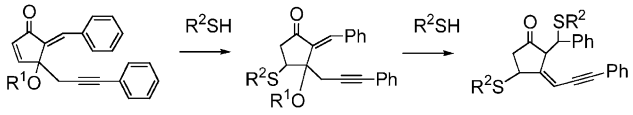
ELSEVIER

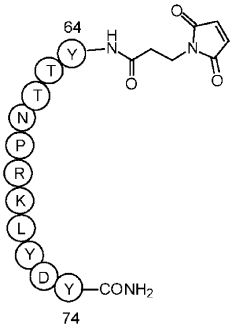
Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 4, 2004

Bioorganic & Medicinal Chemistry Letters

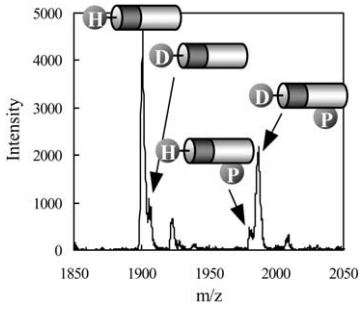
Contents

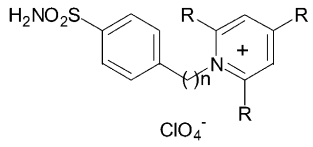
COMMUNICATIONS

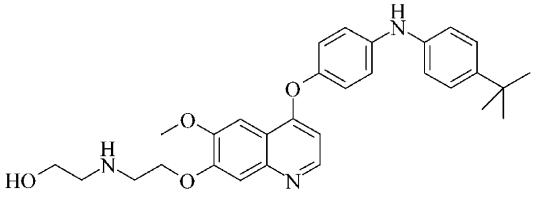


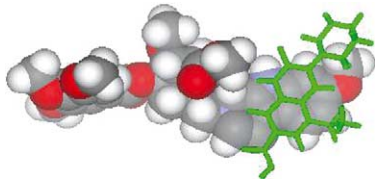


Three peptide fragments of the kringle 5 region of plasminogen and their respective N- and C-terminus maleimido derivatives conjugated to Cys34 of human serum albumin were evaluated in vitro using a human umbilical vein endothelial cell (HUVEC) migration assay and a human plasma stability assay. The N-terminus maleimido derivative of the 64 to 74 segment of kringle 5 conjugated to human serum albumin possessed remarkable in vitro anti-migratory activity.

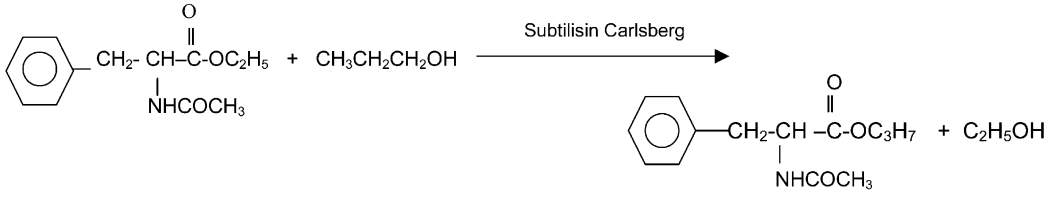




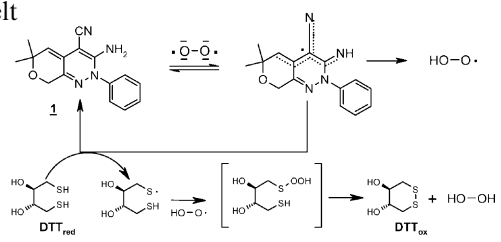




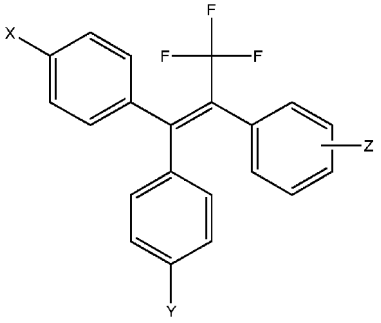
Here we show by molecular modelling that inhibitors of MDR have affinity for substrates of MDR transporters.



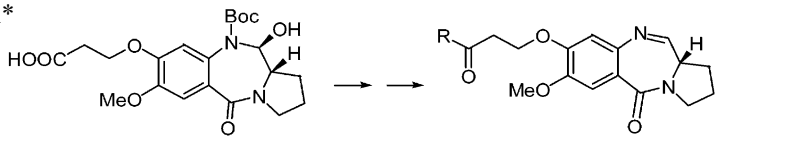
The increase in reaction rates of subtilisin-catalyzed transesterification was achieved by three phase partitioning of the enzyme, followed by either (a) lyophilization in the presence of polyethylene glycol and trehalose or (b) washing the precipitate with *t*-butanol.



Pyridazine analogues cause catalytic oxidation of the reducing agent, generating hydrogen peroxide that oxidizes the active site cysteine on the enzyme, leading to enzyme inactivation.

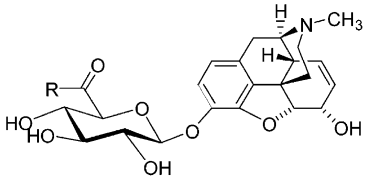


Pharmacophore search for post-coital antifertility activity of 1-trifluoromethyl-1,2,2-triphenylethylenes using E-state index.

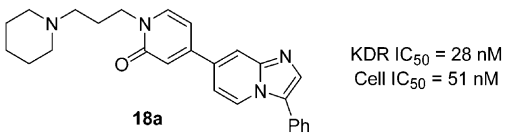


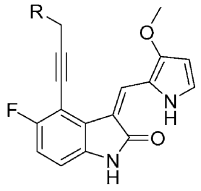
PBD Building Block (**11**) PBD Conjugates: R = Pyrrolidine (**12**), Piperidine (**13**), Indoline (**14**) and Isoindoline (**15**)

A series of novel pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) analogues **12**–**15** has been prepared from a common functionalized building block **11** that can be conveniently synthesized on a large scale and in optically pure form. Isoindoline analogue **15** is the most cytotoxic, has the highest DNA-binding affinity, and shows significant activity in the NCI in vivo hollow fibre assay.

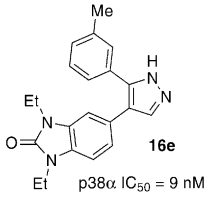


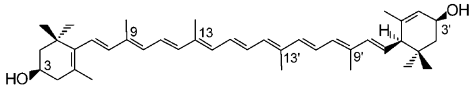
A morphine-3-glucuronide conjugate to octylamine is a lethal compound even at ng/kg doses. However, its closely related amide analogue lacking the octyl chain acts as opioid antagonist in a similar pattern than naloxone.



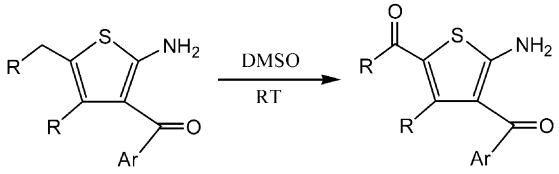


The synthesis and evaluation of a novel and potent series of inhibitors of CDK2 from the oxindole class is described. The members of this new class have heteroatom substituted proprargyl and/or homoproparyl appendages at their C-4 position. The crystal structure of CDK2 complexed with an analogue from this series has been determined and gives insight to the increased potency.

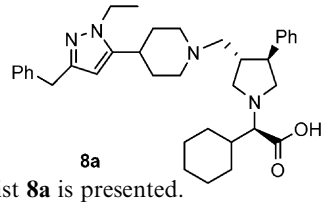




The formation and identification of 3′-epilutein in processed food is reported.

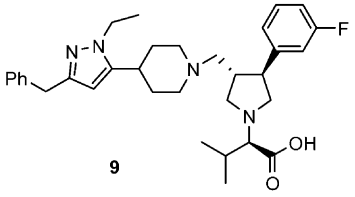


Solutions of 2-amino-3-aroyl-4,5-dialkylthiophenes in DMSO undergo regioselective oxidation of benzylic carbon and are rapidly degraded by horse radish peroxidase and human liver microsomes.



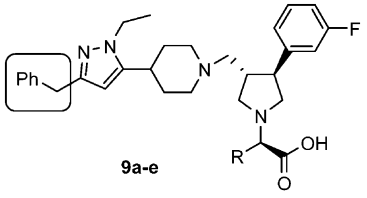
8a

The discovery and SAR study of CCR5 antagonist **8a** is presented.



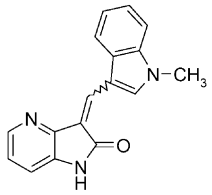
9

Research leading to CCR5 antagonist **9** and ensuing SAR studies are presented.



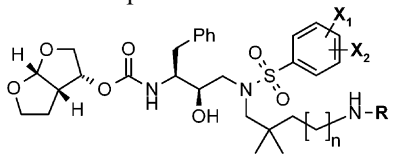
9a-e

Extensive SAR studies on the benzyl segment of **9a**–**e** are presented.

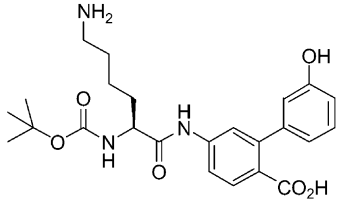


3

The discovery, synthesis, potential binding mode, and in vitro kinase profile of 3-(3-bromo-4-hydroxy-5-(2′-methoxyphenyl)-benzylidene)-5-bromo-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one, 3-[(1-methyl-1*H*-indol-3-yl)methylene]-1,3-dihydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one and related analogues as potent TrkA inhibitors are discussed.

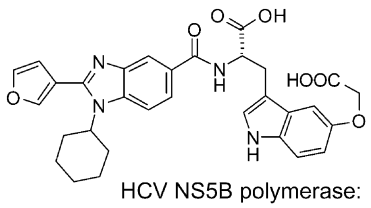


A novel series of P1′ chain-extended arylsufonamides was synthesiszed and evaluated for wild-type HIV protease inhibitory activity and in vitro antiviral activity against wild type virus and two protease inhibitor-resistant mutant viruses. All of the compounds showed dramatic increases in enzyme activity as compared to the currently marketed HIV protease inhibitors amprenavir, indinavir, and nelfinavir. In addition, significant improvements in antiviral potencies against wild type and the two mutant viruses were also realized.

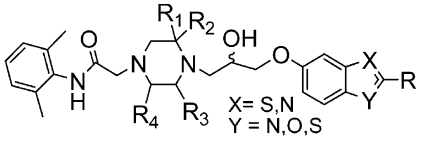


5 IC_{50} = 0.02 nM

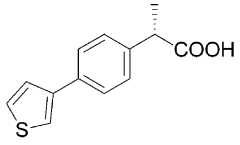
Tetrapeptide KLYD derived from kringle 5 has been shown to capture antiangiogenic activities of kringle 5 in vitro. Further simplification by replacement of the two central amino acids with a 4-aminobenzoic acid spacer group provide compounds with similar in vitro properties to kringle 5 which are able to displace radiolabeled protein from a high affinity binding site on endothelial cells.



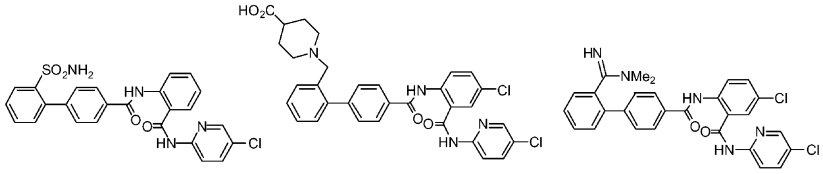
HCV NS5B polymerase:
IC_{50} = 0.019 μM



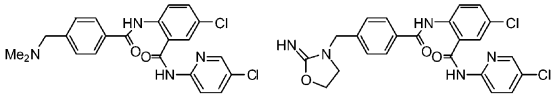
We describe the synthesis of novel fatty acid oxidation inhibitors as potential metabolic modulators for the treatment of stable angina.



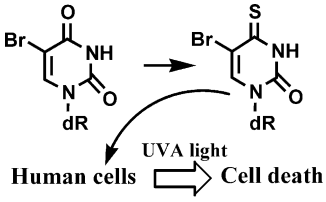
An efficient process for the preparation of *S*-4-(3-thienyl)phenyl-α-methylacetic acid, an enantiomerically pure intermediate of recently approved NSAID atliprofen is reported. The pharmacologically active isomer, *S*-4-(3-thienyl)phenyl-α-methylacetic acid was compared with *S*-ibuprofen by docking studies on COX enzyme structures followed by biological evaluations.



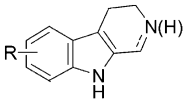
Anthranilamide-based factor Xa inhibitors incorporating substituted biphenyl P4 motifs were designed and synthesized.



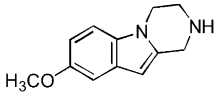
Anthranilamide-based factor Xa inhibitors with improved activity in human plasma thrombin generation assay were designed and synthesized.



The chemical synthesis and cellular incorporation of 4-thio-5-bromo-2′-deoxyuridine (**3a**) are reported, offering therapeutic potential for UVA-induced cell killing.

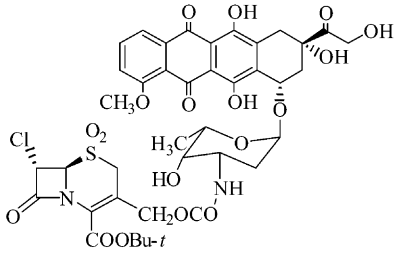


The role of aryl substitution, ring-opening, ring-expansion, and translocation of the piperidine N atom on the I_2 affinity of 3,4-dihydro- and/or 1,2,3,4-tetrahydro-β-carbolines was examined.

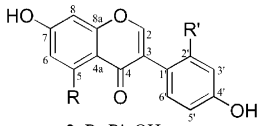


3c

1,2,3,4-Tetrahydropyrazino[1,2-*a*]indole **3c** (8-OMe THPI) has been identified as a novel high affinity ($K_i = 6.2$ nM) I_2 imidazoline receptor ligand with >1000 fold selectivity over I_1 imidazoline and α_2-adrenergic receptors.

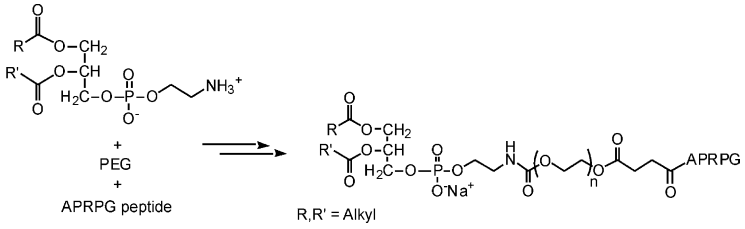


The synthesis and biological properties of doxorubicin prodrug on the basis of cephalosporanate sulfone esters are described.

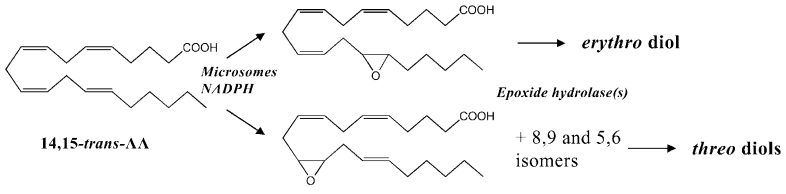


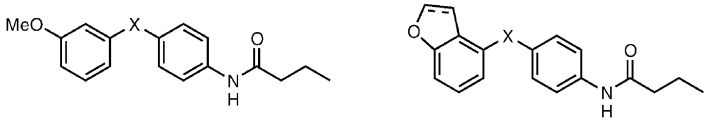
2: R=R'=OH
3: R=OH, R'=OMe
4: R=R'=H
6: R=H, R'=OH

One new isoflavone and several known compounds were isolated from *Crotalaria pallida* and *C. assamica*, respectively. Their anti-inflammatory effects were discussed in this present paper.

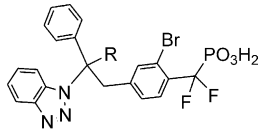


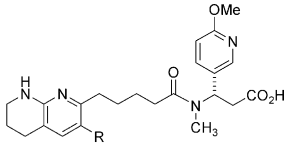
For the purpose of cancer antineovascular therapy, a novel angiogenesis-targeted peptide, Ala-Pro-Arg-Pro-Gly, (APRPG) was attached to hydrophobized polyethylene glycol (distearoylphosphatidylethanolamine [DSPE]-PEG). Liposome modified with this DSPE-PEG-APRPG conjugate highly accumulated in tumor of tumor-bearing mice.



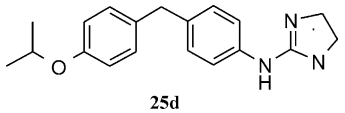


A series of 4-substituted anilides displaying agonism at human melatonin receptors is reported. Several butyramides in the series demonstrate both subnanomolar MT_2 binding affinity and MT_2 selectivity of greater than 70-fold over the MT_1 receptor.





A series of $\alpha_v\beta_3$ antagonists containing 3-substituted tetrahydro-[1,8]naphthyridine were studied. A comparison of their in vitro IC_{50} values to the electron properties of the 3-substituents revealed a good linear Hammett correlation ($\rho = -1.96$, $R^2 = 0.959$).



25d

The 2-(phenylamino)imidazoline **25d** was found to be a high affinity, selective prostacyclin receptor antagonist which demonstrated analgesic activity in the rat.

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).

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