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Synthesis and Pharmacological Activity of Some Schiff Bases Derived from Substituted 1,2,4-Triazoles

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A new series of Schiff bases of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles have been synthesized. Structures of these Schiff bases have been confirmed by analytical and spectral data and they have been screened for antibacterial, antifungal and anti-inflammatory activity.

Key Words: Synthesis, Pharmacological activity, Schiff bases, Substituted 1,2,4-triazoles.

INTRODUCTION

Schiff bases possess various pharmacological activities such as antibacterial[1–3], antifungal[1, 2], antiinflammatory[4], antipyretic[5], antitumor[6–8] and stearase inhibitory activity[9]. Various 1,2,4-triazoles have been reported for their analgesic, carsinostatic[8], antibacterial[10–13], antihypertensive[14], antifungal[10–13] and anti-inflammatory[15, 16] activity.

By considering the above factors it was thought to synthesize Schiff bases of 3-aryloxy-4-amino-5-mercapto-1,2,4-triazoles with furfural, nitrofurfural and 4-dimethylamino benzaldehyde.

Phenol was treated with ethylchloroacetate to give ethylaryloxy acetate (**a**), which on hydrazanolysis gave aryloxyacetylhydrazine (**b**). This compound was converted to corresponding dithiocarbazinate (**c**). Cyclization of **c** in presence of hydrazine hydrate resulted in 3-aryloxy-4-amino-5-mercapto-1,2,4-triazole. The title compounds were synthesized by condensing the above triazoles with various aldehyde.

TABLE-1

Compound	Ar-	—R
1	*p*-Cl-*m*-Cresol	4-dimethylamino benzyl
2	*p*-Cl-*m*-Cresol	furyl
3	*p*-Cl-*m*-Cresol	nitrofuryl
4*	*m*-Cresol	furyl
5^{+}	*m*-Cresol	4-dimethylamino benzyl
6$^{\#}$	*m*-Cresol	nitrofuryl
7	α-Naphthol	4-dimethylamino benzyl
8	α-Naphthol	furyl
9	α-Naphthol	nitrofuryl

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EXPERIMENTAL

Melting points of the newly synthesized compounds was determined by open capillary method and are uncorrected. The ^{1}H NMR spectrum was recorded on Bruker DRX 300 using deuteriated methanol as solvent. The IR spectrum was recorded on Shimadzu 8201 PC. The FAB mass spectrum was recorded on JEOL SX 102/DA-6000 mass spectrometer using Ar/Xe as FAB gas. All compounds were analyzed for C, H and N.

Ethyl Aryloxy Acetate

A mixture of substituted phenol (0.2 mol), ethylchloroacetate (2.5 g, 0.2 mol) and anhydrous potassium carbonate (41.5 g, 0.3 mol) in dry acetone (300 mL) was refluxed on a water bath for 16 h. The reaction mixture was cooled and filtered. From the filtrate excess of acetone was removed by distillation. The reaction mixture was poured into ice-cold water and stirred well. The organic layer was extracted with ether and the ether layer was washed with water and dried over anhydrous sodium sulphate. Ether was removed and the resulting liquid was collected. It was distilled under reduced pressure to give pure ethylaryloxy acetate.

Aryloxyacetyl hydrazine

A mixture of ethylaryloxyacetate (0.1 mol) and hydrazine hydrate (90%, 7.5 mL, 0.15 mol) in ethanol was heated on a water bath for 6 h. Excess of ethanol was removed by distillation. On cooling, aryloxyacetyl hydrazine began to separate. It was collected by filtration and recrystallized from ethanol.

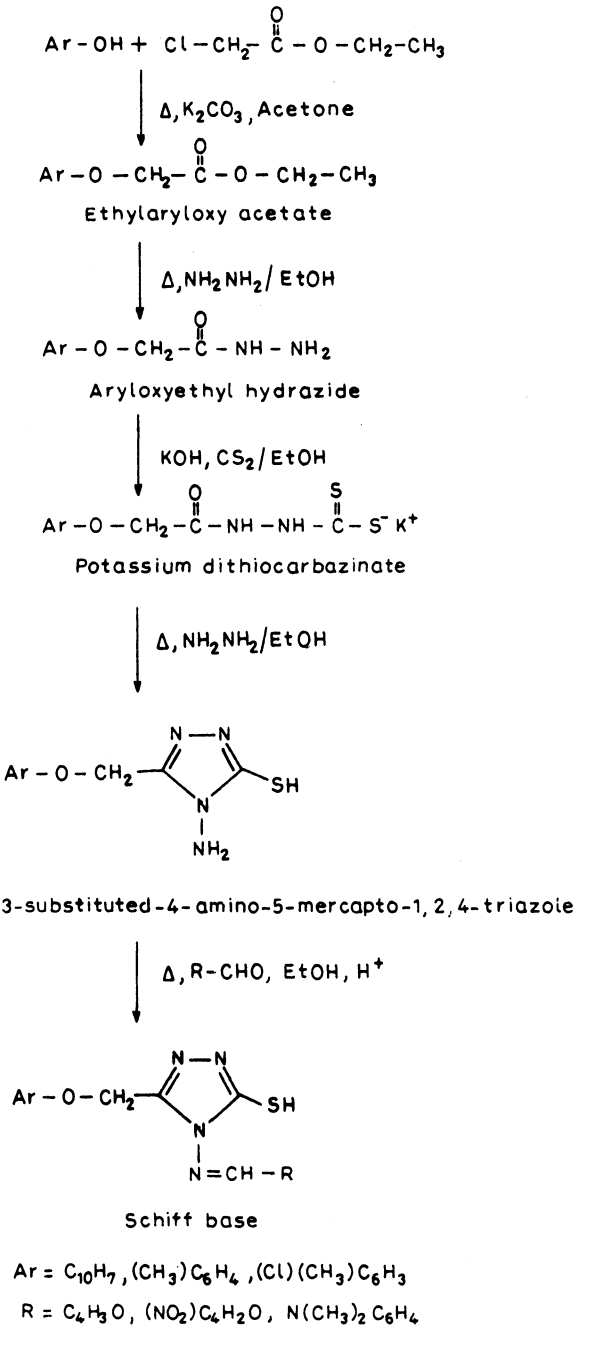
Potassium dithiocarbazinate

Aryloxyacetyl hydrazine (0.1 mol) was added slowly to a solution of potassium hydroxide (8.4 g 0.15 mol) in ethanol. The resulting mixture was stirred well till a clear solution was obtained. Carbon disulphide (11.4 g, 0.15 mol) was added dropwise to it and the contents were stirred vigorously. The temperature was not allowed to rise above 30°C. A solid mass began to separate immediately. It was further stirred for 24 h at room temperature. The resulting mixture was diluted with ether (100 mL) and the precipitate formed was collected by filtration, washed with dry ether and dried at 65°C under vacuum, the salt obtained by this procedure was used in the next reaction without further purification.

3-Aryloxy-4-amino-5-mercapto-1,2,4-triazoles

A mixture containing potassium dithiocarbazinate (0.1 mol), hydrazine hydrate (99%, 0.2 mol) and water (2 mL) was gently heated so that it starts boiling in about 30 min. Heating was continued until evolution of hydrogen sulphide ceased. The reaction mixture was cooled to room temperature and diluted with water (100 mL) and acidified with dil. hydrochloric acid. The solid mass that separated was collected by filtration, washed with water and dried. It was recrystallized from ethanol.

Scheme



Ar = $C_{10}H_7$, $(CH_3)C_6H_4$, $(Cl)(CH_3)C_6H_3$

R = C_4H_3O, $(NO_2)C_4H_2O$, $N(CH_3)_2C_6H_4$

Schiff bases

The triazole (0.01 mol) and aldehyde (0.02 mol) were dissolved separately in ethanol and mixed together. One drop of concentrated sulfuric acid was added and the reaction mixture was refluxed for about 6 h. After cooling the reaction mixture was poured into ice-cold water. The solid mass was filtered and dried. Recrystallisation was done from ethanol. The physical data is shown in Table-2.

TABLE-2

Sample code	m.f.	m. w.	m.p. (°C)	Yield (%)	% Elemental Analysis Cal. (Obs.)		
					C	H	N
1	$C_{19}H_{20}N_5OSCl$	417.7	248 ± 2	68	56.72 (56.47)	4.97 (4.87)	18.77 (18.31)
2	$C_{15}H_{13}N_4OSCl$	348.7	160 ± 2	64	51.60 (51.42)	3.72 (3.60)	16.05 (16.47)
3	$C_{15}H_{12}N_5O_2SCl$	393.7	129 ± 2	72	45.70 (45.23)	3.14 (3.13)	17.78 (17.54)
4*	$C_{15}H_{14}N_4O_2S$	314	125 ± 2	79	57.32 (57.66)	4.45 (4.66)	17.31 (17.20)
5+	$C_{19}H_{21}N_5OS$	367	163 ± 2	70	63.52 (63.60)	6.12 (6.08)	18.06 (18.09)
6#	$C_{15}H_{13}N_5O_4S$	359	170 ± 2	75	51.13 (51.20)	5.02 (5.09)	19.98 (20.01)
7	$C_{22}H_{21}N_5OS$	403	137 ± 2	68	65.50 (65.50)	5.31 (6.15)	17.36 (17.23)
8	$C_{18}H_{14}N_4O_2S$	350	121 ± 2	70	61.70 (60.17)	4.00 (4.47)	16.13 (15.93)
9	$C_{18}H_{13}N_5O_4S$	395	165 ± 2	76	73.22 (73.10)	3.29 (2.94)	17.72 (17.65)

Spectral data

*+#IR: 1596–1618 ν(C=N), 2920–2927 ν(C—H), 3105–3159 ν(N—H), 1020–1027 ν(C=S).

*IR: 1606.5 ν(C=N).

m/z: 314, 220, 121, 107.

^{1}H NMR: δ 2.26 (s, 3H, CH_3), 5.15 (s, OCH_2), 6.8 (d, 2H, *ortho*-protons of *p*-toyl), 7.039 (d, 2H, *meta*-protons of *p*-tolyl), 10.05 (s, 1H, N=CH), 6.65 (quartlet, H, furan-4H proton), 7.13 (d, H, furyl-2H proton), 7.79 (d, H, furyl-5H proton).

+IR: 1596.5 ν(C=N).

m/z: 367, 220, 147, 121, 107.

^{1}H NMR: δ 2.234 (s, 3H, CH_3), 3.05 (s, 6H, $N(CH_3)_2$), 5.126 (s, 2H, OCH_2), 7.65 (d, 2H, *ortho*-proton of 4-dimethylamino phenyl), 7.025 (d, 2H, and *ortho*-protons of *p*-tolyl), 8.84 (d, 2H, *meta*-protons of *p*-tolyl), 6.76 (d, 2H, meta-protons of 4-dimethylamino phenyl), 9.607 (s, 1H, N=CH).

#IR: 1617 ν(C=N).

m/z: 359, 220, 139, 121, 107

^{1}H NMR: δ 2.25 (s, 3H, CH_3), 5.09 (S, 2H, OCH_2), 6.90 (d, 2H, *ortho*-protons of *p*-tolyl), 7.102 (d, 2H, metaprotons of *p*-tolyl), 7.22 (d, H, nitrofuryl-4H proton), 7.53 (d, H, nitrofuryl-3H proton).

Antibacterial activity: Antibacterial activities of the synthesized compound have been summarized in Table-3. The compounds were screened against *S. aureus, B. subtilis, E. coli* and *P. aeuroginosa* using modified Kirby-Bauer method. The compounds were tested at 50 μg level. The result was compared with amoxicillin (10 μg/disk). All compounds showed moderate to good antibacterial activity.

TABLE-3
ZONE OF INHIBITION OF COMPOUNDS 1 TO 9 FOR ANTIBACTERIAL ACTIVITY

Sl. No.	Compound	Diameter of zone of inhibition (mm)			
		P. aeruginosa	*E. coli*	*S. aureus*	*B. subtilis*
1.	**1**	—	12	8	10
2.	**2**	7	14	9	7
3.	**3**	11	19	20	16
4.	**4**	10	9	9	7
5.	**5**	—	16	7	12
6.	**6**	8	22	10	16
7.	**7**	10	8	—	—
8.	**8**	—	8	—	—
9.	**9**	11	21	18	21
10.	Amoxicillin	9	11	14	12
11.	DMSO	—	—	—	—

Antifungal activity: The synthesized compounds were evaluated at 50 μg level for their activity against *Candida albicans* and *Aspergillus niger* using modified Kirby-Bauer method. The result is as shown in Table-4. All the compounds showed moderate to good antifungal activity.

TABLE-4
ZONE OF INHIBITION OF COMPOUNDS 1 TO 9 FOR ANTIFUNGAL ACTIVITY

Sl. No.	Compound	Diameter of zone of inhibition	
		C. albicans	*A. niger*
1.	**1**	7	10
2.	**2**	9	7
3.	**3**	15	14
4.	**4**	10	8
5.	**5**	8	9
6.	**6**	20	12
7.	**7**	—	—
8.	**8**	7	9
9.	**9**	18	12
10.	Griseofulvin	13	16
11.	DMSO	—	—

Anti-inflammatory activity

Winter's hind paw method was used in the present study for the evaluation of anti-inflammatory activity. The compounds were tested at a concentration of 20 mg/kg body weight. Ibuprofen (20 mg/kg body weight) was used as the standard drug. The results are recorded in Table-5. All the compounds, except **4** and **7**, showed moderate anti-inflammatory activity.

TABLE-5
ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS

Sl. No.	Compound	Edema produced after 180 ± SE	Edema inhibited (%)
1.	Control (Acacia mucilage)	0.365 ± 0.015	
2.	Ibuprofen (standard)	0.130 ± 0.020	64.38
3.	**1**	0.310 ± 0.020	15.06
4.	**2**	0.285 ± 0.015	21.91
5.	**3**	0.265 ± 0.024	27.39
6.	**4**	0.335 ± 0.015	8.22
7.	**5**	0.300 ± 0.010	17.81
8.	**6**	0.250 ± 0.010	31.50
9.	**7**	0.210 ± 0.030	42.46
10.	**8**	0.260 ± 0.020	28.77
11.	**9**	0.360 ± 0.010	1.37

Conclusion

The Schiff bases of various 3-(aryloxymethyl)-4-amino-5-mercapto-1,2,4-triazoles with different aldehyde (furfural, nitrofurfural, 4-dimethyl aminobenzaldehyde) were synthesized with object of enhancing biological activity. The structures of these compounds were confirmed by IR, ^{1}H NMR, FAB MASS and elemental analysis.

The synthesized compounds showed remarkable antibacterial and antifungal activity and moderate anti-inflammatory activity. The nitrofuryl derivatives **(3, 6, 9)** showed very good antimicrobial activity. Compound **7** showed good anti-inflammatory activity.

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