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SYNTHESIS AND BIOLOGICAL ACTIVITY OF C-5 MODIFIED DERIVATIVES OF (+)-AJ76 AND (+)-UH232: INCREASED DOPAMINE D_3 RECEPTOR PREFERENCE AND IMPROVED PHARMACOKINETIC PROPERTIES

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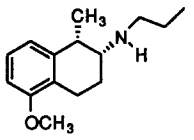
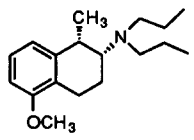
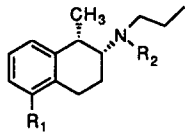
Abstract: A series of (+)-AJ76 and (+)-UH232 analogs with the C-5 methoxy group modified was synthesized and biologically evaluated. Compounds with a triflate or nitrile group were found to be behavioral stimulants with high metabolic stability. The triflate analogs also displayed a 14-fold preference for the D3 receptor site in vitro.



1, (+)-AJ76



2, (+)-UH232



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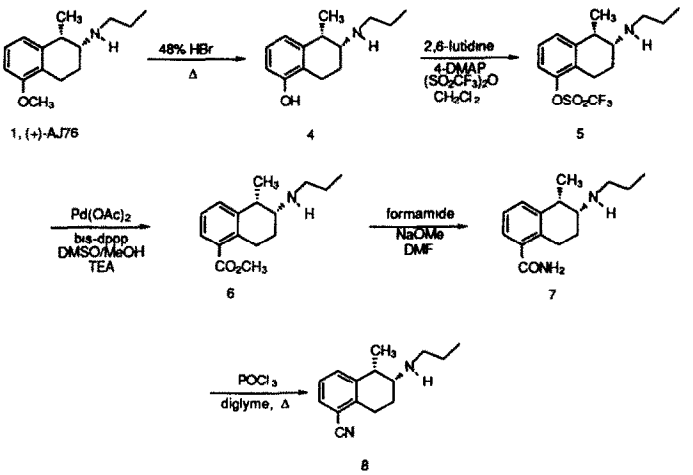
Classical neuroleptics block both presynaptic dopamine (DA) autoreceptors and postsynaptic DA receptors. The DA antagonists *cis*-(+)-1*S*,2*R*-AJ76 (**1**) and *cis*-(+)-1*S*,2*R*-UH232 (**2**) show a preference for the autoreceptors.[1] As a consequence, they produce a weak behavioral activation. The more marked this preference is, the more pronounced is the behavioral stimulation induced by these agents. However, because they also show affinity for the postsynaptic receptors, their stimulating properties are mild as compared to stimulants such as the amphetamines. Moreover, their behavioral action depends on the baseline activity of the animals tested.[1] At a low baseline activity (habituated animals) their stimulating properties are most marked. At a baseline activity pushed very high by means of dopaminergic agents such as apomorphine, amphetamine or cocaine, this new class of agents counteract the behavioral stimulation, apparently because the postsynaptic receptor blockade predominates under these conditions. Most of the data available today stems from experiments on rodents. In monkeys, (+)-AJ76 and especially (+)-UH232 appear to be predominantly inhibitory and neuroleptic-like. However, they appear to act more mildly than classical neuroleptics since they do not

cause torsion dystonia (unpublished findings from our laboratory). The lack of cataleptogenic properties of these agents is well documented in rats.[1] (+)-AJ76 and (+)-UH232 also show a preference in vitro for the D_3 receptor over the D_2 receptor with a ratio of 3-5:1.[2] The relevance of this preference for the behavioral properties of these compounds is unknown.

(+)-AJ76 and (+)-UH232 both display poor oral bioavailability in the rat, which may be due to rapid metabolism (N-dealkylation and O-demethylation) similar to that of other aminotetralins.[3] We have attempted to develop an agent with pharmacodynamic properties similar to (+)-AJ76 and (+)-UH232 but with higher oral bioavailability. Since oxidative demethylation of the methoxy substituent of these compounds is a significant route of metabolism, we decided to investigate a series of analogs (**3**) in which the methoxy group is substituted with different electron withdrawing groups (R_1= OSO_2CF_3, CO_2CH_3, $CONH_2$ and CN).

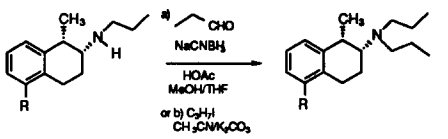
The compounds were synthesized using optically active (+)-AJ76 (**1**)[4] as the starting material.[5] As shown in Scheme 1, (+)-AJ76 was demethylated with 48% HBr in 98% yield. The phenol **4** was converted into the triflate **5** using triflic anhydride, 2,6 lutidine, and 4-dimethylamino-pyridine in methylene chloride (70% yield).[6] The methyl ester **6** was formed using CO, palladium acetate, and 1,3-bis-(diphenylphosphino)propane in triethylamine /DMSO/ MeOH (80% yield).[6] The methyl ester was then converted to amide **7** by heating with formamide and sodium methoxide in DMF.[7] This one-step procedure worked well with a 79% yield. Dehydration of **7** using $POCl_3$ in diglyme[8] yielded the nitrile **8** (70% yield).

Scheme 1



The di-propyl analogs **9** and **10** were synthesized by reductive amination (propionaldehyde, $NaCNBH_3$, HOAc) of **5** and **7**, respectively, as shown in Scheme 2 (yields 71% and 50%, respectively). Compound **11** was prepared by alkylating compound **8** with iodopropane (65% yield).

Scheme 2



5, R=OTf
7, R=$CONH_2$
8, R=CN

9, R=OTf
10, R=$CONH_2$
11, R=CN

PHARMACOLOGICAL RESULTS AND DISCUSSION

The triflates **5** (mono-propyl) and **9** (di-propyl) were the most interesting in this series of analogs. They both displayed a 14 fold preference for the D_3 receptor site over the D_2 in the *in vitro* binding assays. In comparison, (+)-AJ76 and (+)-UH232 have a 3-5:1 preference for the D_3 receptor site. As shown in Table 1, the mono-propyl analog **5** was 4 times less potent at the D_3 and D_2 receptors than the di-propyl analog **9**. The same trend can be seen with (+)-AJ76 and (+)-UH232. *In vivo*, compounds **5** and **9** were found to increase locomotor activity and also increase DOPAC and HVA levels in the striatal and limbic brain regions, indicative of a DA receptor antagonism.[9] Compounds **5** and **9** were, however, considerably less potent than (+)-AJ76 and (+)-UH232, respectively. In contrast to (+)-AJ76 and (+)-UH232,[10] compound **9** was found to be inactive in increasing DA release or synthesis in the nucleus. accumbens at a dose of 200 μmol/kg s.c. when tested in a brain microdialysis model in rats (data not shown).

The metabolic stabilities of the triflates **5** and **9** were studied *in vitro* during incubation with suspensions of freshly isolated rat hepatocytes.[11] As shown in Table 3, the mono-propyl compound **5** and the di-propyl compound **9** were found to be 19 times and 9 times more stable than (+)-AJ76, respectively. Pharmacokinetic studies on **9** revealed that the compound has an absolute oral bioavailability of 9.4% in the rat with the mono-propyl analog **5** as the major metabolite formed. In addition, compound **5** was found to have a oral availability of 62% providing good evidence of its metabolic stability (see Table 3). Sonesson et al., [12] have recently published the triflate functionality as not only a bioisosteric replacement for the hydroxyl group but also one that tends to improve the pharmacokinetic properties in the 2-aminotetralin and the 3-phenyl piperdine series.

The methyl ester **6** had a weak affinity for the 5-HT_{1A} receptor site (Table 1) and was devoid of DA receptor affinity. In the *in vivo* biochemistry assay it produced a weak reduction of 5-HIAA levels. Both nitrile analogs **8** and **11** had very low affinity to the 5-HT_{1A} and D_2 receptors (see Table 1). However, *in vivo* they increased locomotor activity in habituated rats, and at higher doses also increased DOPAC and HVA levels (Table 2). This suggests autoreceptor antagonist activity. Compound **11** also showed a pronounced effect after oral administration (100 μmol/kg). The amides **7** and **10** were found to be inactive in the *in vivo* serotonin and DA metabolism screen in habituated rats (Table 2). This data would suggest that the methyl ester and amide functionalities are not suitable bioisoteres for DA antagonist ligands in the aminotetralin series. The nitrile and triflate substituted analogs, on the other hand, displayed activity in vivo but were less potent in increasing DA metabolites at the doses tested in comparison to (+)-AJ76.

In conclusion, an autoreceptor antagonist more potent than (+)-AJ76 or (+)-UH232 has not been found within this series of analogs. However, with these few modifications of the aromatic substituent, we were able to show an increase in the metabolic stability with the triflate analogs **5** and **9** and, interestingly, also an increased preference of these analogs for the D_3 receptor over the D_2 receptor. In addition, compound **11**, the nitrile analog, was found to be an orally active DA autoreceptor antagonist.

Table 1. Binding Affinities for (+)-AJ76 and (+)-UH232 Derivatives at 5-HT1A and Dopamine Receptors *In Vitro*

Compound	Receptor Binding [a] (Ki nM) 5-HT_{1A}	D_2	D_3	D_4
(+)-AJ76	2331 ±212	145 ±13	26 ±2	117 ±10
(+)-UH232	168 ±11	15 ±0.7	4.2 ±0.3	48 ±2
5	3067±308	2557±245	171±26	621±40
6	287 ±68	2328±191	253±37	1593±106
7	(6720)	NT	NT	NT
8	>1786	IA (16670)	IA	IA
9	>3448	546 ±34	40 ±7	121 ±11
10	NT[c]	NT	NT	NT
11	(5040)	(6670)	NT	NT

[a] All receptor binding measurements were made from cloned mammalian receptors expressed in CHO-K1 cells (using [^{3}H]-U86170 for D_2 receptors and [^{3}H]-spiperone for the D_3 and D_4 receptors). Binding values in parentheses were obtained from rat striatal membrane using [^{3}H]-8-OH-DPAT and [^{3}H]-spiperone for 5-HT_{1A} and D_2 receptors, respectively. [b] IA= inactive: the compound was found to display <50% inhibition at a concentration of 1 μmol/L. [c] NT= not tested.

Table 2. *In Vivo* Behavioral and Biochemical Results in Habituated Rats.

Compd	Dose µmol/ kg s.c	LMA	DOPAC (stri)	HVA (stri)	5-HIAA (limb)
(+)-AJ76	12.5	272±36*	220±13**	251±21**	121±3
	50	354±37**	346±29**	402±29**	127±13
(+)-UH232	12.5	191±17*	176±15**	214±20**	119±12
	50	200±18**			
5	200	167±21	130±10*	135±15*	92±5
6	200	102±22	117±9	120±8	75±11*
7	100	215±61	109±6	105±5	97±5
8	25	165±24	121±9	136±14	102±10
	100	149±23	224±4***	248±5***	100±15
9	200	250±31*	146±6***	163±11***	94±3
10	100	169±16	135±9	128±4	113±3
11	25	125±28	127±2*	134±9*	93±3
	100	334±64*	213±14***	241±16***	95±1
	100[a]	287±23**	128±4*	166±5***	82±8

The locomotor activity (LMA) in rats was measured for 60 min after a 60 min habituation period. The rats were killed and striatal (stri) and limbic brain regions (limb) levels of the DA metabolites DOPAC and HVA as well as the 5-HT metabolite 5HIAA were measured by means of HPLC/EC. DATA are presented as % of saline treated controls (means ± SEM, n=5).* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] oral administration.

Table 3. *In Vitro* Stability and *In Vivo* Absolute Bioavailability of 5 and 9 in the Rat.

Compound	In Vitro Hepatocyte Assay[a]	In Vivo Absolute Bioavailability[b] F (%) ± SEM	T1/2
(+)-AJ76	1	1.6± 0.3	1 h
(+)-UH232	NT	3.7 ± 1.6	2.5 h
5	19	62.2 ±3.2	6 h
9	9	9.4 ± 1.6	6 h

[a] Relative stability to (+)-AJ76. [b]. The absolute oral availability (F) was obtained from blood plasma levels of parent compound analyized by means of GC/MS following 5 µmol/kg, iv, and 40 µmol/kg , po, administration.(see reference 12 for experiment details). The F values were calculated from total area from [C] vs time curves, n=4. T1/2 was estimated from the elimination phase of the oral [C] vs time curves, n=4.

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[5] All new compounds were fully characterized by NMR (300 MHz), IR and either elemental analysis (±0.4%) or high resolution mass spectrometry. Following are the melting points, optical rotations, and ^{1}H NMRs for each new compound as the HCl salt: Compound **5:** m.p.: 202-205 °C; $[\alpha]_D^{25}$ +56° (c 0.923, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.20-7.06 (m, 3H), 3.20-2.61 (m, 7H), 1.90-1.70 (m, 2H), 1.58-1.51 (m, 2H), 1.18-1.16 (d, J= 7.1 Hz, 3H), 0.98-0.93 (t, J= 7.4 Hz, 3H). Compound **6** m.p.: 200-203 °C.;$[\alpha]_D^{25}$ +84°(c 0.1, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.35-7.24 (m, 3H), 3.89 (s, 3H), 3.48-3.0 (m, 5H), 2.5-2.2 (m, 2H), 2.15-2-07 (m, 2H), 1.67-1.65 (m, 2H), 1.50-1.48 (d, J= 6.6 Hz, 3H), 1.08-1.03 (t, J=7.5 Hz, 3H). Compound **7:** hygroscopic solid, sublimation at 175 °C, mp >230 °C.^{1}H NMR (CD_3OD): δ 7.15-7.13 (m, 3H), 3.43-2.94 (m, 6H), 2.15-1.64 (m, 4H), 1.15-1.13 (d, J=7.1 Hz, 3H), 0.96-0.91 (t, J=7.4 Hz, 3H). Compound **8:** m.p.: 268-270 °C; $[\alpha]_D^{25}$ +53° (c 0.81, MeOH);^{1}H NMR ($CDCl_3$): δ 7.55-7.25 (m, 3H), 3.61-1.7 (m, 11H), 1.50-1.48 (d, J= 6.6 Hz, 3H), 0.98-0.93 (t, J=7.4 Hz, 3H). Compound **9:** m.p. 155-158 °C; $[\alpha]_D^{25}$ +50° (c 0.85, MeOH);^{1}H NMR ($CDCl_3$): δ 7.31-7.14 (m, 3H); 3.6-2.8 (m, 8H), 2.36-2.33 (m, 2H), 2.2-1.7 (m, 4H), 1.57-1.54 (d, J= 6.8 Hz, 3H), 1.07-1.00 (two t, J= 7.2 and 6.8 Hz, 6H). Compound **10:** hygroscopic solid, ^{1}H NMR (CD_3OD): δ 7.32-7.22 (m, 3H), 3.6-1.75 (m, 14H), 1.15-1.13 (d, *J*= 7.1 Hz, 3H), 1.08-1.03 (t, *J*= 7.5 Hz, 3H), 0.96-0.91 (t, *J*=7.4 Hz, 3H). Compound **11:** m.p. 150-153 °C; $[\alpha]_D^{25}$ +59° (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.55-7.25 (m, 3H), 3.82-2.9 (m, 8H), 2.4-1.4 (m, 6H), 1.50-1.48 (d, *J*= 6.6 Hz, 3H), 1.07-1.00 (t, *J*= 7.4 Hz, 3H), 0.98-0.93 (t, J=7.4 Hz, 3H).

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[9] For a description of the methods used, refer to reference 1 above.

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[11] This general screening procedure is to assess likely metabolism in vivo by incubating compounds in vitro in the presence of freshly isolated rat hepatocytes (prepared by modification of the method of Reese, J.A; Byard, J.L. *In Vitro* **1981**, 17, 935-940) The rates of metabolism of a compound under this test is determined by HPLC analysis and standardized to that of a reference compound incubated at the same time.

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