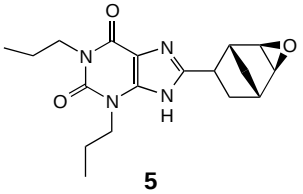
luciferase reporter vector containing androgen DNA response elements, the molecules were shown, unlike bicalutamide, to be full androgen receptor agonists. The authors believe that these molecules represent the first non-steroidal full agonists of androgen receptors reported to date.

A_1 adenosine receptor antagonist

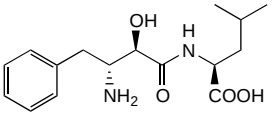
Selective A_1 adenosine receptor antagonists have potential use in the treatment of oedema associated with congestive heart failure. A paper by Petter, R.C. (Biogen, Cambridge, MA, USA) described the highly selective A_1 adenosine receptor antagonist BG9719 (**5**) at the recent *ACS Meeting* in Dallas, TX, USA (Abstr. Medi 094). This potent molecule (K_i = 0.5 nM) is 400, 2,000 and 9,000 times less active at A_{2B}, A_{2A} and A_3 receptor subtypes, respectively, than at the A_1 receptor subtype. The combined potency and selectivity of this compound suggests that it will inhibit proximal-tubule-mediated reabsorption and oppose vasoconstriction of the afferent arterioles in the kidney. Studies using saline-loaded normal rats have shown that BG9719 increases urine output and sodium excretion but does not affect potassium excretion. The drug is presently being evaluated in Phase II clinical trials.



5

Potent nonpeptide aminopeptidase N inhibitors

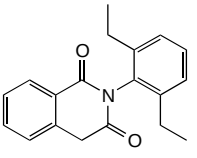
Proteolytic degradation of the extracellular matrix is an important part of the process by which metastasizing tumour cells pass through connective tissue barriers. Aminopeptidase N is an exopeptidase that binds to membranes as an ecto-enzyme. Previous studies have shown that tumour cell invasion is inhibited by monoclonal antibodies to aminopeptidase N, and that bestatin (**6**), a potent inhibitor of aminopeptidase N, inhibits tumour invasion and matrix degradation *in vitro*. Bestatin has also been shown to inhibit metastasis of leukaemia and melanoma in mice.



6

Like several other potent aminopeptidase N inhibitors, bestatin is a pseudodipeptide, which limits its clinical usage because of low bioavailability, proteolytic degradation, biliary excretion and short duration of action. Nonpeptidic analogues of these inhibitors may therefore be useful therapeutic agents.

Miyachi, H. and coworkers have described the discovery of *N*-phenyl cyclic imide derivatives as nonpeptide aminopeptidase N inhibitors [*J. Med. Chem.* (1998) 41, 263–265]. These compounds were shown to be specific inhibitors of aminopeptidase N, with some being more potent than bestatin and other naturally occurring aminopeptidase N inhibitors. The most potent of these molecules, for instance **7** (IC_{50} = 120 ng ml^{-1}), will be useful lead compounds for the future development of low molecular weight, nonpeptidic aminopeptidase N inhibitors for metastasis-preventing therapy.

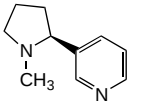


7

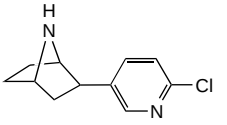
Neuronal nicotinic ACh receptor modulators

Neuronal nicotinic acetylcholine receptors (nAChRs) represent attractive targets for drug discovery [Holladay, M.W. *et al. J. Med. Chem.* (1997) 40, 4169–4194]. Studies in humans and animals have suggested beneficial effects of (*S*)-nicotine (**1**) for several disease states, including Alzheimer's disease, attention deficit hyperactivity disorder, Parkinson's disease, depression and schizophrenia. Moreover, epibatidine (**2**), an alkaloid from the skin of a South American frog, was recently shown to exhibit potent nAChR-mediated analgesic properties in rodents [Badio, B. *et al. Drug Dev. Res.* (1995) 36, 46–59]. Whereas side effects diminish the attractiveness of nicotine or epibatidine as therapeutic agents, the recognition that multiple subtypes of nAChRs exist raises the hope that new chemical entities will be discovered that differentiate beneficial from undesired effects.

The nAChRs are ion channels com-



1

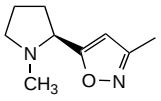


2

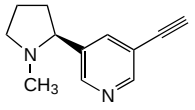
prised of five subunits assembled around a central pore. It has been known for many years that the nAChRs mediating primary motor function in skeletal muscle and those mediating primary neurotransmission in autonomic ganglia are pharmacologically distinct. The existence of multiple subtypes in brain and other tissues has been implicated by the diverse pharmacology exhibited by various ligands. Moreover, numerous nAChR subunits have been identified that are not only differentially distributed in the CNS, but that can also assemble in various combinations in artificial expression systems to form functional ion channels with diverse pharmacological properties. Two of the major subtypes in brain (termed $\alpha4\beta2$ and $\alpha7$ based on their component subunits) have been pharmacologically characterized. While it is clear that neuronal nAChRs are involved in the release of various neurotransmitters, including acetylcholine, dopamine, serotonin, glutamate and

  1359-6446/98/$19.00. PII: S1359-6446(98)01182-9

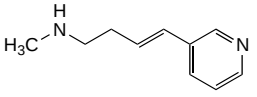
substance P, efforts to correlate specific subtypes with specific neurotransmitters or disease states are incomplete.



3



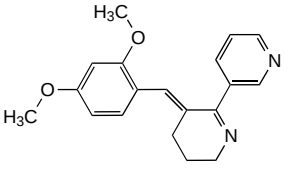
4



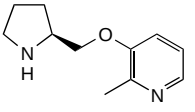
5

Characterization

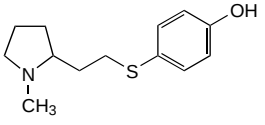
Characterization of novel nAChR modulators in recent years has focused prominently on assays utilizing radioligands specific for the α4β2 subtype, and interactions at α7 have also been measured using radioligand binding. However, the connection between these subtypes and therapeutic endpoints of interest is tenuous. Moreover, selective probes for other putative subtypes in the CNS are not available. By contrast, cell-based functional models exist for measuring interactions with peripheral nAChRs, which mediate effects on the cardiovascular and gastrointestinal systems and on muscle coordination. In addition, dopamine release assays have proven useful for identifying substances with potential in the treatment of Parkinson's disease, and this approach can, in principle, be extended to other diseases for which neurotransmitter augmentation might result in therapeutic benefit. In many instances, whole animal studies have been utilized at an early stage of new compound characterization, both for detecting a desired activity (such as cognition enhancement or analgesia) and also for detecting centrally mediated toxicities (such as hypothermia or locomotor effects). Recently, some programs have implemented high-throughput functional assays at a variety of known or putative nAChR subtypes as a way to identify new lead compounds quickly, although again, it is not clear which nAChR subtypes are of greatest importance for therapeutic indications of interest.



6



7

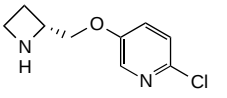


8

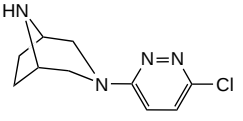
Natural alkaloids

Several natural alkaloids, including nicotine, cytisine, anabasine, anatoxin-a and epibatidine, potently interact with the α4β2 subtype. In principle, all of these could serve as lead compounds for drug discovery, but most also potently interact with other nAChR subtypes, including those in the periphery, and consequently are rather toxic. Following successful medicinal chemistry efforts aimed at preparing compounds with improved therapeutic ratios, several nAChR modulators have recently entered clinical trials or are in advanced preclinical testing for CNS disorders. There are two analogs of *S*-nicotine, ABT418 (**3**) and SIB1508 (**4**), that may have value for Alzheimer's disease and Parkinson's disease, respectively. Also, RJR2403 (**5**), known for some time as a nicotine metabolite, as well as GTS21 (**6**), ABT089 (**7**) and SIB1553 (**8**) [Menzaghi, F. *et al. Soc. Neurosci. Abstracts* (1997) 23, 1200, #477.16] are being investigated for treatment of Alzheimer's disease and other cognitive deficits.

Based on the precedent set by epibatidine, ABT594 (**9**) is under development as a potent, broad-spectrum analgesic agent [Bannon, A.W. *et al. Science* (1998) 279, 77–81]. Structure-activity studies on ABT594 using the mouse hot-plate assay have shown that the azetidine ring and the chloro substituent are crucial for the analgesic effect, whereas the (*R*)-stereochemistry contributes to an enhanced safety profile [Holladay, M.W. *et al. J. Med. Chem.* (1998), 41, 407–412]. Several variants of the epibatidine structure have also been investigated as potential analgesic agents. One recent interesting example is DBO83 (**10**), which shows nAChR-mediated antinociceptive effects in rodent models [Ghelardini, C. *et al. Drug Dev. Res.* (1997) 40, 251–258].



9



10

Currently, efforts are under way to better understand which specific nAChR subtypes are responsible for the beneficial effects of nicotine and the other agents, as well as those responsible for undesirable actions such as addiction and hypothermia. These efforts will be greatly aided by determination of the subunit compositions of minor populations of nAChR subtypes and identification of selective ligands that have suitable, well-defined pharmacokinetic properties. Present indications suggest that work continues to progress on both fronts.

Mark W. Holladay
Neurological and Urological Diseases Research Abbott Laboratories, Abbott Park, IL 60064, USA
tel: +1 847 937 0740
fax: +1 847 937 9195
e-mail: mark.holladay@abbott.com