March 2009 Volume 5 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(1), 2009 [100-103]

Synthesis and antimicrobial activity of 1-(aroyl/aryl sulpho/arylamino methyl)-4-[4′,4″-difluoro diphenyl)- methyl]-piperazines

M.D.Savaliya, J.G.Dobaria , V.N.Patolia, A.U.Patel, D.M.Purohit*

Shree M. & N. Virani Science College, Chemistry Department, Kalawad Road, Rajkot-360005, Gujarat, (INDIA)

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

ABSTRACT

1-Aroyl-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazines**(3a-3j)**;1-Arylsulpho-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazines **(4a-4j)**; 1-Arylaminomethyl-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazines**(5a-5j)** 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 griseofulvin at same concentration 50µg. The structures of the products have been elucidated by IR, ^{1}HNMR, Mass spectral data and elemental analysis.

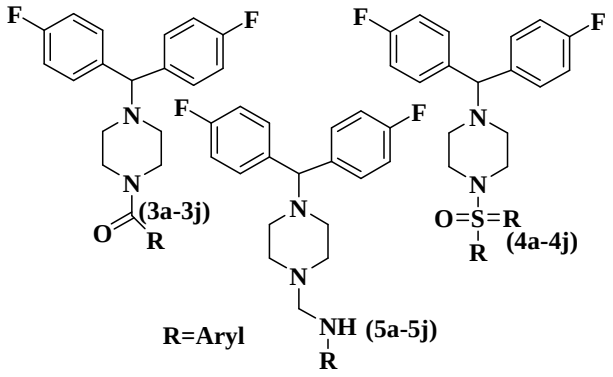
© 2009 Trade Science Inc. - INDIA

KEYWORDS

Arylamide;
Sulphonamide;
Mannich base

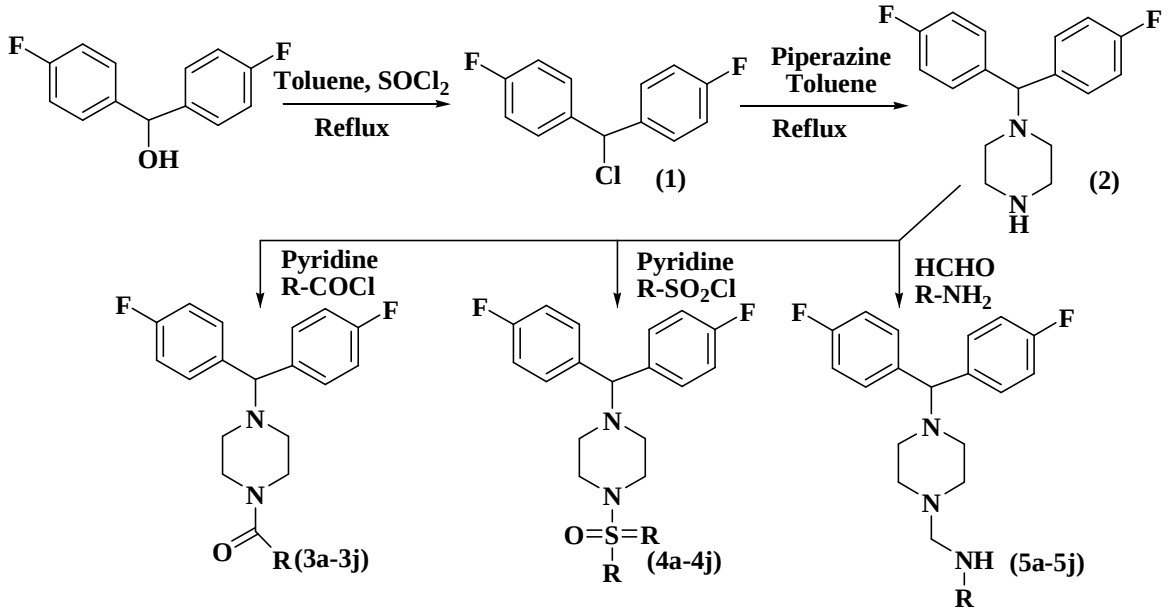
INTRODUCTION

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], antihistaminic[7] etc. In the fact of these interesting biological activities, it appeared of interest to synthesis some new arylamide[8], sulphonamide[9], Mannich base[10] derivatives bearing-1-[(4′,4-difluoro diphenyl)-methyl]-piperazine nucleus.The arylamide have been synthesized by the condensation of 1-[(4′,4″-difluorodiphenyl)-methyl]-piperazine with aroyl chloride. The Sulphonamide have been synthesized by 1-[(4′,4″-difluoro diphenyl)-methyl]-piperazine with aryl sulphonyl chloride. The Mannich base have been synthesized by the condensation of 1- [(4′,4″-difluorodiphenyl)-methyl]-piperazine with different aryl amine in presence of formaldehyde and con.HCl. All the products **(3a-3j)**, **(4a-4j)**, **(5a-5j)**, 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)**, **(5a-5j)**, were tested for their antimicrobial activity by cup-plate method[11] against the Gram positive becteria *Becillus subtillis, Bacillus Cerus,* Gram negative bacteria *Escherichia coli, Escherichia arogen* and for antifungal activity against *Arobactor niger* at a Concentration of



SCHEME

50 μg/ml, using DMF as a solvent. After 24 hrs of incubation at 37^{0}C, the zones of inhibition were measured in mm. The activity was compared with known antibiotics, viz. ampicillin, chloramphenicol, norfloxacin and griseofulvin at the same concentration (50 μg/ml.) which is represented in TABLE 1.

All the synthesized compounds **(3a-3j)**, **(4a-4j), (5a-5j)**, showed moderate to good and remarkable activities with known standared drugs at same concentration, which is represented in TABLE 2.

EXPERIMENTAL

All the melting points were measured in open 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-Chloro-1-(4′,4″-difluorodiphenyl)-methane (1)

A mixture of 1-(4′, 4″-difluorodiphenyl) methanol (2.20 gm, 0.01M) in Toluene (25 ml) with thionyl chloride (1.3 gm, 0.011M) was stirring with at room temp. for 1-2 hrs, than after the reaction mixture refluxed 110-112^{0}C for 8 hrs. Toluene is distilled out completely and remained product is oil form. B.P.321^{0}C; Yield: 82.86 % (Found C: 65.40; H: 3.77; Cl: 14.88); $C_{13}H_9ClF_2$ required C: 65.42; H: 3.80; Cl: 14.89 %).

1 -[(4′,4″-Difluorodiphenyl)-methyl]-piperazine (2)

A mixture of 1-chloro-1-(4′, 4″difluorodiphenyl) -methane(2.38gm, 0.01M), anhydrous piperazine (3.44gm, 0.04M), Toluene (25 ml) was heated under reflux in a oil bath for 8-10 hours. The reaction mixture is cool at room temp. Filter it and filtrate wash with water (25 ml) and separate layers. Take toluene layer and add water (25 ml) than acidify with Con. HCl about 2.0 pH. and separate layers. Take aqueous layer and basify with caustic lye about 13.0 pH. Filter the product and wash with water dried and crystallized from methanol. M.P.92^{0}C; yield 85.72% (Found C: 70.79; H: 6.23; N: 9.70; $C_{17}H_{18}F_2N_2$, required C: 70.83; H: 6.25; N: 9.72 %). I.R. (KBr): 2949(C-H str, asym); 2879 (C-H str, sym); 1452 (C-H def); 3020 (aromatic. C-H str); 1166 (C-H str, i. p def); 821 (C-H str, 0.0.p.); 1325 (C-N str.); 3306 (C-NH str.) ^{1}HNMR (CD_2Cl_2): 2.3-3.0 (8H, d, -CH_2) 6.9-7.5 (8H, m Ar-H); 4.2 (1H, s, C-H). m/z: 56, 91, 109, 155, 183, 208, 273, 288.

1-(4‴-Methoxybenzoyl)-4-[(4′,4″-difluorodiphenyl) -methyl]-piperazine(3e)

A mixture of 1-[(4′, 4″-difluorodiphenyl)-methyl]-

Full Paper

TABLE 1 : The physical data and antimicrobial activity of compunds (3a–3j), (4a–4j), (5a–5j)

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.arogn*	*A.niger*
(3a)	C_6H_5 -	$C_{24}H_{22}ON_2F_2$	184	88.72	7.14	7.10	22	15	21	20	14
(3b)	2-CH_3-C_6H_4 -	$C_{25}H_{24}ON_2F_2$	122	74.52	6.89	6.85	18	22	19	21	16
(3c)	4-CH_3-C_6H_4 -	$C_{25}H_{24}ON_2F_2$	211	74.26	6.89	6.80	17	18	22	16	21
(3d)	2-OCH_3-C_6H_4 -	$C_{25}H_{24}O_2N_2F_2$	121	63.87	6.63	6.60	13	21	22	18	16
(3e)	4-OCH_3-C_6H_4 -	$C_{25}H_{24}O_2N_2F_2$	129	63.71	6.63	6.61	14	21	23	21	17
(3f)	2-Cl-C_6H_4 -	$C_{24}H_{21}ON_2F_2$ Cl	134	73.52	6.56	6.52	19	15	14	12	23
(3g)	2-NO_2-C_6H_4 -	$C_{24}H_{21}O_3N_3F_2$	172	60.11	9.61	9.57	21	15	20	19	19
(3h)	3-NO_2-C_6H_4 -	$C_{24}H_{21}O_3N_3F_2$	152	59.09	9.61	9.55	19	14	16	18	22
(3i)	4-NO_2-C_6H_4 -	$C_{24}H_{21}O_3N_3F_2$	192	60.99	9.61	9.50	16	12	21	24	20
(3j)	3,4-$(OCH_3)_2$-C_6H_3 -	$C_{26}H_{26}O_3N_2F_2$	187	79.55	6.19	6.15	11	19	21	11	24
(4a)	3-COOH-C_6H_4 -	$C_{24}H_{22}O_4N_2F_2$ S	150	71.10	5.93	5.90	19	14	11	18	18
(4b)	5-COOH-2-CH_3-C_6H_3 -	$C_{25}H_{24}O_4N_2F_2$ S	202	66.71	5.76	5.71	21	21	10	21	16
(4c)	3-COOH-4-CH_3-C_6H_3 -	$C_{25}H_{24}O_4N_2F_2$ S	123	61.62	5.76	5.70	21	23	21	21	19
(4d	5-COOH-2-OCH_3-C_6H_3-	$C_{25}H_{24}O_5N_2F_2$ S	200	79.81	5.57	5.52	15	14	12	15	21
(4e)	3-COOH-4-OCH_3-C_6H_3-	$C_{25}H_{24}O_5N_2F_2$ S	227	65.50	5.57	5.50	15	20	19	15	19
(4f)	5-COOH-2-Cl-C_6H_3 -	$C_{24}H_{21}O_4N_2F_2$ ClS	120	66.60	5.53	5.47	19	19	22	19	19
(4g)	3-COOH-4-NO_2-C_6H_3 -	$C_{24}H_{21}O_6N_3F_2$ S	159	76.52	8.12	8.00	21	23	21	21	16
(4h)	3-COOH-5-NO_2-C_6H_3 -	$C_{24}H_{21}O_6N_3F_2$ S	180	62.76	8.12	8.08	15	14	12	19	11
(4i)	5-COOH-2-NO_2-C_6H_3 -	$C_{24}H_{21}O_6N_2F_2$ S	197	74.40	8.12	8.04	15	20	19	21	19
(4j)	4-CH_3-C_6H_4 -	$C_{24}H_{24}O_2N_2F_2$ S	189	75.01	6.33	6.30	14	16	18	19	21
(5a)	C_6H_5 -	$C_{24}H_{25}N_3F_2$	158	70.91	10.68	10.65	15	18	21	22	13
(5b)	2-CH_3-C_6H_4-	$C_{25}H_{27}N_3F_2$	170	78.19	10.31	10.25	21	21	19	21	16
(5c)	3-CH_3-C_6H_4 -	$C_{25}H_{27}N_3F_2$	179	75.16	10.31	10.28	22	20	18	19	15
(5d)	4-CH_3-C_6H_4 -	$C_{25}H_{27}N_3F_2$	180	58.81	10.31	10.32	19	14	21	13	18
(5e)	2-OCH_3-C_6H_4 -	$C_{25}H_{27}N_3F_2O$	154	68.11	9.92	9.89	12	19	22	19	19
(5f)	4-OCH_3-C_6H_4 -	$C_{25}H_{27}N_3F_2O$	210	88.10	9.92	9.85	19	22	22	18	21
(5g)	2-Cl-C_6H_4 -	$C_{24}H_{24}N_3F_2Cl$	176	72.82	9.82	9.79	20	22	19	10	19
(5h)	2-NO_2-C_6H_4 -	$C_{24}H_{24}O_2N_4F_2$	157	65.41	12.78	12.70	17	12	10	12	16
(5i)	3-NO_2-C_6H_4 -	$C_{24}H_{24}O_2N_4F_2$	130	89.16	12.78	12.75	21	17	22	17	11
(5j)	4-NO_2-C_6H_4 -	$C_{24}H_{24}O_2N_4F_2$	163	74.02	12.78	12.72	11	13	14	21	15

TABLE 2: Comparable activity with known standard drugs

Antimicrobial activity : Conclusion : Maximum antimicrobial activity

Compd.	*B.Substillis*	*B.Cerus*	*E.Coli*	*E.arogen*	*A.niger*
(3a-3j)	3a,3f,3g,3h	3b,3c,3d,3e,3j	3a,3b,3c,3d,3e,3g,3i,3j	3a,3b,3e,3i	3c,3f,3h,3j
(4a-4j)	4a,4b,4c,4f,4g	4b,4c,4e,4f,4g,4i	4c,4d,4e,4f,4g,4i	4b,4c,4f,4h,4j	4c,4d,4e,4f,4i,4j
(5a-5j)	5b,5c,5f,5g,5i	5a,5b,5c,5f,5g	5a,5b,5c,5d,5f,5g,5i	5a,5b,5c,5d,5j	5c,5f,5g

Activity of standard drugs

Standard drugs	*B.Substillis.*	*B.Cerus*	*E.Coli*	*E.arogen*	*A.niger*
Ampicillin (50 μg/ml)	21	19	19	21	-
Chloramphanicol (50 μg/ml)	24	20	25	23	-
Norfloxacin (50 μg/ml)	25	20	25	24	-
Griseofulvin (50 μg/ml)	-	-	-	-	24

piperazine (2.88 gm, 0.01M) and 4-methoxybenzoyl chloride (1.70gm, 0.01M), pyridine(10 ml) was heated on an oil bath at 120°C for 5-6 hours. The reaction mixture was cooled and poured in to crushed ice, neutralized with diluted hydrochloric acid, filter it and washed with water. The isolated product was crystallized from methanol. M.P. 129°C; yield 63.71%, (Found : C:71.04; H:5.60; N:6.61; $C_{25}H_{24}F_2N_2O_2$ requried C:71.08; H:5.68; N:6.63 %), IR. (KBr); 2964 (C-H str, asym); 2816 (C-H str, sym); 1462 (C-H def.); 3003 (C-H aromatic); 833 (C-H-o. o.p.); 1369 (C-N str.); 1637 (C=O str.); 1253 (C-O-C str); ^{1}HNMR (CD_2Cl_2): 2.2-3.6 (8H, d, CH_2-) 3.8 (S, 3H, -OCH3); 6.7-7.2 (12H, m, Ar-H); 5.2 (S, C-H). m/z: 91, 155, 183, 203, 243, 273, 287,347, 422.

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

1-[(4‴-Methylphenyl)sulpho]-4-[(4′,4″-difluoro diphenyl)-methyl]- piperazine(4j)

A mixture of 1-[(4′,4″-difluorodiphenyl)-methyl]-piperazine (2.88gm. 0.01M), 4-methylphenylsulphonyl chloride (1.90g, 0.01M), pyridine(10 ml) was heated in a oil bath at 120^{0}C for 5-6 hours. The reaction mixture was cooled and poured into crushed ice, neutralized with diluted hydrochloric acid. The product is filtered, wash with water and crystallized from isopropyl alchohol. M.P. 189^{0}C, yield 75% (Found C:65.10; H:5.41; N:6.30; $C_{24}H_{24}F_2N_2O_2S$, required C:65.15; H:5.42; N:6.33; %). IR. (KBr):); 2962 (C-H str, asym); 2814(C-H str, sym); 1454 (C-H def.); 3010 (C-H aromatic); 829 (C-H- o.o.p.); 1220 (C-N str.); 1329 (S=O str, asym) 1172 (S=O str, sym); ^{1}HNMR (CD_2Cl_2); 4.3-4.9 (11H, m, –CH_3, CH_2-); 8.8-9.5 (12H, m, Ar-H); 6.1 (S, C-H) m/z: 56, 91, 109, 155, 183, 203, 273,287, 347, 442.

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

1-[(4‴-Methoxyphenyl)aminomethyl]-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazine(5f)

A mixture of 1-[(4′, 4″-difluorodiphenyl)-methyl]-piperazine.(2.88gm, 0.01M),4-methoxyaniline(1.23gm, 0.01M),formaldehyde(1 ml), concentrated hydrochloric acid(2 ml) and methanol(25 ml) was refluxed for 6 hrs. The contents were cooled and poured into crushed ice, neutralized with 10% $NaHSO_3$ solution. The isolated product was filtered washed with water. The product was crystallized from ethanol. M.P. 210^{0}C, yield 88.10%. (Found C: 70.88; H:6.30; N:9.85; $C_{25}H_{27}F_2N_3O$ required C:70.92; H:6.38; N:9.92; %). IR (KBr): 2958 (C-H str., asym.); 2877 (C-H str., sym.); 1467 (C-H def.); 3047 (C-H aromatic); 827 (C-H- o.o.p.); 1155 (C-N str.); 1232 (C-O-C str.) 3110 (C-NH); ^{1}HNMR (CD_2Cl_2); 1.9-2.3 (8H d, -CH_2-); 3.8 (S, 3H, -OCH3); 6.8-7.2 (12H, m, Ar-H); 5.2 (S, C-H); 2.7 (S, NH-). m/z: 56, 70, 99, 183, 203, 230, 244, 287,302, 423.

Similarly other compounds **(5a-5j)** were prepared and their physical data are recorded in TABLE 1.

Summary

1-Aroyl-4-[(4′,4″- difluorodiphenyl) - methyl]-piperazines **(3a-3j)**; 1-Aryl sulpho-4 - [(4′,4″-difluorodiphenyl)-methyl] – piperazines **(4a-4j)**; 1-Aryl aminomethyl-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazines **(5a-5j)** have been synthesized. Some of the compounds showed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration 50μg/ml, which is represented in TABLE 2.

ACKNOWLEDGMENT

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**, **1961**, 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)(C1A61k31/215); Chem. Abstr., **101**, 54722j **(1984)**.
[7] M.Puttemans et al.; J.Liqchromato, **7**, 2237 **(1984)**.
[8] M.Masaaki, M.Takashi, K.Nobukiyo, T.Kazuhiko, Igari et al.; Chem.Abstr., **129(9)**, 121754 **(1997)**.
[9] D.M.Purohit, V.H.Shah; Ind.Jou.of Hetero.Chem., **8**, 67-70 **(1998)**.
[10] D.M.Purohit, D.S.Mehata, V.H.Shah; Heterocyclic Communication, **2(5)**, 469-474 **(1996)**.
[11] A.L.Barry; Antimicrobic Succeptibility Test, Principle and Practice, 180-193 **(1993)**.