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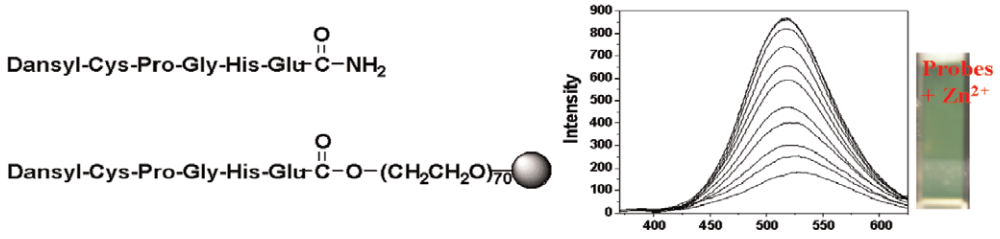
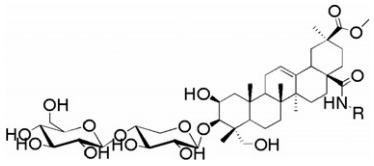
Chemistry
Letters

Bioorganic & Medicinal Chemistry Letters Vol. 17, No. 23, 2007

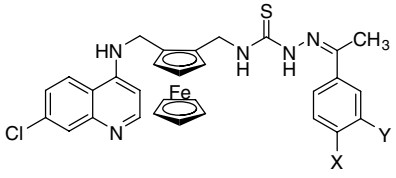
Contents

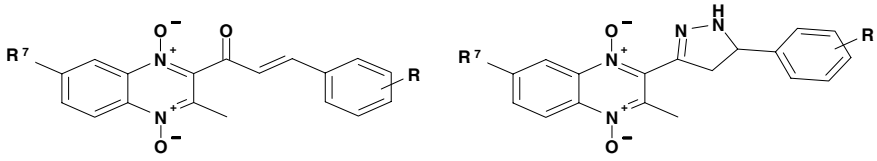
ARTICLES



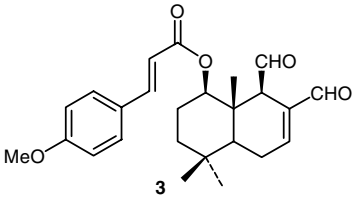


Twenty-one derivatives of Esculentoside A were synthesized. The conversion of the carboxylic acid into amides can highly enhance their inhibitory activity towards COX-2, and also increased the haemolytic activity.





Anti-inflammatory and antioxidant activities of some novel ring substituted 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and of their 4,5-dihydro-(1*H*)-pyrazole analogues are reported.



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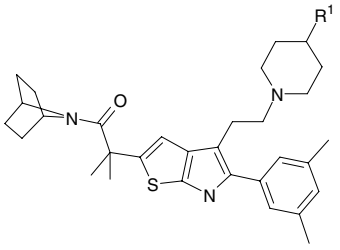
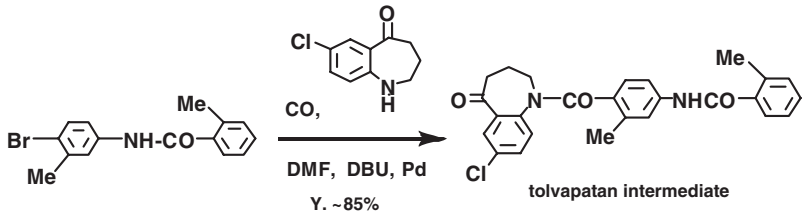
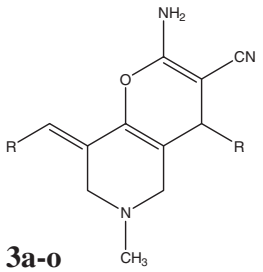
The synthesis and structure–activity relationships (SAR) of GnRH receptor antagonists based on thieno[2,3-*b*]pyrrole scaffold are described. Introduction of a piperidine moiety at C4 position led to compounds combining good in vitro potency and improved pharmacokinetics.

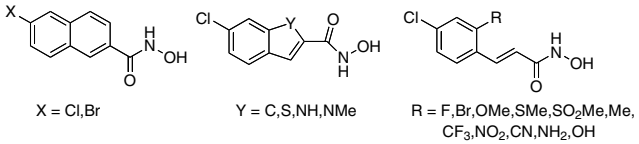




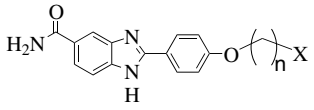
Fifteen tetrahydro-4*H*-pyrano[3,2-*c*]pyridines were prepared and tested for their in vitro activity against three mycobacterial species using the agar dilution method. 2-Amino-4-[4-(dimethylamino)phenyl]-8-(*E*)-[4-(dimethylamino)phenyl]-methylidene-6-methyl-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]-pyridine-3-carbonitrile, was found to be the most potent compound (MIC: 0.43 μM) against MTB and MDR-TB.

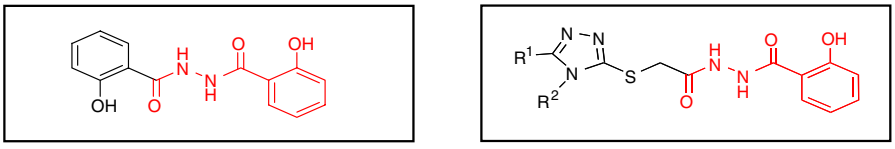


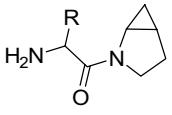
3a-o



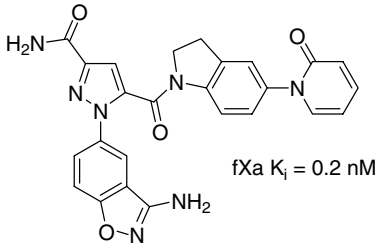
The synthesis and SAR of a series of novel hydroxamate BoNT/A inhibitors is reported.





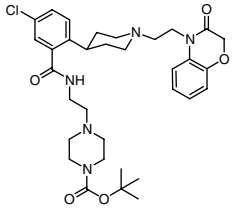


Enzyme inhibitory activity of a series of non-nitrile dipeptides help to discern the nature of individual SAR contributions from P1 and P2 of dipeptide derived DPP4 inhibitors.

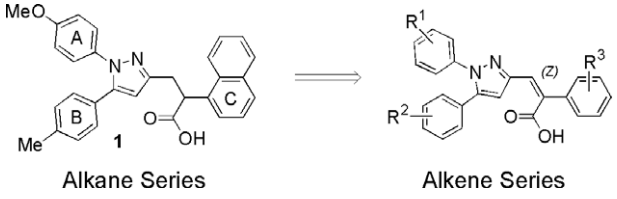


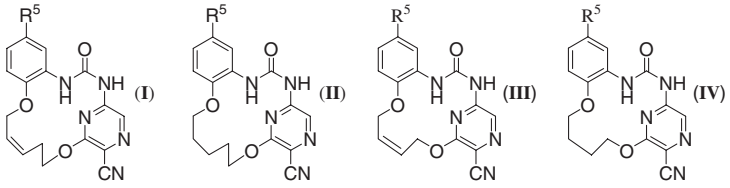
Efforts to optimize clinical candidate razaxaban have led to the discovery of pyrazole-based indoline fXa inhibitors.

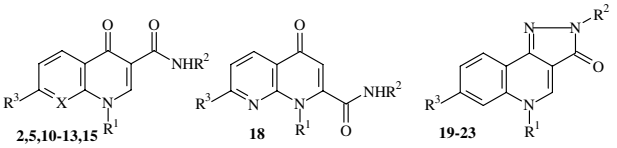
Various 4-phenylpiperidine-benzoxazin-3-ones were synthesized and biologically evaluated as urotensin-II (U-II) receptor antagonists. Compound **12i** was identified from in vitro evaluation as a low nanomolar antagonist against both rat and human U-II receptors. This compound showed in vivo efficacy in reversing the ear-flush response induced by U-II in rats.

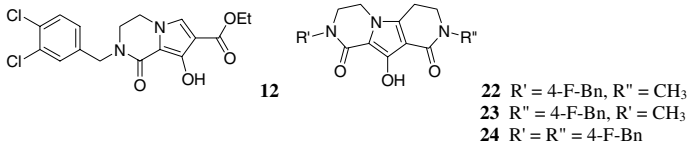


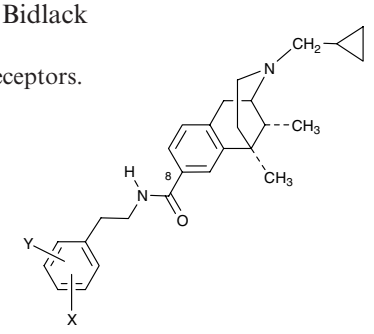
12i

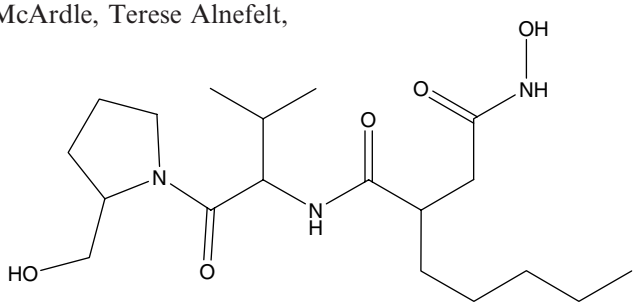


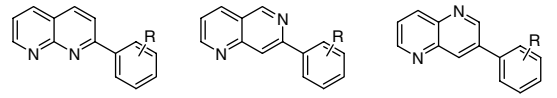






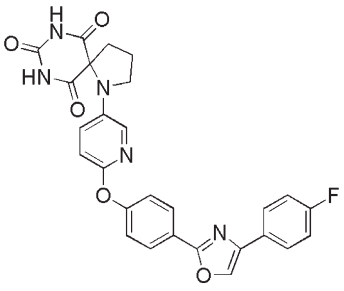






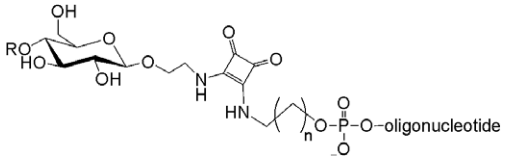
4 5 6

We describe three novel regioisomeric series of aryl naphthyridine analogs, which are potent antagonists of the Class III GPCR mGlu5 receptor. The synthesis and in vitro and in vivo pharmacological activities of these analogs are discussed.



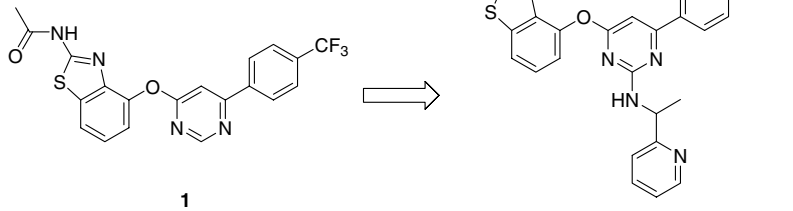
MMP-13 IC_{50} = 0.12 nM
MMP-12 IC_{50} = 143 nM

The discovery of novel, selective spirocyclic inhibitors of MMP-13 is reported.

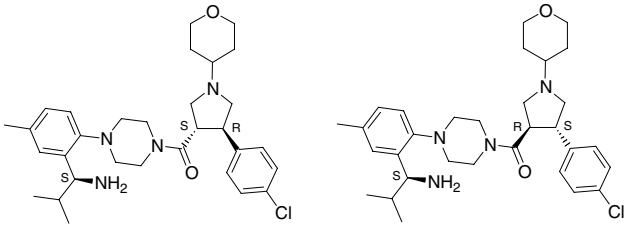


The use of squarate as spacer in the preparation of carbohydrate–oligonucleotide conjugates is reported.

A series of trisubstituted pyrimidines were synthesized to improve aqueous solubility of our first TRPV1 clinical candidate **1**. The structure–activity and structure–solubility studies led to the discovery of **26**.

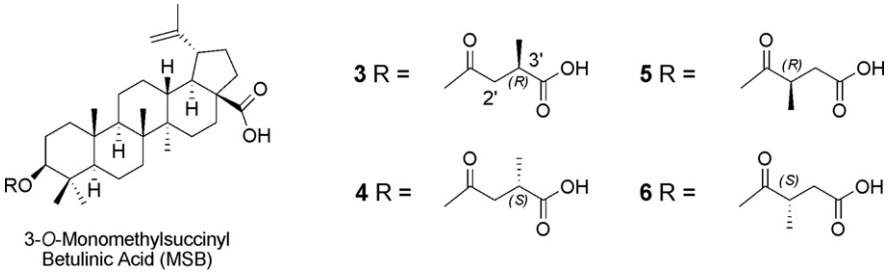


1 (AMG 517) **26**

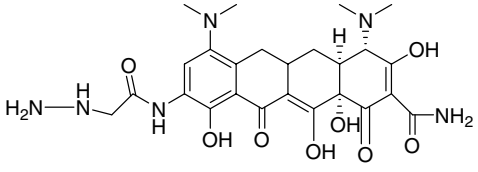


20f-1 (*S,S,R*-isomer): K_i = 11 nM, EC_{50} = 24 nM, IA = 104%

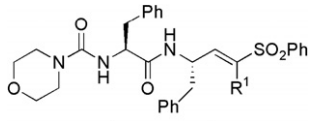
20f-2 (*S,R,S*-isomer): K_i = 8.6 nM, IA = 18%, IC_{50} = 65 nM



3-*O*-Monomethylsuccinyl Betulinic Acid (MSB)

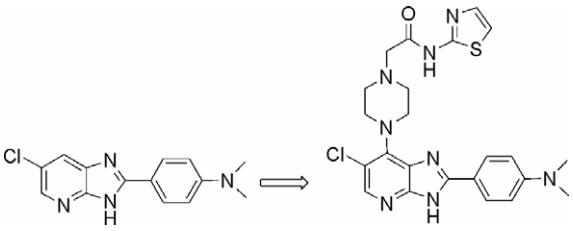


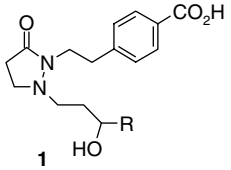
9-Hydrazino-acetyl-amido-MIN, and simpler glycylcycline derivatives, retained minimum inhibitory concentration (MIC) against *Staphylococcus aureus* comparable to minocycline. However, PEG-glycyl-amido-minocyclines showed very low activity.



2, R^1 = H **3**, R^1 = F

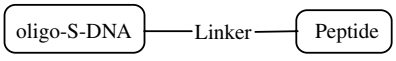
The synthesis of dipeptidyl α-fluorovinyl sulfones is described. Inhibitory assays against a *Leishmania mexicana* cysteine protease revealed low biological activity. Relative rates of Michael additions on vinyl sulfone and α-fluorovinyl sulfone were determined and ab initio calculations on Michael acceptor model structures were performed.



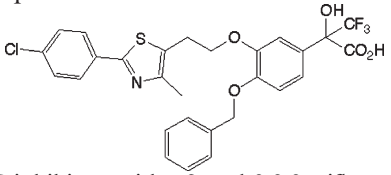


1

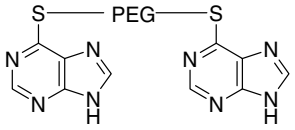
Replacement of the hydroxyl cyclopentanone ring in PGE_2 with chemically more stable heterocyclic rings and substitution of the unsaturated α-alkenyl chain with a metabolically more stable phenethyl chain led to the development of potent and selective analogs of PGE_2. Compound **10f** showed the highest potency and selectivity for the EP_4 receptor.



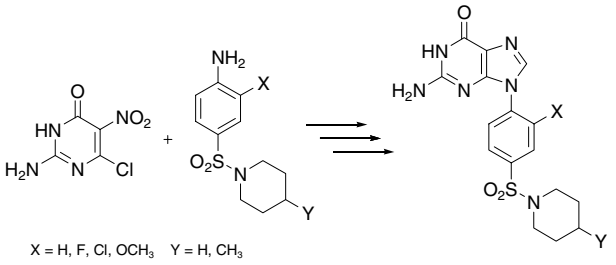
The synthesis of phosphorothioate oligonucleotide–peptide conjugate is reported.



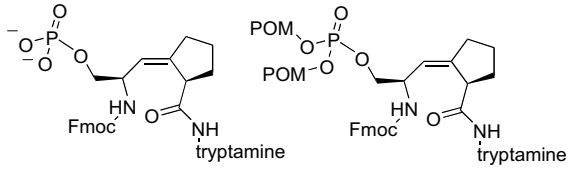
A new series of protein tyrosine phosphatase 1B inhibitors with a 2-aryl-3,3,3-trifluoro-2-hydroxypropionic acid core unit targeted at the enzyme's primary site and a hydrophobic chlorophenylthiazole extension in the 2° site exhibit low-μM inhibitory activity in cell-based assays.

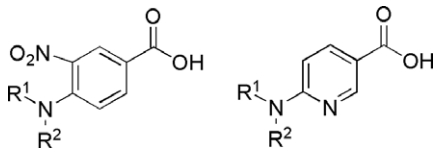


The simple synthesis of a new PEG 6 MP prodrug and its in vivo and in vitro evaluations are described.

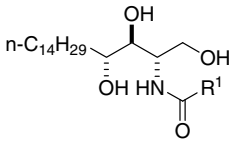


Fmoc-pSer-Ψ[(*Z*)CHC]-Pro-(2)-*N*-(3)-ethylaminoindole **1** showed moderate inhibition towards the mitotic regulator, Pin1 (IC_{50} = 28.3 μM). To improve the cell permeability, the charged phosphate was masked as the bis-pivaloyloxymethyl (POM) phosphate in Fmoc-(bisPOM)-pSer-Ψ[(*Z*)CHC]-Pro-(2)-*N*-(3)-ethylaminoindole **2**. Antiproliferative activity towards A2780 ovarian cancer cells of **1** (IC_{50} = 46.2 μM) was improved significantly in **2** (IC_{50} = 26.9 μM), comparable to the IC_{50} of **1** towards Pin1 enzymatic activity.



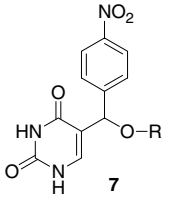


A series of novel functionalized 3-nitro-4-amino benzoic acids and 6-amino nicotinic acids and their agonist activity at GPR109b are reported.



3d, $R^1 = -(CH_2)_3COOCH_3$

Compound **3d** showed the highest enhancement of radiosensitizing effect.



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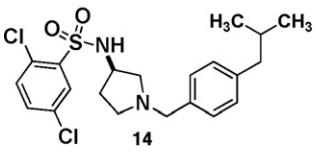
a) R = CH_3
b) R = CH_2CH_3
c) R = $(CH_2)_2CH_3$
d) R = $(CH_2)_3CH_3$
e) R = $(CH_2)_4CH_3$
f) R = $(CH_2)_5CH_3$
g) R = $(CH_2)_6CH_3$
h) R = $(CH_2)_7CH_3$
i) R = $(CH_2)_8CH_3$
j) R = $(CH_2)_9CH_3$
k) R = $(CH_2)_{10}CH_3$
l) R = $(CH_2)_{11}CH_3$
m) R = i-Pr
n) R = s-But
o) R = t-But



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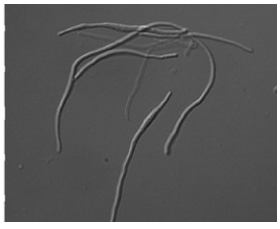
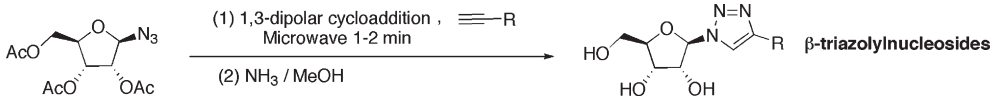
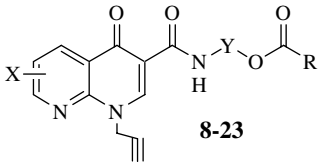
MIC = 10μM; extensive filamentation oberved at 50% MIC



The discovery and preliminary development of a new class of compounds that target bacterial cell division is reported.





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Compounds **12** exhibited high cytotoxicity on HBL-100 (breast) cell line while compounds **17** and **22** have shown high cytotoxicity on KB (oral) and SW-620 (colon) cell lines, respectively.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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