Bioorganic & Medicinal Chemistry Letters 21 (2011) 2161–2182

Contents lists available at ScienceDirect

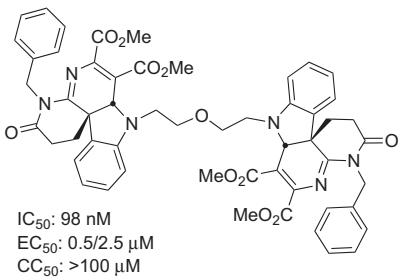
Bioorganic & Medicinal Chemistry Letters

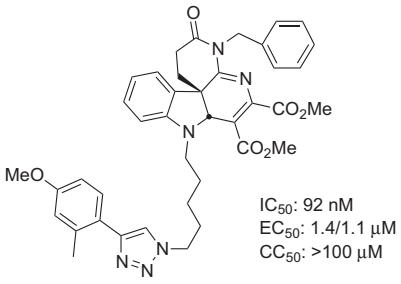
journal homepage: www.elsevier.com/locate/bmcl

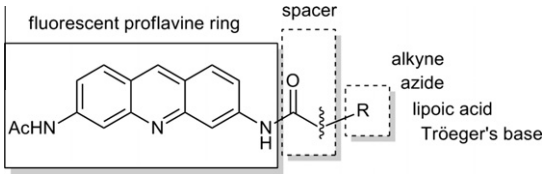
Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 8, 2011

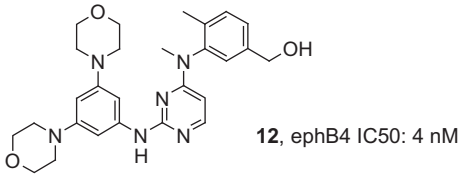
Contents

ARTICLES

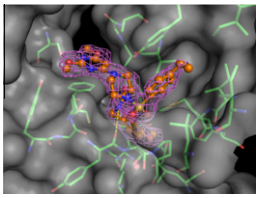


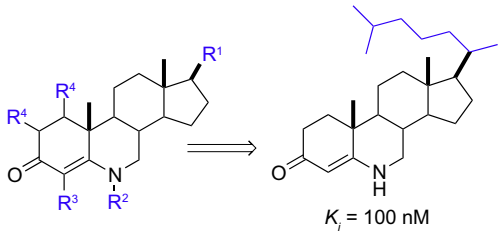


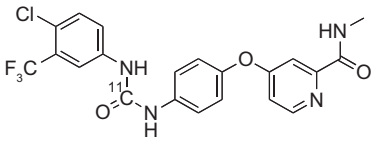




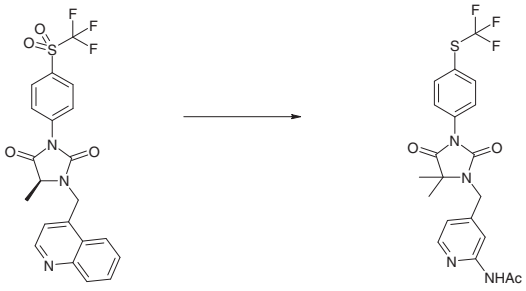
Structure based rationales for the activities of potent *N*-benzyl-4-heteroaryl-1-(phenylsulfonyl)-piperazine-2-carboxamide inhibitors of the hepatitis C viral polymerase are described. Comparison of co-crystal structures of a potent analog with both NS5B genotype 1a and genotype 1b provide possible explanations for the genotype-selectivity observed with this compound class and suggests opportunities for the further optimization of the series.



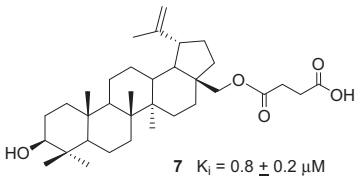




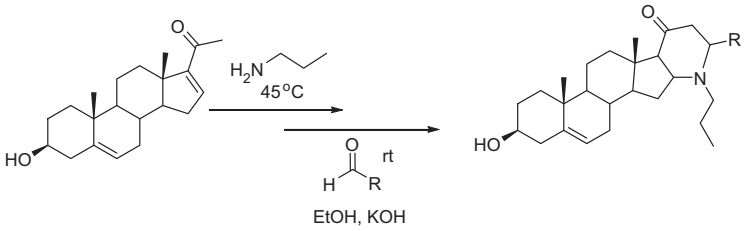
[^{11}C]sorafenib ([^{11}C]**1**)

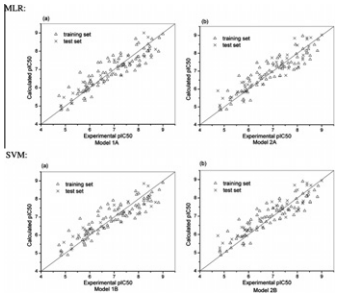


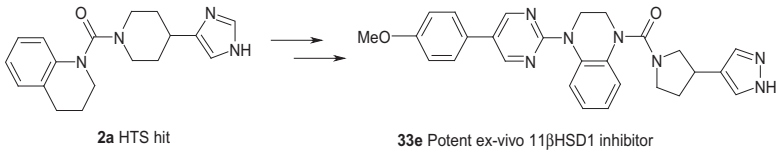
IGF-1R (IC_{50})	0.5 μM	98 nM
IGF-1-induced proliferation (IC_{50})	0.3 μM	8 nM



7 K_i = 0.8 ± 0.2 μM

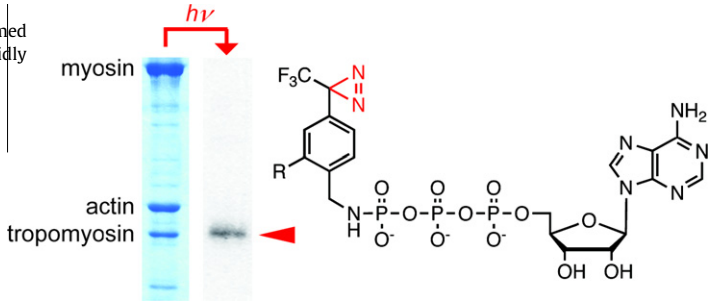


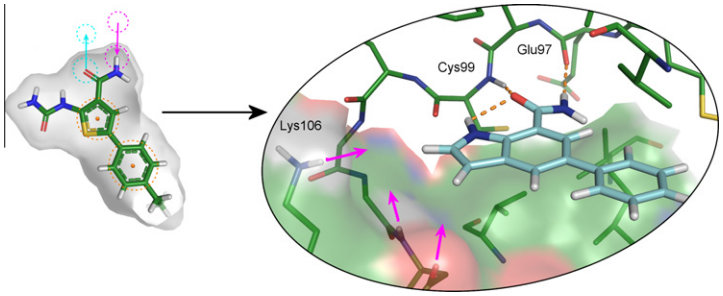


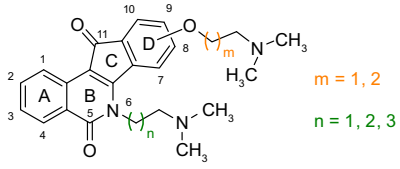


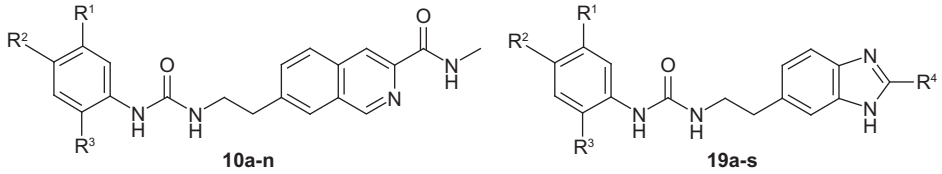
2a HTS hit

33e Potent ex-vivo 11βHSD1 inhibitor

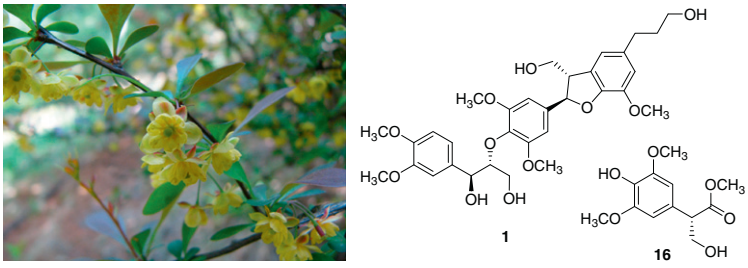




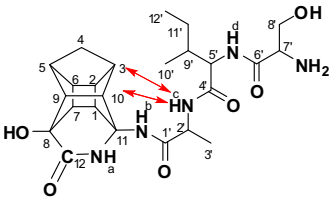




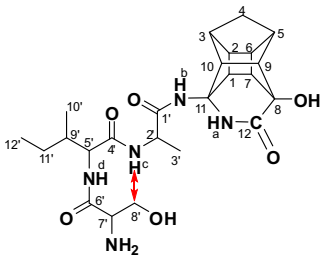
Potent c-RAF inhibitors bearing novel bicyclic heterocycles as key structural elements for the interaction with the hinge region are described.



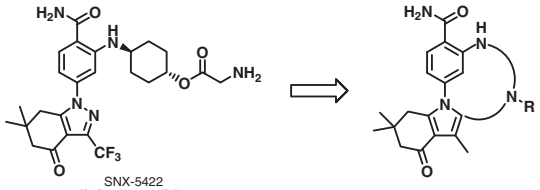
A bioassay-guided fractionation and chemical investigation of the trunk of *Berberis koreana* resulted in the isolation and identification of a new sesquilignan, named berbikonol (**1**), along with 14 known lignan derivatives (**2**–**15**) and a new phenolic compound, named berfussinol (**16**), together with five known ones (**17**–**21**).



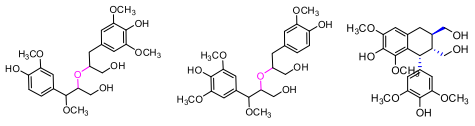
PCU-AISa



PCU-AISb

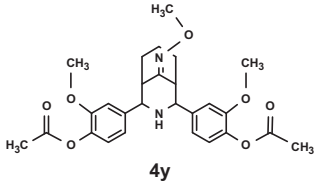


SNX-5422
clinical candidate

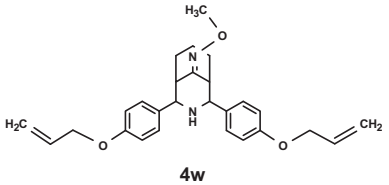


1 2 3

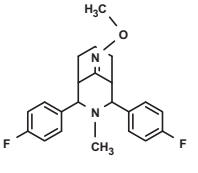
The 80% methanolic extract of *Euonymus alatus* leaves and twigs afforded three new lignans, (−)-*threo*-4,9,4′,9′-tetrahydroxy-3,7,3′,5′-tetramethoxy-8-*O*-8′-neolignan (**1**), (−)-*threo*-4,9,4′,9′-tetrahydroxy-3,5,7,3′-tetramethoxy-8-*O*-8′-neolignan (**2**), (7*R*,8*R*,7′*R*)-(+)-lyoniresinol (**3**), together with seventeen known lignans (**4**–**20**). The structures of **1**–**20** were elucidated by extensive 1D and 2D spectroscopic methods including ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY. All the isolated compounds except for dilignans (**19**, **20**) significantly inhibited nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells.



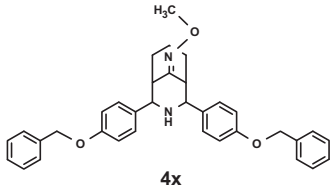
4y
Antioxidant IC_{50} = 0.187 mg/mL



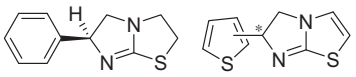
4w
Zone of anti-MTB = 21 mm

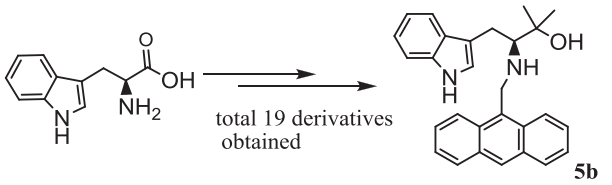


5d
21 mm

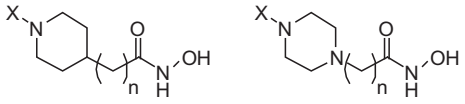


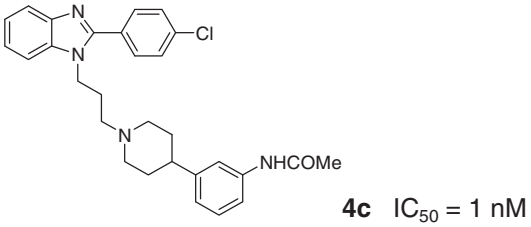
4x
23 mm



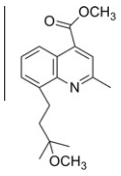


	HL-60	SMMC-7721	A-549	MCF-7	SW480
5b ($IC_{50,}$ μM)	9.55	13.39	11.04	12.50	11.71
DDP ($IC_{50,}$ μM)	1.04	14.99	6.81	24.70	24.34

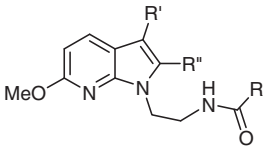




The synthesis and SAR of 2-arylbenzimidazoles as MCH-R1 antagonists are described.

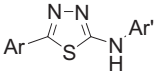


IC_{50} = 29.3 μg ml^{-1}

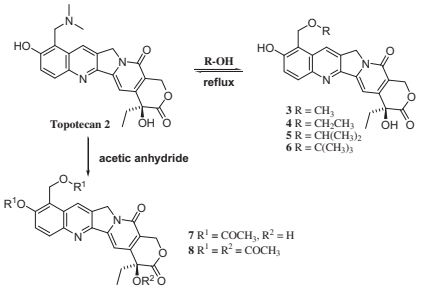


R = Me; R' = R" = H,	Ki(MT_1) = 1.4 nM	Ki(MT_2) = 0.6 nM
R = Et; R' = R" = H,	Ki(MT_1) = 3.3 nM	Ki(MT_2) = 0.28 nM
R = *n*Pr; R' = R" = H,	Ki(MT_1) = 1.3 nM	Ki(MT_2) = 0.3 nM
R = Me; R', R" = -$(CH_2)_4$-,	Ki(MT_1) = 9 nM	Ki(MT_2) = 0.68 nM

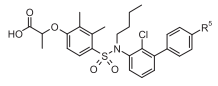
New potent melatonin agonists based on a 7-azaindole scaffold are reported, along with some affinities-dependent pharmacomodulations.



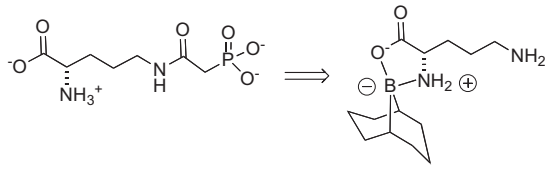
IC_{50} : 4.3 μM - >1.0 mM

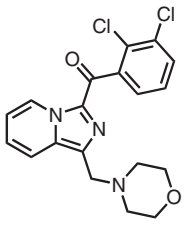


Six derivatives of 10-hydroxycamptothecin were prepared via solvolysis of topotecan in corresponding alcohols and acetic anhydride and evaluated in vitro as anti-tumor agents.



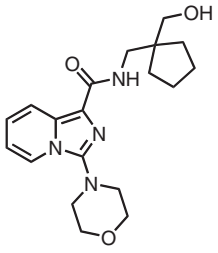
Compound	R^5	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
46	OCF_3	5.0	5.2	7.8	8.6	51
47	CF_3	5.1	5.2	8.2	8.6	59





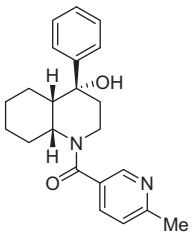
rCB2 cAMP IC_{50} 11 nM
rCB1 cAMP IC_{50} 1068 nM

active in rat CFA pain model



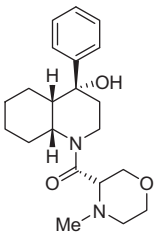
rCB2 cAMP IC_{50} 58 nM
rCB1 cAMP IC_{50} >17000 nM

not active in rat CFA pain model



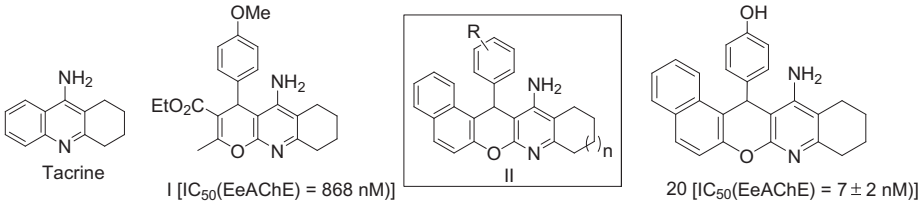
rCB2 cAMP IC_{50} 6.3 nM
rCB1 cAMP IC_{50} 1887 nM

active in rat CFA pain model

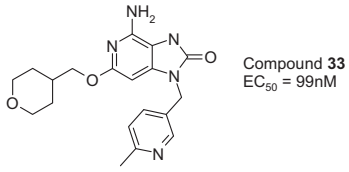


rCB2 cAMP IC_{50} 81 nM
rCB1 cAMP IC_{50} >17000 nM

not active in rat CFA pain model

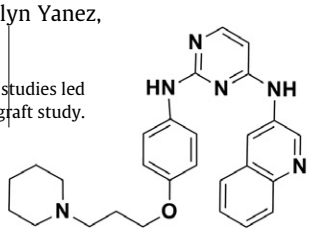


Structure of tacrine, the reference compound **I**, the target molecules {14-aryl-10,11,12,14-tetrahydro-9*H*-benzo[5,6]chromeno[2,3-*b*]quinolin-13-amines} (**II**) and the most potent AChEI (compound **20**) found in this work.

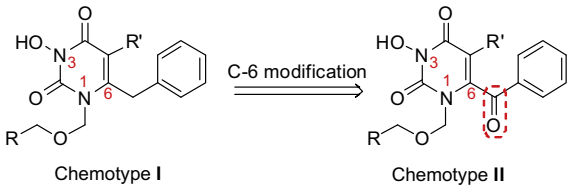


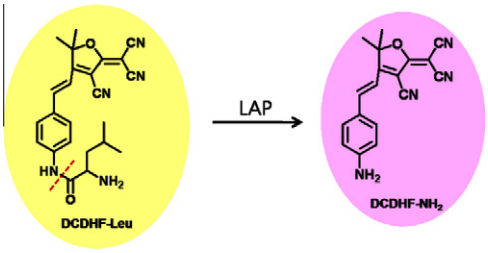
The synthesis and structure–activity relationships of a series of novel interferon inducers are described. Pharmacokinetic studies and efficacy assessment of a series of 8-oxo-3-deazapurine analogues led to the identification of compound **33**, a potent and selective agonist of the TLR7 receptor with an excellent in vivo efficacy profile in a mouse model.

The discovery of 2,4-bis-arylamino-1,3-pyrimidines as IGF-1R inhibitors is described. Optimization studies led to the identification of **26**, which displayed tumor growth inhibition in a mouse Calu-6 tumor xenograft study.

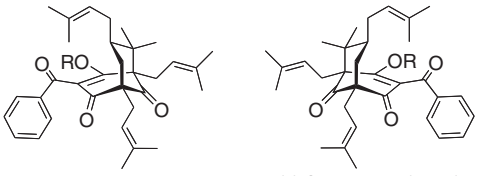


Compound **26**
IGF-1R IC_{50} = 19 nM
huIGF-1R/3T3 IC_{50} = 81 nM

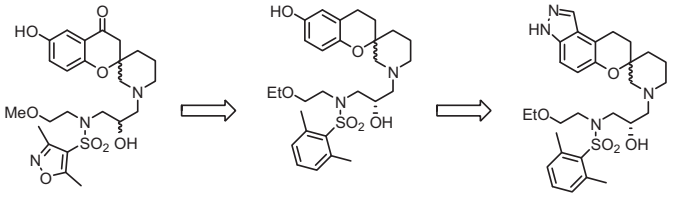


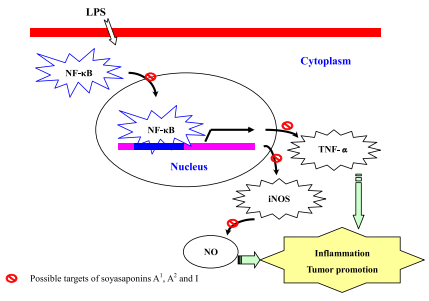


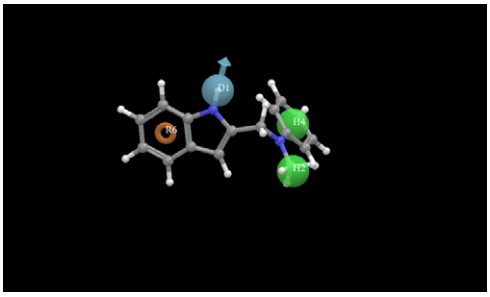
In this paper, we report a small-molecule probe which exhibits colorimetric and fluorogenic changes according to LAP activity.

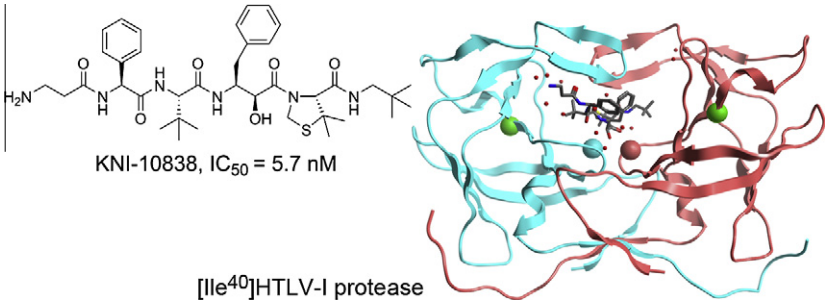


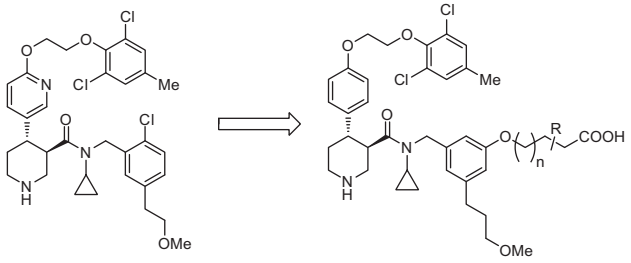
A novel series of spirochromane pan-Akt inhibitors is reported. SAR optimization furnished compounds with improved enzyme potencies and excellent selectivity over the related AGC kinase PKA. Attempted replacement of the phenol hinge binder provided compounds with excellent Akt enzyme and cell activities but greatly diminished selectivity over PKA.

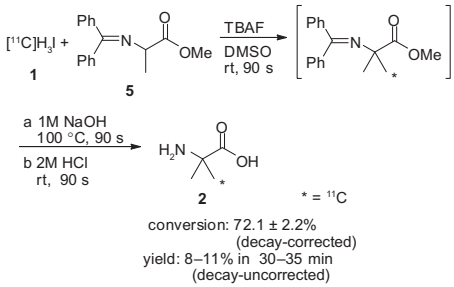


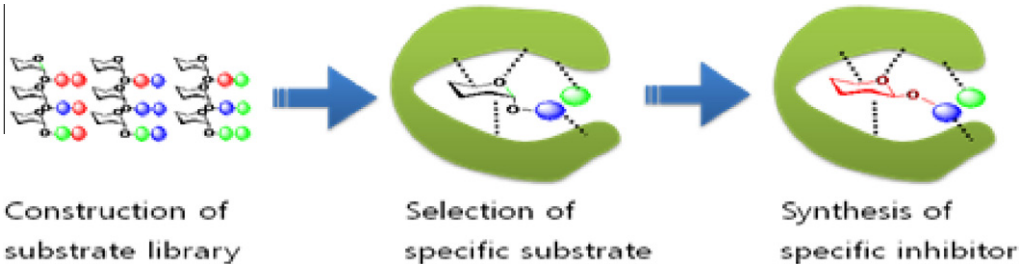


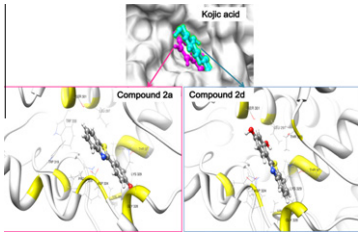


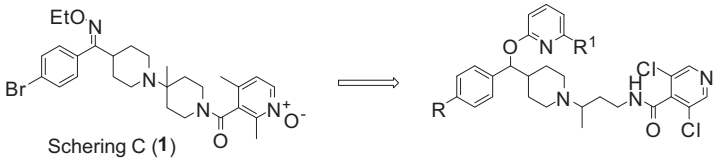


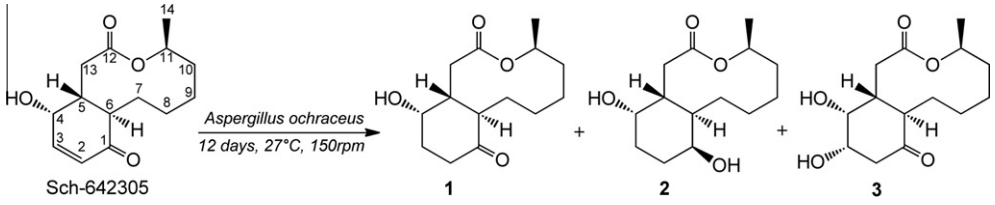


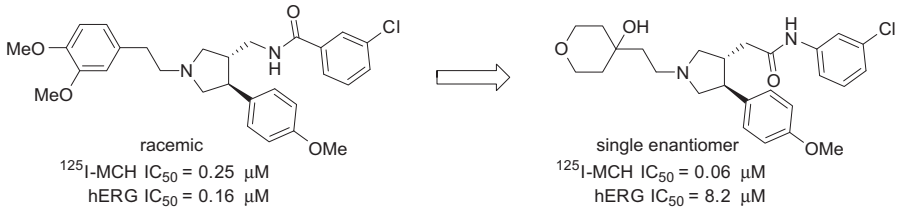


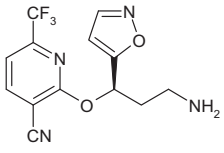








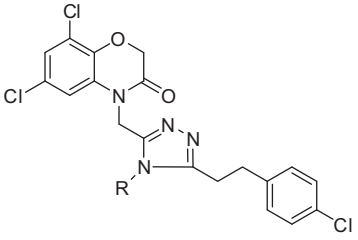




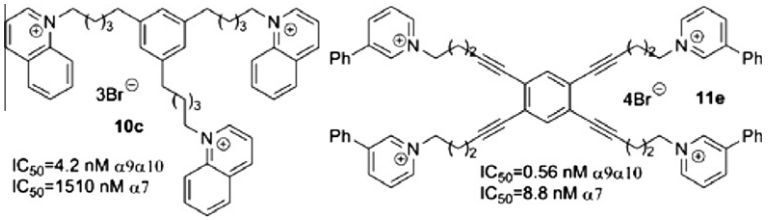
8

By careful analysis of experimental X-ray ligand crystallographic protein data across several inhibitor series we have discovered a novel, potent and selective series of iNOS inhibitors exemplified by compound **8**.

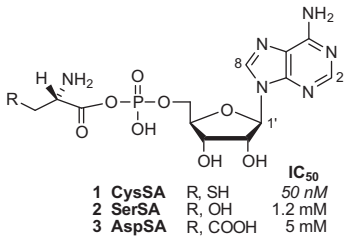
A series of benzothiazinone and benzooxazinone derivatives were discovered as SGLT2 inhibitors. The optimization led to the discovery of compounds **31** and **32**, which exhibited similar potency and better SGLT1selectivity compared to dapagliflozin. These compounds may provide novel promising scaffolds, which are different from phlorizin-based SGLT2 inhibitors.



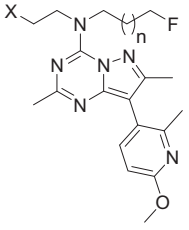
R = $CH_2CH_2CH_3$ **31**
R = $CH_2CH_2CF_3$ **32**

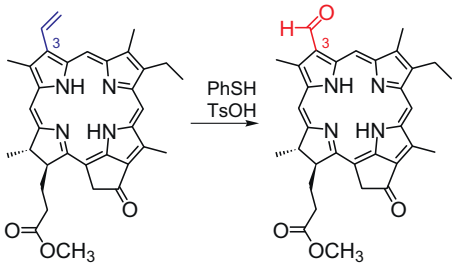


A series of azaaromatic quaternary ammonium analogs has been discovered as potent and selective α9α10 nicotinic acetylcholine receptor (nAChR) antagonists. The preliminary structure–activity relationships of these analogs suggest that increased rigidity in the linker units results in higher potency in inhibition of α9α10 nAChRs and greater selectivity over α7 nAChRs. These analogs represent a new class of analgesic for the treatment of neuropathic and tonic inflammatory pain.

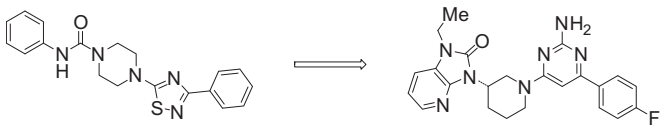


A series of *N*-(3-fluoroalkyl)-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethyl-*N*-alkylpyrazolo [1,5-*a*][1,3,5]triazin-4-amines were prepared and evaluated as potential CRF_1R PET imaging agents. Optimization of their CRF_1R binding potencies and octanol-phosphate buffer phase distribution coefficients resulted in discovery of analog **7e** (IC_{50} = 6.5 nM, log *D* = 3.5).



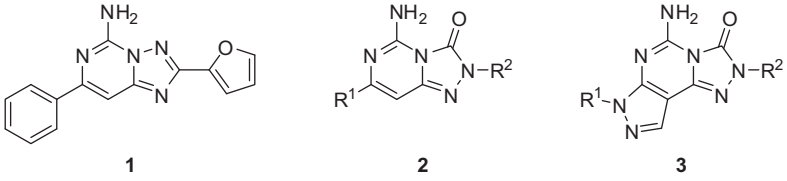


A chlorophyll-*a* derivative (3-vinyl-chlorin) was smoothly converted into the corresponding chlorophyll-*d* derivative (3-formyl-chlorin) under mild conditions: treatment with thiophenol in an acidic solution at room temperature.

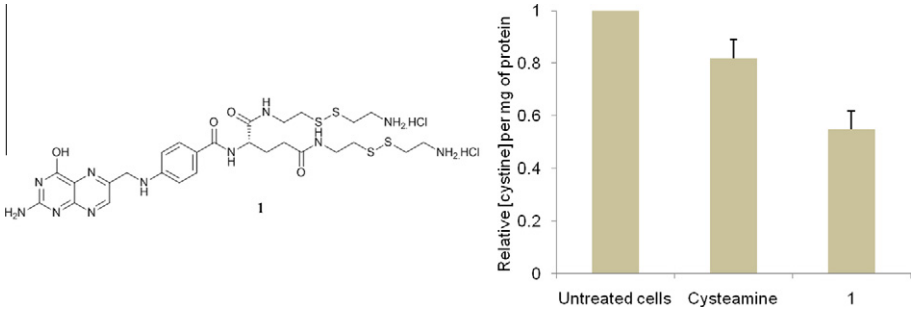


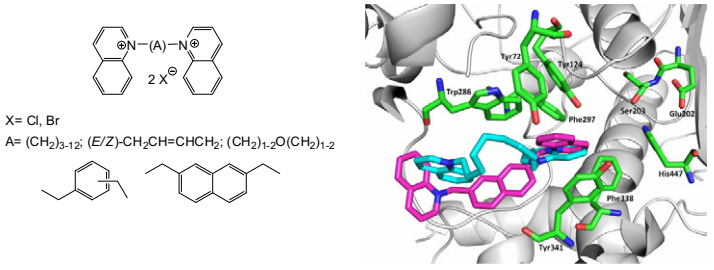
FAAH suicide substrate
IC_{50} = 3 nM

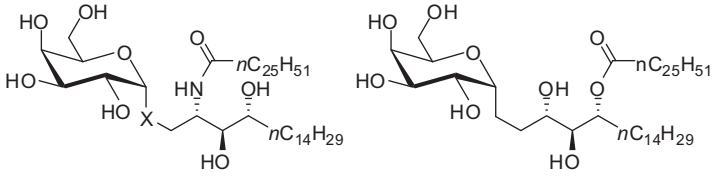
non-covalent FAAH inhibitor
IC_{50} = 14 nM

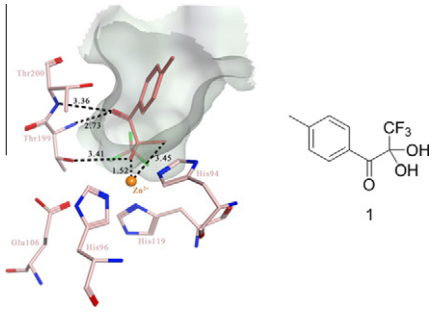


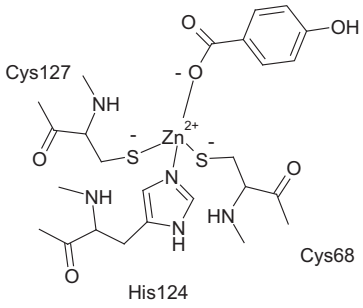
Antagonism of the adenosine A_{2A} receptor affords a possible treatment of Parkinson's disease. In the course of investigating pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine A_{2A} antagonists, we prepared [1,2,4]-triazolo[4,3-*c*]pyrimidin-3-ones with potent and selective (vs A_1) A_{2A} antagonist activity. Structure–activity relationships are described for this series.





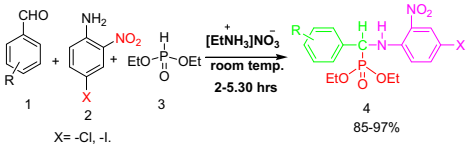


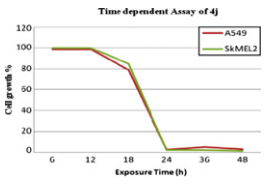


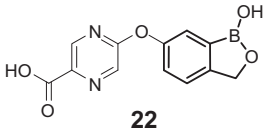


K_I = 7.61 μM (hCA I); 7.28 μM (hCA II); 9.5 nM (Can2); 110 nM (Nce103).

Ionic liquid ethyl ammonium nitrate is used as an excellent catalyst and solvent for three-component one-pot reaction of an aldehydes, amines and diethylphosphite to form novel α-aminophosphonates at room temperature. Among the various catalysts, the preparation of ethyl ammonium nitrate is an environmental friendly, cost effective and recyclable catalyst. Compounds **4b**, **4c**, **4d**, **4f** and **4j** were found more potent antibacterials against pathogenic microorganisms. Whereas, compounds **4a**, **4g**, **4h** and **4j** inhibits growth of active *Escherichia coli* NCIM 2645 and *Salmonella typhi* NCIM 2501. Compound **4j** was found a promising antiproliferative agent against A549 and SK-MEL2 human melanoma cell lines.

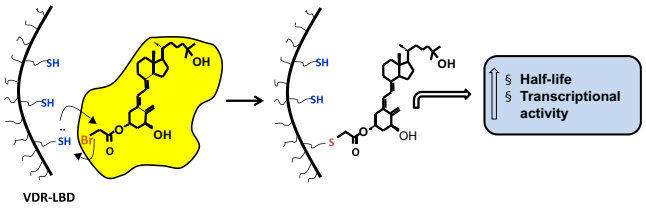






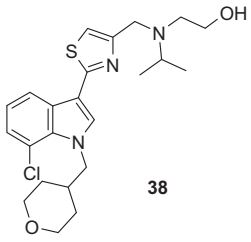
22

A new class of benzoxaborole β-lactamase inhibitors is described. 6-Aryloxy benzoxaborole, **22**, inhibited AmpC P99 and CMY-2 with K_i values in the low nanomolar range. Compound **22** restored antibacterial activity of ceftazidime against *Enterobacter cloacae* P99 expressing AmpC.

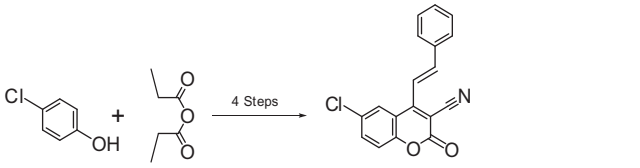


Synthesis of 1α,25-dihydroxyvitamin D_3-3β-bromoacetate, a potential anti-cancer agent, and its probable mechanism of action, denoting its reduced catabolism is presented.

We report an expansion of the structure–activity relationship (SAR) of a novel series of indole-3-heterocyclic CB1 receptor agonists. Starting from the potent but poorly soluble lead, **1**, a rational approach was taken in order to balance solubility, hERG activity and potency while retaining the desired long duration of action within the mouse tail flick test. This led to the discovery of compound **38** which successfully progressed into clinical development.

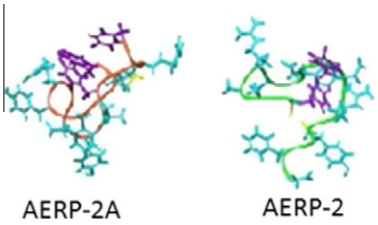


38

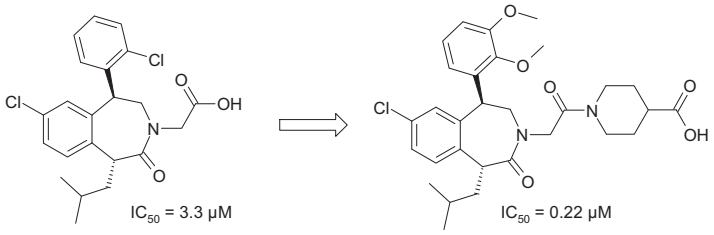


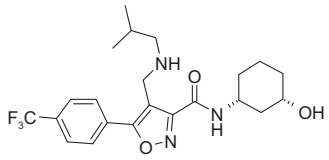
6-chloro-2-oxo-4-[-2-sub.ethenyl]-2*H*-chromene-3-carbonitriles

22 examples



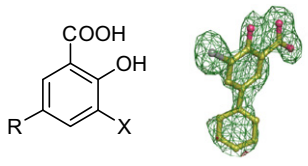
In certain human cancers, EGFR is over-expressed and is related to the metastasic potential of the tumor. We have developed two anti-EGFR receptor-binding peptidomimetics (AERP), as tumor-specific imaging agents. Our newly designed peptidomimetic, AERP, was conjugated to DTPA and labeled with ^{99m}Tc. The in vivo tumor accumulation of [^{99m}Tc] DTPA-AERP-2 was 1.6 ± 0.1 %ID/g and tumor to muscle ratio was 5.5.



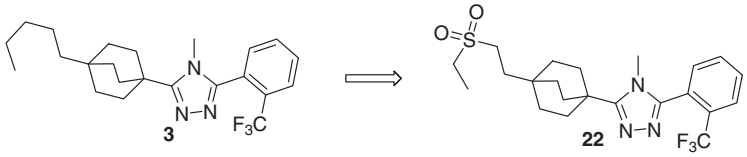


8e

Optimization of a water soluble, moderately potent lead series of isoxazole-3-carboxamides was conducted, affording a compound with the requisite balance of potency, solubility and physicochemical properties for in vivo use. Compound **8e** was demonstrated to be efficacious in a rat model of inflammatory pain, following oral administration.



CPSA: X = Cl, R = Phenyl
DCSA: X = R = Cl



Following the discovery of a metabolic 'soft-spot' on a bicyclo[2.2.2]octyltriazole lead, an extensive effort was undertaken to block the oxidative metabolism and improve PK of this potent HSD1 lead. In this communication, SAR survey focusing on various alkyl chain replacements will be detailed. This effort culminated in the discovery of a potent ethyl sulfone inhibitor with an improved PK profile across species and improved physical properties.

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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¬

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ISSN 0960-894X