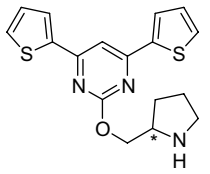
ELSEVIER

Bioorganic & Medicinal Chemistry Letters

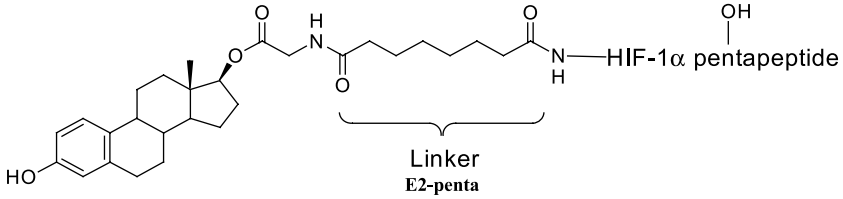
Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 11, 2005

Contents

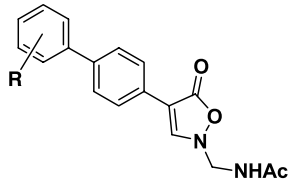
COMMUNICATIONS



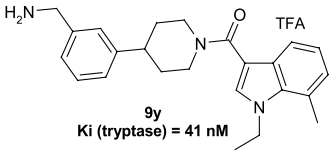
K_S = 450000 M^{-1}
K_R = 190000 M^{-1}

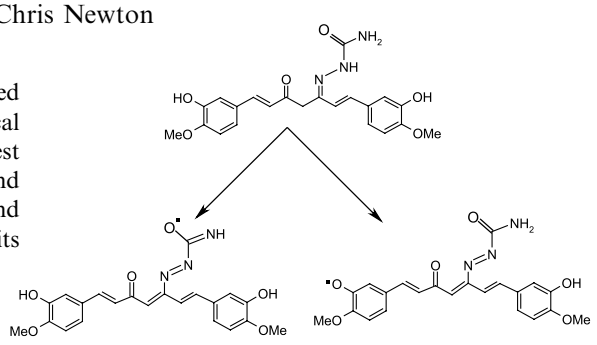


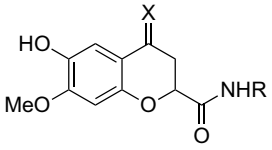
E2-penta is an estradiol-peptide chemical chimera (ER-PROTAC) that binds to the estrogen receptor and targets it for proteolysis via the ubiquitin-mediated proteasome pathway. We show that E2-penta is a novel chemical genetic probe of angiogenesis as it blocks differentiation of vascular endothelial cells and potently inhibits angiogenic sprouting in vivo.



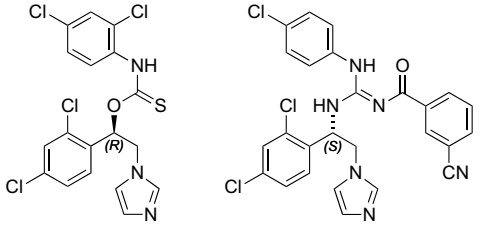
The synthesis and SAR of potent isoxazolinone analogs as antibacterial agents is reported.

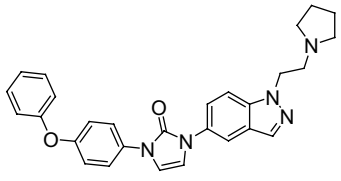


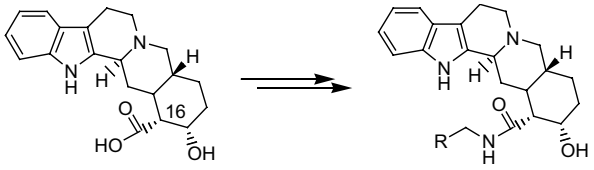


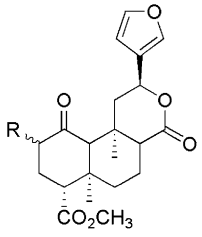


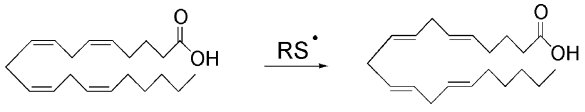
X=H,H or O



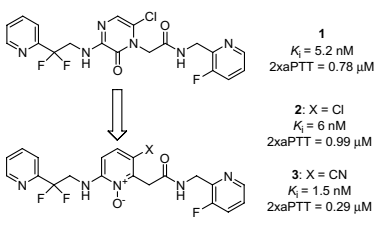




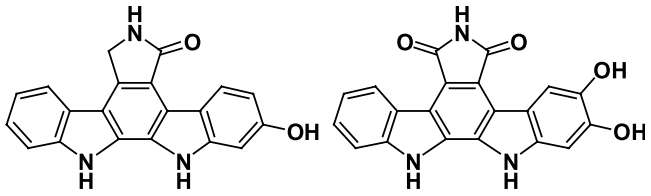




The first synthesis of all-trans isomer of arachidonic acid is reported together with its effects on rabbit platelet aggregation. The all-*trans* PUFA strategy allows a chemical biology approach for the investigation of the effect of the lipid trans geometry in the biological environment.

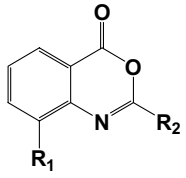


In this study, we demonstrate that the critical hydrogen bonding motif of the established 3-aminopyrazinone thrombin inhibitors can be effectively mimicked by a 2-aminopyridine N-oxide.

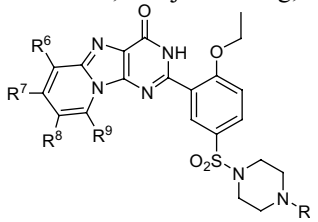


Oxidation of isolated low-density lipoprotein (LDL) or plasma caused fragmentation of apolipoprotein B-100 and decrease in the particle size of LDL. Based on these experiments, we propose that an oxidation reaction is involved in the formation of small dense LDL, an atherogenic LDL subclass.

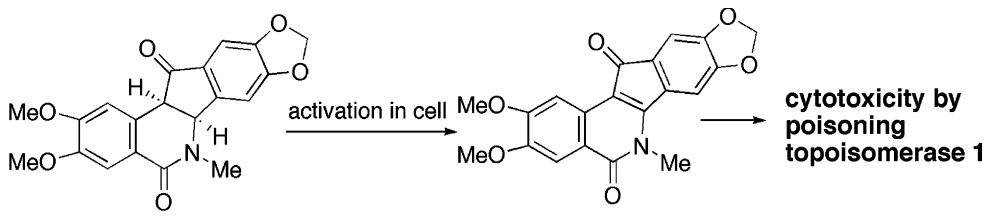
Oxidation of LDL or plasma⟶Fragmentation of apolipoprotein B-100 and decrease in the LDL particle size.

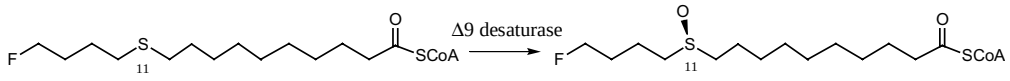


A series of 2,8-disubstituted benzoxazinones were synthesized and subjected to anti-platelet aggregation, inhibition of superoxide anion generation, and inhibition of neutrophil elastase release assays. The results suggested that these compounds can provide the lead compounds for anti-inflammatory agents.

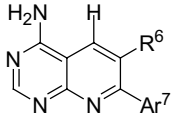


Synthesis and primary SAR of a novel series of 2-phenylpyrido[1,2-*e*]purin-4(3*H*)-one derivatives with piperazinyl sulfonamide substituents were described herein. As potential PDE5 inhibitors for erectile dysfunction (ED) treatment, representative compounds exhibit improved selectivity versus PDE1 and PDE6. Meanwhile, compound **3e** demonstrated functional efficacy on rabbit corpus cavernosum strip in vitro.

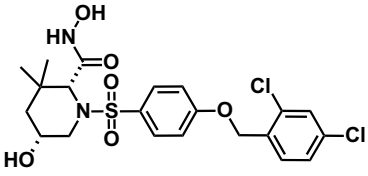


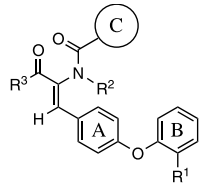


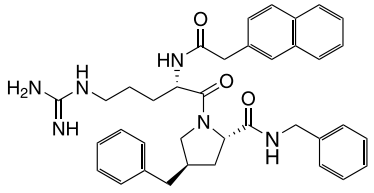
The stereochemistry of fatty acid desaturase-mediated sulfoxidation can be evaluated at micromolar levels of analyte using ^{19}F NMR in combination with a chiral shift reagent: (*S*)-(+)-MPAA.



A series of pipecolic hydroxamate inhibitors of MMP-13 and aggrecanase was discovered based on screening known inhibitors of TNF-α converting enzyme (TACE). Potency versus aggrecanase was optimized by modification of the benzyloxyarylsulfonamide group. Incorporation of geminal alkyl substitution at the 3-position of the piperidine ring improved metabolic stability, presumably by increasing steric hindrance around the metabolically labile hydroxamic acid. This modification also resulted in dramatic improvement of aggrecanase activity with a slight reduction in selectivity versus MMP-1. Synthesis, structure activity relationships, and strategies to reduce metabolic clearance are described.

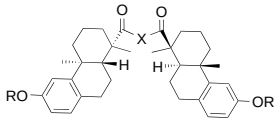






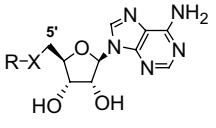
MC4R, Ki=29 nM
MC3R, Ki=258 nM

A series of proline based melanocortin ligands has been developed on the basis of initial piperazine leads by using a more conformationally rigid scaffold. A number of these novel ligands showed significant binding affinity for MC3 and MC4 receptors.



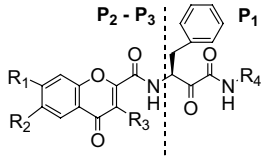
3 (R = H, X = O)
4 (R = Ac, X = O)
5 (R = H, X = NH

Discovery and development of podocarpic acid dimers (e.g., 3–5) are described.

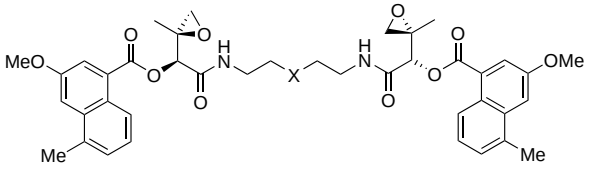


X = S, O, N, O

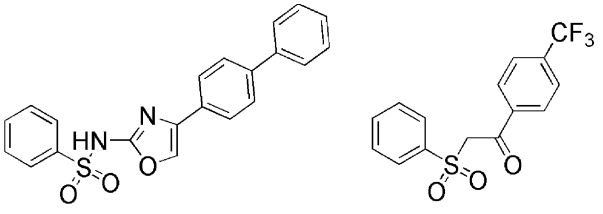
The structure-based design, chemical synthesis, and biological evaluation of novel MTAP substrates are described. These compounds incorporate various C5′-moieties and are shown to have different k_{cat}/K_m values compared with the natural MTAP substrate (MTA).



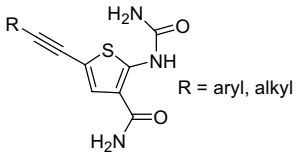
2, Chromone derivatives



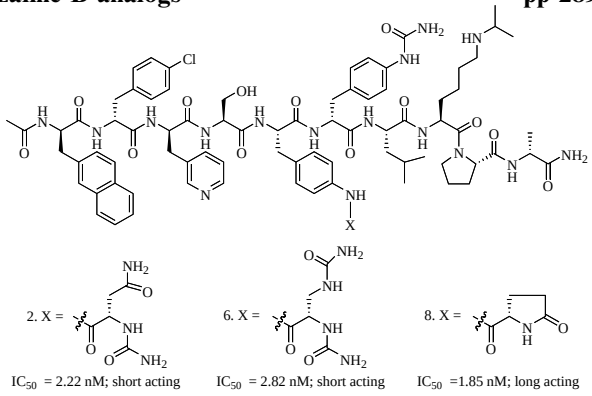
In in vitro assays, it is shown that changing X=CH_2 into X=NMe results in 7–9-fold increase in DNA interstrand cross-linking activity and a 3–10-fold increase in cytotoxicity against human tumour cell lines.

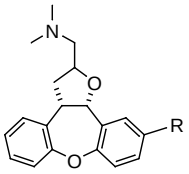


11H IC_{50} = 2.3 μM **13** IC_{50} = 0.19 μM



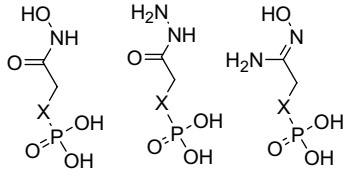
A series of 21 novel 2-[(aminocarbonyl)amino]-5-acetylenyl-3-thiophenecarboxamides were synthesized and evaluated for the inhibition of IKK-2.



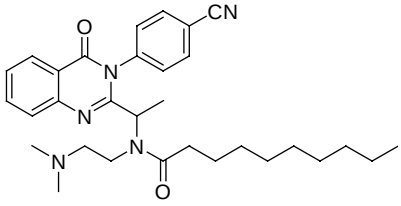


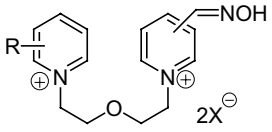
A novel series of *cis*-fused tetrahydrofuran derivatives modified at position C-11 was prepared and evaluated for its potential antidepressant/anxiolytic properties. In vitro affinities for the norepinephrine transporter and for 5-HT_{2A} and 5-HT_{2C} receptors, as well as the ED_{50} values obtained in some in vivo assays predictive for antidepressant and anxiolytic potential are reported.

An array of analogues of the cationic antimicrobial peptide drosocin was synthesized containing substitutions of Tyr6 and Ser7 in order to increase the proteolytic stability. Stabilizing the N-terminus with unnatural amino acids increased the serum stability of analogues by almost a factor 30 over an 8 h period.

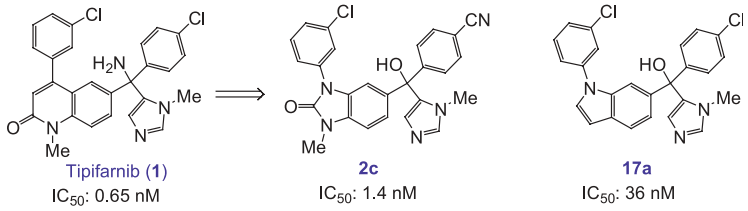


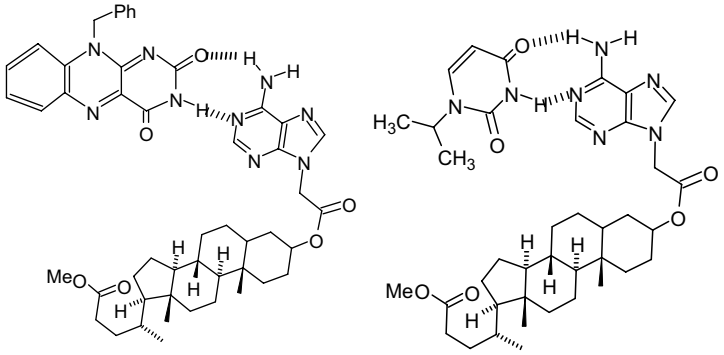
We describe the synthesis and evaluation of three new competitive inhibitors of triose-phosphate isomerase. One of them (phosphoglycoloamidoxime **3a**: K_i = 4.5 μM) is among the best reversible inhibitors so far reported for this enzyme.





New bis-pyridinium oxime reactivators connected with a $CH_2CH_2OCH_2CH_2$ linker between two pyridinium rings were synthesized and their potency to reactivate AChE inhibited by cyclosarin was evaluated.





OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Glycosyldisulfide switching of lectin-carbohydrate interactions. Lectin binding to a modified quartz crystal microbalance surface could be turned on or off by calcium ions or by controlling the redox state of the solution. [Pei, Z.; Aastrup, T.; Anderson, H.; Ramström, O. *Bioorg. Med. Chem. Lett.* **2005**, *15,* 2707.]

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