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PUTATIVE ATYPICAL ANTIPSYCHOTICS WITH MIXED DOPAMINERGIC (D_1, D_2) AND SEROTONERGIC ($5HT_2$) ACTIVITY: THE DESIGN EVOLUTION OF ZD3638

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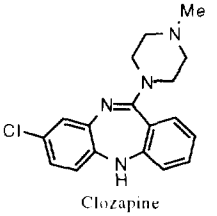
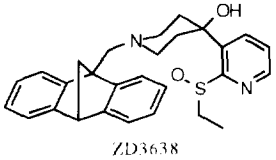
Abstract: The pharmacological activity of a series of 9,10-dihydro-9,10-methanoanthracene methylene amines which function as mixed dopaminergic (D_1/D_2) and serotonergic ($5HT_2$) antagonists is described. The work resulted in a putative atypical antipsychotic, ZD3638, of novel structure and pharmacological profile.

Evolving therapies to treat schizophrenia have centered on two problems with classical treatments: symptomatically heterogeneous movement disorders[1] (particularly tardive dyskinesias and extrapyramidal side effects) and negative or deficit symptoms. An atypical antipsychotic, Clozapine (**1**), successfully addresses some of these problems. Clozapine has both a low propensity to induce movement disorders and has demonstrated efficacy in alleviating psychotic symptoms in treatment resistant schizophrenics.[2] Clozapine is a nonselective antagonist at a variety of neurotransmitter receptors including two classes of dopaminergic receptors, D_1 and D_2[3], and serotonergic $5HT_2$ receptors. Dopamine plays a fundamental role in regulating a broad range of unconditioned, conditioned and psychomotor behaviors.[4] Studies with a variety of antipsychotic drugs demonstrate a high correlation between in vitro affinities for D_2 antagonist binding sites and their clinical potencies in controlling psychotic symptoms.[5] D_1[6] and $5HT_2$[7] receptor activity exert important qualitative control of D_2 dependent behaviors, including motor control. The relationship between endogenous dopaminergic function (acute and chronic) and the impact of subtype selectivity is complex.



Clozapine

1



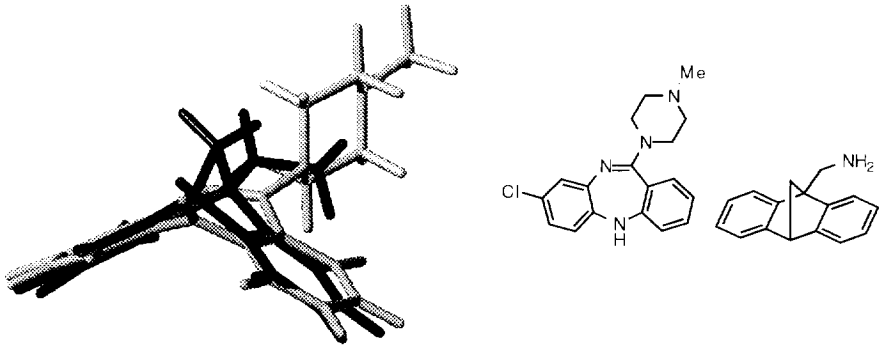
ZD3638

2

In light of the pharmacological profile of clozapine and electrophysiological evidence linking D_1 and D_2 systems, our goal is the development of an orally active $D_1/D_2/5HT_2$ antagonist lacking movement disorders.

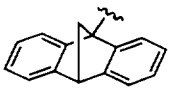
This communication summarizes the medicinal chemistry evolution of the 9,10-dihydro-9,10-methanoanthracene methylene amine series, culminating in the development candidate ZD3638 (**2**).

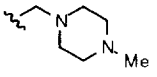
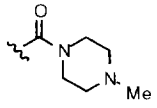
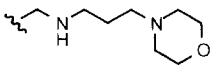
Modeling of clozapine and conformationally restricted dopamine agonists of high D_1 and/or D_2 affinity[8] (dihydrexidine, A69024, A68930, SKF38393, E4101, and the benzergolines) led us to design systems that arrange the aromatic-aromatic centroid distance, the dihedral angle of the aromatic planes, and the position of the basic nitrogen in a geometry shared by most of the agonists (and clozapine). Comparisons were made across conformers within 5 kcal of the global energy minimum (MM2, gas phase calculations). The substructure with the most attractive combination of characteristics was the methanoanthracene methylene amine pictured.



As evidenced by the overlap picture above, the 9,10-dihydro-9,10-methanoanthracene methylene amine compares favorably to clozapine with respect to distance (centroid to centroid and centroid to amine) and planarity ("butterfly" angle) measures. To its advantage the methanoanthracene is conformationally rigid and therefore unambiguous with respect to aromatic-aromatic spatial relationship. It is also readily amenable to synthetic elaboration. Substituted methanoanthracenes are known in the literature to have central nervous system "activity"[9]. However, the compounds contained in these communications had low receptor binding affinity (>1 μM) and no oral activity (> 80 mg/kg ip in dopamine agonist normalization assays).

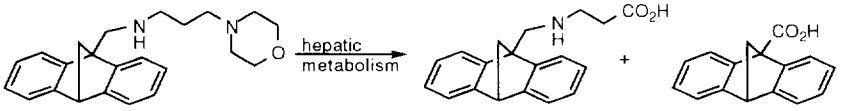
Methanoanthracene methylene piperazines analogous to clozapine (i.e. **4**) lacked appreciable receptor binding affinities (D_1, D_2, $5HT_2$) and functional dopamine antagonism in a normalization assay (i.e. AS: reversal of apomorphine induced swimming ED_{50}s in mg/kg orally)[10].



Compound	D_1 (nM)	D_2 (nM)	$5HT_2$ (nM)	AS (mg/kg)
1 clozapine	250	500	13	40
3 	NA	NA	--	>80
4 	14% @ 2500 nM	18% @ 2500 nM	314	>80
5 	--	0% @ 5000 nM	--	>80
6 	349	222	21	>80

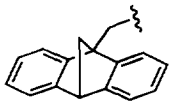
(NA-not active)

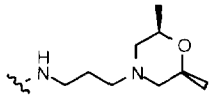
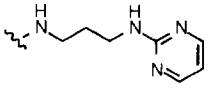
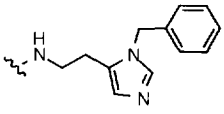
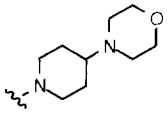
Given the structural similarities by modeling, an explanation of the failure of the amine (**3**) and piperazine derivatives (**4**, **5**) to exhibit clozapine-like binding affinity is unclear. Side chains containing a 1,3-diaminopropyl substructure (compound **6**) displayed clozapine-like binding affinity but with no oral activity. The early reasoning assumed that these conformationally flexible dibasic sidechains contained the flexibility to fit our multicomponent target receptor profile. These dibasic sidechains were extensively modified and displayed a wide variation in binding characteristics, both subtype selective and of mixed receptor affinity. Unfortunately there was consistently little or no functional activity by oral administration. In vivo studies revealed that this type of sidechain was heavily altered by first pass hepatic metabolism. The dominant identified metabolites resulted from N-dealkylation, producing a side chain acid product (**7**) and methanoanthracene acid (**8**).



6 **7** **8**

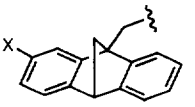
This type of side chain metabolism was addressed by steric blockade of susceptible positions and/or reduction of the distal amine basicity by incorporation into a heterocycle. Some examples of these changes are illustrated in the following table. Marked improvement in the oral activity of the morpholino piperidine **12** prompted us to continue our efforts in this direction. The problem than became one of building D_1 and $5HT_2$ receptor affinity into compounds based on **12**.

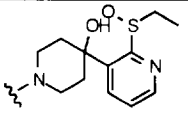
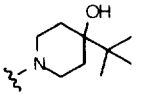
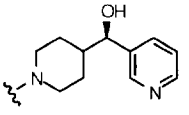
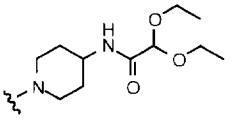
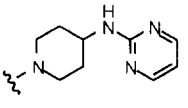


Compound	D_1 (nM)	D_2 (nM)	$5HT_2$ (nM)	AS (mg/kg)
	60	36	11	80
9 				
10 	132	265	227	>80
11 	610	101	84	80
12 	17% @ 1000 nM	57	--	10

Extensive structure/activity relationship studies (to be presented in full paper form) suggested design elements important for $D_1/D_2/5HT_2$ receptor binding affinity and potent oral activity. Oral activity was consistently found with sidechains containing a 4-substituted piperidine. Substituted methanoanthracenes, particularly (9S,10S)-2-chloromethanoanthracenes, similarly improved oral activity. The D_1 binding affinity of aminopyrimidine and imidazole containing sidechains suggested potential hydrogen-bond donor and/or acceptor characteristics within this region of the D_1 receptor. A variety of heteroaromatics could be substituted in the 4 position of the side chain piperidine to improve D_1 receptor binding affinity. In contrast, D_2 and $5HT_2$ binding affinities appeared relatively insensitive to substituents on sidechain piperidines.

A more narrow structure activity relationship profile was created by 4-position substitution of a piperidine methylene methanoanthracene. This resulted in sets of compounds which underwent an extensive electrophysiological and pharmacological characterization on chronic administration. Examples of 4-hydroxy 4-substituted piperidines (e.g. **2**, **13**), 4-hydroxymethyl piperidines (e.g. **14**), amides (e.g. **15**), and aminopyrimidines (e.g. **16**) are represented in the following table.



Compound	X	D_1 (nM)	D_2 (nM)	$5HT_2$ (nM)	AS (mg/kg po)
2  (-) isomer	H	13	42	39	0.6
13 	Cl*	7	5	1	0.6
14 	Cl*	63	14	4	5
15 	Cl*	76	25	40	2.5
16 	Cl*	351	49	2	5

* *(9S, 10S)-stereochemistry*

The pyridyl sulfoxide (**2**), ZD3638, is predicted to have enhanced antipsychotic efficacy and a superior side effect profile as compared to classical antipsychotic agents. The compound is potent by oral administration in tests predictive of antipsychotic efficacy, including normalization assays such as apomorphine climbing swimming and agonist induced contralateral rotation.[11] When administered chronically to rats, ZD3638 produces selective depolarization inactivation of mesolimbic (A10) dopamine neurons (predictive of efficacy) without affecting substantia nigra zona compacta dopamine cells (A9) or zona reticulata GABA cells.[12] It is thought that depolarization inactivation of **both** A9 and A10 neurons by classical agents is responsible for the mix of efficacy and side effects. ZD3638, unlike classical antipsychotic agents, has a reduced liability to cause dystonias (a type of movement disorder) on chronic administration to drug-naive Cebus monkeys. These last two properties are like those of clozapine and are believed predictive of reduced movement disorders of extrapyramidal origin. ZD3638 has entered development and meaningful information on the efficacy and side-effect profile of a mixed $D_1/D_2/5HT_2$ antagonist in the treatment of schizophrenia will soon emerge.

Conclusion

A new class of potent mixed $D_1/D_2/5HT_2$ antagonists based on a methanoanthracene methylene piperidine substructure has been developed. Within certain constraints the side chain can be widely varied, allowing for a range of receptor affinities and in vivo characteristics. The work resulted in ZD3638 which shows considerable promise in advanced pharmacological measures of efficacy and side effect potential.

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10 Additional information concerning many of the detailed compounds, including synthesis, can be found in patent application WO 95/01974 and references therein. The screening described in this communication, for comparison purposes, involved ligand binding assays with the following ligands: D_1 (SCH23390), D_2 (spiroperidol), and $5HT_2$ (ketanserin). The functional dopaminergic test, apomorphine swimming (AS), provides a measure of oral dopaminergic activity, (Migler, B. M.; Warawa, E. J.; Malick, J. B. *Psychopharmacol.* **1993**, *112*, 299).

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