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Discovery of a new series of 5-HT$_{1A}$ receptor agonists

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ABSTRACT

Starting from compounds previously identified as α_1-adrenoceptor antagonists that were also found to bind to the 5-HT$_{1A}$ receptor, in an attempt to separate the two activities, a new series of 5-HT$_{1A}$ receptor agonists was identified and shown to have high potency and/or high selectivity. Of these, compound **13**, which combines high selectivity (5-HT$_{1A}$/α_1 = 151) and good agonist potency (pD_2 = 7.82; E_{max} = 76), was found to be the most interesting.

5-HT$_{1A}$ agonists and partial agonists have been seen to be effective in the treatment of anxiety and depression.[1–5] In addition to therapeutic applications in the psychiatric field, recent preclinical studies have suggested that 5-HT$_{1A}$ receptor agonists also have important neuroprotective properties.[6]

More recently, in animal models, it was observed that 5-HT$_{1A}$ receptor activation is a new molecular mechanism of pain relief and although we are still waiting for proof-of-concept evidence in humans, 5-HT$_{1A}$ receptor agonists may rival the opioids in pain relief therapy.[7]

The 5-HT$_{1A}$ receptor belongs to the class of G-protein coupled receptors (GPCRs), whose members share a number of characteristic amino acid patterns. In particular, the transmembrane amino acid sequence of the 5-HT$_{1A}$ subtype is worthy of note for its high degree of homology to the α_1-adrenergic receptor (approximately 45%).[8] Thus, a great number of ligands show high affinity for receptor systems and poor selectivity.

We reported on a new series of 1,3-dioxolane-based α_1-adrenoceptor antagonists,[9] of which compound **1** showed the highest affinity and selectivity for the α_{1D} subtype. Given the high degree of homology of the amino acid sequence between the α_1-adrenergic and 5-HT$_{1A}$ receptors, further pharmacological investigation of compound **1** was undertaken and unsurprisingly it was found that compound **1** binds to human cloned 5-HT$_{1A}$ receptors with a similarly high affinity (pK_i = 8.45). Moreover, functional experiments showed that compound **1** behaves in the same way as partial agonists (pD_2 = 8.80, %E_{max} = 24). This observation prompted us to conduct further research on this new class of compound with the aim of separating the two activities and very recently we reported on a first structure–activity relationship study.[10] Here, as a continuation of that study, we report on the synthesis of a new set of derivatives (**3–6 and 8–17**) and pharmacological evaluation together with previously synthesised compounds (**2** and **7**).

The compounds under investigation were synthesised (Scheme 1) using standard procedures and characterised by ^{1}H nuclear magnetic resonance (NMR) spectroscopy and elemental analysis. The chloro-derivatives, prepared as described previously,[9,11] were aminated in 2-methoxyethanol in the presence of a catalytic amount of KI, with the appropriate amine either commercially available or prepared in-house by obtaining a reaction between chloroacetamide and the appropriate phenol, followed by reduction with diborane.[12] The free bases were then transformed into the corresponding oxalate salts.

The pharmacological profile of compounds **1**–**17**, and BMY-3748 and 8-OH-DPAT as reference compounds, was determined at the α_1-adrenoceptors on different isolated tissues. Blocking activity was assessed by the antagonism of (−)-noradrenaline-induced contraction of rat prostatic vas deferens (α_{1A}) or thoracic aorta (α_{1D}) and by the antagonism of (−)-phenylephrine-induced contraction of rat spleen (α_{1B}). Radioligand binding assay using [^{3}H]prazosin to label cloned human α_1-adrenoceptors expressed in CHO cells, and [^{3}H]8-OH-DPAT to label cloned human 5-HT$_{1A}$ receptor expressed in HeLa cells was also used. Functional charac-

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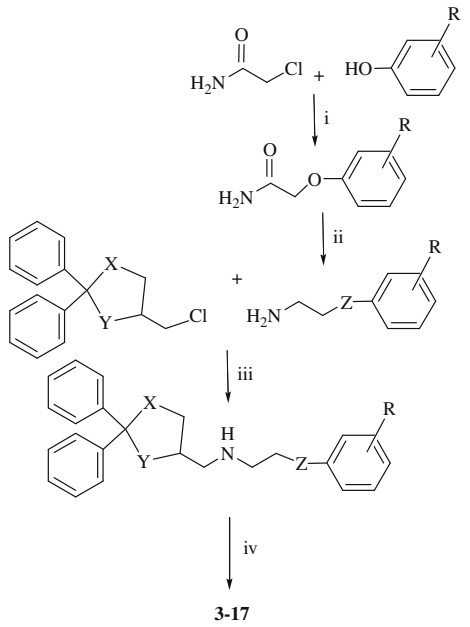

Comp	X	Y	Z	R	Comp	X	Y	Z	R
1	O	O	O	H	**11**	O	O	O	2-OC_2H_5
2	O	O	O	2-OCH_3	**12**	O	O	O	2-*i*OC_3H_7
3	O	O	O	2-CH_3	**13**	O	O	O	2-C_6H_5
4	O	O	CH_2	2-OCH_3	**14**	O	O	O	3-C_6H_5
5	O	O	O	3-OCH_3	**15**	O	O	O	4-C_6H_5
6	O	O	O	4-OCH_3	**16**	S	O	O	2-OCH_3
7	O	O	O	2,6-diOCH_3	**17**	S	S	O	2-OCH_3
8	O	O	O	2,3-diOCH_3					
9	O	O	O	3,4-diOCH_3					
10	O	O	O	3,5-diOCH_3					

Scheme 1. Reagents: (i) Na/C_2H_5OH; (ii) BH_3, diglyme; (iii) KI, 2-methoxyethanol; (iv) $C_2O_4H_2$, Et_2O.

terisation of certain selected compounds at the 5-HT_{1A} receptor was performed according to the method of Stanton and Beer, using [^{35}S]GTPγS binding, in the cell membranes of HeLa cells transfected with human cloned 5-HT_{1A} receptor. For experimental details see Ref. 10.

Preliminary results with enantiomers of compound **1** showed an eudismic ratio of about 2–4 (*R*/*S*), therefore all the compounds were tested as racemates.

Table 1 lists the pharmacological results. As reported previously, in functional studies, compound **1** showed selectivity to the α_{1D} subtype 160- and 324-fold that for the α_{1A} and α_{1B} subtypes, respectively. This selectivity was confirmed, albeit to a lesser extent, in binding studies. Its 2-methoxy derivative **2** shows lower selectivity as a result of an increase in activity/affinity to the α_{1A} and α_{1B} subtypes. The two compounds bind to the 5-HT_{1A} receptor with an even higher affinity than the α_1-adrenergic receptors. Again in this case, compound **2** binds better than compound **1**, indicating the positive role played by the methoxy group in the binding process. However, the agonist potency is negatively affected, since the pD_2 value of 7.36 is about 28 times lower than that of the parent compound **1**. Therefore, as in the case of the α_1-adrenergic receptors, the 2-methoxy group increases binding affinity whilst the potency at the 5-HT_{1A} receptor is reduced more than 10-fold.

The 2-methyl derivative **3** decreases affinity and activity at both receptor systems (α_1 and 5-HT_{1A}) suggesting that the oxygen atom of the methoxy group is primarily responsible for the increased affinity and potency between **1** and **2**. Moreover, the oxygen atom of the phenoxyethyl chain seems to play a similar role. In fact, the O/CH_2 isosteric substitution of compound **2** to obtain compound **4** gives very similar results in terms of both affinity and activity at both the α_1 and 5-HT_{1A} receptors. Particularly, in functional experiments at the α_1-adrenergic receptors the decrease in potency reaches 100-fold as in the case of the α_{1D} subtype. At the 5-HT_{1A} receptors, the 13-fold decrease in affinity is accompanied by a 18-fold decrease in potency (pD_2 = 5.92 vs 7.36 for compound **1**) and efficacy (E_{max}) is halved.

By moving the methoxy group to 3-(**5**) and 4-position (**6**) a general reduction in affinity and potency is observed, indicating its crucial role when in 2-position. The dimethoxy substitution (**7–10**) also seems to determine a general decrease in affinity of the same order of magnitude and of the four disubstituted derivatives the one with the highest affinity, at least at the 5-HT_{1A} receptors, is compound **8**, which maintains the same selectivity for the 5-HT_{1A} receptors as reference compound **2**.

To investigate other substituents at 2-position, we prepared compounds **11**, **12** and **13**. Ethoxy (**11**) and propoxy (**12**) derivatives show a small decrease in 5-HT_{1A} receptor affinity and an increased affinity at the α_1-adrenergic receptor subtypes, thus resulting in a significant decrease in selectivity. In terms of activity, while at the α_1-adrenergic receptor subtypes it is slightly decreased, with the largest variation of about 10-fold observed at the α_{1D} subtype, at the 5-HT_{1A} receptors the agonist potency increases about 50-fold (pD_2 = 9.08 vs 7.36). When a phenyl ring (**13**) replaces the methoxy group, a reduction of affinity is seen at both the receptor systems. At 5-HT_{1A} this reduction is of about threefold, whereas at the α_1-adrenergic receptors it ranges 10–35-fold, resulting therefore in a strong enhancement of selectivity (151). The agonist potency at the 5-HT_{1A} receptors remains unchanged whilst efficacy doubles. Therefore, by replacing the methoxy group with a phenyl ring, a positive effect on selectivity and efficacy of stimulation at the 5-HT_{1A} receptor is observed.

Finally, by replacing the oxygen with a sulfur atom at 3-position to give the 1,3-oxathiolane **16**, the affinity at the α_1- and 5-HT_{1A} receptors is barely affected whereas from a functional point of view a 10-fold decrease at the α_{1A} subtype and 10-fold increase at the α_{1B} subtype are observed. At the 5-HT_{1A} receptors, potency increases 38-fold (pD_2 = 8.94) and efficacy doubles (E_{max} = 76%).

When both oxygens are replaced by sulfur atoms to give 1,3-dithiolane **17**, the affinity at the 5-HT_{1A} increases (fivefold) whereas at the α_1-adrenoceptors it decreases up to 13-fold, as in the case of the α_{1D} subtype, thus raising the selectivity ratio to 158. The antagonist potency at the α_1 subtypes is decreased, whereas at the 5-HT_{1A} potency increases threefold.

These latter results parallel those recently reported[10,13] and seem to confirm that going from 1,3-dioxolane to 1,3-oxathiolane or 1,3-dithiolane one or more pharmacological parameters that favour 5-HT_{1A} receptor activity are clearly observed. In the case of 1,3-oxathiolane, the enhanced parameter is potency whereas in the case of 1,3-dithiolane, selectivity is positively effected. A far larger series of derivatives will have to be studied to ascertain whether or not this is a general trend.

In order to better rationalise the results obtained, a pharmacophoric model was derived, from five of the most potent and selective 5HT_{1A} receptor agonists described in the literature (Chart 1),[1,14–17] and compound **13**, the most interesting of the series.

Starting from the best geometries obtained by conformational analysis, a common alignment was derived using the MOE pharmacophore search module (MOE, Chemical Computing Group Inc., Montreal, H3A 2R7 Canada, http://www.chemcomp.com),