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SYNTHESIS, SPECTRAL STUDY, ANTIMICROBIAL SCREENING OF NEWLY SYNTHESISED AMIDES AND PIPERAZINES MOLECULES

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ABSTRACT

A new series of compounds, namely N-arylamino-5-chloropentanamides (3a-3j) and 1-{4'-[4''-(N-aryl amidopentoxy) phenyl] piperazin-1'-yl}-ethanones (5a-5j), were synthesized. The chemical structures of compounds were confirmed by ^{1}H-NMR, IR, Mass spectral analysis. The compounds **(3a-3j)** and **(5a-5j)** have been evaluated their antimicrobial activity.

KEYWORDS: 5-Chloro-arylamide, Piperazine derivatives, antimicrobial activity (Heterocyclic compounds).

INTRODUCTION

Piperazine contains two nitrogen atom in a six-membered ring which gives polar surface area for their reactivity.[1] Piperazine has a structure that is important for CNS active agent.[2] It is an important class of heterocyclic compounds that found various biological activity,[3] such as Antibacterial,[4] Anti-fungal,[5] Anti –tumor,[6] Anthelmintic,[7] Anti -cancer,[8] Anti-hypertensive,[9] activities. 5-chloropentanoyl chloride reaction with arylamide to form amide derivatives. Which has agriculture and pharmaceutical importance. Amide derivatives have a central carbon atom attached to nitrogen and doble bond with oxygen, the loin pair electron of nitrogen delocalized with carbonyl group stabilized the structure of amide.[10] Carboxamides are widely used in mediational purposes because of their biological

activity such has Anti-inflammatory,[11] Anti-hypertensive,[12] Anti-HIV,[13] Anti-oxidant,[14] Anti-convulsant,[15] Analgesic,[16] activities.

Our research work focus on synthesis of piperazine derivative **(5a-5j)** from 5-chloropentanoyl chloride which has many biological activities and various application in industrial and agriculture use. In our study, we have dedicated our efforts to synthesized amide derivative **(3a-3j)**. Subsequently to evaluated the antimicrobial activity of newly synthesized compounds and compared with standard drugs using the cup-plate method.[17]

MATERIALS AND METHOD

The synthesis process utilized analytical grade (AR) chemicals source from SRL and finar companies, which were employed without any additional purification. All reactions took place under specified conditions. The purity of the synthesized compounds was assessed using TLC with silica gel G (Merk) and the solvent system ethyl acetate:hexane (2:3). The TLC plates were visualized under UV at 260nm. Characterization of the compounds was performed through spectral analysis, including MS (Mass Spectrometry), IR, and ^{1}H-NMR. Mass spectra were recorded using a water Mass spectrometer. Infrared spectroscopy was conducted using KBr on a Shimadzu IR Affinity FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker 400MHz spectrometer in DMSO solvent with TMS as an internal standard. Melting points of the synthesized compounds were determined in open glass capillary tubes and are uncorrected. The antimicrobial activities, of the synthesized compounds **(3a-3j), (5a-5j)** have been taken by the Cup plate method, with known standard drugs utilized for comparison.

General method preparation: 5-chloro-N-(3’-nitrophenyl)pentanamide. (3a)

To a solution containing 5-chloropentanoyl chloride (0.01 m) in acetone, an appropriate 3-nitro aniline (0.01 m) was added. The resulting reaction mixture was stirred at room temperature for 24 hrs. The reaction is monitored by (TLC). After completion of the reaction, the reaction mixture was poured into crushed ice, and filtered, dry it. The obtained product was crystalized in methanol, leading to the formation of the desired compounds (3a). M.P. :150^{0}C; % of Yield :87%.^{1}H NMR (400 MHz, DMSO) δ 10.41 (s, 1H), 8.64 (s, 1H), 7.91 – 7.88 (dd, 2H), 7.59 (t, J = 8.2 Hz, 1H), 3.67 (t, J = 6.0 Hz, 2H), 2.40 (t, J = 6.8 Hz, 2H), 1.77 – 1.72 (m, 4H). IR (cm-) 3082 (C-H Str. Aromatic), 2873-2845 (C-H Str. Alkane), 1456-1313(C-H def. Alkane), 1593(C=C Str. Aromatic), 1296(C-H Def. Aromatic), 1670(C=O Str. Amide), 3315(N-H Str. Amide), 1481(NO2 Str.), 592(C-Cl Str.). MS: at m/z = 256, Anal.

Calcd. for $C_{11}H_{13}ClN_2O_3$ C:51.47,H:5.11,O:18.70,N:10.91.Found C:51.45, H:5.08, O:18.66, N:10.85.

Similarly other **(3a-3j)** compounds have been synthesized.

Reaction scheme: 1

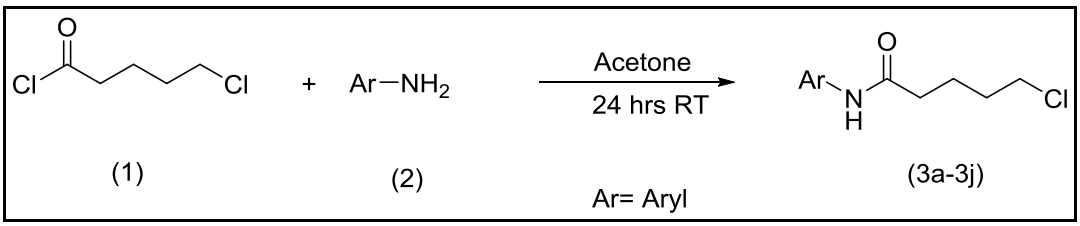

Table 1: Physical and analytical data of N-arylamino-5-chloropentanamides. (3a-3j).

Sr.no	-Ar	M.F	M.W	M.P	%Yield	% of Nitrogen	
						Calcd.	Found
3a	3-NO_2-C_6H_4-	$C_{11}H_{13}ClN_2O_3$	256	150	87	10.91	10.85
3b	4-OCH_3-C_6H_4-	$C_{12}H_{16}ClNO_2$	241	145	90	5.79	5.70
3c	2-NO_2-C_6H_4-	$C_{11}H_{13}ClN_2O_3$	256	130	83	10.91	10.87
3d	4-Cl-C_6H_4-	$C_{11}H_{13}Cl_2NO$	245	160	92	6.65	6.63
3e	4-CH_3-C_6H_4-	$C_{12}H_{16}ClNO$	225	125	88	6.21	6.14
3f	2CH_3-5-NO_2-C_6H_3-	$C_{12}H_{15}ClN_2O_3$	270	170	78	10.35	10.21
3g	4-NO_2-C_6H_4-	$C_{11}H_{13}ClN_2O_3$	256	140	85	10.91	10.78
3h	4-OH-C_6H_4-	$C_{11}H_{14}ClNO_2$	227	100	74	6.15	6.00
3i	4-Br-C_6H_4-	$C_{11}H_{13}BrClNO$	290	155	70	4.82	4.78
3j	3-Br-C_6H_4-	$C_{11}H_{13}BrClNO$	290	167	67	4.82	4.80

General method preparation: 1-{4'-[4''-(N-(3'''-nitrophenyl)amidopentoxy)phenyl] piperazin-1'-yl}-ethanone: (5a)

A solution containing 5-chloro-N-(3'-nitrophenyl)pentanamide (1a) (0.01 mmol) in DMF was mixed with 1-(4'-(4''-hydroxyphenyl)piperazin-1-yl)ethanone (0.01 mmol) and add Anhyd.K_2CO_3 (0.05 mmol). The resulting reaction mixture was refluxed at 150°C for 4 hrs. The progress of the reaction was tracked using TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, filtered, dry it. The obtained product was crystalized in methanol, leading to the formation of the desired compound (5a). M.P. : 160^0C; % Yield : 88%. ^{1}HNMR (400 MHz, DMSO) δ 8.21– 8.08 (m, 4H), 7.79 – 7.65 (m, 4H), 3.71-3.68 (t, J = 5.5 Hz, 4H), 3.55 (t, J = 4.4 Hz, 2H), 2.94-2.87 (t, J = 25.8 Hz, 2H), 2.44 (t, J = 6.3 Hz, 4H), 1.88 – 1.85 (m, 7H). IR (cm-) 3064 (C-H Str. Aromatic), 2922-2864 (C-H Str. Alkane), 1462-1328(C-H def. Alkane), 1523(C=C Str. Aromatic), 1282(C-H Def. Aromatic), 1631(C=O Str.), 1612(C=O Str. Amide), 1246(C-O-C Str.), 1481(NO2 Str.), 3525(N-H Str.

Amide). MS: at m/z = 440. Anal.Calcd. for $C_{23}H_{28}N_4O_5$ C:62.71,H: 6.41,N:12.72,O:18.16 Found C:62.69,H:6.38,N:12.70,O:18.12.

Similarly other **(5a-5j)** compounds have been synthesized.

Reaction scheme: 2

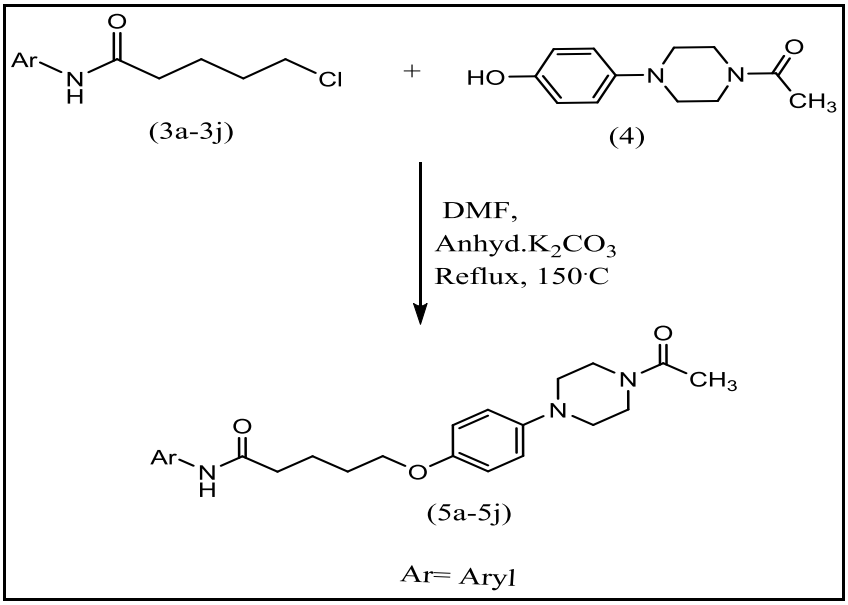

Table 2: physical and analytical data of 1-{4'-[4"-(N-aryl amidopentoxy) phenyl]piperazin-1'-yl}-ethanones. (5a-5j).

Sr.no	-Ar	M.F	M.W	M.P	%Yield	% of Nitrogen	
						Calcd.	Found
5a	3-NO_2-C_6H_4-	$C_{23}H_{28}N_4O_5$	440	160	88	12.72	12.70
5b	4-OCH_3-C_6H_4-	$C_{24}H_{31}N_3O_4$	425	140	92	9.88	9.85
5c	2-NO_2-C_6H_4-	$C_{23}H_{28}N_4O_5$	440	120	83	12.72	12.68
5d	4-Cl-C_6H_4-	$C23H_{28}ClN_3O_5$	429	150	94	9.77	9.75
5e	4-CH_3-C_6H_4-	$C_{23}H_{28}N_4O_5$	409	128	89	10.26	10.23
5f	2-Me-5-NO_2-C_6H_3-	$C_{24}H_{30}N_4O_5$	454	177	78	12.33	12.30
5g	4-NO_2-C_6H_4-	$C_{23}H_{28}N_4O_5$	440	153	85	12.72	12.71
5h	4-OH-C_6H_4-	$C_{23}H_{29}N_3O_4$	411	125	75	10.21	10.19
5i	4-Br-C_6H_4-	$C_{23}H_{28}BrN_3O_3$	473	145	71	8.86	8.81
5j	3-Br-C_6H_4-	$C_{23}H_{28}BrN_3O_3$	473	170	68	8.86	8.83

RESULT AND DISCUSSION

Antimicrobial activity

The antibacterial and antifungal activity is done by the cup plate method through zone of inhibition in mm. The concentration of the compounds & standard drug are 50 µg/ml using DMSO as solvent. The anti-bacterial activity was taken by Gram-positive bacteria Bacillus Subtilis, Staphylococcus aureus & Gram-negative bacteria proteus vulgaris, Escherichia coli.

The anti-fungal activity was taken by Aspergillus niger fungus. The antimicrobial activity compared with known standard drugs Streptomycin, Ampicillin, Tetracycline and nystatin. The Zone of inhibition was measured in mm. Were Zone of inhibition of compounds **(3a-3j) & (5a-5j)** is shown in the table No. 4 to 6.

Table 4: Antimicrobial activity data of N-aryl amino-5-chloropentanamides. (3a-3j).

Sr. No.	Ar	Antibacterial activity, zone of inhibition in m.m.				Antifungal activity, Zone of inhibition in m.m.
		Gram-positive bacteria		Gram-negative bacteria		
		B. subtilis	*S. aureus*	*E. Coli*	*P. Vulgaris*	*A. niger*
3a	3-NO_2-C_6H_4-	20	20	14	11	10
3b	4-OCH_3-C_6H_4-	23	20	12	10	15
3c	2-NO_2-C_6H_4-	20	19	6	13	12
3d	4-Cl-C_6H_4-	19	20	6	11	10
3e	4-CH_3-C_6H_4-	21	22	5	9	6
3f	2-Me-5-NO_2-C_6H_3-	23	21	5	12	5
3g	4-NO_2-C_6H_4-	20	21	7	10	10
3h	4-OH-C_6H_4-	19	20	11	10	10
3i	4-Br-C_6H_4-	18	21	16	13	13
3j	3-Br-C_6H_4-	19	21	22	12	8

Table 5: Antimicrobial activity data of 1-{4'-[4"-(N-aryl amidopentoxy) phenyl] piperazin-1'-yl}-ethanones. (5a-5j).

Sr. No.	Ar	Antibacterial activity, zone of inhibition in m.m.				Antifungal activity, Zone of inhibition in m.m.
		Gram-positive bacteria		Gram-negative bacteria		
		B. subtilis	*S. aureus*	*E. Coli*	*P. vulgaris*	*A. niger*
5a	3-NO_2-C_6H_4-	20	22	18	11	8
5b	4-OCH_3-C_6H_4-	21	22	18	11	10
5c	2-NO_2-C_6H_4-	23	21	18	16	9
5d	4-Cl-C_6H_4-	22	21	18	15	8
5e	4-CH_3-C_6H_4-	20	22	17	14	10
5f	2-Me-5-NO_2-C_6H_3-	21	21	17	13	9
5g	4-NO_2-C_6H_4-	20	20	7	11	9
5h	4-OH-C_6H_4-	22	20	10	15	10
5i	4-Br-C_6H_4-	22	19	6	13	14
5j	3-Br-C_6H_4-	23	19	7	12	12

Table 6: Compounds (3a-3j) (5a-5j) showing antibacterial & antifungal activity compared with known standard drugs.

Compound No.	Antibacterial activity, zone of inhibition in mm.				Antifungal activity, zone of inhibition in mm.
	Gram-positive bacteria		Gram-negative bacteria		
	B. Subtilis	***S. Aureus***	***E. Coli***	***P. vulgaris***	***A. Niger***
(3a-3j)	3a,3b,3c,3e,3f,3g	3e,3f,3g,3i,3j	3j	3c,3i	3b,3c,3i
(5a-5j)	5b,5c,5d,5f, 5h,5i,5j	5a,5b,5c,5d, 5e,5f	5a,5b,5c,5d	5c,5d,5e,5h	5i,5j
Activity of known standard drugs:					
Drugs	***B. Subtilis***	***S. Aureus***	***E. Coli***	***P. vulgaris***	***A. Niger***
Streptomycin	26	27	28	20	0
Ampicillin	25	26	26	19	0
Tetracycline	25	26	27	19	0
Nystatin	0	-	-	-	22

CONCLUSION

We have synthesized the compounds **(3a-3j)** N-aryl amino-5-chloropentanamides and Piperazine derivatives **(5a-5j)** 1-{4'-[4''-(N-aryl amidopentoxy) phenyl] piperazin-1'-yl}-ethanones from 5-chloropentanoyl. The structure confirmed by ^{1}H-NMR, IR, Mass spectra. the synthesized compounds were subjected to antibacterial & antifungal activities. Compounds **3a,3b,3c,3e,3f,3g,3i,3j** and **5a,5b,5c,5d,5e,5f,5h,5i,5j** exhibited good antibacterial activity against Gram-positive bacteria as compared to known standard drugs and Compounds **3c,3i,3j** and **5a,5b,5c,5d,5e,5h** give moderate activity against Gram-negative bacteria as compared to known standard drugs and Compounds **3b,3c,3i** and **5i,5j** displayed moderate antifungal activity as compared to known standard drugs with the same concentration 50 µg/ml.

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