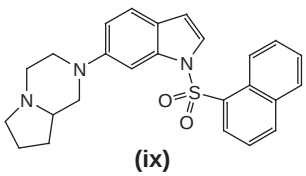
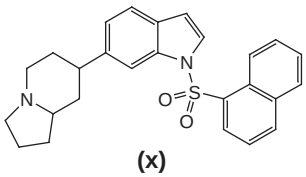
nigra and hippocampus of the brain, as well as the strong affinity of this receptor subtype for several antipsychotic and antidepressant drugs. Furthermore, administration of an antisense oligonucleotide directed towards the 5-HT_6 mRNA in rats has been shown to elicit a behavioral response involving yawning, chewing and stretching that was dose-dependently antagonized by the muscarinic-receptor antagonist atropine. This suggests that the 5-HT_6 receptor might also be implicated in the control of cholinergic neurotransmission. Moreover, 5-HT_6-receptor antagonists might have further use in the treatment of memory dysfunction.

As part of a research effort focused on developing potent and selective 5-HT_6-receptor antagonists, workers from NPS Allelix Corporation (Mississauga, ON, Canada) have identified a novel series of 6-bicyclopiperazinyl-1-arylsulfonylindoles and 6-bicyclopiperidinyl-arylsulfonylindoles, exemplified by (**ix**) and (**x**), respectively. These compounds



(ix)



(x)

have high binding affinities (K_i <6 nM) for human 5-HT_6 receptors expressed in HEK293 cells[4]. The most potent compound (**ix**) was shown to be a competitive antagonist (IC_{50} = 7.2 nM) in a functional adenylate cyclase assay and showed good selectivity for this receptor subtype over several related 5-HT-receptor subtypes. This compound is presently being evaluated for its potential in the treatment of schizophrenia, depression and memory dysfunction.

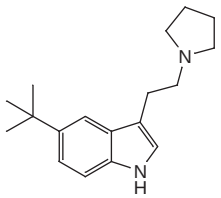
4 Isaac, M. *et al.* (2000) 6-Bicyclopiperazinyl-1-arylsulfonylindole and 6-bicyclopiperidinyl-1-arylsulfonylindole derivatives as novel, potent and selective 5-HT_6 receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 1719–1721

5-HT_{1D}-receptor antagonists for the treatment of migraine

Although the development of sumatriptan has revolutionized the treatment of migraine, a limited number of patients fail to respond to such treatment. Furthermore, a significant number of non-responders suffer from recurrence of headaches within 24 h. Sumatriptan and similar drugs bind to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors with a high affinity.

It has been postulated that the pain associated with migraine is caused by either cranial vasodilation or neural stimulation as a consequence of the stimulation of the trigeminal sensory system that innervate meningeal and cerebral arteries. As the cardiovascular side effects associated with sumatriptan can be attributed to binding to the 5-HT_{1B} receptor, and only the 5-HT_{1D} and 5-HT_{1B} receptors appear to be present in cerebral blood vessels, it has been suggested that selective 5-HT_{1D}-receptor agonists might eliminate the symptoms of migraine without the cardiovascular side effects.

A recent report from Slassi, A. and coworkers describes the synthesis of a series of 5-alkyltrypamines and conformationally constrained 5-alkyl-3-(*N*-methylpyrrolidin-2-yl-methyl) analogues[5]. Evaluation of the binding profile of these compounds using cloned human 5-HT_{1D} and 5-HT_{1B} receptors identified (**xi**) as having a high binding affinity for the 5-HT_{1D} receptor (K_i = 2.5 nM) and >100-fold selectivity for the 5-HT_{1D} over the 5-HT_{1B} receptor subtype. Several derivatives of his analogues, including (**xi**), were shown to possess agonist activity in an isolated rabbit saphenous



(xi)

vein assay with no antagonistic activity. Compound (**xi**) is presently reported to be under further evaluation in animal models for the treatment of migraine.

5 Slassi, A. *et al.* (2000) 5-Alkyltryptamine derivatives as highly selective and potent 5-HT_{1D} receptor agonists. *Bioorg. Med. Chem. Lett.* 10, 1707–1709

Andrew Lloyd

Combinatorial chemistry

NMDA-receptor antagonists

Parkinson's disease, a progressive degenerative CNS disorder, has many debilitating effects such as muscle rigidity, resting tremors and slowness or poverty of movement. This disease affects ≈1% of the population >50 years of age. Parkinson's disease results from degeneration of dopaminergic neurons that lie within the substantia nigra. The treatment of choice has been dopamine replacement therapy, using L-dihydroxyphenylalanine (L-DOPA). However, long-term treatment often results in adverse side effects such as dyskinesias. It has been shown that *N*-methyl-D-aspartate (NMDA)-receptor antagonists can potentiate the effects of L-DOPA in animal models of Parkinson's disease. The use of non-selective NMDA-receptor antagonists also results in several side effects, the most common being ataxia, sedation and cognitive impairments. The recent discovery of multiple subtypes of NMDA receptors, which are differentially expressed throughout the brain, might enable separation of the therapeutic activity from adverse side effects. A solution-phase parallel synthesis approach

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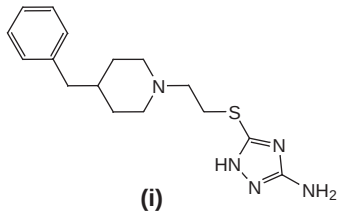
was used to identify NMDA $NR1_A/2B$-subtype-receptor-selective antagonists[1].

A library of 22 individual compounds was prepared in solution and one of the most potent and selective compounds identified was (**i**). This compound had



(i)

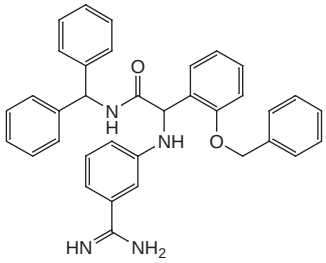
an $NR1_A/2B$ IC_{50} of 35 nM, and possessed selectivity over the following subtypes: $NR1_A/2A$ (>2800-fold) and $NR1_A/2C$ (>2800-fold). This library has enabled the identification of key pharmacophoric elements necessary for potency against $NR1_A/2B$, namely the requirement for a hydrogen bond donor, and a preference for an ethylene link between the piperidine and the thio aryl system of (**i**).

1 Gregory, T.F. *et al.* (2000) Parallel synthesis of a series of subtype-selective NMDA receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 527–529

Molecular evolution in a combinatorial library

The concept of Darwinian selection and evolution has inspired the development and application of evolutionary programming or genetic algorithms to find optimal solutions for combinatorial problems in multi-dimensional and in extensive search spaces. Artificial evolutionary optimization has recently been introduced to find molecules with high biological activity from large, virtual combinatorial libraries of molecules without the need to synthesize and determine the biological activity of all members of this library. Examination of optimization behaviour and performance of genetic algorithms that were used to select molecules from a combinatorial library of potential thrombin inhibitors in 'artificial molecular evolution' experiments has been performed[2].

A combinatorial library of 15,360 individual compounds was synthesized using an Ugi-type three-component reaction of isonitriles, aldehydes and amines to generate putative thrombin inhibitors. Constituent monomers chosen were structurally biased towards the serine protease thrombin and one of the most potent compounds prepared from this library was (**ii**) with a



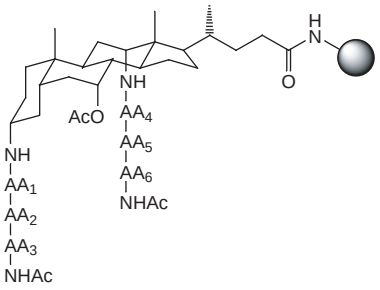
(ii)

K_i of 2 nM against thrombin. This work has demonstrated the benefits of a genetic algorithm-driven approach to the discovery of small-molecule inhibitors of medicinally relevant targets. This type of approach could be useful when dealing with very complex multi-dimensional search spaces.

2 Weber, L. *et al.* (2000) Simulated molecular evolution in a full combinatorial library. *Chem. Biol.* 7, 433–441

Serine protease-like activity

The cleavage of peptide bonds by the serine protease α-chymotrypsin, for example, is a highly efficient and selective reaction compared with its uncatalyzed hydrolysis. Although progress has been made in the development of synthetic hydrolases, substantial improvement is still required. One area of research has been the development of synthetic hydrolases with a focus on gaining a better understanding of the enzymatic process itself. In particular, development of non-peptidic organic molecules possessing an array of functional groups in a suitable geometry for eventual activity. Studies examining serine protease activity are being undertaken using combinatorial techniques in which the two most important catalytic residues, Ser and His of the classic triad (Ser, His, Asp), are each incorporated into one of the two tripeptidic chains generated on a steroidal scaffold (**iii**)[3].



(iii a) AA_1 = Gly; AA_2 = Phe; AA_3 = Ser; AA_4 = Leu; AA_5 =His; AA_6 = Ala
(iii b) AA_1 = Phe; AA_2 = Ser; AA_3 = Phe; AA_4 = Leu; AA_5 =His; AA_6 = Ala
(iii c) AA_1 = Ser; AA_2 = Ser; AA_3 = Phe; AA_4 = Leu; AA_5 =His; AA_6 = Ala

(iii)

A library of 729 compounds in pools of 234 members, prepared using the split–mix synthesis procedure on TentaGel-NH_2 solid-phase resin, revealed three potent mixtures on initial screening against an activated *p*-nitrophenol ester, which was used as a model for the first step of the enzymatic mechanism. Recursive deconvolution identified (**iii a–c**) as the most potent constituents of these mixtures. This work might aid the future design of synthetic hydrolases, which could lead to a better understanding of the mechanism of cleavage and, ultimately, to the synthesis of medicinally relevant compounds.

3 De Clercq, P.J. *et al.* (2000) Application of combinatorial procedures in the search for serine-protease-like activity with focus on the acyl transfer step. *Angew. Chem., Int. Ed. Engl.* 39, 145–148

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