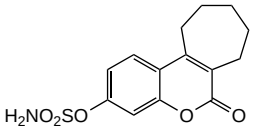
and is currently undergoing preclinical development.



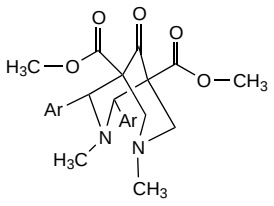
(vi)

6 Woo, L.L. *et al.* (2000) Potent active site-directed inhibition of steroid sulphatase by tricyclic coumarin-based sulphamates. *Chem. Biol.* 7, 773–791

3,7-Diazabicyclononane derivatives as opioid-receptor ligands

Pain is a complex and dynamic process involving multiple, inter-related neurotransmitter and neuromodulator systems in the spinal cord, in ascending and descending spinal pathways, and at supraspinal sites. Although several approaches have been shown to isolate new compounds that are able to effectively treat pain[7], the three major subtypes of the opioid receptors μ, δ and κ, are still primary targets. In particular, κ-agonists were initially thought to be devoid of the side effects of morphine. However, clinical trials showed the presence of dysphoria in several models[8]. This observation has led to the search for peripherally acting κ-agonists.

Researchers from the University of Würzburg (Würzberg, Germany) have previously identified the 2,4-di-2-pyridine-substituted-3,7-dimethyl-3,7-diaza-9-oxo-bicyclo[3.3.1]nonane-1,5-dicarboxylate **(vii)** as a selective κ-ligand that demonstrates strong antinociceptive activity[9]. More recently, they have reported[10] a series of compounds **(viii)**, that have substituted phenyl rings with different moieties at positions 2 and 4.



(vii) Ar = 2-pyridyl
(viii) Ar = substituted phenyl

These new compounds have no affinity for the δ-receptor and show higher affinity for the κ-receptor over the μ-receptor. Compounds that have a *meta*-F (*m*.F) or *meta*-OH (*m*.OH) as well as a *para*-OCH_3 (*p*.OCH_3) on the phenyl rings were found to have a potency comparable with the model **(vii)**, (K_i = 0.015 μM on rat κ-opioid site). However, because of their poor solubility, several compounds could not be tested intravenously in the writhing test. In future, quaternization of the 7-nitrogen, which would direct the compound specifically to peripheral κ-opioid receptors, might aid the development of new peripheral κ-agonists.

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8 Kovaluk, E.A. *et al.* (1998) Novel molecular approaches to analgesia. *Annu. Rep. Med. Chem.* 33, 11–20
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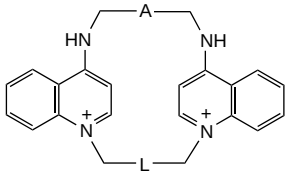
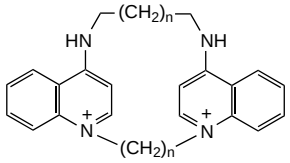
Non-peptidic blockers of apamin-sensitive Ca^{2+}-activated K^+ channels

Small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels occur in many cell types and have a variety of physiological roles. Apamin, a peptidic toxin from bee venom, potently blocks SK_{Ca} channels. However, alternative novel non-peptidic blockers are being sought that could have important therapeutic applications, such as increasing gastrointestinal motility. Moreover, SK_{Ca} channels are involved in the relaxation of blood vessels, and their aberrant expression causes several disorders in myotonic muscular dystrophy. The SK_{Ca} channels are also thought to be responsible for altered responses in the CNS.

Workers from University College London (London, UK) have previously identified a series of *bis*-quinolinium cyclophanes of the general type **(ix)**, as potent blockers of the SK_{Ca} channel[11]. In series **(ix),** A and/or L can be alkylene groups or moieties containing one or two aromatic rings. More recently, the group has reported[12] several *bis*-alkylene cyclophanes **(x)** (*n* = 3–10). These were able to block the SK_{Ca} channels at submicromolar concentrations. The highest activity was observed with the *n* = 5 compound and was significantly decreased in longer and shorter analogues. These results support the previously suggested hypothesis that the linkers do not interact with the channel in a direct way, but control the spatial arrangement of the molecule. In addition to being almost equipotent with apamin for blocking the SK_{Ca} channel in rat sympathetic neurons (IC_{50} = 2.7 ± 0.2 nM), the *n* = 5 compound was also shown to be highly selective for the channel, which makes it a useful tool for further studies.



(ix)



(x)

11 Ganellin, C.R. *et al.* (2000) Synthesis, molecular modelling and pharmacological testing of *bis*-quinolinium cyclophanes: potent, non-peptidic blockers of the apamin-sensitive Ca^{2+}-activated K^+ channel. *J. Med. Chem.* 43, 420–431
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