Bioorganic & Medicinal Chemistry Letters 20 (2010) 1465–1484

Contents lists available at ScienceDirect

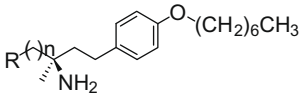
Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 5, 2010

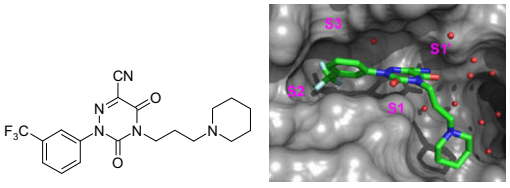
Contents

ARTICLES

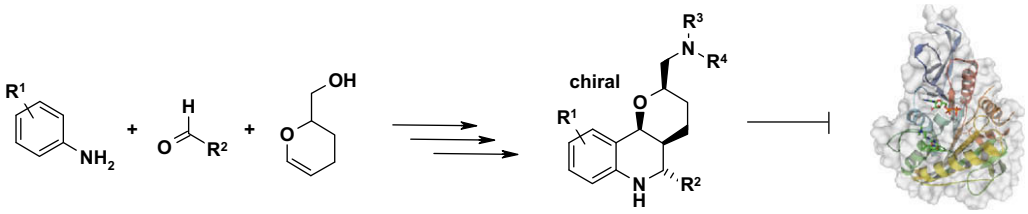


R = CO_2H, $P(O)(OH)_2$, SO_3H, heterocycle
n = 0-2

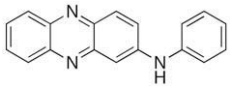
This work describes various carboxylic acids, phosphonic acids, sulfonic acids, tetrazoles as well as sulfonylhydantoins to act as agonists on the $S1P_1$ receptor.



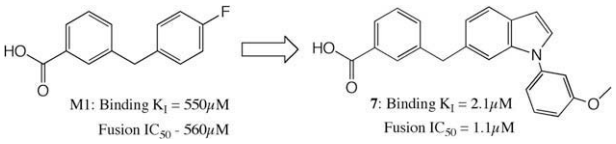
A series of potent and selective dioxo-triazine inhibitors of cathepsin K was identified from HTS.

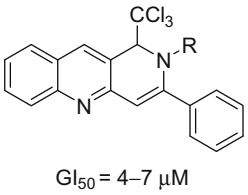


The synthesis, SAR, co-crystal structure and in vivo activity of hexahydro-2*H*-pyrano[3,2-*c*]quinolines (HHPQs) as potent and selective inhibitors of the mitotic kinesin-5 are described.

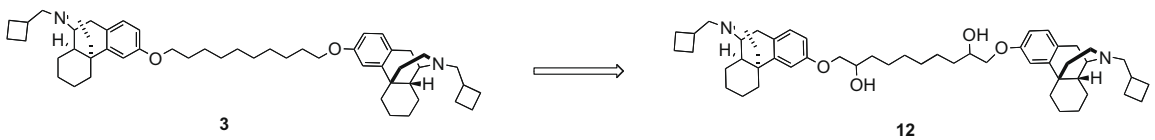


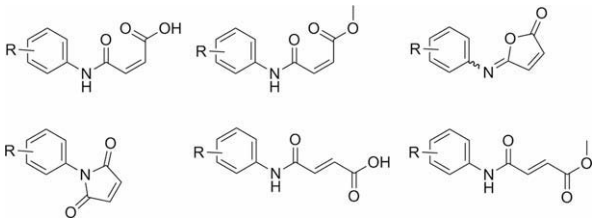
The synthesis and biological activity of *N*-phenylphenazin-2-amine and 4 iodinated derivatives is reported.



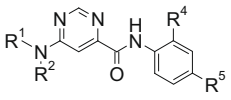


The synthesis and antiproliferative activity of novel 1,2-dihydro-3-phenyl-1-(trichloromethyl)benzo[*b*][1,6]naphthyridines is reported.

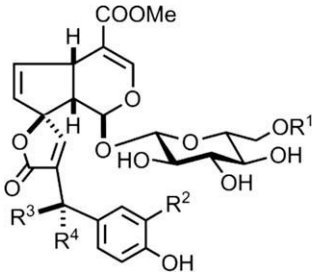




Cytotoxicity and QSAR studies on compounds containing the 1,4-dioxo-2-butenyl moiety viz, *N*-arylmaleamic acids, methyl *N*-arylmaleamates, *N*-arylisomaleimides, *N*-arylmaleimides, *N*-arylfumaramic acids, and methyl *N*-arylfumaramates are reported.

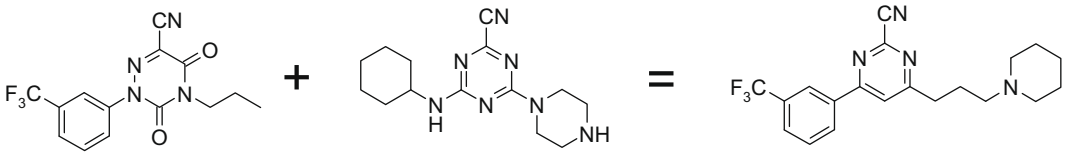


The discovery of a novel series of S1P1 agonists is described. Several single-digit nanomolar S1P1 agonists were discovered, and a selected compound was shown to be able to induce lymphopenia in mice after oral dosing.

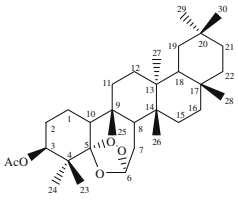


	R^1	R^2	R^3	R^4
1	Ac	OMe	H	OH
2	Ac	H	H	OH
3	H	OMe	H	OH
4	H	H	H	OH
5	H	OMe	=O	=O

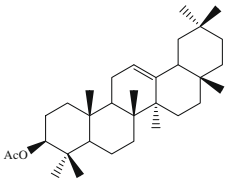
A new phenylpropanoid conjugated iridoid (**1**) together with four known congeners (**2**–**5**) was isolated from the leaves of *Morinda morindoides* as potent anti-malarial principles through bioassay-guided separation.



Morphing structural features of HTS-derived chemotypes led to the discovery of novel 2-cyano-pyrimidine inhibitors of cathepsin K with improved pharmacokinetic profile.

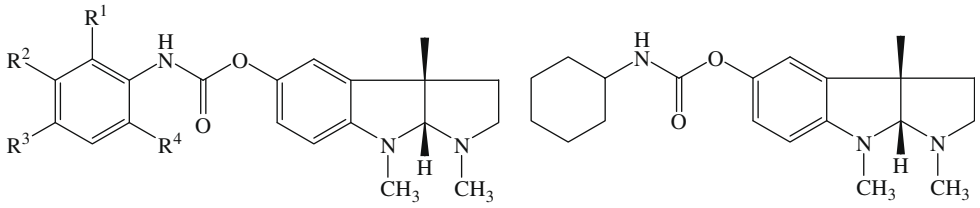


Aceranol acetate (**1**)

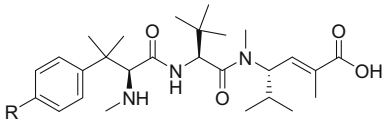


β-Amyrin acetate (**2**)

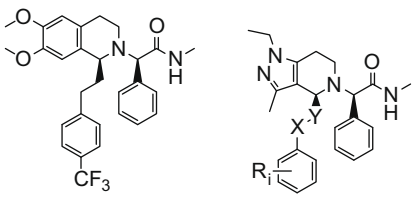
Bioassay-guided fractionation of the MeOH extract led to the isolation of six compounds, including one new triterpene (**1**). Compound **2** reduced the LPS-induced secretion of TNF-α in a RAW264.7 cell line.



A series of physostigmine analogues, were prepared and evaluated for cholinesterase inhibition activities. Compound **17** especially exhibited significantly higher selectivity over BChE than phenserine, a compound currently on clinical trial. Discussion about the relationships between structure and activity of these derivatives was also presented.

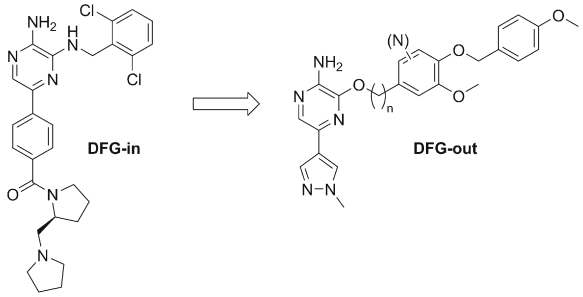


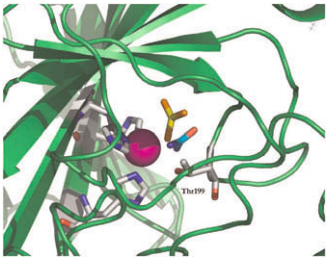
Taltobulin (HTI-286): R = H
HTI-042: R = MeO



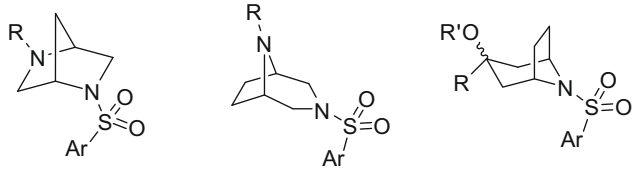
Almorexant
(ACT-078573)

A novel series of dual orexin receptor antagonists was prepared by heteroaromatic five-membered ring system replacement of the dimethoxyphenyl moiety contained in the tetrahydroisoquinoline core skeleton of almorexant, a dual orexin receptor antagonist in phase 3 clinical development.



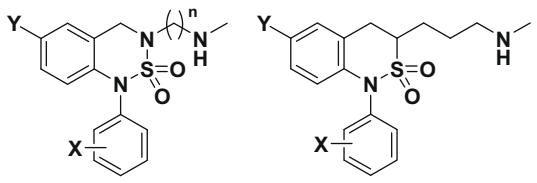


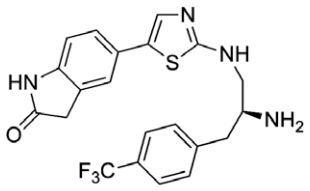
CS_3^{2-}: K_i = 9.7 μM (CA IX); K_i = 120 μM (CA XII); K_i = 660 μM (CA XIV).



Ar = 4-^{t}Bu-phenyl; R, R' = alkyl, cycloalkyl, etc.

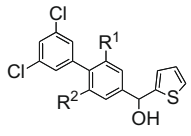
Inhibition of 11β-HSD1 has demonstrated potential in the treatment of various components of metabolic syndrome. We wish to report herein the discovery of novel azabicyclic sulfonamide based 11β-HSD1 inhibitors. Highly potent compounds exhibiting inhibitory activities at both human and mouse 11β-HSD1 were identified. Several compounds demonstrated significant in vivo activity in the mouse cortisone challenge assay.



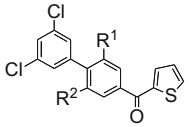


36

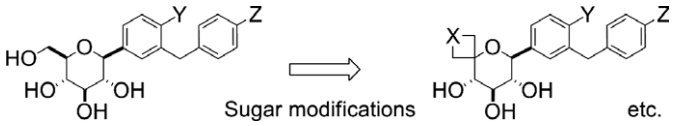
36	IC_{50}, nM
AKT1	18.3±6.4
PKA	167±50
CDK2	185±96
pPRAS40	300±80

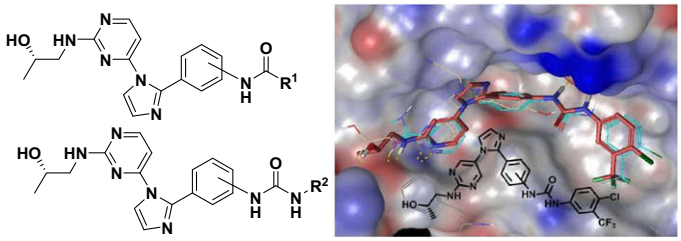


[^{11}C]**2**: $R^1 = O^{11}CH_3$, $R^2 = OCH_3$,
[^{11}C]**3**: $R^1 = O^{11}CH_3$, $R^2 = OH$

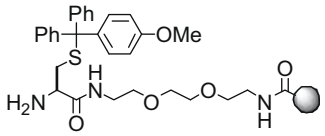


[^{11}C]**4**: $R^1 = O^{11}CH_3$, $R^2 = OCH_3$,
[^{11}C]**5**: $R^1 = O^{11}CH_3$, $R^2 = OH$

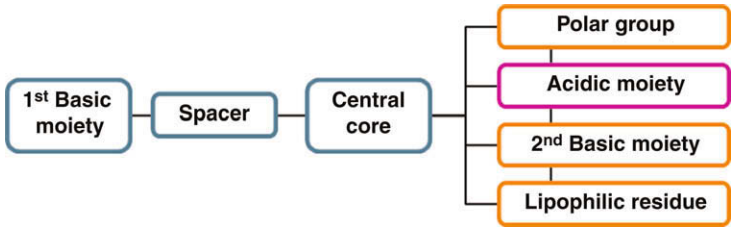


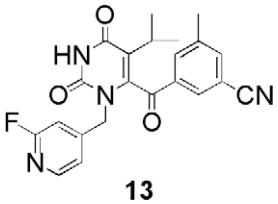


A series of pyrimidin-4-yl-1*H*-imidazol-2-yl derivatives **7, 8, 9** and their antiproliferative activities against A375 human melanoma cell line and WM3629 cell line were described.



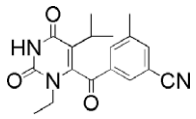
Synthesis of *S*-trityl-L-cysteine (STLC) analogue-immobilized affinity beads and biochemical analysis of the cellular target of STLC derivatives were reported.





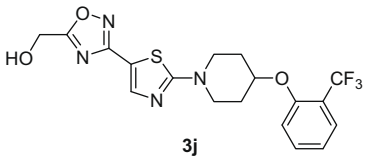
13

A series of N1-heterocyclic pyrimidinediones were evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors, resulting in the discovery of compound **13**.



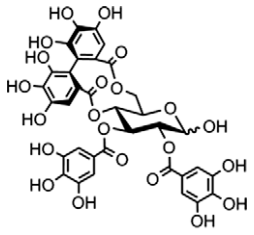
10b

Evaluation of a series of *N*1-alkyl pyrimidinediones as HIV-1 non-nucleoside reverse transcriptase inhibitors identified compound **10b**, which represents the lead compound with pharmacokinetics and antiviral potency that may support once-daily dosing.



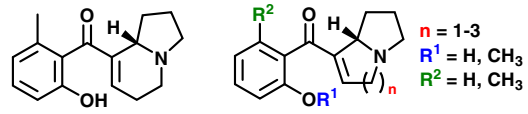
3j

A potent and bioavailable SCD inhibitor, **3j** was identified from optimization of a lead thiazole compound and its in vivo SCD inhibition studies are described.



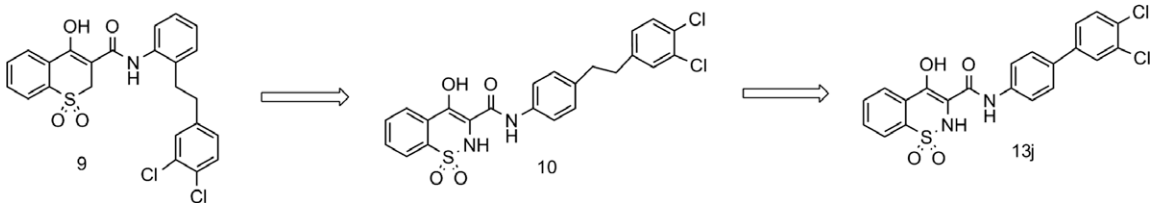
tellimagrandin I (**1**)

Tellimagrandin I (**1**) along with two relative tannins were disclosed as the HCV invasion inhibitors from Rosae Rugosae Flos by use of the model virus expressing the HCV envelopes E1 and E2.



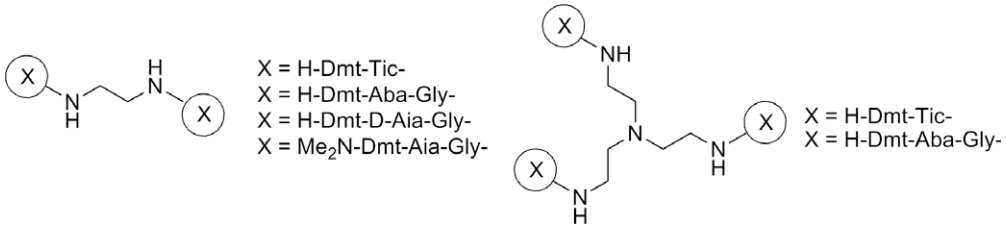
(+)-**elaeocarpenine** **elaeocarpenine analogs**

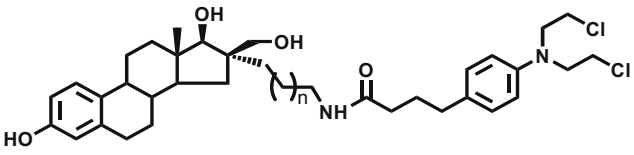
We report the first total synthesis of elaeocarpenine and its analogs and evaluation of their in vitro binding affinities to μ-, δ- and κ-opioid receptor subtypes.



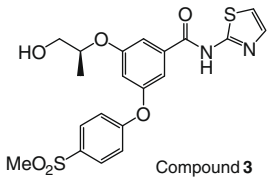
9 10 13j

The design and synthesis of a series of potent and selective mPGES-1 inhibitors based on an oxicam template are described. Our SAR studies allowed us to optimize this series resulting in the identification of compound **13j** which demonstrated potent inhibition in both enzyme and cellular assay. This series of compounds illustrated good mPGES-1 inhibition along with good selectivity over COX-2 and 6-keto $PGF_{1\alpha}$.

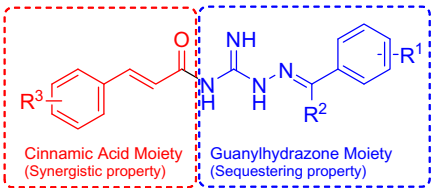




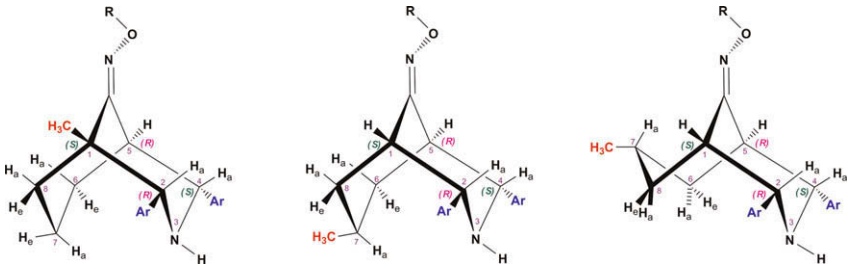
The synthesis of a series of estradiol–chlorambucil hybrids is reported. The hybrids showed significant in vitro anticancer activity when compared to chlorambucil on breast cancer cell lines.

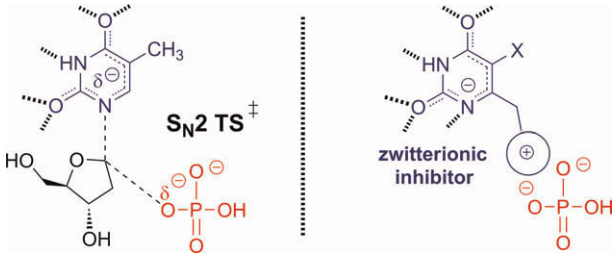


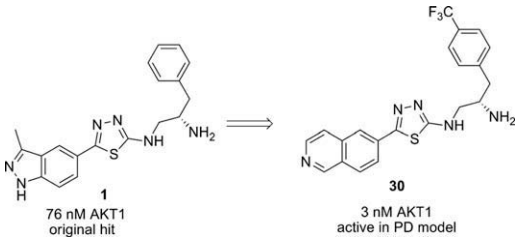
The in vitro covalent binding results that were observed during the course of evaluating the compound **3** for the treatment of type-2 diabetes are described.

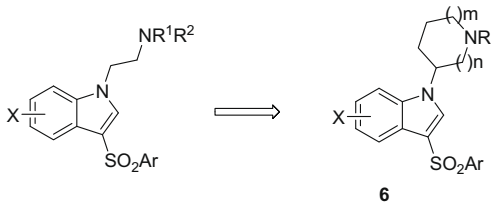


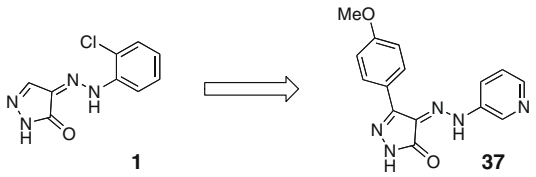
Microwave assisted synthesis of 20 novel phenylacrylamide derivatives incorporating cinnamic acids and guanylhydrazones and in vitro evaluation against *Mycobacterium tuberculosis* is described.



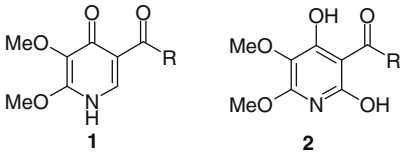




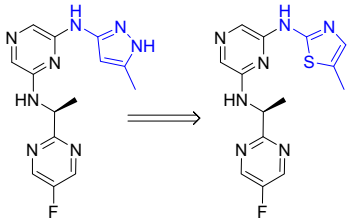


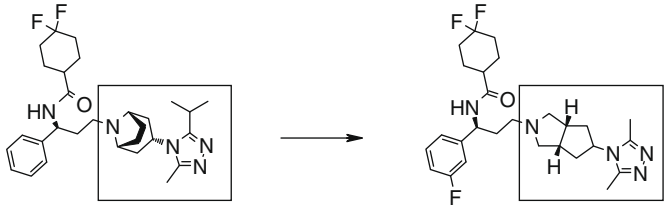


Molecular Weight	222.6	295.3
GSK3β Ki	1.49 μM	0.8 nM
Binding Efficiency Index	26.2	28.0

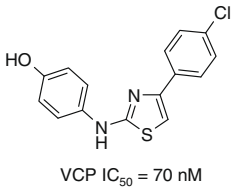


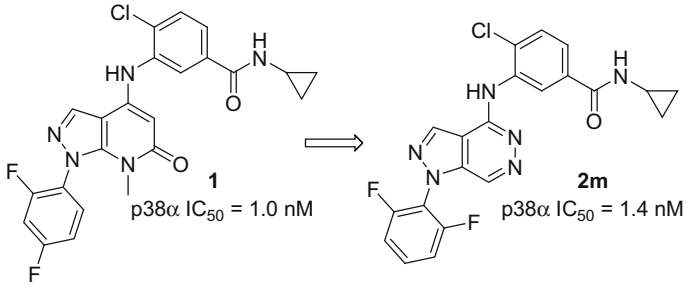
This Letter describes the synthesis of a series of synthetic atpenin analogs of formulae **1** and **2** as potential agricultural fungicides where some compounds showed potent mammalian and fungal mitochondrial complex II inhibition.

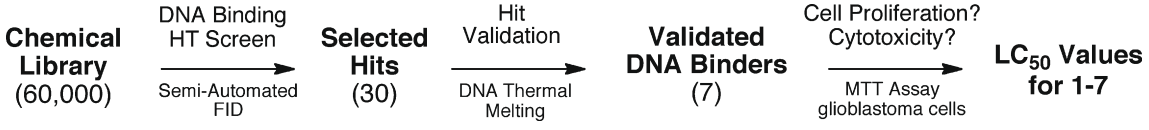




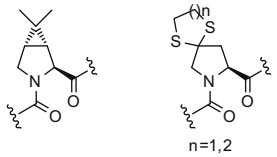
The bicyclic 5-amino-3-azabicyclo[3.3.0]octanes were shown to be effective replacements for the 3-amino-8-azabicyclo[3.2.1]octane found in the CCR5 antagonist maraviroc.

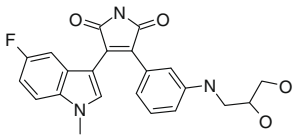






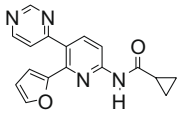
High-throughput fluorescent intercalator displacement (HT–FID) was adapted to the semi-automated screening of a commercial compound library leading to the discovery of cytotoxic DNA-targeted agents.





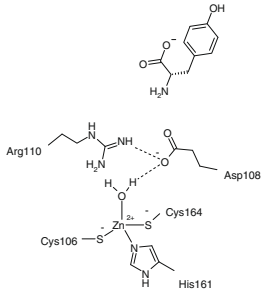
34

A series of maleimides was discovered with high potency and good selectivity for GSK-3β. The most potent compound **34** has an IC_{50} of 0.6 nM for GSK-3β, over 100-fold selectivity against a panel of other kinases, and shows efficacy in rat osteoporosis models.

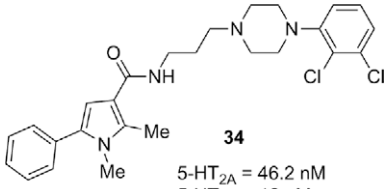


9: A_{2B} Ki = 4±1 nM

The potent and selective A_{2B} adenosine receptor antagonist **9** was shown to have good oral bioavailability in the rat.

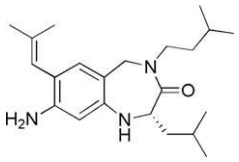


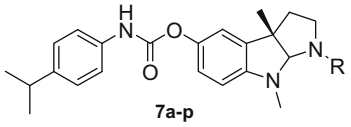
Arylpiperzine-containing pyrrole 3-carboxamide derivatives were synthesized and evaluated as novel antidepressant compounds. The various analogues were efficiently prepared and bio-assayed for binding to 5-HT_{2A}, 5-HT_{2C} receptor, and 5-HT transporter. Based on their in vitro and in vivo activities as well as selectivity over other neurotransmitter receptors and PK profiles, **34** was identified as a lead compound. Consequently, this pyrrole series of compounds appears to be promising enough to warrant further investigation.



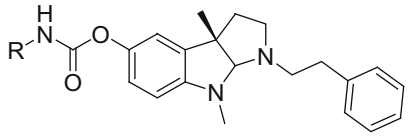
34

5-HT_{2A} = 46.2 nM
5-HT_{2C} = 12 nM
SERT = 61.7 nM

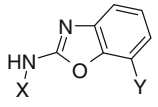




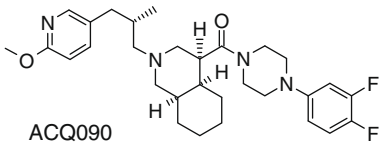
7a-p



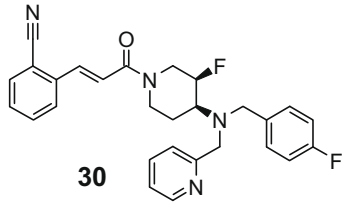
3a-u



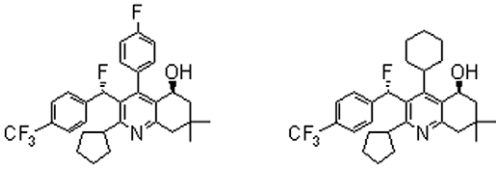
X = aryl
Y = aryl, heteroaryl



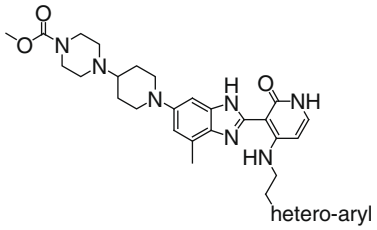
Starting from non-peptidic sst_1-selective somatostatin receptor antagonists, first compounds with mixed sst_1/sst_3 affinity were identified by directed structural modifications. Systematic optimization of these initial leads afforded novel, enantiomerically pure, highly potent and sst_3-subtype selective somatostatin antagonists based on a (4*S*,4a*S*,8a*R*)-decahydro-isoquinoline-4-carboxylic acid core moiety. The representative compound ACQ090 can efficiently be synthesized and shows promising PK properties in rodents.



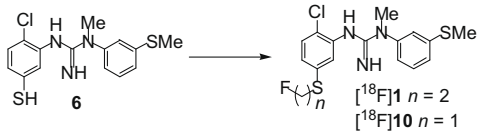
Two series of new PAR1 antagonists have been identified. The first incorporates a cinnamoylpiperidine motif and the second a cinnamoylpyridine pattern. The synthesis, biological activity and structure–activity relationship of these compounds are presented. In each series, one analog showed potent in vivo antithrombotic activity in a rat AV shunt model, with up to 53% inhibition at 1.25 mpk iv for compound **30**.

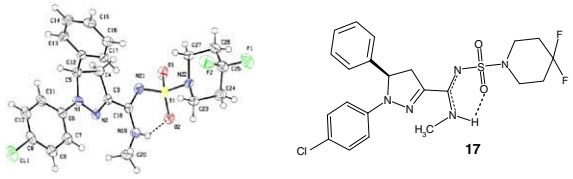


Variations in the 4-position of **4** led to novel CETP inhibitors. The cyclohexyl group was found to be a suitable replacement for the *p*F-phenyl substituent. Compound **11b** was identified as a potent CETP inhibitor with an excellent in vitro and PK-profile.

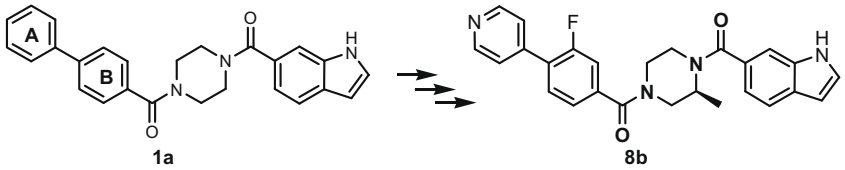


The SAR of PXR transactivation by 3-(benzimidazol-2-yl)-pyridine-2-one based ATP competitive inhibitors of Insulin-like Growth Factor 1 Receptor kinase (IGF-1R) is discussed. Compounds without PXR transactivation, with in vivo antitumor activity, reduced protein binding and improved oral exposure are presented.

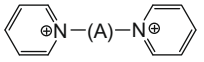




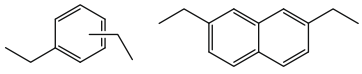
Compound **17** was shown to elicit an unexpected intramolecular H-bonding pattern.

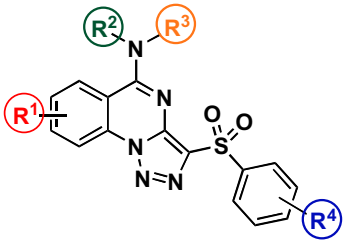


Optimization of the initial growth hormone secretagogue receptor (GHSR) partial agonist **1a** provided the antagonistic tool compound **8b** that featured with improved potency, complete elimination of the partial agonist activity, and suitable PK profiles.

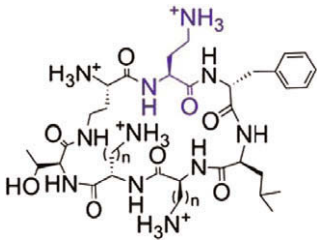


A= $(CH_2)_{1\text{-}12}$; (*E/Z*)-$CH_2CH{=}CHCH_2$; $(CH_2)_{1\text{-}2}O(CH_2)_{1\text{-}2}$



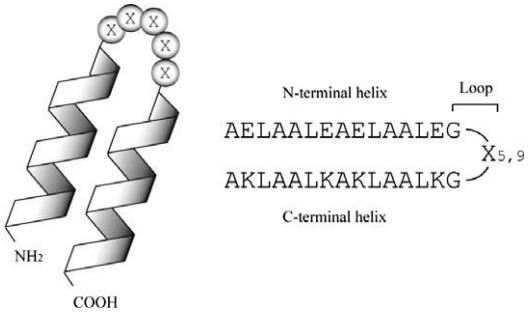


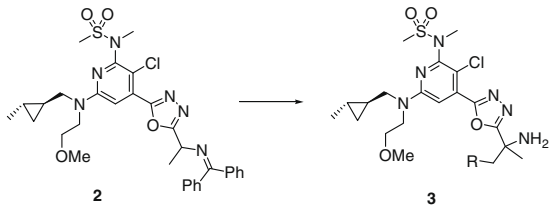
The synthesis and biological evaluation of a focused library of wall teichoic acid biosynthesis inhibitors is reported.



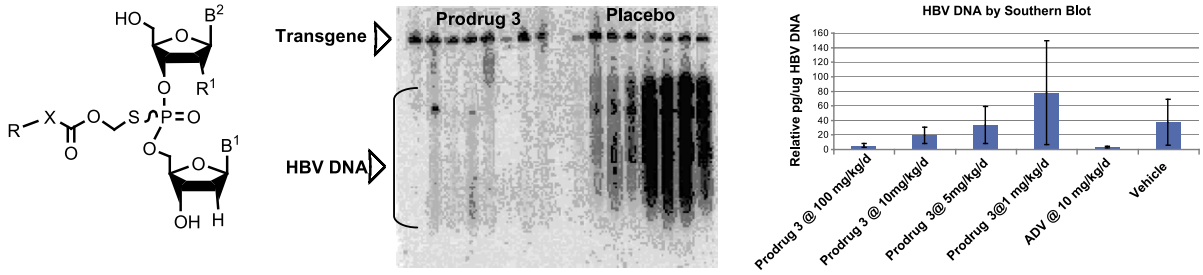
Dab[2] (Dab=L-2,4-Diaminobutyric acid) residue of Polymyxin B heptapeptide plays a critical role in permeation of the outer membrane of *Escherichia coli*.

A phage-displayed library of the loop region in the de novo designed helix–loop–helix peptide was constructed and screened against Aurora-A kinase to provide the inhibitory peptides.

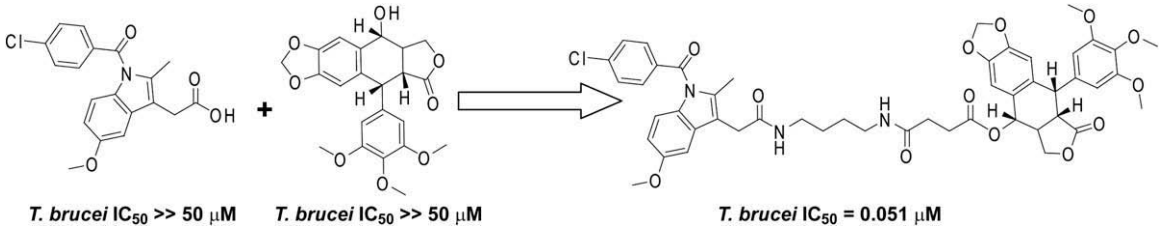


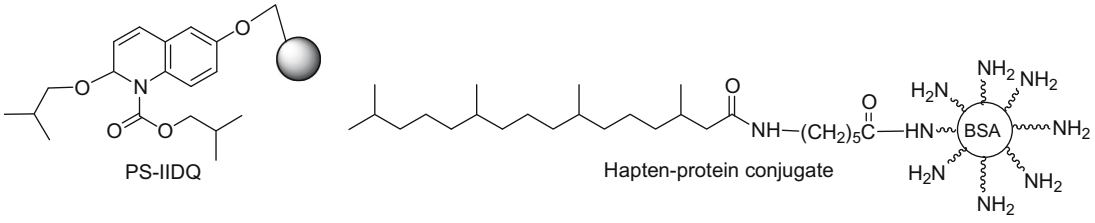


This Letter describes the one pot synthesis of tertiary carbinamine **3** and related analogs of brain penetrant BACE-1 inhibitors via the alkylation of the Schiff base intermediate **2**. Extensive SAR studies led to the identification of a potent BACE inhibitor which is twofold more potent in vitro compared to the lead compound. Significant lowering of CSF Aβ40 was observed in a cisterna magna ported rhesus monkey model with the administration of compound **3**.



Novel acyloxyalkyl dinucleotide prodrugs have been developed as orally bioavailable anti-HBV agents.





Polystyrene supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ), a polymer-supported covalent coupling reagent, was successfully employed for the first time in the bioconjugation of an example hapten (phytanic acid derivative) to a protein (bovine serum albumin (BSA)) within the context of immunogen preparation for antibody development.

*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.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

ELSEVIER

ISSN 0960-894X