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SYNTHESIS AND EVALUATION OF 1,2,4-TRIAZOLE AND PYRROLOPYRAZINE DERIVATIVES FOR VARIOUS BIOLOGICAL ACTIVITIES

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ABSTRACT

In this work some substituted triazole, and pyrrolopyrazine derivatives were synthesized. Triazole were synthesized by using and treating acetaldehyde with pyrazinamide in presence of hydrazine hydrate and total 6 derivatives (A_1-A_6) were prepared by using Ar-NH_2. Pyrrolopyrazine were synthesized by using and treating pyrazinamide with substituted acetaldehyde to obtain corresponding imines, on cyclization by polyphosphoric acid, pyrrolopyrazine derivatives were prepared by mannich reaction(B_1-B_9). All the synthesized compounds were characterized by ^{1}H-NMR, IR and Elemental Analysis. All the compounds were evaluated for antibacterial (*E. coli and S.aureus*) and were measured in terms of zone of inhibition and compared with the standard drug ciprofloxacin for antibacterial activity. All the compounds were evaluated for antitubercular activity (*M. tuberculli*) at 25µg/ml, 50µg/ml and 100µg/ml concentrations. And their results were compared with the standard drug streptomycin from them three compounds have shown promising activity.

Keywords: Pyrrolopyrazine, Triazole, Antibacterial, Antitubercular.

INTRODUCTION

The history of triazoles is less than a century old and starts with work of Bladin who synthesized the first representatives and coined the name for this class of compounds. Over 20,000 triazoles are known but practical applications have been very few until recently. Although most triazoles are readily prepared and stored, expensive starting materials or sensitive intermediates appear to have discouraged industrial synthesis and applications.

The first studies of triazole were concerned with structural isomerism. Modern instrumental and theoretical methods achieved much success in dealing with tautomeric problems, the complexity of which is one of the enduring charms of the chemistry of triazoles. However, some structural and many tautomeric problems require further study, kinetic and other quantitative mechanistic studies are scarce, the stereochemistry and photochemistry of triazole are virtually unexplored.

1,4-Diazoindole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered pyrazine ring fused to a five-membered nitrogen-containing pyrrole ring. 1,4-Diazoindole is a popular component of fragrances and the precursor to many

pharmaceuticals. Recently, 1,4-Diazoindole has been validated as a privileged structure, a scaffold capable of providing useful ligands for diverse receptors.

MATERIALS AND METHODS

ANTI-TUBERCULAR ACTIVITY[3]

The antitubercular screening was carried out by Middle brook 7H9 agar medium against $H_{37}Rv$. Strain. Middle brook 7H9 agar medium containing different derivatives, standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of $H_{37}Rv$ Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth.

ANTIBACTERIAL ACTIVITY

All the compounds were screened for antibacterial activity at 200 µg/ml concentration. However the compounds **A_3, A_6, B_3, B_6** and **B_9**, have shown promising antibacterial activity, while the remaining compounds have also shown moderate antibacterial activity, when compared with the standard drug Ciprofloxacin against *Staphylococcus aureus* (Gram positive) ATCC 29737, and *Escherichia coli* (Gram negative) NCTC 10418. The zone of inhibition was measured in mm.

EXPERIMENTAL SECTION

Melting points were determined in open capillary method and are uncorrected. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR Spectrometer model Avance-II (Bruker) using dimethylsulfoxide-d_6 as solvent and tetramethylsilane as internal standard. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method.

Synthesis of Schiff base from Pyrazinamide. I[1]

A mixture of 0.01mole (1.23g) of pyrazinamide, 18 ml of water & 2.4 ml of conc. aq. NH_3 was vigorously stirred and 1-2 ml of aldehyde was added drop wise with stirring, over a period of 30-60 min..Solid was collected by suction filtration & wash with water. Recrystallise from rectified spirit. melting point-125-130^{0}C, the percentage yield found to be 74%.

Synthesis of Triazole II[2]

A mixture of 0.01 mole (2.41g) of I, hydrazine hydrate 0.01 mole and 2-3 drops of glacial acetic acid was refluxed in absolute ethanol (10 ml) for 6hr.Solid obtained was filtered and recrystallized from ethanol. melting point-210-215^{0}C, the percentage yield found to be 60%.

Synthesis of N-{(1Z)-[4-(3-chloro-2-oxopropoxy) phenyl] methylene} pyrazine-2-carboxamide III[3]

In 250 ml RBF 0.06 mole (2.53g) of II was dissolved, in 15 ml of dry benzene with 2-3 drops of Pyridine,0.5ml of Chloroacetyl chloride was added in dry Benzene under cold condition and refluxed for 2 hr. Solid obtained was filtered. Recrystallized from Acetone Ethanol mixture. melting point-275-280^{0}C, the percentage yield found to be 75%.

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Synthesis of Triazole derivative[1]: (A_1-A_6).

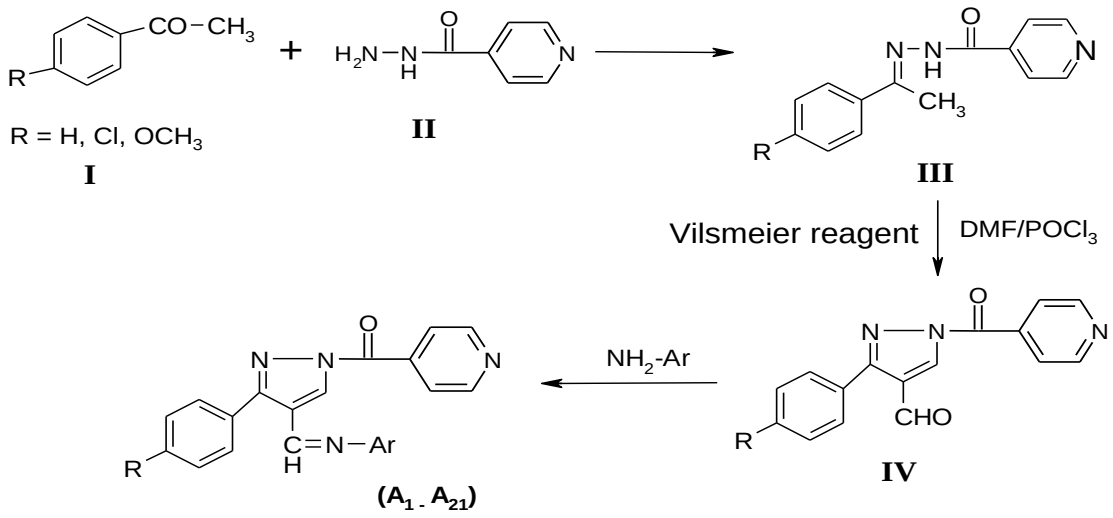
0.01mole of pure sodium bicarbonate,10ml of water, 0.01 mole of amine and 0.01 mole(3.29g) of III was taken in the flask. Heat the flask contents to 90-95^{0}c for 2hrs. solution was kept in cold water, crystals separates, recrystallized from ethanol. Melting points and percentage yields were reported in Table.

RESULT AND DISCUSSION

All the compounds were screened for antitubercular activity by Middle brook 7H9 agar medium as described by Elmer WK et al. against $H_{37}Rv$ Strain. Compounds **A_2, B_2,** and **B_8** have shown promising antitubercular activity. $H_{37}Rv$ strain was used as standard organism. Streptomycin was used as standard drug. However Streptomycin has shown antitubercular activity at 25 ug/ml.

All the compounds were screened for antibacterial activity at 200 µg/ml concentration. However the compounds **A_3, A_6, B_3, B_6** and **B_9,** have shown promising antibacterial activity, while the remaining compounds have also shown moderate antibacterial activity, when compared with standard drug Ciprofloxacin against *Staphylococcus aureus* (Gram positive) ATCC 29737, and *Escherichia coli* (Gram negative) NCTC 10418. The zone of inhibition was measured in mm.

SCHEME



Compd.	R	Ar	Compd.	R	Ar	Compd.	R	Ar
A_1		NH·CO N	A_8		NH·CO N	A_{15}		NH·CO N
A_2		OH COOH	A_9		OH COOH	A_{16}		OH COOH
	H			Cl			$-OCH_3$	
A_3		Cl F	A_{10}		Cl F	A_{17}		Cl F
A_4		F	A_{11}		F	A_{18}		F

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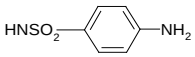
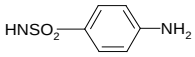
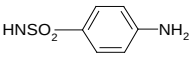
A_5		A_{12}		A_{19}	
A_6		A_{13}		A_{20}	
A_7		A_{14}		A_{21}	

Table No. 1 Analytical, Physico-chemical data of Synthesized Compounds

SL. No.	Compd	Mol. Formula	Mol. Wt.	M.P. ^{0}C	Yield %	CHN (Calcd). Found %			CLogP	CMR
						C	H	N		
1.	A_1	$C_{22}H_{18}N_6O_2$	398.43	205	57	66.32 (66.01)	4.55 (4.45)	21.09 (21.20)	2.26	11.60
2.	A_2	$C_{23}H_{18}N_4O_4$	412.42	149	64	66.66	4.38	13.52	2.80	11.60
3.	A_3	$C_{22}H_{16}N_4ClFO$	406.85	160	59	64.95	3.96	13.17	3.78	11.30
4.	A_4	$C_{22}H_{17}N_4ClO$	388.86	72	49	67.95	4.41	14.41	3.58	11.28
5.	A_5	$C_{22}H_{19}N_5O_3S$	433.49	165	46	60.96 (60.66)	4.24 (4.04)	16.16 (16.02)	1.68	12.3
6.	A_6	$C_{17}H_{14}N_8O$	346.35	217	68	58.95	4.07	32.35	0.09	9.59
7.	A_7	$C_{20}H_{16}N_6O$	356.39	92	75	67.40	4.53	23.58	2.97	12.09
8.	A_8	$C_{22}H_{17}N_6O_2Cl$	432.87	210	47	61.04 (61.22)	3.96 (3.69)	19.41 (19.24)	2.97	12.09
9.	A_9	$C_{23}H_{17}N_4O_4Cl$	488.87	182	53	61.54	3.82	12.48	3.51	12.09
10.	A_{10}	$C_{22}H_{15}N_4Cl_2FO$	441.30	225	43	59.88	3.43	12.70	4.49	11.79
11.	A_{11}	$C_{22}H_{16}N_4Cl_2O$	423.31	95	79	62.42 (62.94)	3.81 (3.52)	13.24 (13.03)	4.29	11.17
12.	A_{12}	$C_{22}H_{18}N_5O_3ClS$	467.94	148	56	56.47	3.88	14.97	2.40	12.52
13.	A_{13}	$C_{17}H_{13}N_8ClO$	380.80	226	52	53.62	3.44	29.43	0.80	10.08
14.	A_{14}	$C_{20}H_{15}N_6ClO$	390.84	214	49	61.46 (61.02)	3.87 (3.55)	21.50 (21.37)	1.69	10.86
15.	A_{15}	$C_{23}H_{20}N_6O_3$	428.45	185	73	68.48	4.71	19.61	2.18	12.22
16.	A_{16}	$C_{24}H_{20}N_4O_5$	444.45	126	76	64.86 (64.45)	4.54 (4.38)	12.61 (12.54)	2.71	12.21
17.	A_{17}	$C_{23}H_{18}N_4O_2ClF$	436.88	178	46	63.23	4.15	12.82	3.70	11.91
18.	A_{18}	$C_{23}H_{19}N_4O_2F$	402.43	152	59	68.65	4.76	13.92	2.92	11.42
19.	A_{19}	$C_{23}H_{21}N_5O_4S$	463.52	162	70	59.60	4.57	15.11	1.60	12.65
20.	A_{20}	$C_{18}H_{16}N_8O_2$	376.38	160	77	57.44 (57.72)	4.28 (4.36)	29.77 (29.57)	0.11	10.20
21.	A_{21}	$C_{21}H_{18}N_6O_2$	386.42	168	71	65.28	4.70	21.75	0.90	10.99

CMR = Constants of Mol. Reactivity. **E:B:C** = Ethyl acetate: Benzene: Chloroform (1:2:1)

The combustion analysis of compounds synthesized is within the limits of permissible errors.

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Table No. 2: Antitubercular and Antimicrobial activities of the synthesized compounds.

Compounds	Antitubercular activity		Antimicrobial activity Zone of inhibition at 200 µg/ml (in mm.)			
	50mcg/mL	100mcg/mL	*A. niger*	*C.albicans*	*E.coli*	*S. aureus*
A_1	+ -	- -	18	19	19	20
A_2	- -	- -	20	21	**24**	**23**
A_3	- -	- -	**22**	**23**	**23**	**24**
A_4	+ -	- -	17	18	15	16
A_5	+ -	- -	19	20	17	19
A_6	+ -	- -	**23**	**24**	**22**	**23**
A_7	- -	- -	21	22	20	21
A_8	+ -	+ -	**24**	**25**	**24**	**23**
A_9	- -	- -	19	20	**24**	**23**
A_{10}	+ -	- -	17	16	17	16
A_{11}	+ -	- -	19	18	18	19
A_{12}	- -	- -	16	15	17	16
A_{13}	- -	- -	19	21	19	20
A_{14}	- +	+ -	**22**	**23**	**24**	**23**
A_{15}	+ -	- -	20	19	20	19
A_{16}	+ -	- -	21	22	18	17
A_{17}	- -	- -	17	16	16	18
A_{18}	+ -	- -	**25**	**26**	19	20
A_{19}	- -	- -	21	22	20	19
A_{20}	+ -	- -	19	17	19	21
A_{21}	+ -	- -	**24**	**25**	**24**	**23**
Streptomycin	- -	- -	**Std-22**	**23**	**Std-23**	**22**

+ +: denotes the growth, + - : denotes growth with less than 20 colonies, - - : denotes no growth
Standard drugs: Norfloxacin for Antibacterial, Griseofulvin for Antifungal.

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SPECTRAL DATA:

A_1: IR (cm^{-1}): 3073 (Ar.C-H Str.), 1653(C-O Str.),1513(-C=N Str.), 1164(N-N-C Str.), 830(C-H def.); **^{1}H NMR (δ ppm):** 8.9 (s,1H, CONH), 7.8-8.2 (m,8H, Pyridyl),7.2-7.6 (m, 5H, Ar-H), 7.1 (s, 1H, CH), 2.2 (s, 1H, Pyrazole).

A_2: IR (cm^{-1}): 3256 (Ar.C-H Str.), 1596(C-O Str.), 1513(C=N Str.), 1173(N-N-C Str.), 834(C-H def); **^{1}H NMR (δ ppm):** 9.3(s, 1H, OH), 9.8(s, 1H, COOH), 7.6-8.2(m, 4H, Pyridyl), 7.2.7.6(m, 11H, Ar-H), 7.1(s, 1H, CH), 2.5(s, 1H, Pyrazole).

A_3: IR (cm^{-1}): 3282 (Ar.C-H Str.), 1653(C-O Str.), 1596(C=N Str.), 1165(N-N-C Str), 827(C-H def.), 742(C-Cl Str.).

A_4: IR (cm^{-1}): 2920 (Ar. C-H Str.), 1653(C-O Str.), 1596(C=N Str), 1165(N-N-C Str.), 827(C-H def.), 742(C-Cl Str.); **^{1}H NMR (δ ppm):** 8.9(m,2H, Pyridine), 2.5 (s,1H, Pyrazole),7.3-7.9(m, 9H, Ar-H), 8.8(s, 1H, CH).

A_5: IR (cm^{-1}): 3475(N-H Str.), 3264(Ar.C-H Str.), 1586(C-O Str), 1500(C=N Str.), 1144(N-N-C Str), 827(C-H def.).

A_6: IR (cm^{-1}): 3387(N-H Str.), 2938(Ar.C-H Str.), 1657(C-O Str.), 1447(C=N Str), 1159(N-N-C Str.), 916(C-H def.).

A_7: IR (cm^{-1}): 3387(N-H Str), 2938(Ar.C-H Str.), 1657(C-O Str.), 1447(-C=N Str.), 1159(N-N-C Str.), 916(C-H def.); **^{1}H NMR (δ ppm):** 8.8(m, 4H, Pyridine), 8.7(m, 2H, Pyrazine)2.5 (s, 1H, Pyrazole), 7.4-7.7(m, 5H, Ar-H), 8.7(s, 1H, CH).

A_8: IR (cm^{-1}): 3186(Ar.C-H Str.), 1670(C-O Str.), 1598(C=N Str.), 1144(N-N-C Str.), 828(C-H def.), 736(C-Cl Str.).

A_9: IR (cm^{-1}): 3187(O-H Str), 3063(Ar.C-H Str.), 1670(C-O Str.), 1595(C=N Str.), 1010(N-N-C Str), 827(C-H def.); **^{1}H NMR (δ ppm):** 12.0(s, 1 H, COOH), 11.8(s, 1 H, Ar-H),2.5 (s, 1H, Pyrazole), 7.5-8(m, 7H, Ar-H), 8.7(s, 1H, CH), 8.8(m, 4H, Pyridyl).

A_{10}: IR (cm^{-1}): 3076(Ar.C-H Str.), 1670(C-O Str.), 1556(C=N Str.), 1089(N-N-C Str.), 828(C-H def.), 735(C-Cl Str.).

A_{11}: IR (cm^{-1}): 3100(Ar.C-H Str.), 1594(C-O Str.), 1501(C=N Str.), 1141(N-N-C Str.), 894(C-H def.), 698(C-Cl Str.); **^{1}H NMR (δ ppm):** 7.7-7.9(m, 4H, Pyridyl), 7.2-7.6(m, 8H, Ar-H), 7.1(s, 1H, CH), 2.5(s, 1H, Pyrazole).

A_{12}: IR (cm^{-1}): 3186(Ar.C-H Str.), 1670(C-O Str.), 1598(C=N Str.), 1144(N-N-C Str.), 828(C-H def.), 736(C-Cl Str.); **^{1}H NMR (δ ppm):** 8.9-9.1(d, 2H, NH_2), 7.7-7.9(m, 4H, Pyridyl), 7.2-7.6(m, 8H, Ar-H), 7.1(s, 1H, CH), 2.5(s, 1H, Pyrazole).

A_{13}: IR (cm^{-1}): 3408(N-H Str.), 3190(Ar.C-H Str.), 1671(C-O Str.), 1515(C=N Str.), 1120(N-N-C Str.), 827(C-H def.), 724(C-Cl Str.); **^{1}H NMR (δ ppm):** 8.8(s, 1H, Pyridyl), 7.5-7.9(m, 4H, Ar-H), 7.5-8(m, 7H, Ar-H), 7.5 (s, 1H, Pyrazole), 6.3(s, 1H,Tetrazole).

A_{14}: IR (cm^{-1}): 3436(N-H Str.), 3110(Ar.C-H Str.), 1671(CO Str.), 1593(C=N Str.), 1121(N-N-C Str.), 829(C-H def.), 723(C-Cl Str.).

A_{15}: IR (cm^{-1}): 3009 (Ar.C-H Str.), 1649(C-O Str.), 1452(C=N Str.), 1298(C-H Str.), 1106(N-N-C Str.), 833(C-H def.); **^{1}H NMR (δ ppm):** 8.8(m, 4H, Pyridine), 7-7.5(m, 4H, Ar-H), 2.5 (s, 1H, Pyrazole), 3.8(s 1H, CH_3).

A_{16}: IR (cm^{-1}): 3184 (Ar.C-H Str.), 1646(C-O Str.), 1541(C=N Str.), 1176(N-N-C Str.), 832(C-H def.); **^{1}H NMR (δ ppm):** 12.0(s, 1 H, COOH), 11.8(s, 1H, Ar-H), 7-7.5(m, 7H, Ar-H), 8.9(s, 1H, Pyridine), 3.8(s 1H, CH_3), 2.5 (s, 1H, Pyrazole); m/z-**449.2** (Mol wt.444.45 Calcd.).

A_{17}: IR (cm^{-1}): 2931 (Ar.C-H Str.), 2773(C-H Str.), 1644(C-O Str.), 1158(N-N-C Str.), 913(C-H def.), 752(C-F Str.); m/z - **434.58** (Mol wt.436.88 Calcd.).

A_{18}: IR (cm^{-1}): 2920 (Ar.C-H Str.), 2990(C-H Str.), 1596(C-O Str.), 1508(-C=N Str.), 1118(N-N-C Str.), 832(C-H def.); **^{1}H NMR (δ ppm):** 7.7-7.9(m, 4H, Pyridyl), 7.2-7.6(m, 8H, Ar.-H), 7.1(s, 1H, CH), 3.7(s, 3H, CH_3), 2.8(s, 1H, Pyrazole).
A_{19}: IR (cm^{-1}): 3430(N-H Str.), 3183 (Ar.C-H Str.), 1649(C-O Str.), 1507(C=N Str.), 1153(N-N-C Str.),832(C-H def.); m/z - **466.5** (Mol wt 463.52 Calcd.).
A_{20}: IR (cm^{-1}): 3430 (Ar.C-H Str.) ,3183(C-O Str.), 1649(C=N Str.), 507(N-N-C Str.), 153(C-H def.), 832(C-Cl Str.); **^{1}H NMR (δ ppm):** 7.7-7.9(m, 4H, Pyridyl), 7.2-7.6(m, 4H, Ar.-H), 7.1(s, 1H, CH), 6.9(s, 3H, NH), 3.9(CH_3),2.8(s, 1H, Pyrazole).
A_{21}: IR (cm^{-1}): 3430 (Ar.C-H Str.), 3183(C-O Str.), 1649(C=N Str.), 1507(N-N-C Str.), 153(C-H def.), 832(C-Cl Str.).

CONCLUSION

In the present scheme we have synthesized 21 new pyrazole derivatives by using Vilsmeirs haak reaction. The structures of the synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis. These compounds were screened for antitubercular, antibacterial and antifungal activities by the standard procedure against standard drugs as reference. Some of these compounds have given promising antitubercular and antimicrobial activities. With suitable molecular modifications of these compounds we can predict promising bioactive molecules in future.

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