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New 2-Substituted 1,2,3,4-Tetrahydrobenzofuro[3,2-*c*]pyridine Having Highly Active and Potent Central α_2-Antagonistic Activity as Potential Antidepressants

Ludo E. J. Kennis,[a,*] François P. Bischoff,[a] Carolus J. Mertens,[a] Christopher J. Love,[a] Frans A. F. Van den Keybus,[a] Serge Pieters,[a] Mirielle Braeken,[a] Anton A. H. P. Megens[b] and Josee E. Leysen[c]

[a]*Department of Medicinal Chemistry, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium*
[b]*Department of General In Vivo Pharmacology, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium*
[c]*Department of Biochemical Pharmacology, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium*

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Abstract—The synthesis and biological activity of a series of benzofuro[3,2-*c*]pyridines and a benzothieno[3,2-*c*]pyridine are described. These compounds exhibit high affinity for the α_2-adrenoceptor, with high selectivity versus the α_1-receptor. Compound **1** also shows potent in vivo central activity and has been selected for further biological and clinical evaluation.

Introduction

The adrenergic system is a well known and frequently studied target and its modulation is of great and varied therapeutic importance. The discovery of the α- and β-receptor subtypes and their further subdivision was an enormous step forward in understanding the complexity of living organisms, however the detailed mechanism of the adrenergic system is not yet clear.

The continuous discovery of new receptor subtypes challenges medicinal chemists to design new selective compounds in order to further unravel and control the complex interactions and functions of this system.

Presynaptic α_2-adrenoceptors modulate the release of norepinephrine and their blockade leads to enhanced norepinephrine (NE) release comparable to that observed with NE uptake inhibitors.[1–3] α_2-Adrenoceptors also modulate release of acetylcholine,[4] 5-hydroxytryptamine (5-HT)[5–7] and dopamine.[8,9] The enhanced release of acetylcholine by α_2-antagonists can have a beneficial effect in pathologies where cortical acetylcholine deficits have been implicated.[4] Based on the hypothesis that augmentation of 5-HT and NE tone will have a beneficial effect in depression, this dual action of α_2-antagonists would make them potential antidepressants.[10]

However, existing α_2-antagonists like idazoxan are still under investigation and other examples such as mirtazapine have, besides their α_2-antagonistic properties, multiple pharmacological activities. In order to investigate further the role of α_2-antagonists in depression there is a need for more selective and potent centrally acting compounds.

Chemistry

1,2,3,4 Tetrahydrobenzofuro[3,2-*c*]pyridines **III** are readily formed by a Fisher-indole-like condensation of 4-piperidone **I** and substituted phenoxyamines **II** (Scheme 1).

However, the use of this scheme is limited by the availability of the substituted phenoxyamines. These products, according to patent literature, can be prepared in yields of 30–50%.[11] Our attempts afforded only low yields (≤15%).

*Corresponding author. Fax: +32−14-60-53-44; e-mail: lkennis@janbe.jnj.com

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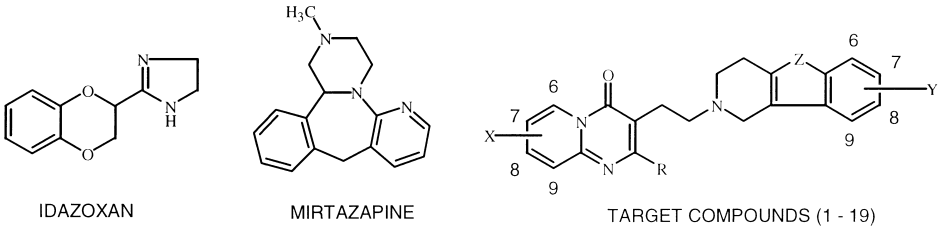
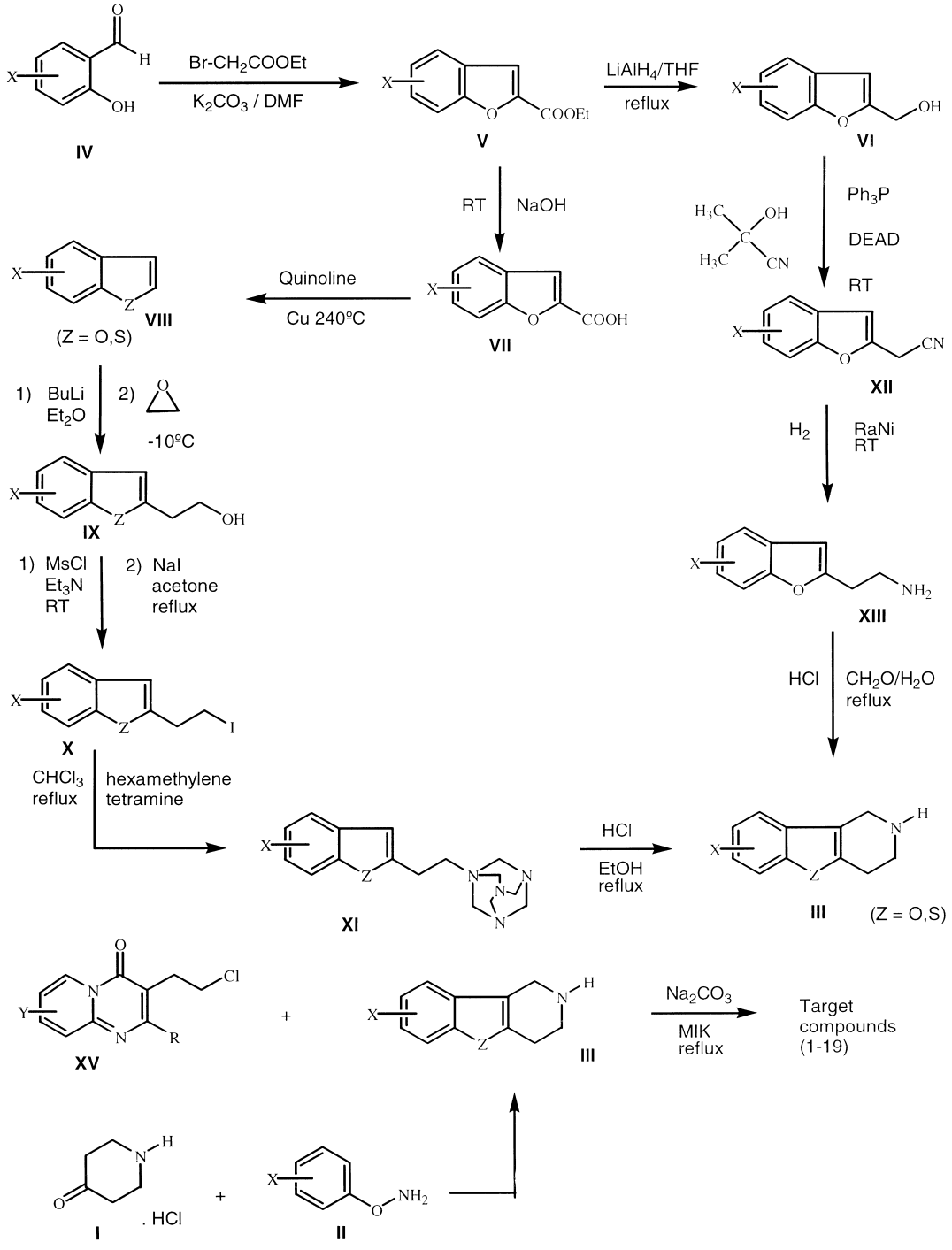

IDAZOXAN
MIRTAZAPINE
TARGET COMPOUNDS (1 - 19)


Br-CH2COOEt
K2CO3 / DMF
LiAlH4/THF
reflux
RT
NaOH
Ph3P
DEAD
RT
Quinoline
Cu 240ºC
(Z = O,S)
1) BuLi
Et2O
2)
-10ºC
1) MsCl
Et3N
RT
2) NaI
acetone
reflux
CHCl3
reflux
hexamethylene
tetramine
H2
RaNi
RT
HCl
CH2O/H2O
reflux
HCl
EtOH
reflux
Na2CO3
MIK
reflux
Target
compounds
(1-19)
. HCl
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
III
XV
I
II

Scheme 1.

An alternative route is also depicted in Scheme 1. Substituted salicylaldehydes **IV** were condensed with ethyl bromoacetate to afford benzofuran-2-carboxylate compounds **V**. The esters were hydrolysed to the acids **VII** in alkaline conditions, and further decarboxylated at 240 °C with Cu in quinoline to the substituted benzofuran compounds **VIII** (Z=O). Alternatively benzofurans and benzothiophenes can also be prepared according to synthetic methods in the literature[12–15] (Z=O; Z=S).

The benzofuran compounds were lithiated with *n*.BuLi and then alkylated with ethylene oxide to form 2-ethanol compounds **IX** selectively. These compounds were transformed via the mesylate to the respective iodides **X** with sodium iodide in acetone. The iodides **X** are quarternised with hexamethylene tetramine and cyclised in acidic conditions to the 1,2,3,4-tetrahydrobenzofuro[3,2-*c*]pyridines **III** (Z=O). Starting from substituted benzothiophene **VIII** (Z=S), the same method was used to afford the 1,2,3,4-tetrahydrobenzothieno-[3,2-*c*]pyridines **III** (Z=S).

The benzofuran 2-carboxylate compounds **V** were reduced with $LiAlH_4$ to the respective benzofuran 2-methanol compounds **VI**. These compounds were transformed under Mitsunobu conditions to the cyano derivatives **XII**.[16] Catalytic reduction with Raney Ni afforded the primary amines **XIII** which were cyclised with formaldehyde in aqueous acid to the 1,2,3,4-tetrahydrobenzofuro[3,2-*c*]pyridines **III** (Z=O).

The final step was a coupling of an annelated pyrimidinone alkylhalide **XV** with the tricyclic amines **III** in an organic solvent and an HCl acceptor such as potassium carbonate. The pyrimidinone alkylhalides **XV** were prepared as described in the literature by Wamhoff et al.[17] The target compounds **1–19** were purified by standard procedures like crystallisation and HPLC. Structures were confirmed with NMR and MS spectroscopy.

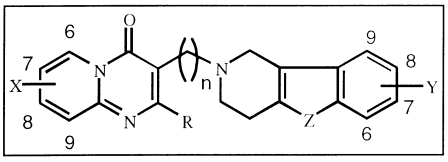
Biological Assays

Receptor binding to the α_1 adrenoceptor was measured using cloned human α_{1A} adrenoceptors stably expressed in CHO cells and (^{3}H) prazosine (0.25 nM). Non-specific binding was assessed in the presence of 1 μM aceperone.

α_2 Adrenoceptor binding was measured on three subtypes: human α_{2A}, human α_{2B} and human α_{2C} adrenoceptors each stably expressed in CHO cells and using (^{3}H) rauwolscine (1 nM) as radioligand. Non-specific binding was assessed in the presence of 1 μM oxymethazoline for α_{2A} and 1 μM spiroxatrine for α_{2B} and α_{2C} adrenoceptors.

Cell membrane preparations and assay conditions were as described by Leysen et al.[18] The test compounds were added at various concentrations in a range of 10^{-5} to 10^{-11}. Data were analysed in inhibition curves and sigmoidal curves were calculated by non-linear regression analysis using polynomials as described by Oestreicher and Pinto[19] pIC_{50} values ($-\log IC_{50}$) were derived from the curves, values are shown in Table 1.

Table 1.



						Receptors pIC_{50}				In vivo (mg/kg s.c.) (*OR)	
	X	Y	R	n	Z	α1	α2A	α2B	α2C	Clonidine	Xylazine
1	H	H	CH_3	2	O	6.46	9.26	8.59	8.77	0.31	0.04
2	H	6 Cl	CH_3	2	O	6.55	9.05	8.36	8.65	0.63	2.5
3	H	8 Cl	CH_3	2	O	—	8.41	7.1	7.56	≥2.5	10*
4	H	H	CH_3	3	O	6.09	7.99	7.97	8.18	≥2.5	≥10
5	H	H	CH_2Ph	2	O	6.69	8.66	8.38	8.57	≥2.5	≥10
6	7-Br	H	CH_3	2	O	6.05	9.45	8.87	9.16	2.5	0.16
7	7-Cl	H	CH_3	2	O	6.14	9.67	9.02	9.14	0.63	0.04
8	9-CH_3	H	CH_3	2	O	6.16	9.22	8.67	8.88	2.5	10
9	7-CH_3	H	CH_3	2	O	6.54	9.46	8.81	8.89	0.63	0.16
10	9-OH	H	CH_3	2	O	6.61	9.16	8.76	8.79	2.5	5
11	8-CH_3	H	CH_3	2	O	6.95	9.35	8.59	8.92	2.5	0.63
12	6-CH_3 8-CH_3	H	CH_3	2	O	6.62	9.47	8.58	9.07	≥2.5	≥10
13	7-CF_3 9-Cl	H	CH_3	2	O	5.23	8.93	8.71	8.44	≥2.5*	≥10*
14	6-CH_3	H	CH_3	2	O	6.4	9.54	8.83	8.97	2.5	0.63
15	7-Cl 9-Cl	H	CH_3	2	O	5.59	9.23	8.9	8.87	≥2.5*	≥10*
16	7-I	H	CH_3	2	O	6.32	9.62	8.68	9.21	≥2.5*	10*
17	9-OCH_3	H	CH_3	2	O	6.94	9.53	8.69	9.15	0.63	0.63
18	7-OCH_3 8-OCH_3	H	CH_3	2	O	5.28	8.45	6.71	7.24	≥0.63	≥10*
19	H	H	CH_3	2	S	6.67	8.76	7.94	7.85	10	2.5
	Idazoxan					5.54	8.08	7.71	7.27	0.63	0.63
	Mirtazapine					5.5	7.07	6.65	6.7	≥10	2.5

In vivo, clonidine (0.04 mg/kg, s.c.) induced antidiarrhoeal action in male rats (200–250 g) challenged simultaneously with castor oil (1 mL p.o.) was assessed 90 min after challenge.[20] Test compounds or solvent were administered 0.5 h before clonidine. Criterion for drug-induced reversal; presence of diarrhoea (not observed in controls; $n \geq 500$). Reversal of the antidiarrhoeal effect of clonidine is obtained with α_2-adrenoceptor blockers.

Xylazine (15 mg/kg, i.v.) induced loss of the righting reflex was recorded up to 120 min after injection in male rats (200–250 g) (modified after Ref. 21). Test compounds or solvent were administered 1 h before xylazine. Criterion for drug-induced antagonism: absence of loss of righting reflex (4.2% false positive controls; $n \geq 300$). Centrally acting α_2-adrenoceptor antagonists antagonize the loss of righting reflex.

Discussion

All of the compounds of Table 1 had high affinities on all three subtypes of the α_2-adrenoceptors, with only minor or no selectivity between the subtypes. The selectivity between the putative presynaptic subtype α_{2A}[22] and the α_1-receptor varies in a range of about 100 (compounds **4** and **5**) and to more than 4000 (compound **15**).

Increasing the length of the chain to $n = 3$ (compound **4**) or replacement of the R substituent by benzyl (compound **5**) results not only in lower selectivity but also in less activity in vivo.

Substitution on the benzofuran[3,2-*c*]pyridine, i.e. compounds **2** and **3**, results in reduced activity in vivo. Substitution on the pyridine of the bicyclic pyridopyrimidinone moiety shows variable results, some substituents, e.g. compounds **6**, **7** and **9**, do have potent in vivo activity, others display dramatic loss of in vivo activity. In some cases compounds had to be orally administered as suspensions and not as solutions, possibly reducing the observed activity. The unsubstituted compound **1** combines high affinity and selectivity for the α_2-adrenoceptor versus the α_1 adrenoceptor with potent central in vivo activity in the xylazine test and was therefore selected for further investigation.

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