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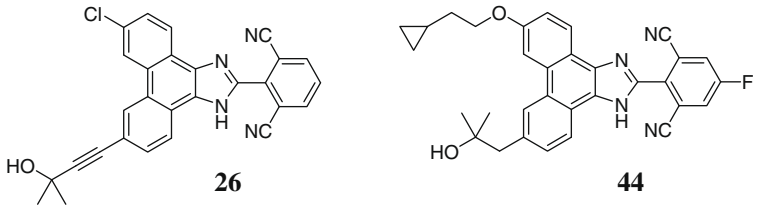
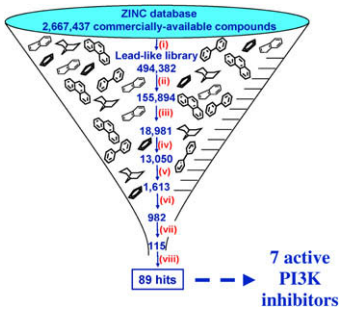
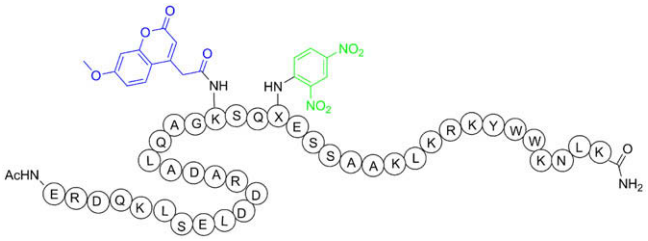
Contents

ARTICLES

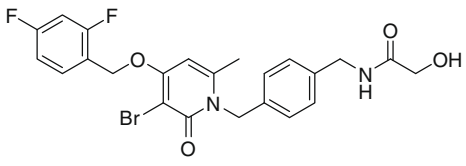


Phenanthrene imidazoles **26** and **44** have been identified as novel potent, selective, and orally active mPGES-1 inhibitors.

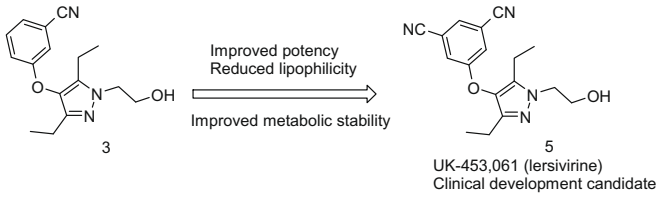




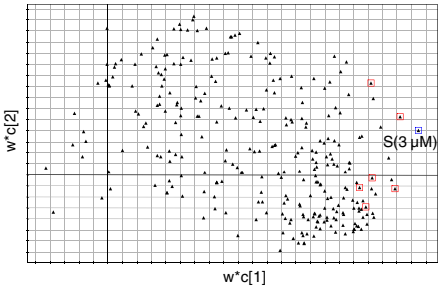
A FRET based synthetic substrate for the botulinum neurotoxin light chain B serotype utilized in both a high and low throughput assay for identification and characterization of inhibitors.

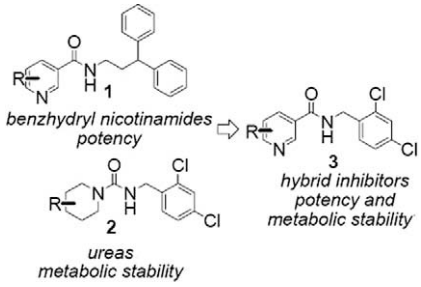


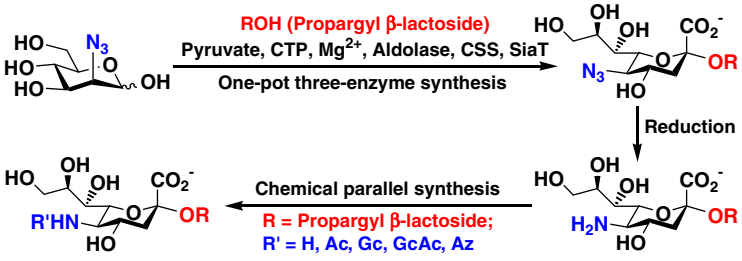
20, p38α IC_{50} = 46 nM



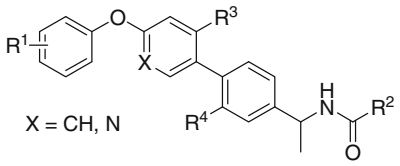
We prepared three discreet cohorts of potent non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) based on the recently reported 3-cyanophenoxypyrazole lead **2**. Several of these compounds displayed very promising anti-HIV activity in vitro, safety, pharmacokinetic and pharmaceutical profiles. We describe our analysis and conclusions leading to the selection of alcohol **5** (UK-453,061, lersivirine) for clinical development.



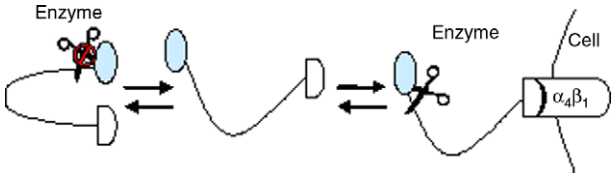


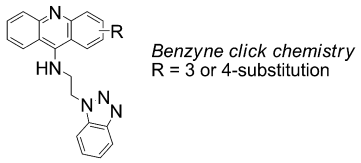


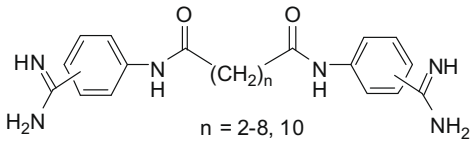
A convenient chemoenzymatic strategy for synthesizing sialosides containing a C5-diversified sialic acid is reported.



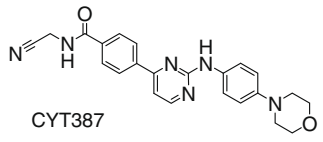
We report potent biphenyl- and 3-phenyl pyridine-based inhibitors of human acetyl-CoA carboxylase (ACC) enzymes 1 and 2.



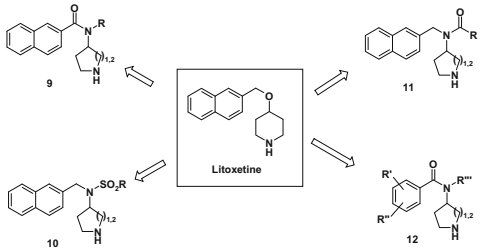




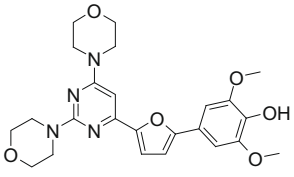
The synthesis and SAR of a series of alkanediamide-linked bisbenzamidines as potent inhibitors of *Trypanosomal brucei* and *Pneumocystis carinii* are described.



Details of SAR studies leading to CYT387, a potent and selective dual JAK1 and JAK2 inhibitor, are reported.

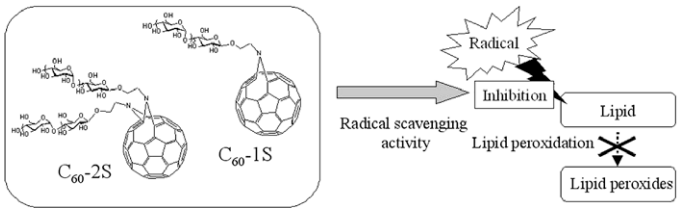


The reported selective serotonin re-uptake inhibitor (SSRI) litoxetine was used as the starting point in the design of a second wave of potent, selective SSRIs with high ease of synthetic accessibility.

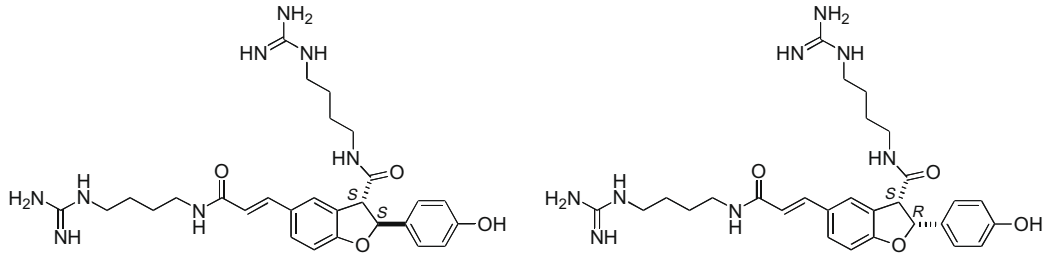


(15)

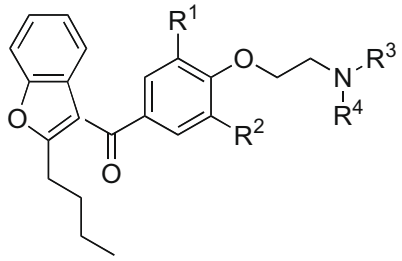
The discovery and optimisation of a novel series of inhibitors of mTOR kinase are described. Compound **15** has low nanomolar potency against mTOR kinase and is highly selective relative to PI3Kα.



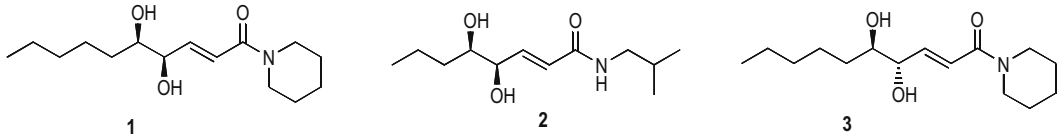
The sugar-pendant fullerene C_{60} derivatives inhibited human plasma lipid peroxidation by scavenging radicals.



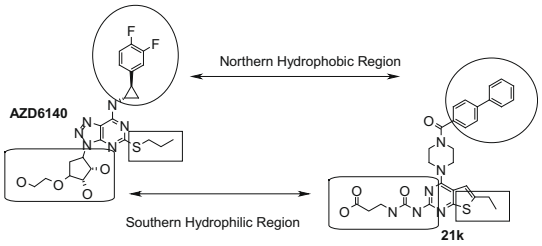
A novel series of tricyclic compounds were designed and synthesized as FBPase inhibitors. SAR studies in this series led to the finding of optimized inhibitors **8l** and **14b**.



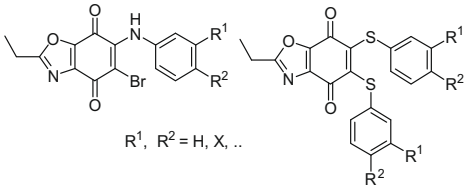
Although amiodarone and its metabolites are capable of stimulating rodent TAAR1, they fail to affect stably expressed unmodified *h*TAAR1 in vitro.



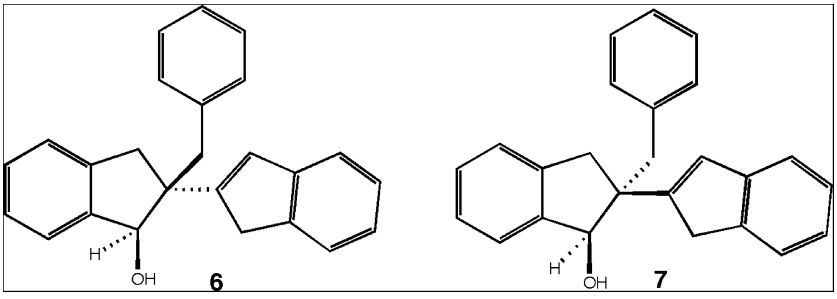
The first stereoselective total synthesis of new natural amide alkaloids **1**–**3** and their anti cancer activity is reported.

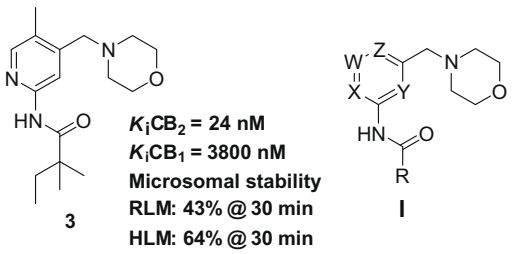


Herein we describe the design and synthesis of a novel series of potent thienopyrimidine $P2Y_{12}$ inhibitors and the negative impact protein binding has on the inhibition of platelet aggregation.

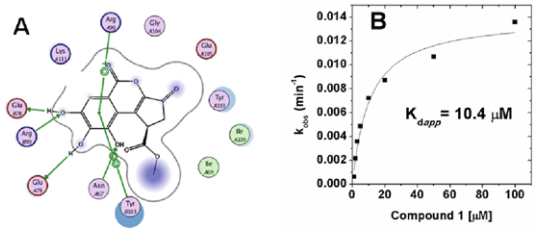


Benzo[*d*]oxazole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. Many of these tested compounds exhibited potent antifungal activity.

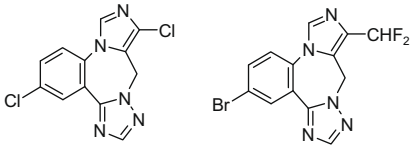




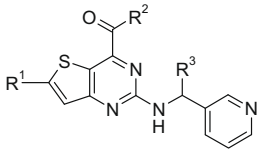
A novel series of pyridine derivatives was synthesized and identified as potent and selective CB_2 agonists.



Kinetic and molecular docking of highly selective inactivation of triosephosphate isomerase from *Trypanosoma cruzi* by brevifolin carboxylate derivatives is reported.

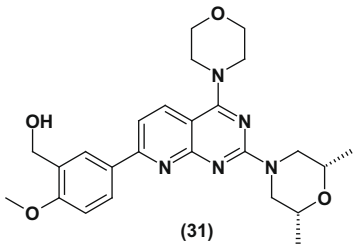


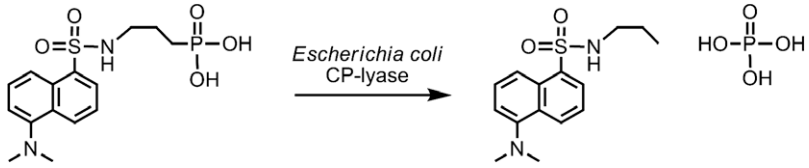
Lead optimisation of the imidazo[1,5-*a*][1,2,4]-triazolo[1,5-*d*][1,4]benzodiazepine class led to the identification of two clinical leads [RO4882224 (**11**) and RO4938581 (**44**)] functioning as novel potent and selective $GABA_A$ α5 inverse agonists. The unique pharmacological profiles and optimal pharmacokinetic profiles resulted in in vivo activity in selected cognition models.

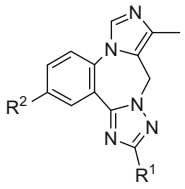


A novel class of antagonists of the human adenosine A_{2B} receptor is described. Offering interesting pharmacokinetic properties, these derivatives may prove useful in elucidating the role of adenosine A_{2B} receptors in a number of human disease conditions.

The discovery and optimization of a novel series of inhibitors of mTOR kinase are described. Compound **31**, KU-63794, has low nanomolar potency against mTOR kinase and is highly selective relative to other PI3K-related kinases.

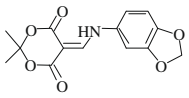






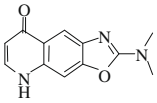
We have discovered a novel class of imidazo[1,5-*a*][1,2,4]-triazolo[1,5-*d*][1,4]benzodiazepines as a promising class of $GABA_A$ α5 ligands which combine both high subtype binding selectivity with a marked inverse agonism. Two compounds (**10e** and **11f**) were found to be active in an in vivo model for cognitive improvement.

Compound **1k**



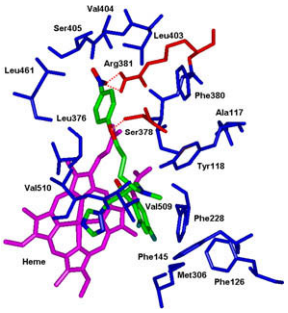
IC_{50} *P. falciparum* (W2) = 10 μM
Specificity Index *P. falciparum* (W2) = 25

Compound **2h**

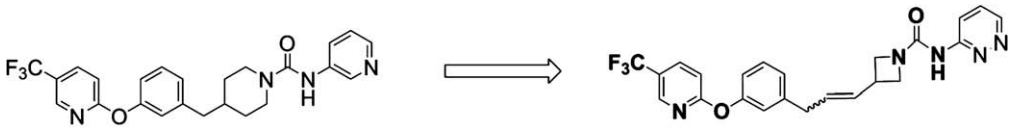


IC_{50} *P. falciparum* (W2) = 40 μM
Specificity Index *P. falciparum* (W2) > 3.1

A series of quinolinones was synthesized by condensation of aminoheterocycle with Meldrum's acid derivatives (yield 90%), followed by thermal cyclization of the resulting synthetic intermediate (yield 58%). One intermediate compound (**1k**) and one final product (**2h**) display interesting antiparasitic activities.



A series of new azoles with excellent in vitro antifungal activity were rational designed and synthesized.



The design and synthesis a series of novel FAAH irreversible azetidine urea inhibitors from PF-3845 are described. Our SAR studies allowed us to optimize this series resulting in the identification of compounds **13** which were potent inhibitors of both human and rat enzyme. This series of compounds illustrated good hydrolase selectivity along with good rat PK properties.

*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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