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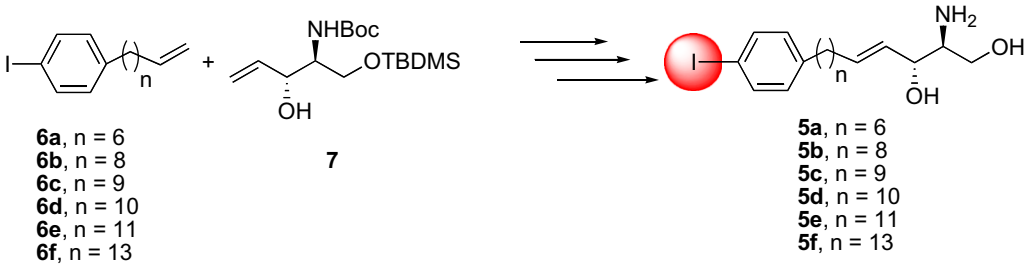
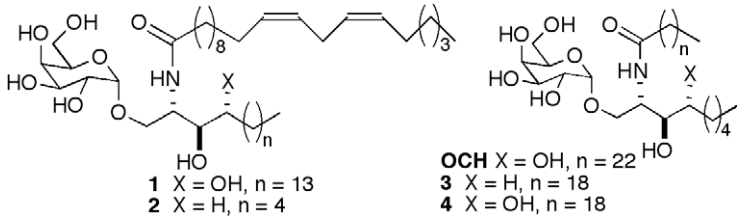
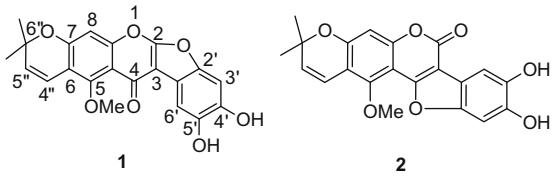
Contents

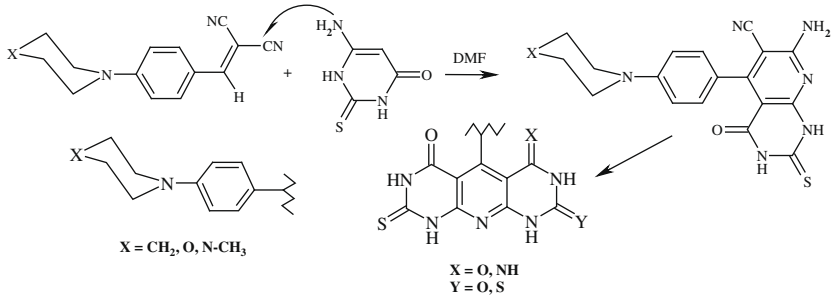
ARTICLES

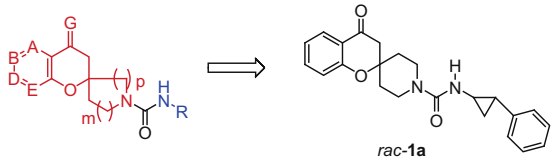




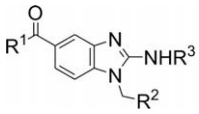


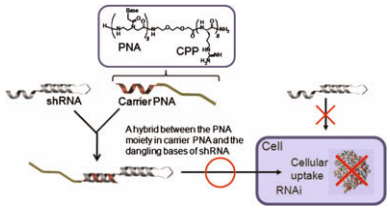
A pair of isomeric isoflavonoid derivatives, Hirtellanines A (**1**) and B (**2**), has been isolated from the roots of *Campylotropis hirtella*. Hirtellanines A showed strong immunosuppressive activities.



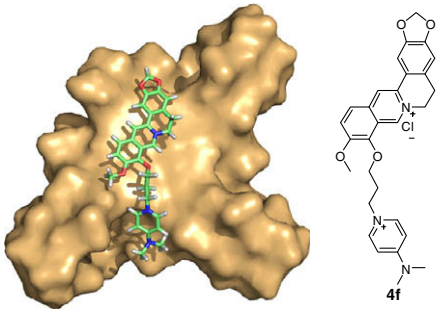


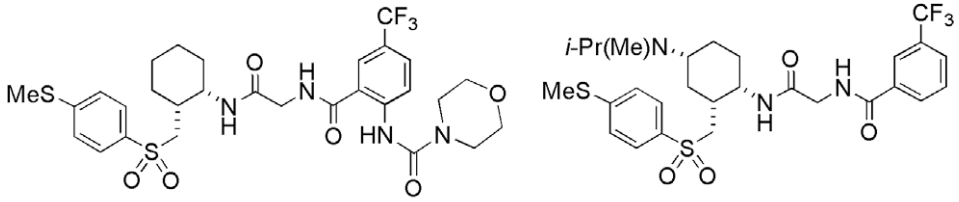
Spirocyclic secondary amine-derived trisubstituted ureas were identified as highly potent, bioavailable and selective soluble epoxide hydrolase (sEH) inhibitors. Despite good oral exposure and excellent ex vivo target engagement in blood, one such compound, *rac*-**1a**, failed to lower blood pressure acutely in spontaneously hypertensive rats (SHRs). This study posed the question as to whether sEH inhibition provides a robust mechanism leading to a significant antihypertensive effect.





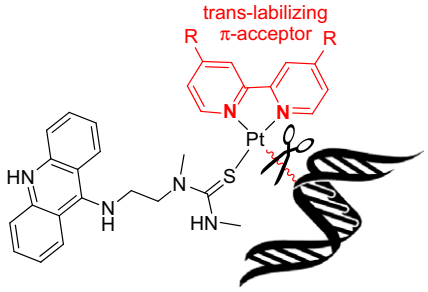
A peptide nucleic acid conjugated to a cell-penetrating peptide (carrier PNA) sequence-specifically binds to an shRNA bearing complementary dangling bases, and the carrier PNA delivers the shRNA effectively into cells.

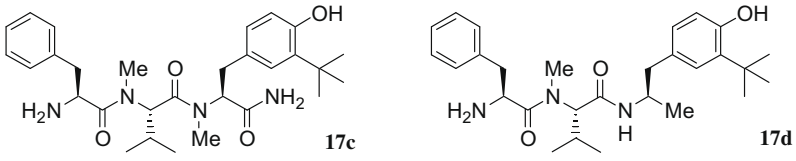




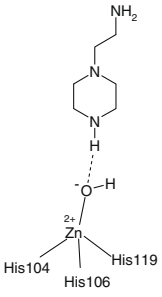
29 CCR2 Bnd IC_{50} = 2.7 nM

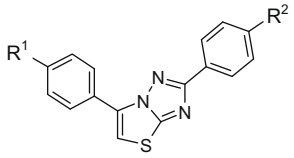
54 CCR2 Bnd IC_{50} = 1.3 nM





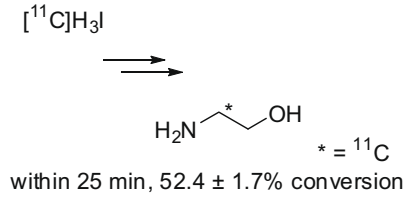
Peptidomimetic motilin antagonists (**17c** and **17d**) were identified. Both compounds dose-dependently suppressed motilin-induced colonic and gastric motility in conscious dogs.



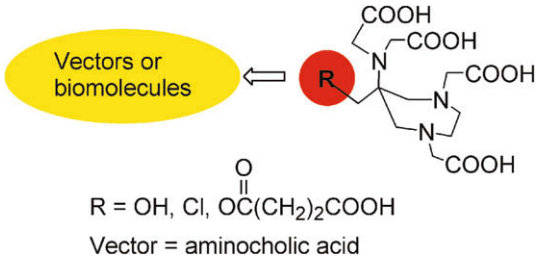


14a: $R^1 = CONHCH_2CH_2\overset{+}{N}HC_5H_{10}$ $R^2 = OCH_2CH_2\overset{+}{N}HC_5H_{10}$ ΔT_m = 11.2 °C
19: $R^1 = OCH_2CH_2\overset{+}{N}HC_5H_{10}$ $R^2 = OCH_2CH_2\overset{+}{N}HC_5H_{10}$ ΔT_m = 8.7 °C

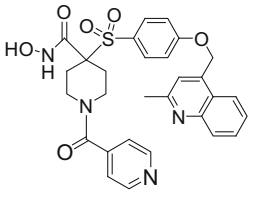
Two of the title compounds (**14a**, **19**) bearing cationic side chains present high selectivity for telomeric G-quadruplex over duplex DNA.



A practical and accessible method for the synthesis of 2-amino[2-^{11}C]ethanol is reported.

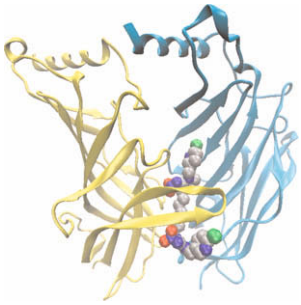


Novel bifunctional ligands based on the AAZTA structure with different functional groups are reported. The Gd-complexes show optimal magnetic properties for Magnetic Resonance-Molecular Imaging applications.

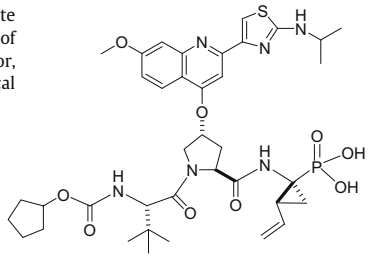


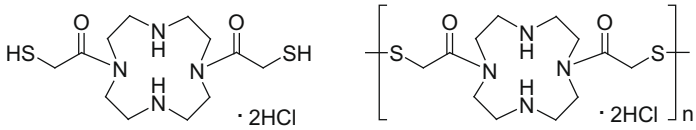
11a-n

The activity of a series of α-sulfone piperidine hydroxamate TACE inhibitors **11a–n** bearing a quinolinyl methyl P1′ group was compared to α-and β-sulfone piperidine hydroxamates with a butynyloxy P1′ group.



The design and preparation of highly potent tricyclic HIV integrase inhibitors are reported. The lead compound has shown good oral bioavailability in both rat and dog. A novel class of phosphonate derivatives was designed to mimic the interaction of product-like carboxylate based inhibitors of HCV NS3 protease. A phosphonic acid was demonstrated to be a potent HCV NS3 protease inhibitor, and a potential candidate for treating HCV infection. The syntheses and preliminary biological evaluation of this phosphonate class of inhibitor are described.

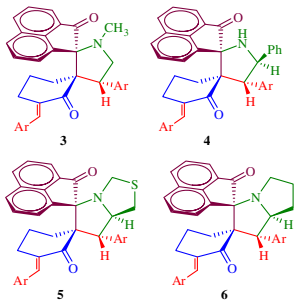


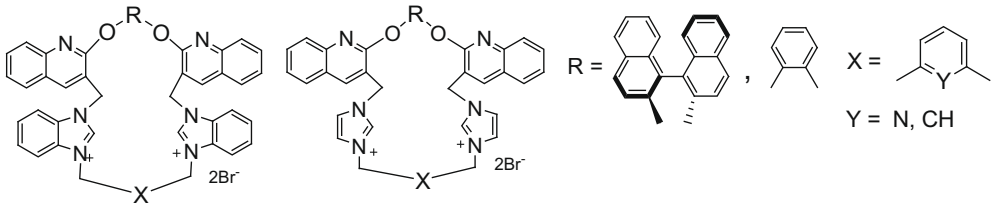


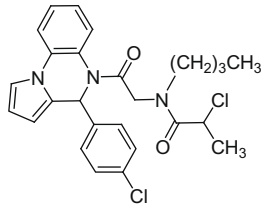
BMAC **PBMAC**

The disulfide bonds-containing polymer (PBMAC) can promote the cleavage of DNA more efficiently than its monomer (BMAC) under physiological conditions.

Twenty eight spiro-cyclohexanones were synthesized via 1,3-dipolar cycloaddition of azomethine ylides to a series of 2,6-bis[(*E*)-arylmethylidene]cyclohexanones and were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Two compounds, 4-(2,4-dichloro-phenyl)-5-phenylpyrrolo-(spiro[2.2″]acenaphthene-1″-one)-spiro[3.2′]-6′-(2,4-dichlorophenylmethylidene)-cyclohexanone (**4i**) and spiro-[5.2″]acenaphthene-1″-one-spiro [6.2′]-6′-(2,4-dichlorophenylmethylidene)-cyclohexanone-7-(2,4-dichlorophenyl)tetrahydro-1 *H*-pyrrolo[1,2-*c*][1,3]thiazole (**5i**) display maximum activity in vitro with MIC of 0.4 μg/mL and were 4 and 15 times more potent than ethambutol and pyrazinamide, respectively.

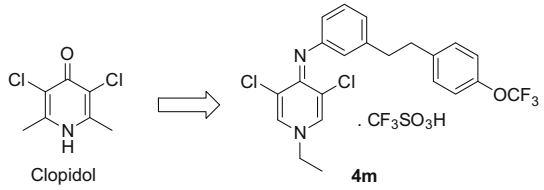






compound **45** CB_1 K_i = 45 nM

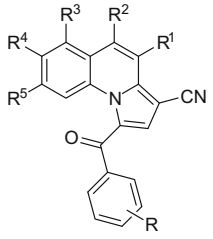
Hit-to-lead optimization of a novel series of *N*-alkyl-*N*-[2-oxo-2-(4-aryl-4*H*-pyrrolo[1,2-*a*]quinoxaline-5-yl)-ethyl]-carboxylic acid amides, derived from a high throughput screening (HTS) hit, are described.



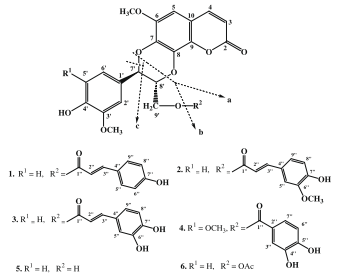
Clopidol **4m**

IC_{50} = 9.73 μM (*P. falciparum* W2) IC_{50} = 0.94 μM (*P. falciparum* W2)

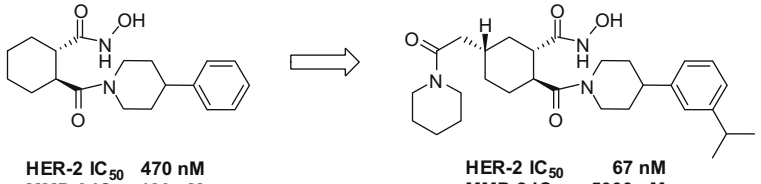
(1*H*-Pyridin-4-ylidene)amines designed as clopidol isosteres were active against *Plasmodium falciparum* W2 (chloroquine-resistant) and FCR3 (atovaquone-resistant) strains in the low micromolar range.

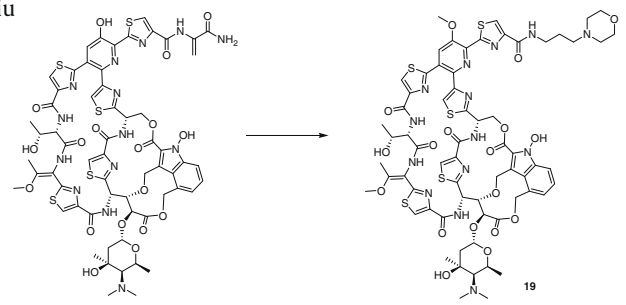


The synthesis and SAR studies of the 4-, 5-, 6-, 7- and 8-positions of apoptosis inducing 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines are reported.

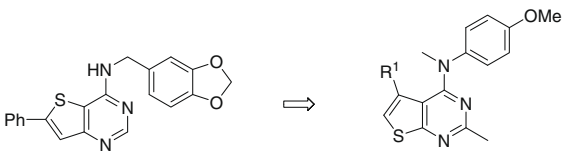


Structures and important mass fragmentation pattern of coumarinolignoids (**1**–**6**).

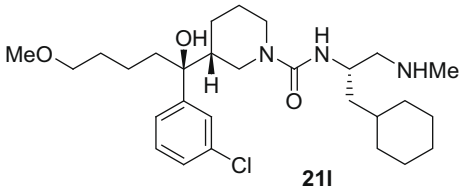




Synthesis and SAR of novel water-soluble amide analogs of nocathiacin **1** are reported. Compound **19** was selected for further evaluation.



The discovery and SAR studies of 4-anilino-*N*-methylthieno[3,2-*d*]pyrimidines and 4-anilino-*N*-methylthieno[2,3-*d*]pyrimidines as potent apoptosis inducers are reported.



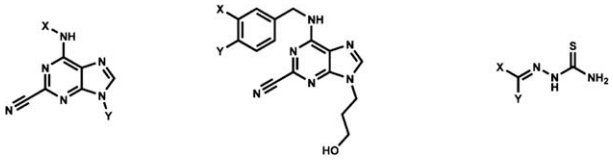
21l

Human renin IC_{50} = 0.47 nM

Plasma renin IC_{50} = 13 nM

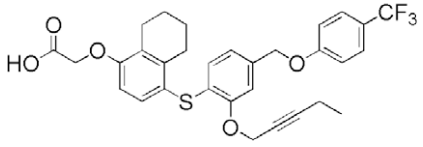
%F (dog) = 38

MW = 508

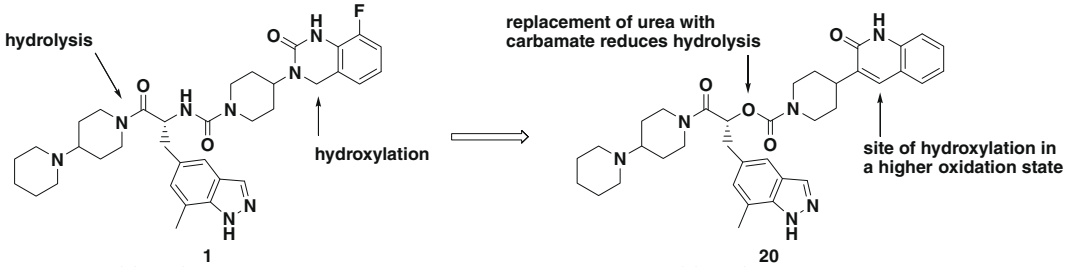


1a-aw 2a-ad 3a-am

Inhibitor 2w
X = acetylamino, Y = H
EC_{50} vs. 3D7, 0 mM pepstatin A = 15 ± 3 μM
EC_{50} vs. 3D7, 10 mM pepstatin A = 6 ± 3 μM
EC_{50} vs. K1, 0 mM pepstatin A = 15 ± 3 μM
EC_{50} vs. K1, 10 mM pepstatin A = 11 ± 5 μM

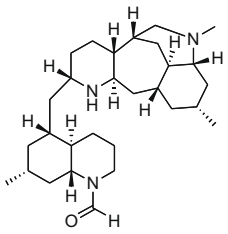


The discovery and optimization of a series of potent PPARδ full agonists with partial agonistic activity against PPARγ is described.

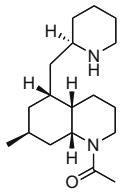


1
CGRP IC_{50} = 0.026 nM

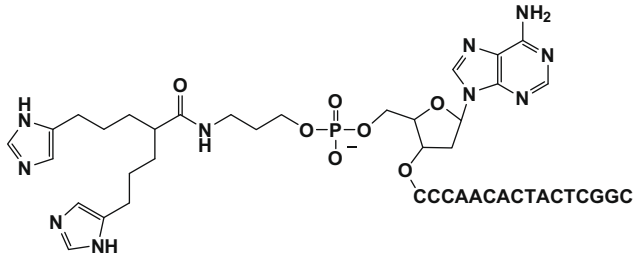
20
CGRP IC_{50} = 0.017 nM



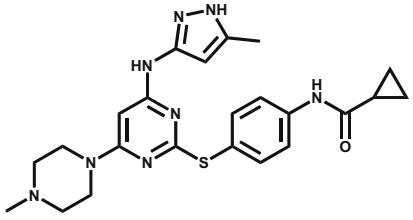
serratezomine D (**1**)



serratezomine E (**2**)

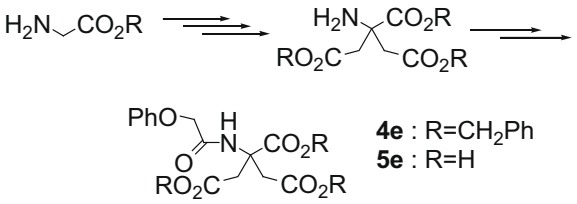


5' bis-imidazole *AS-ODN*



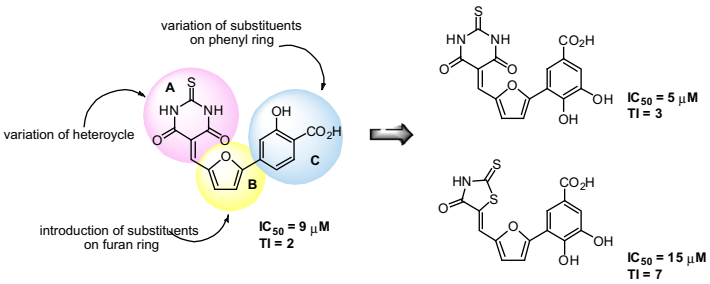
MK-0457 (VX-680)

The identification of a novel series of Aurora kinase inhibitors and exploitation of their SAR, which led to the discovery of MK-0457 (VX-680), is described.

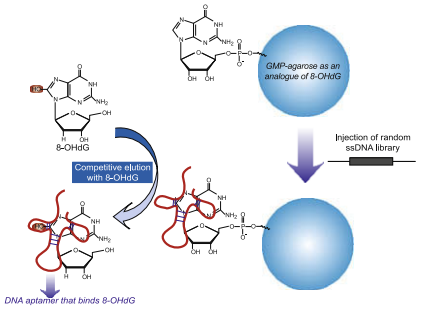


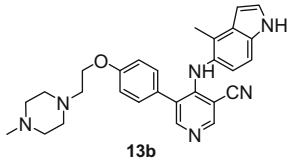
4e : R=CH_2Ph
5e : R=H

The title compounds have been synthesized by alkylation of glycinate imines with bromoacetates, acrylate or fumarate. Their biochemical activity was evaluated against representative β-lactamases of all classes. Out of these molecules, tested as free acids or esters, **5e** and **4e** emerged as modest inhibitor of BS3 and good inhibitor of OXA-10 enzymes respectively. This discovery is consistent with the active site hydrophobic character of class D comparatively to class A β-lactamases.



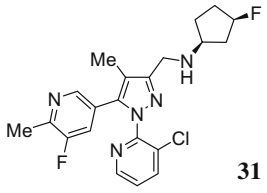
A novel compound inhibiting HIV-1 integrase has been identified by means of virtual screening techniques. A small family of structurally related molecules has been synthesized and biologically evaluated with some of the compounds possessing micromolar activity both in enzymatic and cellular assays.





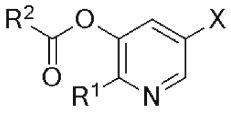
13b

Analog **13b** with a 4-methylindol-5-ylamino group at C-4 and a 4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl group at C-5 had an IC_{50} value of 7.4 nM for the inhibition of PKCθ.

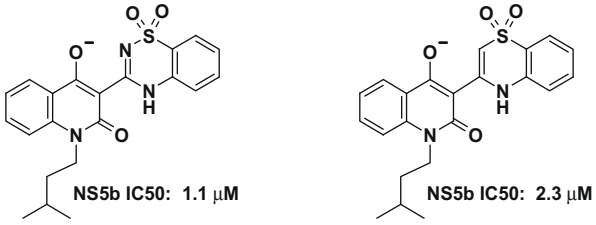


31

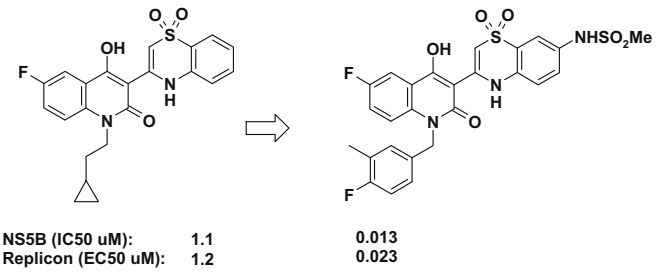
The synthesis and SAR of new ORL1 antagonists is described. Compound **31** displayed high intrinsic potency and selectivity against μ- and κ-opioid receptors, and hERG K^+ channel.

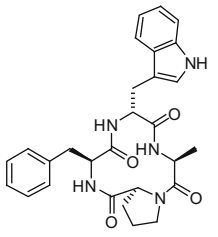


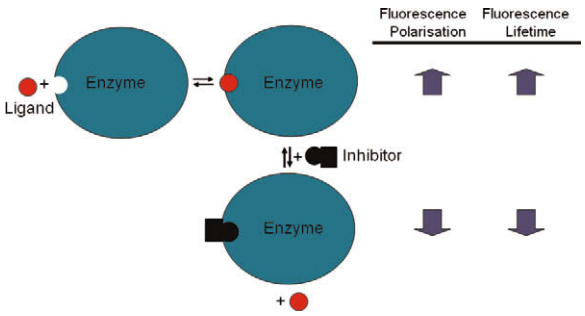
The non-peptidic inhibitors against HRV 3C protease, a series of novel heteroaromatic esters were synthesized and evaluated their activity.

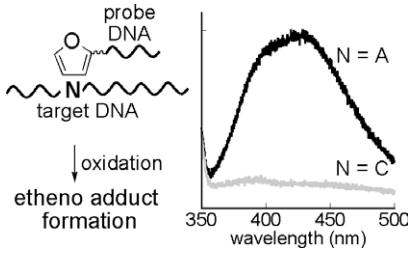


The importance of internal hydrogen bonding in a series of benzothiadiazine and 1,4-benzothiazine NS5b inhibitors has been explored. Computational analysis suggests HCV NS5b polymerase activity is best explained using the anionic forms.

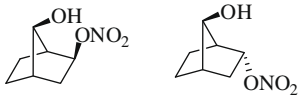




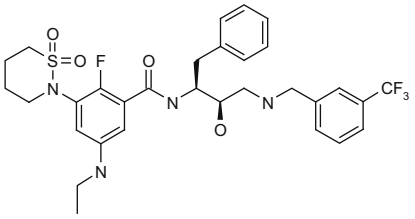




We developed a 1,N^6-ethenoadenosine-forming reaction at a target adenine in DNA duplex and applied it to a mutation diagnosis.

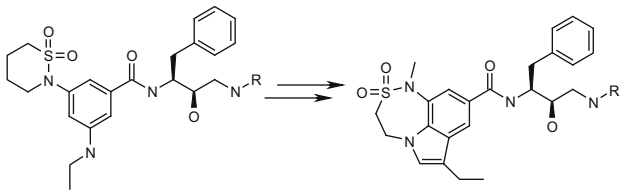


K_i: 13.1 μM K_i: 11.7 μM

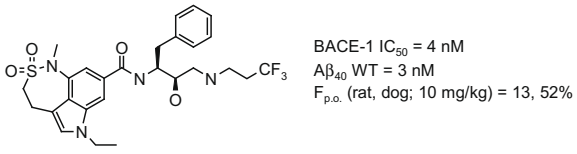


GSK188909
BACE-1 IC_{50} = 2 nM
$A\beta_{40}$ (WT, Swe) = 5, 30 nM
Rat $F_{p.o.}$ (10 mg/kg) = 7%

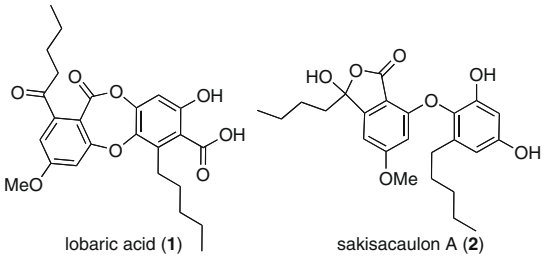
This Letter demonstrates that our first generation of hydroxyethylamine BACE-1 inhibitors was unlikely to deliver a molecule suitable for progression in clinical trials; hence the necessity to discover a second generation of inhibitors with improved pharmacokinetics.



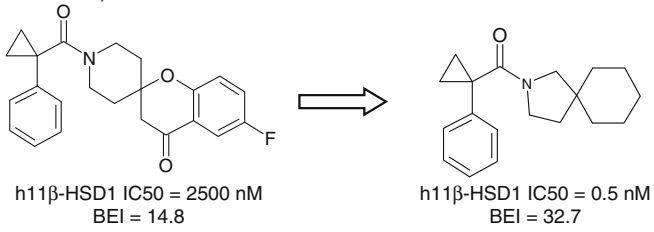
This article discloses the strategy that led to the discovery of a second series of hydroxyethylamine BACE-1 inhibitors with non-prime side substituents of higher binding efficiency.



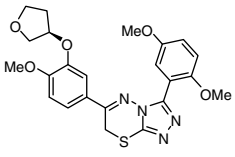
This article discloses the strategy that led to stable hydroxyethylamine BACE-1 inhibitors with nanomolar cell potency and good oral bioavailability and give insights into the design of compounds with the potential of increased brain penetration.



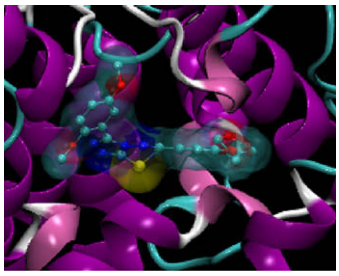
Lobaric acid (**1**) has been isolated from lichen, *Stereocaulon sasakii* together with a new benzofuran, sakisacaulon A (**2**). Lobaric acid (**1**) inhibited the polymerization of tubulin. Structure–activity relationship of lobaric acid and its derivatives on inhibitory activity of tubulin polymerization was discussed.



Structure-based drug design was used to optimise the initial hit yielding a sub-nanomolar IC50 inhibitor (0.5 nM) on human 11β-HSD1 with a high binding efficiency index (BEI of 32.7) which was selective against human 11β-HSD2 (selectivity ratio > 200000).



PDE isoform	*IC_{50} (nM)*
PDE4A1A	0.26
PDE4B	2.3
PDE4B	1.6
PDE4D	1.9



*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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