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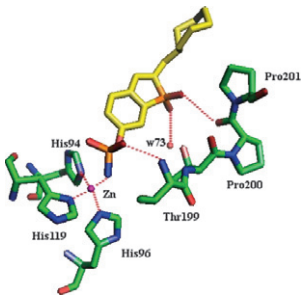
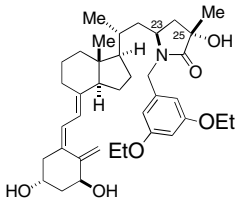
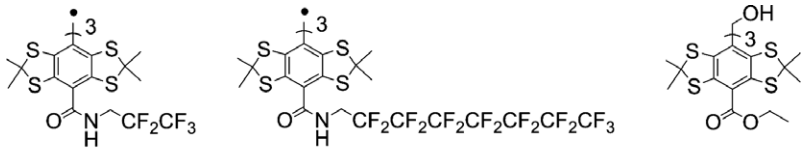
Contents

ARTICLES

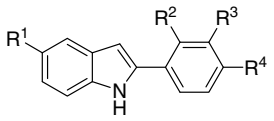




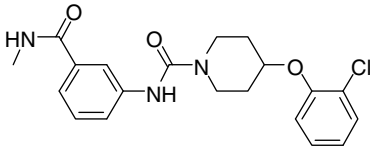
(23*S*,25*S*)-DLAM-1P-3,5(OEt)$_2$



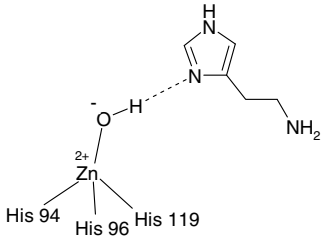
The synthesis of two new persistent fluorinated tetrathiatriarylmethyl (TAM) radicals (**F15T-03** and **F45T-03**) in two steps from ester precursor **1** (95% and 66%, respectively), and preliminary evaluation of their EPR properties are reported.

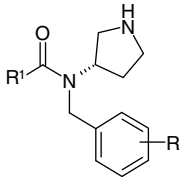


Three new potent indole NorA pump inhibitors and an antibacterial lead compound for *Staphylococcus aureus* are described.

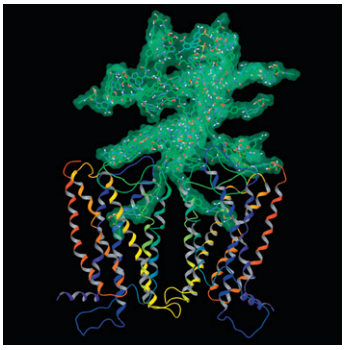


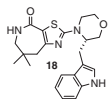
4c IC_{50} < 4 nM (mSCD1)





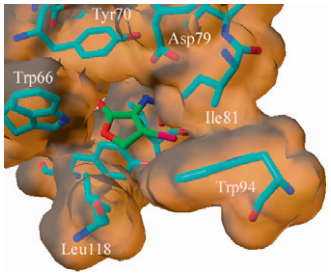
18: R^1 = iPr; R = 2,3-di-Cl
SRI, IC_{50} 12 nM
NRI, IC_{50} 23 nM
DRI, IC_{50} 1270 nM

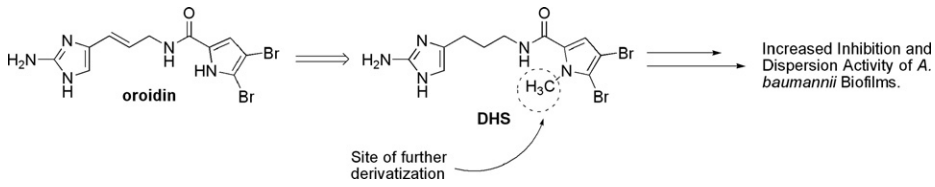




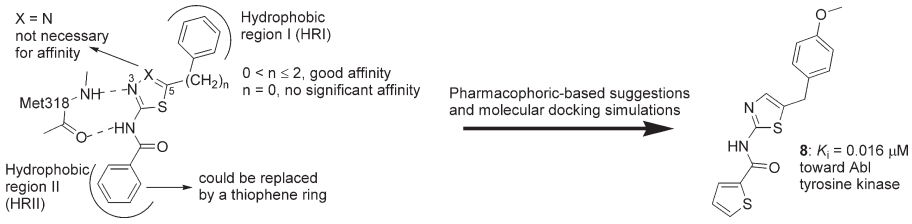
4-(1,3-Thiazol-2-yl)morpholine derivatives have been identified as potent and selective inhibitors of phosphoinositide 3-kinase, compound **18** is shown to demonstrate the utility of this class of compounds in xenograft models of tumor growth.

Amongst some *N*-acyl-3-amino-5*H*-furanone derivatives tested as LuxR-dependent quorum sensing inhibitors, 4-halogenated compounds were found to be the most active. Molecular modelling showed that the presence of the halogen atom could enhance the fitting of the lactone ring through specific interactions with conserved or conservatively replaceable residues in the LuxR protein family.

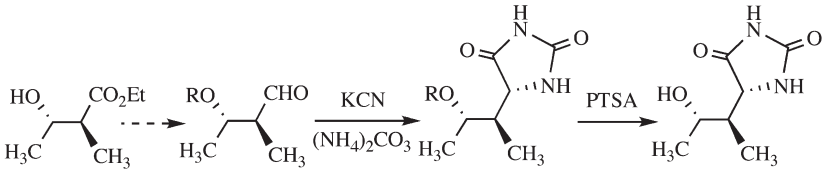


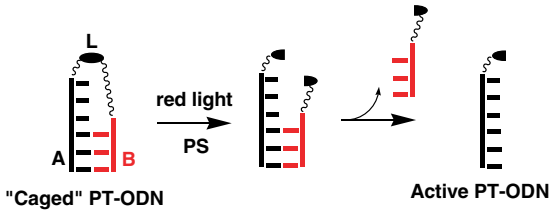


Modification of the alkyl substituent on the pyrrole-based nitrogen of the oroidin template has resulted in derivatives that display more potent anti-biofilm activities than the previous lead compound, DHS.



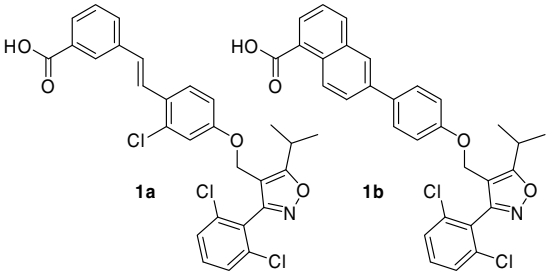
Affinity optimization of thiazole or thiadiazole Abi inhibitors. From 2-benzamido thia(dia)zole compounds to *N*-(thiazol-2-yl)-2-thiophene carboxamide derivatives.

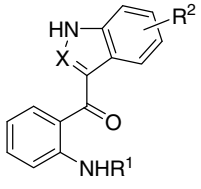




'Caged' phosphothioate oligodeoxyribonucleotides are reported. These compounds do not bind complementary nucleic acids in the dark. Upon irradiation with red light in the presence of chlorine e6 they become efficient binders.

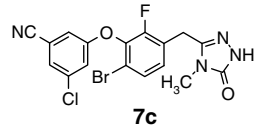
Starting from the known FXR agonist GW 4064 **1a**, a series of stilbene replacements were prepared. The 6-substituted 1-naphthoic acid **1b** was an equipotent FXR agonist with improved developability parameters relative to **1a**. Analog **1b** also reduced the severity of cholestasis in the ANIT acute cholestatic rat model.





X = N or C

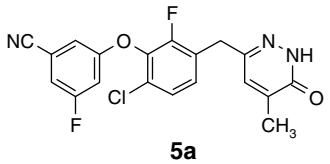
A novel series of potent heteroaryl-ketone derivatives active against VEGFR-2 kinase is described. The best compounds were demonstrated to be inactive against a panel of tyrosine and serine/threonine kinases with the exception of VEGFR-1 kinase. Selected representatives displayed acceptable exposure levels when administered orally to mice.



7c

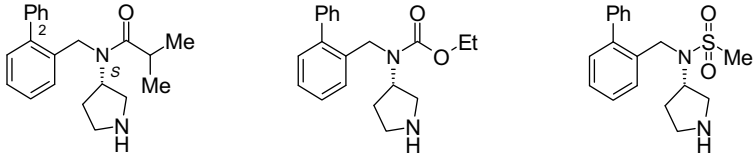
EC_{50} (WT) = 2 nM
PO (2 mg/kg): AUC = 38.4 μM*h
F = 74%

Novel diaryl ether HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) were prepared. Triazolinone compounds that strongly inhibit wild-type and NNRTI-resistant viruses and display excellent pharmacokinetic properties were identified.



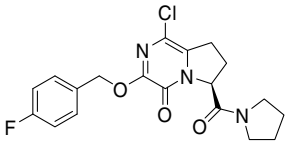
5a

A number of pyridazinones were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). These compounds strongly inhibited the wild-type virus and NNRTI-resistant viruses.



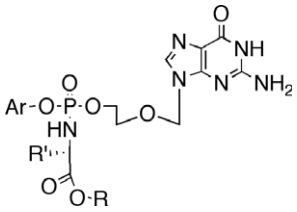
9e **11b** **13a**

Carboxamide **9e**, carbamate **11b** and sulfonamide **13a** were identified as potent NRIs with excellent selectivity over SRI and DRI, good in vitro metabolic stability and weak CYP inhibition. Carbamate **11b** demonstrated superior transit performance in MDCK-mdr1 cell lines with minimal P-gp efflux, which was attributed to reduced HBA capacity. Evaluation in vivo, in rat microdialysis experiments, showed **11b** increased NA levels by 400% over pre-drug levels confirming good CNS penetration.

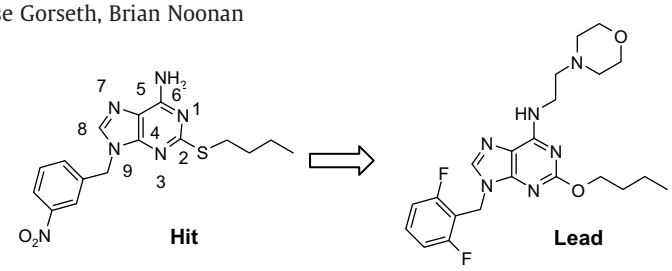


39

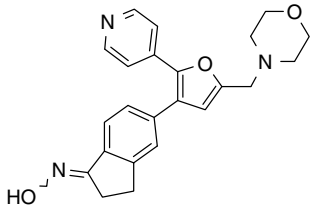
We report the synthesis and in vitro activity of a series of novel pyrrolidinyl pyridones and pyrazinones as potent inhibitors of prolyl oligopeptidase (POP). Within this series, compound **39** was co-crystallized within the catalytic site of a human chimeric POP protein which provided a more detailed understanding of how these inhibitors interacted with key residues within the catalytic pocket.



Low or sub-μM versus HSV-1 and -2 and VZV. Retain full activity versus thymidine kinase mutants proving intracellular phosphate delivery.

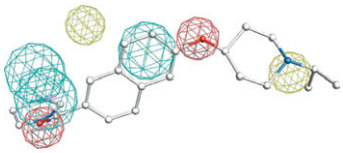


An early SAR study of a screening hit series has generated a series of 9-benzyl purines as inhibitors of bacterial glutamate racemase (MurI) with micromolar enzyme potency and improved physical properties. X-ray co-crystal EI structures were obtained.

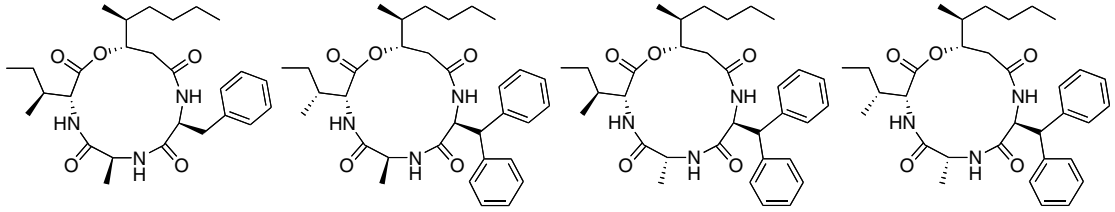


SB-699393 (**17**)

Modification of the potent imidazole-based B-Raf inhibitor SB-590885 resulted in the identification of a series of furan-based derivatives with enhanced CNS penetration. One such compound, SB-699393 (**17**), was examined in vivo to challenge the hypothesis that selective B-Raf inhibitors may be of value in the treatment of stroke.

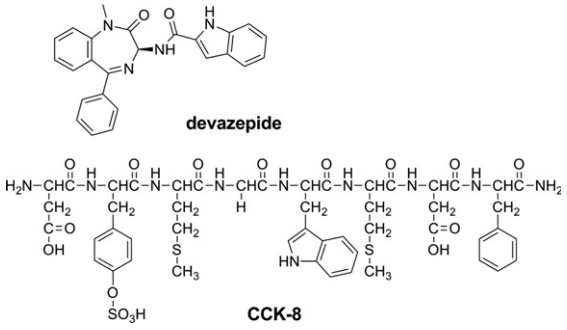


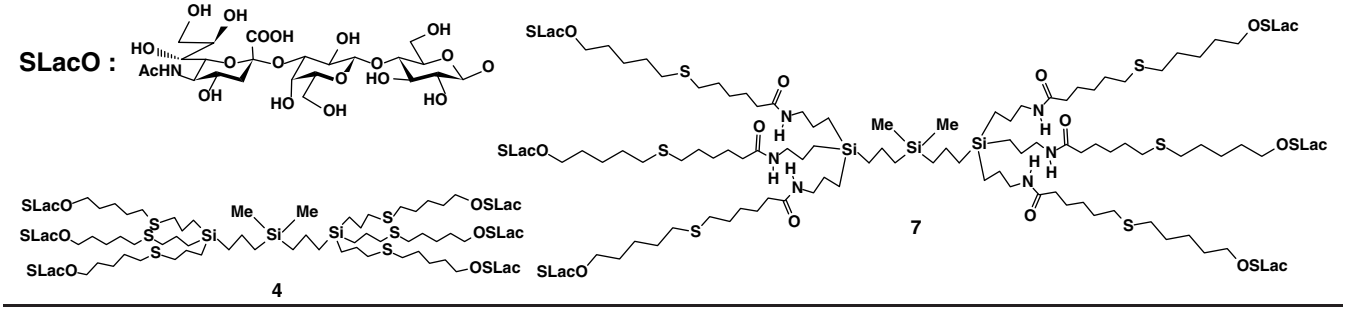
The refined histamine H3 ligand pharmacophore model guided successfully the selection process towards the identification of new, potent and selective naphthalene inverse agonists.

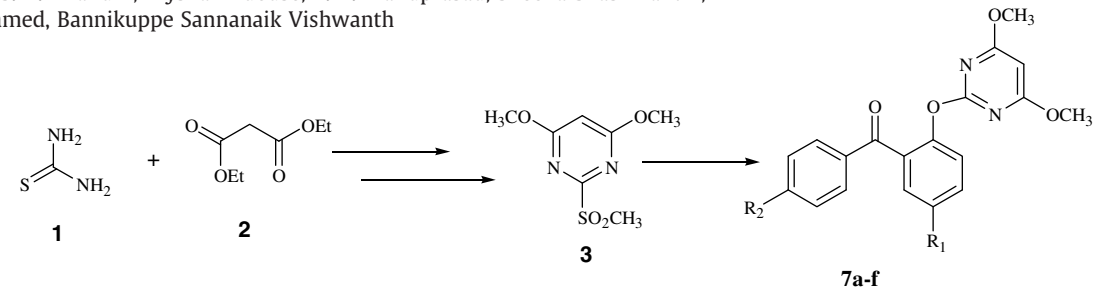


A library of beauveriolide analogues focusing on L-Ala and D-*allo*-Ile of beauveriolide III (**1b**) was synthesized by combinatorial synthesis and their inhibitory activity of CE synthesis in macrophage was tested. Cyclic compounds **7**{*1,3,2*}, **7**{*2,3,1*}, and **7**{*2,3,2*} were 20 times more potent than **1b**.

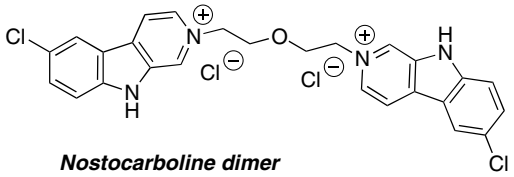
Small molecule benzodiazepine ligands are allosteric modulators of the CCK_1 receptor.



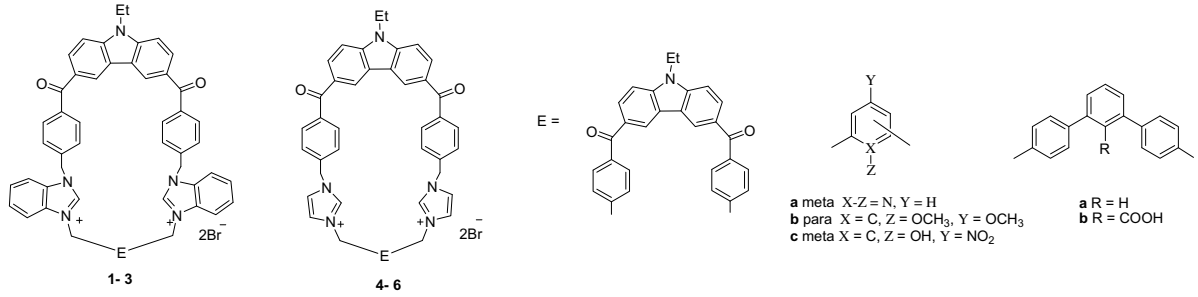


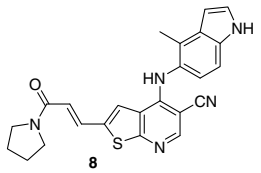


The newly synthesized compounds 2-(2-aroylaroxy)-4,6-dimethoxy pyrimidines **7a–f** were screened for their anti-inflammatory activity and compared with standard drugs.



Nostocarboline dimer
IC_{50} = 18 nM, *Plasmodium falciparum* K1
IC_{50} = 47900 nM, rat myoblasts (L6)
> 2500 fold selectivity

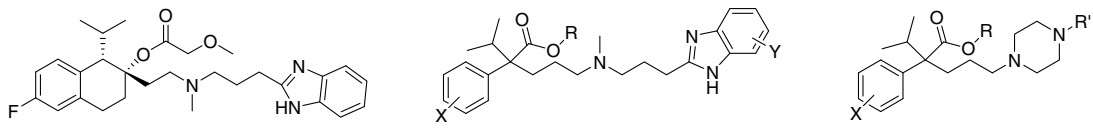




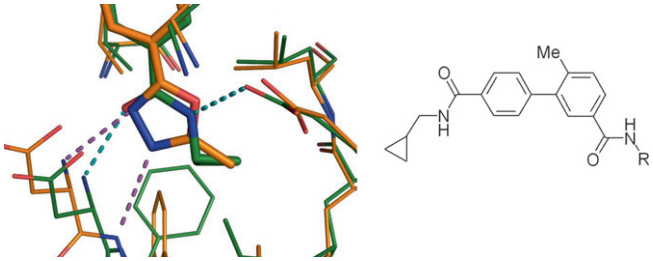
8

PKCθ = 3.8 nM
PKCα, PKCβ, PKCδ, PKCε, PKCη, PKCζ > 1300 nM

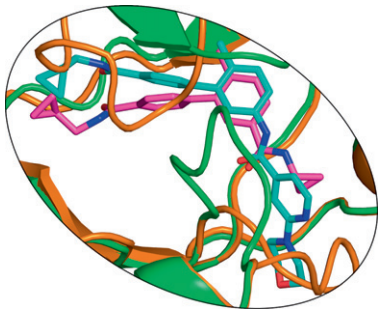
A series of 2-alkenylamide thieno[2,3-*b*]pyridine inhibitors of PKCθ is described. SAR studies led to compound **8** which has excellent selectivity over a variety of PKC isoforms.

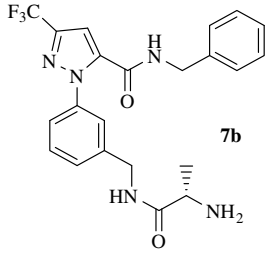


Novel series of α,α′-disubstituted phenylacetate derivatives (**10** and **11**) based on pharmacophore mapping study were prepared and evaluated for T-type calcium channel (α_{1G}) blockers by patch-clamp method. Among them, compound **10e** (X = *p*-Br, Y = H, R = Me) showed higher potency than Mibefradil and competitive PK profiles for further in vivo assay.



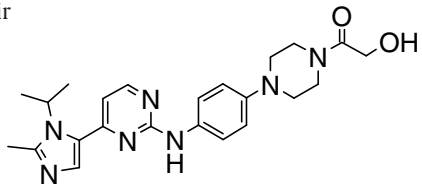
The biphenyl amides (BPAs) are a novel series of p38α MAP kinase inhibitor. The optimisation of the series to give compounds that are potent in an vivo disease model are discussed. SAR is presented and rationalised with reference to the crystallographic binding mode.





7b

This study reports the identification and Hits to Leads optimization of inhibitors of coactivator associated arginine methyltransferase (CARM1). Compound **7b** is a potent, selective inhibitor of CARM1.



2e

MCF-7 IC50 = 0.17 uM

A series of CDK inhibitors with a novel binding mode and good activity in clinically relevant disease models is reported.

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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