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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3201–3204
Bioorganic & Medicinal Chemistry Letters

A new class of selective, non-basic 5-HT$_{2A}$ receptor antagonists

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Received 1 February 2006; revised 13 March 2006; accepted 16 March 2006

Abstract—Based on an existing series of 5-HT$_{2A}$ receptor ligands containing a basic nitrogen, we designed a non-basic lead that had reduced affinity for both the 5-HT$_{2A}$ receptor and the IKr potassium channel. The present paper describes the development of this lead to a novel series of non-basic piperidine sulfonamides and amides that have high affinity for the 5-HT$_{2A}$ receptor, whilst maintaining excellent selectivity over off target activities such as the IKr channel. This work has shown that the proposed pharmacaphore model for the 5-HT$_{2A}$ receptor which suggests that a basic nitrogen is required for the binding of ligands is questionable.

Serotonin (5-HT) is a major neurotransmitter that has been linked to a number of physiological processes, including appetite, emotion, changes in mood and the regulation of the sleep/wake cycle.[1] Hence, it is not too surprising that selective antagonism of the numerous 5-HT receptors has been sought after, and in a number of cases has led to useful drugs. Antagonism of the 5-HT$_2$[2] receptor, in particular, has been implicated in the beneficial effects of some antidepressants as well as antipsychotics.[3] 5-HT$_2$ receptors were first identified in 1979 and since the early 1980s, numerous, structurally diverse antagonists of this receptor have been published (Fig. 1). These include MDL-100907 which has good selectivity for the 5-HT$_{2A}$ subtype. The structural diversity of 5-HT$_{2A}$ ligands presented a challenge in terms of defining a pharmacophore model. However, pharmacophore models that have been proposed agree that two aryl rings and a basic nitrogen are required for binding at the receptor.[4] Using this model, Rowley et al. have suggested that 5-HT$_2$ antagonists can be divided into two classes: (a) those where the aryl rings and the basic nitrogen are in a triangular arrangement (Eplivanserin and **1**) and (b) those where the aryl rings and the basic nitrogen are in a linear disposition (MDL-100907 and **2**).[5]

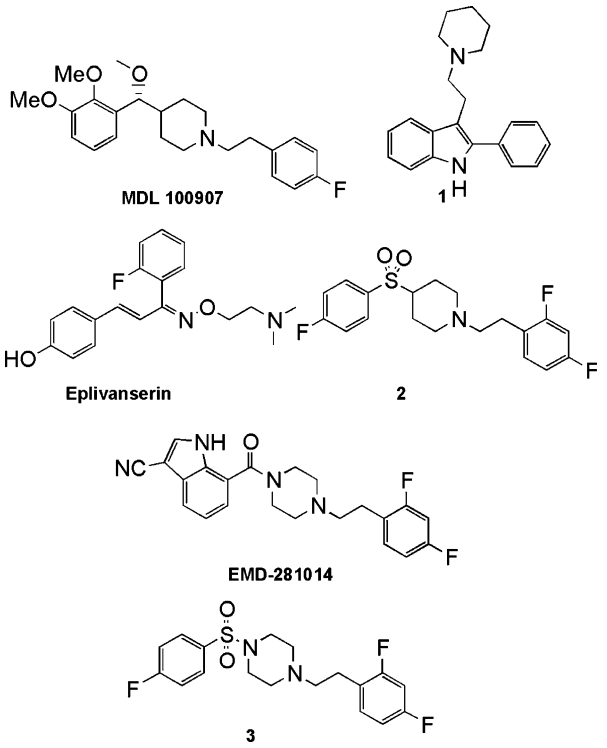

Figure 1. Selected 5-HT$_{2A}$ antagonists.

Site-directed mutagenesis studies have shown that the basic nitrogen in these ligands binds to a charged Asp155 in Helix 3 of the 5-HT$_{2A}$ receptor and is impor-

Keywords: 5-HT$_{2A}$ receptor; Antagonist; Non-basic.
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doi:10.1016/j.bmcl.2006.03.050

tant for the binding of both agonists and antagonists.[6] Hence, 5-HT, Gramine (both agonists), Ketanserin and Spiperone (both antagonists) have no affinity for D155A, D155N and D155Q mutant receptors. More recent work has suggested that the binding interaction of the basic nitrogen may be more complex than originally thought, since there may be an additional interaction of the protonated amine with a Ser159, also on Helix 3.[7] Mutating this serine again affected the binding of some agonists such as 5-HT, whilst others such as lysergic acid were not affected.

Although the basic nitrogen in 5-HT_2 receptor antagonists has been identified as being important for the binding of agonists and antagonists of the receptor, it has also been implicated in a number of undesirable side effects associated with compounds of this class. These include affinity for dopamine receptors and the IKr potassium channel, a voltage gated ion channel involved in control of the heart rhythm. Regulatory agencies are increasingly concerned about cardiovascular events following the chronic dosing of drugs, and require stringent tests to confirm their safety. The atypical antipsychotic sertindole, a compound with dual 5-HT_2/D_2 affinity, was withdrawn from the market due to the prolongation of the corrected QT interval, a consequence of its affinity for the IKr channel.[8] Designing 5-HT_{2A} ligands with little or no affinity for the IKr channel would therefore be beneficial. However, potent IKr channel blockers such as Dofetilide and Terfenadine (Fig. 2) clearly show that the pharmacophore for binding at IKr is similar to the one for binding at the 5-HT_{2A} receptor. Recent work that involved building a predictive pharmacaphore model for the IKr potassium channel concluded that the following features were important for binding: 'one positive ionisable feature, two aromatic rings and one hydrophobic group.'[9]

We have previously shown that in the sulfonylpiperidine series of 5-HT_{2A} antagonists (**2**), reducing the basicity of the piperidine nitrogen together with appropriate aromatic substitution can lead to significantly reduced binding to the IKr channel.[10] We investigated the interaction of the basic nitrogen further by synthesising the amide **4** (Fig. 3) which, although lacking a basic nitrogen that can interact with the charged Asp155, does have an amide which could perhaps interact as a hydrogen bond acceptor with Ser159. The amide **4**, however, had no

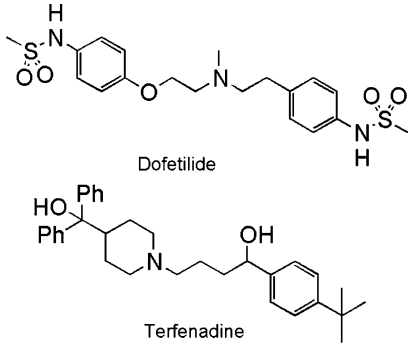


Figure 2. IKr channel blockers.

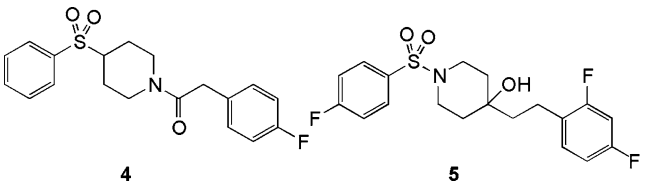
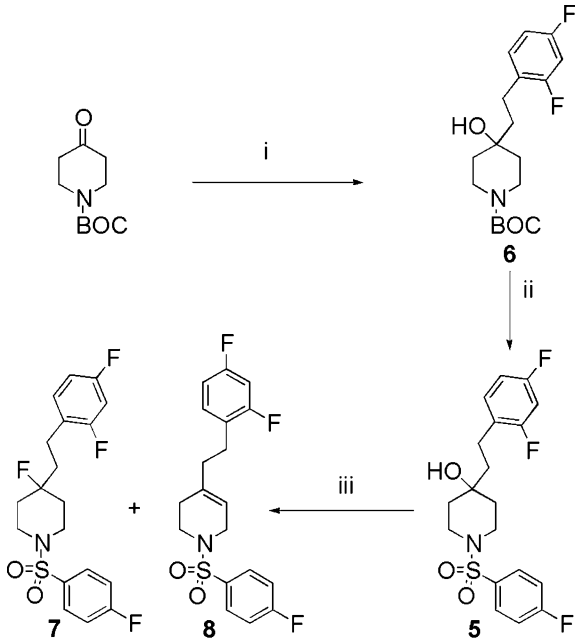


Figure 3.

affinity for 5-HT_{2A} receptors (K_i 5-HT_{2A} >5000 nM). The amide linkage in **4** restricts rotation of the phenethyl side chain and it is possible that the phenyl group is prevented from reaching a suitable position for binding.

From unpublished work in our own laboratories, and known 5-HT_{2A} ligands such as EMD-281014, we knew that piperazine amides and sulfonamides,[11] such as **3**, provide high affinity antagonists analogous to the piperidine sulfones represented by **2**. Consequently, we chose to synthesise compound **5**, again non-basic, but without the conformational restriction of the amide **4** and where the hydroxyl group can serve either as a mimic of the protonated amine or in its own right as a hydrogen bond donor/acceptor that might interact with Ser159. Gratifyingly, we found that **5** had greater affinity for the 5-HT_{2A} receptor (K_i 5-HT_{2A} 190 nM) than the amide **4**. The present paper describes the development of this lead into a novel series of non-basic piperidine sulfonamides and amides to give high affinity, selective ligands, thus disproving the generally accepted view that a basic nitrogen is crucial for binding at the 5-HT_{2A} receptor.

The 4-hydroxypiperidine **5** was synthesised by addition of the requisite Grignard reagent to *N*-BOC piperidone to give **6**, followed by deprotection, and sulfonylation of the resulting trifluoroacetate salt (Scheme 1). Treating **5**



Scheme 1. Reagents: (i) 2,4-difluorophenethyl bromide, Mg, THF; (ii) TFA, Et_3N, 4-F-phenylsulfonyl chloride, CH_2Cl_2; (iii) DAST, CH_2Cl_2.

with DAST gave a mixture of the fluoro compound **7** and the tetrahydropyridine **8** which were separated by HPLC.

The unsubstituted piperidine analogues were synthesised as shown in Scheme 2.

The substituted vinyl pyridine **9** was synthesised from commercially available vinyl pyridine via a Heck reaction.[12] Subsequent hydrogenation gave **10**, which was converted to the TFA salt of piperidine **11** using standard methodology. A small library of amides and sulfonamides was then synthesized, a selection of which is shown.

The SAR for this series of compounds with regard to binding at 5-HT_{2A} and other GPCRs (5-HT_{2C}, hD_2 and hIKr) is summarised in Table 1. The non-basic piperidine **5** lost two orders of magnitude in binding compared to the basic compounds **3** and EMD-281014. Removing the hydrogen bonding hydroxyl group gave an increase in affinity and to our surprise both the fluoro analogue **7** and the tetrahydropyridine **8** were equipotent at the 5-HT_{2A} receptor. This suggested to us that the central ring only functions as a spacer group and that it might be replaced with an unsubstituted piperidine. In fact, **12a** had a similar affinity to **7** and **8**. The 3-fluoro analogue **12b** was shown to be antagonist in the functional assay.[13] A modest increase in affinity was obtained with small substituents at the 2-position of the aryl sulfonamide (see **12c** and **12d**), The 2-cyano analogue **12e** has reduced selectivity for 5-HT_{2A} over 5-HT_{2C}. Both the naphthalene **12f** and the quinoline **12g** are comparable in 5-HT_{2A} affinity to the basic compound **3**. In contrast to the basic compounds, however, the non-basic compounds such as **12g** have improved selectivity over IKr (% inhibition 36% at 10 μM). The quinoline substituent gave the highest selectivity over 5-HT_{2c}. Replacing the sulfonamide linkage with an amide as in **13a** retains affinity for 5-HT_{2A} receptors. However, the quinoline substituent, which gave the best selectivity in the case of the sulfonamide linkage, gave reduced selectivity over 5-HT_{2C} with an amide linkage. All the compounds in this series had excellent selectivity over both the hD_2 receptor and the hIKr potassium channel.

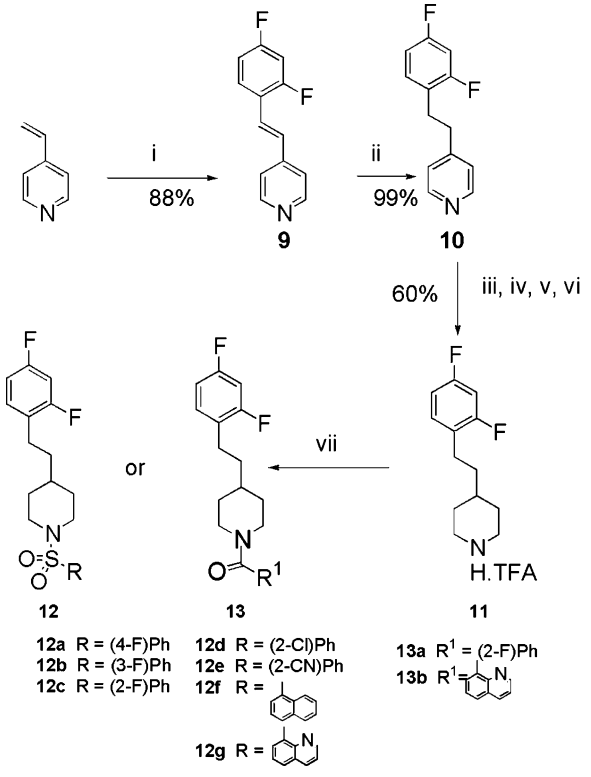
Table 1. Binding affinities

Compound	h5HT_{2A} K_i/nM[a]	h5HT_{2C} K_i/nM[a]	Selectivity[b]	hD_2 K_i/nM[a]	hIKr K_i/nM[a]
2	0.42	92	219	>1000	710
EMD281014	0.87	557	641	>1000	1268
3	4.4	3785	860	>1000	4869
5	190	>4000	—	>1000	>9000
7	24	806	33	>1000	>9000
8	22	449	22	>1000	>9000
12a	52	2033	39	>1000	>9000
12b	14	997	73	>1000	>9000
12c	9.9	239	24	>1000	>9000
12d	6.1	404	66	>1000	>9000
12e	8.1	70	9	>1000	>9000
12f	1.7	96	58	>1000	>9000
12g	2.1	184	84	>1000	>9000
13a	3.9	110	28	>1000	>9000
13b	2.9	28	10	>1000	>9000

[a] h5-HT_{2A}, h5HT_{2C}, hD_2 (dopamine) and hIKr affinities were determined as described in Ref. 3 ($n = 2$).
[b] h5-HT_{2C}/h5-HT_{2A}.

In conclusion, this work has shown that the proposed pharmacophore model for the 5-HT_{2A} receptor which suggests that a basic nitrogen is required for the binding of ligands is questionable. At least in the piperidine sulfone series exemplified by **2**, it is possible to replace the basic piperidine with a non-basic core and still retain high affinity for the 5-HT_{2A} receptor. It could be that in this series of molecules the sulfone or amide moieties present an additional key point of interaction that makes the binding of the basic amine less important. This work also shows that our initial assumption that the amide **4** was not the best compound to test whether a basic nitrogen was necessary for binding at the 5-HT_{2A} receptor was correct.

In fact, replacing the basic piperidine core with a non-basic one has enabled us to retain 5-HT_{2A} affinity whilst significantly reducing binding to the IKr channel. The fact that the basic nitrogen is not needed for 5-HT_{2A} binding in this series of compounds has opened up several possibilities that were hitherto unavailable. This work will be reported in future communications.



Scheme 2. Reagents and conditions: (i) 2,4-difluoro-iodobenzene, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, toluene, 150 °C, 5 h; (ii) Pd/C, EtOAc, H_2 (45 psi); (iii) BnBr, acetone, reflux, 16 h; (iv) $NaBH_4$, MeOH, reflux, 16 h; (v) H_2, HCl (conc.), EtOH, $Pd(OH)_2$, then NaOH, $(BOC)_2O$, dioxane; (vi) TFA; (vii) Et_3N, $ArSO_2Cl$, CH_2Cl_2 or Et_3N, ArCOCl, CH_2Cl_2.

Acknowledgments

The authors thank J. Kingston for the separation of **7** and **8**, K. Wilson for the synthesis of **4** and the CIBE Lead Evaluation group for testing our compounds.

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