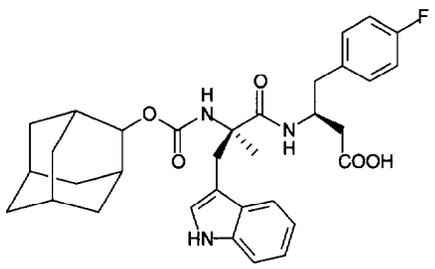
A recent study [Augelli-Szafran, C.E. *et al. Bioorg. Med. Chem.* (1996) 4, 1733–1745] has identified a 4-fluorophenyl analogue of the known CCK_B receptor antagonist CI988 (**5**) with extraordinary binding affinity for the CCK_B receptor (IC_{50} = 0.08 nM) and 940-fold selectivity for the CCK_B receptor over the CCK_A receptor.



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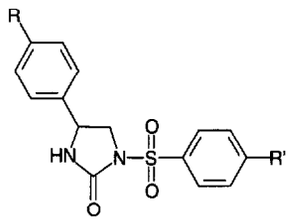
Arylsulphonylimidazolidinones as anticancer agents



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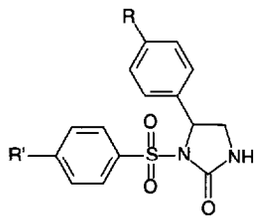

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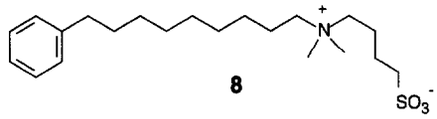
On the basis of recent reports suggesting that diarylsulphonylureas may have therapeutic utility as antineoplastic agents, Jung, S-H. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 2553–2558] have designed and synthesized two series of novel arylsulphonylimidazolidinones based on **6** and **7** containing the sulphonylurea pharmacophore. These compounds were tested against various human solid tumours, murine leukaemia cell lines *in vitro* and murine mammary adenocarcinoma (MM48) *in vivo*. The results suggest that these novel 1-arylsulphonyl-4-phenylimidazolidinones offer potential as lead compounds for the development of anticancer agents based on the sulphonylurea pharmacophore.

Squalene synthetase inhibitors

Shechter, I. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 2585–2588] have described an investigation into the use of sulphobetaines as zwitterionic squalene synthetase inhibitors. These compounds presumably mimic both the carbocationic and anionic moieties of the squalene synthetase reaction intermediates while maintaining overall neutrality. The most effective inhibitors identified by this group are those incorporating aromatic hydrophobic chains such as **8** (IC_{50} = 2 μM) and **9** (IC_{50} = 2 μM).



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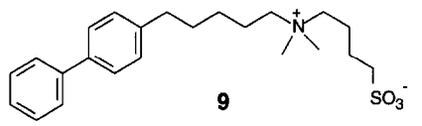
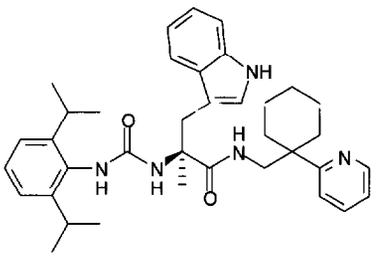


9

Nonpeptide NMB antagonist

Although the neuromedin B (NMB) decapeptide and the structurally related 27-amino-acid gastrin-releasing peptide are thought to mediate a range of biological actions, including autocrine growth, satiety and thermoregulation, the precise physiological role of these peptides has yet to be fully elucidated as a partial consequence of the lack of suitable nonpeptide high-affinity antagonists.

To address this, a group from the Parke-Davis Neuroscience Research Centre (Cambridge, UK) [Eden, J.M. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 2617–2622] have developed a novel series of nonpeptide NMB antagonists, exemplified by **10** (PD165929), using a 'peptoid' drug design strategy.



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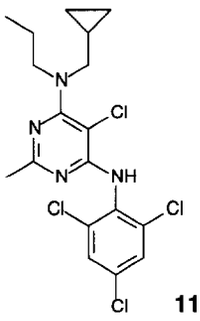
PD165929 was shown to be the first high affinity (K_i = 6.3 nM) competitive antagonist ($_{app}K_b$ = 7.6 nM) at the NMB receptor with greater than 1000-fold selectivity for this receptor over the related gastrin-releasing peptide receptor type.

CRF_1 receptor antagonists

The investigation into the role of corticotropin-releasing factor (CRF) in depression, anxiety and stress-related disorders has also been hampered by the lack of suitable nonpeptide antagonists. The actions of CRF are mediated through a family of G-protein-coupled seven-transmembrane protein receptors of which two subtypes, CRF_1 and CRF_2, have been recently cloned, expressed and characterized. Workers from Neurocrine Biosciences (San Diego, CA, USA) have reported the design and synthesis of a series of high affinity, selective, nonpeptide CRF_1 antagonists based on 4-anilino-6-aminopyrimidines such as **11** [Chen, C. *et al. J. Med. Chem.* (1996) 39, 4358–4360]. These compounds were shown to have low nanomolar affinities for the human CRF_1 receptor subtype and shown to inhibit CRF-stimulated cAMP production in stable cell lines transfected with this subtype *in vitro*. These compounds will be particularly useful for establishing the potential use of CRF_1 receptor antagonists in the treatment of depressive and anxiety-related disorders.



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