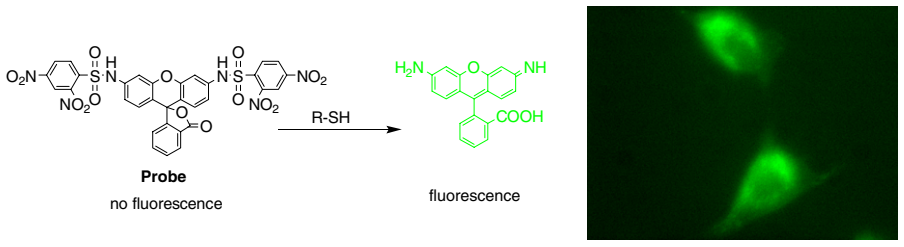
ELSEVIER

Bioorganic & Medicinal Chemistry Letters

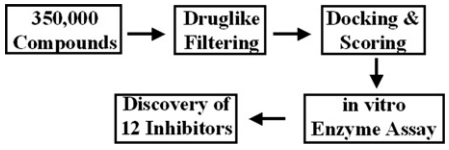
Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 7, 2008

Contents

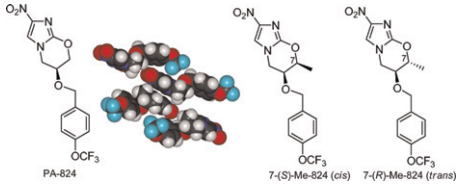
ARTICLES

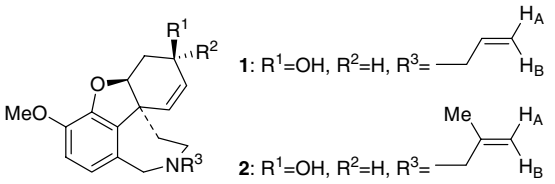


Fluorogenic probe for the detection of intracellular thiols.

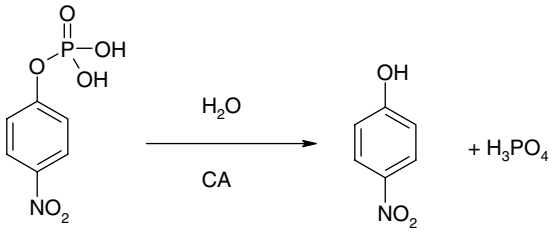


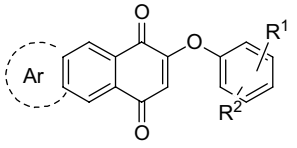
We have discovered 12 novel PRL-3 inhibitors by means of a computer-aided drug design protocol involving homology modeling of the target protein and the virtual screening with docking simulations.





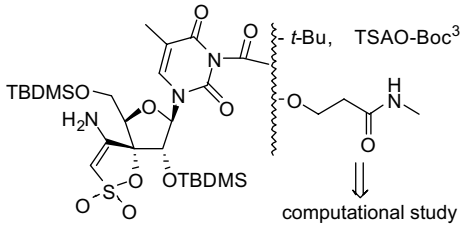
N-Allylnorgalanthamine (**1**) and *N*-(14-methylallyl)norgalanthamine (**2**) inhibit AChE more than the approved drug galanthamine.

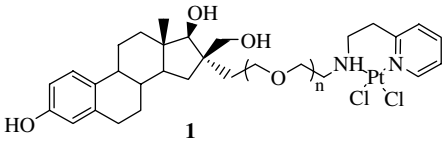




The parallel synthesis of new anti-parasitic compounds is described.

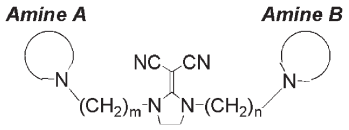
The synthesis and the biological evaluation of the anti-HIV-1 activity of TSAO-Boc^{3}T (**8**) are described. The computational analysis showed that *N*-3 Boc group promotes new interactions in the binding site of the enzyme leading to a good inhibitory value.



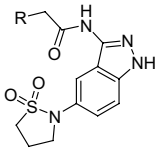


1

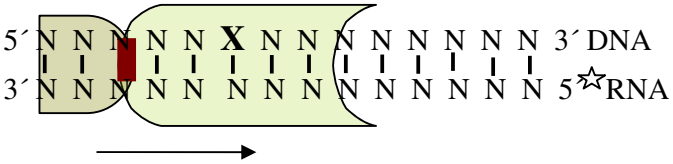
The synthesis of a series of 17β-estradiol-platinum(II) hybrid molecules is reported. The hybrids are made of a PEG linking tether chain of various length and a 2-(2′-aminoethyl)pyridine ligand. MTT assays showed that the derivative with the longest PEG chain showed the best activity against breast cancer cell lines (MCF-7 and MDA-MB-231).



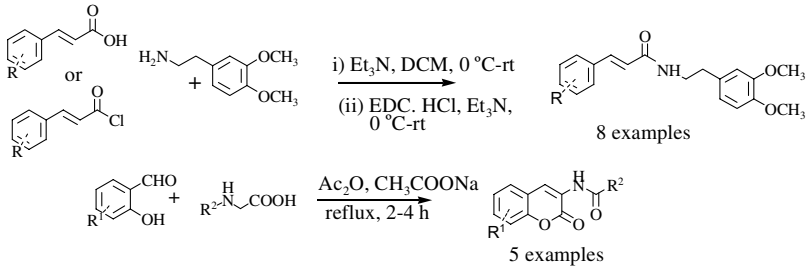
Synthesis of a series of imidazolidinylidene propanedinitrile derivatives as a potent H_3 receptor antagonist is described.

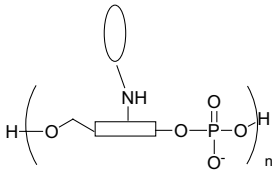


A novel series of 3,5-diaminoindazoles were prepared and found to be CDK inhibitors. Potent inhibitors against CDK1 and CDK2 were obtained by the introduction of $1\lambda^6$-isothiazolidine-1,1-dioxide at 5-position of indazole. Anti-proliferative activities of compounds were evaluated using EJ, HCT116, SW620, and A549 cancer cell lines.

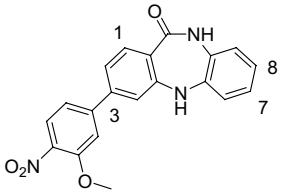


Schematic model of RNase H enzyme (in green) with its cleaving site in red. The horizontal arrow indicates direction of movement of the enzyme and the star indicates P^{32} labelling of the RNA to allow visualization of RNA fragments by gel electrophoresis. The study shows that it is possible to introduce modified nucleotides in an antisense oligonucleotide across RNA cleavage sites, which maintain or even improve RNA cleavage by RNaseH.

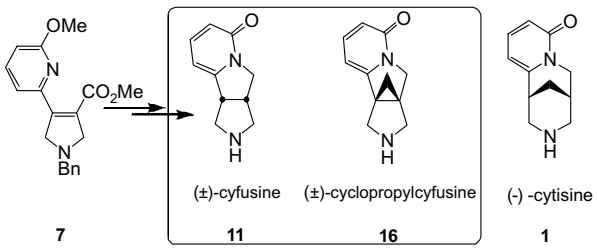


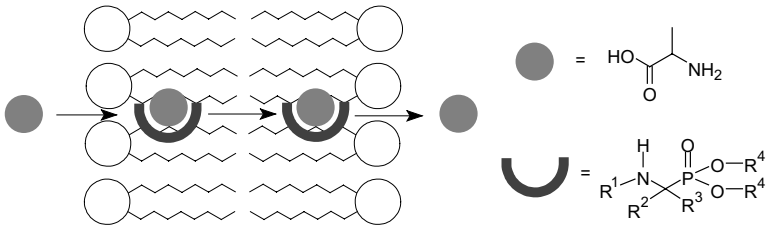


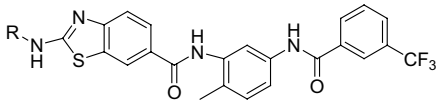
The synthesis of oligomers having several DNA-intercalating units linked by phosphodiester bonds is reported.

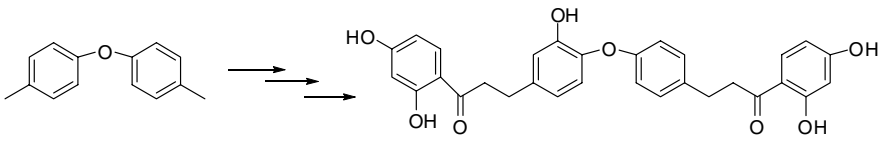


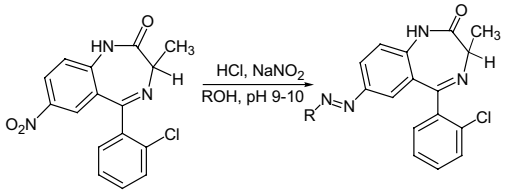
A novel fused tricyclic analog (**11**) of cytisine has been prepared (coined 'cyfusine') and determined to have high affinity at neuronal nicotinic acetylcholine receptors. A [3 + 2] cycloaddition protocol permitted entry into a 3,4-differentially difunctionalized dihydropyrrole (**7**). The penultimate cyclization was accomplished using the modified Van Tamelen conditions developed in our earlier synthesis of (±)-cytisine. Sequential ring-forming reactions ([3 + 2] cycloaddition/cyclopropanation/pyridone cyclization) gives a unique cyclopropyl analog (**16**) possessing a skeleton isoatomic with that of cytisine.

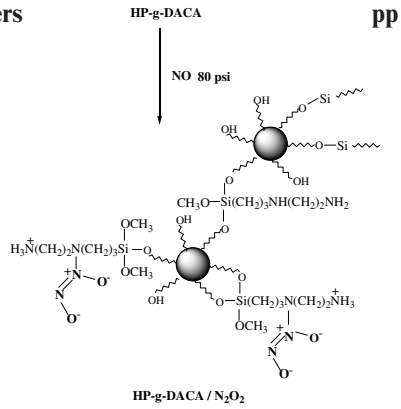


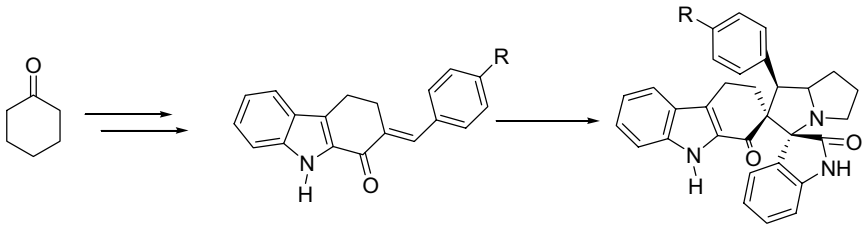


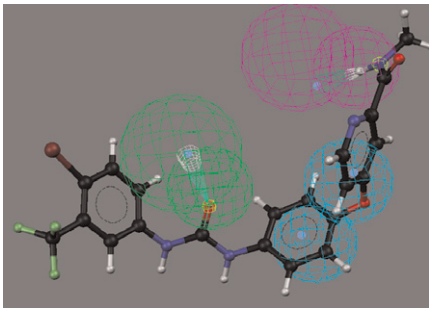


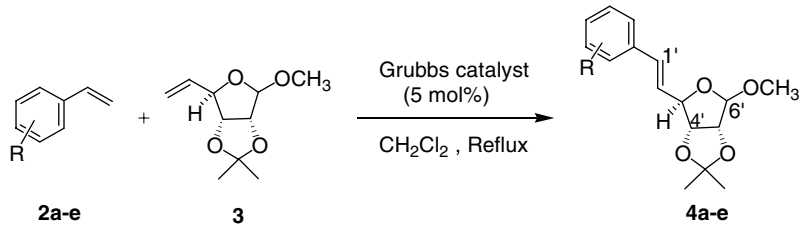




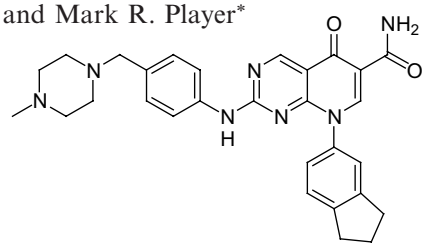


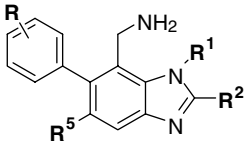


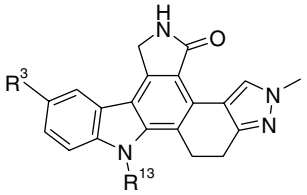




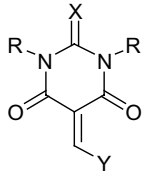
Novel analogues of (+)-varitriol have been synthesized via olefin cross-metathesis reaction using Grubb's catalyst. Newly synthesized compounds were screened for cytotoxicity.



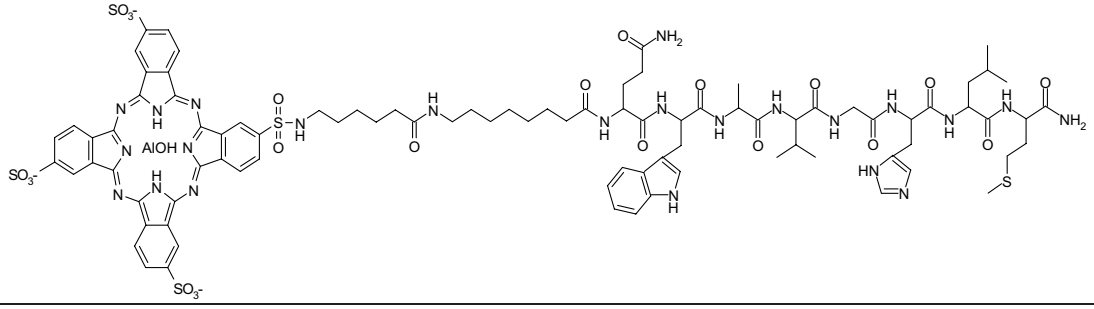


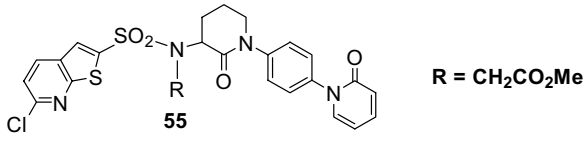


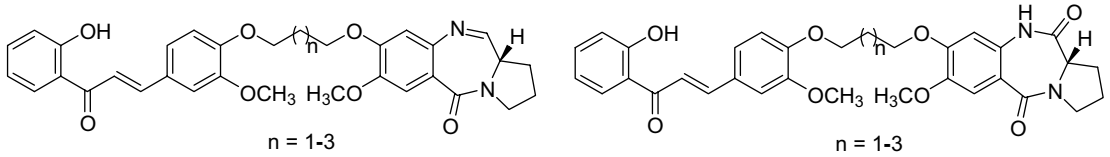
fused pyrrolodihydro-indazolocarbazole

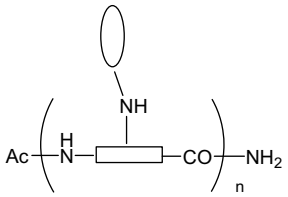


K_i = 50 nM



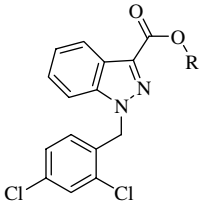


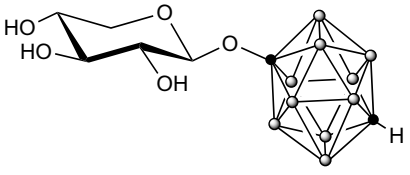


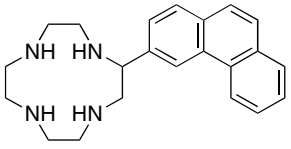


The synthesis of oligomers having several chromophore units linked by amide bonds is reported.

Polyhydric alcohol derivatives of the anticancer agent lonidamine (LND) have been synthesized. The increased water solubility showed by prodrugs **4**, **7**, and **25** together with their log *P* values (2.19, 2.55, and 2.54, respectively) and chemical stability might be beneficial for prodrugs absorption after oral administration. Moreover, the new prodrugs undergo enzymatic hydrolysis in plasma and release LND demonstrating that they are promising candidates for in vivo investigations.

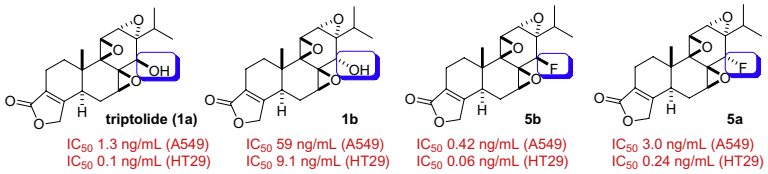


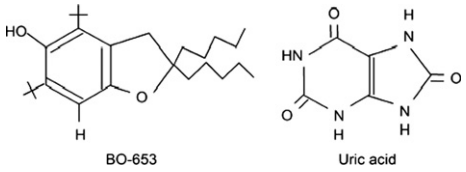




EC_{50} = 1.3 μM

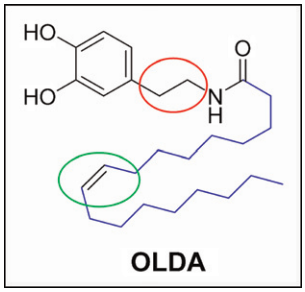
A focused library of C2-substituted-1,4,7,10-tetraazacyclododecanes have been synthesized and shown to have significant in vivo anti-protozoal activity against both trypanosome and malaria parasites.

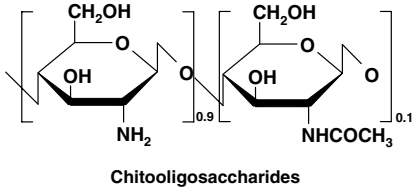




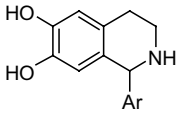
BO-653 was assessed to be much less potent than uric acid by ORAC method, whereas BO-653 exerted much higher antioxidant activity than uric acid against plasma lipid peroxidation.

The structural features of an anthrax lethal factor inhibitor, *N*-oleoyldopamine (OLDA) have been probed. The oleic acid moiety is critical, but, more interestingly, the presence of the double bond and its geometry were found to play an essential role.



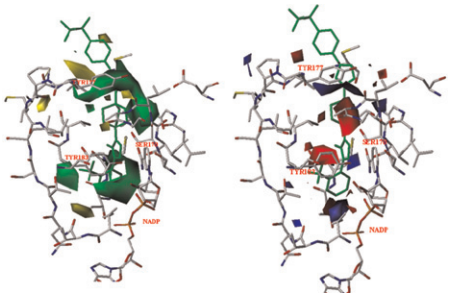


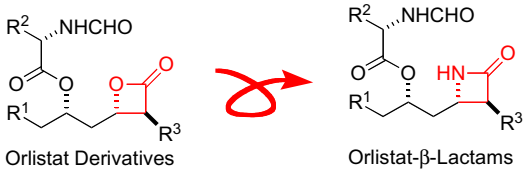
A 90-MMWCOS (MW 1000–5000 Da) showed the highest renin-inhibitory activity with IC_{50} value of 0.51 mg/mL and acted as competitive inhibitor with K_i value of 0.28 mg/mL by Lineweaver-Burk and Dixon plots.

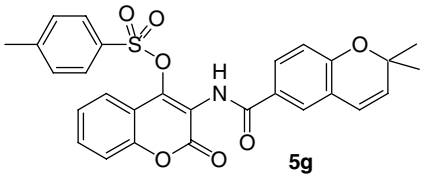


6: Ar = 4-methylphenyl
24: Ar = 3-chlorophenyl
36: Ar = 2-naphthyl

The syntheses and anti-HIV activities of 1-aryl-tetrahydroisoquinoline analogs were described in this paper. Compounds **6**, **24**, and **36** showed potent anti-HIV activities with TI values larger than 95, 159, and 130, respectively.

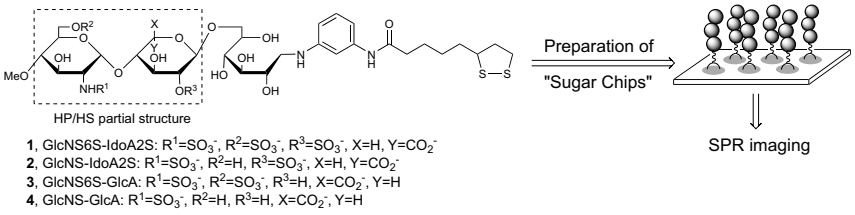


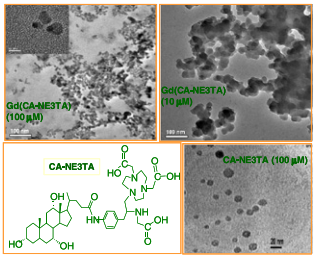




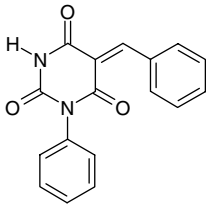
5g

The synthesis and biological activity of a new series of denoviose-coumarins related to novobiocin are described.





A novel series of barbituric acid derivatives were identified as selective inhibitors of α4β7 MAdCAM (mucosal addressin cell adhesion molecule-1) interactions via a high throughput screening exercise. These inhibitors were optimized to submicromolar potencies in whole cell adhesion assays, retaining their selectivity over other integrins.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X