March 2009 Volume 5 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(1), 2009 [96-99]

Synthesis and biological screening of 4-[(4′-chlorophenyl)(phenyl) methyl]piperazine-1-yl-aroylamino/1-arylsulphonamido/-4″-arylidene-2″-(4‴-methoxyphenyl)-5″-oxo-imidazolines

J.V.Guna, V.N.Patolia, A.U.Patel, D.M.Purohit*

Shree M. and N. Virani science college, Chemistry Department , Kalawad Road, Rajkot-5, Gujrat, (INDIA)

Received: 5th March, 2009 ; Accepted: 10th March, 2009

ABSTRACT

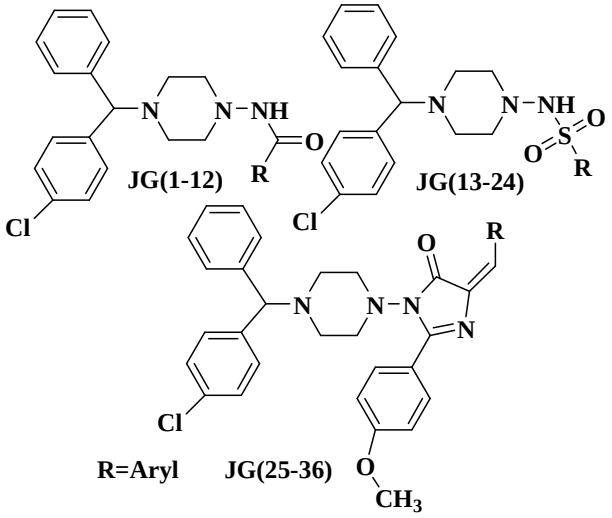
4-[(4'-chlorophenyl)(phenyl) methyl] piperazine-1-yl-aroylamino/aryl sulphonamide/5-oxo-imidazolines have been synthesized. The products have been assayed for their biological activity against Gram +ve, Gram-ve bacteria and fungi. Some of the products showed moderate activity in concentration 50μg/ml. The structures of the products have been elucidated by IR, ^{1}HNMR, Mass spectral data, elemental analysis and thin layer Chromatography.

KEYWORDS

Arylamide;
Sulphonamide;
5-Oxo-imidazoline

INTRODUCTION

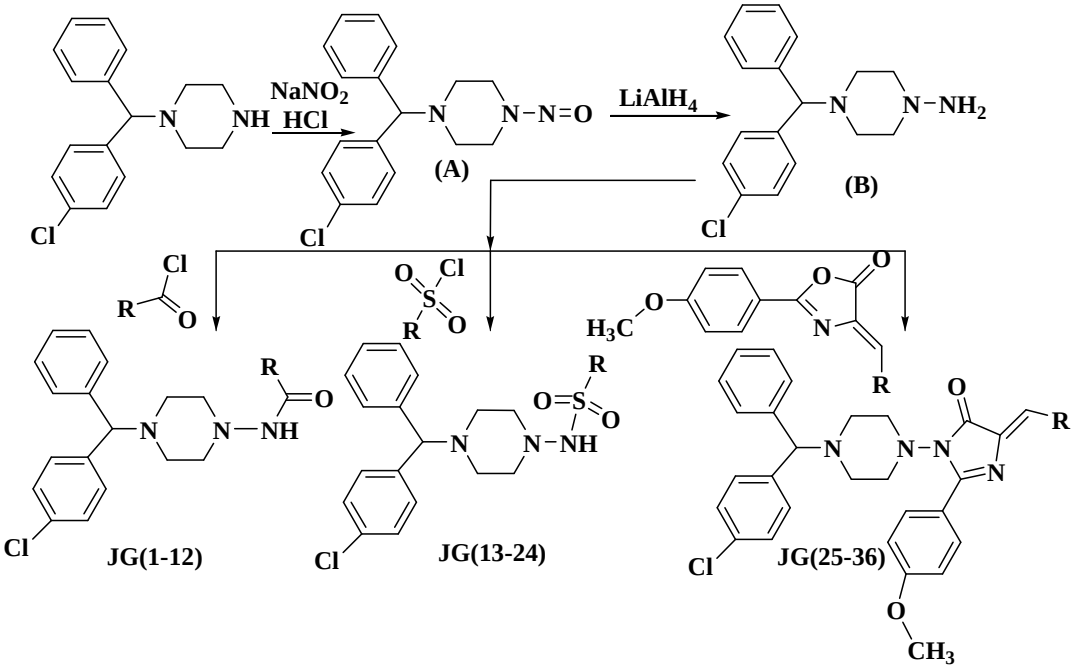
Piperazine derivatives showed a wide variety of biological activities like antimicrobial[1], antiinflammatory[2], insecticidal[3], anthalemintic[4] etc. In view of getting we have synthesized arylamides[5], sulphonamides[6], 5-oxo-imidazoline[7] in piperazine nucleus. More over 4-[(4'-chlorophenyl) (phenyl) methyl] piperazine derivatives are associated with various pharmacological activites. The products arylamide JG (1-12)/Sulphonamide JG (13-24)/5-oxo-imidazoline JG (25-36) have been synthesized and assigned the IR ^{1}HNMR, Mass spectral data, and elemental analysis. The physical data and antimicrobial activities are represented in TABLE 1.



Antimicrobial activity

1-Aroylamino-4-[(4′-Chlorophenyl) (phenyl) methyl]piperazine(JG:1-12)/1-arylsulphonamido-4-[(4′-Chlorophenyl)(phenyl)methyl]Piperazine (JG: 13-24)/N-{4-[(4′-Chlorophenyl) (phenyl) methyl] Piperazine-1-yl}-4″-arylidene-2″-(4‴-methoxy phenyl)-5″-oxo-imidazolines (JG:25-36)products were evaluated in vitro for their antimicrobial activities against *Bacillus Megatarium, Staphylococcus aureus, Escherichia coli , Salmonella typhy ,and Aspergillus niger* using DMF as solvent at 50 μg /ml. concentration by cup plate method[8]. After 24 hrs of incubation at 37^{0}C, the zones of inhibition were measured in mm. The activity was compared with the known antibiotic, viz, Ampicillin, Chloramphenicol, Norfloxacin, Gresiofulvin at same concentration.

All the synthesized compounds (JG: 1-12), (JG: 13-24), (JG: 25-36) showed moderate to good and



SCHEME

remarkable activities with known standard drug at same concentration. The physical data and antimicrobial activities are represented in TABLE 1.

EXPERIMENTAL

All the melting points were measured in open glass capillary method and are uncorrected. I.R. absorption spectra (in cm^{-1}) were recorded on a shimadzu FT-IR 8400-spectrophotometer using KBR pallet and ^1H NMR spectra on BRUKER spectrometer (300 MHz) using TMS as internal standard (chemical shifts in δ ppm) and compounds were routinely checked by TLC using silica gel G.

(A) Synthesis of4-[(4′-chlorophenyl) (phenyl) methyl]-1-nitrosopiperazine(A)

4-[(4′-Chlorophenyl)(Phenyl)methyl]piperazine (8.6 gm,0.03 M) in 50 ml of ice cold water containing 24 ml of diluted HCl is nitrosated with 2.1 gm ,$NaNO_2$ in 10 ml water. The reaction mixture is made alkaline by the addition of NaOH Solution and an oily layer forms. The oily product is separated and crystallized from a mixture of 4.5 ml ethyl acetate-7.0 ml n-heptane. The resultant solid is recystallized from a mixture of 2-propanol and hexane, to give 4-[(4′-chloro phenyl) (phenyl) methyl]-1-nitrosopiperazine m.p.121-123^{0}C

(B) Synthesis of 1-amino-4-[(4′-chlorophenyl) (phenyl) methyl] piperazine(B)

4-[(4′- Chlorophenyl) (Phenyl) methyl]-1-nitroso piperazine (10 gm, 0.03 M) in 140 ml of anhy. ether and 5 ml of benzene is added drop wise to a suspension of 1.9 gm of Lithium aluminium hydride in 140 ml of ether. The reaction mixture is stirred for 1 hrs. at room temperature and then reflux and stirred for 2hrs.The reaction is cooled in an ice bath and excess Lithium aluminum hydride is decomposed by the addition of ethyl acetate. The reaction mixture is hydrolyzed by drop wise addition of 2 ml of water-2ml of 20 % NaOH solution. The inorganic salts are filtered of and washed with ether. The filtrate is dried over sodium sulphate. The solvent is evaporated the residue is dissolved in benzene and the solvent is evaporated once again to give 1-amino-4[(4′-chlorophenyl(phenyl)methyl piperazine. M.P-106-109^{0}C, Yield 55 %.

(C) Synthesis of 4-[(4'-hlorophenyl) (phenyl) methyl]-1-[(4'-methoxyphenyl)-carbamido]pipera zine (JG-7)

A compounds of 1-amino-4 - [(4′-chlorophenyl) (phenyl) methyl] piperazine(3 gm, 0.01M) and 4-methoxy benzoyl chloride (1.07gm, 0.01M) in dry pyridine (20 ml) was refluxed for 8 hrs. The resulting mixture was poured on to crushed ice and neutralized with HCl. The product was filtered, washed with cold water

Full Paper

TABLE 1: The physical data and antimicrobial activity of compounds JG (1-12), JG (13-24), JG (25-36)

Comp.	R	Moleculer formula	M.P ^{0}C	Antimicrobial activity				Antifungl activity	% Of nitrogen	
				B.Mega	*S.aureus*	*E.Coil*	*S.typhi*	*A.niger*	Caled	Found.
JG-1	C_6H_5 -	$C_{24}H_{24}ClN_3O$	172	17	15	14	14	14	10.35	10.28
JG-2	2-CH_3-C6H_4-	$C_{25}H_{26}ClN_3O$	184	14	18	16	12	17	10.01	9.95
JG-3	3-CH_3-C6H_4-	$C_{25}H_{26}ClN_3O$	157	19	12	19	17	17	10.01	9.65
JG-4	4-CH_3-C6H_4-	$C_{25}H_{26}ClN_3O$	118	18	16	13	11	17	10.01	9.79
JG-5	2-OCH_3-C6H_4-	$C_{25}H_{26}ClN_3O_2$	208	13	14	15	12	14	9.64	9.61
JG-6	3-OCH_3-C6H_4-	$C_{25}H_{26}ClN_3O_2$	210	11	14	12	10	13	9.64	9.60
JG-7	4-OCH_3-C6H_4-	$C_{25}H_{26}ClN_3O_2$	138	16	16	16	12	17	9.64	9.62
JG-8	4-NH_2-C6H_4-	$C_{24}H_{25}ClN_4O$	149	11	14	17	13	16	13.31	13.25
JG-9	3-4-$(CH_3)_2$-C6H_3-	$C_{26}H_{28}ClN_3O$	110	18	16	12	16	19	9.68	9.63
JG-10	2-OH-C6H_4-	$C_{24}H_{24}ClN_3O_2$	132	13	11	17	14	15	9.96	9.89
JG-11	4-NO_2-C6H_4-	$C_{24}H_{23}ClN_4O_3$	243	15	13	14	12	16	12.43	12.40
JG-12	$C_4H_3N_2$-(pyrazine)	$C_{22}H_{22}ClN_5O$	228	18	14	17	11	15	17.17	17.14
JG-13	3-COOH-C6H_4-	$C_{24}H_{24}ClN_3O_4S$	118	14	13	17	12	18	8.65	8.61
JG-14	4-OCH_3-3-COOH-C6H_3-	$C_{25}H_{26}ClN_3O_5S$	180	16	18	15	13	16	8.14	8.10
JG-15	5-OCH_3-3-COOH-C6H_3-	$C_{25}H_{26}ClN_3O_5S$	192	19	16	16	17	18	8.14	8.12
JG-16	4-OH-3-COOH-C6H_3-	$C_{24}H_{24}ClN_3O_5S$	196	17	12	18	11	11	8.37	8.32
JG-17	2-OH-5-COOH-C6H_3-	$C_{24}H_{24}ClN_3O_5S$	111	13	15	14	15	17	8.37	8.30
JG-18	4-Cl-3-COOH-C6H_3-	$C_{24}H_{23}Cl_2N_3O_4S$	215	18	11	15	10	14	8.07	8.01
JG-19	2-Cl-5-COOH-C6H_3-	$C_{24}H_{23}Cl_2N_3O_4S$	138	16	13	18	13	15	8.07	8.04
JG-20	4-CH_3-3-COOH-C6H_3-	$C_{25}H_{26}ClN_3O_4S$	181	17	14	13	11	17	8.40	8.31
JG-21	5-CH_3-3-COOH-C6H_3-	$C_{25}H_{26}ClN_3O_4S$	180	17	12	12	14	18	8.40	8.35
JG-22	2-CH_3-5-COOH-C6H_3-	$C_{25}H_{26}ClN_3O_4S$	216	14	10	15	12	17	8.40	8.33
JG-23	2-COOH-$C_4H_2N_2$-(pyrazine)	$C_{22}H_{22}ClN_5O_4S$	110	17	15	17	11	18	14.35	9.91
JG-24	4-NHCOCH$_3$-C6H_3-	$C_{25}H_{27}ClN_4O_3S$	136	14	14	15	13	16	10.23	9.32
JG-25	C_6H_5-	$C_{34}H_{31}ClN_4O_2$	191	19	11	16	12	17	9.95	9.91
JG-26	4-Cl-C6H_4-	$C_{34}H_{30}Cl_2N_4O_2$	135	15	18	12	10	15	9.38	9.32
JG-27	4-F-C6H_4-	$C_{34}H_{30}ClFN_4O_2$	119	13	13	17	12	17	9.64	9.60
JG-28	4-Br-C6H_4-	$C_{34}H_{30}BrClN_4O_2$	140	12	10	16	15	16	8.73	8.71
JG-29	2-OH-C6H_4-	$C_{34}H_{31}ClN_4O_3$	168	16	15	20	17	18	9.68	9.63
JG-30	3- OH-C6H_4-	$C_{34}H_{31}ClN_4O_3$	105	16	17	14	13	16	9.68	9.66
JG-31	4-OH-C6H_4-	$C_{34}H_{31}ClN_4O_3$	101	17	12	16	11	14	9.68	9.65
JG-32	4-OCH_3-C6H_4-	$C_{35}H_{33}ClN_4O_3$	125	15	10	15	17	18	9.20	9.18
JG-33	3-OCH_3-4-OH- C6H_3-	$C_{35}H_{33}ClN_4O_4$	185	17	13	13	10	17	9.45	9.42
JG-34	4-N-$(CH_3)_2$- C6H_3-	$C_{36}H_{36}ClN_5O_2$	120	14	14	16	13	21	11.55	11.52
JG-35	4-NO_2-C6H_4-	$C_{34}H_{30}ClN_5O_4$	177	17	15	14	11	17	11.52	11.50
JG-36	$C_{10}H_7$	$C_{35}H_{32}ClN_5O_6$	171	16	14	18	13	18	10.71	10.70

and crystallized from ethanol. Yield 72%, m.p. 138^{0}C. ($C_{25}H_{26}ClN_3O_2$: required: C 68.88; H, 6.01; N, 9.64; found: C, 68.85; H, 6.00; N, 9.62; %).

IR (KBr); 2958 (C-H str. asym); 2874 (C-H str. sym); 1456 (C-H def); 3072 (C-H aromatic); 829 (C-H-O.O.P.); 1101 (C-N str); 1706 (>C=O str); 3396 (>N-H Str.), 695 (C-Cl str.).

^{1}HNMR (DMF);2.25-2.44 (2H,t,N-CH_2),2.51-2.71 (2H,t,N-CH_2), 3.48-3.49 (2H,t,N-CH_2),4.25-4.35(2H,t,N-CH_2);4.22(1H,s,Ar-CH),3.88(3H,s,Ar-OCH_3), 7.20-7.33(5H,M,Ar-H),8.130(2H,d,Ar-H),8.23-8.28(4H,d,Ar-H),8.28-8.31(2H,d, Ar-H), 8.20(1H,s,N-H). m/z : 436,405,344,329,301,286,272, 216,188,78.

Similarly other aryl amides were synthesized. The physical data are recorded in TABLE 1.

(D) Synthesis of 1-(2′′-methyl-5′′-carboxy)phenyl sulphonamido-4-[(4′- Chlorophenyl)(phenyl) methyl] Piperazines(JG-22)

A compound of 1-amino-4-[(4′-chlorophenyl) (phenyl) methyl] piperazine (2.26gm, 0.01M) and 2-methyl -5-carboxybenzene Sulphonyl Chloride (2.21gm, 0.01m) in the presence of 5ml pyridine.The reaction mixture was refluxe for 5 hrs. in oil bath.The reaction mixture was poured in to crushed ice and filtered, washed with water and crystallized from ethanol. Yield 48% m.p 216^{0}C ($C_{25}H_{26}ClN_3O_4S$: required: C;60.05; H,5.24; N,.8.40; Found:C;60.01;H,5.20; N,.8.33 TLC Solvent System: Ethyl acetate: Hexane (3:7)

IR (KBr); 2963 (C-H str. asym); 2889 (C-H str. sym); 1461 (C-H def); 3082 (C-H aromatic); 849 (C-H-O.O.P.); 1088 (C-N str); 1715 (C=O str); 3390 (N-

TABLE 2: Antimicrobial activity: conclusion: maximum antimicrobial activity

Compd.	*B.mega*	*S.aureus*	*E.Coli*	*S.typhi*	*A.niger*
(JG1-JG12)	JG-3,4,9	JG2,4,7,9	JG-2,3,8,10,12	JG-3,9	JG-2,3,4,7,9
(JG13-JG24)	JG-14,17	JG-14,15,17,23	JG-13,16,19,23	JG-15,17	JG-13,14,15,17,19
(JG25-JG36)	JG25,29,32	JG-26,30,35	JG-27,29,36	JG-28,29,32	JG-25,29,32,34,36
Comparable activity with known standard drugs					
Compd.(50 µg/ml)	***B.mega***	***S.aureus***	***E.Coli***	***S.typhi***	***A.niger***
Ampicillin	22	19	19	22	-
Chloramphanicol	22	23	22	24	-
Norfloxacin	22	22	24	23	-
Greseofulvin	-	-	-	-	22

H Str.), 795 (C-Cl str.).

^{1}HNMR(DMF);1.65 (3H,s,Ar-CH_3);2.30-2.39 (2H,t,N-CH_2);2.59-2.65(2H,t,N-CH_2);3.85-3.84(2H,t,N-CH_2);4.25-4.26(2H,t,N-CH_2);4.14(1H,s,N H); 4.26 (1H, s,Ar-C-H):7.20-7.69(12H,M,ArH):8.64 (1H,s,Ar-COOH). m/z : 500, 456,441,378,353,336,322,301,289,267,251,245,237, 217,165,154,121,104 ,78.

Similarly other sulphonamides were synthesized. The physical data are recorded in TABLE 1.

(E) Synthesis of N-{4-[(4′-Chlorophenyl) (phenyl) methyl] Piperazine-1-yl}-4′′′- N, N-dimethyl amino phenyl)-2′′-(4′′′- methoxy phenyl)-5′′-oxo-imidazolines (JG-34)

A compound of 1-amino-4-[(4′-chlorophenyl) (phenyl) methyl] piperazine (3.0 gm, 0.01M.) and 4-[4′′′-(dimethylamino) benzylidene]-2-(4'-methoxy phenyl) -1, 3-oxazol-5(4H)-one in dry 20 ml pyridine was refluxed for 12 hrs. in oil bath. Resulting mass was poured into crushed ice and neutralized with HCl, filtered and crystallized from dioxan. Yield 69%, mp. 120^{0}C. ($C_{36}H_{36}ClN_5O_2$; Requires: C:71.33; H:5.99; N:11.55%; found:C:71.30;H:5.95;N:11.52%).

IR(KBr); 2959(C-H Str.asym),1448 (C-H def. asym.), 1372(C-H def .asym .), 3050(AromaticC-H Str),1568 (C=C Ring skeletal),1714 (imidazolone C=O str) ,1648 (CH=CH- Str.vinylic),1130(C-O-C Str.),3335 (C-NH Str)1648 (C=Nstr),758 (C-Cl Str).

^{1}HNMR (DMF);2.2-2.29(2H,t,N-CH_2);2.39(6H,s,N-CH_3);2.58-2.69(2H,t,N CH_2) ;2.99-3.03(2H,t,N-CH_2);3.73-3.81(2H,t,N-CH_2);3.87(2H,t,Ar-OCH_3);5.74-5.75 (1H,d,Ar-CH);.6.99 (1H,s,C-H vinylic proton);7.31-7.95(17H,m,Ar-CH); m/z :606,592,578,563,544,478,475,460,417,38,366, 370,343,354,316,298, 286, 253, 237,206,149, 102.

Similarly other 5-oxo-imidazoline have been synthesized. The physical data are recorded in TABLE 1.

Summary

1-Aroylamino-4-[(4′- Chlorophenyl) (phenyl) methyl] Piperazine (JG: 1-12);1-arylsulphonamido-4-[(4′-Chlorophenyl)(phenyl) methyl] Piperazines (JG:13-24); N-{4-[(4′-Chlorophenyl)(phenyl) methyl] Piperazine-1-yl}-4′′-arylidene-2′′-(4′′′-methoxyphenyl) -5′′-oxo-imidazolines (JG:25-36) have been synthesized. Compounds containing JG-3,JG-4,JG-9,JG-14,JG-15,JG-17,JG-29,JG-32 are more comparable antimicrobial activity with known standard drugs compare to other compounds.

ACKNOWLEDGMENT

The authors are thankful to management and Principal Shree M. & N. Virani science college, Rajkot for providing research facilities.

REFERENCES

[1] M.A.Ankhiwala,V.Hathi; Indian J.Heterocycle. Chem., **5**, 229 **(1996)**.

[2] Wang, Zhong-ji, ShiHai-Jain, Shi Haoxin, Hecheng Haxue; **3(3)**, 226 **(1995)**; Chem.Abstr., **124**, 8687d **(1996)**.

[3] D.W.Piotrwoski, K.T.Trains; Acs.Symp.Jer., **584**, 267 **(1995)**; Chem.Abstr., **122**, 154137z **(1995)**.

[4] J.C.Teulade, G.Grassy, J.P.Girard, J.P.Chapat, M.M.S.de Buochberg; Eur.J.Med.Chem., **13**, 271 **(1978)**.

[5] Y.Rival, G.Grassy, A.Taudou, R.Ecalle; Eur.J.Med. Chem., **26**, 13 **(1991)**.

[6] P.kumar, K.N.Dhawan, S.Vrat, K.P.Bhargawa, K. Kishore; Arch.Pharma., **316**, 759, **(1983)**.

[7] F.V.Loffe; Khim.Geterokeiki Sodein, **6**, 1089 **(1968)**; Chem.Abstr., **70**, 72338 **(1986)**.

[8] A.L.Barry, Illus Lee and Febiger; 'The Antimicrobial Succeptibility test', Principal and Practices, Bio.Abstr., **64**, 25183 **(1997)**.