Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 21, pp. 2589-2590, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00374-2

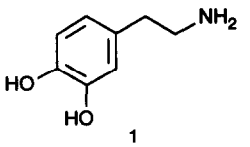
NOVEL HO-DPAT (HYDROXY-2-DIPROPYLAMINOTETRALIN) ISOMERS: STEREOSELECTIVE SYNTHESIS AND RECEPTOR BINDING STUDIES

Peter Gmeiner*, Evi Hummel and Joachim Mierau[$]

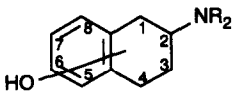
Pharmazeutisches Institut der Universität Bonn, An der Immenburg 4, 53121 Bonn, Germany; [$]Abteilung Biochemische Forschung, Boehringer Ingelheim KG, 55216 Ingelheim / Rhein, Germany

Abstract: The synthesis of the the novel HO-DPAT isomers **2** and **3** from the ß-amino acid **4** is reported. **2** showed strong and selective affinity to the dopamine autoreceptor, labelled with [^{3}H]-pramipexole.

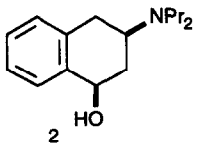
Structure-activity-relationship (SAR) studies by synthesis and receptor binding tests of regioisomers has proved to be a valuable strategy for the discovery of receptor models as well as for optimizing affinity and selectivity of the receptor ligands.[1] In the field of dopamine (**1**) research, conformationally restrained neurotransmitter analogs in different isomeric forms have been investigated with respect to the position of the catechol hydroxyl group(s).[2] It turned out, that one aromatic hydroxyl substituent is sufficient. The position of it, however, is very critical. Among the hydroxy substituted aminotetralins (HO-AT) and its N,N-dipropyl derivatives (HO-DPAT) the 5-hydroxy isomers show the most potent agonistic effects at postsynaptic D-1 and D-2 receptors. On the other hand, 7-HO-DPAT shows only moderate activity at D-1 and postsynaptic D-2 receptors but strong agonistic effects at the presynaptically localized D-2 autoreceptor. Whereas the *(S)*-enantiomers are more active in the 5-OH series the *(R)*-configurated antipodes turned out to be the eutomers for 7-OH-AT and 7-HO-DPAT. For the 6-hydroxy isomers only weak activity is described. Quite different properties have been observed for *(S)*-8-OH-DPAT which is one of the most potent and selective 5-HT$_{1a}$ antagonist and for the 1-HO-ATs revealing inhibitory effects of PNMT (phenylethanolamine N-methyltransferase).[3]



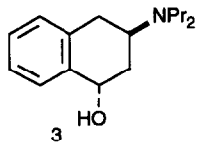
1



R = H: HO-AT
R = Pr: HO-DPAT



2

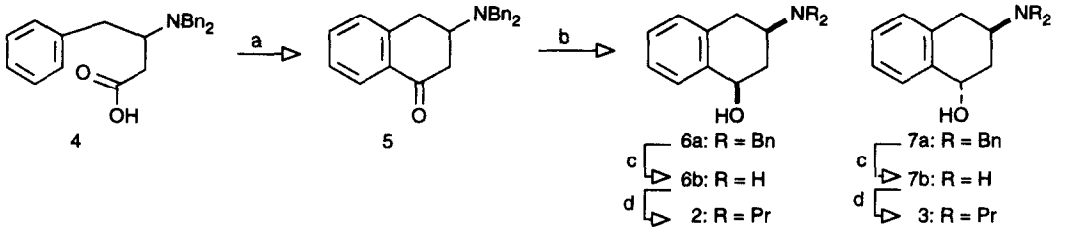


3

As an extension of those studies, we herein report the diastereoselective syntheses and the dopamine receptor binding properties of racemic *cis*- and *trans*-4-HO-DPAT (**2** and **3**).

The construction of the tetralin ring was performed starting from the readily available N,N-dibenzyl protected ß-homophenylalanine **4**. According to our previous results, $SOCl_2$ initiated acid chloride formation and subsequent Friedel Crafts cyclization afforded the aminotetralone **5**.[4,5] For the next step, a diastereoselective reduction of the keto function of **5**, existing predominantly in a half chair conformation with an equatorially positioned dibenzylamino group, was envisioned. We anticipated that a sterically demanding reducing agent should attack from the equatorial side to circumvent 1,3-diaxial interactions. On the other hand, small reagents are supposed to give a favored axial approach which is due to stereoelectronic control.[6] In fact, these assumptions were confirmed when reduction by Li(sBu)$_3$BH led to a 7:1 *trans*-selectivity whereas $LiAlH_4$

resulted in a preferred formation of the *cis*-diastereomer (**6a**:**7a** = 7:1). To avoid formation of 1-naphtol by dibenzylamine elimination as a side reaction it was advantageous to perform the reduction processes at -94° C. Complete separation of **6a** and **7a** required preparative HPLC. However, it was a possible to proceed in the synthesis and to detach the minor isomers at the stage of the final products (**2**,**3**). Removal of the benzyl protecting groups was performed by hydrogenolysis using $Pd(OH)_2/C$ as a catalyst to yield the primary amines **6b** and **7b**. Finally, **6b** and **7b** were converted to the dipropylamines **2** and **3** by treatment with an excess of propionaldehyde and $NaBH_3CN$.



a: ref: 4. b: for **6a**: $LiAlH_4$, THF, 2h, -94°C (50%); for **7a**: $Li(sBu)_3BH$, THF, 2h, -94°C (50%). c: H_2, $Pd(OH)_2/C$, MeOH, 2h, RT (74-82%). d: propionaldehyde, $NaBH_3CN$, MeOH, 20h, RT (37-38%).

For dopamine receptor binding studies rat striatal membranes were employed.[7] The test compounds **2** and **3** were evaluated for their affinity to the dopamine D-1 receptor labelled with [^{3}H]-SCH 23390 and to the D-2 binding sites labelled with [^{3}H]-spiroperidol and [^{3}H]-pramipexole, a compound which pointed out to be an autoreceptor agonist.[8] Both compounds failed to reveal remarkable affinity to the D-1 receptor as well as for the D-2 sites labelled by the antagonist [^{3}H]-spiroperidol (see Table 1). However, both isomers turned out to be potent for displacing the D-2 autoreceptor agonist [^{3}H]-pramipexole when *cis*-4-HO-DPAT **2** showed a 7.3-fold higher affinity (K_i = 35.7 nM) then *trans*-4-HO-DPAT **3**. In comparison, for (-)-PPP [9] a K_i-value of 11.6 nM was determined. Further studies on enantiomerically pure 4-HO-DPAT isomers are in progress.

Table 1:

compd.	D-1 [a]	D-2 [b]	D-2 [c]
(-)-PPP	--------	7800 ± 1000	11.6 ± 0.2
2	> 50000	13950 ± 500	35.7 ± 13.2
3	> 50000	13000 ± 1300	262 ± 12

[a] [^{3}H]-ligand: SCH 23390 (0.3 nM); k_i-values (nM) ± S.E.M.. [b] [^{3}H]-ligand: spiroperidol (0.5 nM); k_i-values (nM) ±S.E.M.. [c] [^{3}H]-ligand: pramipexole; k_i-values (nM) ±S.E.M.

Acknowledgments: This work is supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*.

References and Notes

1 *Comprehensive Medicinal Chemistry*, Vol.3, Hantsch, C.; Sammes, P.G.; Taylor J.B., Eds.; Pergamon Press: Oxford 1990. Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 57.
2 Katerinopoulos, H.E.; Schuster, D.I. *Drugs Fut.* **1987**, *12*, 223.
3 Grunewald, G.L.; Qizhuang, Y. *J. Med. Chem.* **1988**, *31*, 1984.
4 Gmeiner, P. Hummel, E. *Synthesis* **1994**, in press.
5 Previous synthesis of 3-amino-1-tetralols: Violland, R.; Violland-Dupperet, N.; Pacheco, H.; Ghazarian, M. *Bull. Soc. Chim. Fr.* **1971**, 307.
6 Similar observations: Gmeiner, P.; Bollinger, B. *Liebigs Ann. Chem.* **1992**, 273 and ref. cited therein.
7 The studies were performed, according to: Gmeiner, P.; Sommer, J.; Höfner, G.; Mierau, J. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 649 and ref. cited therein.
8 Mierau, J.; Schingnitz, G. *Eur. J. Pharmacol.* **1992**, *215*, 161.
9 Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hacksell, U.; Arviddson, L.-E.; Svensson, U.; Nilsson, J.L.G. *Life Sci.* **1981**, *28*, 1225.

(*Received in Belgium* 25 *July* 1994; *accepted* 27 *September* 1994)