Bioorganic & Medicinal Chemistry Letters, Vol.1, No.5, pp. 257-262, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

C8-SUBSTITUTED DERIVATIVES OF 2-(DIPROPYLAMINO)TETRALIN: PALLADIUM-CATALYZED SYNTHESIS AND INTERACTIONS WITH 5-HT_{1A}-RECEPTORS

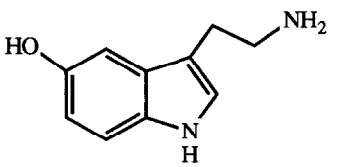
Ye Liu,[a] Björn E. Svensson,[b] Hong Yu,[c] Lourdes Cortizo,[a]
Svante B. Ross,[b] Tommy Lewander,[c] and Uli Hacksell[a,*]

[a] Department of Organic Pharmaceutical Chemistry, Box 574, Uppsala Biomedical Centre, Uppsala University, S-751 23 Uppsala, Sweden,
[b] Research and Development Laboratories, Astra Research Centre, S-151 85 Södertälje, Sweden,
[c] Department of Psychiatry, Ulleråker, Uppsala University, S-750 17 Uppsala, Sweden

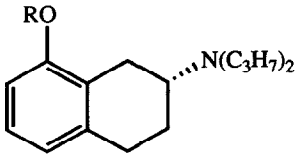
(*Received* 18 *April* 1991)

Abstract: A series of C8-modified analogues of 8-OH-DPAT (**1**) have been prepared by facile palladium-catalyzed reactions of the triflates of the enantiomers of **1**. Several of the new compounds have high affinity for 5-HT_{1A}-receptors and some are potent agonists.

Drugs interacting with the 5-HT_{1A}-subtype[1] of serotonin (5-HT) receptors are of potential clinical interest in the treatment of anxiety and depression.[2] 8-Hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT, **1**)[3] is probably the most thoroughly examined 5-HT_{1A}-receptor agonist. Both enantiomers of **1** are selective agonists of considerable potency,[4] (*R*)-**1** being a full agonist and (*S*)-**1** a partial agonist at 5-HT_{1A}-receptors negatively coupled to adenylate cyclase.[4c] However, neither racemic **1** nor the enantiomers have been considered for drug development, mainly due to their poor bioavailability. Most likely, the poor pharmacokinetic profile of **1** is related to a fast first pass conjugation of the phenolic C8-substituent. It is, therefore, surprising that although the structure of **1** has been varied considerably as the result of research efforts during the ten past years, only few derivatives have appeared in the literature in which the C8-substituent of **1** has been modified.[5] In the present communication we describe a synthetic protocol leading to pure enantiomers of derivatives of **1** containing various substituents in the C8-position. Several of these new derivatives bind with high affinity to 5-HT_{1A}-receptors and some of them seem to be of high potency as 5-HT_{1A}-receptor agonists.

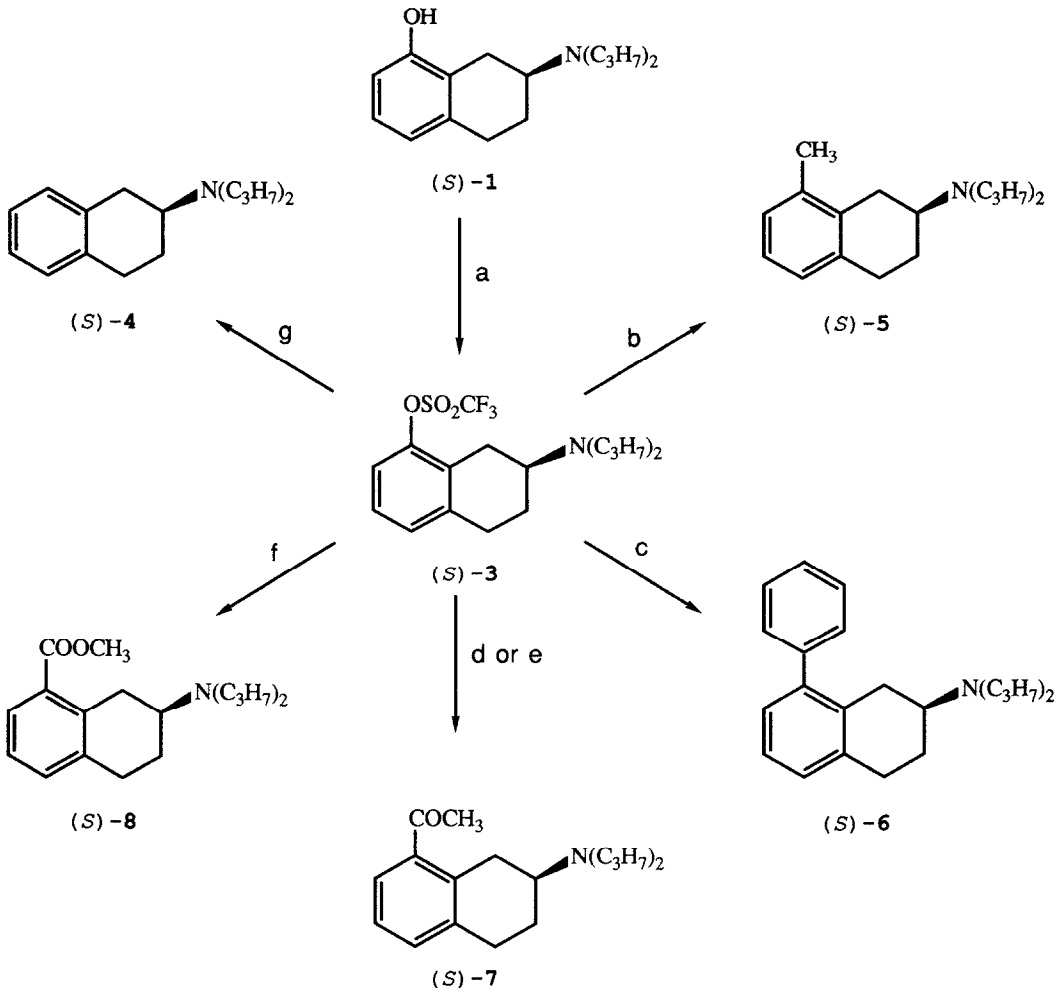


5-HT



(*R*)-**1**: R=H
(*R*)-**2**: R=CH_3

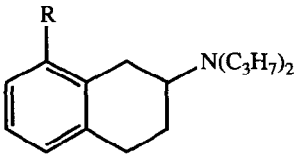
Scheme I*



*Reagents: (a) Triflic anhydride, K_2CO_3, CH_2Cl_2; (b) $(CH_3)_4Sn$, $PdCl_2(Ph_3P)_2$, LiCl, 1,4-dioxane, DMF; (c) $PhSn(n\text{-}C_4H_9)_3$, $Pd(Ph_3P)_4$, LiCl, 1,4-dioxane, DMF; d) $(CH_3)_4Sn$, $PdCl_2$(dppf), CO, LiCl, DMF; (e) i: butylvinylether, $Pd(OAc)_2$, dppp, $N(C_2H_5)_3$, DMF. ii: 10 % HCl; (f) $Pd(OAc)_2$, dppf, $N(C_2H_5)_3$, CH_3OH, CO, DMSO; (g) $Pd(OAc)_2$, dppf, $N(C_2H_5)_3$, HCOOH, DMF.

In the syntheses of the novel derivatives of **1** we utilized efficient palladium-catalyzed transformations of the enantiomers of triflate derivative **3** (Scheme I). An advantage with this synthetic strategy is that the optical purities and absolute configurations of the enantiomers of **1** are retained in the C8-modified analogues. Key intermediates (*S*)- and (*R*)-**3** were produced from the readily available enantiomers of **1**[6] by treatment

Table I. Yields of the Compounds Synthesized and Their Apparent K_i Values and Hill Coefficients for Inhibiting the Binding of [^{3}H]8-OH-DPAT to Membranes from Rat Cerebral Cortex.



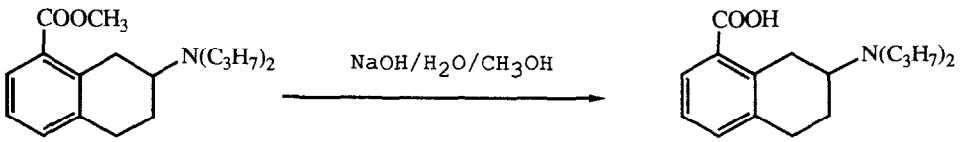
compd[a]	R	yield (%)[b]	mp, °C	recrystn solvent[c]	$[\alpha]_D$[d]	K_i (nM)[e]	(range)	n_H[f]
(*S*)-**1**[g]	OH	-	-	-	-	1.8	(1.6-2.0)	0.86
(*R*)-**1**[g]	OH	-	-	-	-	1.3	(1.1-1.5)	0.97
(*S*)-**2**[g]	OCH_3	-	-	-	-	2.8	(2.7-3.0)	0.96
(*R*)-**2**[g]	OCH_3	-	-	-	-	1.5	(1.4-1.7)	1.11
(*S*)-**3**	OSO_2CF_3	94	114-116	A	-58.9	9.5	(7.4-13.2)	0.83
(*R*)-**3**	OSO_2CF_3	98	113-115	A	+59.6	3.8	(2.8-5.7)	0.79
(*S*)-**4**	H	77	129-130	B	-71.5	56	(46-71)	0.83
(*R*)-**4**	H	41	127-128	B	+71.1	17	(15-19)	0.85
(*S*)-**5**	CH_3	56	129-131	C	-72.5	62	(56-69)	1.04
(*R*)-**5**	CH_3	57	129-131	C	+68.8	34	(32-38)	1.13
(*S*)-**6**	C_6H_5	88	115-117	D	-25.2	24	(22-26)	1.04
(*R*)-**6**	C_6H_5	83	115-116	D	+24.1	7.7	(7.2-8.3)	1.00
(*S*)-**7**	$COCH_3$	44	114-116	A	-123.2	0.7	(0.6-1.0)	0.71
(*R*)-**7**	$COCH_3$	52	115-116	A	+122.7	1.8	(1.6-2.0)	0.96
(*S*)-**8**	$COOCH_3$	59	149-150	A	-115.1	1.7	(1.4-2.1)	1.01
(*R*)-**8**	$COOCH_3$	71	148-150	A	+115.4	4.3	(3.7-4.9)	0.90
(±)-**9**	COOH	97	245-247	C	-	> 300		

[a] All compounds were obtained and tested as the hydrochlorides except (*S*)- and (*R*)-**6** which were obtained and tested as the oxalates. [b] Yields refer to recrystallized compounds. All compounds described have been characterized with ^{1}H and ^{13}C NMR-spectroscopy and give an acceptable elemental analysis. [c] Recrystallization solvent: (A) Chloroform/ether; (B) Acetonitrile/ether; (C) Methanol/ether; (D) Acetone/ether. [d] (*c* 1.0, MeOH), 22°C. [e] Binding of [^{3}H] 8-OH-DPAT (2nM) to rat cerebral cortical membranes was determined as described previously (ref 13). Ki values and approximate standard errors (ranges) were determined from displacement curves based on 6-10 different concentrations in duplicate by using the computer program LIGAND (ref 18). [f] The Hill coefficients were determined from log-logit plots of the inhibition between 10 and 90 %. [g] Included for comparison.

with triflic anhydride in the presence of base.[7] Palladium-catalyzed couplings[8] of (*R*)- or (*S*)-**3** with tetramethyltin and phenyltributylstannane produced the corresponding C8-methylated (**5**) and arylated (**6**) derivatives, respectively. Introduction of methoxycarbonyl and acetyl groups were accomplished by palladium catalyzed carbonylations in the presence of methanol[9] or tetramethyltin.[10] Alternatively, the acetyl group was intro-

duced by a Heck coupling of **3** with butyl vinyl ether[11] and subsequent hydrolysis. The C8-substituent of the enantiomers of **3** was conveniently removed by treatment with formic acid in the presence of a palladium(II) catalyst.[12] Hydrolysis of the racemic methyl ester **8** afforded the carboxylic acid **9** (Scheme II). Yields of the new compounds are given in Table I.

Scheme II



(±)-**8** (±)-**9**

The ability of the derivatives to displace [^{3}H]-8-OH-DPAT from 5-HT_{1A}-receptors is given in Table I.[13] Most of the compounds have high affinity for the 5-HT_{1A}-receptors. In fact, (*S*)-**7** seems to be more potent in this respect than any of the enantiomers of lead compound **1**. Derivatives substituted with a hydroxy, methoxy, acetyl or a methoxycarbonyl group in the C8-position all exhibit high affinity for the 5-HT_{1A}-receptor. The C8-unsubstituted (**4**) and methyl substituted (**5**) derivatives are less potent whereas the triflates (**3**) and the phenyl substituted derivatives (**6**) display intermediate affinity. It is noteworthy that only one derivative, the carboxylic acid (±)-**9**, has low affinity for 5-HT_{1A}-receptors.

The derivatives in Table I show a fairly weak stereoselectivity (about 1.5 - 4 fold) in their interactions with 5-HT_{1A}-receptors. In most derivatives of **1** reported to date, the (*R*)-enantiomers possess the higher affinity but when the C8-substituent is a methoxycarbonyl or an acetyl group, the (*S*)-enantiomers appear to have higher affinity than the (*R*)-antipodes (Table I).

It is well-known[14] that 5-HT_{1A}-receptor agonists decrease the synthesis of 5-HT via activation of somatodendritic autoreceptors. The decrease in synthesis rate may be measured indirectly after inhibition of aromatic *L*-aminoacid decarboxylase (with 3-hydroxybenzylhydrazine; NSD 1015) and subsequent analysis of the 5-HTP levels.[15] In such *in vivo* biochemical experiments in non-pretreated rats, the enantiomers of (*S*)- and (*R*)-**7** behave as receptor agonists, similar in potency to the enantiomers of **1** (Table II). Since none of the enantiomers of **7** affect the DOPA accumulation

in the brain areas studied, they do not appear to activate dopaminergic receptors at the dose tested. In addition, (*R*)- and (*S*)-**7** exhibit similar potencies as the enantiomers of **1** in other tests for 5-HT_{1A}-receptor activity such as reduction of body temperature and induction of the 5-HT behavioral syndrome, which corroborates the biochemical results.[16] Furthermore, preliminary experiments in dogs indicate that the oral bioavailability of **7** is increased about five fold as compared to that of **1**.

Table II. Biochemical Effects *in vivo* of the Enantiomers of **1** and **7** (0.32 μmol/kg, s.c.) in Non-Pretreated Rats.[a]

	5-HTP (ng/g tissue)		DOPA (ng/g tissue)	
Compound	Striatum	Limbic	Striatum	Limbic
(*S*)-**1**	55.8 ± 4.9**	112 ± 4.2**	1136 ± 94	445 ± 14
(*R*)-**1**	51.2 ± 2.6**	102 ± 6.2**	1280 ± 43	414 ± 17
(*S*)-**7**	58.5 ± 7.5*	89.0 ± 8.0**	1098 ± 32	365 ± 19
(*R*)-**7**	62.1 ± 3.1*	111 ± 2.9**	1101 ± 48	399 ± 25
Control	104 ± 4.8	171 ± 7.2	1212 ± 39	440 ± 16

[a] Rats were given test compounds 60 min and benzylhydrazine·HCl (287 μmol/kg, s.c.) 30 min before sacrifice. The values are means ± SEM (n=14 and 4-7 in the control and experimental groups, respectively). Statistics: one way ANOVA followed by Tukey's studentized range (HSD) test; $^{*}p \leq 0.05$, $^{**}p \leq 0.01$ compared with saline treated controls.

The set of compounds presented here may help in the evaluation and refinement of a recently reported 3D-model for 5-HT_{1A}-receptor agonists,[17] provided that the intrinsic activities of the compounds are evaluated. In addition, several of the new compounds may provide leads for drug development.

Acknowledgment. Support for this study was provided by grants from the Swedish Board for Technical Development, the Swedish Natural Science Research Council and Astra Research Centre. L.C. was supported by a grant from DGICYT of the Ministerio de Educación y Ciencia of Spain. We thank Dr Seth-Olov Thorberg for the data on the bioavailability of **1** and **7**.

References and Notes.

1. (a) Fargin, A.; Raymond, J.R.; Lohse, M.J.; Koblika, B.K.; Caron, M.G.; Lefkowits, R.J. *Nature* **1988**, *335*, 358-360, (b) Hartig, P.; Kao, H.-T.; Macchi, M.; Adham, N.; Zgombick, J.; Weinshank, R.; Branchek, T. *Neuropsychopharmacology* **1990**, *3*, 335-347.

2. (a) Traber, J.; Glaser, T. *Trends Pharmacol. Sci.* **1987**, *8*, 432-437, (b) Robinson, D.S.; Alms, D.R.; Shrotriya, R.C.; Messina, M.; Wickramaratne, P. *Psychopathology* **1989**, *22 (Suppl. 7)*, 27-36.
3. (a) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J.L.G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921-923, (b) Hjorth, S.; Carlsson, S.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J.L.G. *J. Neural Transm.* **1982**, *55*, 169-188, (c) Gozlan, H.; El-Mestikawy, S.; Pichat, L.; Glowinsky, J.; Hamon, M. *Nature* **1983**, *305*, 140-142, (d) Middelmiss, D.N.; Fozard, J.R. *Eur. J. Pharmacol.* **1983**, *90*, 151-153.
4. (a) Björk, L.; Backlund-Höök, B.; Nelson, D.L.; Andén, N.-E.; Hacksell, U. *J. Med. Chem.* **1989**, *32*, 779-783, (b) Hacksell, U.; Mellin, C.; Hillver, S.-E.; Björk, L.; Cornfield, L.J.; Nelson, D.L.; Lewander, T. In *Trends in Medicinal Chemistry '90*, Saul, S.; Mechulam, R.; Agranat, I., Eds., Blackwell, in press, (c) Cornfield, L.J.; Lambert, G.; Arvidsson, L.-E.; Mellin, C.; Vallgårda, J.; Hacksell, U.; Nelson, D.L. *Mol. Pharmacol.*, in press.
5. (a) Naiman, N.; Lyon, R.; Bullock, A.; Rydelek, L.; Titeler, M.; Glennon, R.A. *J. Med. Chem.* **1989**, *32*, 253-256, (b) Kline, T.B.; Nelson, D.L.; Namboodiri, K. *J. Med. Chem.* **1990**, *33*, 950-955.
6. Karlsson, A.; Pettersson, C.; Sundell, S.; Arvidsson, L.-E.; Hacksell, U. *Acta Chem. Scand., Ser. B* **1988**, *42*, 231-236.
7. Erhardt, P.W.; Owens, A.H. *Synth. Commun.* **1987**, *17*, 469-475.
8. Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486.
9. Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931-3934.
10. Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1988**, *110*, 1557-1565.
11. Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1990**, *55*, 3654-3655.
12. Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541-5544.
13. The method has been described previously: Liu, Y.; Mellin, C.; Björk. L.; Svensson, B.; Csöregh, I.; Helander, A.; Kenne, L.; Andén, N.-E.; Hacksell, U. *J. Med. Chem.* **1989**, *32*, 3211-3218.
14. Andén, N.-E.; Carlsson, A.; Häggendal, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119-134.
15. Carlsson, A.; Davis, J.N.; Kehr, W.; Lindqvist, M.; Atack, C.V. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1972**, *275*, 153-168.
16. Yu, H.; Liu, Y.; Hacksell, U.; Lewander, T. in manuscript.
17. Mellin, C.; Vallgårda, J.; Nelson, D.L.; Björk, L.; Yu, H.; Andén, N.-E.; Csöregh, I.; Arvidsson, L.-E.; Hacksell, U. *J. Med. Chem.* **1991**, 34, 497-510.
18. Munson, P.J.; Rodbard, D. *Anal. Biochem.* **1980**, 107, 222-239.