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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL SCHIFF AND MANNICH BASES DERIVED FROM 1, 2, 4- TRIAZOLES

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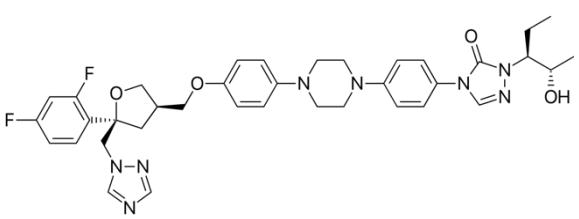
ABSTRACT

This paper reports the synthesis of a series of 3- substituted 1,2,4-triazole Schiff base (3a-b) and amino methylation reactions were performed with formaldehyde and primary, secondary amine furnished Mannich Schiff base (4a-f),(5a-f).The structure of these compounds were established by IR,^{1}HNMR,Mass spectral analysis. The synthesized compounds have been screened for antibacterial activity against *Escherichia coli, S.aureus, P.aeruginosa, B.subtilis* and antifungal activity against *A.flavus, T.mentagrophyts. A.fumigatus. P.Marneffei*. Among the screened compounds 4a,4c,4d,4f,5a and 5d have shown good antibacterial activity.4c,4d,4f and 5d have shown good antifungal activity. The study shows that the synthesized few compounds are potential lead compounds for future drug discovery studies.

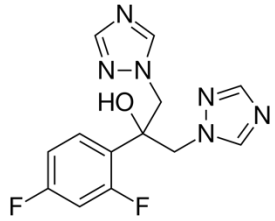
Key words: 1, 2, 4-triazoles, Schiff bases, Mannich bases, Antifungal, Antibacterial activity.

INTRODUCTION

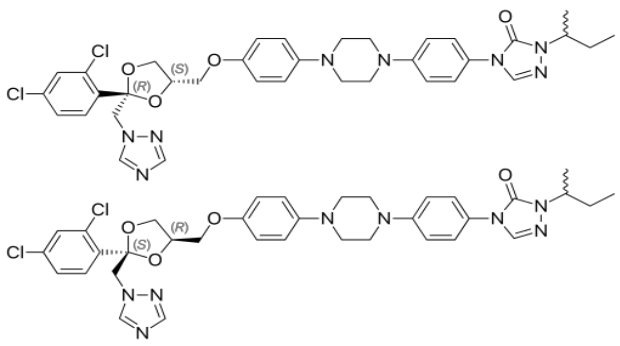
Antimicrobial drugs which at certain concentration inhibit the growth or kill microorganism completely. The progress and expansion of antimicrobial resistance amongst microorganism is a serious concern which has made search of new antimicrobial compounds. All over the world multi-drug resistance bacteria has become major concern. Heterocyclic compounds particularly 1, 2, 4 triazole derivatives by virtue of specific activity compounds be employed in the treatment of infectious disease. Various 1, 2, 4 – triazole derivatives and N- bridged heterocycles are found to be associated with diverse pharmacological activities [1-3]. Schiff bases derived from different heterocycles are reported to possess cytotoxic[4], anticonvulsant[5], antiproliroliperative[6], anticancer and antifungal activities[7]. Mannich bases have been reported to exhibit antitubercular[8], antimalarial[9], vasorelaxing[10], anticancer[11]and analgesic drugs [12]. From the literature it is found that Mannich bases derived from 1, 2, 4 – triazole bearing N-methyl piperazine moiety posses protozoacidal and bactereocidal activity. Drugs such as prazosin[13], Lidoflazine[14] and Urapidil[15] containing piperazine nucleus have shown cardiovascular activity. Several 1, 2, 4 –triazole derivatives are reported to possess anticancer[16], antitubercular[17], analgesic and anti-inflammatory properties[18] .Therefore the synthesis of 1,2,3 triazole Schiff base and mannich base are important target for organic synthesis, These compounds can be tested as an antibacterial and antifungal activity.



Posaconazole



Fluconazole



Iitraconazole

The above antibacterial and antifungal drugs structure strongly encouraging and supporting to choose the idea of synthesizing triazole derivatives containing fluor and chloro on aromatic ring system and morpholine moiety fused with trazole ring system. Prompted by above all these observations, it was decided to synthesize chlorine and fluorine, morpholine containing 1, 2, 4-triazoles derivatives to get high potent molecules.

MATERIALS AND METHODS

Experimental Section

Melting points were determined by the open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}HNMR spectra were recorded using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard either on a Bruker or 300MHz NMR spectrometer. The mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV. The purity of the compounds was checked by completion of the reaction was checked by thin layer chromatography (TLC) on silica gel plate using petroleum ether and ethyl acetate.

Procedure for the preparation of 4-amino-3-(2, 3, 5-trichlorophenyl)-5-mercapto-1, 2, 4-triazole (1)

4-amino-3-(2, 3, 5- trichlorophenyl)-5-mercapto-1, 2, 4-triazole (1) was synthesized by literature method. The solid product obtained was recrystallized from ethanol. Yield 87%, melting point : 168-171^{0}C,IR (KBr) ν/cm^{-1} 3328 (NH_2 asymmetric) 3148 (NH_2 symmetric), 3043 (Ar-H), 1641(C=N), 1459 (C=C), 1112 (C-F), 742 (C-Cl).^{1}HNMR (δ , $CDCl_3$): 4.75 (s, 2H, NH_2), 8.09 (s, 1H), 8.20 (s, 1H) 10.90 (broad singlet, 1H, NH/SH), Mass (%) 294 (M^+), 296 (M+2), 298(M+4, 300(M+6)

General procedure for the preparation of Schiff base 3a and 3b

To a suspension of substituted benzaldehyde (2) (0.01 mol) in methanol (15ml), in equimolar amount of triazole (1) was added. The suspension was heated until clear solution was obtained. Then few drops of Conc. Sulfuric acid was added as catalyst. The solution was refluxed for 3-4 hrs on water bath and the precipitated solid was filtered off, washed with water and recrystallized from ethanol-DMF mixture.

3a: IR (KBr), ν/cm^{-1}: 3082 (Ar-H), 617 and 1493 (C=C), 3071 (NH/SH), 1594 (C=N). ^{1}H-NMR (DMSO) δ: 7.33 (d, 2H, *J* = 8.7 Hz, 4-chlorophenyl), 7.53 (d, 2H, *J* = 8.4 Hz, 4-chlorophenyl), 7.66 (d, 1H, *J* = 2.7 Hz, 2,3,5-trichlorophenyl), 7.91 (d, 1H, *J* = 2.4 Hz, 2,3,5-trichlorophenyl), 9.8 (s, 1H, N=CH) and 14.29 (s, 1H, SH). MS: (M^+, %); m/z, 418 (M^+ 70), 387 (10), 335 (5), 307 (20), 289 (15), 281 (15), 232 (40),

3b: IR (KBr) ν/cm^{-1} 3075 (NH), 3075 (Ar-H), 2910 (C-H), 1601 (C=N), 612 and 1486 (C=C) 785 and 628 (C=Cl). ^{1}HNMR (δ $CDCl_3$) : 7.1-7.14 (t, 2H, *J* = 10.4 Hz, 4-fluorophenyl), 7.474 (d, 1H, *J* = 2.7 Hz, 2,3,5-trichlorophenyl), and 7.68 (d, 1H, *J* = 2.4 Hz, 2,3,5-trichlorophenyl), 7.7-7.74 (m, 2H, 4-fluorophenyl), 10.34 (s, 1H, N=CH), 11.29, (s, 1H, SH). MS: (M^+, %); m/z, 400 (M^+ 100), 383 (20), 307 (30), 280 (50),

General procedure for the synthesis of Mannich bases (4 & 5)

The Schiff base **3** (0.01 mol) was dissolved in methanol, then formaldehyde (40%, 1.5 ml) and primary /secondary amine (0.01mol) were introduced to this solution. The mixture was stirred for 2-3 h and kept overnight at room temperature. The resulting solid was collected by filtration, washed with cold ethanol and recrystallized from ethanol and DMF to yield the titled compound.

4a: **IR (KBr),** ν/cm^{-1}: 1594 (C=N), 1270 (C=S), 867 (C-Cl). : **^{1}H-NMR ($CDCl_3$),** δ: 2.86-2.89 (t, 4H, -CH_2-O-CH_2-), 3.72-3.73 (t, 4H, -CH_2-N-CH_2), 5.293 (s, 2H, --CH_2-), 7.09-7.14 (t, 2H, *J* = 8.4, Fluorophenyl), 7.464 (d, 1H, *J* = 2.7 Hz, 2,3,5-trichlorophenyl), 7.68 (d, 1H, *J* = 2.4 Hz, 2,3,5-trichlorophenyl), 7.689-7.733 (m, 2H, 4-Fluorophenyl), 10.38 (s, 1H, -N=CH-). **FAB MS: (M^+, %)**; m/z, 501 (M^+, 60), 415 ((12), 403(30), 379(5), 260(22), 235(20).

4f: **IR (KBr),** ν/cm^{-1}: 1594(C=N), 1270 (C=S), 867 (C-Cl): **^{1}H-NMR (DMSO)**, δ : 2.148 (s, 3H, N-CH_3), 2.333-2.505 (t, 4H, -CH_2-N-CH_2-), 2.505-2.771 (t, 4H, -CH_2-N-CH_2-), 5.201 (s, 2H. N-CH_2-N), 7.584 (d, 2H, *J* = 8.4 Hz, 4-chlorophenyl), 7.77 (d, 2H, *J* = 8.4 Hz, 4-chlorophenyl), 7.94 (d, 1H, *J* = 2.7Hz, 2, 3, 5-trichlorophenyl), 8.17 (d, 1H, *J* = 2.4 Hz, 2, 3, 5-trichlorophenyl), 9.963 (s, 1H, N=CH). **FAB MS: (M^+, %);** m/z, 530 (M^+, 100), 419 ((40), 385 (3), 307 (12), 289 (22), 281 (10).

5d: IR (KBr), ν/cm^{-1}: 3360 (NH), 1890 (C=N), 1298 (C=S), 1200, (C-F). **^{1}H-NMR (DMSO)** δ: 5.52-5.54 (t, 1H, NH), 5.75-5.78 (d, 2H, N-CH_2-NH-), 6.58-6.75(t, 1H, *J* = 10.7, trifluoromethylphenyl), 6.8-6.95 (t, 1H, *J* = 10.4, trifluoromethylphenyl), 7.22-7.32 (d, 1H, *J* = 8.4, trifluoromethylphenyl), 9.941 (s, 1H, N=CH), 7.58-7.61 (d, 1H, *J* = 8.4, trifluoromethylphenyl), 7.580-7.609 (d, *J*=8.7 Hz, 1H, 4-chlorophenyl), 7.765 -7.793 (d, *J* = 8.4, 1H, 4-chlorophenyl), 7.848 (d,1H, *J* = 2.7 Hz, 2,3,5-trichlorophenyl), 8.154 (d, 1H, *J* = 2.4 Hz, 2,3,5-trichlorophenyl).

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Psuedomonus aeruginosa* (ATTC-27853) and *Bacillius subtilis* (recultured) bacterial stains by disc diffusion method[20, 21]. The discs

measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140° C for an hour. The test compounds were prepared with different concentrations using dimethylformamide. 1ml containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24h. Tetracycline was used as the standard drug at concentration of 10µg/ml. Solvent and growth controls were kept and zones of inhibition was noted. The results of such studies are given in the Table-II.

Antifungal activity

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus* (NICM No.524), *trichophyton mentagrophytes* (Recultured), *Aspergillus fumigatus* (NCIM No.902) and, *Penicillium marneffei* (recultured) and in DMSO by serial plate dilution method[22, 23]. Sabourands agar media was prepared by dissolving peptone (1g), D-glucose (4g) and agar (2g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3ml saline to get a suspension of corresponding species, 20 ml of agar media was poured in to each petridishes. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1hr. using an agar punch wells were made in to each well labeled. A control was also prepared in triplicate and maintained at 37 °C for 3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Flucanazole as the standard.

RESULT AND DISCUSSION

Chemistry

4-amino-3-(2, 3, 5-tirchlorophenyl)-5-mercapto-1, 2, 4-triazole (1) was synthesized from 2, 3, 5- trichlorobenzoic acid as per the literature[19]. Compound **1** was treated with substituted aromatic aldehydes (**2**) in presence of acetic acid to yield Schiff base (**3**). Compound **3** when treated with primary and secondary amines in presence of formaldehyde gave Mannich bases (4 and 5) in good yields. The reaction sequence outlined in S**cheme 1.** The characterization data of Schiff bases (**3**) and Mannich bases (4 and 5) are given in Table 1, under supplementary information.

The antibacterial and antifungal activity data of the synthesized compounds are given in table.2 and 3. Among the screened compounds **4a, 4c, 4d, 4f, 5a** and **5d** have shown good activity against all the tested organisms. Among the screened compounds **4c, 4d, 4f** and **5d** have shown good antifungal activity.

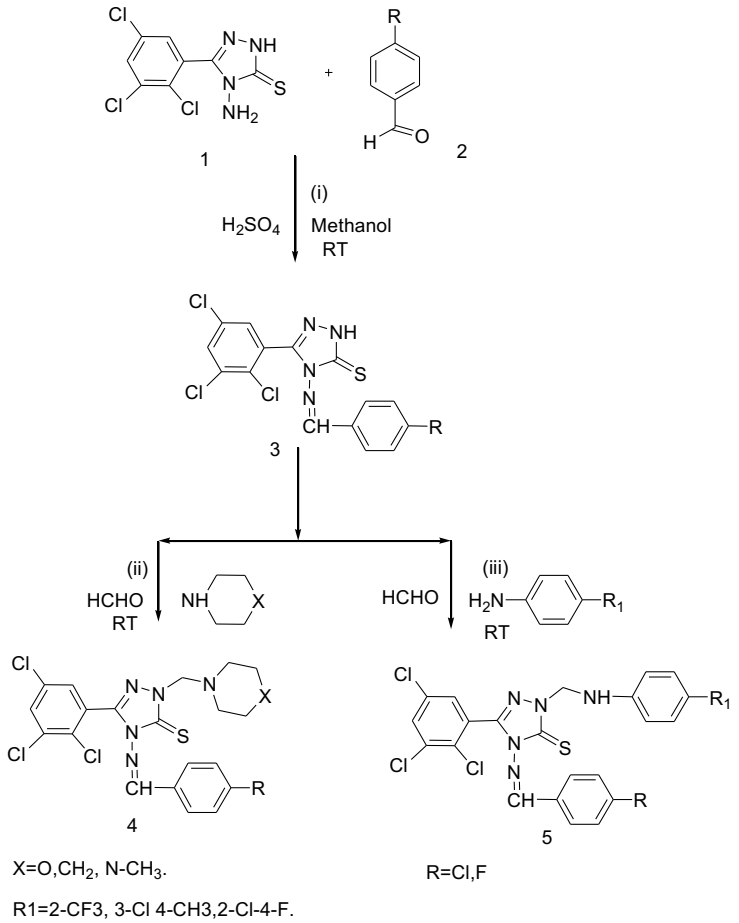


Fig.1: Synthesis of Schiff base and Mannich base

Biological results

The results of antibacterial and antifungal activity of compounds 3(a-b),4(a-f) and 5(a-f) have shown in the table 2 and 3.The results indicates that compound 4b,4g,4f,5c display an excellent activity against Escherichia coli(inhibitory zone matching with standard tetracycline (12.5mm),remaining compounds exhibiting moderate activity against E-coli bacteria(inhibitory zone less than 12.5mm),compounds 5c,5e and 4e shows high activity against Bacillus subtilis bacteria(inhibitory zone greater than 12.5mm).The tested compounds such as 4c,4f,5b and 5e indicates high antifungal activity against Aspergillus flavus(inhibitory zone showing greater than 22mm),similarly, 4fd,4e,5d, compounds are strongly showing high activity against Trichophyton mentagrophytes(inhibitory zone showing greater than 19mm).4e compound exhibiting strong activity against Aspergillus fumigatus(inhibitory zone displaying greater than 26mm respectively.

Table 1: Characterization data of the prepared compounds 3a, 3b, (4a-4f) and (5a-5f)

Compd	R	X	R1	Mol. Formula	Yield	MP	Found(Calculated)		
							C	H	N
3a	Cl	--	-	$C_{15}H_8N_4Cl_4S$		210-212	43.00 (42..98)	1.91 (1.88)	13.42 (13.39)
3b	F	--	-	$C_{15}H_8N_4Cl_3FS$		231-232	45.00 (44.97)	2.01 (1.98)	14.00 (13.97)
4a	F	O	-	$C_{19}H_{17}N_5C_{13}FOS$	(80)	184-86	47. 89 (47. 90)	4.0 (3.39)	13.98 (13.97)
4b	F	CH_2	-	$C_{20}H_{19}N_5C_{13}FS$	(85)	168-70	51.34 (51.33)	3.85 (3.86)	14.26 (14.25)
4c	F	N-CH_3	-	$C_{10}H_{20}N_6C_{13}FS$	(86)	176-78	49.01 (49.02)	3.88 (3.89)	16.33 (16.34)
4d	Cl	O	-	$C_{19}H_{17}N_5C_{14}OS$	(85)	182-84	46.43 (46.42)	3.29 (3.28)	13.54 (13.53)
4e	Cl	CH_2	-	$C_{20}H_{19}N_5C_{14}S$	(80)	180-82	48.91 (48.92)	3.67 (3.68)	13.59 (13.60)
4f	Cl	N-CH_3	-	$C_{19}H_{20}N_6C_{14}S$	(85)	196-98	47.53 (47.55)	3.76 (3.76)	15.83 (15.86)
5a	F	--	2-CF_3	$C_{23}H_{14}N_5C_{13}F_4S$	(90)	160-62	48.01 (48.01)	2.41 (2.44)	12.13 (12.14)
5b	F	--	3-Cl, 4-CH_3	$C_{23}H_{16}N_5C_{14}FS$	(80)	153-55	49.73 (49.75)	2.87 (2.87)	12.60 (12.64)
5c	F	--	2-Cl,4-F	$C_{22}H_{13}N_5C_{14}F_2S$	(85)	140-42	47.23 (47.23)	2.31 (2.33)	12.51 (12.51)
5d	Cl	--	2-CF_3	$C_{23}H_{14}N_5C_{14}F_3S$	(80)	182-84	46.71 (46.71)	2.35 (2.37)	11.85 (11.86)
5e	Cl	--	2-Cl, 3-CH_3	$C_{23}H_{16}N_5Cl_5S$	(82)	180-82	48.41 (48.44)	2.81 (2.83)	12.27 (12.29)
5f	Cl	--	2-Cl,4-F	$C_{22}H_{13}N_5C_{15}S$	(75)	196-98	45.90 (45.91)	2.25 (2.27)	12.16 (12.16)

Table 2: Antibacterial activity data of prepared compounds (3a-b), (4a-j) & (5a-f)

Compounds	Zone of inhibition in mm			
	E. coli	*S. aureus*	*P. aeruginosa*	*B. subtilis*
3a	6.25(12.5)	6.25(12.5)	----	6.25(25)
3b	----	-------	12.5(50)	-----
4a	6.25(12.5)	6.25(12.5)	6.25(12.5)	6.25(25)
4b	12.5(100)	------	-----	----
4c	6.25(25)	6.25(12.5)	6.25(12.5)	6.25(25)
4d	6.25(25)	6.25(12.5)	6.25(6.25)	6.25(25)
4e	12.5(100)	-------	6.25(12.5)	12.5(100)
4f	12.5(25)	6.25(12.5)	12.5(12.5)	6.25(25)
5a	6.25(25)	12.5(50)	6.25(12.5)	6.25(25)
5b	6.25(6.25)	6.25(25)	-----	6.25(25)
5c	12.5(50)	------	6.25(12.5)	12.5(25)
5d	6.25(12.5)	6.25(12.5)	6.25(12.5)	6.25(12.5)
5e	6.25(25)	----	6.25(12.5)	12.5(25)
5f	---	-----	12.5(50)	-----
Standard	12.5(25)	6.25(12.5)	6.25(12.5)	12.5(25)

-- indicates bacteria are resistant to the compounds greater than100µg/ml. MIC (µg/ml) = minimum inhibitory concentration, that is the lowest concentration to completely inhibit bacterial growth. MBC (µg/ml) = minimum bacterial concentration, that is lowest concentration to completely kill bacteria.

Table 3: Antifungal activity data of prepared compounds (3a-f), (4a-j) & (5a-5f)

Compounds	Zone of inhibition in mm			
	A. flavus	*T. mentagrophytes*	*A. fumigatus*	*P. marneffei*
3a	14	17	12	17
3b	20	15	21	22
4a	--	16	---	---
4b	21	19	22	17
4c	22	18	24	21
4d	--	21	26	20
4e	20	20	27	14
4f	22	19	24	20
5a	17	11	19	16
5b	22	---	--	--
5c	19	14	15	15
5d	20	21	23	19
5e	22	18	20	19
5f	--	--	25	--
Standard	22	19	26	23

_ indicates fungus is resistant to the compounds > 100µg/ml, Zone of inhibition in mm.

Structure activity relationship

On the studying the effect of the substitution on the antifungal and antibacterial activity relationship can be seen. If you compare the above mentioned drugs like Posaconazole, Fluconazole, Iitraconazole, An electron withdrawing groups such as chlorine and fluorine placed para position in aromatic ring system and incorporating morpoline containing triazole derivatives like 4a, 4c, 4d, 4f and 5a, 5d showing more antibacterial activity. Similarly results were found with incorporation of morpoline and trifluoro group substituted primary and secondary amine on aromatic ring system increases the antibacterial activity. On the considering the relationship of the antifungal activity of substituted triazole derivatives. It was observed that same morpoline and substuted chlorine and fluorine groups increases the antifungal activity.

CONCLUSION

In this paper, a series of novel 1, 2, 4 triazole Schiff base and Mannich bases were synthesized and tested antibacterial, antifungal activity against four bacterial strains, four fungal strains. The results are indicated that among the 14 compounds 4a, 4c, 4d, 4f, 5a and 5d have shown more antibacterial activity against all the tested organisms, along with that among screened compounds 4c, 4d, 4f and 5d have shown good antifungal activity. Specifically, 4f could be promising lead molecules for development of more potent and safer antibacterial drugs. Similarly 4f and 5d showed antifungal effect superior to clinical candidate's fluconazole. Therefore the above mentioned said drugs may be the better pharmacophore to explore the development of new antibacterial and antifungal active moieties.

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