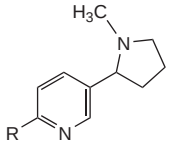
Monitor: molecules and profiles

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

New nicotine derivatives can antagonize its own analgesic action

Nicotine (**i**, R = H) is believed to produce some of its effects through nicotinic acetylcholine (nACh) receptors. Neuronal nicotinic receptors are involved in several physiological processes, including appetite, memory, analgesia, anxiety and other neurological disorders [1–3]. Several side-effects associated with nicotine have led to the search for less toxic nACh agents.



(i-vi)

Glennon and collaborators have reported [4,5] that 6-methylnicotine is more potent than nicotine in *in vivo* assays that are indicative of nicotinic activity, although its affinity is no greater than that of nicotine. In addition, the 6-halogenated analogues of nicotine were found to be more potent than expected on the basis of their affinities.

The same group has now investigated [6] a series of 6-alkylsubstituted analogues of nicotine (compounds **ii–vi**), where the R group ranges from methyl to *n*-pentyl. The compounds were tested in binding experiments as well as in three functional assays: (1) the tail-flick assay (a common test for analgesic properties), (2) spontaneous activity assay in mice, and (3) a substitution in a drug discrimination assay in rats trained to discriminate (–)nicotine from saline vehicle.

Binding data showed that affinity decreases from 6-methylnicotine (**ii**; K_i = 1.8 nM) to 6-*n*-pentylnicotine (**vi**; K_i =72 nM). In the same assay, nicotine showed a K_i value of 1.3 nM. Unexpectedly, in *in vivo* tests (tail-flick and spontaneous activity assays in mice) compound (–)**iii** (R = ethyl, K_i = 5.6 nM) was more potent than nicotine (ED_{50} 2.1 μmol kg^{-1} and 1.4 μmol kg^{-1} versus ED_{50} = 9.9 μmol kg^{-1} and 4.9 μmol kg^{-1} for nicotine, respectively in the two assays), while (–)**iv** (R = *n*.propyl, K_i = 22 nM) was inactive in producing antinociceptive effects up to doses of 70 μmol kg^{-1}. Compounds (–)**v** (R = *n*.butyl, K_i = 21 nM) and **vi** were also inactive in *in vivo* assays.

In further experiments, compound (–)**iv** was found to antagonize the antinociceptive action of 2.5 mg kg^{-1} of (–)nicotine (tail-flick assay; AD_{50} = 4.9 μmol kg^{-1}). By contrast, (–)**iv** did not antagonize either the spontaneous activity or stimulus effects of nicotine at doses up to 35 μmol kg^{-1} and 50 μmol kg^{-1}, respectively.

If multiple subtypes of nACh receptors are involved in the different actions of nicotinic agonists, compound (–)**iv** and other nicotinic competitive antagonists that are able to selectively block different nicotinic effects, could be useful tools in the study of nACh receptor-mediated events.

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Novel antitumour molecules

New antitumour xanthen-9-one-4-acetic acid analogues

Flavone-8-acetic acid (FAA; compound **i**) is a synthetic flavonoid with an unusual pharmacological profile. It is characterized by low activity against fast-growing tumours, such as leukaemias, but broad activity against slow-growing solid tumours. These slow-growing tumours are

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