December 2010 ISSN: 0974 - 7516 Volume 6 Issue 4

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 6(4), 2010 [267-271]

Synthesis and antimicrobial activity of 1-N-(arylideneamino)/1-N-(arylmethylamino)-4-[(4', 4''-difluorodiphenyl)- methyl]-piperazines

M.D.Savaliya, J.G.Dobaria, D.M.Purohit*

Shree M. & N. Virani Science College, Chemistry Department, Kalawad Road, Rajkot - 360 005 (Guj.), (INDIA)

E-mail: purohitdm@yahoo.com

Received: 1st July, 2010 ; Accepted: 10th July, 2010

ABSTRACT

1-N-arylideneamino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazines **(3a-3j)**; 1-N-arylmethyl amino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazines **(4a-4j)** have been synthesized. The products have been assayed for their antimicrobial screening against Gram +ve, Gram –ve becteria and fungi. Some of the products showed moderate activity compare with known standard drugs viz. ampicillin, chloramphenicol, norfloxacin and greseofulvin at same concentration 50μg/ml. The structures of the products have been elucidated by IR, ^{1}HNMR, Mass spectral data and elemental analysis.

© 2010 Trade Science Inc. - INDIA

KEYWORDS

Schiff's bases;
Arylmethylamine
(Heterocyclic chemistry).

INTRODUCTION

Piperazine derivatives play a vital role largely due to the wide ranging biological activities. Piperazine are known to exhibit wide spectrum of biodynamic activity. Taking into consideration diverse biodynamic activities analgesic[1], antibacterial[2], antidiabatic[3], antifungal[4], antiulcer[5,6], antihistamine[7], anthelmintic[8], anti-inflammatory[9] etc. In the fact of these interesting biological activities, it appeared of interest to synthesis some new Schiff's base[10-12] derivatives bearing 1-amino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazine nucleus. The arylidene amino (Schiff's base) derivatives have been synthesized by the condensation of 1-amino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazine with different aromatic aldehydes. The arylmethylamino derivatives have been synthesized by the selective reduction of (imine group) Schiff's base of 1-N-arylideneamino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazines with sodium borohydride. All the products **(3a-3j)**, **(4a-4j)** were assigned the IR, ^{1}HNMR, Mass spectra, TLC and elemental analysis. The physical data and antimicrobial activities are represented in TABLE 1.

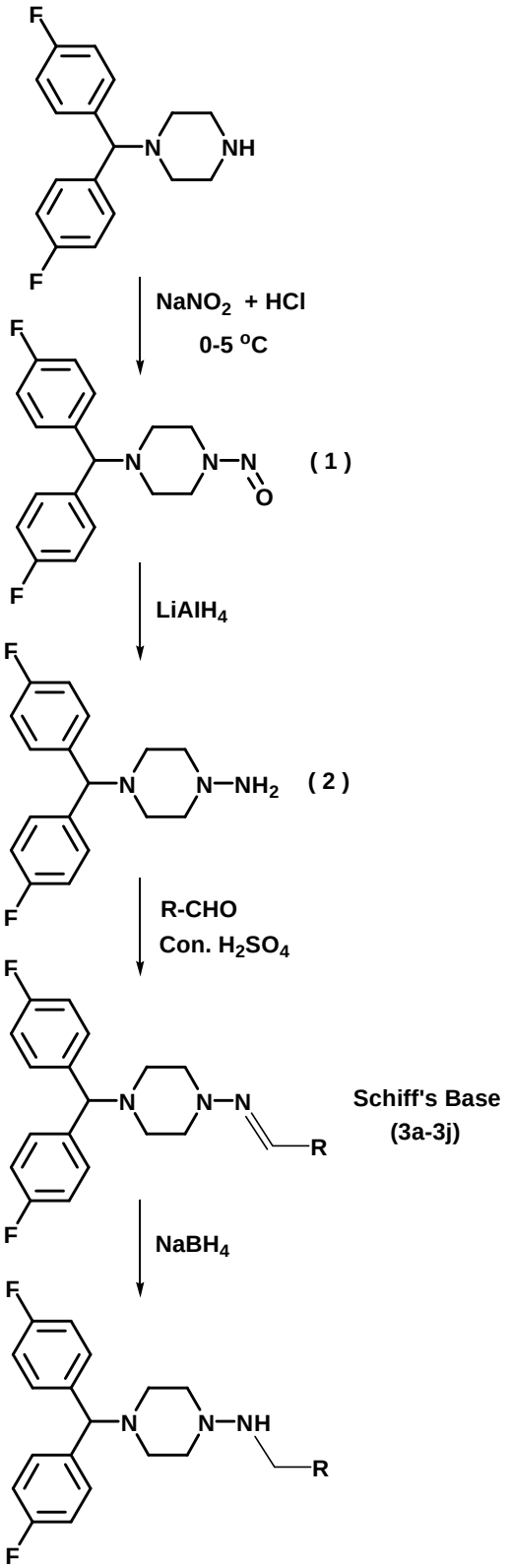
ANTIMICROBIAL ACTIVITY

All the products **(3a-3j)**, **(4a-4j)** were tested for their antimicrobial activity by cup-plate method[13] against the Gram positive becteria *Bacillus subtillis, Bacillus Cerus,* Gram negative bacteria *Escherichia coli*, *Enterobacter aerogen* and for antifungal activity against *Aspergillus niger* at a Concentration of 50 μg/ml, using DMF as a solvent. After 24hrs of incubation at 37°c, the zone of inhibition were measured in mm. The activity was compared with known standard drugs viz. ampicillin, chloramphenicol, norfloxacin and greseofulvin at the same concentration (50 μg/ml.) which is represented in TABLE 1.

All the synthesized compounds **(3a-3j)**, **(4a-4j)** showed moderate to good and remarkable activities

Full Paper

Reaction Scheme



with known standard drugs at same concentration, which is represented in TABLE 2

EXPERIMENTAL SECTION

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 I.R. – 435 spectrophotometer using KBr pellet method and ^{1}HNMR spectra on Hitachi R-1200 (300MHZ) spectrometer using TMS as internal starndard (chemical shifts in δ ppm) and Mass spectra on a Joel 300 ev.The compounds were routinely checked by TLC using silica gel G.

1-Nitroso-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine (1)

A compound of 1-[(4',4"-difluorodiphenyl)-methyl]-piperazine (8.6 gm, 0.03M) 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 5 ml ethyl acetate - 70 ml n-heptane. The resultant solid is recystallized from a mixture of 2-propanol and hexane, to give 1-nitroso-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine. M.P.153-155°C; Yield: 80.56 % ($C_{17}H_{17}N_3F_2O$; Found C: 64.30; H: 5.37; N: 13.22; required C: 64.34; H: 5.40; N:13.24 %).

1-Amino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine (2)

A compound of 1-nitroso-4-[(4',4"-difluorodiphenyl)-methyl]-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 refluxed and stirred for 2 hrs. The reaction mixture 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 and washed with ether. The filtrate is dried over sodium sulphate. The solvent is evaporated, the residue is dissolved in ben-

TABLE 1 : The physical data and antimicrobial activity of compunds (3a–3j), (4a–4j):

Comp.	R	Molecular Formula	M.P °C	Yield %	Nitrogen %		Antibacterial Activity Zone of Inhibition in mm				Anti fungal Activity Zone of Inhibition in mm
					Calcd.	Found	B. Substillis	B. cerus	E. coli	E. aerogen	A.niger
3a	C_6H_5 -	$C_{24}H_{23}N_3F_2$	214	62.21	10.73	10.70	19	14	19	16	20
3b	2-OH-C_6H_4-	$C_{24}H_{23}ON_3F_2$	187	66.00	10.31	10.27	22	20	20	14	17
3c	4-OH-C_6H_4 -	$C_{24}H_{23}ON_3F_2$	139	76.29	10.31	10.25	19	22	14	20	21
3d	2-OCH_3-C_6H_4 -	$C_{25}H_{25}ON_3F_2$	165	75.87	9.97	9.91	23	13	22	14	17
3e	4-OCH_3-C_6H_4 -	$C_{25}H_{25}ON_3F_2$	146	76.54	9.97	9.94	17	23	16	19	23
3f	2-Cl-C_6H_4 -	$C_{24}H_{22}N_3F_2Cl$	132	60.47	9.87	9.85	24	16	23	21	18
3g	4-F-C_6H_4 -	$C_{24}H_{22}N_3F_3$	178	55.74	10.26	10.22	14	22	17	17	21
3h	2-NO_2-C_6H_4 -	$C_{24}H_{22}O_2N_4F_2$	187	59.25	12.84	12.80	20	15	19	16	14
3i	3-NO_2-C_6H_4 -	$C_{24}H_{22}O_2N_4F_2$	196	60.12	12.84	12.82	24	22	21	20	22
3j	C_4H_3O -	$C_{22}H_{21}ON_3F_2$	193	65.00	11.02	10.97	23	14	14	22	15
4a	C_6H_5 -	$C_{24}H_{25}N_3F_2$	186	72.28	9.66	9.62	15	14	19	17	19
4b	2-OH-C_6H_4-	$C_{24}H_{25}ON_3F_2$	171	69.40	10.26	10.22	22	22	23	20	22
4c	4-OH-C_6H_4 -	$C_{24}H_{25}ON_3F_2$	179	73.49	10.26	10.24	18	16	15	14	16
4d	2-OCH_3-C_6H_4 -	$C_{25}H_{27}ON_3F_2$	157	65.38	9.92	9.88	23	21	22	19	23
4e	4-OCH_3-C_6H_4 -	$C_{25}H_{27}ON_3F_2$	175	82.00	9.92	9.89	17	15	16	16	15
4f	2-Cl-C_6H_4 -	$C_{24}H_{24}N_3F_2Cl$	127	80.47	9.82	9.85	21	20	20	22	17
4g	4-F-C_6H_4 -	$C_{24}H_{24}N_3F_3$	108	85.11	10.21	10.19	19	16	15	15	17
4h	2-NO_2-C_6H_4 -	$C_{24}H_{24}O_2N_4F_2$	161	69.87	12.78	12.75	14	23	15	21	21
4i	3-NO_2-C_6H_4 -	$C_{24}H_{24}O_2N_4F_2$	117	74.12	12.78	12.73	24	13	17	18	18
4j	C_4H_3O -	$C_{22}H_{23}ON_3F_2$	172	78.00	10.96	10.94	23	20	21	22	21

TABLE 2 : Comparable activity with known standard drugs :

Antimicrobial Activity:

Conclusion:

Maximum antimicrobial activity:

Compd.	B.Substillis	B.Cerus	E.Coli	E.aerogen	A.niger
(3a-3j)	3b,3d,3f,3h,3i,3j	3b,3c,3e,3g,3i	3b,3d,3f,3i,	3c,3e,3f,3i,3j	3c,3e,3g,3i
(4a-4j)	4b,4d,4f,4i,4j	4b,4d,4f,4h,4j	4b,4d,4f,4j	4b,4d,4f,4h,4i,4j	4b,4d,4h,4j

Activity of standard drugs:

Standard Drugs	B.Substillis	B.Cerus	E.Coli	E.aerogen	A.niger
Ampicillin (50 μg/ml)	23	22	21	19	-
Chloramphanicol (50 μg/ml)	22	23	21	20	-
Norfloxacin (50 μg/ml)	24	21	23	22	-
Griseofulvin (50 μg/ml)	-	-	-	-	23

zene and the solvent is evaporated once again to give 1-amino-4-[(4',4''-difluorodiphenyl)-methyl]-piperazine. M.P.126-129°C; Yield 57.72% ($C_{17}H_{19}F_2N_3$; Found C: 67.27; H: 6.29; N: 13.83; required C: 67.31; H: 6.31; N: 13.85 %). I.R. (KBr): 2910(C-H str, asym); 2837 (C-H str, sym); 1454 (C-H def); 3033 (aromatic. C-H str); 1197 (C-H str, i. p def); 759 (C-H str, 0.0.p.); 1361 (C-N str.); 3274 (C-NH str.); 1606 (C-NH ben.); 3330 (N-H str.); ^{1}HNMR (DMF): 2.19-2.23 (4H, d d, N-CH_2); 2.66-2.71 (4H,

Full Paper

d d, N-CH_2); 6.93-7.21 (8H, m, Ar-H); 5.19 (1H, s, C-H); 2.57 (2H, s, N-NH_2). m/z: 53, 76, 95, 127, 177, 205, 219, 230, 257, 269, 282, 303.

Synthesis of 1-N-[(4"'-methoxybenzylidene)-amino]-4-[(4',4"-difluorodiphenyl)-methyl] –piperazine (3e)

A mixture of 1-amino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine (3.03gm, 0.01M) and 4-methoxybenzaldehyde (1.36 gm, 0.01M) dissolved in ethanol (20 ml) in presence of catalytic amount of concentrated sulphuric acid (0.2 ml).The reaction mixture was refluxed for 8 hrs. The contents were cooled and poured in crushed ice product was isolated and re-crystallized from ethanol. Yield: 76.54%, M.P. 146°C. ($C_{25}H_{25}ON_3F_2$; Required: C: 71.24; H: 5.98; N: 9.97; Found: C: 71.20; H: 5.95; N: 9.94%), IR.(KBr); 2948(C-H str.asym.), 2881(C-H str.sym.), 1450(C-H def. asym.), 1369(C-H def. sym.), 3024(C-H str. aromatic), 1487(C=C str. aromatic), 1130(C-H i.p. def.), 757(C-F str.), 1323(C-N str. piperazine), 1265(C-O-C str.), 1089(C-N str.), 1589(C=N str.).; ^{1}HNMR($CDCl_3$): 2.50-2.59 (4H, d, N-CH_2), 2.73-2.77 (4H, d, N-CH_2), 3.75 (3H, s, Ar-OCH_3), 5.20 (1H, s, C-H), 6.89-6.89 (4H, d, Ar-H), 7.08-7.10 (2H, d, Ar-H), 7.14-7.28 (4H, t, Ar-H), 7.37-7.44 (2H, d, Ar-H), 8.11 (1H, d, C-H).; m/z : 86, 96, 108, 112, 137, 150, 167, 203, 208, 220, 228, 238, 254, 275, 288, 303, 318, 329, 338, 344, 352, 400, 408, 421.

Similarly other compounds **(3a -3j)** were prepared and their physical data are recorded in TABLE 1

Synthesis of 1- N - [(4"'- methoxyphenyl) - methylamino]- 4 -[(4', 4"- difluorodiphenyl)-methyl]-piperazine (4e)

Sodium borohydride (0.57gm, 0.015M) was added to a methanolic solution of 1 - N - [(4"'-methoxybenzylidene) - amino] - 4 - [(4',4"-difluorodiphenyl) - methyl] -piperazine (4.21gm, 0.01M) over a period of 30 minutes at temperature 5-10°C with constant stirring. The reaction mixture was kept over night at room temp with constant stirring. The excess sodium borohydride was neutralized by adding water and the product was extracted with ether. The ether layer was washed with water untill become neutral, then dried over anhydrous Na_2SO_4 and finally the ether was evaporated to give aminomethyl derivatives. Yield: 82.00%, M.P. 175°C. ($C_{25}H_{27}ON_3F_2$; Required: C: 70.90; H: 6.43; N: 9.92; Found: C: 70.87; H: 6.39; N: 9.89 %), IR.(KBr); 2910(C-H str.asym.), 2837(C-H str.sym.), 1454(C-H def. asym.), 1396(C-H def. sym.), 2655(-CH_2 str. alkene), 3033(C-H str. aromatic), 1496(C=C str. aromatic), 1197(C-H i.p. def.), 759(C-F str.), 1361(C-N str. piperazine), 1250(C-O-C str.), 1606(C-N str.), 1522(N-H bend.), 3330(N-H str.); ^{1}HNMR($CDCl_3$): 2.30-2.38 (4H, d, N-CH_2), 2.61-2.67 (4H, d, N-CH_2), 3.70 (3H, s, Ar-OCH_3), 4.01 (2H, s, C-H), 5.10 (1H, s, C-H), 6.93-6.96 (2H, d, Ar-H), 7.04-7.06 (4H, t, Ar-H), 7.18-7.27 (2H, d, Ar-H), 7.39-7.48 (4H, t, Ar-H), 8.10 (1H, d, N-H).; m/z : 86, 96, 108, 115, 130, 137, 150, 157, 176, 194, 204, 208, 219, 233, 275, 288, 303, 330, 359, 387, 393, 423.

Similarly other compounds **(4a-4j)** were prepared and their physical data are recorded in TABLE 1

CONCLUSION

1 - N - arylideneamino - 4 - [(4', 4" - difluorodiphenyl) - methyl] - piperazines **(3a-3j)**; 1-N-arylmethylamino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazines **(4a-4j)** have been synthesized and some of the compounds **(3b)**, **(3c)**, **(3f)**, **(3i)**, **(3j)**, **(4b)**, **(4d)**, **(4f)**, **(4h)**, **(4j)** showed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and greseofulvin at same concentration 50µg/ml, which is represented in TABLE 2.

ACKNOWLEDGEMENTS

The authors are thankful to management and principal shree M. & N. virani science college, Rajkot for providing research facilities.

REFERENCES

[1] Vos C.De et al.; Ann.Allexgy, **59**, 278 **(1987)**.
[2] Baltyl et al.; J.Org.Chem., **14**, 775 **(1949)**.
[3] F.F.Roth, W.M.Govier; J.Pharmcol.Exp.Ther., **124**, 347 **(1958)**.

[4] Hanna; Toxics Appl.Pharmacol., **3**, 3936 **(1961)**.
[5] J.Hoffmann et al.; Pharma.Sci., **72**, 1342 **(1983)**.
[6] Tashio Pharmaceutical Co. Ltd. Japan Koho JP, 59,12,094 (84,12,094) (C1A 61k31/215); Chem. Abstr., **101**, 54722j **(1984)**.
[7] M.Puttemans et al.; J.Liqchromato., **7**, 2237 **(1984)**.
[8] J.C.Teulade, G.Grassy, J.P.Girard, J.P.Chapat, M.M.S.de Buochberg; Eur.J.Med.Chem., **13**, 271 **(1978)**.
[9] P.Ducommun, S.D.Lehmann; Rev.Can.Boil, 11298, **1952**, Chem.Abstr., **47**, 1292f **(1953)**.
[10] Ram Tilak, Ritu Tyagi, Bhawna Goel, K.K.Saxena, V.K.Shrivastava, Ashok Kumar; Indian Drugs, **35(4)**, 216-221 (Eng.) **(1998)**; Chem.Abstr., **129**, 9, 641, 109052r **(1998)**.
[11] Perumal Panneerselvam, Bilal Ahmad Rather, Dontireddy Ravi Sankar Reddy, Natesh Ramesh Kumar; European Journal of Medicinal Chemistry, **44(5)**, 2328-2333 May, **(2009)**.
[12] S.J.Wadher, M.P.Puranik, N.A.Karande, P.G.Yeole; International Journal of Pharm.Tech.Research, **1(1)**, 22-23, Jan-March, **(2009)**.
[13] A.L.Barry; The Antimicrobial Succeptibility Test, Principal and Practices, Edited by Illus Lea and Febiger 180, Bio.Abstr., **64**, 25183 **(1976)**.