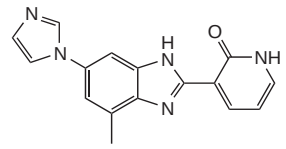
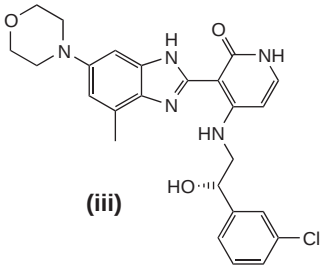


(ii)



(iii)

Further structural refinements, guided by crystallographic data from co-crystallization of **(ii)** with truncated IGF-1R, led to the identification of compound **(iii)** (BMS-536924), a potent inhibitor of IGF-1R (IC_{50} = 100 nM) with a good overall kinase selectivity profile (although inhibitory activity against the insulin receptor was observed, IC_{50} = 73 nM). Growth inhibitory activity in the submicromolar IC_{50} range was observed for compound **(iii)** in a range of cell lines where there is good evidence of the involvement of IGF-1R signalling. Compound **(iii)** exhibited strong *in vivo* activity in the IGF-1R Sal tumour model following oral administration (100–300 mg/kg once a day for 14 days) and showed efficacy in the Colo205 human colon carcinoma model. The potential disruption of glucose homeostasis, arising from inhibition of the insulin receptor, was investigated by an oral glucose-tolerance test (OGTT); a twofold window between antitumour efficacy and glucose elevation was observed *in vivo*. Furthermore, evaluation of pharmacokinetic parameters in multiple species demonstrated good oral bioavailability. Compound **(iii),** therefore, represents a novel class of IGF-1R inhibitor with promising *in vitro* and *in vivo* antitumour activity and it is a useful tool for probing the cellular effects of IGF-1R inhibition.

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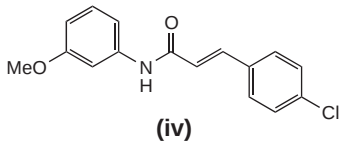
New TRPV1-targeting agents for pain management

The vanilloid receptor, TRPV1, belongs to a large family of non-voltage-gated cation channels that are involved in sensory signalling. It acts as a molecular integrator of various noxious chemicals (vanilloids and acids) and physical stimuli (especially heat). Additionally, this receptor is activated by a series of inflammatory mediators, including bradikinin and lipoxygenase products, as well as by the endocannabinoid (anandamide). There is a growing body of research that identifies the potential of TRPV1 modulators, both agonists and antagonists, for the treatment of a wide range of debilitating conditions, such as chronic inflammatory and neuropathic pain, irritable bowel syndrome, asthma and urinary incontinence [5].

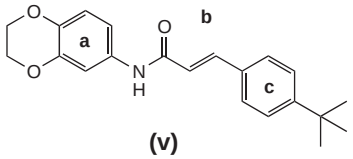
Since the cloning of TRPV1 in 1997, considerable efforts have focused on developing antagonists for this receptor [6,7] from several compound families, including the capsaicin-competitive TRPV1 antagonist family and the group of noncompetitive channel blockers. The capsaicin-competitive TRPV1 antagonist family comprises compounds related to vanilloid agonists, such as capsazepine and the 5-iodinated resiniferatoxin, as well as diverse structurally unrelated small molecules (mostly urea and thiourea derivatives), which have emerged from high throughput screening (HTS) programmes. Some of these small molecules were highly active in animal models of chronic pain but some of them lack selectivity towards other voltage- and ligand-gated ion channels, or their selectivity profiles have not been defined in detail. Within the family of noncompetitive channel blockers, apart from the classical, nonselective broad spectrum stain (ruthenium red), a number of cationic molecules have recently been identified as potent vanilloid channel blockers, shown to possess significant antinociceptive and antihyperalgesic effects in different animal assays.

The arena of the TRPV1 modulators has been recently amplified with the discovery of novel, potent and selective antagonists that have a central cinnamide core. On one hand, Gunthorpe *et al.* [8] have recently reported on the *in vitro* pharmacology of compound **(iv),** SB-366791, that acts as a competitive TRPV1 antagonist, able to inhibit the multimode (capsaicin-, acid- and heat-mediated) activation of the receptor in the nanomolar range. In addition, SB-366791 was shown to be highly selective because it produces little or no effect on a wide array of therapeutically relevant biological targets, including different ion channels and G-protein-coupled receptors (GPCRs).

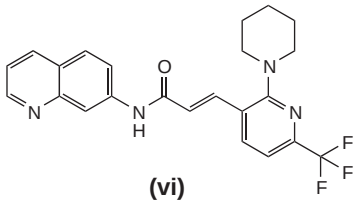
On the other hand, at Amgen, the screening of a combinatorial library led to the identification of compound **(v)**, AMG 9810, that has a very



(iv)



(v)



(vi)

closely related structure to that of the GSK molecule **(iv)** [9]. Detailed biochemical characterization of AMG 9810 demonstrated that it is a potent, competitive antagonist of capsaicin activation that also blocks other modes of TRPV1 activation, including protons, heat and different endogenous ligands. Moreover, this compound shows no significant inhibition of ligand binding to the recombinant TRP family members, a panel of ion channels, GPCRs or transporter proteins. *In vitro* assays demonstrated that compound **(v)** blocks the capsaicin-evoked depolarization and the calcitonin gene-related peptide release, whereas *in vivo* studies show a positive response in capsaicin-induced eye wiping and reduced CFA-driven thermal and mechanical hyperalgesia in a model of inflammatory pain. Because AMG 9810 suffers from high first-pass metabolism and poor oral absorption, the investigation was pursued with an extensive SAR study looking at modifications of the three main areas of the molecule **(v)**: the aniline moiety (indicated by the letter a), the acrylamide core (indicated by the letter b) and the phenyl ring (indicated by the letter c) [10]. The findings can be summarized as follows:

- The 7-quinoline ring was identified as the best substitution for the benzodioxane moiety of compound **(iv)**.
- The appendage of substituents at the α position was detrimental to activity, whereas it can accommodate aliphatic and aromatic substituents at the β position.
- Preferred substituents for the phenyl ring of the cynnamide were *p*-t-Bu, *p*-i-Pr, and *p*-CF_3. Moreover, *o*,*p*-disubstituted 3-pyridyl rings were also well tolerated.

The combination of optimum modifications resulted in compound **(vi)**, the most potent cinnamide antagonist within this series. This compound showed an improved pharmacokinetic profile over the lead compound **(v)**.

These competitive antagonists, as well as the recently described noncompetitive TRPV1 channel blockers, could serve as pharmacological useful tools for unambiguously defining the physiological role of TRPV1 receptors and, ultimately, might yield promising therapeutic agents for the management of chronic and neuropathic pain.

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