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Synthesis and biological screening of 1-N-{4'-[(4",4"'-difluoro diphenyl)- methyl]-piperazine-1'-yl}-4-arylidene-2-(4""-methoxyphenyl)-5-oxo-imidazolines

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ABSTRACT

1-N-{4'-[(4",4"'-difluorodiphenyl)-methyl]-piperazine-1'-yl}-4-arylidene-2-(4""-methoxy phenyl)-5-oxo-imidazolines **(3a-3j)** have been synthesized by the condensation of 1-amino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine with different oxazolones. 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.

KEYWORDS

5-oxo-imidazolines
(Heterocyclic chemistry).

INTRODUCTION

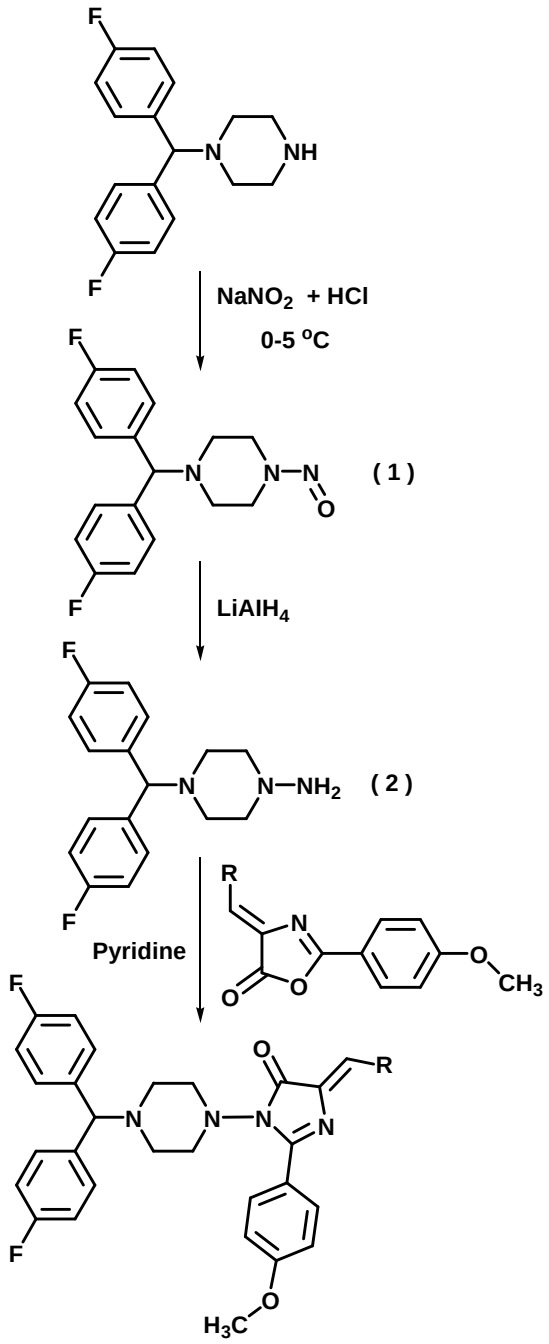
Piperazine derivatives play a vital role largely due to the wide ranging biological activities. Piperazine are known to exhibit wide spectrum of biodynamic activity. Taking into consideration diverse biodynamic activities analgesic[1], antibacterial[2], antidiabatic[3], antifungal[4], antiulcer[5,6], antihistamine[7], anthelmintic[8], anti-inflammatory[9] etc. In the fact of these interesting biological activities, in view of getting to synthesised some new 5-oxo-imidazoline[10-13] derivatives bearing 1-amino-4-[(4',4"-difluoro diphenyl)-methyl]-piperazine nucleus. 5-oxo-imidazoline derivatives have been synthesized by the condensation of 1-amino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine with different oxazolones. All the products **(3a-3j)** 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)** were tested for their antimicrobial activity by cup-plate method[14] 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)** showed moderate to good and remarkable activities with known standard drugs at same concentration, which is represented in TABLE 2

Reaction Scheme



5-oxo-imidazolines (3a-3j) **R = Aryl**

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 benzene 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

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

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 -	$C_{34}H_{30}O_2N_4F_2$	164	64.22	9.92	9.90	16	19	14	22	18
3b	2-OH-C_6H_4-	$C_{34}H_{30}O_3N_4F_2$	127	66.37	9.65	9.60	22	16	22	18	21
3c	4-OH-C_6H_4 -	$C_{34}H_{30}O_3N_4F_2$	130	71.42	9.65	9.62	13	20	18	16	15
3d	2-OCH_3-C_6H_4 -	$C_{35}H_{32}O_3N_4F_2$	152	70.65	9.42	9.41	20	17	20	16	22
3e	4-OCH_3-C_6H_4 -	$C_{35}H_{32}O_3N_4F_2$	117	69.52	9.42	9.40	19	22	16	20	18
3f	2-Cl-C_6H_4 -	$C_{34}H_{29}O_2N_4F_2Cl$	154	64.43	9.35	9.32	21	15	23	14	16
3g	4-F-C_6H_4 -	$C_{34}H_{29}O_2N_4F_3$	172	65.75	9.62	9.60	17	23	20	22	23
3h	2-NO_2-C_6H_4 -	$C_{34}H_{29}O_4N_5F_2$	168	59.00	11.49	11.46	24	15	17	15	14
3i	3-NO_2-C_6H_4 -	$C_{34}H_{29}O_4N_5F_2$	145	60.45	11.49	11.45	23	16	22	21	21
3j	C_4H_3O -	$C_{32}H_{28}O_3N_4F_2$	135	68.71	10.10	10.08	14	22	20	17	17

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	3c,3e,3g,3j	3b,3d,3f,3g,3i,3j	3a,3b,3e,3g,3i	3b,3d,3g,3i

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

(DMF): 2.19-2.23 (4H, d d, N-CH_2); 2.66-2.71 (4H, 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 4-(4"-methoxybenzylidene)-2-(4'-methoxyphenyl)-5-oxazolone

A mixture of [(4-methoxybenzoyl)amino]-acetic acid (6.06gm, 0.029M), acetic anhydride (3.26gm, 0.032M), sodium acetate(2.62gm, 0.032M**)** and 4-methoxy benzaldehyde (4.35gm, 0.032 mol) was heated on a water bath for 4 hrs. Resulting mass poured into ice cold water, filtered and crystallized from acetone and water. Yield: 82%, M.P. 185°C.

Similarly, other oxazolones have been prepared by Erlen Meyer oxazolone method[15].

Synthesis of 1-N-{4'-[(4", 4"'- difluorodiphenyl) - methyl] - piperazine - 1'-yl}- 4 -(4""'-methoxybenzylidene)-2-(4""-methoxyphenyl)-5-oxo-imidazolines (3e)

A mixture of 1-amino-4-[(4',4"-difluorodiphenyl)-methyl]-piperazine (3.03gm, 0.01M) and 4-(4"-methoxybenzylidene)-2-(4'-methoxyphenyl)-5-oxazolone (3.09 gm, 0.01 M) in dry pyridine (20 ml) was refluxed for 12 hrs. in oil bath. Resulting mass was poured into crushed ice and neutralized with dil. HCl, filtered and the product was recrystallized from 1,4-dioxan.Yield: 69.52 %, M.P.117°C. ($C_{35}H_{32}O_3N_4F_2$; Required : C: 70.69; H: 5.42; N: 9.42; Found : C: 70.67; H: 5.39; N: 9.40 %), IR.(KBr); 2937(C-H str.asym.), 2866(C-H str.sym.), 1469(C-H def. asym.), 1377(C-

H def. sym.), 3055(C-H str. aromatic), 1579(C=C str. aromatic), 1259(C-H i.p. def.), 761(C-F str.), 1311(C-N str. piperazine), 1228(C-O-C str.), 1099(C-N str.), 1608(C=N str.), 1633(C=O str.).; ^{1}HNMR($CDCl_3$): 2.50-2.51 (8H, d, N-CH_2), 3.73 (6H, s, Ar-OCH_3), 5.20 (1H, s, C-H), 6.68-6.70 (2H, d, Ar-H), 6.91-6.99 (2H, d, Ar-H), 7.27-7.34 (4H, t, Ar-H), 7.55-7.59 (4H, t, Ar-H), 7.66-7.73 (2H, d, Ar-H), 7.89-7.93 (2H, d, Ar-H), 8.47 (1H, s, C-H).; m/z : 84, 96, 108, 123, 134, 180, 194, 204, 220, 276, 288, 303, 318, 332, 380, 392, 404, 430, 448, 475, 488, 500, 550, 594.

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

CONCLUSION

1-N-{4'-[(4'',4'''-difluorodiphenyl)-methyl]-piperazine-1'-yl}-4-arylidene-2-(4''''-methoxy phenyl)-5-oxo-imidazolines **(3a-3j)** have been synthesized and some of the compounds **(3b)**, **(3d)**, **(3g)**, **(3i)**, 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.

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