

Original Article**An efficient, Method for the Synthesis of 4H-Pyrido-[1, 2]-Pyrimidine Derivatives and their anticancer activity**Jyothi Vantikommu*¹ Sadanandam Palle ²¹Research and Development Centre, Velarix Life Sciences Private Limited, Hyderabad.²Research and Development Centre, Hepa Pharma Private Limited, Hyderabad.Email: jyothi.vantikommu@gmail.com

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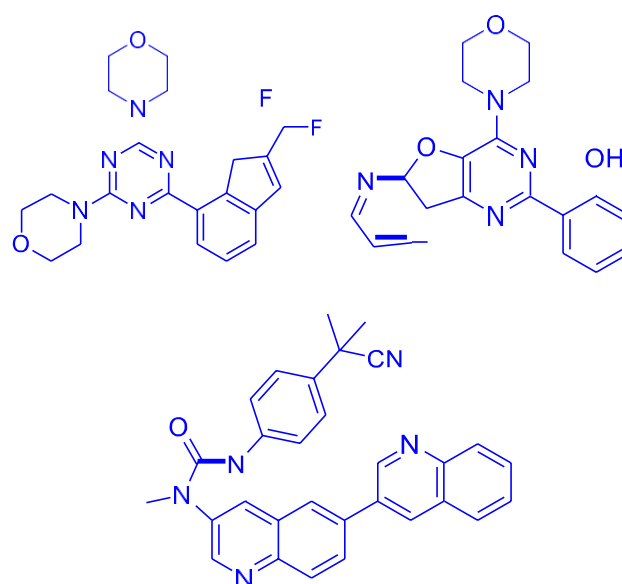
ABSTRACT

A library of 4H-pyrido-[1,2]-pyrimidine derivatives were synthesised via one pot three component method, in this reaction involves a simple condensation of 2-minopyrimidines, aldehydes and ketones in the presence of ethanol reflux by using cost effective and ecofriendly catalyst sulphamic acid. These synthesised compounds were submitted for the anti proliferative activity against various human cancer cell lines, among these 2, 3, 8 and 12 compounds were showed excellent activity. Range between 1.15- 1.95 μ M.

Keywords: Anti-Cancer, pyrimidine, Anti-proliferative**1. INTRODUCTION**

The pyrimidine are having high sort in the medicinal chemistry to the development of novel active therapeutics. It has a wide range of interest in the pharmacology, ^{1, 2} such as antibacterial, antiviral including anti-HIV, anticancer, analgesic and anti-inflammatory properties.³⁻⁶ Multicomponent reactions (MCRs) are implicated in various interesting and difficult conversion in organic synthesis⁷⁻¹², and it have much importance in the synthetic organic chemistry because of their generality of the products now these are called as precursors of the drug discovery. Most of the applications were already well-known those are Biginelli reaction, Mannich, Ugi reaction¹³⁻¹⁵. Whatever the development of novel multicomponent reaction have great need in the field of medicinal and synthetic organic chemistry for the generating novel active scaffolds, ^{16, 17}. As per our best of our knowledge there is no report of the synthesis of 4H-Pyrido-[1, 2]-pyrimidine derivatives by using this ecofriendly method, Here the catalyst can recyclable and reusable upto 3-4 times without any loss and properties of the

Catalyst. Our present method develops and to prepare fourteen compounds of new heterocycles it extends to develop by willingly existing carbonyl compounds.

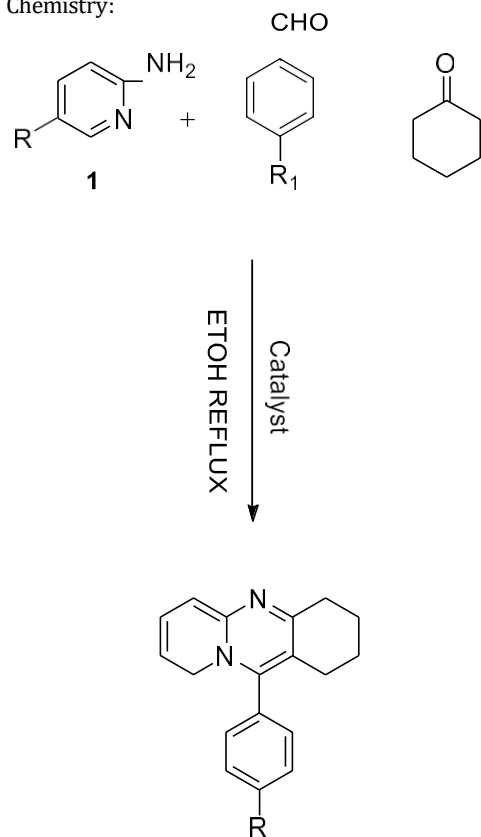
**Fig: 1 biologically active pyrimidine derivatives*****Corresponding Author:**

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Results and discussions:

Chemistry:



Here model reaction was done with 2-aminopyridine (1.0 mmol), aldehydes (1.0 mmol) and ketones (2.0 mmol) by using sulphamic acid as a recyclable and reusable catalyst in the presence of ethanol as a solvent reflux then add catalyst, under nitrogen condition the reaction mixture was stirred with reflux for 5h this reaction was monitored by the TLC. After completion of the reaction. Then solvent Ethanol was removed from the reaction by rotavacuum pressure. Resultant reaction mixture extracts with ethyl acetate and water, the organic layer washed with sodium sulphate then it evaporate solid compound was formed then it was purified by the column chromatography by using Ethyl acetate and Hexane mobile phase, afforded final desired product (compound-1d). And yields are good to excellent.

Table-1: Optimization of reaction conditions for the synthesis of 4H-Pyrido-[1, 2]- pyrimidine derivatives.

S.No	Solvent	Temp- (°C)	Time (hr)	Yield % ^a
1	methanol	RT	12	20
2	water	RT	12	15
3	ethanol	RT	12	25
4	methanol	60	6	40
5	-----	120	6	50
6	ethanol	80	5	80
7	water	100	5	55
8	methanol	80	5	50

^a-isolated yields

Table-1: Optimization of reaction conditions for the synthesis of 4H-Pyrido-[1,2]- pyrimidine derivatives.

S.No	R	R1	R2	Yield% ^a
1	H	H	H	70
2	H	4-CL	H	72
3	H	4-F	H	77
4	H	4-NO ₂	H	68
5	H	3-NO ₂	H	65
6	H	3-Cl	H	70
7	H	3-F	H	75
8	H	4-OME	H	78
9	H	4-Me	H	65
10	4-Cl	H	H	76
11	4-Cl	4-Cl	H	80
12	4-Cl	4-F	H	82
13	4-Cl	4-NO ₂	H	76
14	4-Cl	3-NO ₂	H	72

^a-isolated yields

Table-2: Synthesis of 4H-Pyrido-[1, 2]-pyrimidine derivatives by condensation of 2- aminopyrimidines, aldehydes and ketones.

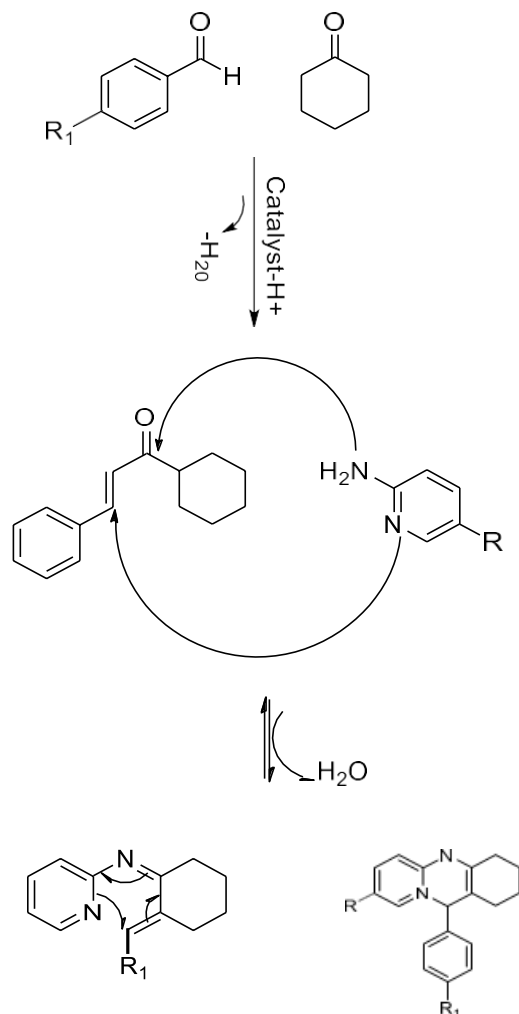
Mechanism:

Fig 2: Mechanism for 4H-prido-[1,2-] pyrimidine synthesis.

This procedure plausible mechanism for the formation of 4H-prido-[1,2-] pyrimidine from 2- aminopyrimidines, aldehydes and ketones by using recyclable and reusable catalyst (sulphamic acid) shown in the figure-2 first aldehyde and acetophenones are couple then form intermediate with elimination of water molecule. Then this intermediate was reacts with 2-aminopyridine by using proton from acidic catalyst again it eliminates the water molecule, then final the double bond pi- electrons of 2-aminopyridine migrates to the aldehyde carbon finally cyclized product was formed.

Antiproliferative activity

Cytotoxicity assay was performed 18 was performed to estimate the cytotoxic prospective of these compounds neighbouring to selected human cancer cell lines which include HeLa (cervical), (liver) A549, prostate (DU 145) and MCF-7 (breast). These compounds showed noteworthy cytotoxic activity with IC50 values ranging from 1.15-1.95 μ M against

different cancer cell lines. The results are concise as IC50 values in Table 3

S.no	A549	Temp-(°C)	Time (hr)	Yield % ^a
1	3.54	3.13	4.37	3.65
2	1.99	1.93	2.09	1.15
3	1.91	2.81	6.90	3.51
4	4.90	3.89	5.25	5.97
5	6.50	7.47	5.90	5.24
6	4.90	3.75	6.14	7.38
7	5.57	4.54	7.06	8.74
8	1.75	1.96	2.87	3.08
9	4.13	3.31	5.68	7.03
10	4.70	704	6.78	7.93
11	7.56	5.29	10.2	6.90
12	2.61	1.94	1.81	4.01
13	6.75	7.94	8.87	4.08
14	7.08	4.09	4.90	5.39
Control	1.31	1.81	2.13	1.25

Table. 3 Antiproliferative activity for the synthesised derivatives

Experimental procedure:

The reaction was done with 2-aminopyridine (1.0 mmol), aldehydes (1.0 mmol) and ketones (2.0 mmol) by using sulphamic acid as a recyclable and reusable catalyst in the presence of ETOH as a solvent reflux then add catalyst, under nitrogen condition the reaction mixture was stirred with reflux for 5 hours this reaction was monitored by the TLC. After completion of the reaction. Then solvent Ethanol was removed from the reaction by rotavacuum pressure. Resultant reaction mixture extracts with ethyl acetate and water, the organic layer washed with sodium sulphate then it evaporate solid compound was formed then it was purified by the column chromatography by using Ethyl acetate and Hexane mobile phase, afforded final desired product. And yields are good to excellent.

11-(4-Nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-1

77 %; white solid, mp: 148–151 oC; ¹H NMR: δ 8.25–8.22 (m, 2H), 7.54–7.45 (m, 3H), 7.34–7.29 (m, 1H), 7.07 (d, 1H, J = 6.3), 6.46 (t, 1H, J = 6.3), 5.72 (s, 1H), 2.53–2.37 (m, 2H), 1.91–1.61 (m, 6H); MS (ESI): m/z 308.4 [M + H⁺].

11-(p-Tolyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-2

68 %; yellow solid, mp: 120–123 oC; ¹³C NMR: δ 148.01, 139.1, 138.2, 136.2, 135.9, 133.4, 129.6, 126.1, 123.5, 108.2, 106.5, 66.3, 30.2, 26.7, 23.2, 22.7, 21.2; ¹H NMR: δ 7.24–7.11 (m, 4H), 6.87 (t, 1H, J = 7.8), 6.73–6.65 (m, 2H), 5.96 (t, 1H, J = 6.6), 5.32 (s, 1H), 2.32–2.30 (m, 5H), 1.79–1.58 (m, 6H); MS (ESI): m/z 276.2 [M + H⁺].

11-(4-Methoxyphenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-3

65 %; cream solid, mp: 83–88 oC; ¹³C NMR: δ 159.7, 148.9, 136.6, 135.4, 135.1, 133.4, 128.3, 123.5, 114.2, 108.6, 107.0, 67.9, 55.3, 30.2, 26.7, 23.2, 22.8; ¹H NMR: δ 7.27–7.21 (m, 2H), 6.88–6.84 (m, 3H), 6.76–6.68 (m, 2H), 5.99 (t, 1H, J = 6.6), 5.32 (s, 1H), 3.79 (s, 3H), 2.39–2.29 (m, 2H), 1.77–1.57 (m, 6H); MS (ESI): m/z 293.56 [M + H⁺].

11-(4-fluorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] quinazoline-4

70 %; pale yellow solid, mp: 88–90 oC; ¹³C NMR: δ 148.8, 141.9, 137.5, 135.2, 134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; ¹H NMR: δ 7.50–7.21 (m, 7H), 6.62 (t, 1H, J = 6.0), 5.64 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); MS (ESI): m/z 297.9 [M + H⁺].

11-(4-Nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-5

75 %; yellow solid, mp: 148–152 oC; ¹H NMR: δ 8.20–8.22 (m, 2H), 7.44–7.35 (m, 3H), 7.34–7.20 (m, 1H), 7.07 (d, 1H, J = 6.3), 6.36 (t, 1H, J = 6.3), 5.62 (s, 1H), 2.53–2.37 (m, 2H), 1.91–1.61 (m, 6H); MS (ESI): m/z 308.6 [M + H⁺].

11-(3-Chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] quinazoline-6

78 %; brown solid, mp: 86–89 oC; ¹H NMR: δ 7.40–7.31 (m, 7H), 6.52 (t, 1H, J = 6.0), 5.64 (s, 1H), 2.37–2.36 (m, 2H), 1.88–1.61 (m, 6H); ¹³C NMR: δ 148.8, 141.9, 137.5, 135.2, 134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; MS (ESI): m/z 297.88 [M + H⁺].

11-(3-Chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] quinazoline-7

65%; yellow solid, mp: 80–83 oC; ¹H NMR: δ 7.55–7.21 (m, 7H), 6.67 (t, 1H, J = 6.0), 5.54 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); ¹³C NMR: δ 148.8, 141.9, 137.5, 135.2, 134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; MS (ESI): m/z 297.7 [M + H⁺].

8-Chloro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-8

76 %; light solid, mp: 129–133 oC; ¹³C NMR: δ 146.8, 140.4, 136.6, 134.9, 134.8, 132.5, 129.4, 128.3, 124.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; ¹H NMR: δ 7.35–7.32 (m, 2H), 7.27–7.22 (m, 2H), 6.89–6.85 (m, 1H), 6.78 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34–2.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 330.3 [M + H⁺].

8-Chloro-11-(3-nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b] quinazoline-11

80 %; cream solid, mp: 120–122 oC; ¹³C NMR: δ 143.8, 140.4, 136.6, 135.9, 133.8, 132.5, 129.4, 128.3, 122.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; ¹H NMR: δ 7.32–7.26 (m, 2H), 7.27–7.22 (m, 2H), 6.89–6.75 (m, 1H), 6.78 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34–2.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 330.4 [M + H⁺].

8-Chloro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] quinazoline-12

82 %; white solid, mp: 80–83 oC; ¹³C NMR: δ 147.8, 142.9, 137.5, 134.2, 133.5, 131.0, 129.4, 128.3, 123.6, 105.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; ¹H NMR: δ 7.40–7.21 (m, 7H), 6.52 (t, 1H, J = 6.0), 5.44 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); MS (ESI): m/z 296.9 [M + H⁺].

8-Fluoro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-13

76 %; white solid, mp: 127–130 oC; ¹³C NMR: δ 143.8, 136.4, 131.6, 125.9, 124.8, 122.5, 119.4, 118.3, 114.6, 105.3, 104.4, 68.0, 29.9, 26.6, 22.9, 22.5; ¹H NMR: δ 7.25–7.12 (m, 2H), 7.27–7.22 (m, 2H), 6.49–6.85 (m, 1H), 6.18 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34–2.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 329.27 [M + H⁺].

8-Nitro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-14

72 %; yellow solid, mp: 129–135 oC; ¹³C NMR: δ 146.8, 140.4, 136.6, 134.9, 134.8, 132.5, 129.4, 128.3, 124.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; ¹H NMR: δ 7.45–7.42 (m, 2H), 7.37–7.22 (m, 2H), 6.89–6.75 (m, 1H), 6.68 (s, 1H), 6.45 (d, 1H, J = 2.1), 5.12 (s, 1H), 2.34–2.13 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 329.8 [M + H⁺].

Conclusion:

In summery we developed of 4H-prido-[1,2-] pyrimidine derivates from the 2- aminopyrimidines, aldehydes and ketones by using recyclable and reusable catalyst it under go one pot the component system to formation of 4H-prido-[1,2-] pyrimidine compounds these are good to excellent yields and it is the more efficient and simple method for scope of organic chemistry synthesis.

Materials and methods:

All chemicals and reagents were obtained from Aldrich Lancaster (Alfa Aeser, Johnson Matthey Company, Ward Hill, MA, USA), or Spectrochem Pvt. Ltd. (Mumbai, India) and were used without further purification. Reactions were performer by TLC performed on silica gel glass plate containing 60 GF-254, and visualization was achieved by UV light or iodine indicator. ¹H and ¹³C NMR spectra were determined in CDCl₃ by using Varian and Avance instruments. Chemical shifts are expressed in parts per million (δ in ppm) downfield from internal TMS and coupling constants are expressed in Hz. ¹H NMR spectroscopic data coupling constants in Hz, number of protons. ESI mass spectra were recorded on a Micro mass Quattro LC using ESI+ software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected.

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