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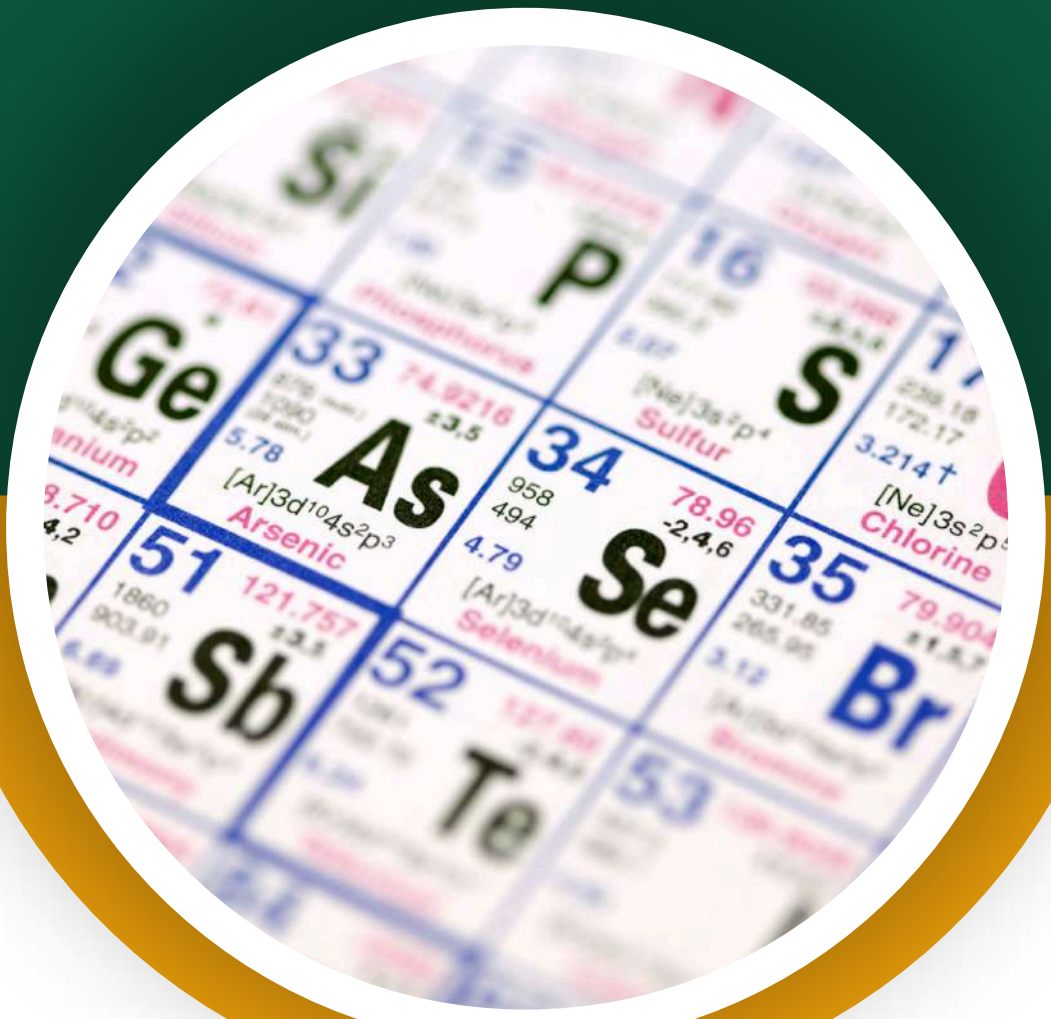
HANDBOOK ON

ADVANCES OF 2-HETERYL / HETEROALKYL-QUINAZOLIN-4(3*H*)-ONES



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BIOGRAPHY

Prof. Mittapelli Vasantha obtained her Ph.D. from Osmania University. Initially, she worked as a Lecturer in Department of Chemistry, P.G. Section, N.B. Science College, Hyderabad, after a spell of more than 3 years, she moved to Mylan Laboratories, Hyderabad and worked as R&D Executive to Senior Manager (R&D) for about nine years. She joined as Associate Professor in the Department of Chemistry, Mahatma Gandhi University, Nalgonda and got promoted as Professor.

She has about 31 years of research experience including 9 years in Pharmaceutical Industry and more than 15 years of academic as well as administrative experience in various positions at Mahatma Gandhi University. She has organized 12 Seminars/Conferences.

Prof. M. Vasantha has published 31 research papers in national and international Journals and 1 Book Chapter. She completed 3 research projects and was awarded one Ph.D. & 7 P.G Dissertations under her guidance. Her research areas are Bioactive Nitrogen Heterocycles, Biofuels, and Nano Chemistry.

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PREFACE

This book describes the synthesis and importance of 2-heteryl / heteroalkyl / heteroaryl-quinazolin-4(3*H*)-ones. The promise exhibited by these compounds as drug candidates has encouraged extensive research on quinazolin-4(3*H*)-one, and the literature is abounding with syntheses and pharmacological activity.

We are now aiming to consolidate and present an overview of various strategies known in literature up to September 2023 for the synthesis of 2-heteryl / heteroalkyl / heteroaryl-quinazolin-4(3*H*)-ones along with their importance in medicine and industry. A tentative classification of the compounds proposed for inclusion in the chapter is indicated below, and it is based on the nature of the 2-heteryl substituent in the quinazolin-4(3*H*)-one ring. For this purpose, the compounds have been mainly classified as Heterylquinazolin-4(3*H*)-ones, Heterylalkenyl / Heterylalkyl group, Heterylamine/aminoalkyl/phenyl group, Heterylcarbonyl/ Heterylcarbonylalkyl and Ether& thioether linkages. Further classification is based on the size of the ring attached- three membered, four membered, five membered, six membered and seven membered, nature of the heteroatom (N, O and S) and number of hetero atoms present in the ring.

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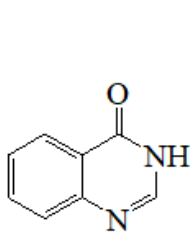
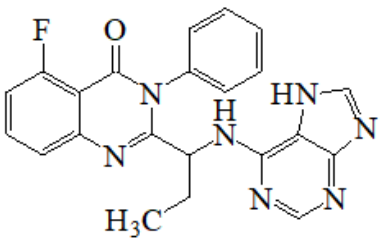
1. Introduction

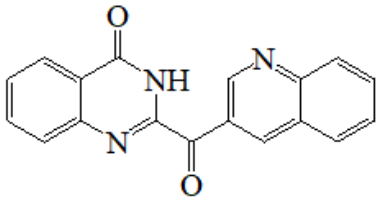
4-Oxo derivative of 1,3-diazanaphthalene is called quinazolin-4(3*H*)-one. Several quinazolin-4(3*H*)-one derivatives are sold as drugs. For example, Idelalisib, sold under the brand name Zydelig is a medication used to treat certain blood cancers, Luotonin F for the treatment of rheumatism and various other inflammatory conditions, Bouchardatine, Orirenierine A, and Orirenierine B are adipogenesis/lipogenesis inhibitors.



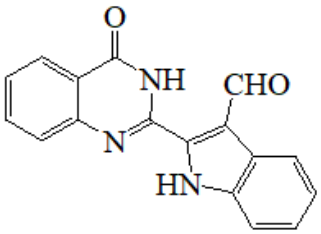
Quinazolin-4(3*H*)-one



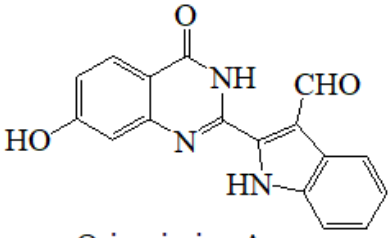
Idelalisib



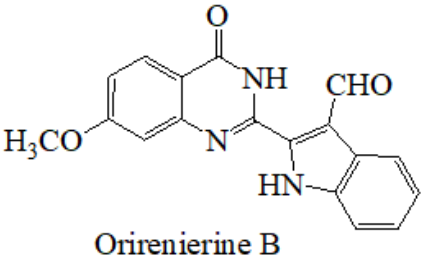
Luotonin F



Bouchardatine



Orirenierine A



Orirenierine B

A number of 2-heteryl, heteroalkyl and heteroaryl-quinazolin-4(3*H*)-ones exhibited a wide range of pharmacological properties such as:

- **PI3Kd** [4, 8, 66, 67, 68, 80, 81,119]
- **antiproliferative** [4, 31, 128, 131]
- **antifeedant** [5]
- **Rock/PKA inhibitors** [6]
- **anti-osteoarthritis** [7]
- **HDAC6 inhibitor** [8]
- **anti-inflammatory** [9, 16,25, 26, 27, 30, 32,33, 37,42, 64, 89, 90, 98, 115, 121, 122, 123]
- **PARP inhibitors** [10]
- **antimicrobial** [11,29, 43, 83, 107, 116, 117, 121, 124]
- **cytotoxic** [12, 14, 18, 44, 102, 104]
- **COX-2inhibitors** [12, 71, 89]
- **AChE inhibitor with anti-inflammatory** [13]
- **adipogenesis/lipogenesis inhibitors** [15]
- **analgesic** [16, 26, 27, 42,71, 78, 89, 98, 121]

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- **body temperature lowering agent**[16]
- **antibacterial** [17, 24, 51, 52, 85]
- **antifungal** [5, 17, 35, 48, 109]
- **piscicidal** [17]
- **MurA inhibitory** [19, 65]
- **PARP-1 inhibitor** [20, 91, 101]
- **anticholinergic** [21]
- **α-Glucosidase and α-Amylase** [22]
- **antitumor** [23,39, 118, 120]
- **anticancer** [25, 47, 54, 70, 105, 111, 114, 125]
- **NF-kB and AP-1 inhibitors** [25, 32, 33]
- **MAO-A and MAO-B inhibitors**[28]
- **antidepressant** [28]
- **antiviral** [31, 40]
- **antitrypanosomal** [34]
- **antileishmanial** [34, 106]
- **Human Methionine Aminopeptidase-1 Inhibitor** [36]
- **CYP1B1 inhibitors**[38]
- **hypnotic** [41, 42, 59, 61]
- **anticonvelsant**[42]
- **sedative** [42]
- **muscle relaxant** [42, 59, 61]
- **DNAPK** [45]
- **osteogenesis** [46]
- **anti-influenza** [49]
- **induce myeloid differentiation** [50]
- **diuretic agents** [53]
- **dyes** [55]
- **AMPA receptor antagonist** [56, 57, 60, 63, 87]
- **anti-tubercular agents** [58, 82, 117]
- **plasmotic** [59]
- **anticonvulsant** [59, 61]
- **tranquilising** [59]
- **homologous recombinase RAD51**[62]
- **antihistamine**[69, 78, 93]
- **COX-171, ulcerogenic** [71, 84, 98]
- **heat resistant** [72]
- **CCK antagonists** [73,74,75]
- **PET Imaging of PDE 10A** [76]
- **PDE10A inhibitors** [77]
- **hypotensive** [78]

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- antihypotensive [79]
- HDAC inhibitor [80]
- hypoglycemic [86]
- CXCR3 antagonist [88]
- radioligand for histamine H3 receptor occupancy [92]
- fiber reactive dyes [94]
- chemosensor [95]
- PDE V inhibitor [96, 97, 132]
- PDE II inhibitor97, cycloxygenase [98]
- NR2B selective NMDA receptor antagonists [99]
- (MMP)-13 zinc-binding inhibitor [100]
- ZAP70 and Syk kinases inhibitor [103]
- DHFR inhibitor [108, 110]
- antiulcer [112, 118, 129, 130]
- antihelmentic [113]
- allosteric Chk1 kinase inhibitors [126]
- antioxidant [127]
- VEGFR-2 inhibitor [128]

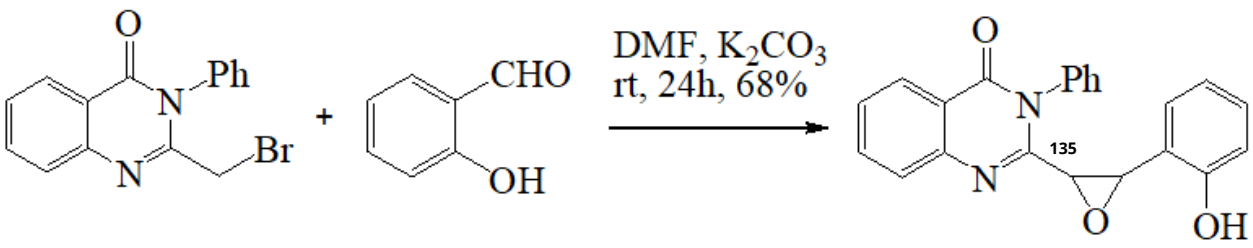
The promise exhibited by these compounds as a drug candidate has encouraged extensive research on quinazolin-4(3*H*)-one, and the literature is abounding with novel syntheses and transformations of this ring system. Our laboratory has been engaged in the design and synthesis of new 2-heteryl-quinazolin-4(3*H*)-ones in search of 'drug candidates' and published several papers including two review articles.[133, 134] We are now aiming to consolidate and present an overview of various strategies known in literature for the synthesis of 2-heterylquinazolin-4(3*H*)-ones along with their importance in medicine and industry. A tentative classification of the compounds is based on the nature of the 2-heteryl substituent in the quinazolin-4(3*H*)-one ring.

2 Heterylquinazolin-4(3*H*)-ones

2.1 Three membered heteryl ring

2.1.1 Oxiranyl-4(3*H*)-quinazolinone

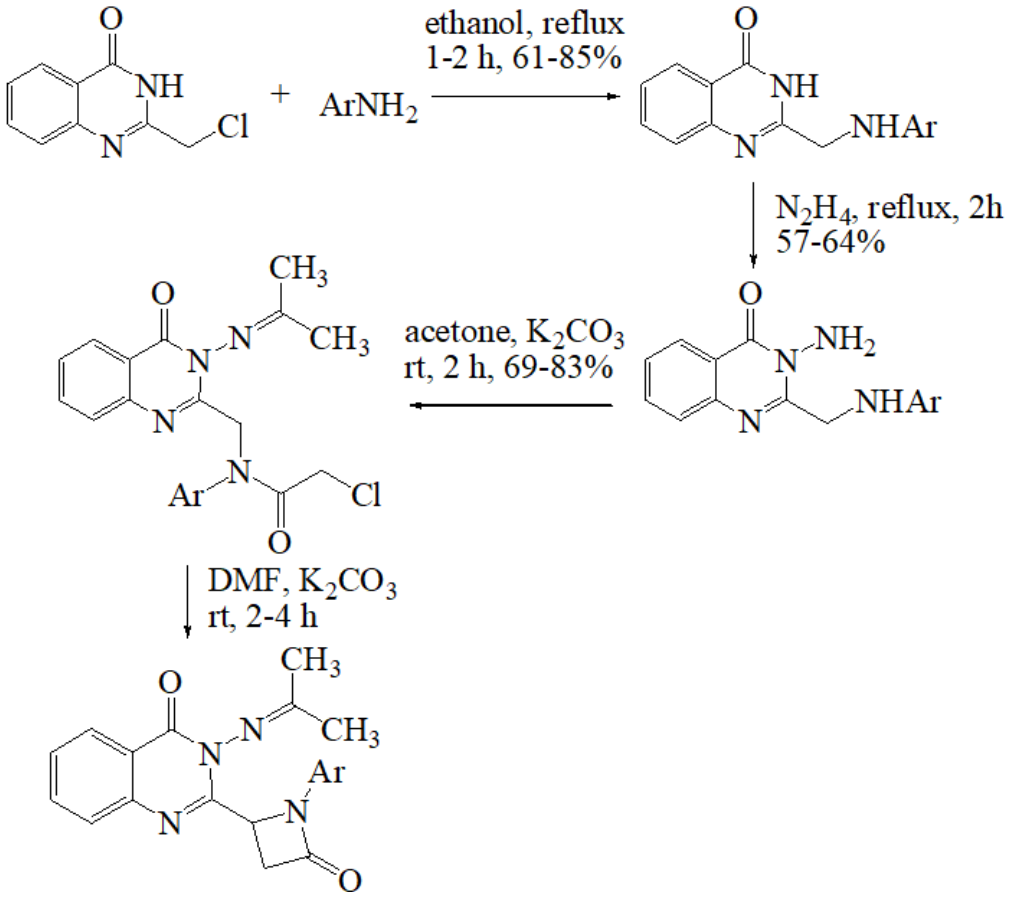
Ismail and Sayed reported the formation of 2-[3-phenyl-4(3*H*)-quinazolinone-2-yl]-3-(2-hydroxyphenyl)oxirane in the reaction of 2-bromomethyl-3-phenyl-4(3*H*)-quinazolinone and 2-hydroxybenzaldehyde, conducted at room temperature in DMF containing anhydrous potassium carbonate. The reaction mechanism is analogous to Darzens condensation.



2.2 Four Membered heteryl ring

2.2.1 Azetidinylquinazolin-4(3*H*)-ones

This 1-aryl-4-[isopropylideneamino/methyl-4(3*H*)-oxoquinazolin-2-yl]azetidin-2-ones were prepared starting from 2-chloromethyl-4(3*H*)-quinazolinone. Reaction of chloromethyl compound with arylamine yielded 2-arylaminomethyl-4(3*H*)-quinazolinone. Conversion of arylamine derivative to 3-amino-2-arylaminomethyl-4(3*H*)-quinazolinone, and its chloroacetyl derivative - 2-*N*-chloroacetylarylaminomethyl-3-isopropylidineamino-4(3*H*)-quinazolinone, are the key steps in the synthesis of 2-(azetidin-2-one-4-yl)-4(3*H*)-quinazolinone. Base catalyzed dehydrochlorinative cyclization of the resultant compounds to target compounds was achieved by stirring in DMF containing K_2CO_3 at room temperature.[136]



Potent PI3Kd and cell proliferative 5-substituted-2-(1-(2-alkyl-4-amino-5-cyanopyrimidine-6-yl)azetidin-2-yl)-quinazolin-4(3*H*)-ones were obtained from 2-amino-6-bromobenzoic acid. The reaction of 2-amino-6-bromobenzoic acid with a (*S*)-1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid in the presence of triphenyl phosphite and pyridine and subsequent addition of aniline to the reaction mixture resulted in formation of Boc protected 2-((*S*)-azetidin-2-yl)-5-bromo-3-phenylquinazolin-4(3*H*)-one. Deprotection with TFA followed by alkynyl of substituted quinazolinones via a Sonagashira coupling of aryl bromide under $Pd(PPh_3)_2Cl_2$/CuI yielded the corresponding terminal alkynes. Incorporation of the hinge binder motif was accomplished by the nucleophilic displacement of substituted 4-chloro-pyrimidines in the presence of DIPEA at 130-160°C under microwave irradiation and the title compounds were obtained in 76-79% yields.[4]

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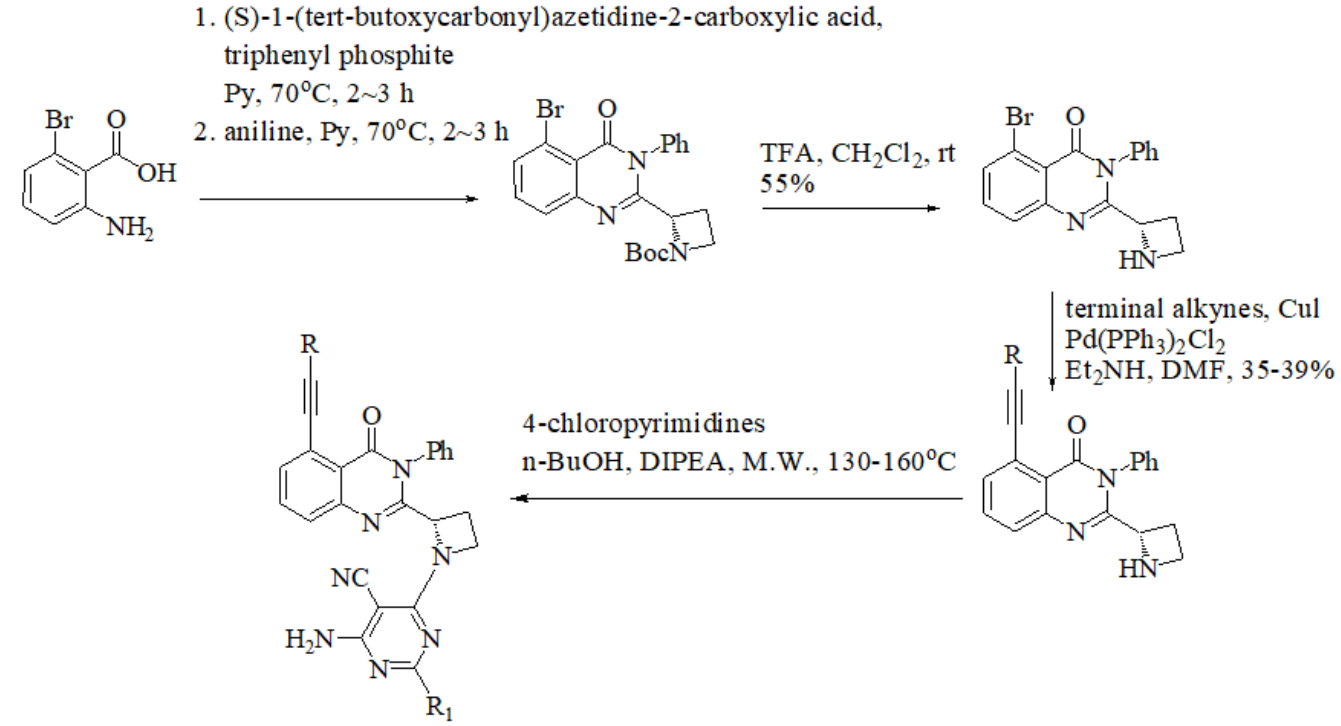
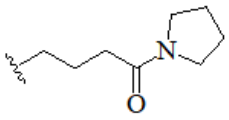
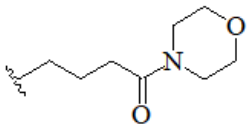
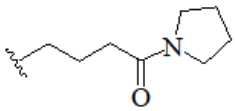
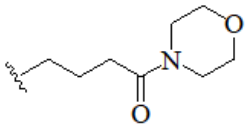


R	R1	Yield(%)	R	R1	Yield(%)
	H	77		H	76
	NH_2	79		NH_2	78

Reddy et.al reported the synthesis of [bis-(4-(3-methylquinazolin-4(3*H*)-one-2-yl)azetidin-2-one-yl)]phenyl/biphenyl/diphenylmethane. 2-Chloromethylquinazolin-4(3*H*)-one was reacted with arylamine to yield [*N,N*'-bis((3-methylquinazolin-4(3*H*)-one-2-yl)methyl)aryldiamine. Conversion of amine derivative to *N,N*'-dichloroacetyl-[*N,N*'-bis((3-methylquinazolin-4(3*H*)-one-2-yl)-methyl)] aryldiamine with chloroacetyl chloride followed by base catalyzed dehydrochlorinative cyclization with K_2CO_3 in DMF to isolate compound corresponding bis (quinazolinonyl-β-lactams). 3,3'-Dimethyl -4,4'-[*N,N*'-dichloroacetyl-N,N'-bis((3-methylquinazolin-4(3*H*)-one-2-yl)methyl)] diaminobi-phenyl is the most promising with 66.26% antifeedant activity even at 6.25µg/cm^{2}concentration.[5, 137]

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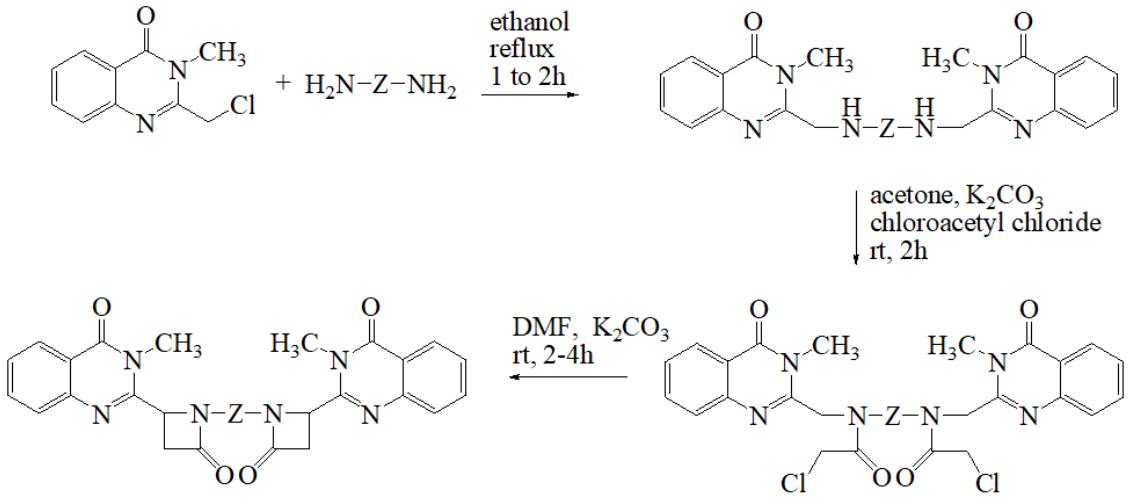
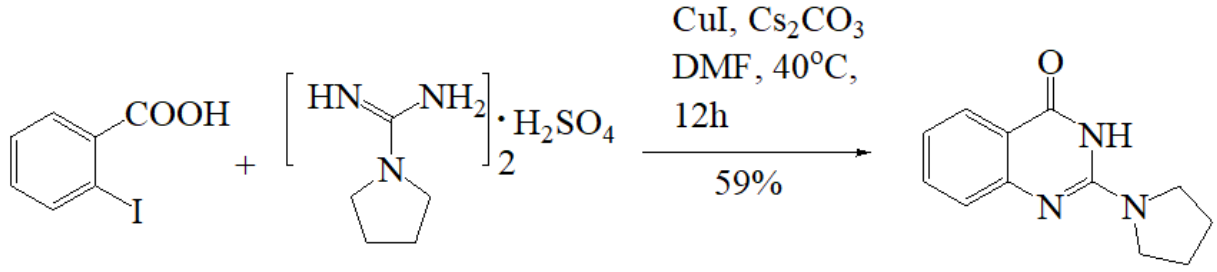


5	a	b	c	d	e
Z	1,4-C_6H_4-	4,4'-C_6H_4-C_6H_4-	4,4'-C_7H_6-C_7H_6-	4,4'-C_6H_4-CH_2-C_6H_4	4,4'-C_7H_6O-CH_2-C_7H_6O
Yield	80	70	85	83	72

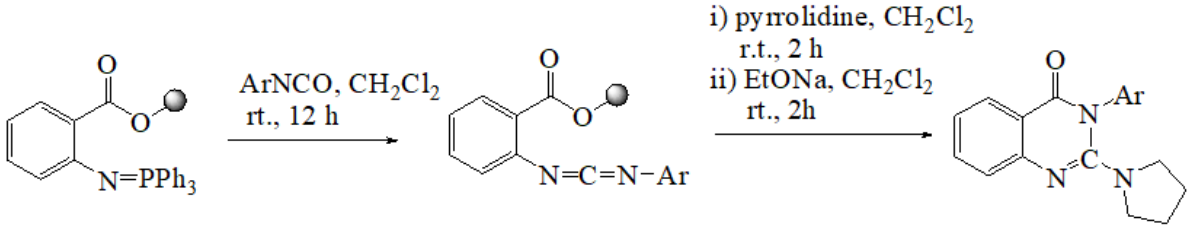
2.3 Five-Membered heteryl ring

2.3.1 Pyrrolidinylquinazolin-4(3*H*)-ones

2-Iodobenzoic acid was reacted with pyrrolidine-1-carboxamidine salt in *N,N*-dimethylformamide in presence of CuI and Cs_2CO_3 under nitrogen atmosphere to isolate 2-(pyrrolidin-1-yl)-quinazolin-4(3*H*)-one. The yield of the reaction increased to 72% at reaction temperature of 80°C.[138]

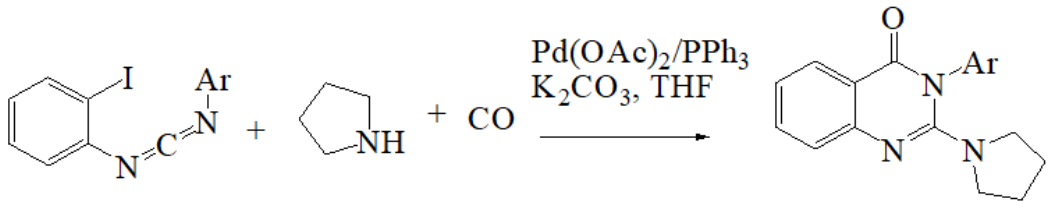


Xie et.al prepared 2-(pyrrolidin-1-yl)-3-arylquinazolin-4(3*H*)-one from poly(ethylene glycol) (PEG) supported aza-Wittig reaction. Quinazolinones were synthesized efficiently by reaction of secondary amine with PEG-supported carbodiimides, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes with isocyanates.[139]



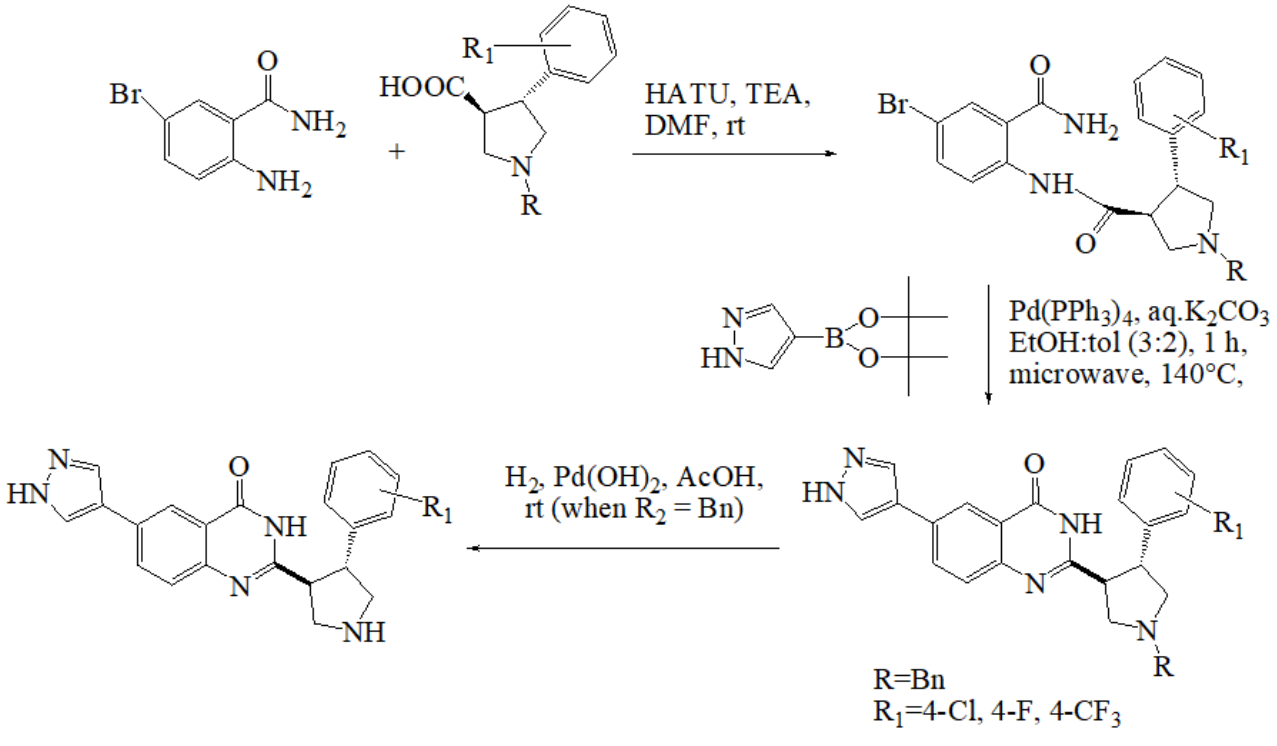
Ar	Ph	4-ClC_6H_4	4-FC_6H_4
Yield(%)	81	75	88

Synthesis of 3-aryl-2-(pyrrolidin-1-yl)quinazolin-4(3*H*)-one by palladium-catalyzed inter molecular addition and intramolecular cyclocarbonylation cascade reaction of *N*-(2-iodophenyl)-*N*′-aryldicarbodiimide with pyrrolidine was reported.[140]



Ar	yield (%)
Ph	96
4-$CH_3OC_6H_4$	93
4-ClC_6H_4	92
1-Naph	70

Rock/PKA inhibitors 2-(4-arylpyrrolidin-3-yl)-6-(1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one derivatives were obtained by coupling of an 2-amino-5-bromobenzamide with Bn-L-proline derivatives, palladium-catalyzed Suzuki coupling to get *N*-protected 2-(4-arylpyrrolidin-3-yl)quinazolin-4(3*H*)-one derivatives followed by deprotection using $Pd(OH)_2$ in AcOH.[6]



A new method for the preparation of 2-((3-(*N*-tertiarybutyloxycarbonyl-*N*-methyl)amino) pyrrolidin-1-yl)-6-phenoxy-quinazolin-4(3*H*)-one is described by warming a mixture of an tert-butyl (*E*)-1-amidinopyrrolidin-3-ylmethylcarbamate and carbonyl diimidazole in acetonitrile results in formation of a putative *N*-amidinoisocyanate intermediate which undergoes a 6p-electron electrocyclic reaction with the aryl ring.[141]

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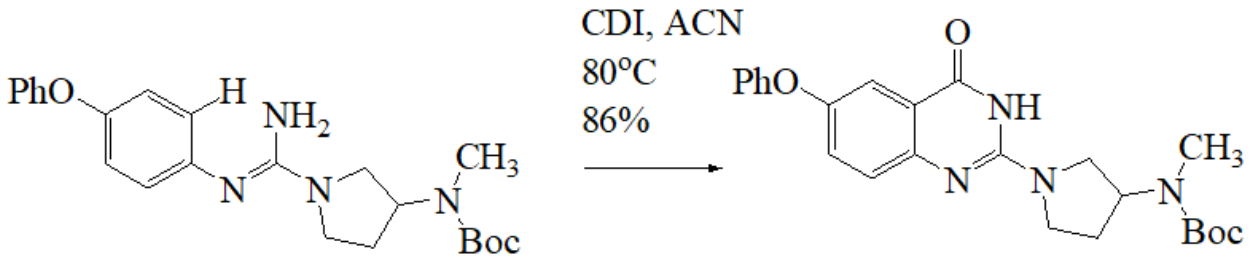
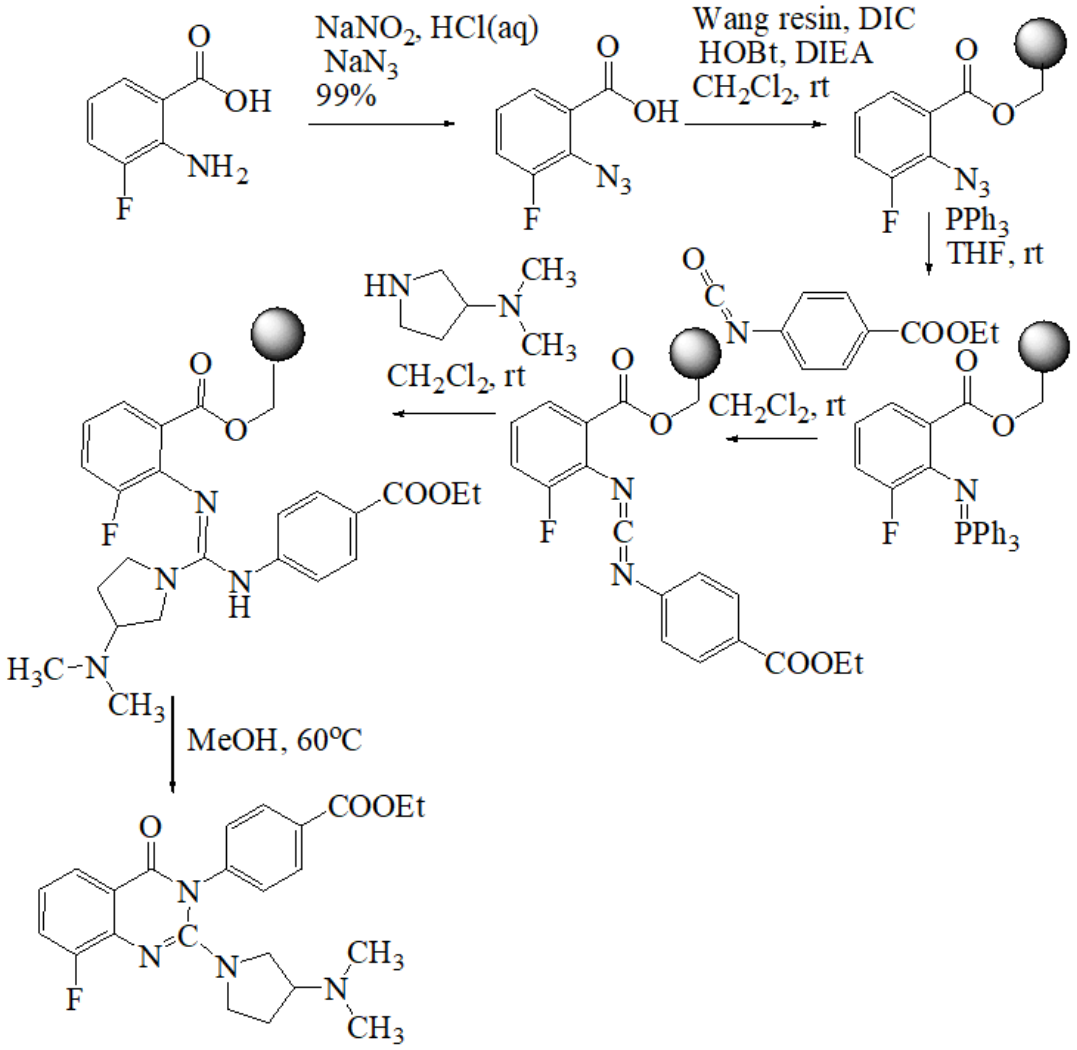


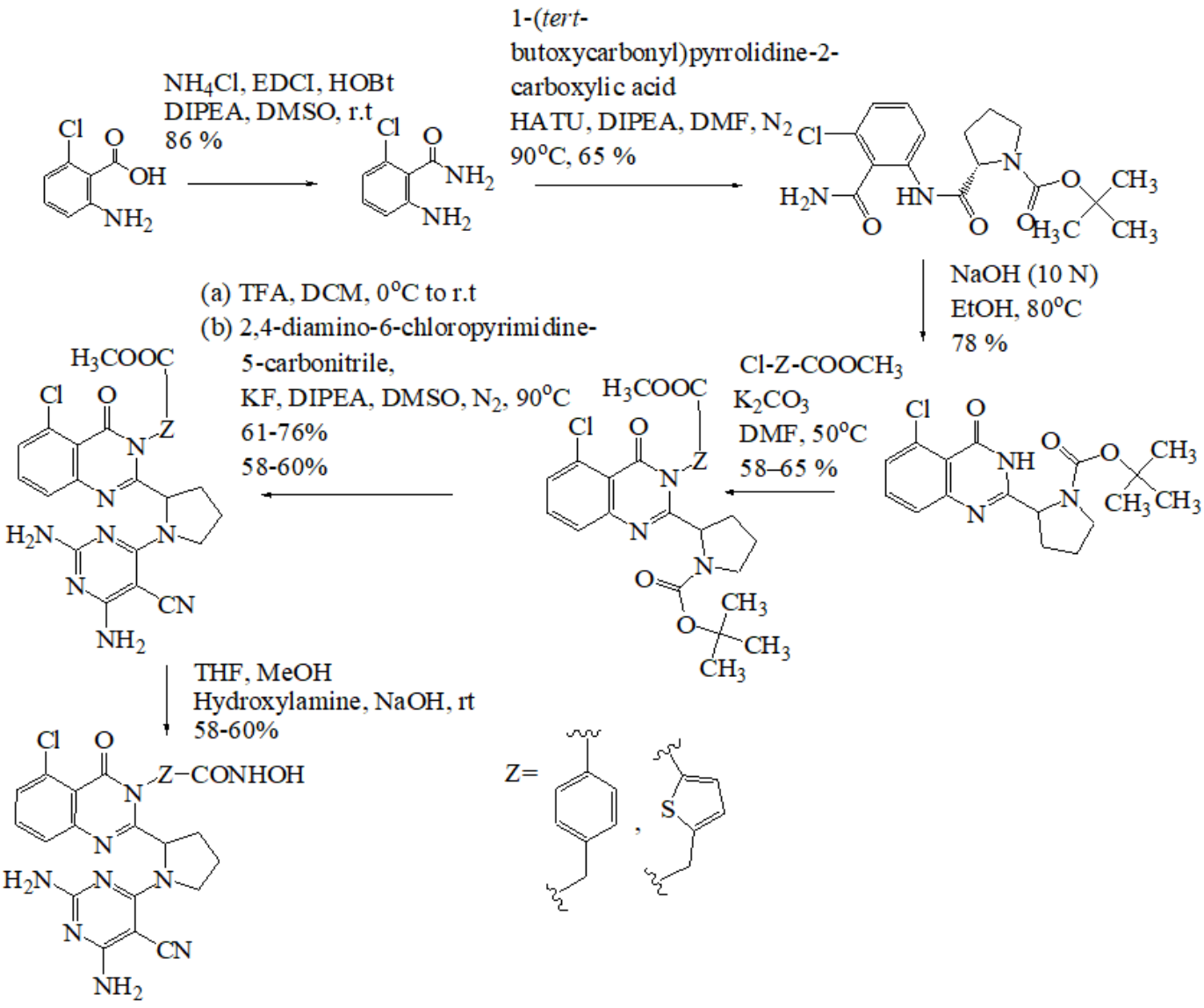
Azidation of the easily available 2-amino-3-fluorobenzoic acid under Sandmeyer conditions gave 2-azido-3-fluorobenzoic acid, coupling using typical amidation conditions with dicyclohexylcarbodiimide to afford the corresponding polymerboundortho-azide ester.

Exposing the azide with PPh_3 in tetrahydrofuran at room temperature to iminophosphorane, followed by isocyanate, to give carbodiimide derivative. Finally, treatment with pyrrolidine derivative, followed by intramolecular cyclization and simultaneous cleavage from the resin, provided the 8-fluoro-2-(3-(dimethylamino)pyrrolidin-1-yl)-3-(4-ethoxycarbonyl phenyl)quinazolin-4(3*H*)-one. These compounds have exhibited anabolic activity toward chondrogenic differentiation and provide relief against articular cartilage damage i.e anti-osteoarthritis.[7]

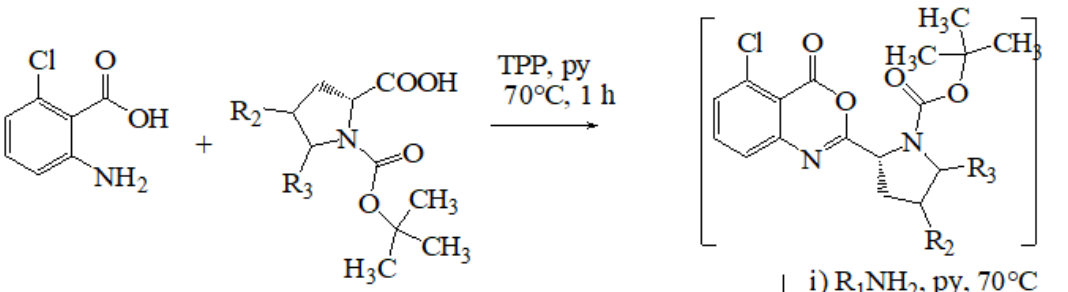


2.3.2 Pyrimidinylpyrrolidinylquinazolin-4(3*H*)-one

2-Amino-6-chlorobenzoic acid was converted into corresponding amide upon the treatment with NH_4Cl in the presence of EDCI, HOBt and DIPEA. The newly formed intermediate was subsequently condensed with 1-(tert-butoxycarbonyl) pyrrolidine-2-carboxylic acid leading to the generation of the diamide. The intramolecular cyclization under basic condition and nucleophilic substitution at 2° nitrogen with chlorinated ester derivatives was furnished with the corresponding quinazolinone derivatives. After unmasking the amino group of pyrrolidine moieties, SNAr reaction with 2,4-diamino-6-chloropyrimidine-5-carbonitrile to provided 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-pyrrolidin-2-yl)-3-(((4-methoxycarbonyl)phenyl)methyl) -5-chloroquinazolin-4(3*H*)-one and 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-pyrrolidin-2-yl) -3-((5-(methoxycarbonyl)thiophene-2-yl)methyl)-5-chloroquinazolin-4(3*H*)-one followed by reaction with hydroxylamine to afford 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-pyrrolidin-2-yl)-3-(((4-hydoxylaminocarbonyl)phenyl)methyl)-5-chloroquinazolin-4(3*H*)-one & 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-pyrrolidin-2-yl)-3-((5-(hydoxylaminocarbonyl)thiophene-2-yl)methyl)-5chloroquinazolin- 4(3*H*)-one. These compounds are PI3Kδ and HDAC6 inhibitors.[8]



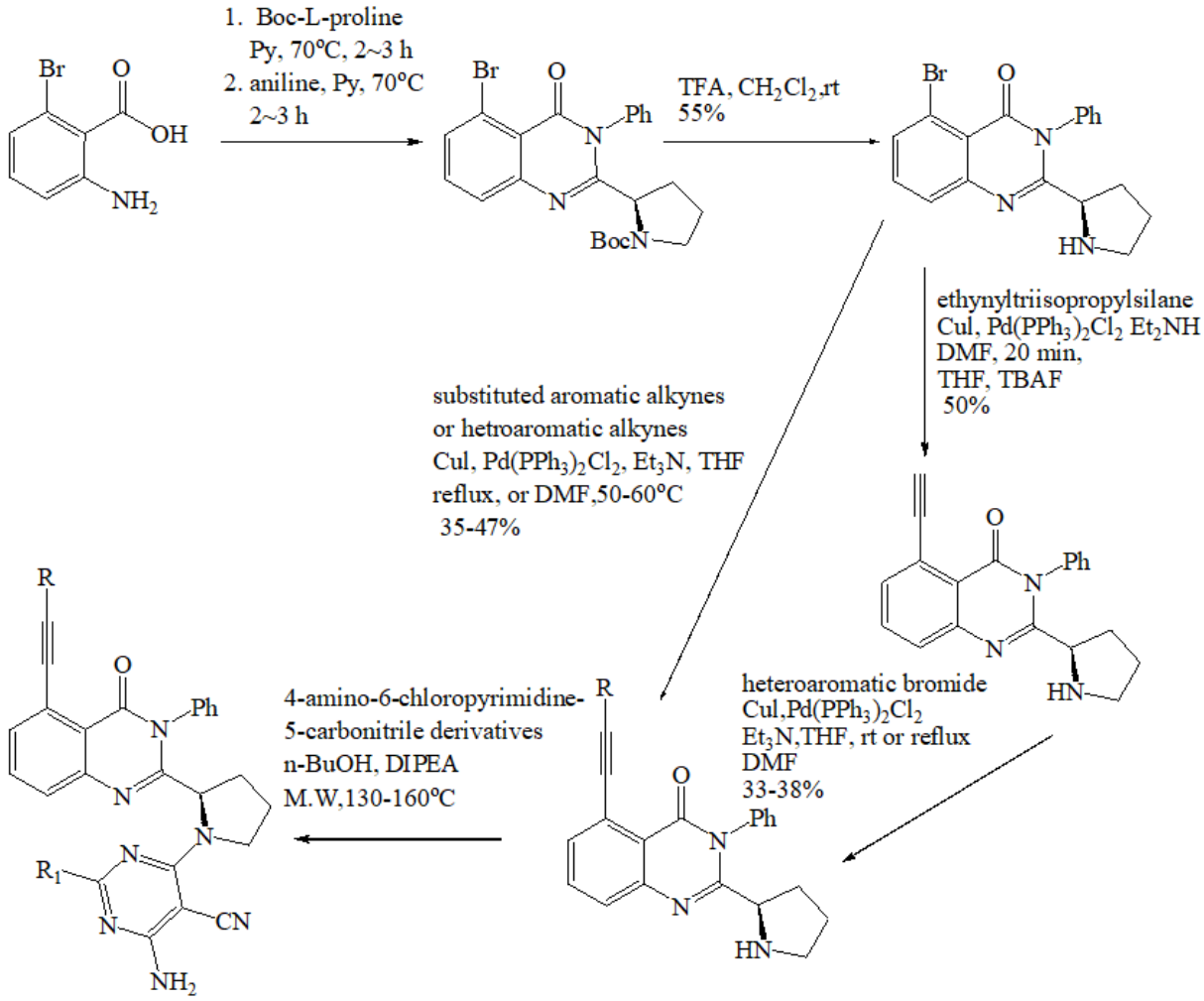
In similar lines, the quinazolinone cores were prepared via one-pot, two step dehydrative cyclization, by treatment of 2-amino-6-chlorobenzoic acid and the BOC-L-proline derivatives with triphenyl phosphate (TPP) and pyridine stirred at 70°C under nitrogen for 1h, followed by addition of the appropriate amino compounds. The *N*-Boc deprotection of resultant compounds with concentrated hydrochloric acid afforded the key amine intermediates- 2-(pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives. The key amine intermediates were reacted with the 4-amino-6-chloro-pyrimidine-5-carbonitrile in the presence of triethylamine and n-butyl alcohol to generate desired 2-(1-(pyrimidin-4-yl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives. These compounds have been shown promising anti-inflammatory activity.[9]

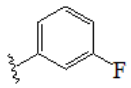
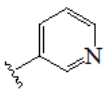
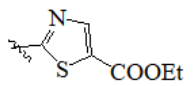
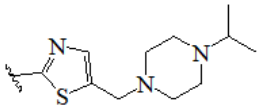
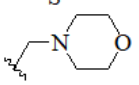
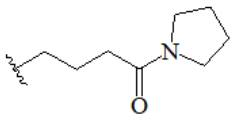
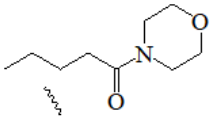


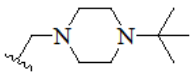
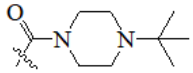
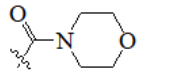
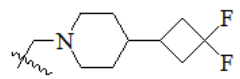
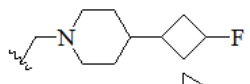
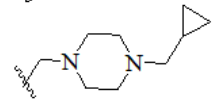
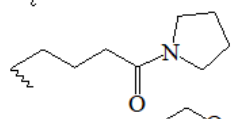
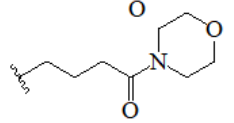
R_1	R_2	R_3	yield(%)
Ph	cyclopropyl	H	72
Ph	vinyl	H	72
Ph	(R)(allyloxy)	H	53
Ph	difluoro	H	82
Ph	H	CH_3	80
3-F-phenyl	H	CH_3	82
3-pyridyl	H	CH_3	67
morpholinyl	H	CH_3	79

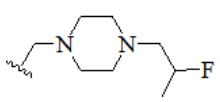
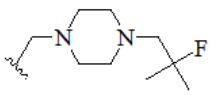
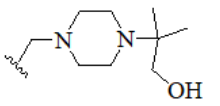
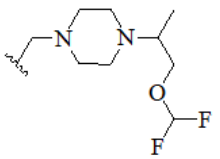
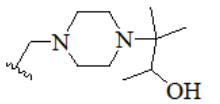
Compounds with potent PI3Kd and cell proliferation activities were obtained from 2-amino-6-bromobenzoic acid. The reaction of 2-amino-6-bromobenzoic acid with a Boc-L-proline in the presence of triphenyl phosphite containing pyridine and subsequent addition of aniline to the reaction mixture resulted in formation of (*S*)-tert-butyl 2-(5-bromo-3,4-dihydro-4-oxo-3-phenylquinazolin-2-yl)pyrrolidine-1-carboxylate. Deprotection with TFA to 5-bromo-3-phenyl-2-((*S*)-pyrrolidin-2-yl)quinazolin-4(3*H*)-one followed by alkynyl via palladium-catalyzed Sonagashira coupling of 5-bromo-3-phenyl-2-((*S*)-pyrrolidin-2-yl)quinazolin-4(3*H*)-one with ethynylsilane, coupling of resulting alkyne with appropriate heteryl / heteroalkyl bromides under Pd $(PPh_3)_2Cl_2$/CuI followed by condensation with 4-amino-6-chloropyrimidine-5-carbonitrile derivatives under microwave irradiation at 130-160 °C yielded 5-substituted-2-(1-(2-alkyl-4-amino-5-cyanopyrimidine-6-yl)pyrrolidin-2-yl)-quinazolin-4(3*H*)-ones.[4]

DOI: https://doi.org/10.5281/zenodo.13644773



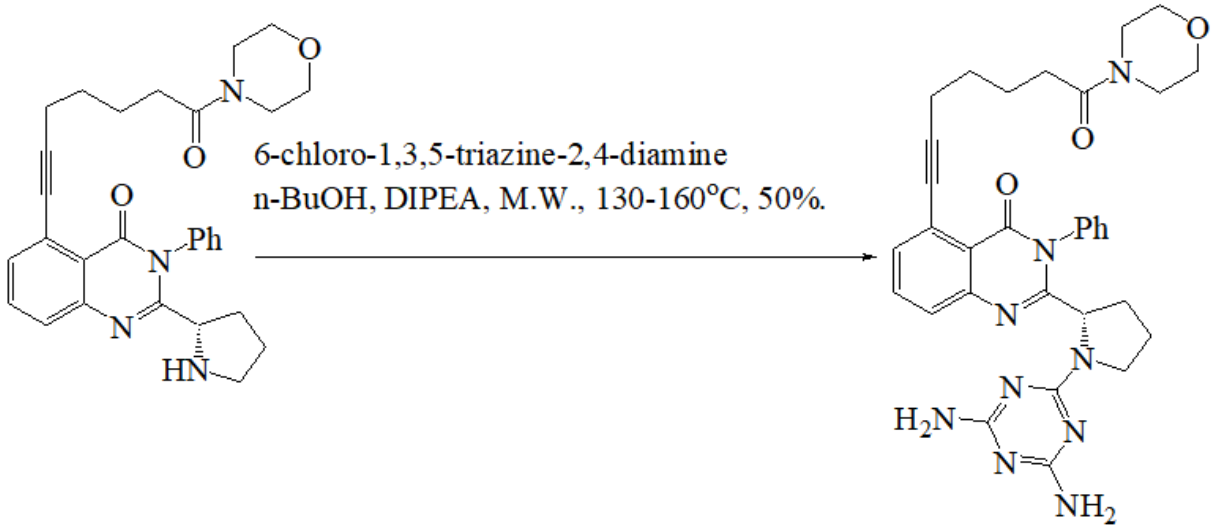
R	R1	Yield(%)
	H	71
	H	73
	H	70
	H	66
	H	69
	H	65
	H	80
	H	68
	H	75

R	R1	Yield(%)
	H	77
	H	74
	H	65
	H	66
	H	73
	H	79
	H	79
	NH_2	79
	NH_2	73

R	R1	Yield(%)
	H	77
	H	79
	H	67
	H	68
	H	66

2.3.3 Triazinylpyrrolidinylquinazolin-4(3*H*)-one

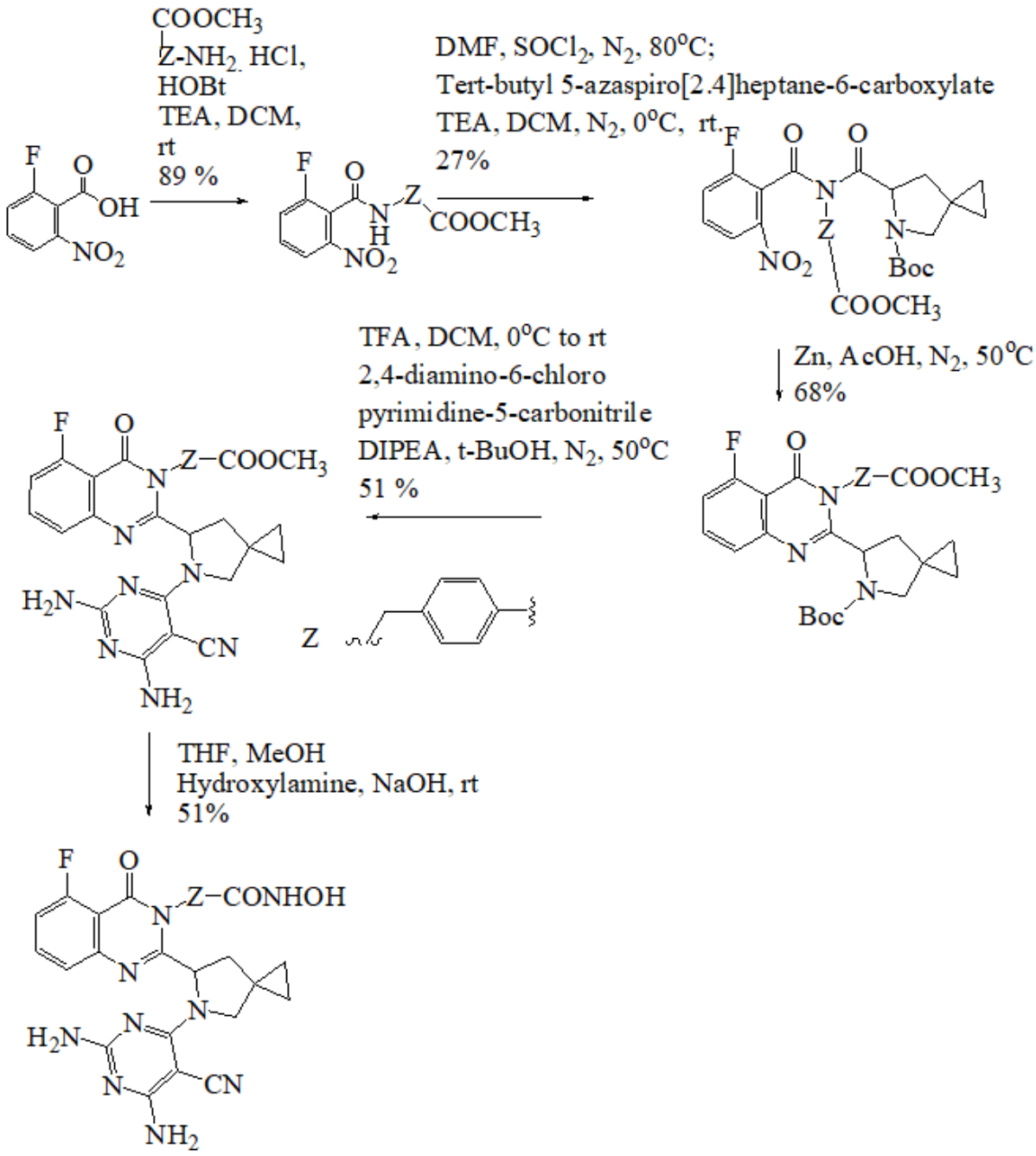
2-(1-(4,6-Diamino-1,3,5-triazin-2-yl)pyrrolidin-2-yl)-5-(7-morpholino-7-oxohept-1-ynyl)-3-phenylquinazolin-4(3*H*)-one with potent PI3Kd and cell proliferation activities was obtained by the reaction of 5-(7-morpholino-7-oxohept-1-ynyl)-3-phenyl-2-(pyrrolidin-2-yl)quinazolin-4(3*H*)-one with 6-chloro-1,3,5-triazine-2,4-diamine in the presence of DIPEA at 130-160 °C under microwave irradiation.[4]



2.3.4 Pyrimidinylazaspiroheptanylquinazolin-4(3*H*)-one

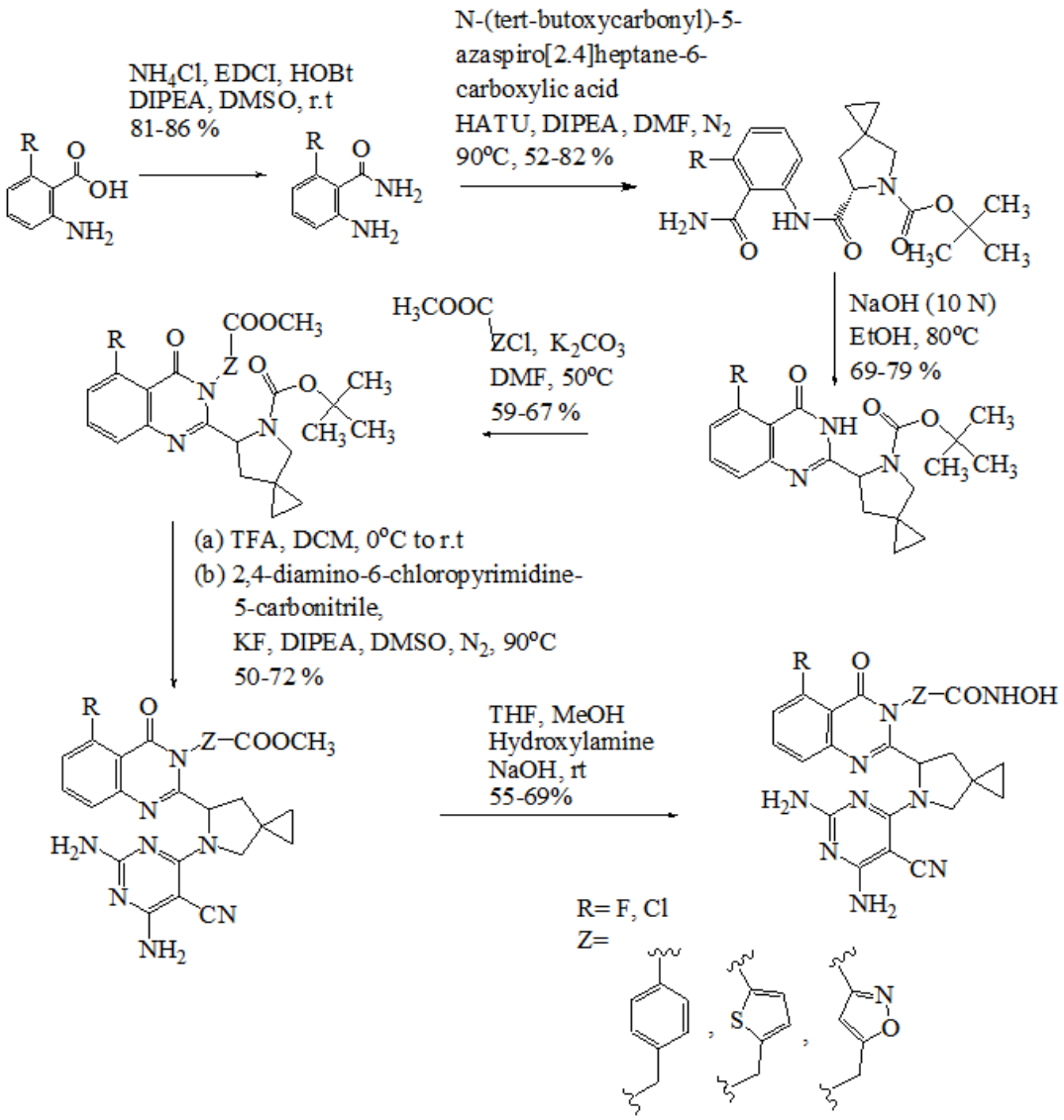
The PI3Kδ and HDAC6 inhibitors are synthesized from 2-fluoro-6-nitrobenzoic acid. The 2-fluoro-6-nitrobenzoic acid is condensed with methyl 4-(aminomethyl)benzoate hydrochloride to afford the amide intermediate. Subsequently, it was converted into imidoyl chlorides, which underwent an in situ Mumm rearrangement after the treatment with tert-butyl 5-azaspiro[2.4]heptane-6-carboxylate to generate the corresponding imide. The imide was then subjected to a one-pot reduction of the nitro moiety and the intramolecular cyclization, there by furnishing the quinazolone derivative. After unmasking the amino group, SNAr reaction with 2,4-diamino-6-chloropyrimidine-5-carbonitrile to get 2-(5-(2,6-diamino-5-cyanopyrimidin-4-yl)-5-azaspiro[2.4]heptan-6-yl)-3-(((4-methoxycarbonyl)phenyl)methyl)-5-fluoro-quinazolin-4(3*H*)-one followed by reaction with hydroxylamine provided 2-(5-(2,6-diamino-5-cyanopyrimidin-4-yl)-5-azaspiro[2.4]heptan-6-yl)-3-(((4-hydroxylaminocarbonyl)phenyl)methyl)-5-fluoro-quinazolin-4 (3*H*)-one.[8]

DOI: https://doi.org/10.5281/zenodo.13644773



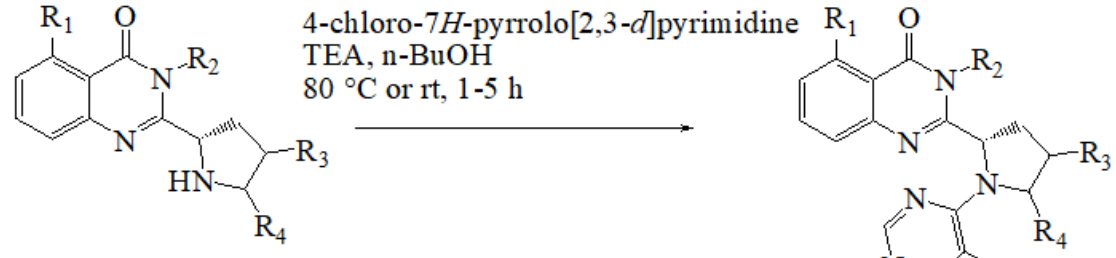
Alternatively, pyrimidinylazaspiroheptanylquinazolin-4(3*H*)-one derivatives were prepared from 2-aminobenzoic acid derivatives. The anthranilic acid derivatives were converted into corresponding amides upon the treatment with NH_4Cl in the presence of EDCI, HOBt and DIPEA. The newly formed intermediates were subsequently condensed with *N*-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid leading to the generation of the diamide derivatives. The following intramolecular cyclization under basic condition and nucleophilic substitution with corresponding bromomethyl or chloromethyl substituted aryl carboxylic ester furnished the 2, 3, 5-trisubstituted quinazolone derivatives. After unmasking the amino group, SNAr reaction with 2,4-diamino-6-chloropyrimidine-5-carbonitrile to get 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-5-azaspiro[2.4]heptan-6-yl)-4(3*H*)-quinazolinone derivatives followed by reaction with hydroxylamine provided corresponding hydroxylamine derivatives. The 2-(*N*-(2,6-diamino-5-cyanopyrimidin-4-yl)-5-azaspiro[2.4]heptan-6-yl)-3-(((4-methoxycarbonyl)phenyl)methyl)-5-chloro-quinazolin-4(3*H*)-one is a potent PI3Kδ and HDAC6 inhibitor.[8]

DOI: https://doi.org/10.5281/zenodo.13644773



2.3.5 Pyrrolopyrimidinylpyrrolidinylquinazolin-4(3*H*)-ones

2-(Pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives were reacted with the 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine in the presence of triethylamine and n-butyl alcohol to generate desired 2-((*S*)-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives. These compounds have been shown promising anti-inflammatory activity.[9]

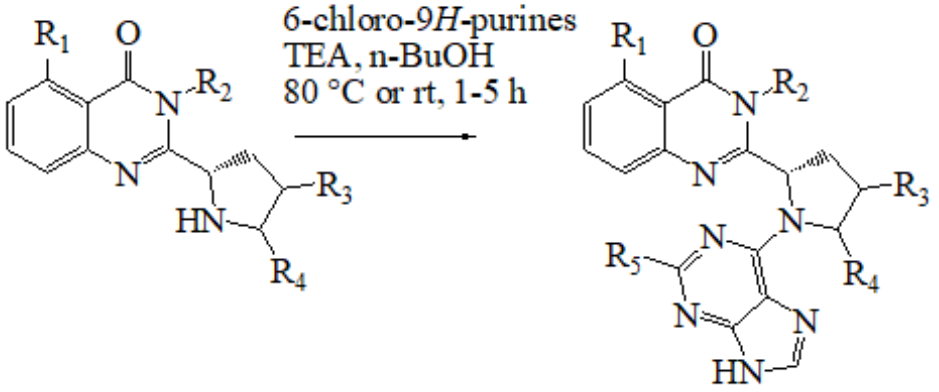


S.No	R_1	R_2	R_3	R_4	yield(%)
12	Cl	Ph	cyclopropyl	H	42
16	Cl	Ph	vinyl	H	42
20	Cl	Ph	(R)(allyloxy)	H	34
24	Cl	Ph	difluoro	H	62
49	Cl	3-fluorophenyl	H	CH_3	45

DOI: https://doi.org/10.5281/zenodo.13644773

2.3.6 Purinylpyrrolidinylquinazolin-4(3*H*)-ones

2-(Pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives were reacted with the 6-chloro-9*H*-purine derivatives in the presence of triethylamine and n-butyl alcohol to generate desired 2-((*S*)-1-(9*H*-purin-6-yl)pyrrolidin-2-yl)quinazolin-4(3*H*)-one derivatives. These compounds have been shown promising anti-inflammatory activity.[9]

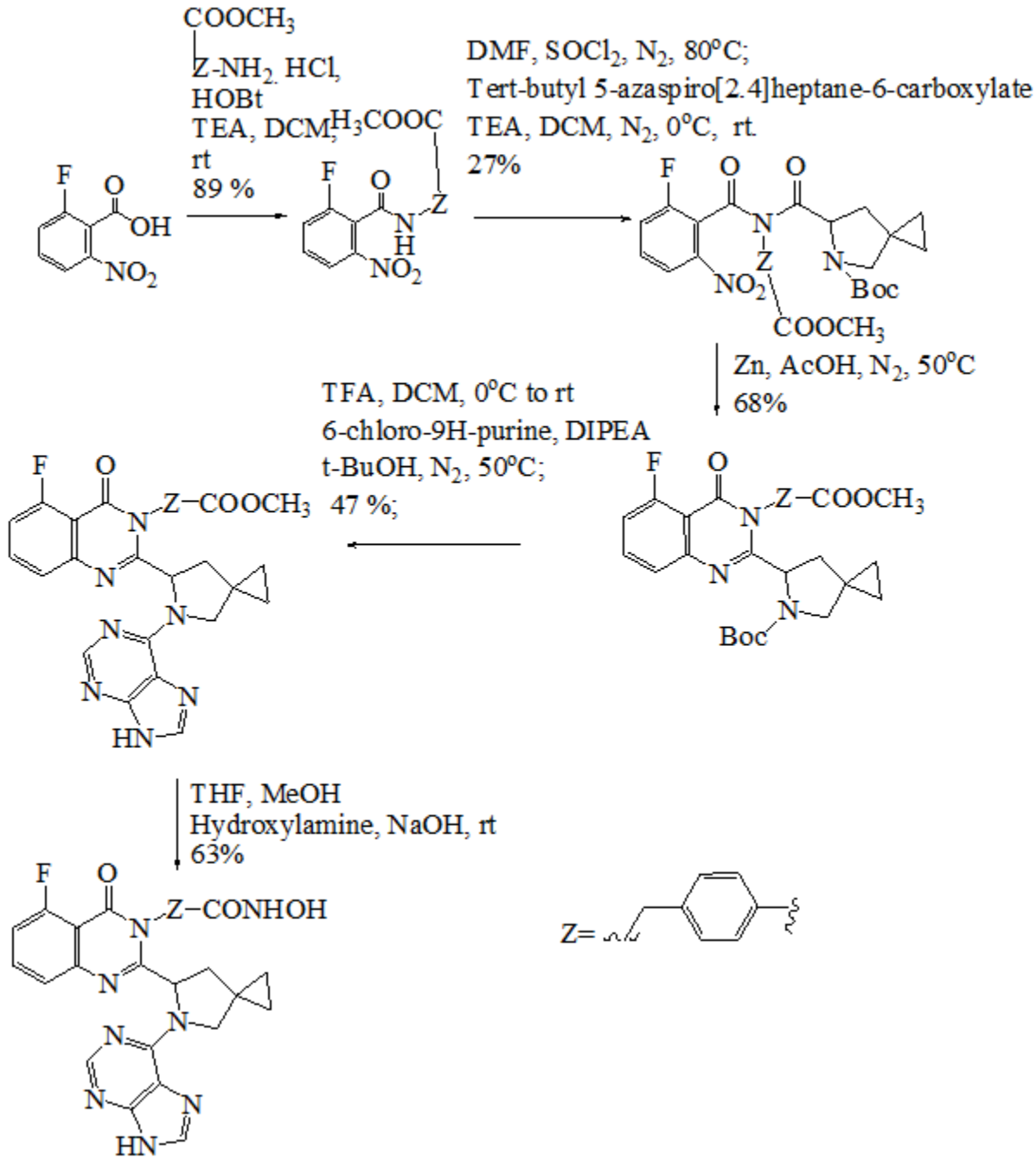


S.No	R_1	R_2	R_3	R_4	R_5	yield(%)
10	Cl	Ph	H	H	NH_2	43
11	Cl	Ph	cyclopropyl	H	NH_2	37
13	Cl	Ph	cyclopropyl	H	H	46
15	Cl	Ph	vinyl	H	NH_2	33
17	Cl	Ph	vinyl	H	H	37
19	Cl	Ph	(R)(allyloxy)	H	NH_2	27
21	Cl	Ph	(R)(allyloxy)	H	H	22
23	Cl	Ph	difluoro	H	NH_2	49
25	Cl	Ph	difluoro	H	H	41
43	Cl	Ph	H	CH_3	NH_2	33
48	Cl	3-fluorophenyl	H	CH_3	NH_2	32
50	Cl	3-fluorophenyl	H	CH_3	H	46

2.3.7 Purinylazaspiroheptanylquinazolin-4(3*H*)-one

2-Fluoro-6-nitrobenzoic acid was condensed with methyl 4-(aminomethyl)benzoate hydrochloride to afford the amide intermediates. Subsequently, they were converted into imidoyl chlorides, which underwent an in situ Mumm rearrangement after the treatment with tert-butyl 5-azaspiro[2.4]heptane-6-carboxylate to generate the corresponding imide. The imide was then subjected to a one-pot reduction of the nitro moiety and the intramolecular cyclization, thereby furnishing the quinazolone derivative. After unmasking the amino group, SNAr reaction with 6-chloro-9*H*-purine-5-carbonitrile to yield 2-(5-(9*H*-purin-6-yl)-5-azaspiro[2.4]heptan-6-yl)-3-(((4-methoxycarbonyl)phenyl)methyl)-5-fluoro-quinazolin-4(3*H*)-one followed by reaction with hydroxylamine provided 2-(5-(9*H*-purin-6-yl)-5-azaspiro[2.4]heptan-6-yl)-3-(((4-hydroxyaminocarbonyl)phenyl)methyl)-5-fluoro-quinazolin-4(3*H*)-one and is a PI3Kδ and HDAC6 inhibitor.[8]

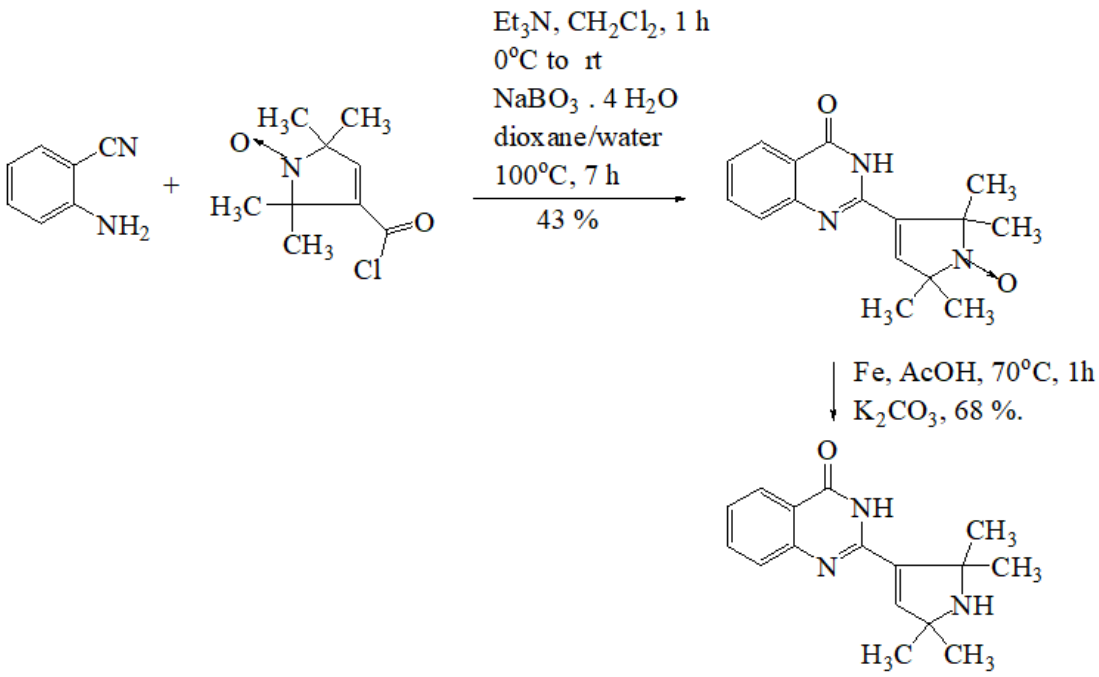
DOI: https://doi.org/10.5281/zenodo.13644773



2.3.8 Dihydropyrrolylquinazolin-4(3*H*)-one

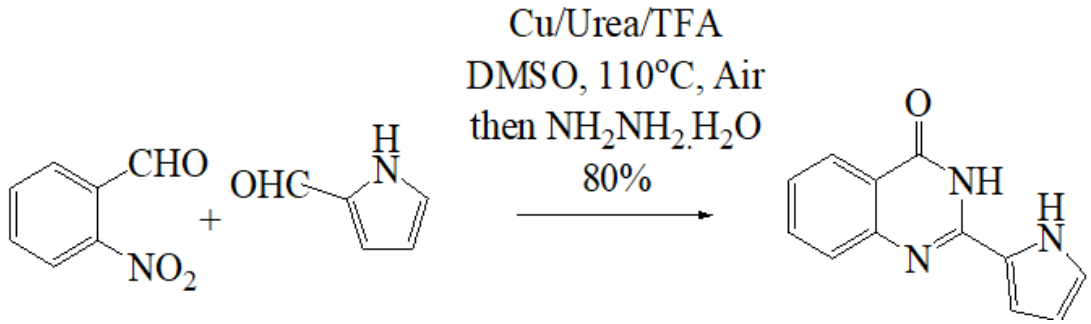
Reaction of 2-aminobenzonitrile with 1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrole-3-carbonyl chloride in CH_2Cl_2 containing Et_3N followed by treatment with $NaBO_3.4H_2O$ yielded the 2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-quinazolin-4(3*H*)-one radical. The resultant nitroxide compound was reduced with Fe powder in acetic acid to isolate 2-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-quinazolin-4(3*H*)-one. These compounds are PARP inhibitors.[10]

DOI: https://doi.org/10.5281/zenodo.13644773

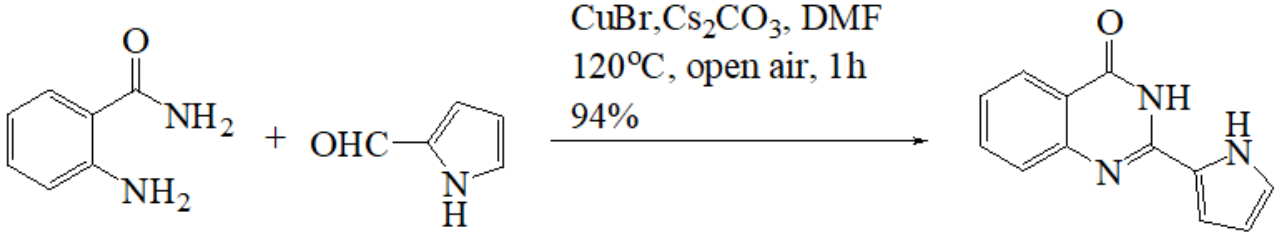


2.3.9 Pyrrolylquinazolin-4(3*H*)-one

2-Nitrobenzaldehyde was treated with urea, Cu(OAc)$_2$ and TFA in a DMSO solvent at 110°C, then hydrazine hydrate and 1*H*-pyrrole-2-carbaldehyde were added sequentially at the same temperature and stirred at room temperature for 12–16 h to isolate 2-(1*H*-pyrrol-2-yl)quinazolin-4(3*H*)-one.[142]

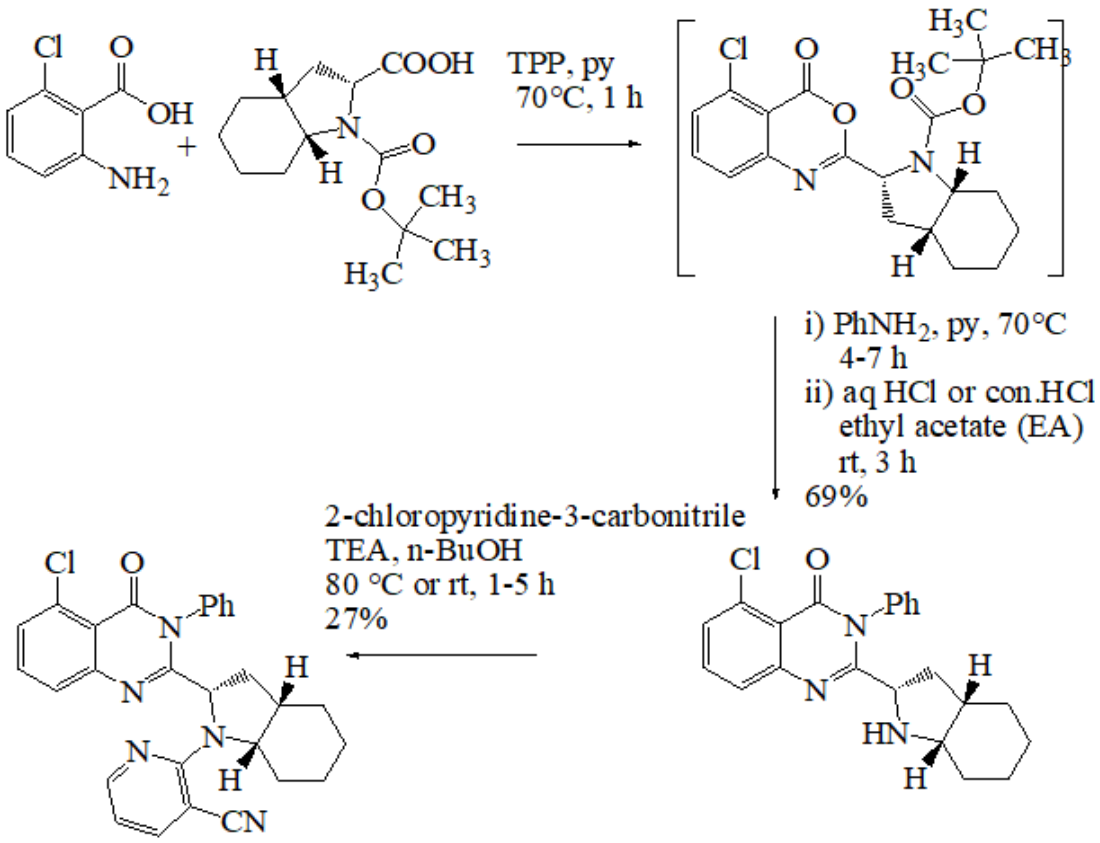


R. Nagarajan et.al reacted 1*H*-pyrrole-2-carbaldehyde with anthranilamide through copper(I) bromide mediated aerobic oxidation reaction to produce the 2-(1*H*-pyrrol-2-yl)quinazolin-4(3*H*)-one.[143]



2.3.10 Pyridinyloctahydroindolylquinazolin-4(3*H*)-one

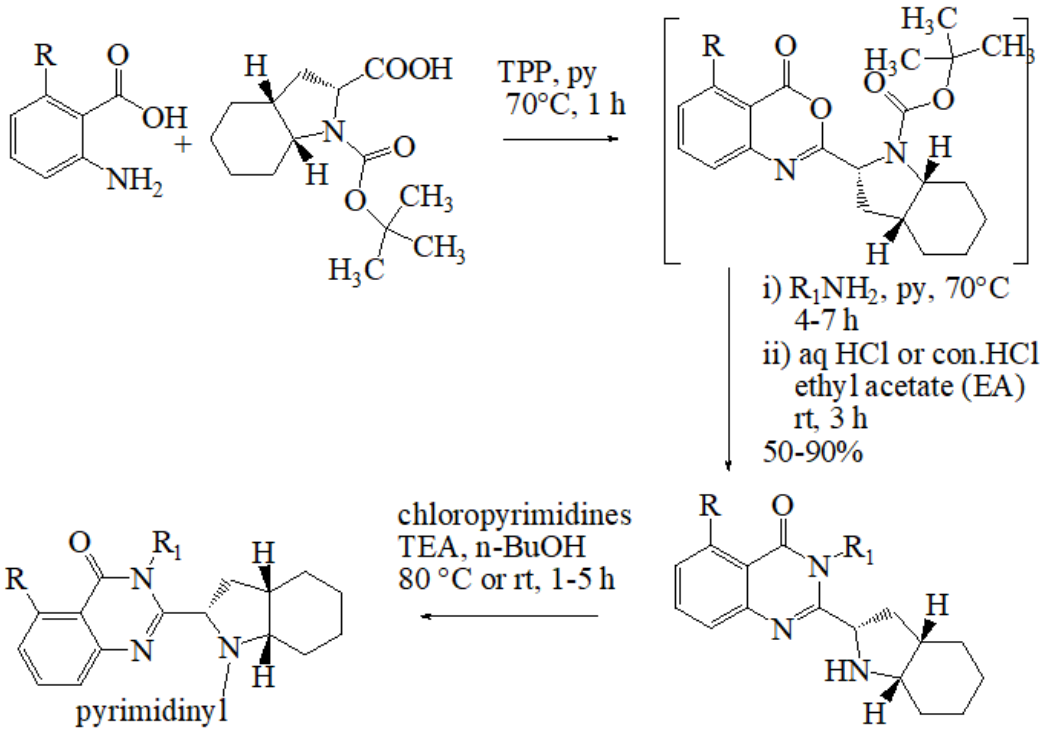
The quinazolinone core was prepared via one-pot, two step dehydrative cyclization, by treatment of 2-amino-6-chlorobenzoic acid and the (2*R*,3a*R*,7a*R*)-1-(tert-butoxycarbonyl)-octahydro-1*H*-indole-2-carboxylic acid with triphenyl phosphate (TPP) and pyridine stirred at 70 °C under nitrogen for 1h, followed by addition of the aniline. The *N*-Boc deprotection of resultant compound with concentrated hydrochloric acid afforded the (*S*)-5-chloro-3-phenyl-2-((2*S*,3a*S*,7a*S*)-octahydro-1*H*-indol-2-yl)quinazolin-4(3*H*)-one. The key amine intermediate was reacted with the 2-chloropyridine-3-carbonitrile in the presence of triethylamine and n-butyl alcohol to generate desired 5-chloro-2-((2*S*,3a*S*,7a*S*)-octahydro-1-(3-cyanopyridin-2-yl)-1*H*-indol-2-yl)-3-phenyl-quinazolin-4(3*H*)-one. This compound has been shown promising anti-inflammatory activity.[9]



2.3.11 Pyrimidinyloctahydroindolylquinazolin-4(3*H*)-ones

The quinazolinone core was prepared via one-pot, two step dehydrative cyclization, by treatment of 2-amino-6-chlorobenzoic acid or 2-amino-6-fluorobenzoic acid and the (*2R,3aR,7aR*)-1-(tert-butoxycarbonyl)-octahydro-1*H*-indole-2-carboxylic acid with triphenyl phosphate (TPP) and pyridine stirred at 70 °C under nitrogen for 1h, followed by addition of the aniline. The *N*-Boc deprotection of resultant compound with concentrated hydrochloric acid afforded the (*S*)-5-chloro/fluoro-3-phenyl-2-((*2S,3aS,7aS*)-octahydro-1*H*-indol-2-yl)quinazolin-4(3*H*)-one. The key amine intermediate was reacted with the 2-chloropyridine-3-carbonitrile in the presence of triethylamine and n-butyl alcohol to generate desired 3-substituted 5-chloro/fluoro-2-((1-pyrimidin-2/6-yl)-(*2S,3aS,7aS*)-octahydro-1*H*-indol-2-yl)-quinazolin-4(3*H*)-ones. These compounds have been shown promising anti-inflammatory activity.[9]

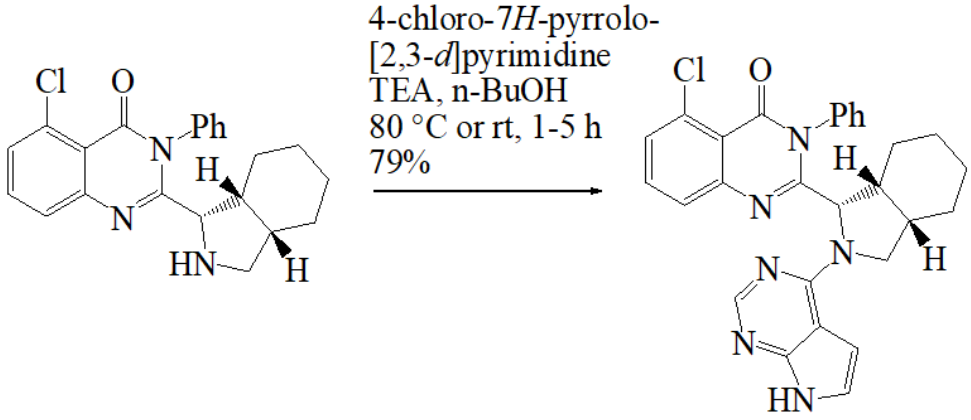
DOI: https://doi.org/10.5281/zenodo.13644773



R	R_1	pyrimidinyl	yield(%)
Cl	phenyl	4-Amino-5-cyano-pyrimidin-6-yl	88
Cl	phenyl	4-methylpyrimidin-2-yl	21
Cl	phenyl	4-chloropyrimidin-2-yl	19
Cl	phenyl	4-Aminopyrimidin-2-yl	13
Cl	3-tri-F-methoxyphenyl	4-Amino-5-cyano-pyrimidin-6-yl	69
Cl	3-F-phenyl	4-Amino-5-cyano-pyrimidin-6-yl	72
Cl	3,5-di-F-phenyl	4-Amino-5-cyano-pyrimidin-6-yl	74
Cl	3-pyridyl	4-Amino-5-cyano-pyrimidin-6-yl	47
Cl	morpholinyl	4-Amino-5-cyano-pyrimidin-6-yl	68
F	3,5-di-F-phenyl	4-Amino-5-cyano-pyrimidin-6-yl	75

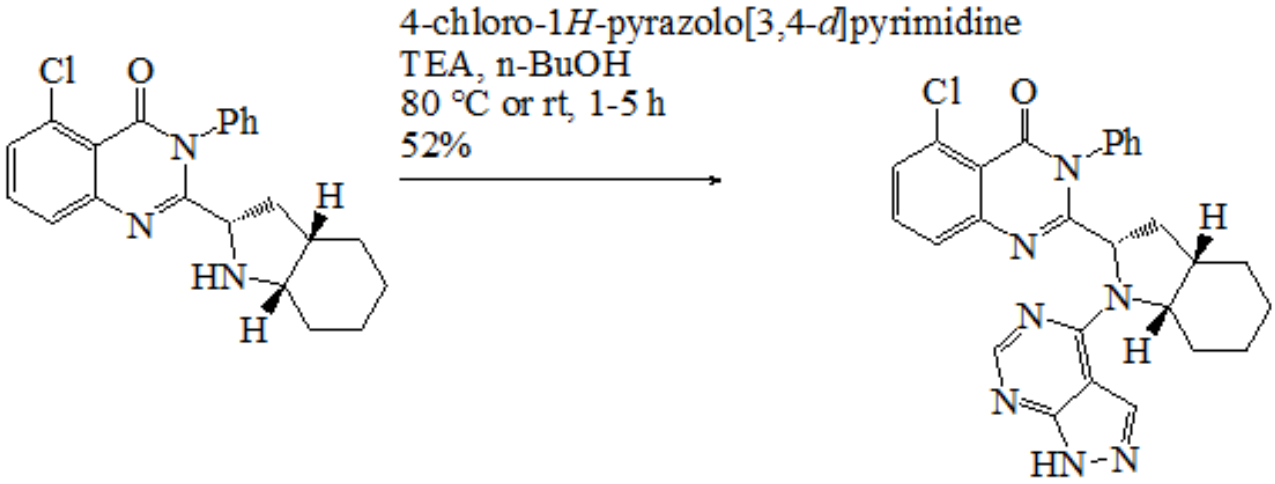
2.3.12 Pyrrolopyrimidinyloctahydroisoindolylquinazolin-4(3*H*)-one

Promising anti-inflammatory compound, 5-chloro-2-((2-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl))(*1S,3aS,7aR*)octahydro-1*H*-isoindol-1-yl)-3-phenylquinazolin-4(3*H*)-one, was prepared by reacting (*S*)-5-chloro-3-phenyl-2-((*2S,3aS,7aS*)-octahydro-1*H*-indol-2-yl)quinazolin-4(3*H*)-one with the 4-chloro-7*H*-pyrrolo-[2,3-*d*]pyrimidine in the presence of triethylamine and n-butyl alcohol in good yield.[9]



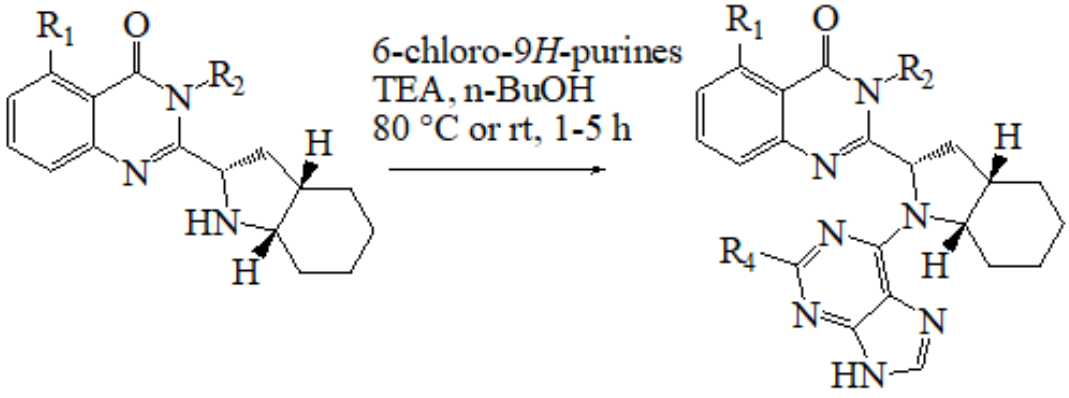
2.3.13 Pyrazolopyrimidinyloctahydroindolyl)quinazolin-4(3*H*)-one

The (*S*)-5-chloro-3-phenyl-2-((*2S,3aS,7aS*)-octahydro-1*H*-indol-2-yl)quinazolin-4(3*H*)-one was reacted with the 4-chloro-1H-pyrazolo[3,4-d]pyrimidine in the presence of triethylamine and n-butyl alcohol to generate 2-((2*S*,3a*S*,7a*S*)-1-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)octahydro-1*H*-indol-2-yl)-5-chloro-3-phenylquinazolin-4(3*H*)-one and is exhibited promising anti-inflammatory activity.[9]



2.3.14 Purinyloctahydroindolylquinazolin-4(3*H*)-ones

Lijuan Chen et.al reported the synthesis of promising anti-inflammatory compounds, 2-((*2S,3aS,7aS*)-octahydro-1-(9*H*-purin-6-yl)-1*H*-indol-2-yl)quinazolin-4(3*H*)-one derivatives, by reacting (*S*)-5-chloro-3-phenyl-2-((*2S,3aS,7aS*)-octahydro-1*H*-indol-2-yl)quinazolin-4(3*H*)-ones with the 6-chloro-9*H*-purines in the presence of triethylamine and n-butyl alcohol.[9]

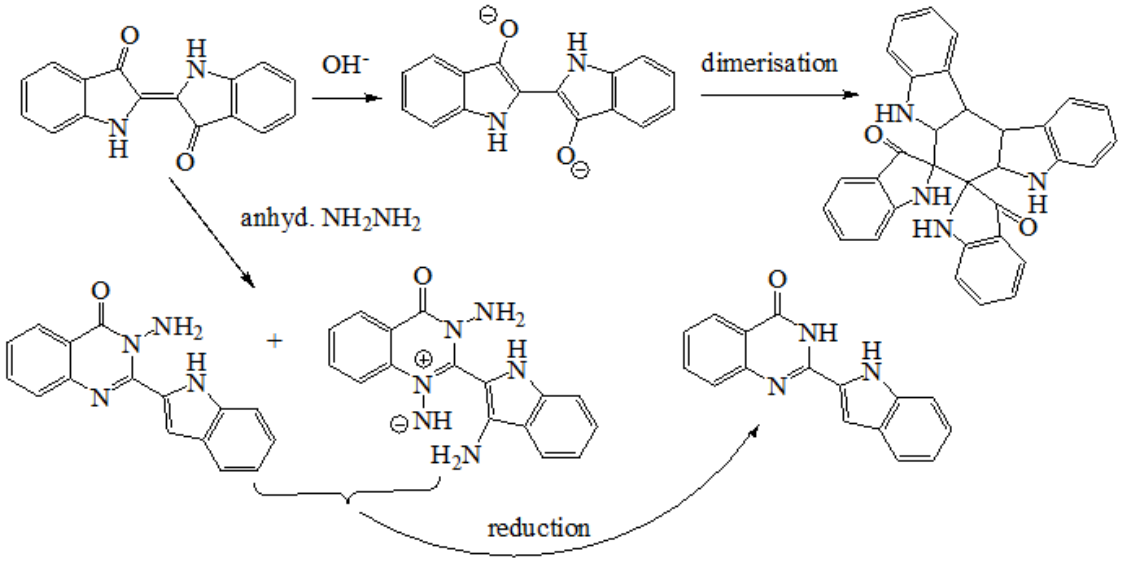


S.No	R_1	R_2	R_4	yield(%)
27	Cl	Ph	NH_2	62
29	Cl	Ph	H	47
36	Cl	Ph	Cl	49

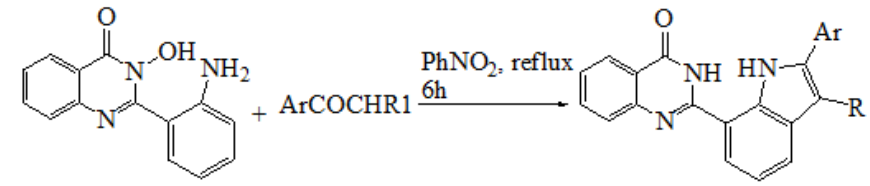
2.3.15 Indolylquinazolin-4(3*H*)-one

Bergman et.al studied the reaction of indigo and hydrazine under basic conditions. In the presence of a strong base, the anion was formed and rapidly underwent oxidative dimerisation. However, anhydrous hydrazine converts indigo to 3-amino-2-(2'-indolyl)-quinazolin-4(3*H*)-ones, depending on the temperature at which the reaction was conducted. Reduction of these two compounds with Raney nickel gave 2-(2'-indolyl)-quinazolin-4(3*H*)-ones.[144, 145]

DOI: https://doi.org/10.5281/zenodo.13644773

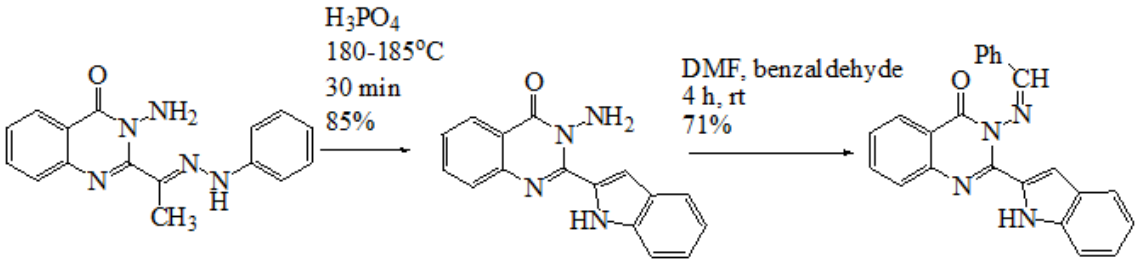


A novel bisazaheterocycle, indolyl-quinazolin-4(3*H*)-ones were synthesized in our laboratory. When a mixture of 2-(2-aminophenyl)-3-hydroxy-4(3*H*)-quinazolinone and an aryl ketone was refluxed in nitrobenzene, 2-(2-aryl-1*H*-7-indolyl)-3,4-dihydro-4-quinazolinone was obtained in one- step.[146]



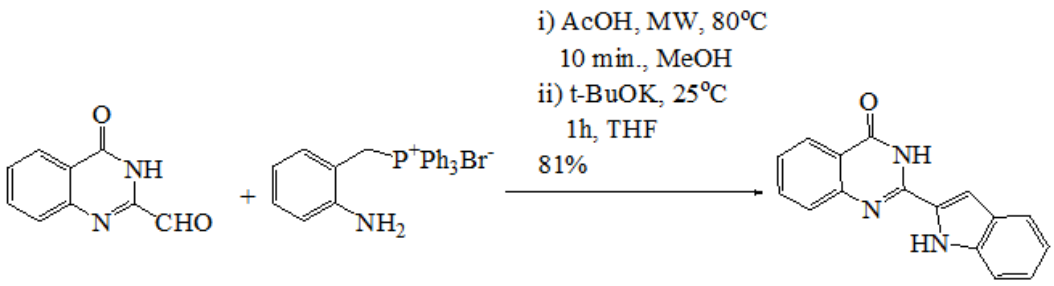
R	H	H	H	H	H	CH_3	C_6H_5
Ar	C_6H_5	4-$CH_3C_6H_4$	4-ClC_6H_4	4-$NO_2C_6H_4$	2-HOC_6H_4	H	$CH_2C_6H_5$
Yield (%)	68	81	78	74	71	69	79

Fischer indolization of 3-amino-2-(1-phenylhydrazonoethyl)-quinazolin-4(3*H*)-one in presence of 85% phosphoric acid yielded 2-(2-indolyl)-3-amino-quinazolin-4(3*H*)-one and was condensation with benzaldehyde to afford corresponding 2-(2-indol-2-yl)-3- benzyli deneaminoquinazolin-4(3*H*)-one. [147]

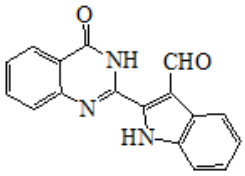


Alternatively, Lee et.al have reported a synthesis of compound 2-(2-indolyl)- quinazolin-4(3*H*)-one by the cyclization of aromatic aldehyde with (2-aminobenzyl)triphenylphosphonium bromides in methanol containing acetic acid under micro wave irradiation followed by treatment with potassium t-butoxide. They were shown significant inhibitory activities on COX-2 and on cell growth of CCRF-CEM.12 [148]

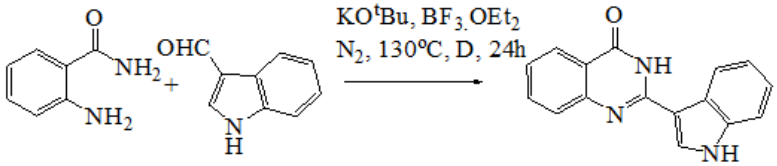
DOI: https://doi.org/10.5281/zenodo.13644773



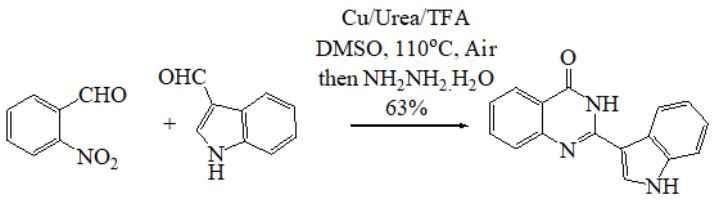
Wattanapiromsakula et.al have been isolated Bouchardatine as yellow amorphous powder from the aerial parts of Bouchardatia neurococca.[149]



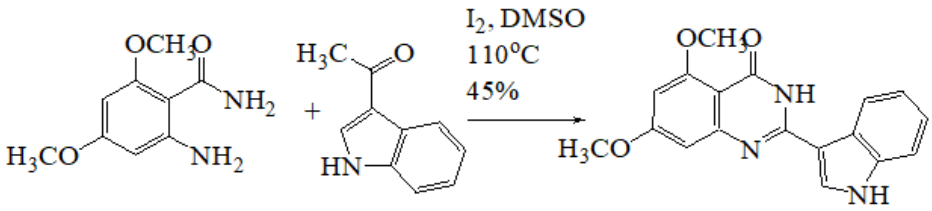
The KO^t Bu-BF_3.OEt_2 mediated synthesis of 2-(1*H*-indol-3-yl)quinazolin-4(3*H*)-one from 2-amino benzamide with 1*H*-indole-3-carbaldehyde is described.[150]



2-Nitrobenzaldehyde was treated with urea, $Cu(OAc)_2$ and TFA in a DMSO solvent at 110°C, then hydrazine hydrate and 1*H*-indole-3-carbaldehyde were added sequentially at the same temperature and stirred at room temperature for 16h to isolate 2-(1*H*-indol-3-yl)quinazolin-4(3*H*)-one.[142]



A novel AChE inhibitor with anti-inflammatory activity, 2-(1*H*-indol-3-yl)-5,7-dimethoxy quinazolin-4(3*H*)-one, was prepared by the reaction of 2-amino-4,6-dimethoxy benzamide with 1-(1*H*-indol-3-yl)ethanone in I_2 containing DMSO.[13]



Nagarajan etal., described the total synthesis of 2-(3-formylindol-2-yl)quinazolin-4(3*H*)-one alkaloid bouchardatine and some of the quinazolinone derivatives. Synthesis of bouchardatine,

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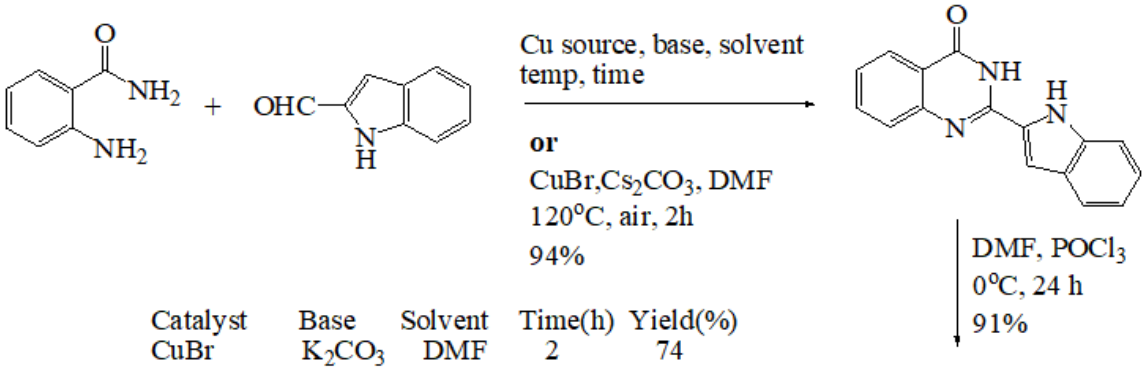
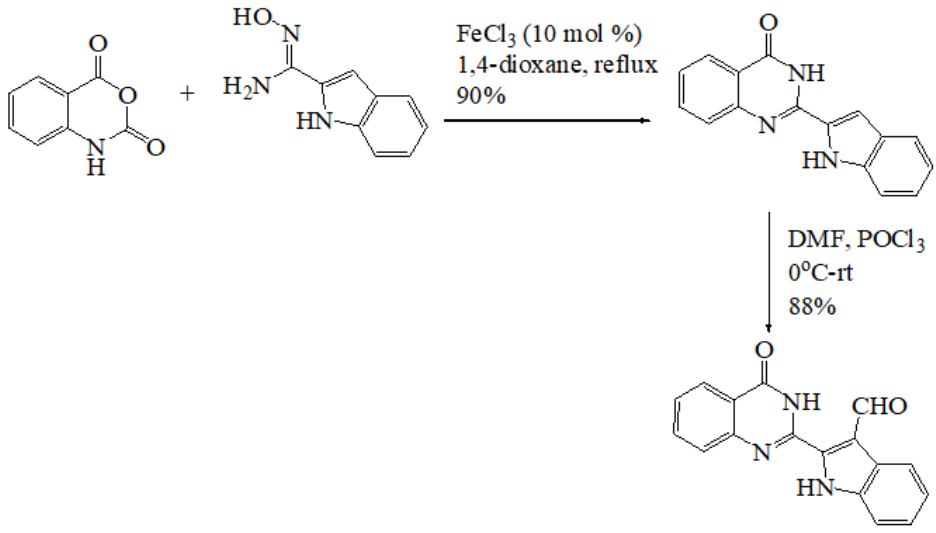
starting from indole-2-aldehyde with anthranilamide through copper(I) bromide mediated aerobic oxidation reaction followed by Vilsmeier-Haack formylation gives the natural product bouchardatine alkaloid in good yield.[143]



Catalyst	Base	Solvent	Time(h)	Yield(%)
CuBr	K_2CO_3	DMF	2	74
CuBr	KOAc	DMF	6	48
CuI	Cs_2CO_3	DMF	4	85
CuBr	Cs_2CO_3	NMP	8	10
$Cu(OAc)_2$	Cs_2CO_3	DMF	6	84
CuBr	Cs_2CO_3	DMF	2	94
CuI	Cs_2CO_3	DMSO	8	20
CuBr	Na_2CO_3	DMF	12	72
CuCl	Cs_2CO_3	DMSO	12	35
CuBr	Cs_2CO_3	Toluene	12	22
CuI	K_2CO_3	DMF	4	72
-	Cs_2CO_3	DMF	12	-
CuBr	Cs_2CO_3	DMF	5	68

Alternatively, a Bouchardatine natural product i.e 2-(3-formylindol-2-yl)quinazolin-4(3*H*)-one was synthesized by refluxing a mixture of isatoic anhydride and aqueous hydroxylamine derivative in 1,4-dioxane in presence of iron(III) chloride catalyst to isolate 2-(indol-2-yl)quinazolin-4(3*H*)-one followed by formylation. Circumdatin H, 8-Norrutaecarpine and, Luotonin B and E are few natural products can be synthesized by this methodology. [151]



Urea/thiourea has been identified as an effective ammonia surrogate in the construction of quinazolin-4(3*H*)-one ring. This strategy afforded a simple and catalyst free synthesis of

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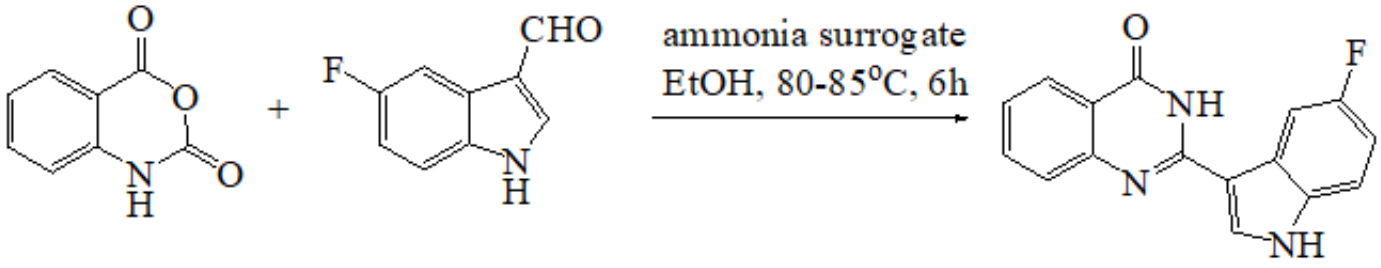
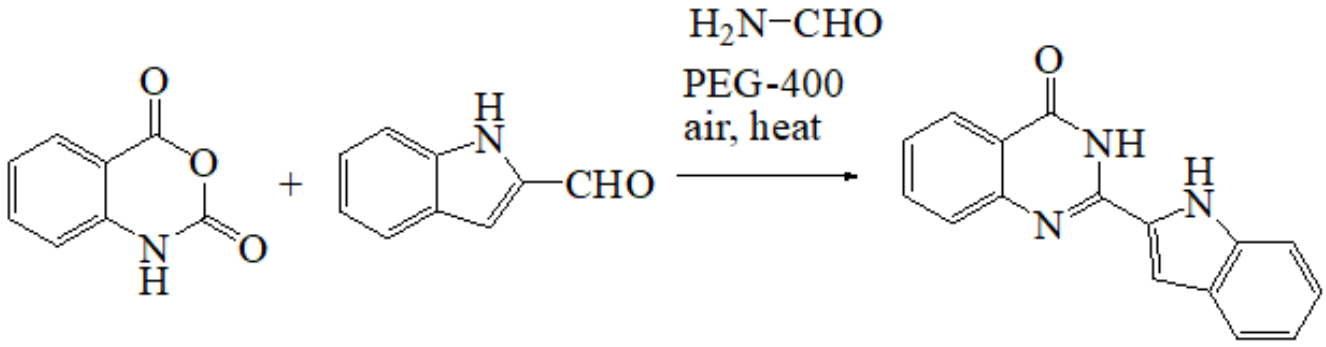
2-(5-fluoro-1*H*-indol-3-yl)-2,3-dihydroquinazolin-4(1*H*)-one and 2-(5-fluoro-1*H*-indol-3-yl)quina zolin-4(3*H*)-one via the reaction of isatoic anhydride and 5-fluoro-1*H*-indole-3-carbaldehyde in the presence of urea or thiourea in ethanol. The reaction proceeded well to afford the quinazolin-4(3*H*)-one or its dihydro derivative, depending on the nature of carbonyl compound employed.[152]



Ammonia surrogate	Yield(%)
Urea	88
Thiourea	80

A remarkably rapid but microwave/ultrasound/catalyst-free method has been developed for the construction of a quinazolin-4(3*H*)-one ring using formamide as an efficient ammonia precursor and PEG-400 as an effective solvent. The methodology afforded various 2-substituted quinazolin-4(3*H)*-one derivatives in good yield via a three-component reaction of isatoic anhydride, aldehydes and formamide in air. [153]



Indole-quinazolinone hybrids with active amides were synthesized, characterized, and assessed for their cytotoxicity. Two molecules displayed substantial activity in sulphorhodamine B assay method.[14]

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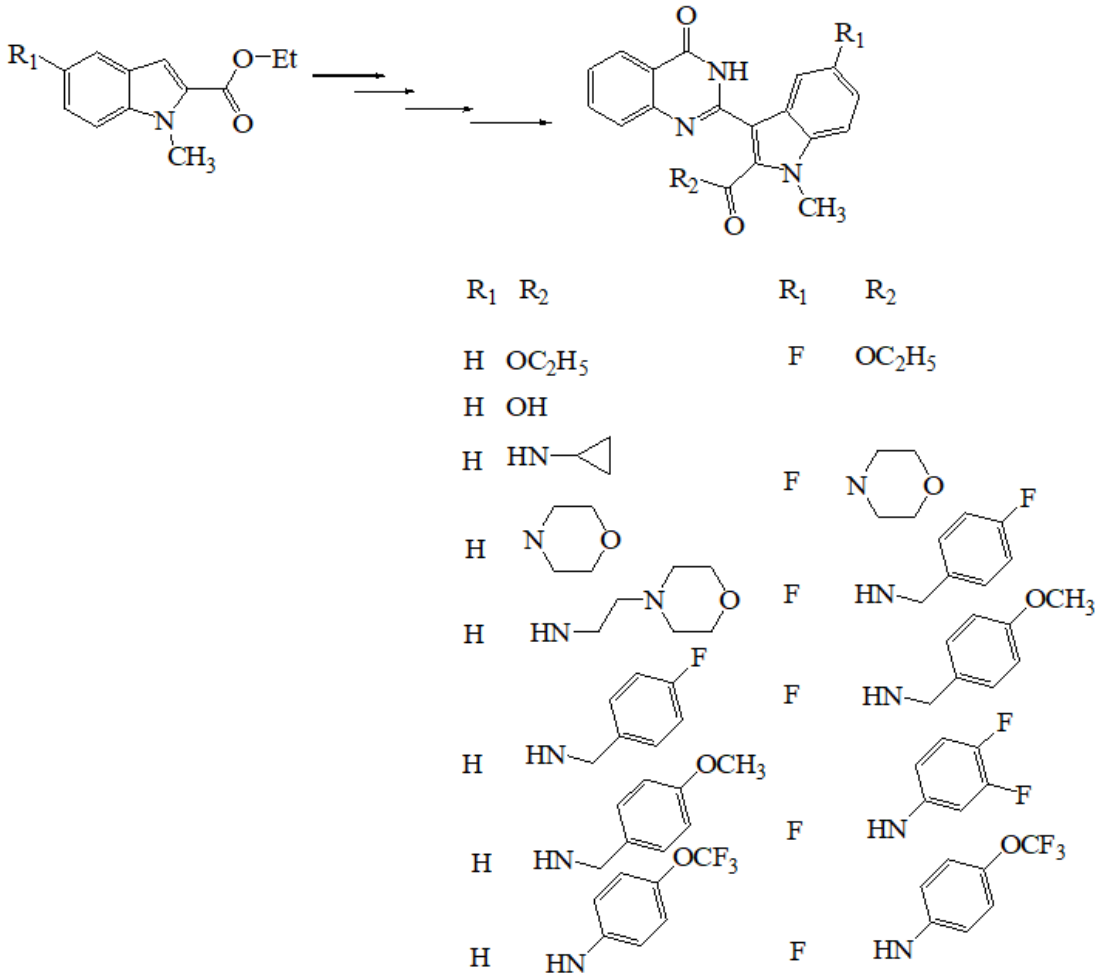
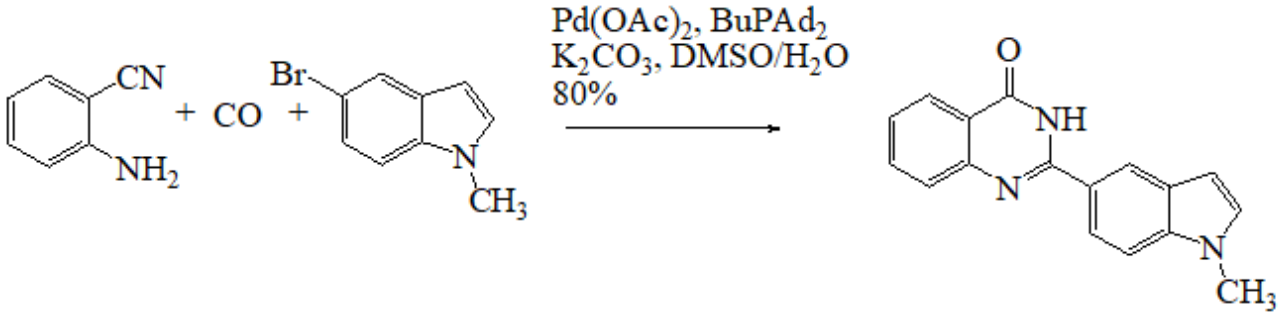
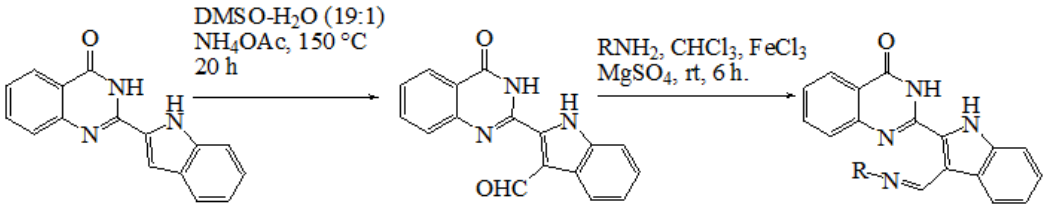


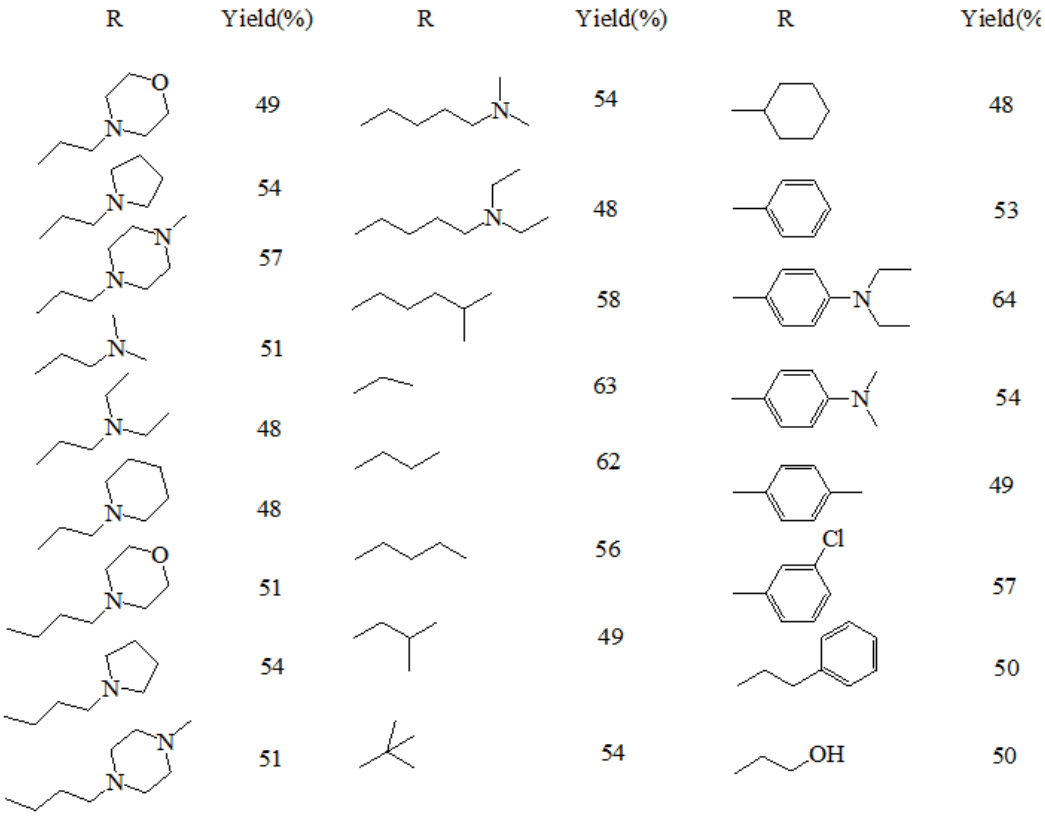
A cascade synthesis of quinazolinones from 2-aminobenzonitriles and heteryl bromides through a palladium-catalyzed carbonylation reaction has been developed. Example, The 2-(1-methyl-1*H*-indol-5-yl)quinazolin-4(3*H*)-one was synthesized by the condensation of 5-bromo-1-methyl-1*H*-indole with 2-aminobenzonitriles. The reactions go through aminocarbonylation of aryl bromides–hydration of nitriles–cyclization sequence.[154]



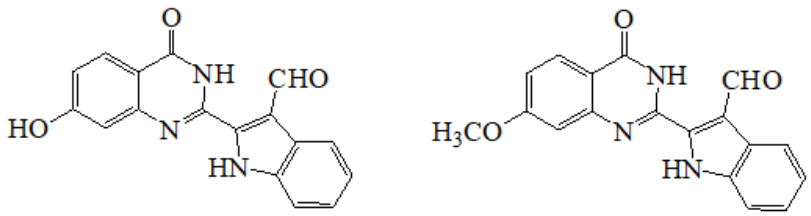
Lipid-lowering agents 2-(3-((heteryl/arylimino)methyl)-1*H*-indol-2-yl)quinazolin-4(3*H*)-one were produced by the formylation of 2-(1*H*-indol-2-yl)quinazolin-4(3*H*)-one with ammonium acetate and DMSO-water to get 2-(3-formylindol-2-yl)quinazolin-4(3*H*)-one and converted to a series of imine side chain substituted quinazolinone derivatives with different amines and showed better lipid-lowering activity than 2-(3-formylindol-2-yl)quinazolin-4(3*H*)-one.[15]

DOI: https://doi.org/10.5281/zenodo.13644773





The two alkaloids Orirenierine A and Orirenierine B were isolated from the methanol extract of the stems of Oricia renieri and showed low antibacterial, antifungal and cytotoxic activity.[3]



Orirenierine A

Orirenierine B

2.3.16 Indolizinylquinazolin-4(3*H*)-ones

3-Substituted benzyl-2-methyl-quinazolin-4(3*H*)-ones was reacted with pyridine derivatives in presence of iodine to form Zwitter ion followed by cyclization/aromatization with chalcones in presence of $FeCl_3$ to afford the desired product 3-substituted benzyl-2-(1-benzoyl-2-aryl-indolizin-3-yl)quinazolin-4(3*H*)-ones in moderate to very good yield. This approach is a highly efficient and convenient way to get derivatives of indolizines from readily accessible substrate under relatively mild reaction conditions.[155]

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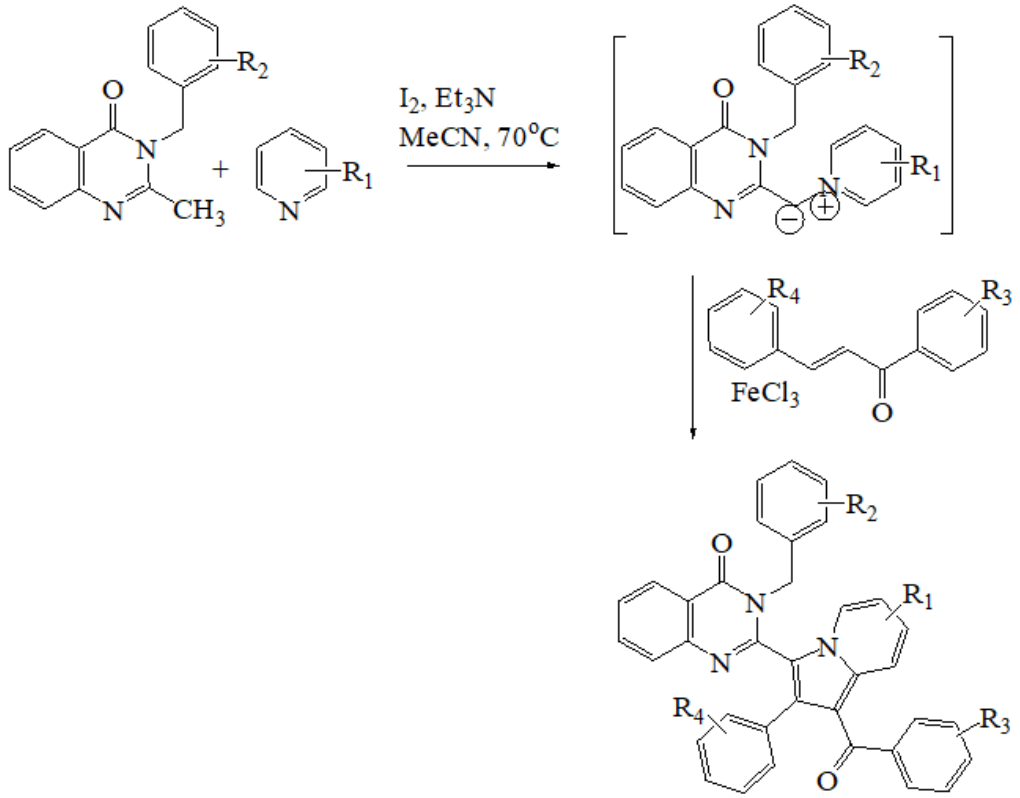
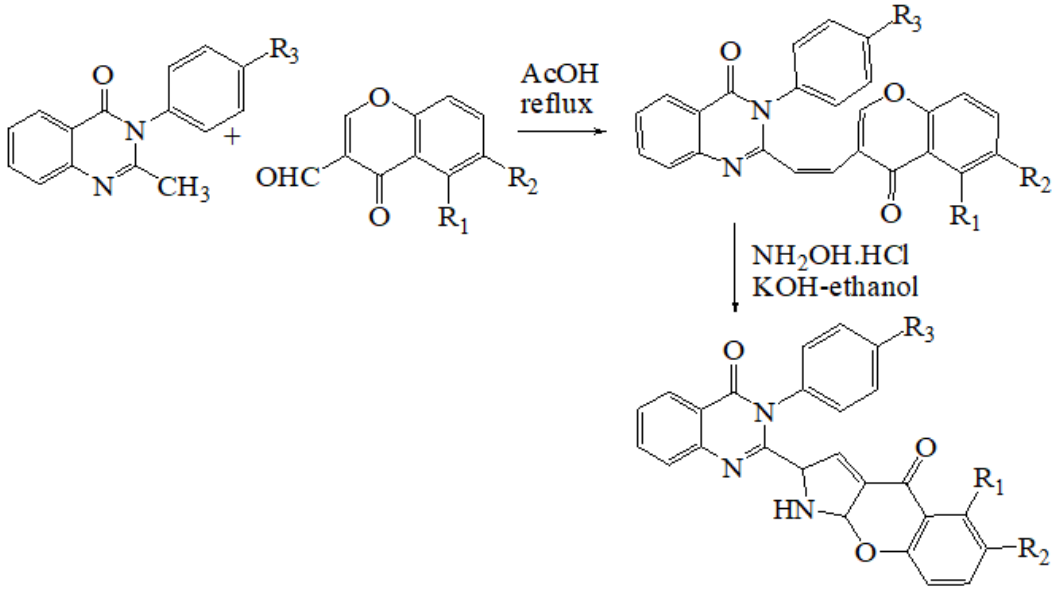


2.3.17 Pyrrolinodihydrobenzopyranonylquinazolinon-4(3*H*)-ones

Acid catalysed condensation of 3-formylchromones with 3-aryl-2-methyl-quinazolin-4(3*H*)-ones yielded the styryl derivatives, which reacted with hydroxylamine hydrochloride in alcoholic potassium hydroxide to yield the corresponding 2-(pyrrolino[5,4-*b*]-2,3-dihydro-4*H*-[1]-benzopyran-4-one-2-yl)-3-aryl-quinazolin-4(3*H*)-ones. These compounds showed significant antimicrobial activity.[11]

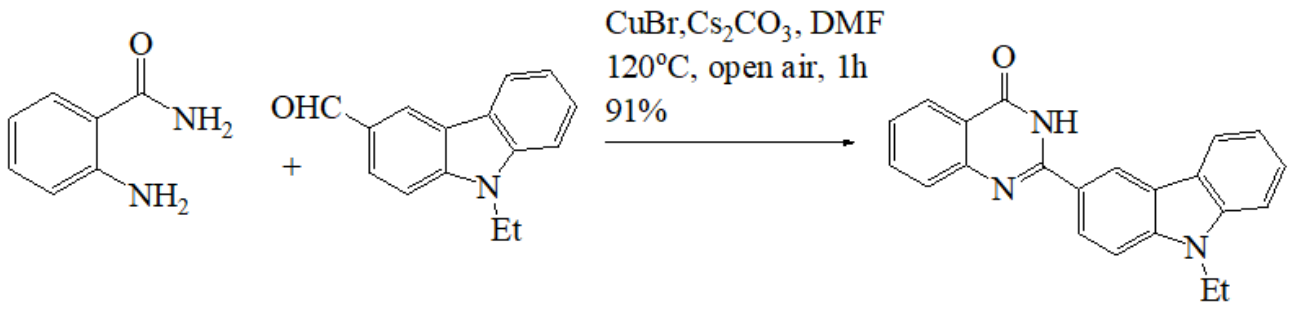


R_1	H	H	H	CH_3	H	H	H	CH_3	H	H	H	CH_3
R_2	H	Cl	CH_3	Cl	H	Cl	CH_3	Cl	H	Cl	CH_3	Cl
R_3	H	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3	Br	Br	Br
Yield (%)	56	60	58	62	64	55	62	55	55	62	65	64

DOI: https://doi.org/10.5281/zenodo.13644773

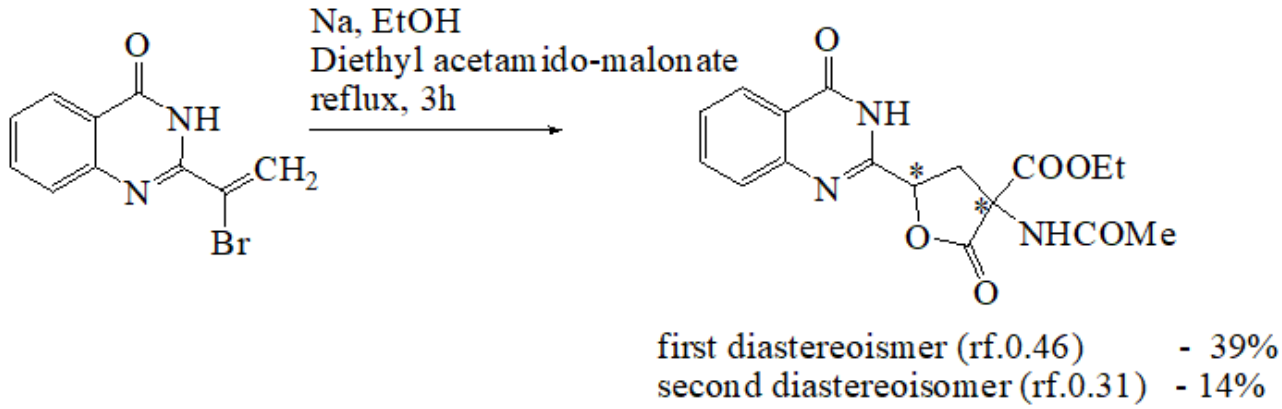
2.3.18 Carbazolylquinazolin-4(3*H*)-one

2-(9-Ethyl-9*H*-carbazol-3-yl)quinazolin-4(3*H*)-one was synthesized from 9-ethyl-9*H*-carbazole-3-carbaldehyde with anthranilamide through copper(I) bromide mediated aerobic oxidation reaction. [143]

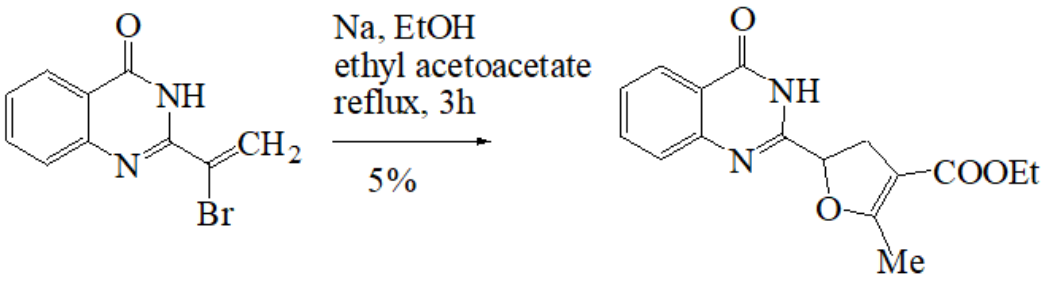


2.3.19 Tetrahydrofuranylquinazolin-4(3*H*)-ones

Two diastereomers, 3-acetylamino-2-oxo-5-(quinazolin-4(3*H*)-one-2-yl)-tetrahydrofuran-3-carboxylic acid ethyl ester (first diastereoismer (rf.0.46) in 39% yield and second diastereoisomer (rf.0.31) in 14% yield), were isolated by column chromatography from the residue, which was obtained by the reaction of vinylquinazolinone with diethyl acetamidomalonate in ethanol containing sodium metal. [156]



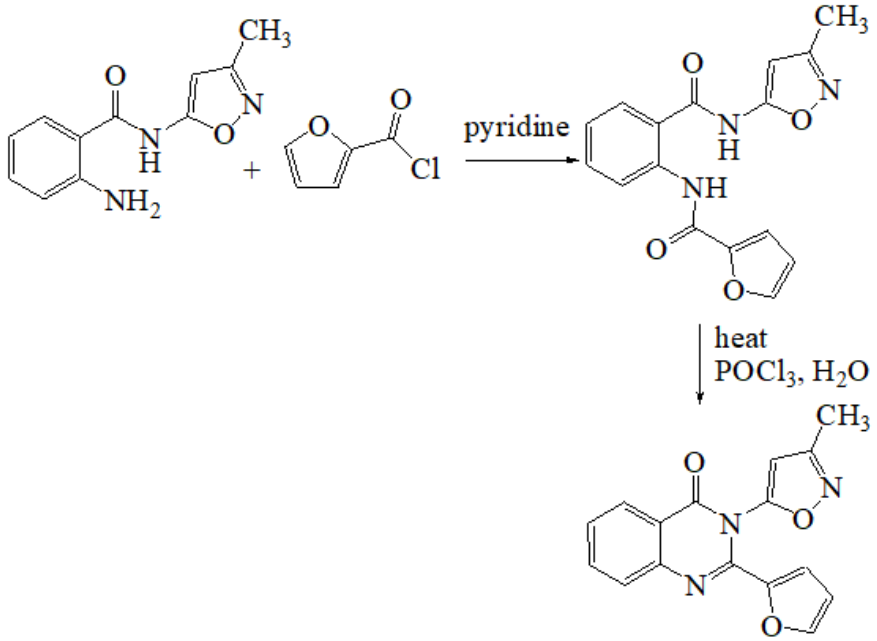
Methyl-5-(quinazolin-4(3*H*)-one-2-yl)-4,5-dihydro-furan-3-carboxylic acid ethyl ester was prepared by the reaction of vinylquinazolinone with ethyl acetoacetate in ethanol containing sodium metal.[156]



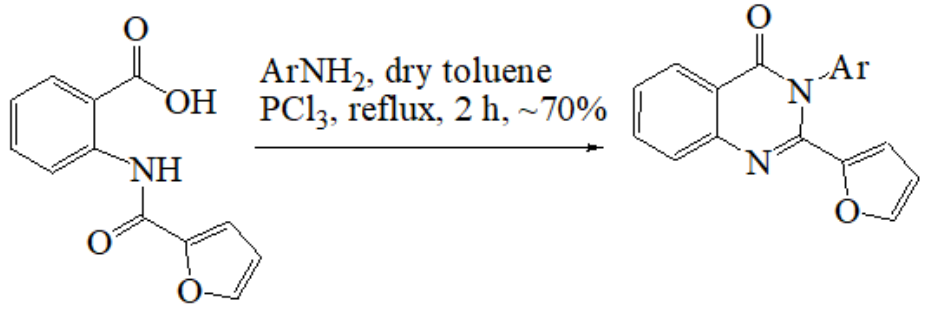
DOI: https://doi.org/10.5281/zenodo.13644773

2.3.20 Furanylquinazolin-4(3*H*)-ones

3-(3-Methyl-5-isoxazolyl)-2-(2-furyl)-4(3*H*)-quinazolinone is an useful analgesic, antiinflammatory and body temperature lowering agent. 5-[(2-Aminobenzoyl)amino]-3-methylisoxazole was reacted with furfuroyl chloride in pyridine to obtain 5-[2-(2-furoylamino)benzoylamino]-3-methylisoxazole. Dehydrative cyclization of resultant compound to yield title compounds was achieved by heating in $POCl_3$.[16]



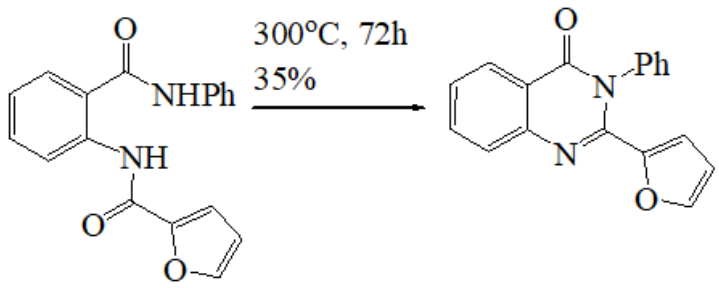
Subba Rao prepared 2-(2-furyl)-3-aryl-4(3*H*)-quinazolinone derivatives by condensing *N*-(2-furoyl)anthranilic acid with primary amines. The quinazolinones showed antibacterial, antifungal, and piscicidal activity.[17]



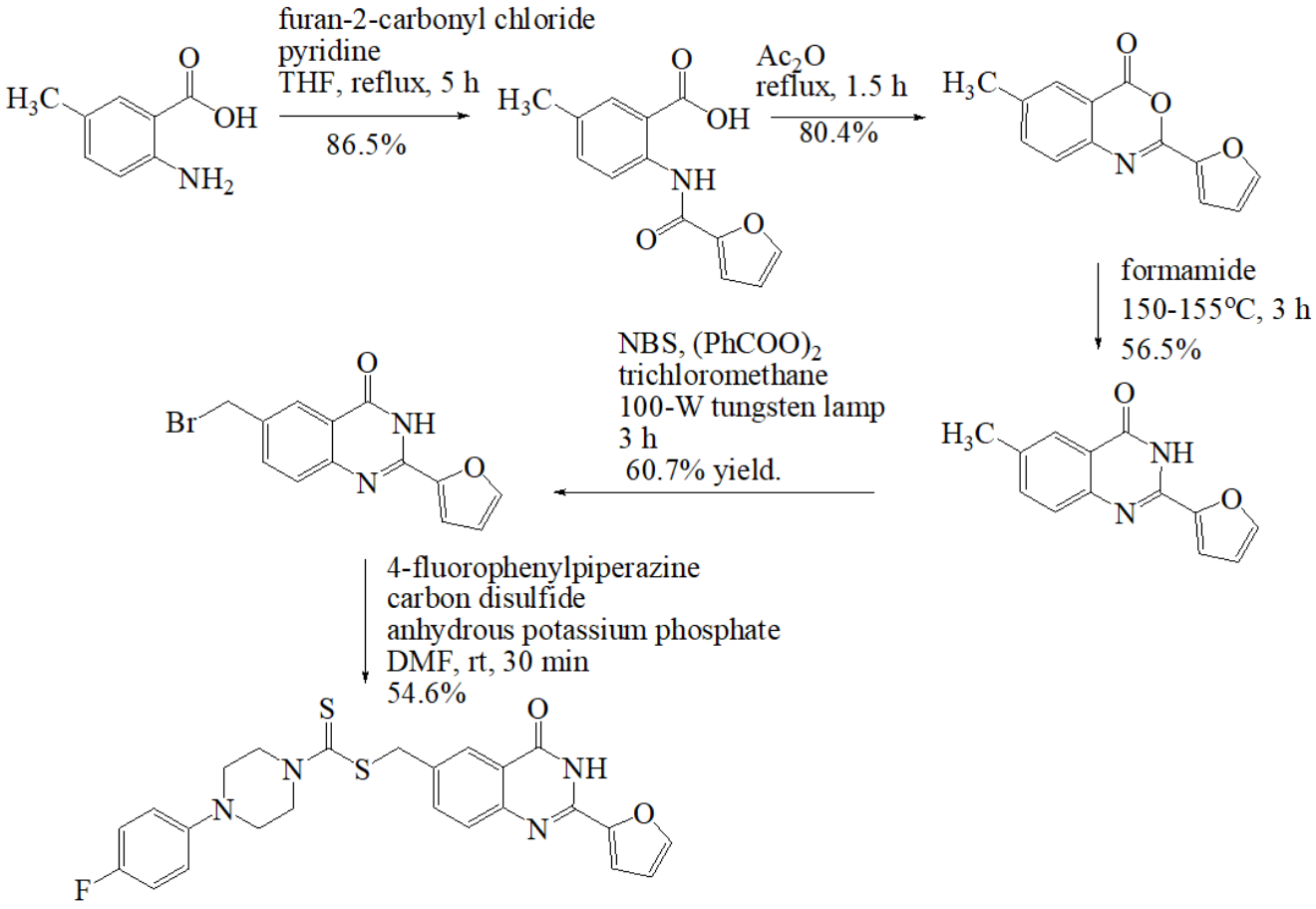
Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4,2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, 2,4,6-$Br_3C_6H_2$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$

Ramana and Yuvaraj reported ortho interaction of the anilide function and *N*-acyl group in 2-(2-furoylamino)benzanilide, under electron impact, that led to dehydrative cyclization of the molecular ion. The mechanism and the ion structures proposed in the mass spectral study are supported by high resolution data and Collision Activated Decomposition (CAD)-B/E linked scan spectra. This observation was successfully translated into a laboratory synthesis by the thermolysis of benzanilide derivative and isolating 2-(2-furyl)-4(3*H*)-quinazolinone from the pyrolysate in 35% yield.[157]

DOI: https://doi.org/10.5281/zenodo.13644773

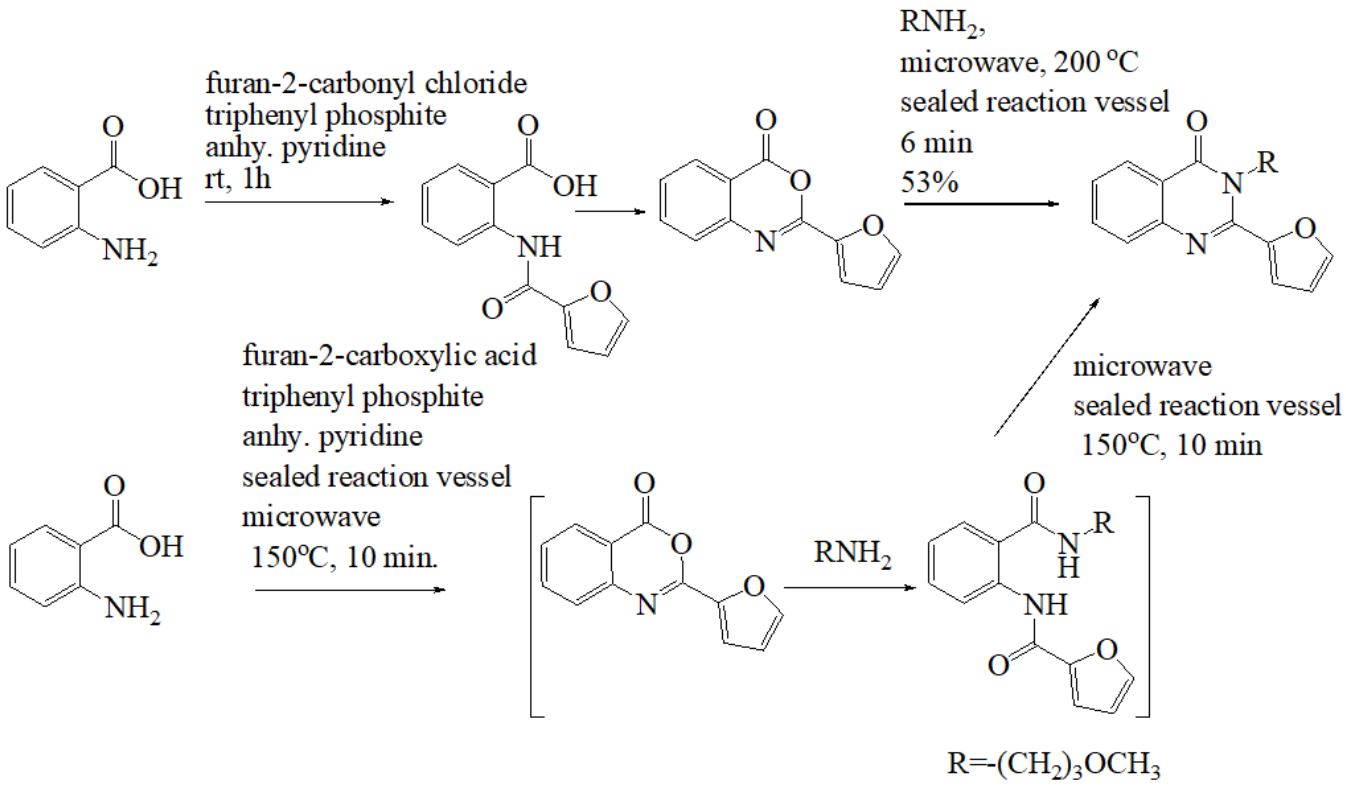


(2-(Furan-2-yl)-quinazolin-4(3*H*)-one-6-yl)methyl-4-(4-fluorophenyl)piperazine-1 carbodithioate was prepared by reacting 2-amino-5-methylbenzoic acid with acyl chloride to yield 2-(furan-2-carboxamido)-5-methylbenzoic acid. Conversion to 2-(furan-2-yl)-6-methyl-4*H*-benzo[*d*] [1,3]oxazin-4-one with acetic anhydride, reaction with formamide to 2-(furan-2-yl)-6-methylquinazolin-4(3*H*)-one, α-halogenation with NBS to bromo derivative, and coupling with 4-fluorophenylpiperazine and carbon disulfide in *N, N*-dimethylformamide in presence of anhydrous potassium phosphate are the key steps in the synthesis of final compound. The prepared compound has been screened for its in-vitro cytotoxicity against A-549 (human cell lung cancer), HCT-8 (human colon cancer), HepG2 (human liver cancer), and K562 (human myelogenous leukaemia) cell lines and results revealed that the replacement of methyl at the C2 position of quinazolin-4(3*H*)-one with other heteroaryl group led to a decrease in cytotoxic activity.[18]

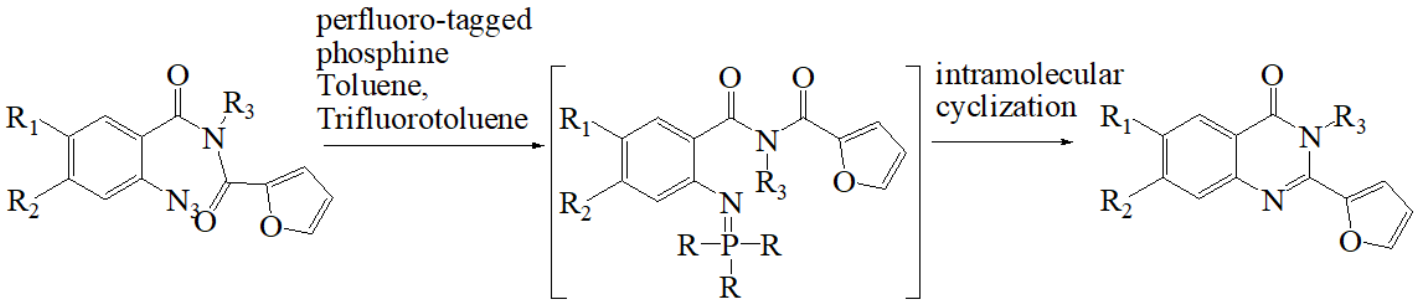


DOI: https://doi.org/10.5281/zenodo.13644773

Ji-Feng et.al have developed an efficient microwave promoted, one-pot, two-step synthesis of 2-(furan-2-yl)-quinazolin-4(3*H*)-one from anthranilic acid, carboxylic acid or acyl chloride, and amine.[158]



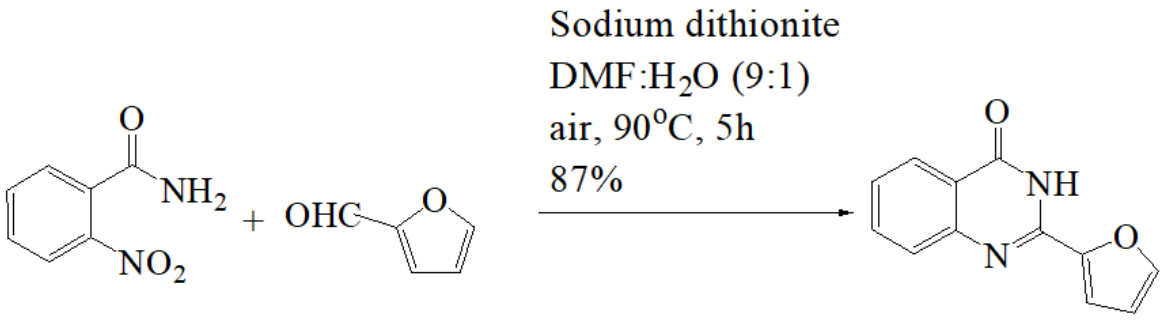
In a Staudinger reaction, the 2-azidobenzamide derivative reacted quantitatively with the perfluoro-tagged phosphine leading to the iminophosphoranes followed by cyclisation by an intramolecular Aza-Wittig reaction to the desired quinazoline derivatives. Though solid-phase bound phosphine derivative used instead of perfluoro-tagged phosphine, the yields in this reaction are not improved much (56-94%).[159]



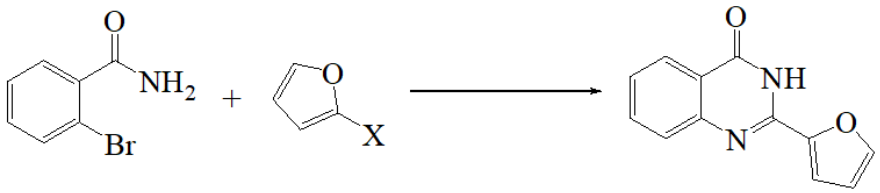
R_1	H	H	I	OCH_3
R_2	H	H	H	OCH_3
R_3	$CH_2C_6H_5$	$CH_2C_4H_3S$	$CH_2C_4H_3S$	$CH_2C_4H_3S$
Yield (%)	72	93	77	92

DOI: https://doi.org/10.5281/zenodo.13644773

A simple one-pot procedure for the preparation of 2-furylquinazolin-4(3*H*)-ones starting from readily available 2-nitrobenzamides and furan-2-carbaldehyde is described. Sodium dithionite is used as the reducing agent for the nitro group, and its decomposition in situ in aqueous *N, N*-dimethylformamide leads to the final oxidation step that gives the desired heterocyclic compounds.[160]

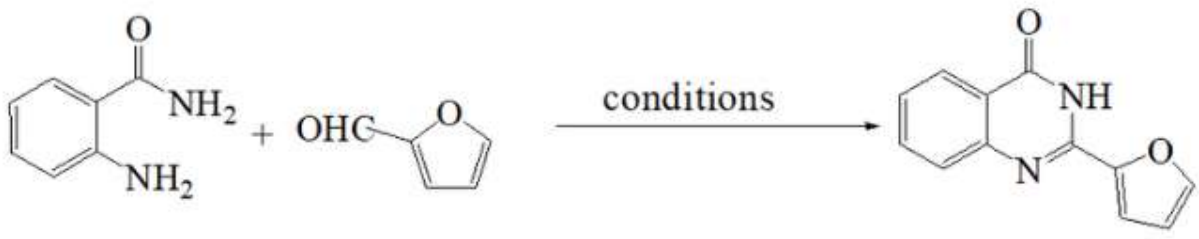


A novel and efficient Cu(I)-catalyzed ligand and base-free multipathway domino strategy has been developed for the synthesis of 2-(furan-2-yl)quinazolin-4(3*H*)-one. The reaction utilizes 2-bromobenzamide and multiform substrates such as aldehydes and alcohols for a one-pot protocol, whereas $TMSN_3$ is used as a nitrogen source.[161]



X	conditions	Yield (%)
—CHO	$TMSN_3$, CuI, air DMSO, 80°C	78%
—CH_2OH	$TMSN_3$, CuI, DMSO, air TBHP, 80°C	75%

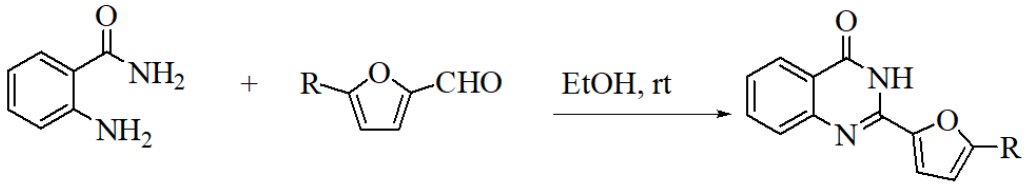
Alternatively, 2-furyl-quinazolin-4(3*H*)-one was prepared by condensation of furfural and anthranilamide under various conditions.



DOI: https://doi.org/10.5281/zenodo.13644773

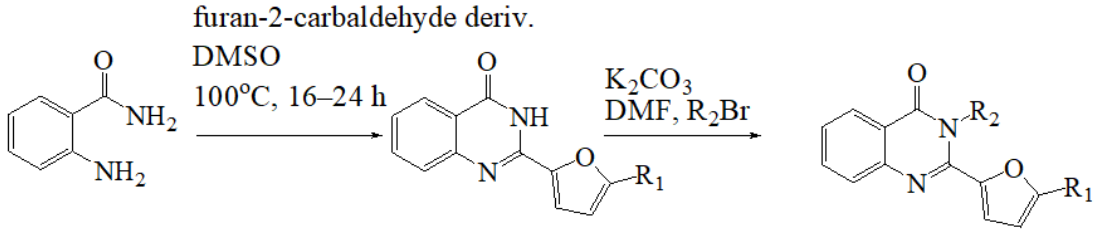
Conditions and yield	Reference
$VO(acac)_2$, air, DMA, 120°C, 15h, 92%	162
Cp_2ZrCl_2, DMF, 80-100°C, 46%	163
$CoCl_2$, CH_3CN,reflux, 7h,78%	164
$Cu(NO_3)_2.3H_2O$, CH_3CN, 80°C, 10h, 77%	165
air, 120°C, 24h, 88%	166
DMSO, 100°C, open flask	167

Zaytsev et.al also reported the synthesis of 2-furylquinazolin-4(3*H*)-one derivatives from the condensation of anthranilamide with 5-bromo and 5-iodofurancarboxaldehydes in EtOH at room temperature.[168]



R	Yield(%)
Br	38
I	38

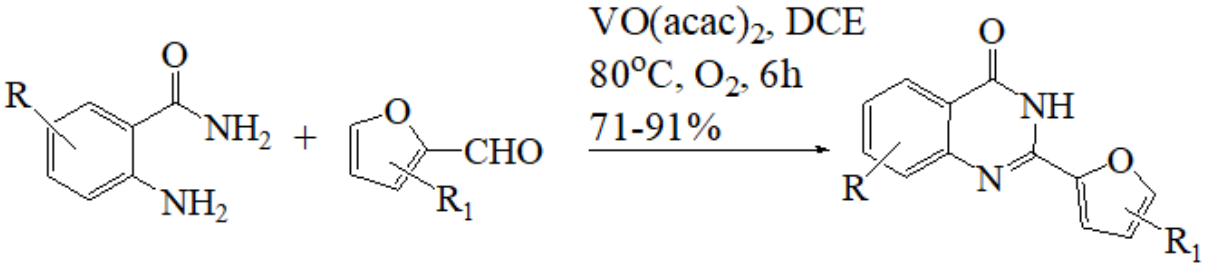
Promising antimicrobial activities concomitant with their MurA inhibitory, 2-furylquinazolin-4(3*H*)-one derivatives, were prepared from anthranilamide and furan-2-carbaldehyde derivatives in dimethylsulphoxide (DMSO) via aerobic oxidative cyclisation followed by alkylation was carried out using various alkyl bromides in dimethylformamide (DMF) under basic conditions.[19]



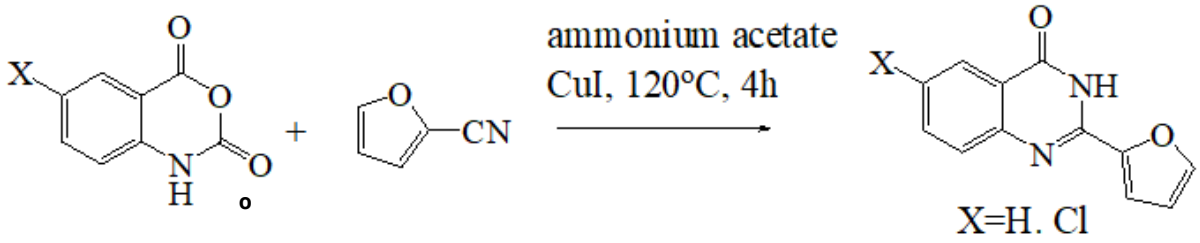
R_1	R_2	R_1	R_2
H	H	H	CH_3
CH_3	H	H	$CH(CH_3)_2$
Br	H	NO_2	$CH(CH_3)_2$
NO_2	H		

DOI: https://doi.org/10.5281/zenodo.13644773

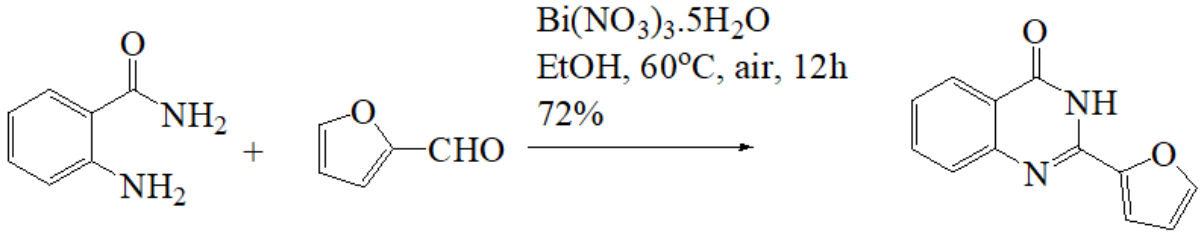
An efficient and simple $VO(AcAc)_2$ - catalyzed approach to the synthesis of various substituted 2-furyl-quinazolin-4(3*H*)-ones from 2-aminobenzamides with alcohols or aldehydes in good to excellent yields with molecular oxygen as the oxidant.[169]



A novel and efficient approach for the synthesis of 2-furyl-quinazolin-4(3*H*)-ones through a one-pot copper-catalyzed three-component reaction of isatoic anhydride or 6-chloroisatoic anhydride, furan-2-carbonitrile and ammonium acetate under solvent-free conditions in good yields has been described.[170]

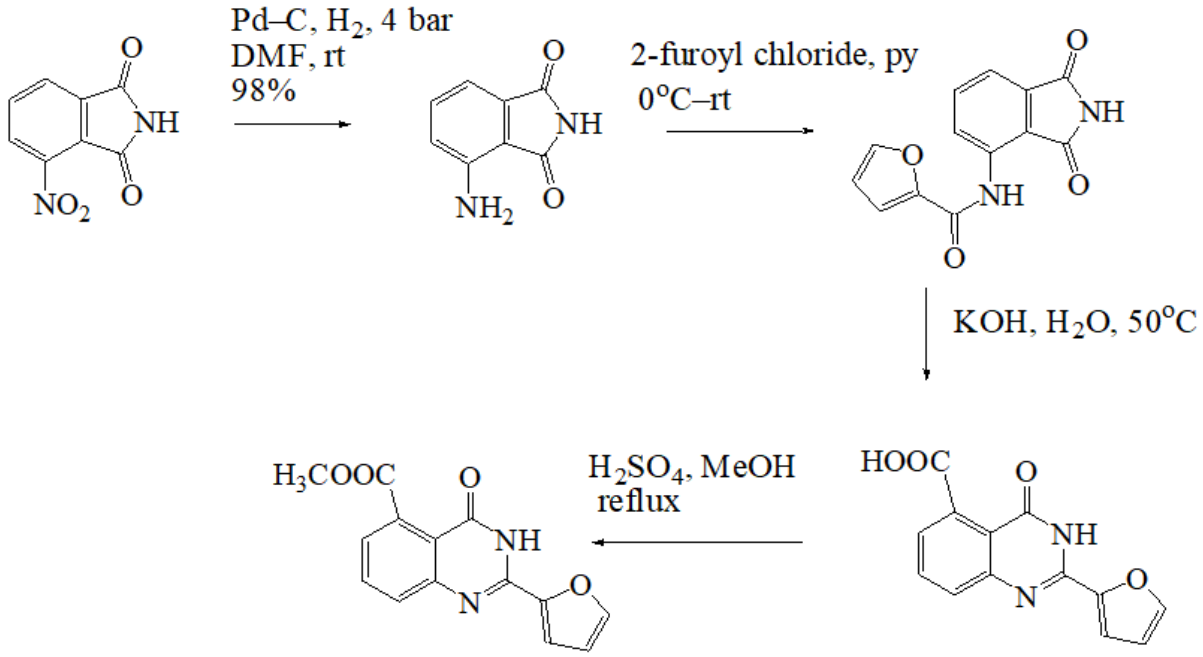


The oxidative cyclocondensation of 2-aminobenzamide with furan-2-carbaldehyde in presence of $Bi(NO_3)_3.5H_2O$ at 60° C in ethanol for 12 h to isolate 2-(furan-2-yl)quinazolin-4(3*H*)-one was explored.[171]

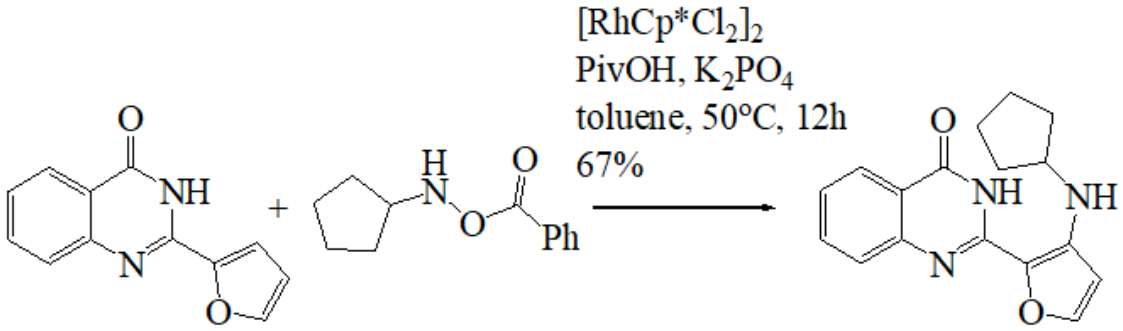


4-Nitroisoindoline-1,3-dione was reduced with Pd/C-H_2 to yield 4-aminoisoindoline-1,3-dione. Acylation with 2-furoyl chloride, a novel ring opening-reclosing reaction with KOH solution followed by esterification with methanol affording the corresponding ester - 5-methoxy carbonyl -2-(furan-2-yl)quinazolin-4(3*H*)-one and is a new class of PARP-1 inhibitors.[20]

DOI: https://doi.org/10.5281/zenodo.13644773

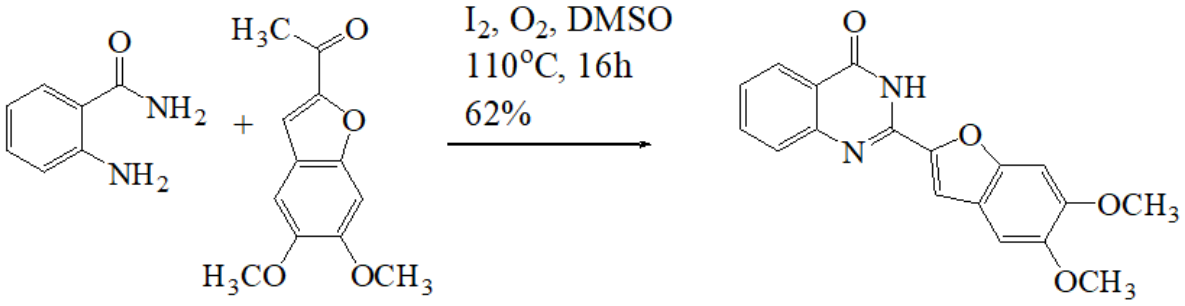


The ortho C-H amination of 2-(furan-2-yl)quinazolin-4(3*H*)-one was achieved with *N*-benzoyloxycyclopentylamine in presence of Rh-catalyzed to isolate 2-(3-(cyclopentyl amino)furan-2-yl)quinazolin-4(3*H*)-one.[172]



2.3.21 Benzofuranylquinazolin-4(3*H*)-one

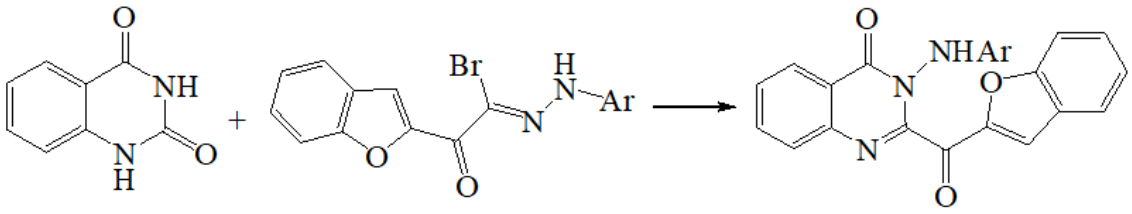
Molecular iodine catalyzed oxidative coupling of 2-aminobenzamides with 1-(5,6-dimethoxybenzofuran-2-yl)ethanone produced 2-(5,6-dimethoxybenzofuran-2-yl)quinazolin-4(3*H*)-one. [173]



2.3.22 Carbobenzofuryl-quinazolin-4(3*H*)-ones

Abdelhamid et.al reported a facile one-step synthesis of 2-(2-carbobenzofuryl)-3-(4-arylamino)-quinazolin-4(3*H*)-ones by condensing isatoic anhydride with 2-bromobezofurylglyoxal-2-arylhydrazones.[174]

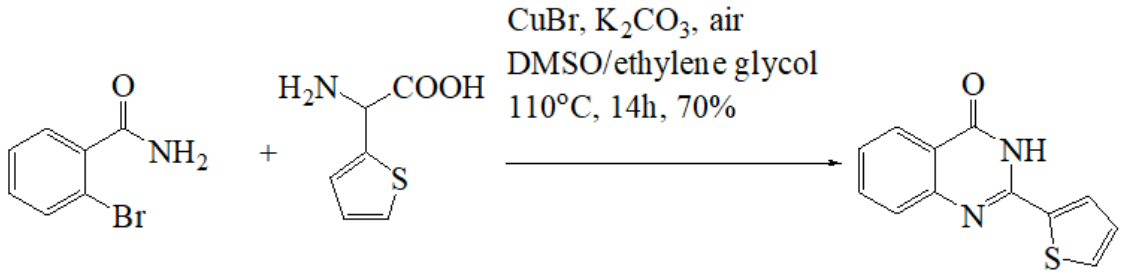
DOI: https://doi.org/10.5281/zenodo.13644773



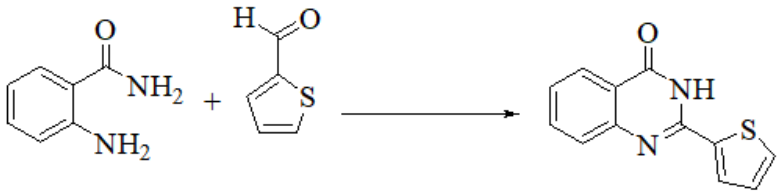
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

2.3.23 Thiophenylquinazolin-4(3*H*)-ones

Xu and Fu prepared 2-(2-thiophenyl)-quinazolinone-4(3*H*)-one by copper-catalyzed domino method on reaction of 2-bromobenzamide with *R*-2-amino-2-(thiophen-2-yl)acetic acid. The domino process underwent Ullmann-type *N*-arylation, decarboxylation, aerobic oxidation, and intramolecular addition for the construction of heterocycles.[175]



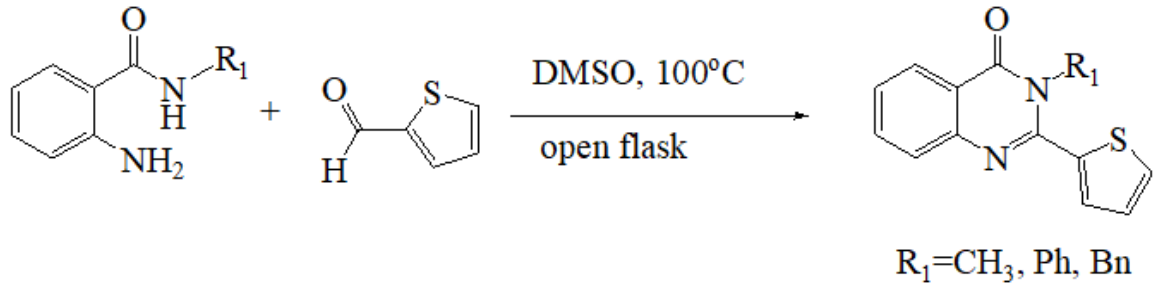
A simple and efficient synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one from the condensation and oxidative cyclization of 2-aminobenzamide with 2-thiophene carboxaldehyde was reported in various conditions.



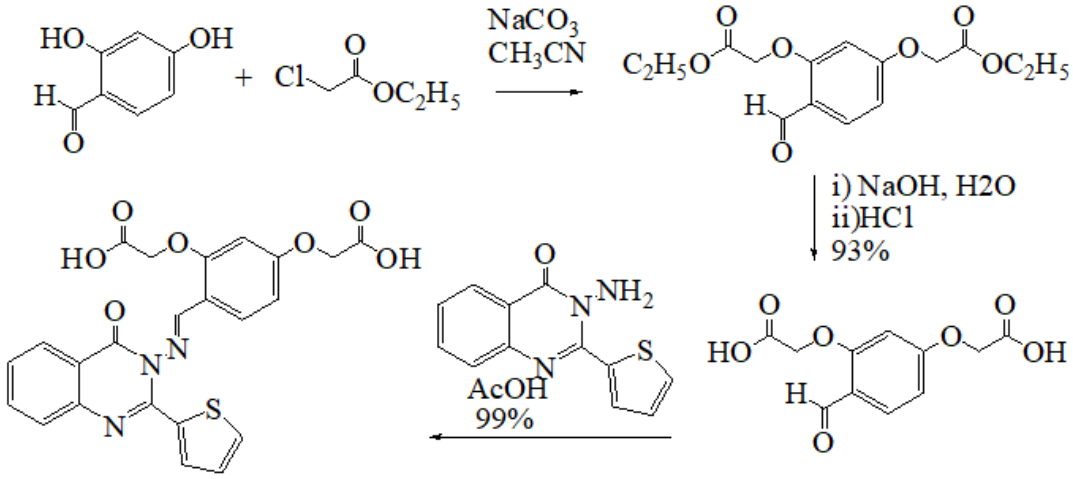
Conditions and yield	Reference
I_2, O_2, DMSO, 110°C,16h, 65%	173
$CeCl_3$, dimethylcarbonate/air, 100°C, 7h, 70%	176
DMSO, 100°C, 16–24 h	19
air, 120°C, 24h, 96%	166
$Y(OTf)_3$, DMSO, 110°C, 89%	177
Cp_2ZrCl_2, DMF, 80-100°C, 39%	163

Cheon and Kim developed an efficient, user-friendly and highly environmentally benign protocol for the synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one from anthranilamides and thiophene-2-carbaldehyde via aerobic oxidative cyclization in wet DMSO without any additives.[167]

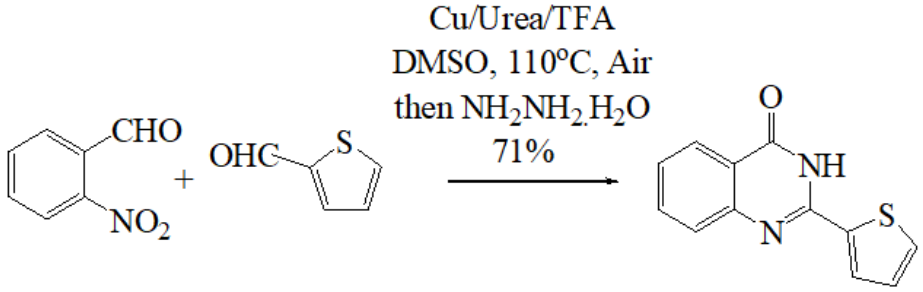
DOI: https://doi.org/10.5281/zenodo.13644773



The compound with anticholinergic properties, 2-(thiophene-2-yl)-3-(((2,4-bis(carboxy methoxy))benzylidene)amino)-quinazolin-4(3H)-one, was synthesized with excellent yield by the reaction of 2,4-dihydroxy benzaldehyde with ethylchloro acetate, hydrolysis followed by condensation of the resultant 2,2'-(4-formyl-1,3-phenylene)bis(oxy)diacetic acid with 2-(thiophene-2-yl)-3-amino-quinazolin-4(3*H*)-one in glacial acetic acid for an hour.[21]

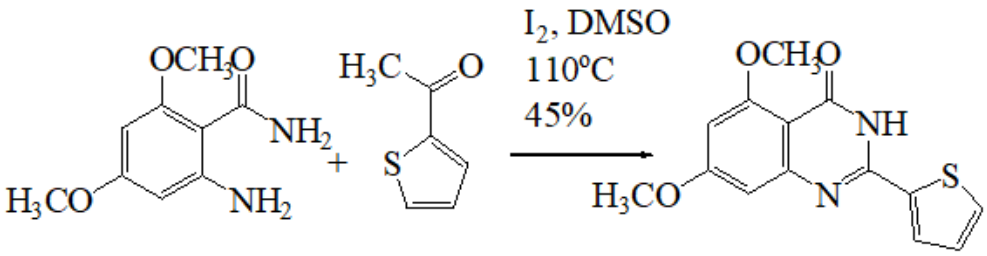


2-Nitrobenzaldehyde was treated with urea, $Cu(OAc)_2$ and TFA in a DMSO solvent at 110°C, then hydrazine hydrate and thiophene-2-carbaldehyde were added sequentially at the same temperature and stirred at room temperature for 16h to isolate 2-(thiophen-2-yl)quinazolin-4(3*H*)-one.[142]

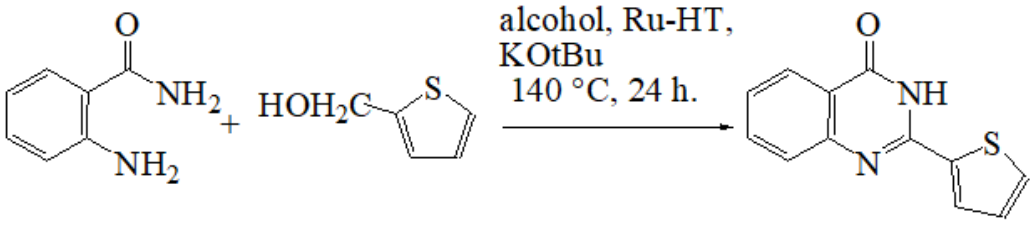


A novel AChE inhibitor with anti-inflammatory activity, 5,7-dimethoxy-2-(thiophen-2-yl)quinazolin-4(3*H*)-one, was prepared by the reaction of 2-amino-4,6-dimethoxybenzamide with 1-(thiophen-2-yl)ethanone in I_2 containing DMSO.[13]

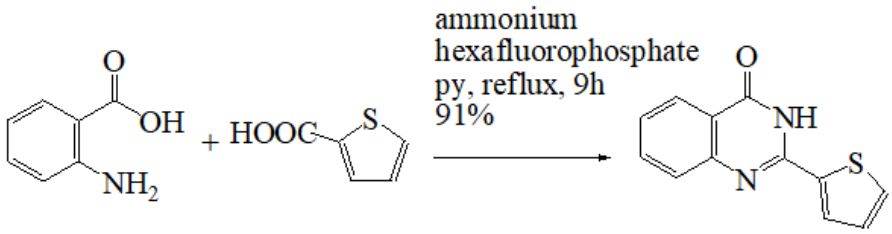
DOI: https://doi.org/10.5281/zenodo.13644773



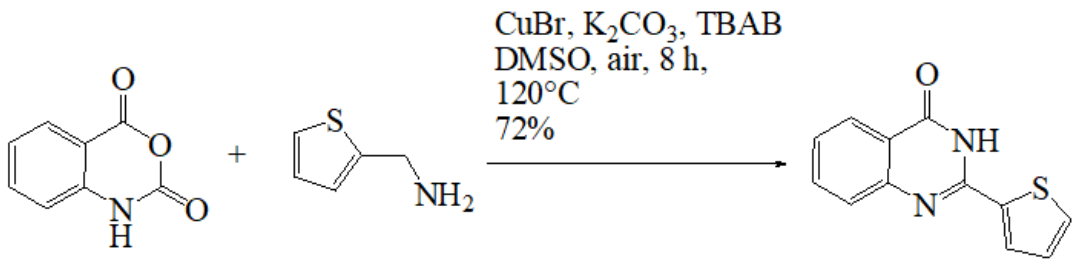
An efficient Ru doped hydrotalcite catalyzed *N*-alkylation of 2-aminobenzamide with (thiophen-2-yl)methanol via borrowing hydrogen catalysis to afford 2-(thiophen-2-yl)quinazolin-4(3*H*)-one is illustrated.[178]



A mixture of 2-aminobenzoic acid, thiophene-2-carboxylic acid, ammonium hexafluoro phosphate was refluxed in pyridine for 9 h to isolate 2-(thiophen-2-yl)quinazolin-4(3*H*)-one.[179]

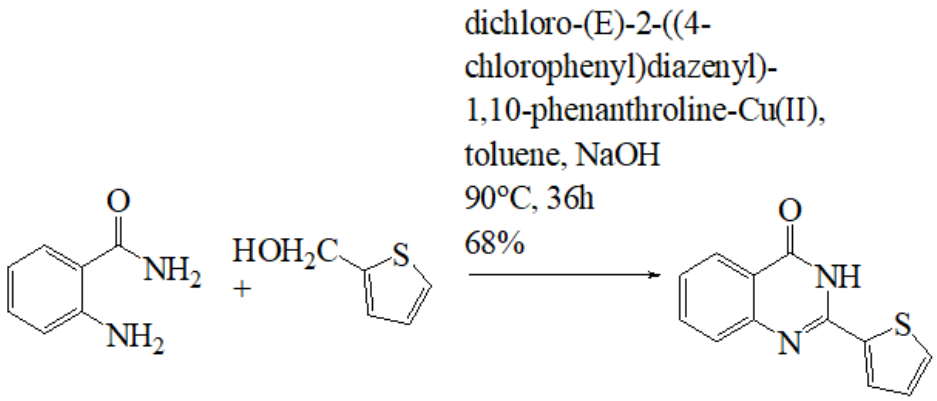


Alternatively, novel and straightforward method for the synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one from the reaction of isatoic anhydride and (thiophen-2-yl)methanamine for the formation of *N*-substituted anthranilamides, which under aerobic conditions in the presence of CuBr undergo an in situ oxidation–cyclization reaction.[180]

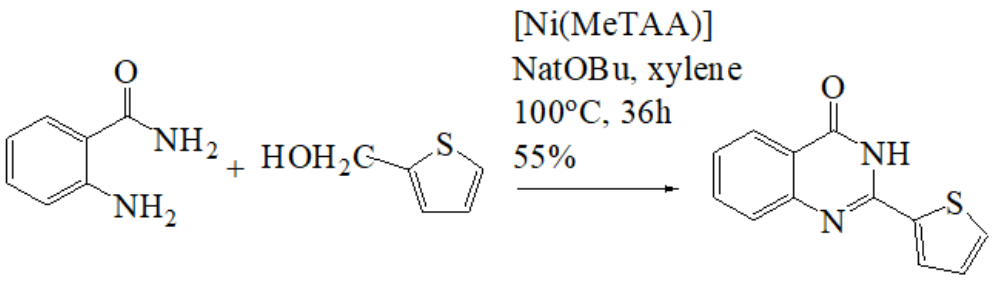


Nanda D. Paul et.al reported the dehydrogenative coupling of 2-aminobenzamide and (thiophen-2-yl)methanol to afford 2-(thiophen-2-yl)quinazolin-4(3*H*)-one in presence of dichloro-(*E*)-2-((4-chlorophenyl)diazenyl)-1,10-phenanthroline-Cu(II) catalyst in toluene containing NaOH at 90° C for 36h.[181]

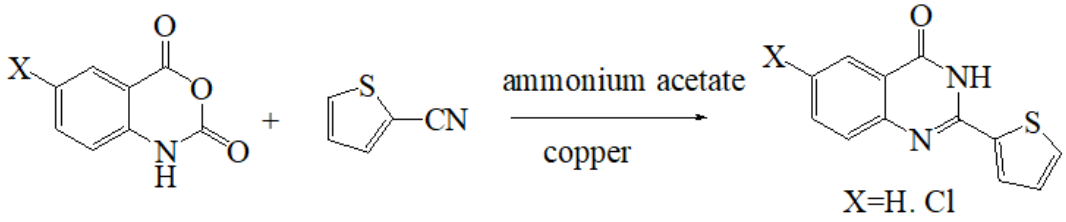
DOI: https://doi.org/10.5281/zenodo.13644773



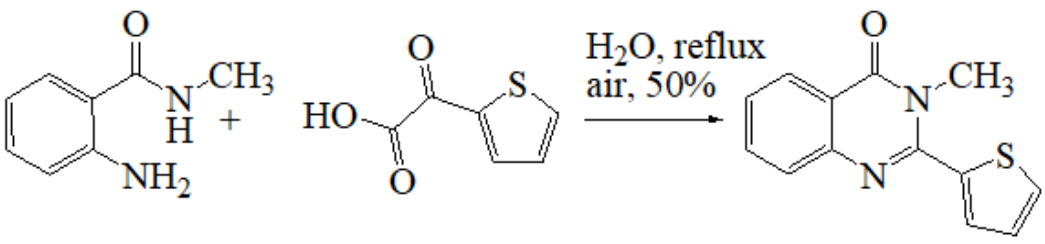
The cascade synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one via acceptor less de hydrogenative cyclization of o-aminobenzamide with (thiophen-2-yl)methanol using [Ni(MeTAA)] as the catalyst is reported.[182]



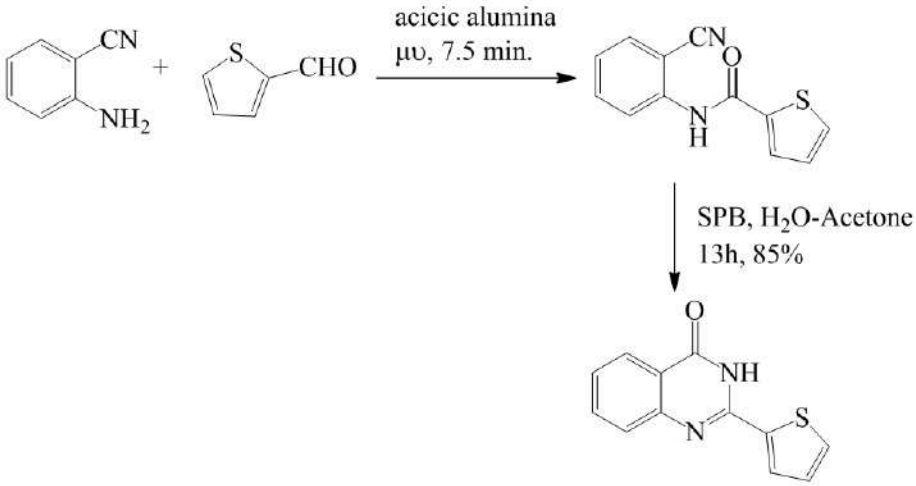
Rahim et.al have developed a novel and efficient approach for the synthesis of 2-(thiophen-2-yl)quinazoline-4(3*H*)-ones I [X = H, Cl] through a one-pot copper-catalyzed three-component reaction of isatoic anhydride or 6-chloroisatoic anhydride, thiophene-2-carbonitrile and ammonium acetate under solvent-free conditions in good yields. [170]



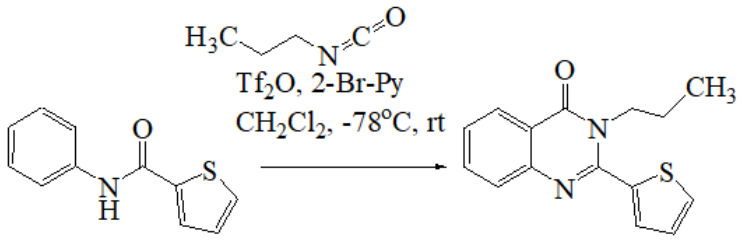
A green oxidant and catalyst-free reaction between 2-oxo-2-(thiophen-2-yl)acetic acid and 2-amino-*N*-methylbenzamide in pure water at reflux provided 3-methyl-2-(thiophen-2-yl)quinazolin-4(3*H*)-one. The yield of the product has been increased from 50% to 71% under O_2 atmosphere. [183]



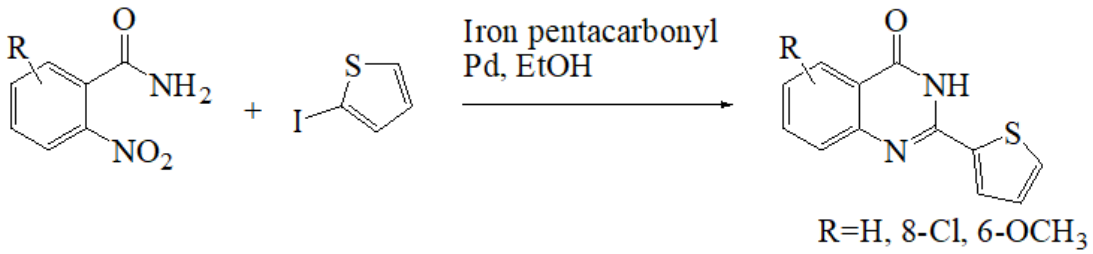
An environmentally benign approach for the synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one by reacting 2-aminobenzonitrile with thiophene-2-carbaldehyde in ethanol containing acidic alumina under microwave irradiation followed by cyclized in acetone - water employing sodium perborate (SPB) as catalyst.[184]



Huang et.al developed a chemoselective activation of the secondary amide *N*-phenylthiophene-2-carboxamide with Tf_2O/2-Br-Pyr, the sequential addition of 1-isocyanatopropane and cyclization to afford 3-propyl-2-(thiophen-2-yl)quinazolin-4(3*H*)-one.[185]

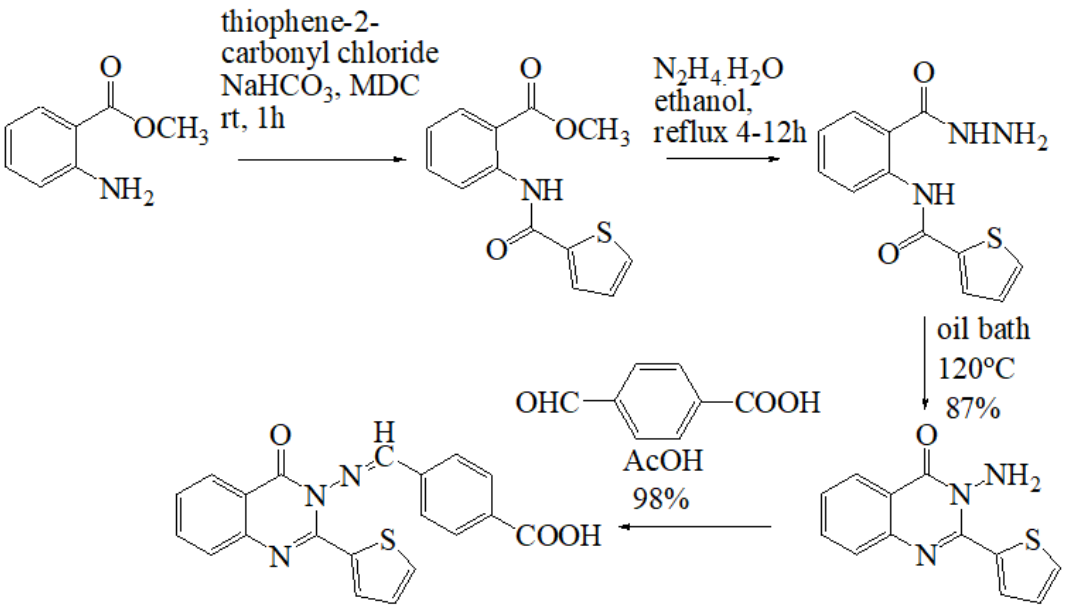


A direct and unconventional method for the synthesis of quinazolinones by using iron pentacarbonyl as a reducing agent and a carbon monoxide source under microwave irradiation is described. The reaction of 2-iodothiophene with 2-nitrobenzamide derivative successfully delivered a wide variety quinazolinones.[186]

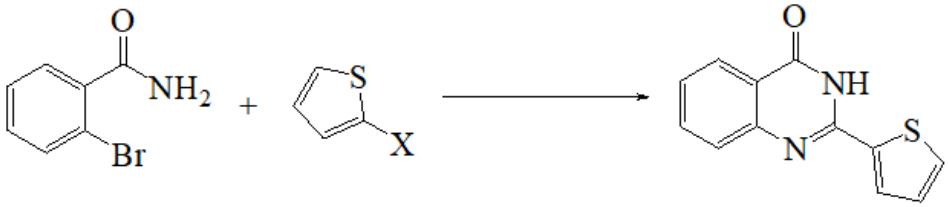


The α-Glucosidase and α-Amylase enzymes inhibitory activity compound was synthesized from methyl anthranilate. Methyl anthranilate was reacted with thiophene-2-carbonyl chloride in dichloromethane containing sodium bicarbonate to get methyl 2-(thiophene-2-carboxamido)benzoate, reaction with hydrazinium hydroxide in ethanol at reflux for 4–12h to get 2-(thiophene-2-carboxamido)benzohydrazide, heat in an oil bath at 120°C for two hours without any solvent core to get 3-amino-2-(thiophen-2-yl)quinazolin-4(3*H*)-one followed by reaction with 4-formylbenzoic acid in glacial acetic acid at reflux for an hour to afford 3-(4-carboxybenzylideneamino)-2-(thiophen-2-yl)quinazolin-4(3*H*)-one in good yield.[22]

DOI: https://doi.org/10.5281/zenodo.13644773



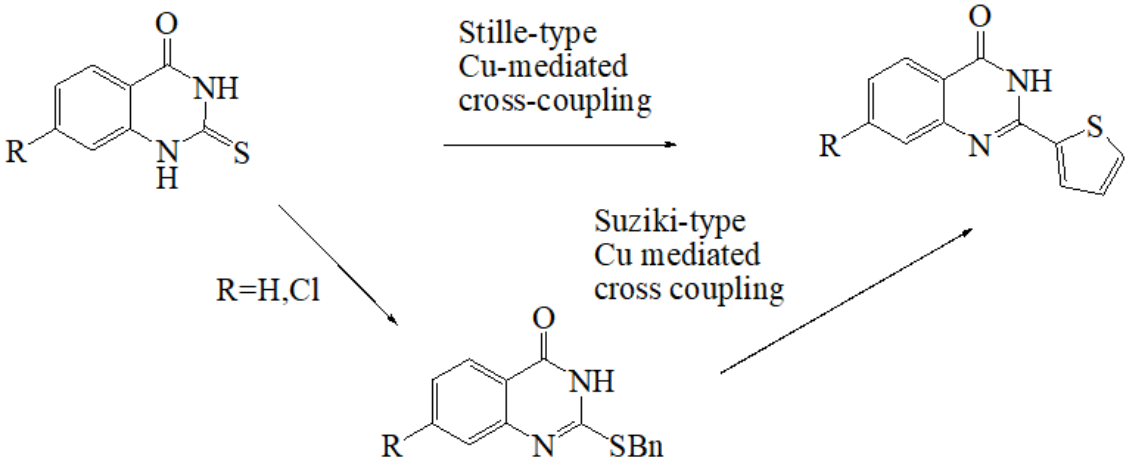
Tripathi et.al have reported a novel and efficient Cu(I)-catalyzed ligand- and base-free synthesis of 2-(thiophen-2-yl)quinazolin-4(3*H*)-one. The reaction utilizes 2-bromobenzamide and multiform substrates such as aldehydes, alcohols, and methyl arenes for a one-pot protocol, whereas $TMSN_3$ is used as a nitrogen source. [161]



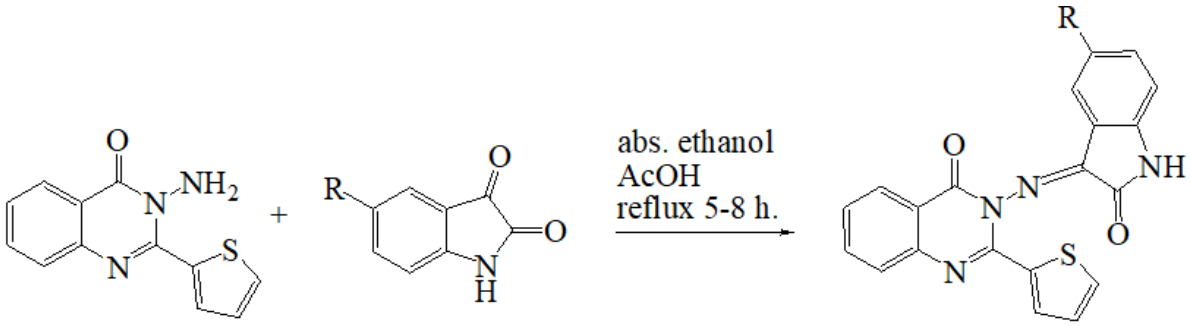
X	condition	Yield (%)
—CHO	$TMSN_3$, CuI, air DMSO, 80°C	81%
—CH_2OH	$TMSN_3$, CuI, DMSO, air TBHP, 80°C	76%
—CH_3	$TMSN_3$, CuI, DMSO, air TBHP, 80°C	49%

With the purpose of searching for new heterocyclic building blocks, a new method to access *N*(3)-unsubstituted 2-(thiophen-2-yl)quinazolin-4(3*H*)-one from 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one derivatives was developed. The synthetic protocol was based on the copper-mediated palladium-catalysed cross-coupling reactions of 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one derivatives with (het)arylstannanes or their 2-(benzylthio)quinazolin-4(3*H*)-one derivatives with (het)arylboronic acids, using CuBr·Me_2 S and CuMeSal as promoters, respectively.[187]

DOI: https://doi.org/10.5281/zenodo.13644773

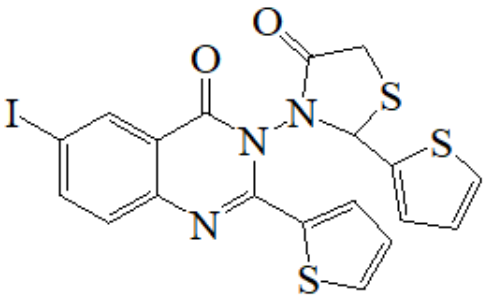


A. M. Alafeefy et.al synthesized (*Z*)-3-(substituted oxoindolin-3-ylideneamino)-2-(thiophen-2-yl)quinazolin-4(3*H*)-ones by the reaction of 3-amino-2-arylquinazolin-4(3*H*)-one with substituted indoline-2,3-dione. All five compounds tested antitumor activity against most of the tested cell lines, Daoy, UW228-2, Huh-7, Hela and MDA-MB231. (*Z*)-3-(2-Oxoindolin3-ylideneamino)-2-(thiophen-2-yl)quinazolin-4(3*H*)-one was active only against one tumor cell line.[23]



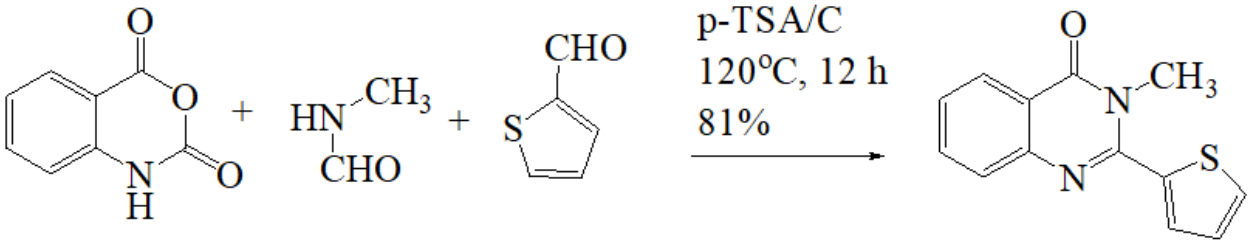
R	H	Cl	CH_3	OCH_3	NO_2
Yield(%)	64	62	52	47	51

Srinivas et.al reported that 6-iodo-3-(4-oxo-2-(thiophen-2-yl)thiazolidin-3-yl)-2-(thiophen-2-yl)quinazolin-4(3*H*)-one was proved to be the most active broad spectrum antibacterial agents.[24]

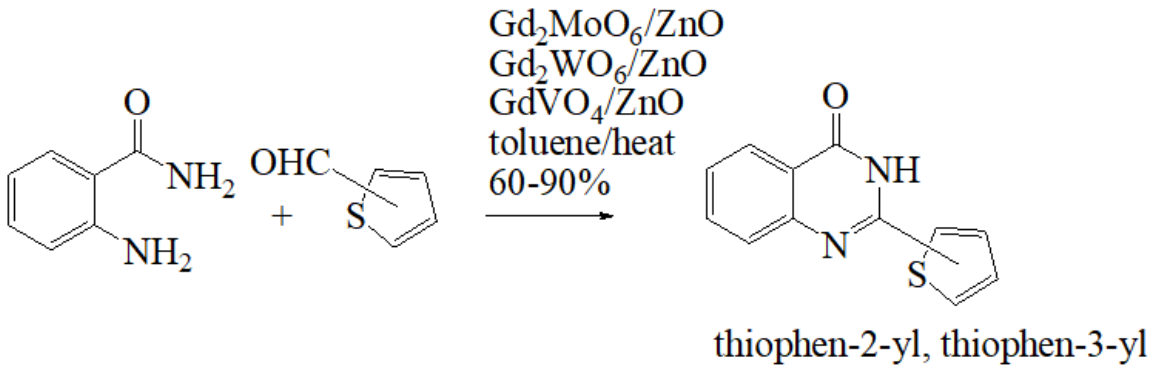


The Straightforward preparation of 3-methyl-2-(thiophen-2-yl)quinazolin-4(3*H*)-one via the reusable carbon-supported acid-catalyzed direct amidation and cascade annulation of isatoic anhydride with *N*-methylformamide and 4- thiophene-2-carbaldehyde is reported.[188]

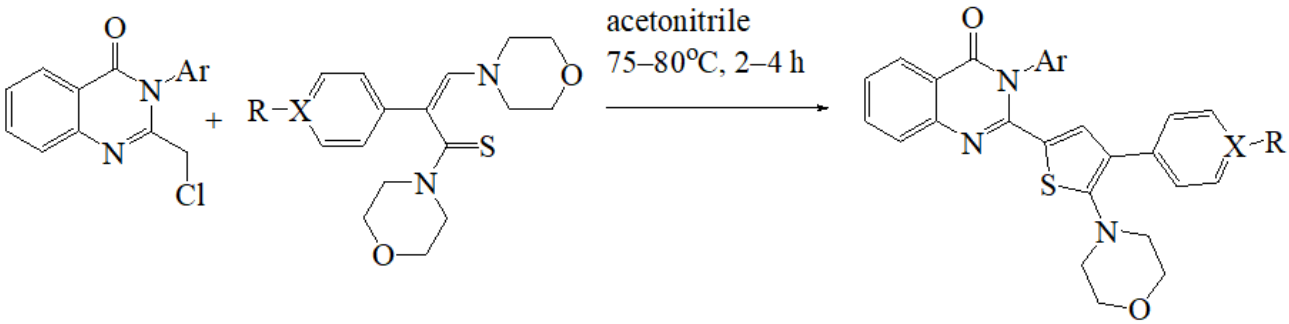
DOI: https://doi.org/10.5281/zenodo.13644773



New protocol was developed for synthesis of 2-(thiophen-2-yl)/(thiophen-3-yl)/quinazolin-4(3*H*)-one by condensation of anthranilamide with thiophene-2-carbaldehyde/ thiophene-3-carbaldehyde catalysed by rare earth metal oxide namely Gd_2MoO_6 doped on ZnO in toluene in 60–90% yield. The catalysts could be reused at least four times without loss of catalytic activity.[189]



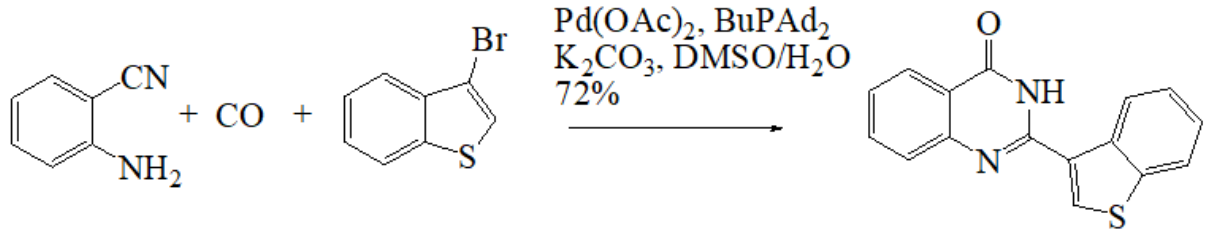
Potential anti-inflammatory, anti-cancer and inhibitors of NF-kB and AP-1 mediated transcriptional activation quinazolinone derivatives, 2-(5-morpholin-4-yl-4-(aryl/pyridinyl)-thiophene-2-yl)-3-aryl-quinazolin-4(3*H*)-ones were prepared by the reaction of 2-chloromethyl-3-aryl-quinazolin-4(3*H*)-ones with 1,3-dimorpholin-4-yl-2-substituted-propenethiones.[25]



Ar	X	R	Yield (%)	Ar	X	R	Yield (%)
C_6H_5	C	H	58	4-$CH_3C_6H_4$	C	SO_2CH_3	57
C_6H_5	C	Cl	51	4-$CH_3C_6H_4$	C	SCH_3	42
C_6H_5	C	$NHCOCH_3$	57	4-$CH_3C_6H_4$	N	-	39
C_6H_5	C	SO_2CH_3	58.4	2-$CH_3OC_6H_4$	C	H	43
C_6H_5	C	SCH_3	46	2-$CH_3OC_6H_4$	C	SO_2CH_3	55
C_6H_5	N	-	38	2-$CH_3OC_6H_4$	N	-	41
2-$CH_3C_6H_4$	C	H	54	3-$CH_3OC_6H_4$	C	SO_2CH_3	57
2-$CH_3C_6H_4$	C	Cl	53	4-$CH_3OC_6H_4$	C	SO_2CH_3	56
2-$CH_3C_6H_4$	C	SO_2CH_3	56	2-ClC_6H_4	N	-	39
2-$CH_3C_6H_4$	C	SCH_3	56	4-ClC_6H_4	C	H	54
2-$CH_3C_6H_4$	N	-	39	4-ClC_6H_4	C	Cl	55
3-$CH_3C_6H_4$	C	Cl	56	4-ClC_6H_4	C	$NHCOCH_3$	54
3-$CH_3C_6H_4$	C	$NHCOCH_3$	52	4-ClC_6H_4	C	SO_2CH_3	57
3-$CH_3C_6H_4$	C	SO_2CH_3	54.5	4-ClC_6H_4	N	-	39
3-$CH_3C_6H_4$	C	SCH_3	43	4-$CH_3COC_6H_4$	C	H	52
3-$CH_3C_6H_4$	N	-	36	4-$CH_3COC_6H_4$	C	Cl	50
4-$CH_3C_6H_4$	C	H	54	4-$CH_3COC_6H_4$	C	SO_2CH_3	54
4-$CH_3C_6H_4$	C	Cl	51	4-$CH_3COC_6H_4$	N	-	42
4-$CH_3C_6H_4$	C	$NHCOCH_3$	40				

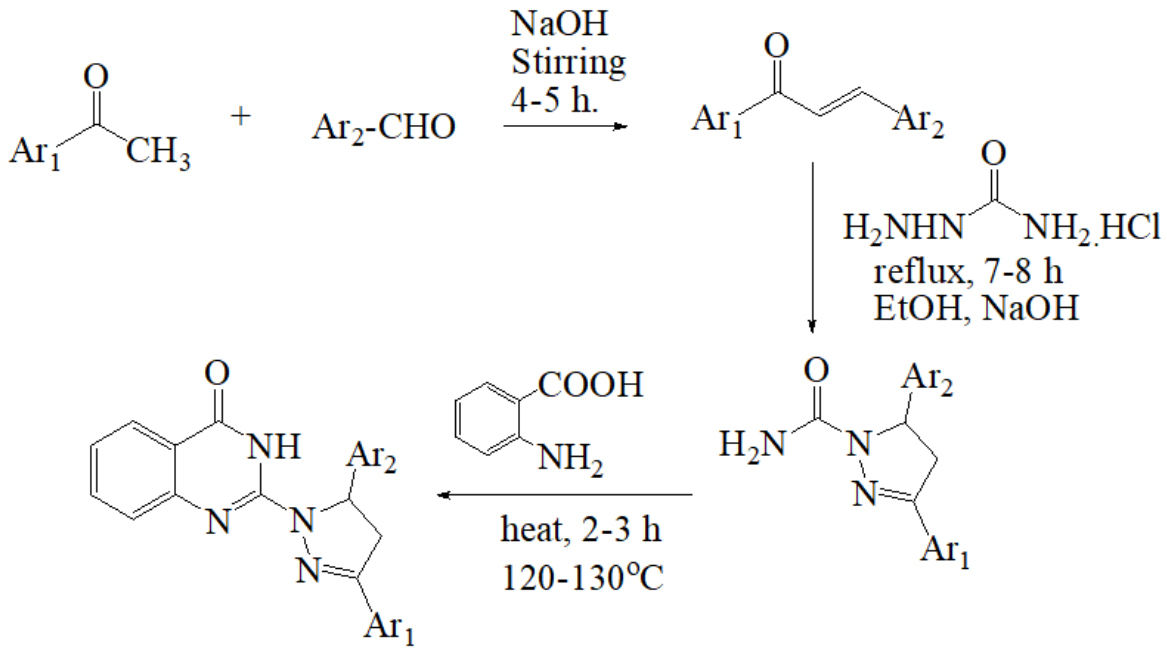
2.3.24 Benzothiophenylquinazolin-4(3*H*)-one

Xiao-Feng Wu et.al reported the a cascade synthesis of 2-(benzo[*b*]thiophen-3-yl)quinazolin-4(3*H*)-one from 2-aminobenzonitrile and 3-bromobenzo[*b*]thiophene through a palladium-catalyzed carbonylation reaction has been developed. The reactions go through aminocarbonylation of aryl bromides–hydration of nitriles–cyclization sequence.[154]



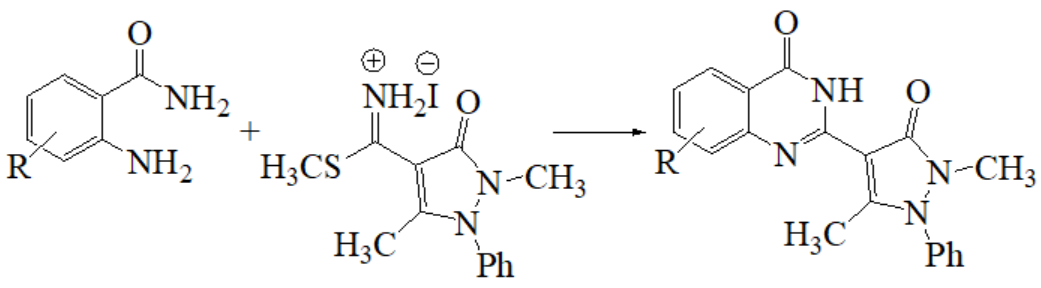
2.3.25 Dihydropyrazolylquinazolin-4(3*H*)-ones

Analgesic and anti-inflammatory activities of pyrazoline bearing quinazolin-4(3*H*)-one derivatives were prepared by Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone with aromatic aldehyde in the presence of aqueous alkali, cyloaddition of obtained chalcone with semicarbazide HCl to yield amide derivative followed by cyclization reaction with anthranillic acid to yield 2-(3, 5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)quinazoline-4(3*H*)-one.[26]



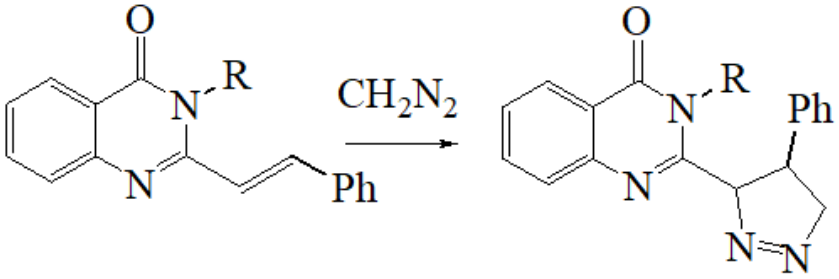
Ar_1	Ar_2	Yield(%)	Ar_1	Ar_2	Yield(%)
C_6H_5	C_6H_5	69	C_6H_5	$4\text{-}ClC_6H_4$	57
C_6H_5	$4\text{-}(CH_3)_2NC_6H_4$	59	$4\text{-}BrC_6H_4$	$4\text{-}ClC_6H_4$	60
$4\text{-}BrC_6H_4$	$2\text{-}ClC_6H_4$	52	$4\text{-}BrC_6H_4$	$4\text{-}(CH_3)_2NC_6H_4$	59
$4\text{-}NH_2C_6H_4$	$4\text{-}ClC_6H_4$	64	$4\text{-}NH_2C_6H_4$	$2\text{-}ClC_6H_4$	60
$4\text{-}HOC_6H_4$	$4\text{-}ClC_6H_4$	53	$4\text{-}HOC_6H_4$	$2\text{-}ClC_6H_4$	57

Reaction of an anthranilic acid with 4-thioimidemethiodidoantipyrine was found to be the most feasible route for preparing 2-(4-antipyrinyl)-quinazolin-4(3*H*)-ones.[190]



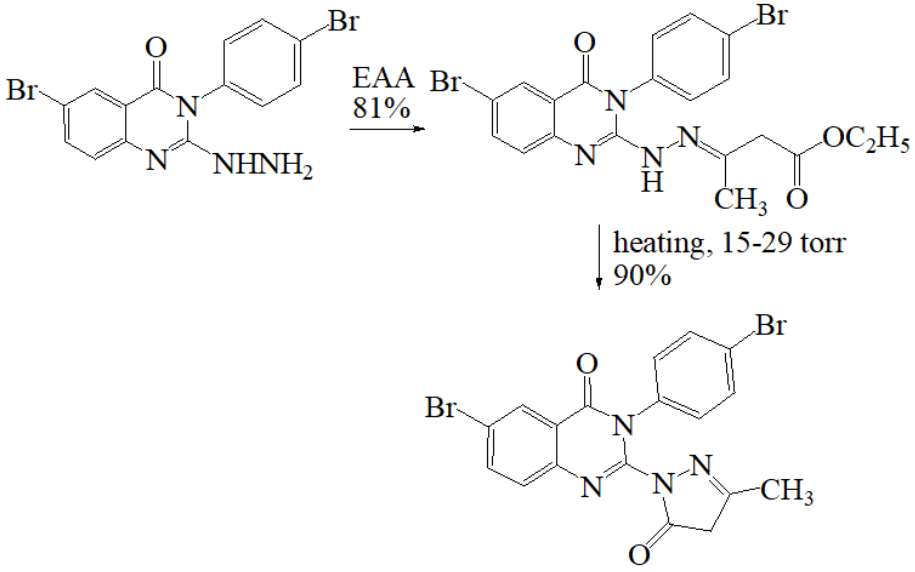
R = H, 6-Cl, 7-Cl, 6-Br, 6-CH_3

In an alternative synthesis, 1,3-dipolar addition of diazomethane to C=C bond in 3-alkyl-2-styryl-4(3*H*)-quinazolinone yielded 3-aryl-2-(4-phenylpyrazolin-3-yl)-quinazolin-4(3*H*)-ones in good yields. No further details are reported about this reaction.[191]



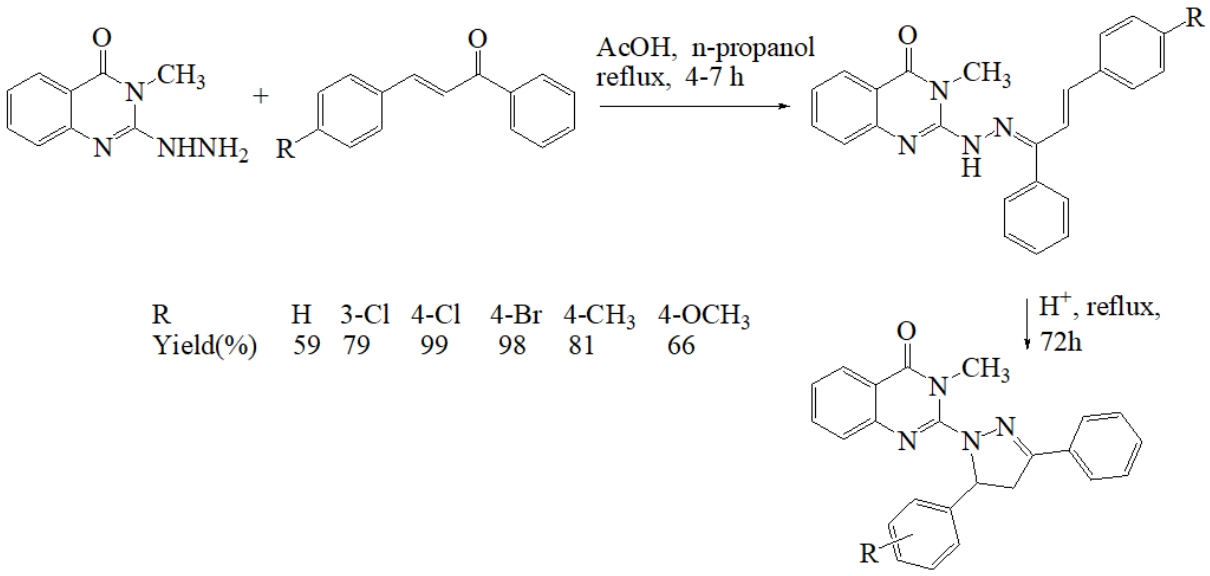
R = C_4H_9, C_6H_5, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 3-$NO_2C_6H_4$

2-(1-(3-Methylpyrazolyl))-4(3*H*)-quinazolinone was prepared in two-steps from 6-bromo-3-(4-bromo-phenyl)-2-hydrazino-4(3*H*)-quinazolinone. First, hydrazine derivative was condensed with ethyl acetoacetate (EAA) and the resultant hydrazone was isolated in 81% yield on heating in vacuum (15-20 torr) at its melting point.[192]



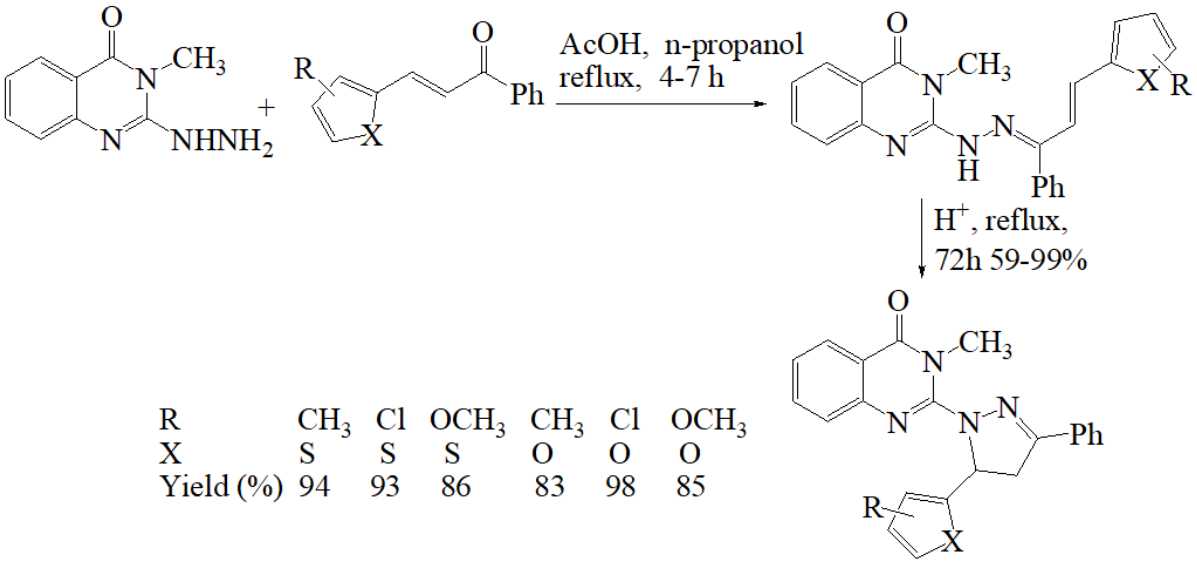
Acid catalyzed condensation of 2-hydrazino-3-methylquinazolin-4(3*H*)-one and α,β-unsaturated ketones yielded 2-(1-phenyl-3-aryl-2-propenylidene)hydrazino-3- methylquinazolin-4(3*H*)-ones. Subsequent cyclisation in glacial acetic acid afforded 2-(5-aryl-3-phenyl-2-pyrazolin-1-yl)-3-methylquinazolin-4(3*H*)-one derivatives and have showed anti-inflammatory and analgesic activity.[27]

DOI: https://doi.org/10.5281/zenodo.13644773



R	H	3-Cl	4-Cl	4-Br	4-CH_3	4-OCH_3
Yield(%)	59	79	99	98	81	66

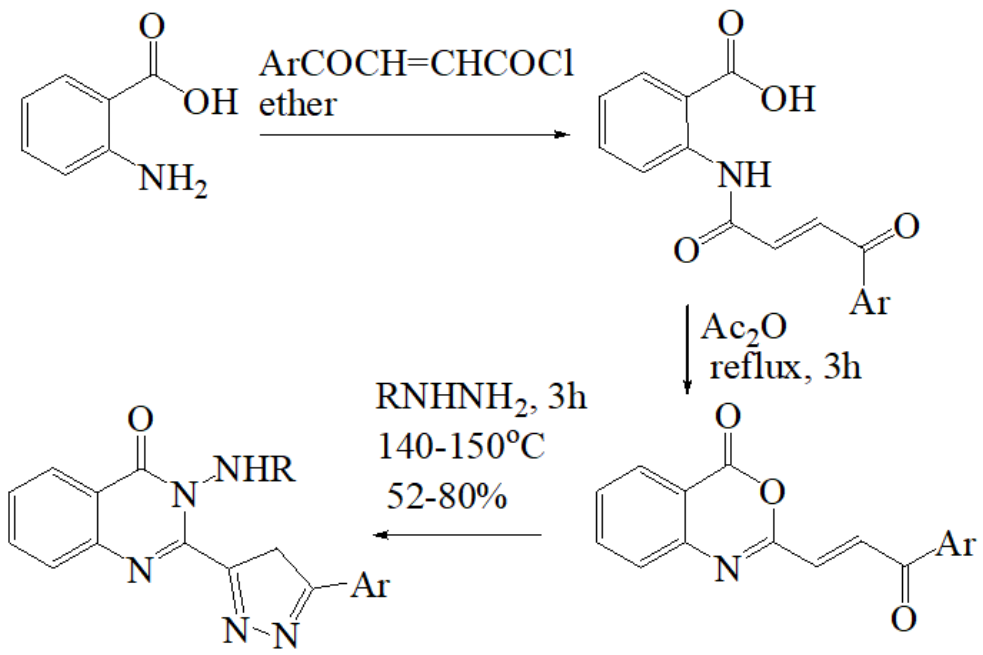
A mixture of 2-hydrazino-3-methylquinazolin-4(3*H*)-one and chalcones were refluxed under acidic conditions for the formation of hydrazones and subsequent addition of *N–H* on the olefinic bond of the propenone moiety that form the ring-closed final products- 2-(3-substituted phenyl-5-heteroaryl-2-pyrazoline-1-yl)-3-methylquinazolin-4(3*H*)-one derivatives. Most of the synthesized compounds showed high activity against both the MAO-A and the MAO-B isoforms. However, only 2-[10-(4-chlorophenyl)-3-thienyl-2-propenylidene] hydrazine-3-methyl)-quinazolin-4(3*H*)-one have showed antidepressant activity.[28]



R	CH_3	Cl	OCH_3	CH_3	Cl	OCH_3
X	S	S	S	O	O	O
Yield (%)	94	93	86	83	98	85

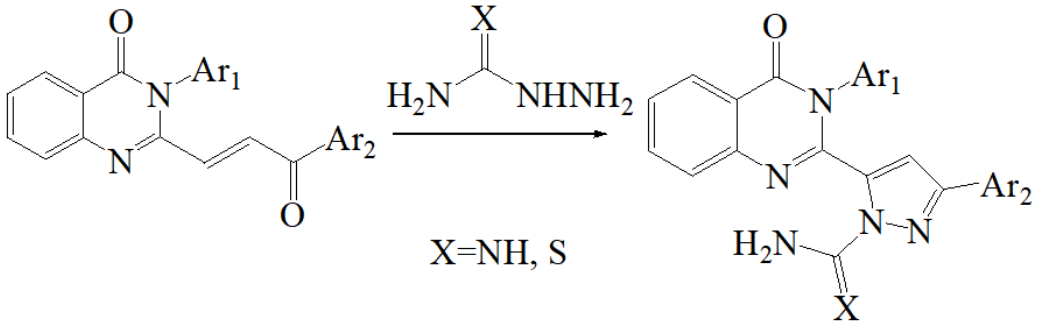
Soliman et.al reported the synthesis of 2-pyrazolyl-quinazolin-4(3*H*)-ones starting from 3-aroylpropenoyl chloride on reacting with anthranilic acid in ether, resultant benzoic acid derivative was cyclized to the benzoxazinone by refluxing in acetic anhydride for 3 h, then reacted with hydrazine hydrate and with phenylhydrazine to yield 2-[5'-(3'-aryl-4',5'-dihydropyrazolyl)]-3-amino-quinazolin-4(3*H*)-ones and 2-(1'-phenyl-3'-aryl-4',5'-dihydropyrazolyl)-3-phenylamino-quinazolin-4(3*H*)-ones respectively. These compounds have shown antimicrobial activity.[29, 193, 194]

DOI: https://doi.org/10.5281/zenodo.13644773



NHR = 4-ClC_6H_4CH=N, 4-$CH_3OC_6H_4CH$=N, $(CH_3)_2C$=N, $C_6H_{11}NHCONH$, $C_6H_5CONHCONH$, NH_2;phthalimido, Ar = 2, 4, 6-$(CH_3)_3C_6H_2$
R = H, Ph; Ar = 4-$CH_3C_6H_4$, 2, 4-$(CH_3)_2C_6H_3$

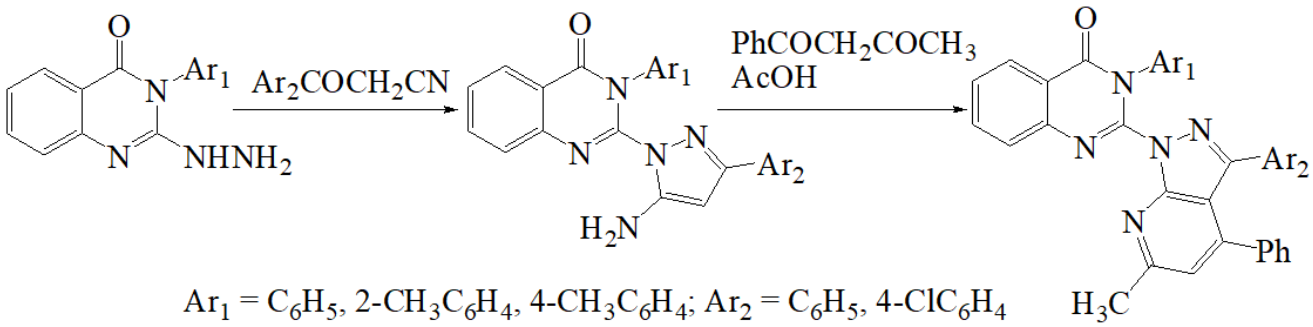
Khilil et.al prepared two novel quinazolinones from the key intermediate, 3-aryl-2-(3-oxopropenyl)-quinazolin-4(3*H*)-ones. For example, the key intermediate reacted with aminoguanidine to give 3-aryl-2-(3-aryl-1-iminocarbamoyl-1*H*-pyrazol-5-yl)-quinazolin-4(3*H*)-ones. With thiosemicarbazide, the key intermediate yielded 3-aryl-2-(3-aryl-thiocarbamoyl-1*H*-pyrazol)-quinazolin-4(3*H*)-ones. The antiinflammatory activity of representatives of these compounds is comparable to or higher than that of proquazone.[30]



Ar_1 = C_6H_5, 4-$CH_3C_6H_4$, 4-BrC_6H_4; Ar_2 = C_6H_5, 4-$CH_3C_6H_4$

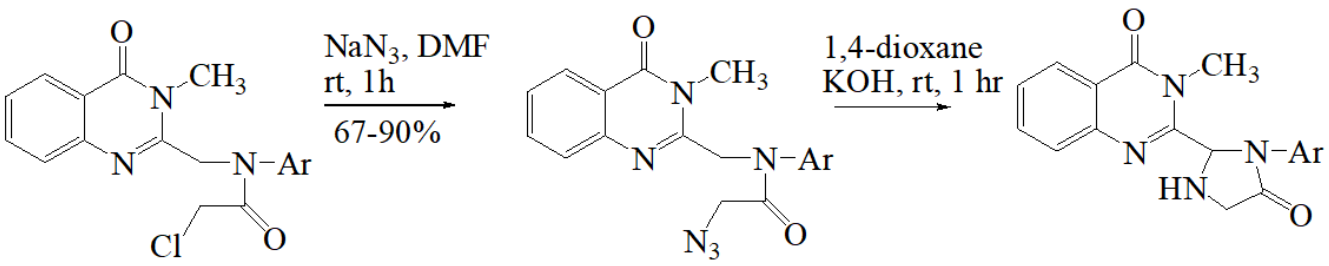
El-Feky synthesized 2-pyrazolo[3,4-*b*]pyridylquinazolinones starting from 2-hydrazino-3-aryl-quinazolin-4(3*H*)-ones. The hydrazine condensed with cyanoacetophenones to give 2-(3-aryl-5-aminopyrazolyl)-3-aryl-quinazolin-4(3*H*)-ones. Subsequent reaction with benzoylacetone in glacial acetic acid afforded the title compounds.[195]

DOI: https://doi.org/10.5281/zenodo.13644773



2.3.26 Imidazolidinonylquinazolin-4(3*H*)-ones

The 2-*N*-azidoacetylarylaminomethyl-3-methylquinazolin-4(3*H*)-one, which was prepared by stirring a mixture of 2-*N*-chloroacetyl-(4-aryl)aminomethyl-3-methylquinazolin-4(3*H*)-one and sodium azide in DMF, was easily underwent cyclisation in basic medium to afford 2-imidazolidinonylquinazolin-4(3*H*)-one.[196]

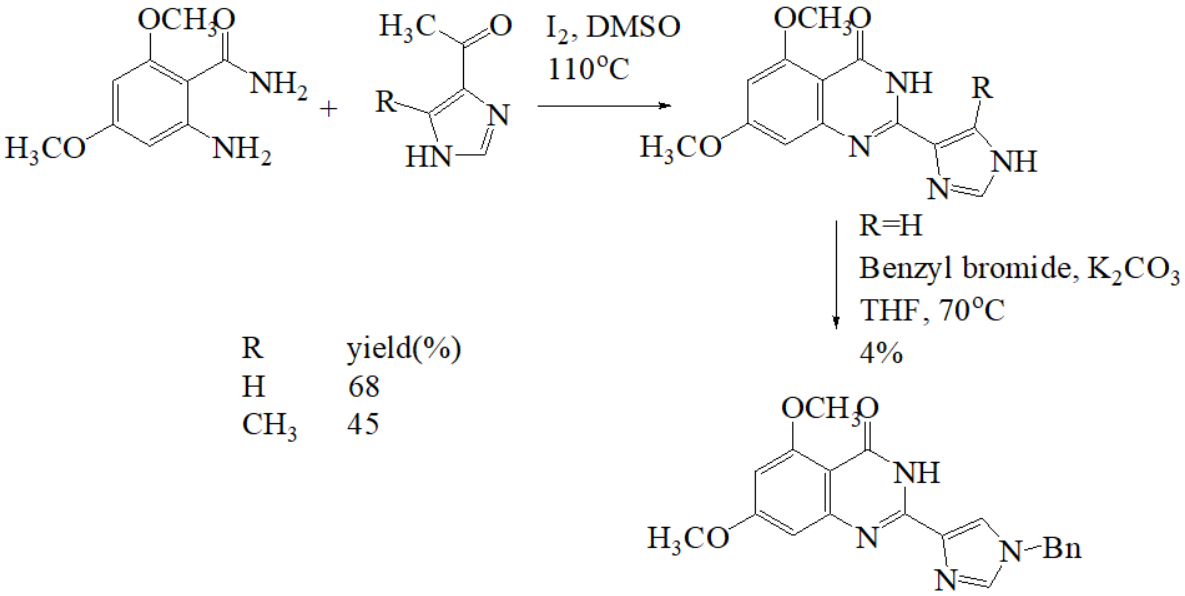


Ar	C_6H_5	4-$CH_3C_6H_4$	4-$C_2H_5C_6H_4$	4-ClC_6H_4
Yield(%)	92	94	72	97

2.3.27 Imidazolylquinazolin-4(3*H*)-one

A novel AChE inhibitors with anti-inflammatory activities were prepared by the reaction of 2-amino-4,6-dimethoxybenzamide with 1-(1*H*-imidazol-4-yl)ethanone under I_2 to give 2-(1*H*-imidazol-4-yl)-5,7-dimethoxyquinazolin-4(3*H*)-one derivatives. Further one of the resultant compound 2-(1*H*-imidazol-4-yl)-5,7-dimethoxyquinazolin-4(3*H*)-one was benzylated with benzyl bromide to produce 2-(1-benzyl-1*H*-imidazol-4-yl)-5,7-dimethoxyquinazolin-4(3*H*)-one.[13]

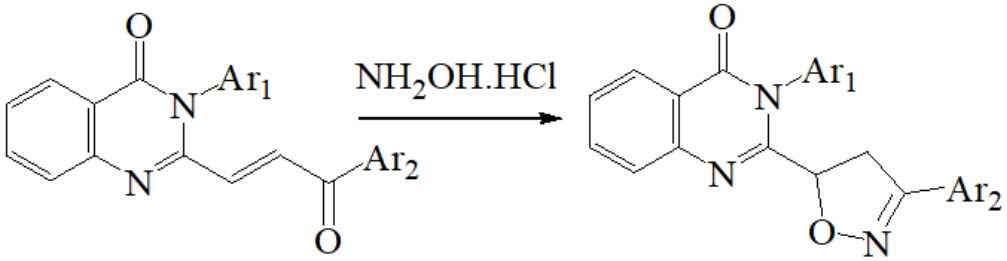
DOI: https://doi.org/10.5281/zenodo.13644773



R	yield(%)
H	68
CH_3	45

2.3.28 Oxazolylquinazolin-4(3*H*)-ones

3-Aryl-2-(3-oxopropenyl)-quinazolin-4(3*H*)-ones reacted with hydroxylamine hydrochloride to yield 3-aryl-2-(3-aryl-4,5-dihydro-1,2-oxozol-5-yl)-quinazolin-4(3*H*)-ones. The antiinflammatory activity of representatives of these compounds is comparable to or higher than that of proquazone.[30]

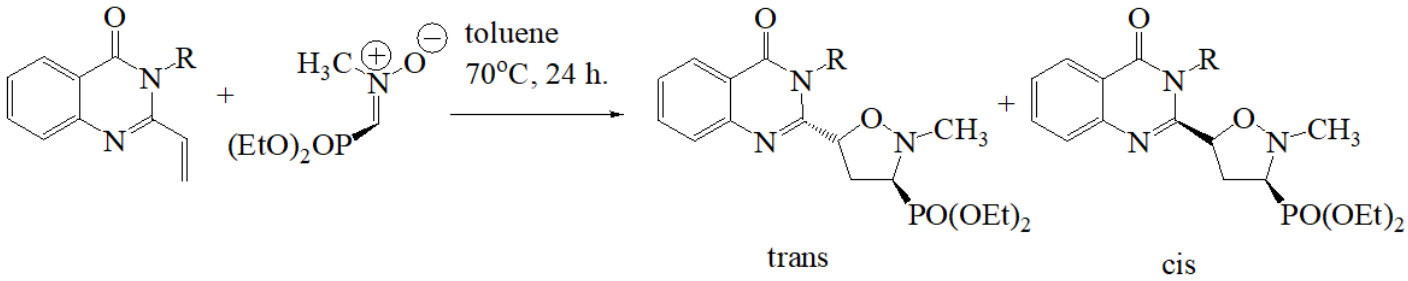


$Ar_1 = C_6H_5$, 4-$CH_3C_6H_4$, 4-BrC_6H_4; $Ar_2 = C_6H_5$, 4-$CH_3C_6H_4$

2.3.29 Isoxazolidinylquinazolin-4(3*H*)-ones

An antiproliferative agents- (*3S,5R*)-diethyl 5-(quinazolin-4(3*H*)-one-2-yl)-2-methylisoxazolidin-3-yl-3-phosphonates were synthesized by the 1,3-dipolar cycloaddition of *N*-methyl-C-(diethoxyphosphoryl)nitrone with N_3 -substitued 2-vinylquinazolin-4(3*H*)-ones in toluene 70°C. All isoxazolidines were assessed for antiviral activity against a broad range of DNA and RNA viruses. Isoxazolidines trans-2-F/cis-2-F (90:10), trans-4-F and trans-2,4-diF/cis-2,4-diF (97:3) showed weak activity (EC_{50} = 6.84, 15.29 and 9.44 M) toward VZV (TK+ strain) which was only one order of magnitude lower than that of acyclovir used as a reference drug. Phosphonates trans-benzyl/cis-benzyl (90:10), trans-2-nitro, trans-4-nitro/cis-4-nitro (90:10) and trans-3-F appeared slightly active toward cytomegalovirus (EC_{50}= 27–45 M). Compounds containing benzyl substituents at N_3 in the quinazolinone skeleton exhibited slight antiproliferative activity towards the tested immortalized cells with IC_{50} in the 21–102 M range[31]

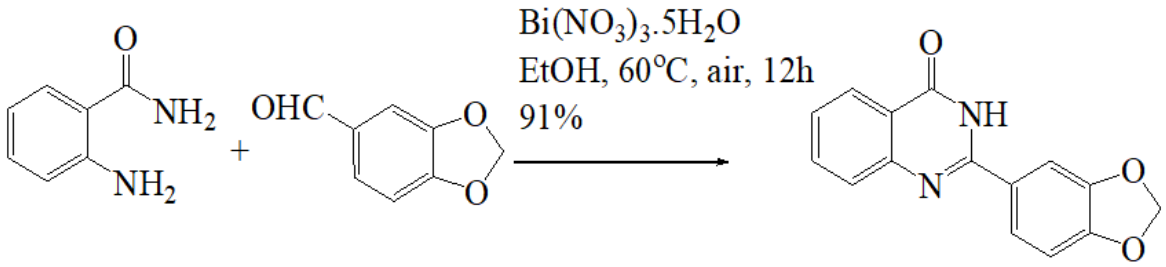
DOI: https://doi.org/10.5281/zenodo.13644773



R	Trans:Cis	trans Yield (%)	trans and cis Yield (%)
H	92:08	23	70
C_6H_5-CH_2	90:10	--	84
2-NO_2-C_6H_4-CH_2	90:10	20	73
3-NO_2-C_6H_4-CH_2	92:08	--	98
4-NO_2-C_6H_4-CH_2	90:10	--	91
2-F-C_6H_4-CH_2	90:10	--	94
3-F-C_6H_4-CH_2	90:10	07	89
4-F-C_6H_4-CH_2	90:10	22	70
2,4-diF-C_6H_3-CH_2	92:08	--	94
Me	94:06	19	78
Et	92:08	--	86

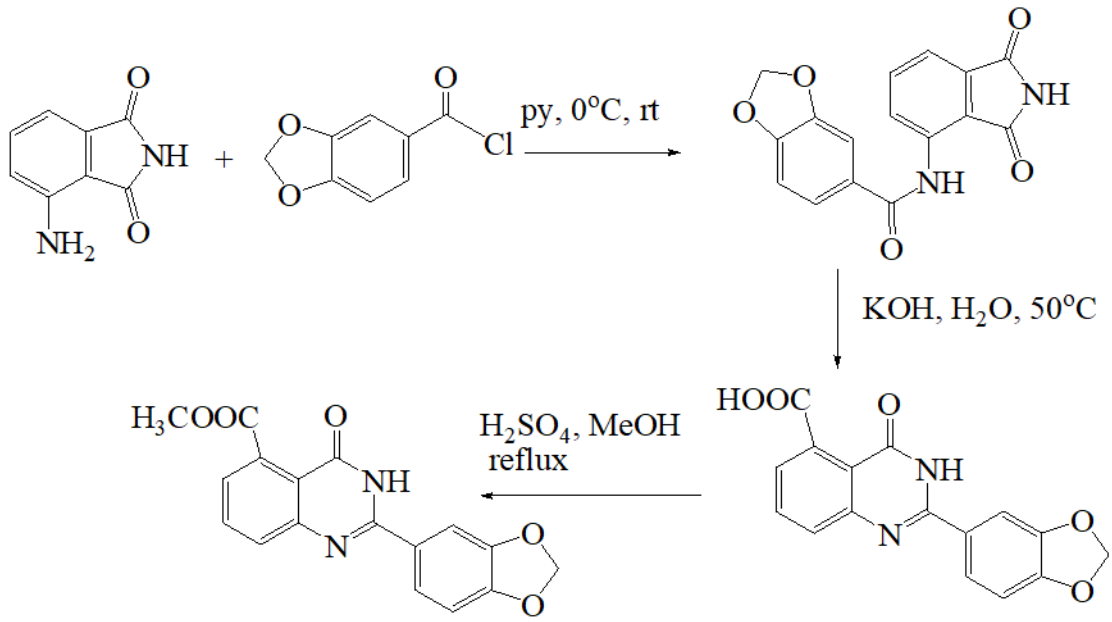
2.3.30 Benzodioxolylquinazolin-4(3*H*)-one

The oxidative cyclocondensation of 2-aminobenzamide with benzo[*d*][1,3]dioxole-5-carbaldehyde in presence of $Bi(NO_3)_3.5H_2O$ at 60° C in ethanol for 12 h to isolate 2-(benzo[*d*][1,3]dioxol-5-yl)quinazolin-4(3*H*)-one was explored.[171]



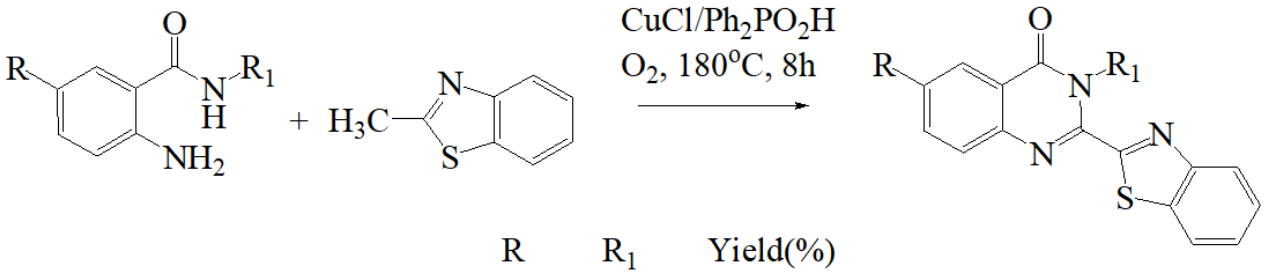
The synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)-5-methoxycarbonylquinazolin-4(3*H*)-one was reported by the acylation of 4-aminoisoindoline-1,3-dione with benzo[*d*][1,3]dioxole-5-carbonyl chloride, a novel ring opening-reclosing reaction with KOH solution followed by esterification with methanol. These are a new class of PARP-1 inhibitors.[20]

DOI: https://doi.org/10.5281/zenodo.13644773



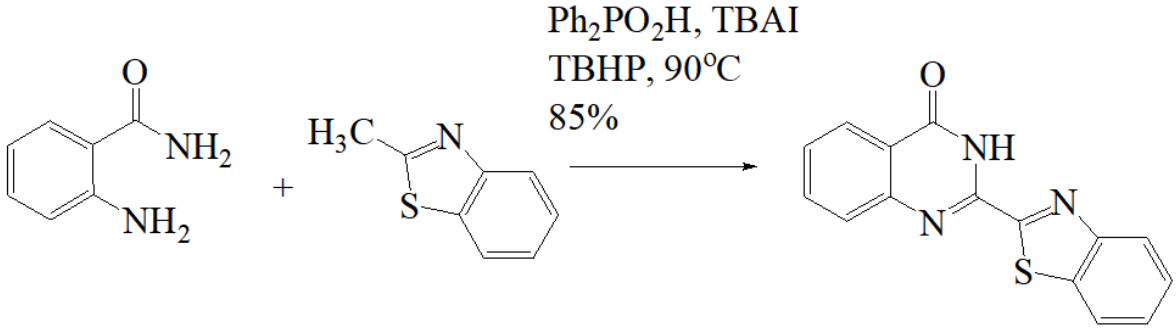
2.3.31 Benzothiazolylquinazolin-4(3*H*)-one

An efficient synthesis of 2-(benzothiazol-2-yl)quinazolin-4(3*H*)-ones via copper-catalyzed direct aerobic oxidative amination of sp3C–H bonds has been developed. This tandem oxidation–amination– cyclization transformation represents a Straightforward protocol to prepare 2-(benzothiazol-2-yl)quinazolin-4(3*H*)-ones from easily available 2-aminobenzamides and 2-methylbenzothiazole.[197]



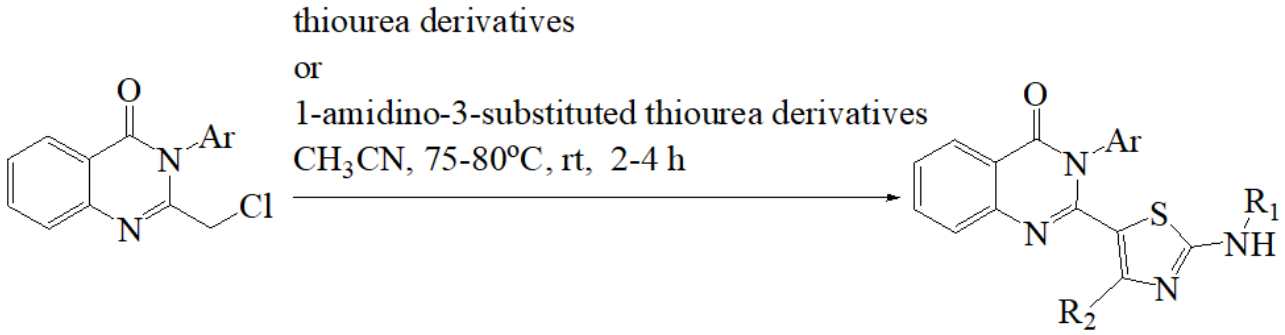
R	R_1	Yield(%)
CH_3	H	56
H	H	85
H	CH_3	34

An alternative method under transition metal-free conditions with mild conditions from 2-aminobenzamides and 2-methylbenzo[*d*]thiazole is described. The oxidation of 2-methylbenzo[*d*]thiazole to (benzo[*d*]thiazol-2-yl)methanol is proposed as the key step in this transformation.[198]



2.3.32 Thiazolylquinazolin-4(3*H*)-ones

Rajan et.al synthesized 2-(2-alkylamino/arylamino-4-alkyl/phenyl/amino-thiazole- 5-yl)-3-aryl-quinazolin-4(3*H*)-one derivatives by condensing 2-chloromethyl-3-aryl-quinazolin-4(3*H*)-one with thiourea derivatives or 1-amidino-3-substituted thiourea derivatives in acetonitrile. The quinazolinone derivatives are identified as inhibitors of NF-kB and AP-1 mediated transcription activation and as potential anti-inflammatory agents.[32, 33]



Ar	R_1	R_2	Yield (%)
C_6H_5	C_6H_5	CH_3	72.36
C_6H_5	4-ClC_6H_4	CH_3	39
2-$CH_3C_6H_4$	CH_3	CH_3	30
2-$CH_3C_6H_4$	C_6H_5	CH_3	49
2-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	54
3-$CH_3C_6H_4$	CH_3	CH_3	30
3-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	51
4-$CH_3C_6H_4$	4-ClC_6H_4	CH_3	55
2-$CH_3OC_6H_4$	4-ClC_6H_4	CH_3	41
4-$CH_3OC_6H_4$	4-ClC_6H_4	CH_3	38
2-ClC_6H_4	C_6H_5	CH_3	44
2-ClC_6H_4	4-ClC_6H_4	CH_3	41
2-ClC_6H_4	CH_3	CH_3	41
4-ClC_6H_4	C_6H_5	CH_3	51
4-ClC_6H_4	4-ClC_6H_4	CH_3	35
4-$CH_3COC_6H_4$	CH_3	CH_3	30

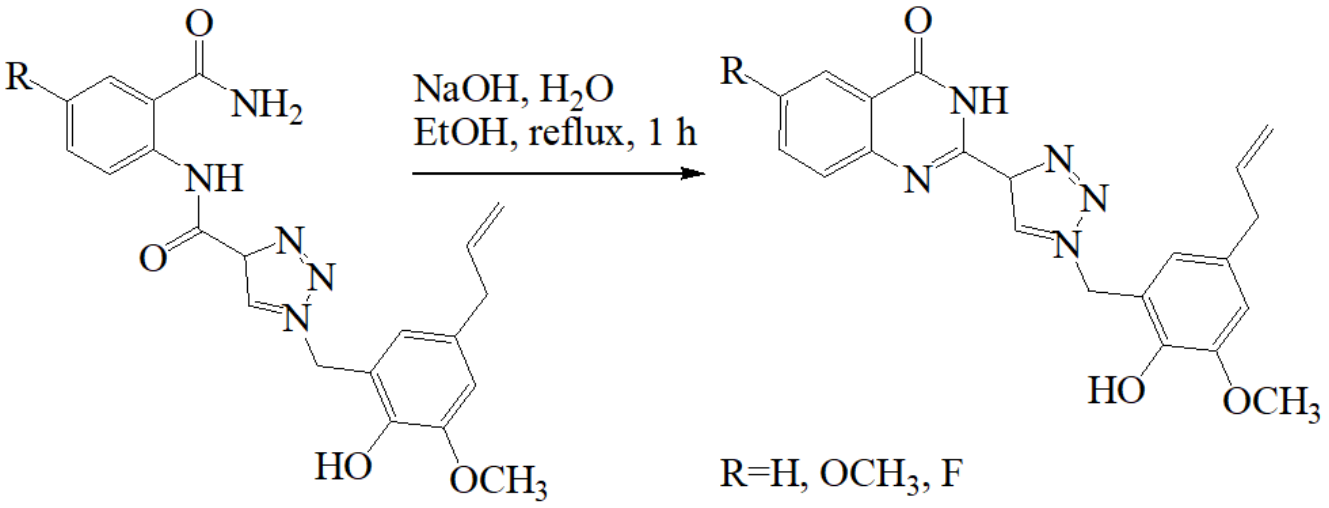
DOI: https://doi.org/10.5281/zenodo.13644773

4-$CH_3COC_6H_4$	C_6H_5	CH_3	48
4-$CH_3COC_6H_4$	4-ClC_6H_4	CH_3	43
4-ClC_6H_4	4-ClC_6H_4	NH_2	34
4-$CH_3COC_6H_4$	4-ClC_6H_4	NH_2	32
C_6H_5	4-ClC_6H_4	C_6H_5	71
2-$CH_3C_6H_4$	4-ClC_6H_4	C_6H_5	57
2-ClC_6H_4	4-ClC_6H_4	C_6H_5	51
4-ClC_6H_4	4-$CH_3C_6H_4$	C_6H_5	27
4-$CH_3COC_6H_4$	CH_3	C_6H_5	44
4-$CH_3COC_6H_4$	4-ClC_6H_4	C_6H_5	44
C_6H_5	$COOC_2H_5$	C_6H_5	79
C_6H_5	CH_3	C_6H_5	48
C_6H_5	C_6H_5	C_6H_5	78
C_6H_5	CO C_6H_5	C_6H_5	75
C_6H_5	4-ClC_6H_4	C_6H_5	71
4-$CH_3OC_6H_4$	$COOC_2H_5$	C_6H_5	46
4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	49
4-$CH_3OC_6H_4$	CO C_6H_5	C_6H_5	57
4-$CH_3OC_6H_4$	4-Cl C_6H_4	C_6H_5	52
4-ClC_6H4	$COOC_2H5$	CH_3	46
4-ClC_6H_4	CH_3	CH_3	41
4-ClC_6H4	C_6H_5	CH_3	51
4-ClC_6H_4	4-ClC_6H_4	CH_3	-
4-ClC_6H_4	$COOC_2H_5$	C_6H_5	50
4-ClC_6H_4	CH_3	C_6H_5	45
4-ClC_6H_4	C_6H_5	C_6H_5	53
4-ClC_6H_4	COC_6H_5	C_6H_5	53
4-ClC_6H_4	4-ClC_6H_4	C_6H_5	39

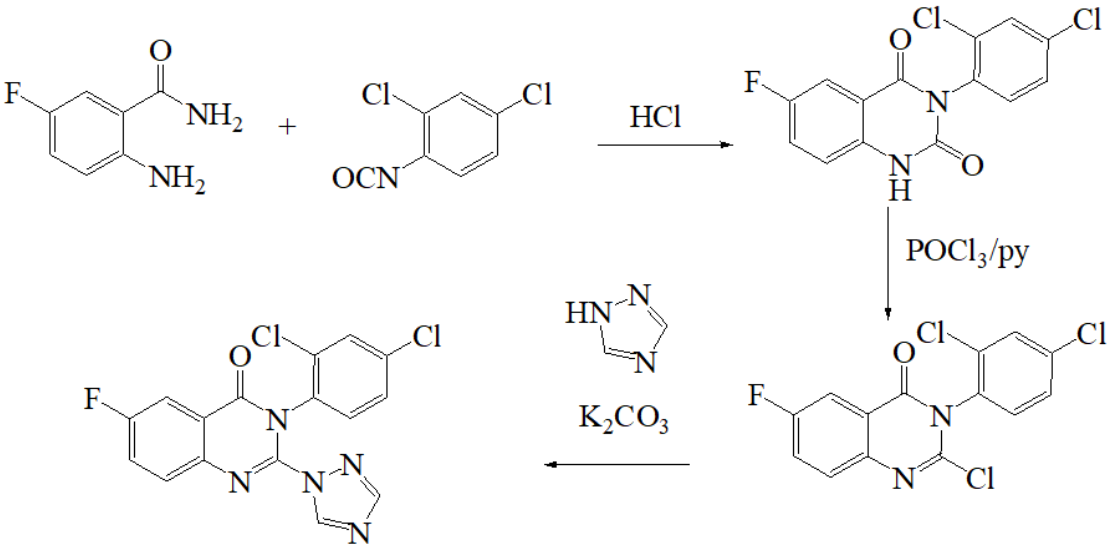
2.3.33 Triazolylquinazolin-4(3*H*)-ones

The cyclocondensation of 2-acylamino anthranilamides in hot ethanol containing aqueous NaOH afforded 2-(1-(5-allyl-2-hydroxy-3-methoxybenzyl)-1*H*-1, 2, 3-triazol-4-yl)-quinazolin-4(3*H*)-ones in quantitative yield. These compounds have shown antitrypanosomal and antileishmanial activities.[34]

DOI: https://doi.org/10.5281/zenodo.13644773

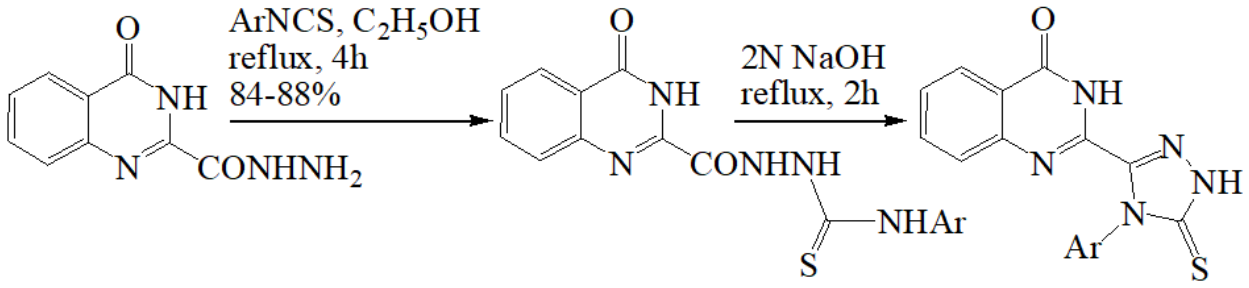


The fungicide, 3-(2,4-dichlorophenyl)-6-fluoro-2-(1*H*-1,2,4-triazol-1-yl)quinazolin-4(3*H*)-one (Fluquinconazole), is synthesised from the rection of 2-amino-5-fluorobenzamide with 2,4-dichloro-1-isocyanatobenzene in presence of hydrochloric acid to afford 3-(2,4-dichlorophenyl)-6-fluoroquinazoline-2,4(1*H*,3*H*)-dione, rection of the resultant compound with $POCl_3$ in pyridine gave 2-chloro-3-(2,4-dichlorophenyl)-6-fluoroquinazolin-4(3*H*)-one followed by reaction with triazole containing potassium carbonate. Fluquinconazole is a selective protectant and curative fungicide used to control various endophytic diseases mainly on cereals applied as a seed dressing to canola before sowing.[35]



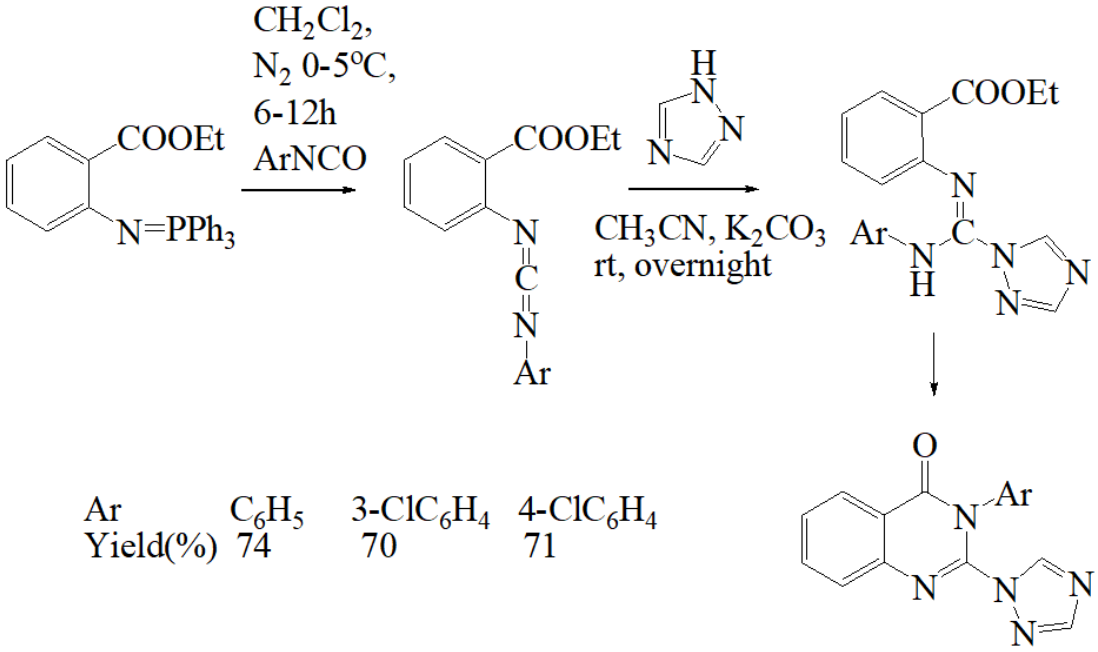
The single report concerning the preparation of 2-(arylthiotriazolyl)-3-aryl-quinazolin-4(3*H*)-ones, involves the condensation of 2-hydrazinocarbonyl-quinazolin-4(3*H*)-ones with arylisothiocyanates in refluxing ethanol. The resulting 4-aryl-1-[4(3*H*)-quinazolinone-2-yl]-2-carbonylthiosemicarbazides were cyclized to final compounds by refluxing in 2*N* sodium hydroxide solution.[199]

DOI: https://doi.org/10.5281/zenodo.13644773



Ar	C_6H_5	4-$CH_3OC_6H_4$	4-ClC_6H_4	4-BrC_6H_4
Yield (%)	84	85	80	82

Iminophosphorane was reacted with aromatic isocyanate to give functionalized carbodiimide derivatives. The reaction of 1,2,4-triazole with carbodiimides under solid K_2CO_3 provide a convenient and regiospecific route to 3-aryl-2-(triazol-1-yl)-quinazolin-4(3*H*)-ones.[200]

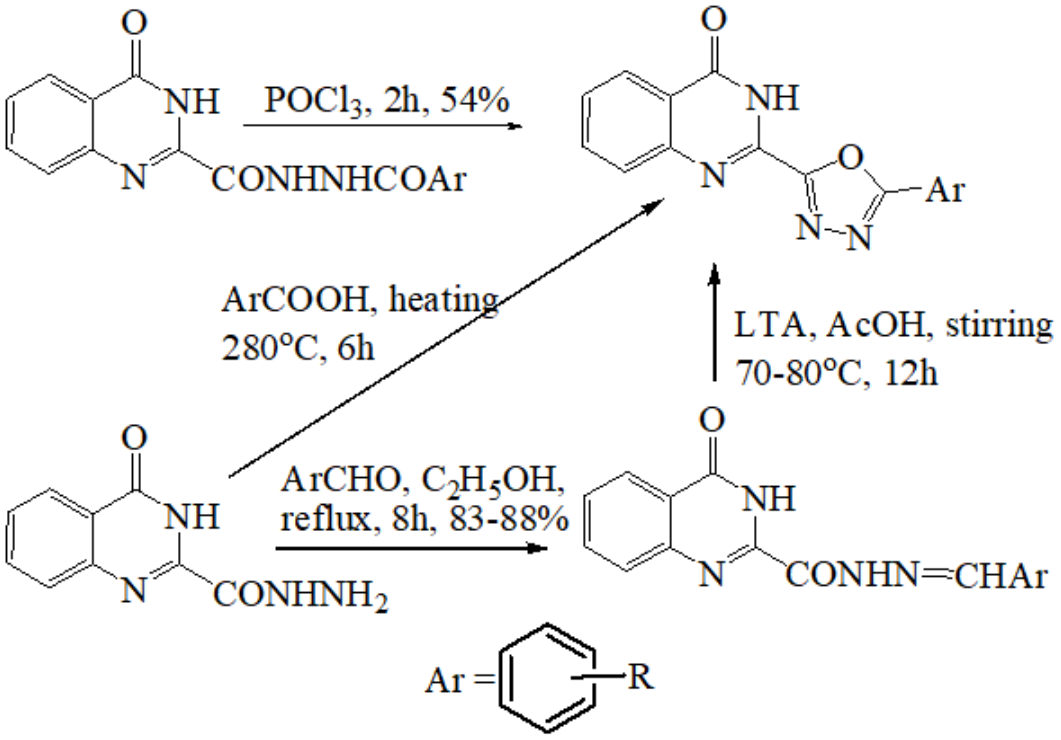


Ar	C_6H_5	3-ClC_6H_4	4-ClC_6H_4
Yield(%)	74	70	71

2.3.34 Oxadiazolylquinazolin-4(3*H*)-ones

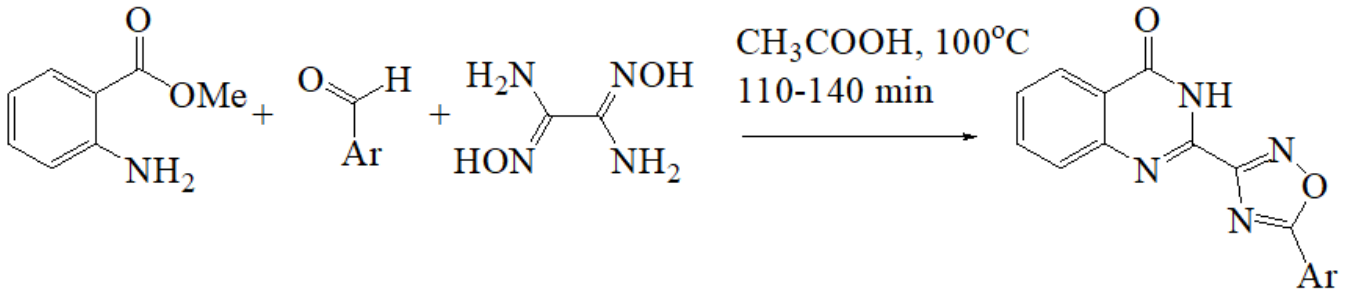
Synthesis of 2-[2-(5-aryl-1,3,4-oxadiazolyl)-quinazolin-4(3*H*)-ones was first reported by George et.al by reacting aroylhydrazinocarbonyl-quinazolin-4(3*H*)-ones with $POCl_3$. As an alternative synthesis, Reddy and Reddy prepared the same by lead tetraacetate (LTA) oxidation of 2-arylidenehydrazinocarbonyl-quinazolin-4(3*H*)-ones. The required hydrazone was obtained by reacting hydrazide with aromatic aldehydes in ethanol medium. They also synthesized 2-oxadiazolyl-quinazolin-4(3*H*)-ones in one-step by dry heating a solid mixture of hydrazide and aromatic acid at 280^{0}C for 6 h. The yields, however, were 42 – 48% in this thermal reaction. [201, 202]

DOI: https://doi.org/10.5281/zenodo.13644773



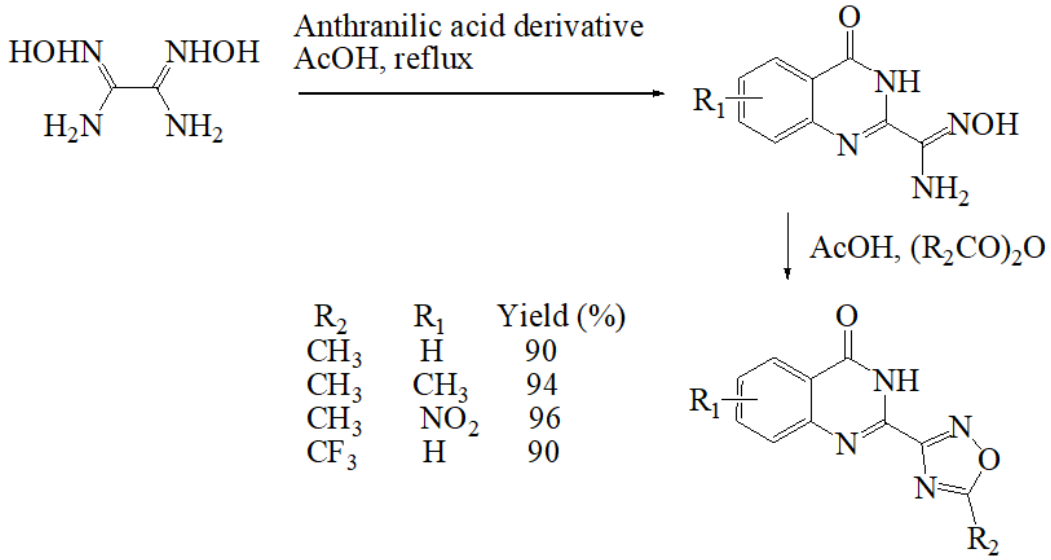
R	H	4-CH_3	4-OCH_3	3-NO_2	4-NO_2	3-Cl	4-Cl
Yield (%) pyrolysis	45	46	48	42	44	40	45
Yield (%) LTA	66	68	70	60	66	62	65

Abolghasem Moghimi and Ahmad Shaabani were described a one-pot three-component approach starting from diaminoglyoxime, aldehydes and methyl 2-aminobenzoate in the presence of acetic acid at 100⁰C to afford 2-[5-(aryl)-1,2,4-oxadiazol-3-yl]quinazolin-4(3*H*)-ones.[203]



Alternatively, new and efficient approache is developed for the synthesis of a series of 2-(5-alkyl-1,2,4-oxadiazol-3-yl)quinazolin-4(3*H*)-ones in good yields, via the reactions of diaminoglyoxime and anthranilic acid derivatives in acetic acid as the solvent under reflux conditions to yield 3,4-dihydro-*N*'-hydroxy-4-oxoquinazoline-2-carboxamidine. These new reactions between anhydride and carboxamidine derivative were undertaken to add an oxadiazole ring to the 2 position of the quinazolinone derivatives. The reactions were straightforward and 2-(5-alkyl-1,2,4-oxadiazol-3-yl)quinazolin-4(3*H*)-one derivatives were obtained.[204]

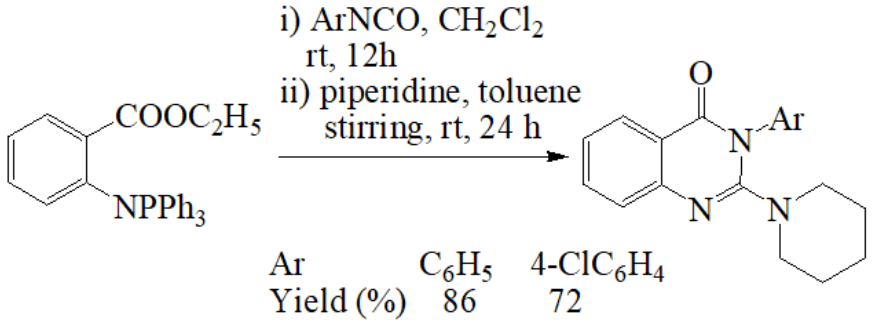
DOI: https://doi.org/10.5281/zenodo.13644773



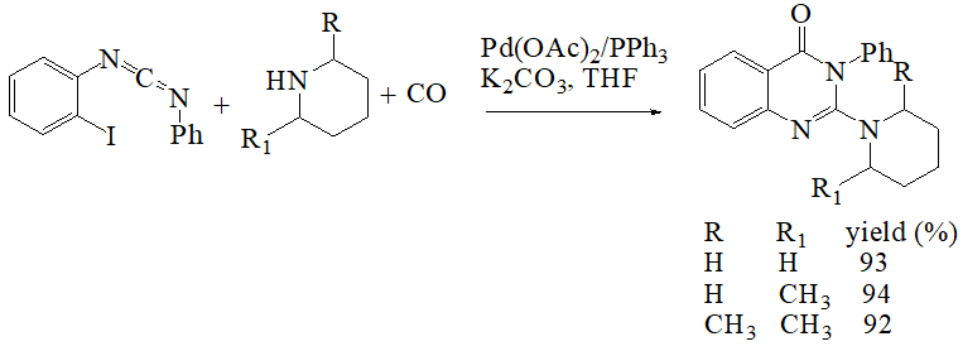
2.4 Six-Membered heteryl ring

2.4.1 Piperidinylquinazolin-4(3*H*)-ones

2-Piperidino-3-aryl-quinazolin-4(3*H*)-ones were prepared by an aza-Wittig reaction of ethyl anthranilate ylide with aryl isocyanates and piperidine under mild conditions.[205]

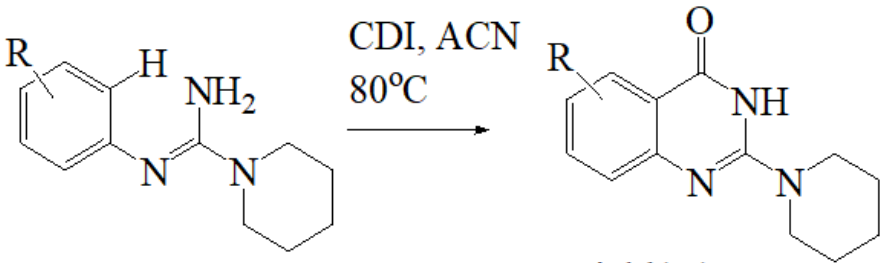


Synthesis of 3-phenyl-2-(piperidin-1-yl)quinazolin-4(3*H*)-one by palladium-catalyzed intermolecular addition and intramolecular cyclocarbonylation cascade reaction of *N*-(2-iodophenyl)-*N*′-phenyldicarbodiimide with piperidine / 2-methyl piperidine / 2,6-dimethyl piperidine was reported.[140]



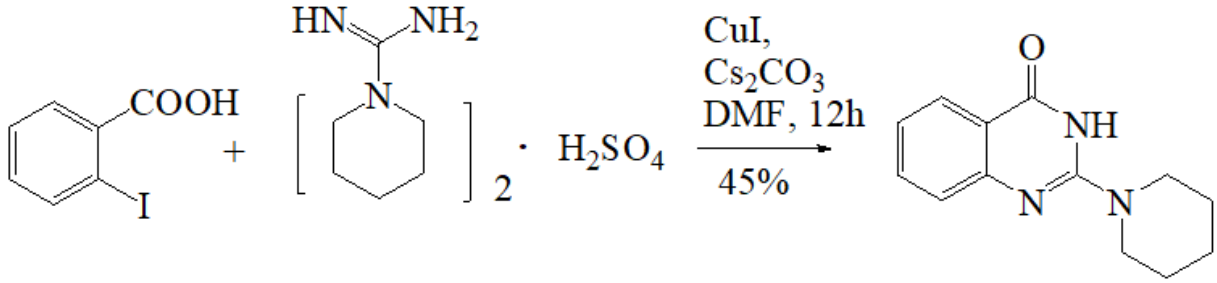
Alternatively, a new method for the preparation of 2-(piperidin-1-yl)quinazolin-4(3*H*)-ones is described by warming a mixture of an (*E*)-*N*′-arylpiperidine-1-carboxamidine and carbonyl diimidazole in acetonitrile results in formation of a putative *N*-amidinoisocyanate intermediate which undergoes a 6p-electron electrocyclic reaction with the aryl ring.[141]

DOI: https://doi.org/10.5281/zenodo.13644773

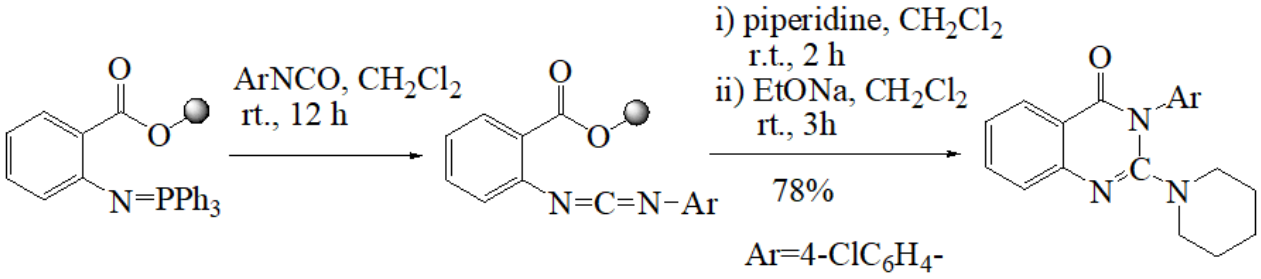


R	yield(%)
8-Br	89
6-OPh	0

2-Iodobenzoic acid was reacted with piperidine-1-carboxamidine salt in *N,N*-dimethylformamide in presence of CuI and Cs_2CO_3 to isolate 2-(piperidin-1-yl)-quinazolin-4(3*H*)-one. The yield of the reaction increased to 70% at reaction temperature of 80°C.[138]

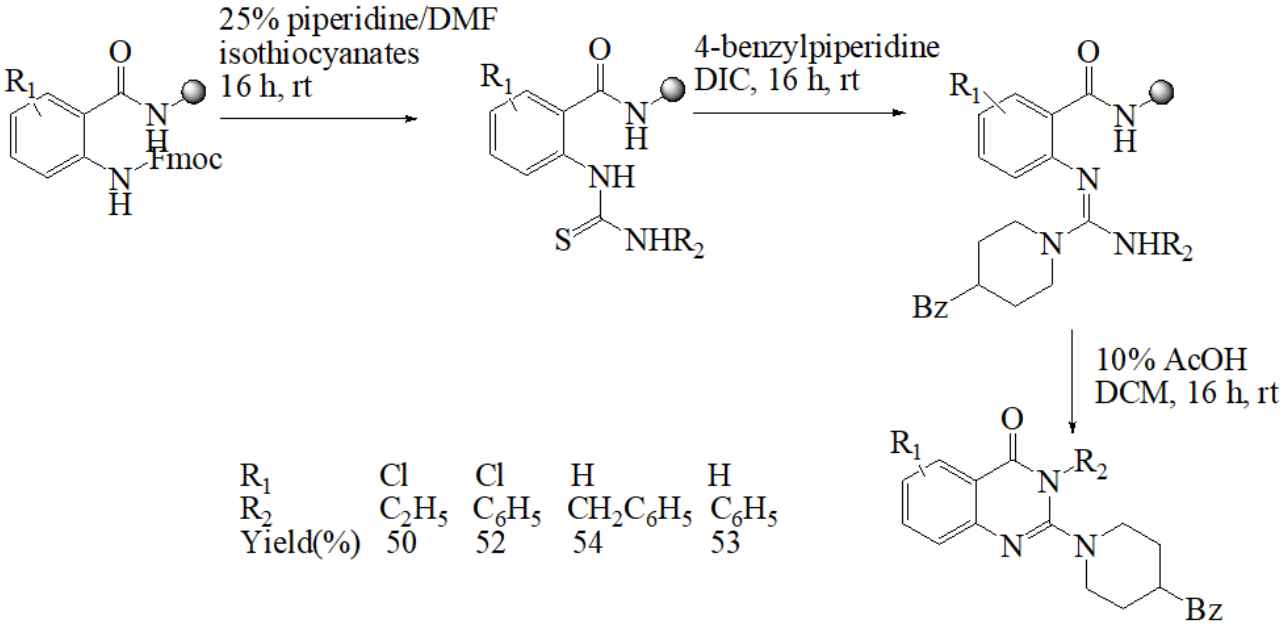


Xie et.al prepared 2-(piperidin-1-yl)-3-aryl-quinazolin-4(3*H*)-one from poly(ethyleneglycol) (PEG) supported aza-Wittig reaction. Quinazolinones were synthesized efficiently by reaction of secondary amine with PEG-supported carbodiimides, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes with isocyanates.[139]

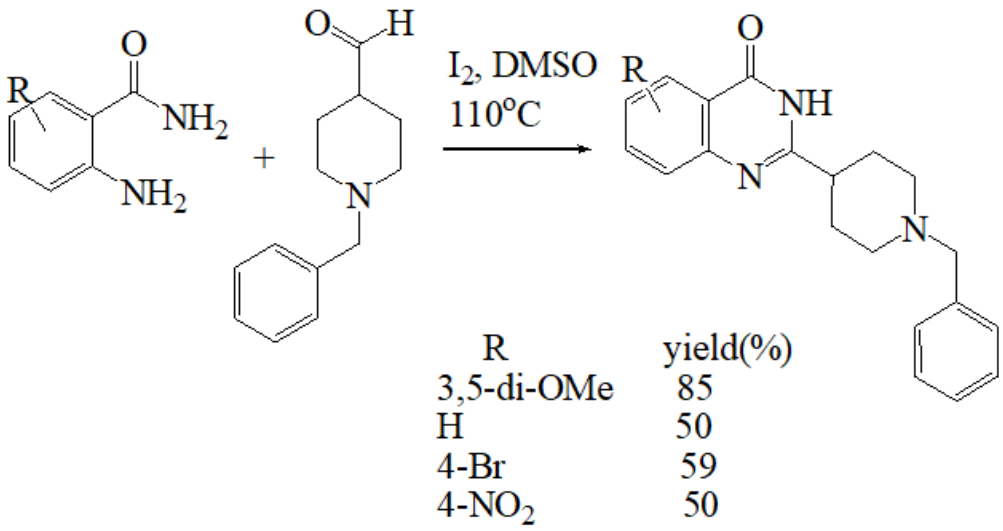


A versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones has been developed using immobilized arylguanidines. The latter were obtained by treating the amino group of polymer-linked anthranilamide with isothiocyanates followed by coupling the resultant amide with secondary amines in the presence of DIC to generate amine derivative. Finally a cyclative cleavage strategy was applied to give the desired quinazolinones in high yields and purities. [206]

DOI: https://doi.org/10.5281/zenodo.13644773



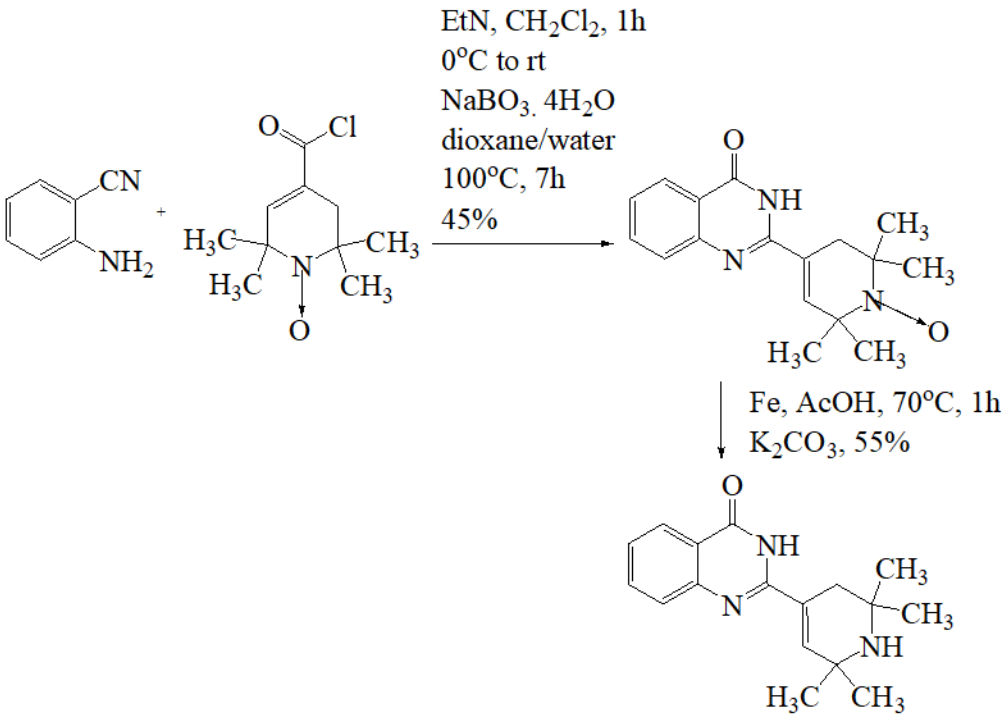
A novel AChE inhibitors with anti-inflammatory activities, 2-(1-benzylpiperidin-4-yl)quinazolin-4(3*H*)-ones, were prepared by the reaction of 2-aminobenzamide derivatives with 1-benzylpiperidine-4-carbaldehyde in I_2 containing DMSO.[13]



2.4.2 Tetrahydropyridinylquinazolin-4(3*H*)-one

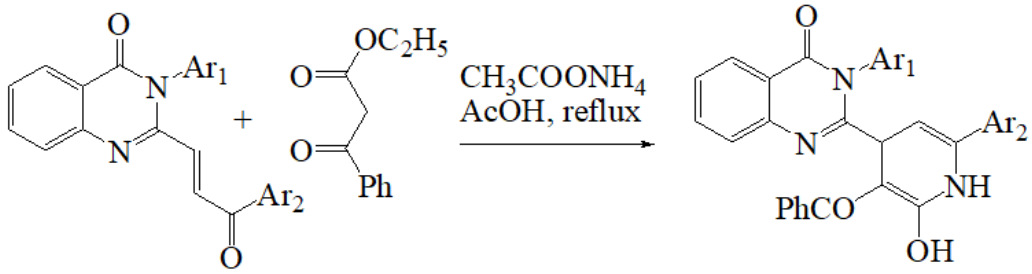
Reaction of 2-amino-benzonitrile with 1-oxyl-1,2,3,6-tetrahydro-2,2,6,6-tetramethyl pyridine-4-carbonyl chloride followed by treatment with $NaBO_3.4H_2O$ yielded the 2-(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)-quinazolin-4(3*H*)-one radical. The resultant nitroxide was reduced with Fe powder in acetic acid to isolate 2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)-quinazolin-4(3*H*)-one. These are the PARP inhibitors.[10]

DOI: https://doi.org/10.5281/zenodo.13644773



2.4.3 Piperidinonylquinazolin-4(3*H*)-ones

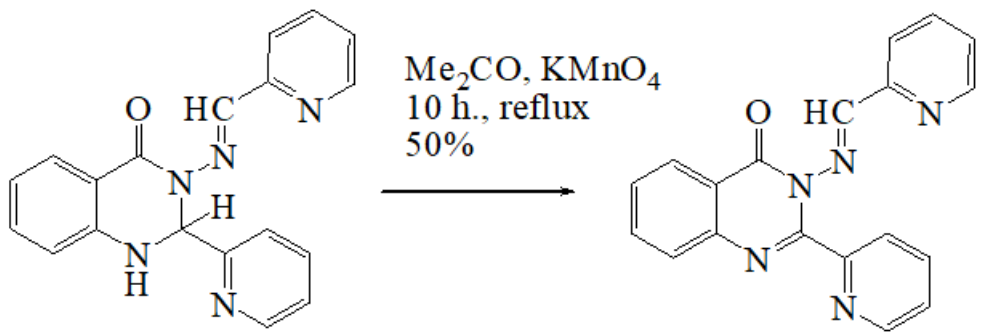
Salem et.al reported the synthesis of several 2-heterylquinazolinone derivatives by Michael addition of active methylene nucleophiles to 2-[(3-chloro-4-methylbenzoyl)vinyl-3-(4-methylphenyl)-quinazolin-4(3*H*)-ones. Thus, 2-piperidinonyl-3-(4-methylphenyl)-quinazolin-4(3*H*)-ones were the products when the quinazolinone derivative was refluxed with ethyl benzoylacetate in acetic acid containing ammonium acetate.[207]



$Ar_1 = 4\text{-}CH_3C_6H_4$; $Ar_2 = 3\text{-}Cl\text{-}4\text{-}CH_3C_6H_3$

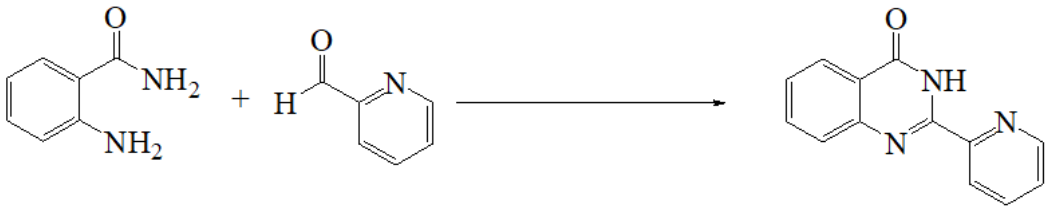
2.4.4 Pyridylquinazolin-4(3*H*)-ones

Kalagouda et.al have oxidized 2-pyridin-2-yl-3-(pyridine-2-carboxylideneamino)-1,2-dihydroquinazolin-4(3*H*)-one with $KMnO_4$ in hot acetone to isolate 2-pyridine- 2-yl-3-(pyridine-2-carboxylideneamino)-quinazolin-4(3*H*)-one.[208]



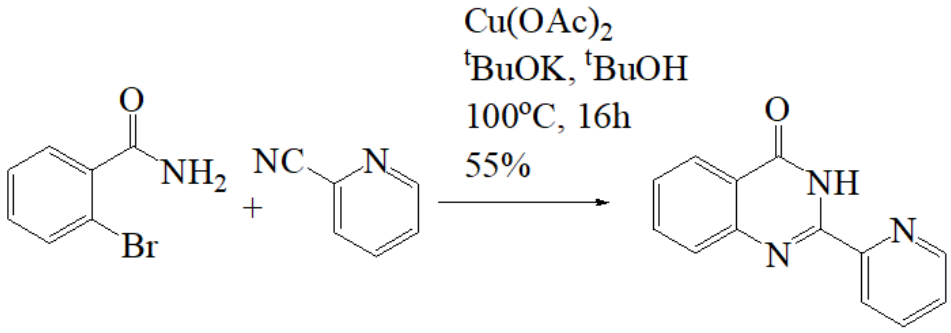
DOI: https://doi.org/10.5281/zenodo.13644773

The synthesis of 2-(pyridin-2-yl)quinazolin-4(3*H*)-one by the condensation of 2-aminobenzamide with picolinaldehyde in various conditions is reported.

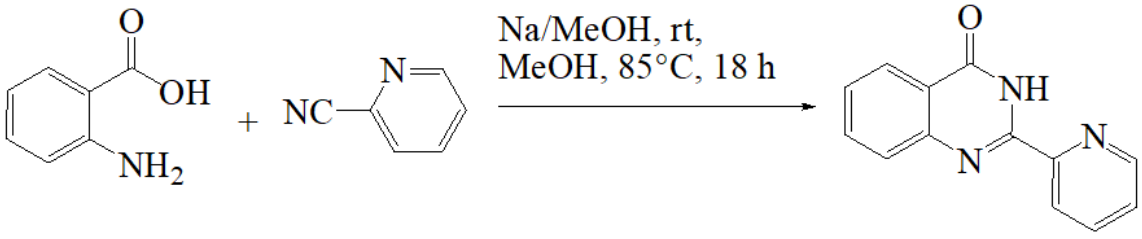


Conditions and yield	Reference
$H_3PW_{12}O_{40}$, H_2O, C_2H_5OH (2:1), 100°C	209
air, 120°C, 24h, 92%	166
CuBr, Cs_2CO_3, DMF 120°C, open air, 30 min, 92%	143
KOtBu, $BF_3.OEt_2$, N_2, 130°C, 24h, 49%	150

M. Bao et.al reacted 2-bromobenzamide and picolinonitrile in presence of $Cu(OAc)_2$, ^tBuOK and ^tBuOH at 100°C under nitrogen atmosphere for 16h to isolate 2-(pyridin-2-yl)quinazolin-4(3*H*)-one.[210]



Human Methionine Aminopeptidase-1 Inhibitor, 2-pyridylquinazolin-4(3*H*)-one, was prepared by the reaction of 2-cyanopyridines with sodium in methanol to generate methyl pyridine-2-carboximidate in situ followed by condensed with anthranilic acid.[36]

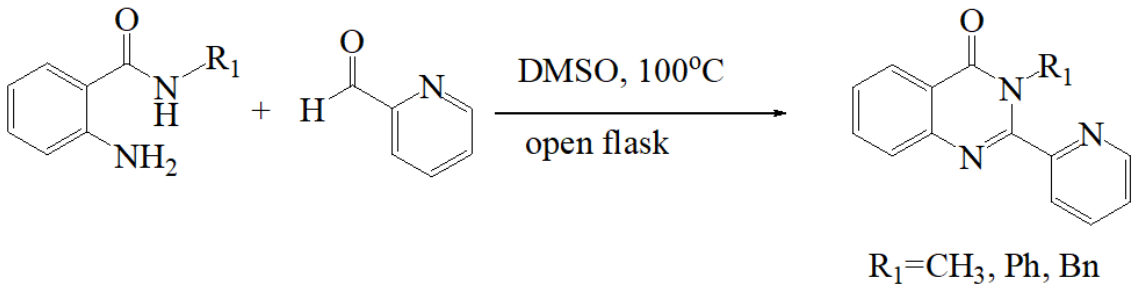


2-(Pyridin-2-yl)quinazolin-4(3*H*)-one was synthesized by heating of (pyridin-2-yl)methanol and 2-aminobenzamide under various conditions.

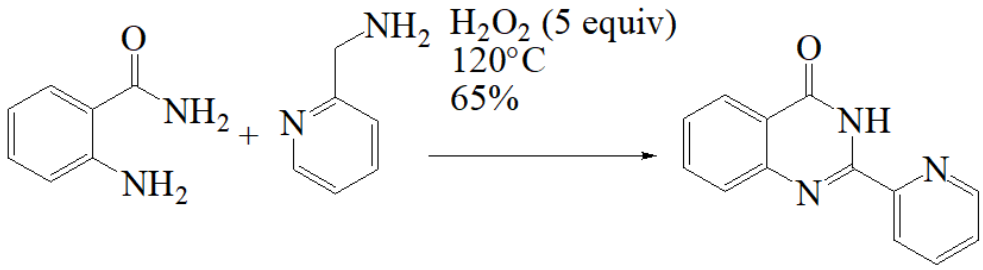
DOI: https://doi.org/10.5281/zenodo.13644773

Conditions and yield	Reference
TBHP, 110°C, 12h, 83%	211
dichloro-(E)-2-(phenyldiazenyl)-1,10-phenanthroline-Cu(II), toluene, NaOH, 90°C, 36h, 56%	181
$FeCl_3$, p-TsOH, MeCN, H_2O, rt, 8h, 68%	212
[Ni(MeTAA)]NatOBu, xylene, 100oC, 36h, 56%	182

Cheon and Kim developed an efficient, user-friendly and highly environmentally benign protocol for the synthesis of 2-(pyridin-2-yl)quinazolin-4(3*H*)-one from anthranilamides and picolinaldehyde via aerobic oxidative cyclization in wet DMSO without any additives.[167]

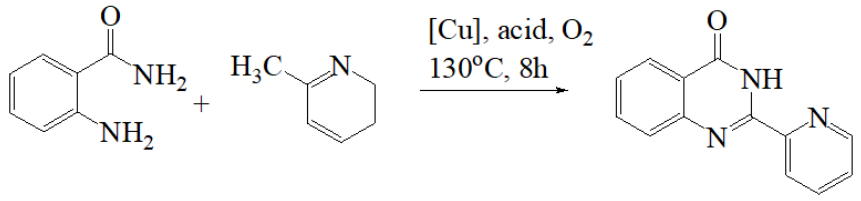


A convenient and transition-metal free protocol for 2-(pyridin-2-yl)quinazolin-4(3*H*)-one synthesis with o-aminobenzamide and (pyridin-2-yl)methanamine using H_2O_2 as the oxidant under metal- and additive-free conditions was developed in good yield.[213]



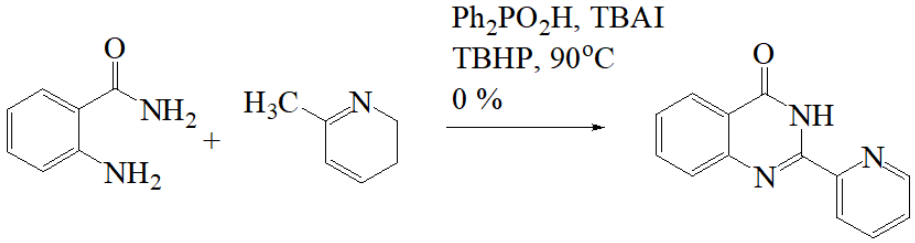
As a model reaction, the reaction of 2-aminobenzamide with 2-methylpyridine under oxygen atmosphere (1 atm) was investigated first, disclosing that a catalytic amount of copper and Ph_2PO_2H could promote the reaction efficiently. An extensive screening of the reaction conditions revealed that 2-(pyridin-2-yl)quinazolin-4(3*H*)-one was generated in 80% yield in the presence of a catalytic amount of CuCl and Ph_2PO_2H. All the copper catalysts, acid and oxygen are essential for this reaction. The absence of any of them led to failure of the formation of the desired product.[197]

DOI: https://doi.org/10.5281/zenodo.13644773

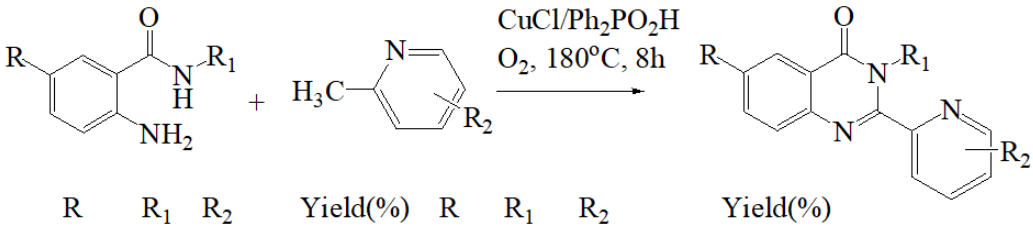


[Cu]	acid	solvent	Yield(%)	[Cu]	acid	solvent	Yield(%)
--	--	C_6H_5Cl	none	CuCl	--	C_6H_5Cl	none
--	Ph_2PO_2H	C_6H_5Cl	none	CuCl	Ph_2PO_2H	C_6H_5Cl	none
CuCl	Ph_2PO_2H	C_6H_5Cl	80	CuCl	Ph_2PO_2H	C_6H_5Cl	55(76)
CuCl	Ph_2PO_2H	C_6H_5Cl	35	CuCl	Ph_2PO_2H	C_6H_5Cl	40
CuBr	Ph_2PO_2H	C_6H_5Cl	32	CuI	Ph_2PO_2H	C_6H_5Cl	22
$CuCl_2$	Ph_2PO_2H	C_6H_5Cl	68	$CuBr_2$	Ph_2PO_2H	C_6H_5Cl	31
$Cu(OAc)_2$	Ph_2PO_2H	C_6H_5Cl	27	CuCl	$PhCO_2H$	C_6H_5Cl	47
CuCl	$PhCH_2CO_2H$	C_6H_5Cl	60	CuCl	CF_3CO_2H	C_6H_5Cl	35
CuCl	Ph_2PO_2H	MeCN	27	CuCl	Ph_2PO_2H	THF	21
CuCl	Ph_2PO_2H	DCE	11	CuCl	Ph_2PO_2H	toluene	57
CuCl	Ph_2PO_2H	dioxane	65	CuCl	Ph_2PO_2H	C_6H_5Cl	43

Chen Ma et.al described a new method for the synthesis of 2-hetarylquinazolin-4(3*H*)-ones from 2-aminobenzamides and (2-azaaryl)methanes under transition metal-free conditions. This protocol features a wide substrate scope with a broad range of functional group tolerance under mild conditions. The oxidation of (2-azaaryl)methanes to (2-azaaryl)methanals is proposed as the key step in this transformation.[198]



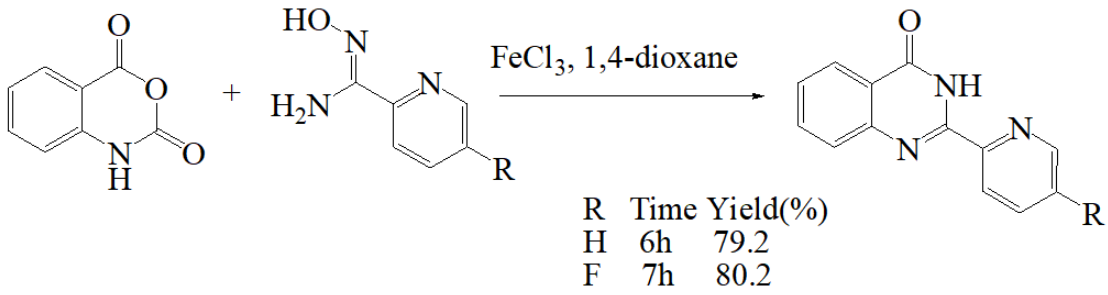
An efficient synthesis of 2-(pyridin-2-yl)quinazolin-4(3*H*)-one via copper-catalyzed direct aerobic oxidative amination of sp3C–H bonds has been developed. This tandem oxidation–amination– cyclization transformation represents a straightforward protocol to prepare 2-(pyridin-2-yl)quinazolin-4(3*H*)-one from easily available 2-aminobenzamides and (2-azaaryl)methanes.[197]



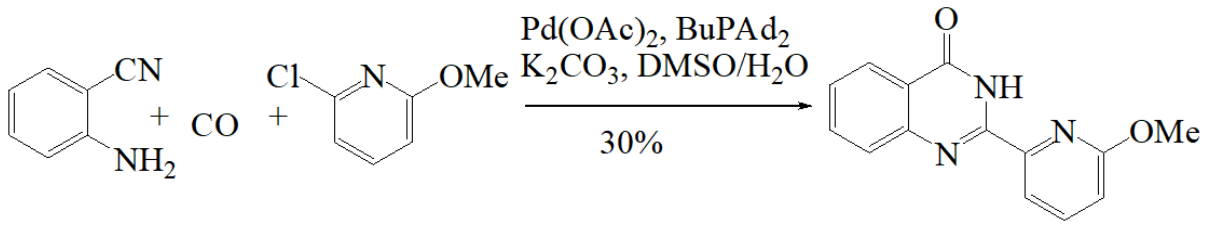
R	R_1	R_2	Yield(%)	R	R_1	R_2	Yield(%)
H	H	H	76	Cl	H	H	79
H	H	5-ethyl	61	Cl	H	6-methyl	83
H	H	6-methyl	92	H	CH_3	H	65
CH_3	H	6-methyl	39				

A simple and highly efficient synthesis of 2-(pyridin-2-yl)quinazolin-4(3*H*)-one derivatives by the iron(III) chloride catalyzed reaction of isatoic anhydride with various amidoxime derivatives was developed.[214]

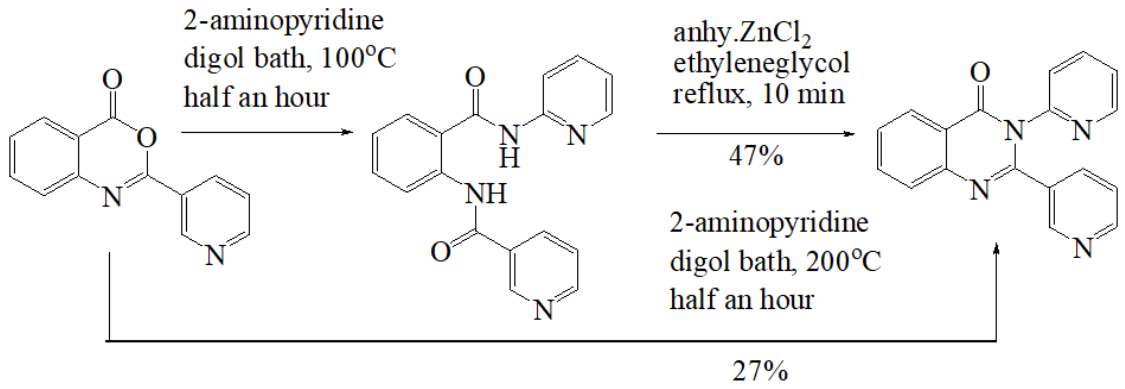
DOI: https://doi.org/10.5281/zenodo.13644773



Wu et.al developed an interesting and straightforward one-pot cascade procedure for the carbonylative synthesis of 2-pyridinylquinazolin-4(3*H*)-one from commercially available 2-aminobenzonitriles and chloropyridine derivative in 30% yield.[154]

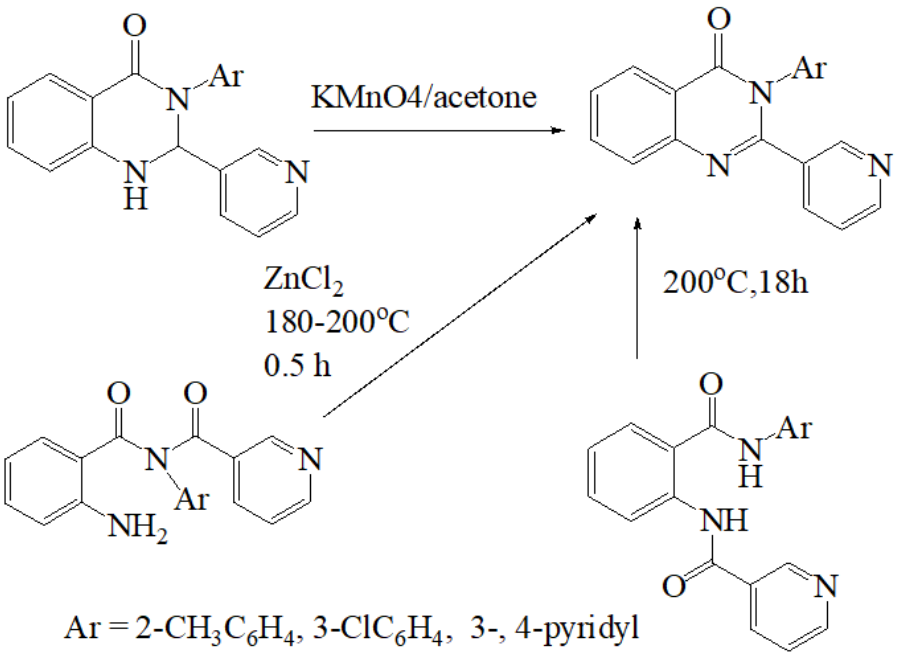


Heating the mixture of 2-(pyridin-3-yl)-3,1-benzoxazin-4(3*H*)-one and 2-aminopyridine yielded diamide under milder conditions, while at higher temperatures the cyclized product quinazolin-4(3*H*)-one was isolated. However, diamide converted the final quinazolinones by using a catalytic amount of anhydrous zinc chloride. The compounds exhibited anti-inflammatory activity.[37]

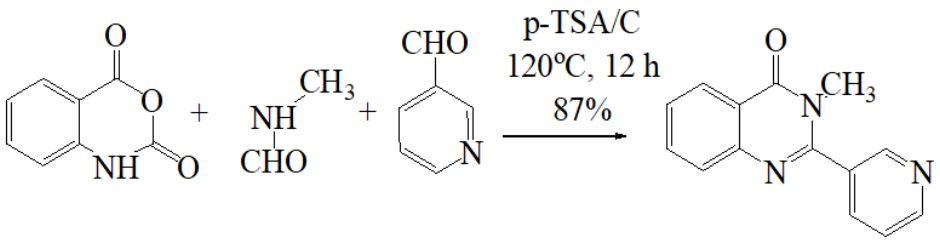


Alternatively, 2-(3-pyridyl)-3-(2-tolyl)-quinazolin-4(3*H*)-ones were synthesised by permanganate oxidation of 2-(3-pyridyl)-3-(2-tolyl)-1,2-dihydro-quinazolin-4(3*H*)-ones in acetone. The title compounds also can be prepared by cyclization of 2-amino-*N*-acylbenzanilides or 2-nicotinamidobenzanilide.[215, 216, 217]

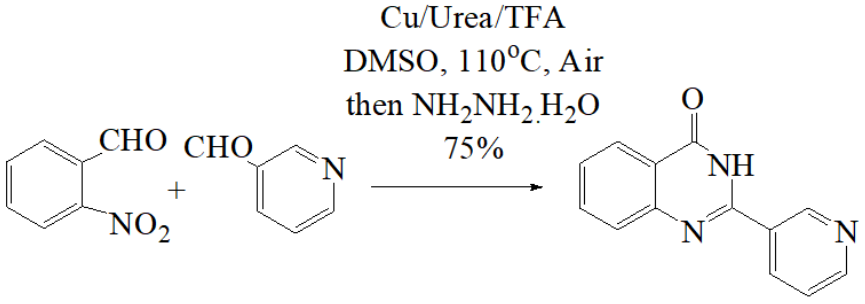
DOI: https://doi.org/10.5281/zenodo.13644773



The straightforward preparation of 3-methyl-2-(pyridin-3-yl)quinazolin-4(3*H*)-one via the reusable carbon-supported acid-catalyzed direct amidation and cascade annulation of isatoic anhydride with *N*-methylformamide and 4- nicotinaldehyde is reported.[188]



S. Pal and S. Sahoo were treated the 2-nitrobenzaldehyde with urea, Cu(OAc) $_2$ and TFA in a DMSO solvent at 110 °C, then hydrazine hydrate and nicotinaldehyde were added sequentially at the same temperature and stirred at room temperature for 12−16 h to isolate 2-(pyridin-3-yl) quinazolin-4(3*H*)-one.[142]



The 3-benzyl-2-(pyridin-3-yl)quinazolin-4(3*H*)-one was prepared by the direct arylation of 3-benzylated quinazolin-4(3*H*)-one with 3-iodopyridine in DMF in presence of CuI, LiO^{t}Bu and catalytic amount of Pd(OAc)$_2$ at 120°C for 12 h. [218, 219]

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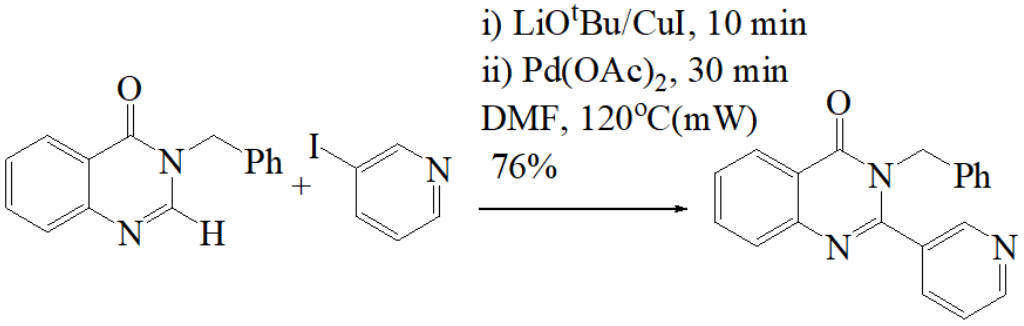
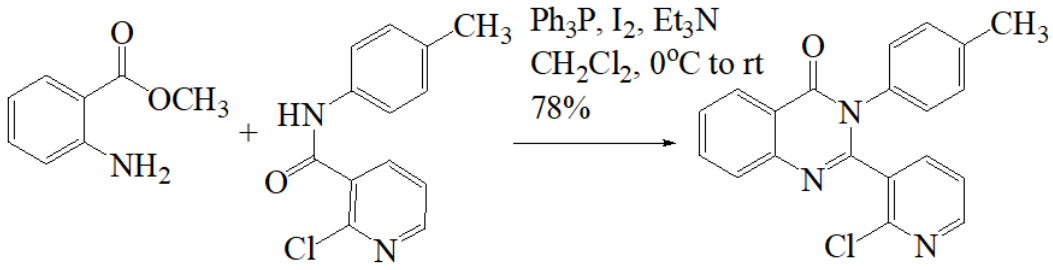
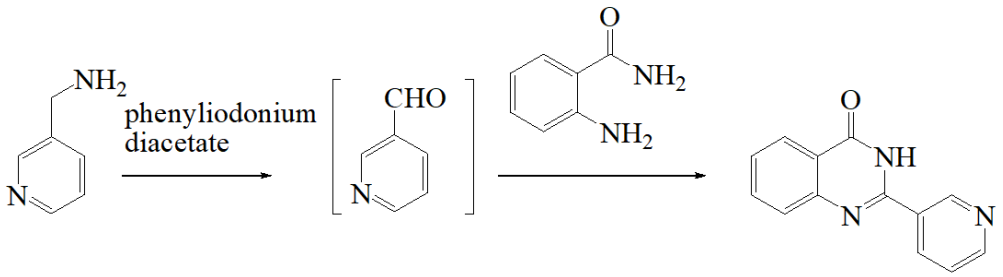


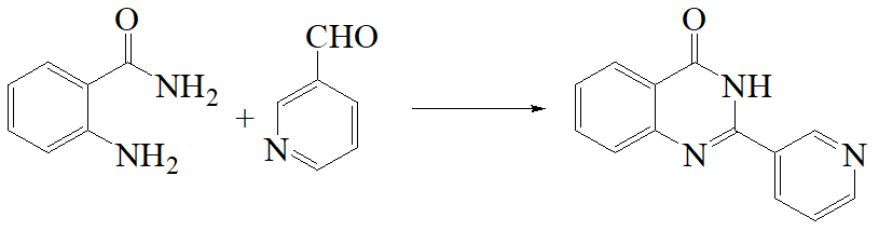
Methyl anthranilate and 2-chloro-*N*-p-tolylpyridine-3-carboxamide were reacted in CH_2 Cl_2 containing iodine, triphenylphosphine and triethylamine at 0°C and allowed to warm up to room temperature to afford 2-(2-chloropyridin-3-yl)quinazolin-4(3*H*)-one in good yield.[219]



An efficient metal-free, one-pot protocol was developed for the synthesis of 2-(pyridin-3-yl)quinazolin-4(3*H*)-one. This protocol proceeds via oxidation of (pyridin-3-yl)methanamine, resulting in in-situ aldehyde formation followed by the condensation with o-aminobenzamide to the corresponding heterocycles using a mild oxidant phenyliodonium diacetate (PIDA). A new strategy for C-N bond cleavage and formation in the absence of transition-metal reagent or ligand under environmentally benign reaction conditions is described.[220]



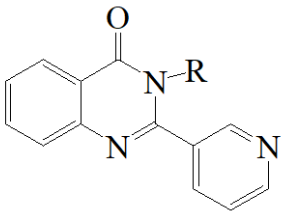
Selective CYP1B1 inhibitor, 2-(pyridin-3-yl)quinazolin-4(3*H*)-one, was prepared by the condensation of 2-aminobenzamide with nicotinaldehyde using various conditions in good yields.



DOI: https://doi.org/10.5281/zenodo.13644773

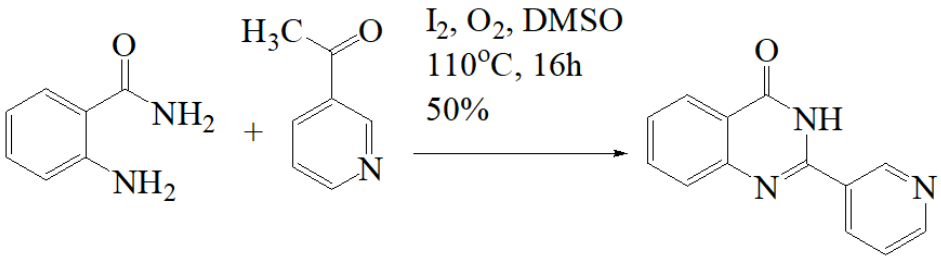
Conditions and yield	Reference
I_2, Sodium acetate, DMF, 60-70°C, 24h	38
Cp_2ZrCl_2, DMF, 80-100°C, 60%	163

Siddharth Sharma et.al reported the synthesis of quinazolinones by using a versatile Pd/Fe_3O_4 supported on *N*-doped reduced graphene oxide (N-rGO) catalyst to carry out under extremely mild conditions through isocyanide insertion cascades. The supported Pd/Fe_3O_4nanoparticles could be easily recovered from the reaction mixture and reused several times without any loss in catalytic activity.[221]



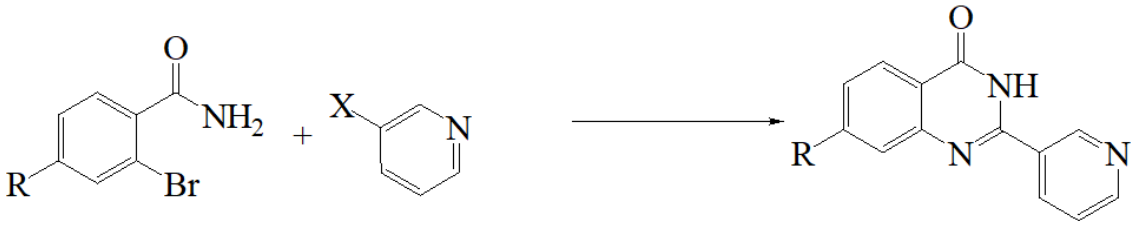
R = H, $C_6H_5CH_2$, 4-$CF_3C_6H_4CH_2$

Molecular iodine catalyzed oxidative coupling of 2-aminobenzamides with 1-(pyridin-3-yl)ethanone produced 2-(pyridin-3-yl)quinazolin-4(3*H*)-one.[173]



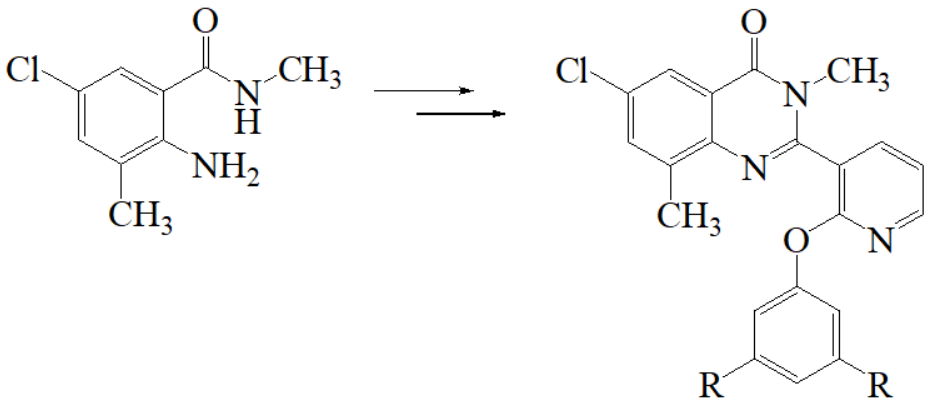
A novel and efficient Cu(I)-catalyzed ligand- and base-free multipathway domino strategy has been developed for the synthesis of 2-(3-pyridyl)quinazolin-4(3*H*)-ones. The reaction utilizes 2-bromobenzamide and multiform substrates such as aldehydes and alcohols for a one-pot protocol, whereas $TMSN_3$ is used as a nitrogen source.[161]

DOI: https://doi.org/10.5281/zenodo.13644773



X	condition	R	Yield (%)
—CHO	$TMSN_3$, CuI, air DMSO, 80°C	H	65%
—CHO	$TMSN_3$, CuI, air DMSO, 80°C	CH_3	62%
—CH_2OH	$TMSN_3$, CuI, DMSO, air TBHP, 80°C	H	60%

A series of novel 2-(2-(phenoxy)pyridin-3-yl)quinazolin-4(3*H*)-one derivatives were designed, synthesized as antitumor agents. The pharmacological screening results revealed that many compounds exhibited moderate levels of antitumor activities against four cancer cell lines, especially 6-chloro-2-(2-(3,5-dimethylphenoxy)pyridin-3-yl)-3,8-dimethylquinazolin-4(3*H*)-one displayed promising activities against A549 (IC_{50} = 12.47±2.86 μM) than Gefitinib (IC_{50} = 17.37±6.01 μM).[39]



Xingwen et.al was reacted 2-(4-pyridinyl)-4*H*-benzo[*d*][1,3]oxazin-4-one with 80% $NH_2NH_2.H_2O$ and the resultant 3-amino-2-arylquinazolin-4(3*H*)-one was condensed with appropriate

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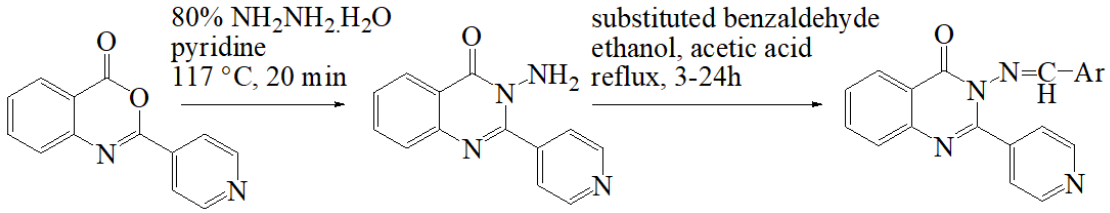
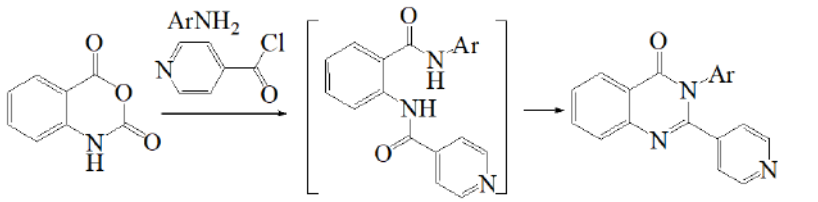
substituted benzaldehyde in ethanol to isolate 2-(4-pyridinyl)-3-(arylamino)-quinazolin-4(3*H*)-one. These compounds exhibited weak antifungal and antiviral activities.[40]

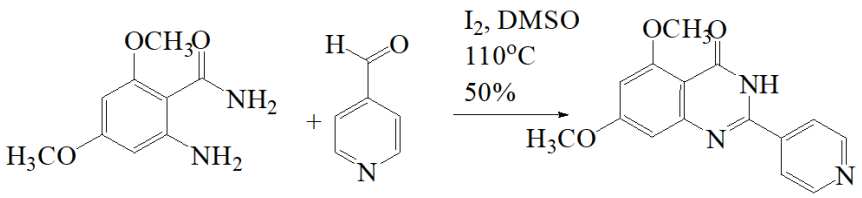


Ar	Ph	2-ClC_6H_4	4-FC_6H_4	2,3-$Cl_2C_6H_3$
Yield (%)	67	69	89	89

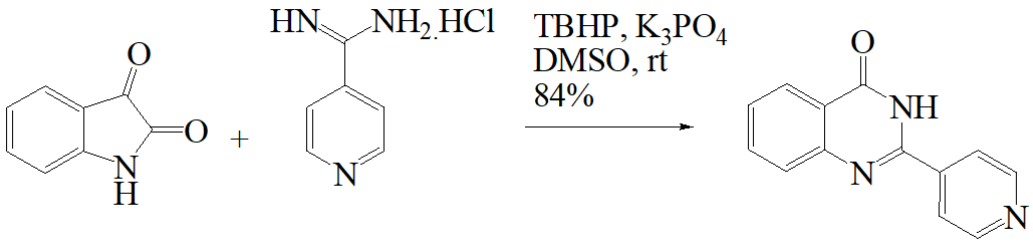
Hisano et.al have also reported a one-pot synthesis of 2-(4-pyridyl)-3-aryl-4(3*H*)-quinazolinone by reacting isatoic anhydride with isonicotinoyl chloride and aromatic amines. These compounds showed promising hypnotic effect in intraperitonial doses above 100 mg/kg.[41]



A novel AChE inhibitor with anti-inflammatory activity, 5,7-dimethoxy-2-(pyridin-4-yl)quinazolin-4(3*H*)-one, was prepared by the reaction of 2-amino-4,6-dimethoxybenzamide with isonicotinaldehyde in I_2 containing DMSO.[13]

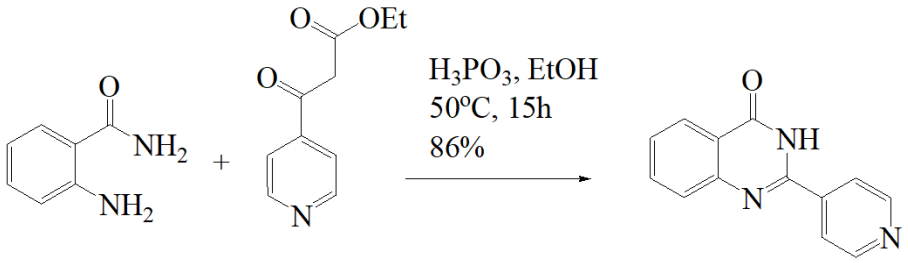


An-Xin Wu et.al have been developed a synergetic tert-butyl hydroperoxide/K_3PO_4 -promoted oxidative cyclization for the facile synthesis of 2-(pyridin-4-yl)quinazolin-4(3*H*)-one from commercially available isatins and amidine hydrochlorides at room temperature.[222]

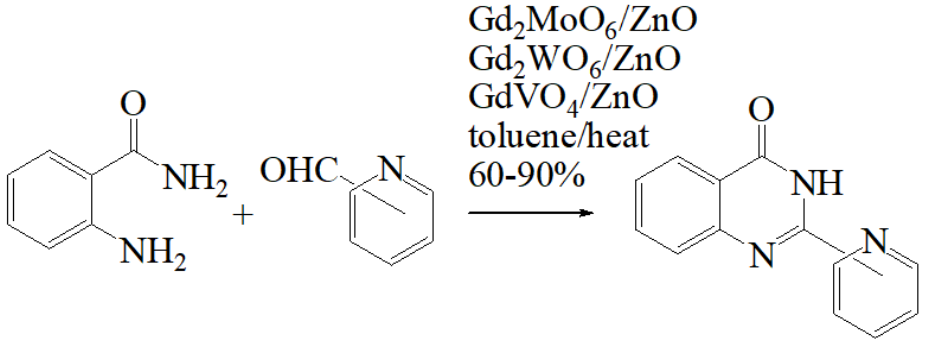


DOI: https://doi.org/10.5281/zenodo.13644773

Efficient phosphorous acid-catalyzed cyclocondensation of ethyl 3-oxo-3-(pyridin-4-yl)propanoate with o-aminobenzamide via selective C–C bond cleavage leading to formation of 2-(pyridin-4-yl)quinazolin-4(3*H*)-one.[223]

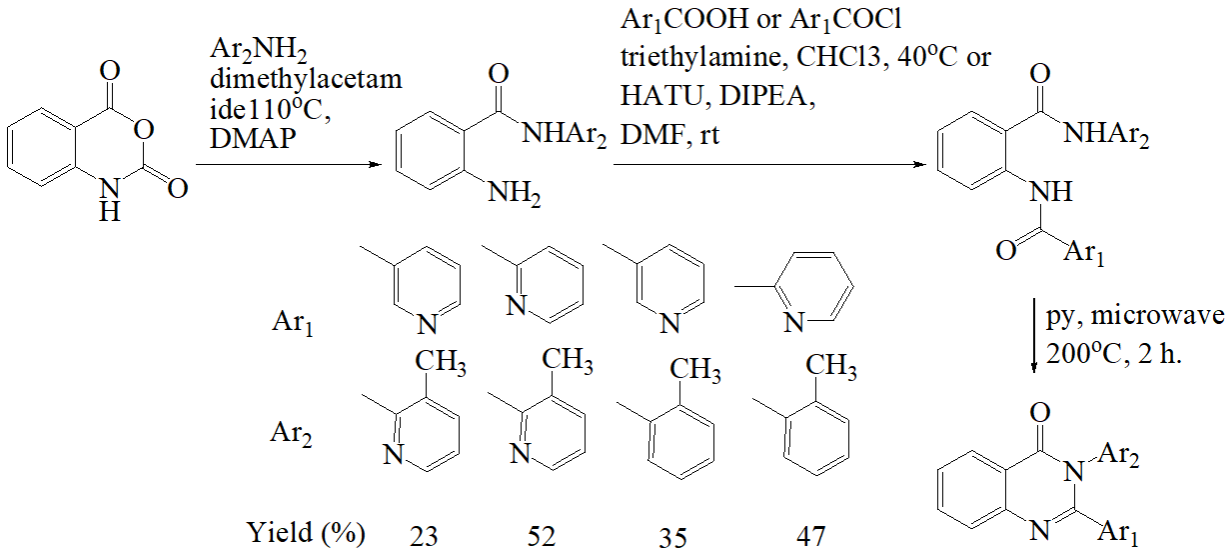


Prof. M. Swaminathan et.al were developed a new protocol for synthesis of 2-(pyridin-2-yl/pyridin-4-yl)quinazolin-4(3*H*)-one by condensation of anthranilamide with picolinaldehyde/isonicotinaldehyde catalysed by rare earth metal oxide namely Gd_2MoO_6 doped on ZnO in toluene in 60–90% yield. The catalysts could be reused at least four times without loss of catalytic activity.[189]

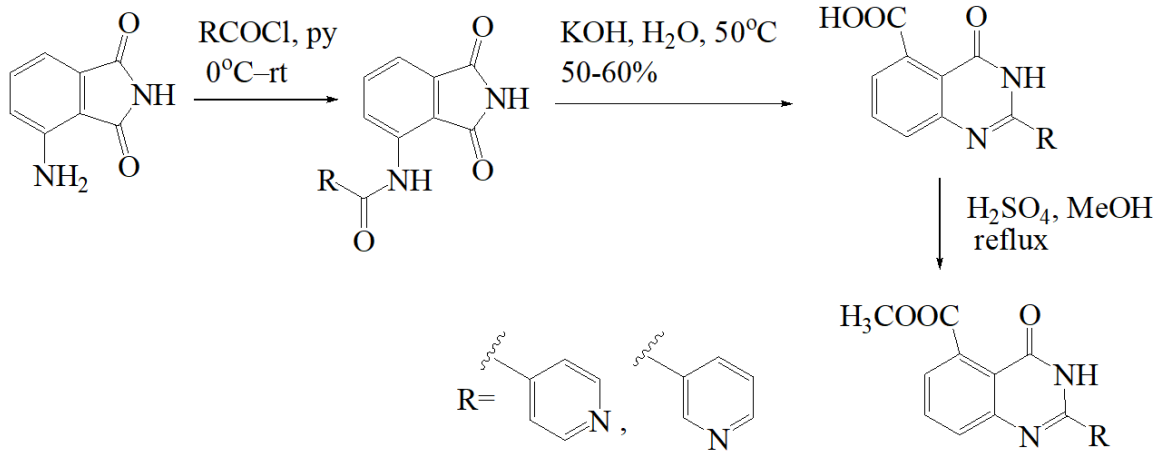


pyridin-2-yl, pyridin-4-yl

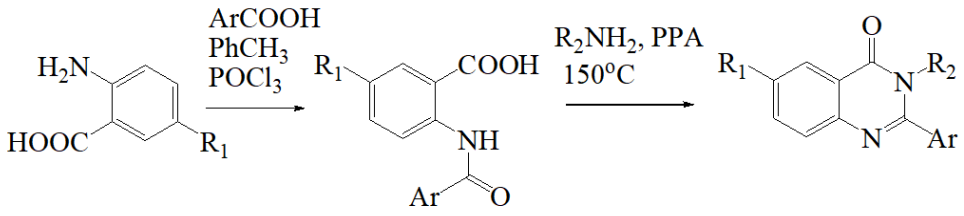
A series of diamides were prepared by condensation of the appropriate amine with isatoic anhydride followed by coupling of the resulting amines with an acyl chlorides or carboxylic acids. The diamides were converted to the corresponding 2,3-diarylquinazolin-4(3*H*)-ones by microwave heating in pyridine at 200°C. The yields were low to moderate.[224]



A new class of PARP-1 inhibitors were synthesized by the acylation of 4-aminoisoindoline-1,3-dione with nicotinoyl chloride or isonicotinoyl chloride, a novel ring opening-reclosing reaction with KOH solution followed by esterification with methanol affording the 5-methoxycarbonyl-2-(pyridin-3-yl or pyridin-4-yl)quinazolin-4(3*H*)-one.[20]

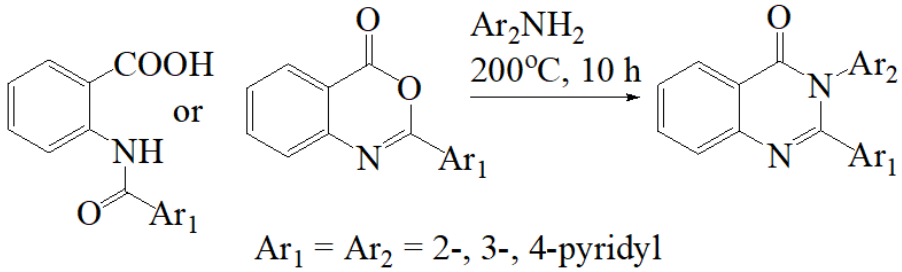


The three isomers - 2-(2/3/4-pyridyl)-3-alkyl-quinazolin-4(3*H*)-ones have exhibited hypnotic, analgesic, anti-inflammatory, anticonvulsant, sedative, anaesthetic and muscle relaxant properties. Hisano et.al reported the preparation of 2-(2-pyridyl)-3-aryl-quinazolin-4(3*H*)-ones from 2-nicotinaminobenzoic acids and arylamines. The required amides were obtained by reacting anthranilic acid with picolinic acids in toluene containing phosphorous oxychloride. Use of 3-picolinic acid in the reaction yielded the isomer.[42]



R_1 = H, NO_2; R_2 = 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$; Ar = 2-, 3-, 4-pyridyl

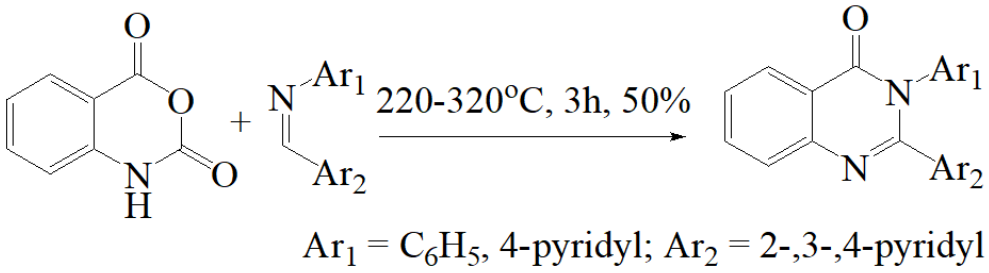
Noda et.al prepared 2,3-bis(pyridyl)quinazolinones by heating *N*-pyridylcarboxyl-anthranilic acids or 2-pyridylbenzoxazinones with pyridylamines at 200°C for 10 h.[225]



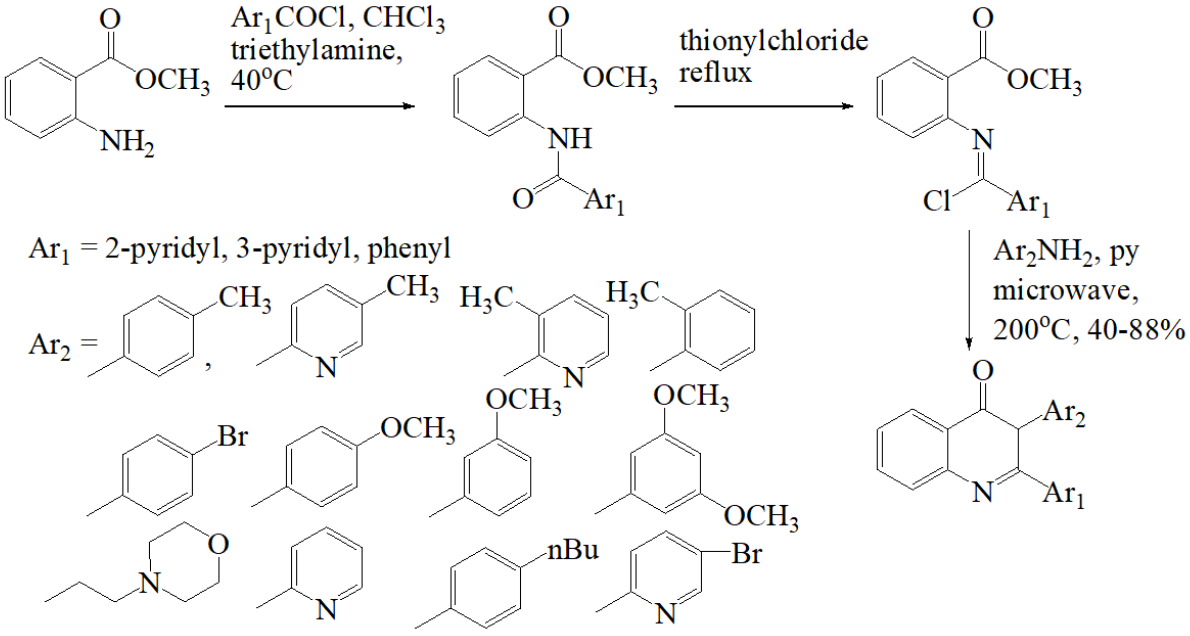
Ar_1 = Ar_2 = 2-, 3-, 4-pyridyl

3-Aryl-2-pyridyl-quinazolin-4(3*H*)-ones were also prepared by heating isatoic anhydride with arylideneanilines.[226]

DOI: https://doi.org/10.5281/zenodo.13644773

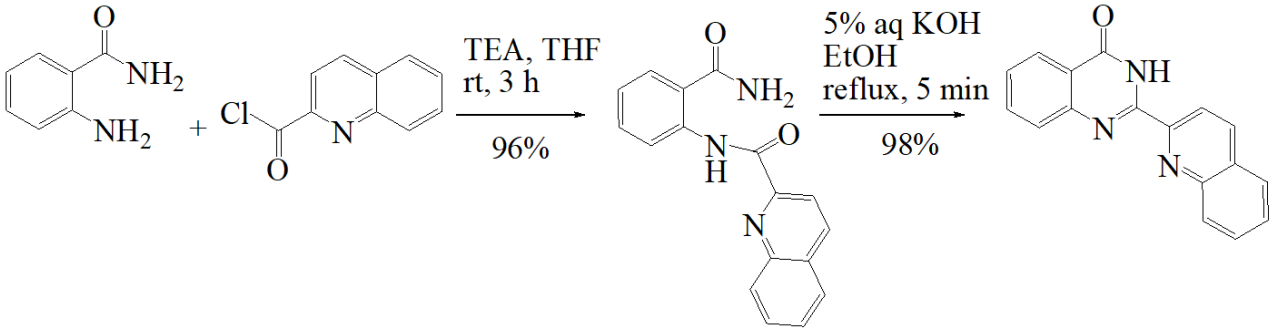


However, a practical and efficient three step synthetic route has been developed by microwave-assisted condensation of an imidoyl chloride with an aryl amine to isolate 2,3-diarylquinazolin-4(3*H*)-ones in quantitative yield. The imidoyl chloride was synthesized by acylation of methyl anthranilate with acyl chloride and subsequently treated the amide derivative with thionyl chloride to afford imidoyl chloride.[224]

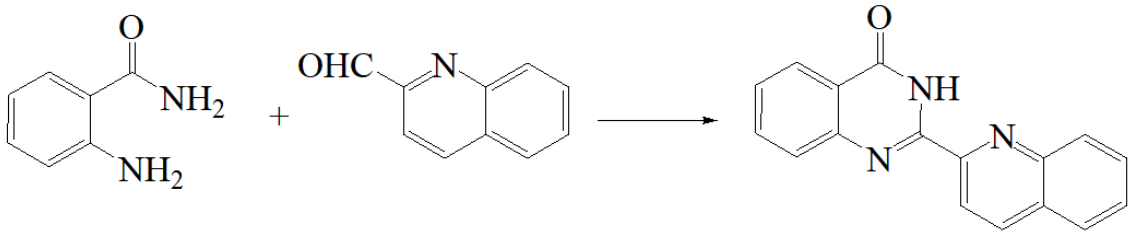


2.4.5 Quinolinylquinazolin-4(3*H*)-ones

Antimicrobial agent, 2-(2-quinolinyl)-quinazolin-4(3*H*)-one, was synthesized by reacting anthranilamide and 2-quinolinecarbonyl chloride in presence of triethylamine to obtain 2-(2-aminocarbonylquinolinyl)benzamide followed by cyclisation under basic conditions.[43]

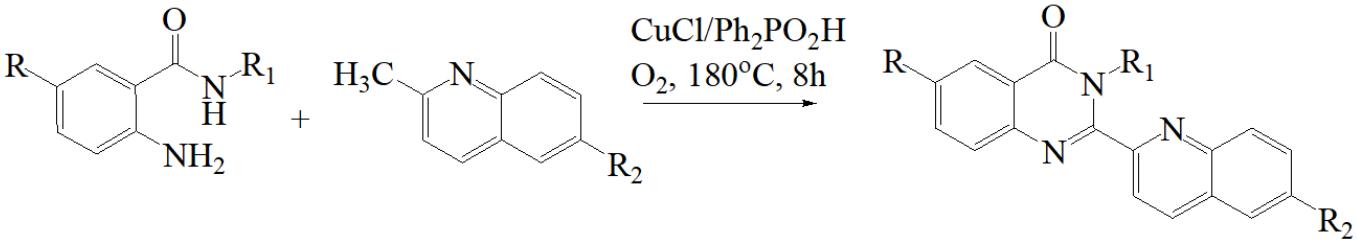


An environment-friendly, catalyst free, solventless, one-step synthesis of 2-(quinolin-2-yl)quinazolin-4(3*H*)-one is presented. The process involves heating of aldehydes and anthranilamides under air as cheap oxidant and as key promoter of reaction. The protocol is suitable for both aromatic and aliphatic aldehydes. This novel synthetic method may be applied to a wide range of educts, offering high yields at low cost while characterized by minimum environmental impact.



conditions and yield	reference
air, 120°C, 24h, 99%	166
CuBr, Cs_2CO_3, DMF 120°C, open air, 1h, 95%	143

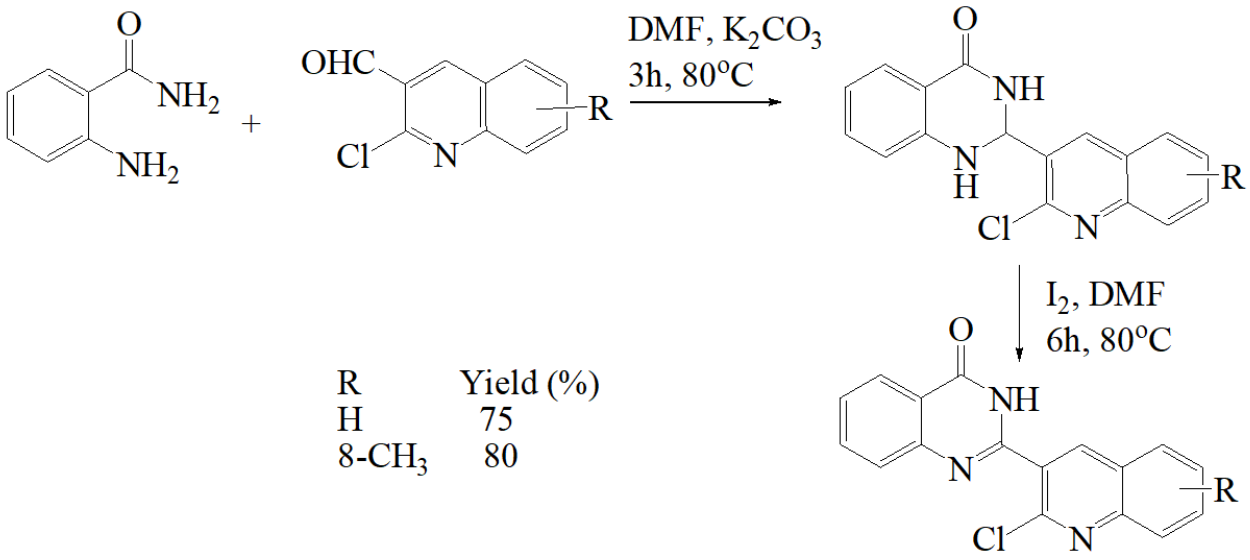
Shuang-Feng Yin et.al reported a direct straightforward tandem oxidation–amination–cyclization transformation via copper-catalyzed from easily available 2-aminobenzamides and (2-azaaryl)methanes to yield 2-(quinolin-2-yl)quinazolin-4(3*H*)-one derivatives.[19]
[7]



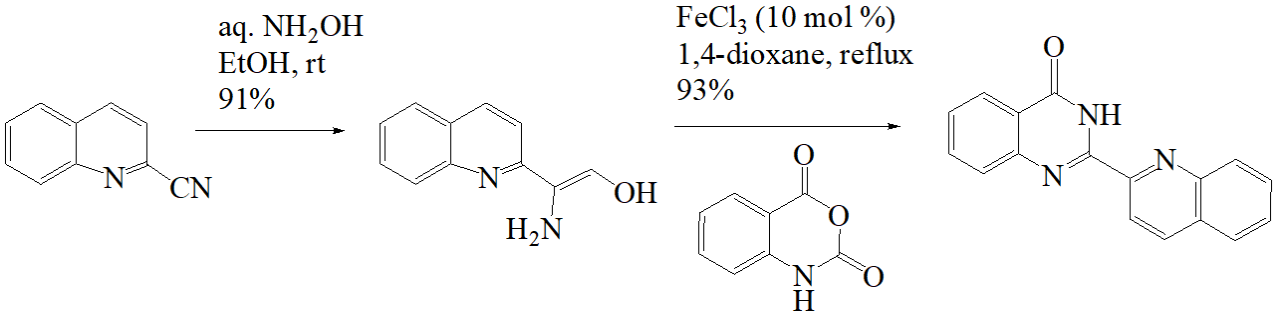
R	R_1	R_2	Yield(%)	R	R_1	R_2	Yield(%)
Cl	H	H	75	H	H	H	86
H	H	OCH_3	56	CH_3	H	H	56
H	CH_3	H	65				

An efficient and high yielding protocol is reported for the synthesis of new class of 2-(2-chloroquinolin-3-yl)quinazolin-4(3*H*)-one derivatives by the reaction of 2-aminobenzamide with 2-chloroquinoline-3-carbaldehydes followed by oxidation.[227]

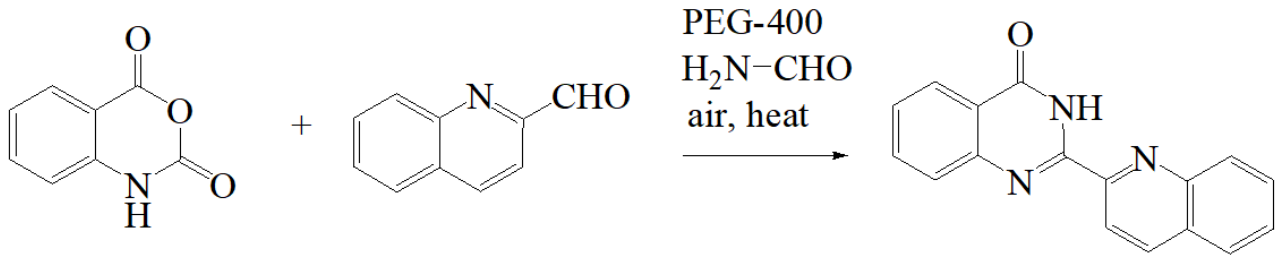
DOI: https://doi.org/10.5281/zenodo.13644773



Ramamohan Mekala et.al described a novel and efficient method for the synthesis of 2-(quinolin-2-yl)quinazolin-4(3*H*)-one by utilizing Iron(III) Chloride catalyzed in a key step.[151]



A remarkably rapid but microwave/ultrasound/catalyst-free method has been developed for the construction of a quinazolin-4(3*H*)-one ring using formamide as an efficient ammonia precursor and PEG-400 as an effective solvent. The methodology afforded 2-(quinolin-2-yl)quinazolin-4(3*H*)-one in good yield via a three-component reaction of isatoic anhydride, aldehydes and formamide in air.[153]

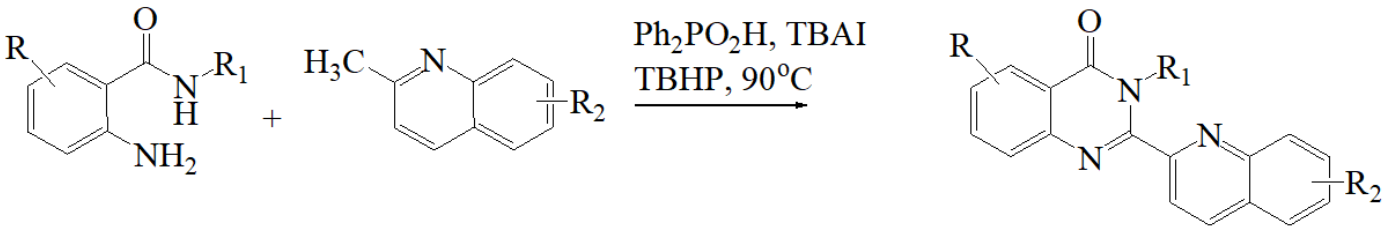


Rama Pati Tripathi et.al reported a novel and efficient Cu(I)-catalyzed ligand- and base-free multipathway domino strategy for the synthesis of 2-(quinolin-4-yl)quinazolin-4(3*H*)-one by utilizing 2-bromobenzamide and multiform substrates such as aldehydes and alcohols for a one-pot protocol, whereas $TMSN_3$ is used as a nitrogen source.[161]

DOI: https://doi.org/10.5281/zenodo.13644773

X	condition	Yield (%)
—CHO	$TMSN_3$, CuI, air DMSO, 80°C	61%
—CH_2OH	$TMSN_3$, CuI, DMSO, air TBHP, 80°C	58%

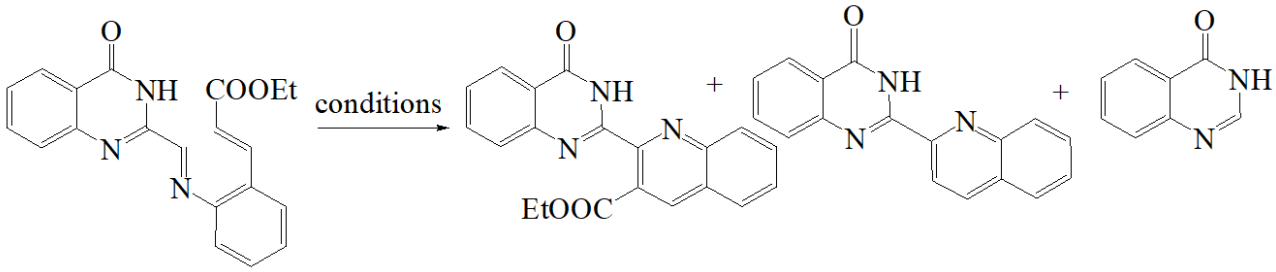
A new method for the synthesis of 2-(quinolin-4-yl)quinazolin-4(3*H*)-one from 2-aminobenzamides and 2-methylquinolines under transition metal-free conditions under mild conditions is described. The oxidation of 2-methylquinolines to corresponding aldehyde is proposed as the key step in this transformation.[198]



R	R1	R2	Yield(%)	R	R1	R2	Yield(%)
H	H	H	93	6-CH_3	H	H	93
6-Cl	H	H	78	5-Cl	H	H	72
6-F	H	H	90	6-OCH_3	H	H	80
6-I	H	H	67	C≡CPh	H	H	95
H	CH_3	H	87	H	n-C_3H_7	H	85
H	i-C_3H_7	H	82	H	$CH_2C_6H_5$	H	82
H	tetrahydrofuran-2-yl)methyl	H	77	H	3,4-dimethoxy phenethyl	H	72
H	H	7-Cl	86	H	H	6-Br	66
H	H	7-F	79	H	H	6-CH_3	90
H	H	8-benzyloxy	75				

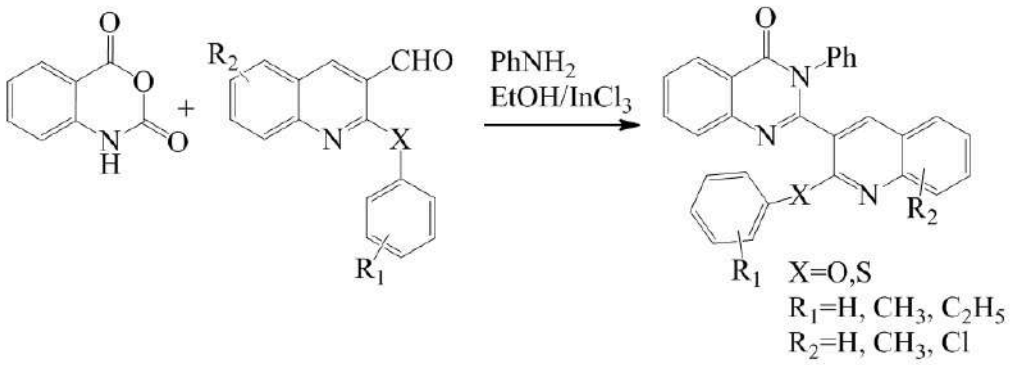
Cheol-Hong Cheon et.al were reported a procedure to synthesis 2-(quinolin-4-yl)quinazolin-4(3*H*)-ones by heating aldimine at 200 °C in 1,2,4-trichlorobenzene for 24 h in 20% yield. This was accompanied by the formation of several unexpected side products decarboxylated compound and quinazolinone.[228]

DOI: https://doi.org/10.5281/zenodo.13644773



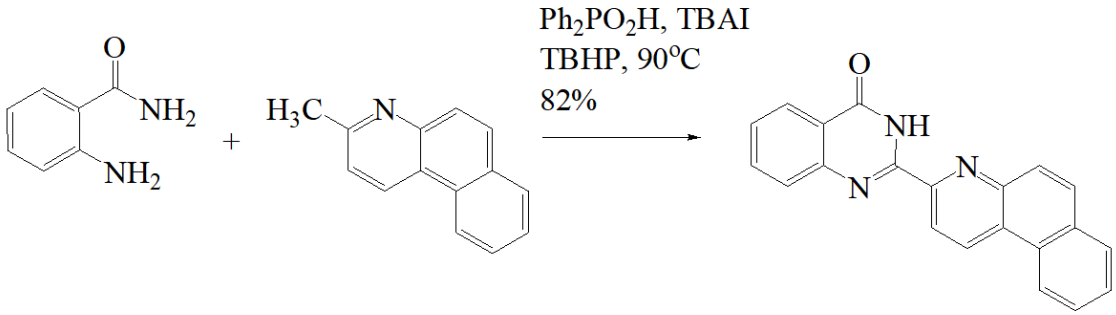
conditions	result
1,2,4-$C_6H_3Cl_3$, air, 200 °C, 24 h	23% + 27%+ 26% + unidentifiable Mixture
1,2,4-$C_6H_3Cl_3$, MW (100 W), <150 °C, 10 h	no reaction
1,2,4-$C_6H_3Cl_3$, MW (100 W), 160 °C, 10 h	42% + 12% + 15%) + unidentifiable mixture
1,2,4-$C_6H_3Cl_3$, MW (100 W), 180 °C, 10 h	28% + 18% + 21% + unidentifiable mixture
1,2,4-$C_6H_3Cl_3$, MW (100 W), 200 °C, 10 h	19% + 28% + 25% + unidentifiable mixture

The compounds with antibacterial activity, 3-phenyl-2-(quinolin-3-yl)quinazolin-4(3*H*)-one derivatives, were synthesized by the cyclocondensation reaction of isatoic anhydride, aniline with 2-substituted-quinoline-3-carbaldehyde derivatives in ethanol in presence of In(III)-catalyst in high yields.[24]



2.4.6 Benzoquinolinylquinazolin-4(3*H*)-one

A new method for the synthesis of 2-(benzo[*f*]quinolin-3-yl)quinazolin-4(3*H*)-one from 2-aminobenzamides and 3-methylbenzo[*f*]quinoline under transition metal-free conditions and mild conditions is described. The oxidation of 3-methylbenzo[*f*]quinoline to corresponding aldehyde is proposed as the key step in this transformation.[198]

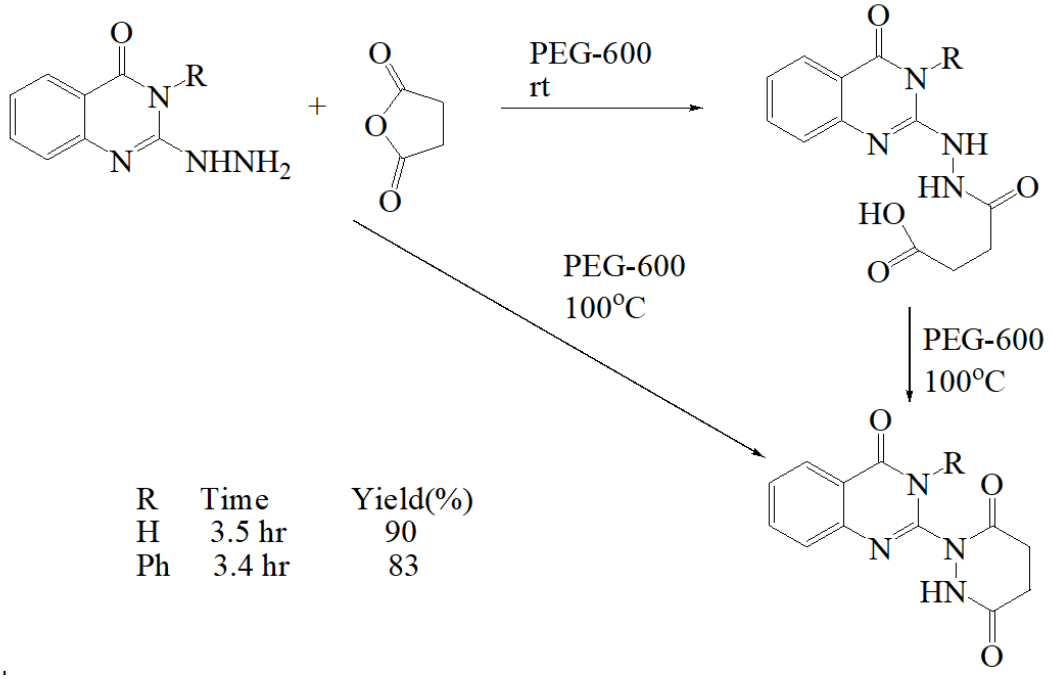


2.4.7 Hexahydropyridazinylquinazolin-4(3*H*)-ones

2-Hydrazinoquinazolin-4(3*H*)-ones were reacts with succinic anhydride in PEG-600 at RT to yield 4-oxo-4-(2-(4-oxo-3,4-dihydroquinazolin-2-yl)hydrazinyl)butanoic acid derivatives and the resultant compoundshave been transformed into 2-(4,5-dihydropyridazine-3,6-dione-1-yl)quinazolin-4(3*H*)-ones. The final compounds have also been prepared alternatively

DOI: https://doi.org/10.5281/zenodo.13644773

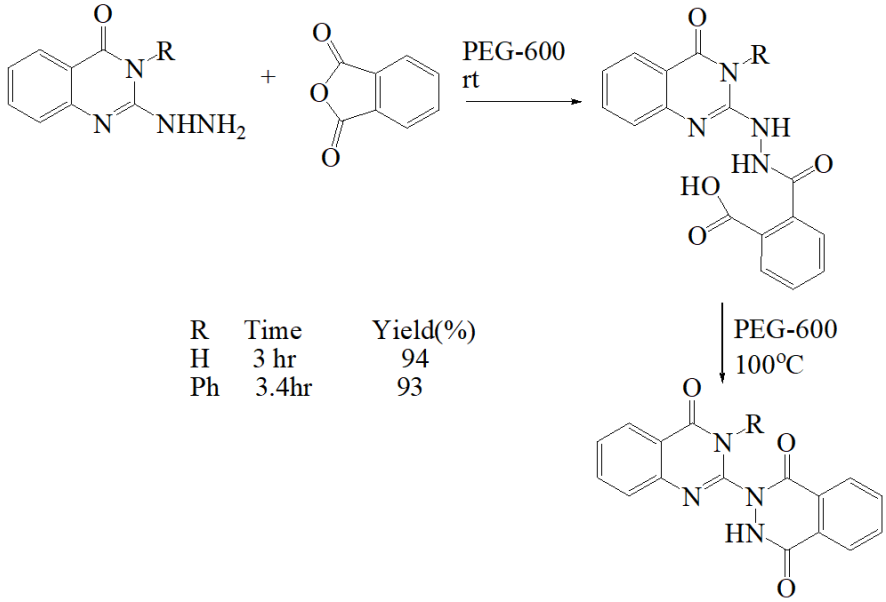
by reacting 2-hydrazinoquinazolin-4(3*H*)-ones with succinic anhydride in PEG-600 at 100°C. [229]



R	Time	Yield(%)
H	3.5 hr	90
Ph	3.4 hr	83

2.4.8 Dihydrophthalazinedioneylquinazolin-4(3*H*)-ones

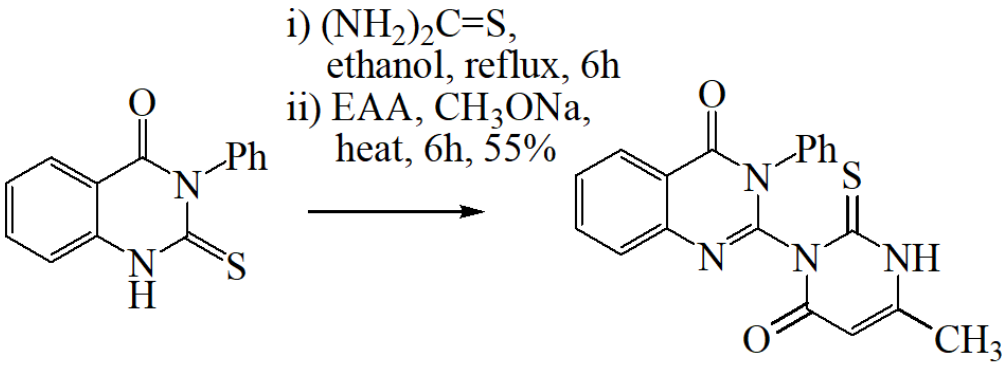
Md. Rafeeq et.al were reacted 2-hydrazinoquinazolin-4(3*H*)-ones with phthalic anhydride in PEG-600 at RT to yield 2-(3,4-dihydro-4-oxoquinazolin-2-ylaminocarbamoyl)benzoic acid derivatives and the resultant compounds have been transformed into 2-(2,3-dihydrophthalazine-1,4-dione-2-yl)quinazolin-4(3*H*)-ones in PEG-600 at 100°C. [229]



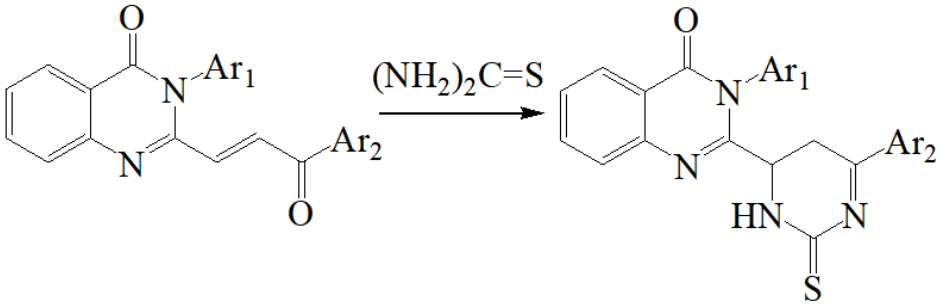
R	Time	Yield(%)
H	3 hr	94
Ph	3.4hr	93

El-Desuky et.al reported a one pot synthesis of 3-phenyl-2(4-methyl-6-oxo-2-thioxo-1-pyrimidinyl-4(3*H*)-quinazolinone by reacting 3-phenyl-2-thioxo-4-oxo-1, 2, 3, 4-tetrahydroquinazoline with thiourea and ethyl acetoacetate (EAA). The mechanism involves the initial formation of a pyrimidine which then substitutes the thiol group at C-2 of the quinazolinone moiety. [230]

DOI: https://doi.org/10.5281/zenodo.13644773



Khilil et.al prepared 3-aryl-2-(4-aryl-2-thio-1, 2, 5, 6-tetrahydro-1,3-pyrimidin-6-yl)-quinazolin-4(3*H*)-ones by reacting the key intermediate, 3-aryl-2-(3-oxopropenyl)-quinazolin-4(3*H*)-ones and thiourea.[30]



Ar_1 = C_6H_5, 4-$CH_3C_6H_4$, 4-BrC_6H_4, Ar_2 = C_6H_5, 4-$CH_3C_6H_4$

2.4.9 Pyrimidinylquinazolin-4(3*H*)-one

A novel cytotoxic compounds-2-(2-amino-6-arylpyrimidin-4-yl)quinazolin-4(3*H*)-ones were designed and accessed via guanidine condensation with the quinazolinonyl aryl enones that were in turn derived from 2-acetyl quinazolin-4(3*H*)-one. The screening results revealed that 2-(2-amino-6-(2,4,6-trimethoxyphenyl)pyrimidin-4-yl)quinazolin-4(3*H*)-one,2-(2-amino-6-(4-(methylthio)phenyl)pyrimidin-4-yl)quinazolin-4(3*H*)-one and 2-(2-amino-6-(3-bromophenyl) pyrimidin-4-yl)quinazolin-4(3*H*)-one inhibited biofilm formation efficiently in MRSA (IC_{50} ~ 20 µM). The cytotoxicity assay of the active compounds revealed that compounds 2-(2-amino-6-(3-bromophenyl) pyrimidin-4-yl)quinazolin-4(3*H*)-one was highly toxic to the cells.[44]

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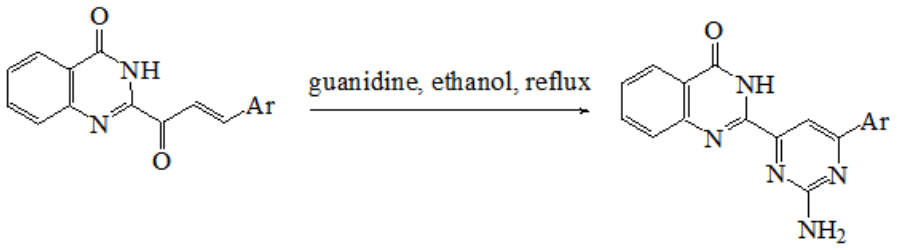
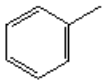
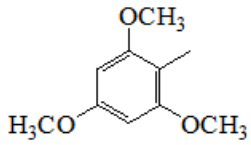
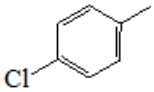
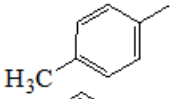
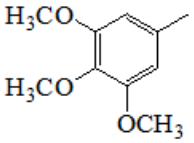
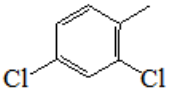
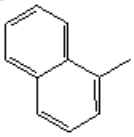
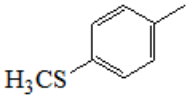
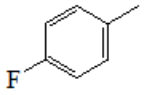
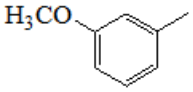
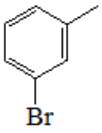
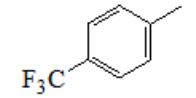
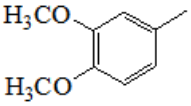
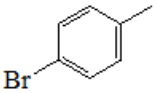
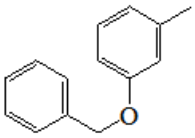
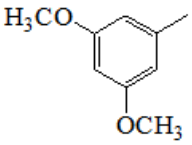
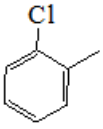
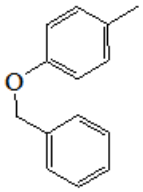
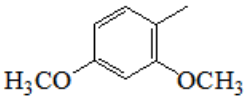
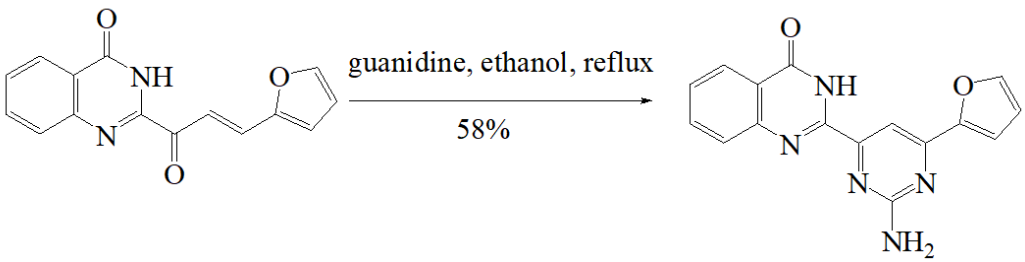


Ar	yield (%)	Ar	yield (%)	Ar	yield (%)
	89		63		43
	53		55		41
	54		40		66
	86		49		47
	52		54		49
	84		37		51
	37				

2.4.10 Furanylpyrimidinylquinazolin-4(3*H*)-one

S. Rasapalli et.al was designed a novel 2-(2-amino-6-(furan-2-yl)pyrimidin-4-yl)quinazolin-4(3*H*)-one and accessed via guanidine condensation with the 2-((*E*)-3-(furan-2-yl)acryloyl)quinazolin-4(3*H*)-one in refluxed ethanol.[44]



2.4.11 Thiophenylpyrimidinylquinazolin-4(3*H*)-one

Condensation of guanidine with the 2-(3-(thiophen-2-yl)acryloyl)quinazolin-4(3*H*)-one in refluxed ethanol gave 2-(2-amino-6-(thiophen-2-yl)pyrimidin-4-yl)quinazolin-4(3*H*)-one in moderate yield.[44]

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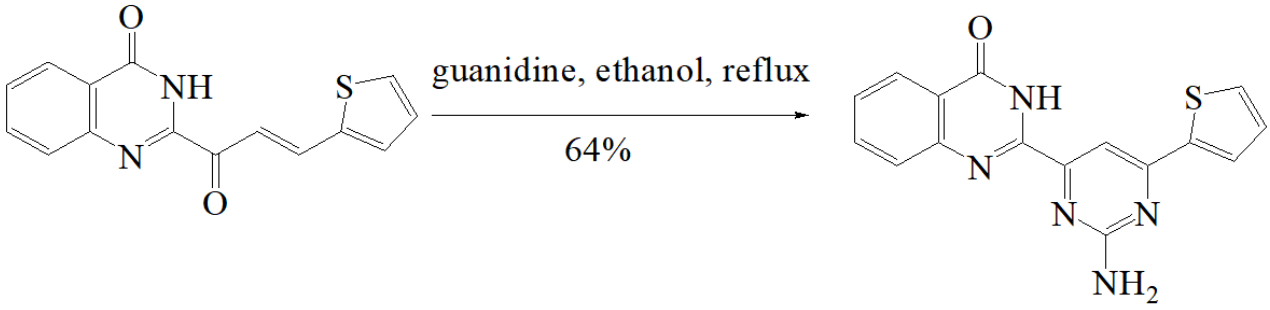
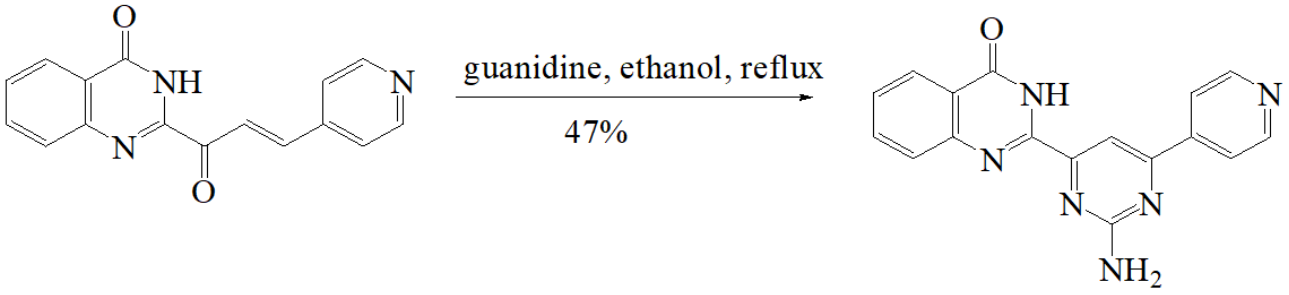


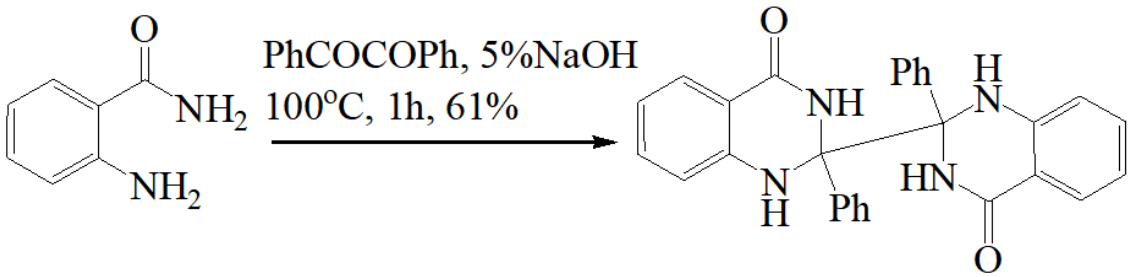
2.4.12 Pyridinylpyrimidinylquinazolin-4(3*H*)-one

2-(3-(Pyridin-4-yl)acryloyl)quinazolin-4(3*H*)-one was condensed with guanidine in refluxed ethanol to provide 2-(2-amino-6-(pyridin-4-yl)pyrimidin-4-yl)quinazolin-4(3*H*)-one. [44]



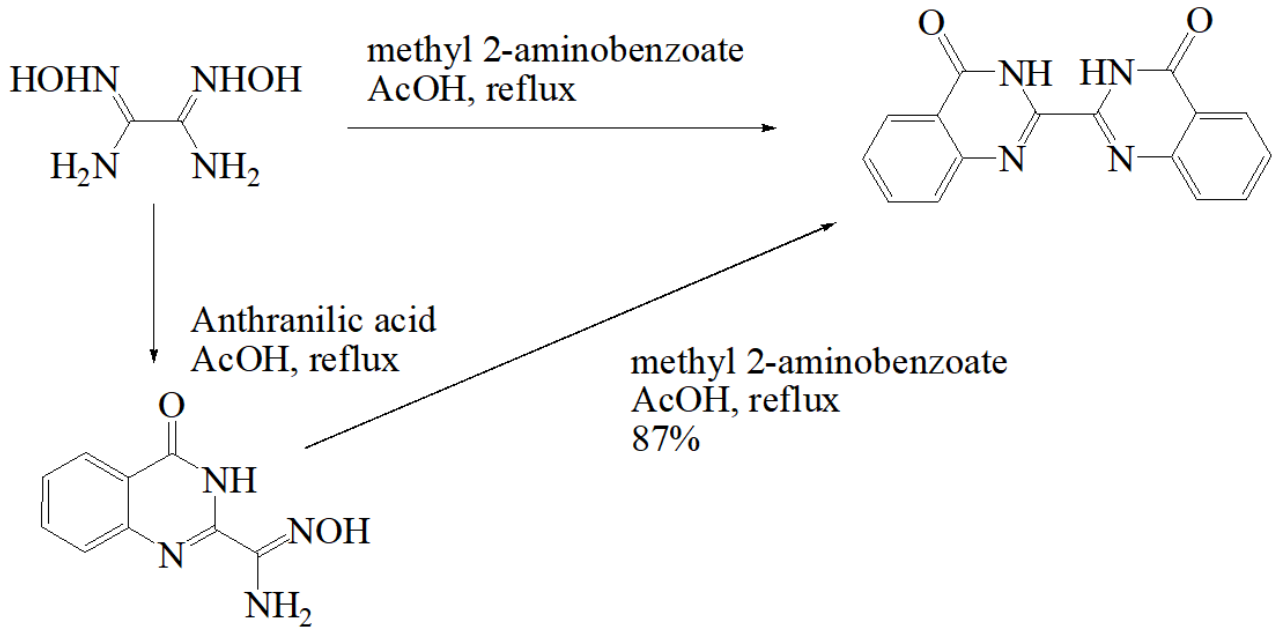
2.4.13 2,2'-Bisquinazolin-4(3*H*)-ones

Anthranilamide also reacts with benzil to give 2,2'-diphenyltetrahydro-2,2'-bisquinazolin-4,4'-dione in 61% yield.[231]

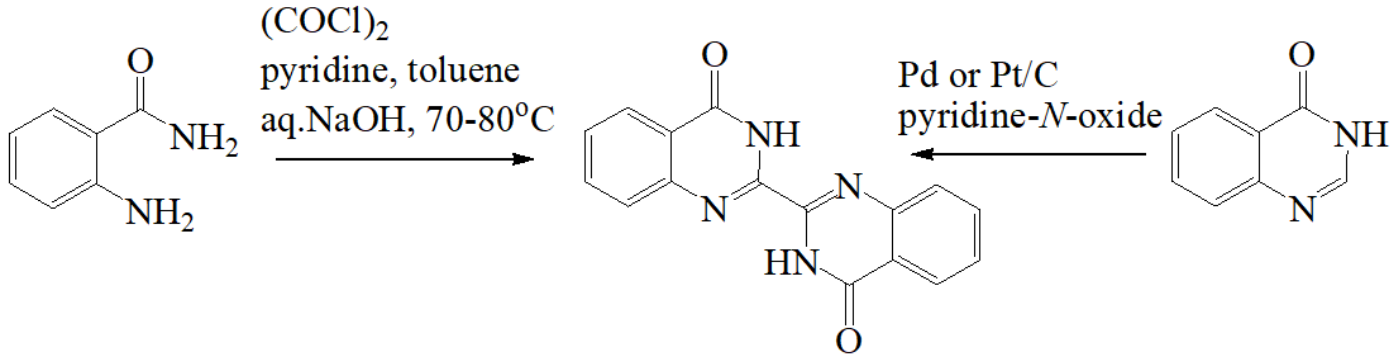


A new and efficient approaches are developed for the synthesis of 4,4'(3*H*,3*H*')-quinazolinone in good yields, via the reactions of diaminoglyoxime and methyl 2-aminobenzoate in acetic acid as the solvent under reflux conditions or diaminoglyoxime and anthranilic acid in acetic acid under reflux conditions followed by reaction of resultant 3,4-dihydro-*N*'-hydroxy-4-oxoquinazoline-2-carboxamidine with methyl 2-aminobenzoate in acetic acid under reflux conditions in 87% yield. [204]

DOI: https://doi.org/10.5281/zenodo.13644773

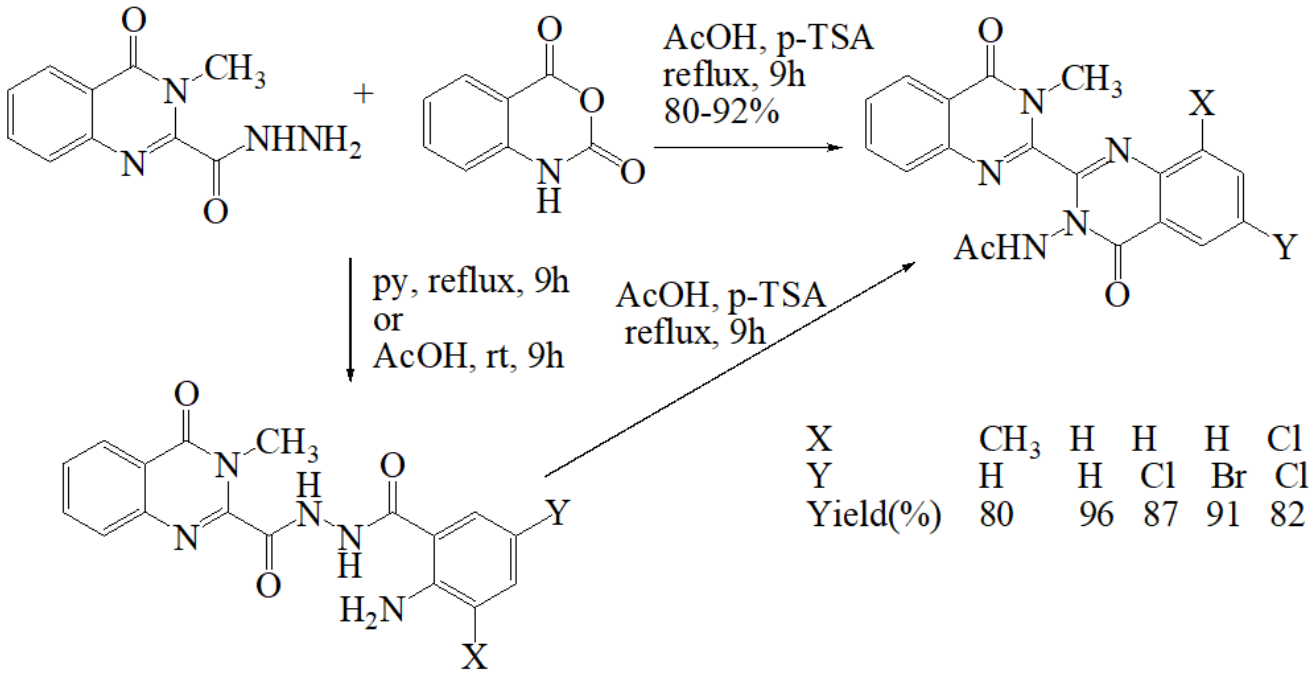


Symmetrical 2,2'-bis-4(3*H*)-quinazolinone is useful as a heat resistant whitening agent. It was prepared by a base catalysed reaction of 2-aminobenzamide with oxalyl chloride. An alternative method involves dimerisation of 4(3*H*)-quinazolinone in the presence of pyridin-1-oxide and Pd or Pt/C.[232, 233]



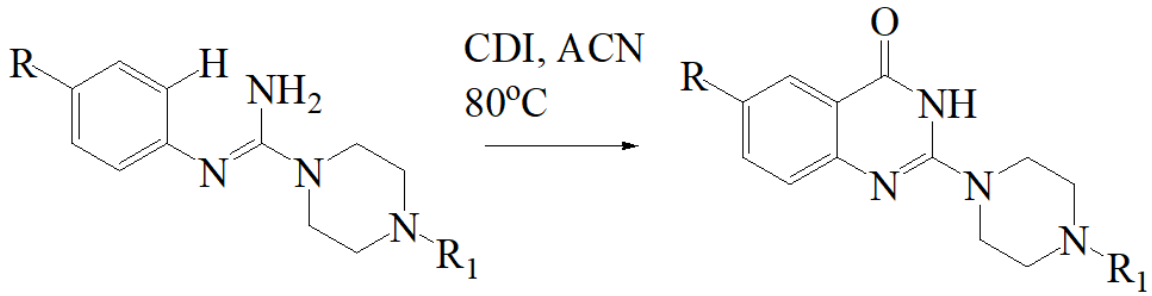
Refluxing a mixture of 2-hydrazinocarbonyl-3-methylquinazolin-4(3*H*)-one and isatoic anhydrides in acetic acid yielded 3'-acetamido-3-methyl-2,2'-bisquinazolin-4(3*H*)-one derivatives. The same compounds were obtained by starting materials in pyridine or acetic acid at room temperature followed by cyclizing the resulting 2-[(2-aminobenzoyl)hydrazinocarbonyl] -3-methylquinazolin-4(3*H*)-one in acetic acid at reflux. 3'-Acetamido-6'-bromo-3-methyl-2,2'-bisquinazolin-4(3*H*)-one has exhibited 70.25% antifungal activity against *macrophomina sorgina* at 25µg/disc.5,[234]

DOI: https://doi.org/10.5281/zenodo.13644773



2.4.14 Piperazinylquinazolin-4(3*H*)-ones

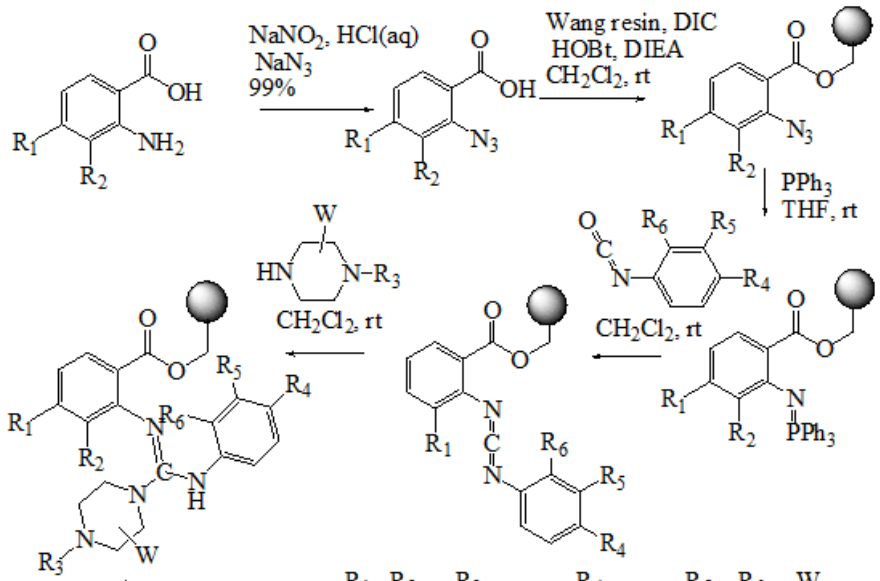
A new method for the preparation of 2-(piperazin-1-yl)quinazolin-4(3*H*)-ones is described by warming a mixture of an (*E*)-*N*'-phenylpiperazine-1-carboxamidinesand carbonyl diimidazole in acetonitrile results in formation of a putative *N*-amidinoisocyanate intermediate which undergoes a 6p-electron electrocyclic reaction with the aryl ring.[141]



R	R_1	yield(%)
Cl	$CH_2C_6H_5$	57
OPh	$C_6H_4COCH_3$	95

Azidation of the easily available anthranilic acid derivatives under Sandmeyer conditions gave orthoazido benzoic acids, coupling using typical amidation conditions with dicyclohexylcarbodiimide to afford the corresponding polymer bound *ortho*-azide esters. Exposing the azides with PPh_3 in tetrahydrofuran at room temperature to iminophosphoranes, followed by isocyanate, to give carbodiimide derivatives. Finally, treatment with various piperazine derivatives, followed by intramolecular cyclization and simultaneous cleavage from the resin, provided the 3-aryl-2-(piperazin-1-yl)quinazolin-4(3*H*)-one derivatives. These compounds have exhibited anabolic activity toward chondrogenic differentiation and provide relief against articular cartilage damage i.e anti-osteoarthritis.[7]

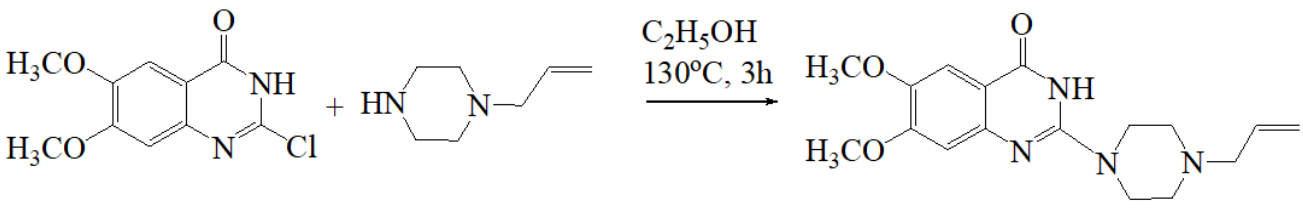
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	R_2	R_3	R_4	R_5	R_6	W
H	Cl	CH_3	Cl	H	H	H
H	Cl	CH_3	CH_3	H	H	H
H	Cl	CH_3	H	CH_3	H	H
H	Cl	CH_3	H	H	CH_3	H
H	Cl	CH_3	COOEt	H	H	H
H	F	CH_3	COOEt	H	H	H
H	H	CH_3	OCH_3	H	H	H
H	Br	CH_3	COOEt	H	H	H
H	OCH_3	CH_3	CH_3	H	H	H
H	F	$CH(CH_3)_2$	COOEt	H	H	H
F	H	H	OCH_3	H	H	H
F	H	CH_3	OCH_3	H	H	H
F	H	C_2H_5	OCH_3	H	H	H
F	H	CH_3	CF_3	H	H	(S)-3-$CH(CH_3)_2$
F	H	CH_3	CF_3	H	H	(S)-3-$CH_2CH(CH_3)_2$
F	H	CH_3	CF_3	H	H	3, 3-$(CH_3)_2$
F	H	CH_3	CF_3	H	H	3-cyclopropyl
F	H	CH_3	CF_3	H	H	Beta-2-CH_3
F	H	CH_3	F	H	H	3-oxo
H	F	CH_3	CF_3	H	H	H
H	F	CH_3	$CH(CH_3)_2$	H	H	H
H	F	CH_3	OCF_3	H	H	H
H	F	CH_3	SCF_3	H	H	H

2.4.15 Diazino-quinazolin-4(3*H*)-ones

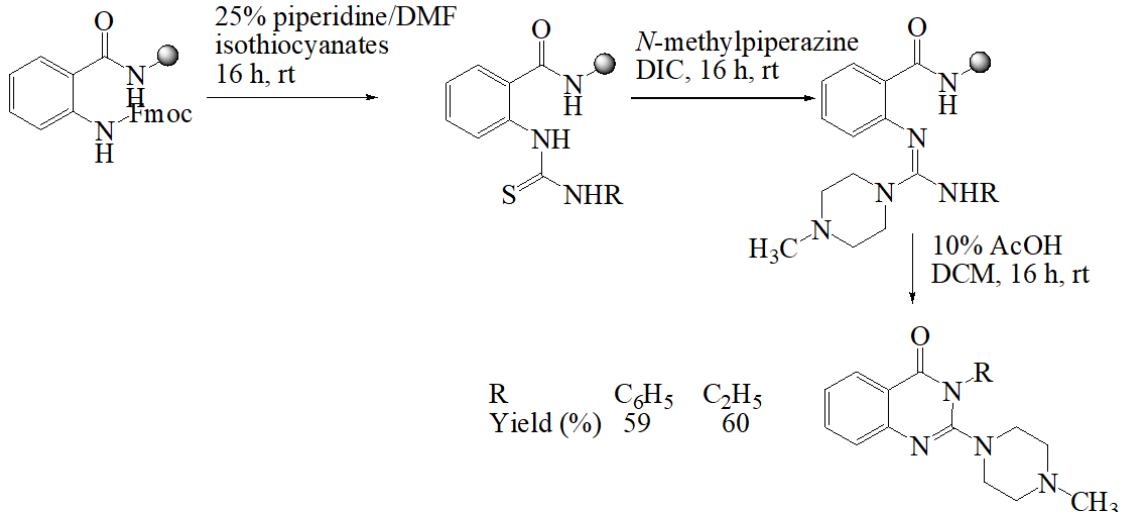
2-(4-Allyl-1-piperazinyl)-4(3*H*)-quinazolinone showed promising antihypertensive activity. It was prepared by heating 2-chloro-6,7-dimethoxy-4(3*H*)-quinazolinone with *N*-allyl piperazine in ethanol in a pressure bottle at 130 ^{0} C for 3 h.[235]



A versatile method for the solid-phase synthesis of differentially substituted quinazolin-4(3*H*)-ones has been developed using immobilized arylguanidines. The latter were obtained by treating the amino group of polymer-linked anthranilamide with isothiocyanates followed by coupling the resultant amide with secondary amines in the presence of DIC to generate pyrazine derivative. Finally a cyclative cleavage strategy was applied to give the desired 2-(4-methyl

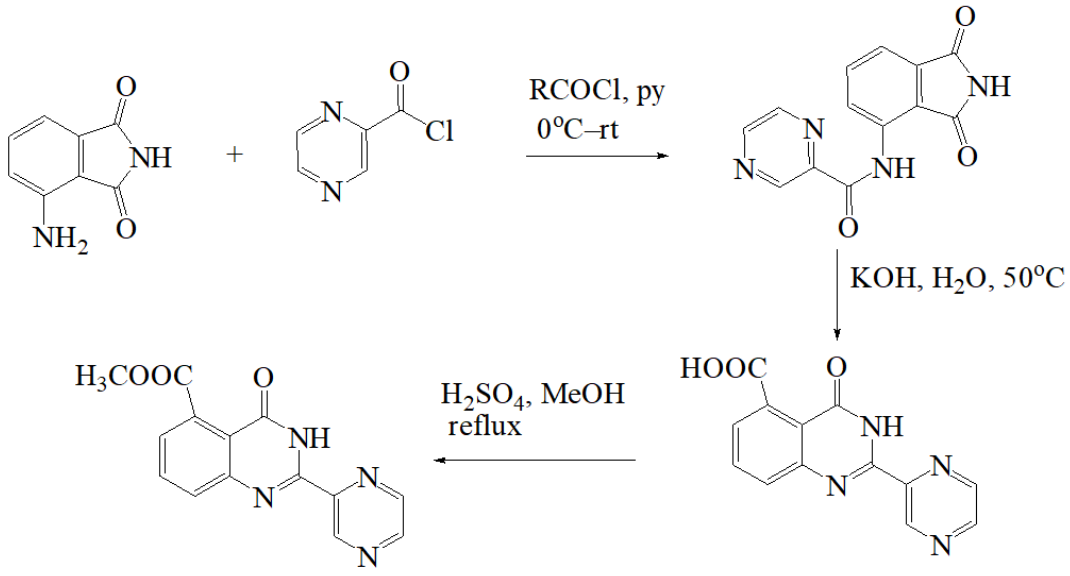
DOI: https://doi.org/10.5281/zenodo.13644773

piperazin-1-yl)-quinazolin-4(3*H*)-ones in high yields and purities.[206]

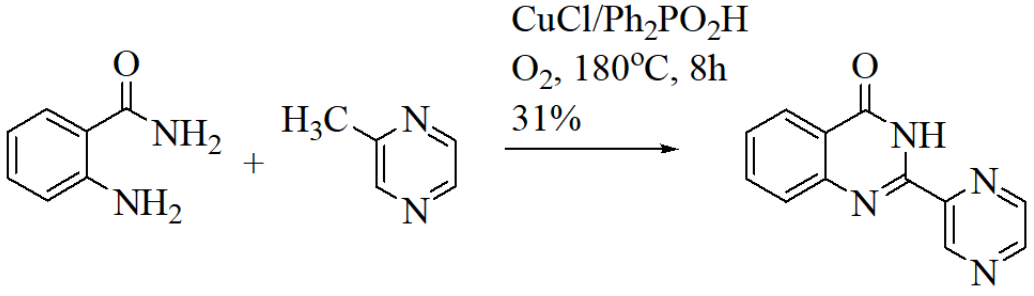


2.4.16 Pyrazinylquinazolin-4(3*H*)-ones

A new class of PARP-1 inhibitor was synthesized by the acylation of 4-aminoisoindoline-1,3-dione with pyrazine-2-carbonyl chloride, a novel ring opening-reclosing reaction with KOH solution followed by esterification with methanol affording the 5-methoxycarbonyl-2-(pyrazin-2-yl)-quinazolin-4(3*H*)-one.[20]

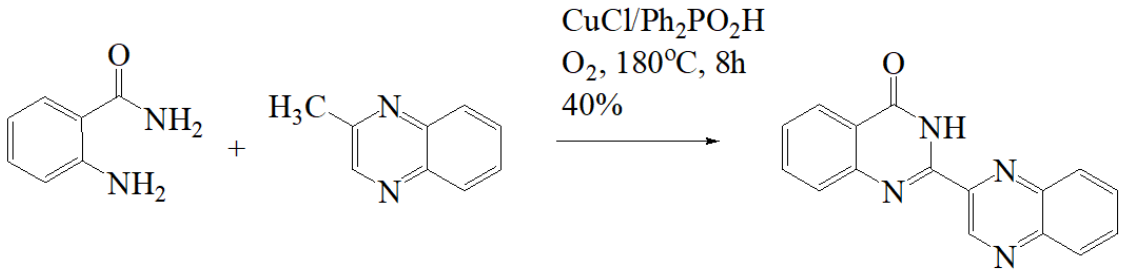


A direct Straightforward tandem oxidation–amination–cyclization transformation via copper-catalyzed from easily available 2-aminobenzamides and 2-methylpyrazine to 2-(pyrazin-2-yl)quinazolin-4(3*H*)-one has been developed.[197]

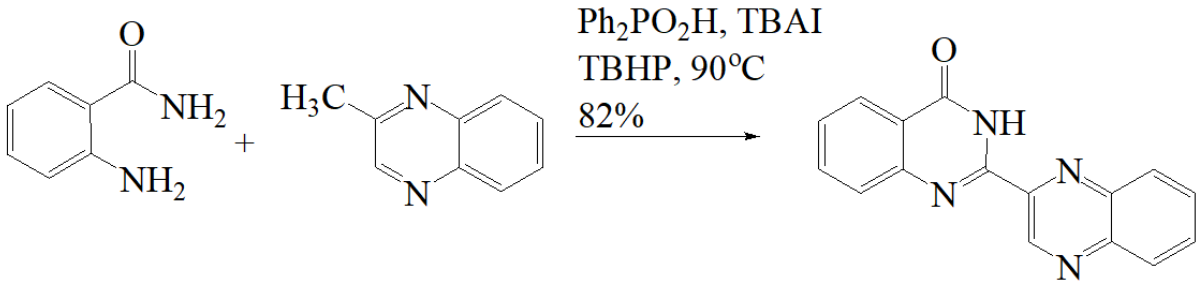


2.4.17 Quinoxalinylquinazolin-4(3*H*)-ones

2-(Quinoxalin-3-yl)quinazolin-4(3*H*)-one was synthesized by a direct Straightforward tandem oxidation– amination– cyclization transformation via copper-catalyzed from easily available 2-aminobenzamides and 2-methylquinoxaline.[197]

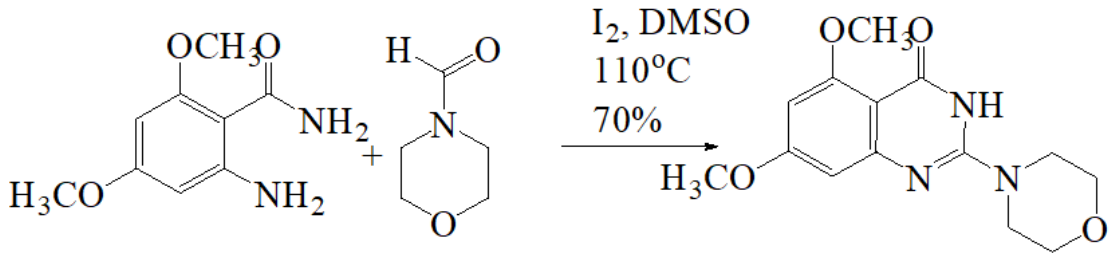


Alternatively, a new method for the synthesis of 2-(quinoxalin-3-yl)quinazolin-4(3*H*)-one from 2-aminobenzamides and 2-methylquinoxaline under transition metal-free conditions is described. The oxidation of 2-methylquinoxaline to corresponding aldehyde is proposed as the key step in this transformation.[198]



2.4.18 Morpholinoquinazolin-4(3*H*)-one

A novel AChE inhibitor with anti-inflammatory activity, 5,7-dimethoxy-2-morpholinoquinazolin-4(3*H*)-one, was prepared by the reaction of 2-amino-4,6-dimethoxybenzamide with morpholine-4-carbaldehyde in I_2 containing DMSO.[13]



A new method for the preparation of 5,6-dichloro-2-morpholinoquinazolin-4(3*H*)-one and 6,7-dichloro-2-morpholinoquinazolin-4(3*H*)-one is described by warming a mixture of an ((*E*)-*N*'-(3,4-dichlorophenyl)morpholine-4-carboxamidine and carbonyl diimidazole in acetonitrile results in formation of a putative *N*-amidinoisocyanate intermediate which undergoes a 6p-electron electrocyclic reaction with the aryl ring.[141]

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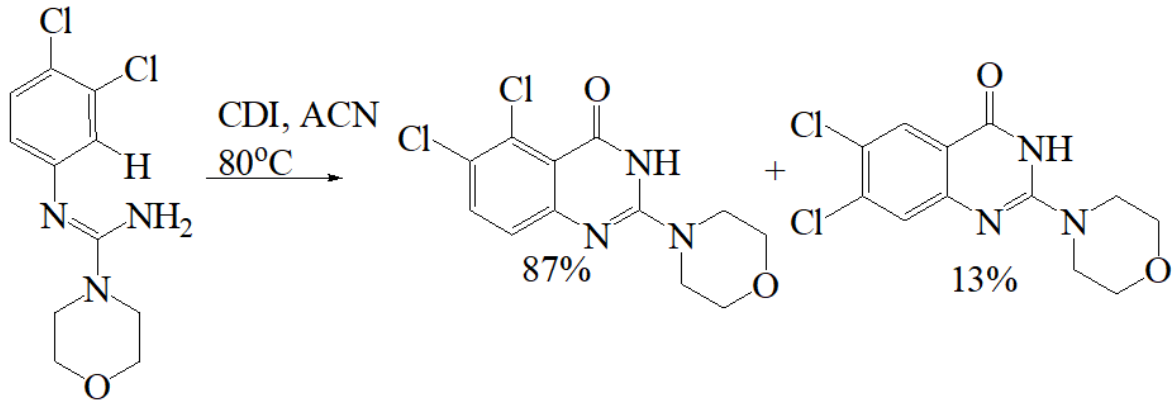
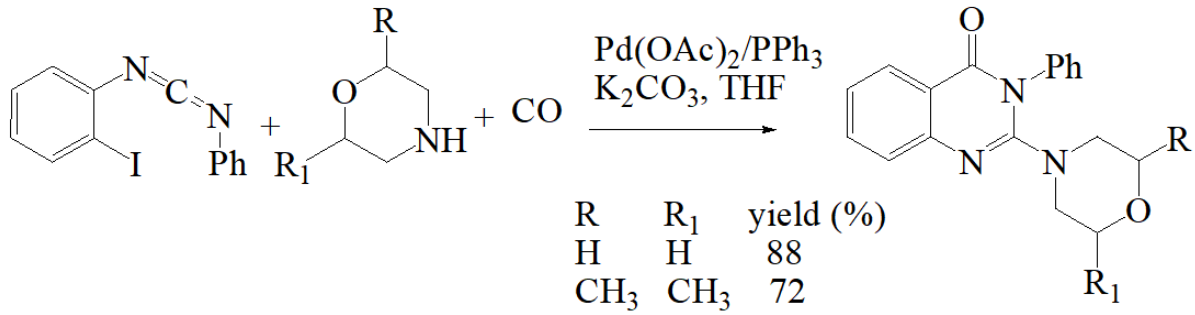
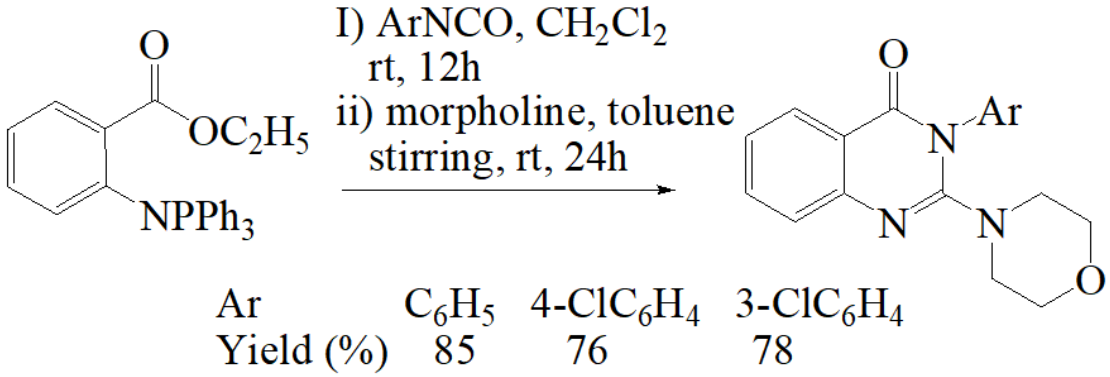


Synthesis of 2-morpholino-3-phenylquinazolin-4(3*H*)-one by palladium-catalyzed inter molecular addition and intramolecular cyclocarbonylation cascade reaction of *N*-(2-iodophenyl)-*N′*-phenyldicarbodiimide with morpholine/2,6-dimethylmorpholine was reported.[140]

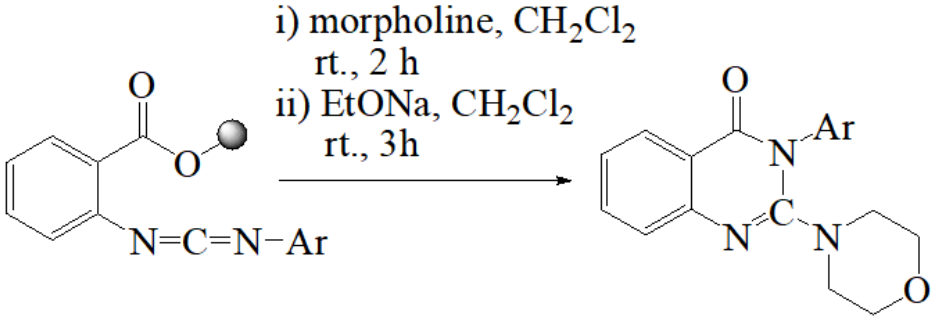


Ming-Wu Ding et.al prepared 2-morpholinyl-3-aryl-quinazolin-4(3*H*)-ones by aza-Wittig reaction of ethyl anthranilate ylide with a mixture of aromatic isocyanates and morpholine under mild conditions.[205]



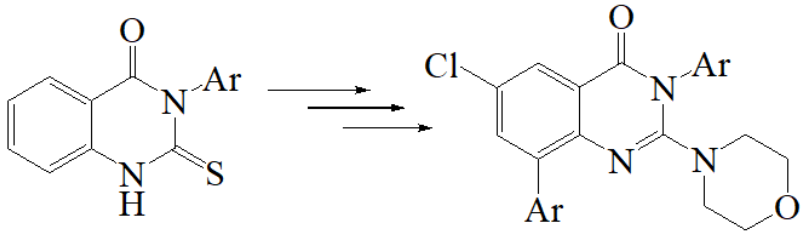
Xie et.al prepared 3-aryl-2-(*N*-morpholinyl)-quinazolin-4(3*H*)-one from poly(ethylene glycol) (PEG) supported aza-Wittig reaction. Quinazolinones were synthesized efficiently by reaction of morpholine with PEG-supported carbodiimides.[139]

DOI: https://doi.org/10.5281/zenodo.13644773



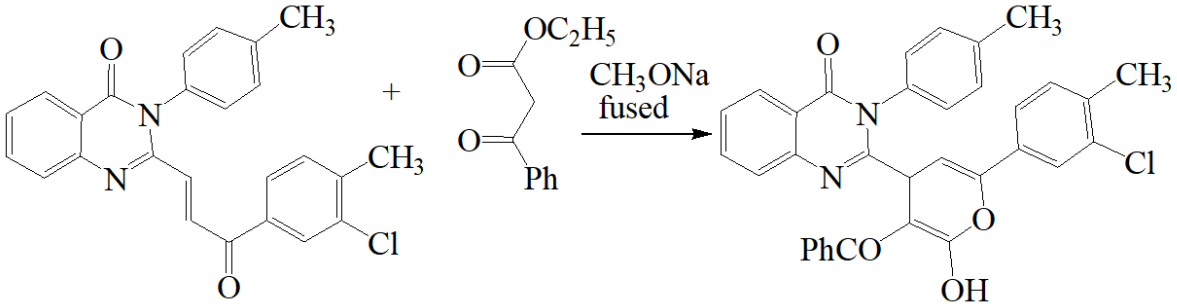
Ar	4-ClC_6H_4	4-FC_6H_4
Yield(%)	83	72

A series of novel 8-aryl-2-morpholino quinazolines were synthesized from the precursor 2-thioxo quinazolin-4(3*H*)-ones. These compounds exhibited DNAPK, PI3K and cytotoxicity.[45]



2.4.19 Pyranyl-quinazolin-4(3*H*)-ones

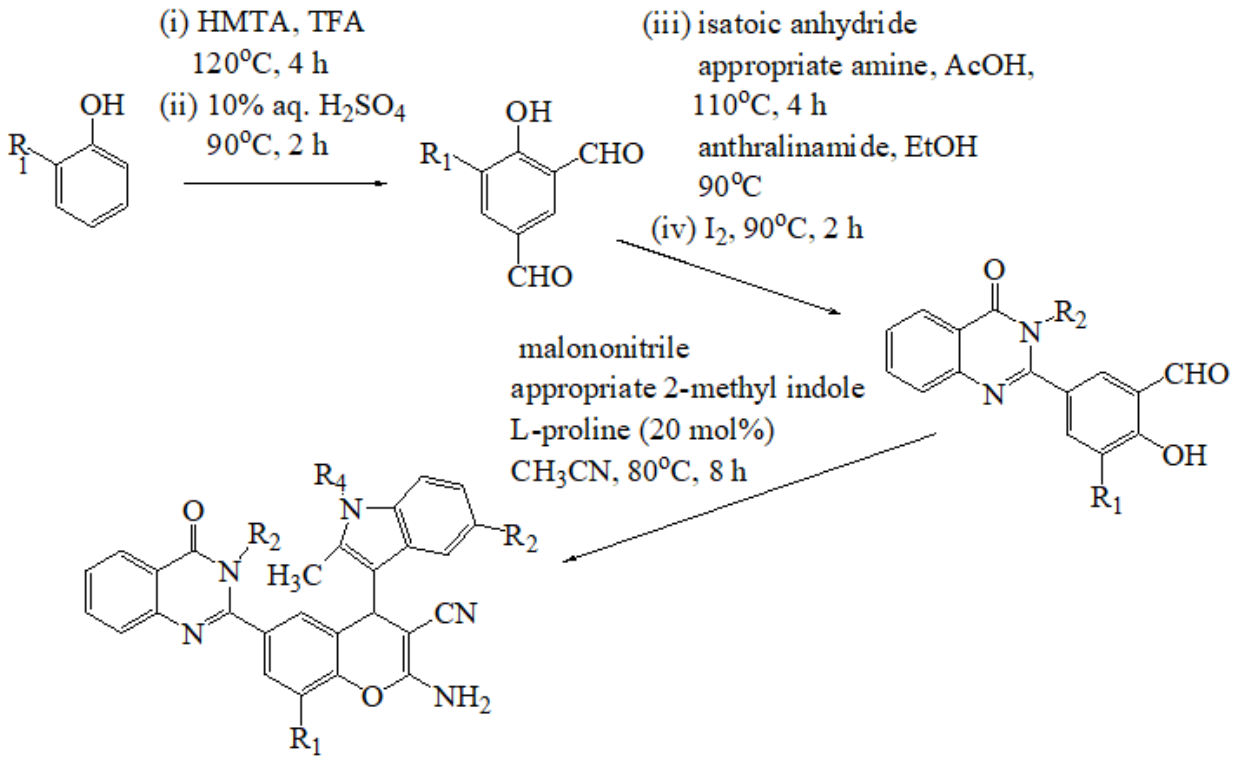
Salem et.al reported the synthesis of 3-(4-methylphenyl)-2-[4-(3-benzoyl-6-(3-chloro-4-tolyl)-5-ene-3,4-dihydro-2-oxo-2*H*-pyran-4-yl)]-quinazolin-4(3*H*)-ones by the reaction of 2-[(3-chloro-4-methylbenzoyl)vinyl-3-(4-methylphenyl)-quinazolin-4(3*H*)-ones with ethyl benzoylacetate in the presence of sodium methoxide.[207]



2.4.20 Indolylchromeneylquinazolin-4(3*H*)-ones

A solution of 2-alkyl phenol and hexamethylenetetramine in trifluoroacetic acid was heated at 120°C for 4 h followed by treatment with 10% aqueous H_2SO_4 at 90°C for 2 h to isolate 4-hydroxy-5-alkyl isophthalaldehydes. Reaction of the resultant compounds with isatoic anhydride and appropriate alkylamines in acetic acid at 110°C for 4h followed reaction with molecular iodine at 90° C for 2 h afford 5-(3,4-dihydro-4-oxoquinazolin-2-yl)-2-hydroxybenzaldehydes. These quinazolinone derivatives used as a key intermediate and performed a multi component reactions with substituted 2-methyl indoles and malononitrile in the presence of L-proline as a catalyst in acetonitrile to give 2-((4-(2-methyl-1*H*-indol-3-yl))2-amino-3-cyano-4*H*-chromene-6-yl)-quinazolin-4(3*H*)-ones. These compounds promoting osteogenesis through BMP2 upregulation.[46]

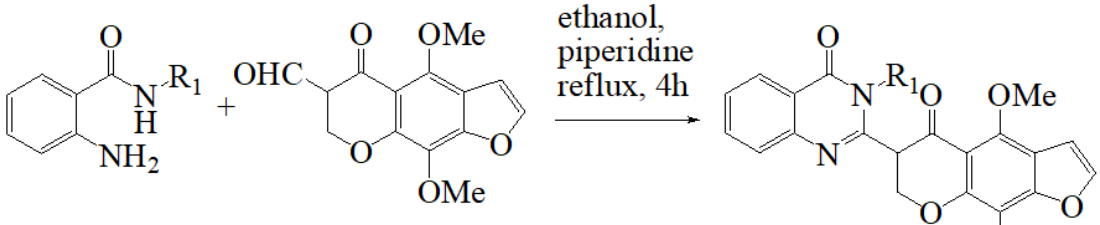
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	R_2	R_3	R_4	yield(%)	R_1	R_2	R_3	R_4	yield(%)
t-Bu	CH_3	H	H	79	t-Bu	CH_3	Cl	H	72
t-Bu	C_2H_5	H	H	76	t-Bu	H	OCH_3	H	72
t-Bu	H	H	H	69	t-Bu	CH_3	OCH_3	H	75
t-Bu	C_2H_5	OCH_3	H	68	t-Bu	H	Cl	H	67
i-Pr	CH_3	H	H	72	i-Pr	CH_3	Cl	H	74
i-Pr	CH_3	OCH_3	H	71	i-Pr	C_2H_5	H	H	68
n-Pr	CH_3	H	H	67	n-Pr	CH_3	Cl	H	73
n-Pr	CH_3	OCH_3	H	71	n-Pr	C_2H_5	H	H	68
Et	CH_3	H	H	70	Et	CH_3	Cl	H	77
Et	CH_3	OCH_3	H	73	Et	C_2H_5	H	H	75
Et	H	H	H	64	CH_3	CH_3	H	H	76
CH_3	CH_3	Cl	H	72	CH_3	CH_3	OCH_3	H	68
CH_3	C_2H_5	H	H	72	CH_3	C_2H_5	H	CH_3	78
CH_3	C_2H_5	H	C_2H_5	76					

2.4.21 Furochrominylquinazolin-4(3*H*)-ones

A mixture of equimolar amounts of 2-amino-*N*-substituted benzamide and 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-4-aldehyde in ethanol were refluxed in the presence of piperidine as catalytic amount to isolate 2-(6,7-dihydro-4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)-quinazolin-4(3*H*)-one. These compounds have showed high activity against Gram positive, Gram negative and fungi as well.[43]

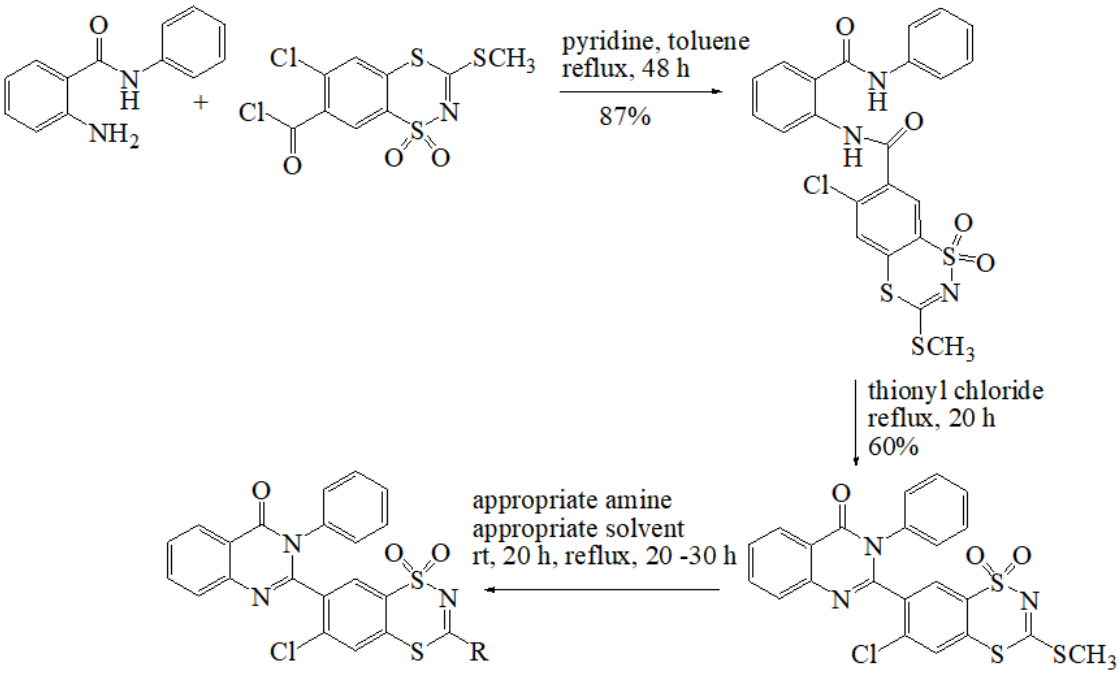


R_1=C_6H_5, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$

DOI: https://doi.org/10.5281/zenodo.13644773

2.4.22 Benzodithiazinylquinazolin-4(3*H*)-ones

Pomarnacka et.al prepared potent antiproliferative and anti-cancer agents- 2-[6-chloro-3-(substituted amino)-1,1-dioxo-1,4,2-benzodithiazin-7-yl]-3-phenylquinazolin-4(3*H*)-ones. 2-Aminobenzanilide and 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazin-7-carbonyl chloride were refluxed in anhy. toluene containing pyridine to isolate *N*-[2-(phenylcarbamoyl)-phenyl]-6-chloro-1,1-dioxo-3-methylthio-1,4,2-benzo- dithiazin-7-carboxamide and then treated with thionyl chloride to isolate 2-(6-chloro-1,1-dioxo-3-methylthio-1,4,2-benzodithiazin-7-yl)-3-phenylquina zolin-4(3*H*)-one. The resultant compound was treated with the appropriate amine in the appropriate solvent to isolate title compounds. The bioassay indicated that the few derivatives possess cancer-cell growth-inhibitory properties.[47]



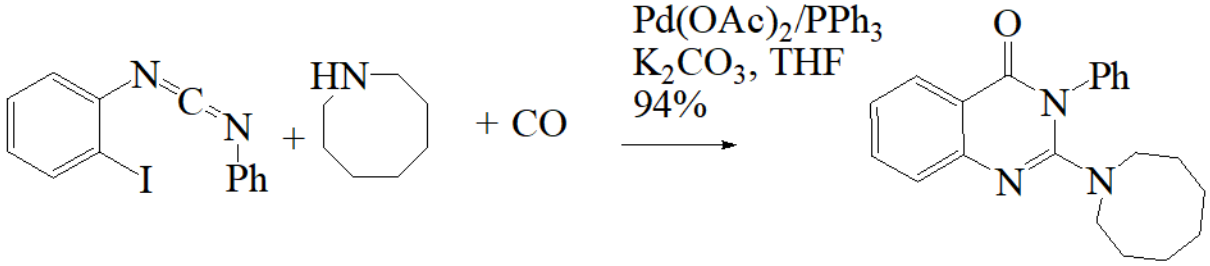
Appropriate amine (RH)	Appropriate solvent	Yield (%)	Appropriate amine (RH)	Appropriate Solvent	Yield (%)
piperidine	benzene	58	propargylamine	Benzene	63
morpholine	benzene	55	benzylamine	Methanol	67
pyrrolidine	benzene	48	phenethylamine	Methanol	63
1-phenyl piperazine	benzene	40	tolylamine	Benzene	27
2-aminopropane	methanol	59	3-(aminomethyl) pyridine	Methanol	37
3-amino-1-propanol	methanol	57	2-(2-aminoethyl) pyridine	methanol,	52
allylamine	benzene	68			

DOI: https://doi.org/10.5281/zenodo.13644773

2.5 Seven Membered ring

2.5.1 Azocanylquinazolin-4(3*H*)-one

Synthesis of 2-(azocan-1-yl)-3-phenylquinazolin-4(3*H*)-one by palladium-catalyzed intermolecular addition and intramolecular cyclocarbonylation cascade reaction of *N*-(2-iodophenyl)-*N*′-phenyldicarbodiimide with azocane was reported.[140]

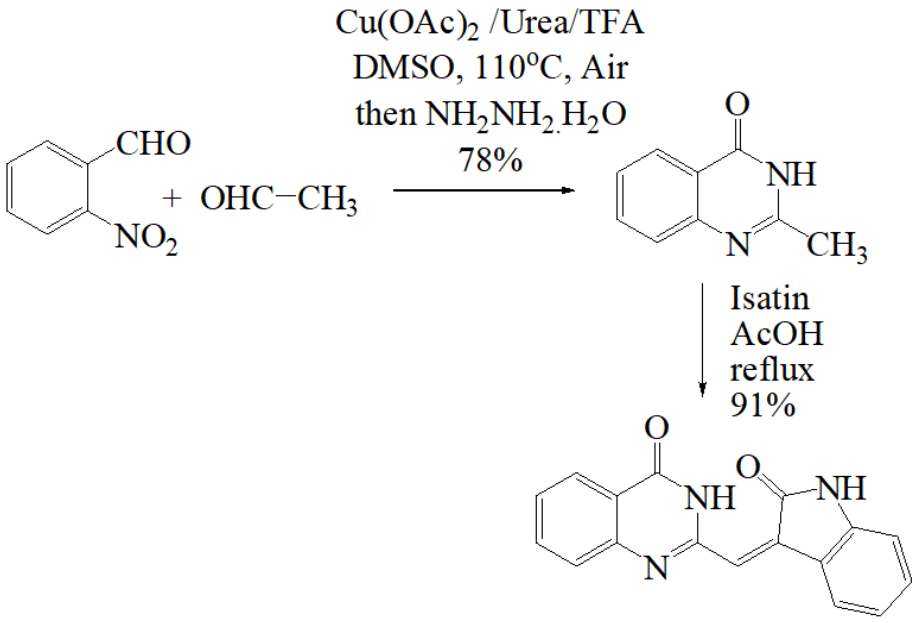


3. Heterylalkenyl / Heterylalkyl group

3.1 Heterylidenemethyl

3.1.1 Indolinylidenemethylquinazolin-4(3*H*)-one

2-Nitrobenzaldehyde was treated with urea, Cu(OAc)$_2$ and TFA in a DMSO solvent at 110°C, then hydrazine hydrate and acetaldehyde were added sequentially at the same temperature and stirred at room temperature for 12−16 h to isolate 2-methylquinazolin-4(3*H*)-one. Then the resultant 2-methylquinazolin-4(3*H*)-one was reacted with isatin in AcOH at reflux for 4 h to afford 2-((*Z*)-(2-oxoindolin-3-ylidene)methyl)quinazolin-4(3*H*)-one (Schizocommunin) in good yield.[142]



3.1.2 Triazolylmethylindolinylidenemethylquinazolin-4(3*H*)-one

An efficient and highly diastereoselective synthesis of schizocommunin analogues has been achieved through an iron-catalyzed C(sp3)-H/C(sp3)-H cross-dehydrogenative coupling reaction between 2-methyl quinazolinones and indolin-2-ones. This method requires air (molecular oxygen) as an oxidant instead of chemical equivalent oxidising agents and prefunctionalized

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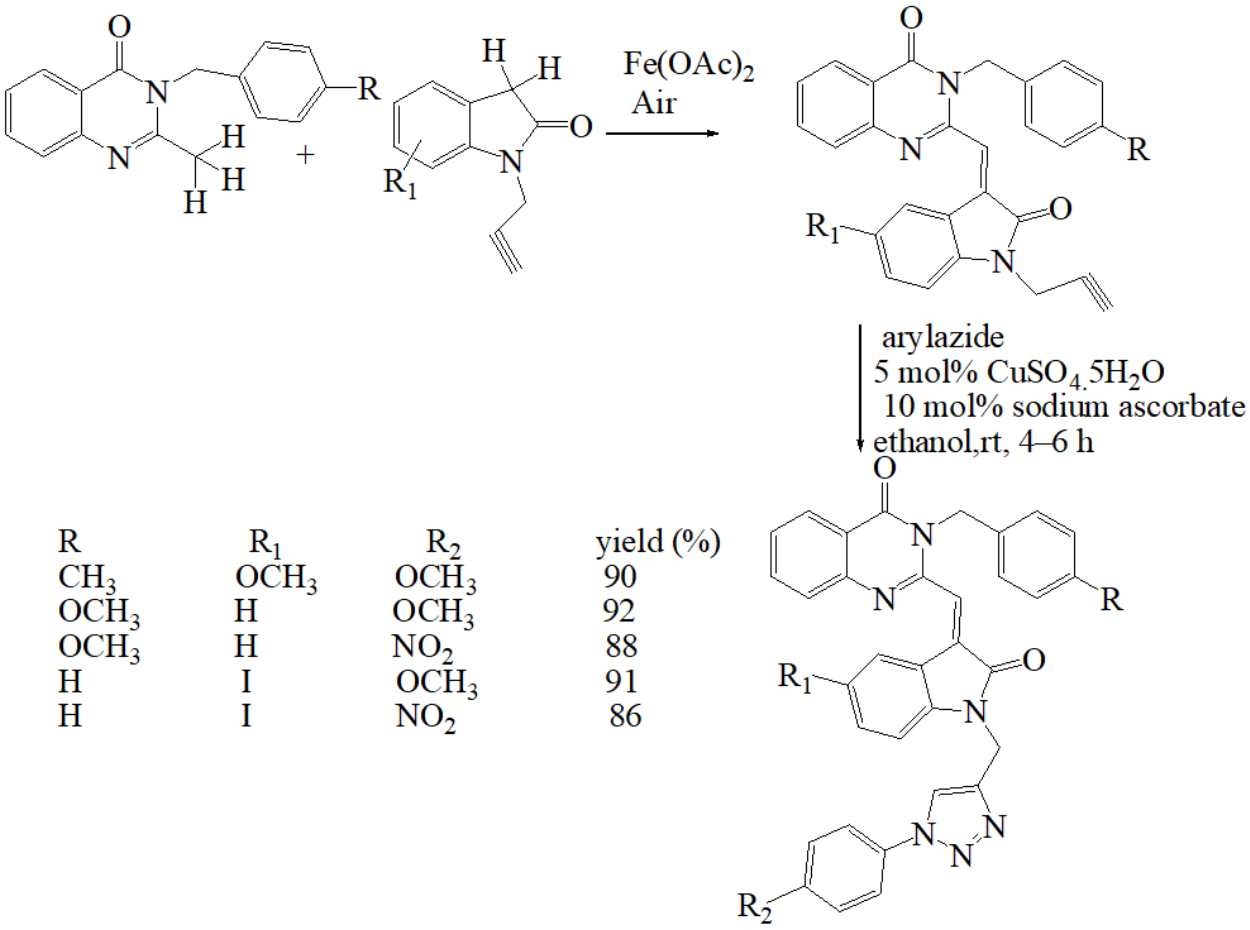
coupling partners like arylazides. The developed schizocommunin analogues were reacted to obtained in good to excellent yields and various kinds of functional groups were tolerated. It is worthy to note that schizocommunin, a bioactive natural product displaying broad spectrum of biological properties in which anticancer property is one of them. 2-((*Z*)-(1-((1-(4-Nitrophenyl)1*H*-1,2,3-triazol-4-yl)methyl)-5-methoxy-2-oxoindolin-3-ylidene)methyl)-3-((4 methyl phenyl)methyl)-quinazolin-4(3*H*)-one one is potent among them.[236]

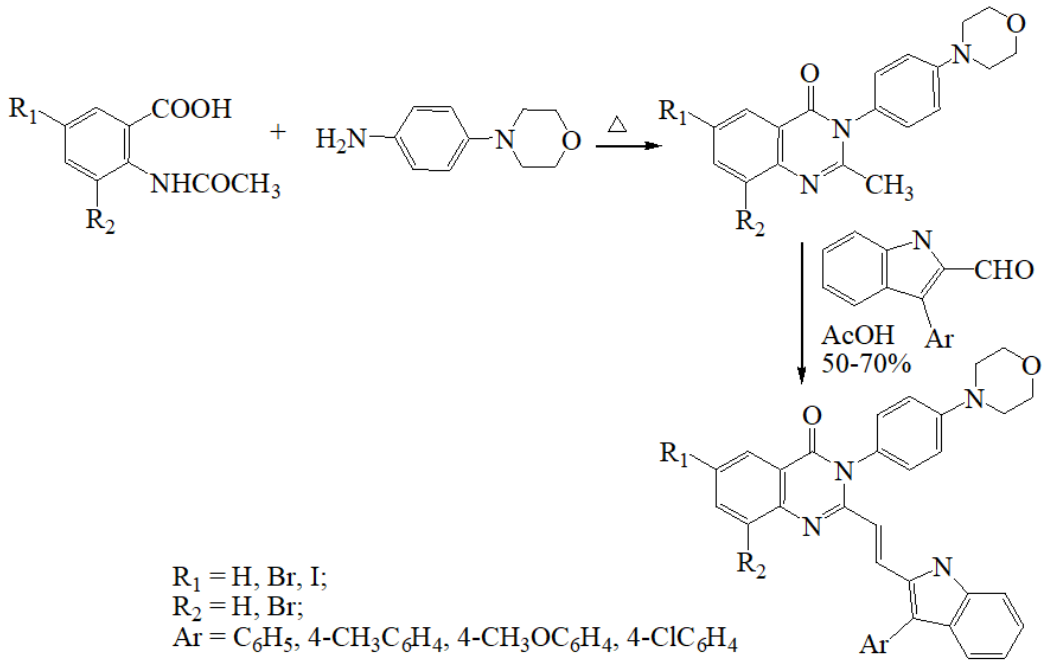


R	R_1	R_2	yield (%)
CH_3	OCH_3	OCH_3	90
OCH_3	H	OCH_3	92
OCH_3	H	NO_2	88
H	I	OCH_3	91
H	I	NO_2	86

3.1.3 Indolylethylenyl-quinazolin-4(3*H*)-ones

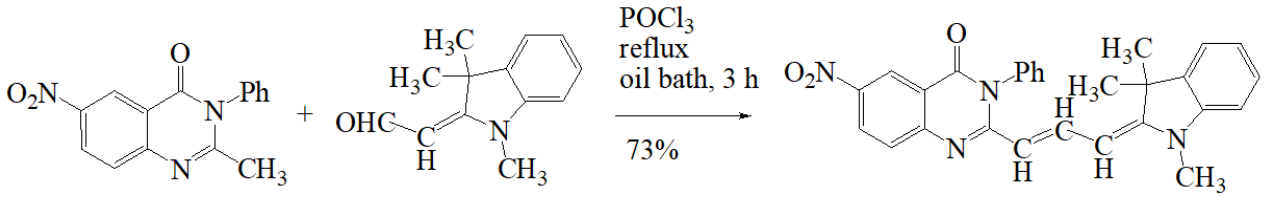
2-[2-(2-Arylindole-3-yl)ethylene]-3-[4-(4-morpholino)phenyl]-6,8-disubstituted-quinazolin-4(3*H*)-ones are useful as CNS active, psychotropic and anti-inflammatory agents. These heteroalkenyl quinazolinones were synthesized by Knoevenagel condensation of 2-methyl-3-(4-morpholinophenyl)-quinazolin-4(3*H*)-ones and 2-arylindol-3-carboxaldehyde in the presence of acetic acid. The key compound 2-methyl-4(3*H*)-quinazolinone derivatives were prepared by fusion of *N*-acetylanthranilics acid with 4-morpholinoaniline.[237, 238]

DOI: https://doi.org/10.5281/zenodo.13644773



3.1.4 Indolinylidenepropenylquinazolin-4(3*H*)-one

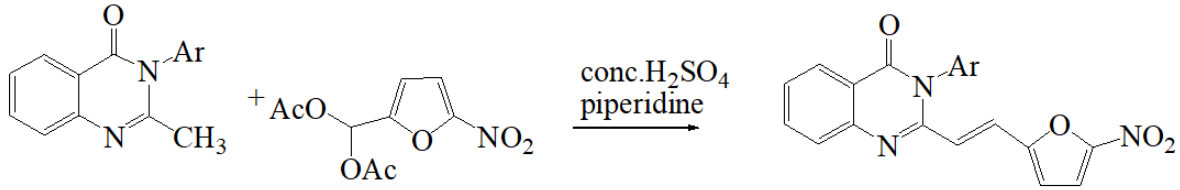
Bhatti and Seshadri were prepared styryl dyes, 2-(3-(indolin-2-ylidene)prop-1-enyl)- quinazolin-4(3*H*)-one by reacting 2-methyl-6-nitro-3-phenylquinazolin-4(3*H*)-one and 2-(1,3,3-tri methylindolin-2-ylidene)acetaldehyde in presence of phosphorus oxychloride.[55]



3.2 Heterylalkenyl

3.2.1 Furylvinyl-quinazolin-4(3*H*)-ones

2-Methyl-3-arylquinazolin-4(3*H*)-one was condensed with nitrofurfural diacetate in the presence of piperidine and drops of concentrated sulphuric acid to afford 2-(2-(furan-2-yl)vinyl)-quinazolin-4(3*H*)-ones and have shown potent antifungal activity.[48]

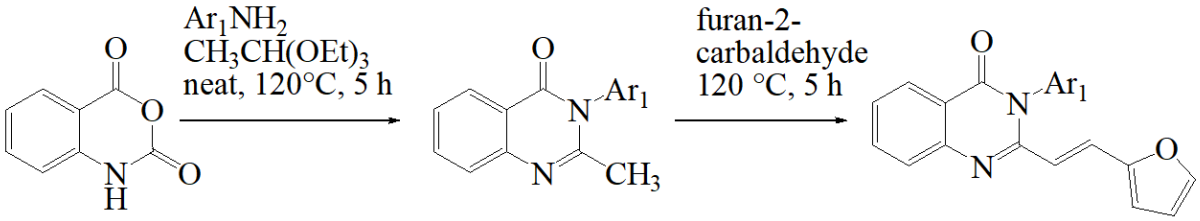


Ar	Ph	4-BrC$_6$H$_4$	4-MeC$_6$H$_4$	3-ClC$_6$H$_4$	3-Cl-4-FC$_6$H$_3$
Yield(%)	80	81	78	57	81

Ar	2-MeOC$_6$H$_4$	3-MeC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	2,5-Cl$_2$C$_6$H$_3$
Yield(%)	51	68	50	53

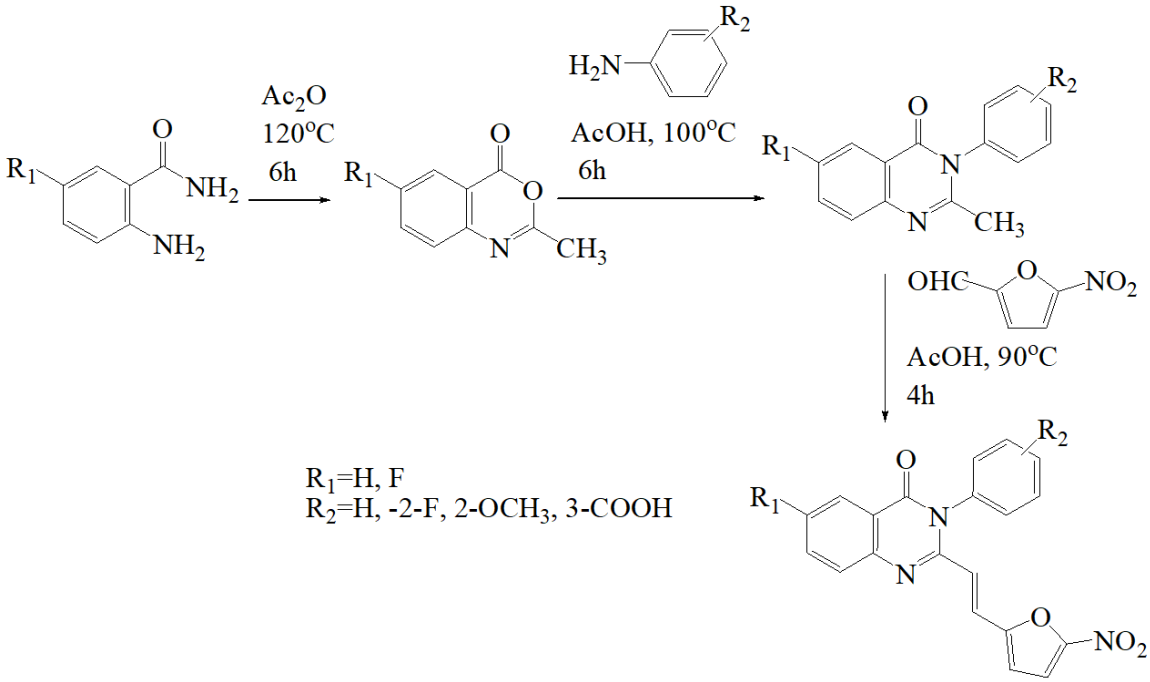
Anti-influenza agents, 2-(-2-(furan-2-yl)vinyl)quinazolin-4(3*H*)-ones, were synthesized by heating the mixture of isatoic anhydride, aryl amine/NH_4OAc and triethyl orthoacetate under neat condition at 120 °C followed by addition of aldehydes.[49]

DOI: https://doi.org/10.5281/zenodo.13644773

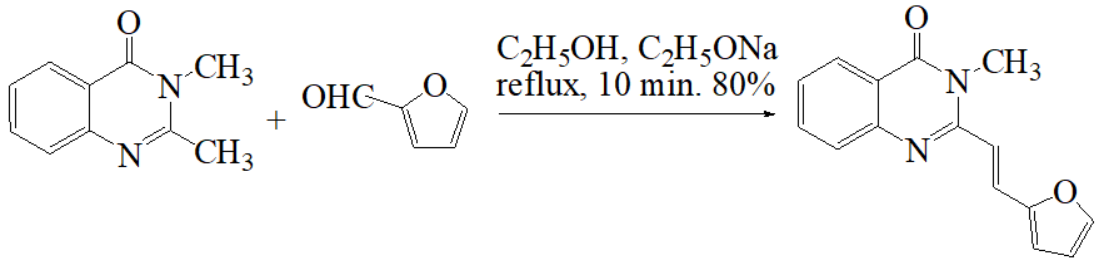


Ar_1	Yield(%)	Ar_1	Yield(%)
4-MeS-C_6H_4	75	4-MeO-C_6H_4	71
2,3,4-Tri-OMe-C_6H_4	74	Ph	66

The compounds, 2-(2-(furan-2-yl)vinyl)-3-phenylquinazolin-4(3*H*)-ones, with induce myeloid differentiation were synthesized by the cyclisation of the anthranilic acid with acetic anhydride, treatment with respective aniline under reflux followed by heating with particular aldehydes in acetic acid. The 6-fluoro-3-(2-methoxyphenyl)-2-(2-(5-nitrofuran-2-yl)vinyl)quinazolin-4(3*H*)-one was found to be the potent derivative for inducing myeloid differentiation in HL-60 cells.[50]

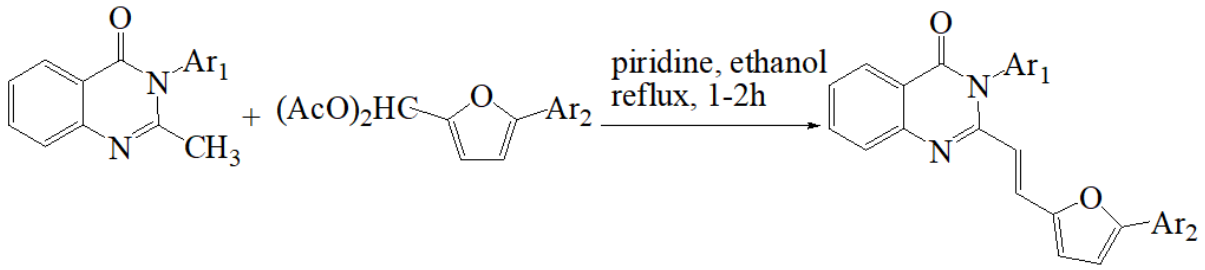


2-(2-Furylvinyl)-3-alkyl-quinazolin-4(3*H*)-ones were obtained in 80-90% yields by Knoevenagel condensation of 2-methyl-3-alkyl-quinazolin-4(3*H*)-ones with furfural in absolute ethanol containing sodium ethoxide.[239, 240]



DOI: https://doi.org/10.5281/zenodo.13644773

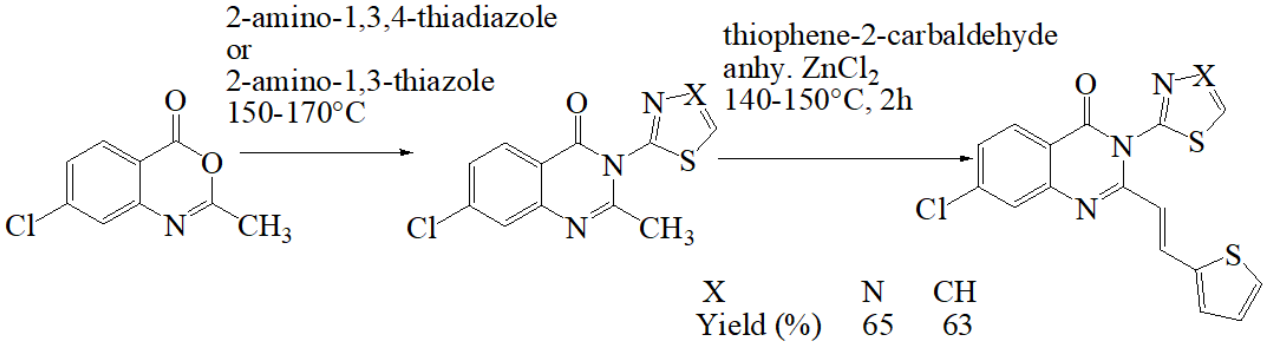
Holla et.al reported the synthesis and antibacterial activity of 3-aryl-2-{2-[2-(5-nitrofuryl)]vinyl}-quinazolin-4(3*H*)-ones. Condensation of 3-aryl-2-methyl-quinazolin-4(3*H*)-ones with 5-substituted furaldehyde diacetate in absolute ethanol followed by refluxing with piperidine for 1-2 h provided 2-heteryl-quinazolin-4(3*H*)-ones. They also reported the preparation of 3-aryl-2-{2-[2-(5-arylfuryl)]vinyl}-quinazolin-4(3*H*)-ones following the same procedure. [51, 52]



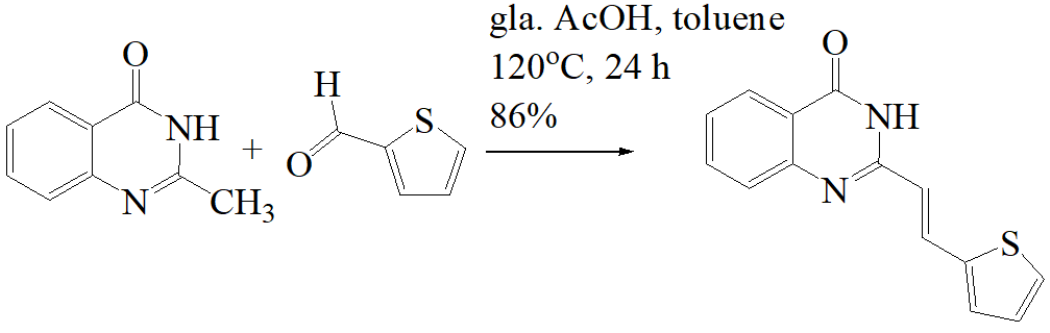
Ar_1 = 2-ClC_6H_4, 2-$CH_3C_6H_4$, , 4-$NO_2C_6H_4$, 4-ClC_6H_4; Ar_2 =$_4$-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$

3.2.2 Thiophenylvinylquinazolin-4(3*H*)-one

An intimate mixture of the 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one and 2-amino-1,3,4-thiadiazole or 2-amino-1,3-thiazole was heated at 150-170°C followed by condensation of the resultant 7-chloro-2-methyl-3-(1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones with thiophene-2-carbaldehyde in presence of anhyd. zinc chloride to afford 2-(2-thienylvinyl)-7-chloro-3-(1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones. These compounds are diuretic agents.[53]



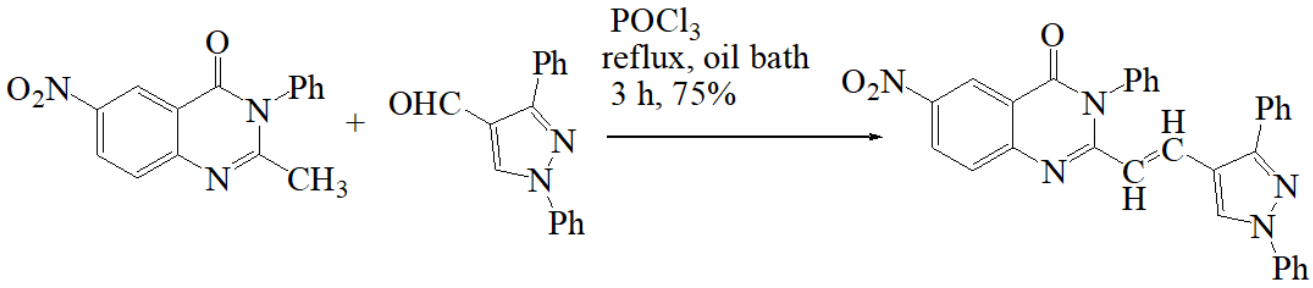
Knoevenagel type condensation of 2-methylquinazolin-4(3*H*)-one with thiophene-2-carbaldehyde in toluene containing glacial acetic acid at 120°C for 24h to isolate 2-((*E*)-2-(thiophen-2-yl)vinyl)quinazolin-4(3*H*)-one and is potential therapeutic hit for oral cancer. [54]



DOI: https://doi.org/10.5281/zenodo.13644773

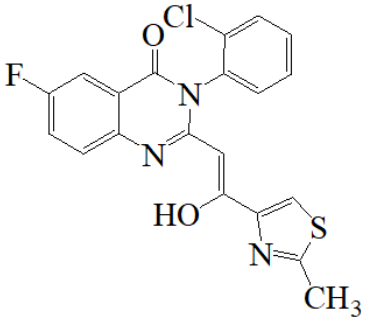
3.2.3 Pyrazolylvinylquinazolin-4(3*H*)-one

Bhatti and Seshadri were prepared styryl dyes, 6-nitro-3-phenyl-2-((E)-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)vinyl)-quinazolin-4(3*H*)-one, by reacting 2-methyl-6-nitro-3- phenylquinazolin-4(3*H*)-one and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde in presence of phosphorus oxychloride.[55]

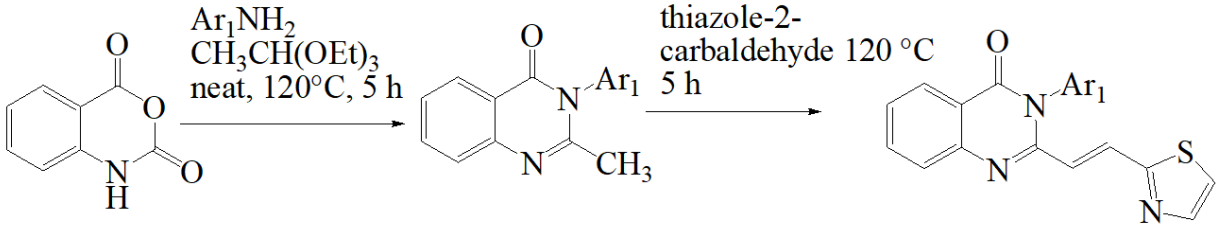


3.2.4 Thiazolylvinylquinazolin-4(3H)-ones

3-(2-Chlorophenyl)-6-fluoro-2-(2-hydroxy-2-(2-methylthiazol-4-yl)vinyl)-quinazolin-4(3*H*)-ones is a neuroprotective agent and a potent AMPA receptor antagonist. The details of its synthesis are patented and are not available.[56, 57]



The mixture of isatoic anhydride, amine/NH_4OAc and triethyl orthoacetate was heated under neat condition at 120 °C followed by addition of aldehyde and continued stirring to isolate the 2-(2-(thiazol-2-yl)vinyl)quinazolin-4(3*H*)-one. These quinazolinones area novel class of potent anti-tubercular agents.[58]

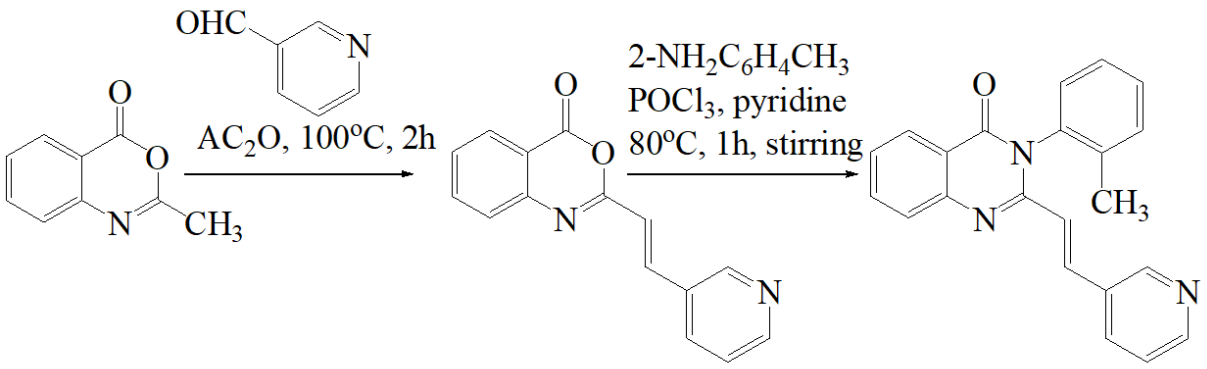


Ar_1	Yield(%)	Ar_1	Yield(%)
4-MeS-C_6H_4	73	2,3,4-Tri-OMe-C_6H_4	75
4-MeO-C_6H_4	74	Ph	70

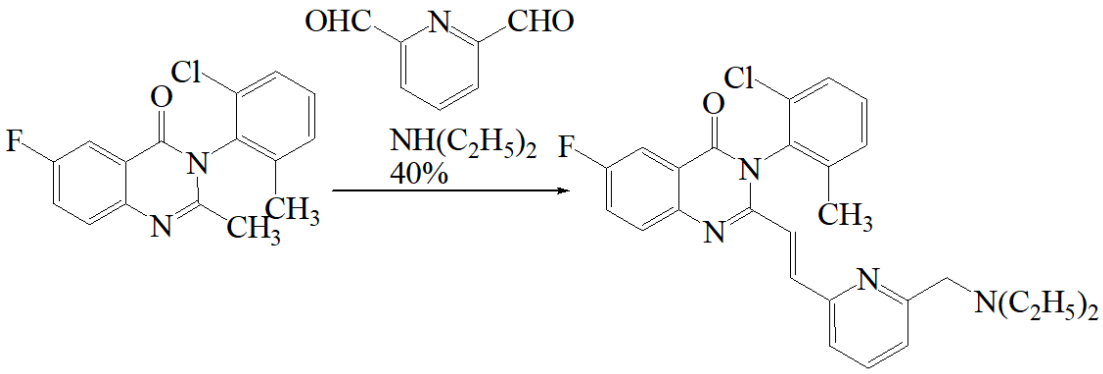
3.2.5 Pyridinylvinylquinazolin-4(3*H*)-one

2-[2-(3-Pyridylvinyl)-3-(2-tolyl)-quinazolin-4(3*H*)-ones showed plasmotic, anticonvulsant, hypnotic, tranquilising and muscle relaxant activity. They were prepared in two-steps- (i) condensation of 2-methyl-3,1-benzoxazin-4-one with 3-pyridine carboxaldehyde, to isolate 2-[2-(3-pyridylvinyl)]-3,1-benzoxazin-4-one followed by with o-toluidine.[59]

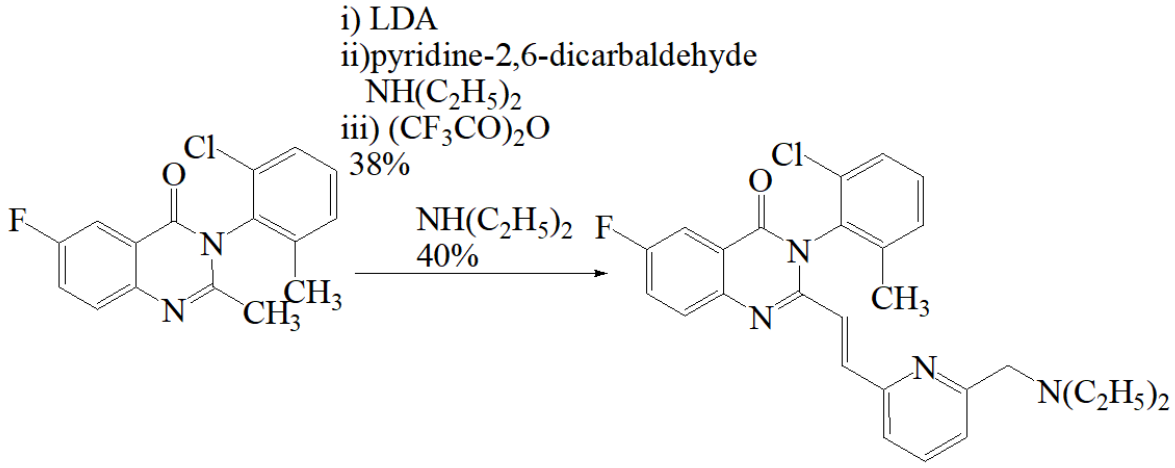
DOI: https://doi.org/10.5281/zenodo.13644773



Welch and Devries have prepared the atropisomers, (*S*)-isomer of 3-(2-chlorophenyl)-6-fluoro-2-[2-(6-diethylaminomethylpyridyl)vinyl]quinazolin-4(3*H*)-one which is useful as AMPA antogonists, particularly in the treatment of neurodegenerative and CNS-trauma related conditions. The isomer was prepared by reacting 3-(2-chlorophenyl)-6-fluoro-2-methyl-quinazolin-4(3*H*)-ones and 2,6-pyridinedicarboxaldehyde in diethylamine.[60, 241, 242, 243]



Chenard et.al also prepared the same compound by reacting 3-(2-chlorophenyl)-6-fluoro-2-methyl-quinazolin-4(3*H*)-ones and 2,6-pyridinedicarboxaldehyde in the presence of LDA/ diethylamine followed by $(CF_3CO)_2O$ mediated dehydration.[244]



Dai and Virgil have synthesized a quinazolinone phosphine bidentate ligand starting from monodentate ligand. The monodentate ligand was reacted with 1.2 equivalents of n- BuLi in

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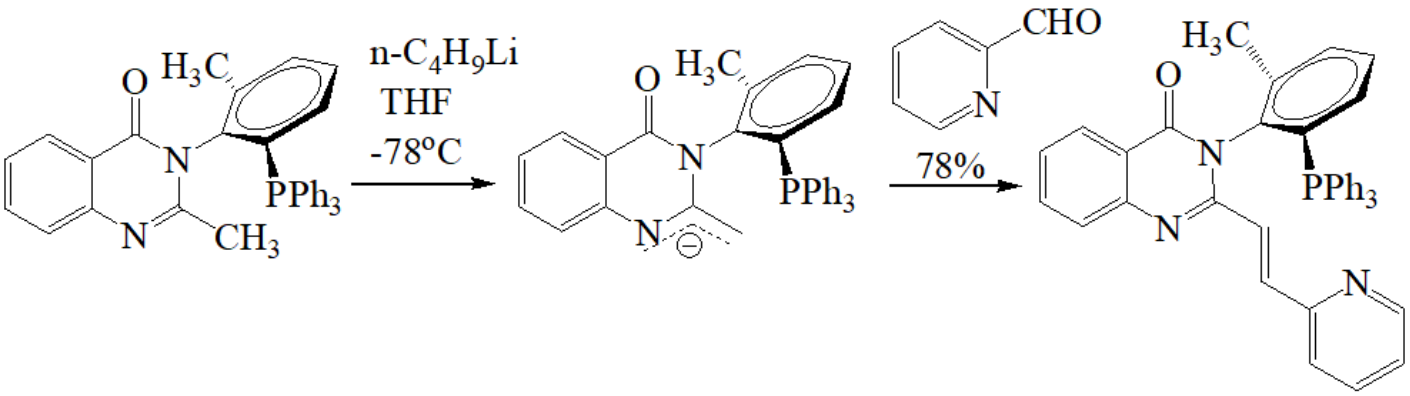
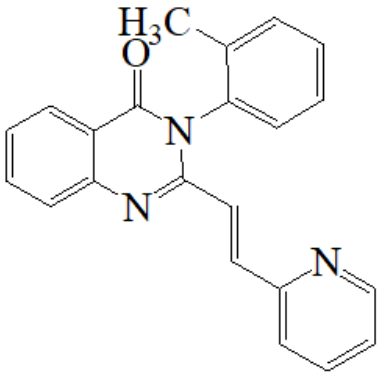
THF at –78°C to generate the anion, which was submitted to Claisen-Schmidt reaction with 2-pyridyl aldehyde to yield the bidentate ligand in 78% yield.[245]

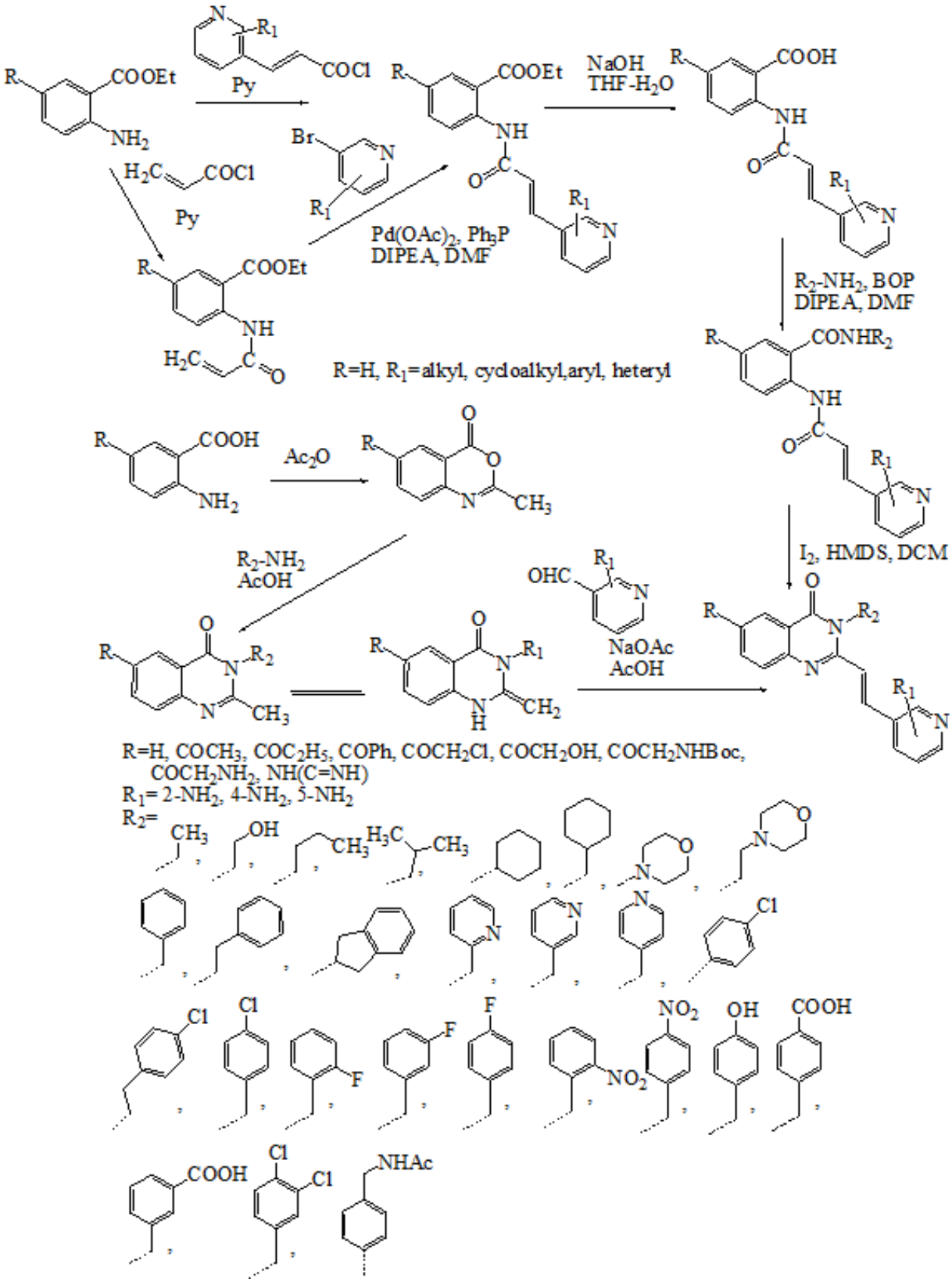


2-{2-[(2-Pyridyl)vinyl]-3-o-tolyl}-4(3*H*)-quinazolinone showed anticonvulsant, hypnotic and muscle relaxant activity, and was sold as a drug under the trade name piriqualone.[61]



Two general strategies (I and II) were implemented for the synthesis of quinazolinone derivatives as inhibitors of homologous recombinase RAD51. In statergie-1, the common intermediate 2-(3-(pyridin-3-yl)acrylamido)benzoic acid derivatives were assembled by coupling ethyl anthranilate derivatives with the corresponding 3-(pyridin-3-yl)acryloyl chloride to ethyl 2-(3-(pyridin-3-yl)acrylamido)benzoate derivatives, followed by ester hydrolysis. Depending on the availability of the building blocks, the ethyl 2-(3-(pyridin-3-yl)acrylamido)benzoate derivatives were also constructed by Heck coupling of the corresponding 3-bromopyridine with ethyl 2-(acrylamido)benzoate derivatives. After introducing amine through amide coupling to 2-(3-(pyridin-3-yl)acrylamido)-*N*-substitutedbenzamides, the intermediates were cyclized under mild dehydration conditions with iodine and hexamethyldisilazine to give the desired 3-substituted-2-((*E*)-2-(pyridin-3-yl)vinyl)quinazolin-4(3*H*)-ones. In stategy-II, a one-pot synthesis from anthranilic acids to 2-methylquinazolinones, through the mixed anhydride 2-methyloxazinones followed by condenation with nicotinaldehyde.[62]

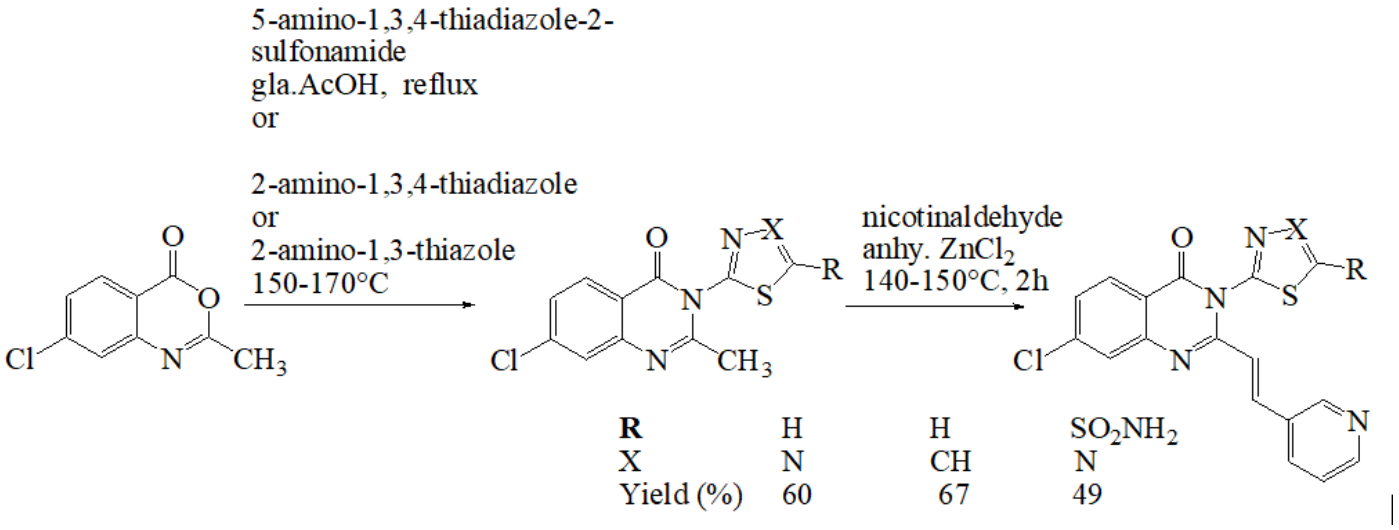
DOI: https://doi.org/10.5281/zenodo.13644773



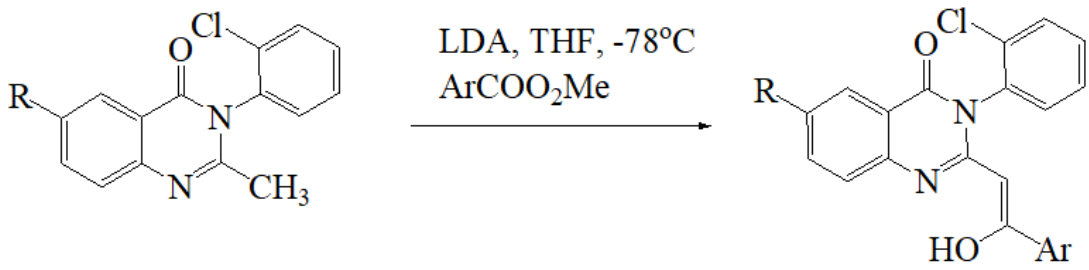
A mixture of 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one and 5-amino-1,3,4-thiadiazole-2-sulfonamide or 2-amino-1,3,4-thiadiazole or 2-amino-1,3-thiazole was heated at 150-170°C followed by condensation of the resultant 7-chloro-2-methyl-3-(2-sulfamoyl-1,3,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones with nicotinaldehyde in presence of anhyd. zinc chloride to afford 2-(2-(pyridine-3-yl)vinyl)-7- chloro-3-(2-sulfamoyl-1,3,4-

DOI: https://doi.org/10.5281/zenodo.13644773

thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl or thiazol-2-yl)-quinazolin-4(3*H*)-ones.[53]



Chenard et.al were used LDA or NaH for the deprotonation of 2-methylquinazolin-4(3*H*)-one and the obtained carbanion was quenched with various aromatic esters to produce quinazolin-4(3*H*)-one derivative and are potent noncompetitive AMPA receptor antagonists.[63]



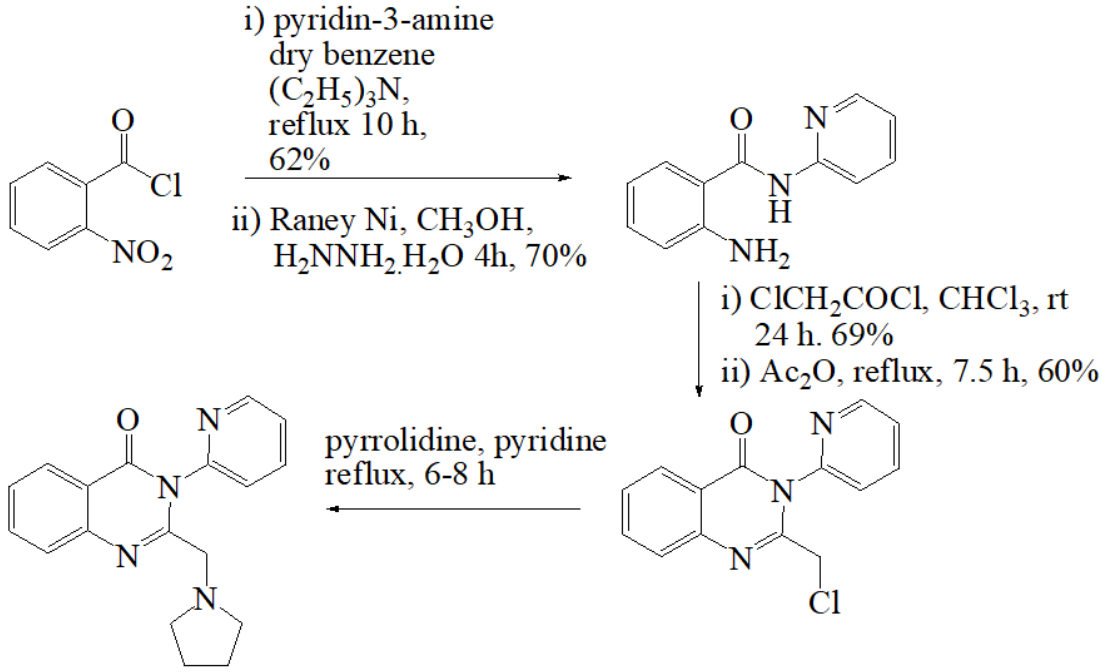
R	H	F	F	F	F
Ar	pyrid-2-yl	pyrid-2-yl	3-cyanopyrid-2-yl	6-methylpyrid-2-yl	3-cyano-6-methylpyrid-2-yl

3.3 Heterylalkyl group

3.3.1 Pyrrolidinylmethylquinazolin-4(3*H*)-ones

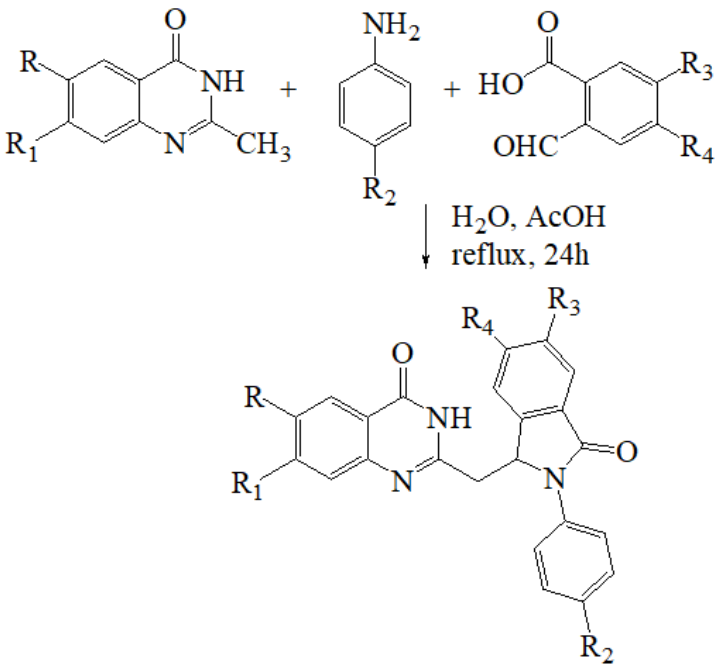
3-(2-Pyridyl)-quinazolin-4(3*H*)-ones linked to pyrrole, piperidine, 4-methylpiperidine, and morpholine at C2 via a methylene group showed significant contraceptive activity. These heterocycles were prepared starting from 2-nitrobenzoyl chloride. For example, reaction of 2-nitrobenzoyl chloride with 2-aminopyridine followed by reduction of the nitro group gave 2-amino-*N*-(2-pyridyl)benzamide. Chloroacetylation of the amine followed by cyclization afforded 2-chloromethyl-3-(2-pyridyl)-quinazolin-4(3*H*)-ones which reacts with a NH bearing heterocycle to yield 2 - heteralkyl quinazolinone. For example, reaction of 2-chloromethyl-3-(2-pyridyl)-quinazolin-4(3*H*)-ones with pyrrolidine yielded pyrrolidinylmethyl-3-(2-pyridyl)-quinazolin-4(3*H*)-ones.[246]

DOI: https://doi.org/10.5281/zenodo.13644773



3.3.2 Isoindolinylmethylquinazolin-4(3*H*)-one

A novel, green and one-pot three-component synthesis of 2-((2-aryl-3-oxoisoindolin-1-yl)methyl)quinazolin-4(3*H*)-one by reacting 2-methylquinazolin-4(3*H*)-ones, aryl amines and 2-formylbenzoic acids through a sequential condensation, sp3 CAH bond functionalization and cyclization reactions in aqueous media in good to excellent yields is reported.[247]



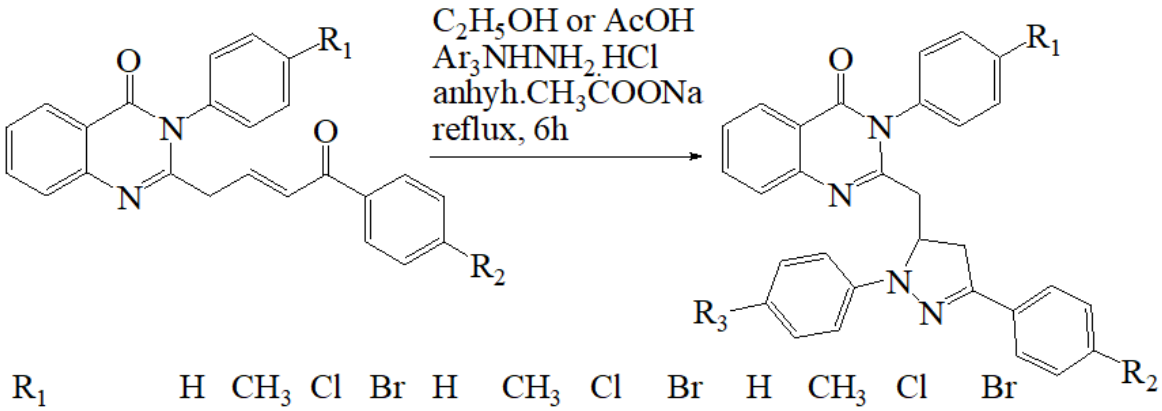
R	R_1	R_2	R_3	R_4	yield(%)
H	H	H	H	H	87
H	H	CH_3	H	H	92
H	H	C_2H_5	H	H	90
H	H	OCH_3	H	H	87
H	H	F	H	H	82
CH_3	CH_3	H	H	H	90

R	R_1	R_2	R_3	R_4	yield(%)
H	Cl	H	H	H	87
H	Cl	CH_3	H	H	84
H	Cl	C_2H_5	H	H	88
H	Cl	OCH_3	H	H	85
H	Cl	F	H	H	80
H	Cl	H	OCH_3	OCH_3	90
H	Cl	CH_3	OCH_3	OCH_3	80

DOI: https://doi.org/10.5281/zenodo.13644773

3.3.3 Pyrazolylmethyl-quinazolin-4(3*H*)-ones

2-(3-Pyrazolyl)methyl-3-aryl-quinazolin-4(3H)-ones are useful as non-steroidal antiinflammatory agents. They were prepared by the condensation of 2-[3-(1-arylacryloyl)] methyl-3-aryl-quinazolin-4(3*H*)-ones with hydrazine hydrate.[64]

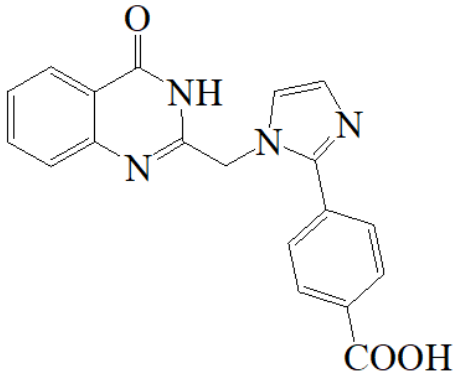


R_1	H	CH_3	Cl	Br	H	CH_3	Cl	Br	H	CH_3	Cl	Br
R_2	H	H	H	H	CH_3	CH_3	CH_3	CH_3	H	H	H	H
R_3	H	H	H	H	H	H	H	H	CH_3	CH_3	CH_3	CH_3
Yield (%)	80	69	78	72	79	68	82	76	72	81	77	67

R_1	H	CH_3	Cl	Br	H	CH_3	Cl	Br	H	CH_3	Cl	Br
R_2	CH_3	CH_3	CH_3	CH_3	H	H	H	H	CH_3	CH_3	CH_3	CH_3
R_3	CH_3	CH_3	CH_3	CH_3	Br	Br	Br	Br	Br	Br	Br	Br
Yield (%)	79	75	68	82	80	72	76	68	69	76	72	78

3.3.4 Imidazolylmethylquinazolin-4(3*H*)-one

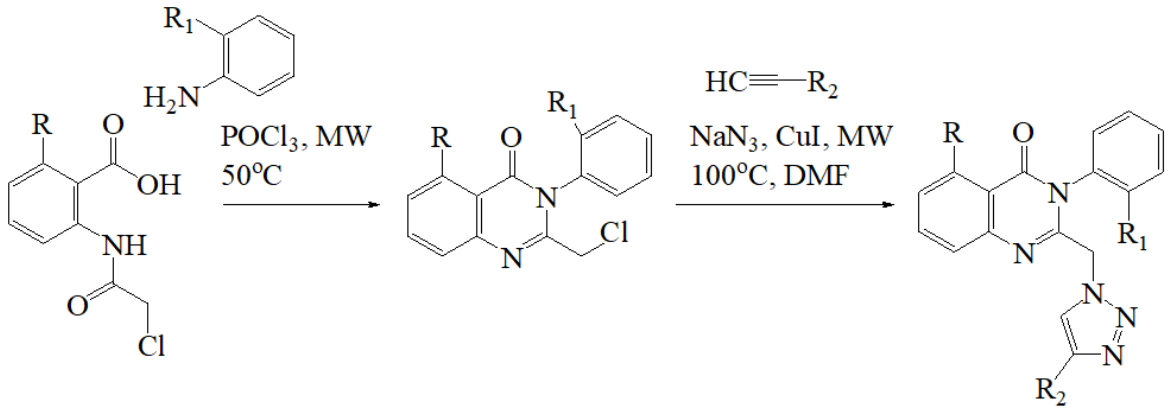
4-(1-((3,4-Dihydro-4-oxoquinazolin-2-yl)methyl)-1*H*-imidazol-2-yl)benzoic acid, consisting of three rings, is a new inhibitor of *E.coli MurA* and discovered by structure-based virtual screening. They are dihydroquinazolinone and imidazole rings and benzoic acid function, which are connected directly or via short linker. This is corresponded to Lipinski rule of five.[65]



3.3.5 Triazolylmethylquinazolin-4(3*H*)-ones

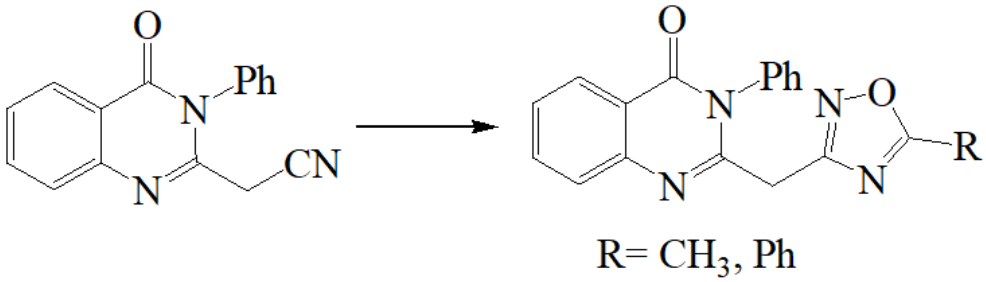
The introduction of a triazole substituent at C-2 position of quinazolinones structure, 5-substituted-2-((aryl-1*H*-1,2,3-triazol-1-yl)methyl)-3-(aryl)quinazolin-4(3*H*)-ones, were achieved from 2-(chloromethyl)-5-substituted-3-(o-tolyl)quinazolin-4(3H)-ones, sodium azide and phenylacetylenes in presence of CuI in DMF solvent.[248]

DOI: https://doi.org/10.5281/zenodo.13644773



R	R_1	R_2	Yield (%)	R	R_1	R_2	Yield (%)
CH_3	CH_3	phenyl	80	H	CH_3	(3-methylphenoxy)methyl	78
CH_3	CH_3	2-fluorophenyl	78	H	CH_3	(4-methoxyphenoxy)methyl	76
CH_3	CH_3	4-methylphenyl	76	H	CH_3	(3,5-bis(trifluoromethyl))phenyl	75
CH_3	CH_3	4-bromophenyl	75	H	CH_3	biphenyl	80
CH_3	CH_3	4-trifluoromethoxyphenyl	73	H	CH_3	2-fluorophenyl	76
CH_3	CH_3	2-trifluoromethylphenyl	77	H	CH_3	(3-fluorophenoxy)methyl	70
CH_3	CH_3	2-methyl-4-methoxyphenyl	75	H	CH_3	2-trifluoromethylphenyl	72
CH_3	CH_3	biphenyl	78	H	CH_3	((4-methoxyphenyl)sulphonylamino)methyl	78
CH_3	CH_3	3-pyridinyl	80	H	CH_3	((2,4-difluorophenyl)sulphonylamino)methyl	72
CH_3	CH_3	(4-chloro-3-methylphenoxy)methyl	77	CH_3	CF_3	2-methyl-4-methoxyphenyl	78
CH_3	CH_3	(phenylsulphonylamino)ethyl	75	CH_3	CF_3	phenyl	80
H	CH_3	4-bromophenyl	78	CH_3	CF_3	3-pyridinyl	71
H	CH_3	phenyl	72	CH_3	CF_3	3,4-dimethylanilinomethyl	73

El-Feky prepared 2-[(5-methyl / phenyl-1,2,4-oxadiazol-3-yl)methyl]-3-phenyl-quinazolin-4(3*H*)-ones from 2-cyanomethyl-3-phenyl-quinazolin-4(3*H*)-ones and aldehydes via the amide oxime derivatives.[249]



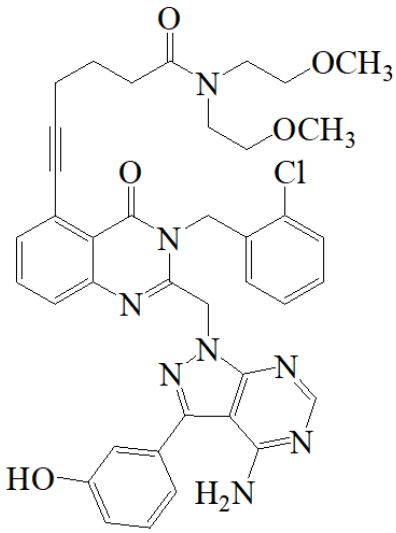
R= CH_3, Ph

3.3.6 Pyrazolopyrimidinylmethylquinazolin-4(3*H*)-one

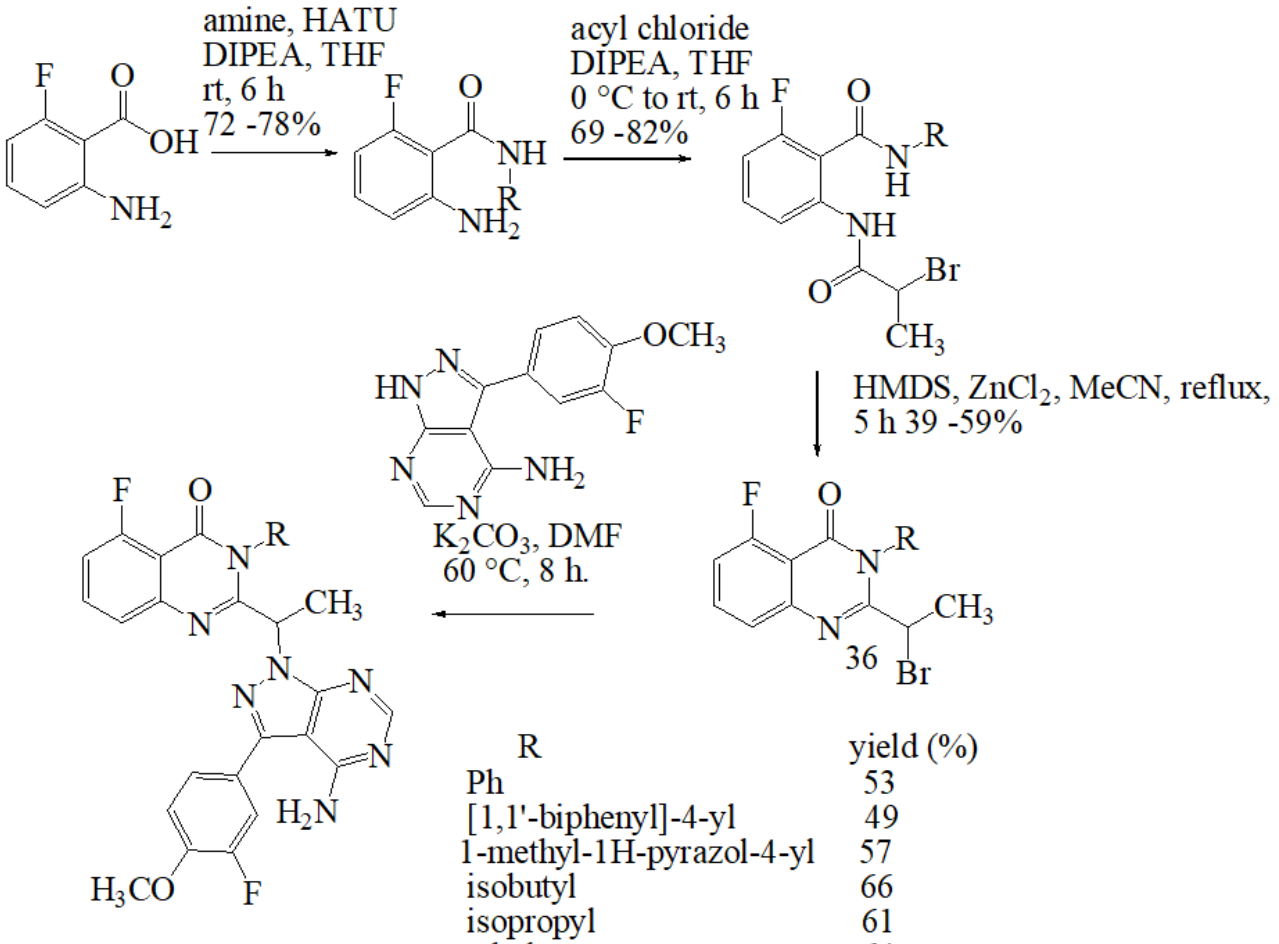
2-(6-(2-((4-Amino-3-(3-hydroxyphenyl)-1*H*-pyrazolo(3,4-*d*)pyrimidin-1-yl)methyl))-3-(2-chlorobenzyl)-5-(*N*,*N*-bis(2-methoxyethyl)-4-yn-hexanamide-5-yl)-quinazolin-4(3*H*)-one(RV-1729) is a clinical stage PI3Kγδ inhibitor that is being investigated for the potential treatment of inflammatory lung diseases.[66]

DOI: https://doi.org/10.5281/zenodo.13644773

Potent and Selective PI3Kδ Inhibitors, 2-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-5-fluoro quinazolin-4(3*H*)-ones, were synthesized from the 2-amino-6-fluorobenzoic acid. The 2-amino-6-fluorobenzoic acid was treated with aniline in anhydrous THF in presence of HATU and DIPEA at room temperature for 6h to yield 2-amino-6-fluorobenzamide derivative. The product was acylated with 2-bromopropanoyl chloride in anhydrous THF containing DIPEA at 0°C for 1h and at room temperature for 6h to afford 2-bromopropanamido)-6-fluoro benzamide followed by cyclisation to produce 2-(1-bromoethyl)-5-fluoroquinazolin-4(3*H*)-one. The heterylation of the resultant product with 3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-amine in anhydrous DMF in presence of K_2CO_3 at 60^{0}C for 8h furnished 2-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-5-fluoroquinazolin-4(3*H*)-ones.[67]



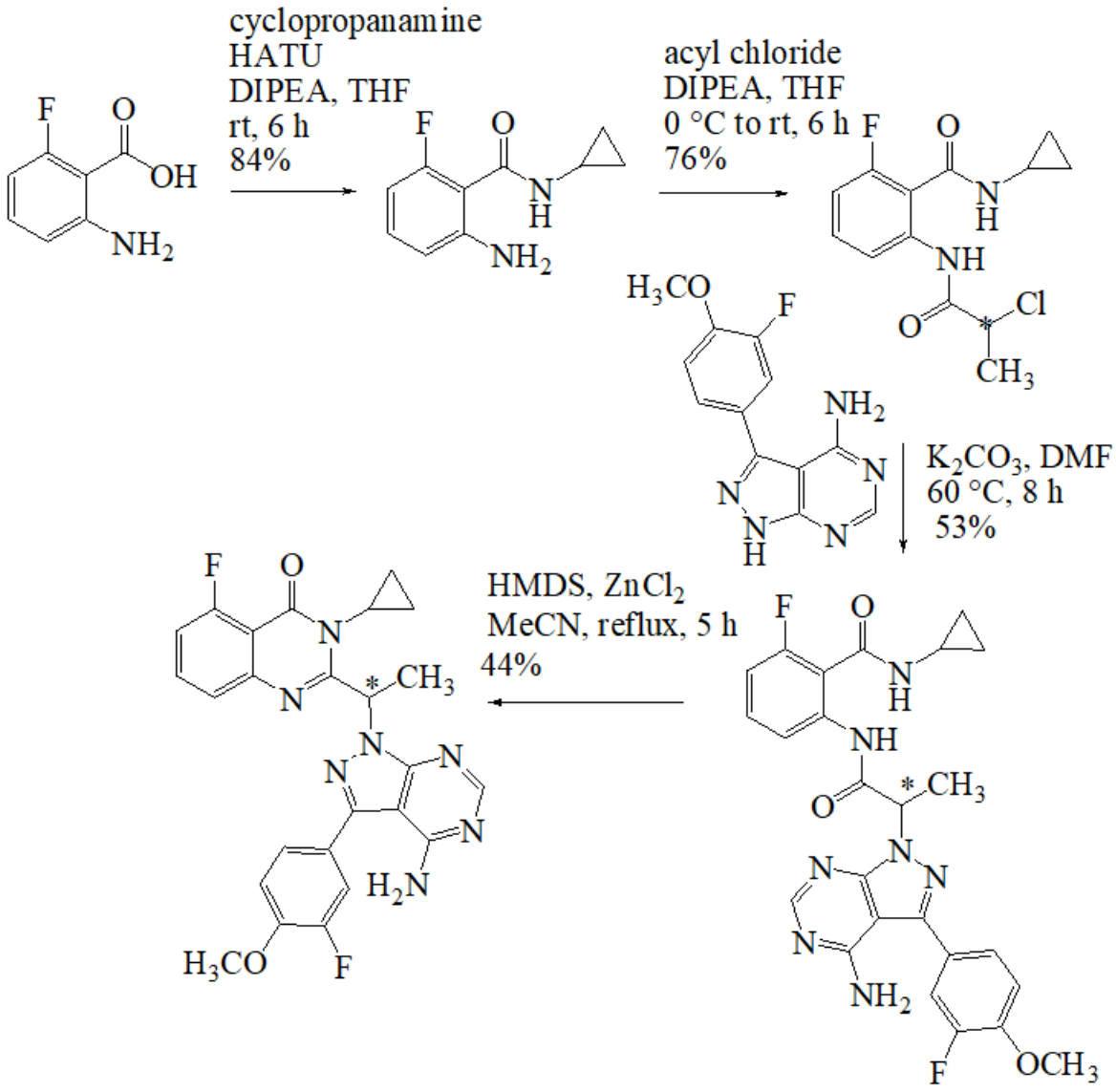
RV-1729



R	yield (%)
Ph	53
[1,1'-biphenyl]-4-yl	49
1-methyl-1H-pyrazol-4-yl	57
isobutyl	66
isopropyl	61
ethyl	64
methyl	60

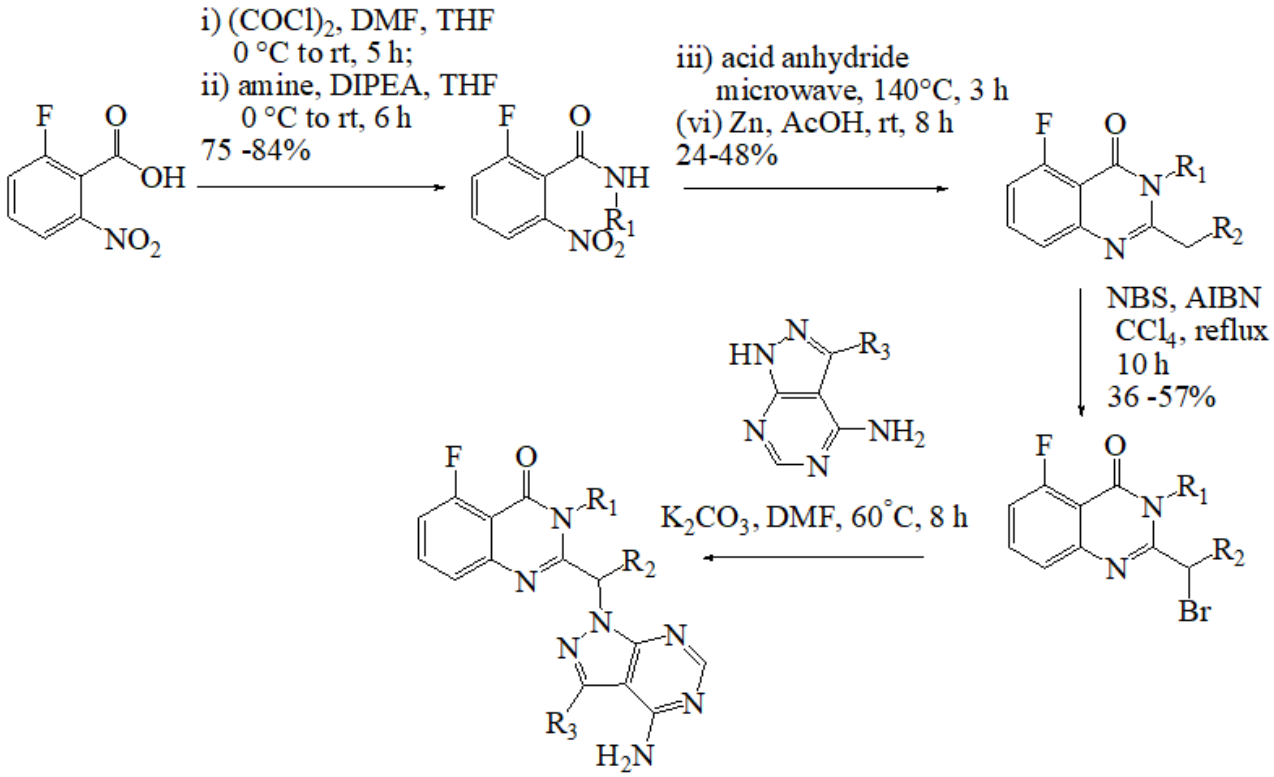
DOI: https://doi.org/10.5281/zenodo.13644773

2-(1-(4-Amino-3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-cyclopropyl-5-fluoroquinazolin-4(3*H*)-one also prepared by the reaction of 2-amino-6-fluorobenzoic acid with cyclopropalamine, acylation with 2-chloropropanoyl chloride, heterylation of the resultant product with 3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine followed by cyclisation.[67]



Alternatively,2-(1-(4-amino-3-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)-3-subs tituted-5-fluoro-quinazolin-4(3*H*)-ones were synthesized by the treatment of 2-fluoro-6-nitrobenzoic acid with oxalyl dichloride and then with amines to 2-fluoro-*N*-substituted-6-nitrobenzamide, reduction and acylative cyclisation with acid anhydride to 2,3-disubstituted quinazoline-4(3*H*)-ones, α-halogenation with NBS in presence of AIBN to 2-(1-bromoethyl)-5-fluoroquinazolin-4(3*H*)-one derivatives, then heterylation with 3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amines. The (S)-2-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazolo-[3,4-*d*]pyrimidin-1-yl)propyl)-3-cyclopropyl-5-fluoroquinazolin-4(3*H*)-one is a novel potent and isoform selective PI3Kδ inhibitor compound (S)-18 through a fragment hybridization strategy.[67]

DOI: https://doi.org/10.5281/zenodo.13644773

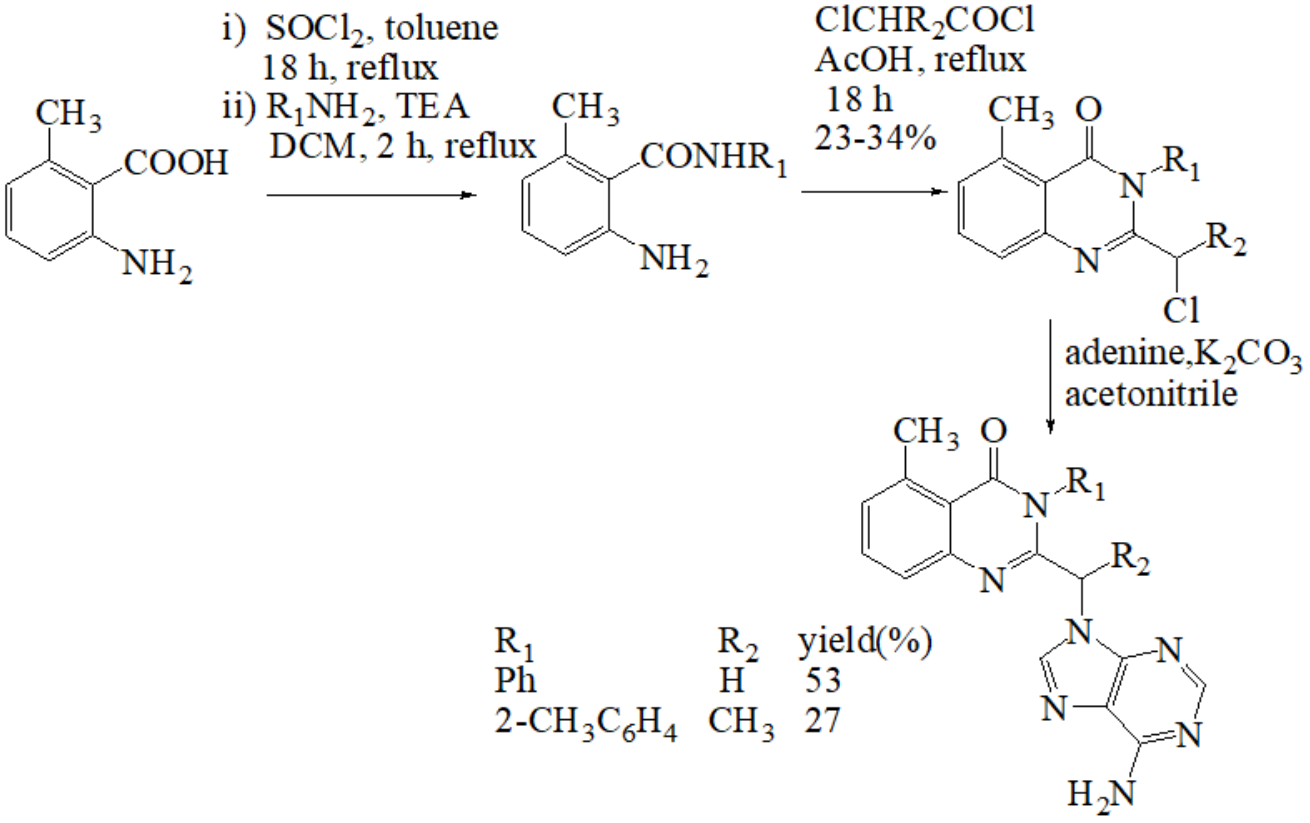


R_1	R_2	R_3	yield (%)	R_1	R_2	R_3	yield (%)
benzyl	CH_3	3-fluoro-4-methoxyphenyl	54	cyclopropyl	C_2H_5	4-methoxy-3-methylphenyl	52
cyclohexyl	CH_3	3-fluoro-4-methoxyphenyl	56	cyclopropyl	C_2H_5	3-fluoro-4-isopropoxyphenyl	48
cyclopentyl	CH_3	3-fluoro-4-methoxyphenyl	55	cyclopropyl	C_2H_5	N-methylbenzamide	64
cyclobutyl	CH_3	3-fluoro-4-methoxyphenyl	54	cyclopropyl	C_2H_5	phenylacetamide	62
cyclopropyl	C_2H_5	3-fluoro-4-methoxyphenyl	65	cyclopropyl	C_2H_5	benzo[d][1,3]dioxaol-5-yl	55
cyclopropyl	C_2H_5	H	58	cyclopropyl	C_2H_5	quinolin-3-yl	46
cyclopropyl	C_2H_5	phenyl	60	cyclopropyl	C_2H_5	1-methyl-1H-pyrazol-4-yl	57
cyclopropyl	C_2H_5	4-methoxyphenyl	63	cyclopropyl	C_2H_5	thiophen-3-yl	65
cyclopropyl	C_2H_5	3,4-dimethoxyphenyl	57				

3.3.7 Purinylmethylquinazolin-4(3*H*)-ones

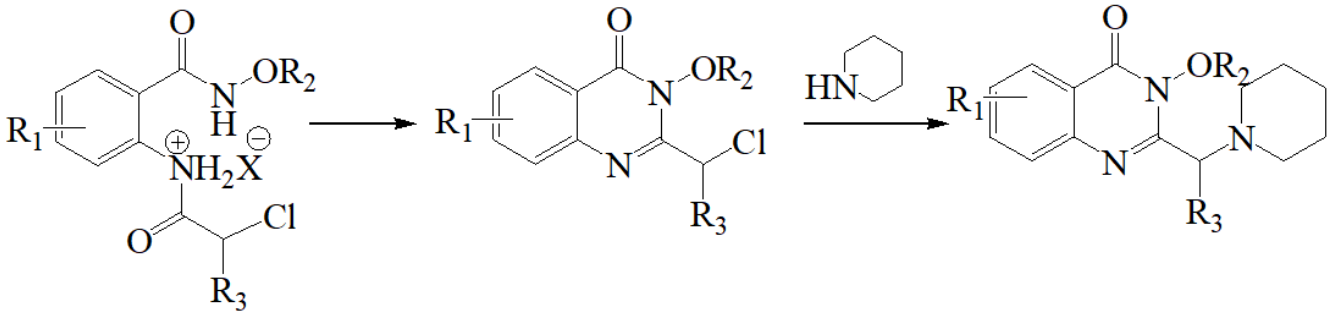
The PI3Kδ inhibitors, 2-((6-amino-9*H*-purin-9-yl)methyl)-5-methyl-3-arylquinazolin-4(3*H*)-ones and (a*S*, *S*)-2-((6-amino-9*H*-purin-9-yl)ethyl)-5-methyl-3-arylquinazolin-4(3*H*)-ones, were pre pared by the reaction of 2-amino-6-methylbenzoic acid with thionyl chloride to corresponding acid chloride and then reacted with the suitable anilines to afford 2-amino-6-methyl-*N*-arylbenzamides, reaction with a 2-chloroacetyl chloride derivatives in refluxing acetic acid to 2-(1-chloroethyl)-5-methyl-3-arylquinazolin-4(3*H*)-ones and finally reacted with adenine in the presence of K_2CO_3[68].

DOI: https://doi.org/10.5281/zenodo.13644773



3.3.8 Piperidinylmethylquinazolin-4(3*H*)-ones

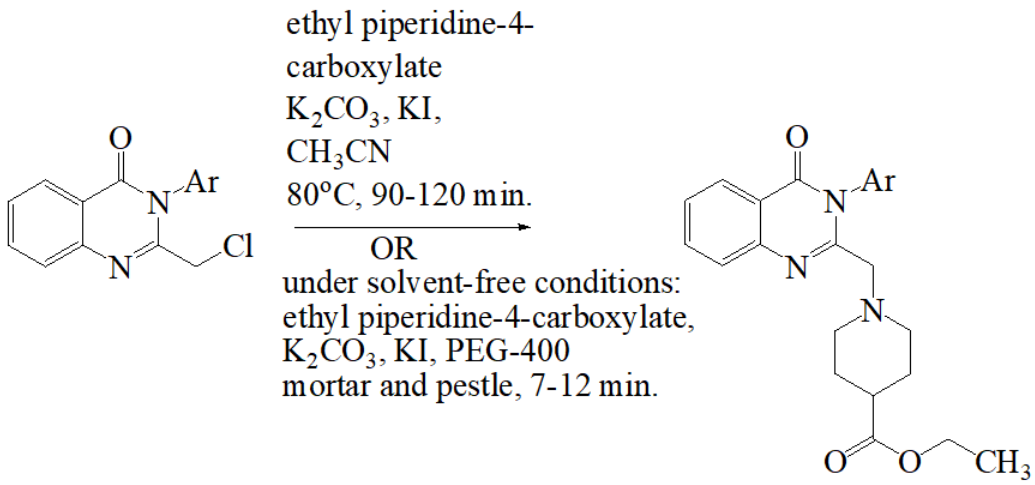
The salts of 2-(*N*-acylamino)benzoylhydroxamates were cyclized to 3-alkoxyquinazolinones, nucleophilic substitution of the halogen by piperidine afforded 2-(1-piperidinemethyl)-3-alkoxy-quinazolin-4(3*H*)-ones.[250]



R_1 = H, 6-NO_2, 2-Br, 7-Cl; R_2 = CH_3, $CH_2C_6H_5$, C_3H_7; R_3 = CH_3, C_6H_5; X = Cl, Br

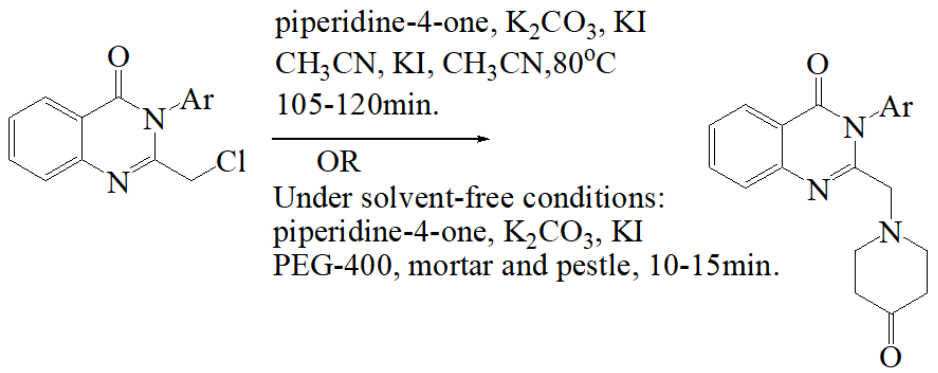
A mixture of 2-(chloromethyl)-3-arylquinazolin-4(3*H*)-one and ethyl piperidine- 4-carboxylate were heated to isolate 1-[3-aryl-quinazolin-4(3*H*)-one-2-yl-methyl]piperidine-4-carboxylic acid ethyl ester. The yield of the reaction have been increased by carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle.[251]

DOI: https://doi.org/10.5281/zenodo.13644773



Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	80	78	84	78
	Solvent-free	90	92	91	89

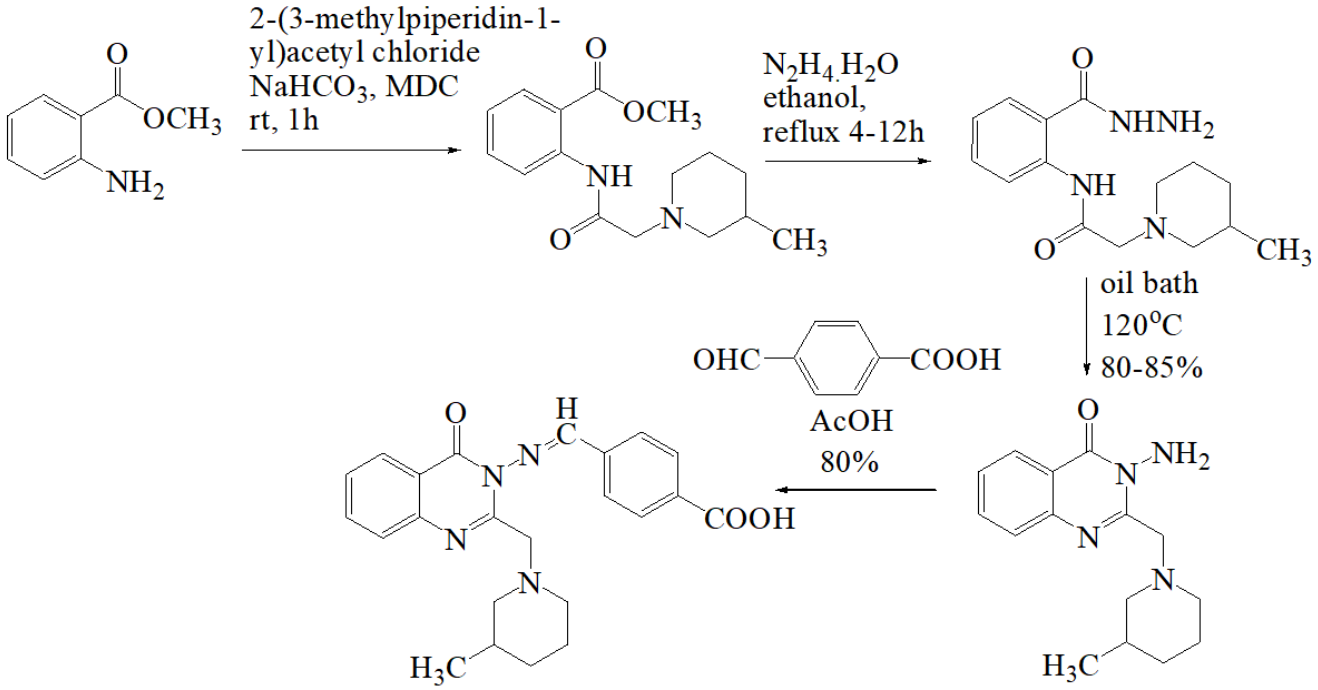
A mixture of 2-(chloromethyl)-3-arylquinazolin-4(3*H*)-one and piperidine-4-one were heated to isolate 3-aryl-2-(4-oxo-piperidin-1-ylmethyl)-quinazolin-4(3*H*)-one. The yield of the reaction have been increased by carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle.



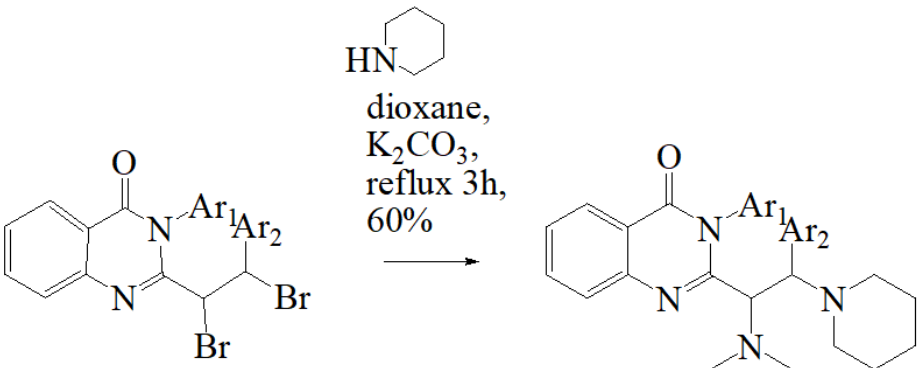
Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	84	80	80	75
	Solvent-free	92	94	90	88

Methyl anthranilate was reacted with 2-(3-methylpiperidin-1-yl)acetyl chloride in dichloromethane containing sodium bicarbonate to get methyl 2-(2-(3-methylpiperidin-1-yl)acetamido)benzoate, reaction with hydrazinium hydroxide in ethanol at reflux for 4–12h to get 2-(2-(3-methylpiperidin-1-yl)acetamido)benzohydrazide, heat in an oil bath at 120°C for two hours without any solvent core to get 3-amino-2-((3-methylpiperidin-1-yl)methyl)quinazolin-4(3*H*)-one followed by reaction with 4-formylbenzoic acid in glacial acetic acid at reflux for an hour to afford 3-(4-carboxybenzylideneamino)-2-((3-methylpiperidin-1-yl)methyl)quinazolin-4(3*H*)-one in good yield. The compound showed α-Glucosidase and α-Amylase enzymes inhibitory activity.[22]

DOI: https://doi.org/10.5281/zenodo.13644773



2-α,β-Di-(1-piperidine)-β-arylethyl–3-aryl-quinazolin-4(3*H*)-ones exhibited significant anti inflammatory activity, and were prepared by refluxing α,β-dibromoarylethyl-quinazolin-4(3*H*)-ones with piperidine in dioxane containing K_2CO_3 for 3 h.[252]

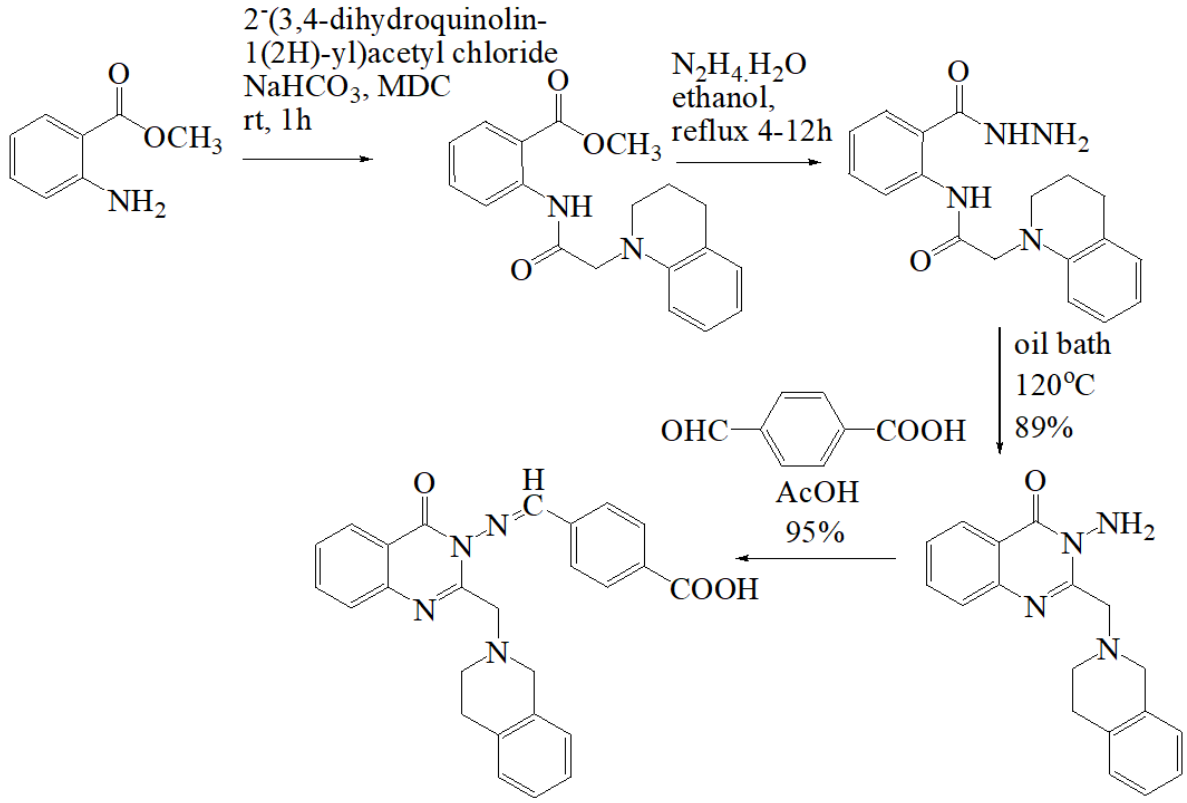


Ar_1= 2-ClC_6H_4, 2-$CH_3C_6H_4$, 2-$CH_3C_6H_4$
Ar_2= 2-$CH_3OC_6H_4$, 2-HOC_6H_4, 3-ClC_6H_4

3.3.9 Dihydroisoquinolinylmethylquinazolin-4(3*H*)-one

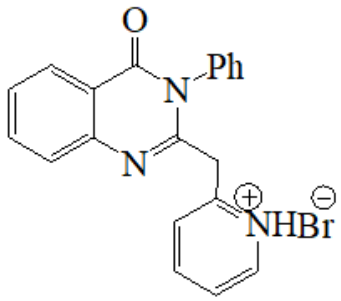
Methyl anthranilate was reacted with 2-(3,4-dihydroquinolin-1(2*H*)-yl)acetyl chloride in dichloromethane containing sodium bicarbonate to get methyl 2-(2-(3,4-dihydroquinolin-1(2*H*)-yl)acetamido)benzoate, reaction with hydrazinium hydroxide in ethanol at reflux for 4–12h to get 2-(2-(3,4-dihydroquinolin-1(2*H*)-yl)acetamido)benzohydrazide, heat in an oil bath at 120°C for two hours without any solvent core to get 3-amino-2-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)quinazolin-4(3*H*)-one followed by reaction with 4-formylbenzoic acid in glacial acetic acid at reflux for an hour to afford 3-(4-carboxybenzylideneamino)-2-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)quinazolin-4(3*H*)-one in good yield. The compound showed α-Glucosidase and α-Amylase enzymes inhibitory activity.[22]

DOI: https://doi.org/10.5281/zenodo.13644773



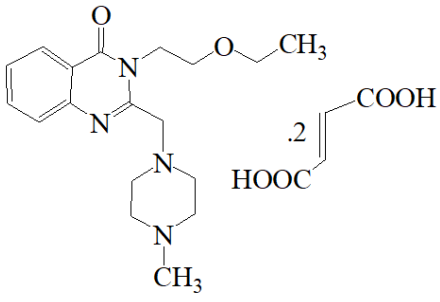
3.3.10 Pyridiniummethylquinazolin-4(3*H*)-one

Barakat synthesized 3-phenyl-2-pyridiniummethyl-4(3*H*)-quinazolinone bromides.[253]



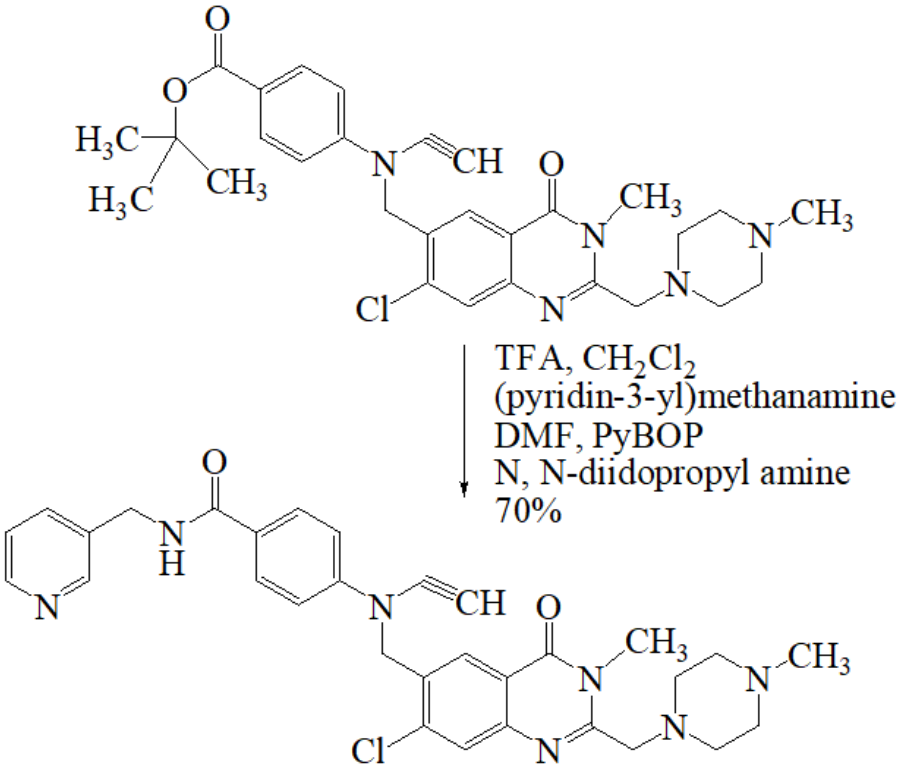
3.3.11 Piperazinylmethylquinazolin-4(3*H*)-ones

3-(2-Ethoxyethyl)-2-((4-methylpiperazine-1-yl)methyl)-4(3*H*)-quinazolinone difumarate, isolated from guinea Pig ileum, was active in vitro against histamine induced contractions.[69]



3-Methyl-2-(4-methylpiperazin-1-ylmethyl)-6-[*N*-(4-(3-pyridylmethylaminocarbonylphenyl)-*N*-(propyn-2-yl)amino)methyl]-7-chloro-4(3*H*)- quinazolinone was prepared by hydrolysis of

quinazolinone was prepared by hydrolysis of tert-butyl-4-[(*N*-(3-methyl-2-(4-methylpiperazine-1-yl methyl)-7-chloro-4(3*H*)-quinazolinon-6-ylmethyl))-*N*-(propyn-2-yl)amino]benzoate with TFA in $CHCl_3$ followed by amidation with 3-(aminomethyl)pyridine in DMF using PyBOP in the presence of *N,N*-diisopropylamine. Quinazolinone derivative inhibits thymidylate synthase (TS) albeit poorly when compared to the known anticancer agents CB3717 (IC_{50} compound / IC_{50} CB3717 > 2500). It is however active against the W1L2 and W1/2:C1 cell lines, including W1L2 cells incubated in the presence of folate metabolites with IC_{50} values of 0.49 nm, 0.28 nm, and 0.32 nm, respectively.[70]



Dr. F. S. Tokali was reacted methyl anthranilate with 2-(piperazin-1-yl)acetyl chloride derivatives in dichloromethane containing sodium bicarbonate to get methyl 2-(2-(4-methyl/phenylpiperazin-1-yl)acetamido)benzoate, reaction with hydrazinium hydroxide in ethanol at reflux for 4–12h to get 2 2-(2-(4-methyl/phenylpiperazin-1-yl)acetamido) benzohydrazide, heat in an oil bath at 120°C for two hours without any solvent core to get 3-amino-2-((4-methyl/phenylpiperazin-1-yl)methyl)quinazolin-4(3*H*)-one followed by reaction with 4-formylbenzoic acid in glacial acetic acid at reflux for an hour to afford 3-(4-carboxybenzylideneamino)-2-((4-methyl/phenylpiperazin-1-yl)methyl)quinazolin-4(3*H*)-one in good yield. The 3-(4-carboxybenzylideneamino)-2-[(4-phenylpiperazin-1-yl)methyl]-quinazolin-4(3*H*)-one has the strongest inhibitory effect for α-Glucosidase and α-Amylase enzymes.[22]

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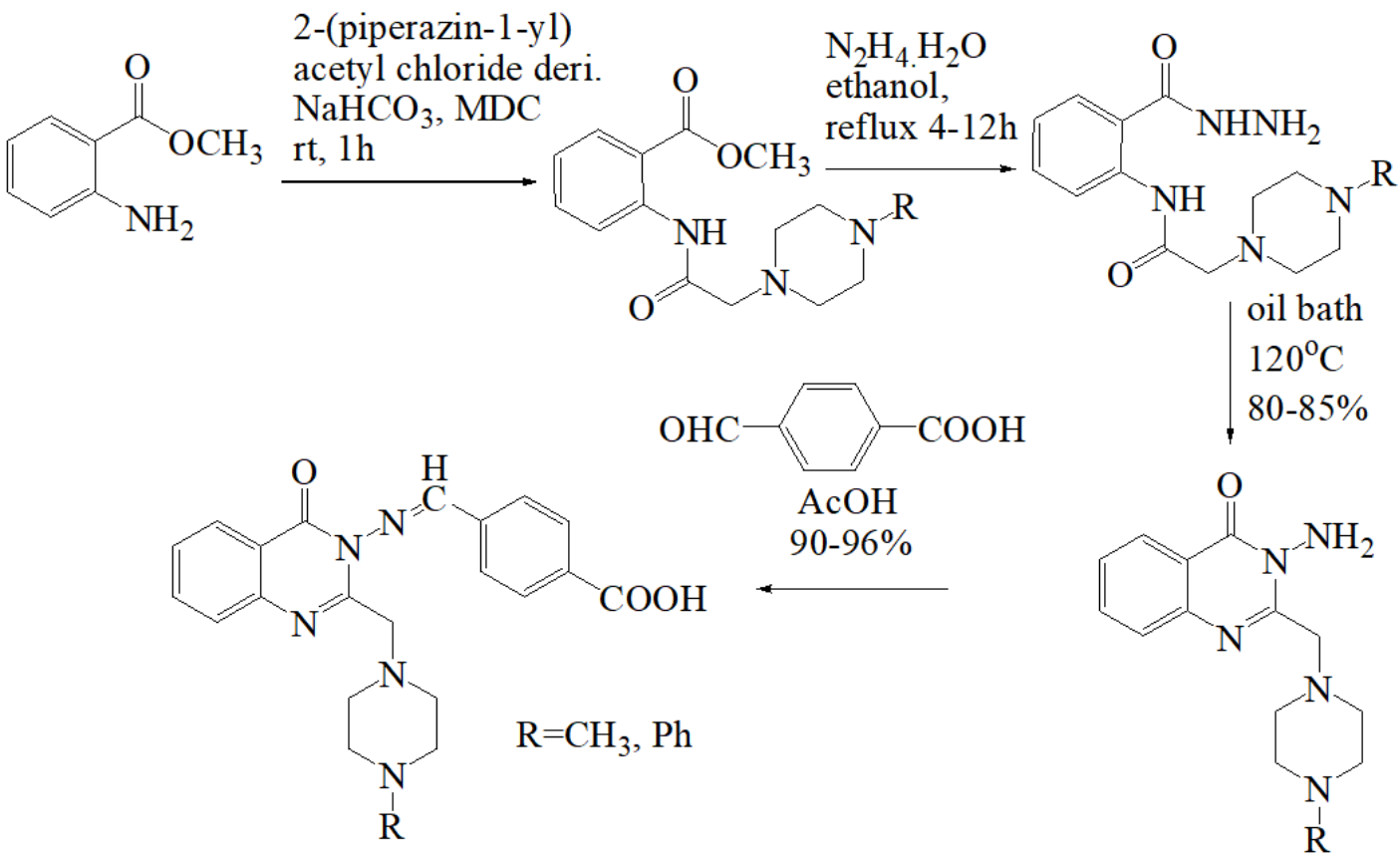
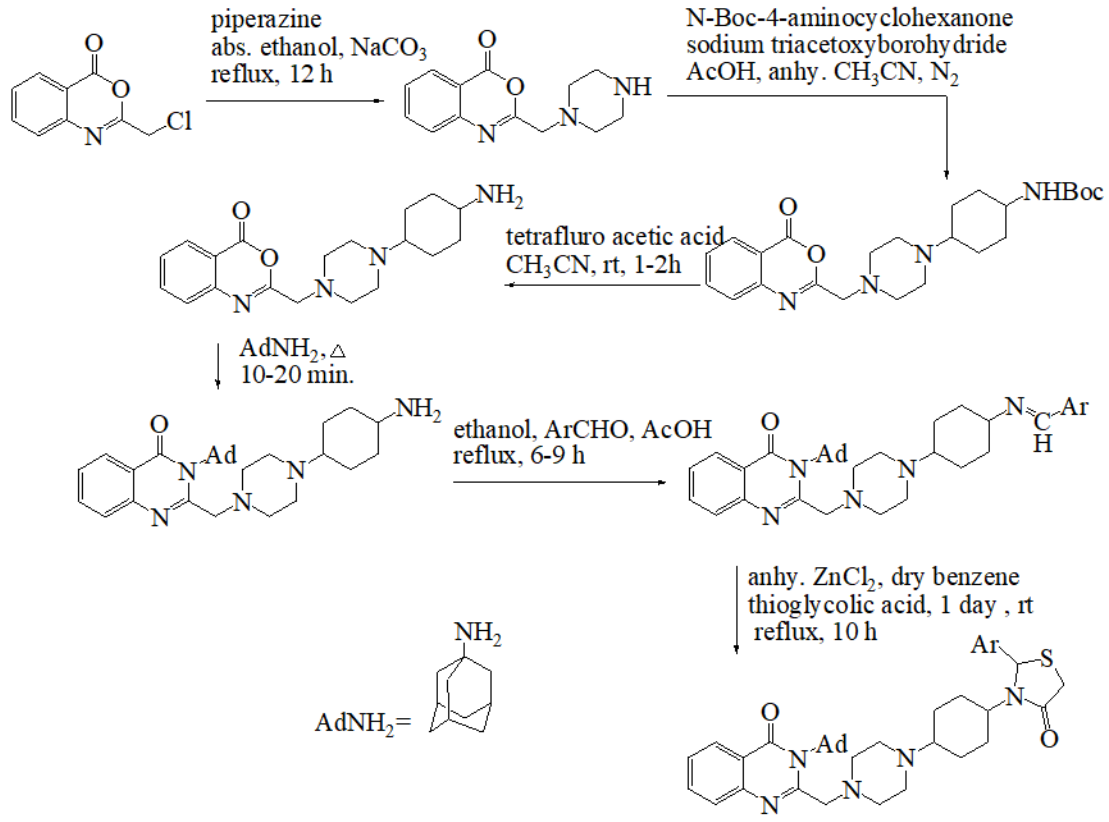


2-Chloromethylbenzo[*d*][1,3]oxazin-4-one was condensed with piperazine to isolate 2-(piperazinyl)methylbenzo[*d*][1,3]oxazin-4-one. Then treated with *N*-Boc-4-aminocyclohexanone to give 2-[4-{(tert-butylcarbamte)cyclohexyl}piperazinyl]methylbenzo-[*d*][1,3]oxazin-4-one, deprotection of amine function to isolate 2-[4-(cyclohexylamine)piperazinyl] methylbenzo[*d*] [1,3]oxazin-4-one, condensation with amantadine to 3-(admantan-1-yl)-2-[{4-(4-amino cyclo hexyl)piperazin-1-yl}methyl]- quinazolin-4(3*H*)-one, reaction with substituted benzaldehydes in the presence of few drops of glacial acid to isolate 3-[(admantan-1-yl)-2-{4-(4-arylidenamino)cyclohexyl)- piperazin-1-yl}methyl]-quinazolin-4(3*H*)-ones and finally cyclisation with thioglycolic acid to afford 3-[(admantan-1-yl)-2-[4-{4-(2-phenyl-4-oxo-1,3-thiazolidinyl) cyclohexyl}piperazin-1-yl]methyl]-quinazolin-4(3*H*)-ones. These compounds exhibited moderate to good COX-1 and COX-2 inhibitory activity, antibacterial, antifungal, anti-inflammatory, analgesic and ulcerogenic activities.[71]

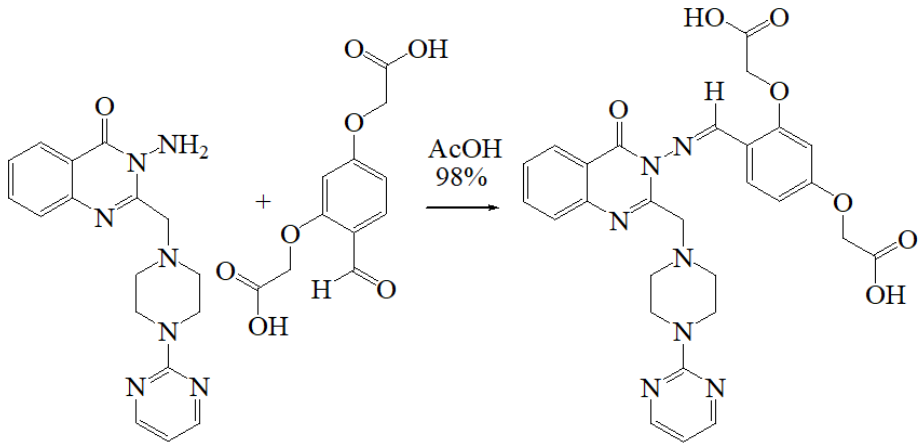
DOI: https://doi.org/10.5281/zenodo.13644773



Ar	C_6H_5	2-ClC_6H_4	3-ClC_6H_4	4-ClC_6H_4	2-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	2-HOC_6H_4
Yield (%)	56	43	40	44	50	48	55	45

3.3.12 Pyrimidinylpiperazinylmethylquinazolin-4(3*H*)-one

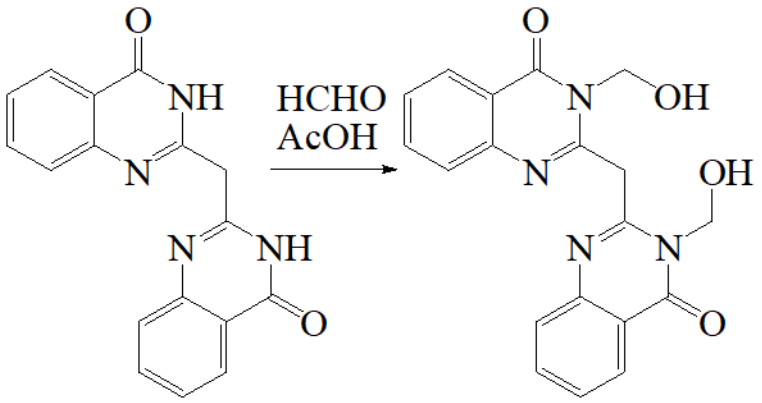
2-((4-(Pyrimidin-2-yl)piperazin-1-yl)methyl)-3-(((2,4-bis(carboxymethoxy))benzylidene)amino)-quinazolin-4(3*H*)-one with anticholinergic properties was synthesized with excellent yield by the reaction of 2,2'-(4-formyl-1,3-phenylene)bis(oxy)diacetic acid with 2-((4-(pyrimidin-2-yl)piperazin -1-yl)methyl)-3-amino-quinazolin-4(3*H*)-one in refluxed glacial acetic acid for an hour. This is the most effective compound against AChE and BChE both enzymes.[21]



3.1.13 2,2'-Methylenebisquinazolin-4(3*H*)-ones

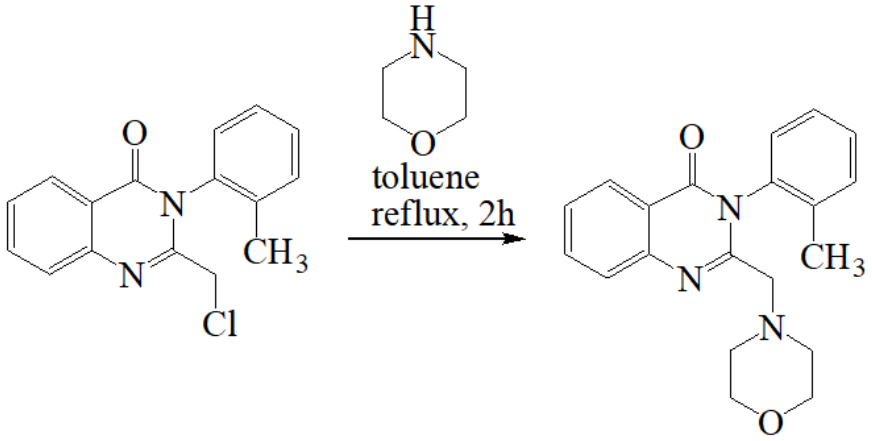
Reaction of 2,2'-methylenebisquinazolin-4(3*H*)-one with formaldehyde in acetic acid gave 2,2'-methylenebis[3-methylolquinazolin-4(3*H*)-one]derivative. Copolymerisation with adiponitrile in H_2SO_4 medium gave a good heat resistant polyamide.[72]

DOI: https://doi.org/10.5281/zenodo.13644773

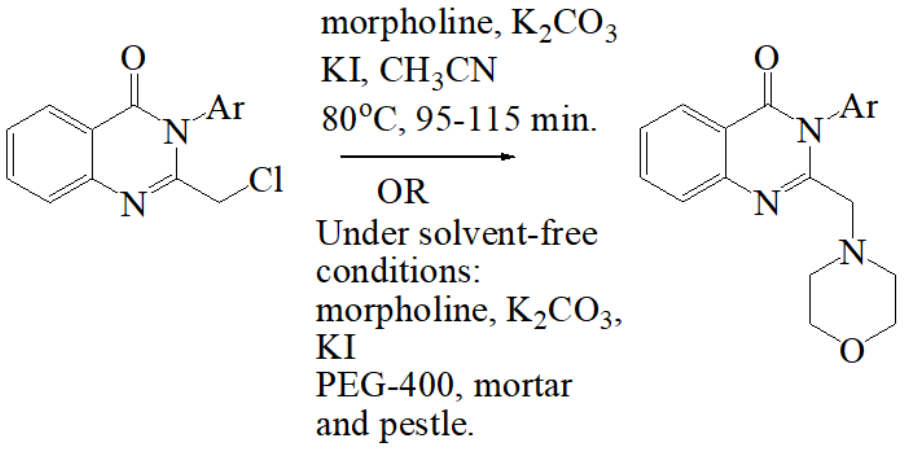


3.3.14 Morpholinomethylquinazolin-4(3*H*)-ones

2-Morpholinomethyl-3-(2-tolyl)-quinazolin-4(3*H*)-ones exhibited hypnotic and anticonvulsant activity. They were prepared by reacting 2-chloromethyl-3-(2-tolyl)-4(3*H*)-quinazolinone with morpholine in boiling toluene.[254]



The 2-chloromethyl-3-aryl-4(3*H*)-quinazolinone was reacted with morpholine in basic medium to isolate 3-aryl-2-morpholin-4-yl-methylquinazolin-4(3*H*)-one. The same reaction has been carried out under solvent-free conditions in the presence of PEG-400 by simple physical grinding in a mortar and pestle with improved yield. [53, 251]



Ar		3-$CH_3OC_6H_4$	C_6H_5	2-$CH_3C_6H_4$	2-$CF_3C_6H_4$
Yield (%)	Solution phase	86	80	82	76
	Solvent-free	95	94	92	90

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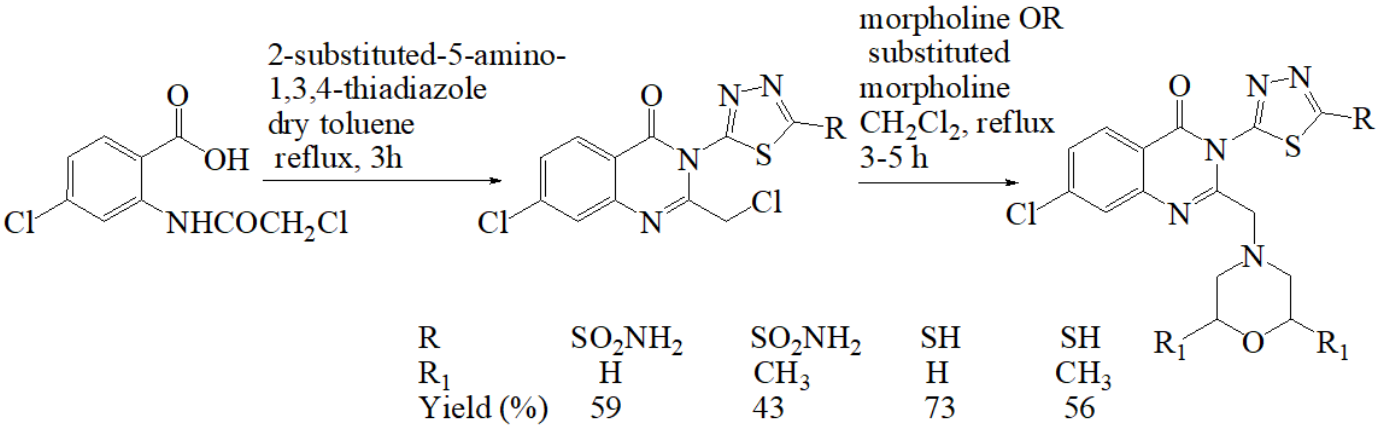
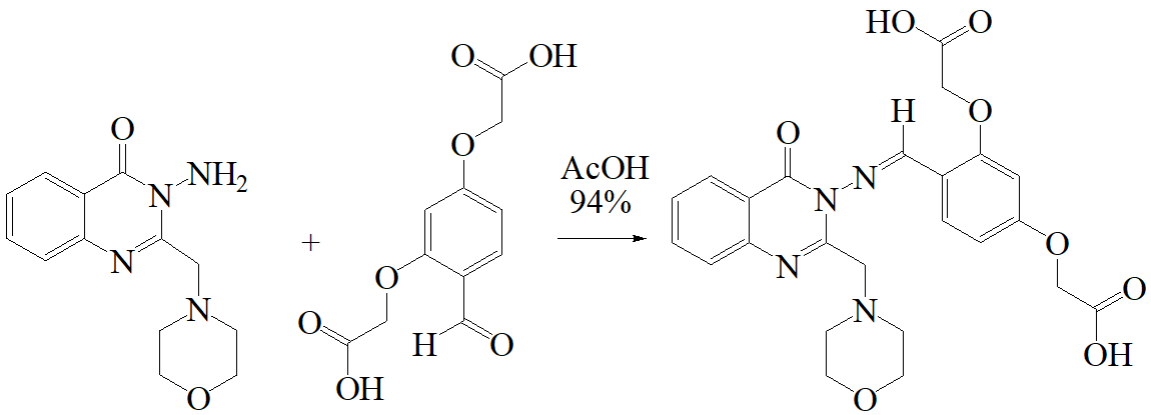
4-Chloro-2-chloroacetylaminobenzoic acid and 2-substituted-5-amino-1,3,4- thiadiazole were reacted in dry toluene in presence of phosphorous trichloride and the resultant 7-chloro-2-chloromethyl-3-(2-substituted-1,3,4-thiadiazol-5-yl)-quinazolin-4(3*H*)-ones and morpholine or substituted morpholine was refluxed to afford 7-chloro-2-(morpholinomethyl or 2,6-dimethylmorpholinomethyl)-3-(2-substituted- 1,3,4-thiadiazol-5-yl)-quinazolin-4(3*H*)-ones.[53]



2-Morpholinomethyl-3-(((2,4-bis(carboxymethoxy))benzylidene)amino)-quinazolin-4(3*H*)-one with anticholinergic properties was synthesized with excellent yield by the reaction of 2,2'-(4-formyl-1,3-phenylene)bis(oxy)diacetic acid with 2-(morpholinomethyl)-3-amino-quinazolin-4(3*H*)-one in refluxed glacial acetic acid for an hour.[21]



Methyl anthranilate was reacted with 2-morpholinoacetyl chloride in dichloromethane containing sodium bicarbonate to get methyl 2-(2-morpholinoacetamido)benzoate, reaction with hydrazinium hydroxide in ethanol at reflux for 4–12h to get 2-(2-morpholino acetamido)benzohydrazide, heat in an oil bath at 120°C for two hours without any solvent core to get 3-amino-2-(morpholinomethyl)quinazolin-4(3*H*)-one followed by reaction with 4-formylbenzoic acid in glacial acetic acid at reflux for an hour to afford 3-(4-carboxy benzylideneamino)-2-(morpholinomethyl)quinazolin-4(3*H*)-one in good yield. The compound showed α-Glucosidase and α-Amylase enzymes inhibitory activity.[22]

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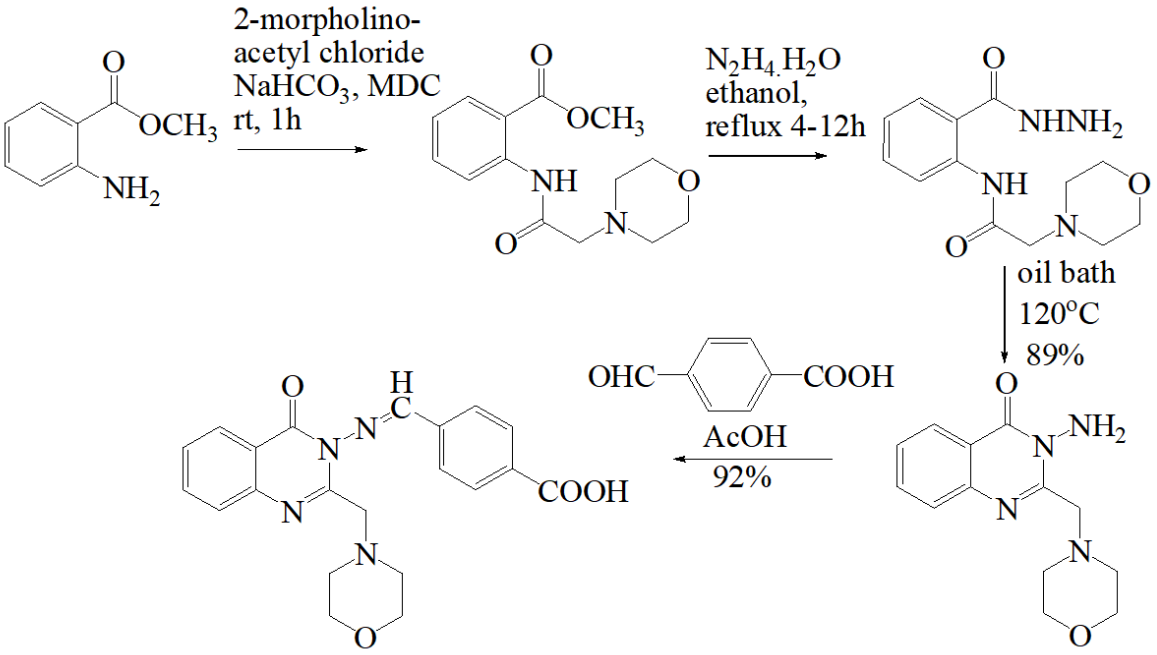
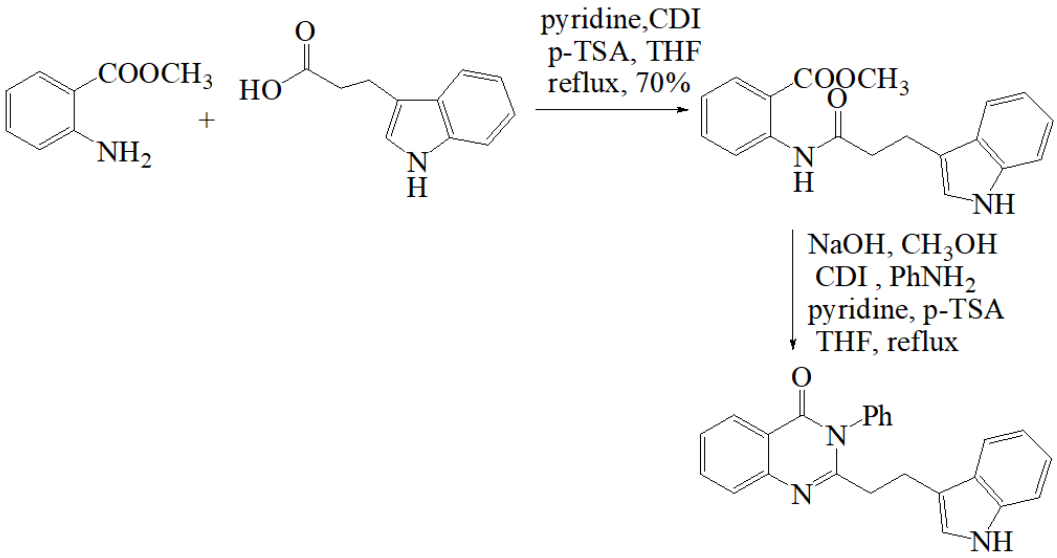


3.3.15 Indolylethyl-quinazolin-4(3*H*)-ones

Melvin et.al reported the synthesis of 2-[2-(3-indolyl)ethyl]-3-phenyl-quinazolin-4(3*H*)-ones that are useful in the treatment of gastrointestinal and appetite disorders, as CCK antagonists and decreases the number of spontaneously active dopamine neurons. Reaction of methyl anthranilate with 3-(3-indolyl)propionic acid in the presence of 1,1'-carbonyldiimidazole and pyridinium p-toluenesulfonate in boiling THF yielded 3-(3-indolyl)-*N*-(2-carbomethoxy phenyl)propionamide. The compound was treated with methanol containing sodium hydroxide, aniline, 1, 1'-carbonyldiimidazole and pyridinium p-toluenesulfonate in refluxing in THF to give title compound.[73,74]



Melvin extended the above synthesis to prepare quinazolinone based cholecystokinin/gastro receptor ligands. Reaction of 2-amino-*N*-(3-carboisobutanonylphenyl)benzamide with 5-(3-indolylmethyl)-1,3-dioxane-4,6-dione in pyridine containing pyridinium tosylate unde reflux in nitrogen atmosphere for 48 h gave 2-(3-butanoylphenyl)-4(3*H*)-quinazolinone. The X-Ray crystallographic analysis (R = H, IC_{50}= 0.026 mM) showed an extended structure with two

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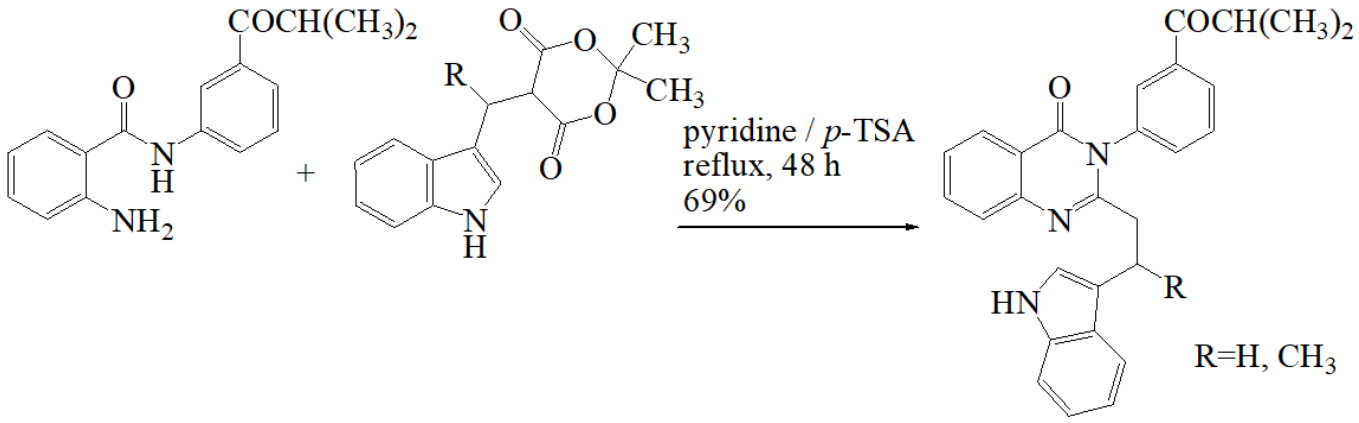
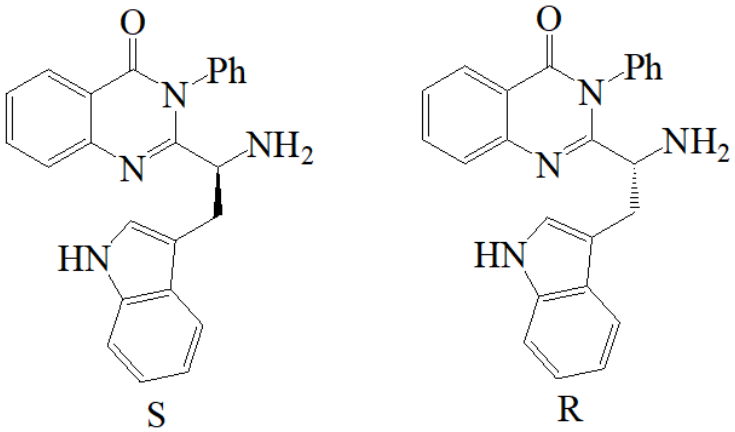
heterocyclic rings adopting an antiperiplanar arrangement around the s bond of the ethane link, whereas the solid-state conformation for the less active analog (R=CH_3 , IC_{50} =9.1 mM) is folded with two heteroaromatic systems adopting a synclinal orientation. However, MMZ force field calculations (Macro Model V.30) suggest that the energy difference between such unfavourable steric interactions may account for the difference in receptor affinity.[75]



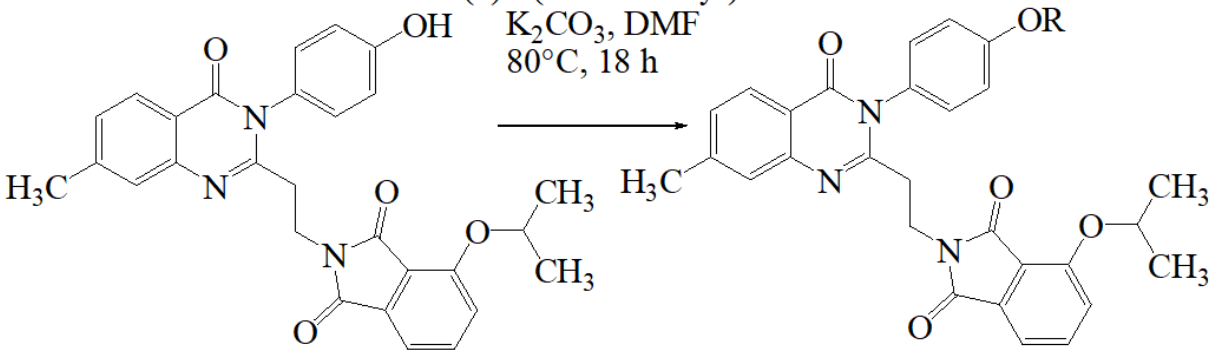
The enantiomeric isomers 2-((*S*)-1-amino-2-(1*H*-indol-3-yl)ethyl)-3-phenylquinazolin-4(3*H*)-one and 2-((*R*)-1-amino-2-(1*H*-indol-3-yl)ethyl)-3-phenyl quinazolin-4(3*H*)-one were separated by chiral HPLC using Method: HPLC (RegisPak, ethanol/n-hexane/triethylamine = 49.95/50/0.05, flow rate = 1.0 mL/min, l = 280 nm) tR = 10.4 min (R- isomer), tR = 13.6 min (S- isomer). 255



3.3.16 Isoindolinedioneylethylquinazolin-4(3*H*)-one

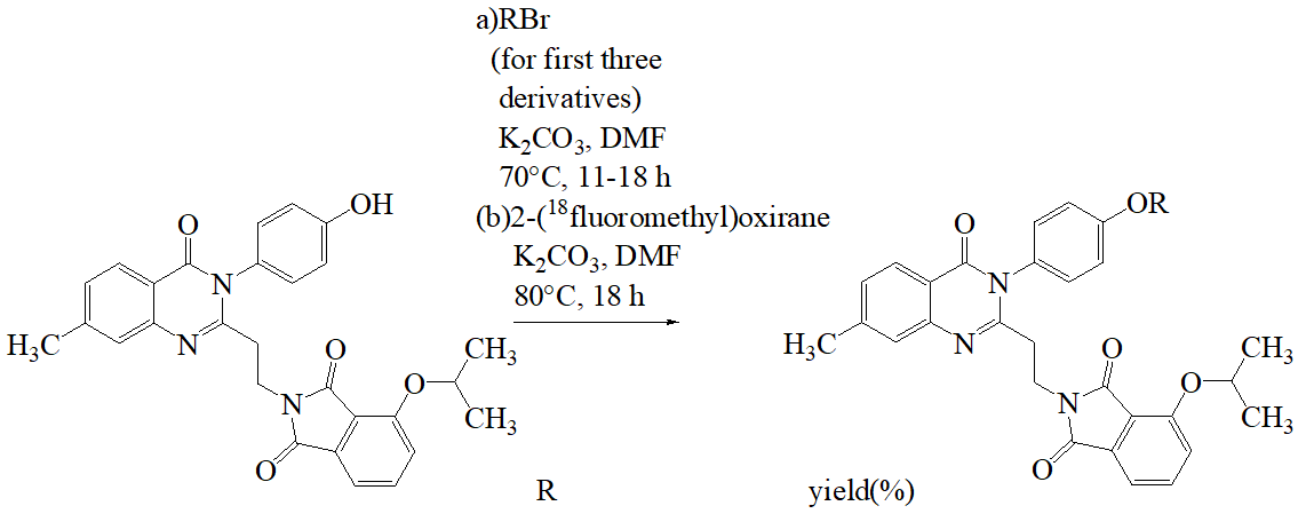
The novel 3-(4-fluoroalkyloxy analogues of phenyl)-7-methyl-2-(2-(4-isopropoxyisoindoline-1,3-dione-2-yl)ethyl)quinazolin-4(3*H*)-ones, were synthesized using the same phenol precursor: 7-methyl-3-(4-hydroxyphenyl)-2-(2-(4-isopropoxyisoindoline-1,3-dione-2-yl)ethyl)quinazolin-4 (3*H*)-one with fluoropropyl tosylate/fluoromethyl tosylate in the presence of K_2CO_3 at 70 °C and opening reaction of epifluorohydrin and K_2CO_3 at 80°C for 18 h. These compounds are useful for Positron-Emission-Tomography Imaging of Phosphodiesterase 10A in the Brain.[76]

DOI: https://doi.org/10.5281/zenodo.13644773



R	yield(%)
$CH_2CH_2CH_2F$	78
CH_2F	27
CD_2F	24
$CH_2CH(OH)CH_2F$	30

The lipophilicity (log D) values are in the range normally considered as suitable for PET ligands in brain imaging. When the size of the fluoroalkyl group shrank, the lipophilicity was also reduced in this series of compounds. Because of these compounds' promising in vitro profiles, radiolabeled with 18F quinazolinones derivatives were synthesized and performed in vivo evaluation of PET imaging of PDE10A. Of these PET ligands, two fluoromethoxy analogues 3-(4-([18F]Fluoroethoxy)phenyl)-7-methyl-2-(2-(4-isopropoxyisoindoline-1,3-dione-2-yl)ethyl) quinazolin-4(3*H*)-one and 3-(4-([18F]Fluoromethoxy-d2)phenyl)-7-methyl-2-(2-(4-isopropoxyiso indoline-1,3-dione-2-yl)ethyl)quinazolin-4(3*H*)-one showed potent affinity for PDE10A and adequate lipophilicity.[76]

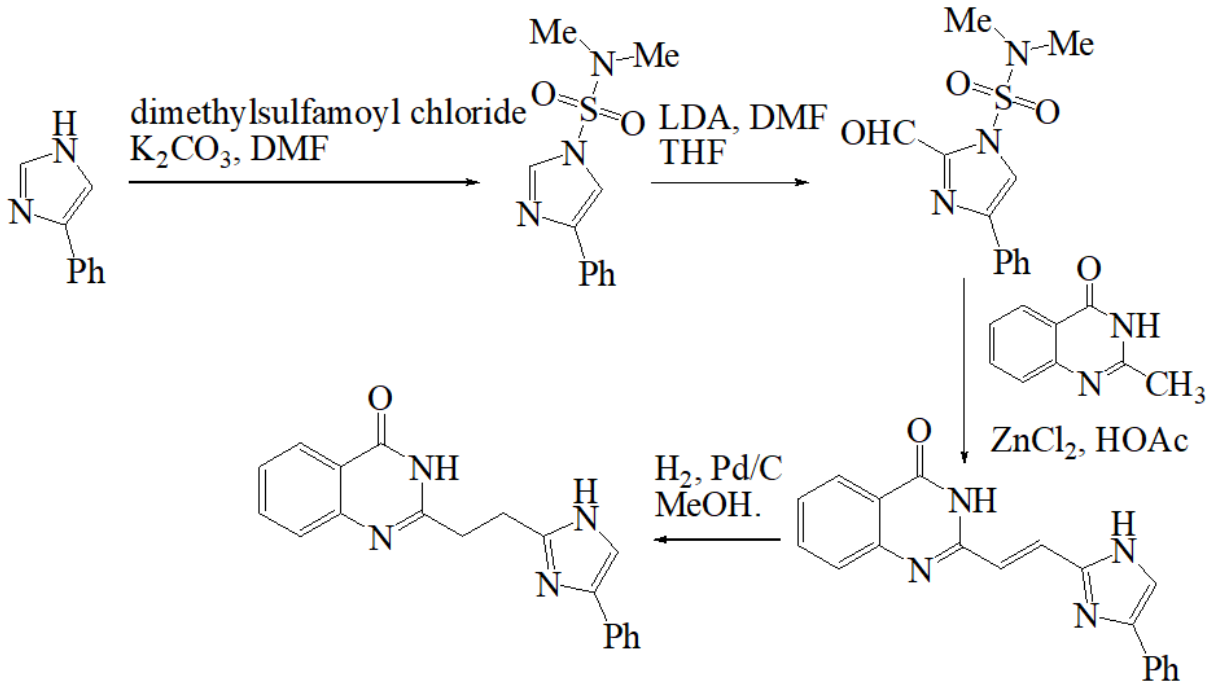


R	yield(%)
$CH_2CH_2CH_2{}^{18}F$	7
$CH_2{}^{18}F$	9
$CD_2{}^{18}F$	10
$CH_2CH(OH)CH_2{}^{18}F$	2

DOI: https://doi.org/10.5281/zenodo.13644773

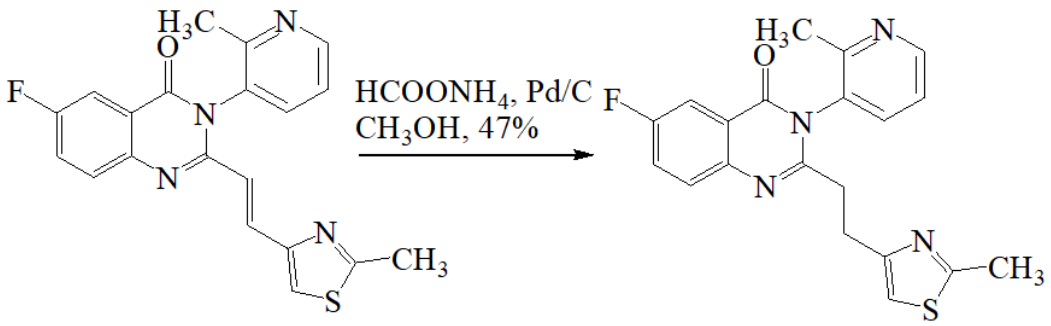
3.3.17 Imidazolylethylquinazolin-4(3*H*)-one

Douglas F. Burdi et.al are reported the synthesis of highly potent, selective orally bioavailable inhibitors of PDE10A, 2-(2-(4-phenyl-1*H*-imidazol-2-yl)ethyl)quinazolin-4(3*H*)-one. Sulfony lation of 5-phenyl-1*H*-imidazole with dimethylsulfamoyl chloride, formylation at the 2-position of 5-phenyl-1*H*-imidazole using LDA/DMF, coupling the formyl group with 2-methylquinazolin-4(3*H*)-one using zinc chloride in acetic acid and catalytic hydrogenation afforded target molecule.[77]



3.3.18 Thiazolylethylquinazolin-4(3*H*)-one

Chenard et.al prepared the atropisomer, (*S*)-3-(2-methylpyridine)-6-fluoro-2-[2-(2-methyl thiazol-4-yl)ethyl]-4(3*H*)-quinazolinone mesylate in 47% yield by refluxing (*S*)-3-(2-methyl pyridine)-6-fluoro-2-[2-(2-methylthiazol-4-yl)vinyl]-quinazolin-4(3*H*)-ones with ammonium formate and Pd/C in CH_3OH and, followed by saltification with CH_3SO_3H.[241]



3.3.19 Pyridinylethylquinazolin-4(3*H*)-one

Chenard and Welch have reported the preparation of the quinazolinone derivative. 3-(2-Chloro-phenyl)-6-fluoro-2-methyl-4(3*H*)-quinazolinone was reacted with BuLi, diisopropylamine in methanol, and ethyl picolinate to get 3-(2-chlorophenyl)-6-fluoro-2-[2-hydroxy-2-(2-pyridinyl) ethyl]-4(3*H*)-quinazolinone.[242]

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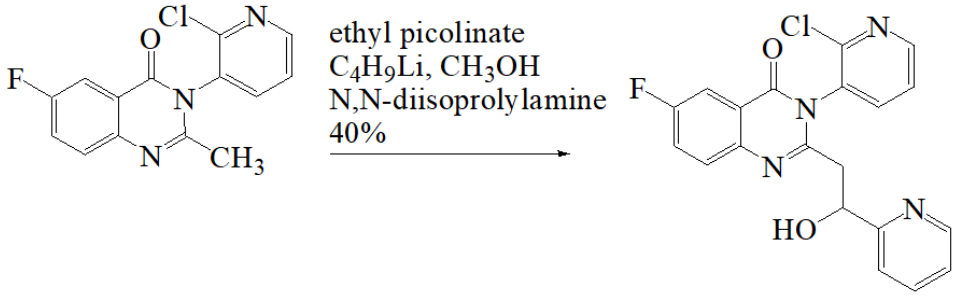
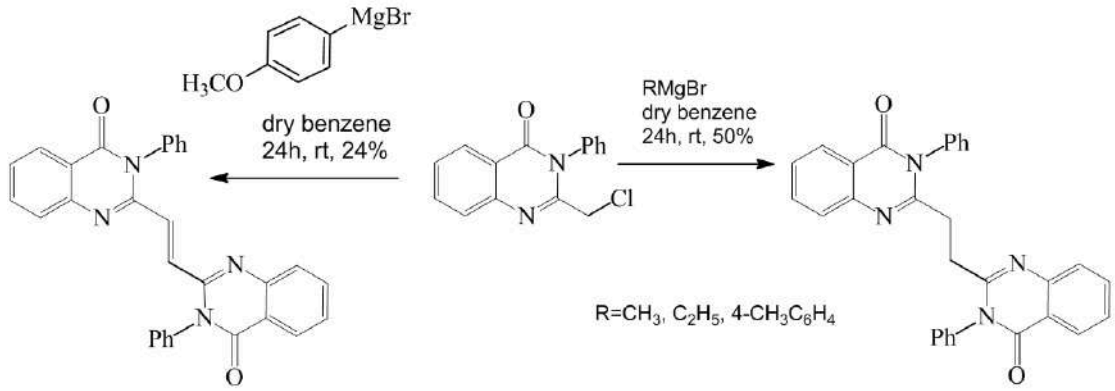
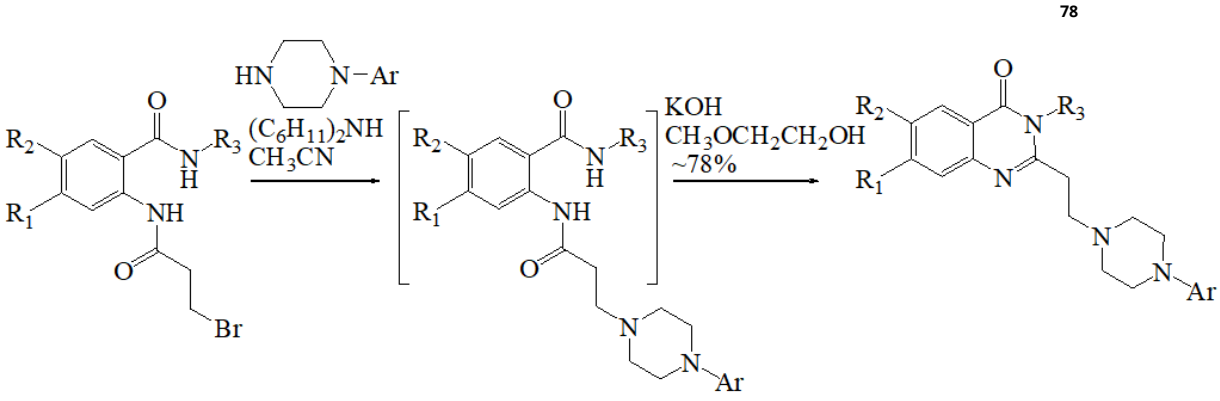


The 1,2-bis[3-phenylquinazolin-4(3*H*)-one-2-yl]ethane was prepared by Ismail et.al by treating 2-(chloromethyl)-3-phenylquinazolin-4(3*H*)-one with RMgBr (R=CH , C H and 4-CH C H). When 4-methoxyphenylmagnesiumbromide was used to generate carbanion, the reaction yielded 1,2-bis[3-phenylquinazolin-4(3*H*)-one-2-yl]ethylene.[135]



3.3.20 Piperazinylethylquinazolin-4(3*H*)-ones

Amschler et.al prepared 2-[1-(4-aryl)piperazino]ethyl-4(3*H*)-quinazolinone derivatives by treating a suitably substituted 2-carbamoylanilide with 1-arylpiperazine in acetonitrile containing dicyclohexylamine, followed by dehydrative cyclization. These compounds showed hypotensive, antihistamine and analgesic properties with slight sedative effect.



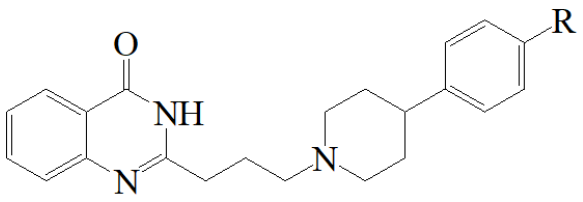
[78]

$R_1 = R_2 = H, CH_3, OCH_3$; $R_3 = CH_3, C_6H_5CH_2CH_2, (CH_3)_2CHCH_2CH_2$
Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4
3-$CF_3C_6H_4$, 2-$C_2H_5OC_6H_4$

3.3.21 Piperidinylpropylquinazolin-4(3*H*)-ones

2-(3-((4-Aryl)piperidin-1-yl)propyl)quinazolin-4(3*H*)-one is the most potent PARP-1 inhibitor, effectively improved the sensitivity of cisplatin-resistant human gastric cancer cells to cisplatin by inhibiting PARP-1 catalytic activity.[91]

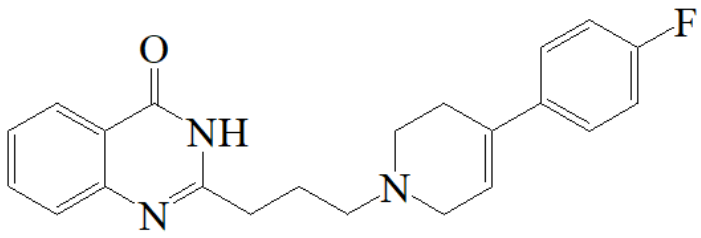
DOI: https://doi.org/10.5281/zenodo.13644773



R	IC_{50}	R	IC_{50}
Cl	0.388	H	0.079

3.3.22 Tetrahydropyridinylpropylquinazolin-4(3*H*)-one

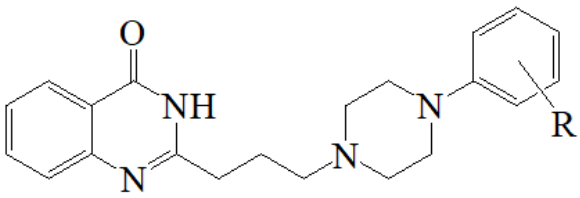
Hyun-Ju Park etal also identified potent Poly(ADP-ribose)polymerase-1 (PARP-1) inhibitor 2-(4-(4-(4-fluorophenyl)-5,6-dihydropyridin-1(2*H*)-yl)propyl)quinazolin-4(3*H*)-one with IC_{50}-0.304 through pharmacophore-based virtual screening of Korean Chemical Database.[91]



IC_{50}- 0.304

3.3.23 Piperazinylpropylquinazolin-4(3*H*)-ones

The most potent PARP-1 inhibitor, 2-(3-(4-(4-fluorophenyl)piperazin-1-yl)propyl)quinazolin-4(3*H*)-one effectively improved the sensitivity of cisplatin-resistant human gastric cancer cells to cisplatin by inhibiting PARP-1 catalytic activity [91]

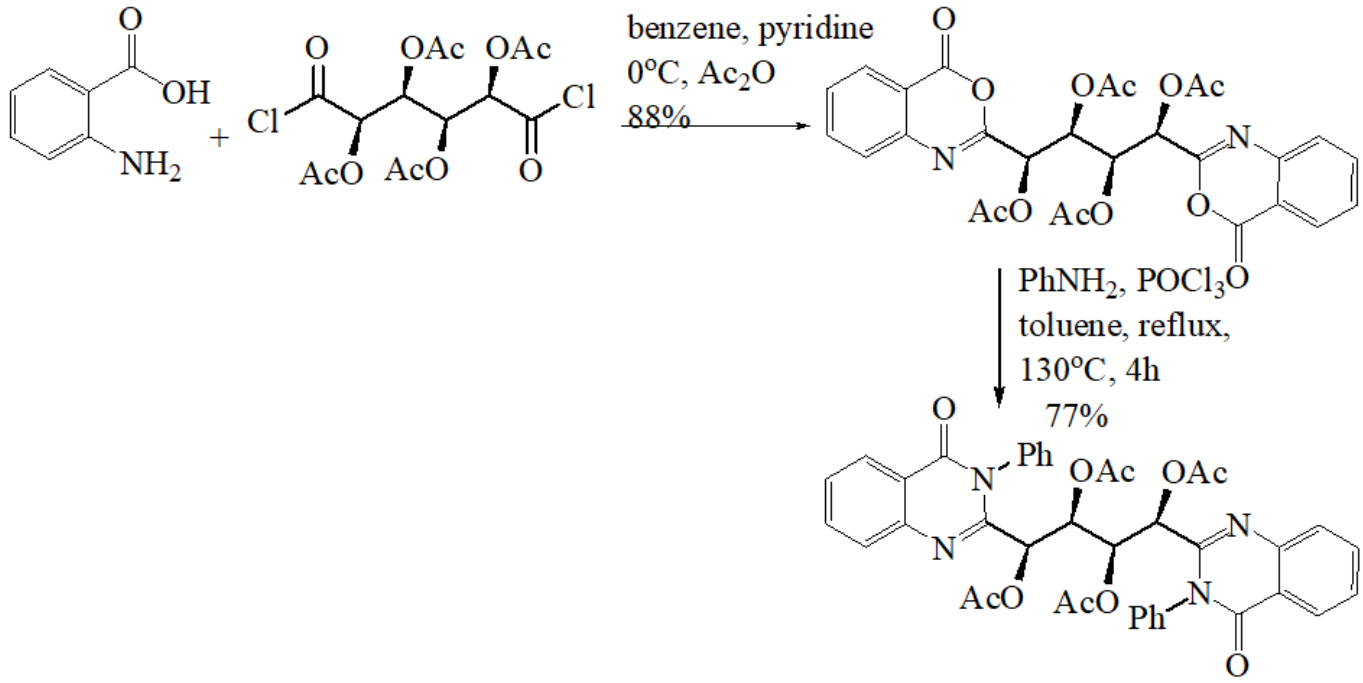


R	IC_{50}	R	IC_{50}	R	IC_{50}
2-OCH_3	0.189	3-Cl	1.008	4-F	0.077

3.3.24 Quinazolinonylbutylquinazolin-4(3*H*)-one

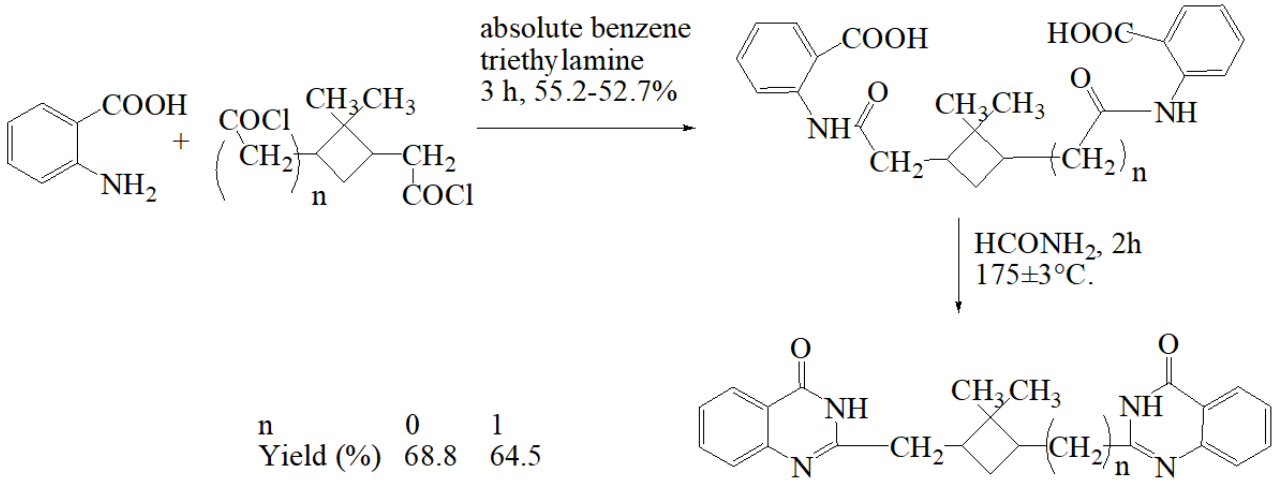
A novel approach to the synthesis of C-nucleoside analogs involves building of benzoxazine rings at the terminus of a carbohydrate moiety. 2,3,4,5-Tetra-O-acetylgalactoryl chloride was condensed with anthranilic acid in benzene containing pyridine at 0^0C and the condensed product underwent dehydrative cyclization in acetic anhydride to form 1,2,3,4-tetra-O-acetyl-1,4-bis(benzoxazin-4-on-2-yl)galactotetritol. The bisbenzoxazine on reacting with aniline in the presence of $POCl_3$ in toluene afforded 1,4-bis-(3-phenyl-4(3*H*)-quinazolinone-2-yl)-1,2,3,4-tetra-O-acetylgalactotetritol.[256]

DOI: https://doi.org/10.5281/zenodo.13644773



3.3.25 Bis(quinazolin-4(3*H*)-onylalkyl)cyclobutanes

2,2-Dimethyl-1-[quinazolin-4(3*H*)-one-2-yl]methyl-3-[quinazolin-4(3*H*)-one-2-yl]cyclobutane (n=0) and 2,2-dimethyl-1,3-di[quinazolin-4(3*H*)-one-2-ylmethyl]cyclobutane (n=1) were prepared by reacting anthranilic acid with diacid chloride to corresponding anthramilic acid derivative and subsequent treatment with formamide.[257]



n	0	1
Yield (%)	68.8	64.5

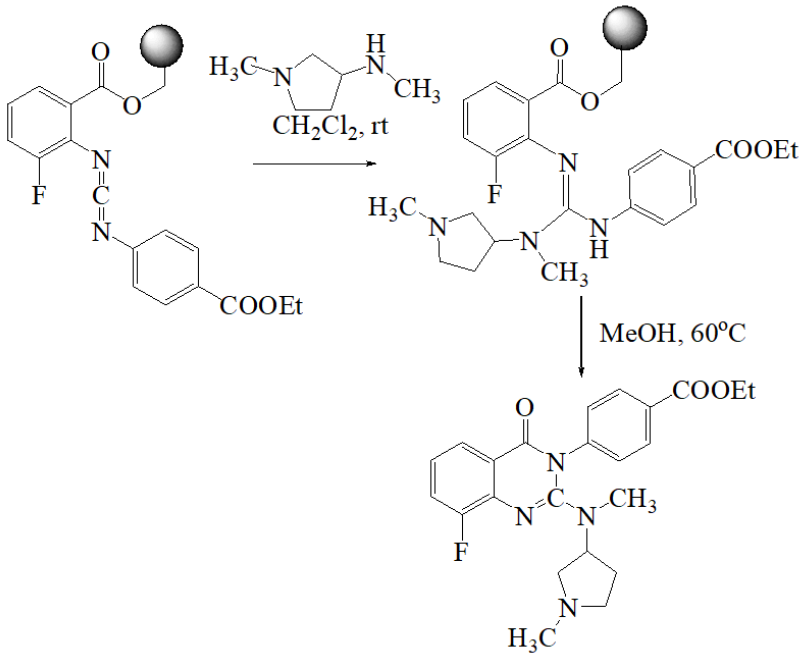
4 Heterylamine/aminoalkyl/phenylgroup

4.1 Heterylamine

4.1.1 Pyrrolidinylaminoquinazolin-4(3*H*)-one

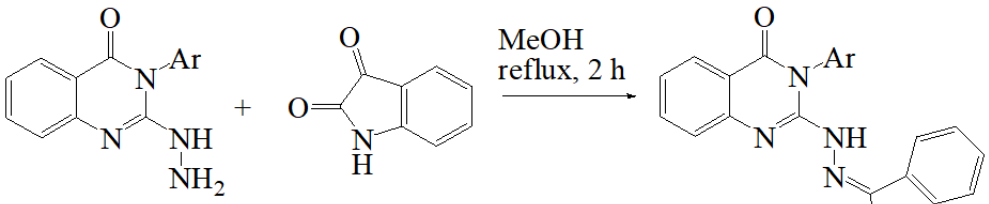
The polymer bound carbodiimide treated with various *N*,1-dimethylpyrrolidin-3-amine followed by intramolecular cyclization and simultaneous cleavage from the resin, provided the 8-fluoro-2-(*N*-methyl-*N*-(1-methylpyrrolidin-3-yl)amino)-3-(4-ethoxycarbonyl phenyl)-quinazolin-4(3*H*)-one. These compounds have exhibited anabolic activity toward chondrogenic differentiation and provide relief against articular cartilage damage.[7]

DOI: https://doi.org/10.5281/zenodo.13644773



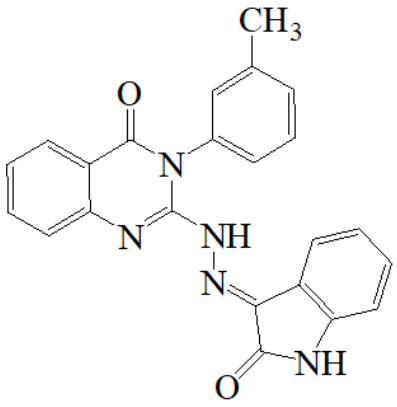
4.1.2 Isatinhydrazonylquinazolin-4(3*H*)-ones

Antimicrobial compounds, 3-aryl-2-(isatinhydrazone-3-yl)-quinazolin-4(3*H*)-ones, were Synthesized by refluxing a mixture of 3-aryl-2-hydrazino-quinazolin-4(3*H*)-one and isatin in methanol.[83]



Ar	Ph	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	4-ClC_6H_4
Yield (%)	69	71	69	69

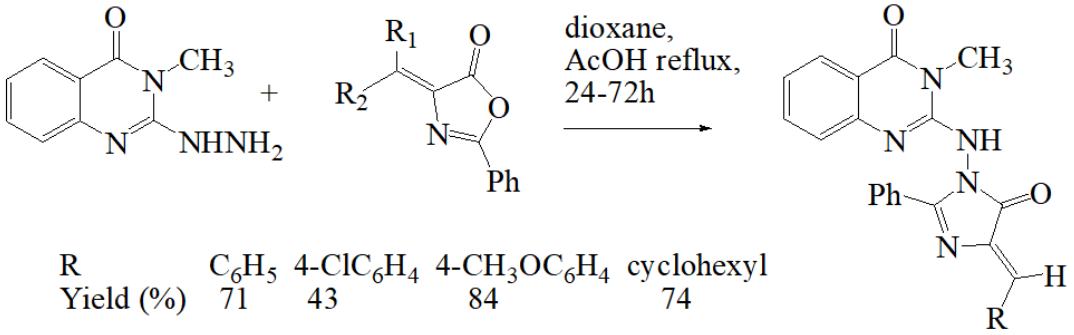
The desirability-based MOOP method indicated the presence of bulky alkyl substituents at the C-2 position of the quinazoline displayed a positive role on the ulcerogenic ability.[84]



4.1.3 Dihydroimidazolylaminoquinazolin-4(3*H*)-ones

Hamidian et.al reacted 2-hydrazino-3-methyl-quinazolin-4(3*H*)-one with 5(4*H*)-oxazolone derivative in acetic acid at reflux to afford 3-methyl-2-({5-oxo-2-phenyl-4-[1-arylmethyli dene]-4,5-dihydro-1*H*-imidazol-1-yl}amino)-quinazolin-4(3*H*)-one.[258]

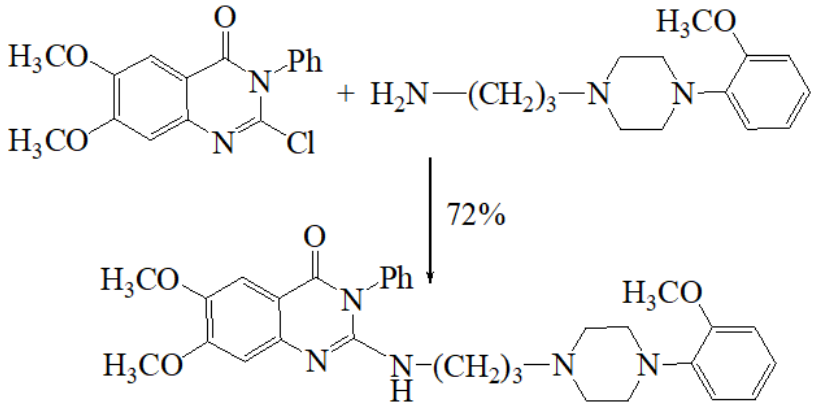
DOI: https://doi.org/10.5281/zenodo.13644773



R	C_6H_5	4-ClC_6H_4	4-$CH_3OC_6H_4$	cyclohexyl
Yield (%)	71	43	84	74

4.1.4 Pyrazinylpropylaminoquinazolin-4(3*H*)-one

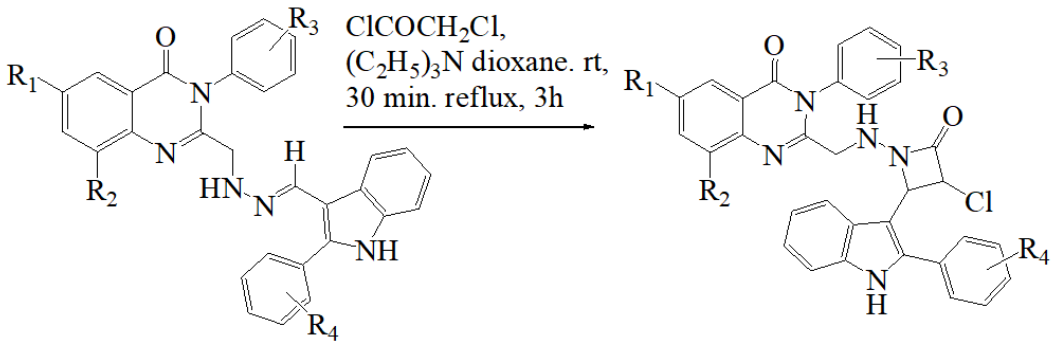
Antihypertensive, 2-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propylamino)-6,7-dimethoxy-3-phenylquinazolin-4(3*H*)-one, was obtained in 72% yield by reacting 2-chloro-3-phenyl-6,7-dimethoxy-4(3*H*)-quinazolinone with 1-(3-aminopropyl)-4-(2-methoxyphenyl)piperazine.[79]



4.2 Heterylaminoalkyl

4.2.1 Indolylazetidinylaminomethylquinazolin-4(3*H*)-ones

6,8-Disubstituted 3-aryl-2-{3'-[3"-(2"-arylindolylmethylene)]hydrazinomethyl}-quinazolin-4(3*H*)-ones served as an ideal starting material for synthesizing these class of compounds. For example, chloroacetylation of starting material in triethylamine medium afforded 6-bromo-2-1'-(3'-chloro–4'-(3"-(2"-arylindolyl))azetidin-2'-one)aminomethyl)-3-aryl-quinazolin-4(3*H*)-ones.[259]

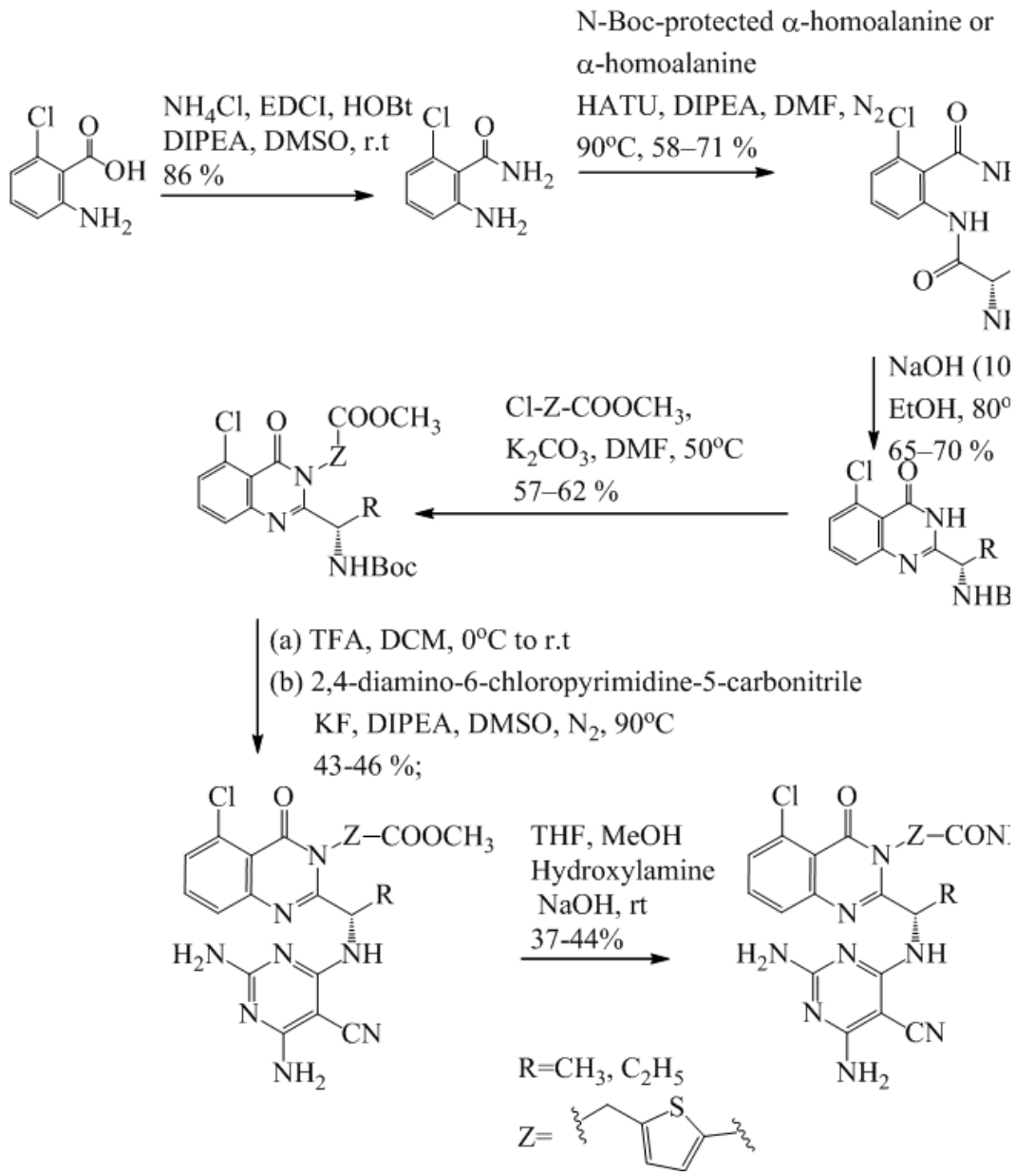


R_1	I	I	Br	Br	Br	Br	I	I	Br	Br	H
R_2	H	H	H	H	Br	Br	H	H	H	H	H
R_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	4-Cl	4-Cl	3-Cl	3-Cl	NH_2
R_4	H	4-CH_3	H	4-CH_3	H	4-CH_3	H	4-CH_3	H	4-CH_3	H

4.2.2 Pyrimidinylaminomethylquinazolin-4(3*H*)-ones

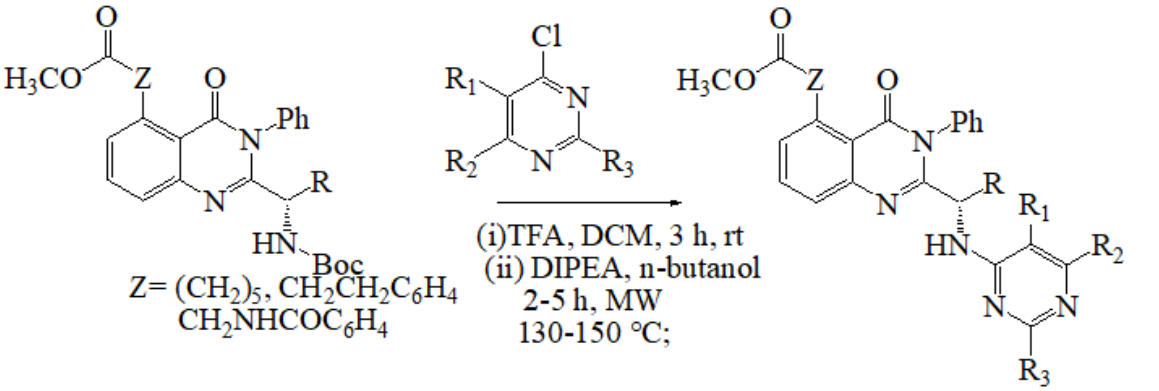
2-Amino-6-chlorobenzoic acid, as the starting material, was converted into corresponding amide

upon the treatment with NH_4Cl in the presence of EDCI, HOBt and DIPEA. The newly formed intermediates were subsequently condenced with corresponding *N*-Boc-protected α-homoalanine or α-homoalanine leading to the generation of the diamides. The following intramolecular cyclization under basic condition and nucleophilic substitution with corresponding bromomethyl or chloromethyl substituted aryl carboxylic ester furnished the 2, 3, 5-trisubstituted quinazolone derivatives. After unmasking the amino group, SNAr reaction with 2,4-diamino-6-chloropyrimidine-5-carbonitrile provided corresponding 2-(1-((2,4-diamino-5-cyano-pyrimidine-6-yl)amino)ethyl)-3-((5-(methoxycarbonyl)thiophene-2-yl)methyl)-5-chloro quinazolin-4(3*H*)-one and 2-(1-((2,4-diamino-5-cyano-pyrimidine-6-yl)amino)propyl)-3-((5-(methoxycarbonyl)thiophene-2-yl)methyl)-5-chloroquinazolin-4(3*H*)-one followed by reaction with hydroxyl amine afforded 2-(1-((2,4-diamino-5-cyano-pyrimidine-6-yl)amino)ethyl)-3-((5-(hydroxyaminocarbonyl)thiophene-2-yl)methyl)-5-chloroquinazolin-4(3*H*)-one and 2-(1-((2,4-diamino-5-cyano-pyrimidine-6-yl)amino)propyl)-3-((5-(hydroxyaminocarbonyl)thiophene-2-yl)methyl)-5-chloroquinazolin-4(3*H*)-one. These compounds showed PI3Kδ and HDAC6 inhibition activity.[8]



DOI: https://doi.org/10.5281/zenodo.13644773

5-Substituted-3-phenyl-2-((pyrimidin-4-ylamino)methyl)quinazolin-4(3*H*)-one derivatives were synthesized from compounds 5-substituted-(((tert-butoxycarbonyl)amino)methyl)-3-phenyl-quinazolin-4(3*H*)-one by attaching the pyrimidine kinase binding moieties using SNAr reactions and converting resulting esters to corresponding (((tert-butoxycarbonyl) amino)methyl)-3-phenyl-quinazolin-4(3*H*)-one-5-hydroxamic acids derivatives. These series of quinazolin-4-one-based hydroxamic acids were synthesized for the dual inhibition of PI3K and HDAC enzymes. Particularly, (*S*)-4-(((2-(1-((2-amino-5-cyano-6-methylpyrimidin-4-yl)amino)-propyl)-4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)amino)-methyl)-*N*-hydroxybenzamide was identified as a potent dual inhibitor with high kinome selectivity and potent antiproliferative activity against various cancer cell lines, including leukemia, melanoma, renal, nonsmall cell lung cancer, central nervous system (CNS) cancer, and breast cancer. Dual inhibitor also showed good potency in inducing cell death via necrosis in multiple AML cell lines, including the FLT3-ITD mutant and FLT3-inhibitor resistant cell lines, and primary cells from AML patients. [80]

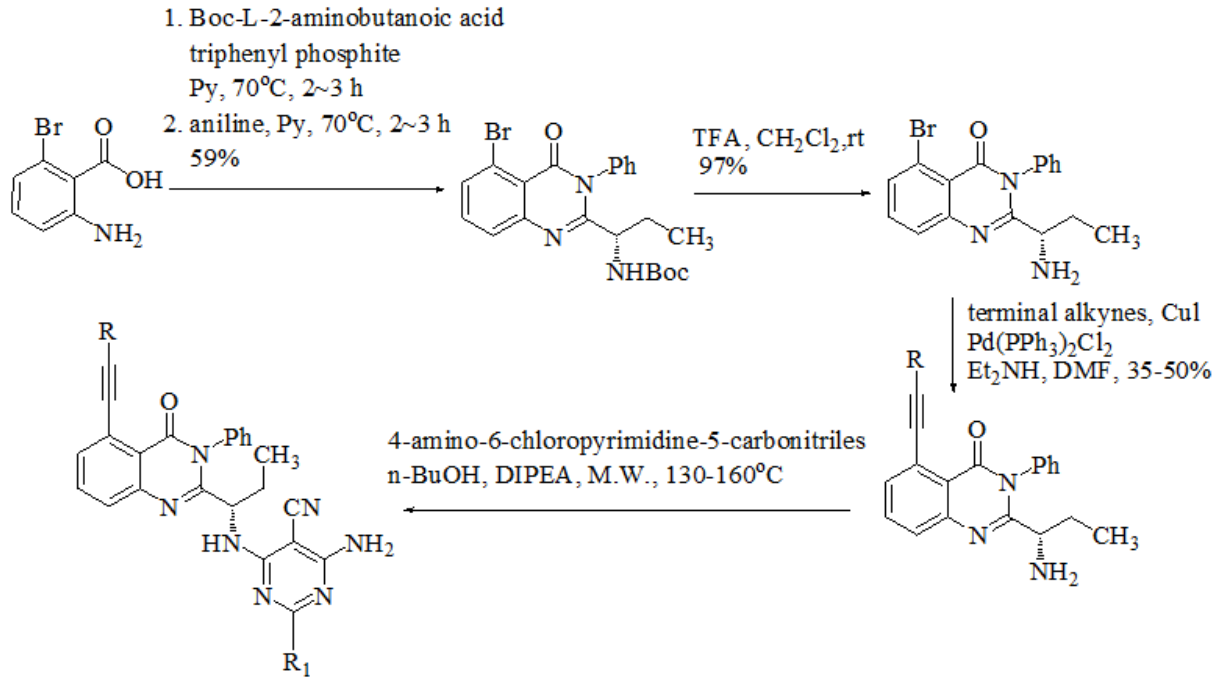


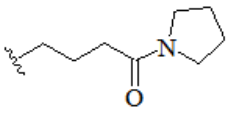
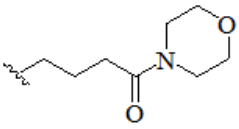
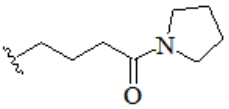
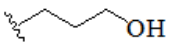
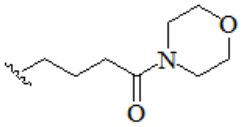
Z	R	R_1	R_2	R_3	yield(%)
$(CH_2)_5$	C_2H_5	CN	NH_2	NH_2	61
$(CH_2)_5$	C_2H_5	CN	CH_3	NH_2	69
$(CH_2)_5$	C_2H_5	CH_3	H	NH_2	70
$CH_2CH_2C_6H_4$	C_2H_5	CN	NH_2	NH_2	40
$CH_2NHCO(CH_2)_3$	C_2H_5	CN	CH_3	NH_2	82
$CH_2NHCOC_6H_4$	C_2H_5	CN	NH_2	NH_2	42
$CH_2NHCOC_6H_4$	C_2H_5	CN	CH_3	NH_2	52
$CH_2NHCOC_6H_4$	C_2H_5	H	CH_3	NH_2	42
$CH_2NHCOC_6H_4$	C_2H_5	CN	NH_2	H	39
$CH_2NHCOC_6H_4$	C_2H_5	Cl	NH_2	H	80
$CH_2NHCOC_5H_3N$	C_2H_5	Cl	NH_2	H	36
$CH_2NHCOC_6H_4$	C_2H_5	Cl	CH_3	NH_2	88
$CH_2NHCOC_6H_4$	C_2H_5	CN	NH_2	CH_3	64
$CH_2NHCOC_6H_4$	C_2H_5	Cl	NH_2	NH_2	40
$CH_2NHCOC_6H_4$	C_2H_5	CN	CF_3	NH_2	41
$CH_2NHCOC_6H_4$	C_2H_5	CN	cyclopropyl	NH_2	59
$CH_2NHCOC_6H_4$	C_2H_5	CN	CHF_2	NH_2	30
$CH_2NHCOC_6H_4$	CH_3	CN	NH_2	NH_2	64
$CH_2NHCOC_6H_4$	CH_3	CN	CH_3	NH_2	52

Compounds with potent antiproliferative activity against T lymphoblast MOLT-4 were obtained from 2-amino-6-bromobenzoic acid. Reaction of 2-amino-6-bromobenzoic acid with a (*S*)-2-(tert-butoxycarbonylamino)butanoic acid in the presence of triphenyl phosphite and pyridine and subsequent addition of aniline to the reaction mixture resulted in formation of Boc protected

DOI: https://doi.org/10.5281/zenodo.13644773

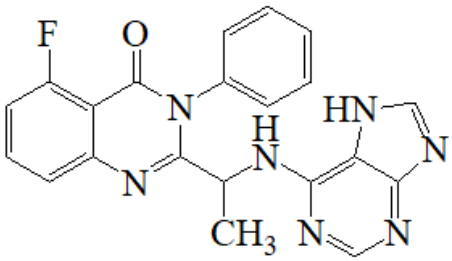
2-((*S*)-1-aminopropyl)-5-bromo-3-phenylquinazolin-4(3*H*)-one. Deprotection with TFA to get corresponding bromoquinazolinone derivative followed by reaction with terminal alkynyl via a Sonagashira coupling of under $Pd(PPh_3)Cl_2/CuI_2$ to yield corresponding quinazolinone derivatives. Incorporation of the hinge binder motif was accomplished by the nucleophilic displacement of substituted 4-amino-6-chloropyrimidine-5-carbonitrile in the presence of DIPEA at 130-160^{0}C under microwave irradiation and the target compounds, 5-substituted-2-((*S*)-1-((2-alkyl-4-amino-5-cyanopyrimidine-6-yl)amino)propyl)-3-phenyl-quina-zolin-4(3*H*)-one were obtained.[4]



R	R_1	Yield(%)	R	R_1	Yield(%)
	H	80		NH_2	77
	NH_2	78		NH_2	47
	H	76			

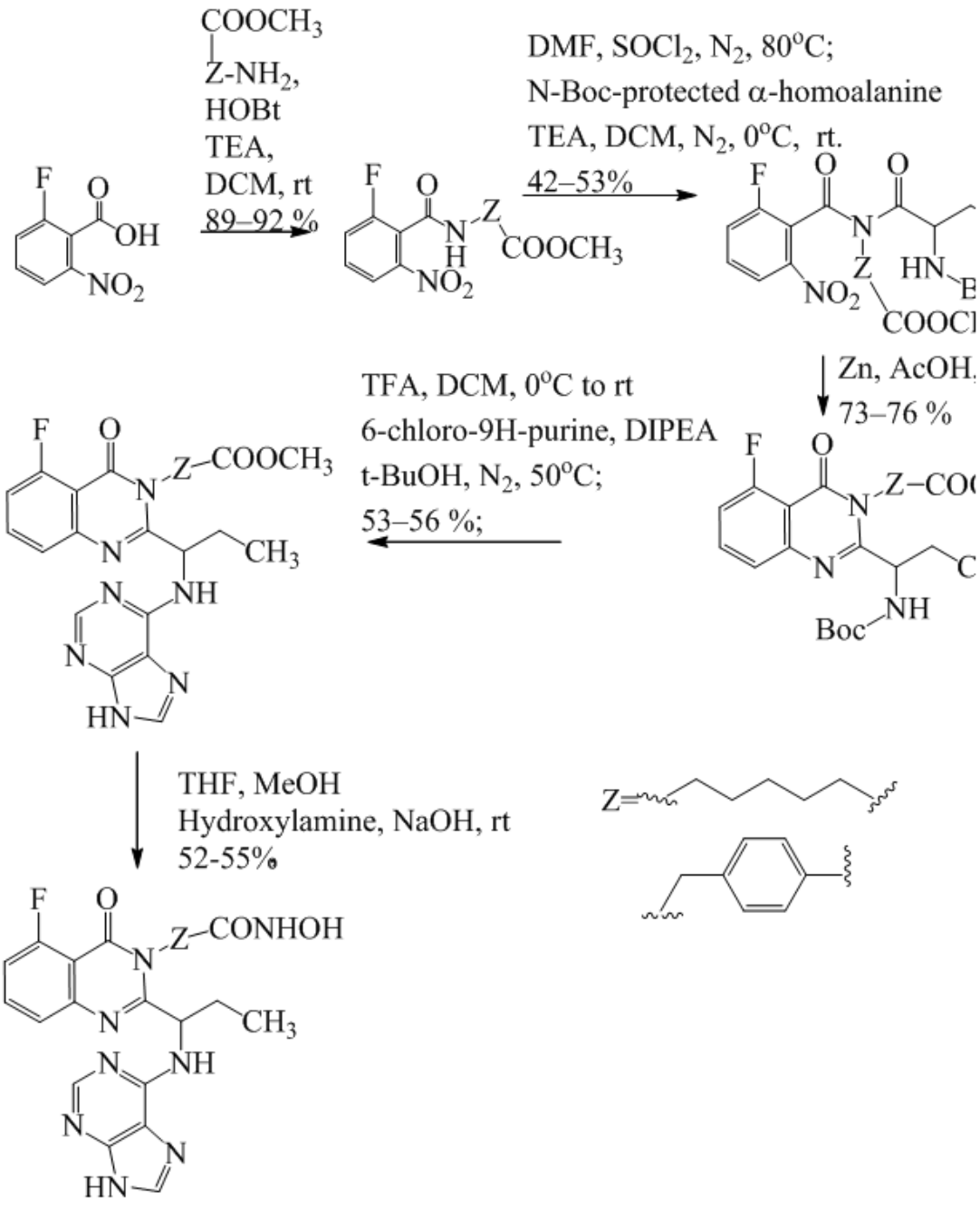
4.2.3 Purinylaminomethylquinazolin-4(3*H*)-one

Duvelisib-(2-(1-(7*H*-purin-6-ylamino)ethyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one) is a Phosphoinositide 3-kinase inhibitor, specifically of the delta and gamma isoforms of PI3K.[81]



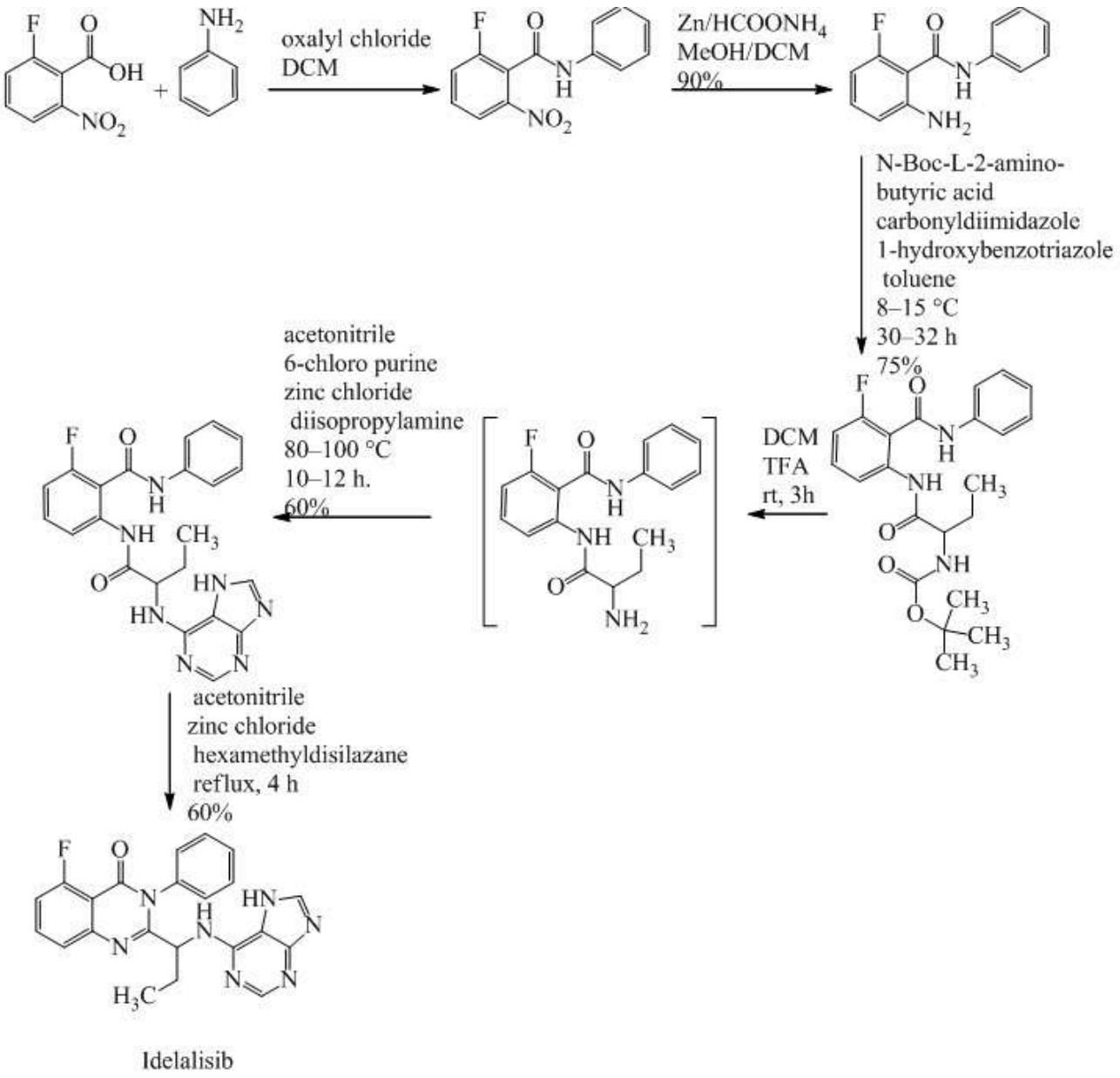
DOI: https://doi.org/10.5281/zenodo.13644773

2-Fluoro-6-nitrobenzoic acid was condensed with methyl 6-aminohexanoate hydrochloride or methyl 4-(aminomethyl)benzoate hydrochloride to afford the amide intermediates. Subsequently, they were converted into imidoyl chlorides, which underwent an in situ Mumm rearrangement after the treatment with corresponding *N*-Boc-protected α-homoalanine to generate the corresponding imides. The imides were then subjected to a one-pot reduction of the nitro moiety and the intramolecular cyclization, thereby furnishing the quinazolone derivatives. After unmasking the amino group, the SNAr reaction with 6-chloro-9*H*-purine to get 2-(1-(9*H*-purin-6-ylamino)propyl)-5-fluoroquinazolin-4(3*H*)-one derivatives followed by reaction with hydroxylamine provided 2-(1-(9*H*-purin-6-ylamino)propyl)-3-*N*-(hydroxyaminocarbonylpentyl) -5-fluoroquinazolin-4(3*H*)-one and 2-(1-(9*H*-purin-6-ylamino)propyl)-3-(((4-hydroxy amino carbonyl) phenyl)methyl)-5-fluoroquinazolin-4(3*H*)-one. These compounds exhibited PI3Kδ and HDAC6 activity.[8]



DOI: https://doi.org/10.5281/zenodo.13644773

Krishna Murthy et.al treated 2-fluoro-5-nitro benzoic acid with oxalylchloride followed by condensation with aniline in DCM to afford the corresponding 2-fluoro-6-nitro-*N*-phenylbenzamide. The reduction of nitro group for the preparation of amino intermediate is carried out by zinc and ammonium formate to afford the 2-amino-6-fluoro-*N*-phenylbenzamide. *N*-Boc-L-2-amino butyric acid was coupled with 2-amino-6-fluoro-*N*-phenylbenzamide at ambient temperature and achieved >98% purities with reasonably good yield to get Boc protected 2-{[(2S)-2-aminobutanoyl]amino}-6-fluoro-*N*-phenylbenzamide. Deprotection with TFA followed by reaction with 6-chloro purine to yield 2-{[(2S)-2-amino(7*H*-purin)butanoyl]amino}-6-fluoro-N-phenylbenzamide then cyclisation of resulting diamide afford the 5-fluoro-3-phenyl-2-[(1S)-1-(9*H*-purin-6-ylamino)propyl]-quinazolin-4(3*H*)-one (idelalisib).[260]

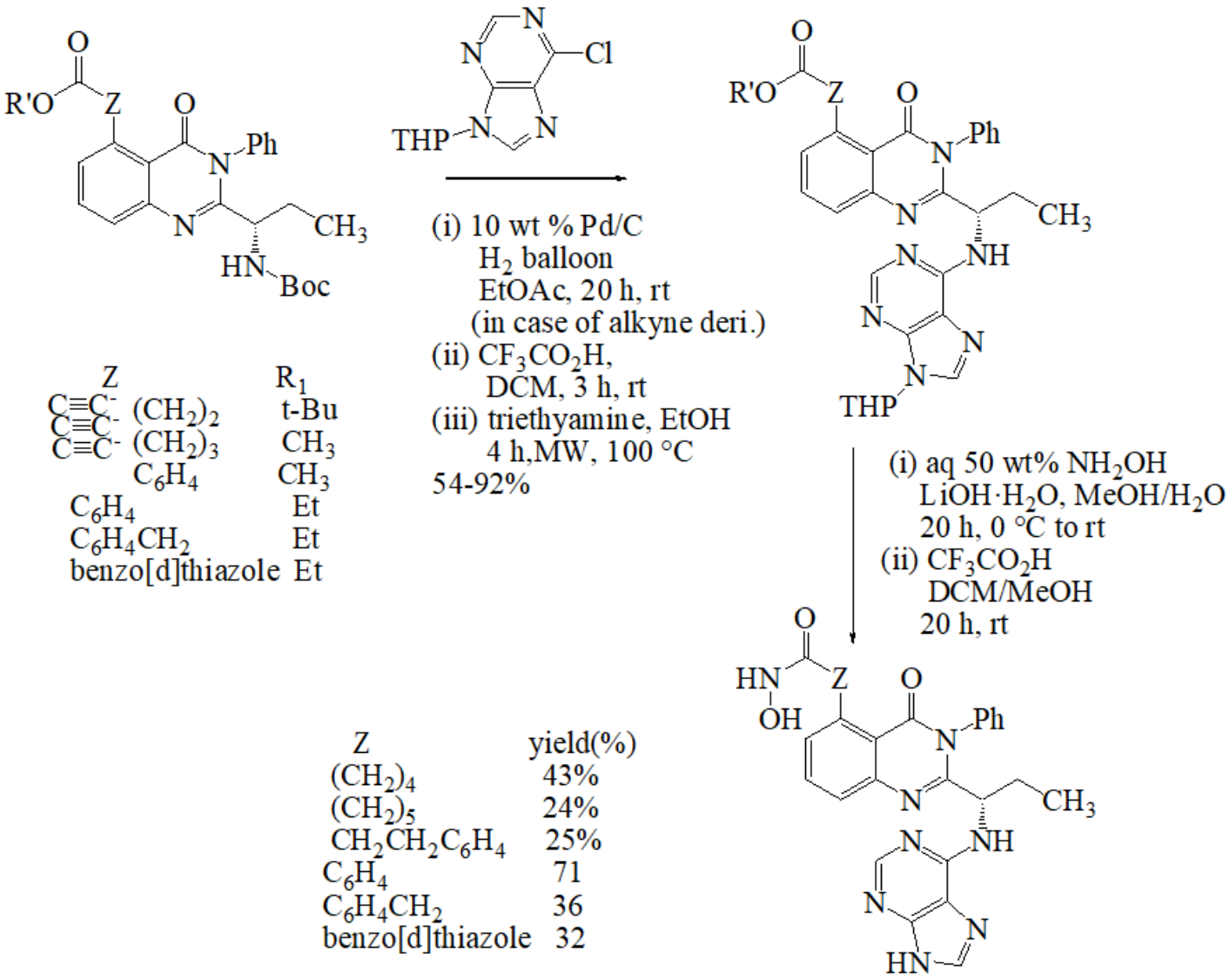


Idelalisib

Idelalisib is PI3K Delta Inhibitor for the treatment of three indolent B-cell neoplasms: relapsed/refractory chronic lymphocytic leukemia (CLL, in combination with rituximab), relapsed follicular lymphoma, and relapsed small lymphocytic lymphoma.[1]

DOI: https://doi.org/10.5281/zenodo.13644773

Hydrogenation of alkyne derivative followed by Boc-deprotection and nucleophilic aromatic substitution on purine afforded compounds 2-((*S*)-1-(9*H*-purin-6-ylamino)propyl)-3-phenyl quinazolin-4(3*H*)-one ester derivatives. Target compounds were derived by either: (a) hydrolyzing the alkyl ester to carboxylic acid, coupling with NH_2OTHP followed by deprotection of THP-protecting groups using TFA, or (b) converting the alkyl ester directly to hydroxamic acid using aq NH_4OH/LiOH and subsequent removal of the THP-protecting group using TFA. These compounds synthesized as novel dual PI3K/HDAC inhibitors by incorporating an HDAC pharmacophore into a PI3K inhibitor (Idelalisib) via an optimized linker.[80]

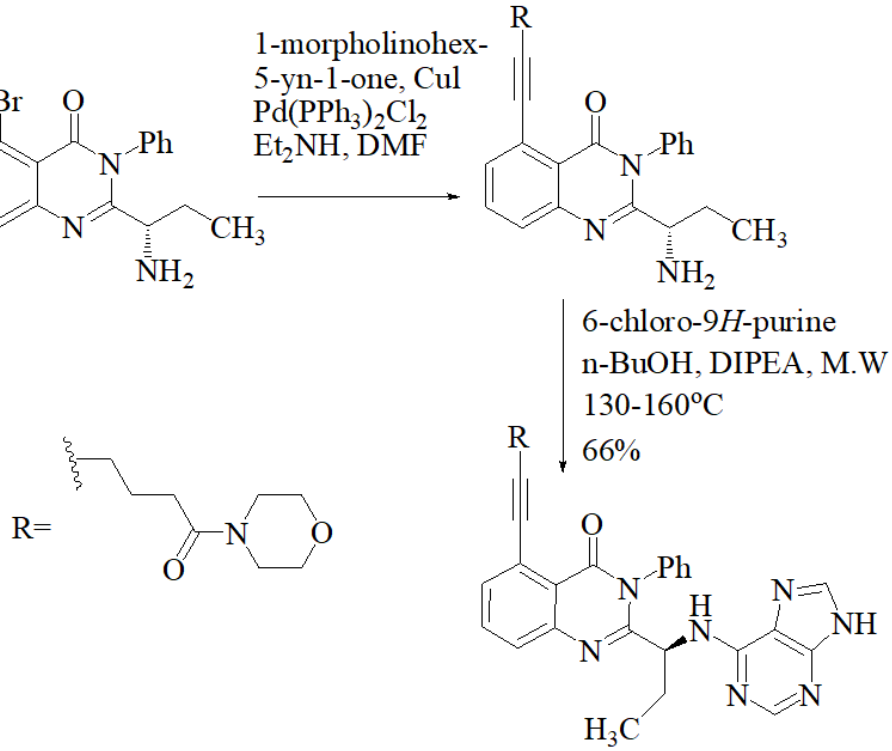


Z	R_1
$C\equiv C$	t-Bu
$C\equiv C-(CH_2)_2$	t-Bu
$C\equiv C-(CH_2)_3$	CH_3
C_6H_4	CH_3
C_6H_4	Et
$C_6H_4CH_2$	Et
benzo[d]thiazole	Et

Z	yield(%)
$(CH_2)_4$	43%
$(CH_2)_5$	24%
$CH_2CH_2C_6H_4$	25%
C_6H_4	71
$C_6H_4CH_2$	36
benzo[d]thiazole	32

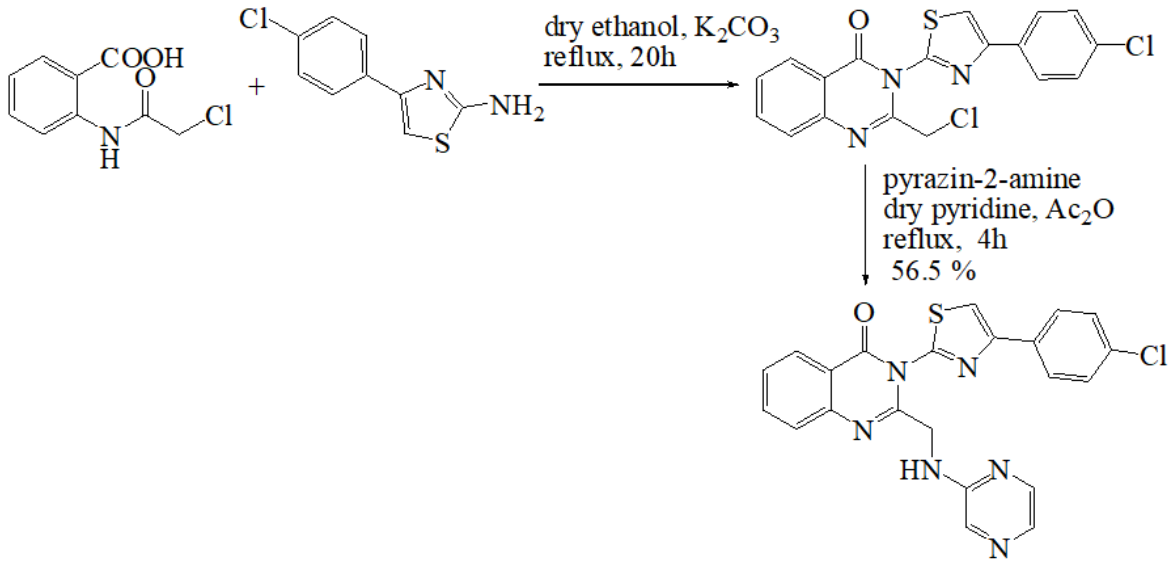
Ao Zhang etal reacted 1-morpholinohex-5-yn-1-one via a Sonagashira coupling of bromoquinazolinone derivative under $Pd(PPh_3)_2Cl_2$/CuI to yield the corresponding terminal alkyne derivative. Incorporation of the hinge binder motif was accomplished by the nucleophilic displacement of 6-chloro-9*H*-purine in the presence of DIPEA at 130-160°C under microwave irradiation and the target 2-((*S*)-1-(9*H*-purin-6-ylamino)propyl)-5-(6-morpholino-6-oxohex-1-ynyl)-3-phenylquinazolin-4(3*H*)-one was obtained. These are the compounds with potent PI3Kd and cell proliferation activities.[4]

DOI: https://doi.org/10.5281/zenodo.13644773



4.2.4 Pyrazinylaminomethylquinazolin-4(3*H*)-one

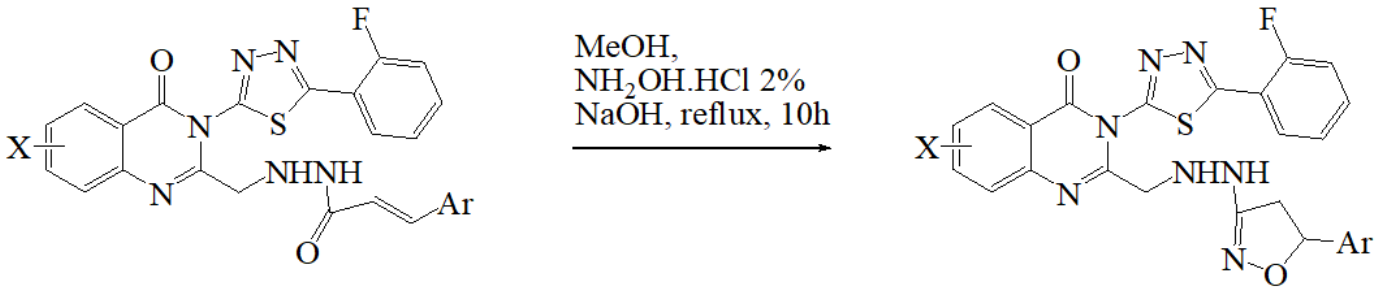
Potent Antitubercular agents, *N*-3-(4-(4-chlorophenyl)thiazol-2-yl)-2-((pyrazin-2-yl)amino methyl)-quinazolin-4(3*H*) -one derivatives, were prepared by reacting *N*-chloro acetylanthranilic acid with 4-chlorophenyl thiazole to 2-chloromethyl-3-[4-(4-chlorophenyl) thiazol-2-yl]-quinazolin-4(3*H*)-one followed by condensation with pyrazin-2-amine.[82]



4.2.5 Dihydroisoxazolylhydrazinylmethylquinazolin-4(3*H*)-ones

Hemlata et.al reacted 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5- (un/substituted hetetocyclic/arylchalconyl)-hydrazinyl)methyl)-substituted quinazolin- 4(3*H*)-one with hydro - xyl amine hydrochloride at reflux in methanol in presence of 2% NaOH solution to isolate potent antipsychotic and anticonvulsant agents, 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-((2-(5-(unsubstituted heterocyclic/aryl)-4,5-dihydroisoxazol-2-yl)hydrazinyl)methyl) substituted quinazolin-4(3*H*)-one. These compounds have exhibited antibacterial activity.[85]

DOI: https://doi.org/10.5281/zenodo.13644773

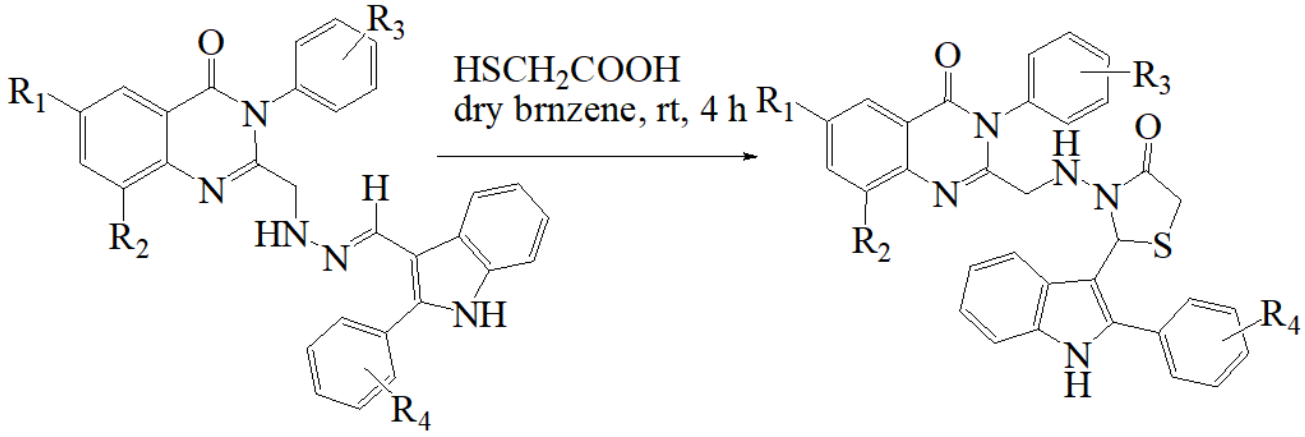


X	H	6-Br	6,8-di Br	H	6-Br
Ar	2-pyridyl	2-pyridyl	2-pyridyl	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
Yield (%)	74	78	77	69	71

X	6,8-di Br	H	6,8-di Br
Ar	4-$CH_3OC_6H_4$	4-CH_3Oindol-3-yl	4-CH_3Oindol-3-yl
Yield (%)	79	77	75

4.2.6 Indolylthiazolylaminomethylquinazolin-4(3*H*)-ones

Reaction of 6,8-disubstituted 3-aryl-2-{3'-[3"-(2"-arylindolylmethylene)]hydrazinomethyl}-quinazolin-4(3*H*)-ones with thioacetic acid in dry benzene yielded 6,8-disubstituted-3-aryl-2-{[2'-(2"-arylindol-3"-yl)-4'-oxothiazolidin-1'-yl]aminomethyl}-quinazolin-4(3*H*)-ones.[261]

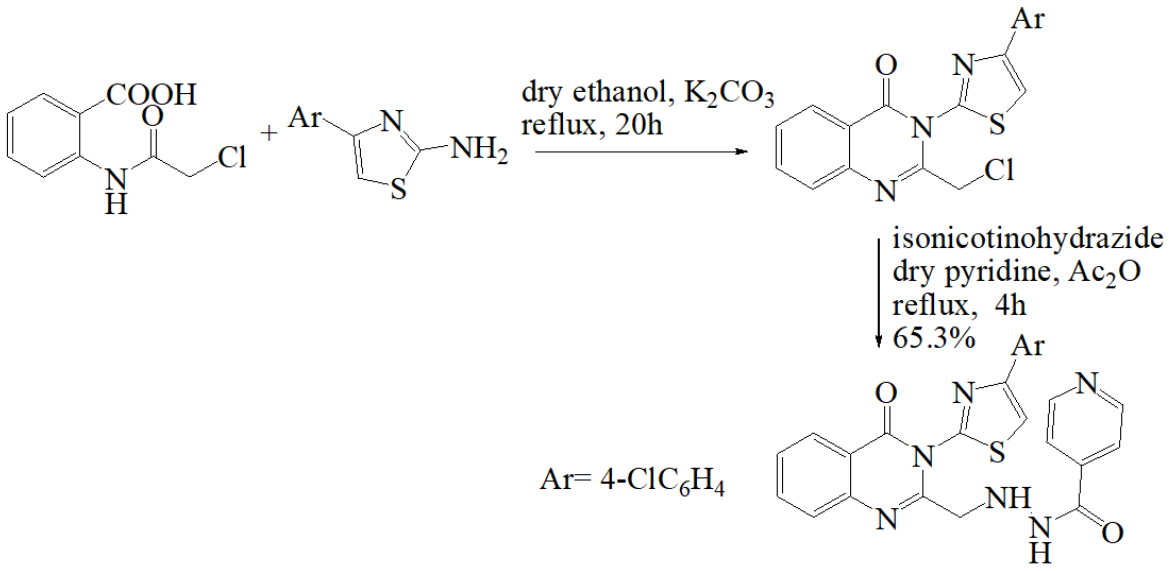


R_1	I	I	Br	Br	Br	Br	I	I	Br	Br	H
R_2	H	H	H	H	Br	Br	H	H	H	H	H
R_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	2-CH_3	4-Cl	4-Cl	3-Cl	3-Cl	NH_2
R_4	H	4-CH_3	H	4-CH_3	H	4-CH_3	H	4-CH_3	H	4-CH_3	H

4.2.7 Isonicotinoylhydrazinylquinazolin-4(3*H*)-one

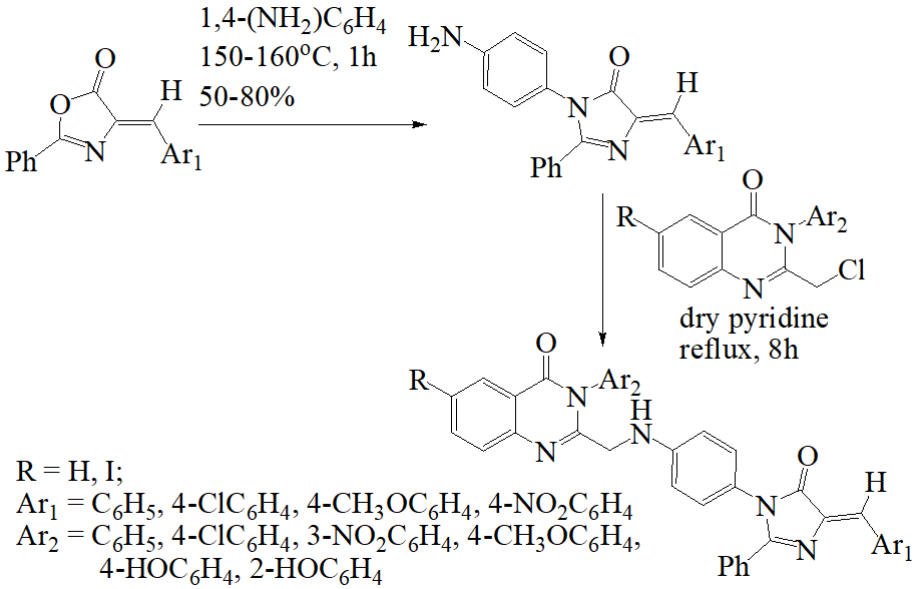
Potent antitubercular agent, *N*'-((3-(4-(4-chlorophenyl)thiazol-2-yl)-quinazolin-4(3*H*)-one-2-yl)-methyl)isonicotinohydrazide, was prepared by reacting *N*-chloroacetyl anthranilic acid with 4-chlorophenyl thiazole in presence of potassium to isolate 2-chloromethyl-3-[4-(4-chlorophenyl)-thiazol-2-yl]-quinazolin-4(3*H*)-one followed by refluxing the resultant compound with isonicotinohydrazide in dry pyridine and acetic anhydride.[82]

DOI: https://doi.org/10.5281/zenodo.13644773



4.2.8 Imidazolylphenylaminomethylquinazolin-4(3*H*)-ones

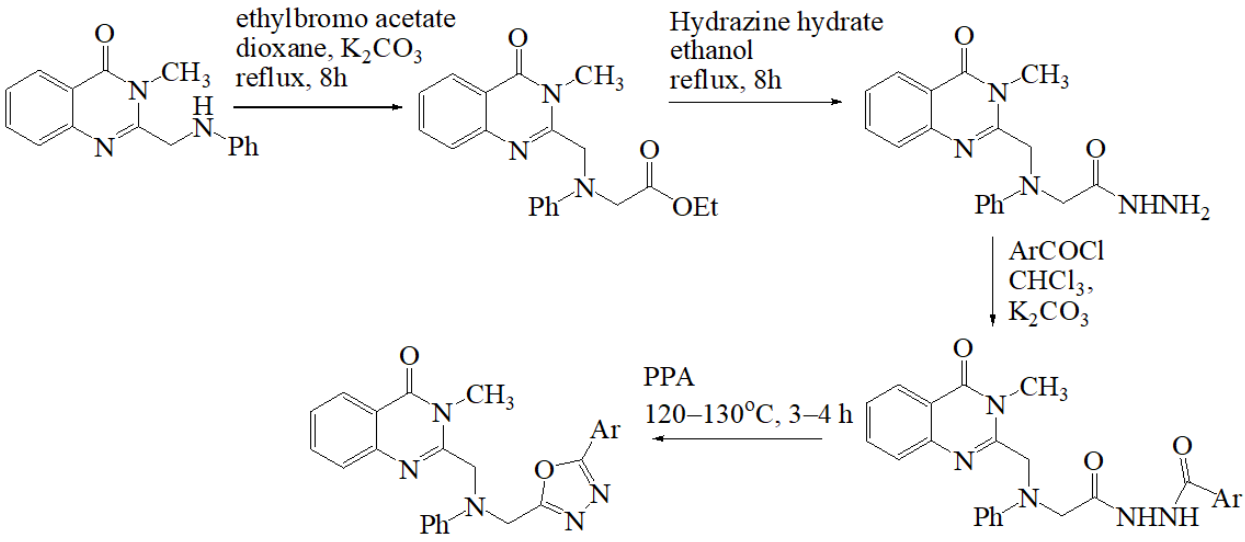
A number of 2-{1'-{4'-[4"-(arylmethylene)-4",5"-dihydro-2"-phenylimidazol-5"-one]phenyl} amino - methyl}-3-aryl-quinazolin-4(3*H*)-ones showed significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. The title compounds were synthesised by first condensing 1,4-phenylenediamine with the lactone phenyl(benzylidene)oxazolinones to isolate 1-(4-aminophenyl)-2-phenyl-(4-arylmethylene)imidazol-5-ones and its subsequent reaction with 3-aryl-2-chloro-methyl-quinazolin-4(3*H*)-ones.[262]



4.2.9 Oxadiazolylmethylaminomethylquinazolin-4(3*H*)-ones

Alkylation of 2-phenylaminomethyl-3-oxadiazolylquinazolin-4(3*H*)-one with ethylbromo acetate to ethyl 2-(*N*-((3-methylquinazolin-4(3*H*)-one-2-yl)methyl)-*N*- phenylamino)acetate followed by hydrazinolysis with hydrazine hydrate furnished 2-{[(3-methylquinazolin-4(3*H*)-one-2-yl)methyl]-aniline}ethanohydrazide. Aroylation of hydrazide compound to corresponding compounds and ring formation on reaction with polyphosphoric acid (PPA) at 120-130°C to isolate 3-methyl-2-({[5-aryl-1,3,4-oxadiazol-2-yl)methyl]aniline}methyl)-quinazolin-4(3*H*)-ones.[263]

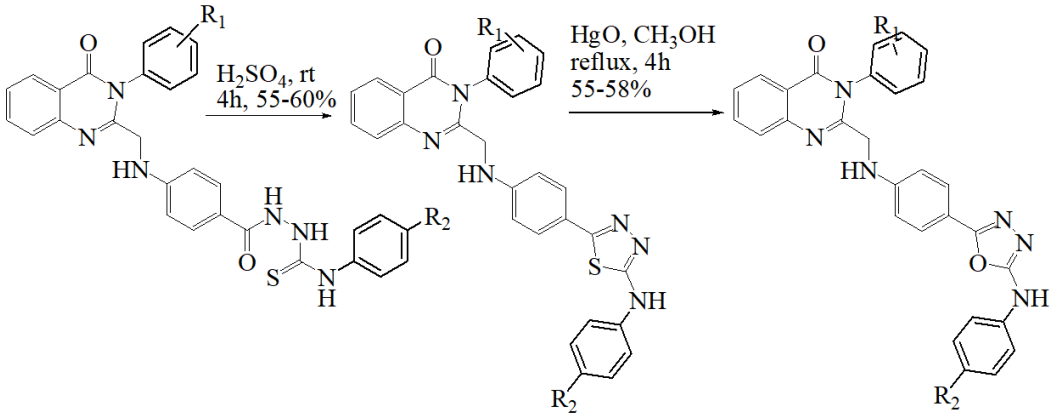
DOI: https://doi.org/10.5281/zenodo.13644773



Ar	Ph	4-MeC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	3-MeC_6H_4	3-ClC_6H_4
Yield(%)	66	67	60	51	52	59

4.2.10 Oxadiazolylphenylaminomethylquinazolin-4(3*H*)-ones

Hussain and Jamali prepared the hypoglycemic agents, 2-{4'-[5"-(2"-arylamino-1",3",4"-thiadiazolyl)]-phenyl}aminomethyl-3-aryl-quinazolin-4(3*H*)-ones, by cyclizing the thiosemicarbazides in concentrated sulfuric acid at room temperature. The thiadiazole derivatives were converted to the corresponding oxadiazole derivatives, 2-{4'-[5"-(2"-arylamino-1",3",4"-oxadiazole)]phenyl)}aminomethyl-3-aryl-quinazolin-4(3*H*)-ones by refluxing in methanol containing mercuric oxide.[86]

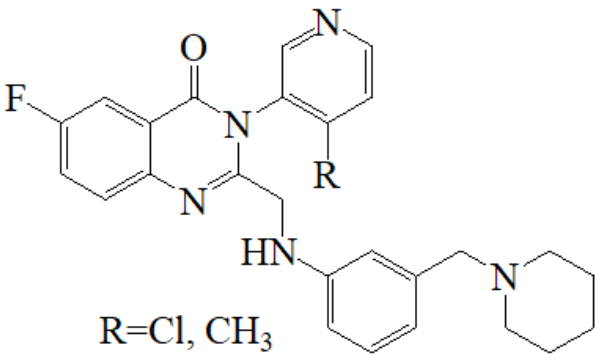


R_1	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3
R_2	H	H	H	CH_3	CH_3	CH_3	OCH_3	OCH_3
R_1	4-NO_2	2-CH_3	4-OCH_3	4-NO_2	2-CH_3	4-OCH_3		
R_2	OCH_3	Cl	Cl	Cl	Br	Br		

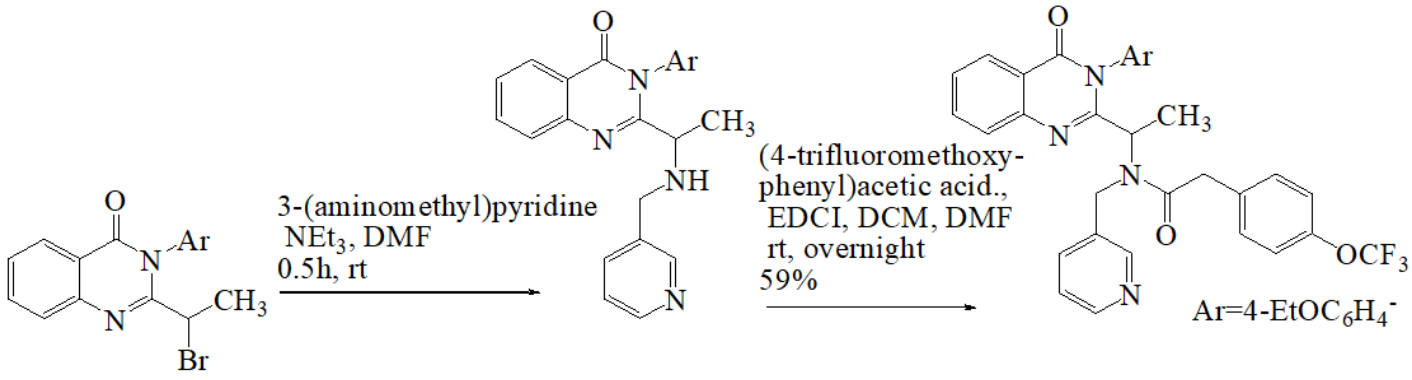
4.2.11 Pyrrolidinomethylphenylaminomethylquinazolin-4(3*H*)-ones

3-(2-Chlorophenyl)-6-fluoro-2-[3-(1-pyrrolidinomethyl)phenylaminomethyl]quinazolin-4(3*H*)-one and 3-(2-methylpyridyl)-6-fluoro-2-(3-(1-pyrrolidinomethyl)phenylaminomethyl quinazolin-4(3*H*)-one are neuroprotective agents, a potent AMPA receptor antagonist with an IC_{50} value < 5mM against AMPA receptor activation induced 45 Ca^{+2} uptake in rat cerebella granule cell cultures.[87]

DOI: https://doi.org/10.5281/zenodo.13644773



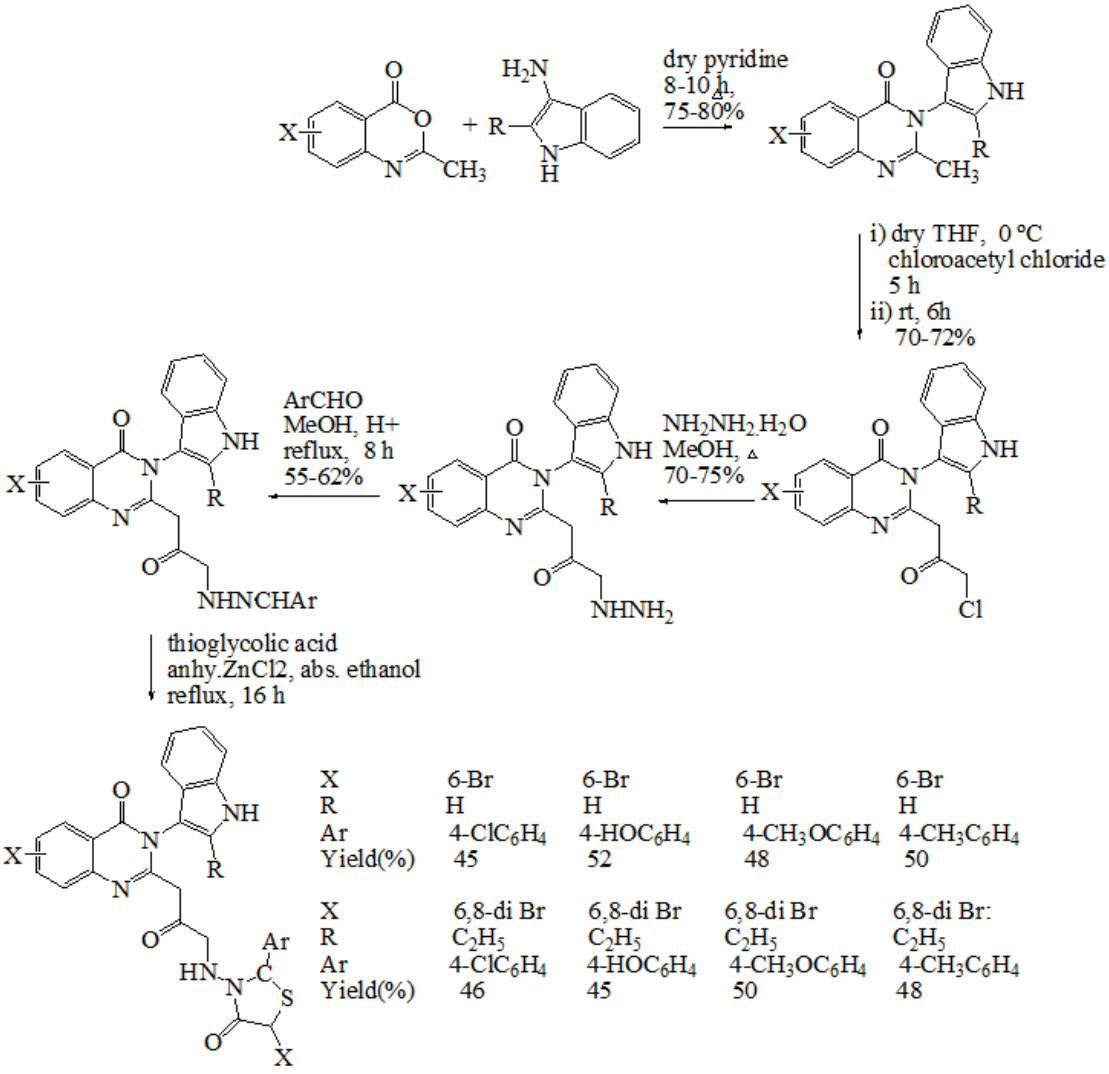
Stefania et.al prepared CXCR3 receptor antagonists, *N*-{1-[3-(4-ethoxy-phenyl)-quinazolin-4(3*H*)-one-2-yl]-ethyl}-*N*-pyridin-3-ylmethyl-2-(4-trifluoromethoxy phenyl)-acetamide on reaction of 2-(1-bromoethyl)-3-aryl-quinazolin-4(3*H*)-one with 3-(aminomethyl)pyridine and condensation of resultant 3-(aryl)-2-{1-[(pyridin-3-ylmethyl)-amino]-ethyl}-quinazolin-4(3*H*)-one with (4-tri fluoromethoxy-phenyl)-acetic acid.[88]



4.2.12 Thiazolidinylaminoacetylmethylenylquinazolin-4(3*H*)-ones

Potent anti-inflammatory, analgesic and COX-II Inhibitors derivatives, 2-(*N*-(5-substituted 2-aryl-4-oxo-3-thiazolidinyl)aminoacetylmethyl)-3-(2-substitutedindol-3-yl)-substituted quinazolin-4(3*H*)-ones were prepared from 2-methylsubstituted benzoxazines. Reaction of benzoxazines with 2-substituted-3-aminoindoles, treatment with chloroacetyl chloride to corresponding compound, reaction with hydrazinehydrate to 2-hydrazinoacetylmethylene-3-(2'-substitute dindol-3'-yl)-substituted quinazolin-4(3*H*)-ones, condensation with substituted benzaldehyde to 2-(substituted phenylmethyleneimino)aminoacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones and finally reacted with thioglycolic acid in the presence of anhydrous $ZnCl_2$ to yield compound.[89,90]

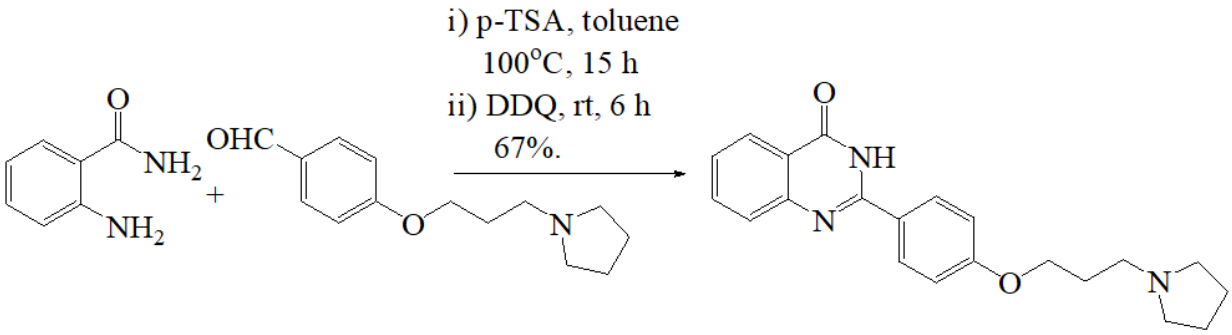
DOI: https://doi.org/10.5281/zenodo.13644773



4.3 Heterylphenyl

4.3.1 Pyrrolidinylpropyloxyphenylquinazolin-4(3*H*)-one

The anthranilamide was thermally condensed with 4-[3-(pyrrolidin-1-yl)propoxy] benzaldehyde in presence of a catalytic amount of p-toluenesulfonic acid, followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone to furnish the 2-(4-{[3-(1-pyrrolidinyl)propyl]oxy}phenyl)-quinazolin-4(3*H*)-one. This is identified as a potent and selective radioligand for histamine H_3 receptors.[92]



4.3.2 Thiophenylphenylquinazolin-4(3*H*)-one

The reaction of the 2-methoxy-6-(thiophen-3-yl) benzaldehyde and *N*-(3,5-bis (trifluoromethyl) benzyl)-2-aminobenzamide under the catalysis of the chiral phosphoric acid with a catalyst loading of 10 mol % and following oxidation by DDQ, the corresponding

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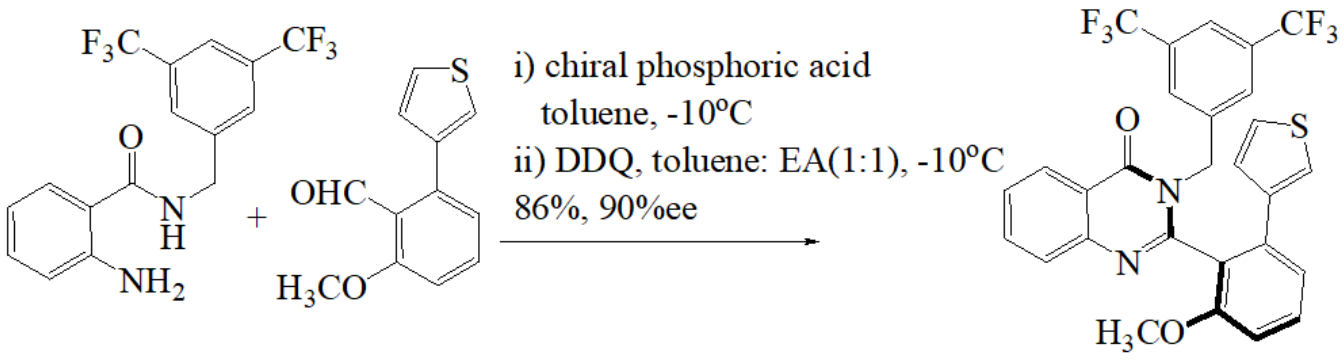
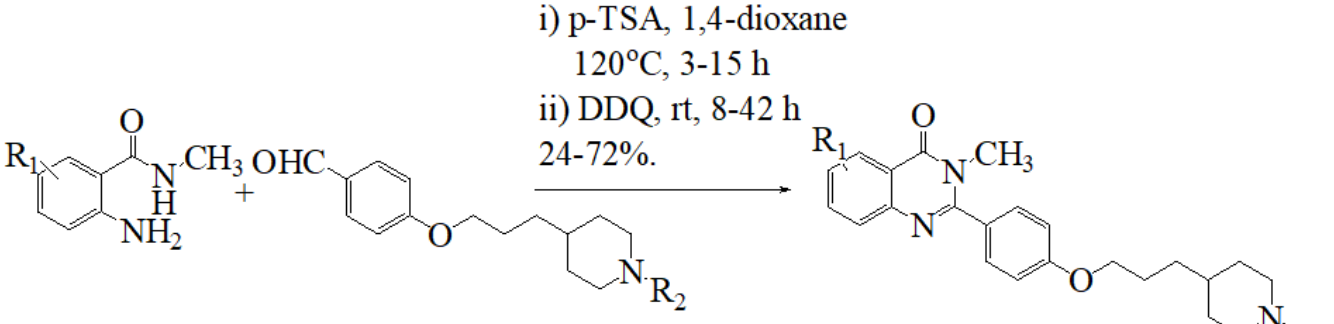
3-(3,5-bis(trifluoromethyl)benzyl)-2-(2-methoxy-6-(thiophen-3-yl)phenyl)quinazolin-4(3*H*)-one constructed with excellent outcomes in terms of yield and ee value.[264]



4.3.3 Piperidinylpropoxyphenylquinazolin-4(3*H*)-ones

The benzamide derivative was thermally condensed with 4-aminoalkoxy benzaldehyde in presence of a catalytic amount of p-toluenesulfonic acid followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone to furnish the 2-[4-(aminoalkoxy)phenyl]-quinazolin-4(3*H*)-one derivatives. These derivatives were identified as potent human H_3 receptor inverse agonists.[93]

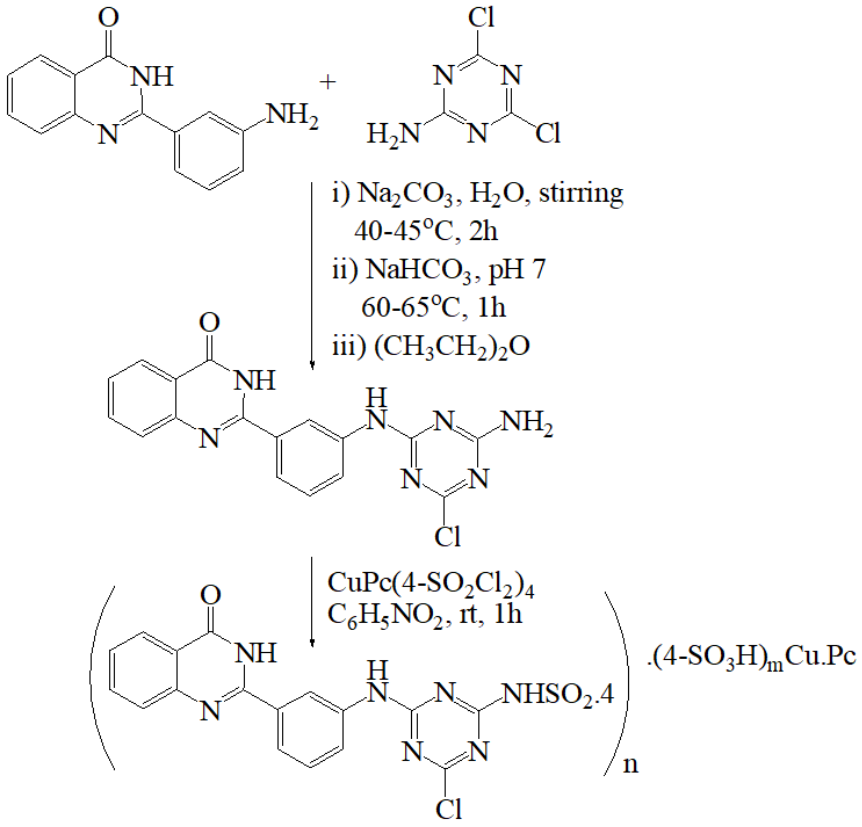


R_1 = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, $CH_2C_6H_5$, C_6H_5
R2 = cyclobutyl, cyclopentyl

4.3.4 Triazolylaminophenylquinazolin-4(3*H*)-ones

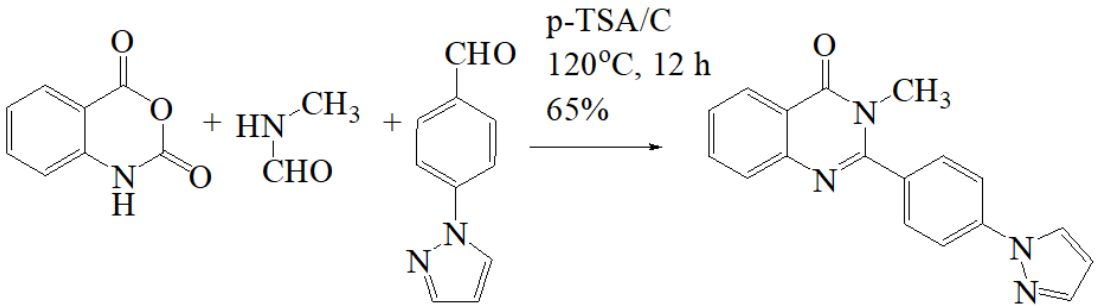
2-Amino-4,6-dichloro-s-triazine was reacted with 2-(3-aminophenyl)-quinazolin-4(3*H*)-ones in aqueous sodium carbonate solution at room temperature to give 2-{3'-[4"-(2"-amino-6"-chloro-*S*-triazine)]aminophenyl}-quinazolin-4(3*H*)-ones. They were derivatized with copper phthalo cyanine and the resulting products are useful as fiber reactive dyes.[94]

DOI: https://doi.org/10.5281/zenodo.13644773



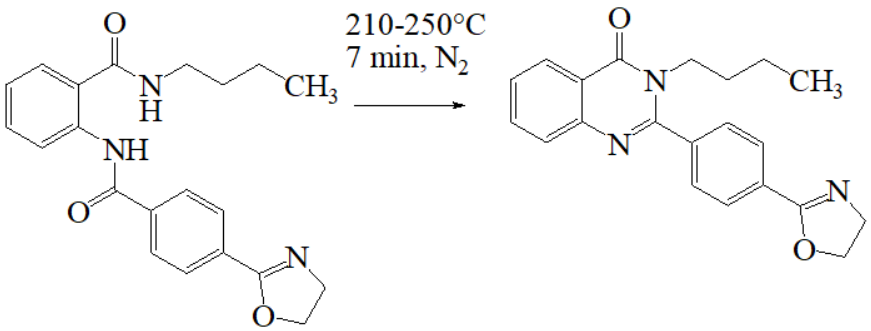
4.3.5 Pyrazolylphenylquinazolin-4(3*H*)-one

The straightforward preparation of 2-(4-(1*H*-pyrazol-1-yl)phenyl)-3-methyl quinazolin-4(3*H*)-one via the reusable carbon-supported acid-catalyzed direct amidation and cascade annulation of isatoic anhydride with *N*-methylformamide and 4-(1*H*-pyrazol-1-yl)benzaldehyde is reported.[188]



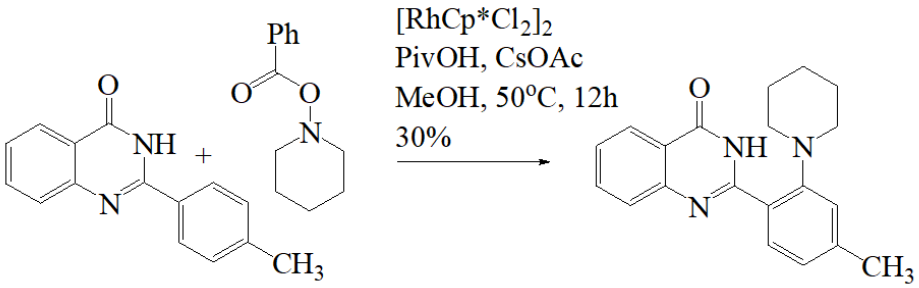
4.3.6 Dihydrooxazolylphenylquinazolin-4(3*H*)-one

Jakisch et.al heated the 2-(4-(4,5-dihydrooxazol-2-yl)benzoylamino-*N*-butylbenzamide for 7 min under nitrogen in a small glass tube at 210° C (below 250° C) to yield 3-butyl-2-(4-(4,5-dihydrooxazol-2-yl)phenyl)-quinazolin-4(3*H*)-one. The reaction at 250°C yielded a mixture of staring material and product.[265]

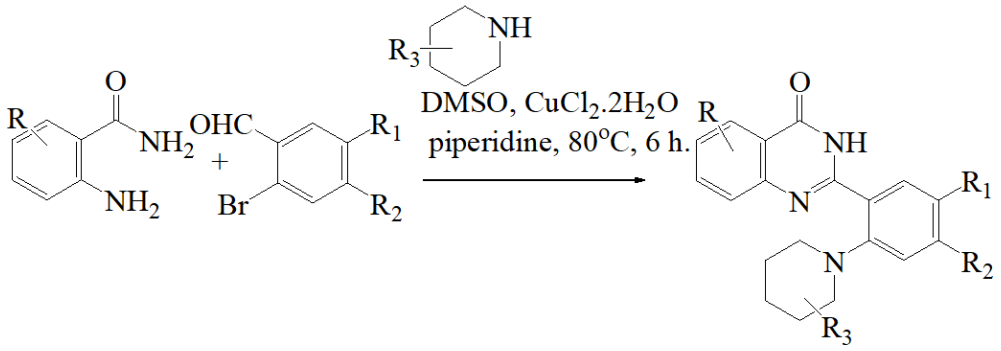


4.3.7 Piperidinylphenylquinazolin-4(3*H*)-ones

The ortho C-H amination of 2-p-tolylquinazolin-4(3*H*)-one was achieved with *N, N*-benzoyl oxypiperidine in presence of Rh-catalyzed to isolate 2-(4-methyl-2-(piperidin-1-yl)phenyl)quinazolin-4(3*H*)-one.[172]



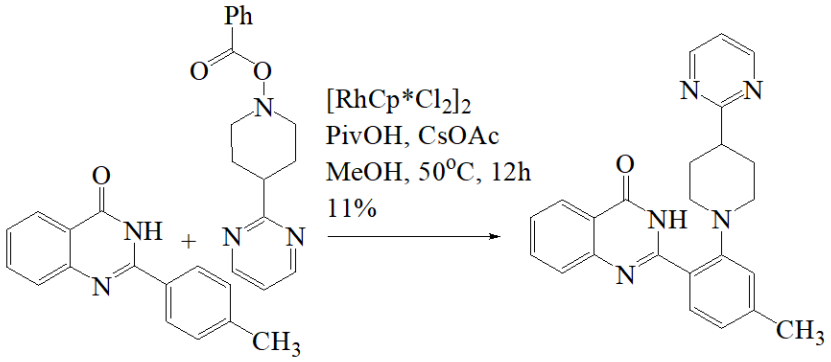
A mixture of 2-bromo benzaldehyde, anthranilamide and piperidine was reacted in DMSO containing $CuCl_2.2H_2O$ at 80° C temperature for 6 h to provide 2-(2-(piperidin-1-yl)phenyl)quinazolin-4(3*H*)-ones.[266]



R	R_1	R_2	R_3	yield(%)	R	R_1	R_2	R_3	yield(%)
H	H	H	H	85	H	OCH_3	OCH_3	H	72
H	H	H	4-CH_3	74	H	OCH_3	H	H	77
H	H	H	3-CH_3	73	H	OCH_2O		H	81
H	H	H	4-CH_2Ph	76	H	NO_2	H	H	56
6-Cl	H	H	H	84					

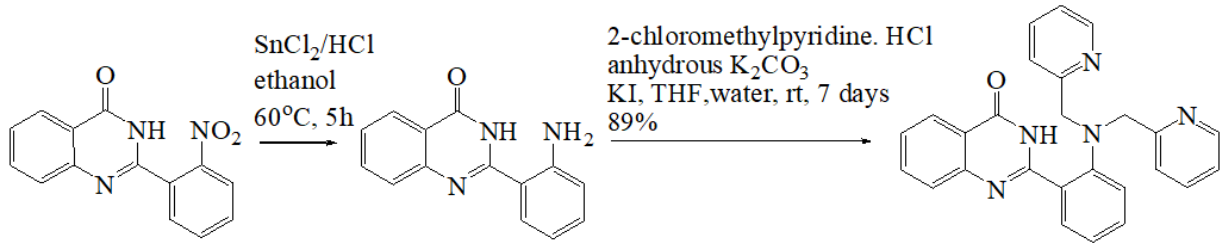
4.3.8 Pyrimidinylpiperidinylphenylquinazolin-4(3*H*)-one

The ortho C-H amination of 2-p-tolylquinazolin-4(3*H*)-one was achieved with 2-(1-benzoyloxypiperidin-4-yl)pyrimidine in presence of Rh-catalyzed to isolate 2-(4-methyl-2-(4-(pyrimidin-2-yl)piperidin-1-yl)phenyl)quinazolin-4(3*H*)-one.[172]



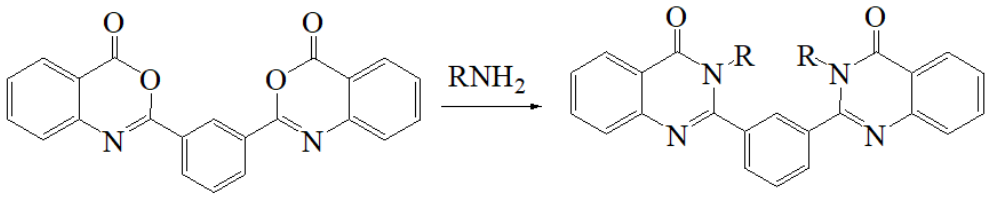
4.3.9 Bispyridinylmethylaminophenylquinazolin-4(3H)-one

2-(2-Nitrophenyl)-quinazolin-4(3*H*)-one was reduced with tin dichloride and the resultant 2-(2-aminophenyl)-quinazolin-4(3*H*)-one was treated with 2-chloromethyl- pyridine hydrochloride to afford 2-(2-(bispyridin-2-ylmethyl)aminophenyl)-quinazolin-4(3*H*)-one. These quinazoline useful as chemosensor for cobalt(II) recognition based on excited-state intramolecular proton transfer.[95]

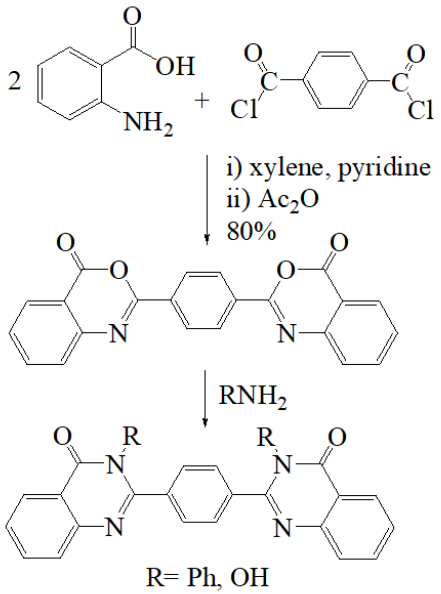


4.3.10 {2,2"-Bis[quinazolin-4(3*H*)-one]}benzenes

1',3'-{2,2"-Bis[quinazolin-4(3*H*)-one]}benzene and its *N*-substituted derivatives showed broad spectrum of antibacterial activity and were synthesized by amine insertion reaction with 1',3'-[2,2"-bis(3,1-benzoxazin-4-one)]benzene.[267]



In a similar way, 1',4'-{2,2"-bis[quinazolin-4(3*H*)- one]}benzenes were prepared by the insertion of aniline with 1',4'-[2,2"-bis(3,1-benzoxazin-4-one)]benzene. Use of hydroxylamine in the reaction yields the 3-hydroxy derivative. The benzoxazin derivative was prepared in 80% yield from the reaction anthranilic acid and terephthaloyl chloride in xylene containing pyridine and subsequent treatment with Ac_2O.[268]



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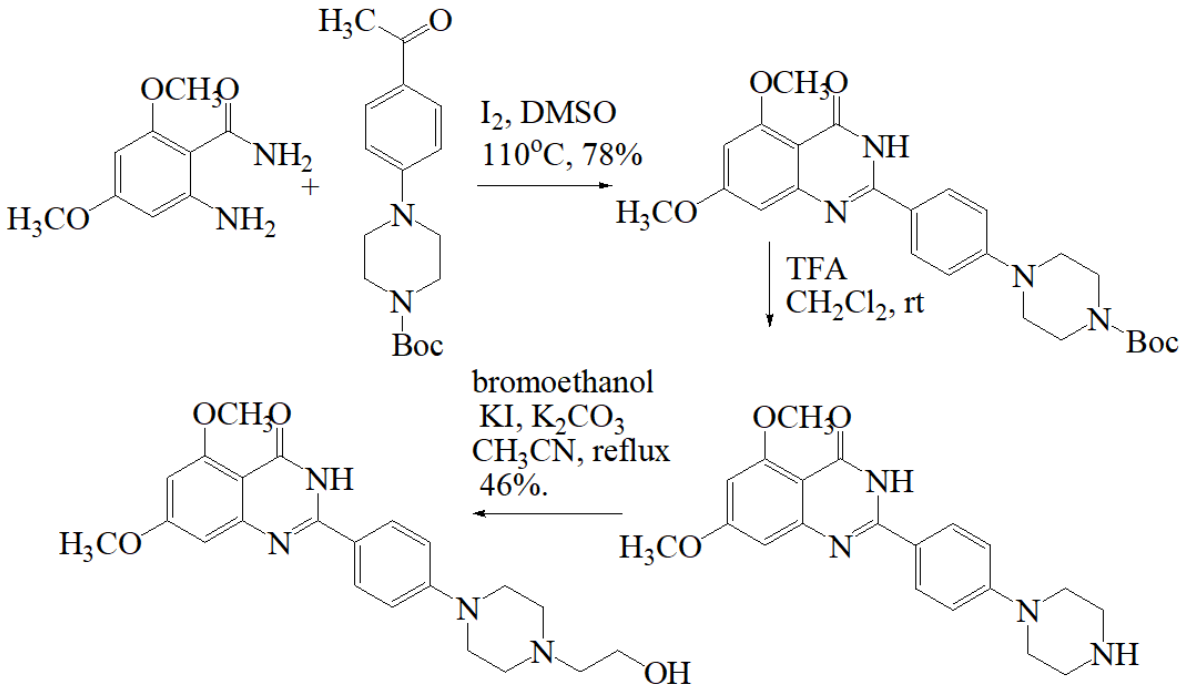
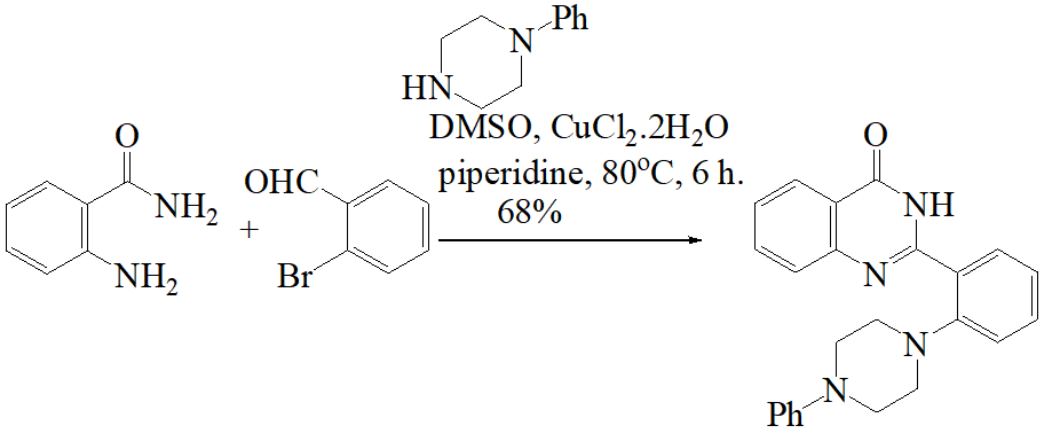
4.3.11 Piperazinylphenylquinazolin-4(3*H*)-one

The tert-butyl 4-(4-acetylphenyl)piperazine-1-carboxylate was reacted with 2-amino-4,6-dimethoxybenzamide in I_2 containing DMSO to provide tert-butyl 4-(4-(3,4-dihydro-5,7-dimethoxy-4-oxoquinazolin-2-yl)phenyl)piperazine-1-carboxylate. The Boc group was removed under TFA to provide 5,7-dimethoxy-2-(4-(piperazin-1-yl)phenyl)quinazolin-4(3*H*)-one which was further substituted by bromoethanol to yield 2-(4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one smoothly in presence of K_2CO_3 and KI. This compound has shown AChE inhibitor with anti-inflammatory activity.[13]



A mixture of 2-bromo benzaldehyde, anthranilamide and 1-phenylpiperazine was reacted in DMSO containing $CuCl_2.2H_2O$ at 80°C temperature for 6 h to provide 2-(2-(4-phenylpiperazin-1-yl)phenyl)quinazolin-4(3*H*)-one.[266]

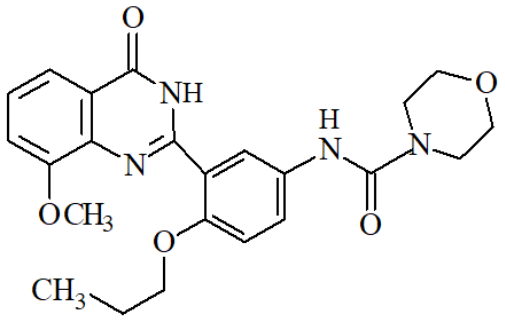


4.3.12 Morpholinylcarbaminoarylquinazolin-4(3*H*)-one

***N*-[3-(8-Methoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-4-propoxyphenyl]morpholine-4-carbamide is a lead drug for the treatment of heart failure and other cardiovascular and respiratory**

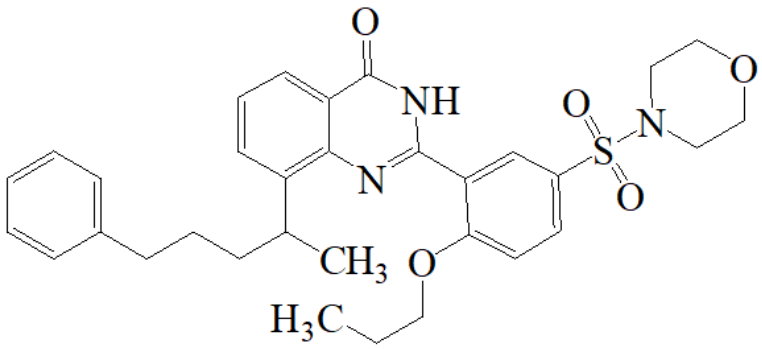
DOI: https://doi.org/10.5281/zenodo.13644773

tract / allergic disorders, with potent cGMP phosphodiesterase (PDE V) inhibitory activity. [96]

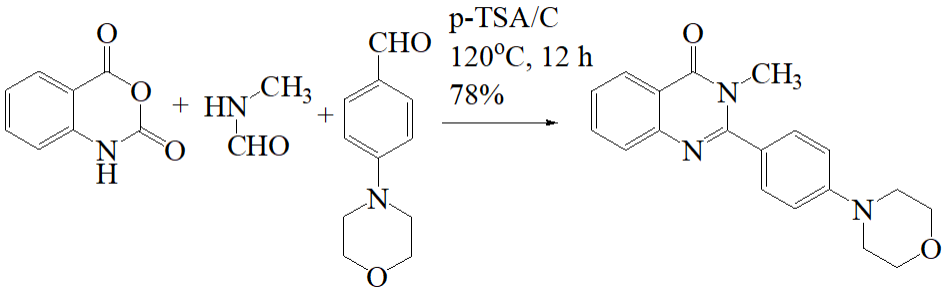


4.3.13 Morpholinylsulfonylarylquinazolin-4(3*H*)-one

8-(1-Methyl-4-phenylbutyl)-2-[5-(morpholinylsulfonyl)-2–propoxyphenyl]-4(3*H*)-quinazolinone is used for the treatment of cardiovascular and thromboembolic disorders that exhibits potent in vitro inhibition of phosphodiesterase type II to V (and PDE V) activity.[97]

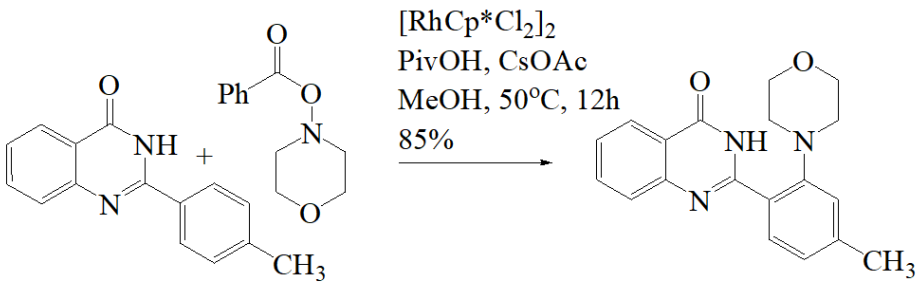


The straightforward preparation of 3-methyl-2-(4-morpholinophenyl)quinazolin-4(3*H*)-one via the reusable carbon-supported acid-catalyzed direct amidation and cascade annulation of isatoic anhydride with *N*-methylformamide and 4-morpholinobenzaldehyde is reported.[188]

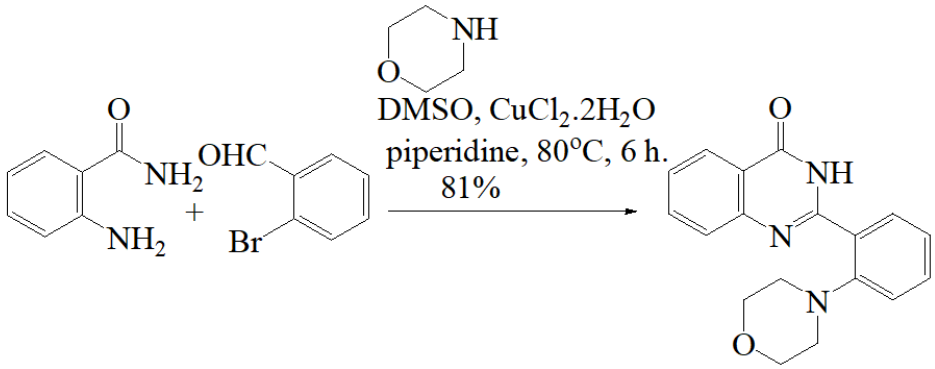


The ortho C-H amination of 2-p-tolylquinazolin-4(3*H*)-one was achieved with *N*-benzoyloxymorpholine in presence of Rh-catalyzed to isolate 2-(4-methyl-2-morpholino phenyl)quinazolin-4(3*H*)-one.[172]

DOI: https://doi.org/10.5281/zenodo.13644773

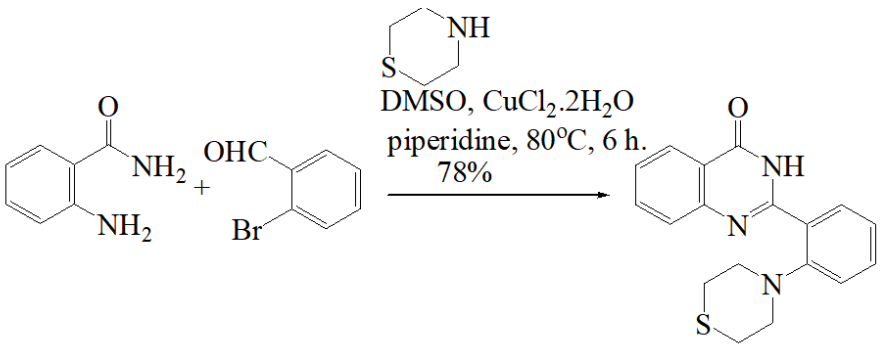


A mixture of 2-bromo benzaldehyde, anthranilamide and morpholine was reacted in DMSO containing $CuCl_2.2H_2O$ at 80° C temperature for 6 h to provide 2-(2-morpholinophenyl)quina zolin-4(3*H*)-one.[266]



4.3.14 Thiomorpholinophenylquinazolin-4(3*H*)-one.

A mixture of 2-bromo benzaldehyde, anthranilamide and thiomorpholine was reacted in DMSO containing $Cu_2Cl_2.2H_2O$ at 80°C temperature for 6 h to provide 2-(2-thiomorpholinophenyl) quinazolin-4(3*H*)-one.[266]

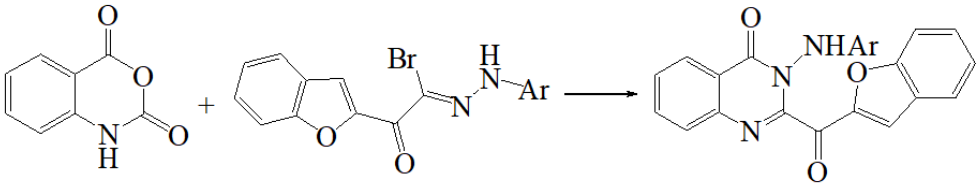


5 Heterylcarbonyl/ Heterylcarbonylalkyl

5.1 Heterylcarbonyl

5.1.1 Carbobenzofurylquinazolin-4(3*H*)-ones

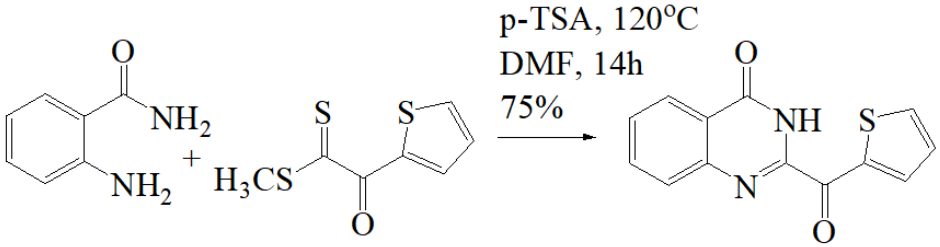
Abdelhamid et.al reported a facile one-step synthesis of 2-(2-carbobenzofuryl)-3-(4-arylamino)-quinazolin-4(3*H*)-ones by condensing 2-bromobezofurylglyoxal-2-arylhydrazones with isatoic anhydride.[174]



Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

5.1.2 Thiophenylcarbonylquinazolin-4(3*H*)-one

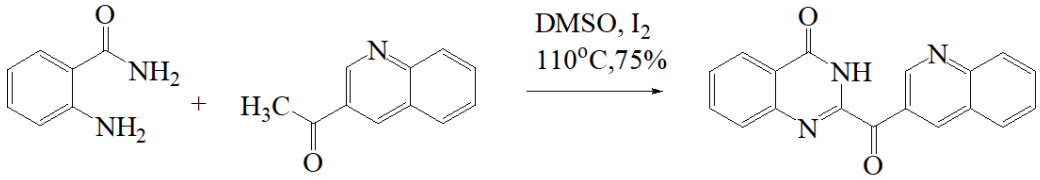
Acid catalysed cyclization of o-aminobenzamide and α-oxodithioesters (ex-methyl 2-oxo-2-(thiophen-2-yl)ethanedithioate) in a highly regioselective fashion to give 2 (thiophen-2-yl)carbonylquinazolin-4(3*H*)-one is achieved in DMF containing p-TSA at 120°C in 75% yield.[269]



5.1.3 Quinolinylcarbonylquinazolin-4(3*H*)-one

Luotonin F (2-((quinolin-3-yl)carbonyl)quinazolin-4(3*H*)-one) is an alkaloid found in the aerial parts of the P. nigellastrum Bunge, a plant used in traditional Chinese medicine for the treatment of rheumatism and various other inflammatory conditions. It demonstrates cytotoxicity against leukemia P-388 cells (IC_{50} =2.3 μM) through a mechanism that involves stabilizing the DNA topoisomerase I-DNA complex.[2, 270]

Luotonin F was synthesized by an efficient one-pot synthetic protocol from easily available starting materials involving multifundamental reactions (iodination, Kornblum oxidation, and annulation) in one-pot. The procedure involves the reaction of 1-(quinolin-3-yl)ethanone with iodine in DMSO followed by reaction with 2-aminobenzamide to isolate Luotonin F in good yield.



5.2 Heterylcarbonylalkyl

5.2.1 Pyrazolinylacetylmethylquinazolin-4(3H)-ones

2-Methyl-3-aryl-substituted quinazolin-4(3*H*)-ones were reacted with chloroacetyl chloride to 2-chloroacetylmethylene-3-aryl-substituted quinazolin-4(3*H*)-one, conversion into 2-hydrazino acetylmethyl-3-aryl-substituted quinazolin-4(3*H*)-one with hydrazine hydrate (99 %)

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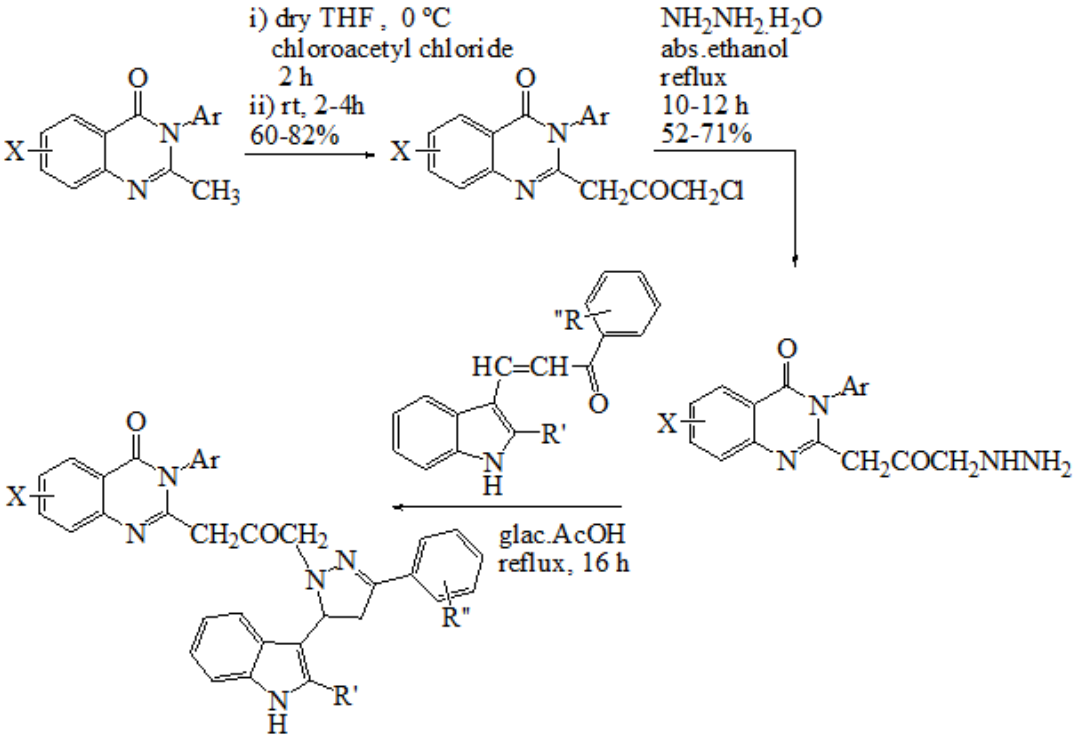
followed by reaction with 2-substituted indol-3-yl-substituted chalcones in glacial acetic acid at reflux to afford 3-aryl-2-((3-aryl-5-(2-substituted indol-3-yl)-2-pyrazolinyl)acetylmethylene)-substituted quinazolin-4(3*H*)-one. These compounds exhibited potent antiinflammatory, analgesic, ulcerogenic, cycloxygenase and toxicity activities.[98, 271]



X	H	H	6-Br	6,8-di Br
Ar	3-ClC$_6$H$_4$	2,4-Cl$_2$C$_6$H$_3$	3-CH$_3$OC$_6$H$_4$	3-CH$_3$OC$_6$H$_4$
R'	CH$_3$	CH$_3$	CH$_3$	CH$_3$
R"	2-OCH$_3$	2-OCH$_3$	H	H
Yield (%)	52	48	51	60

X	H	6-Br	6,8-di Br	H
Ar	2,4-Cl$_2$C$_6$H$_3$	3-CH$_3$OC$_6$H$_4$	3-CHH$_3$OC$_6$H$_4$	3-ClC$_6$H$_4$
R'	C$_6$H$_5$	C$_6$H$_5$	C$_6$H$_5$	H
R"	2-OCH$_3$	H	H	2-OCH$_3$
Yield (%)	50	42	44	47

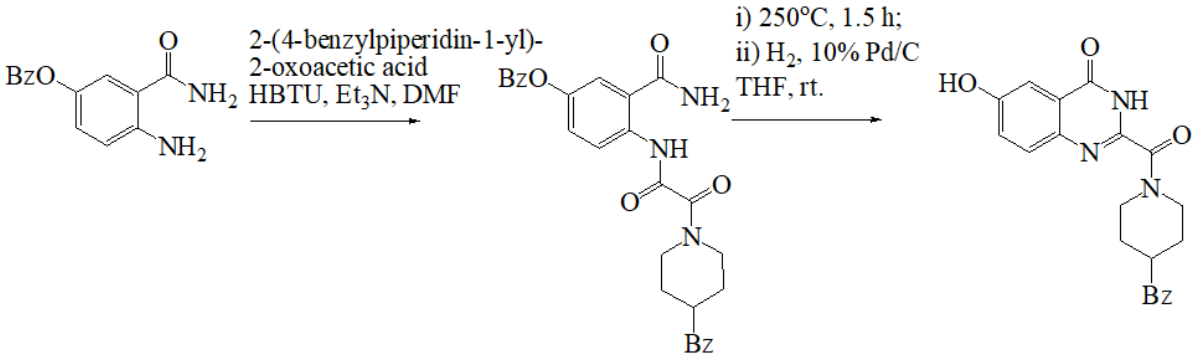
X	H	6-Br	6,8-di Br	H
Ar	2,4-Cl$_2$C$_6$H$_3$	3-CH$_3$OC$_6$H$_4$	3-CH$_3$OC$_6$H$_4$	3-ClC$_6$H$_4$
R'	H	H	H	C$_6$H$_5$
R"	2-OCH$_3$	H	H	2-OCH$_3$
Yield (%)	51	42	60	39

5.3 Amide linkage

5.3.1 Piperidinyloxomethylquinazolin-4(3*H*)-one

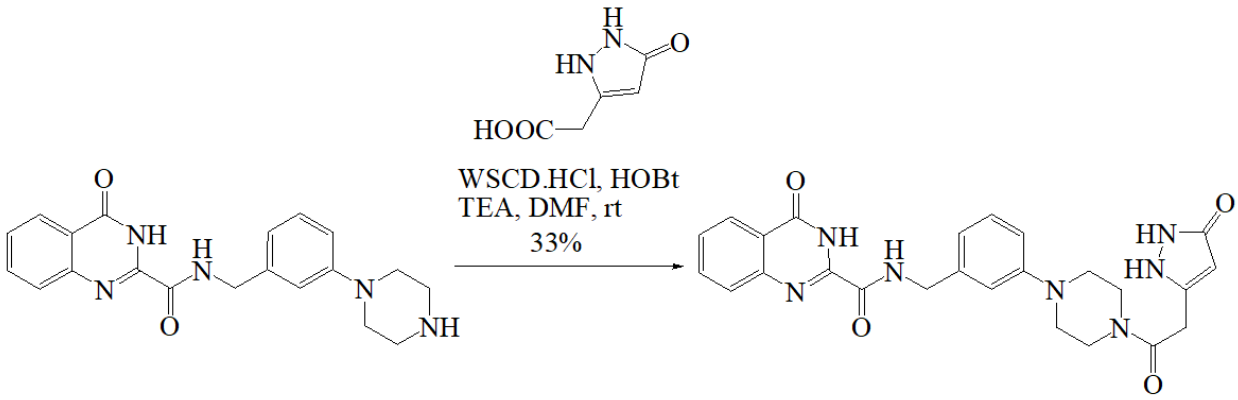
Novel NR_2B selective NMDA receptor antagonists were prepared by the condensation of anthranilamide derivative with 2-(4-benzylpiperidin-1-yl)-2-oxoacetic acid in presence of HBTU, Et_3N in DMF medium followed by thermal condensation of the obtained oxalic acid diamide and catalytic hydrogenolysis of O-benzyl protecting group to afforded 2-(4-benzylpiperidin-1-yl)-oxomethylquinazolin-4(3*H*)-one.[99]

DOI: https://doi.org/10.5281/zenodo.13644773



5.3.2 Dihydro-5-oxo-pyrazolylacetylpiperazinylbenzylmethylaminocarbonyl quinazoline-4(3*H*)-one

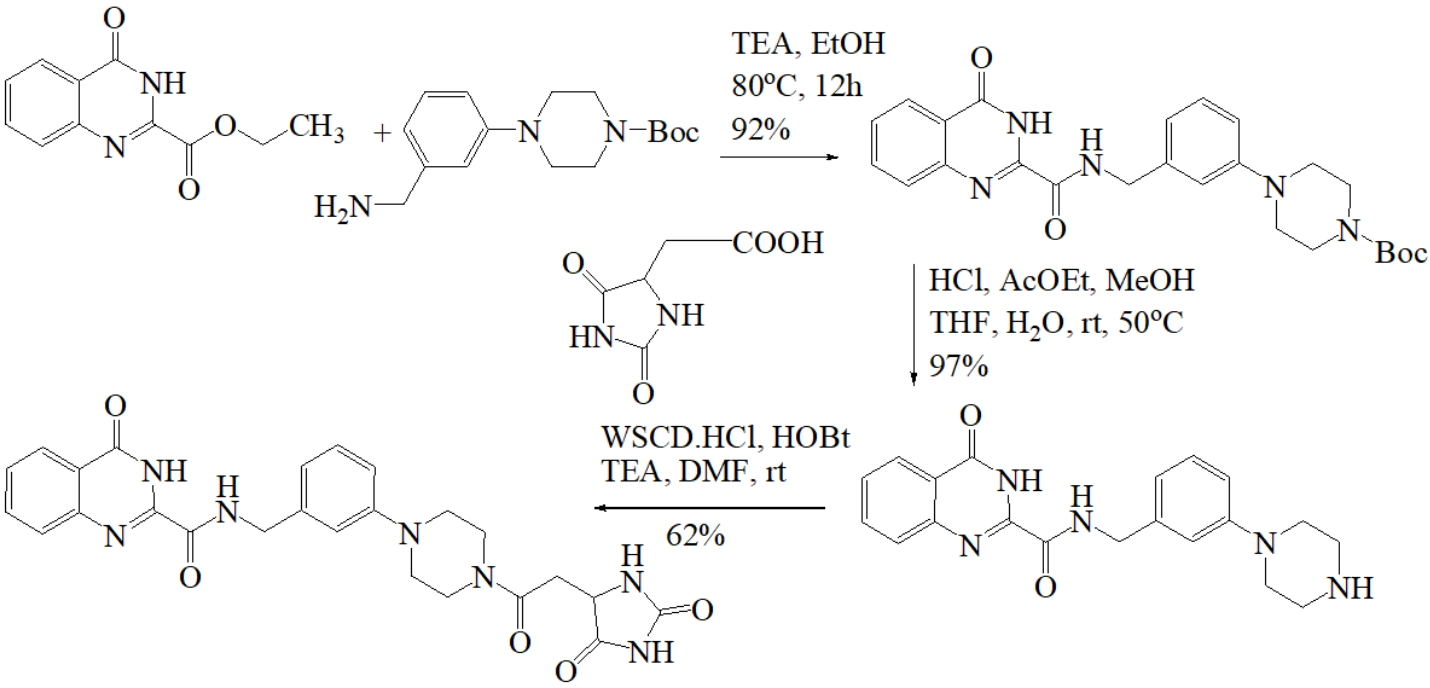
The 2-(((3-(piperazin-1-yl)benzyl)amino)carbonyl)quinazoline-4(3*H*)-one and 2-(2,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetic acid were coupled to isolate 2-(((3-(4-(2-(2,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetyl)piperazin-1-yl)benzyl)amino)carbonyl)quinazoline-4(3*H*)-one and is a matrix metalloproteinase (MMP)-13 zinc-binding inhibitor.[100]



5.3.3 Imidazolidinylacetylpiperazinylbenzylmethylaminocarbonylquinazoline-4 (3*H)*-one

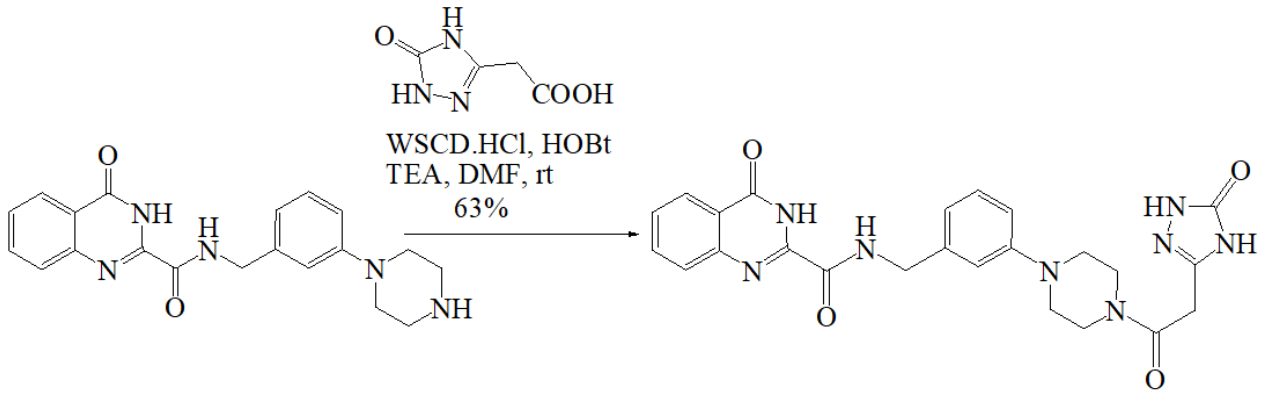
Matrix metalloproteinase (MMP)-13 zinc-binding inhibitor 2-((*N*-(3-(4-(2-(2,5-dioxoimidazolidin -4-yl)acetyl)piperazin-1-yl)benzyl)amino)carbonyl)-quinazolin-4(3*H*)-one was synthesized by reacting the 1,1-dimethylethyl 4-[3-(aminomethyl)phenyl]piperazine-1-carboxylate and ethyl quinazolin-4(3*H*)-one-2-carboxylate in ethanol containing triethylamine to isolate Boc protected *N*-(3-(piperazin-1-yl)benzyl)-quinazolin-4(3*H*)-one-2-carboxamide then deprotection followed by coupling of the resultant compound with 2-(2,5-dioxoimidazolidin-4-yl)acetic acid.[44,9]

DOI: https://doi.org/10.5281/zenodo.13644773



5.3.4 Dihydro-5-oxotriazolyl acetyl piperazinyl benzyl methyl amino carbonyl quinazoline-4 (3*H*)-one

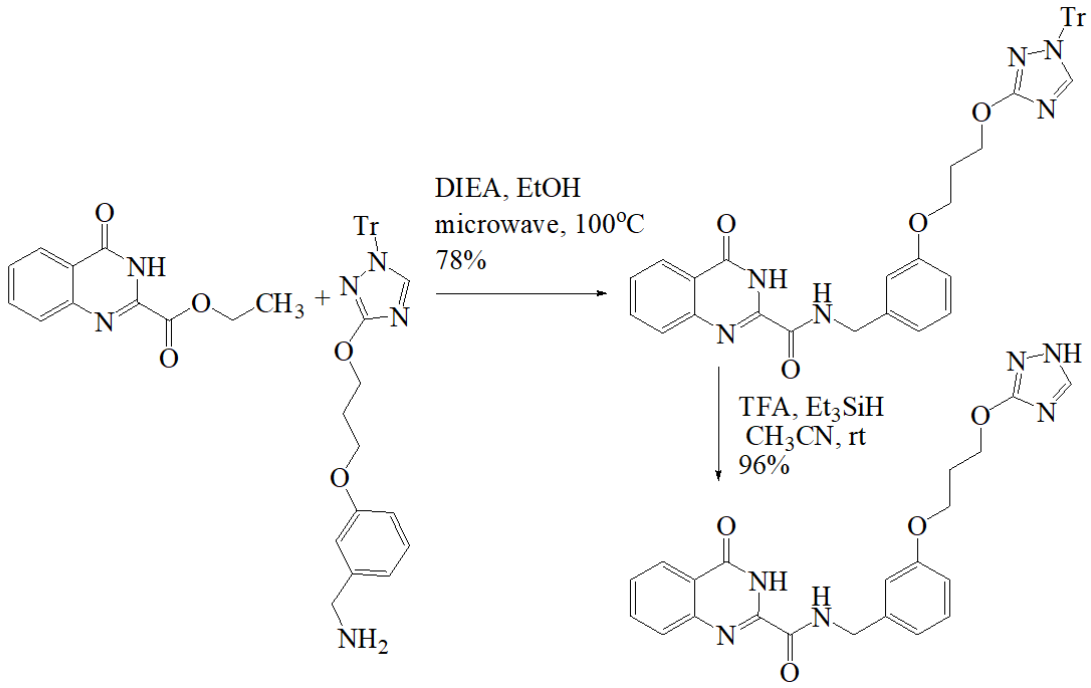
Hiroshi et.al reported the synthesis of 2-(3-(4-(2-(4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)acetyl)piperazin-1-yl)benzyl)methylaminocarbonyl-quinazoline-4(3*H*)-one by condensing 2-(((3-(piperazin-1-yl)benzyl)amino)carbonyl)quinazoline-4(3*H*)-one and 2-(4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)acetic acid and is a matrix metalloproteinase (MMP)-13 zinc-binding inhibitor.[100]



5.3.5 Triazolyloxypropoxybenzylaminocarbonylquinazoline-4(3*H*)-one

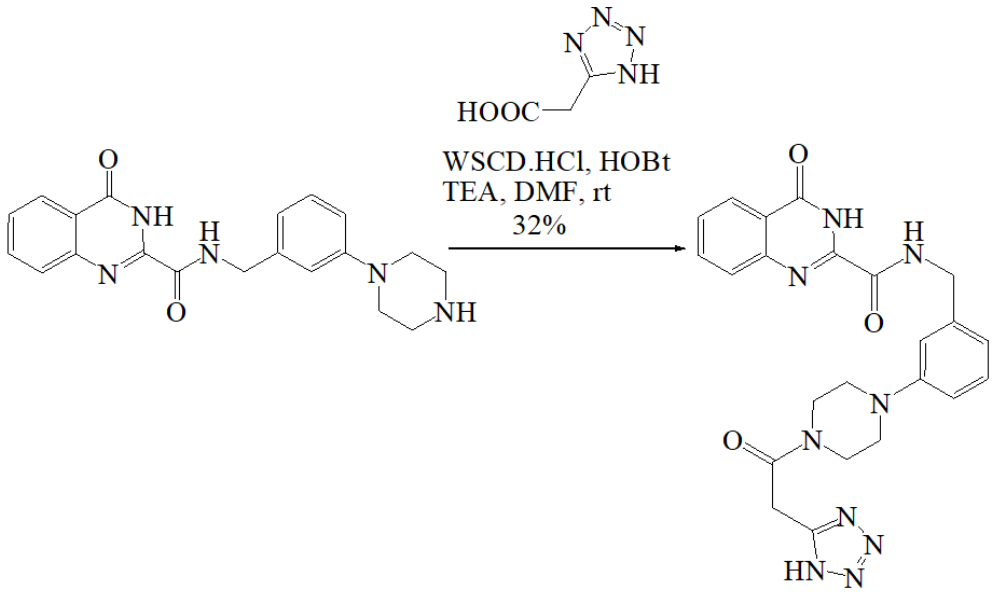
Quinazolin-4(3*H*)-one-2-carboxylic acid ethyl ester was subjected to aminolysis by treatment with 3-(3-(1-trityl-(1*H*-1,2,4-triazol-3-yloxy)propoxy)phenyl)methanamine in EtOH to afford compound trityltriazole derivative, which was deprotected to 1,2,4-triazole under acidic condition to yield 2-(3-(3-(1*H*-1,2,4-triazol-3-yloxy)propoxy)benzylaminocarbonyl)-quinazoline-4(3*H*)-one and are matrix metalloproteinase (MMP)-13 zinc-binding inhibitors.[100]

DOI: https://doi.org/10.5281/zenodo.13644773



5.3.6 Tetrazolylacetylpiperazinylbenzylmethylaminocarbonylquinazoline-4(3*H*)-one

A matrix metalloproteinase (MMP)-13 zinc-binding inhibitor 2-(3-(4-(2-(1*H*-tetrazol-5-yl)acetyl)piperazin-1-yl)benzyl)methylaminocarbonyl-quinazoline-4(3*H*)-one was prepared from the condenation of 2-(((3-(piperazin-1-yl)benzyl)amino)carbonyl)quinazoline-4(3*H*)-one and 2-(1*H*-tetrazol-5-yl)acetic acid in DMF.[100]

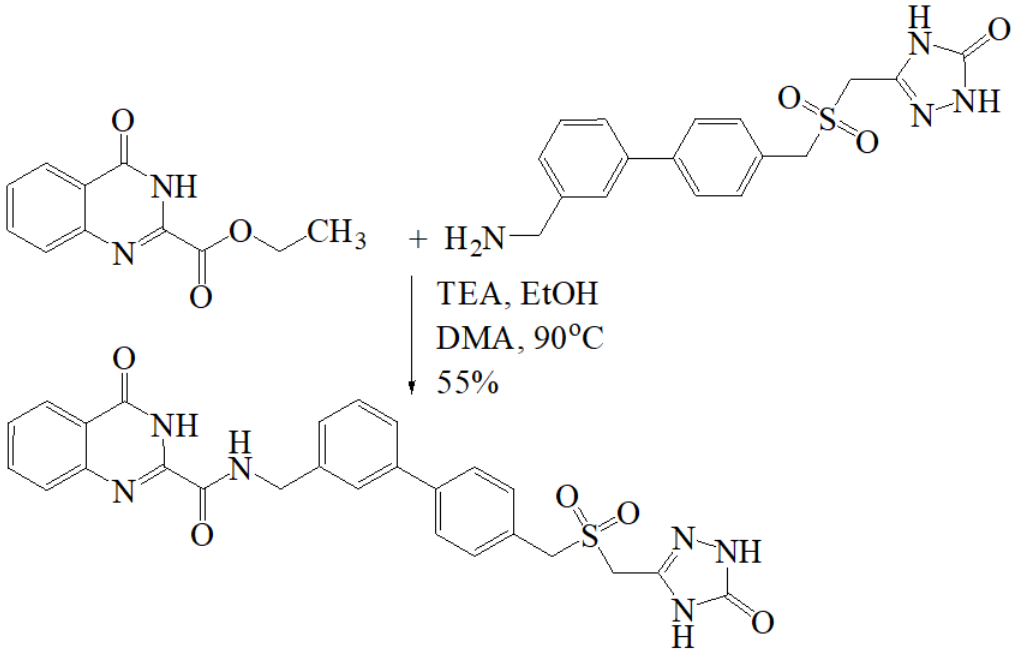


5.3.7 Triazoloneylmethylsulfonylmethylbiphenylylmethylaminocarbonyl-quinazolin-4(3H)-one

Hiroshi Nara et.al condensed the 3-(4'-(((2*H*-1,2,4-triazol-3(4*H*)-one-5-yl)methylsulfonyl) methyl) phenyl)benzylamine with quinazolin-4(3*H*)-one-2-carboxylic acid ethyl ester in basic condition to afford 2-(3-(4'-(((2*H*-1,2,4-triazol-3(4*H*)-one-5-yl)methylsulfonylmethyl))phenyl)

DOI: https://doi.org/10.5281/zenodo.13644773

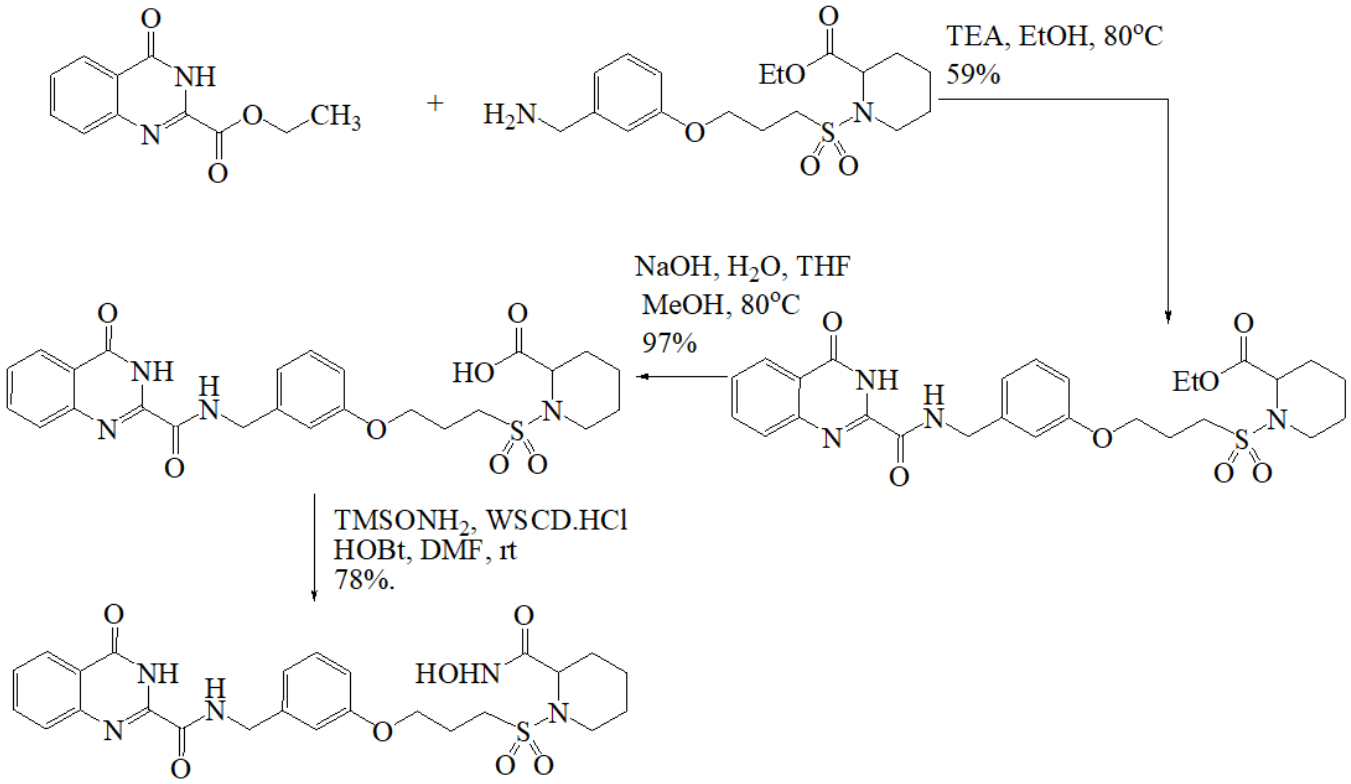
benzylaminocarbonyl)-quinazoline-4(3*H*)-one and has exhibited excellent potency (IC_{50} = 0.071 nM) and selectivity (greater than 170-fold) over other MMPs (MMP-1, 2, 3, 7, 8, 9, 10, 12, and 14) and tumor necrosis factor-a converting enzyme (TACE) and are matrix metalloproteinase (MMP)-13 zinc-binding inhibitors.[100]



5.3.8 Piperidinyl sulfonyl propoxy benzylaminocarbonyl quinazolin-4(3*H*)-one

Matrix metalloproteinase (MMP)-13 zinc-binding inhibitor 2-(3-(((2-hydroxyamino carbonyl piperidine-1-yl)sulfonyl)propoxy)benzylaminocarbonyl)-quinazoline-4(3*H*)-one synthesized by the condensation of 3-(((2-ethoxycarbonylpiperidine-1-yl)sulfonyl)propoxy)benzylamine with quinazolin-4(3*H*)-one-2-carboxylic acid ethyl ester in ethanol containing TEA to isolate 2-(3-(((2-ethoxycarbonylpiperidine-1-yl)sulfonyl)propoxy)benzylamino-carbonyl)-quinazoline-4(3*H*)-one followed by hydroloysis and reaction with O-(trimethylsilyl)hydroxylamine.[100]

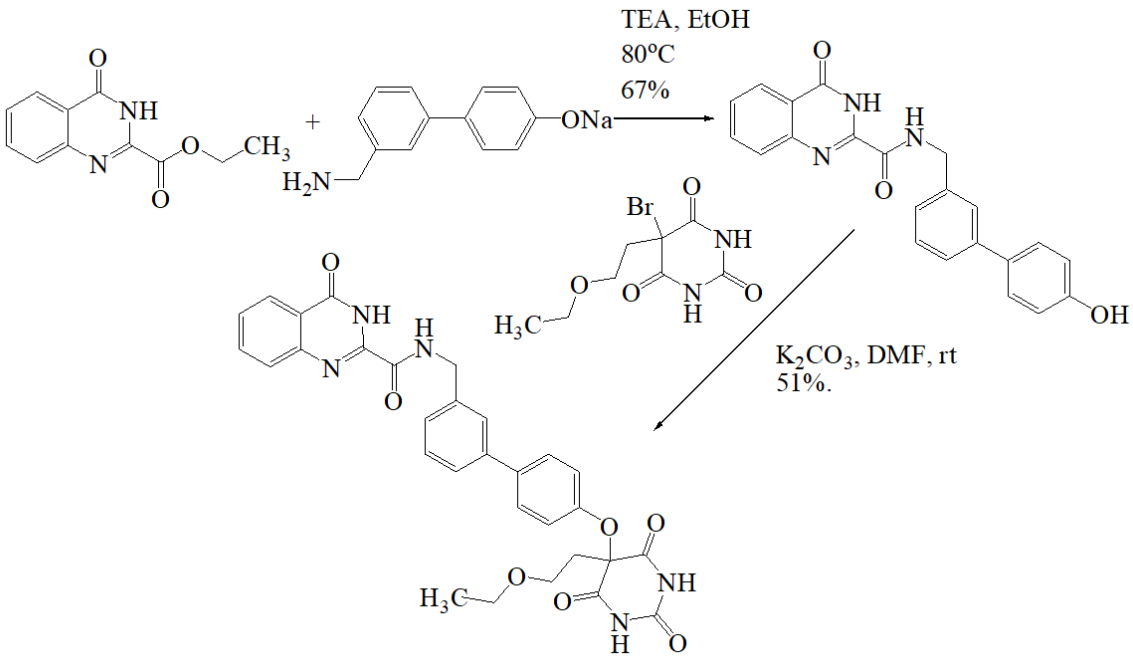
DOI: https://doi.org/10.5281/zenodo.13644773



5.3.9 Pyrimidinetrioneyloxybiphenylylmethylaminocarbonylquinazolin-4(3*H*)-one

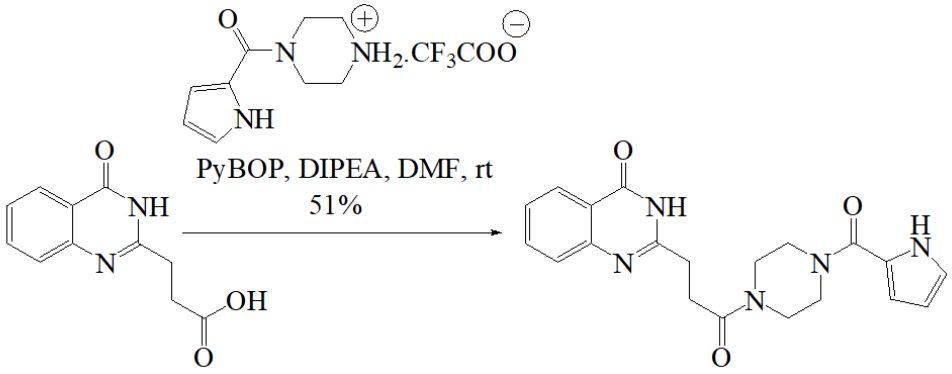
Hiroshi et.al reported the synthesis of 2-((((((4'-5-(2-ethoxyethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione-5-yl)oxy)biphenyl-3-yl)-methyl)amino)carbonyl)-quinazolin-4(3*H*)-one to introduce a barbiturate functionality into the quinazoline-2-carboxamide via a biphenyl linker using 4-[3-(aminomethyl)phenyl]phenol as a starting material. Condensation of 4-[3-(aminomethyl) phenyl]phenol as a sodium salt with quinazoline-2-carboxylic acid ethyl ester followed by installation of the the barbiturate functionality by using 5-bromo-5-(2-ethoxyethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione under basic condition to provide quinazolin-4(3*H*)-one derivative. The quinazolin-4(3*H*)-one derivative demonstrated good PAMPA permeability, good stability against liver microsomes, and acceptable oral bioavailability (F% > 30) in rats. However, showed a very low volume of distribution, which may reflect high plasma protein binding and are matrix metalloproteinase (MMP)-13 zinc-binding inhibitors.[100]

DOI: https://doi.org/10.5281/zenodo.13644773

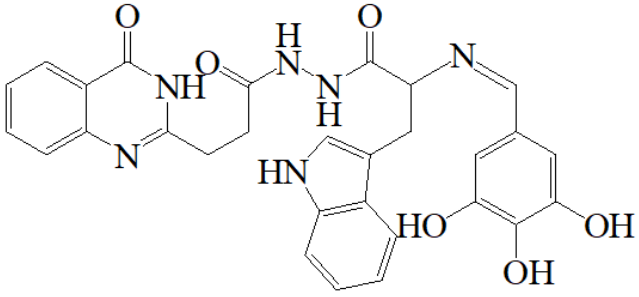


5.3.10 Pyrrolylcarbonylpiperazinylcarbonylethylquinazolin-4(3*H*)-one

Giuseppe Giannini et.al reported a synthesis of 2-(3-oxo-3-(4-((pyrrol-2-yl)carbonyl)piperazin-1-yl)propyl)quinazolin-4(3*H*)-one by coupling of quinazolin-4(3*H*)-one-2-propanoic acid with (pyrrol-2-yl)(piperazin-1-yl)methanone trifluoroacetate and showed potent PARP-1 inhibitory activity.[101]



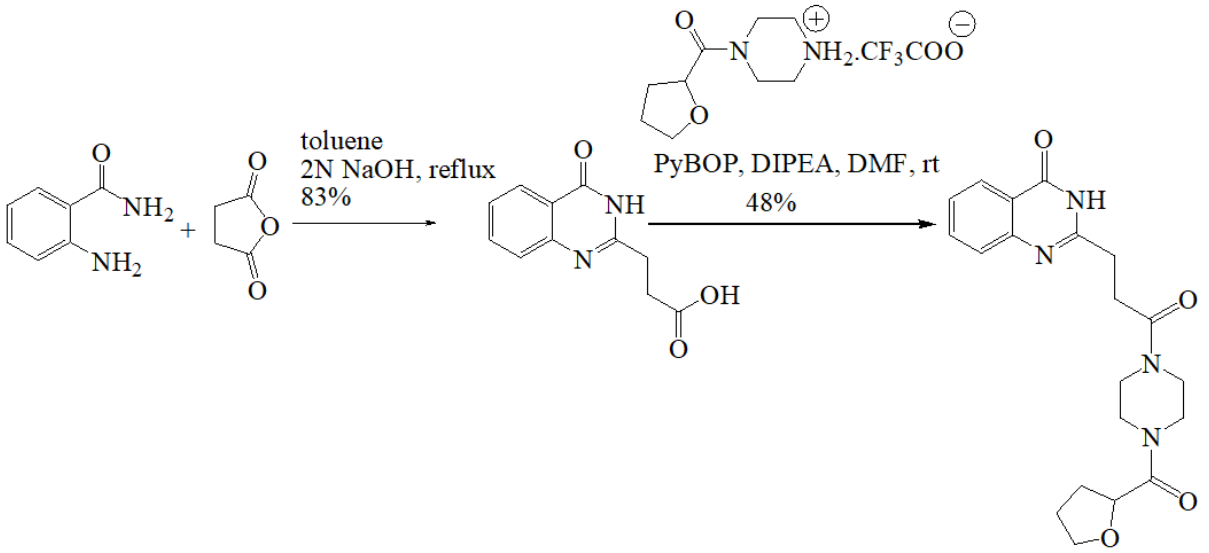
The N_2-(3-(3,4-dihydro-4-oxoquinazolin-2-yl)propaneoyl)-2-(3,4,5-trihydroxybenzylidene-amino)-3-(1*H*-indol-3-yl)propanehydrazide is reported in the literature with high cytotoxicity against tested cell lines.[102]



IC_{50}=78.919 nM against HepG2

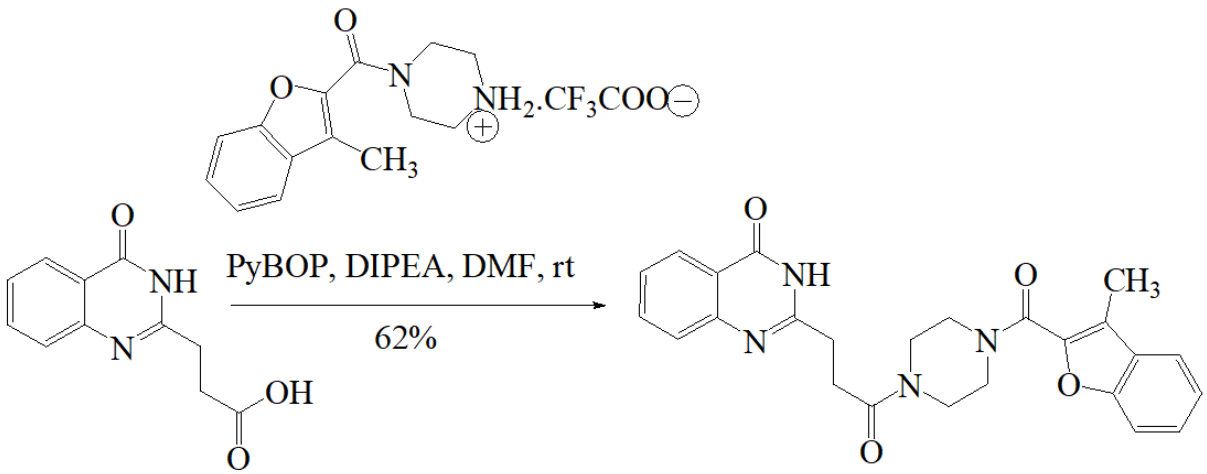
5.3.11 Tetrahydrofuranylcarbonylpiperazinylcarbonylethylquinazolin-4(3*H*)-one

A new potent PARP-1 inhibitor 2-(((4-((tetrahydrofuran-2-yl)carbonyl)piperazin-1-yl)carbonyl) ethyl)quinazolin-4(3*H*)-one, which was identified from virtual screening of commercial libraries, was synthesized by reacting anthranilamide and succinic anhydride in refluxing toluene in presence of NaOH to obtain quinazolin-4(3*H*)-one-2-propanoic acid followed by coupling with (tetrahydrofuran-2-yl)(piperazin-1-yl)methanone trifluoroacetate.[101]



5.3.12 Benzofuranylcarbonylpiperazinylcarbonylethylquinazolin-4(3*H*)-one

Quinazolin-4(3*H*)-one-2-propanoic acid reacted with (3-methylbenzofuran-2-yl)(piperazin-1-yl)methanone trifluoroacetate to produce a new potent PARP-1 inhibitor 2-(3-(4-(3-methyl benzofuran-2-carbonyl)piperazin-1-yl)-3-oxopropyl)quinazolin-4(3H)-one [101]



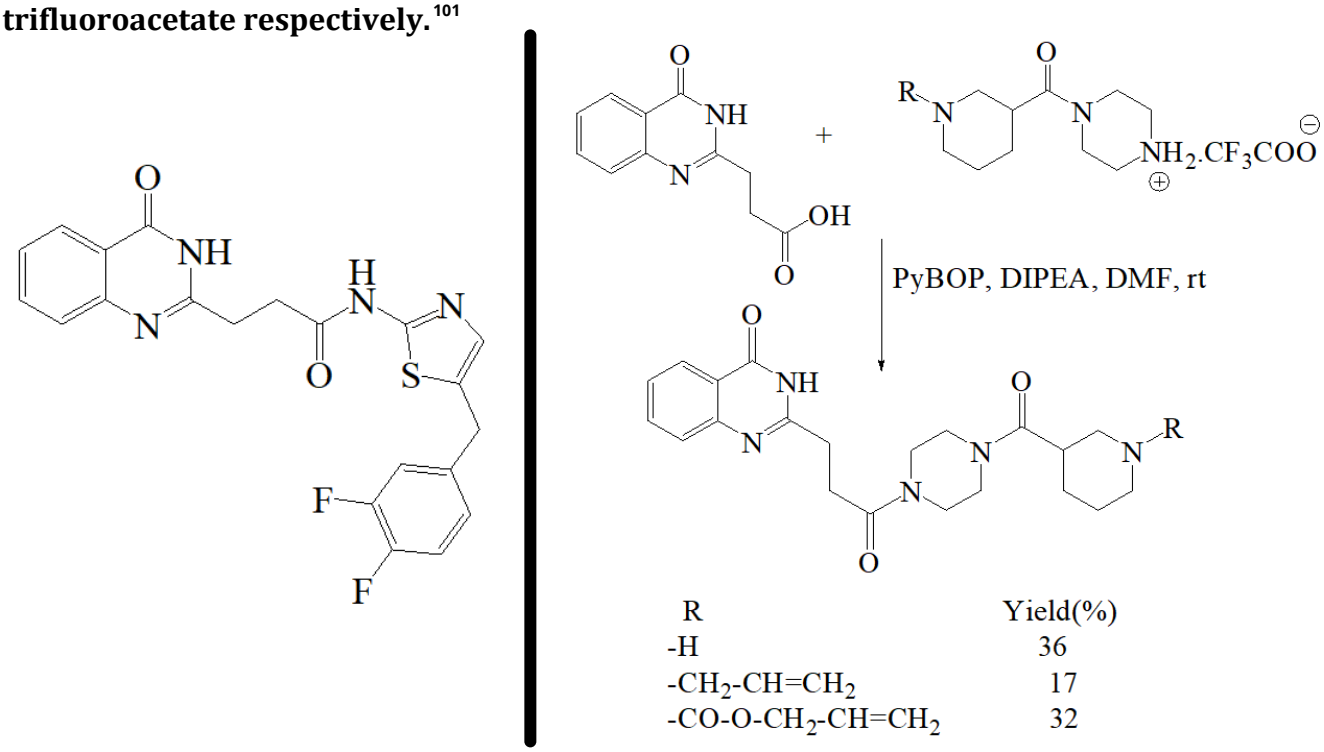
5.3.13 Thiazolylaminocarbonylethylquinazolin-4(3*H*)-one

Amedeo Caflisch and Hongtao Zhao have discovered a novel inhibitor of the Syk and ZAP70 kinases by high-throughput docking into a rare DFG-in, C-helix-out conformation of Syk. The 2-((*N*-(5-(3,4-difluorobenzyl)thiazol-2-yl)-propanamide)-3-yl)-quinazoline-4(3*H*)-one is single digit µM inhibitors of ZAP70 and JAK2. Its slightly higher potency for ZAP70 than Syk is likely to originate from the C-helix-out conformation being more populated by ZAP70 than Syk.[103]

DOI: https://doi.org/10.5281/zenodo.13644773

5.3.14 Piperidinylcarbonylpiperazinylcarbonylethylquinazolin-4(3*H*)-ones

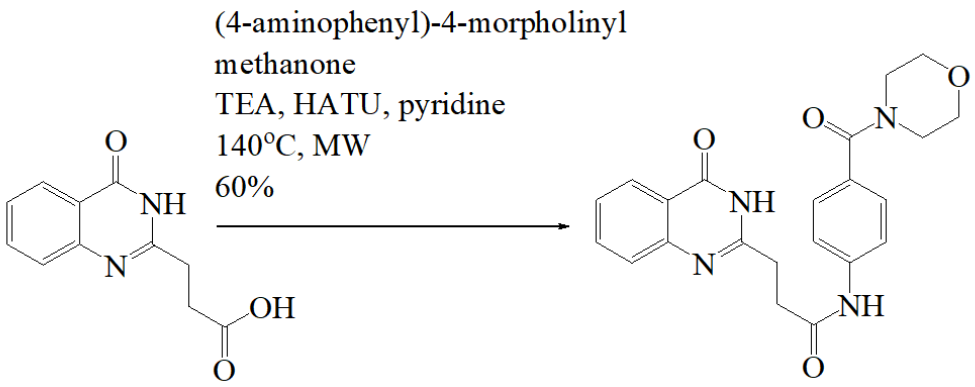
A new potent PARP-1 inhibitors 2-(3-oxo-3-(4-((piperidin-3-yl)carbonyl)piperazin-1-yl)propyl) quinazolin-4(3*H*)-one, 2-(3-oxo-3-(4-((1-allylpiperidin-3-yl)carbonyl)piperazin-1-yl)propyl) quinazolin-4(3*H*)-one and 2-(3-oxo-3-(4-(((1-allyloxycarbonyl)piperidin-3-yl)carbonyl)piperazin-1-yl)propyl)quinazolin-4(3*H*)-one, which were identified from virtual screening of commercial libraries, were synthesized by coupling of quinazolin-4(3*H*)-one-2-propanoic acid with (piperazin-1-yl)(piperidin-3-yl)methanone trifluoroacetate, (1-allylpiperidin-3-yl)(piperazin-1-yl)methanone trifluoroacetate and allyl-3-((piperazin-1-yl)carbonyl)piperidine-1-carboxylate trifluoroacetate respectively.[101]



R	Yield(%)
-H	36
$-CH_2-CH=CH_2$	17
$-CO-O-CH_2-CH=CH_2$	32

5.3.15 Morpholinylcarbonylphenylaminocarbonylethylquinazoline-4(3*H*)-one

A new potent PARP-1 inhibitor 2-(2-(4-((morpholine-4-yl)carbonyl)phenyl)aminocarbonyl) ethylquinazoline-4(3*H*)-one was synthesized by reacting quinazolin-4(3*H*)-one-2-propanoic acid with (4-aminophenyl)-4-morpholinylmethanone.[101]



5.3.16 Pyridinylmethylcarbonylaminomethylquinazolin-4(3*H*)-one

Rock inhibitor 6-(1*H*-pyrazol-4-yl)-2-(1-(((*R*)-(pyridin-3-yl)acetyl)amino)-2-(4-chlorophenyl)-ethane-1-yl)-quinazolin-4(3*H*)-one was synthesised by EDC mediated coupling of 2-((*R*)-1-amino-2-(4-chlorophenyl)ethyl)-6-(1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one with 2-(pyridin-3-yl)acetic acid followed by reverse phase preparative HPLC purification.[6]

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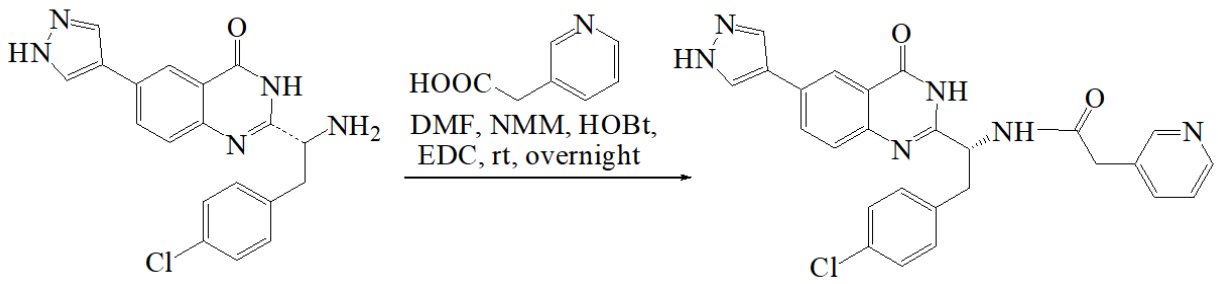
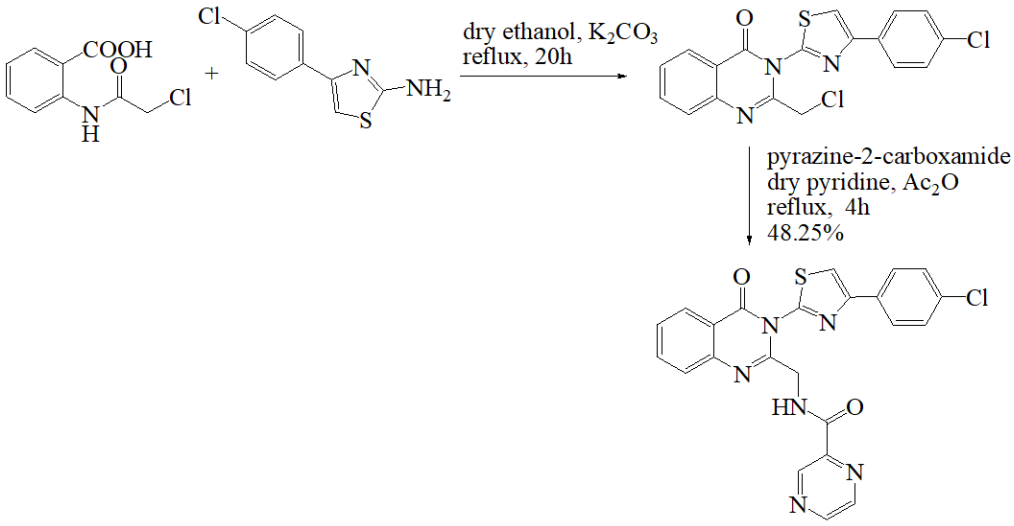


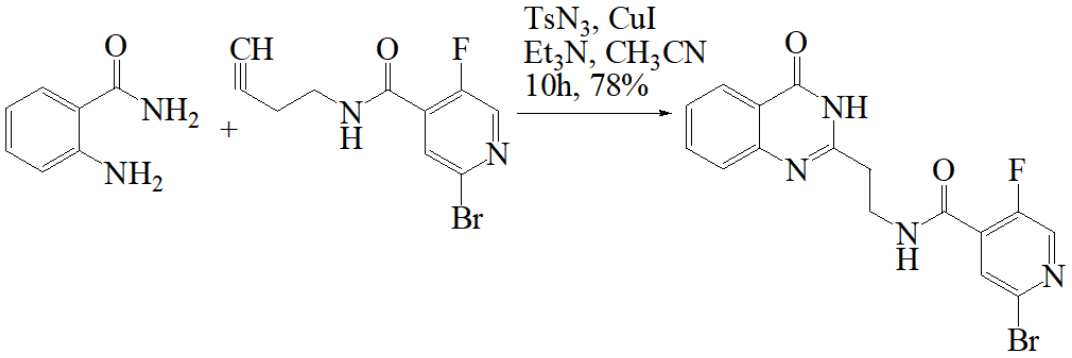
5.3.17 Pyrazinyloxomethylaminomethylquinazolin-4(3*H*)-one

Potent Antitubercular agent, 3-(4-(4-chlorophenyl)thiazol-2-yl)-2-((2-pyrazinoyl)aminomethyl) quinazolin-4(3*H*)-one, was prepared by reacting *N*-chloroacetylanthranilic acid with 4-chlorophenyl thiazole amine to 2-chloromethyl-3-[4-(4-chlorophenyl)thiazol-2-yl]-quinazolin-4(3*H*)-one followed by condensation with. pyrazine-2-carboxamide.[82]



5.3.18 Pyridinylcarbonylaminoethylquinazolin-4(3*H*)-one

A simple and highly efficient copper iodide catalyzed one-pot synthesis of 2-(2((2-bromo-5-fluoro-pyridin-4-yl)carbonylamino)ethyl)-quinazolin-4(3*H*)-one have been developed by reacting anthranilamide, 2-bromo-*N*-(but-3-ynyl)-5-fluoropyridine-4-carboxamide and tosyl azide using copper iodide in THF containing triethylamine for 10h at room temperature.[272]

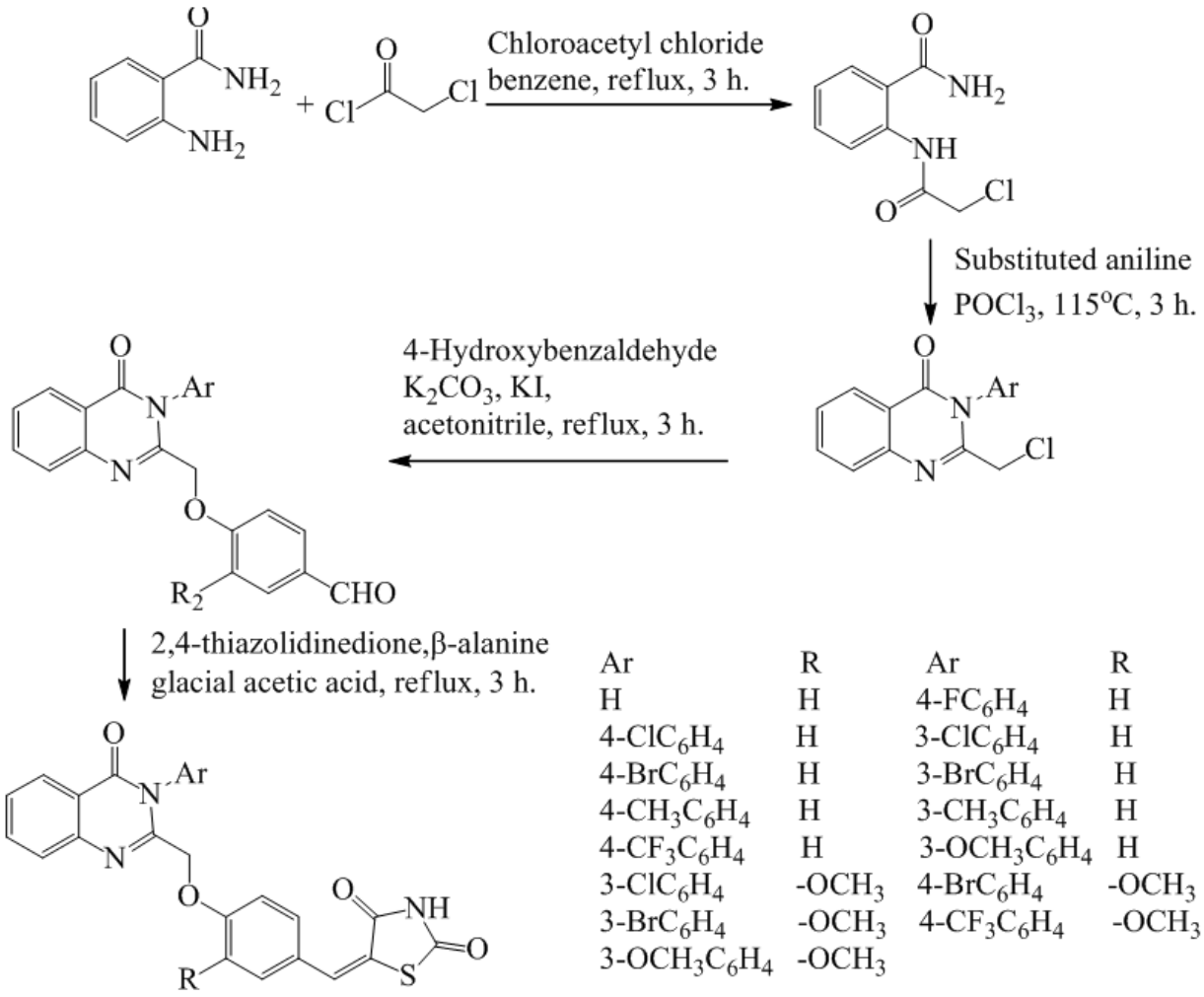


6 Ether and thioether linkage

6.1 Ether linkage

6.1.1 Thiazolidinylidenemethylphenoxymethylquinazolin-4(3*H*)-one

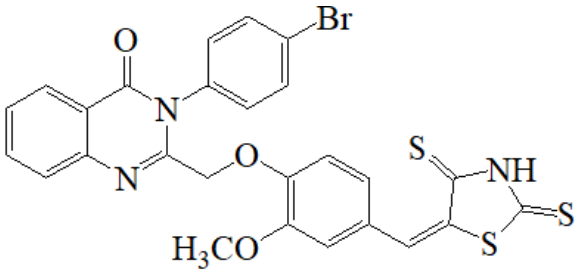
Kamel Metwally reported the synthesis of 2-((4-(thiazolidine-2,4-dione-5-ylidenemethyl) phenoxy)methyl)-quinazolin-4(3*H*)-ones. Chloroacetylation of anthranilic acid was performed using chloroacetyl chloride in dry benzene under reflux conditions to afford the corresponding *N*-chloroacetyl anthranilic acids in high yields. The required cyclization was achieved by heating the chloroacetylated derivatives with the appropriate anilines in presence of phosphorus oxychloride to give the key intermediates in moderate yields. The aldehydes derivatives were obtained in good yields through reaction of the chloromethyl derivatives with 4-hydroxybenzaldehyde under the basic conditions of potassium carbonate and in the presence potassium iodide as a catalyst. Knoevenagel-type condensation of the obtained aldehydes with 2,4-thiazolidinedione using β-alanine as a condensing agent afforded the desired product in moderate yields and are potential cytotoxic agents.[104]



Ar	R	Ar	R
H	H	4-FC_6H_4	H
4-ClC_6H_4	H	3-ClC_6H_4	H
4-BrC_6H_4	H	3-BrC_6H_4	H
4-$CH_3C_6H_4$	H	3-$CH_3C_6H_4$	H
4-$CF_3C_6H_4$	H	3-$OCH_3C_6H_4$	H
3-ClC_6H_4	-OCH_3	4-BrC_6H_4	-OCH_3
3-BrC_6H_4	-OCH_3	4-$CF_3C_6H_4$	-OCH_3
3-$OCH_3C_6H_4$	-OCH_3		

The 2-((2-methoxy-4-(thiazolidine-2,4-dithione-5-ylidenemethyl)phenoxy)methyl)-3-(4-bromo-phenyl)quinazolin-4(3*H*)-one (compound B) is reported in the literature with high cytotoxicity against tested cell lines.[102]

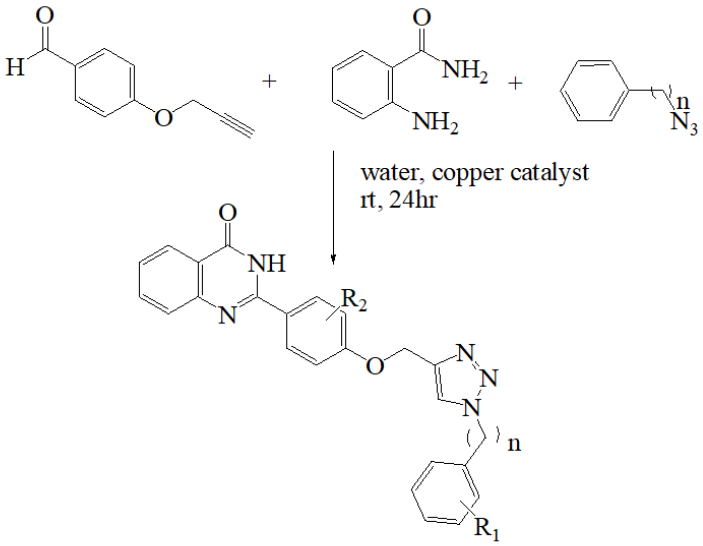
DOI: https://doi.org/10.5281/zenodo.13644773



IC_{50}=1.2 mM against HL-60
IC_{50}=1.5 mM against K-562
IC_{50}=100 mM against AG01523 normal celld

6.1.2 Triazolylmethoxyphenylquinazolin-4(3*H*)-ones

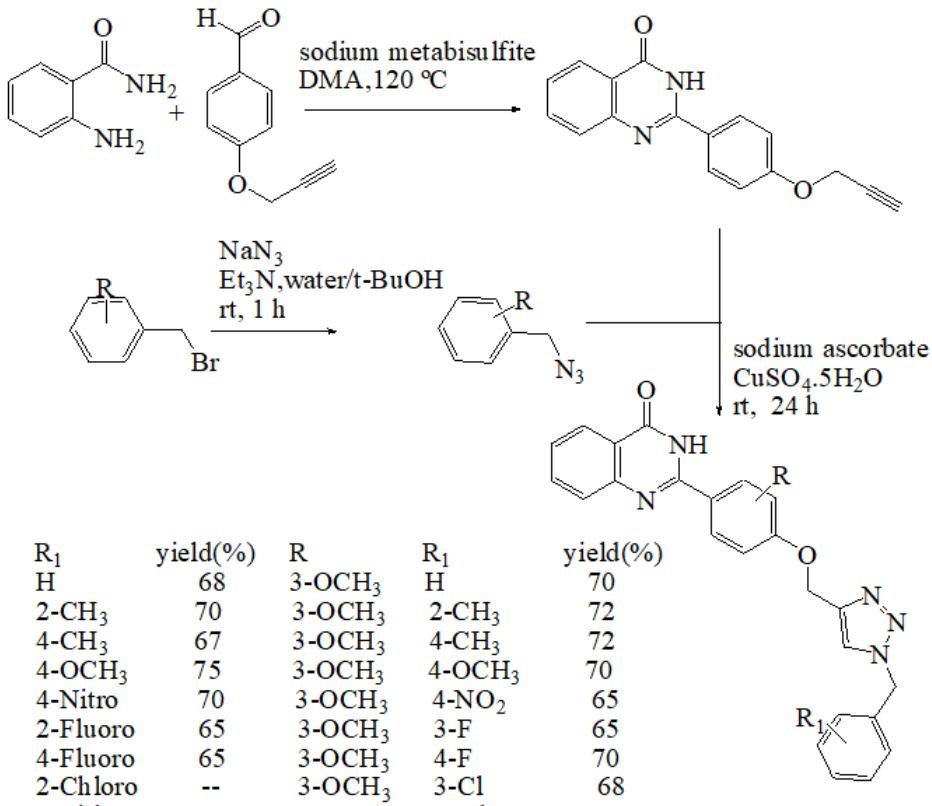
The green and one pot synthesis of 2-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)quinazolin-4(3*H*)-one derivatives is reported by adding 4-(prop-2-yn-1-yloxy) benzaldehyde, azide derivative and 2-aminobenzamide in water followed by addition of 1.5 mol% of [Cu@BCD@SiO_2@SPION] and stirred for 24 h at room temperature.[273]



R_1	R_2	n	Yield (%)	R_1	R_2	n	Yield (%)
H	H	1	83	4-F	H	1	87
4-Me	H	1	80	3,4-Cl_2	H	1	85
4-NO_2	H	1	79	2,3-Cl_2	H	1	81
H	2-OMe	1	88	4-Me	2-OMe	1	84
4-F	2-OMe	1	82	2-Me	2-OMe	1	85
4-Cl	H	0	80				

Mohammad Mahdavi et.al reacted the 2-aminobenzamide with 4-(prop-2-yn-1-yloxy)benzaldehyde derivative and sodium metabisulfite in DMA at 120^{0}C to isolate 2-(4-(prop-2-ynyloxy)phenyl)quinazolin-4(3*H*)-one. Next, a solution of arylmethylchloride/bromide, sodium azide and Et_3N in the mixture of water /t-BuOH was stirred at room temperature for 1 h to get 1-(azidomethyl)benzene derivatives. Subsequently, a mixture of 2-(4-(prop-2-ynyloxy)phenyl)quinazolin-4(3*H*)-one, sodium ascorbate, and $CuSO_4.5H_2O$ was reacted with freshly prepared azide derivatives at room temperature for 24 h to afford 2-(4-((1-aryl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)quinazolin-4(3*H*)-ones. These compounds exhibited anticancer activity.[105]

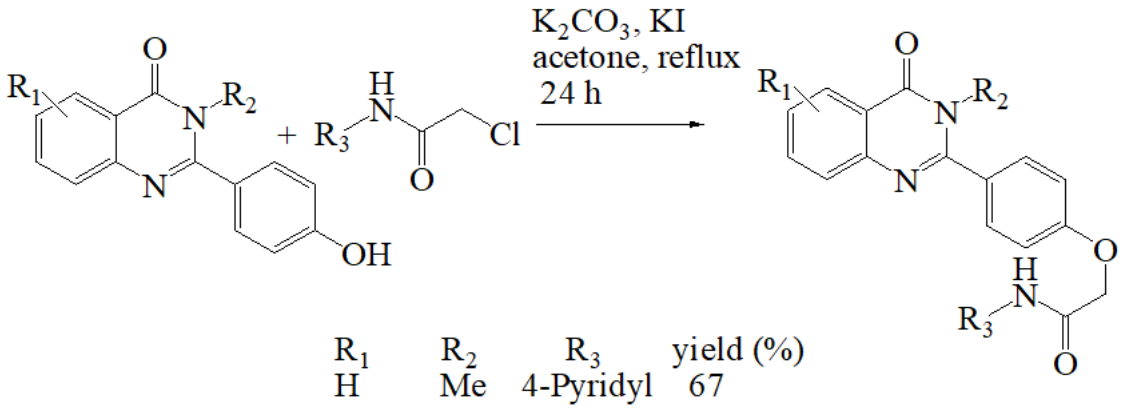
DOI: https://doi.org/10.5281/zenodo.13644773



R	R_1	yield(%)	R	R_1	yield(%)
H	H	68	3-OCH_3	H	70
H	2-CH_3	70	3-OCH_3	2-CH_3	72
H	4-CH_3	67	3-OCH_3	4-CH_3	72
H	4-OCH_3	75	3-OCH_3	4-OCH_3	70
H	4-Nitro	70	3-OCH_3	4-NO_2	65
H	2-Fluoro	65	3-OCH_3	3-F	65
H	4-Fluoro	65	3-OCH_3	4-F	70
H	2-Chloro	--	3-OCH_3	3-Cl	68
H	3-Chloro	72	3-OCH_3	4-Cl	68
H	4-Chloro	70	3-OC_2H_5	2,3-dichloro	70
H	2,3-Dichloro	75	3-OCH_3	2,4-dichloro	70
H	2,4-Dichloro	74	3-OCH_3	3,4-dichloro	72
H	3,4-Dichloro	65	3-OCH_3	4-bromo	75
H	4-Bromo	73			

6.1.3 Pyridinylaminocarbonylmethoxyphenylquinazolin-4(3*H*)-ones

The 2-(4-hydroxyphenyl)quinazolin-4(3*H*)-ones and the 2-chloro-*N*-(pyridin-2/4-yl)acetamides were reacted in anhydrous acetone containing anhydrous K_2CO_3 and KI (0.08 mmol) and was refluxed for 24 h to isolate 2-(4-((((pyridin-2/4-yl)amino)carbonyl)methoxy)phenyl)-quinazolin-4(3*H*)-ones in good yield. The 3-methyl-2-(4-((((pyridin-2-yl)amino)carbonyl)methoxy)phenyl)-quinazolin-4(3*H*)-one demonstrated remarkable anti-leishmanial activity towards intracellular *L. donovani amastigotes* in vitro.[106]

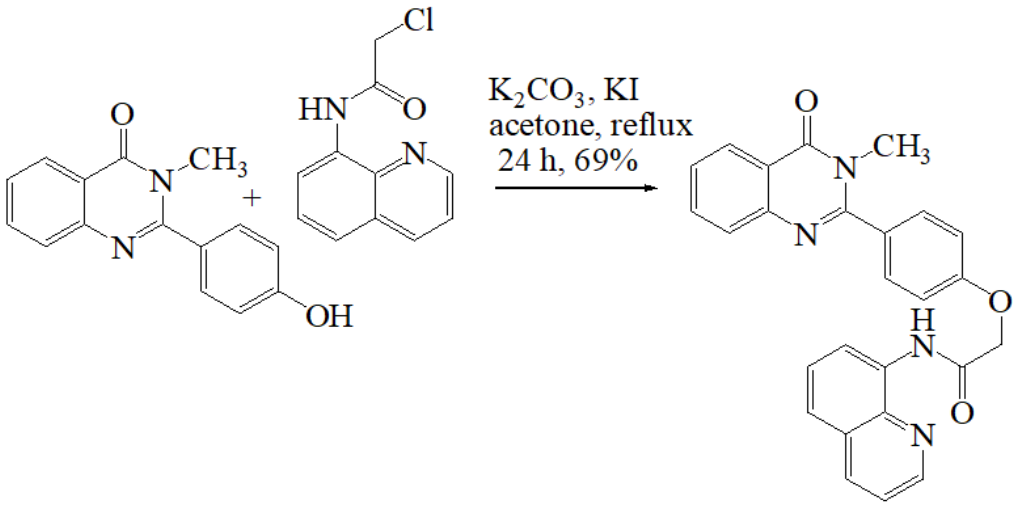


R_1	R_2	R_3	yield (%)
H	Me	4-Pyridyl	67
H	Me	2-Pyridyl	69
H	Et	2-Pyridyl	68
7-F	Me	2-Pyridyl	65
6-Cl	Me	2-Pyridyl	66

DOI: https://doi.org/10.5281/zenodo.13644773

6.1.4 Quinolinylaminocarbonylmethoxyphenylquinazolin-4(3*H*)-one

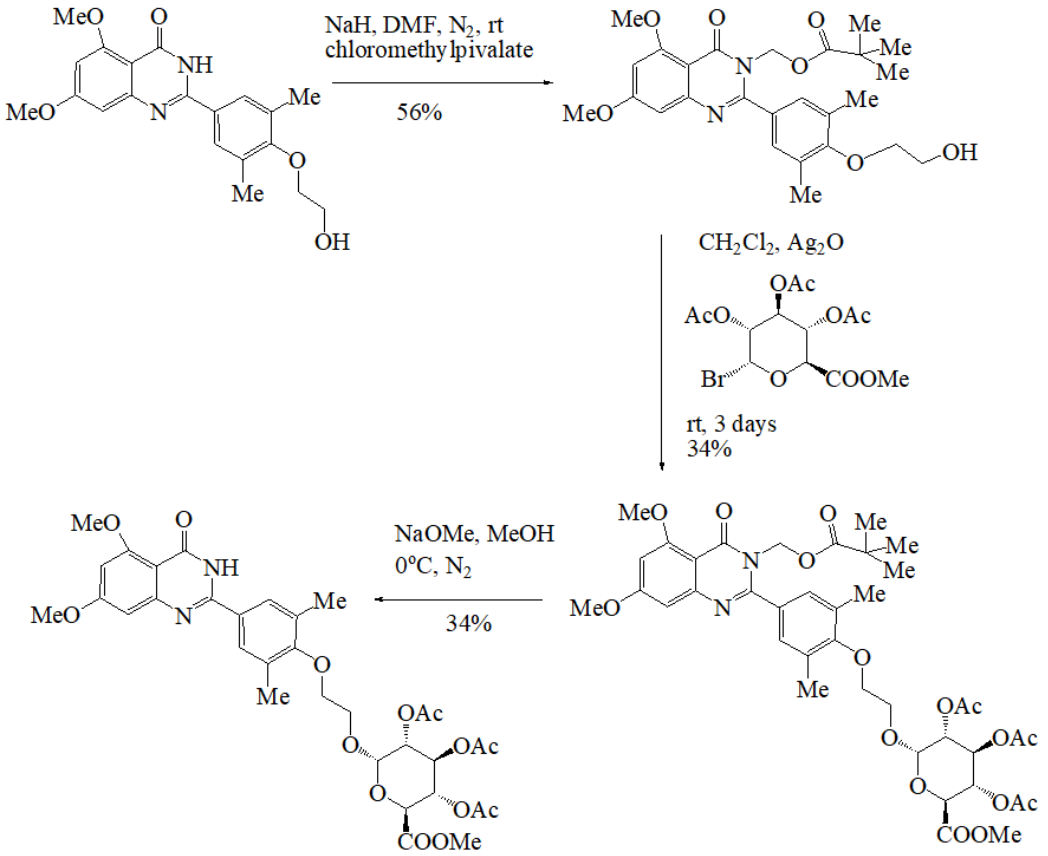
The remarkable anti-leishmanial activity towards intracellular *L. donovani amastigotes* in vitro compound, 2-(4-((((quinolin-8-yl)amino)carbonyl)methoxy)phenyl)-quinazolin-4(3*H*)-one, is synthesized by reacting 2-(4-hydroxyphenyl)quinazolin-4(3*H*)-one with 2-chloro-*N*-(quinolin-8-yl)acetamide in anhydrous acetone containing anhydrous K_2CO_3 and KI and was refluxed for 24 h.[106]



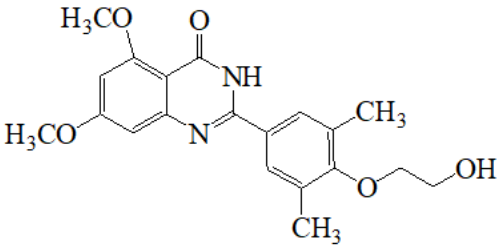
6.1.5 Tetrahydropyranyloxyethoxyphenylquinazolin-4(3*H*)-one

2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one was reacted with chloromethylpivalate to isolate 2,2-dimethylpropionic acid 2-(4-(2- hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one-3-ylmethyl ester. The obtained compound was then treated with (2*S*,3*S*,4*S*,5*R*,6*R*)-3,4,5- triacetoxy-6-bromotetrahydropyran-2-carboxylic acid methyl ester in presence of silver (I) oxide to give 3,4,5-triacetoxy-6-(2-(4-(3-(2,2-dimethylpropionyloxymethyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one-2-yl)-2,6-dimethyl phenoxy)ethoxy)tetrahydropyran-2-carboxylic acid methyl ester and the N_3 - group is deprotected with sodium methoxide to give 6-(2-(4-(5,7-dimethoxy-quinazolin-4(3*H*)-one-2-yl)-2,6-dimethyl phenoxy)ethoxy)-3,4,5-trihydroxytetrahydropyran-2-carboxylic acid. This compound is predominant metabolites of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (RVX-208).[274]

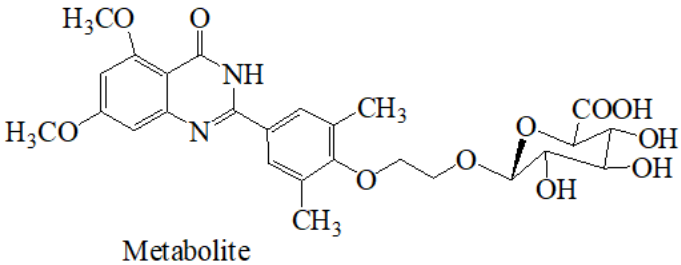
DOI: https://doi.org/10.5281/zenodo.13644773



The structure of predominant metabolite 2-(4-(2-((tetrahydro-3,4,5-trihydroxy-2*H*-pyran-2-carboxylic acid-)6-yl)oxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (M4) of RVX-208, observed both in vitro human and animal liver microsomal incubations, as well as in plasma from animal in vivo studies, was determined.[274]



RVX 208



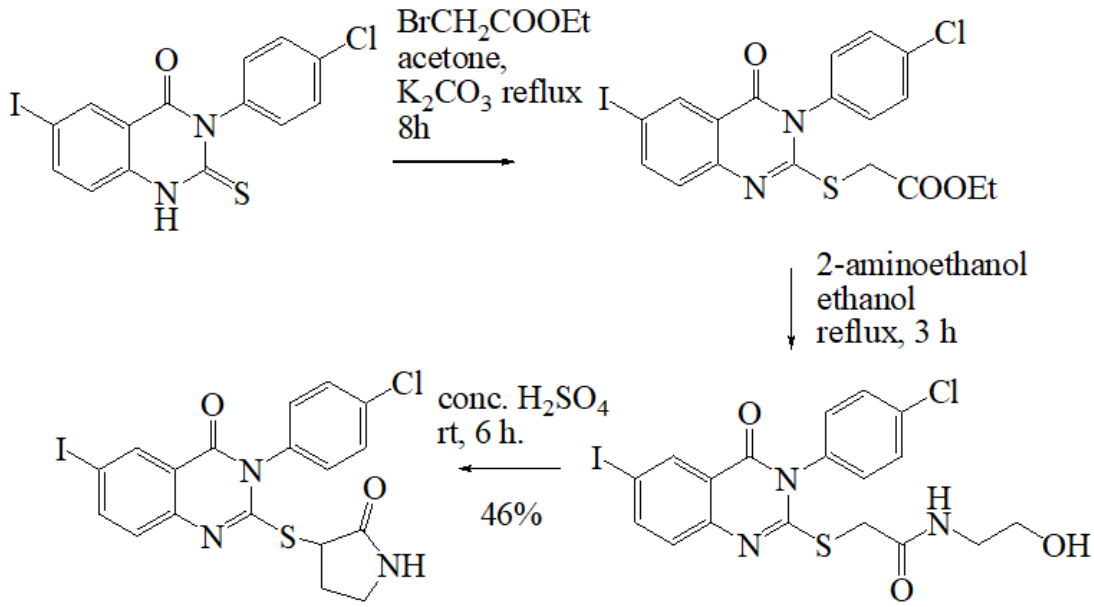
Metabolite

6.2 Thioether linkage

6.2.1 Pyrrolidinylthioquinazolin-4(3*H*)-one

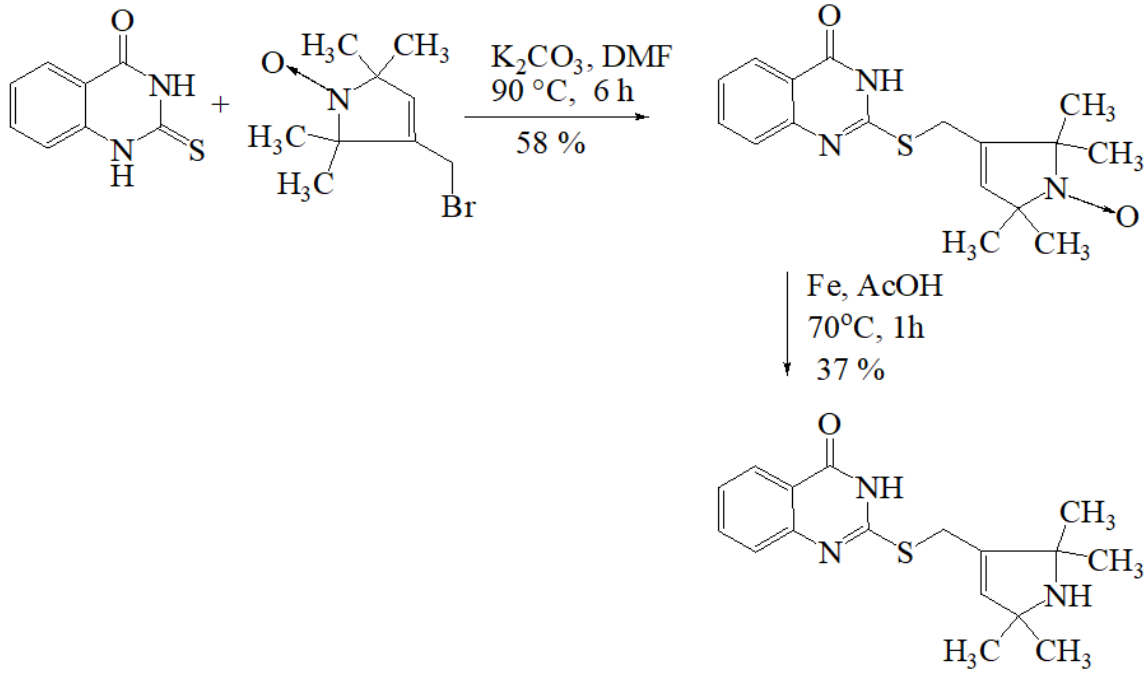
A mixture of 2-mercapto-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one, ethyl bromoacetate and anhydrous potassium carbonate in dry acetone was heated under reflux to isolate 2-(ethoxycarbonylmethyl)thio-3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one. The resultant compound was reacted with 2-aminoethanol to get *N*-(2-hydroxyethyl)-2-[(3-(4-chloro)phenyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide and was cyclized with conc. H_2SO_4 to yield 2-[(2-oxopyrrolidin-3-yl)thio]-3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one. This compound show ed a remarkably broad spectrum of antimicrobial activity.[107]

DOI: https://doi.org/10.5281/zenodo.13644773



6.2.2 Dihydropyrrolylmethylthioquinazolin-4(3*H*)-one

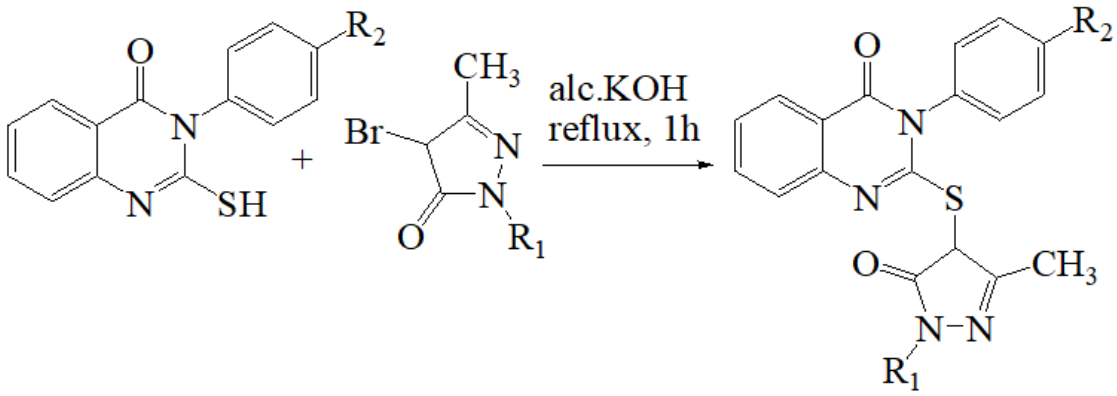
2-Mercaptoquinazolin-4(3*H*)-one was condensed with 1-oxyl-3-(bromomethyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrole to yield 2-{[(1-oxyl-2,2,5,5-tetramethyl-2,5- dihydro-1*H*-pyrrol-3-yl)methyl]thio}-quinazolin-4(3*H*)-one radical. The resultant nitroxide was reduced with Fe powder in acetic acid to isolate 2-{[(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]thio}-quinazolin-4(3*H*)-one.[10]



6.2.3 Pyrazolylthioquinazolin-4(3*H*)-ones

Potential fungicidal quinazolinone derivatives, 2-[(1'-alkyl-3'methyl-5'-oxo-pyrazolin-4'-yl)thio]-3-aryl-quinazolin-4(3*H*)-ones were prepared by the reaction of 2-mercapto-3-aryl-quinazolin-4(3*H*)-ones with 4-bromo-2-pyrazolin-5-one in alcoholic alkali. They are fungitoxic against the rice blast pathogen *Pyricularia oryzae* and brown leaf spot pathogen *Helmenthosporium oryzae*.[275]

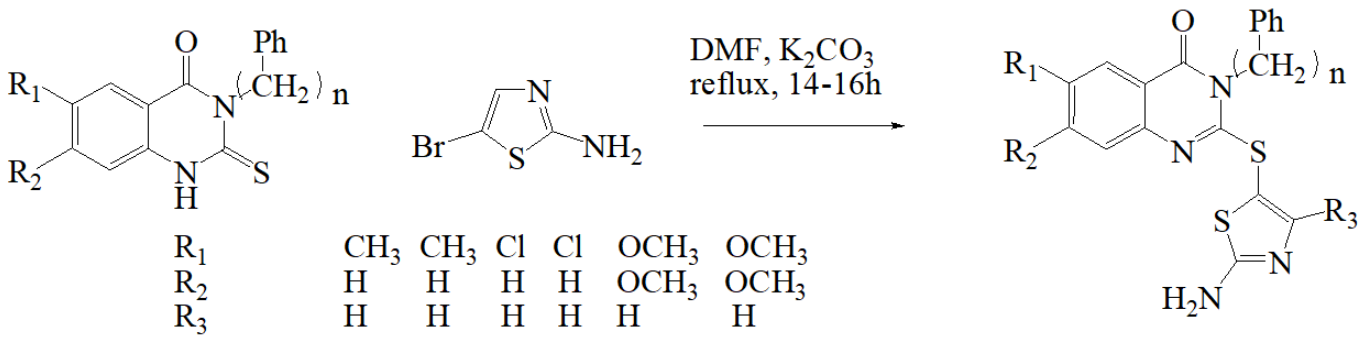
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	H	H	H
R_2	H	4-Cl	3-Cl	2-Cl	4-NO_2	4-OCH_3	2-OCH_3	4-CH_3	H	4-Cl	3-Cl
Yield (%)	80	70	50	65	55	50	45	50	75	65	60
R_1	H	H	H	H	H	Ph	Ph	Ph			
R_2	2-Cl	4-NO_2	4-CH_3	4-OCH_3	2-OCH_3	2-COOH	4-COOH	4-OC_2H_5			
Yield (%)	55	60	65	60	40	40	50	30			

6.2.4 Thiazolylthioquinazolin-4(3*H*)-ones

Al-Omary et.al condensed 2-thioxo-quinazoline analogs with 2-amino-5-bromothiazole in basic medium to afford 2-amino-5-(3-phenyl/benzyl)- substituted quinazolin-4(3*H*)-one-2-ylthio) thiazole. These compounds showed active dihydrofolate reductase (DHFR) inhibition, antimicrobial, and antitumor activities.[108]



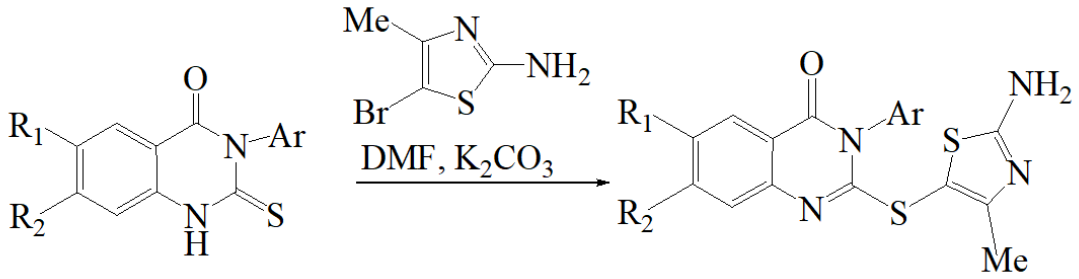
R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
R_3	H	H	H	H	H	H
n	0	1	0	1	0	1
Yield(%)	42	25	56	48	55	30

,

R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
R_3	COOEt	COOEt	COOEt	COOEt	COOEt	COOEt
n	0	1	0	1	0	1
Yield(%)	44	63	31	37	63	49

The remarkable broad-spectrum antimicrobial and antitumor active quinazolinone derivatives, 2-(2-amino-4-methylthiazol-5-yl-thio)-3-substituted-6-substituted or 6,7-disubstituted-quinazolin-4(3*H*)-ones were prepared by alkylating the 2-thioxo-function of the substituted-2-thioxo-2,3-dihydro-quinazolin-4(1*H*)-ones with 2-amino-5-bromo-4-methylthiazole in dimethyl formamide (DMF) in presence of potassium carbonate. These are anti-osteoarthritis compunds.[7]

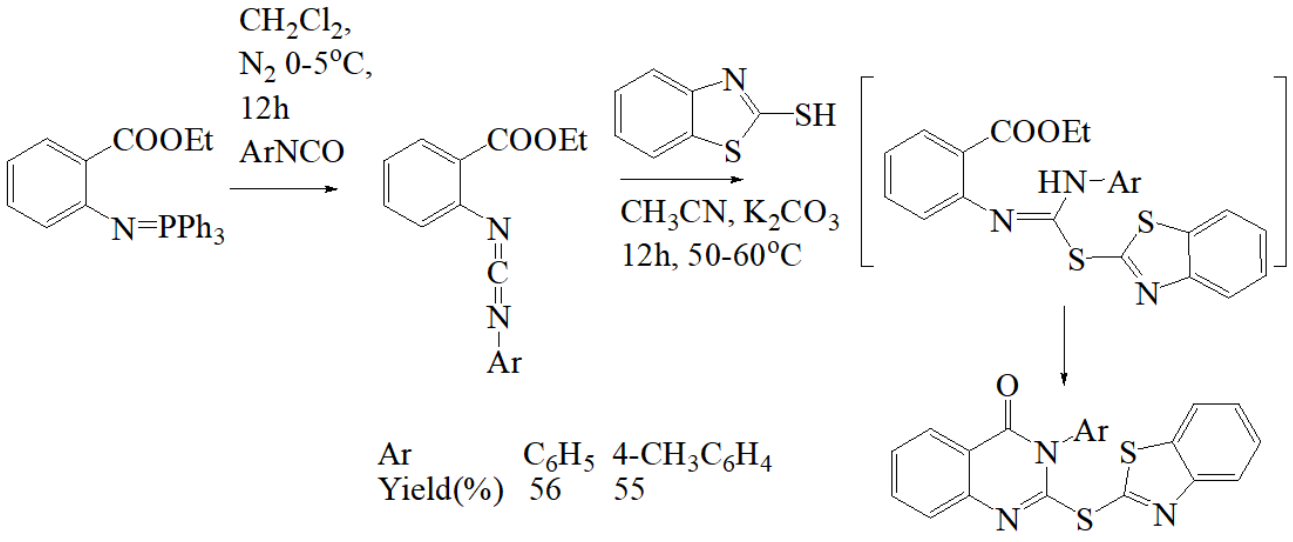
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	R_2	Ar	Yield (%)	R_1	R_2	Ar	Yield (%)
CH_3	H	C_6H_5	62	Cl	H	4-ClC_6H_4	58
CH_3	H	4-$CH_3C_6H_4$	54	Cl	H	4-$OC_6H_5C_6H_4$	69
CH_3	H	4-$OCH_3C_6H_4$	59	OCH_3	OCH_3	C_6H_5	58
CH_3	H	4-ClC_6H_4	50	OCH_3	OCH_3	4-$CH_3C_6H_4$	55
CH_3	H	4-$OC_6H_5C_6H_4$	55	OCH_3	OCH_3	4-$OCH_3C_6H_4$	49
Cl	H	C_6H_5	64	OCH_3	OCH_3	4-ClC_6H_4	62
Cl	H	4-$CH_3C_6H_4$	43	OCH_3	OCH_3	4-$OC_6H_5C_6H_4$	68
Cl	H	4-$OCH_3C_6H_4$	59	CH_3	H	$CH_2C_6H_5$	68
Cl	H	$CH_2C_6H_5$	72	OCH_3	OCH_3	$CH_2C_6H_5$	56

6.2.5 Benzothiazolylthioquinazolin-4(3*H*)-ones

2-(2-Benzothiazolylthio)-quinazolin-4(3*H*)-ones were synthesized by base catalytic reactions of 2-mercaptobenzothiazole with carbodiimides, which were obtained via aza-Wittig reaction of iminophosphorane with aromatic isocyanates. The compounds exhibited fungicidal activity.[109]

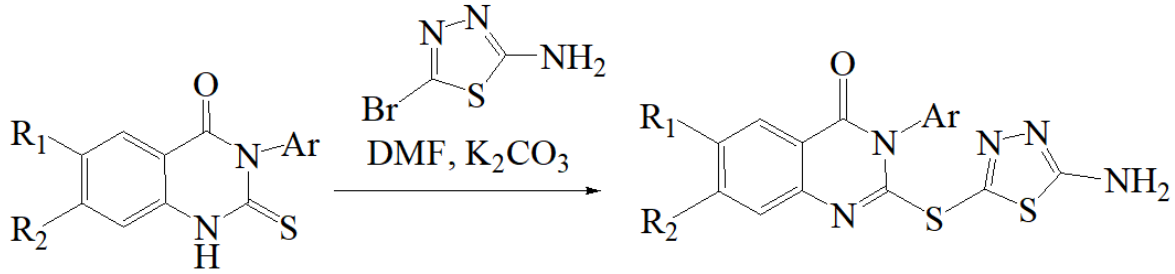


Ar	C_6H_5	4-$CH_3C_6H_4$
Yield(%)	56	55

6.2.6 Thiadiazolylthioquinazolin-4(3*H*)-one

The most active DHFR inhibitors, remarkable broad-spectrum antimicrobial and antitumor active quinazolinone derivatives, 2-(5-amino-1,3,4-thiadiazol-2-yl-thio)-quinazolin-4(3*H*)-ones were prepared by alkylated the 2-thioxo-function of the substituted-2-thioxo-2,3-dihydro-quinazolin-4(1*H*)-ones with 2-amino-5-bromo-1,3,4-thiadiazole in dimethylformamide (DMF) in presence of potassium carbonate.[110]

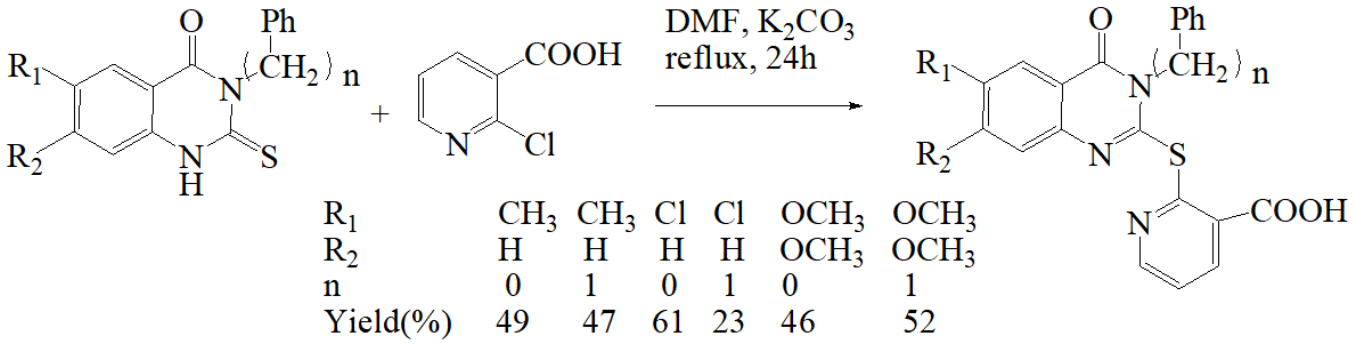
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	R_2	Ar	Yield(%)	R_1	R_2	Ar	Yield(%)
CH_3	H	C_6H_5	54	Cl	H	$4\text{-}ClC_6H_4$	75
CH_3	H	$4\text{-}CH_3C_6H_4$	66	Cl	H	$4\text{-}OC_6H_5C_6H_4$	79
CH_3	H	$4\text{-}OCH_3C_6H_4$	52	OCH_3	OCH_3	C_6H_5	45
CH_3	H	$4\text{-}ClC_6H_4$	60	OCH_3	OCH_3	$4\text{-}CH_3C_6H_4$	55
CH_3	H	$4\text{-}OC_6H_5C_6H_4$	74	OCH_3	OCH_3	$4\text{-}OCH_3C_6H_4$	68
Cl	H	C_6H_5	44	OCH_3	OCH_3	$4\text{-}ClC_6H_4$	51
Cl	H	$4\text{-}CH_3C_6H_4$	59	OCH_3	OCH_3	$4\text{-}OC_6H_5C_6H_4$	70
Cl	H	$4\text{-}OCH_3C_6H_4$	49	CH_3	H	$CH_2C_6H_5$	41
Cl	H	$CH_2C_6H_5$	53	OCH_3	OCH_3	$CH_2C_6H_5$	39

6.2.7 Pyridinylthioquinazolin-4(3*H*)-one

The 2-thioxo-function of the 2-mercapto-quinazolin-4(3*H*)-ones was alkylated using halogenated pyridine derivatives in dimethylformamide containing potassium carbonate to afford 2-(3-benzyl-6-substituted (or 6,7-dimethoxy)-4-oxo-3,4-dihydroquinazoline-2-ylthio)nicotinic acid derivatives. 2-(3-Benzyl-3,4-dihydro-6-methyl-4-oxoquinazolin-2-ylthio)pyridine-3-carboxylic acid showed broad spectrum antitumor activity toward several tumor cell lines with GI values range of 25.8-41.2%.[108]

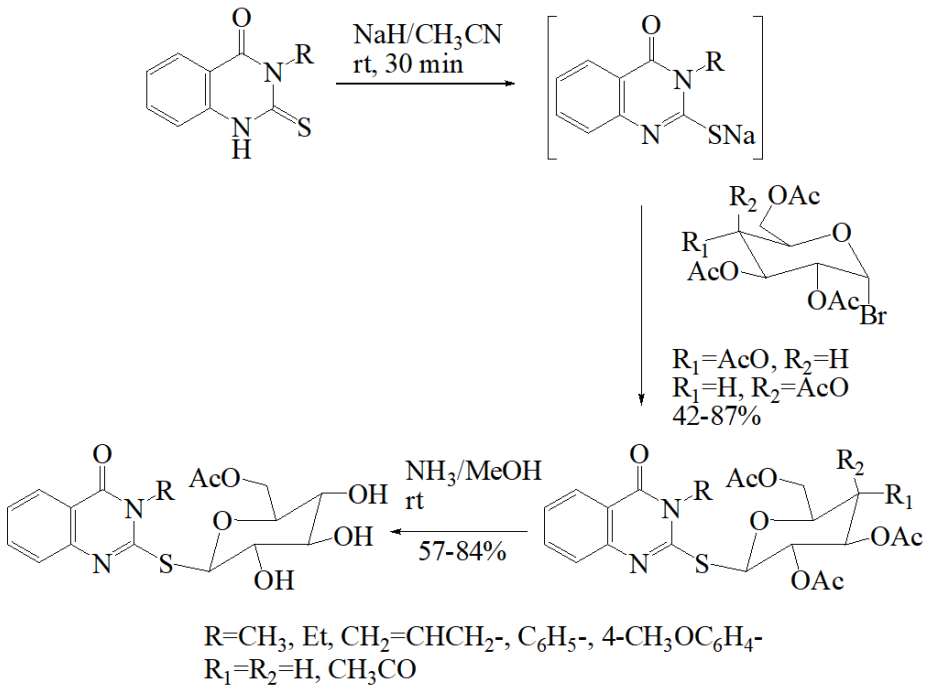


R_1	CH_3	CH_3	Cl	Cl	OCH_3	OCH_3
R_2	H	H	H	H	OCH_3	OCH_3
n	0	1	0	1	0	1
Yield(%)	49	47	61	23	46	52

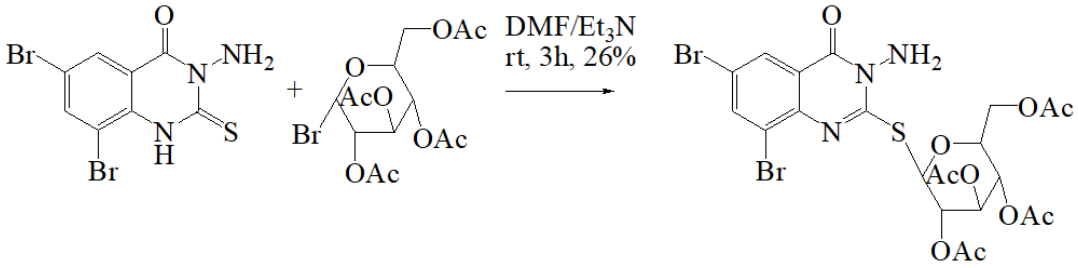
6.2.8 Glucopyranosylthioquinazolin-4(3*H*)-ones

Anticancer agents, 3-substituded-2-(β-D-glucopyranosylsulfanyl)-quinazolin-4(3*H*)-ones, were synthesized by the treatment of 3-substituted 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones with NaH in anhydrous acetonitrile furnished the sodium thioxo-4-thiazolidinones, which in turn were treated with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide followed by removal of the acetyl groups with a saturated 5% NH_3 /MeOH solution at room temperature.

DOI: https://doi.org/10.5281/zenodo.13644773

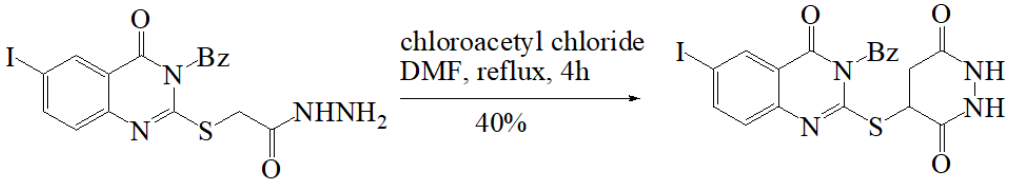


The coupling of 3-amino-6,8-dibromo-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one with (2,3,4,6-tetra-O-acetyl-α-D-gluopyranosyl)bromide in DMF gave 3-amino-6,8- dibromo-2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thioxo-2,3-dihydro-1*H*-quinazolin-4-one.[276]



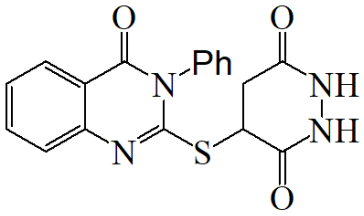
6.2.9 Pyridazinylthioquinazolin-4(3*H*)-one

***N*-[2-(3-Benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl]hydrazine was reacted with chloroacetyl chloride in dimethylformamide under reflux to isolate 2-[(3,6-dioxopyridazin-4-yl)thio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one. This compound could be considered as useful templates for future development to obtain more potent antitumor agent.[114]**



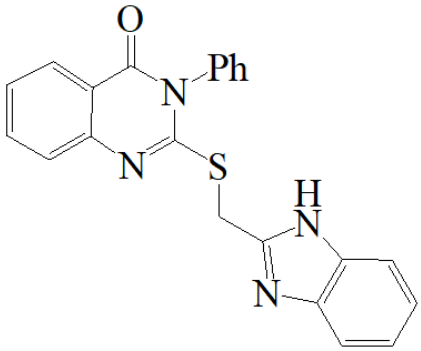
Quinazolinones linked at C-2 to heteryl moieties such as 1,3,4-oxadiazine, 1,2,4-triazine, pyrazolidine-3,5-dione, 1,2,4,5-tetrazine-3-one, pyridazine-3,6-dione , pyrazole, 1,2,4-triazine-5-one and triazole were synthesized as antitumor agents. They were tested the in vitro against *Ehrlich Ascites Carcinoma* cells and were found to be bacteriostatic, the most active being piperazine-3, 6-dione.[120]

DOI: https://doi.org/10.5281/zenodo.13644773

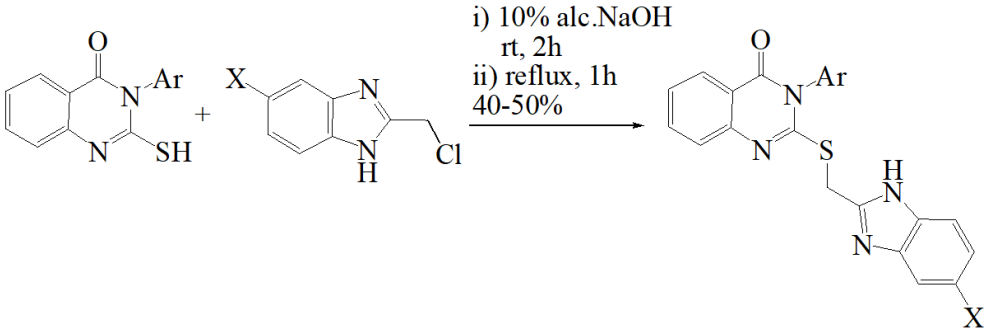


6.2.10 Imidazolylmethylthioquinazolin-4(3*H*)-ones

3-Phenyl-2-(2-benzimidazolyl)methylthio-4(3*H*)-quinazolinone is a potent antiulcer agent which suppresses domathacine induced ulcers by 90% in mice at 100 mg/Kg. The suppressive effect of cimitidine at the same dose is 40%.[112]



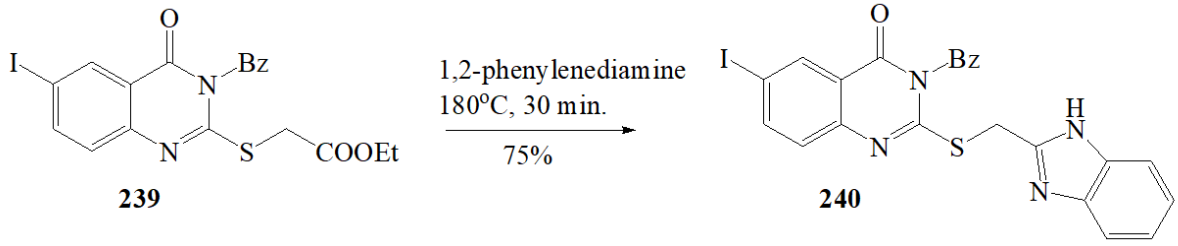
A mixture of 3-aryl-2-mercapto-quinazolin-4(3*H*)-ones and 2-chloromethylbenzimidazole was stirred for 2 h in 10% alcoholic NaOH, kept over-night and then was refluxed for 1 h to give 3-aryl-2-(2-benzimidazolyl)methylthio-4(3*H*)-quinazolinone. The compounds are potential antihelmentic agents.[113]



Ar	C_6H_5	4-ClC_6H_4	4-BrC_6H_4	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-$CH_3OC_6H_4$	-naphthyl
X	H	H	H	H	H	H	H

Ar	cyclohexyl	C_6H_5	4-ClC_6H_4	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-$CH_3OC_6H_4$
X	H	Cl	Cl	Cl	Cl	Cl

Equimolar amounts of 2-(ethoxycarbonylmethyl)thio-3-benzyl-6-iodo-quinazolin-4(3*H*)-one and 1,2-phenylenediamine were fused at 180°C to generate 2-[(2-benzimidazole)methylthio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one which are anticancer agents.[114]

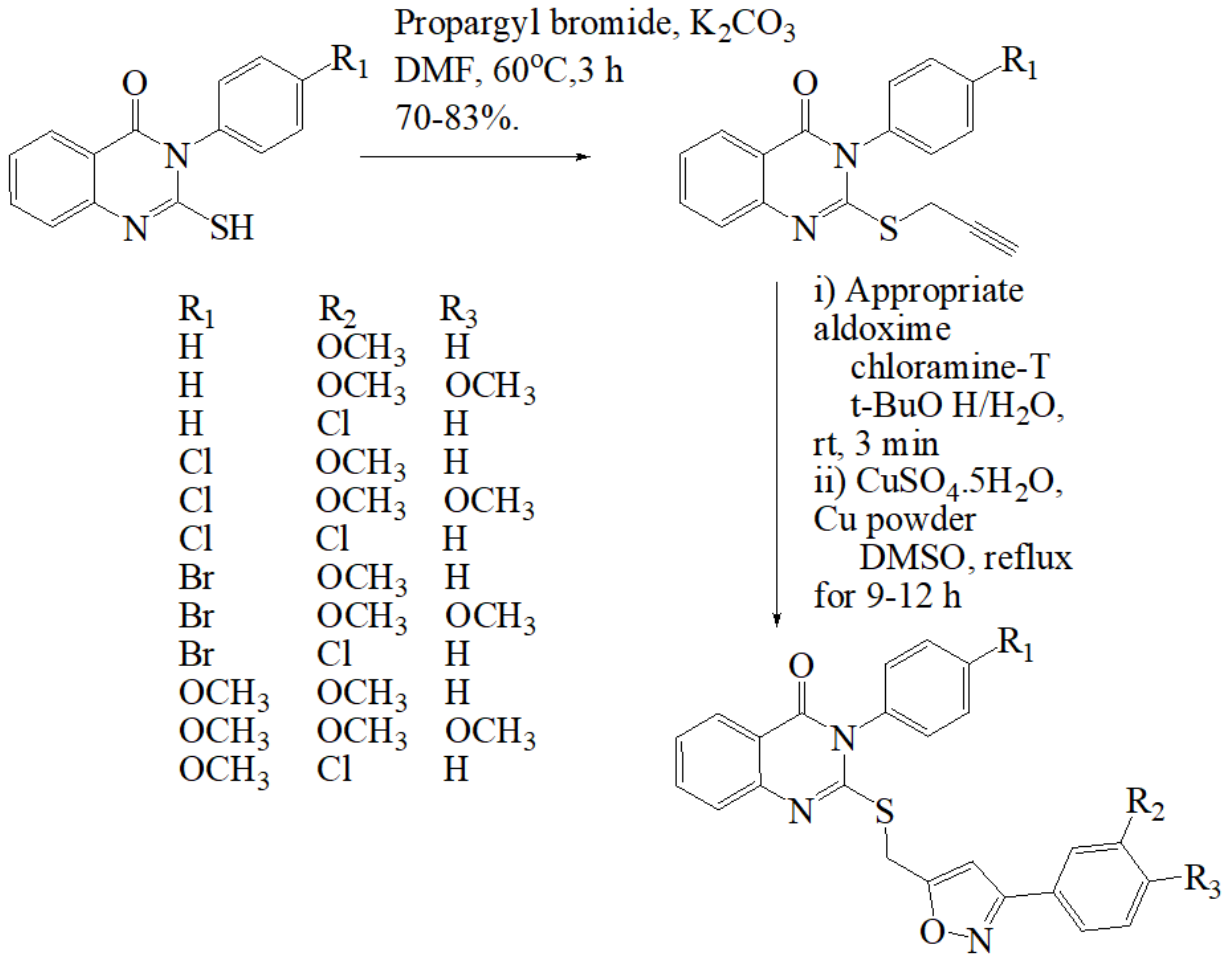


239 **240**

DOI: https://doi.org/10.5281/zenodo.13644773

6.2.11 Isoxazolylmethylthioquinazolin-4(3*H*)-ones.

Reaction of mercapto-3-substituted phenyl-quinazolin-4(3*H*)-ones with propargyl bromide in the presence of anhydrous potassium carbonate in DMF gave 3-aryl-2-(prop-2-ynylthio)quinazolin-4(3*H*)-one followed by 3 + 2 cycloaddition reaction with various aldoximes in the presence of chloramine-T, $CuSO_4$ and Cu powder furnished 2-((3-arylisoxazol-5-yl)methylthio)-3-arylquinazolin-4(3*H*)-ones. These compounds are anti-inflammatory agents.[115]

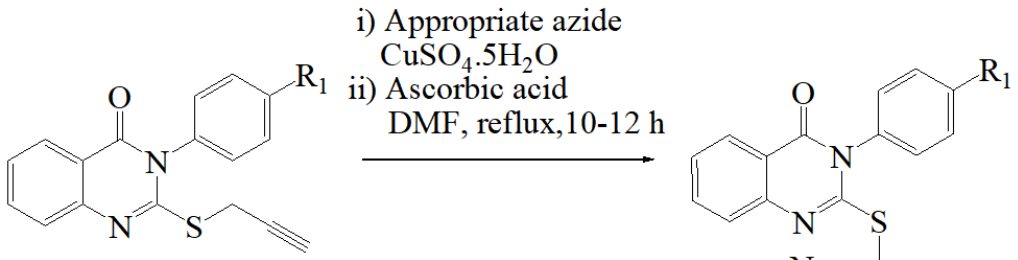


R_1	R_2	R_3
H	OCH_3	H
H	OCH_3	OCH_3
H	Cl	H
Cl	OCH_3	H
Cl	OCH_3	OCH_3
Cl	Cl	H
Br	OCH_3	H
Br	OCH_3	OCH_3
Br	Cl	H
OCH_3	OCH_3	H
OCH_3	OCH_3	OCH_3
OCH_3	Cl	H

6.2.12 Triazolylmethylthioquinazolin-4(3*H*)-ones.

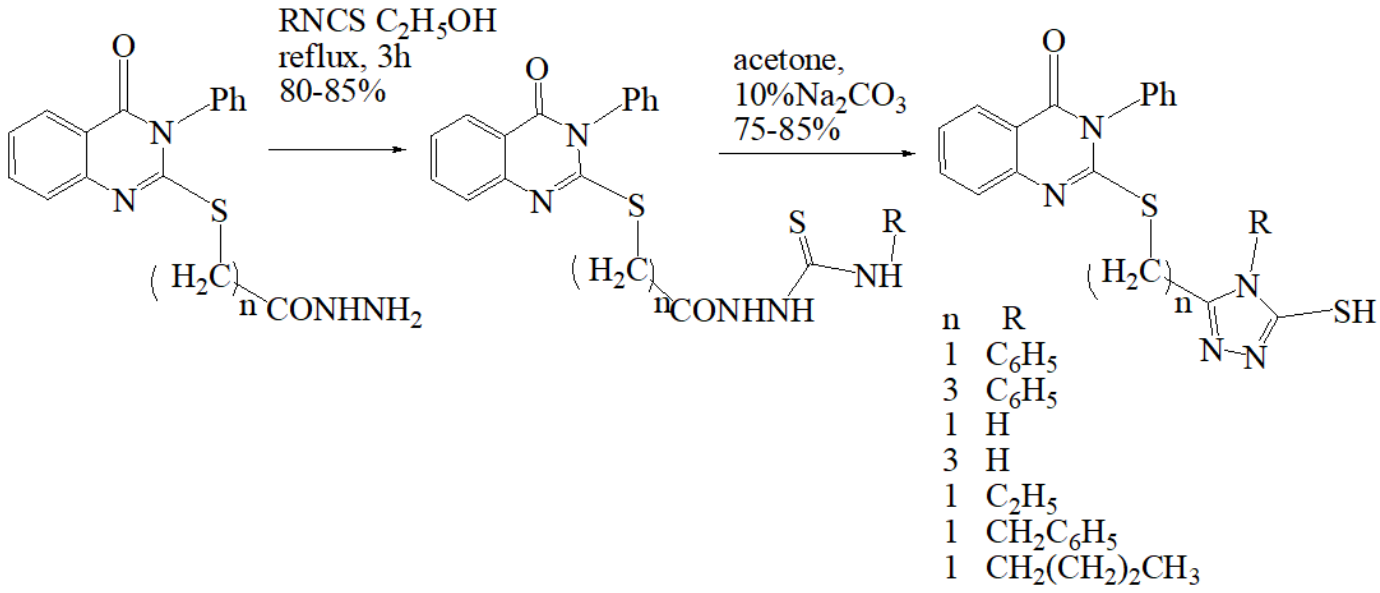
1,3-Dipolar cycloaddition reactions between 3-aryl-2-(prop-2-ynylthio)quinazolin-4(3*H*)-ones and aromatic azides were carried out by refluxing in DMF in the presence of $CuSO_4$/ascorbic acid as a catalyst producing 2-((1-aryl-1*H*-1,2,3-triazol-4-yl)methylthio)-3-arylquinazolin-4(3*H*)-ones. These compounds are anti-inflammatory agents.[115]

DOI: https://doi.org/10.5281/zenodo.13644773



R_1	R_2	R_1	R_2
H	H	Br	H
H	Cl	Br	Cl
H	Br	Br	Br
H	COOH	Br	COOH
Cl	H	OCH_3	H
Cl	Cl	OCH_3	Cl
Cl	Br	OCH_3	Br
Cl	COOH	OCH_3	COOH

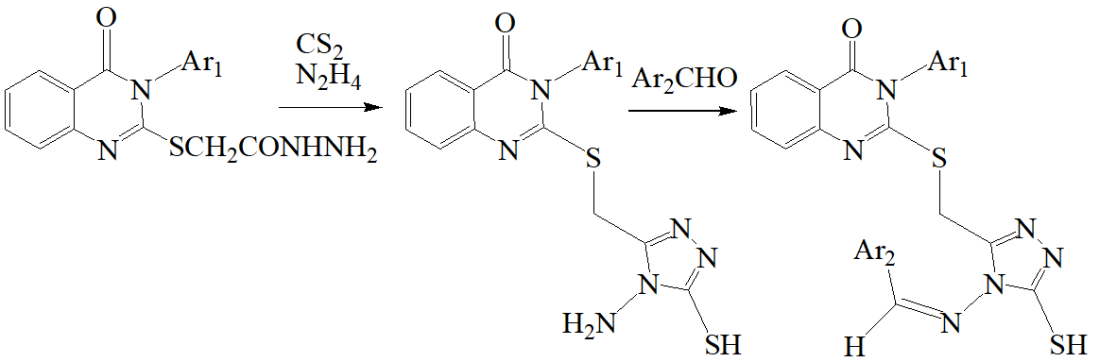
2-[(5-Thione-4-aryl-1,2,4-triazol-3-yl)methylthio]-3-aryl-quinazolin-4(3*H*)-ones are useful as antibacterial agents. They were prepared in two steps starting from [3-aryl-4(3*H*)-quinazolinone-2-yl]thioacetylhydrazine. Reaction of the hydrazine derivative with phenyl isothiocyanate gave 4-[(6-substituted-3-aryl-4(3*H*)-quinazolinone-2-yl)thioacetyl]-1-arylthio semicarbazide, and the side chain at second position was subsequently subjected to ring closure in the presence of 10% Na_2CO_3.[116, 277]



n	R
1	C_6H_5
3	C_6H_5
1	H
3	H
1	C_2H_5
1	$CH_2C_6H_5$
1	$CH_2(CH_2)_2CH_3$

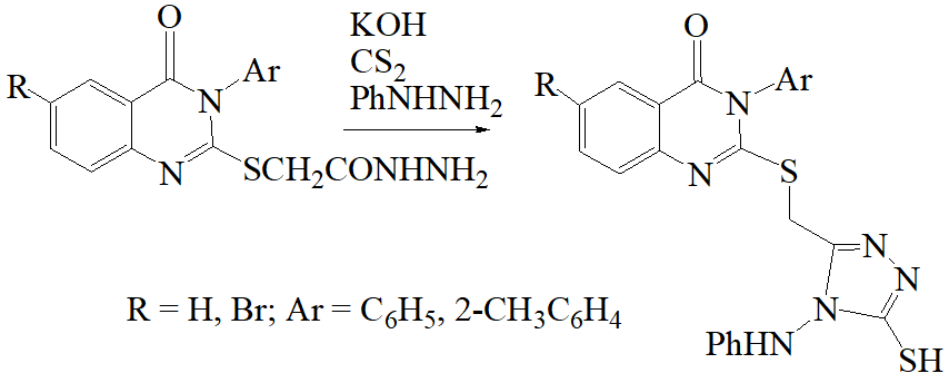
El-Feky et.al used similar compounds i.e., [3-aryl-4(3*H*)-quinazolinone-2-yl]thioacetylhydrazine for the preparation of 2-triazolylmethylthio-quinazolin-4(3*H*)-ones. In this method, the hydrazide was reacted with hydrazine and carbon disulphide to obtain 2-[(4-amino-5-thiol-4*H*-1,2,4-triazol-3-yl)-methylthio]-3-aryl-quinazolin-4(3*H*)-ones, which were converted to the corresponding Schiff's bases.[278]

DOI: https://doi.org/10.5281/zenodo.13644773



Ar_1 = C_6H_5, 2-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$
Ar_2 = C_6H_5, 4-$CH_3OC_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-HOC_6H_4, 2-HOC_6H_4

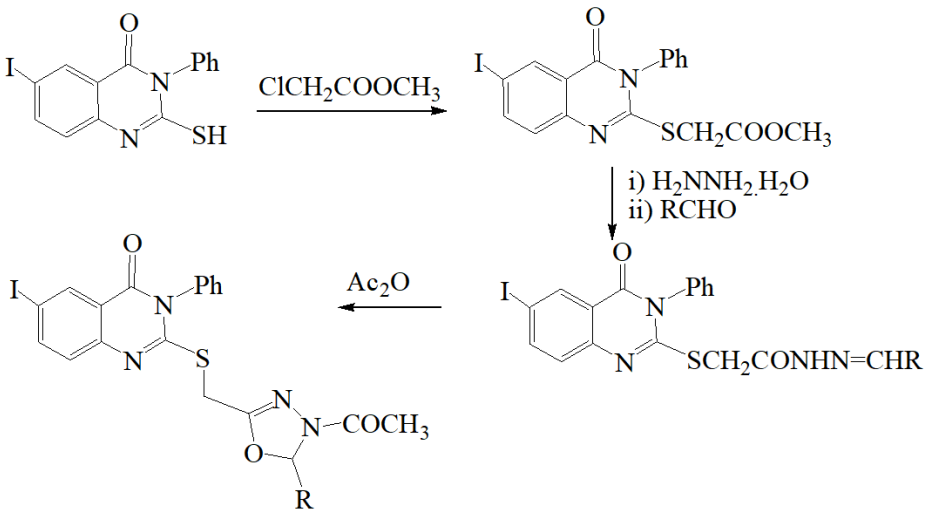
The antibacterial agents triazolylquinazolinones were also prepared from the key intermediate, (3-aryl-4(3*H*)-quinazolinone-2-yl)thioacetylhydrazine. Reaction with phenylhydrazine and carbon disulfide in alkaline medium yielded 2-((4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)methylthio)-3-aryl-quinazolin-4(3*H*)-ones in one-step.[279]



R = H, Br; Ar = C_6H_5, 2-$CH_3C_6H_4$

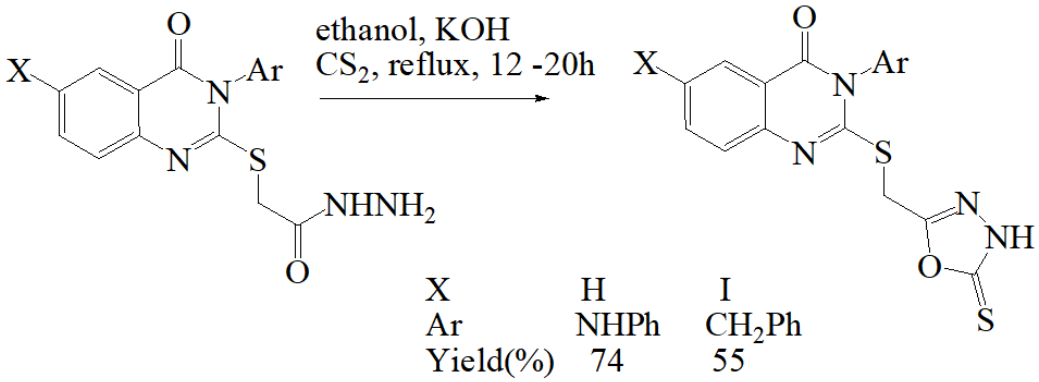
6.2.13 Oxadiazolylmethylthioquinazolin-4(3*H*)-ones

Abdel-Hamide et.al reported a multi-step synthesis of 2-[(3-(5-substituted 4-acetyl-1,3,4-oxadiazole))methylthio]-3-phenyl-6-iodo-quinazolin-4(3*H*)-ones. Reaction of 2-mercapto-3-phenyl-6-iodo-4(3*H*)-quinazolinone with methyl chloroacetate gave 2-methoxycarbonyl methylthio-3-phenyl-6-iodo-quinazolin-4(3*H*)-ones which on treatment with hydrazine hydrate followed by condensation with aldehydes afforded the hydrazone. In the presence of acetic anhydride, hydrazone cyclized to oxadiazole derivatives.[280]

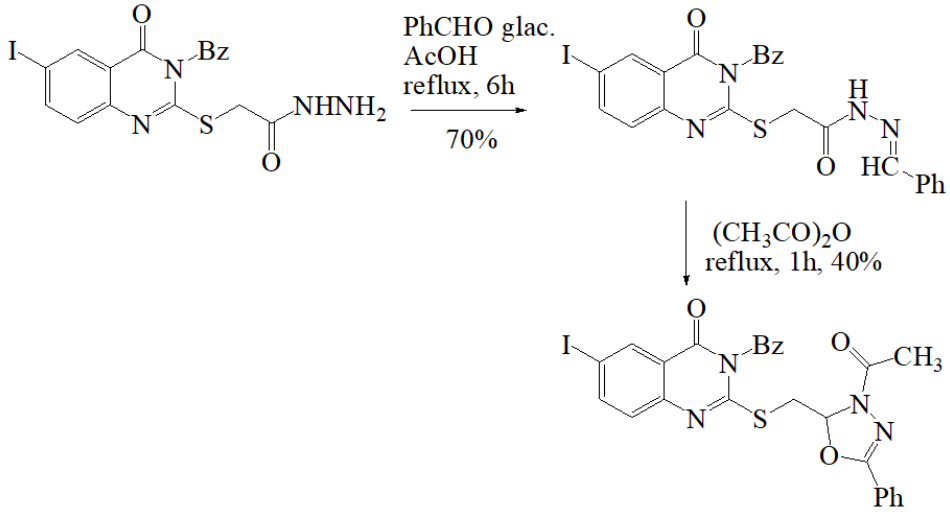


6.2.14 Dihydrooxadiazolylmethylthioquinazolin-4(3*H*)-ones

Treatment of (3-substituted quinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide with methanolic KOH and carbon disulphide afforded 3-substituted-2-(((4,5-dihydro- 5-thioxo-1,3,4-oxadiazol-2-yl)-methyl)sulfanyl)-quinazolin-4(3*H*)-one.[114, 124]



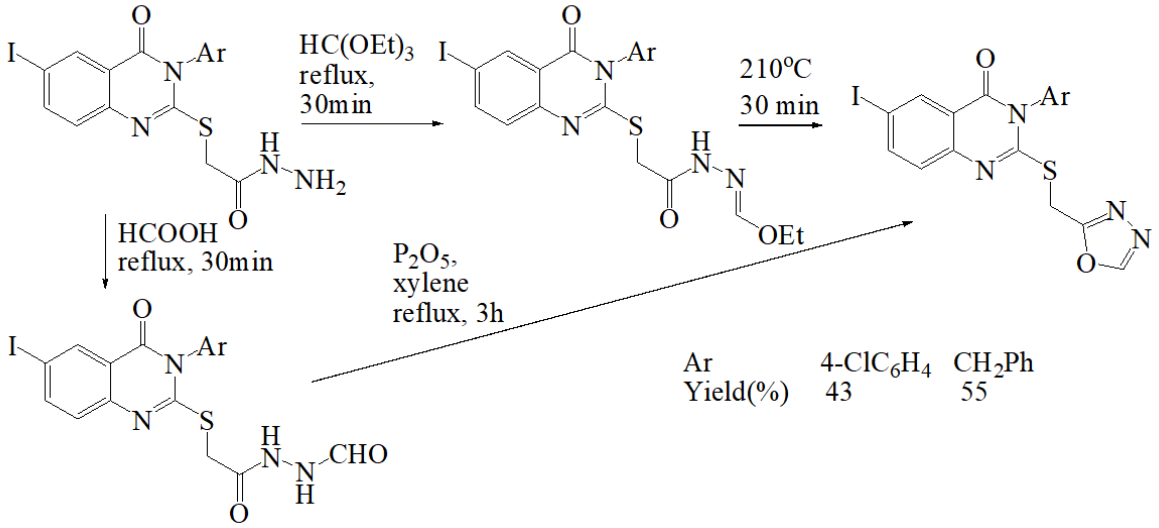
A mixture of 2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thio]acetylhydrazine and benzaldehyde in glacial AcOH was heated under reflux to isolate *N*-benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine followed by cyclization in acetic anhydride at reflux to isolate 2-[(3-acetyl-5-phenyl-1,3,4-oxadiazolin-2-yl)methylthio]-3-benzyl-6-iodo-quinazolin-4(3*H*)-one.[114]



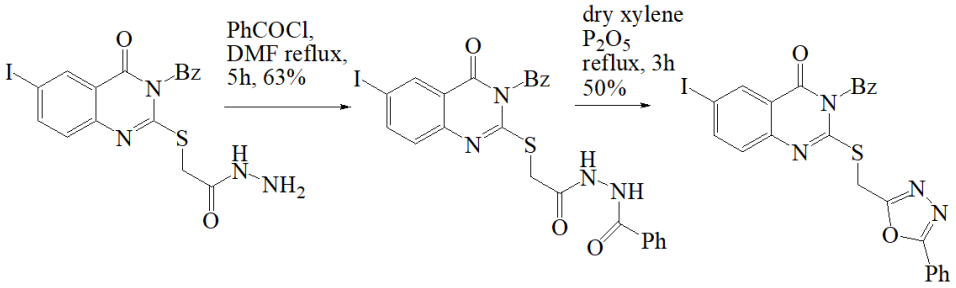
2-[(3-(4-Chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine and triethylorthoformate were refluxed to isolate *N*-ethoxymethine-*N'*-[2(3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine followed by thermal cyclisation yielded 2-((1,3,4-oxadiazol-2-yl)methylthio)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one.

Alternatively, acetylhydrazine derivative in formic acid was heated under reflux and the resultant *N*-formyl-*N*-(2-(3-(4-chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl]-hydrazine cyclised with phosphorus pentoxide to afford target compounds. These compounds showed a remarkably broad spectrum of antimicrobial activity.[107, 114]

DOI: https://doi.org/10.5281/zenodo.13644773

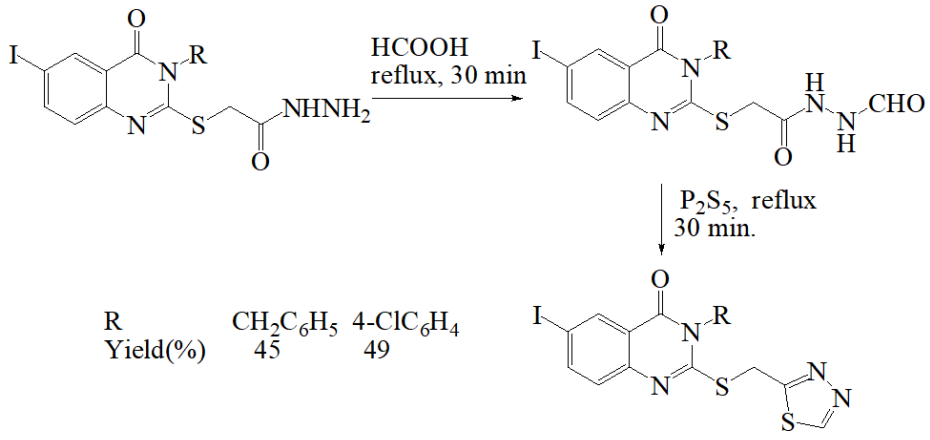


Khalil et.al developed an alternative method for the preparation of 2-((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)-3-benzyl-6-iodoquinazolin-4(3*H*)-one by benzoylating the compound hydrazide to corresponding compound followed by cyclisation with phosphorus pentoxide.[114]



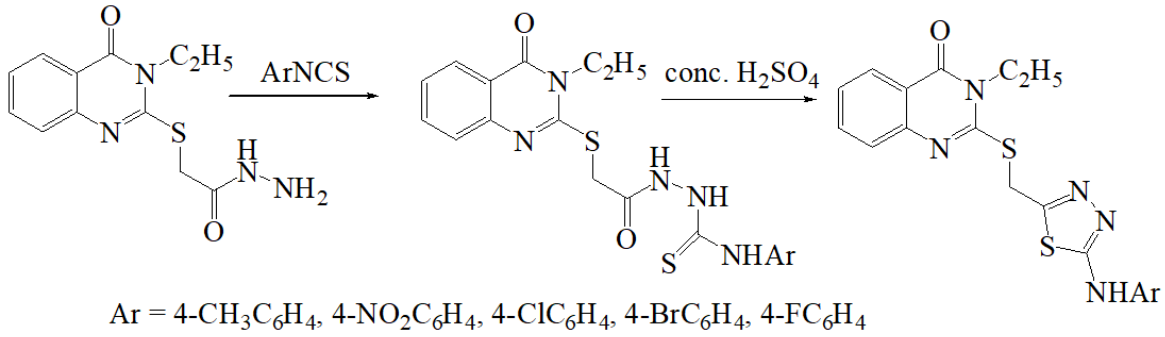
6.2.15 Thiadiazolylmethylthioquinazolin-4(3*H*)-ones

Khalil et.al were reacted 2-[(3-substituted-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thio] acetyl-hydrazine with formic acid under reflux to isolate *N*-formyl-*N*-[2-(3-substituted-6-iodoquinazolin-4(3*H*)-one-2-yl)-thioacetyl]hydrazine followed by treatment with phosphorus pentasulfide in xylene to isolate 2-[(1,3,4,-thiadiazol-2-yl)methylthio]-3-substituted-6-iodo-quinazolin-4(3*H*)-ones. These compounds identified as antitumor and antimicrobialagents.[107,114]



2-[(5-Arylamino-1,3,4-thiadiazole-2-yl)methylthio]-3-ethyl-quinazolin-4(3*H*)-ones are useful as antifungal agents. They were prepared by cyclizing 4-(3-ethyl-4(3*H*)-quinazolinone-2-yl)thioacetyl)-1-arylthiosemicarbazide in conc. H_2SO_4.[116]

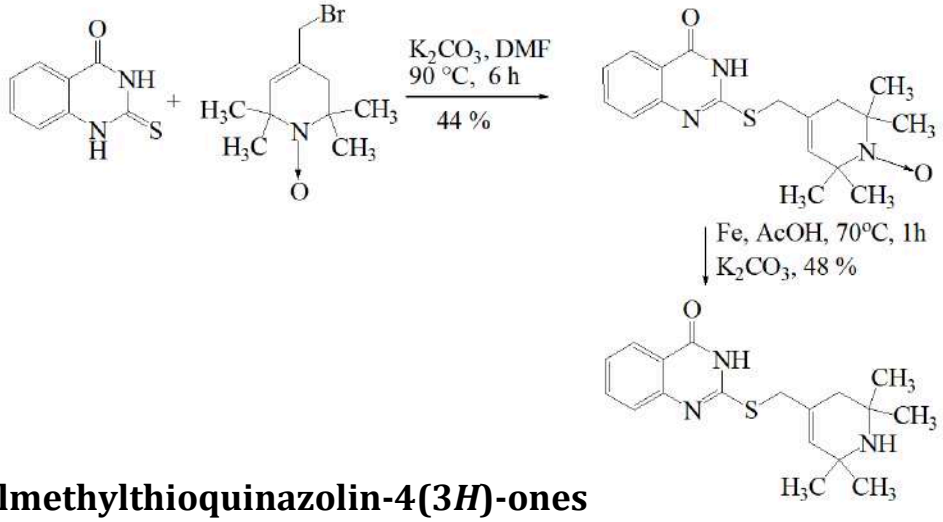
DOI: https://doi.org/10.5281/zenodo.13644773



Ar = 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4

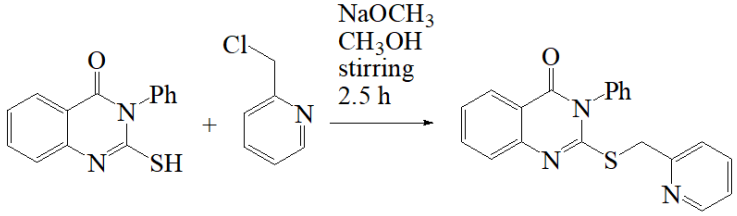
6.2.16 Tetrahydropyridinylmethylthioquinazolin-4(3*H*)-one

2-Mercaptoquinazolin-4(3*H*)-one was condensed with 1-oxyl-4-(bromomethyl)-1,2,3,6-tetrahydro-2,2,6,6-tetramethylpyridine to yield 2-{[(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl]thio}-quinazolin-4(3*H*)-one radical. The resultant nitroxide was reduced with Fe powder in acetic acid to isolate 2-{[(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl]thio}-quinazolin-4(3*H*)-one.[10]

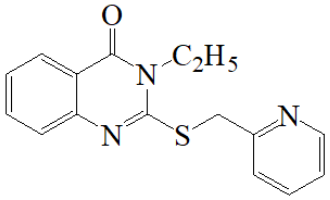


6.2.17 Pyridylmethylthioquinazolin-4(3*H*)-ones

3-Phenyl-2-(2-pyridylmethylthio)quinazolin-4(3*H*)-one was found to possess antiulcer properties. It was obtained from the reaction of 2-mercapto-3-phenyl-quinazolin-4(3*H*)-ones with 2-chloromethyl pyridine hydrochloride in the presence of sodium methoxide in methanolic solution.[131]

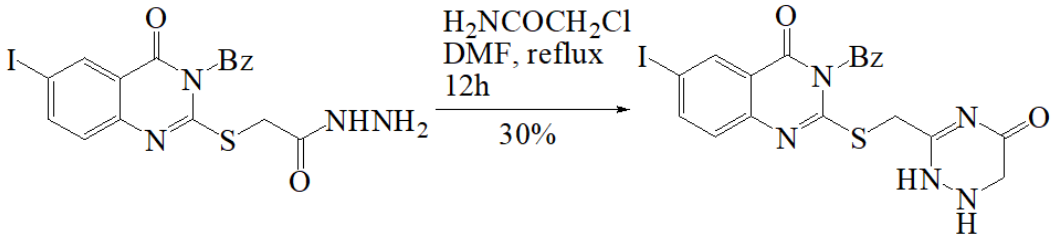


3-Ethyl-2-(2-pyridylmethylthio)-4(3*H*)-quinazolinone is a potent antiulcer agent which suppresses in domathacine induced ulcers by 90% in mice at 100 mg/Kg.[112]

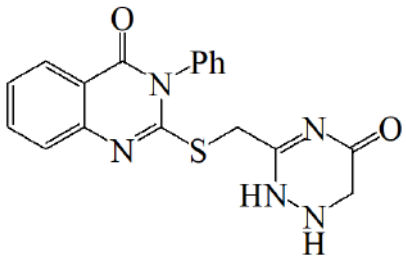


6.2.18 Dihydrotriazinylmethylthioquinazolin-4(3*H*)-one

An equimolar mixture of *N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)-thioacetyl] hydrazine and chloroacetamide in dimethylformamide was heated under reflux to isolate [(5-oxo-1,6-dihydro-6*H*-1,2,4-triazin-2-yl)methylthio]-3-benzyl-6-iodoquinazolin-4(3*H*)-one. These compounds identified as antitumor agents.[114]

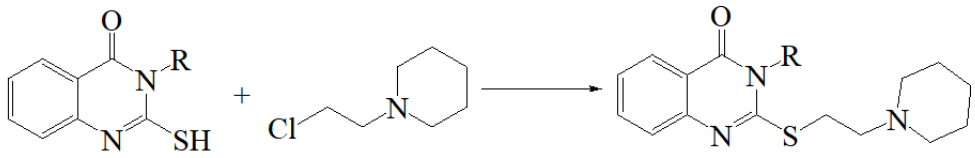


Quinazolinones linked at C-2 to heteryl moieties such as 1,3,4-oxadiazine, 1,2,4-triazine, pyrazolidine-3,5-dione, 1, 2, 4, 5-tetrazine-3-one, pyridazine-3,6-dione, pyrazole, 1, 2, 4-triazine-5-one and triazole were synthesized as antitumor agents. They were tested the in vitro against Ehrlich Ascites Carcinoma cells and were found to be bacteriostatic, the most active being 1, 2-dihydro-1, 2, 4-triazin-5(6*H*)-one.[120]



6.2.19 Piperidinoethylthioquinazolin

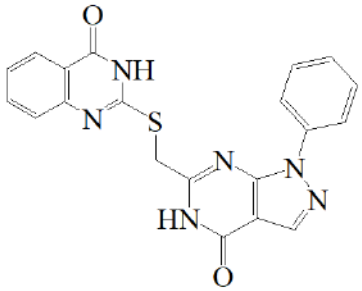
Bhargava and Singh prepared 2-(1-piperidinoethylthio)-3-aryl/alkyl-quinazolin-4(3*H*)-ones from the reaction of 3-aryl-2-mercapto-quinazolin-4(3*H*)-ones with piperidinoethyl chloride. These quinazolinone derivatives inhibited *Mycobacterium tuberculosis*.[117]



R = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, CH_3, C_2H_5, C_4H_9

6.2.20 Pyrazolopyrimidinonylmethylthioquinazolin-4(3*H*)-one

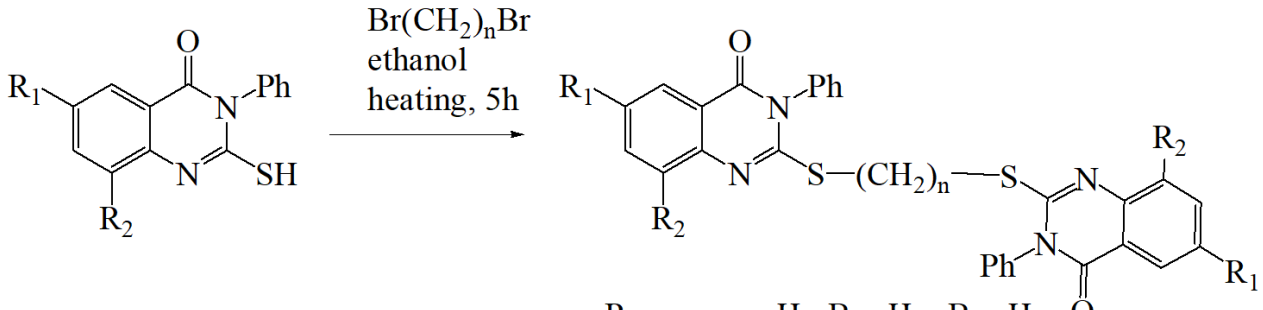
L. Yang et.al reported 2-(((4,5-dihydro-4-oxo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl) methyl)sulfanyl)quinazolin-4(3*H*)-one as tumor growth inhibitor and apoptosis inducer.[118]



DOI: https://doi.org/10.5281/zenodo.13644773

6.2.21 2,2'-Bis-[quinazolin-4(3*H*)-one-sulfides]

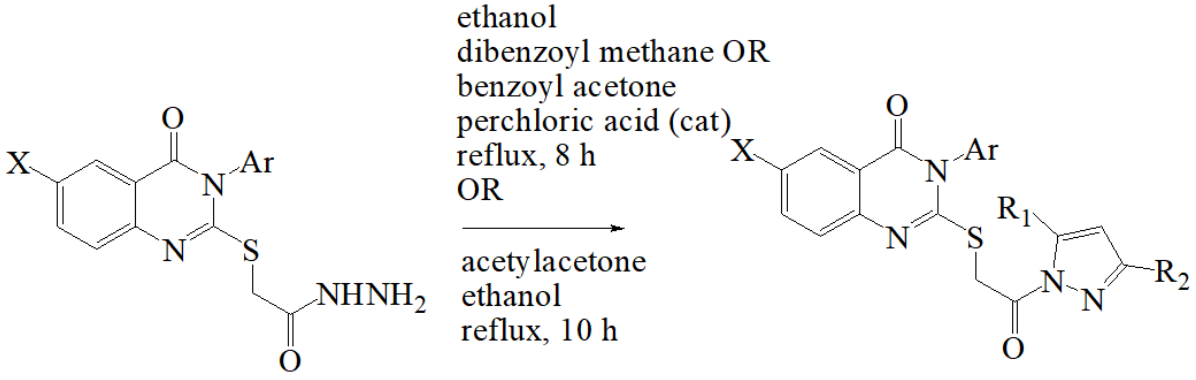
2,2'-Bis[6,8-disubstituted 3-phenyl-4(3*H*)-quinazolinonyl]sulfide derivatives were obtained from the reaction of 6,8-disubstituted 2-mercaptoquinazolin-4(3*H*)-ones and 1,2-dibromoalkane in ethanol medium.[281]



R_1	H	Br	H	Br	H
R_2	H	Br	H	Br	H
n	1	1	2	2	3
Yield (%)	68	75	80	78	70

6.2.22 Pyrazoloxoethylthioquinazolin-4(3*H*)-ones

The (3-arylquinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide on reaction with benzoyl acetone or dibenzoyl methane furnished the corresponding 2-[2-(pyrazol-1-yl)-2-oxo-ethylthio]-3-arylquinazolin-4(3*H*)-ones. The 2-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl-thio)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one (X=I, R_1 =R_2=CH_3, Ar=4-Cl-C_6H_4) showed a remarkably broad spectrum of antimicrobial activity.[124, 261]

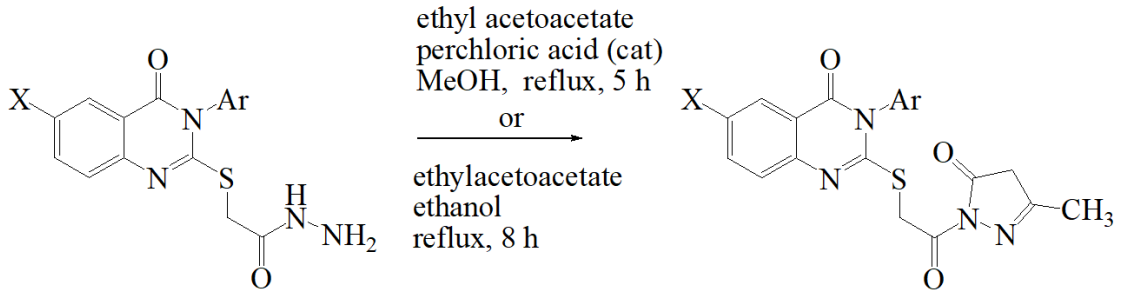


X	H	H	I	I
R1	Ph	CH_3	CH_3	CH_3
R2	Ph	Ph	CH_3	CH_3
Ar	NHPh	NHPh	4-ClC_6H_4	CH_2Ph
Yield(%)	80	72	62	55

6.2.23 Dihydropyrazolyloxoethylthioquinazolin-4(3*H*)-ones

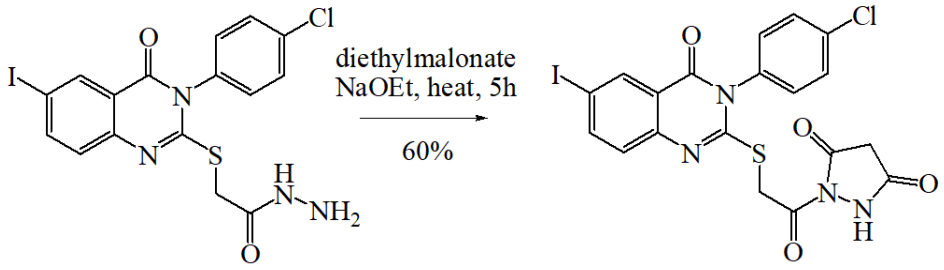
The (3-arylquinazolin-4(3*H*)-one-2-ylthio)acetic acid hydrazide on reaction with ethyl acetoacetate yielded 2-[2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxoethylthio]-3-aryl quinazolin-4(3*H*)-ones.[107, 114, 124]

DOI: https://doi.org/10.5281/zenodo.13644773



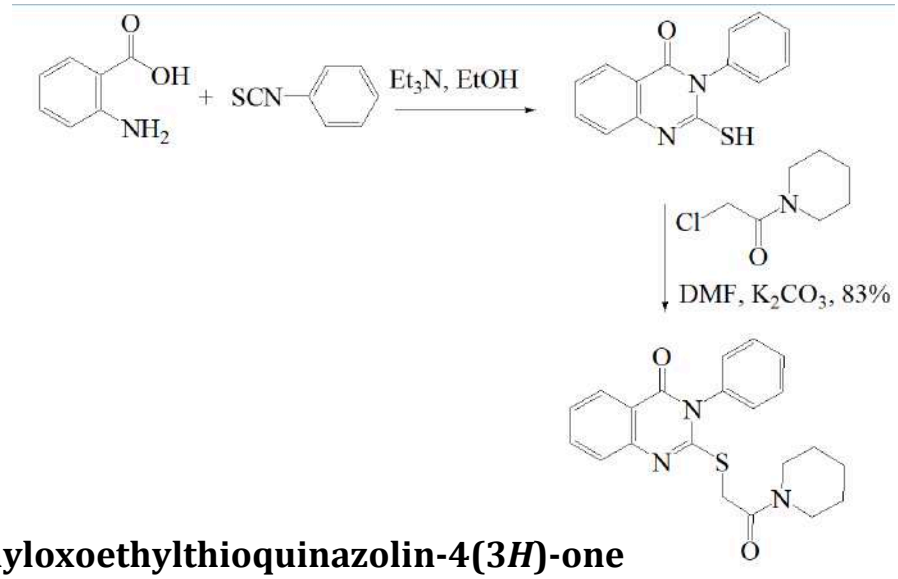
6.2.24 Dioxopyrazolidinylcarbonylmethylthioquinazolin-4(3*H*)-one

2-[(3-(4-Chlorophenyl)-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine was reacted with diethylmalonate in presence of sodium ethoxide to yield 2-[3,5-dioxo-pyrazolidin-1-yl)carbonylmethylthio]-3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one.[107]



6.2.25 Piperidinylcarbonylmethylthioquinazolin-4(3*H*)-one

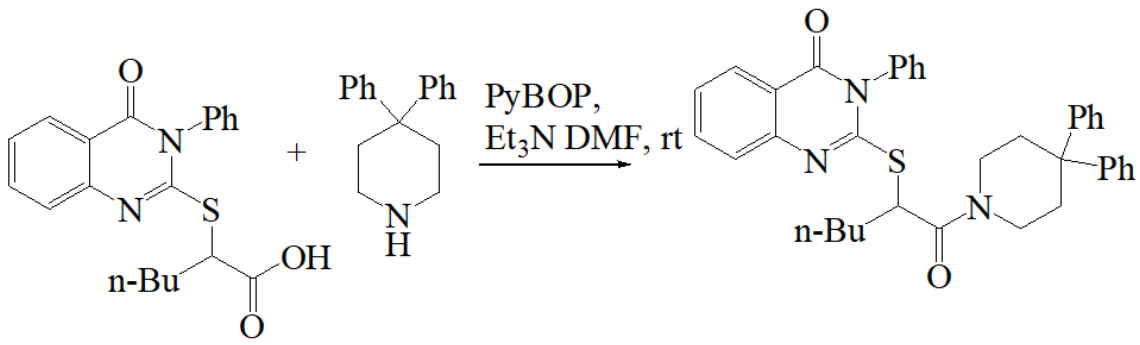
2-Aminobenzoic acid and phenylisothiocyanate were condensed in ethanol containing triethylamine. The resultant 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones was alkylated using 2-chloro-1-(piperidin-1-yl)ethan-1-one in dimethylformamide in presence of anhydrous potassium carbonate to afford 2-(2-oxo-2-(piperidin-1-yl)ethylthio)-3-phenylquinazolin-4(3*H*)-one.[125]



6.2.26 Piperidinyloxoethylthioquinazolin-4(3*H*)-one

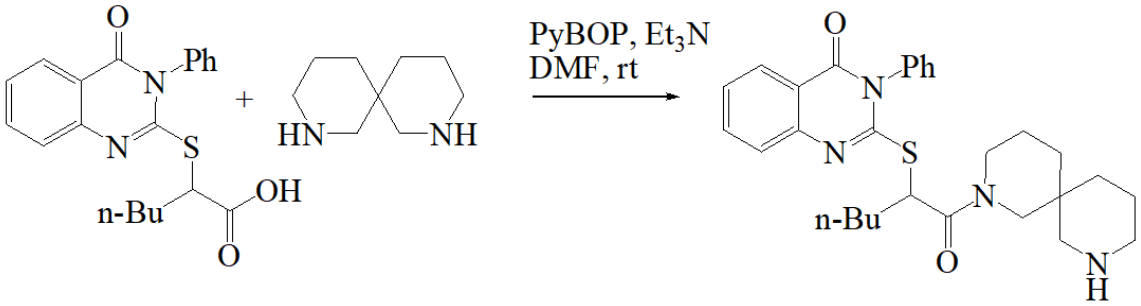
2-(3-Phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid and 4,4-diphenylpiperidine were condensed in basic medium to produce 2-(1-oxo-1-(4,4-diphenyl piperidin-1-yl)-hexan-2-ylthio))-3-phenylquinazolin-4(3*H*)-one. This compound has showed moderate antiallosteric Chk1 kinase activity.[126]

DOI: https://doi.org/10.5281/zenodo.13644773



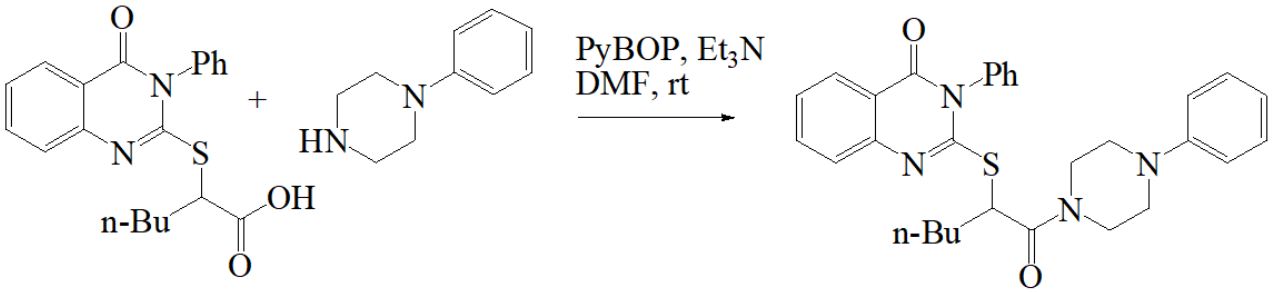
6.2.27 Diazaspiro[5.5]undecanyloxoethylthioquinazolin-4(3*H*)-one

Greatest potential allosteric Chk1 kinase inhibitors have been prepared by condensing 2-(3-phenylquinazolin-4(3*H*)-2-ylthio)hexanoic acid with 2,8-diazaspiro[5.5]undecane in basic medium to produce 2-(1-oxo-1-(2,8-diazaspiro[5.5]undecane-2-yl)hexan-2-ylthio)-3-phenyl quinazolin-4(3*H*)-one[126]



6.2.28 Piperazinylhexanoylthioquinazolin-4(3*H*)-one

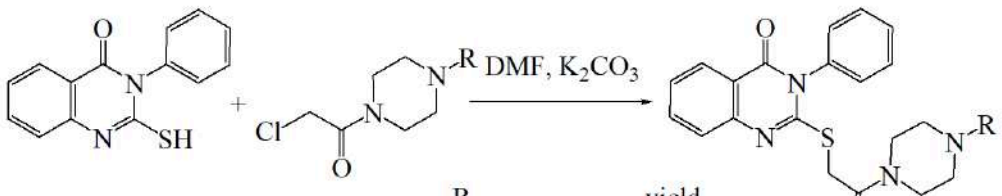
Reaction of 2-(3-phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid with phenylpiperazine yielded 2-(1-oxo-1-(4-phenylpiperazin-1-yl)hexano-2-ylthio)-3-phenyl quinazolin-4(3*H*)-one which is a potential allosteric Chk1 kinase inhibitor.[126]



6.2.29 Piperazinylcarbonylmethylthioquinazolin-4(3*H*)-one

The 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one was alkylated using 2-chloro-1-(piperazin-1-yl)ethanone in dimethylformamide (DMF) in presence of anhydrous potassium carbonate to afford 2-(2-oxo-2-(piperazin-1-yl)ethylthio)-3-phenylquinazolin-4(3*H*)-one. The compounds 2-(2-(4-allylpiperazin-1-yl)-2-oxoethylthio)-3-phenylquinazolin-4(3*H*)-one and 2-(2-(4-acetylpiperazin-1-yl)-2-oxoethylthio)-3-phenylquinazolin-4(3*H*)-one were exhibited potent anti-proliferative activity against three human cancer cell lines and HSP90 inhibition activity.[125]

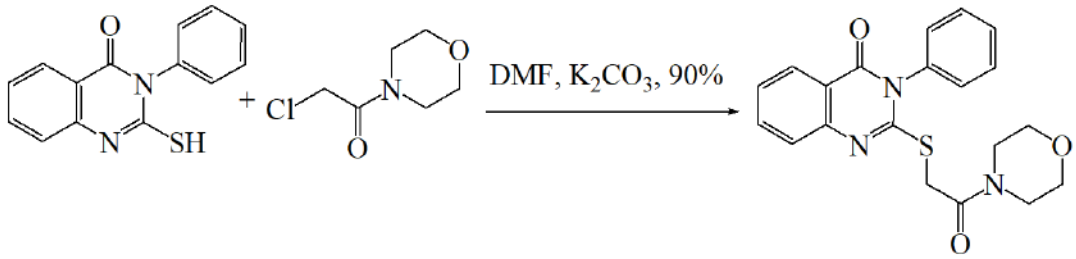
DOI: https://doi.org/10.5281/zenodo.13644773



R	yield
CH_2CH_3	84
CH_2-CH=CH_2	98
$COCH_3$	81
$COOC(CH_3)_3$	63
C_6C_{11}	97
$C_4H_3N_2$	96

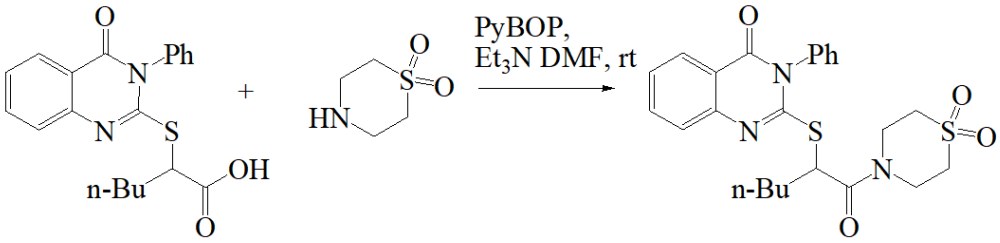
6.2.30 Morpholinylcarbonylmethylthioquinazolin-4(3*H*)-one

The potent anti-proliferative activity against three human cancer cell lines and HSP90 inhibition activity compound 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones was alkylated using 2-chloro-1-morpholinoethan-1-one in dimethylformamide in presence of anhydrous potassium carbonate to afford 2-(2-morpholino-2-oxoethylthio)-3-phenylquinazolin-4(3*H*)-one.[125]



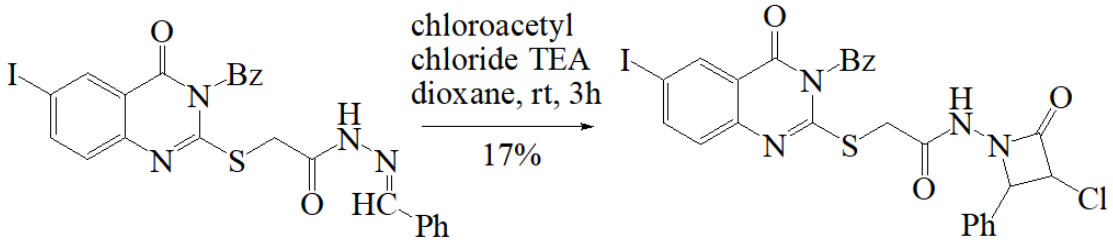
6.2.31 Thiomorpholinylhexanylthioquinazolin-4(3*H*)-one

2-(3-Phenylquinazolin-4(3*H*)-one-2-ylthio)hexanoic acid was reacted with thiomorpholine-1,1-dioxide to isolate 2-(1-oxo-1-(thiomorpholine-1,1-dioxide-4-yl)hexan-2-ylthio)-3-phenyl quinazolin-4(3*H*)-one.[126]



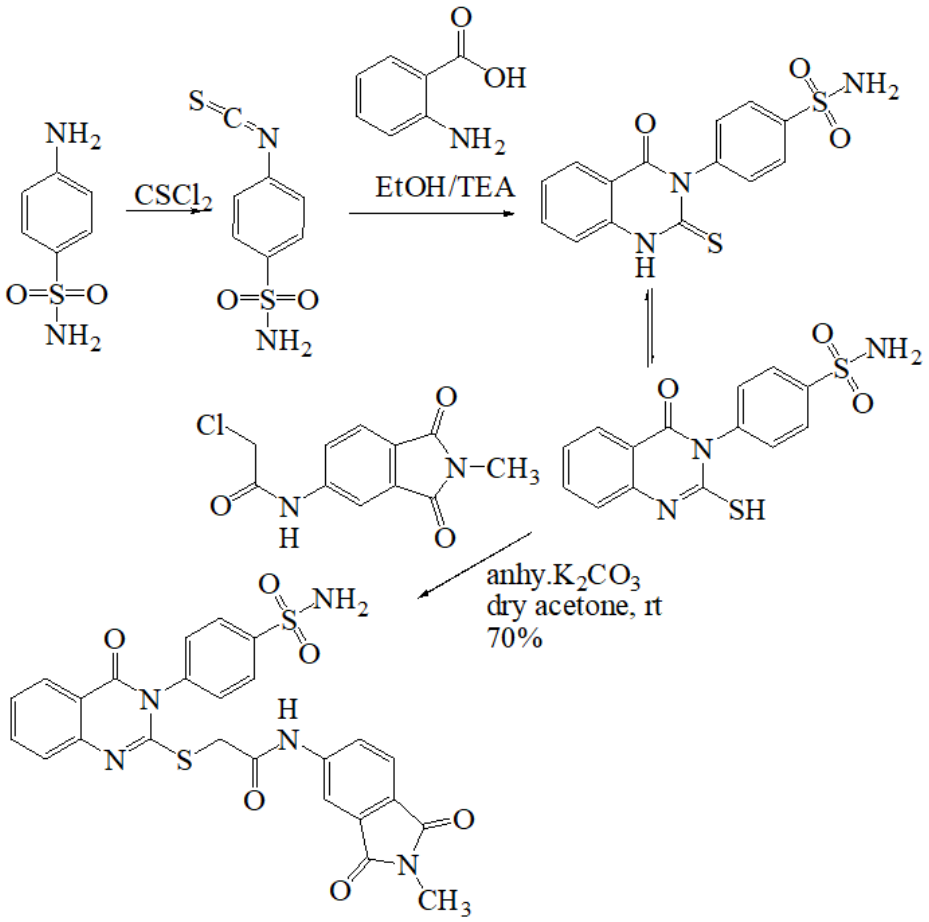
6.2.32 Azetidinylaminooxoethylthioquinazolin-4(3*H*)-one

***N*-Benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine was reacted with chloroacetyl chloride in triethylamine to isolate *N*-(2-oxo-3-chloro- 4-phenylazetidin-1-yl)-2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide.[114]**



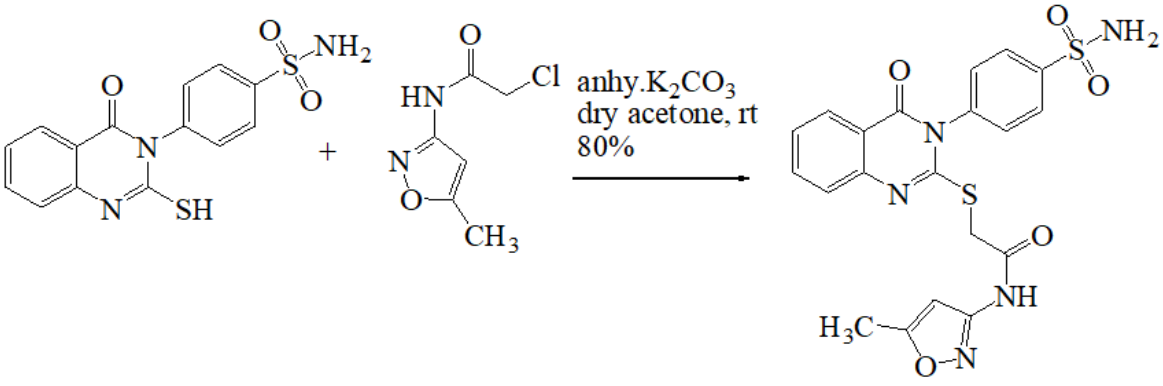
6.2.33 Isoindolinylaminocarbonylmethylthioquinazolin-4(3*H*)-one

The 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one was utilized in the synthesis of 2-((((2-methyl-1,3-dioxoisoindolin-5-yl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one through the reaction with 2-chloro-*N*-(2-methyl-1,3-dioxoisoindolin-6-yl)acetamide in dry acetone and an equimolar amount of anhydrous K_2CO_3 at room temperature. This compound has shown antioxidant activity.[127]



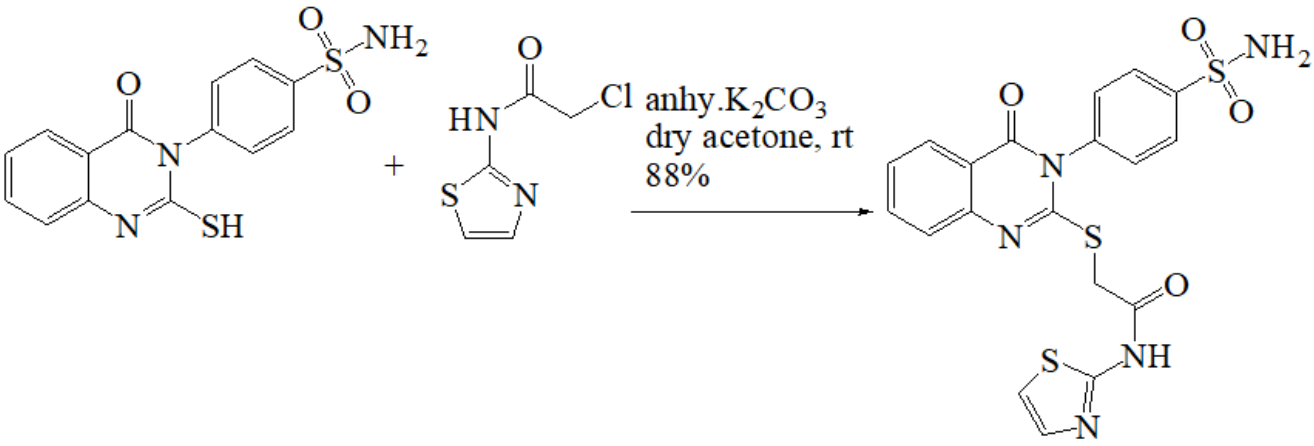
6.3.34 Isoxazolylaminocarbonylmethylthioquinazolin-4(3*H*)-one

The compound, 2-((((5-methylisoxazol-3-yl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one, with antioxidant activity has synthesized by reacting 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-(5-methylisoxazol-3-yl)acetamide in dry acetone containing anhy. K_2CO_3 at room temperature.[127]



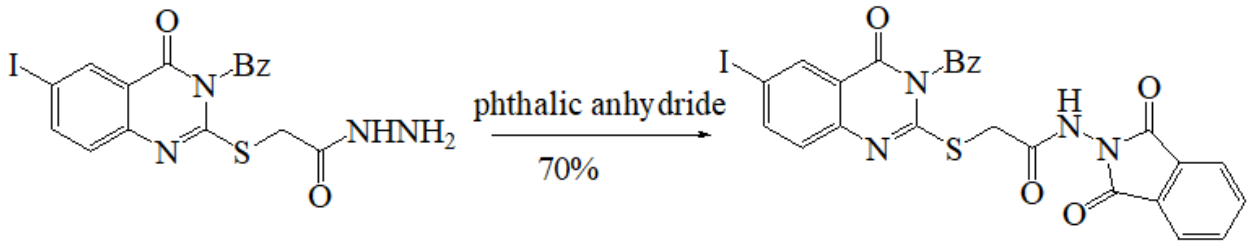
6.2.35 Thiazolylaminocarbonylmethylthioquinazolin-4(3*H*)-one

Aiten M. Soliman et.al were described the reaction of 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-(thiazol-2-yl)acetamide in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-((((thiazol-2-yl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one. This compound has shown antioxidant activity.



6.2.36 Dioxoisoindolinylaminooxoethylthioquinazolin-4(3*H*)-one

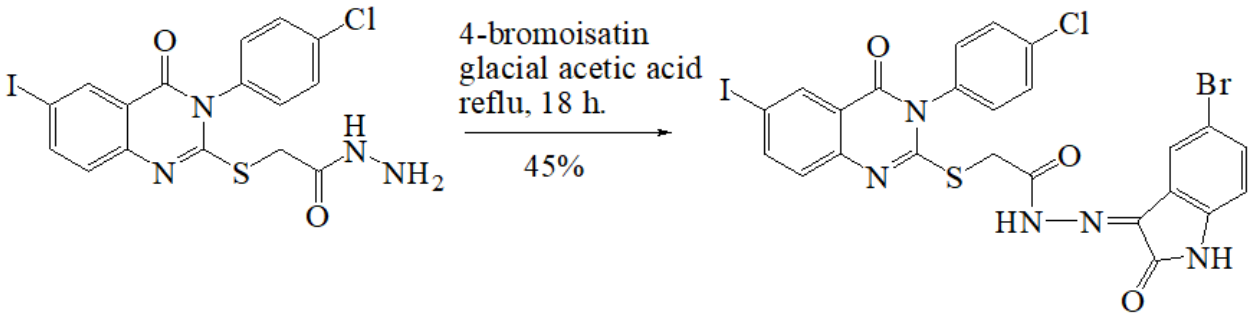
The 2-(3-benzyl-6-iodoquinazolin-4(3*H*)-one-2-ylthio)acetohydrazide was reacted with phthalic anhydride to give 2-(3-benzyl-6-iodoquinazolin-4(3*H*)-one-2-ylthio)-*N*-(1,3-dioxo-isoindolin-2-yl)-acetamide.[114]



6.2.37 Indolinylidenehydrazinooxoethylthioquinazolin-4(3*H*)-one

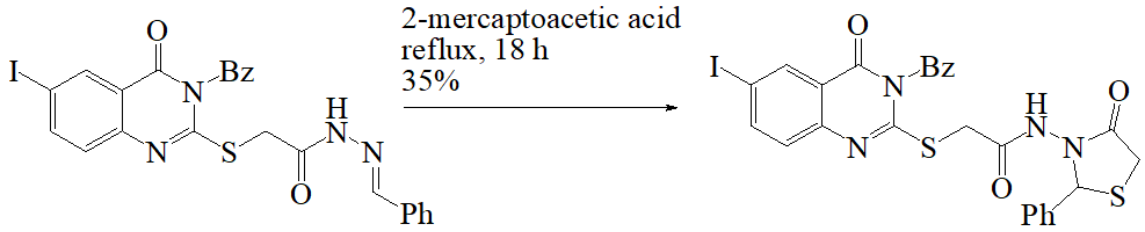
2-[(3-(4-Chlorophenyl)-6-iodoquinazolin-4(3*H*)-one-2-yl)thio]acetylhydrazine and 4-bromoisatin were refluxed in acidic medium to afford (*E*)-*N*-(5-bromo-2-oxoindolin-3-ylidene)-2-[3-(4-chlorophenyl)-6-iodoquinazolin-4(3*H*)-one-2-ylthio]acetohydrazide.[107]

DOI: https://doi.org/10.5281/zenodo.13644773



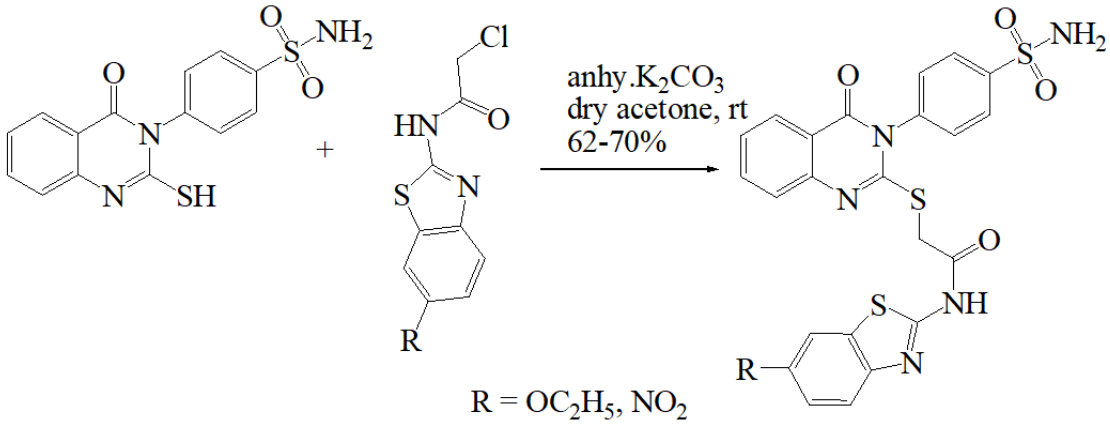
6.2.38 Thiazolidinylaminooxoethylthioquinazolin-4(3*H*)-one

***N*-Benzylidine-*N*-[2-(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thioacetyl]hydrazine and thioglycolic acid in dioxane was heated under reflux to isolate *N*-(2-phenyl-4-oxo-1,3-thiazolidin-3-yl)-2-[(3-benzyl-6-iodo-quinazolin-4(3*H*)-one-2-yl)thio]acetamide.[114]**



6.2.39 Benzothiazolylaminocarbonylmethylthioquinazolin-4(3*H*)-ones

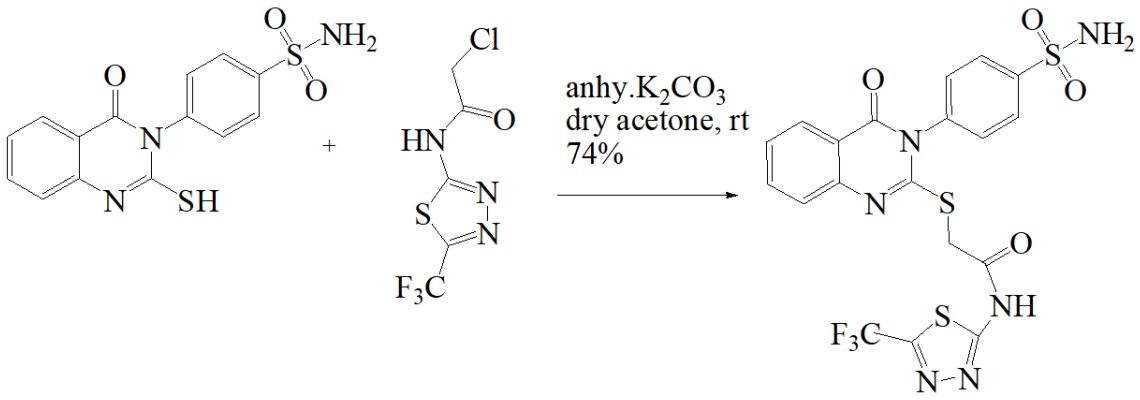
The antioxidant activity compounds, 2-((((6-ethoxy/nitrobenzo[*d*]thiazol-2-yl)amino) carbonyl) methylthio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-ones, were synthesized by reacting 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-(6-ethoxy/nitrobenzo [*d*] thiazol-2-yl)acetamide in dry acetone containing anh. K_2CO_3 at room temperature.[127]



6.2.40 Thiadiazolylaminocarbonylmethylthioquinazolin-4(3*H*)-one

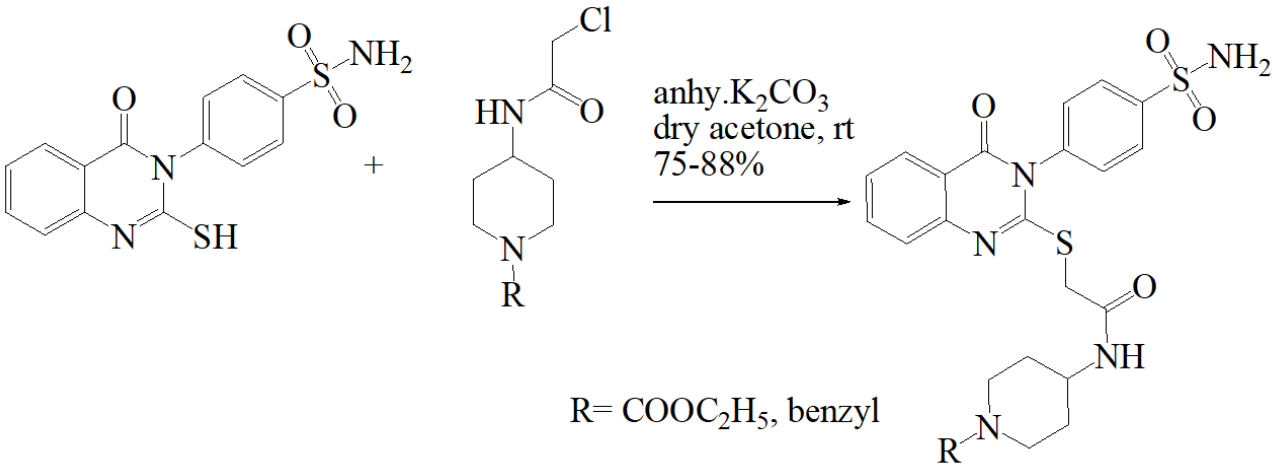
The 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one was reacted with 2-chloro-*N*-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)acetamide in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-(((((trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)carbonyl)methyl thio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one. This compound has shown anti-oxidant activity.[127]

DOI: https://doi.org/10.5281/zenodo.13644773



6.2.41 Piperidinylaminocarbonylmethylthioquinazolin-4(3*H*)-ones

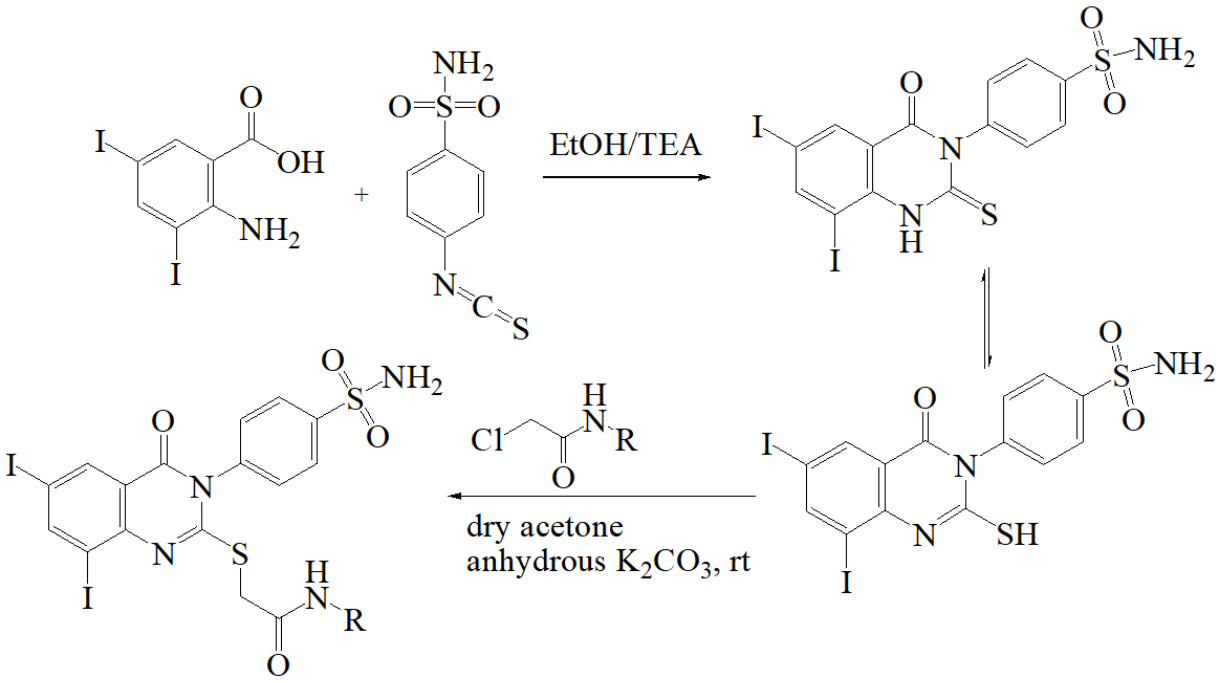
Aiten M. Soliman et.al were reacted 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-(piperidin-4-yl)acetamide derivatives in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-((((piperidin-4-yl)amino)carbonyl)methylthio)-3-(4-sulfamoyl phenyl)-quinazolin-4(3*H*)-ones. These compounds have shown antioxidant activity.[127]



6.2.42 Pyridinylaminocarbonylmethylthioquinazolin-4(3*H*)-ones

A novel 2-((((pyridin-2-yl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-6,8-diiodo-quinazolin-4(3*H*)-one derivatives as antioxidants that protects against the harmful effect of radiation were prepared by coupling of 2-amino-3,5-diiodobenzoic acid with 4-isothio cyanato benzenesulfonamide to yield 4-(6,8-diiodo-2-mercapto-4-quinazolin-3(4*H*)-oneyl)benzene sulfon amide followed by alkylation with 2-chloro-*N*-pyridinylacetamides in dry acetone and anhydrous K_2CO_3[127]

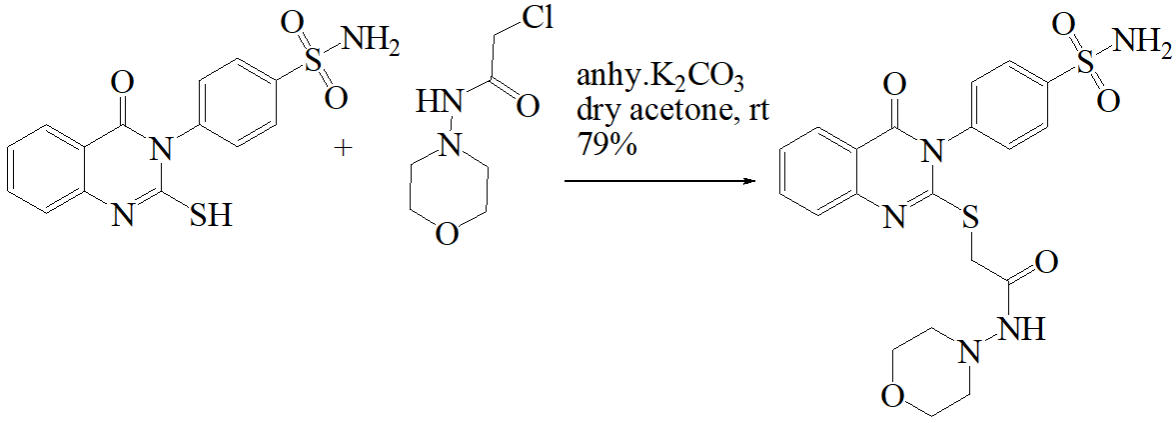
DOI: https://doi.org/10.5281/zenodo.13644773



2-pyridyl, 3-pyridyl, 4-pyridyl, 2-chloro-3-pyridyl, 5-chloro-2-pyridyl

6.2.43 Morpholinoaminocarbonylmethylthioquinazolin-4(3*H*)-one

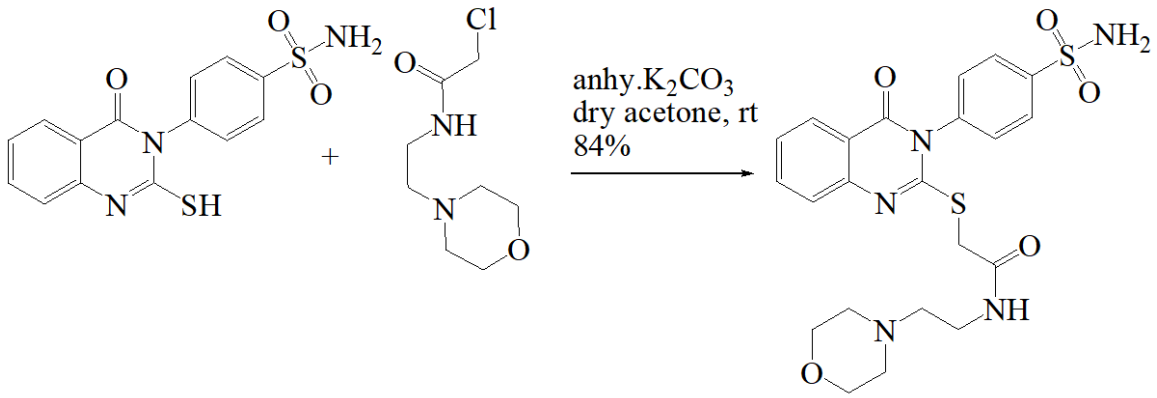
The antioxidant compound, 2-((((morpholino)amino)carbonyl)methylthio)-3-(4-sulfamoyl phenyl)-quinazolin-4(3*H*)-one, was synthesized by reacting 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-morpholinoacetamide in dry acetone containing anhy. K_2CO_3 at room temperature.[127]



6.2.44 Morpholinoethylaminocarbonylmethylthioquinazolin-4(3*H*)-one

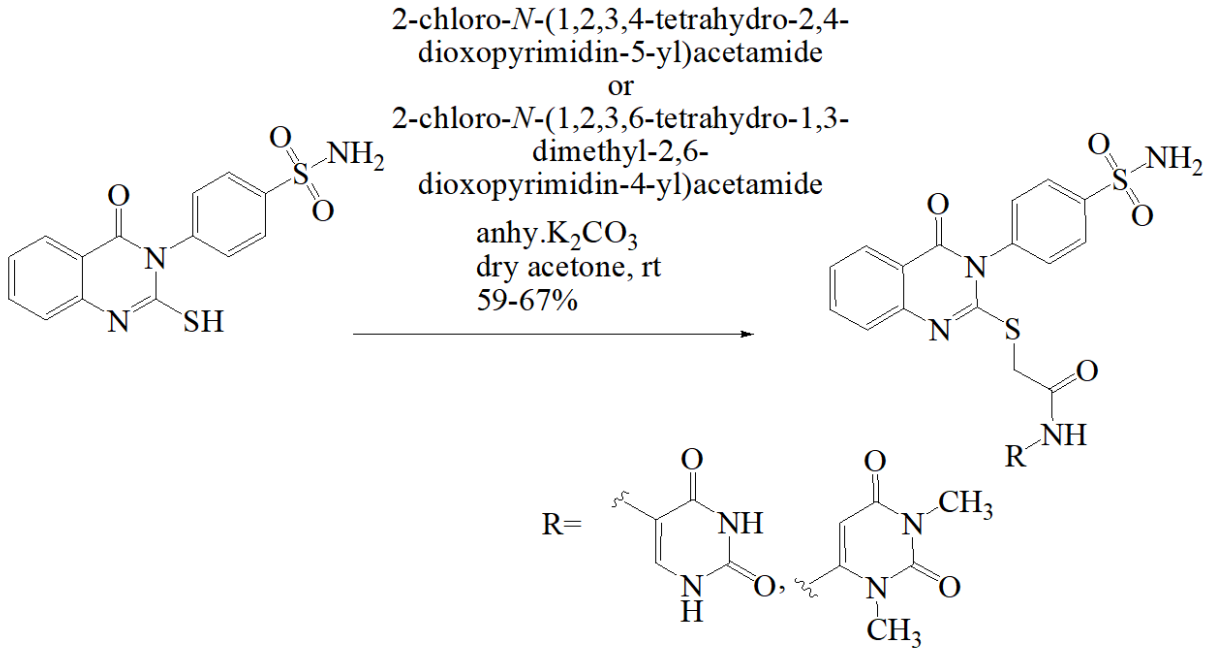
The 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one was reacted with 2-chloro-*N*-(2-morpholinoethyl)acetamide in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-((((2-morpholinoethyl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one. This compound has shown antioxidant activity.[127]

DOI: https://doi.org/10.5281/zenodo.13644773



6.2.45 Tetrahydrodioxopyrimidinylaminocarbonylmethylthioquinazolin-4(3*H*)-ones

The 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one was reacted with 2-chloro-*N*-(1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)acetamide or/and 2-chloro-*N*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidin-4-yl)acetamide in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-((((1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)amino)carbonyl)methyl thio)-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one and 2-((((1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopyrimidin-4-yl)amino)carbonyl)methylthio)-3-(4-sulfamoylphenyl)-quin-azolin-4(3*H*)-one respectively. These compounds have shown antioxidant activity.[127]



6.2.46 Pyrazinylaminocarbonylmethylthioquinazolin-4(3*H*)-one

Aiten M. Soliman et.al were reacted 2-mercapto-3-(4-sulfamoylphenyl)-quinazolin-4(3*H*)-one with 2-chloro-*N*-(pyrazin-2-yl)acetamide derivatives in dry acetone containing anhy. K_2CO_3 at room temperature to afford 2-((((pyrazin-2-yl)amino)carbonyl)methylthio)-3-(4-sulfamoyl phenyl)-quinazolin-4(3*H*)-one. This compound has been screened for its antioxidant activity using DPPH assay in comparison to ascorbic acid. It was the most active compound in this

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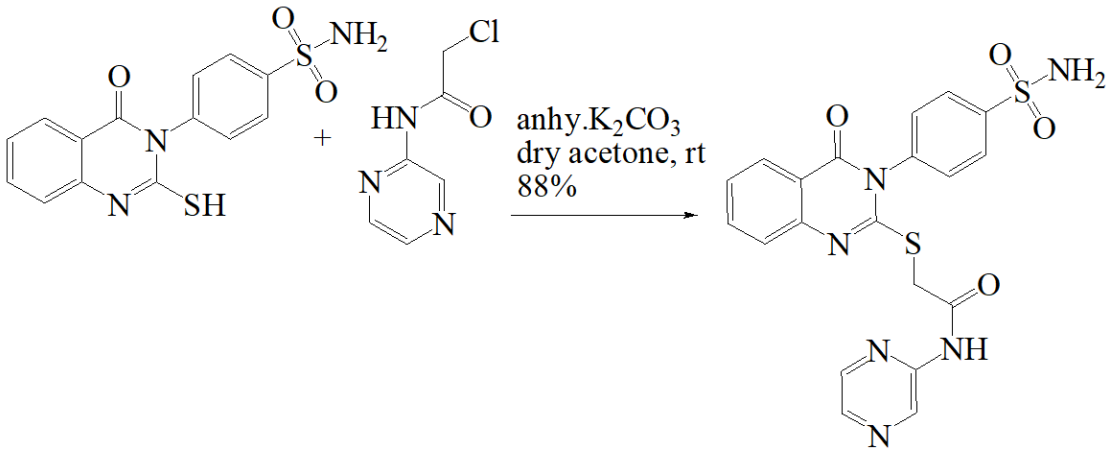
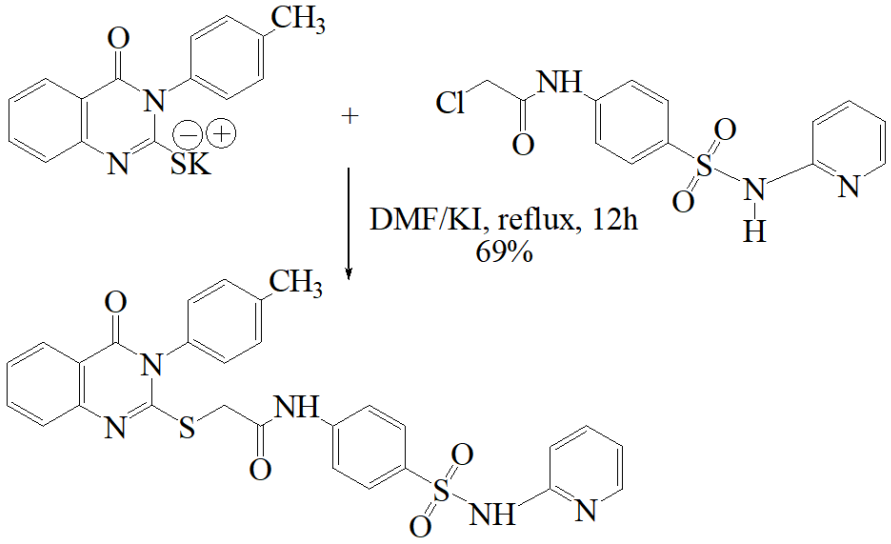
series with IC_{50} = 45.76 mM. The current in vivo studies revealed that this has median lethal dose (LD_{50}) = 200 mg/kg.[127]



6.2.47 Pyridinylaminosulfonylphenylaminocarbonylmethylthioquinazolin-4(3*H*)-one

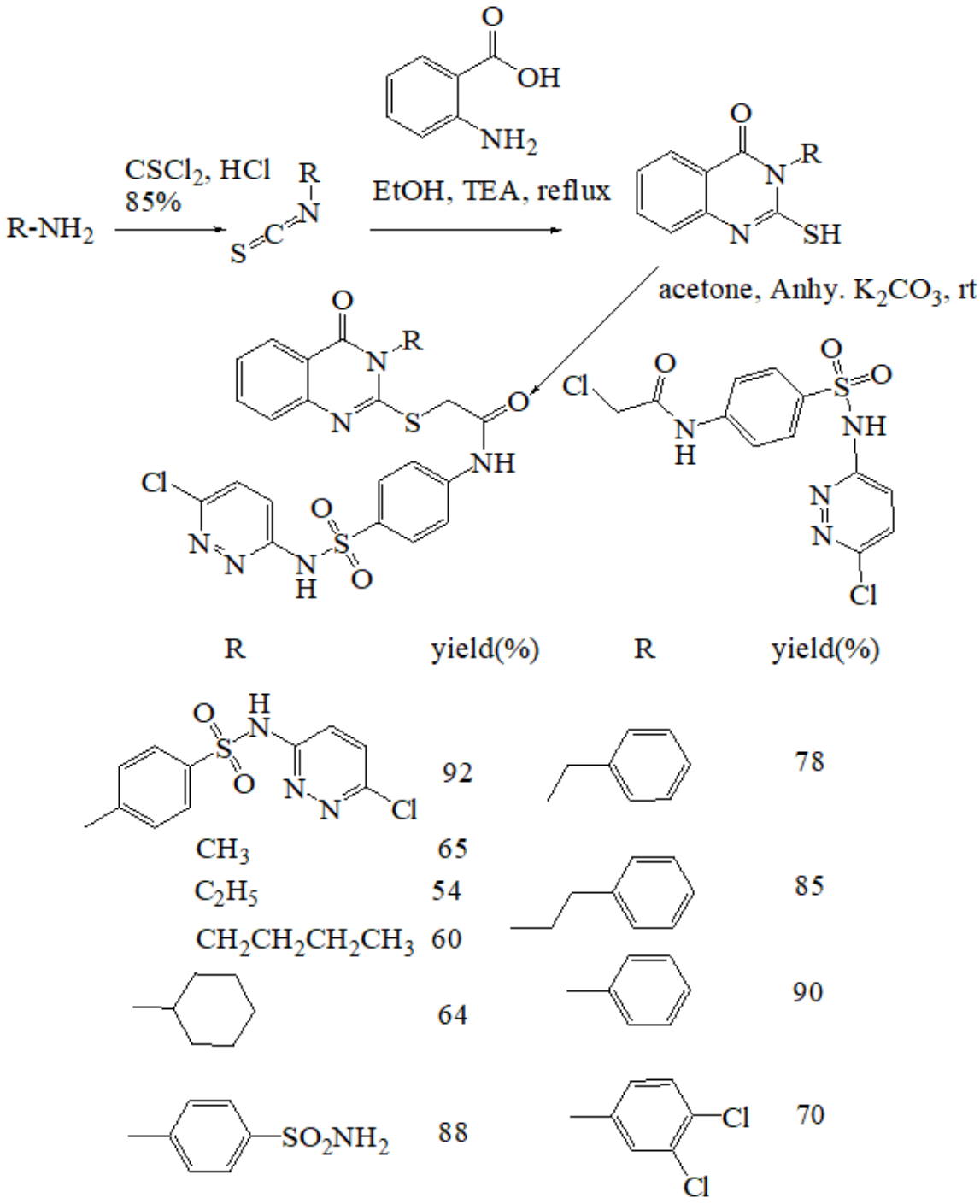
A mixture of potassium salt of 2-mercapto-3-(4-methylphenyl)quinazolin-4(3*H*)-one and 2-chloro-*N*-(4-(*N*-(pyridin-2-yl)sulfamoyl)phenyl)acetamide in DMF was heated on a water bath for 12h to afford 3-(4-methylphenyl)-2-(((((4-(((pyridin-2-yl)amino)sulfonyl)- phenyl)amino) carbonyl) methyl)thio)-quinazolin-4(3*H*)-one.[128]



6.2.48 Pyridazinylsulfamoylphenylaminocarbonylmethylthioquinazolin-4(3*H*)-one

Antiproliferative, antiangiogenic and apoptotic agents,2-((((4-(*N*-(6-chloropyridazin-3-yl) sulfamoyl)phenyl)amino)carbonyl)methylthio)-3-substituted-quinazolin-4(3*H*)-one, were synthesized by reacting isothiocyanate with 2-aminobenzoic acid in refluxed ethanol containing triethylamine to isolate 3-substituted-2,3-dihydro-2-thioxoquinazolin-4(1*H*)-one followed by the alkylation of the resultant SH group with 2-chloro-*N*-(4-(*N*-(6-chloropyridazin-3-yl)sulfamoyl) phenyl)acetamide in dry acetone and anhydrous K_2CO_3.[131]

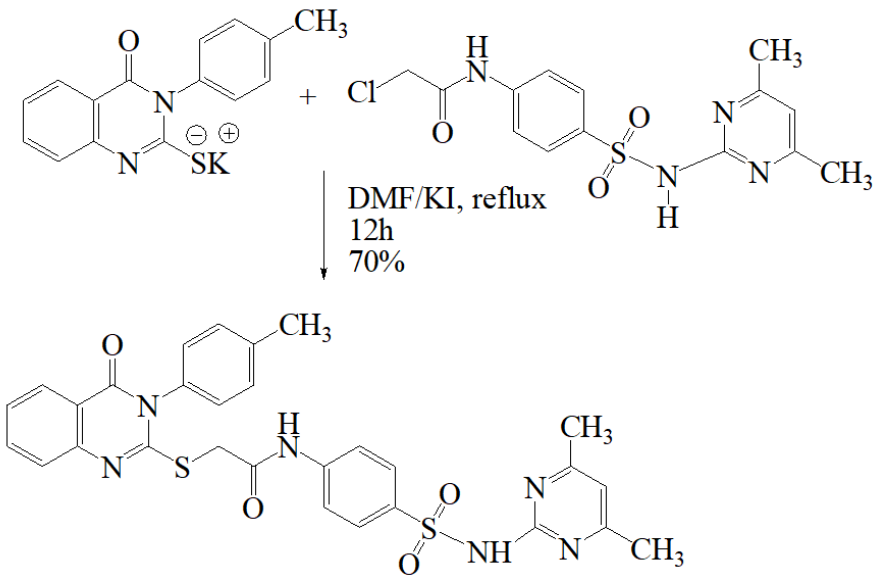
DOI: https://doi.org/10.5281/zenodo.13644773



6.2.49 Pyrimidinylaminosulfonylphenylaminocarbonylmethylthioquinazolin-4(3*H*)-one

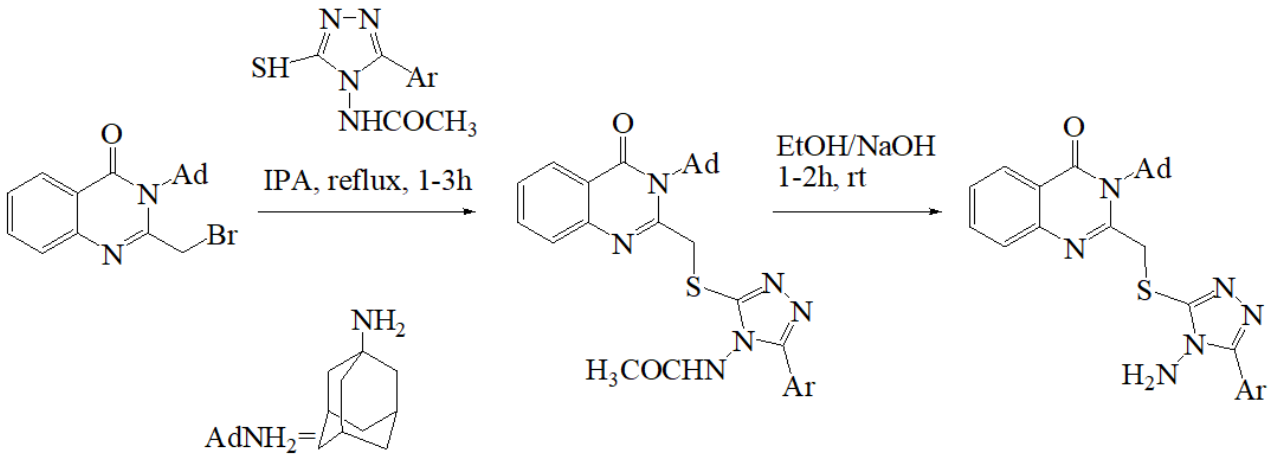
Excellent anti-proliferative activities against HepG2 and HCT-116 cell lines compound, 3-(4-methylphenyl)-2-(((((4-(((4,6-dimethylpyrimidin-2-yl)amino)sulfonyl)-phenyl)amino)carbonyl) methyl)thio)-quinazolin-4(3*H*)-one, was prepared by heating potassium salt of 2-mercapto-3-(4-methylphenyl)quinazolin-4(3*H*)-one and 2-chloro-*N*-(4-(*N*-(4,6-dimethylpyrimidin-2-yl)sulfa moyl)phenyl) acetamide in DMF on a water bath for 12 h.[128]

DOI: https://doi.org/10.5281/zenodo.13644773



6.2.50 Triazolylthiomethylquinazolin-4(3*H*)-ones

Potent antimicrobial, anti-inflammatory and analgesic activities derivatives 3-amantadinyl-2-[(4-amino-3-aryl-5-ylthio)-1,2,4-triazolo]methyl)-quinazolin-4(3H)-one were prepared by reacting 3-amantadinyl-2-bromomethylquinazolin-4-(3*H*)-ones with 3-aryl-4-acetamido-5-mercapto-tria-zoles to afford 3-amantadinyl-2-[(4-acetamido-3-aryl-5-ylthio)-1,2,4-triazolo]methyl)-quina-zolin-4(3*H*)-one followed by deprotection in ethanolic–sodium hydroxide.[121]



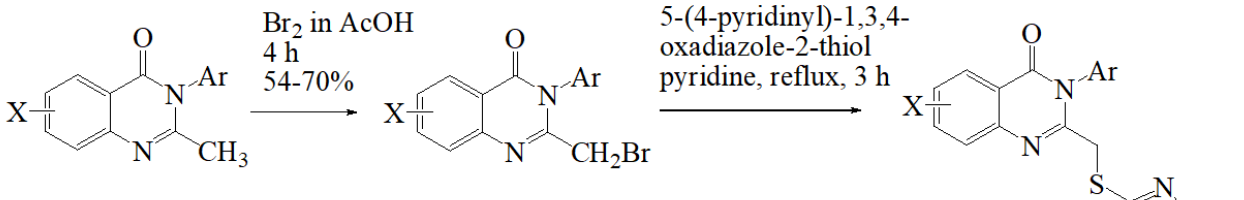
Ar	C_6H_5	2-HOC_6H_4	3-HOC_6H_4	4-HOC_6H_4	4-$C_2H_5OC_6H_4$
Yield (%)	60	60	58	62	63

Ar	4-$HOCH_2C_6H_4$	4-$C_2H_5OCH_2C_6H_4$l	2-ClC_6H_4	4-ClC_6H_4
Yield (%)	57	60	57	53

6.2.51 Pyridinyloxadiazolylthiomethylquinazolin-4(3*H*)-ones

Antiinflammatory, 2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-ylthiomethyl]-3-substituted aryl-6- substituted quinazolin-4(3*H*)-ones were prepared by reacting 2-methyl-3-aryl-6-substituted quinazolin-4(3*H*)-ones with bromine in acetic acid to isolate 2-bromomethyl-3-substituted aryl-6-substituted quinazolin-4(3*H*)-ones followed by reaction with 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol in pyridine at reflux.[122]

DOI: https://doi.org/10.5281/zenodo.13644773

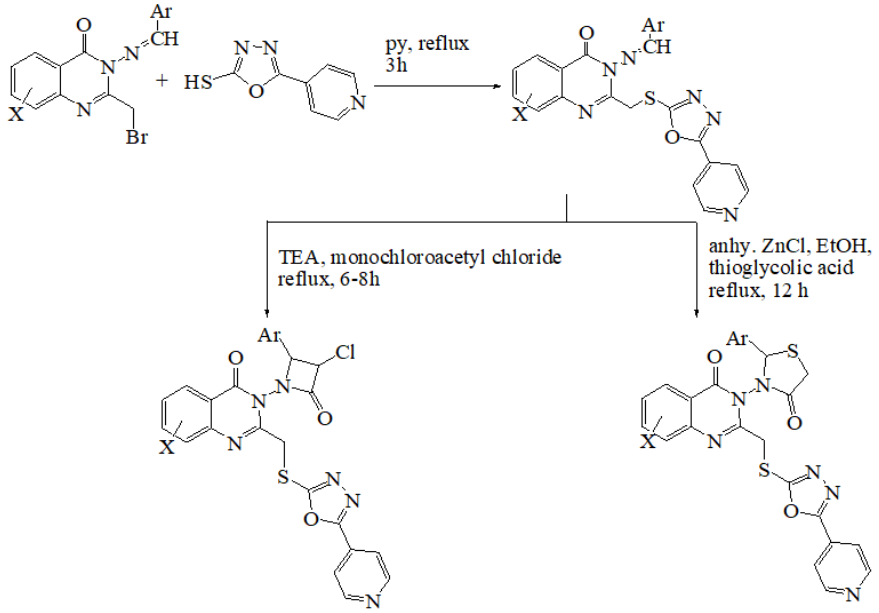


X	H	H	H	H	H	6-I	6-I
Ar	C_6H_5	2-ClC_6H_4	4-ClC_6H_4	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	2-ClC_6H_4
Yield (%)	59	45	40	38	55	56	44

X	6-I	6-I	6-I	6-Br	6-Br	6-Br
Ar	4-ClC_6H_4	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	2-ClC_6H_4	4-ClC_6H_4
Yield (%)	51	52	57	58	49	52

X	6-Br	6-Br
Ar	2-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
Yield (%)	46	50

2-Bromomethyl-3-(arylideneamino)-substituted-3*H*-quinazolin-4-ones and 5-(4-pyridinyl) 1,3,4-oxadiazole-2-thiol were refluxed in pyridine to isolate 2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(arylidene-amino)-substituted quinazolin-4(3*H*)-one. The resultant compound was reacted with i) monochloroacetyl chloride in presence of triethylamine ii) thioglycolic acid containing $ZnCl_2$ to afford 3-(3-chloro-2-oxo-4-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4(3*H*)-ones and 3-(4-oxo-2-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4(3*H*)-one respectively. All the compounds exhibited anti-inflammatory activity at the dose 50 mg/kg p.o. varying degree from 16.3 to 36.3% inhibition of oedema.[123]



X	H	H	H	H
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-OHC_6H_4
Yield(%)	50	55	40	45

X	6-Br	6-Br	6-Br
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$
Yield(%)	52	55	40

X	6-Br
Ar	4-OHC_6H_4
Yield(%)	55

X	H	H	H	H
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$	4-OHC_6H_4
Yield(%)	55	50	40	48

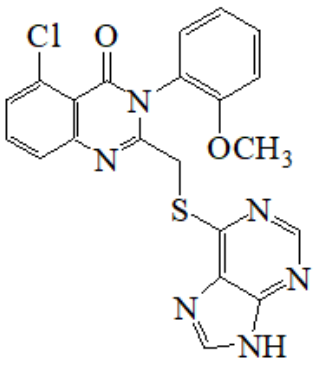
X	6-Br	6-Br	6-Br
Ar	Ph	4-ClC_6H_4	4-$CH_3OC_6H_4$
Yield(%)	52	56	40

X	6-Br
Ar	4-OHC_6H_4
Yield(%)	55

DOI: https://doi.org/10.5281/zenodo.13644773

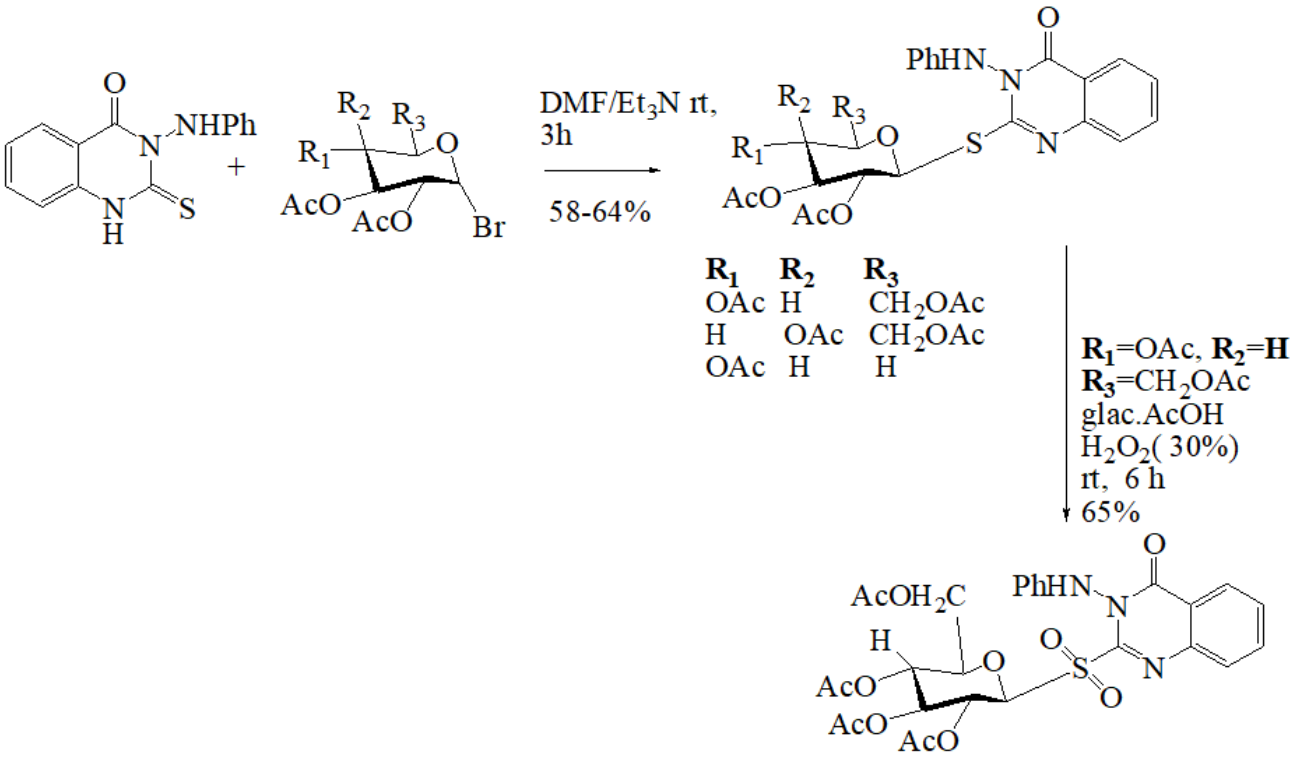
6.2.52 Purinylthiomethylquinazolin-4(3*H*)-one

Roger L Williams et.al reported the mechanisms for selectivity and potency of new PI (3) K inhibitor, 2-((9*H*-purin-6-ylthio)methyl)-5-chloro-3-(2-methoxyphenyl)quinazolin-4(3*H*)-one, for p110 delta.[119]



6.2.53 Glucopyranosylsulphonylquinazolin-4(3*H*)-one

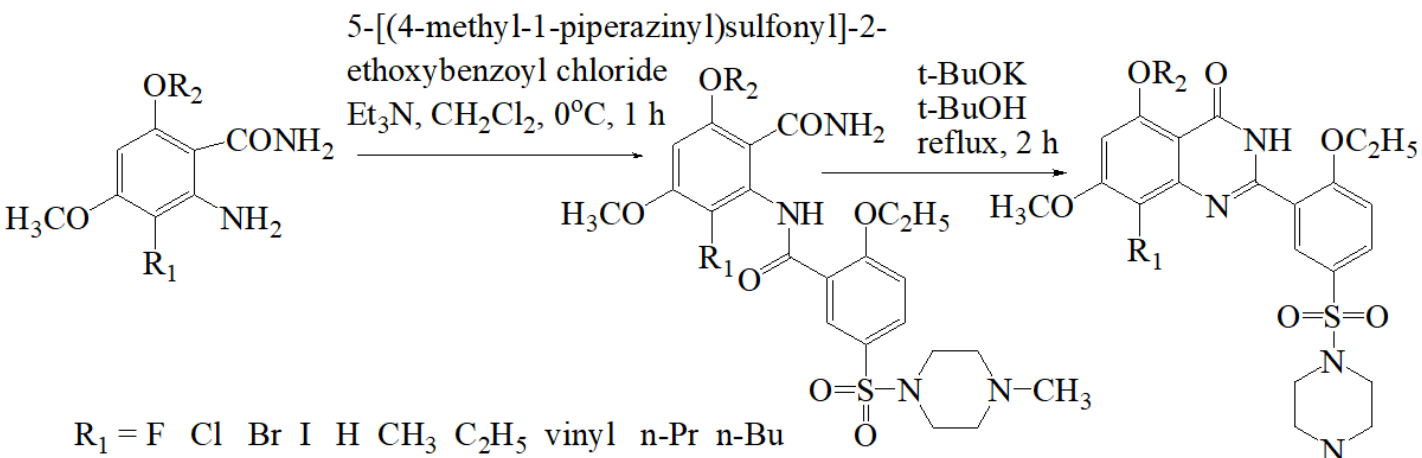
Saleh et.al prepared most pronounced inhibitory effect when tested against *S. aureus.* 3-Phenylamino-2-thioxo-3*H*-quinazolin-4-one was reacted with substituted pyranosyl bromide to yield S-glycoside derivatives. Oxidation of S-glucoside with H_2O_2 afforded the corresponding sulphone; 2-(2,3,4,6,tetra-O-acetyl-β-D-glucopyranosylsulphonyl)-3-phenylaminoquinazolin-4 (3H)-one.[124]



6.2.54 Piperazinylsulfonylphenylquinazolin-4(3*H*)-ones

A class of potent PDE5 inhibitors with high selectivity versus PDE6, 2-phenylquinazolin-4(3*H*)-one derivatives, have been prepared by coupling 2-aminobenzamide derivatives with 5-[(4-methyl-1-piperazinyl)sulfonyl]-2-ethoxybenzoyl chloride followed by dehydrative cyclization by using ^{t}-BuOK as base, in refluxing ^{t}-BuOH.[132]

DOI: https://doi.org/10.5281/zenodo.13644773

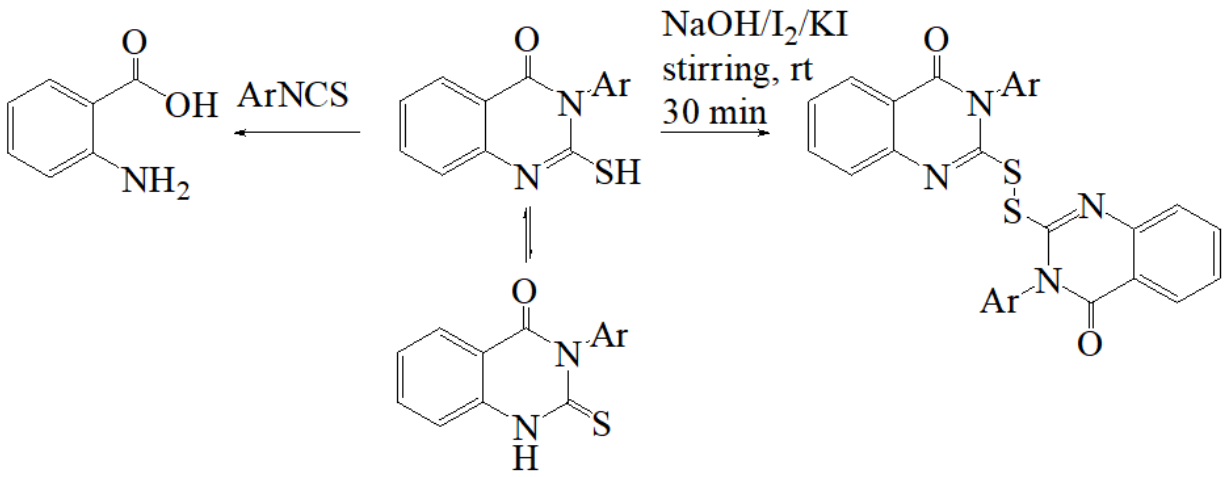


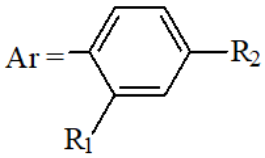
R_1 = F Cl Br I H CH_3 C_2H_5 vinyl n-Pr n-Bu
R_2 = H H H H H H H H H H

R_1 = F Cl Br I H CH_3 C_2H_5 vinyl n-Pr n-Bu
R_2 = CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3 CH_3

6.2.55 Dithiobis[quinazolin-4(3*H*)-ones]

2.2'-Dithiobis[3-aryl-quinazolin-4(3*H*)-ones]) were prepared from 2-mercapto-3-arylquinazolinone-4(3*H*)-one, which in-turn were easily obtained by addition of arylisothiocyanate to anthranilic acid. Oxidation of resulting compound using I_2 /KI, afforded end product.[281, 282]



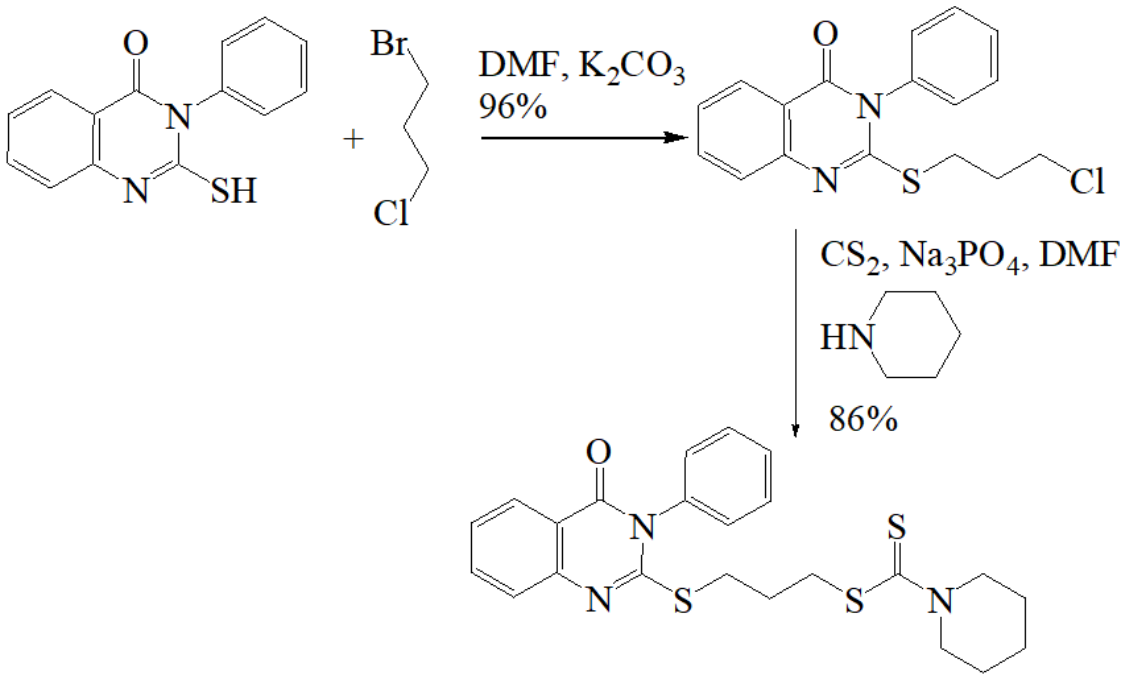
Ar = 

R_1	H	Br	I	Cl	Br
R_2	H	Br	H	H	CH_3
Yield (%)	85	80	82	74	87

6.2.56 Piperidineylthiocarbonylthiopropylthioquinazolin-4(3*H*)-one

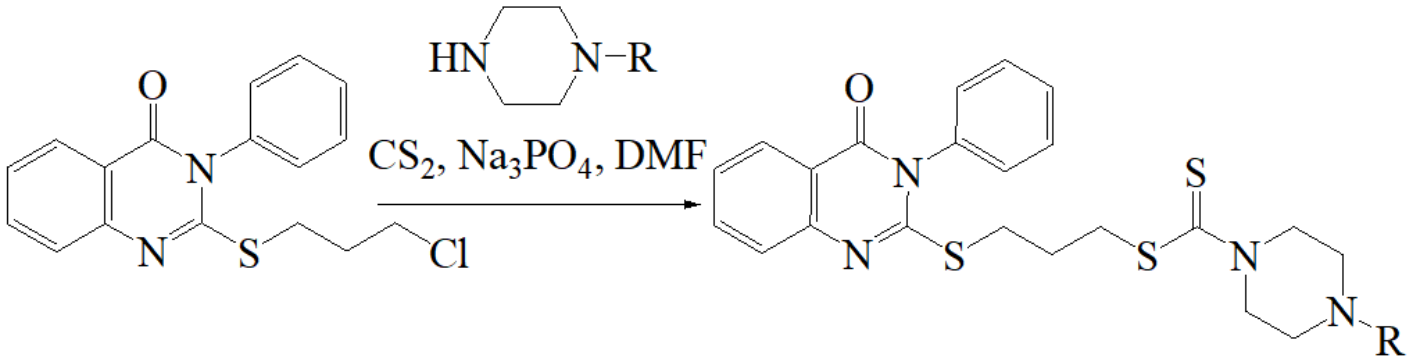
Shahenda M. El-Messery et.al were reacted 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one with 1-bromo-3-chloropropane in DMF containing anhydrous potassium carbonate at room temperature to isolate 2-[(3-chloropropyl)thio]-3-phenylquinazolin-4(3*H*)-one was obtained in excellent yield. The target 2-((3-(((piperidine-1-yl)thiocarbonyl)thio)propyl)thio)-3-phenylquinazolin-4(3*H*)-one was synthesized by reacting the key intermediate with carbon disulfide, sodium phosphate and piperadine in DMF.[125]

DOI: https://doi.org/10.5281/zenodo.13644773



6.2.57 Piperazineylthiocarbonylthiopropylthioquinazolin-4(3H)-ones

The 2-((3-((piperazine-1-yl)thiocarbonylthio)propyl)thio)-3-phenylquinazolin-4(3*H*)-ones were synthesized by reacting the 2-[(3-chloropropyl) thio]-3-phenylquinazolin-4(3*H*)-one with carbon disulfide, sodium phosphate and piperazines in DMF. The 2-((3-((4-(2-ethoxyphenyl)piperazine-1-yl)thiocarbonylthio)propyl)thio)-3-phenylquinazolin-4(3*H*)-one was exhibited excellent anti-proliferative activity against three human cancer cell lines and HSP90 inhibition activity.[125]

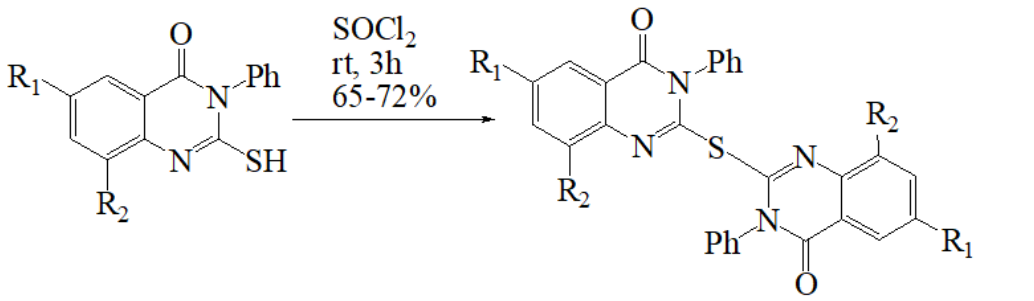


R	yield (%)	R	yield (%)
CH_3	74	CH_2CH_3	70
CH_2-CH=CH_2	63	$COCH_3$	71
C_6C_{11}	58	C_6H_5	85
(2-OC_2H_5)C_6H_4	89	$C_4H_3N_2$	69

6.2.58 2,2'-Bis-[quinazolin-4(3*H*)-ones]sulfones

2,2'-Bis[6,8-disubstituted 3-phenyl-4(3*H*)-quinazolinonyl]sulfones showed promising CNS depres- sant activity. Dimerisation of 6,8-disubstituted 2-mercaptoquinazolin-4(3*H*)-ones followed by oxidation afforded the bisquinazolinone derivatives.[281]

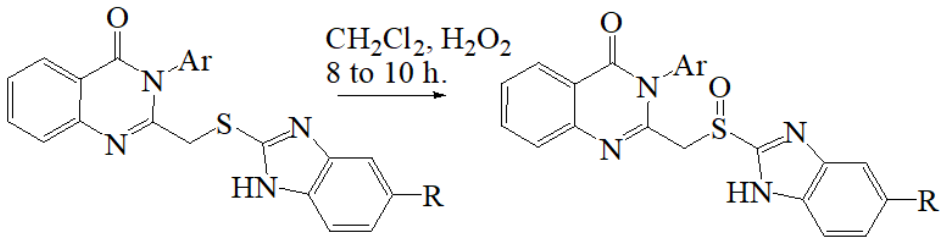
DOI: https://doi.org/10.5281/zenodo.13644773



R_1	H	Br	I	Br
R_2	H	Br	H	H
Yield (%)	72	70	70	65

6.2.59 Benzoimidazolylsulfinylmethylquinazolin-4(3*H*)-ones

Patil et.al prepared 2-[{1*H*-benzo(*d*)imidazol-2-ylsulfinyl]methyl}-3-aryl quinazolin-4(3*H*)-one by oxidizing 2-[{1*H*-benzo(*d*)imidazol-2-ylthio}methyl]-3-arylquinazolin-4(3*H*)-one with hydro gen peroxide. These compounds have shown antiulcer activity.[129]



R	H	H	H	H	H	H	H
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	45	40	48	35	46	41	42

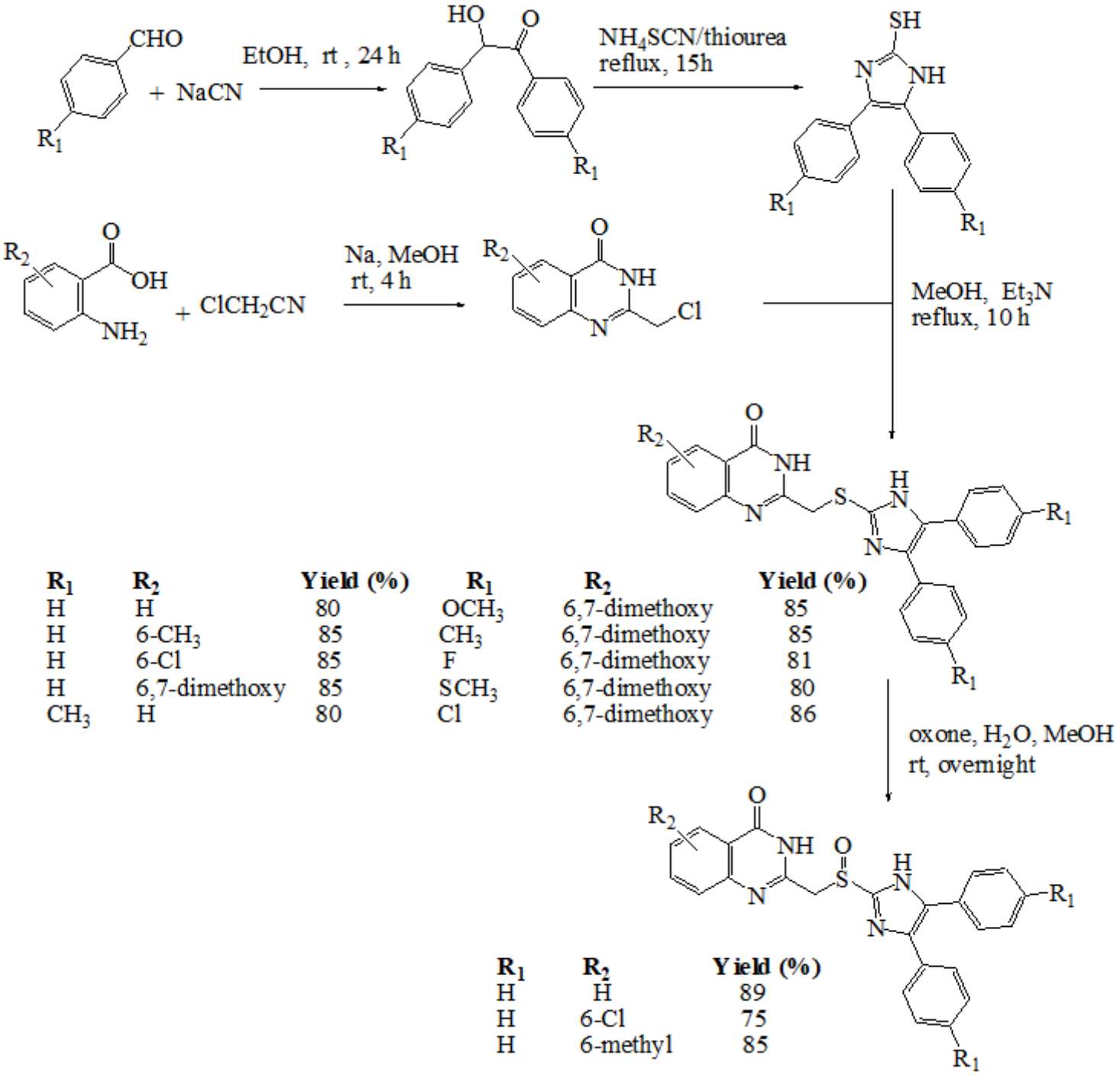
R	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	35	45	40	38	42	42	46

R	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$	$OCHF_2$
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3COC_6H_4$	4-$CH_3OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_4	4-ClC_6H_4
Yield (%)	42	40	48	38	38	42	43

DOI: https://doi.org/10.5281/zenodo.13644773

6.2.60 Imidazolylsulfinylmethylquinazolin-4(3*H*)-one

The key intermediate 4,5-diaryl-1*H*-imidazole-2-thiols were prepared through benzoin condensation of aryl aldehyde followed by reaction with thiocyanate in presence of thiourea in n-butanol under reflux condition. The second key intermediate 2-(chloromethyl)quinazolin-4(3*H*)-ones were prepared from anthranilic acids and chloroacetonitrile in sodium containing methanol. 2-((4,5-Diaryl-1*H*-imidazol-2-ylthio)methyl)quinazolin-4(3*H*)-ones were prepared from SN_2 reaction of imidazole-2-thione derivatives and different quinazolinones in methanol as the solvent and the presence of small amounts of triethylamine. The oxidation of sulfur atom in resultant compound was carried out by oxone in methanol for conversion to 2-((4,5-diaryl-1*H*-imidazol-2-ylsulfinyl)methyl)quinazolin-4(3*H*)-one.[283]



R_1	R_2	Yield (%)	R_1	R_2	Yield (%)
H	H	80	OCH_3	6,7-dimethoxy	85
H	6-CH_3	85	CH_3	6,7-dimethoxy	85
H	6-Cl	85	F	6,7-dimethoxy	81
H	6,7-dimethoxy	85	SCH_3	6,7-dimethoxy	80
CH_3	H	80	Cl	6,7-dimethoxy	86

R_1	R_2	Yield (%)
H	H	89
H	6-Cl	75
H	6-methyl	85

DOI: https://doi.org/10.5281/zenodo.13644773

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