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Bioorganic & Medicinal Chemistry Letters

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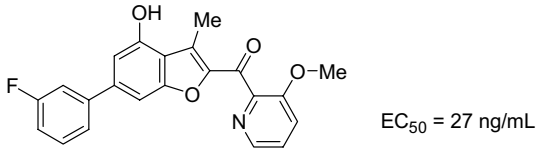
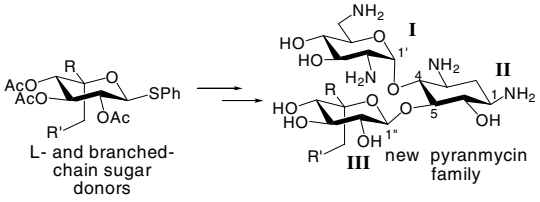
Contents

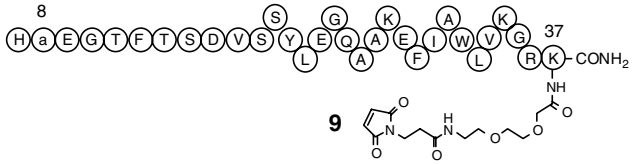
COMMUNICATIONS



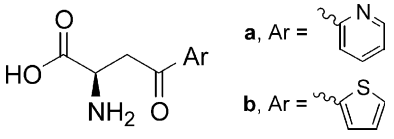
A compound library for structure optimization was synthesized employing solution-phase parallel synthesis to find highly potent derivatives.



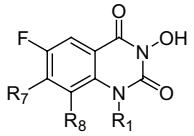
The syntheses of a challenging branched-chain sugar and several L-sugars have been accomplished. Their application in the studies of the antibacterial activity of pyranmycins is reported, which could provide new strategies for the future design of aminoglycoside antibiotics.



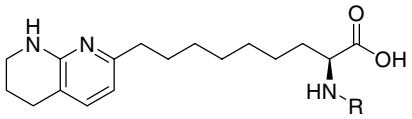
A series of analogs of GLP-1(7–36) amide containing a *N*ε-(2-{2-[2-(3-maleimidopropylamido)ethoxy]ethoxy}acetyl)-lysine has been synthesized and the resulting derivatives were bioconjugated to Cys34 of human serum albumin (HSA). The GLP-1-HSA bioconjugates were analyzed in vitro to assess the stabilizing effect of bioconjugation in the presence of DPP-IV as well as GLP-1 receptor binding and activation. Compound **9** (CJC-1131) having the point of attachment to albumin at the *C*-terminal of GLP-1 and a D-alanine substitution at position 8 was identified as having the best combination of stability and bioactivity.



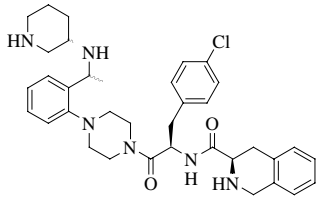
New *N*-heteroarylcarbonylalanines of the D-series were stereoselectively prepared from enoates derived from D-mannitol. Their activities in binding and functional assays for the NMDA sub-type of glutamate receptors are described.



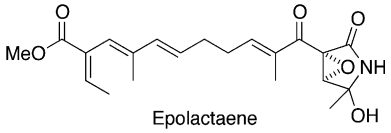
The synthesis and SAR of the 3-hydroxyquinazoline diones, a novel class of bacterial topoisomerase inhibitors, is reported.



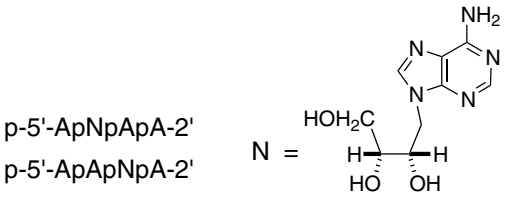
A series of $\alpha_v\beta_3$ receptor antagonists lacking the amide bond of previously-reported 'chain-shortened' compounds is described. Replacement of the lone amide bond with two methylene groups in this series yields more lipophilic compounds that have longer half-lives, lower clearance, and greater oral bioavailability when administered to dogs.

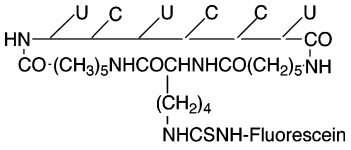


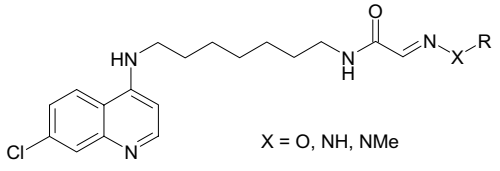
13g, EC_{50} = 3.8 nM



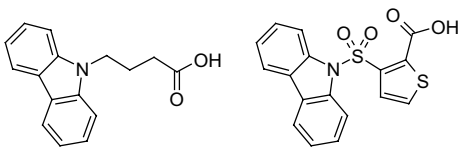
Epolactaene derivatives were synthesized and their ability to inhibit the growth of human cancer cell lines was tested. These derivatives were further analyzed for their ability to affect human heat shock protein 60 (Hsp60). We discovered the structural characteristics important for the ability to bind to Hsp60 and the fundamental role of α,β-unsaturated ketone in inhibiting Hsp60 chaperone activity.

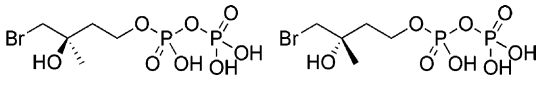


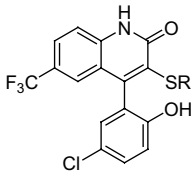


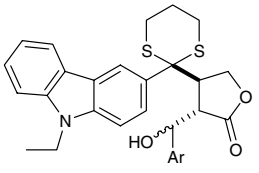


Low micromolar human A-FABP inhibitors were found by utilizing a fluorescence polarization assay, X-ray crystallography and modeling. The carbazole- and indole-based inhibitors displayed approximately 10-fold preferences over human H-FABP and E-FABP, and are highly selective against I-FABP. This communication describes the SAR for drug-like synthetic inhibitors of human A-FABP.

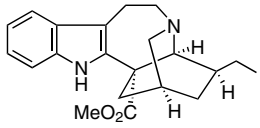




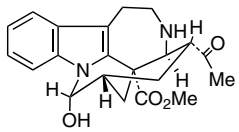




The inhibitory activity of lignanolides and intermediates on HIV replication, NF-κB and Tat dependent HIV-LTR activation is evaluated.

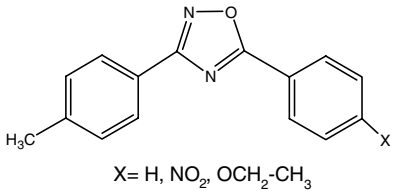


coronaridine

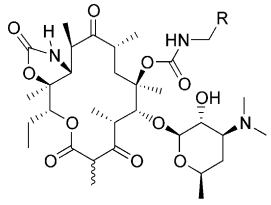


dippinine B

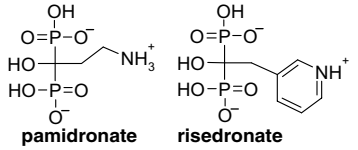
Five ibogan alkaloids (coronaridine, heyneanine, 19-*epi*-heyneanine, dippinine B, and dippinine C), out of a total of 25 tested, showed appreciable activity in reversing resistance in vincristine-resistant KB cells.



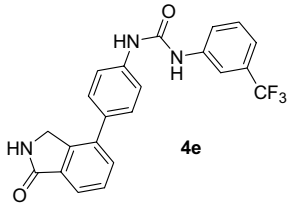
A novel and convenient microwave-assisted synthesis of 1,2,4-oxadiazoles is described. Conventional heating and microwave irradiation of the reactions are compared. Moreover, the importance of some coupling reagents was evaluated.



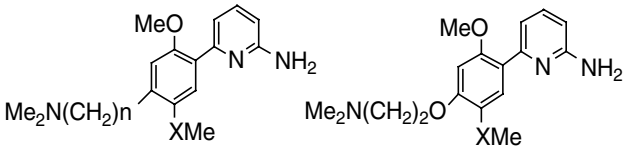
A new series of ketolides is reported, which features the use of a C-6 carbamate for tethering the arylalkyl sidechain to the macrolide core. The best members of this series display in vitro and in vivo activity comparable to telithromycin.



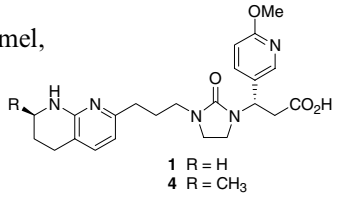
Bisphosphonates were tested as inhibitors of *Trypanosoma cruzi* hypoxanthine-guanine phosphoribosyltransferase by computational modeling and enzymatic assays. The two most potent inhibitors were **pamidronate** and **risedronate** with K_i values of 50.6 and 23.2 μM, respectively.



The evaluation of KDR kinase inhibitor **4e** (IC_{50} 7 nM) and related analogs is reported.

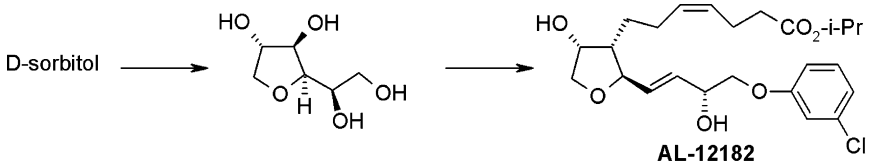


The synthesis and nNOS/eNOS activity of 6-(4-(dimethylaminoalkyl)/-(4-(dimethylaminoalkoxy)-5-ethyl-2-methoxyphenyl)-pyridin-2-ylamines and 6-(4-(dimethylaminoalkyl)/-(4-(dimethylaminoalkoxy)-2,5-dimethoxyphenyl)-pyridin-2-ylamines **1**–**8** are described. These compounds are potent inhibitors of the human nNOS isoform.

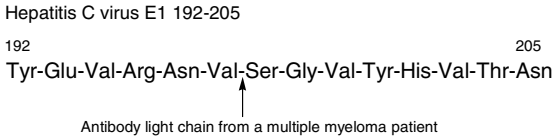


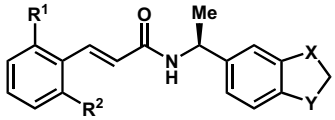
Subtle modifications were incorporated into the structure of clinical candidate **1**. These changes were designed to maintain potency and selectivity while inducing changes in physical properties leading to improved pharmacokinetics in three species. This approach led to the identification of **4** as a potent, selective $\alpha_v\beta_3$ receptor antagonist that was selected for clinical development based on an improved PK profile and efficacy demonstrated in an in vivo model of bone turnover.

Syntheses and excellent anti-MRSA activities of the mansonone F analogs are reported. In addition, the minimal structural requirements for its anti-MRSA activities as well as its structure–activity relationship including the C3 substituents effects on anti-MRSA activity are also described.



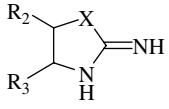
3 μg dose, 40% drop in monkey IOP





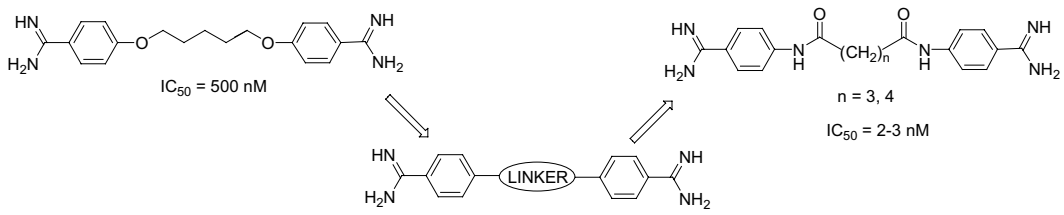
(*S*)-3: R^1 = Cl, R^2 = H; X = Y = O
(*S*)-4: R^1 = R^2 = F; X = CH_2; Y = O
(*S*)-5: R^1 = F, R^2 = H; X = CH_2; Y = NH

The synthesis and the KCNQ2 opener activity of a novel series of acrylamides are described.

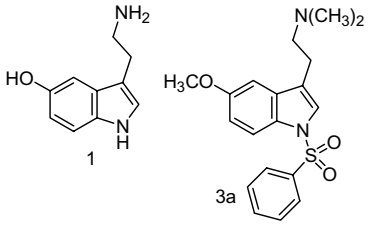


X = S, CHR_1

Synthesis and evaluation of pyrrolidin-2-imines (X = CHR_1) and 1,3-thiazolidin-2-imines (X = S) as inhibitors of nitric oxide synthase (NOS) are discussed.

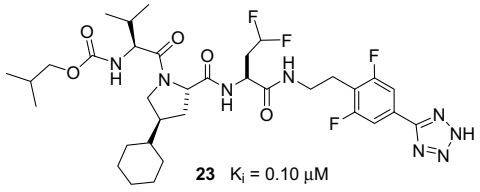


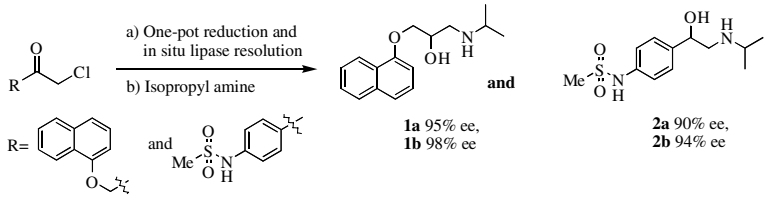
Modifications of the linker between the benzamidine moieties led to the discovery of several new highly potent anti-*Pneumocystis carinii* agents.

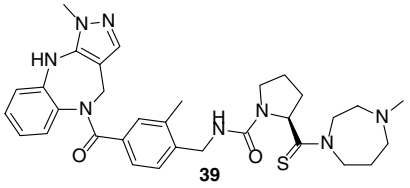


A homology model of human 5-HT$_6$ receptors was constructed and N_1-arylsulfonyltryptamines (e.g., **3a**) were found to bind in a different manner than the tryptamine agonist serotonin (**1**).

The development of phenethylamide **23** (K_i 0.1 μM) is described together with the pharmacokinetics behavior of this and related compounds.







The first non-peptide, low molecular weight agonists of the hormone oxytocin (OT) are reported. The most potent compound, **39**, showed an $EC_{50} = 33$ nM and was selective for the OT receptor.

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 htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].

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