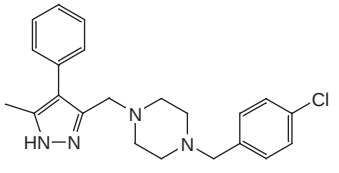
Monitor: molecules and profiles

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.

Substituted pyrazoles as novel D_4 receptor ligands

As described previously in this column, ligands that bind to dopamine D_4 receptors may have uses as antipyschotic agents. Workers from Merck, Sharp & Dohme Laboratories (Harlow, UK) have described the synthesis of two novel series of 3-(heterocyclylmethyl)pyrazoles and evaluated these as potential D_4 ligands using clonal cell lines [Bourrain, S. *et al. Bioorg. Med. Chem.* (1998) 6, 1731–1743]. Both series, exemplified by **1** and **2** respectively, showed high affinity and selectivity for the human D_4 (hD_4) receptor.

These studies showed that for series I the piperazine *N*-benzyl substituent is essential for high affinity hD_4 binding whereas in series II the second basic nitrogen is not essential. Studies on the affinity of these compounds for ion channels and other receptors showed that compound **2** had no measurable affinity for calcium, sodium or potassium (IK_R) channels nor for the $5HT_2$, $5HT_{1A}$ and sigma receptors. This compound would therefore be a useful tool for further evaluating the pharmacology of the hD_4 receptor.



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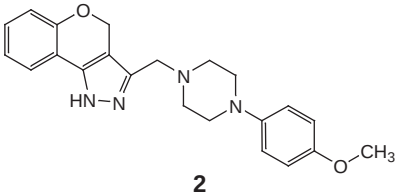

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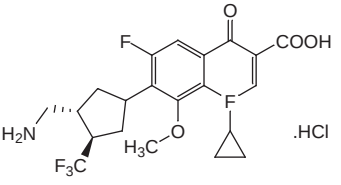
Novel fluoroquinolone antibiotics

Antibacterial fluoroquinolones are widely used in the anti-infective chemotherapy field. However frequent clinical use of these compounds has led to the development of quinolone- and methicillin-resistant strains. Recent work has therefore focused on the development of fluoroquinolones with activity against such quinolone- and methicillin-resistant organisms. Fukui, H. and coworkers have recently described the synthesis and antimicrobial activity of a novel series of 7-(3-substituted-3- or 4-trifluoromethyl-1-pyrrolidinyl)-8-methoxyfluoroquinolones [*Bioorg. Med. Chem. Lett.* (1998) 8, 2819–2824]. These studies have identified **3** (S34109) as a promising candidate for further evaluation, as it has superior activity against quinolone- and methicillin-resistant *Staphylococcus aureus* and lower cytotoxicity and mutagenicity potential compared with other members of the series.



3

MEK inhibitors

Although steroids have been used for many years to treat inflammation, the side effects of these drugs are a major cause for concern. As part of an intensive programme to identify novel anti-inflammatory drugs with alternative mechanisms of action, workers from DuPont Pharmaceuticals Company (Wilmington, DE, USA) have been investigating the potential of inhibiting the transcription factors AP-1 and NF-κB, which regulate the transcription of immune response genes.

During the screening of the DuPont library, the group identified a compound

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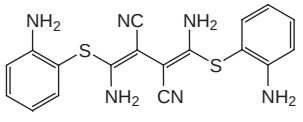
(**4**, U0126) that inhibits AP-1 transcription activity [Duncia, J.V. *et al. Bioorg. Med. Chem. Lett.* (1998) 8, 2839–2844]. Further studies of the cell signalling cascades led to the discovery that this compound also inhibits the MAP kinase kinase MEK, and other recently reported studies confirm the ability of this compound to block the production of inflammatory cytokines and matrix metalloproteinases [DeSilva, D.R. *et al. J. Immunol.* (1998) 160, 4175–4181]. Structure–activity studies have shown that despite the propensity of this compound to undergo isomerization and cyclization, the *Z,Z*-isomer of **4** appears to be the active moiety. Further studies are presently being undertaken to elucidate the efficacy of this compound in animal models of inflammation.



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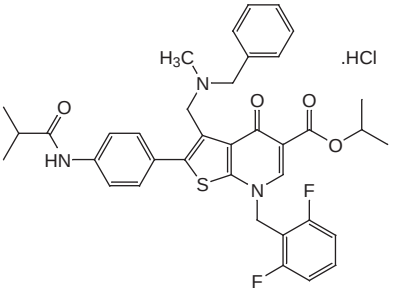
LHRH receptor antagonist

Luteinizing hormone-releasing hormone (LHRH) is secreted from the hypothalamus where it stimulates the anterior pituitary gland to release leuteinizing hormone (LH) and follicle-stimulating hormone (FSH), which ultimately elicit gonadal production of sex steroids and gametogenesis. LHRH therefore has an important role in the regulation of sexual function. As a result there has been considerable interest in using this agent and related synthetic analogues for the treatment of endocrine-based diseases such as prostate cancer.

Chronic administration of LHRH receptor agonists results in depletion of the gonadotropins and downregulates the receptor in the pituitary gonadotrophs resulting in suppression of steroid hormones. Such treatment requires chronic administration over two to four weeks, but this could be avoided by administration of LHRH antagonists because these agents should suppress gonadotropin release from onset and avoid the possibility of the initial hormonal surge associated with early stage administration of LHRH agonists. Although work over the past two decades has recently led to the development of several peptide-based, potent and safe antagonists, these agents have poor oral bioavailability.

Cho, N. and coworkers have recently reported the design, synthesis and biological evaluation of isopropyl 3-(*N*-benzyl-*N*-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-isobutyrylaminophenyl)-4-oxothienol[2,3-b]pyridine-5-carboxylate hydrochloride (**5**, T98475) as an orally active, highly potent human LHRH antagonist [*J. Med. Chem.* (1998) 41, 4190–4195]. This compound clearly overcomes the problems associated with the existing LHRH antagonists and it should lead to better treatments for sex hormone-dependent pathologies.



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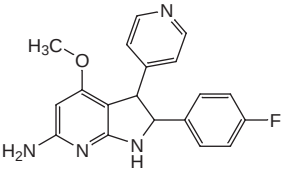
p38 kinase inhibitor

The mitogen-activated protein (MAP) kinase homologue p38 plays important roles in the production of the monocyte-derived proinflammatory cytokines, tumour necrosis factor α (TNF-α) and interleukin 1β (IL-1β), and in the signalling cascades associated with the TNF-α and IL-1 receptors. Thus p38 kinase has been proposed as a potential therapeutic target for the treatment of many inflammatory disorders including rheumatoid arthritis, inflammatory bowel disease and psoriasis.

A recent report from The R.W. Johnson Pharmaceutical Research Institute (Raritan, NJ, USA) describes the identification of 6-amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl) 1H-pyrrolo(2,3-b)pyridine (**6**, RWJ68354) as a potent and selective p38 kinase inhibitor [Henry, J.R. *et al. J. Med. Chem.* (1998) 41, 4196–4198].

This compound was shown to be a potent inhibitor of cellular p38 kinase activity (IC_{50} = 9 nM), LPS-stimulated TNF-α and IL-1β production from human peripheral blood mononuclear cells (IC_{50} = 6.3 nM and 26 nM, respectively) *in vitro* and LPS-stimulated TNF-α production in mice (ED_{50} <10 mg kg^{-1} p.o.) and rats (ED_{50} <25 mg kg^{-1} p.o.). This compound is clearly a potential Phase I compound and deserves further preclinical evaluation.



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In short…

Genentech (South San Francisco, CA, USA) and **Magainin Pharmaceuticals** (Plymouth Meeting, PA, USA) enter into a collaborative research and option agreement in asthma. Genentech will have access to a therapeutic target (IL-9), which is in Magainin's Asthma Gene Database, and the companies will collaborate to evaluate the potential of a blocking antibody to IL-9 in suppressing the asthmatic response. Genentech made an initial equity investment in Magainin of $2 million, purchasing Common Stock at a 10% premium to the 20-day average closing price. At completion of the collaborative research program, Genentech has the option to enter into a development and commercialization agreement, which could provide for payments to Magainin of up to $35 million.