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SYNTHESIS AND EVALUATION OF N-SUBSTITUTED 1-(5-FLUORO-2-PYRIMIDINYL)PIPERAZINE DERIVATIVES AS POTENTIAL ANTI-ISCHEMIC AGENTS

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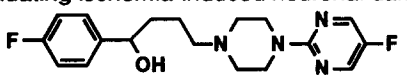
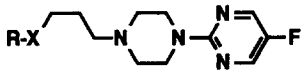
Abstract: A number of N-substituted 1-(5-fluoro-2-pyrimidinyl)piperazine derivatives were prepared and evaluated for binding to sigma and serotonin 5-HT_{1A} and 5-HT_2 receptor subtypes as well as for their protection against nitrogen anoxia-induced lethality in rats. Although various compounds exhibited good binding affinity and/or anti-anoxic effects, there was no obvious correlation between their receptor binding and in vivo effects.

We have previously described BMY-14802 (**1**, also designated BMS-181100[1]) and analogs as having affinity for sigma binding sites as well as pharmacological properties suggestive of possible antipsychotic utility[1,2]. Other studies have corroborated the sigma site interaction of **1**[3] or have shown it to be efficacious in animal models of cerebral ischemia[4,5,6]. Insofar as **1** acts as a partial agonist at the 5-HT_{1A} serotonin receptor subtype[7,8,9], the compound's anti-ischemic activty may be ascribed to either its sigma or 5-HT_{1A} component or both. There is a growing body of evidence which indicates that the sigma "receptor" may modulate excitatory amino acid neurotransmission, especially that mediated via the NMDA receptor[6,7,10,11,12]; the role of NMDA receptor activation in ischemia and neurodegeneration is well-established by an enormous wealth of published empirical data. Although the importance of serotonergic neurotransmission in the pathophysiology of ischemic events such as stroke and the potential value of serotonergic agents in the treatment of neurodegenerative disorders remain to be elucidated, recent investigations have shown 5-HT_{1A} agonists to be as effective as NMDA antagonists and calcium channel blockers in attenuating ischemia-induced neuronal damage in rodents[13].



1, BMY-14802



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In order to determine the effects of structural permutations of the BMY-14802 molecule upon both receptor binding and anti-ischemic activity, we have

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prepared a number of compounds of type I. While these agents retain the 1-(5-fluoro-2-pyrimidinyl)piperazine pharmacophore, they bear side chains in which structural elements of **1** have been modified or replaced. Among such modifications relative to the BMY-14802 prototype are changing of the 4-fluorophenyl group to another aromatic, heteroaromatic or aliphatic moiety and/or O-acylation of the carbinol or replacement of CHOH by CH_2, O, S or CHNHR. The compounds were synthesized by the different routes depicted in Scheme 1. The key step in the preparation of several carbinol derivatives was α–acylation of γ-butyrolactone to afford intermediates II which underwent ring opening and decarboxylation upon treatment with HCl to give the γ-chloroketones III; the latter were elaborated to the target compounds by one of several alternative pathways as shown. Conversion of the carbinols to the corresponding azides was followed by catalytic reduction to the amines, IV, which were acylated or sulfonylated.

Representative compounds were tested for 5-HT_2 as well as for sigma and 5-HT_{1A} binding, employing previously cited methods[6]; IC_{50} values (drug concentration required to inhibit specific binding by 50%) were determined by measuring displacement of radioligand at 5 different test drug concentrations and are reported in Table 1. Values for BMY-14802 are also presented for comparison. Potential neuroprotective activity was assessed by a test compound's ability to block nitrogen (N_2) anoxia induced lethality in male Sprague-Dawley rats. Drugs were administered i.p. 15 minutes prior to a one minute exposure to an atmosphere of 100% nitrogen which causes all non-drug treated controls to expire within 4-5 minutes. Table 1 shows the maximal protection against N_2 lethality (number of animals surviving 2 hours after N_2 exposure/ number in test group (8 or more) X 100) at the lowest drug dose required to achieve it .

Affinity for both sigma and 5-HT_{1A} binding sites was increased ca. 10 fold as the result of replacing the fluorophenyl ring of **1** by a cyclohexyl ring (compound **2**) showing that an aromatic group at the terminus of the side chain is not essential for receptor recognition. Affinities for the 5-HT_{1A} and 5-HT_2 receptor subtypes were significantly enhanced in several analogs in which the carbinol moiety of **1** was replaced by a methylene, ether or thioether (**7, 8, 9** respectively). These same modifications appeared to increase recognition at the sigma site as well although sigma binding was totally abolished by the introduction of the sulfone moiety (compound **10**). The limited data for compound **11** suggests that the effects of combining two structural changes, each of which singularly imparts increased affinity, may be detrimental. O-acetylation of BMY-14802 (**5**) resulted in contrasting effects, i.e. a two fold drop in sigma binding but increased 5-HT receptor binding whereas both sigma and 5-HT_{1A} binding were

Scheme 1

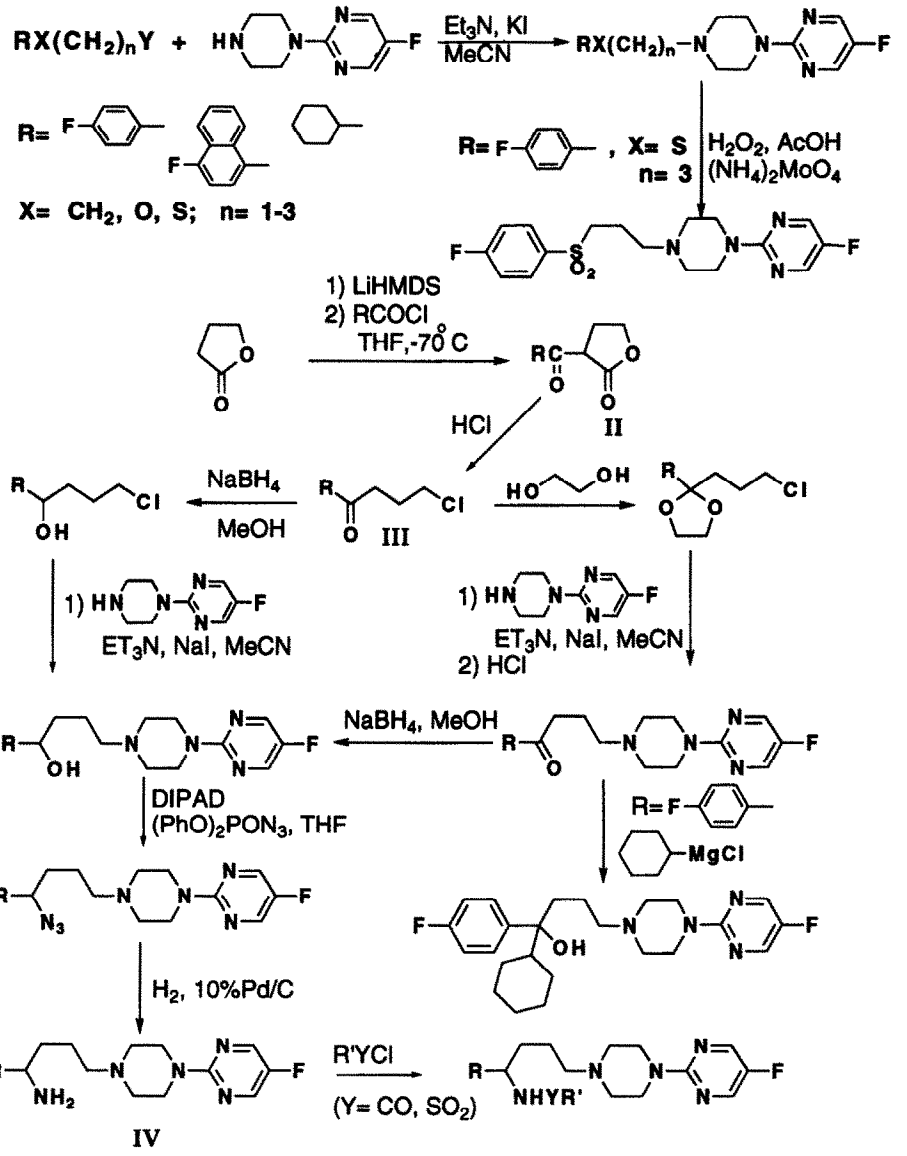
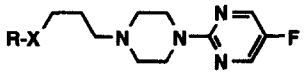

RX(CH2)nY + HN N N F
Et3N, KI
MeCN
RX(CH2)n N N N F
R= F
F
X= CH2, O, S; n= 1-3
R= F , X= S
n= 3
H2O2, AcOH
(NH4)2MoO4
F S O2 N N N F
1) LiHMDS
2) RCOCl
THF,-70° C
HCl
II
NaBH4
MeOH
III
HO OH
1) HN N N F
ET3N, NaI, MeCN
1) HN N N F
ET3N, NaI, MeCN
2) HCl
NaBH4, MeOH
DIPAD
(PhO)2PON3, THF
R= F
MgCl
H2, 10%Pd/C
R'YCl
(Y= CO, SO2)
IV

Table 1



Cmpd. No.	R	X	IC50 (nM) Sigma[a]	5-HT1A[b]	5-HT2[c]	% protection against N2 lethality (dose, mg/kg, i.p)
Carbinols & esters						
1 (BMY-14802)	4-F-C_6H_4	CHOH	112	320	1700	63 (50/100)
2	c-C_6H_{11}	CHOH	12	30	--	100 (40)
3	4-F-$C_{10}H_6$[d]	CHOH	88	562	1012	100 (100)
4	4-F-C_6H_4	c-C_6H_{11}CHOH	--	50	336	75 (40)
5	4-F-C_6H_4	CHOCOMe	227	46	504	100 (80)
6	4-F-C_6H_4	CHOCOPh	3500	581	--	63 (80)
Alkanes, ethers, thioethers, sulfones						
7	4-F-C_6H_4	CH_2	23	71	212	75(40)
8	4-F-C_6H_4	O	89	145	141	25(40)
9	4-F-C_6H_4	S	51	129	--	13(40)
10	4-F-C_6H_4	SO_2	>45K	461	--	25(40)
11	c-C_6H_{11}	CH_2	--	315	--	75(80)
12	4-F-$C_{10}H_6$	CH_2	213	414	590	100(20)
Amines & their acyl &sulfonyl derivatives						
13	4-F-C_6H_4	CHNHCOMe	>49K	289	--	13(40)
14	4-F-C_6H_4	CHNHCO-4-F-C_6H_4	>100K	106	468	88(40)
15	4-F-C_6H_4	CHNHSO2-4-F-C_6H_4	1520	1810	3400	100(80)
16	c-C_6H_{11}	$CHNH_2$	52	257	>1K	50(20)
17	c-C_6H_{11}	CHNHCO-4-F-C_6H_4	>2K	>1K	760	50(20)
18	c-C_6H_{11}	CHNHSO2-4-F-C_6H_4	504	>1K	760	50(20)
19	4-F-$C_{10}H_6$	$CHNH_2$	215	345	>1K	88(40)
20	4-F-$C_{10}H_6$	CHNHSO2-4-F-C_6H_4	>1K	--	--	38(40)

[a] vs. [^{3}H]3-PPP in whole guinea pig brain; [b] vs. [^{3}H]8-OH-DPAT in rat hippocampus; [c] vs. [^{3}H] spiperone in rat cortex; [d] 4-fluoro-1-naphthyl.

negatively impacted by the bulkier O-benzoyl group (**6**). In general, the introduction of an N-acetylated or sulfonylated amino functionality caused a marked attenuation in receptor recognition. Within this series of compounds, there is poor correlation between in vitro sigma and/or 5-HT_{1A} binding and in vivo protection against nitrogen lethality. While compounds **2** and **12** which had the highest in vivo potency and efficacy, exhibited good to moderate sigma and 5-HT_{1A} binding, several congeners that bound well at both sites (e.g. **8, 9**) showed rather weak in vivo activity. In contrast the benzamide **14** and sulfonamide **15** exhibited very effective anti-anoxic activity despite the fact that both lack sigma site affinity and **15** is also a poor ligand at the 5-HT receptor subtypes. These ambiguous findings raise some doubt as to whether the sigma or 5-HT_{1A} components of BMY-14802 are relevant to its anti-ischemic properties. There are however caveats; although the nitrogen-induced lethality test may be useful as a rapid through-put screen, it may not be a reliable predictor of activity in more stringent in vivo paradigms such as middle cerebral artery occlusion. Moreover, efforts to correlate in vitro data with whole animal test results are often complicated by pharmacokinetic and metabolic parameters. The generally weak 5-HT_2 binding of the compounds in this series suggests that interaction at the 5-HT_2 receptor is not responsible for their in vivo pharmacological effects.

In summary, it was found that both the sigma and 5-HT_{1A} receptors were tolerant toward a number of structural variations in the side chain of the lead compound, BMY-14802. While both the in vitro receptor binding affinities and the in vivo anti-anoxic effects of the latter were surpassed by those exhibited by other (5-fluoro-2-pyrimidinyl)piperazine derivatives, no nexus was clearly established between the in vitro and in vivo activities of these compounds.

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