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DOPAMINE RECEPTOR BINDING PROPERTIES OF SOME 2,3,4,5-TETRAHYDRO-1*H*-3-BENZAZEPINE-7-OLS WITH NON-AROMATIC SUBSTITUENTS IN THE 5-POSITION

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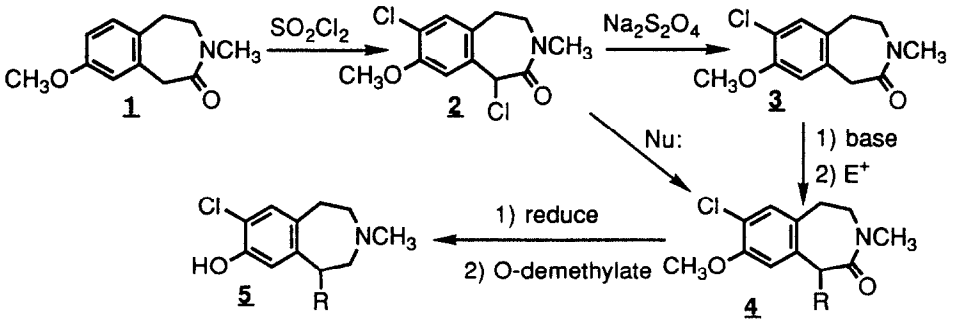
Abstract: 2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-ols related to the selective dopamine D-1 antagonist SCH 23390, but bearing non-aromatic substituents in the 5-position possess considerable affinity and selectivity for D-1 vs. D-2 receptors.

Selective antagonists of the dopamine D-1 receptor hold considerable promise as antipsychotic agents lacking any significant propensity for causing the therapeutically limiting neurological side-effects observed with most agents of this type in current clinical use.[3] The D-1 subset of dopamine receptors is defined biochemically by its selective antagonist (5R)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol (SCH-23390).[4] Indeed, most of the selective ligands for this receptor , both agonists and antagonists, are members of this series[5,6] or very closely related compounds.[7,8] More recently, selective non-benzazepine D-1 ligands have been reported.[9-12] It is believed that high D-1 receptor affinity requires the presence of a non-phenolic aromatic ring thought to be complimentary either for a secondary π-complexing domain[13] or a charged site[14] of the receptor. Indeed, studies in the benzazepine agonist series have indicated that replacement of the pendant phenyl group by other aryl, alkyl, or cycloalkyl groups decrease or abolish activity.[5,13] However, it has been very recently demonstrated that replacement of the aromatic pendant group with other lipophilic moieties in a series of D-1 agonist benzopyrans can result in conservation of receptor affinity.[15] Our interest in the benzazepines prompt us to now report on the effect of replacement of aromatic substituents on D-1 receptor affinity and selectivity in this series.

The preparation of the target compounds (Scheme 1) proceeded from the lactam **1**, m.p. 104-5°, prepared by modification of the procedure reported by Wilson.[5,16] Treatment of **1** with sulfuryl chloride in CH_2Cl_2 introduces chlorine into both the 5- and 8-positions to give **2**, m.p. 162-164°. The 5-chloro group in **2** could be removed by treatment with sodium dithionite to give **3**, m.p. 117-118°. Treatment of **2** with nucleophiles and subsequent elaboration of the resulting lactams **4** gave rise to **5e-g** (Table 1). Treatment of the enolates of **3** with electrophiles similarly gave the remaining target compounds. Vinylic substituents (**5n-o**) were introduced into **3** via Pd^0 complexes prepared from an appropriate enol triflate. The cycloheptatriene moiety (**5p**) was introduced via tropylium tetrafluoborate; no other cycloheptatriene isomers were detected in this or subsequents steps. The bidentate electrophile 1,4-dibromobutane ultimately gave spiro compound **5i**. Reduction of lactams **4** was effected with DIBAL followed by $Na(CN)BH_3$ at pH 5, $LiAlH_4$, or BH_3,

depending on the nature if the substituent. O-demethylation was accomplished with either sodium ethanethiolate in DMF at 120° or 48% HBr at 130° to furnish the target 7-hydroxy compounds **5.**

Scheme 1. Synthesis of 2,3,4,5-tetrahydro-1H-3-benzazepine-7-ols

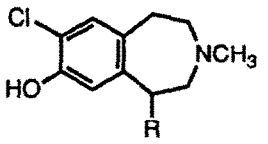


The unsubstituted compound **5a** was found to posess considerably diminished D-1 affinity and poor selectivity compared to **5q** (SCH 23390) (Table 1). However, considerable D-1 affinity and selectivity were conferred upon introduction of a simple n-propyl substituent at position 5 (**5b**). Unsaturation in the chain (**5c-d**) did not greatly alter this profile, although introduction of S,O, or N into the chain (**5e-g**) resulted in attenuation of affinity. Placement of a tertiary nitrogen at the end of the chain (**5h**) resulted in considerable loss of affinity . The spiro analog **5i** also showed attenuated activity.

In order to more closely emulate the pendant phenyl ring, compounds bearing cycloalkyl substituents with varying degrees of unsaturation (**5j-p**) were synthesized. In all cases, including fully cycloaliphatic rings, good activity and selectivity are retained. Several compounds possessed activity in the rat conditioned avoidance paradigm[17], thus confirming their antidopaminergic properties.

Thus, the dopamine D-1 receptor affinity of the benzazepine antagonists does not depend on the presence of an aromatic substituent at the 5-position. The putative accessory binding site believed to interact with the pendant substituent would seem to be generally accommodative of lipophilic moieties.

Table 1. SAR of 5-Substituted 2,3,4,5-Tetrahydro 1*H*-3-benzazepine-7-ols.



Cpd	R	K_i (nM) D-1	K_i (nM) D-2	Rat CAR mpk(sc)	m.p. °C.
5a	H	46	265	1.0	243-4[b]
5b	n-C_3H_7	3.3	1160	0.3	132-4
5c	$CH_2CH{=}CH_2$	5.7	284	0.1	141-3
5d	CH_2CCH	8.7	626	1.0	150-70
5e	SC_2H_5	33	2710	NT[a]	amorphous
5f	OC_2H_5	24	>10000	1.0	235-6[c]
5g	1-piperidyl	100	>10000	3.0	232-4[c]
5h	$(CH_2)_3NMe_2$	>1000	>100000	NT	145-60[c]
5i	-$(CH_2)_4$-	23	2250	1.0	155-8
5j	cyclo-C_5H_9	13	2050	1.0	164-6
5k	cyclo-C_6H_{11}	10	1780	0.3	144-7
5l	cyclo-C_7H_{13}	7.6	1190	1.0	233-6[c]
5m	2-cyclohexenyl	2.0	581	0.3	170-90[c,d]
5n	1-cyclohexenyl	2.1	1600	0.1	177-9
5o	1-cyclopentenyl	5.1	1540	NT	186-8
5p	cycloheptatrien-1-yl	3.7	1800	0.1	246-7[c]
5q	phenyl	0.3[e]	760[e]	0.02	

Binding to the D-1 and D-2 receptors was measured by the ability of a test compound to displace ^{3}[H]SCH 23390 and ^{3}[H]spiperone, respectively, from receptors in rat striatal tissue.[4] Data are reported as the mean of at least three determinations. Behavioral data are reported as the minimal dose producing a statistically significant ($P<0.05$ compared to a vehicle treated group) reduction in avoidance responding 1 hr. after drug treatment.

[a] Not tested [b] HBr salt [c] HCl salt [d] mixture of two racemates [e] (R)-enantiomer , Ref. 6

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