Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

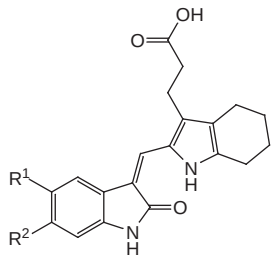
Molecules

Angiogenic growth factor inhibitors

Angiogenesis plays an important role in supporting the growth of solid tumors. This process provides capillaries around the tumour mass to (1) supply nutrients and growth factors for rapid tumour growth and (2) remove waste products of tumour metabolism. Such capillaries also provide a carrier to enable the transport of tumour cells to other sites within the body leading to the formation of metastases. Various growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), as well as their associated receptor tyrosine kinases, have been directly or indirectly implicated in tumour angiogenesis. The has led to the widespread investigation into the use of growth factor receptor inhibitors of these tyrosine kinases as therapeutic agents for the treatment of cancer.

Workers at the New York University Medical Center (New York, NY, USA) have recently reported the synthesis and evaluation of novel 3-substituted indolin-2-ones containing a tetrahydroindole moiety as specific inhibitors of the receptor kinases associated with VEGF, FGF and PDGF receptors[1]. Structure–activity relationships were developed by evaluating the inhibitory properties of these novel compounds with respect to the VEGF-R2 (Flk-1/KDR), FGF-R1, PDGF-Rβ, p60$^{c\text{-}Src}$ and epidermal growth factor receptor (EGF-R) tyrosine kinases. Furthermore, their ability to inhibit growth factor-stimulated cell proliferation was evaluated using human umbilical vein endothelial cells (HUVECs) or 3T3 mouse fibroblasts *in vitro*.

The most potent inhibitors of VEGF, FGF and PDGF receptor kinases were those with a propionic acid group at the C-3′ position of the tetrahydroindole ring. Compounds (**i**), (**ii**) and (**iii**) were found to be the most active against VEGF-R2 (Flk-1) (IC_{50} = 4 nM), FGF-R1 (IC_{50} = 80 nM) and PDGF-Rβ (IC_{50} = 4 nM), respectively. All of these compounds were inactive when tested against EGF-R tyrosine kinase. In addition, compounds (**iii**) and (**iv**) inhibited both growth factor-dependent cell proliferation and biochemical kinase activity for all three targets. These compounds might therefore be useful leads for the development of agents for both the inhibition of tumor angiogenesis and for the treatment of other PDGF and FGF-related disorders.



(i) R^1 = COOH, R^2 = H
(ii) R^1 = H, R^2 = 2-OCH_3phenyl
(iii) R^1 = Br, R^2 = H
(iv) R^1 = H, R^2 = H

1 Sun, L. *et al.* (2000) Identification of substituted 3-[(4,5,6,7-tetrahydro-1*H*-indol-2-yl)methylene]-1,3-dihydroindol-2-ones as growth factor receptor inhibitors for VEGF-R2 (Flk-1/KDR), FGF-R1 and PDGF-Rβ tyrosine kinases. *J. Med. Chem.* 43, 2655–2663

α_{1A}-Adrenoceptor antagonist

The urological disorder benign prostatic hyperplasia (BPH), which causes urinary obstruction, is presently treated using non-subtype-selective α_1-adrenoceptor antagonists. However, the use of such agents is limited by several cardiovascular side effects caused by vascular α_1-adrenoceptor blockade. As

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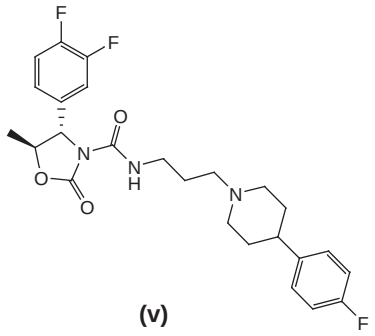
the α_{1A} subtype is the predominant receptor subtype associated with the prostate, it has been suggested that selective α_{1A}-receptor antagonists might provide more effective symptomatic relief of BPH by avoiding the cardiovascular complications. Although several α_{1A}-receptor subtype-selective antagonists have been reported in recent years, these compounds generally show poor bioavailability (0–30%) and short plasma half-lives (<4 h) in rats and dogs[2].

A recent publication by Lagu, B. and coworkers describes the *de novo* design, synthesis and *in vitro* and *in vivo* evaluation of a novel oxazolidinone analogue (**v**) as a potent and selective



(v)

α_{1A}-receptor antagonist[2]. This compound has subnanomolar binding affinity for the recombinant human (K_i = 0.17 nM), rat (K_i = 0.36 nM) and dog (K_i = 0.23 nM) α_{1A} receptor with >700-fold selectivity for the human α_{1A} receptor over human α_{1B} and α_{1D} receptors. In functional assays, this compound potently antagonized A61603- and phenylephrine-induced contraction of human, rat and dog prostate tissue. In anesthetized rats, the compound showed higher functional potency than the α_{1A}-receptor antagonist terazosin and improved selectivity for prostate α_1-adrenoreceptor over cardiovascular receptors. Unlike terazosin, this compound failed to show any hypotensive effects in the dog, even at high doses of 300 μg kg^{-1}. The compound also offered improved oral bioavailability and plasma half-life in rats (25% and 6 h) and dogs (74% and >12 h).

The high binding affinity and selectivity for the α_{1A} adrenoceptor coupled with the pharmacokinetic and pharmacodynamic profiles presented in this paper suggest that this compound will be a useful lead for the future development of α_{1A}-adrenoceptor antagonists for the treatment of BPH.

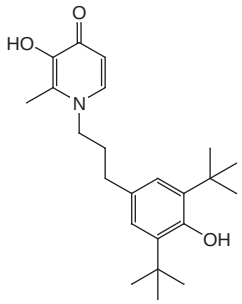
2 Lagu, B. *et al.* (2000) *De novo* design of a novel oxazolidinone analogue as a potent and selective α_{1A} adrenergic receptor antagonist with high oral bioavailability. *J. Med. Chem.* 43, 2775–2778

Lipid peroxidation inhibitors

Increasing evidence suggests that free radical generation is associated with various disorders including stroke, Parkinson's disease and Alzheimer's disease. Free radical scavenging antioxidants might therefore have a role as neuroprotective agents for the treatment of such diseases. However, the use of these agents is limited by the continued generation of free radicals by various metal ion-associated reactions such as the iron-catalyzed Fenton reaction. Various reports have suggested that ion chelators might act synergistically with radical scavengers to protect tissue against oxidative stress.

To test the hypothesis that a hybrid molecule containing both iron chelation and antioxidant functionality would offer advantages over the co-administration of antioxidants and iron chelators, workers at Cerebrus (Winnersh, Wokingham, UK) have synthesized and evaluated a series of hybrid systems based on the combination of 3-hydroxy-4(1*H*)-pyridinones and 2,6-disubstituted phenols[3].

These studies resulted in the identification of compound (**vi**) as a potent inhibitor of lipid peroxidation in rat brain homogenates (IC_{50} = 1 μM). Furthermore, it is also effective at protecting cerebellar granule cells against iodoacetic acid-induced oxidative stress (EC_{50} = 280 nM).



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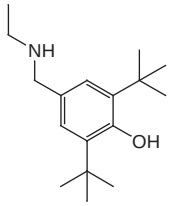

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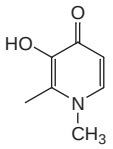


(viii)

This agent was more effective than dual administration of the radical scavenger di-*tert*-butylphenol (**vii**) and the iron chelator 1,2-dimethyl-3-hydroxy-4(1*H*)-pyridinone (**viii**). Consequently, these novel hybrid systems are presently under evaluation for the treatment of neurodegenerative disorders.

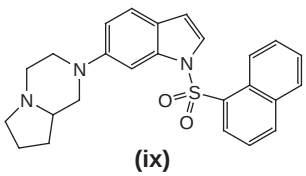
3 Bebbington, D. *et al.* (2000) 3,5 Disubstituted-4-hydroxyphenyls linked to 3-hydroxy-2-methyl-4(1*H*)-pyridinone: potent inhibitors of lipid peroxidation and cell toxicity. *J. Med. Chem.* 43, 2779–2782

5-HT_6-receptor antagonists for schizophrenia, depression and memory dysfunction

Recent studies have shown that the 5-HT_6 receptor might be a useful therapeutic target for the treatment of schizophrenia and depression. This suggestion is based on studies of the localization of the 5-HT_6 receptor mRNA in the nucleus accumbens, striatum, olfactory tubercle, substantia

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



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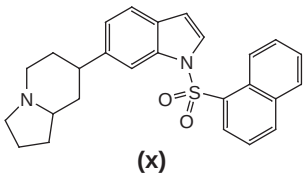


(x)

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.

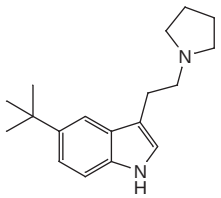
4 Isaac, M. *et al.* (2000) 6-Bicyclopiperazinyl-1-arylsulfonylindole and 6-bicyclopiperidinyl-1-arylsulfonylindole derivatives as novel, potent and selective 5-HT_6 receptor antagonists. *Bioorg. Med. Chem. Lett.* 10, 1719–1721

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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