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Synthesis and Studies of 1-[2-(Aryl Amino-2-Oxo Ethyl) Amino]-4-(N-Methyl Piperazino)-Benzene Derivatives

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Abstract 1-[2-(Aryl Amino-2-Oxo Ethyl) Amino]-4-(N-Methyl Piperazino)-Benzene Derivatives were synthesized. The synthesized compounds were screened for their antibacterial activities against *S.aures* and *E.coli* by cup plat method. From screening result some compounds found highly active against both Gram-positive and Gram-negative bacteria while other compounds possess feeble to moderate activity.

Key words: Synthesis and antibacterial activity, piperazine,

Introduction

The reaction of N-Chloro acetyl aryl amines with N- [4-Amino Phenyl] –N-methyl piperazine gives the 1-[2-(Aryl amino–2–oxo ethyl) amino]-4-(N-methyl piperazino)-benzenes.

Piperazine belongs to the family of medicines called anthelmintics. Anthelmintics are used in the treatment of worm infections. Piperazine derivatives have also been shown to possess diverse biological properties including antihistamine, anti kationic, anticonvulsant, anti HIV¹ and as potential cocaine-abuse therapeutic agent²⁻³. The two nitrogens of the piperazine molecules are present in rigid conformation structures, which probably favors their involvement to the dopamine receptors.

A large number of antibiotics contain amide linkage. Several derivatives of amides were prepared and found to possess antimicrobial activities. Literature survey reveals that various drugs e.g. penicillin⁴ (antibacterial), Pyrazinamide⁵ (anti tubercular), Indinavir⁶, Ritonavir⁷ etc. (protease inhibitors as anti AIDS) contains their particular activities due to the amide linkage present in their structures.

Considering these findings, we thought to synthesize the amide derivatives of different amines⁸⁻⁹.

(I)

The above amide derivatives of amines condensed with N-[4-Amino phenyl]-N-methyl piperazine gave 1-[2-(Aryl amino-2-oxo ethyl) amino]-4-(N-methyl piperazino)-benzenes(II).

(II)

Scheme

Step -I

Step-II

Step-III

Step-IV **Experimental***Step-1 Preparation of N-[4-nitrophenyl]-N-methyl piperazine.*

A mixture of N-methyl piperazine (0.01mole), 4-chloro nitro benzene (0.01mole) and anhydrous K_2CO_3 in methanol was refluxed with stirring. After the completion of reaction the resultant mixture was cooled to room temperature. Then it was poured into ice-cold water with constant stirring. The solid separated was purified by recrystallisation. M.P. 220-222°C.

Step-2 Preparation of N-[4-aminophenyl]-N-methyl piperazine.

A mixture of N-[4-nitrophenyl]-N-methyl piperazine (0.01mole), iron dust (0.01mole), HCl (0.01 mole) and water (2 ml) was refluxed with stirring. After the completion of reaction it was filtered, washed with water and neutralized with Na_2CO_3 . The solid separated was purified by recrystallisation. M.P. 65-69°C.

Step-3 Preparation of N-Chloro acetyl aryl amines.

In benzene (30.00ml) chloro acetyl chloride (0.03M, 2.4ml.) was added and the mixture was stirred in water bath. The solution of aryl amines (0.02M) in benzene (30.0 ml) was added drop wise and refluxed for 2 hours. Then cooled the reaction mixture. The resulting white precipitates were filtered by recrystallisation from alcohol. Physical data of N-Chloro acetyl aryl amines are given in **Table 1**.

Step-4 Preparation of 1-[2-(Aryl amino-2-oxo ethyl) amino]-4-(N-methyl piperazino)-benzene.

A mixture of N-Chloro acetyl aryl amine (0.01M), N-[4-Amino phenyl]-N-methyl piperazine (0.01M, 1.91 gm.) and anhydrous K_2CO_3 were refluxed in acetone. After the completion of reaction the resulting mixture was cooled to room temperature. Then it was poured in to ice cold water with constant stirring. The solid separated was purified by recrystallisation from ethanol. Physical and analytical data of title compound and its other substituted derivatives are given in **Table-2**.

Table 1. Physical and analytical data of n-chloroacetyl aryl amines

No.	R	M.F.	M.W.	M.P. ^o C	%Analysis Calc. (found)		
					C	H	N
1	H	C ₈ H ₈ NOCl	169.5	80	56.64 (56.63)	4.72 (4.68)	8.26 (8.24)
2	2-Cl	C ₈ H ₇ NOCl ₂	204.0	68	47.05 (47.04)	3.43 (3.39)	6.83 (6.71)
3	3-Cl	C ₈ H ₇ NOCl ₂	204.0	87	47.05 (47.04)	3.43 (3.40)	6.83 (6.73)
4	4-Cl	C ₈ H ₇ NOCl ₂	204.0	150	47.05 (47.04)	3.43 (3.40)	6.83 (6.70)
5	2-NO ₂	C ₈ H ₇ N ₂ O ₃ Cl	214.5	91	44.76 (44.68)	3.26 (3.22)	13.05 (13.04)
6	3-NO ₂	C ₈ H ₇ N ₂ O ₃ Cl	214.5	90	44.76 (44.70)	3.26 (3.24)	13.05 (13.02)
7	4-NO ₂	C ₈ H ₇ N ₂ O ₃ Cl	214.5	118	44.76 (44.71)	3.26 (3.22)	13.05 (13.04)
8	2-CH ₃	C ₉ H ₁₀ NOCl	183.5	87	58.85 (58.81)	5.45 (5.40)	7.63 (7.50)
9	3-CH ₃	C ₉ H ₁₀ NOCl	183.5	85	58.85 (58.83)	5.45 (5.40)	7.63 (7.53)
10	4-CH ₃	C ₉ H ₁₀ NOCl	183.5	130	58.85 (58.80)	5.45 (5.38)	7.63 (7.52)

Table-2. Physical, analytical data and antibacterial activity of 1-[2-(Aryl amino-2-oxo ethyl) amino]-4-(N-methyl piperazino)-benzene.

No.	R	M.F.	M.W.	M.P	Yield %	C%		H%		N%	
						Req.	Found	Req.	Found	Req.	Found
1	H	C ₁₉ H ₂₄ N ₄ O	324	170	64	70.37	70.35	7.40	7.38	17.28	17.26
2	2-Cl	C ₁₉ H ₂₃ N ₄ OCl	358.5	192	70	63.59	63.56	6.41	6.38	15.62	15.58
3	3-Cl	C ₁₉ H ₂₃ N ₄ OCl	358.5	169	72	63.59	63.54	6.41	6.36	15.62	15.60
4	4-Cl	C ₁₉ H ₂₃ N ₄ OCl	358.5	181	75	63.59	63.47	6.41	6.34	15.62	15.56
5	2-NO ₂	C ₁₉ H ₂₃ N ₅ O ₃	369	152	60	61.78	61.74	6.23	6.21	18.97	18.92
6	3-NO ₂	C ₁₉ H ₂₃ N ₅ O ₃	369	165	69	61.78	61.70	6.23	6.20	18.97	18.90
7	4-NO ₂	C ₁₉ H ₂₃ N ₅ O ₃	369	194	65	61.78	61.76	6.23	6.18	18.97	18.89
8	2-CH ₃	C ₂₀ H ₂₆ N ₄ O	338	317	60	71.00	70.95	7.69	7.65	16.56	16.53
9	3-CH ₃	C ₂₀ H ₂₆ N ₄ O	338	330	64	71.00	70.80	7.69	7.60	16.56	16.50
10	4-CH ₃	C ₂₀ H ₂₆ N ₄ O	338	341	68	71.00	70.82	7.69	7.55	16.56	16.42

Spectral Data

NMR spectra: δ (CDCl_3)

2.34 (3H, s, $-\text{CH}_3$)
 2.41 (2H, s, $-\text{CH}_2$, f)
 2.98 (8H, bs, $-(\text{CH}_2\text{CH}_2)_2\text{N}-$, a,b,c,d)
 6.68 to 7.32 (4H, m, Ar H at h)
 7.64 (2H, d, Ar H at i, k)
 7.76 (2H, s, Ar H at j, l)
 9.8 (1H, s, $>\text{NH}$, g)
 10.24 (1H, s, $>\text{NH}$, e)

IR Spectra:

IR Spectra shows (C-N Stretching in piperazine) at about 1615 cm^{-1} , ($-\text{NH}$ stretching in aromatic amine) 3215 cm^{-1} , (C=O stretching in aryl ketone) 1676 cm^{-1} , (CH_2 active methyl group) 1486 cm^{-1} (C-H [asym] deformation in methyl group at 1490 cm^{-1})

Results and Discussion

The entire synthesised compounds were screened for their antibacterial activities against *S.aures* and *E.coli* by cup plat method. Tetracycline and Chloramphenicol were used as standard drugs. The compounds were tested at the concentration of $40\text{ }\mu\text{g/ml}$ and DMF as a solvent.

From screening result it was observed that the compounds 2,4,6,7,10 found highly active against both Gram-positive and Gram-negative bacteria while other compounds possess feeble to moderate activity. Compounds 2,4,10 showed maximum zone of inhibition respectively (12,12,13) for *E.coli* while compounds 1,2 showed maximum zone of inhibition respectively (12,12) for *S.aures* as well as compound 6,8 showed maximum zone of inhibitions (11,11) for *S.typhi* respectively.

Table-3. Antibacterial activity of newly synthesized compounds

Comp. No.	Zone of inhibition in mm at 40 µg/ml conc.				
	E. coli	S. aureus	S. typhi	B.subtilis	
1	-	12	10	-	
2	12	12	09	09	
3	08	-	-	-	
4	12	08	08	09	
5	08	06	09	09	
6	10	10	11	10	
7	10	11	09	10	
8	-	-	11	07	
9	08	09	-	-	
10	13	11	10	09	
Standard Drugs					
Tetracycline		15	19	24	21
Chloramphenicol		18	25	24	20

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