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NOVEL BENZOPYRANO[3,4-*c*]PYRROLE DERIVATIVES AS POTENT AND SELECTIVE DOPAMINE D_3 RECEPTOR ANTAGONISTS

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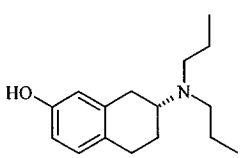
Abstract: A new series of benzopyrano[3,4-*c*]pyrrole derivatives were synthesized and evaluated for their interaction with dopamine D_3 *versus* D_2 receptors. Amongst these compounds, **4x** (S 33084) was found to be a potent and selective dopamine D_3 receptor antagonist.

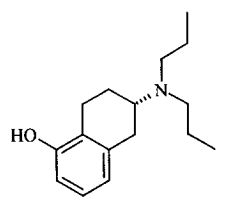
Recent advances in molecular biology have established the existence of two families of dopamine receptor: a D_2-group comprising D_2, D_3 and D_4 receptors, and a D_1-group incorporating D_1 and D_5 receptors[1]. Antipsychotic agents are thought to exert their therapeutic actions at least partially via antagonism of mesolimbic dopamine D_2 receptors. However, blockade of striatal and hypophyseal populations of dopamine D_2 receptors provokes extrapyramidal motor and endocrine side-effects respectively[2].

In contrast to D_2 receptors, dopamine D_3 receptors display a preferential localization in limbic areas of the brain[3]. Moreover, many antipsychotic agents show high affinity for dopamine D_3 as well as dopamine D_2 receptors[4]. These observations raise the possibility that a selective dopamine D_3 receptor antagonist might possess antipsychotic properties in the relative absence of neurological and endocrine side-effects.

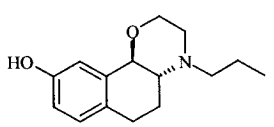
Early studies identified the N,N-di-n-propyl derivatives of the 5- or 7-hydroxy-2-aminotetralin e.g.: (R)-(+)-7-OH-DPAT **1** and (S)-(-)-5-OH-DPAT **2** as potent D_3 receptor ligands[5]:



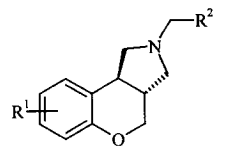
1 (R)-(+)-7-OH-DPAT



2 (S)-(-)-5-OH-DPAT



3 (+)-PD128907



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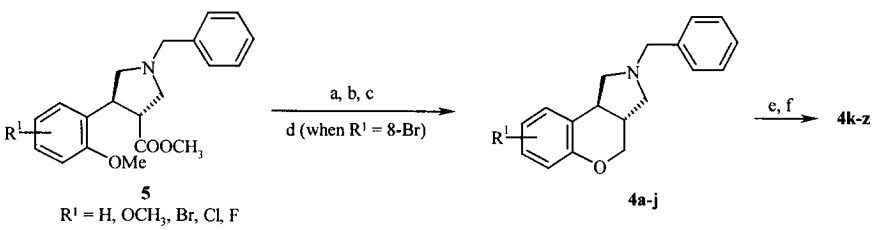
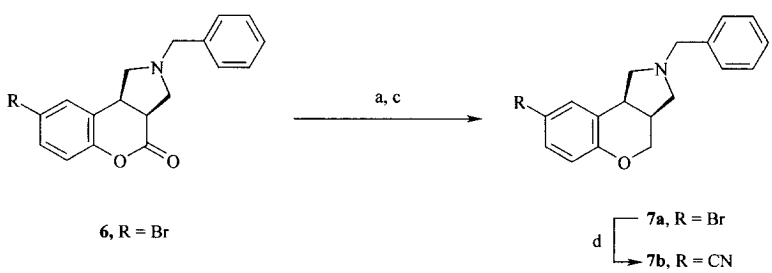
Subsequently, this N,N-di-n-propyl-2-aminotetralin framework has served as a structural basis for the design of numerous dopaminergic agents[6]. However, the presence of two alkyl chains on the nitrogen is associated with limited metabolic stability. Therefore, in order to obtain more rigid and stable derivatives, tricyclic compounds in which the basic nitrogen atom is incorporated in a cyclic structure (as in compound **3**) have been developed[7].

In a recent report, we described the synthesis of novel pyrrolidine derivatives via a 1,3-dipolar cycloaddition using a non-stabilized azomethine ylide and an activated double bond[8]. In the present paper, we describe the utilization of these intermediates in the synthesis of novel tricyclic benzopyrano[3,4-*c*]pyrrolidine derivatives. The compounds described herein differ from the tricyclic compounds mentioned above as concerns the position of the nitrogen on the third ring. The two fused rings of the benzopyrano[3,4-*c*]pyrrolidines documented herein exist in two distinct configurations: *cis* and *trans*. In molecular modeling studies (not shown), the *trans* compounds **4** behaved as conformationally constrained derivatives of **1** or **2**. Compounds **4** were evaluated for their affinities at cloned human (h) dopamine D_3 and D_2 receptors.

Scheme 1



Scheme 2



a: $LiAlH_4$, THF, 10°C; b: EtSNa, DMF, 140°C; c: DEAD, Ph_3P, THF, r.t.; d: $Zn(CN)_2$, $Pd(Ph_3P)_4$, DMF, 80°C; e: HCl/EtOH, H_2-Pd/C, 40°C; f: R^2-CHO, $NaBH(OAc)_3$, 1,2-dichloroethane.

Trans compounds **4** were prepared from the disubstituted *trans* pyrrolidines **5**[8] (Scheme1). After reduction of the ester function with $LiAlH_4$, an O-demethylation was performed on the

crude alcohol with EtSNa[9]. Subsequently, the ring closure in benzopyrane was realized *via* an intramolecular Mitsunobu reaction. The 8-cyano derivatives **4g** were obtained after displacement of the corresponding bromine using $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF[10]. After debenzylation, various substituents were introduced onto the nitrogen atom *via* reductive amination with the appropriate aldehydes to yield the final compounds **4k-z**. Resolution was undertaken for the bromo derivatives and the *trans* 8-bromo **4e** was resolved into its two enantiomers by separation of the crystalline diastereoisomeric salts obtained with the D and L dibenzoyl tartaric acids. Several recrystallisations of each salt permitted complete enrichment (ee $\geq$ 99%). Finally a tetrahydronaphthalene derivative **8** (see table I), which is a strict bioisoster of **4g** was prepared for comparison[11].

The *cis* derivatives **7a** and **7b** were prepared starting from the tricyclic lactone **6** (Scheme 2). **6** was obtained via application of a stereoselective cycloaddition[8] to a 6-bromocoumarine[12].

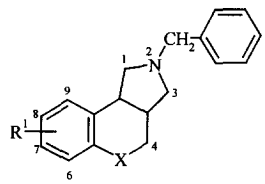
Biological Results and Discussion

All compounds were tested for their ability to displace the radioligand [^{125}I]-iodosulpiride from hD_3 and hD_2 receptors transfected into CHO cells[13]. Table I summarizes the influence of the various benzopyrane substituents. The majority of compounds were potent ligands at hD_3 receptors (pK_is between 7.8 and 8.4 for: **4c**, **4d**; **4e** and **4g**). Further, they showed a modest preference for hD_3 *versus* hD_2 sites. The introduction of a cyano substituent on the 8- or 7-position in the *trans* series yielded the most potent (**4g**) and the most selective compound (**4j**) respectively. While maintaining this cyano substituent at the 8-position of the *trans* isomer, we studied the influence of replacement of the N-unsubstituted benzyl group by various side-chains. The replacement of the oxygen atom in the benzopyrano ring by a carbon atom led to a relative increase in dopamine D_2 receptor affinity, and hence loss of selectivity (**4g** $\rightarrow$ **8**).

The role of the side chain is illustrated by results shown in Table II. The N-benzyl derivatives (**4g**, **4k**, **4n**) exhibited good affinity for hD_3 *vs* hD_2 sites, a finding also obtained for the N-n-propyl compound **4q**. Elongation of the chain by one carbon led in the case of the 4-acetamido derivative **4n** to a marked increase in dopamine D_3 receptor affinity (**4r**). This difference was not as clear with other phenyl substituents (data not shown). Replacement of the acetyl group in **4r** by a sulfonyl (**4u**) or a benzoyl group (**4v**) yielded less selective compounds. Finally the most interesting derivatives were obtained by grafting the 4-(4-phenylbenzoylamino)butyl chain[14] onto the nitrogen atom of the pyrrolidine ring (**4w**). With regard to stereochemical relationships, the *cis* compounds, for which the pyrrolidine ring projects above the plane of the molecule, were poorly recognized by hD_3 receptors

(compounds **7a**, **7b**). On the other hand, there was only a marginal preference for the (3aR,9bS) *trans* enantiomer *versus* the (3aS,9bR) *trans* enantiomer, underlining the quasi-plane form of the structure (**4l** → **4m**; **4o** → **4p**; **4s** → **4t**; **4x** → **4y**).

Table I: Affinities of the N-benzyl derivatives at hD_3 *versus* hD_2 receptors.



Compound[a]	R^1	X	Stereochemistry	pK_i[b]	
				hD_3	hD_2
4a	H	O	*trans*	6.9	6.5
4b	8-OCH_3	"	"	7.1	6.7
4c	8-F	"	"	8.1	7.6
4d	8-Cl	"	"	7.8	7.5
4e	8-Br	"	"	7.8	7.3
4f	7-OCH_3	"	"	7.1	6.6
4g	8-CN	"	"	8.4	7.6
4h	8-CN	"	(3aR, 9bS)	8.6	7.7
4i	8-CN	"	(3aS, 9bR)	8.2	7.5
4j[15]	7-CN	"	*trans*	7.6	6.3
7a	8-Br	"	*cis*	7.0	6.3
7b	8-CN	"	"	7.0	6.5
8	8-CN	C	*trans*	8.2	8.0

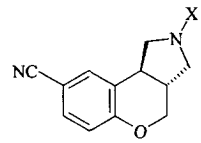
a: all compounds had satisfactory IR, MS and ^{1}H-NMR analyses.
b: pK_i values shown are means of least two independent determinations.

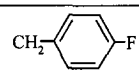
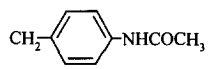
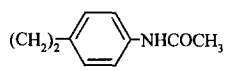
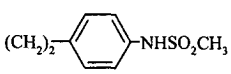
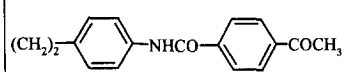
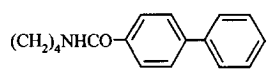
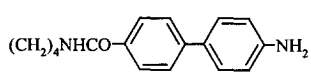
The majority of the compounds, including **4w**, **4x** and **4y**, were tested for their ability either to themselves stimulate [^{35}S]GTPγS binding at hD_3 and hD_2 receptors, or to block its induction by dopamine[16]. All behaved as antagonists[17].

In conclusion, in a series of benzopyrano[3,4-*c*]pyrrole derivatives, we have discovered novel, potent and selective hD_3 receptor antagonists. Of these, **4x**[18] is a highly potent and selective hD_3 *vs* hD_2 receptor antagonist which displays > 100-fold selectivity over hD_1, hD_4 and hD_5 receptors, as well as all other (> 30) receptors as yet evaluated. The potential therapeutic

utility of **4x**, which possesses satisfactory brain penetration and expresses antagonistic properties *in vivo,* is currently under exploration[17].

Table II: Affinities of the *trans* 8-CN derivatives at hD_3 *versus* hD_2 receptors.



Compound[a]	X	Stereochemistry	pK_i[b]	
			hD_3	hD_2
4k		(±)	8.1	7.1
4l	"	(3aR, 9bS)	8.2	7.6
4m	"	(3aS, 9bR)	7.8	7.4
4n		(±)	7.9	7.6
4o	"	(3aR, 9bS)	8.0	7.9
4p	"	(3aS, 9bR)	7.7	7.5
4q	CH_2-CH_2-CH_3	(±)	7.8	6.9
4r		(±)	9.0	7.4
4s	"	(3aR, 9bS)	9.0	7.5
4t	"	(3aS, 9bR)	8.5	7.4
4u		(±)	8.8	7.6
4v		(±)	9.1	7.7
4w		(±)	9.1	7.1
4x	"	(3aR, 9bS)	9.5	7.5
4y	"	(3aS, 9bR)	9.2	7.3
4z		(3aR, 9bS)	9.7	7.7

a: all compounds had satisfactory IR, MS and ^{1}H-NMR analyses.
b: pK_i values shown are means of at least two independent determinations.

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18. Analytical data for compound **4x** (hydrochloride form): $[\alpha]_D^{20}$ = 12.62 (DMSO, [c] = 1%); I.R. (nujol): 3422, 2800-2300, 2221, 1639, 1544 cm^{-1}; ^{1}H-NMR (DMSO-d6 + NaOD) δ: 7.95 (d, 2H), 7.7 (d, 4H), 7.6-7.3 (m, 5H), 6.95 (d, 1H), 4.35 (2dd, 2H), 3.3 (m, 3H), 2.9 (m, 2H), 2.7-2.5 (m, 4H), 2.1 (m, 1H), 1.55 (m, 4H); Anal. Calc. For $C_{29}H_{30}ClN_3O_2$: C, 71.37; H, 6.20; Cl, 7.26; N, 8.61. Found: C, 71,32; H, 6.21; Cl, 7.39; N, 8.57.