ELSEVIER

Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 8, 2004

Bioorganic & Medicinal Chemistry Letters

Special Section: Symposium-in-Print

Neuronal Nicotinic Receptors and Ligands

Guest Editors: Rao S. Rapaka and William A. Corrigall

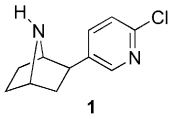
Division of Neuroscience & Behavioral Research, National Institute on Drug Abuse, Room 4282, MSC-9555, 6001 Executive Blvd, Bethesda, MD 20892, USA

Contents

There are many different nicotinic acetylcholine receptor subtypes constructed from a variety of different subunit combinations. This extensive diversity offers an excellent opportunity for chemists who are producing nicotinic ligands. Subunit specific ligands could have wide and varied effects in the laboratory as experimental tools and in the clinic as therapeutic agents.

Nicotine

Progress towards the development of α4β2 nicotinic acetylcholinergic (nACh) receptor pharmacophores is reviewed from the early Beers and Riech model to the more recent vector models.

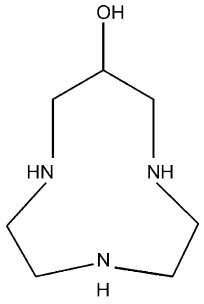


1

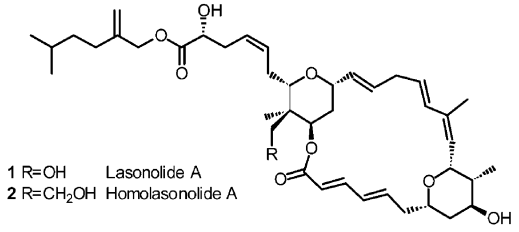
Epibatidine (**1**) is a potent but nonselective nAChR agonist. Its biological effects appear to be mediated largely by α4β2 nAChRs. Surprisingly, only a limited number of epibatidine analogues have been synthesized and evaluated in in vitro assays. Even fewer analogues have received in vivo pharmacological evaluation. In this paper, SAR studies directed toward epibatidine analogues will be reviewed.

Consideration of the activation and desensitization properties of neuronal nicotinic acetylcholine receptors (nAChRs) predicts that there should be a range of concentrations over which low ambient levels of agonist can continuously open nAChR channels. These findings support the idea that postsynaptic nAChRs may participate in unconventional cellular signaling mediated by the release of acetylcholine from diffusely distributed non-synaptic cholinergic varicosities.

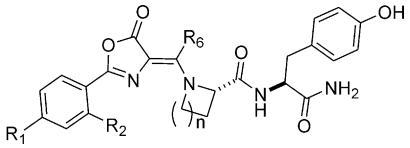
REGULAR COMMUNICATIONS



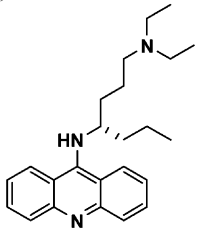
Antitumor activity evaluations of nickel and cobalt complex with triaza macrocyclic ligand were presented.



Homolasonolide A (**2**) was synthesized, and it was found that **2** was less active than lasonolide A (**1**).

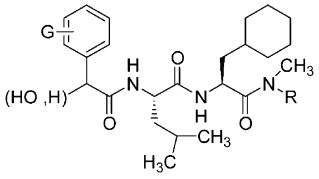


The preparation and structure–activity relationships (SARs) of potent and selective small molecule inhibitors of bacterial methionyl-tRNA synthetase (MetRS) derived from an oxazolone–dipeptide scaffold are described.

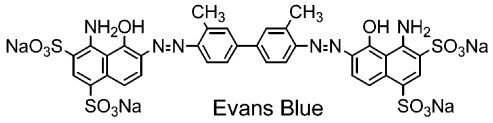


10

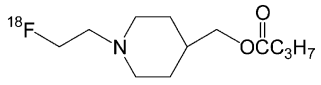
Compounds such as **10** ($IC_{50} = 9$ nM) are high-affinity ligands of the $\alpha_2\delta$ subunit of voltage gated calcium channels.

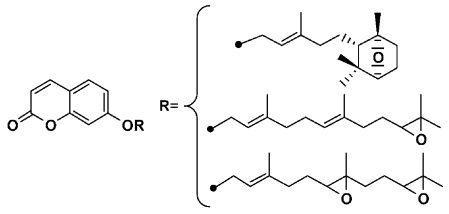


Structure–activity relationships of γ-secretase inhibitors are reported.

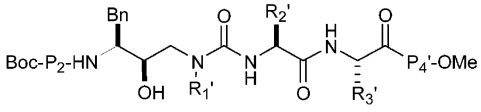


Commonly used dyes including Evans Blue and Trypan Blue were found to inhibit protein tyrosine phosphatases. Of the 13 dyes tested, four exhibited IC_{50} of less than 10 μM, with Evans Blue lowest IC_{50} of 1.3 μM against PTP1B.

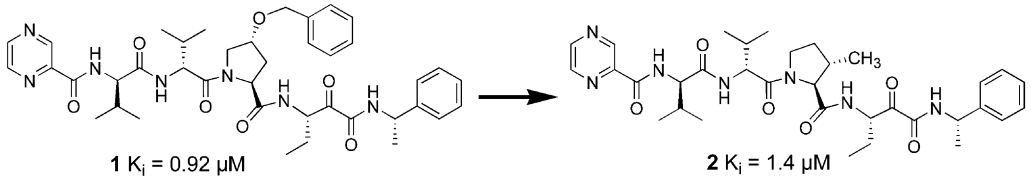




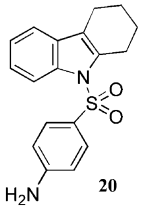
The coumarin core proved a good starting structure for the design of new SHC inhibitors. An epoxide function at the end of the prenyl chain increased the inhibitory effect, revealing a critical detail for molecular recognition.



(Hydroxyethyl)urea peptidomimetics are potent inhibitors of γ-secretase that are readily accessible. Systematic alteration of P2–P4′ revealed that the corresponding S2–S4′ active site pockets accommodate a variety of substituents, consistent with the fact that this protease cleaves a variety of single-pass membrane proteins. A compound spanning P2–P3′ was identified as a low nM inhibitor of γ-secretase activity both in cells and under cell-free conditions.

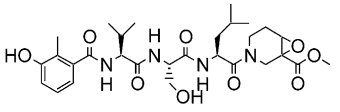


A series of potent HCV NS3·4A protease inhibitors incorporating novel 3-substituted proline moieties at the P_2 position are described.



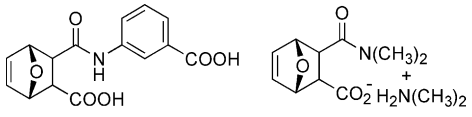
20

N_9-(4-Aminobenzenesulfonyl)-1,2,3,4-tetrahydrocarbazole (**20**; p$A_2 = 7.0$ for antagonism of cAMP hydrolysis) was demonstrated to represent a member of a novel class of 5-HT$_6$ receptor antagonists.



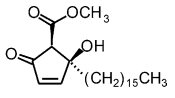
Proteasome inhibitor **2**

A series of C-terminal methyl 3,4-epoxypiperidine-3-carboxylate tripeptide derivatives were synthesized to evaluate their inhibitory capacity against active sites of the proteasome.

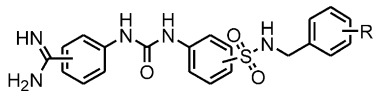


10 **16**

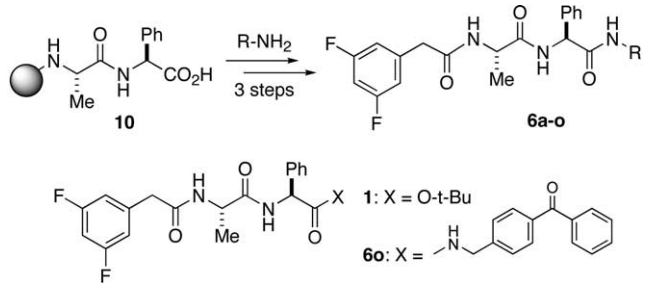
Fourteen modified norcantharidin analogues have been synthesized and screened for their ability to inhibit the serine/threonine protein phosphatases 1 and 2A. The most potent compounds found were **10** (PP1 $IC_{50} = 13 \pm 5$ μM; PP2A $IC_{50} = 7 \pm 3$ μM) and **16** (PP1 $IC_{50} = 18 \pm 8$ μM; PP2A $IC_{50} = 3.2 \pm 0.4$ μM). Overall, only analogues possessing at least one acidic residue at the former anhydride warhead displayed any PP1 or PP2A inhibitory action.



Untenone A (1)
IC_{50} 4.3 μM



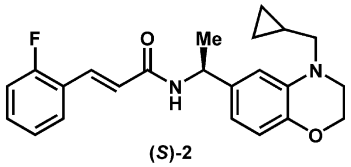
A novel structural class of antimalarial compounds was discovered. The most potent compound was more active (8 nM) in an antimalaria proliferation assay as Chloroquine (17 nM).



Parallel synthesis of the C-terminal modified DAPT (**1**) derivatives **6a**–**o** was accomplished by condensation of the polymer bound *N*-acylamino acid **10** with several amines.

A unique peptide sequence of HGGHHG screening from a combinatorial synthetic peptide library showed a good chelating ability to bind a transition metal on a chip better than hexa-His peptide. It was directly conjugated with a His-Tagged proteins onto a chip in a mild aqueous solution and can be used this chip as a high throughput technique for protein array in order to detect and purify the His-Tagged proteins.

(*S*)-*N*-[1-(4-Cyclopropylmethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl]-3-(2-fluoro-phenyl)-acrylamide ((*S*)-**2**) was identified as a potent and efficacious KCNQ2 opener. This compound demonstrated significant activity in reducing neuronal hyperexcitability in rat hippocampal slices, and the inhibition mediated by (*S*)-**2** was reversed by the KCNQ blocker linopirdine.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by ***Indraneel Ghosh****, Department of Chemistry, University of Arizona.* The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htB1 (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htB1 (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1389].

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X