Orally Active Central Dopamine and Serotonin Receptor Ligands: 5-, 6-, 7-, and 8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralins and the Formation of Active Metabolites *in Vivo*

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The racemic triflate derivatives **5–8** of the 5-, 6-, 7-, and 8-hydroxylated 2-(di-n-propylamino)-tetralins **1–4** were shown to possess similar pharmacological profiles to their phenolic counterparts in *in vitro* binding and *in vivo* biochemical and behavioral assays in rats. Consequently, subcutaneous administration of the 5-, 6-, and 7-triflates displayed essentially dopaminergic agonist properties, while the 8-triflate was shown to be a selective 5-HT$_{1A}$ receptor agonist. With respect to their agonist activities, the triflates were less potent than their phenolic analogs. The absolute oral bioavailability of compound **8** (8-triflate) was 4–5 times greater than the corresponding hydroxylated compound. Interestingly, in the *in vivo* biochemical assay compound **8** was found to be more potent after oral than after subcutaneous administration, indicating formation of one or more active metabolites. Following a study of the metabolism of compound **8** in rat hepatocytes, the monopropyl analog **9** was identified as the major metabolite and was suprisingly found to be more potent than compound **8**. Oral administration of compound **5** (5-triflate) resulted in behavioral and biochemical effects indicative of mixed DA/5-HT$_{1A}$ agonist properties not seen after subcutaneous administration. These results may also be indicative of the formation of active metabolites.

Introduction

8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT (**4**), Figure 1) is a potent and selective 5-HT$_{1A}$ receptor agonist.[1–3] Its triflate derivative **8** has been reported by Liu et al. to retain high affinity for this receptor subtype.[4] No further pharmacological data on compound **8** or any other triflate derivative has as yet been reported. The scope of this study was to investigate the pharmacological effects of **8** and of its isomers **5–7**. The oral activity of 8-OH-DPAT in the rat is low, mainly due to extensive first pass elimination via *O*-glucuronidation.[5] The oral bioavailability of **10** [5-hydroxy-2-[N-propyl-N-(2-thienylethyl)amino]tetralin, N-0437] and its stereoisomers has been extensively studied, the main metabolite in the rat being the *O*-glucuronide.[6,7] One way to avoid or delay glucuronidation is to mask the phenol as a carboxylic ester

derivative, which were found to act as prodrugs.[8,9] In addition, den Daas briefly studied the isopropyl sulfonate
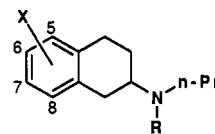
compd	X	R	compd	X	R
1	5-OH	n-Pr	9	8-OSO$_2$CF$_3$	H
2	6-OH	n-Pr	10	5-OH	2-thienylethyl
3	7-OH	n-Pr	11	5-OSO$_2$CH(CH$_3$)$_2$	2-thienylethyl
4	8-OH	n-Pr	12	5-OMe	n-Pr
5	5-OSO$_2$CF$_3$	n-Pr	13	6-OMe	n-Pr
6	6-OSO$_2$CF$_3$	n-Pr	14	7-OMe	n-Pr
7	7-OSO$_2$CF$_3$	n-Pr	15	8-OMe	n-Pr
8	8-OSO$_2$CF$_3$	n-Pr			

Figure 1. Structures discussed.

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Table I. Physical Data of Compounds 5–9

compd	yield %	mp,[a] °C	formula	analysis
5	78	126–130	$C_{17}H_{24}F_3NO_3S \cdot HCl$	CHN
6	84	178–182	$C_{17}H_{24}F_3NO_3S \cdot HCl \cdot$ $0.5(CH_3CH_2)_2O^b$	CHN
7	82	193–195	$C_{17}H_{24}F_3NO_3S \cdot HCl$	CHN
8	88	135–136	$C_{17}H_{24}F_3NO_3S \cdot C_2H_2O_2$	CHN
9	45	224–225	$C_{14}H_{18}F_3NO_3S \cdot HCl$	CHN

[a] Recrystallization solvents were EtOH/isopropyl ether for compounds 5, 7, and 9 and MeOH/ether for compounds 6 and 8. [b] Verified by ^{1}H NMR.

analog of 10 (compound 11).[10] This compound was found not to be hydrolyzed to 10 by esterases *in vitro*. However, it exhibited postsynaptic DA receptor stimulatory effects in 6-hydroxydopamine-lesioned rats with a long duration of action.

Previous experience from our group indicates that conversion of a phenol group to a triflate yields compounds with improved oral availability.[11] In addition, biological data suggests that the DA receptor agonist properties are attenuated, while DA receptor antagonistic properties are amplified, or at least unchanged, in comparison with those of the corresponding phenols.[11] Since the dopaminergic potencies of 5- and 7-OH-DPAT (1 and 3, respectively) are very high, there may be some margin for an affinity and/or potency reduction, provided that, at the same time, the oral availability is increased.[12,13] The same reasoning is valid also for the 8-substituted compound 8, as compared to its phenol 4, with respect to 5-HT$_{1A}$ receptor activation. In this initial study, we evaluated the racemic analogs in *in vitro* binding and metabolism and *in vivo* pharmacological models.

Another objective of this study was to gain some insight into the pharmacokinetic properties of these triflates. This was achieved by measurement of plasma concentrations after oral and intraveneous administration of compounds 4, 5, and 8. In addition, the *in vitro* metabolism of compounds 5 and 8 was investigated in an isolated rat hepatocyte system.[14]

Chemistry

The triflates were synthesized from the known hydroxylated 2-(n-alkylamino) tetralins by treatment with triflic anhydride in the presence of a base (Table I).[3, 15]

Pharmacology

In Vivo Biochemistry. The *in vivo* biochemical test utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[16] The synthesis rate of the catecholamines dopamine (DA) and norepinephrine (NE) is decreased by agonists and increased by antagonists via an agonist and antagonist action at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT$_{1A}$ receptor agonists.[17-19] 5-Hydroxytryptophan accumulation (5-HTP), following decarboxylase inhibition by (3-hydroxybenzyl)hydrazine (NSD 1015), was used as an indicator of the 5-HT synthesis rate in the three brain areas (Table II). In addition, the DOPA accumulation was used as an indicator of the DA synthesis rate in the DA-rich areas (i.e. the limbic system and corpus striatum)[20] and the NE synthesis rate in the NE-rich hemispheres (mainly cortex). For this study we used

Table II. Effects on Rat Brain DA and 5-HT Synthesis Rates (DOPA and 5-HTP Accumulation) *in Vivo* in Reserpinized Rats[a]

compd	ED$_{50}$ (μmol/kg)[a]					
	DOPA acc			5-HTP acc		
	limb.	stri	hem.	limb.	stri	hem.
1 sc[e]	0.01	0.01	I (13.5)[c]	I (13.5)	I (13.5)	I (13.5)
1 po	0.7[b] (0.4–1.0)	0.5 (0.4–0.7)	4.0 (1.8–6.0)	I (7.6)	I (7.6)	I (7.6)
2 sc[f]	0.2	0.2	I (45)	I (45)	I (45)	I (45)
3 sc[f]	0.03	0.03	I (11.0)	I (11.0)	I (11.0)	I (11.0)
4 sc[f]	I (45)	I (45)	I (45)	0.05	0.04	0.07
4 po	P (61)[d]	P (61)	I (61)	3.0 (0.9–7.5)	7.9 (5.7–12)	7.6 (5.4–15)
5 sc	0.4 (0.2–0.6)	0.5 (0.5–0.6)	P (3.1)	I (50.0)	I (50.0)	P (50.0)
5 po	6.2 (5.2–7.2)	7.9 (6.5–9.0)	P (12.5)	3.0 (2.5–4.0)	P (50)	5.4 (4.5–6.3)
6 sc	2.0 (1.3–2.7)	1.3 (1.0–1.8)	I (50.0)	I (50.0)	I (50.0)	I (50.0)
7 sc	1.6 (1.2–2.0)	0.4 (0.4–0.6)	P (12.5)	P (50.0)	34 (25–44)	27 (23–33)
8 sc	P (50)	P (50)	I (50)	5.9 (3.6–8.0)	15 (11–20)	10 (7–15)
8 po	P (50)	P (50)	30 (24–40)	1.2 (0.8–1.9)	1.5 (0.8–2.5)	1.2 (0.7–2.0)
9 sc	P (50)	P (50)	P (50)	1.2 (1.0–1.7)	0.8 (0.3–1.3)	1.1 (0.9–1.3)
12 sc[e]	0.01	0.02	I (45)	I (45)	I (45)	I (45)
12 po	0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.3 (0.2–0.4)	0.4 (0.2–0.6)	0.5 (0.2–0.7)	0.3 (0.2–0.6)
14 sc	P (50)	P (50)	I (50)	P (50)	P (50)	I (50)
15 sc[f]	I (45)	I (45)	I (45)	0.3	0.3	0.2
15 po	5.5 (3.0–8.5)	12.5 (8.0–15.0)	I (50)	3.2 (1.8–5.5)	3.2 (0.8–7.0)	2.3 (1.6–4.2)

[a] The animals received reserpine 18 h before the test drug and NSD 1015, which were given 30 min before decapitation. Shown are the values producing a half-maximal decrease in the accumulation of DOPA and 5-HTP in the limbic, striatal, and hemispheral brain areas. [b] ED$_{50}$ values with graphically estimated deviation (shown in parentheses) based on SEM for each dose. [c] I means inactive at the highest dose tested (given in parentheses as μmol/kg). [d] P means partial response at the highest dose tested, shown in parentheses. [e] Data were taken from ref 21. [f] Data were taken from ref 1. [g] Data were taken from ref 3.

reserpine-pretreated rats (5 mg/kg sc, 18 h). This model is designed to detect directly acting agonists (with various degrees of intrinsic activity) at central monoamine receptors through both biochemical and behavioral effects. Compound 5 was also evaluated in non-pretreated rats in order to study possible antagonistic effects.

Locomotor Activity and Gross Behavioral Observations. Postsynaptic agonistic effects of the test compounds were assessed by the increase in locomotor activity (reversal of reserpine-induced hypokinesia). 5-HT$_{1A}$ agonists induce the 5-HT behavioral syndrome (flat body posture and forepaw treading), while postsynaptic dopamine agonists induce locomotor activity and stereotypies (rearing and sniffing). Motor activity recordings were carried out as previously described with the use of motility meters (Table III).[21] The gross behavior of the animals was observed through semi-transparent glass windows.

In Vitro Binding. The abilities of the test compounds to displace the radioactively labeled ligands [3H]-8-OH-DPAT (5-HT$_{1A}$ agonist), [3H]spiperone (D2-antagonist), and [3H]-N-0437 (D2-agonist) were assessed *in vitro* in homogenized rat brain tissue (Table IV).

Bioanalysis. The absolute oral availabilities of the test compounds were determined by means of analysis of actual plasma concentrations after oral and intravenous administration. Blood samples were collected at various time intervals up to 12 h after drug injection. The doses were

Table III. Locomotor Activity in Reserpinized Rats

compd	dose (μmol/kg, sc)	counts/30 min (mean ± SEM)	behavioral observations 5-HT[a]	DA[a]
ctrls		3 ± 1		
1	0.08	60 ± 20*,[b]		++
2	2.2	100 ± 20		+
3	1.0	160 ± 4		+
4	0.2	66 ± 20*	++	
5[c]	50	170 ± 40*		++
6	12.5	80 ± 30*		+
7	50	170 ± 20*	+	++
8	50	110 ± 20*	++	
9	50	120 ± 40*	++	

[a] The gross behavior of the animals was observed during the motility recordings. The DA agonist induced behavior was characterized by increased locomotion, sniffing, and licking, whereas the 5-HT behavioral syndrome consisted of flat body posture and forepaw treading. The symbols + and ++ denote low or high intensity of the behavioral effects, respectively. [b] Statistics according to ANOVA (n = 5) followed by Fischer's PLSD test. * $p < 0.005$ versus reserpine controls. [c] The LMA was decreased to 76 ± 23% * of controls in non-pretreated rats (50 μmol/kg).

Table IV. *In Vitro* Binding Data

compd	K_i (nM)[a] D_2 ([³H]spiperone)	D_2 ([³H]-N-0437)	5-HT$_{1A}$ ([³H]-8-OH-DPAT)
1	10.8 ± 2.3[d,e]	NT[c]	1040[b]
2	340[b]	NT	3260[b]
3	54 ± 12[d,e]	NT	2800[b]
4	1357 ± 275[d,e]	NT	8.7 ± 5.8[d,e]
5	64 ± 8[d]	28 ± 9[d]	160 ± 10[d]
6	1570[b]	99[b]	16000[b]
7	1300 ± 160[d]	150 ± 50[d]	360 ± 10[d]
8	670[b]	NT	9.6 ± 2.3[d]
9	1360 ± 90[d]	NT	3.8 ± 0.2[d]
12	100[b]	NT	440[b]
15	160[b]	NT	10[b]

[a] K_i values for displacement of the dopamine D_2 receptor antagonist spiperone, the dopamine D_2 receptor agonist N-0437, and the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT. [b] Values are the mean of six drug concentrations (10^{-4}–10^{-9} M) determined from a single experiment. [c] Not tested. [d] Values are the mean of six drug concentrations (10^{-4}–10^{-9} M) in which each value was determined in triplicate. [e] Reference 39.

Table V. Pharmacokinetic Data for Compounds 4, 5, and 8 in the Rat

compd	AUC ratio po/iv (%)[a]	half-life, min[b]
4	2.4 ± 0.9	72
5	8.5 ± 1.5	90
8	11.2 ± 5.2	90

[a] Blood samples were taken from rats with arterial catheters at various time intervals between 5 min and 12 h. The absolute oral availability was estimated by comparing the areas under the curves (AUC) in graphs where the drug concentrations were plotted against time ($n = 4$ for both iv and po administration). The doses were 40 μmol/kg (po) and 5 μmol/kg (iv) for compounds 5 and 8 and 20 μmol/kg (po) and 1 μmol/kg (iv) for compound 4. [b] The half-lives were estimated graphically from the elimination phase of the blood concentration-time curves after oral administration.

40 μmol/kg (po) and 5 μmol/kg (iv) for compounds 5 and 8 and 20 μmol/kg (po) and 1 μmol/kg (iv) for compound 4. Compounds were administered orally to the animals via gavage (Table V).

In Vitro **Metabolism.** The metabolism of compounds 5 and 8 was studied following incubation with suspensions of isolated rat hepatocytes. The metabolite profiles were examined by thermospray (TSP) LC/MS with or without β-glucuronidase/sulfatase treatment. Structural information on metabolites was obtained by MS/MS daughter ion analysis.
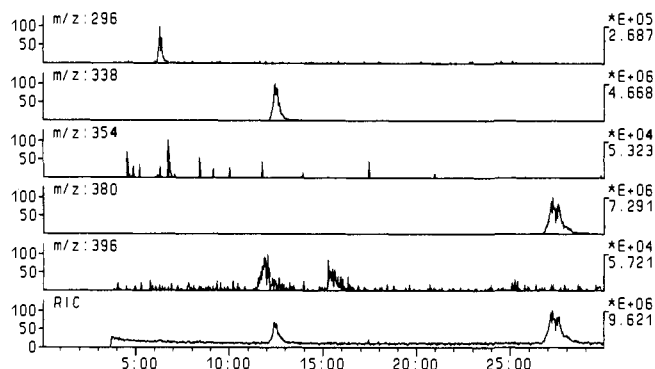

Figure 2. Mass chromatogram of 30-min rat hepatocyte incubation of compound 8 following treatment with β-glucuronidase/sulfatase. Units on the right hand axis are ion current in exponential notation, those on left are arbitrary. RIC refers to reconstituted ion current over the whole scan range.
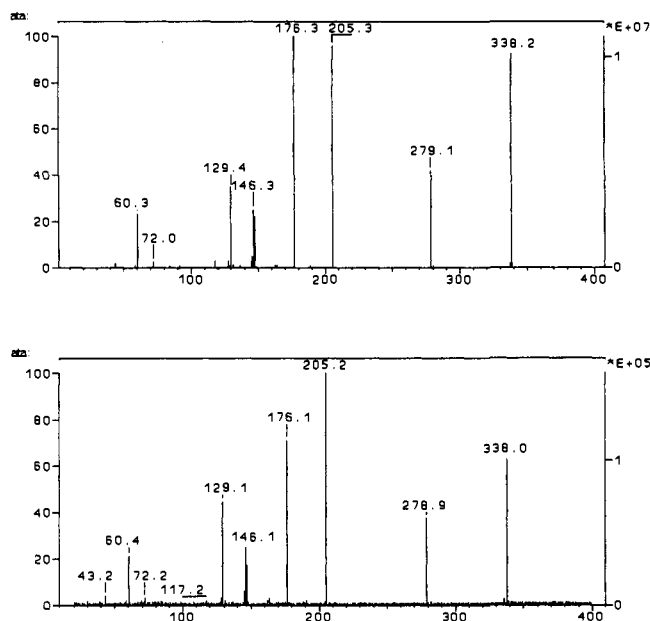

Figure 3. MS/MS spectra (daughters of m/z 338) of the authentic metabolite, compound 9 (top), and M1, the major metabolite from incubation of compound 8 with rat hepatocytes (bottom).

Results and Discussion

Structure–Activity Relationships. The data in Tables II-IV suggest that the pharmacological profiles of compounds 5–8 are similar to those of their corresponding phenols (1–4). Thus, the 5-, 6-, and 7-substituted triflates are dopamine receptor agonists with a trend in the potency of $5 \geq 7 > 6$, both *in vivo* (Tables II and III) and *in vitro* (Table IV), while compound 8 is a selective 5-HT$_{1A}$ receptor agonist. The dopaminergic compounds 5–7 elicited typical and marked postsynaptic DA-receptor stimulatory effects, i.e. increased locomotion and stereotypies (Table III). However, in a single-dose study in non-pretreated animals, compound 5 produced a submaximal reduction in DOPA accumulation in normal rats (50 μmol).[22] Furthermore, a weak hypoactivity was noted (Table III). This suggests that compound 5 is a partial DA agonist in normal rats. Interestingly, compound 7 seems to be slightly more potent in striatum than in the limbic region as a DA receptor agonist (decrease in DOPA accumulation *in vivo*, Table II). There is no obvious explanation for this finding.

The substituent constants and the nature of sulfonate esters can best be discussed by separating the physico-chemical properties into electron-withdrawing and elec-

Figure 4. MS/MS spectrum (daughters of m/z 296) of M2 from incubation of compound 8 with rat hepatocytes and interpretation of fragmentation.

Figure 5. Mass chromatogram of 120-min rat hepatocyte incubation of compound 8 following treatment with β-glucuronidase/sulfatase. Units on right hand axis are ion current in exponential notation, those on the left are arbitrary. RIC refers to reconstituted ion current over the whole scan range.

tron-donating ability and comparison with hydroxy and methoxy substituents, as shown in Table VI. The positive signs of the Hammett σ_p and σ_I constants for the triflate and the mesylate groups indicate that the sulfonate esters are electron withdrawing groups. However, they are ortho–para directing as seen from the negative sign of σ_R. This observation is in accordance with experimental evidence which shows that the phenyl triflate is first nitrated at the 4 position and then at the 2 position, but only under forcing conditions.[23] The hydroxy and methoxy substituents are electron-donating according to the negative sign of σ_p constants (Table VI). In addition, aryltriflates may be able, through their polarizable electronic clouds with H-bond accepting properties, to participate in H-bonding in the drug–receptor interaction. Such H-bonds will be weaker than those developed from a phenolic group, which can both donate and accept a hydrogen bond, and may confer other pharmacological properties upon the triflate derivatives than those displayed by the corresponding phenols.

An interesting physicochemical effect of the triflate substituent is its influence on lipophilicity. We have calculated the ClogP values for compounds 4, 8, and 15 to be 3.9, 5.8, and 4.5, respectively.[24] This indicates that the triflate group increases the lipophilicity, as compared to the 8-OH compound 4, more so than the methyl group in the 8-methoxy analog 15.

Figure 6. Proposed metabolic pathway of compound 8 in isolated rat hepatocytes.

Table VI. Physicochemical Parameters for Sulfonic Ester and Hydroxy/Methoxy Substituents

substituent	σ_p	σ_R	σ_I	ref
CH₃SO₂O	+0.33	−0.28	+0.61	23
CF₃SO₂O	+0.47	−0.36	+0.84	23
MeO	−0.27	−0.47	+0.21	36, 37
HO	−0.37	−0.40	+0.32	36, 38

As shown in Table II, it is not necessary to have a hydrogen bond donating substituent on the aromatic ring (e.g. compare 1 and 12) for dopaminergic activity. This indicates that hydrogen-bond acceptance is sufficient for DA receptor stimulation. The biochemical ED_{50} value for the 5-triflate analog 5 is approximately 15 to 20 times higher than the corresponding value for the 5-methoxy analog 12. However, the *in vitro* binding affinities for 5 and 12 are roughly the same. One explanation for these observations could be that the triflation makes the compound bind well (increased lipophilicity) but diminishes the functional potency (intrinsic efficacy) at the DA receptors. In addition, it may be speculated that by triflatation, the S-enantiomer of 1, which is a full agonist, may become a partial agonist, while the antagonistic properties of the R-enantiomer of 1 are retained in R-5.[25] Thus, the potential agonistic properties of S-5 may possibly be counteracted by the potential antagonistic properties of R-5. This is supported by data from normal rats, where racemic 5 behaves as a partial agonist. In order to understand fully the influence of the triflate functionality in the SAR of DA receptors, it is important to resolve compound 5 and to investigate further the pharmacological activity of the enantiomers of this compound.

The electronic density of the aromatic ring does not

seem to be as important for 5-HT$_{1A}$ agonists as for DA agonists. Romero et al.[26] have reported that 8-CONH$_2$-DPAT is a highly potent 5-HT$_{1A}$ agonist ([^{3}H]-8-OH-DPAT, K_i = 6.1). The carboxamide group is a powerful electron-withdrawing group and it has the capability to act as a hydrogen-bond donor.

The most intriguing result from this study is that oral administration of compound 8 resulted in a 5–10 times *higher potency* than did subcutaneous administration. Furthermore, the maximal reduction in 5-HTP accumulation was about 75% of controls for compound 8 po, whereas most other 5-HT$_{1A}$ agonists produce only approximately 50% of the maximal reduction. At first glance, this seems to indicate that compound 8 is a prodrug of 8-OH-DPAT (4). However, no 8-OH-DPAT (4) was found in the blood from the animals in the pharmacokinetic study performed. In order to gain some insight into the possible metabolic pathways of compounds 5 and 8, incubations were performed with isolated rat hepatocytes. A sample obtained following 30 min incubation of compound 8 was treated with β-glucuronidase/sulfatase. LC/MS analysis of this sample (Figure 2) revealed several compounds not detected in the blank (hepatocytes without drug). Assuming equal response factors, the largest peak had the same [M + H]$^+$ ion (m/z 380) and retention time as compound 8. The major metabolite (M1) exhibited an [M + H]$^+$ ion at m/z 338 consistent with it being the secondary amine product (9) of N-despropylation of compound 8. An authentic sample of this putative metabolite (9) was subsequently shown to exhibit an [M + H]$^+$ ion of m/z 338 at the same retention time. Comparision of the MS/MS spectra of M1 and compound 9 (daughters of m/z 338; Figure 3) confirmed the identity of M1. The second most abundant ion in the mass chromatogram (Figure 2) was m/z 296, which corresponded to a putative primary amine metabolite (M2). This could arise from further N-despropylation of the major metabolite. Although no authentic standard of the primary amine (M2) was available, the MS/MS spectrum (daughters of m/z 296) was entirely consistent with this assignment. An interpretation of the fragmentation, along with the spectrum, is given in Figure 4. Two minor metabolites of compound 8 were also observed with [M + H]$^+$ ions at m/z 396. These were thought to be oxidatation products of compound 8. There was insufficient material to obtain MS/MS data on these proposed metabolites.

Analysis of a sample obtained after 120-min incubation (Figure 5) revealed that M2 was slightly more abundant than M1. A further metabolite (M3) was observed at m/z 354 which was thought to be an oxidation product of M1. MS/MS analysis (daughters of 354), while not providing a definitive assignment, was suggestive of hydroxylation having taken place at a benzylic position.

The relative amounts of the metabolites with or without β-glucuronidase/sulfatase treatment did not appear to change. It is therefore concluded that glucuronide or sulfate conjugation was not significant pathway in this model system. The proposed metabolic pathway for compound 8 is given in Figure 6. Data obtained from studies with compound 5 suggested that this compound also undergoes N-despropylation to the primary amine;[27] however no evidence for any oxidized metabolites was found.

When the monopropyl compound 9 was tested in reserpinized rats, it was suprisingly found to be more potent

as a 5-HT$_{1A}$ agonist than the dipropyl analog (8) (Table II). The *in vitro* binding study further supports this finding (Table IV). Based on these results, we suggest that the active metabolite, when compound 8 is administered orally, is the monopropyl analog 9. Since 8-substituted aminotetralins, in general, are more potent with a dipropyl than with a monopropyl substitution on the nitrogen,[3] this finding constitutes an important contribution to the SAR for compounds with affinity to the 5-HT$_{1A}$ receptor.

The effect of the triflate substituent on the metabolism of aminotetralins is unclear. The increase in lipophilicity would allow greater penetration of the lipid-rich smooth endoplasmic reticulum (containing the cytochrome P450 superfamily) in the liver, which may have resulted in a more extensive first pass metabolism in this organ. However, the electron-withdrawing properties of the triflate group may result in a decrease in aromatic hydroxylation, as compared with an electron-donating substituent such as a hydroxy group[28] and likely a methoxy group also. Overall, oxidation appeared to be a minor pathway for compounds 5 and 8 *in vitro*, although aromatic hydroxylation could not be ruled out. This may contribute toward the increased oral bioavailability of the triflates. Furthermore, it has been reported that aryltriflates are chemically stable compounds with respect to solvolysis.[29]

The oral bioavailabilites of compounds 5 and 8 are 8.5% and 11%, respectively (Table V). This is higher than that of 8-OH-DPAT (4) (2.4%), indicating that the triflates are more stable *in vivo*. On the basis of pharmacological data presented in this paper, it is possible that the oral availability of compound 9 would be considerably greater than 11%. There were no major differences in plasma half-life among compounds 4, 5, and 8.

In addition, oral administration of compounds 5 and 12 resulted in behavioral and biochemical effects indicative of mixed DA/5-HT$_{1A}$ agonist properties, which is not seen after subcutaneous administration. This also indicates the formation of active metabolites. It has been reported in the literature that 5-methoxyaminotetralin (primary amine) displays 5-HT$_{1A}$ effects in behavior and biochemical assays.[30] It is speculated that the active metabolite of compounds 5 and 12 might be respective primary amines, and these are responsible for the 5-HT$_{1A}$ activity.

In conclusion, we present the triflate group as an interesting bioisostere of a methoxy and/or a hydroxy group in both serotonergic and dopaminergic compounds. As discussed, triflates are chemically stable, electron-withdrawing groups conferring increased lipophilicity, as compared to the parent methoxy and/or hydroxy compound. These data are compatible with increased metabolic stability with respect to aromatic hydroxylation, and direct O-glucuronidation can no longer occur. This is demonstrated both by the *in vitro* hepatocyte data and the absolute bioavailability data of compound 8 (F = 11%), as compared to 8-OH-DPAT (F = 2.4%). However, the triflate functionality seems to reduce the potency. As shown with the 8 substituted analogs, the triflate analog 8 is about 100 times less potent biochemically than the corresponding hydroxy analog 4. Compound 8 was found to be more active after oral administration than after subcutanous administration thus indicating the possibility of an active metabolite. The monopropyl analog 9 was postulated to be the active metabolite and was subse-

quently found to be more potent than compound 8. However, in order to understand fully the influence of the triflate functionality in the SAR of DA and 5-HT$_{1A}$ agonists/antagonists, it is important to resolve compounds 5, 8, and 9 and to investigate further the pharmacological activity of the enantiomers of these compounds.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ at 300 and 75.4 MHz, respectively, with a Varian XL 300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Low resolution mass spectra were obtained on a HP 5970A instrument operating at an ionization potential of 70 eV and interfaced with a HP5700 gas chromatograph. A fused silica column (11 m, 0.22 mm i.d.) coated with cross-linked SE-54 (film thickness, 0.3 m; He gas, flow, 40 cm/s) was used. Elemental analyses were obtained from Mikro Kemi AB, Uppsala, Sweden. Melting points were determined with a melting point microscope (Reichert Thermovar) and are uncorrected. For flash chromatography silica gel 60 (0.040–0.063 mm, E. Merck, no. 9385) was used.

Materials. All monohydroxylated and monomethoxylated aminotetralins were prepared according to the literature procedures.[3,12,15] Chemicals used were commercially available (Aldrich) and were used without further purification.

(±)-5-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralin (5). A solution of 5-hydroxy-2-(di-n-propylamino)tetralin (1) (75 mg, 0.302 mmol) and triethylamine (34 mg, 0.332 mmol) in 2 mL of CH$_2$Cl$_2$ was cooled to –30 °C. Then the triflic anhydride (94 mg, 0.332 mmol) in 0.5 mL of CH$_2$Cl$_2$ was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h at 25 °C. The reaction mixture was then quenched with water. The layers were separated, and the organic phase was washed with 2 portions of 10% HCl solution (v/v). Following a wash of the organic portion with brine and drying (MgSO$_4$) the solvent was removed under reduced pressure. The residue (99 mg, 86%) was chromatographed on a silica column with MeOH/CH$_2$Cl$_2$ (1:19, v/v) as eluent and afforded 89 mg (78%) of pure triflate as an oil. The amine was converted into the HCl salt and recrystallized from ethanol/ether: mp 126–30 °C (HCl); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, 6H), 1.5 (sext, 4H), 1.7 (m, 1H), 2.1 (m, 1H), 2.5 (t, 4H), 2.7–3.2 (m, 5H), 7.08 (d, J = 7.5 Hz, 1H), 7.11–7.24 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 12, 22.3, 24.5, 25.3, 32.7, 53.0, 56.2, 118.4, 119.1 (q, J = 315 Hz), 127.2, 129.6, 130.2, 141.5, 148; MS m/z (relative intensity, 70 eV) 379.2 (9.0, M$^+$), 350.2 (100), 217.0 (29.0), 188.0 (46.4), 145.0 (65.2).

(±)-6-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralin (6). Triflation of 6-hydroxy-2-(di-n-propylamino)tetralin (2) (63 mg, 0.255 mmol) was performed according to the procedure given for the production of 5 above and gave an oil after extractive workup. Chromatography on a column of silica gel using a mixture of CH$_2$Cl$_2$/MeOH (19:1, v/v) as eluent gave the title compound (81 mg, 84%): mp 178–82 °C (HCl); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, 6H), 2.0 (m, 4H), 2.55 (m, 1H), 3–3.7 (m, 10 H), 7.04 (d, J = 2 Hz, 1H), 7.1 (dd, J_1 = 2 Hz, J_2 = 9 Hz, 1H), 7.22 (d, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 12.0, 18.5, 24.2, 29.1, 29.9, 52.5, 59.2, 118.5 (q, J = 320 Hz), 120.0, 121.6, 131.8, 133.7, 137.9, 148.5; MS m/z (relative intensity, 70 eV) 379.2 (9.3, M$^+$), 350.2 (61.4), 279.0 (20.6), 246.2 (100), 188.0 (18.0).

(±)-7-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralin (7). Triflation of 7-hydroxy-2-(di-n-propylamino)tetralin (3) (65 mg, 0.263 mmol) was performed according to the procedure given for the production of 5 above and gave an oil after extractive workup. Chromatography on a column of silica gel using a mixture of CH$_2$Cl$_2$/MeOH (19:1, v/v) as eluent gave the title compound (82 mg, 82%): mp 193–95 °C (HCl); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.0 (t, 6H), 2.0 (m, 5H), 2.6 (m, 1H), 2.9–3.1 (m, 8H), 3.63 (m, 1H), 7.1 (d, J = 9.3 Hz, 1H), 7.2 (d, J = 9.2 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.0, 18.0, 23.9, 28.0, 29.8, 52.0, 59.0, 118.5 (q, J = 320 Hz, CF$_3$)), 119.9, 122, 130.3, 134.4, 135.0, 148.0; MS m/z (relative intensity, 70 eV) 379.2 (6.8, M$^+$), 350.0 (100), 279.0 (19.4), 217.1 (43.7), 188.1 (23.6).

(±)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(di-n-propylamino)tetralin (8). Triflation of 8-hydroxy-2-(di-n-propylamino)tetralin (4) (102 mg, 0.412 mmol) was performed according to the procedure given for the production of 5 above and gave an oil after extractive workup. Chromatography on a column of silica gel using a mixture of CH$_2$Cl$_2$/MeOH (19:1, v/v) as eluent gave the title compound (138 mg, 88%): mp 135–36 °C (oxalate); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.01 (t, J = 7.1, 6H), 1.47 (m, 4H), 1.68 (m, 1H), 2.03 (m, 1H), 2.48 (t, J = 7.2, 4H), 2.61 (m, 1H), 2.92 (m, 4H), 7.05–7.18 (m, 3H); MS m/z (relative intensity, 70 eV) 379.2 (6.1, M$^+$), 350.8 (100), 217.6 (55.9), 188.5 (38.2), 146.4 (87.7).

(±)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(n-propylamino)tetralin (9). Triflation of 8-hydroxy-2-(n-propylamino)tetralin (260 mg, 1.27 mmol) was performed according to the procedure given for the production of 5 above and gave an oil after extractive workup. Chromatography on a column of silica gel using a mixture of CH$_2$Cl$_2$/MeOH (12:1, v/v) as eluent gave the title compound (192 mg, 45%): mp 224–25 °C (HCl); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, 3H), 1.55 (m, 2H), 1.68 (m, 1H), 2.1 (m, 1H), 2.7 (t, 2H), 2.7–3.2 (m, 5H), 7.05–7.2 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.7, 22.9, 27.8, 28.2, 30.0, 48.7, 52.7, 118.4, 118.5 (q, J = 320 Hz, CF$_3$), 126.9, 128.2, 128.6, 139.7, 148.3; MS m/z (relative intensity, 70 eV) 337.0 (28, M$^+$), 308.0 (100), 279.0 (23), 204.15 (41), 69.0 (22).

Pharmacology. Animals. Animals used in the biochemical and motor activity experiments were male rats of the Sprague–Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were housed five per cage with free access to water and food, for at least 1 week from arrival until used in the experiments. The animals treated orally with drug were fasted 18 h before the experiment.

Materials. All substances to be tested were dissolved in physiological (0.9%, w/v) saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 mL/kg, and all solutions had neutral pH values (except for the solutions of reserpine).

Biochemistry. The biochemical experiments and the determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed as previously described.[31,32] Separate dose–response curves based on four to six dose levels for each substance and each brain area were constructed. From these graphs, the dose of the drug yielding a half-maximal decrease (ED$_{50}$ value) of the 5-HTP (the maximal effect, expressed as percent of controls, was as follows: limbic system, striatum, and the hemispheres = –50%) and the DOPA (the maximal effect, expressed as percent of controls, was as follows: limbic system = –65%, striatum = –80%, and the hemispheres = 50%) levels were estimated separately (Table II). Control values for the 5-HTP data were (ng/g, mean ± SEM; n = 4) as follows; limbic system = 160 ± 20, striatum = 120 ± 10, and the hemispheres 100 ± 10. The DOPA levels were (ng/g, mean ± SEM, n = 10) as follows; limbic system = 810 ± 60, striatum = 3700 ± 200, and the hemispheres = 170 ± 10.

Motor Activity. The motor activity was measured by means of photocell recordings (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm) as previously described.[21] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were subcutaneously injected in the neck region with reserpine (5 mg/kg sc). The different test compounds were also administered subcutaneously in the neck region (n = 4). Immediately after drug administration, the rats were put into the motility meters (one rat/cage). The activity was then followed and recorded for the subsequent 30 min (reserpine control values 3 ± 1 counts/30 min, mean ± SEM; n = 13; Table III. Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors.

5-HT$_{1A}$ Radioligand Binding.[33] Male Sprague–Dawley rats (160–225 g) were killed by decapitation, and the whole brain with the exception of the brain stem and cerebellum was rapidly removed, weighed, and chilled in ice-cold 0.9% NaCl. Each brain was homogenized (Ultra-Turrax for 20 s) in 10 mL of ice-cold 50 mM Tris buffer (pH 8.0 at 25 °C) containing 120 mM NaCl, 4

mM $CaCl_2$, and 4 mM $MgCl_2$ and centrifuged at 20000g at 4 °C for 10 min. Pellets were resuspended in 10 mL of fresh buffer and preincubated for 10 min at 37 °C (water bath) and then recentrifuged. Final pellets were homogenized in 100 volumes (w/v) of Tris buffer (as described above) containing 10 μM pargyline. The incubation tubes (triplicates) were kept on ice and received 100 μL of drug solution in water (or water for total binding) and 1 mL of membrane suspension (corresponds to 10 mg of original tissue). The binding experiment was initiated by addition of 100 μL of [^{3}H]-8-OH-DPAT (specific activity, 143–158 Ci/mmol) in ascorbic acid (the final incubation concentration was 1 nm [^{3}H]-8-OH-DPAT in 0.1% ascorbic acid). After incubation for 15 min at 37 °C, the reaction was terminated by separation of the free radioligand from bound by rapid vacuum filtration using cell-harvester equipment (O.M. Teknik, Denmark). The tubes were rinsed with 4 mL, and the filters (Whatman GF/F 25 mm) were washed twice with 4 mL, ice-cold 0.9% NaCl (w/v).

The radioactivity of the filters was measured in a liquid scintillation counter (efficiency 41%, LKB 1215 Rackbeta, Pharmacia-Sweden) in 5 mL of Picofluor TM15. Specific binding (70–75% of total binding) was defined as the radioactivity displaced by 10 μM 5-HT. IC_{50} values were calculated by semilog plot and linear regression analysis.

Inhibition of [^{3}H]Spiperone Binding. Binding of [^{3}H]-spiperone (specific activity, 21–24 Ci/mmol) to rat striatal membrane was, with a few exceptions, determined as described by Hyttel and Arnt.[34] Briefly, membranes were isolated in 50 mM potassium phosphate buffer (pH 7.4 at 25 °C) by homogenization and centrifugation at 20000g (10 min, 4 °C). The final pellets were homogenized in 1300 volumes of 50 mM potassium phosphate buffer, and the membrane suspension was incubated with 0.5 nM [^{3}H]spiperone in a final volume of 4.2 mL (3 mg of original tissue) for 10 min at 37 °C. Specific binding was 70–80% of total binding and was obtained by adding 10 μM 6,7-ADTN to the membrane suspension.

Inhibition of [^{3}H]-N-0437 binding. Male Wistar (Mol:Wist) rats (125–250 g) were sacrificed and their corpora striata were dissected and weighed. The tissue was homogenized (Ultra Turrax 10–15 s) in 10 mL of ice-cold 50 nM Tris buffer, pH 7.5 (at 25 °C), containing 1 mM Na_2EDTA, 5 mM KCl, and 2 mM $CaCl_2$. The homogenate was incubated for 15 min at 37 °C and then centrifuged twice at 20000 g for 10 min at 4 °C, with rehomogenization of the pellet in 10 mL of ice-cold buffer. The final pellet was homogenized in 1600 vol (w/v) of ice-cold buffer. Incubation tubes (triplicates) kept on ice received 100 μL of drug solution in water (or water for total binding) and 2 mL of tissue suspension (final tissue content corresponding to 1.25 mg of original tissue). The binding experiment was initiated by addition of 100 μL of [^{3}H]-N-0437 (from Amersham International plc., England; specific activity, approximately 80 Ci/mmol, final concentration, 0.2 nM) and by placing the tubes in a 25 °C water bath. After incubation for 90 min, the samples were filtered under vacuum (100–200 mbar) through Whatman GF/F filters (25 mm). The tubes were rinsed with 5 mL of ice-cold buffer which was then poured on the filters. Thereafter, the filters were washed with 5 mL of buffer. The filters were placed in counting vials, and 4 mL of appropriate scintillation fluid (e.g. Picofluor 15) was added. After shaking for 1 h and storage for 2 h in the dark, the content of radioactivity was determined by liquid-scintillation counting. Specific binding was obtained by subtracting the nonspecific binding in the presence of 1 μM of 6,7-ADTN. For determination of the inhibition of binding, five concentrations of drugs covering 3 decades were used. The measured cpm's were plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve was drawn. The IC_{50} value was determined as the concentration at which the binding was 50% of total binding in control samples minus the nonspecific binding in the presence of 1 μM 6,7-ADTN.

Estimation of Oral Bioavailability. Blood levels of 4, 5, and 8 were measured by means of gas chromatography (Hewlett-Packard 5890)–mass spectrometry (VG Trio II). The doses were 40 μmol/kg (po) and 5 μmol/kg (iv) for compounds 5 and 8 and 20 μmol/kg (po) and 1 μmol/kg (iv) for compound 4. The compounds were administered orally to the animals via gavage. The blood samples (150 μL) were collected from arterial catheters

in male Sprague–Dawley rats (300 g). The experiment was started 24 h after the operation, and blood samples were collected at various time intervals up to 12 h after drug injection. The samples were diluted with 1 mL of water followed by addition of 50 μL of internal standard [(S)-(–)-3-[[3-(Trifluoromethyl)sulfonyl]-oxy]phenyl-N-ethylpiperidine[11]); 10 pmol/μL was added. The pH was adjusted to 11.0 by the addition of saturated Na_2CO_3 solution. After mixing, the samples were extracted with 4 mL of dichloromethane by shaking for 30 min. The organic layer was transferred to a smaller tube and evaporated to dryness under a stream of nitrogen. The residue was redissolved in 40 μL of toluene for GC–MS analysis. A standard curve over the range 2–1000 pmol/mL was prepared by adding appropriate amounts of 5 or 8 standard to blank blood samples. A set of control samples at two different concentrations (made up in bulk and kept frozen) were included in each assay. GC was performed on cross-linked PS 264 capillary column (15 m × 0.25 mm) and a 2-μL sample was injected in the splitless mode. The GC temperature was held at 90 °C for 1 min following injection and was then increased by 30 °C/min to a final temperature of 290 °C. Each sample was run in duplicate. The absolute oral availability of the compounds was assessed by comparing the areas under the curves (AUC), for po (n = 4) and iv (n = 4) administration, from plots of concentration in blood versus time. Rats treated orally with drug were deprived of food 18 h before the experiment.

Hepatocytes. Hepatocytes were isolated from male Sprague-Dawley rats (Charles River, Margate, UK; body weight $\approx$ 200 g) by *in situ* collagenase perfusion based on the method of Seglen.[35] Cell viability was determined by Trypan blue dye exclusion (typically 85–90%). Isolated hepatocytes were suspended at 5 × 10^6 viable cells mL^{-1} in 10 mM phosphate buffered saline (pH 7.4 at 4 °C; prepared from tablets obtained from Sigma Chemical Co., Poole, UK) containing 1% (w/v) glucose.

Incubation of Hepatocytes with Compounds 5 and 8. A 5-mL aliquot of hepatocyte suspension was dispensed into a polycarbonate 25-mL conical flask. Following pre-incubation for 5 min at 37 °C in a shaking water bath ($\approx$120 strokes/min), 100 μL of a solution of compound 5 or 8 (as the ethane dioate salt, 1 mg/mL equivalents in dimethyl sulfoxide) was added and the incubation continued for a further 120 min. After 30 and 120 min, samples (2 mL) were withdrawn from the flask into 2 mL of 0.1 M sodium acetate buffer (pH 5.0 at 37 °C) and ultrasonicated for 5 min. The samples were then stored at –20 °C overnight. A sample of hepatocyte suspension without drug was processed as above to act as a blank.

Incubation of samples with β-Glucuronidase. Following thawing, samples were divided into equal aliquots and incubated with or without 50 μL of a β-glucuronidase/sulfatase preparation (Type H3, from *H. pomatia*; Sigma). Protein was precipitated with acetonitrile (2 mL) followed by centrifugation at 12000g for 5 min. Removal of acetonitrile *in vacuo* yielded an aqueous residue ($\approx$1 mL).

Mass Spectrometry. Samples were analyzed by thermospray (TSP) LC/MS using a Finnigan MAT TSQ 70 mass spectrometer coupled via a TSP II interface (both Finnigan MAT, Paradise, Hemel Hempstead, UK) to a reversed phase HPLC system. The spectrometer was operated in Q3 MS mode to collect the TSP/LC/MS data and in TSP/LC/MS/MS mode to obtain the collisionally induced dissociation (CID) data.

HPLC Conditions: injector, manual U6K (Millipore); pump, Waters 600MS (Millipore, Watford, UK); guard column, Brownlee RP8 15 × 3.2 mm (Anachem, Luton, UK); column, Zorbax Rx C8 250 × 4.6 mm (Hichrom, Reading, UK); mobile phase, 33% (v/v) acetonitrile, 0.1% (v/v) trifluoroacetic acid in Milli-Q water (Millipore); flow rate, 1.5 mL/min; injection volume, 100 μL; equivalent to 100 μL of the original incubate.

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