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TETRACYCLIC ANALOGUES OF [+]-S 14297: SYNTHESIS AND DETERMINATION OF AFFINITY AND SELECTIVITY AT CLONED HUMAN DOPAMINE D_3 vs D_2 RECEPTORS

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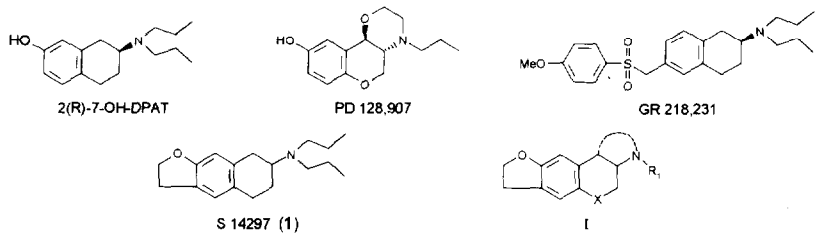
Abstract: Starting from the structure of the preferential D_3 antagonist S 14297 (**1**), we have prepared a series of *cis* and *trans* tetracyclic derivatives of general formula **I** in order to improve potency and selectivity for D_3 receptors. The *trans* oxazino derivative **2c**, showed slightly increased affinity at D_3 receptors and double the selectivity for D_3 over D_2 receptors, in comparison to S 14297. *Cis* derivatives and compounds where R_1 is aralkyl were totally devoid of activity. © 1997 Elsevier Science Ltd.

Since its discovery by Sokoloff and Schwartz[1], the dopamine D_3 receptor has attracted a great deal of interest. In view of its location in limbic areas, such as the nucleus accumbens and the islets of Calleja, this novel dopamine receptor may play an important role in the pathogenesis and potential treatment of psychiatric disorders. However, despite considerable efforts directed towards the discovery of selective ligands, relatively few agonists (2(R)-7-OH-DPAT and PD 128,907)[2,3] or antagonists (nafadotride, U99194, GR 218,231)[4-6] are sufficiently selective to allow for an investigation of the functional role of D_3 receptors.

Scheme I



Recently, we identified a family of tetralin derivatives, of which [+]-S 14297 (**1**) showed a significant degree of selectivity for D_3 over D_2 receptors, permitting a broad characterization of its pharmacological profile[7,8,9]. As **1** also displayed substantial selectivity against other receptor types[8], the structure of [+]-S 14297 was considered a worthy starting point to find more selective compounds.

Among the different strategies pursued towards this goal, one consisted of the rigidification of the parent structure, where the nitrogen atom of [+]-S 14297 was included in a fourth ring (Scheme I).

In view of their relatively easy chemical accessibility, furo[2,3-b] 1,4-oxazino[3,2-h]naphthalene derivatives, **2a-h** were first prepared to assess the influence of the nature of the R_1 side-chain upon potency at D_3 receptors and selectivity towards the D_2 subtype.

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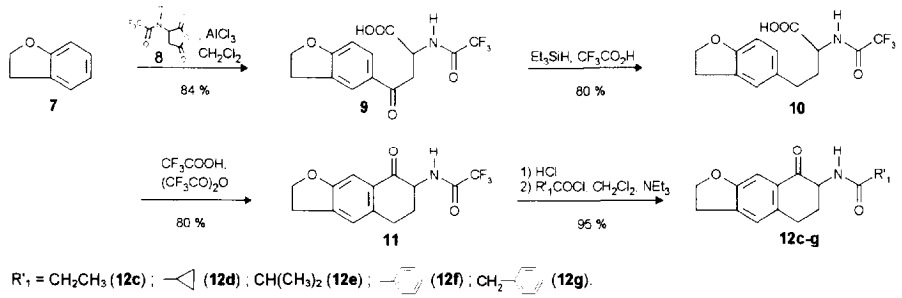
Jones et al.[10] have prepared *N*-substituted 1,4-oxazino [3,2-h] naphthalene derivatives in five steps, starting from the appropriately substituted 2-amido-1-tetralones. It was found necessary to prepare the required amido-tetralones **12**, using a non classical method for the introduction of an amino function at the α position of the tetralone, since the Neber reaction, or the action of isoamylnitrite was unsuccessfull on tetralone **6** [11]. We therefore decided to introduce the amino function as early as possible in the synthesis, and found that the most convenient way to obtain the key intermediates **12c-g** was as depicted in Scheme II. A Friedel-Crafts reaction between 2,3-dihydrobenzo[b]furan and the racemic anhydride **8** led exclusively to the regioisomer **9,** which allowed incorporation of the amino function at C-2, as required. Reduction of the ketone directly into the

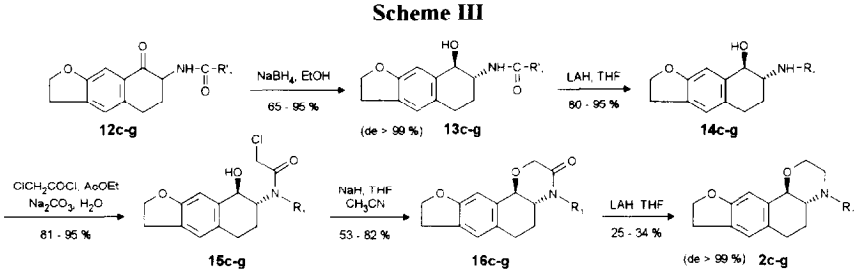
Scheme II



corresponding methylene derivative **10** was best achieved with triethylsilane in trifluoroacetic acid, using the conditions described by West[12]. Cyclisation of the acid **10**, by an intramolecular Friedel-Crafts reaction, led to the amido-ketone **11**, in high yield when the reaction was performed in a mixture of trifluoracetic anhydride and trifluoroacetic acid. This protocol was superior to the more classical procedures such as PPA, H_2SO_4/H_3PO_4 or H_2SO_4 alone. Finally, removal of the trifluoroacetyl protective group and acylation with the appropriate acid chlorides led to the desired amido-ketones **12c-g**

Construction of the *trans* oxazine ring system according to the method of Jones et al.[10] (Scheme III) required the preparation of the *trans* amido-alcohols **13c-g** which were obtained by sodium borohydride reduction of the

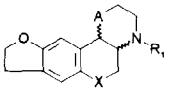
Scheme III



ketones **12c-g**, in > to 99 % de. Annulation of the resulting amino-alcohols **14c-g** (Scheme III) gave the oxazines **2c-g** in modest overall yields, since reduction of the amides **16** led to the formation of by-products[13]. The secondary amine **2a** was obtained by hydrogenolytic cleavage of the benzyl derivative **2f**, and transformed by reductive alkylation (CH_2O/$NaBH(OAc)_3$/THF), into the *N*-methyl derivative **2b**.

From an analysis of the data in Table I, it can be seen that the most potent and selective analogue is the n-propyl derivative **2c**. The nature of the R_1 side-chain thus influences both D_3 potency and selectivity. The *N*-cyclopropylmethyl and the *N*-isobutyl groups maintained the high selectivity of **2d** and **2e** but lost affinity at D_3 receptors. Moreover, D_3 affinity also diminished when the chain was shortened (**2 b**) or eliminated (**2a**). Finally, a phenyl ring in the side-chain led to a complete loss of D_3 and D_2 activity (**2f** and **2g**).

Table I. Dopamine D_3 and D_2 Receptor Affinities and Selectivities for Compounds **2a-h** and **3-5**.



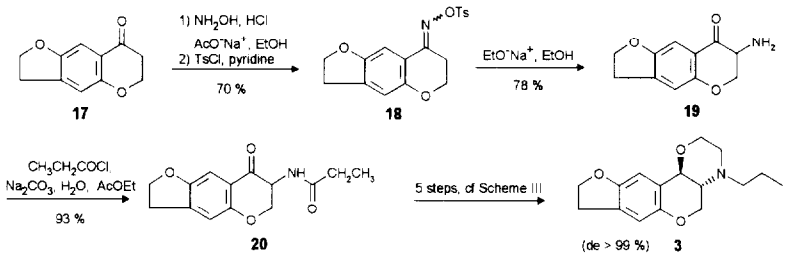
Entry	X	A	Ring-junction	R_1	Affinity (pKi)[a] hD_2	Affinity (pKi)[a] hD_3	Selectivity[b] D_3 vs D_2
2a	CH_2	O	trans	H	6.0	6.7	5
2b	CH_2	O	trans	CH_3	6.4	7.1	5
2c	CH_2	O	trans	$(CH_2)_2CH_3$	6.4	8.0	40
2d	CH_2	O	trans	CH_2-cyclopropyl	5.6	7.2	40
2e	CH_2	O	trans	$CH_2CH(CH_3)_2$	5.3	6.9	43
2f	CH_2	O	trans	CH_2-phenyl	< 5	< 5	-
2g	CH_2	O	trans	$(CH_2)_2$-phenyl	< 5	< 5	-
2h	CH_2	O	cis	$(CH_2)_2CH_3$	< 5	< 5	-
3	O	O	trans	$(CH_2)_2CH_3$	4.9	6.3	25
4	O	O	cis	$(CH_2)_2CH_3$	< 4	< 5	-
5	CH_2	CH_2	trans	$(CH_2)_2CH_3$	6.3	7.6	20
1					6.6	7.9	20

[a] pKis are derived from two to five independant determinations each performed in triplicate. Experiments were undertaken on membranes of CHO cells stably transfected with cloned human dopamine D_2 and D_3 receptors. [^{125}I]-iodosulpride was used as the radioligand.

[b] Selectivity is expressed by the ratio of Ki (nM) values at D_2 and D_3 receptors.

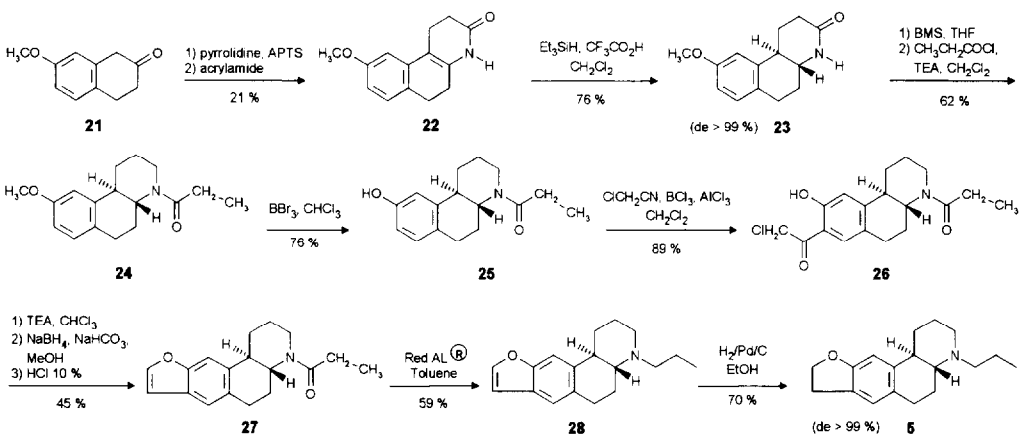
Since PD 128,907 is the most selective D_3 agonist currently known, it was also decided at this point to include in this study the furo [2,3-g] 1,4-oxazino[5,6-c] benzopyran derivative **3**, which can be viewed as an oxo analog of compound **2c**. In this case, the synthetic strategy developed by Jones et al.[10] could be applied in its entirety, starting from the chromanone **17**, since the Neber rearrangement led to **19** in good yield (Scheme IV).

Scheme IV



Finally, it was decided to complete this series of *trans* derivatives by preparing the furo [2,3-b] azaphenanthrene derivative **5**, a methylene analogue of compound **2c**, following the synthetic pathway depicted in Scheme V. The key intermediate **22** was prepared by an aza-annulation method, first described by Stork[14] and used by Cannon[15] on various substituted tetralones. Access to the *trans*-fused lactam **23** requires a stereoselective reduction of the olefinic bond. Kursanov[16] has used ionic hydrogenation using triethylsilane and trifluoroacetic acid to obtain predominantly the *trans*-ring geometry in this kind of system. Applying the conditions developed by Cannon[17], in

Scheme V

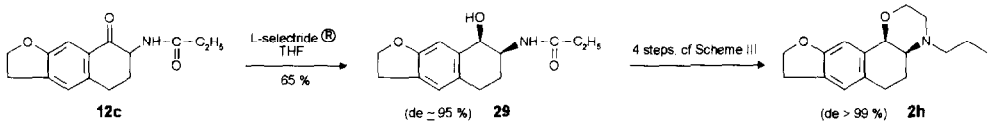


preference to those used by Ninomiya[18], to tetralone **21**, led to **23** which showed a diastereomeric purity in excess of 99 % de. Transformation of **23** in **24** proceeded without difficulty. Next, we speculated that the construction of the furan ring might be envisaged via a Houben-Hoesch reaction starting from **25**. Ortho orientation was expected, due to the presence of boron trichloride. The reaction proceeded with complete regioselectivity for the required ortho position. This allowed for the preparation of the furan ring in four steps and in excellent yield. Initially, reduction of the amide **27** was troublesome, as both LAH and BMS led to

intractable materials. However, reduction with Red Al® gave the tertiary amine **28** in reasonable yield. Finally, catalytic hydrogenation led to **5**. These close analogues of **2c** were disappointing since **3** was only weakly potent at D_3 receptors (pKi = 6.3) though its selectivity to D_2 sites was of the same order of magnitude as for S 14297. Moreover, compound **5** exhibited only half the selectivity of **2c**, due to a slight decrease of affinity at D_3 receptors (pKi = 7.6).

In order to assess the influence of the nature of the ring-junction upon potency and selectivity, we next prepared the *cis* derivatives **2h** and **4**, diastereoisomers of **2c** and **3** respectively. Reduction of **12c** using L-Selectride®, instead of sodium borohydride, as shown in Scheme III, afforded the key *cis* amido-alcohol **29**, in close to 95 % de,

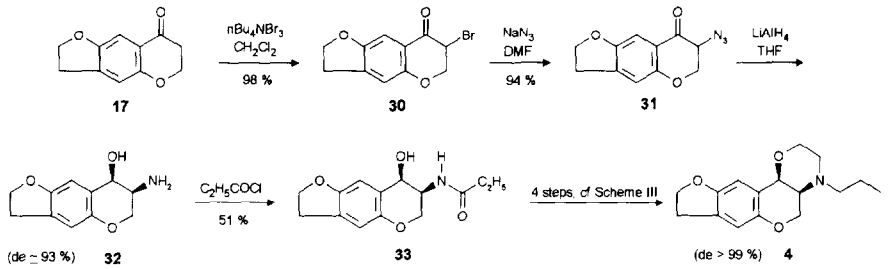
Scheme VI



which was subsequently transformed to **2 h** (Scheme VI), according to the same procedures used for the preparation of the *trans* derivatives.

To obtain **4,** the key *cis* amido-alcohol **33** was prepared (Scheme VII), starting from the chromanone **17**. Reduction of the azido-ketone **31** by LAH afforded the *cis* amino-alcohol **32** in 93 % de. The same functional

Scheme VII



group transformations depicted in Scheme III led to the desired *cis* analogue **4** which showed a diastereoisomeric purity > to 99 % de. As shown in Table I, *cis* derivatives are unfortunately completely devoid of activity at D_3 and D_2 receptors.

Conclusion

Rigidification by cyclisation of the parent compound [+]- S 14297 has led, as expected, to an improvement of selectivity, provided the ring-junction is *trans*, the cyclisation includes an oxygen atom and the side chain is propyl. Compound **2c** showed a selectivity double that of S 14297. *Cis* derivatives and compounds where the side chain bears a phenyl residue were devoid of activity at D_3 and D_2 receptors.

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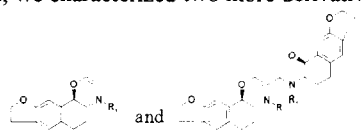
13. Besides the expected compounds, we characterized two more derivatives : 
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