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THE DISCOVERY OF A SERIES OF NEW NON-INDOLE 5HT1D AGONISTS

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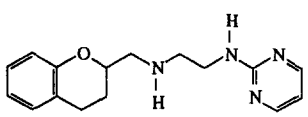
Abstract

The synthesis and SAR of a series of non-indole $5HT_{1D}$ agonists is described. The most interesting molecule of this series is compound **13**, alniditan. It is active as a constrictor of the saphenous vein of the dog and of the pig basilar artery with ED_{50} values of 9.09×10^{-9}M and 2.29×10^{-8}M respectively, and it has high affinities to the $5HT_{1D}$-receptor and to the $5HT_{1D}$-receptor with pK_i values of 8.6 and 8.3 respectively.

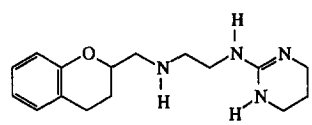
Introduction

Since the discovery of sumatriptan[1], a number of selective $5HT_{1D}$ agonists are described in the literature. Most of them are substituted indoles.[2]

As part of a broad screening program, we found that compounds **1** and **2** are potent constrictors of isolated dog saphenous vein[3] with ED_{50} values of 4.94×10^{-8}M respectively 6.00×10^{-8}M.



1



2

A preliminary evaluation of the selectivity of these two lead compounds showed that besides their activity on the saphenous vein, they also had a marked constrictor activity on the basilar artery of the pig[3]. These results pointed to the involvement of the $5HT_{1D}$ receptor.[4] Indeed, it was found that both compounds bind with high activity to the $5HT_{1D}$ receptor (of calf substantia nigra)[5], pK_i's of 7.5 and 7.2. They also bind with comparable affinity to the $5HT_{1A}$ receptor (cloned human expressed in Ha7 cells)[6] (pK_i's of 7.5 and 7.8)whereas their affinity towards a variety of other neurotransmitter and neuropeptide receptors[6] was much lower ($pK_i < 6$).

These findings prompted us to start a synthesis program around these structures, including variations in the benzopyran-, the aminopyrimidine- and the ethanediamine spacer-parts.

Chemistry

All analogs were synthesised as depicted in Scheme 1.

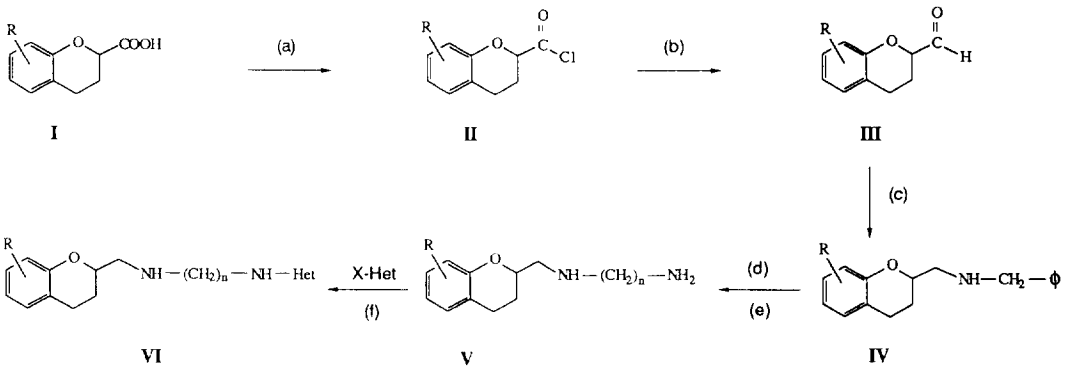
The starting substituted benzopyran-2-carboxylic acids I were either commercially available or were synthesised using methods described in literature.[7] Non-benzopyran analogs (see table 3) were synthesised following the same procedure, again starting from the corresponding acids.[8]

The diamines V were reacted selectively on the primary amine with a number of CH_3S- or chloro-substituted heterocycles to give the endproducts VI.

Compound **25** was prepared by catalytic hydrogenation of **24** and the tetrahydropyrimidines were also obtained by hydrogenation of the hydrochloric- or oxalic acid salts of the corresponding pyrimidines.

Compound **31** was prepared via hydrolysis of **30**.

Scheme 1



(a) $SOCl_2$/toluene; (b) H_2/Pd/C, DMF, thiophene sol.; (c) NH_2-CH_2-  , CH_3OH, H_2/Pd/C, thiophene sol.; (d) K_2CO_3/DMF, or, if n = 3, addition of $CH{=}CH_2CN$ inEtOH, ΔT; (e) H_2/RaNi in CH_3OH; (f) K_2CO_3 in EtOH (X = Cl) or, ΔT, MeOH (X = SCH_3)

The enantiomers of the most promising compounds were prepared starting from the enantiomerically pure 2(S)- and 2(R)-benzopyran-2-carboxylic acid[9] following the same scheme.

Results

All compounds were tested for binding to the $5HT_{1D}$ and $5HT_{1A}$ receptors and for their ability to induce constriction of dog saphenous vein segments. The results are summarized in Tables 1 to 3 and the potencies of these compounds can be compared to those of sumatriptan shown in Table 1.

As illustrated in Table 1, extension of the spacer chain length to C3 gives a marked improvement of the activity on the dog saphenous vein and of the binding to both receptor subtypes. Although further extension of the chain length still gives highly potent compounds, there seems to be no further improvements.

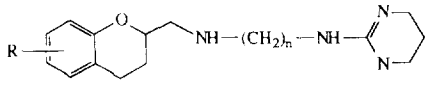
Other variations in this spacer part, not shown in the Table, such as alkyl substitution on one or both nitrogen atoms, or introduction of branched alkyl chains give a marked decrease in activity. The same is true when cyclic spacers such as piperazine, 3- or 4-aminopiperidine, 1,2-, 1,3- or 1,4-diaminocyclohexane are introduced or when the spacer part is linked to the benzopyran by an amide or an ethylenebridge instead of a methylenebridge. Also the replacement of one of the spacer nitrogen atoms by an oxygen results in a loss of activity.

The influence of substitution on the benzopyran is also exemplified in Table 1; a -OCH_3 substituent on the 5- or 6-position results in less active compounds whereas the 7- or 8-substituted compounds are highly active.This is also true for other substituents (not all shown in the table) such as alkyl, hydroxy, halogen or nitrile. (The 6-F compound **10** is an exception as it is equipotent to the parent compound).

In fact, out of the mono substituted analogs the 7-ethyl compound **11** is the most active in both receptor assays, as well as in the dog saphenous vein and the pig basilar artery assay (ED_{50}: 3.46×10^{-9} M).

Alkyl substitution in the 2-position (ex.**12**) leads to inactive compounds.

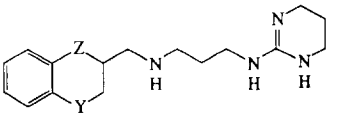
Table 1 :



Compound	R	n	configuration	$5HT_{1D}$[6] pIC_{50}	$5HT_{1A}$[5] pIC_{50}	dog saphenous vein[3] ED_{50}(M)
2	H	2		7.2	7.8	4.94×10^{-8}
3	H	3		8.5	7.9	4.53×10^{-9}
4	H	4		7.9	8.1	1.10×10^{-8}
5	H	5		8.0	8.3	1.52×10^{-8}
6	5-OCH_3	3		<6	<6	$>10^{-6}$
7	6-OCH_3	3		<6	<6	$>10^{-6}$
8	7-OCH_3	3		8.5	7.9	1.78×10^{-8}
9	8-OCH_3	3		9.1	8.3	2.09×10^{-9}
10	6-F	3		8.1	7.6	1.97×10^{-8}
11	7-C_2H_5	3		9.5	8.4	1.93×10^{-9}
12	2-CH_3	3		<6	<6	$>10^{-6}$
13	H	3	R	8.6	8.3	9.09×10^{-9}
14	H	3	S	7.8	7.3	5.15×10^{-8}
Sumatriptan				7.0	6.4	1.6×10^{-7}

Table 2 gives an overview of the various benzopyran like structures that were synthesised. With the exception of the benzodioxan which retains some activity, all other molecules were markedly less active or almost inactive.

Table 2 :



Compound	Z	Y	5HT1D pIC50	5HT1A pIC50	dog saphenous vein ED_{50}(M)
15	O	O	7.6	7.7	6.65×10^{-8}
16	O	-	6.9	7.3	$>10^{-6}$
17	CH_2	CH_2	7.4	6.9	6.15×10^{-7}
18	O	CH_2-CH_2	<6	<6	$>10^{-6}$
19	CH_2	O	<6	<6	$>10^{-6}$
20	NCH_3	CH_2	<6	<6	$>10^{-6}$
21	O	NH	<6	<6	$>10^{-6}$

As shown in table 3 quite a number of amidine or guanidine replacements for the 2-aminopyrimidine part of **22** are compatible with activity .
We synthetised the enantiomers of some of the more intersting compounds: **3, 1, 21, 22, 23** and **29.** In all cases the R-isomer was more active than the S-enantiomer as is illustrated in Table 1 for the enantiomers of **3.**

Compound **13**, alniditan, is at least 10 times more potent than sumatriptan, as well in binding to the 5HT1D receptor, as in the dog saphenous vein (see table 1) and the pig basilar artery assays (ED_{50} 2.92×10^{-8}M versus 5.58×10^{-7}M for sumatriptan). It is selected out of this series and it is currently undergoing clinical trials as a candidate antimigraine drug.

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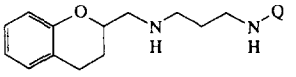
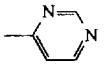
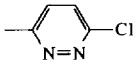
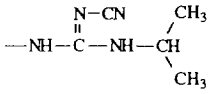
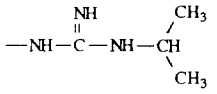
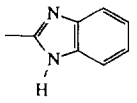
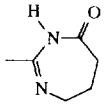
Table 3 :



Q	Comp.	$5HT_{1D}$ pIC_{50}	$5HT_{1A}$ pIC_{50}	saphenous vein ED_{50}(M)
	**22**	8.8	8.7	$>10^{-7}$
	**23**	8.2	7.9	3.15×10^{-8}
	24	8.3	8.9	3.8×10^{-7}
	**25**	8.4	8.2	1.70×10^{-8}
	**26**	8.0	8.3	7.87×10^{-8}
	**27**	8.0	8.4	1.55×10^{-8}
	**28**	8.7	9.4	$>10^{-7}$
	**29**	8.1	8.8	5.70×10^{-7}
	**30**	7.3	7.8	1.15×10^{-7}
	**31**	8.5	8.1	4.80×10^{-9}
	**32**	<6	<7	$>10^{-6}$
	**33**	6.8	8.7	$>10^{-6}$

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   Similarly, basilar artery segments taken from pigs were used in this manner. Contractions were here induced with serotonin ($3x10^{-7}$M). After refreshing the organ bath solution, the compounds to be tested were added and the response was expressed as the percentage of the response to serotonin. ED_{50} values are defined as the concentration of the compound tested causing 50% contraction relative to the reference response.
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