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

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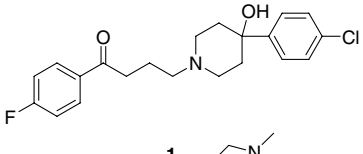
Abstract—Chronic low-dose treatment of rats with the psychomimetic drug, phencyclidine, induces regionally specific metabolic and neurochemical changes in the CNS that mirror those observed in the brains of schizophrenic patients. Recent evidence suggests that drugs targeting serotoninergic and muscarinic 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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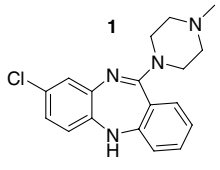

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Keywords: Anti-schizophrenic; M4 receptor agonist; 5HT7 receptor antagonist; Tetrahydroisoquinolines; Amidines.
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clozapine and other recently introduced drugs such as olanzapine.

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.

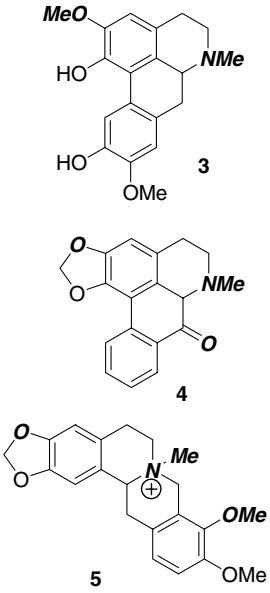


Figure 1. Alkaloids from natural product screening that contributed to the design of serominic compounds. The atoms in bold italics indicate the conceptual binding determinants for the relevant receptors: 5-HT_7 in **3** and **5**; M_4 in **4** and **5**.

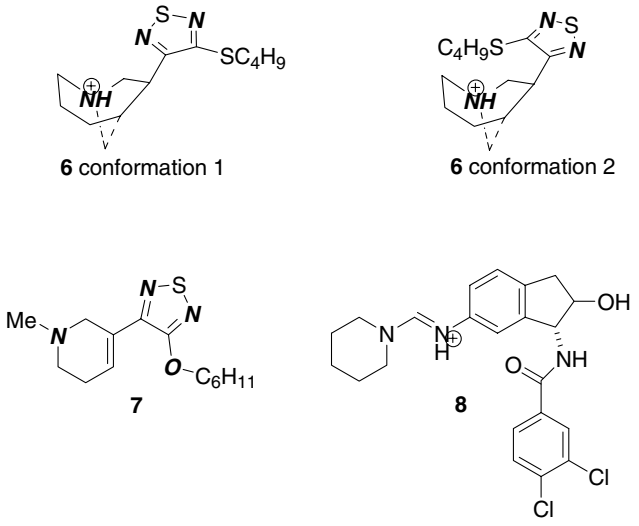


Figure 2. Structural and conformational relationships in M_4 agonists. The several binding determinants corresponding to those of berberine (Fig. 1, **5**) are shown in bold italics.

These arguments suggest that the requirements for serominic compounds (Fig. 3) can be satisfied by a combination of two subunits, merged at N^+ with geometries consistent with the patterns shown in Fig. 2. In the 5-HT_7 component, X represents a hydrogen bond acceptor, in particular an alkoxy group. In the M_4 binding component, Y represents a hydrogen bond acceptor or, based upon PTAC, a thioether.

Compound design and synthesis. We have studied two series of compounds that embody the seroninic concept and avoid structural relationships with haloperidol or clozapine. Series A includes indolylethylamine and tetrahydrocarboline derivatives that bear hydrogen bond acceptors or sulfur substituent in the side chain. This series was designed to investigate new types of molecular scaffold differing significantly from structures that had so far shown activity. As such, this represents the more speculative series (Scheme 1). Series B contains tetrahydroisoquinoline and benzylamine analogues of the Lilly M_4 agonist (**8**). Muscarinic antagonists from polycyclic alkaloid analogues have been described[18] and aporphine derivatives that bind strongly to the 5-HT_7 receptor also[19] but seroninic dual activity is novel. We propose that acceptable properties of a seroninic are (i) similar binding affinities for both 5-HT_7 and M_4 receptors and (ii) at least 50-fold selectivity for 5-HT_7 over D_2 receptors (Scheme 2).

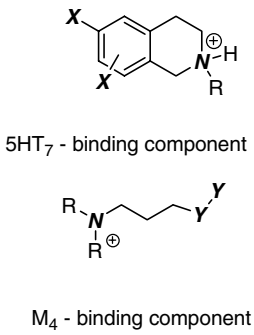
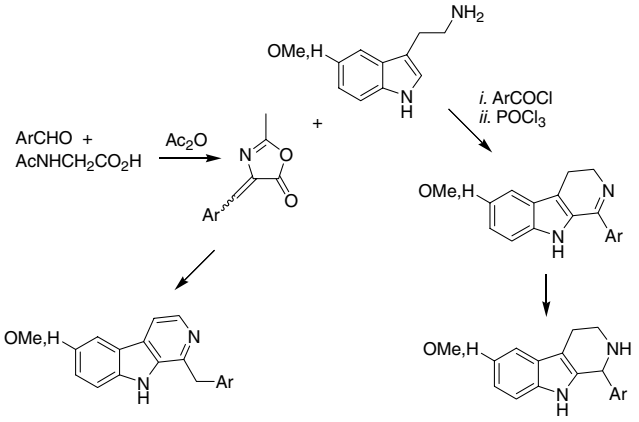


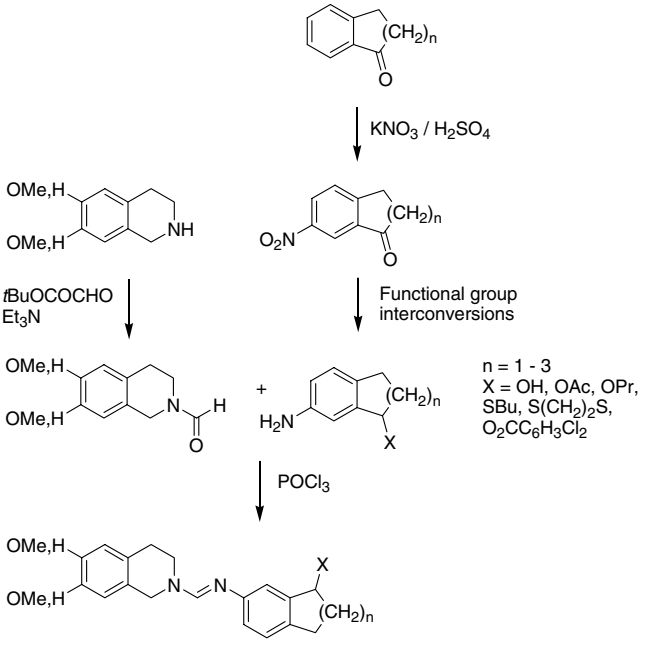
Figure 3. Proposed structural components of seroninic compounds.

The synthesis of series A compounds followed two routes. For the aryl carbazoles (**9**–**14**), 5-methoxytryptamine was acylated with the appropriate carboxylic acid (>95%) and the resulting amide cyclised with phosphorus oxychloride to give dihydrocarbazoles (53–84%).[20] The tetrahydrocarbazoles were obtained by reduction with sodium borohydride. The benzyl carbazoles (**15**–**22**) were prepared by condensation of 5-methoxytryptamine (9–96%) with a series of arylidene oxazolones themselves prepared from the corresponding aryl carboxaldehyde and *N*-acetylglycine (9–95%).[21] The complete series of compounds, **9**–**22**, is shown in Table 1.

Series B is a more extensive collection of compounds that takes the tetrahydroisoquinoline structure as its

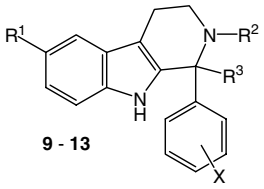
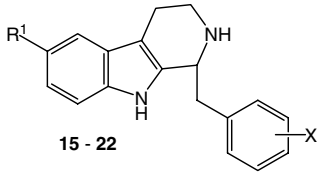
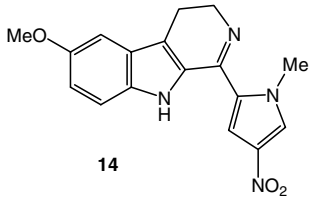


Scheme 1. Generalised synthetic scheme for series A.



Scheme 2. Generalised synthetic scheme for series B.

Table 1. Carboline derivatives[a]

Compound	R^1	R^2 R^3	X	5-HT_7 K_i (μM)	M_4 K_i (μM)	D_2 K_i (μM)	D_2/5-HT_7 ratio
9	H	..=..	3-OMe	0.8	42	31	39
			 **9 - 13**				
10	H	H H	3-OH	1.1	>30	88	80
11	OMe	..=..	3-OMe	3.5	78	25	7
12	H	H H	H	97	>300	>300	>3
13	H	H H	3-OMe	1.7	>300	nt	—
14	OMe	..=..	Nitropyrrole	7.8	70	200	26
			 **15 - 22**				
15	H		3-OMe	0.026	35	1.6	62
16	OMe		3-OMe	0.045	18	1.5	33
17	H		3,4-OCH_2O	0.009	24	4.6	511
18	OMe		3,4-OCH_2O	0.036	12	1.9	53
19	H		2-SPr	0.02	94	nt	—
20	H		2-SMe	0.035	95	nt	—
21	H		4-SMe	0.17	68	nt	—
22	H		2-OH,3-F	0.046	>300	nt	—
			 **14**				

[a] 5-HT_7, M_4 and D_2 receptor binding assays were performed using tritiated 5-CT, *N*-methylscopolamine and spiperone, respectively (see Supplementary material). $n = 1–5$, variation <20%.

basis in place of the tetrahydrocarboline of series A compounds. The structural variations include the substituents on the tetrahydroquinoline, the ring size of the benzofused system connected through the amidine, and the substitution pattern of the alicyclic ring. A variety of benzofused alicyclic compounds were required; indanes, tetralins and benzocycloheptanes and the corresponding ketones were obtained by adaptations of standard methods.[22] The amines required for amidine preparation were obtained by nitration[23] of the appropriate benzofused alicyclic compounds, functional group modification of the nitro compounds to afford the required alicyclic ring substituents (acetates, dichlorobenzoates, ethers, thioethers and thioacetals). Hydrogenation of the functionalised nitro compounds over palladium on carbon afforded the corresponding aromatic amines, which were converted into the required amidines by condensation with the appropriate formamide in the presence of phosphorus oxychloride.[24] Typical yields for the amidine formation were 40–60%. Formylations of tetrahydroquinolines were facilitated with the use of trimethylacetic formic anhydride.[25] It should be pointed out that alcohols like **29**, **30** cannot be used as precursors to make different esters as the amidine group in the structure is very sensitive to acetyl chloride, benzoyl chloride and acetic anhydride.

Evaluation of compounds. Although series A (Table 1) did not contain a compound that satisfied all of the requirements for a serominic described above, it has nevertheless provided important pointers towards the required properties. The aryl dihydrocarbolines **9**, **11** and **14** show measurable binding activity in each assay but the aryl tetrahydrocarbolines **10** and **13** have no measured M_4 activity. On the other hand, substituted benzyl tetrahydrocarbolines have binding activity in both assays. Tetrahydro-β-carbolines bind strongly to 5-HT_7 receptors [e.g., **15**, **16** and **18**]; they also indicate

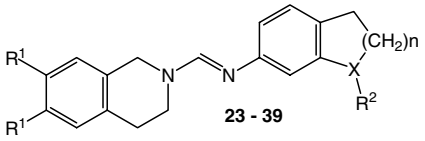
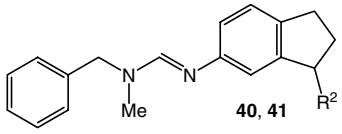
that a single nitrogen atom can act as the cationic site to elicit both 5-HT_7 and M_4 activity. **17** and **18** were prepared with the methylenedioxy ring which is an isostere of the thiadiazole ring of PTAC. These compounds demonstrate very effective binding to 5-HT_7 receptor compared with D_2 binding activity; **17**, for example, is more than 500-fold selective for the 5-HT_7 receptor compared with the D_2 receptor but, like others in series A showed insufficient M_4 binding activity for further investigation. For comparison of affinity and selectivity, the K_is of PTAC at 5-HT_7 and M_4 receptors were determined in our assays to be 3.8 and 0.002 μM, respectively, whilst those of the 5-HT_7 selective ligand, SB2598741, were 0.02 and 4.3 μM, respectively.

For the series B compounds, the coupling of a tetrahydroisoquinoline with a substituted benzocycloalkane led to a number of dual active compounds (serominics). Thus several compounds (**23**, **26**, **29**, **30**, **33**, **34**, **38** and **39**) all incorporate the required units and shown significant binding activity to both 5-HT_7 and M_4 receptors. The tetrahydroisoquinolines may be unsubstituted or substituted with alkoxy groups and a variety of hydroxy and alkoxy substituents are acceptable in the cycloalkane ring. Encouragingly, in some compounds D_2 binding activity was significantly lower (**23**, **25**, **29** and **30**) but in others, D_2 activity remained close to that at the 5-HT_7 and M_4 receptors (**27** and **34**). The compound with the most promising profile was **29**, which was greater than 750-fold selective for the 5-HT_7 receptor; it was taken further, together with **26**, into functional assays (see below).

Bearing in mind the likely significance of sulfur in the binding of PTAC to the M_4 receptor, compounds **35**–**38** were prepared to explore the role of sulfur in binding in series B. Table 2 shows that compounds **35** and **38** have similar binding affinities to the oxygen containing compounds described above but **36** and **37** are markedly less effective in binding activity. The vinyl sulfide **36** might have been predicted to be closer in Lewis basicity to the sulfur in PTAC, but clearly in our compounds, sulfur bound to a tetrahedral carbon provides more effective binding to M_4 receptors. The bulkier dithiane groups in **35** and **39** might have caused steric problems for binding but this appears not to be the case. However, the most intriguing change seen with **36** and **37** is the low binding affinities for 5-HT_7 receptors.

The results of a ligand binding assay do not show whether a compound is behaving as an agonist or antagonist. The most promising compounds from the ligand binding assays were therefore evaluated in a functional

Table 2. Amidine derivatives[a]

Compound	R^1	R^2	*n*	X	5-HT_7 K_i (μM)	M_4 K_i (μM)	D_2 K_i (μM)	D_2/5-HT_7 ratio
				 **23 - 39**				
23	H	OAc	2	CH	0.2	1.4	2.4	12
24	OMe	$CO_2{}^tBu$	1	N	2.2	50.0	54.0	24
25	OMe	OAc	2	CH	0.4	0.2	11.0	28
26	OMe	OAc	3	CH	0.5	0.2	14.0	28
27	OMe	OPr	2	CH	5.3	12.0	42.0	8
28	OMe	CO_2Me	1	N	25.0	2.0	14.0	0.6
29	OMe	OH	1	CH	0.4	0.3	>300	>750
30	H	OH	1	CH	2.7	2.8	>300	>111
31	H	$O_2CC_6H_3Cl_2$	1	CH	>30	160.0	nt	—
32	OMe	$O_2CC_6H_3Cl_2$	1	CH	>30	5.3	>300	—
33	OMe	OAc	1	CH	1.0	0.2	12.0	12
34	H	OAc	1	CH	0.1	1.6	1.7	17
35	OMe	$S(CH_2)_2S$	2	C	0.3	0.7	>100	>333
36	OMe	SBu	(alkene)	C	>300	11.0	8.2	<0.03
37	OMe	SBu	1	CH	36.0	4.5	3.1	0.09
38	OMe	OH	3	CH	0.8	0.3	1.7	2.1
39	OMe	$S(CH_2)_2S$	1	C	0.2	0.3	>100	>500
				 **40, 41**				
40		OAc			0.1	4.5	1.6	16
41		OH			3.6	19.0	59.0	16

[a] 5-HT_7, M_4 and D_2 receptor binding assays were performed using tritiated 5-CT, *N*-methylscopolamine and spiperone, respectively (see Supplementary material). *n* = 1–5, variation <20%.

assay using mouse N1E-115 cells, which produce a pure population of M_4 receptors.[25] Known muscarinic agonists such as oxotremorine and acetylcholine act on muscarinic M_4 receptors coupled to an inhibition of adenylyl cyclase, leading to reduced cAMP levels.[26] While full dose–response curves were not obtained for each agonist, the maximum response observed with **26** and **29** was similar to that found for PTAC suggesting that both **26** and **29** behave as full agonists. Because it is unclear to what extent neutral or intrinsic 5-HT_7 activity is central to our serominic hypothesis, full functional characterization of **26** and **29** at this receptor has not been carried out.

As shown in Fig. 4, both **26** and **29** at nM concentrations caused a substantial reduction of cAMP levels to less than 50% of control; this decrease was blocked by the muscarinic antagonist, atropine. To demonstrate in vivo antipsychotic activity, three compounds, **25**, **29** and **33**, were examined in the amphetamine induced hyperactivity test in rats; this test is widely used for assessing antipsychotic activity.[27] The selection of these compounds was in part due to the higher affinity of **25** and **33** at the D_2 receptor compared with **29**. Compounds **25**, **29** and **33** were tested at a concentration of 10 mg/kg ip. Although very similar in structure, the small differences between these three compounds were found to have major effects on their activity in this test in a manner that was not predictable (Fig. 5a). It would not be expected that all compounds that showed an appropriate profile in receptor binding assays would be active *in vivo* because such assays take no account of bioavailability and metabolism. However, the most active compound, **29**, was found to suppress hyperactivity in a dose dependent manner (Fig. 5b) with an ED_{50} of around 8 mg/kg ip (95% confidence limits). Interestingly **29** had the most pronounced effect in the amphetamine test, whereas **25** and **33** appeared ineffective. The activity of compound **29** is unlikely to be related to antagonism of dopamine receptors since this compound has minimal binding

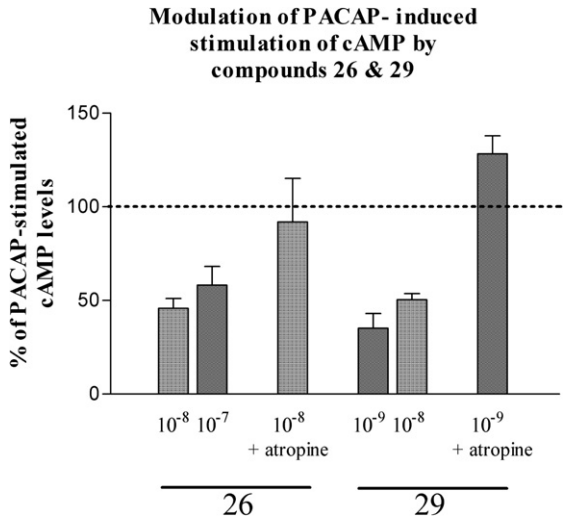


Figure 4. Functional assay of **26** and **29**. Modulation of PACAP-induced stimulation of cAMP by low concentrations (10^{-9} and 10^{-8} M). Antagonism by atropine (10^{-4} M) is clearly indicated.

affinity for the D2 receptor ($K_i > 300\mu M$) in contrast to compounds **25** and **33**, which were both measurably active.

Beginning from studies of brain metabolism, through lead generation by screening of natural products, ligand binding and functional assays, we have demonstrated in vivo the potential of the serominic concept as a valid basis for the discovery of new antipsychotic compounds. Future studies will address whether compounds acting at these targets display activity in our chronic PCP model of metabolic hypofunction thereby assessing our ability to predict an improved therapeutic profile over existing antipsychotic drugs. The antipsychotic activity of **29** without appreciable D_2 antagonist activity is a striking finding that demonstrates the potential of serominic compounds as novel antipsychotic agents.

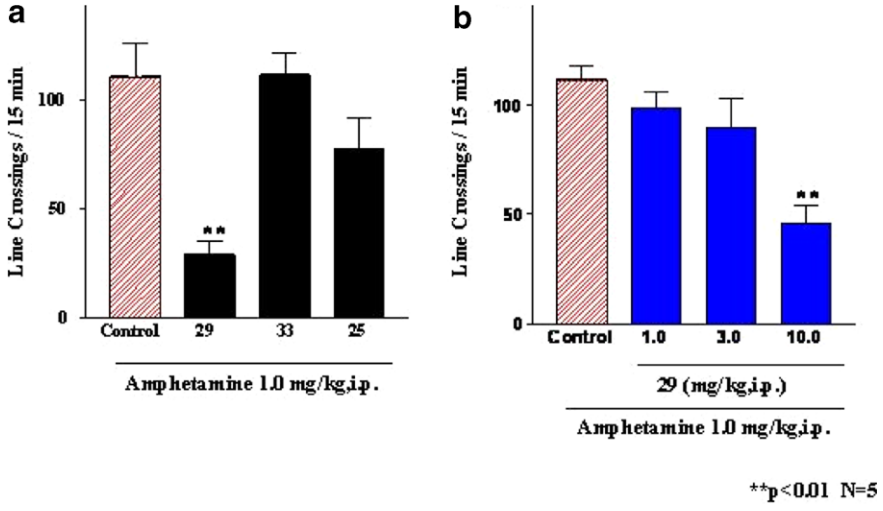


Figure 5. Demonstration of serominic activity by the amphetamine induced hyperactivity test. (a) Left: effect of compounds **23**, **33** and **25** at 10 mg kg^{-1}. (b) Right: dose–response of compound **29**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.01.093.

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