New, centrally acting dopaminergic agents with an improved oral bioavailability

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Concluding remarks

Both newly synthesised and previously known compounds were tested for their affinity at cloned human dopamine D_2 and D_3 receptors. Compounds with an interesting binding profile were selected for *in vivo* testing. For a number of these compounds, their relative oral bioavailabilities were determined.

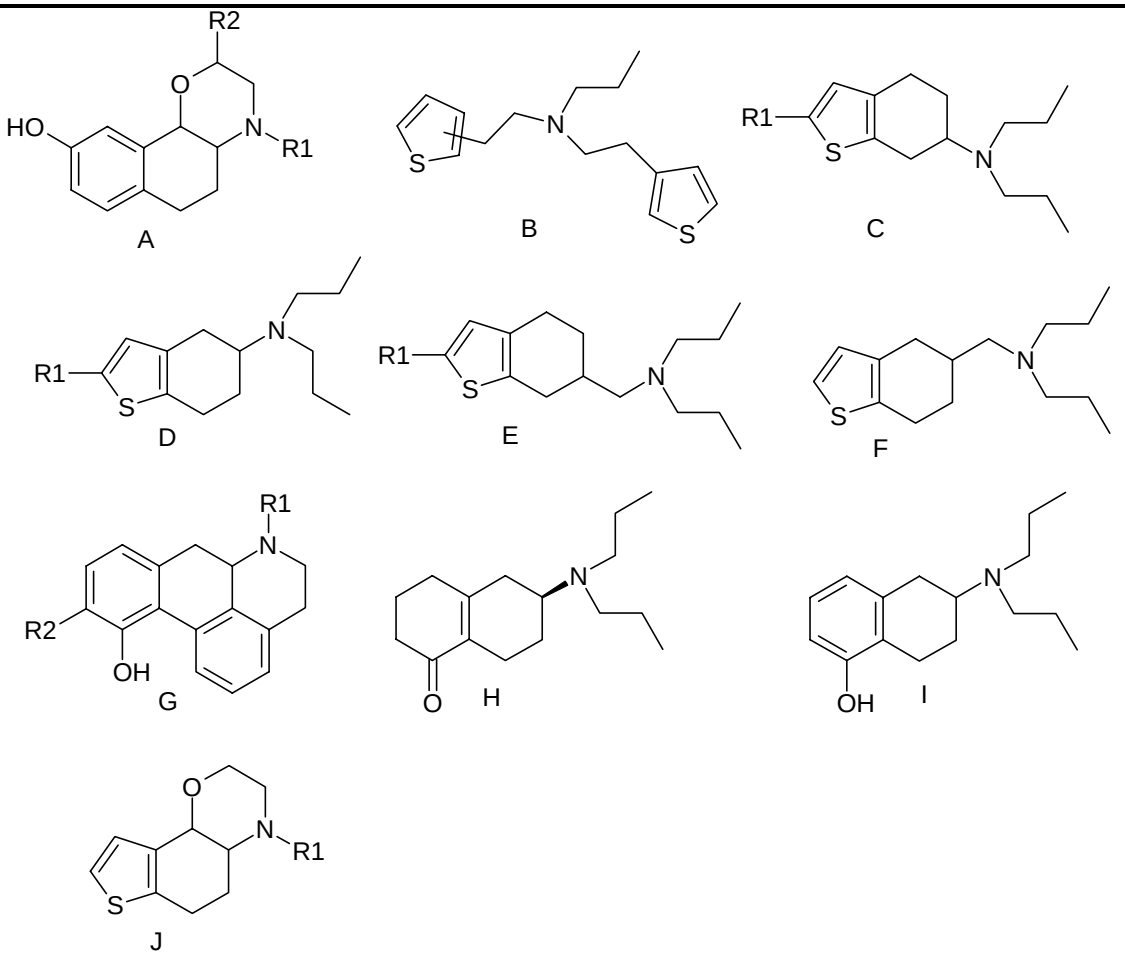
The binding affinities of the hexahydronaphthoxazines of type A showed that a large substituent on the nitrogen gives a compound which lacks affinity for the dopamine receptors (compound **27b**, Table 8.1). However, the compound with a thienylethyl moiety on the nitrogen possesses affinity for the dopamine D_3 receptor. This led us to hypothesise that a thienylethylamine moiety could act as a pharmacophore for the dopamine receptor. To test this hypothesis a series of thiophene containing compounds were synthesised (compounds **29**, **30**, **34** and **35**). These compounds possessed affinity for the dopamine receptors, but their affinities were lower than those of the corresponding phenolic analogues. This diminished affinity might be caused by I) the less tight H-bonding of the sulfur atom, as compared to a hydroxyl moiety; II) the non-optimal distance between the hydrogen bond forming moieties on the aromatic site and the nitrogen atom; III) by the fact that the essential atoms of the ligands have an interaction with alternative interaction points of the dopamine receptor. The results of compounds **29**, **30**, **34** and **35** confirmed the hypothesis that a thienylethylamine can act as a dopamine receptor pharmacophore. Although the distances between the sulfur atom and the nitrogen atom in the hexahydrothianaphthoxazines **38** and **39** are comparable with those in compound **35**, the introduction of a morpholine ring gave a dramatic decrease in the dopamine D_2 and D_3 receptor affinity.[239]

Since the tetrahydrobenzo[*b*]thiophenes **34** and **35** possess a diminished affinity for the dopamine receptors, as compared to hydroxylated 2-aminotetralins, a number of compounds were synthesised of which was expected that they would possess a higher affinity for the dopamine receptors. We have used two methods for such a strategy; i.e. I) increasing the distance between the sulfur and the nitrogen (compounds **36** and **37**); II) introduction of another and better H-bond forming moiety on the 2-position of the thiophene ring (compounds **65**, **66**, **67**, **68**, **69**, **70** and **71**). Introduction of substituents on the 2-position in 6-(N,N-di-*n*-propyl)amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene **34** lead to compounds with no affinity for the dopamine D_2 receptors and moderate to high affinity for the dopamine D_3 receptors. Therefore, they are very selective for the dopamine D_3 receptor. The same introduction in 5-(N,N-di-*n*-propyl)amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene **35** gives compounds with low to no affinity for the dopamine D_2 and D_3 receptors. Such a difference in affinity, which is not seen with the parent compounds **34** and **35**, might be explained from the fact that compounds **65**, **66**, and **67** are structurally comparable with the dopamine D_3 receptor preferring agonist

7-OH-DPAT, while compounds **68** and **69** are structurally more comparable with the less-active dopamine receptor ligand 6-OH-DPAT.[98,205]

Also the introduction of a methylene group between the aliphatic ring and the nitrogen atom in compound **34** gives a compound with selectivity and a moderate affinity for the dopamine D_3 receptor, which resides in the (+)-enantiomer. Substitution of the 2-position of compound **36** gives compounds without affinity for the dopamine D_2 and D_3 receptors.

Table 1 Binding affinities and relative oral bioavailabilities of dopamine receptor ligands used in this thesis.



Compound	Structural type	R1	R2	Ki (nM) D_2	Ki (nM) D_3	Relative oral bioavailability (%)
27a	A	*n*-propyl	H	6.24	0.21	NT
27b	A	phenylethyl	H	> 3676	1566	NT
27c	A	2-thienylethyl	H	3676	83	NT
28	A	*n*-propyl	phenyl	375	12	NT
29	B	2-thienyl		1080	117	NT

Table 1, continued

Compound	Structural type	R1	R2	Ki (nM) D_2	Ki (nM) D_3	Relative oral bioavailability (%)
30	B	3-thienyl		439	108	NT
34	C	H		27	28	10 %
65	C	CHO		>10000[a]	40	NT
66	C	CH_2OH		968	9	NT
67	C	CHNOH		>10000[a]	113	NT
35	D	H		20	40	≥ 10 %
68	D	CHO				NT
69	D	CH_2OH				NT
36	E	H		3107	60	NT
(+)-36	E	H		100/-7	50/43	NT
(–)-36	E	H		100/8	50/17	NT
70	E	CHO				NT
71	E	CH_2OH				NT
37	F			2037	247	NT
11	G	CH_3	OH	3.7		1 %
79	G	CH_3	H	58[a]		NT
80	G	*n*-propyl	OH	1.5		1 %
12	G	*n*-propyl	H	5.3		3 %
83	H					3-30 %
9	I			14	0.54	1-3 %
38	J	H		>4780	3000	NT
39	J	*n*-propyl		630	240	NT

Footnotes: [a] IC_{50}; NT: not tested.

Using microdialysis experiments the relative oral bioavailabilities of the compounds **34**, **35**, **11**, **80**, **12**, **83** and **9** could be calculated. These data show that a compound with a catechol or a phenol possesses a low relative oral bioavailability (compounds **11**, **80**, **12** and **9**). To circumvent such a low relative oral bioavailability a bioisostere of a phenol could be introduced or a prodrug approach could be applied. Compounds **34** and **35** are examples of a bioisosteric replacements and compound **83** is a prodrug of a catecholic or a phenolic 2-aminotetralin. Both types of compounds show an improved relative oral bioavailability, as compared to the hydroxylated 2-aminotetralins.[215,276]

In conclusion, the thienylethylamine moiety can act as a pharmacophore at the dopamine receptor and introduction of such a moiety yields compounds with an improved relative oral bioavailability, as compared to the hydroxylated 2-aminotetralins. The synthesised and tested thiophene analogues of 2-aminotetralins possess a diminished affinity for the dopamine

receptors, but this could be partly compensated by their higher relative oral bioavailability. Also the concept of a new kind of prodrug leads to a compound with a significantly improved relative oral bioavailability. Aporphines are still interesting and potent dopamine receptor agonists, however, they possess a low relative oral bioavailability.