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(DIPROPYLAMINO)-TETRAHYDRONAPHTHOFURANS: CENTRALLY ACTING SEROTONIN AGONISTS AND DOPAMINE AGONISTS-ANTAGONISTS

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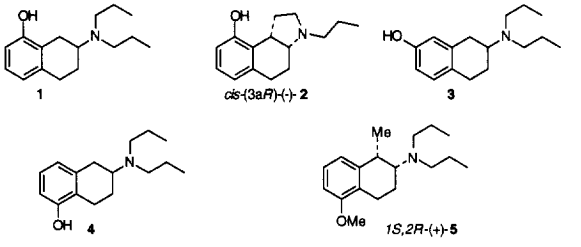
Abstract. CNS-active aminotetralins containing phenolic moieties were transformed in a simple two-step procedure to the corresponding benzofurans. The compounds were tested in *in vitro* binding studies at serotonin 5-HT_{1A} and 5-HT_2 and dopamine D_2, D_3 and D_4 receptors. These studies revealed that the furan homologs showed overall lower affinities than the phenol counterparts. This was also reflected *in vivo* in biochemical studies. The benzofuran compounds retained most of the agonist/antagonist activities but with lower potency.

Phenolic aminotetralins and their corresponding methoxy derivatives have been widely used as pharmacological tools in CNS-research, in both the dopaminergic and serotonergic areas. 8-Hydroxy-2-(dipropyl)-aminotetralin (**1**, 8-OH-DPAT) is a very potent serotonin 5-HT_{1A} agonist and is the ligand of choice for binding experiments at the 5-HT_{1A} receptor.[1-4] The pyrrolidino fused compound *cis*-(3a*R*)-(-)-**2** has also been reported as a high affinity 5-HT_{1A} receptor agonist.[5] Similarly 7-OH-DPAT (**3**) and 5-OH-DPAT (**4**) have been widely used in the dopamine area, the former lately as a dopamine D_3 agonist and the latter as a dopamine D_2 agonist.[1,6-14] The 1-methylated 5-methoxy derivative (*cis-1S,2R*-(+)-**5**, UH232) is reported as a dopamine autoreceptor antagonist.[15,16] This type of compounds, especially the phenolic, suffers from poor oral bioavailability.[17-22]

Fig. 1



In a series of articles, it has been demonstrated that indolic aminotetralins and derivatives thereof, not only mimic the action of phenolic aminotetralins but also possess superior pharmacokinetic properties in terms of oral bioavailability.[21,23,24] In this preliminary investigation, we have synthesized similar benzofuran isosteres to the mentioned hydroxy and methoxy compounds for comparison in terms of *in vitro* and *in vivo* assessment. There are several possible approaches to benzofurans. Since phenolic compounds were readily available, both "in house" and from fine chemicals suppliers, we sought a method for converting these phenolic compounds directly

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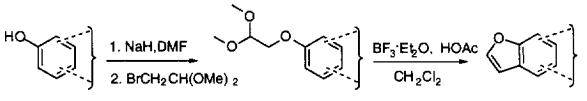
to their corresponding benzofurans. It has been reported that benzthiophenes and indoles can be produced from the corresponding thiols and anilines by alkylation with bromoacetaldehyde diethyl acetal followed by boron trifluoride diethyl etherate catalyzed cyclization in trifluoroacetic anhydride.[25]. The authors found that in the case of benzofuran homologs only polymeric material was obtained. We tried a similar procedure and used after some initial experiments a more inert solvent for the cyclization step, dichloromethane. Several acidic catalysts were tested in the cyclization step but only boron trifluoride diethyl etherate resulted in desired products (Scheme 1,Table 1)[26]. Included in the study is also α-napthtol, as a comparision starting material without an amino functionality.

Scheme 1.



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In fig. 2, the compounds synthesized by this method, are shown. The yields were almost quantitative in the first alkylation step. In the second step however, it seemed that also in this case amounts of the raw product were obtained as polymers as in ref.[25]. This renders the method somewhat unpredictable in terms of expected yields (Table 1). A deeper synthetic-technical evaluation of the utility and yield optimization possibilities of this cyclization method is therefore desired. Notable is also that compound **3** yielded both compound **8** and its isomeric furan fused to the other side of the oxygen. The latter compound was detected but could not successfully be separated and isolated in its pure form (LC, HPLC). Yields were not improved significantly when the reaction was performed on α-napthtol, giving compound **11**.

Fig 2.

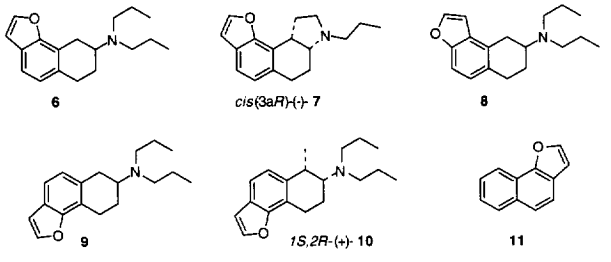

Table 1. Compounds synthesized.

Compound synthesized[a]	LC elute[b]	Recrystn. solvent[c]	m.p. (°C)	Isol. Yield (%)[d]
6-HCl	A	A	215-218	11
cis-(3a*R*)-(-)-**7**-HCl	B	B	208-209	21
8-HCl	C	A	240-243	13 (of 30 tot)[f]
9-(free base)	C	-	oil	13
cis-1S,2R-(+)-**10** (free base)[g]	D	-	oil	13
11	E	-	oil	30

[a]Spectral data in Note 26. [b]A=CH_2Cl_2/*i*-PrOH (9:1), B=Hexane/Acetone (4:1), C=CH_2Cl_2/MeOH (19:1), D=CH_2Cl_2/MeOH (9:1), E=*iso*-octane/EtOAc (19:1). [c]A=MeOH/Et_2O, B=EtOAc/Hexane/MeOH(trace). [d]Yield of purified product for the two steps. [e]Hygroscopic. [f]Yield in parenthesis include compound **8** and its isomeric furan [g]The phenolic precursor was synthesised from UH232 (*cis-1S,2R*-(+)-**5**) by reflux in conc HBr for 3 hrs, evaporation and basic work-up.

The furan derivatives were tested *in vitro* for their ability to displace ^{3}[H]-8-OH-DPAT, ^{3}[H]-ketanserin, ^{3}[H]-U86170[27] and ^{3}[H]-spiperone from 5-HT_{1A}, 5-HT_2, D_2, D_3 and D_4 receptor sites respectively, expressed in cloned Chinese Hamster Ovarial (CHO) cells (Table 2). The compounds were also tested for *in vivo* agonist activity in serotonergic, dopaminergic and noradrenergic systems of reserpine pretreated rats (Table 3). Dopamine autoreceptor antagonist activity was assessed in non-pretreated rats (Table 4). In both *in vivo* methods the synthesis rate of neurotransmitter precursors (5-HTP and DOPA accumulation after decarboxylase inhibition by means of NSD1015) was used as indices of agonist/antagonist activity. Motor activity was recorded in an electronic motility meter. The benzofurans were compared with their corresponding phenols.

Table 2. *In vitro* binding affinities.

Compound	5-HT_{1A}	5-HT_2	D_2	D_3	D_4
			Ki (nM)[a]		
1	0.4±0.2	1614±493	86±8	259±80	>1515
cis-(3a*R*)-(-)-**2**[d]	0.2±0.1	1637±732	769±94	>4762	>4067
3	47±18	NT[b]	2.5±0.5	1.4±0.6	148±27
4	344±58	NT	0.7±0.05	4.4±0.3	NT
cis-1S,2R-(+)-**5**	168±11[g]	NT	15±0.7[g]	4.2±0.3[g]	48±2[g]
6	6.1±1.1	I	32±2	16.2±2	I
cis-(3a*R*)-(-)-**7**	3.9±0.9	146±21	150±46	323±245	>4067
8	7.8±1.1	I	64±7	45±8	I
9	210±18	I	18±2	56±11	I
cis-1S,2R-(+)-**10**	120±18	70±7	46±2	27±6	55±7

[a]Ki values followed by SEM. [b]NT=Not Tested. [c]I=Inactive (less than 50% inhibition at 1μM) [d]Binding values from ref.[5]. [e]^3[H]-8-OH-DPAT-labelled 5-HT_{1A}-sites in bovine hippocampus. [f]^3[H]-raclopride-labelled D_2-sites in rat striatum. [g]Data from ref.[28]

Table 3. *In vivo* effects on 5-HT and DA synthesis in rat brain as measured by 5-HTP and DOPA accumulation in reserpine pretreated animals.

	DOPA accumulation[a]			5-HTP-accumulation[a]		
	Limb.	Stri.	Hem.	Limb.	Stri.	Hem.
Compound[b]	ED_{50} (μmol/kg)[c]			ED_{50} (μmol/kg)[c]		
1[d]	P[e](45)	P(45)	P(45)	0.052	0.063	0.052
3[d]	0.027	0.03	I[f](11)	I(11)	I(11)	I(11)
4[d]	0.011	0.009	I(13.5)	I(13.5)	I(13.5)	I(13.5)
6	P(50)	P(50)	I(50)	3.24 (5.48±0.36)	3.18 (5.49±0.34)	2.26 (5.64±0.32)
cis-(3a*R*)-(-)-**7**	I(12.5)	P(12.5)	I(12.5)	0.41 (6.38±0.38)	0.40 (6.39±0.50)	0.66 (6.18±0.23)
8	4.47 (5.34±0.35)	13.05 (4.88±0.40)	I(50)	4.56 (5.34±0.21)	2.12 (5.67±0.70)	6.08 (5.22±0.82)
9	0.74	0.98	I(50)	I(50) (6.13±0.16)	I(50) (6.01±0.21)	I(50)

[a]limb=limbic regions. stri=corpus striatum. hem=hemispheres. [b]Compound 2 has not been tested in these models. [c]ED_{50} values calculated as in ref.23 [d]Data from ref. 1. [e]P=Partial effects in the highest dose tested (Dose in parenthesis). [f]I=Inactive in the highest dose tested (dose in parenthesis).

Table 4. *In vivo* DA effects in non-pretreated rats. DA synthesis (DOPA accumulation) and locomotor activity

Compound	DOPA accumulation[a] (% of saline control) (50μmol/kg)		Locomotor activity[a] (% of saline control) (50μmol/kg)
	limbic regions	striatum	
cis-1S,2R-(+)-**5**[b]	245***	370***	70±13**
cis-1S,2R-(+)-**10**	121±8[c]	161±8***	107±11[c]

[a] ***Denotes p<0.001, ** p<0.01, * p<0.05. [b] Data from ref 29. [c] Not significant.

In general, the biological responses for the benzofuran derivatives were comparable to the corresponding phenolic derivatives even though the potencies were lower. Also, for certain benzofurans, the selectivity was altered. Compound **6** retained some of the 5-HT_{1A} affinity of 8-OH-DPAT, **1** (10 times lower affinity) and was still quite selective *in vivo* for 5-HT responses, however, was less potent. In addition this compound **6** possessed some affinity for dopaminergic receptors. Compound *cis*-(3a*R*)-(-)-**7** was also a quite potent 5-HT_{1A} agonist which is reflected both *in vitro* and *in vivo* results. The dopaminergic activity of 5-OH-DPAT **4**, was retained although with lower potency and affinities in its corresponding benzofuran derivative **9**. The benzofuran derivative **8** of 7-OH-DPAT, **3**, showed mixed dopaminergic and serotonergic agonist effects which are more similar to its indole homolog (see refs. [21,24]) than to 7-OH-DPAT. Notable is that also compound *cis-1S,2R*-(+)-**10** retained some of the biochemical antagonist activity of its methoxy counterpart UH232 *cis-1S,2R*-(+)-**5**, see Table 4) as judged by elevated DOPA formation.

In summary, a convenient but not optimized synthetic method to prepare furans from phenolic compounds is reported.[30] The prepared furan analogs of the biologically active phenols, in general retained some of the activity of the phenolic compounds, although with lower potency.

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(26) A typical procedure was as follows: a mixture of the phenolic compound (1 eq) and sodium hydride (4 eq, 60% in mineral oil, washed with hexane and dried) in DMF (approx. 1M solution of phenol) was stirred at r. t. for 1 hr. Bromoacetaldehyde dimethylacetal was added and the mixture was stirred at 70 °C for 4-12 h, cooled and quenched with 15% NaOH. After drying, filtration and concentration of the organic phase, the resulting acetal (I, Scheme 1) was dissolved in HOAc and concentrated. The HOAc-salt was dissolved in CH_2Cl_2 and treated with approx. 4 eq BF_3-Et_2O and stirred for 24 h. The progress of the reaction was followed by GC (unidentified intermediates were observed). The mixture was treated with 15% NaOH. Additional extractions (CH_2Cl_2), followed by drying, filtration and concentration yielded a residue, which was purified on silica to give II (Scheme 1, Table 1). **Compound 6:** Dipropyl-(6,7,8,9-tetrahydronaphtho[*1,2-b*]furan-8-yl)amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.5 (sixtet, 4H), 1.8

(octet, 1H), 2.05 (br.d, 1H), 2.55 (t, 4H), 2.7-3.3 (m, 5H), 6.7 (d, J=2.2 Hz, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.33.d (8.0, 1H), 7.57 (d, J=2.2 Hz, 1H); MS *m/e* 271 (M+, 30), 242 (100), 171 (75), 128 (15), 141 (13), 115 (12), C,H*,N. **Compound 7:** 8-Propyl-7,7a,8,9,10,10a-hexahydro-6*H*-1-oxa-8-aza-dicyclopenta[*a,h*] naphthalene. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.4-3.2 (m, 13H), 3.74 (?, J=8.6 Hz, 1H), 6.70 (d, J=2.2 Hz, 1H), 6.97 (d, J=7.9 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.55 (d, J=2.2 Hz, 1H); MS *m/e* 255 (M+,), 226(100), 169 (6), 141 (6); $[\alpha]_D^{20}$ -91.0° (c=0.9, Methanol, free base), C,H,N. **Compound 8:** Dipropyl-(6,7,8,9-tetrahydronaphtho[*2,1-b*]furan-8-yl)amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.5 (sixtet, 4H), 1.7 (octet, 1H), 2.1 (br.d, 1H), 2.55 (t, 4H), 2.7-3.2 (m, 5H), 6.75 (dd, J=0.9, 2.2 Hz, 1H), 7.0 (d, J=8.6 Hz, 1H), 7.5.d (8.3, 1H), 7.57 (d, J=2.3 Hz, 1H); MS *m/e* 271 (M+, 11), 171 (100), 242 (57), 128 (23), 115 (17), 141 (15), C,H*,N. **Compound 9:** Di-*n*-propyl-(6,7,8,9-tetrahydronaphtho[1,2-*b*]furan-7-yl)-amine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sixt, 4H), 1.70 (oct, 1H), 2.2 (br.d, 1H), 2.55 (t, 4H), 2.8-3.2 (m's, 4H), 3.3 (d of d, 1H), 6.70 (d, J=2.1 Hz, 1H), 6.98 (d, J=8.1 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.56 (d, J=2.2 Hz, 1H); MS *m/e* 271 (M+, 9), 171 (100), 242 (45), 128 (26), 115 (18), 141 (18), 145 (15), HRMS. **Compound 10:** (6-Methyl-6,7,8,9-tetrahydronaphtho[1,2-*b*]furan-7-yl)-dipropyl-amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.2 (d, 3H), 1.5 (m, 4H), 1.9 (m, 1H), 2.55-2.75 (m, 4H), 2.8-3.1 (m, 3H), 3.25 (m, 2H), 6.72 (d, J=2.2 Hz, 1H), 7.0 (d, J=8.0 Hz, 1H), 7.4 (d, J=8.0 Hz, 1H), 7.6 (d, J=2.0 Hz, 1H); MS *m/e* 285 (M+, 36), 256 (100), 185 (96), 158 (36), 128 (16); $[\alpha]_D^{20}$ +33.4° (c=1.0, Methanol, free base), HRMS. **Compound 11:** Naphtho[1,2-*b*]furan ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J=1.5 Hz, 1H), 7.54 (t, J=8.1 Hz, 1H), 7.65 (t, J=8.1 Hz, 1H), 7.81 (d, J=2.2 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 8.38 (d, J=8.1 Hz, 1H); MS (*m/e* 168 (M+, 100), 139 (62), 140 (26), 63 (14).* Denotes that value deviates 0.5-0.6 %

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(30) During the course of this work a similar approach (using Amberlyst 15 as catalyst) for cyclization appeared in the literature: Knölker, H-J; Fröhner, W. *Tetrahedron Lett.* **1996**, 37, 9183-9186. By following that procedure we could prepare and isolate compound **11** from α-naphthol in 48% yield, whereas the phenol **3** yielded no product (**8ab**). Although very promising, this method needs to be modified to suit phenolic compounds having an amino moiety.

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