Synthesis and Properties of Some 2,3-Disubstituted 6-Fluoro-7-(4-methyl-1-piperazinyl)quinoxalines

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The 2,3-disubstituted 6-fluoro-7-(4-methyl-1-piperazinyl)- quinoxalines (**3-11**) were synthesized for bioassay *via* reaction of 1.2-diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**2**) with the appropriate 1,2-dicarbonyl compounds. However, none of the tested compounds **3-11** showed significant *in vitro* activity against *E. coli* ATCC11229, *S. aureus* ATCC6538 and *C.albicans* SATCC10231.

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Introduction.

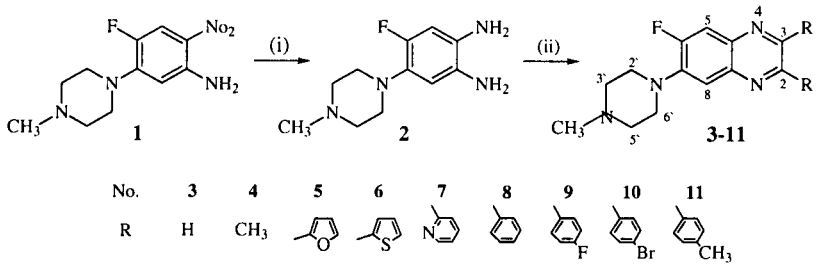
A number of quinoxaline derivatives possess antifungal [1] and anticancer [2,3] activities. Moreover, several quinoxaline derivatives show antidiabetic [4], antiallergic [5,6], angiotensin II receptor antagonistic [7] properties as well as adenosine binding [8] and benzodiazepine receptor binding [9] activities. However, quinoxalines incorporating both, fluorine and piperazine substituents at 6- and 7-positions have not been hitherto described in the literature. Such substituents might together enhance and/or modify the bioactivity of the substituted quinoxalines. This is deduced from the fact that the presence of both, fluorine and piperazine as substituents in the 4-quinolone core/moiety led to considerable enhancement of the antibacterial potency of the second generation 'Fluoroquinolones' such as Ciprofloxacin [10] and Amifloxacin [11]. On this basis, and continuing our research in the field of synthesis and bioassay of appropriately substituted heterocycles [12-16], we report here the synthesis of some of 2,3-disubstituted 6-fluoro-7-(4-methyl-1-piperazinyl) quinoxalines (3-11) for bioassay.

Results and Discussion.

The target quinoxalines **3-11** were synthesized by the reaction of 4-fluoro-5-(4-methyl-1-piperazinyl)-1,2-phenylenediamine (**2**) with the appropriate 1,2-dicarbonyl compounds (Scheme 1). The required diamine **2** is obtained by reduction of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**1**) with stannous chloride in concentrated hydrochloric acid. The steps involved in the preparation of the *o*-nitroaniline precursor **1** have been previously described [16]. Physical and analytical data for the new compounds **3-11** are shown in Table 1.

All the new quinoxaline derivatives (**3-11**) were further transformed into the respective hydrochlorides and tested *in vitro* against *E. coli* ATCC11229, *S. aureus* ATCC6538 and *C.albicans* SATCC10231. The *in vitro* antibacterial activity was evaluated by the minimal inhibitory concentration (MIC) technique according to the macrodilution method [17]. The positive control was the commercial antibacterial Ciprofloxacine. However, none of the above compounds showed any significant activity at concerntrations <80 μg/ml.

Scheme 1



(i): $SnCl_2$ + concentrated HCl, NaOH; (ii): RCO-COR / EtOH.

Table 1
Experimenta and Analytical Data

Compound	Yield (%)	mp°	Molecular Formula	[M]+	Analysis (Calcd./Found) C	H	N
3	82	224-225	$C_{13}H_{15}N_4F$	246	63.40	6.14	22.75
					63.37	6.13	22.68
4	85	176-177	$C_{15}H_{19}N_4F$	274	65.67	6.98	20.42
					65.60	6.95	20.36
5	89	131-133	$C_{21}H_{19}N_4FO_2$	378	66.66	5.06	14.18
					66.53	5.01	14.69
6	75	169-170	$C_{21}H_{19}N_4FS_2$	410	61.44	4.66	13.65
					61.38	4.61	13.64
7	89	215-217	$C_{23}H_{21}N_6F$	400	68.98	5.29	20.99
					68.96	5.24	20.93
8	77	165-167	$C_{25}H_{23}N_4F$	398	75.35	5.82	14.06
					75.23	5.80	13.99
9	80	178-180	$C_{25}H_{21}N_4F_3$	434	69.11	4.87	12.90
					68.97	4.90	13.00
10	73	208-209	$C_{25}H_{21}N_4FBr_2$	556	53.98	3.80	10.07
					53.91	3.81	9.99
11	84	219-221	$C_{27}H_{27}N_4F$	426	76.03	6.38	13.14
					75.95	6.38	13.11

EXPERIMENTAL

The 1,2-dicarbonyl compounds used in this work were commercial samples, and 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (1), required in the present work, is prepared from 3-chloro-4-fluoroaniline by a sequence of steps involving acylation, nitration and deacylation followed by reaction with *N*-methylpiperazine according to puplished procedures [16]. Melting points were determined on an electrothermal melting temperature apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Bruker AM 250 MHz instrument in deuteriochloroform ($CDCl_3$) using TMS as internal standard. Mass spectra (electron impact) were obtained on a Varian CH-7 spectrometer at 70 eV; the temperature of the ion source was 200°.

1,2-Diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**2**).

This key intermediate was prepared by reducing 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (1) (5.0 g, 20 mmol) with stannous chloride (22.44 g, 120 mmol) in concentrated hydrochloric acid (100 ml) as described in the literature [12]. Yield 2.7 g (61%); mp 97-98° (lit[12] mp 96-97°).

2,3-Disubstituted 6-fluoro-7-(4-methyl-1-piperazinyl)quinoxalines **3-11**.

General Procedure.

To a stirred solution of 4-fluoro-5-(4-methyl-1-piperazinyl)-1,2-phenylenediamine (**2**) (1.12 g, 5.0 mmol) in ethanol (5 ml) was added dropwise at room temperature a solution of the corresponding 1,2-dicarbonyl compound (5.1 mmol); in the case of compound 3, 2,3-dihydrodioxine was added in ethanol (5 ml). The mixture was stirred overnight. The resulting precipitate was collected and recrystallized from dichloromethane/petroleum ether to give the title compounds. The following compounds were prepared by the above procedure:

6-Fluoro-7-(4-methyl-1-piperazinyl)quinoxaline (**3**).

This compound was obtained as brown prisms; ^1H nmr: d 2.39 (s, 3H, N-CH_3), 2.67 (bt, 4H, C3'-H/ C5'-H), 3.32 (bt, 4H, C2'-H/ C6'-H), 7.45 (d, 1H, H-8, J_{H-F} = 9.2 Hz),7.66 (d, 1H, H-5, J_{H-F} = 13.4 Hz), 8.66 (d, 1H, H-2, J = 2.1 Hz), 8.72 (d, 1H, H-2, J = 2.1 Hz); ms m/z: 246 (M+, 100%).

6-Fluoro-2,3-dimethyl-7-(4-methyl-1-piperazinyl)quinoxaline (**4**).

This compound was obtained as white prisms; ^1H nmr: d 2.37 (s, 3H, N-CH_3), 2.60-2.70 (m., 10H, C2-CH3, C3-CH3, C3'-H/ C5'-H), 3.24 (bt, 4H, C2'-H/ C6'-H), 7.34 (d, 1H, H-8, JH-F = 9.2 Hz),7.51 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 274 (M+, 100%).

6-Fluoro-2,3-di(2-furyl)-7-(4-methyl-1-piperazinyl)quinoxaline (**5**).

This compound was obtained as yellow needles; ^1H nmr: d 2.39 (s, 3H, N-CH_3), 2.66 (bt. 4H, C3'-H/ C5'-H), 3.33 (bt, 4H, C2'-H/ C6'-H), [6.54-6.62 (m, 4H), 7.60-7.66 (m, 2H), and furyl H-3, H-4, H-5], 7.51 (d, 1H, H-8, J_{H-F} = 8.9 Hz),7.69 (d, 1H, H-5, J_{H-F} = 13.4 Hz); ms m/z: 378 (M+, 100%).

6-Fluoro-7-(4-methyl-1-piperazinyl)-2,3-di(2-thienyl)quinoxaline (**6**).

This compound was obtained as yellow needles; ^1H nmr: d 2.39 (s, 3H, N-CH_3), 2.66 (bt, 4H, C3'-H/ C5'-H), 3.32 (bt, 4H, C2'-H/ C6'-H), [7.00-7.05 (m, 2H), 7.17-7.21 (m, 2H), 7.42-7.49 (m, 3H), H-8, and thienyl H-3, H-4, H-5], 7.64 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 410 (M+, 33%).

6-Fluoro-7-(4-methyl-1-piperazinyl)-2,3-di(2-pyridyl)quinoxaline (**7**).

This compound was obtained as yellow prisms; ^1H nmr: d 2.40 (s, 3H, N-CH_3), 2.68 (bt, 4H, C3'-H/ C5'-H), 3.36 (bt, 4H, C2'-H/ C6'-H), [7.20-7.27 (m, 2H), 7.74-7.89 (m, 5H), 8.38-8.43 (m, 2H), H-5, and pyridyl H-3, H-4, H-5, H-6], 7.60 (d, 1H, H-8, J_{H-F} = 7.60 Hz); m/z: 400 (M+; 100%).

6-Fluoro-7-(4-methyl-1-piperazinyl)-2,3-diphenylquinoxaline (**8**).

This compound was obtained as yellow needles; ^{1}H nmr: d 2.40 (s, 3H, N-CH_3), 2.67 (bt, 4H, C3'-H/ C5'-H), 3.33 (bt, 4H, C2'-H/ C6'-H), [7.30-7.34 (m, 6H), 7.46-7.50 (m, 4H), C2- and C3-phenyl], 7.55 (d, 1H, H-8, J_{H-F} = 8.9 Hz), 7.73 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 398 (M+, 100%).

6-Fluoro-2,3-di(4-fluorophenyl)-7-(4-methyl-1-piperazinyl)-quinoxaline (**9**).

This compound was obtained as yellow prisms; ^{1}H nmr: d 2.31 (s, 3H, N-CH_3), 2.58 (bt, 4H, C3'-H/ C5'-H), 3.25 (bt, 4H, C2'-H/ C6'-H),[6.91-6.99 (m, 4H), 7.35-7.44 (m, 5H), H-8 and C2- and C3-(4-fluorophenyl)], 7.61 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 434 (M+, 100%).

2,3-Di(4-bromophenyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-quinoxaline (**10**).

This compound was obtained as yellow needles; ^{1}H nmr: d 2.31 (s, 3H, N-CH_3), 2.58 (bt, 4H, C3'-H/ C5'-H), 3.24 (bt, 4H, C2'-H/ C6'-H), [7.25 (d, 2H, Hz = 1.2), 7.28(d, 2H, Hz = 1.2), 7.37-7.42 (m, 5H), H-8 and C2- and C3-(4-bromopheny)], 7.60 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 556 (M+, 10%).

6-Fluoro-7-(4-methyl-1-piperazinyl)-2,3-di(4-tolyl)quinoxaline (**11**).

This compound was obtained as yellow prisms; ^{1}H nmr: d 2.36 (s, 6H, Ph-CH_3, Ph'-CH_3) 2.52 (s, 3H, N-CH_3), 2.86 (bt, 4H, C3'-H/ C5'-H), 3.43 (bt, 4H, C2'-H/ C6'-H), [7.14 (d, 4H, J = 8.6 Hz), 7.38(d, 4H, J = 8.2 Hz) C2- and C3-(4-tolyl)], 7.54 (d, 1H, H-8, J_{H-F} = 8.9 Hz), 7.71 (d, 1H, H-5, J_{H-F} = 13.1 Hz); ms m/z: 426 (M+, 100%).

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