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Synthesis and Evaluation of Antimicrobiological Activity of Novel 1,2,4-Triazoles

Saritha Garrepalli*, Swarnalatha Katherasala, B. Yamini and A.Mounika
St.Peter's College Of Pharmacy, Madikonda, Hyd. Road, Warangal, A.P, INDIA.

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ABSTRACT

In the present investigation, a series of new Schiff bases IV (a-d) were synthesized by the condensation of 4-amino-5-mercapto-3-pyridine-1,2,4-triazole (III) with various substituted aromatic aldehydes in ethanol using catalytic amount of glacial acetic acid. The starting material isonicotinic acid hydrazide (I) reacted with carbon disulphide and alcoholic KOH to give potassium dithiocarbazinate (II). The formed potassium dithiocarbazinate was treated with hydrazine hydrate gives product (III). Newly synthesized compounds were characterized by IR, TLC, NMR and mass spectra. All the compounds were evaluated for their antibacterial and antifungal acitivity using zone of inhibition method. Few of the compounds were found to be biologically active.

Key words: *Triazole derivatives, ^{1}HNMR, IR and Antibacterial activity.*

INTRODUCTION

The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications, such as propellants, explosives and especially in chemotherapy. In the medicinal chemistry, azole are widely used and studied class of antimicrobial agents due to their safety profile and high therapeutic index. Among there, conazoles are a major class of azole based drugs such as itraconazole, fluconazole and vorconazole etc.

A large large number of ring system containing 1,2,4-triazoles have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulant, sedative, anti-anxiety, antimicrobial agent and antimycotic agent. Also there are some known drugs containing 1,2,4-triazole moiety example triazolam, alprazolam, furacyclin, hexaconazole and fluotrimazole.

A detailed literature survey revealed that, Schiff bases possess diverse type of biological activities. Some Schiff bases bearing aryl groups exhibited interesting biological acitivities. Keeping in view of the above facts and in continuation of our research on biologically potent molecules, we here in report the synthesis of some new 1,2,4-triazole derivatives and their antimicrobial and antifungal activity.

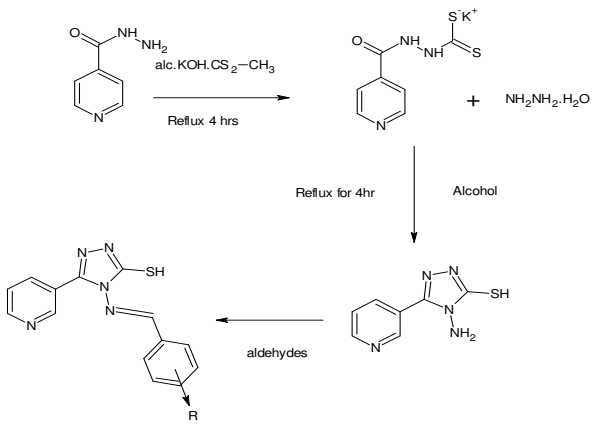
MATERIAL AND METHOD

Synthesis of triazole derivatives involved following steps. In the first step isonicotinic acid hydrazide was treated with alcoholic KOH and carbon disulphide to give potassium dithiocarbazinate (II). In the next step2 potassium dithiocarbazinate (II) was reacted with hydrazine hydrate in the presence of ethanol to give 4-amino-5-mercapto-3-pyridine-1,2,4-triazole (III) which was further reacted with different substituted aromatic aldehydes in the presence of glacial acetic acid and ethanol as solvent to give 4-(4-substituted benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol(IV a – d).

The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus. The homogeneity of all newly synthesized compounds was checked by TLC on silica gel G coated plates using chloroform: ethyl acetate (1:1) solvent system. IR spectra (KBR pellet) were recorded on FTIR paragon 500 (Perkin Elmer) instrument. ^{1}HNMR spectra were recorded on JEOL, GSX_ 400 FT NMR instrument at 400 MHZ in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard.

***Corresponding author:**
Saritha Garrepalli
St.Peter's College Of Pharmacy, Madikonda,
Hyd. Road, Warangal, A.P, INDIA. Mobile No. 9951936457.
**E-Mail: sarithagarrepalli@gmail.com*

Experimental Procedure:
Scheme:



Synthesis of Triazole Derivatives:

Step-1: Synthesis of potassium dithiocarbazinate (II):

An equimolar amount of isonicotinic acid hydrazide and carbon disulphide were taken in a round bottom flask and dissolved in alcoholic potassium hydroxide (1.5 moles) for reflux about 6 hrs. after cooling the separated potassium dithiocarbazinate was taken out. Dried and used directly for the next step without further purification.

Percentage Yield: 80%, ***M.P;*** 144-146°C, ***Rf;*** 0.7 (chloroform and Methanol)

Step-2: Synthesis of 4-amino-5-mercapto-3-pyridine-1,2,4-triazole (III):

An equimolar amount of potassium dithiocarbazinate and hydrazine hydrate were taken in a round bottom flask and dissolved in alcohol and refluxed for about 6 hrs when profuse evaluation of hydrogen sulphide was observed. The reaction mixture was cooled and poured in cold water on acidification with hydrochloric acid, the

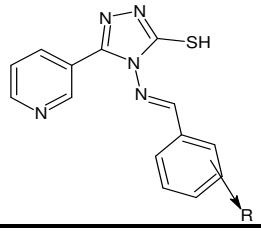
compound obtained which was filtered and washed with cold water and recrystalized from ethanol.

Percentage Yield; 70%, ***M.P;*** 144-146°C, ***Rf;*** 0.5 (chloroform and ethyl acetate)

Step-3: Synthesis of 4-(4-substituted benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol (IV a-d):

The 4-amino-5-mercapto-3-pyridine-1,2,4-triazole (III, 0.01mol) and appropriate aromatic aldehydes (0.015mol) in alcohol(20ml) with 2 to 3 drops of acetic acid, heated under reflux on a water bath for one hour. The solvent was removed to possible extent by distillation under reduced pressure. The product thus obtained was filtered, washed with water dried and purified by recrystallization from suitable solvent to produce the compounds IV (a-d). The physical data of these benzoxazole derivatives were given in table1

Table No. 1: Physical data of 4-(4-substituted benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol



S. No.	Compound	R	Mol. Formula	Melting point	% Yield
1	**IV a**	**4 - OH**	$C_{14}N_5H_{11}OS$	210	70
2	**IV b**	**4 - Cl**	$C_{14}N_5H_{10}ClS$	205	78
3	**IV c**	**4 - OCH_3**	$C_{15}N_5H_{13}OS$	180	60
4	**IV d**	**4 - $N(CH_3)_2$**	$C_{16}N_6H_{16}S$	190	72

Compound IV a:

4-(4-Hydroxy benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol:

IR (KBr, cm-1): 3150 (OH), 3060(C-H aromatic), 2932 (C-H str in CH_2), 1592 (C=N), 1059 (N-N); 2560 (S-H str).

^{1}H-NMR ($CDCl_3$) δ: 7.4 – 8.2 (s, 4H, Pyridine-H); 6.82-7.06(m,4H,Ar-H); 6.18 (s, 1H, =CH); 2.98 (s,1H, SH);4.20 (s, 1H, OH); MS (EI). m/z 298 (M+1).

Compound IV b:

4-(4-Chloro benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol:

IR (KBr, cm-1): 3100(C-H aromatic), 2982 (C-H str in CH_2), 1582 (C=N), 1029 (N-N); 2500 (S-H str).

^{1}H-NMR ($CDCl_3$) δ: 7.4 – 8.0 (s, 4H, Pyridine-H); 6.72-7.16(m,4H,Ar-H); 6.28 (s, 1H, =CH); 3.0 (s,1H, SH): MS (EI). m/z 316 (M+1).

Compound IV c:

4-(4-methoxy benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol:

IR (KBr, cm-1): 3080(C-H aromatic), 2952 (C-H str in CH_2), 1572 (C=N), 1079 (N-N); 2560 (S-H str): MS (EI). m/z 312 (M+1).

Compound IV d:

4-(4-dimethyl amino benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol:

IR (KBr, cm-1): 3060(C-H aromatic), 2962 (C-H str in CH_2), 1592 (C=N), 1059 (N-N); 2600 (S-H str): MS (EI). m/z 329 (M+1).

Antimicrobial Activity:

All the newly synthesized compounds were evaluated for their antimicrobial activities against various microorganisms representing Gram – Positive bacteria (S. aureus), Gram – negative bacteria (E. coli) and fungus (C. arbicans) were carried out by cup – plate agar diffusion method using nutrient agar. The compounds were tested in – vitro for their antibacterial activity against two microorganisms viz. Escherichia coli and Staphylococcus aureus which are pathogenic to human beings. The anti fungal screening was carried out by cup – plate agar diffusion method using nutrient agar. Inoculation of the test organism Candida albicans fungal cultures were made in the Sabouraud – Dextrose agar and then incubated at 37 °C for 18 – 24 hrs standard drugs Norfloxacin and griseofalvin were used. The concentration was 200 µg/ml.

RESULTS AND DISCUSSION

Formation of 4-(4-substituted benzylidene amino)-5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiol (IV a-d) was confirmed by recording their IR, NMR and Mass spectral analysis. IR spectrum of compound IVa showed absorption bands at 3150,3060, 2932, 1592, 1059 and 2560 cm-1 which is due to the O-H, C-H aromatic, C-H str in CH_2, C=N, N-N and S-H groups, respectively. The 1HNMR spectrum of IV a showed a singlet at δ: 7.4 – 8.2 corresponds to pyridine CH(4H). A doublets was observed δ 6.82-7.06 due to aromatic CH (4H). A singlet observed at δ 6.18 due to N = CH and A siglet appeared at δ 2.98 due to SH. Similarly the mass spectrum was recorded and reported as (M + 1) values. For the compound IV a molecular weight 297 is consistent with the molecular formula $C_{14}N_5H_{11}OS$. The values for the remaining compounds have been presented under the experimental part.

All the newly synthesized compounds were screened for their antibacterial and antifungal activities. For antibacterial studies, microorganisms employed were S. aureus and E. coli. For antifungal studies, microorganism employed was C.albicans. both antimicrobial studies were assessed by cup – plate method.

From the antimicrobial activity study, it was found that compounds IVb and IVd exhibited the promising activity as that of the standard drug norfloxacin against S.aureus and E.coli and IVa and IVc exhibited the moderate activity as that of standard drugs. The antifungal activity of compounds IVb and IVd against C.albicans was found to be higher than that of the Iva and IVc.

The observed activity in IVb and IVd was may be due to the presence of chloro and dimethyl amino groups.

Table No. 2: Antibacterial activities of the synthesized compounds

S.NO	COMPOUNDS	ZONE OF INHIBITION AT 200 Mg/ml		
		E.Coli	S. aureus	C.albicans
1	**IVa**	18	17	19
2	**IVb**	22	21	23
3	**IVc**	19	19	21
4	**IVd**	23	22	23
5	**Norflaxacin**	25	25	----
6	**griseofulvin**	-----	-----	24

Compounds IVb and IVd have shown promising antibacterial and antifungal activity. Norfloxacin and griseofulvin were used as standard drugs.

CONCLUSION

A novel series of Schiff bases bearing 1,2,4-triazole ring systems were synthesized. These were characterized by IR, NMR, TLC and Mass spectrometry. All the compounds were screened for their antibacterial and antifungal activity by cup – plate method. Compounds IVb and IVd exhibited promising activity as that of the standard drug norfloxacin and griseofulvin.

REFERENCES:

1. Jing Chen, Xian-Yu Sun, Kyu-Yun Chai, Zin-Seok Lee, Mi-Sun Song and Zhe-Shan Quan. Bioorganic and Medicinal Chemistry, **2007**; 15: 6775-6781.
2. N.Demirbas, SA. Karaoglu, A. Demirbas. Medicinal Chemistry, **2004**; 39: 793.
3. Bn. Goswami, Jcs. Kataky, Baruah. Hetero Cyclic Chemistry, **1986**; 23: 1439.
4. R.Guptha, S.Sudan, V.Meng. Indian Journal of Chemistry, **1996**: 3513, 621.
5. VN. Britsun And M.O. Lozinskii. Hetero Cyclic Compounds, **2004;** 40: 1092.
6. Bakavoli, M. Davoodnia, A. Rahimizadeh. J. Chemistry. Res., **2002**; 4: 178.
7. A. Khirsaga, Mp. Toraskar, Vm. Kulkarney, S. Dhanashire. International Journal of Chemtech Research, **2008**; 1: 696-701.
8. Brucato, A. Copoola, A. Gianguzza, S. Provenzano. P.M, **2008**; 54: 88-90.
9. Chavez, D.E, Parrish. D, A. Journal of Heterocyclic Chemistry, **2009**; 46: 88-90.
10. D.L. Coffen, R.I. Fryer: U.S. Patent. Chem., **1974**; 3: 849, 434.
11. A.Y. Hassan. Elem, 2009; 184(11): 2759-2776.
12. B.S. Holla, B.S. Rao, K. Shridhara. Farmaco, **2000**; 55: 338-344.
13. A.M. Isloor, B. Kalluraya, P. Shetty; Eur. J. Med. Chem, **2009**; 44: 3784-3787.

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