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# $M_4$ agonists/5HT$_7$ antagonists with potential as antischizophrenic drugs: Serominic compounds

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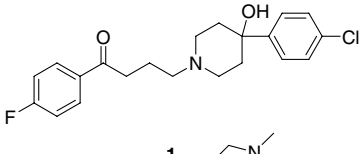
**Abstract**—Chronic low-dose treatment of rats with the psychomimetic drug, phencyclidine, induces regionally specific metabolic and neurochemical changes in the CNS that mirror those observed in the brains of schizophrenic patients. Recent evidence suggests that drugs targeting serotoninergic and muscarinic receptors, and in particular 5-HT$_7$ antagonists and $M_4$ agonists, exert beneficial effects in this model of schizophrenia. Compounds that display this combined pattern of activity we refer to as *serominic* compounds. Based upon leads from natural product screening, we have designed and synthesised such serominic compounds, which are principally arylamidine derivatives of tetrahydroisoquinolines, and shown that they have the required serominic profile in ligand binding assays and show potential antipsychotic activity in functional assays.


Schizophrenia is a widespread disorder that affects approximately 1% of the population worldwide. Currently available treatments for psychotic diseases including schizophrenia have a limited response from patients but also have significant side effects.[1] The first generation antipsychotic drugs including haloperidol (**1**) are effective to some extent against the so-called positive symptoms of schizophrenia, which include hallucinations and delusions. However such compounds are ineffective against the so-called negative symptoms, which include loss of emotional responsiveness, lack of motivation and social withdrawal, and also in the remediation of cognitive defects in working memory, attention and executive function. It is generally accepted that conventional antipsychotic drugs are dopamine $D_2$ antagonists, a property that has been associated with their activity against positive symptoms but also with side effects such as motor defects and hyperprolactinemia.[2] The introduction of clozapine (**2**) offered an improved clinical profile against the cognitive deficits and negative symptoms. However clozapine is a weak $D_2$ antagonist at clinical doses.[3] This clearly indicates that antipsychotic activity is associated with much more than $D_2$ antagonist activity. Several mechanisms have been proposed to explain the atypicality of clozapine. These include relatively strongers 5-HT$_{2A}$ receptor affinity compared with dopamine $D_2$ receptor affinity[3] and 'fast dissociation' from the $D_2$ receptor.[4] However, there is no general agreement on the mechanisms underlying the atypical antipsychotic profile of



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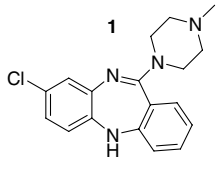

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clozapine and other recently introduced drugs such as olanzapine.

In order to establish a new basis for the discovery of antischizophrenic compounds, we demonstrated that chronic intermittent exposure to phencyclidine induces schizophrenia-like patterns of activity in the rat brain and distinguishes between the behaviour of haloperidol and clozapine.[5,6] Moreover metabolic activity measured by 2-deoxyglucose autoradiography identified hypoactivity in the prefrontal cortex (hypofrontality), thalamus and temporal lobes. The regionally specific changes together with the associated cognitive deficits mirror those observed in schizophrenic patients.[5,6] $M_4$ muscarinic acetylcholine receptors located in the prefrontal cortex have been implicated in the pathology of schizophrenia.[7,8] Some of the more effective atypical antipsychotic drugs have significant 5-$HT_7$ affinity in their pharmacological profile and 5-$HT_7$ receptors are highly localized in the thalamic nuclei[9] and prefrontal cortex where their level of expression may be altered in schizophrenia. Based upon this information, we hypothesised that a favourable primary profile for an antischizophrenic drug would be 5-$HT_7$ antagonist activity, $M_4$ agonist activity and low affinity for the $D_2$ receptor. We call this the serominic concept. Importantly, neither 5-$HT_7$ antagonists alone nor $M_4$ antagonists alone have shown activity in animal models predictive of the negative symptoms of schizophrenia although some activity has been claimed against positive symptoms.[10,11] The selective targeting of muscarinic receptor subtypes as an approach to novel therapies for psychotic disorders has been highlighted.[12] and the difficulty in obtaining selective compounds has also been argued.[13] The importance of the dual acting compound expressed by the serominic concept therefore appears strong.

*Lead identification.* Radioligand 5-$HT_7$, $M_4$ and $D_2$ receptor binding assays were established using tritiated 5-CT (5-carboxytryptamine), *N*-methylscopolamine and spiperone, respectively.[14] About 2000 plant extracts from the natural products library of SIDR, University of Strathclyde, were screened in these ligand binding assays. Extracts displaying significant activity in both the 5-$HT_7$ and $M_4$ receptor binding assays were fractionated by solvent partitioning and purified by HPLC before being reassayed. Several active compounds were identified by NMR spectroscopy. Significant activity in the 5-$HT_7$ screen was identified in aporphines of which liliotulipiferine **3** was one of the strongest binding ($K_i$ 80 nM). In the $M_4$ assay, whilst aporphines themselves were inactive, the introduction of an oxygen atom in ring C to give oxoaporphines, exemplified by liriodenine **4**, gave compounds with activity in the micromolar range. The common structural elements in **3** and **4** associated with the isoquinoline suggested that it might be possible to obtain serominic compounds designed by a conceptual fusion of the two structures. In support of this concept, we found that berberine **5** showed both measurable 5-$HT_7$ ($K_i \sim 5\mu M$) and $M_4$ ($K_i \sim 2\mu M$) activity.

Further consideration of these structures, those of the natural ligands and those of known synthetic ligands led to the following definitions of structural requirements anticipated for serominic activity (Fig. 1).

1. a *framework* that contains an $N^+$.
2. a *5-$HT_7$ responsive group*, which would typically be an aromatic system possibly with alkoxy substituents.
3. an $M_4$ *responsive group*, which would typically be a hydrogen bond acceptor such as methylenedioxy, thiadiazole, or alkoxy.
4. the three components should be joined in such a way as to provide an approximately planar or slightly puckered molecule with some but limited conformational flexibility.

Of the known semi-selective $M_4$ agonists, PTAC (**6**),[10] and xanomeline (**7**)[15] can adopt two primary conformations (Fig. 2) but only conformation 1 is available for the $M_4$ agonist **8** introduced by Lilly.[16] In PTAC and xanomeline, it is also possible to identify the same nominal separation between the positively charged nitrogen atom and a hydrogen bond acceptor as that noted in berberine (**5**) above. Interestingly, xanomeline and PTAC have been proposed as candidate antipsychotic drugs.[15,17] The Lilly $M_4$ agonist **8** does not conform to the same nominal pattern but, in view of its activity proven for a required component of a serominic compound, substructures from **8** were included in the design of compounds (see below). These structural concepts, although loosely drawn from screening and published information, were sufficient to stimulate the design and synthesis of compounds to evaluate the serominic concept as a novel approach to antipyschotic drugs.

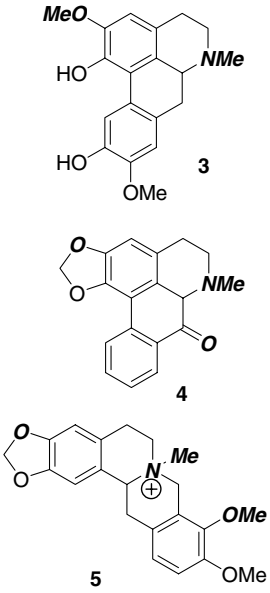


**Figure 1.** Alkaloids from natural product screening that contributed to the design of serominic compounds. The atoms in bold italics indicate the conceptual binding determinants for the relevant receptors: 5-$HT_7$ in **3** and **5**; $M_4$ in **4** and **5**.