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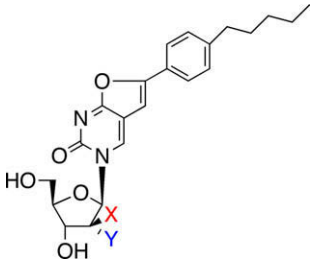
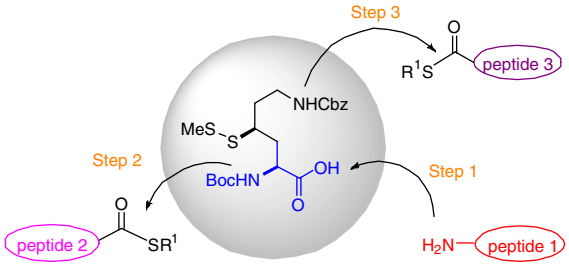
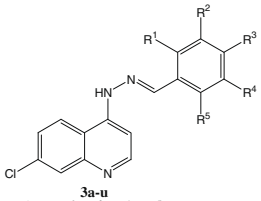
Contents

ARTICLES



Only the beta fluoro analogue (X = F, Y = H) retains potent anti-VZV activity.

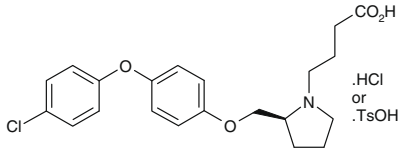




3a-u
R^1= X; R^2 =R^3 =R^4 = R^5 = H
R^2= X; R^1 =R^3 =R^4 = R^5 = H
R^3= X; R^1 =R^2 =R^4 = R^5 = H
X= H; Cl; F; Br; OMe; OH; CN; NO_2

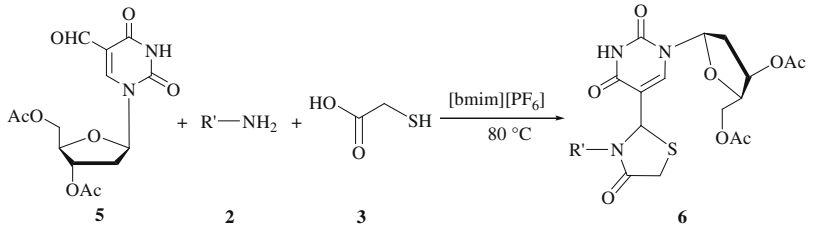
MIC= 12.5- 2.5μg/mL

A series of twenty-one quinoline derivatives have been synthesized and evaluated against *Mycobacterium tuberculosis*. Three compounds exhibited a significant activity (2.5 μg/mL), which can be compared with that of the first line drugs, ethambutol (3.12 μg/mL) and rifampicin (2.0 μg/mL).



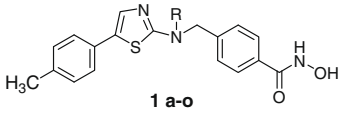
DG-051 (HCl salt) or DG-051B (TsOH salt)

The identification and synthesis of two CYP mediated metabolites of DG-051 are reported.



5 2 3 6

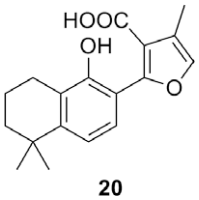
Novel pyrimidine nucleoside–thiazolidinone hybrids with antiparasitic activities were synthesized via an eco-friendly and efficient three-component reaction in [bmim][PF_6].



1 a-o

R=alkyl, phenoxyalkyl or tolyloxyalkyl

The discovery of a series of potent and selective *N*-hydroxybenzamide-based HDAC inhibitors is reported.



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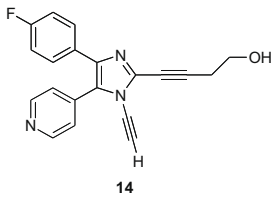
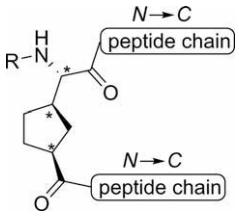
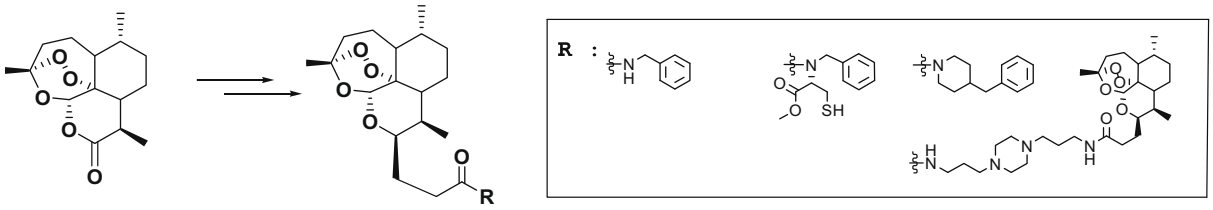


14

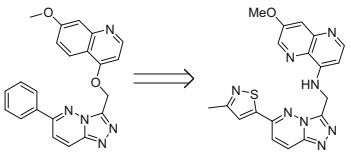
The dialkynylimidazole **14** is a potent (IC_{50} = 200 nM) and selective inhibitor that covalently modifies p38α.



Peptide constructs decreasing the Id protein level and stimulating α-actin expression in SMCs in the low-micromolar range are reported.

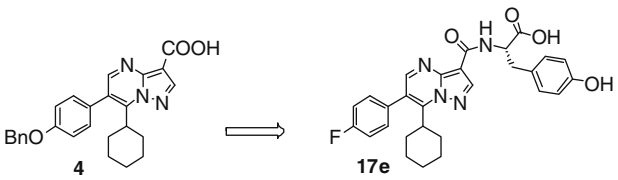


Novel amide derivatives of non-acetal deoxoartemisinin were synthesized. Some of the derivatives had potent in vitro anticancer activity and the deoxoartemisinin amide trimer had potent in vivo antiangiogenic activity.

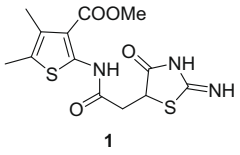


1 24

Deregulation of the receptor tyrosine kinase c-Met has been implicated in several human cancers and is an attractive target for small molecule drug discovery. We previously showed that O-linked triazolopyridazines can be potent inhibitors of c-Met. Herein, we report the discovery of a related series of N-linked triazolopyridazines which demonstrate nanomolar inhibition of c-Met kinase activity and display improved pharmacodynamic profiles. Specifically, the potent time-dependent inhibition of cytochrome P450 associated with the O-linked triazolopyridazines has been eliminated within this novel series of inhibitors. N-linked triazolopyridazine **24** exhibited favorable pharmacokinetics and displayed potent inhibition of HGF-mediated c-Met phosphorylation in a mouse liver PD model. Once-daily oral administration of **24** for 22 days showed significant tumor growth inhibition in an NIH-3T3/TPR-Met xenograft mouse efficacy model.

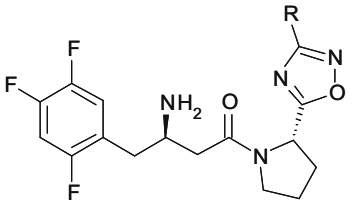


Synthesis and optimization of novel pyrazolo[1,5-*a*]pyrimidine HCV polymerase inhibitors are described.



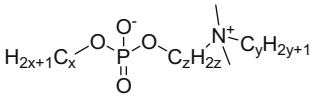
1

Identification of iminooxothiazolidines as secreted frizzled related protein-1 inhibitors and the SAR requirements are reported.

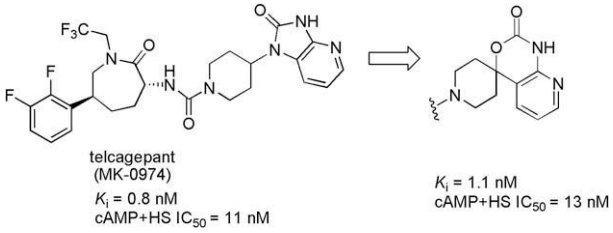


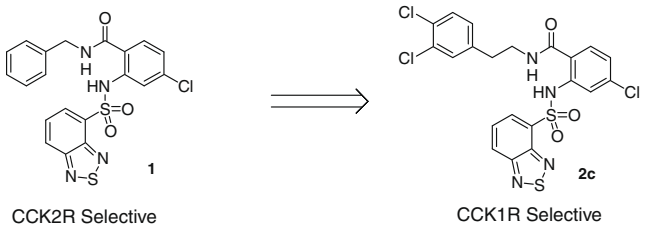
6b-6m

For a series of β-homophenylalanine based inhibitors of dipeptidyl peptidase IV ADME properties were improved by the incorporation of amide replacements. These efforts led to a novel series of potent and selective inhibitors of DPP-4 that exhibit an attractive pharmacokinetic profile and show excellent efficacy in an animal model of diabetes.

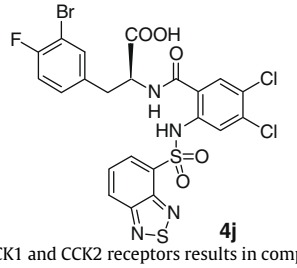


The synthesis and antiprotozoal, antimycotic, and cytotoxic activity of dialkylphosphocholines are reported.



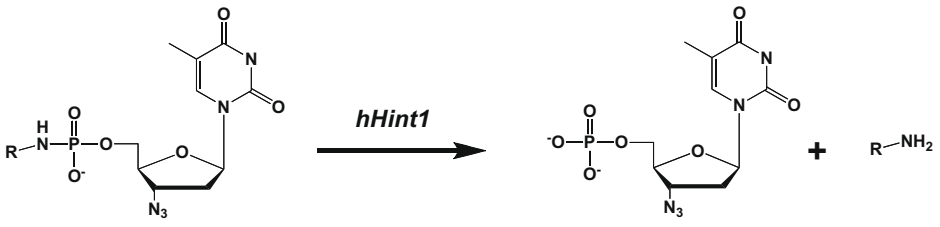


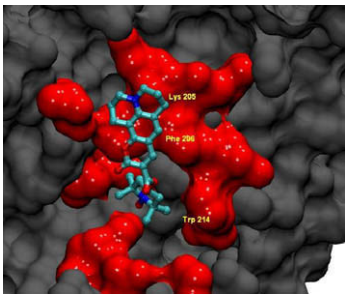
Cholecystokinin receptor subtype selectivity is shown to be reversed in the anthranilic sulfonamide series of antagonists via specific manipulation of the amide side chain.



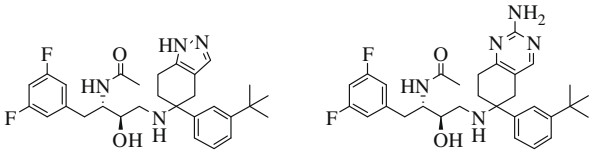
CCK1R pK_I = 6.8
CCK2R pK_I = 8.0
Reduction in plasma amylase = 67% @ 30 μmol/kg
Inhibition of gastric acid production ED_{50} = 1.6 μmol/kg

Optimization of affinity for both CCK1 and CCK2 receptors results in compounds that both inhibit pancreatic enzyme secretion and inhibit the production of gastric acid in animal models.



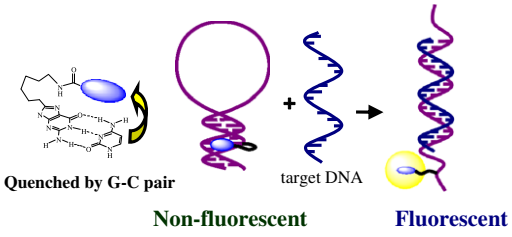


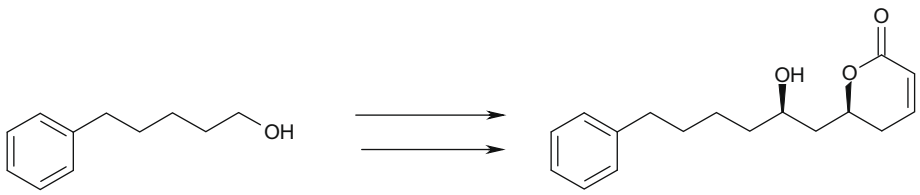
Kinetic rate constant values for the nitroxide reduction bound to Human serum albumin reveal influence of environment and accessibility factors on the antioxidant ability to repair protein free radicals.

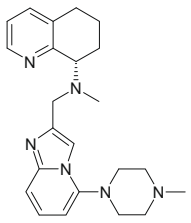


56 **57**

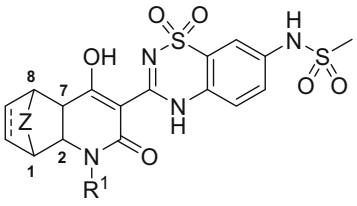
Using structure-guided design, hydroxyethylamine BACE-1 inhibitors were optimized to nanomolar Aβ cellular inhibition with selectivity against cathepsin-D. X-ray crystallography illuminated the *S1′* residues critical to this effort, which culminated in compounds **56** and **57** that exhibited potency and selectivity but poor permeability and high P-gp efflux.



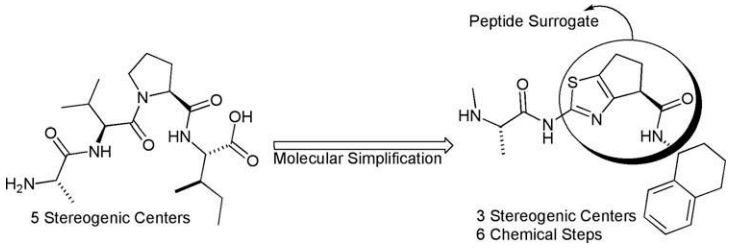




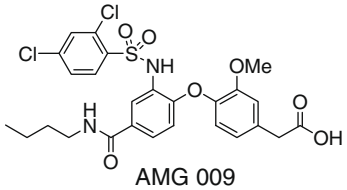
Synthesis of several novel imidazopyridine-5,6,7,8-tetrahydro-8-quinolinamine derivatives with potent activity against HIV-1 are described.



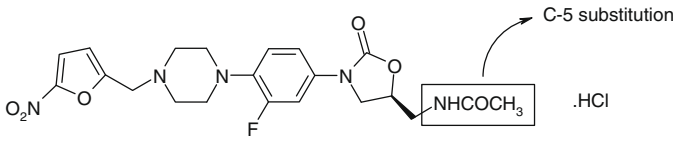
Z = CH_2, CH_2CH_2, O



Based on tetrapeptide AVPI we were able to design and synthesize a new simplified scaffold to inhibit the BIR3 domain of the XIAP protein at low micromolar range.

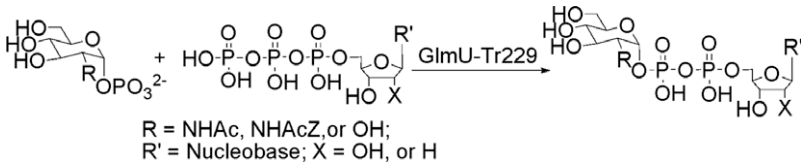


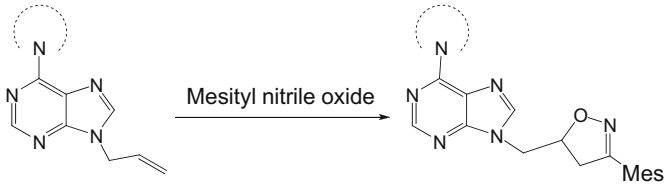
A series of phenylacetic acid derivatives was discovered as CRTH2 antagonists. Modification of the series led to compounds that are also antagonists of DP. Since activation of CRTH2 and DP are believed to play key roles in mediating responses of asthma and other immune diseases, this series was optimized to increase the dual antagonistic activities and improve pharmacokinetic properties. These efforts led to selection of AMG 009 as a clinical candidate.



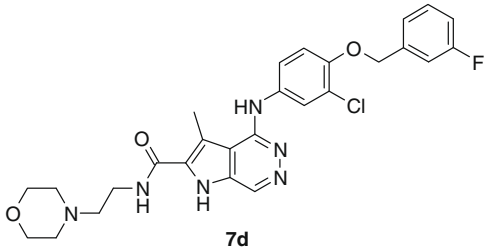
Ranbezolid

A number of 5-substituted derivatives of Ranbezolid, a novel oxazolidinone were synthesized and their antibacterial activity reported.



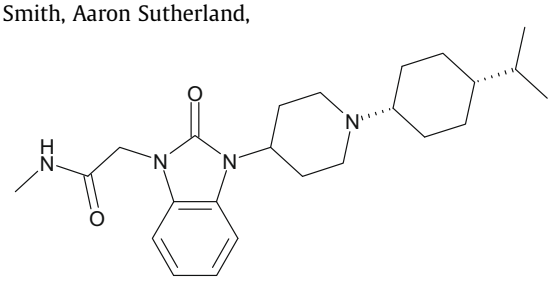


The synthesized compounds act as lipid peroxidation inhibitors and potent thrombin inhibitors.



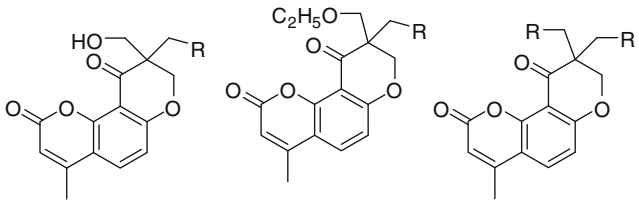
7d

A series of novel pyrrolopyridazine derivatives have been discovered to be HER-2 inhibitors. These compounds selectively inhibited HER-2 kinase activity at low nanomolar concentrations. Compound **7d** was identified as a potent HER-2 inhibitor with an IC_{50} of 4 nM.

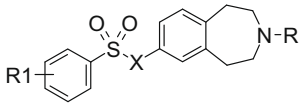


51

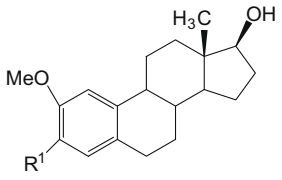
A knowledge based approach was applied to explore novel NOP receptor agonists with simplified hydrophobes. Compound **51** was identified as a high affinity, potent NOP receptor agonist.



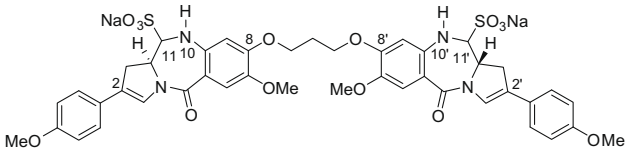
7a-c **8a-h** **9a-h**



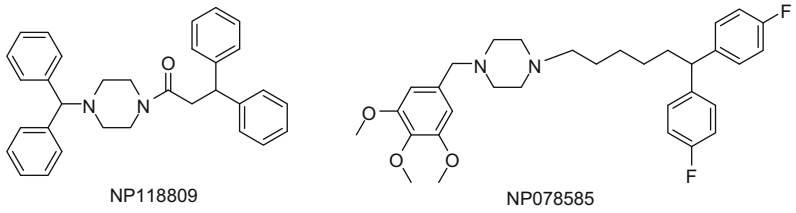
Novel benzazepine sulfonamides and sulfones are potent, selective motilin receptor agonists. Hit identification and lead optimisation of this new peptide GPCR ligand series is described.



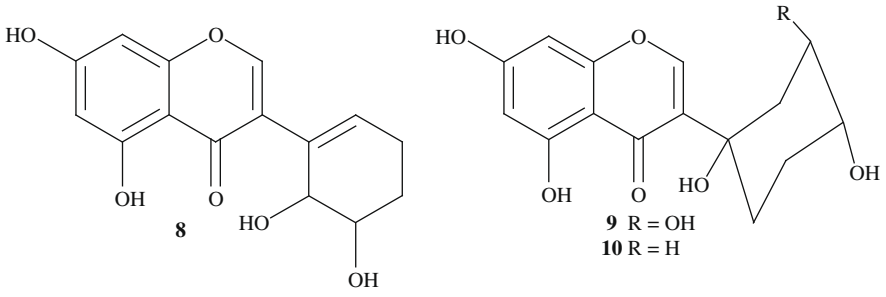
A lead-generation series of analogs of 2-methoxyestradiol modified at the 3-position were designed, synthesized and evaluated for antiproliferative, antiangiogenic, and estrogenic properties.

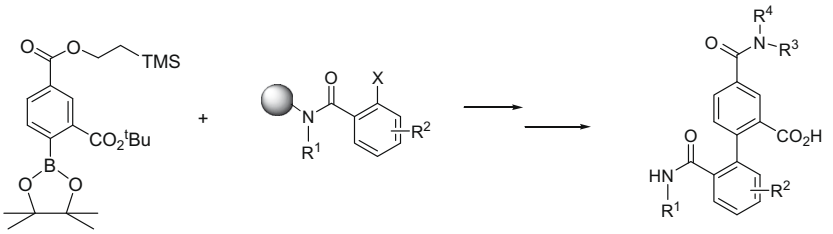


Novel C11/C11′-bisulfite prodrug (SG2285, **17**) of the N10–C11/N10′–C11′ bis-imine PBD dimer (**16**) with enhanced water solubility and a slower rate of reaction with DNA.



Discovery of **NP118809** and **NP078585** as N-type selective calcium channel blockers resulting from the scaffold optimization of flunarizine and lomerizine are reported.





A novel and efficient method for synthesizing a highly functionalized aryl boronic acid reagent in large scale was developed. A hug biphenyl scaffold library for trypsin-like serine protease inhibitor by solid-phase synthesis is described.

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.]

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