Bioorganic & Medicinal Chemistry Letters 20 (2010) 4961–4982

Contents lists available at ScienceDirect

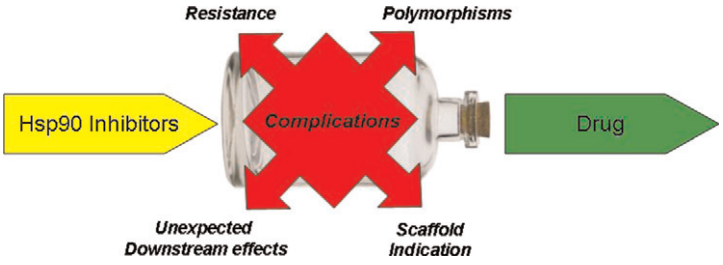
Bioorganic & Medicinal Chemistry Letters

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

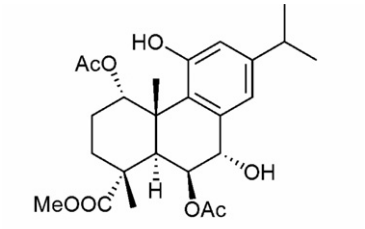
Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 17, 2010

Contents

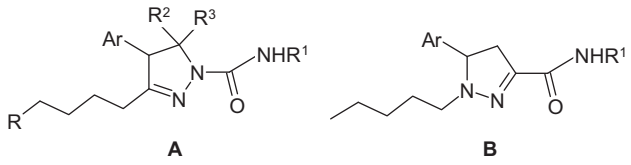
BMCL DIGEST



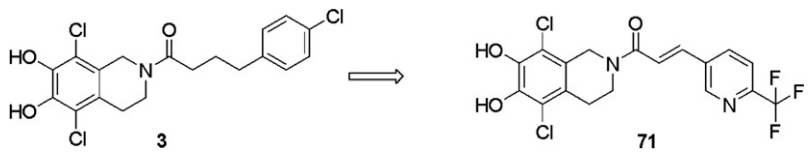
REGULAR ARTICLES



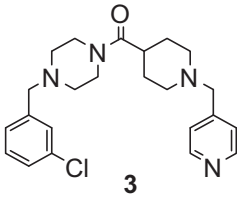
Staphylococcus aureus (MIC=22 μg/mL)
Aspergillus fumigatus (MIC=89 μg/mL)



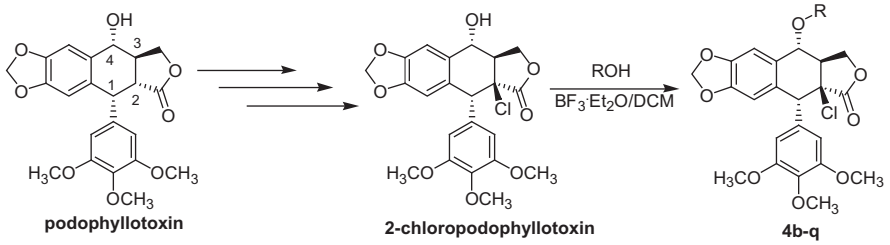
The synthesis and SAR of two novel CB_1 receptor agonist classes A and B are described.



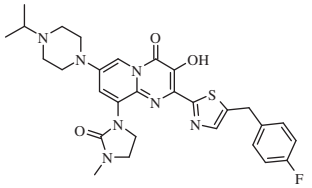
The discovery and synthesis of bronchodilator **71** using a functional tissue assay is described.



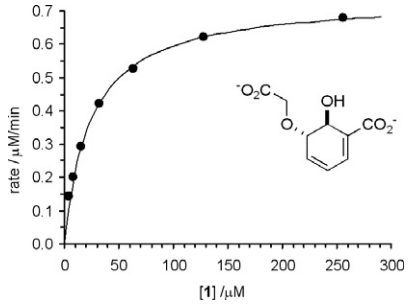
A structure–activity relationship study of the lead piperazinylcarbonylpiperidine compound **3** has resulted in the identification of 4-benzimidazolyl-piperidinylcarbonyl-piperidine **6h** as a histamine-3 (H_3) receptor antagonist. Additional optimization of **6h** led to the identification of compounds **11i–k** with K_i < 0.5 nM and good in vivo activity.

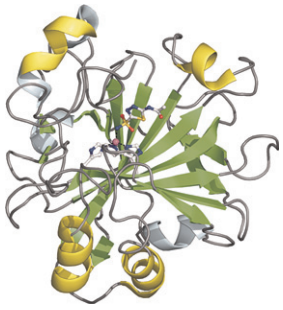


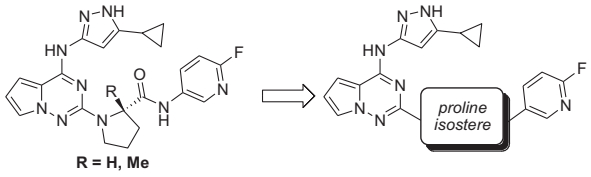
Some derivatives exhibited more promising and pronounced insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach*. It was clearly demonstrated that the length of straight-chain or branched-chain alkyloxy, and heteroatom-containing cycloalkyloxy at the C-4 position of 2-chloropodophyllotoxin were very important for the insecticidal activity.



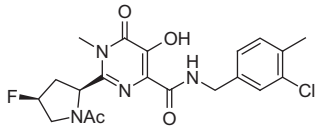
33 **EC_{50} HIV (WT-integrase) 6.8nM**
EC_{50} HIV (WT –integrase +50% NHS) 8.5nM
EC_{50} HIV (QHGS -integrase) 21nM
EC_{50} HIV (NHEQ -integrase) 8.9nM





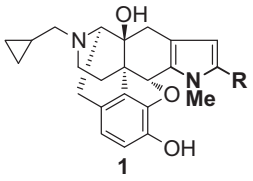


Analogs utilizing proline isosteres in IGF-1R/IR inhibitors are disclosed. X-ray co-crystallography of selected analogs reveals information key to target potency.



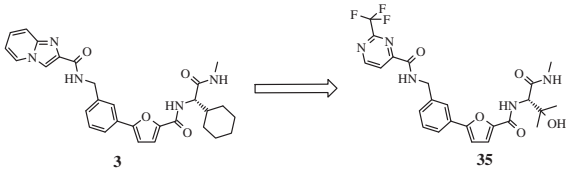
13 Spread CIC_{95} (50% NHS) = 46 nM

The identification of the promising agent against HIV-1 **13** is reported.



1

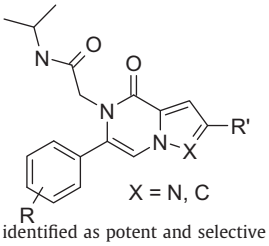
Pyrrolomorphinans **1** were synthesized to examine whether the pyrrole ring might be an accessory site in the κ receptor selective antagonist, nor-binaltorphimine.



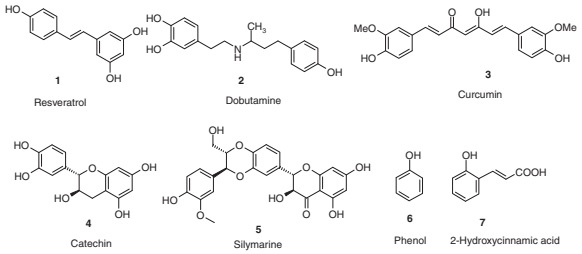
3 MMP-13 IC_{50}: 100 nM

35 MMP-13 IC_{50}: 5 nM
>200-fold selectivity over other MMPs

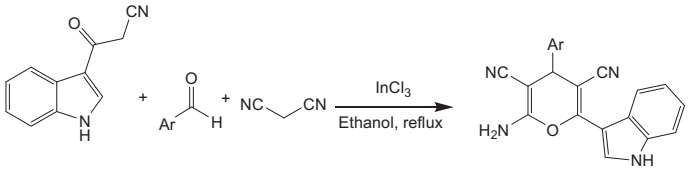
SAR studies to improve the selectivity and metabolic stability of a class of recently discovered non-Zn-chelating MMP-13 inhibitors are reported.



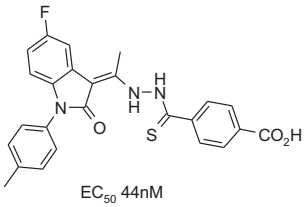
Novel series of pyrrole-pyrazinone and pyrazole-pyrazinone have been identified as potent and selective Vasopressin$_{1b}$ receptor antagonists. Exploration of the substitution pattern around the core of these templates allowed generation of compounds with high inhibitory potency at Vasopressin$_{1b}$ receptor including examples that showed good selectivity with respect to Vasopressin$_{1a}$, Vasopressin$_2$, and Oxytocin receptors subtype.



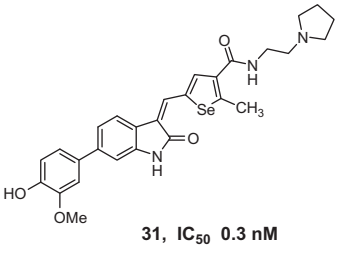
K_Is of 380 nM–12.02 μM against CA I–CA XV.



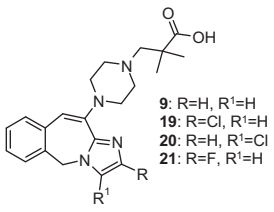
A simple and convenient method for the one-pot three-component synthesis of 3-pyranyl indoles has been accomplished by tandem Knoevenagel–Michael reaction of 3-cyanoacetyl indole, various aromatic aldehydes and malononitrile catalyzed by $InCl_3$ in ethanol under reflux conditions. The newly synthesized 3-pyranyl indoles were evaluated for anti-microbial, antioxidant, and anticancer activities. Some of the compounds are showed good anticancer activity against MCF-7 breast cancer cell lines on comparison with of standards drugs.



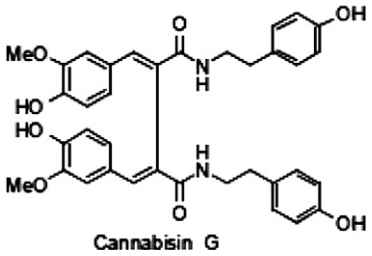
Oxoindolin-3-ylidene ethyl benzothiohydrazides as small molecule c-mpl agonists is reported.



A series of selenophene derivatives (i.e., **31**) are reported as potent inhibitors of CHK1 kinase.

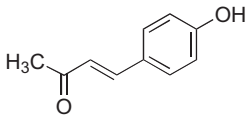


Application of a zwitterionic approach successfully delivered a class of high quality leads, 3-[4-(3-R^1-2-R-5H-imidazo[1,2-*b*][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acids (e.g., **9**, **19**, **20**, and **21**), characterized by potent and balanced H_1/5-HT_{2A} receptor antagonist activities and good developability profiles.

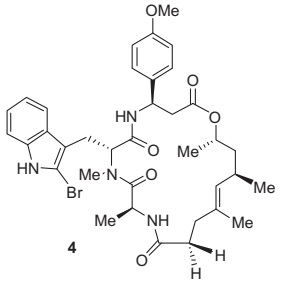


Cannabisin G

Cannabisin G (**1**), a naturally occurring lignanamide, was synthesized in 45% overall yield starting from 3-*tert*-butyl ethyl ferulate (**6**). An oxidative coupling by potassium ferricyanide in an alkaline media serves as the key step to construct the biphenylbutadiene skeleton of **1** with high regioselectivity.

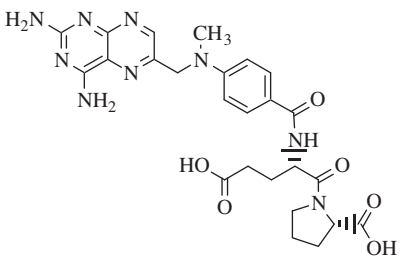


Structure-based engineering of benzalacetone synthase from *Rheum palmatum* is reported.

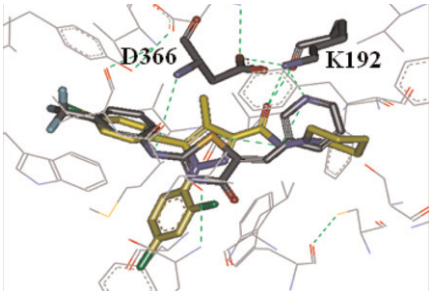


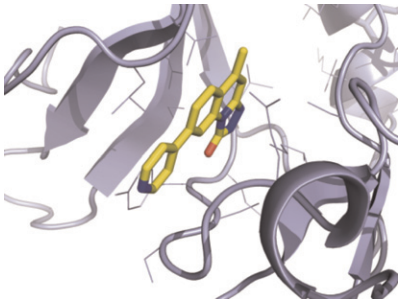
4

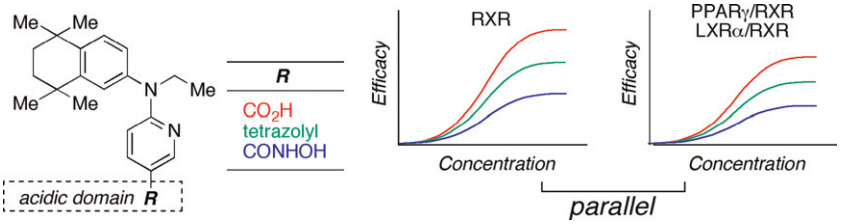
Eight new jasplakinolide derivatives were synthesized and evaluated for antitumor activity by measuring their ability to interfere with the actin cytoskeleton. Simplified derivative **4** is essentially as active as natural jasplakinolide.



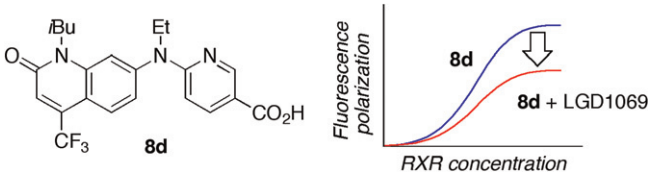
Pro-MTX



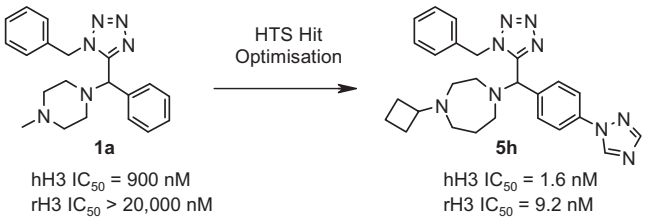




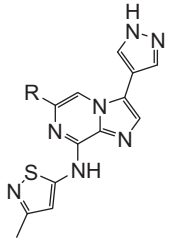
Modification at the acidic domain of RXR agonists has little or no effect on permissive RXR-heterodimer activation. This information may be useful for creating RXR agonists with improved absorption, distribution, metabolism, and excretion (ADME) characteristics.

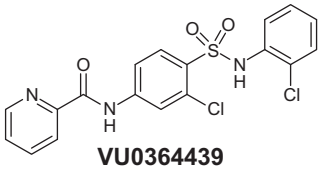


Fluorescent retinoid X receptor (RXR) agonist 6-[ethyl-(1-isobutyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-7-yl)amino]-nicotinic acid (**8d**) was synthesized by modification of the lipophilic domain of general RXR agonists. Compound **8d** showed fluorescence polarization (FP) in the presence of RXR and the FP was reduced in the presence of an RXR agonist, LGD1069.

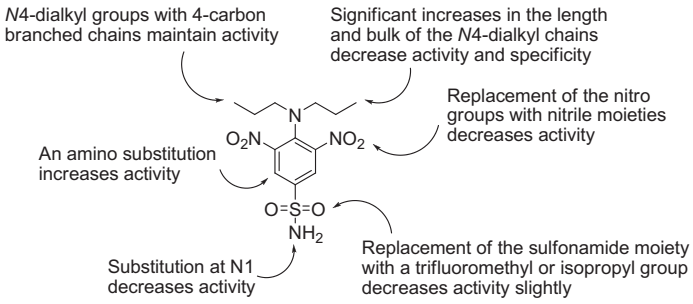


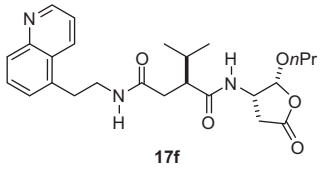
The synthesis and structure–activity relationships (SAR) of novel, potent imidazo[1,2-*a*]pyrazine-based Aurora kinase inhibitors are described. The X-ray crystal structure of imidazo[1,2-*a*]pyrazine Aurora inhibitor **1j** is disclosed. Compound **10i** was identified as good lead compound with an attractive in vitro DMPK profile.





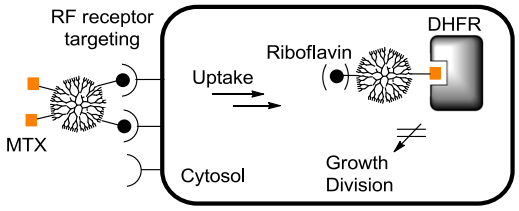
Herein we disclose the synthesis and SAR of a series of 4-(phenylsulfamoyl)phenylacetamide compounds as $mGlu_4$ positive allosteric modulators (PAMs) that were identified via a functional HTS. An iterative parallel approach to these compounds culminated in the discovery of VU0364439 (**11**) which represents the most potent (19.8 nM) $mGlu_4$ PAM reported to date.



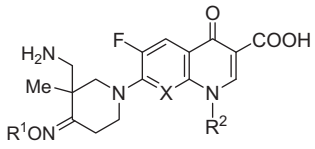


17f

Succinic acid amides have been found to be effective P2–P3 scaffold replacements. ICE inhibitors based on this framework were synthesized and evaluated and the in vivo active ICE inhibitor **17f** is reported.

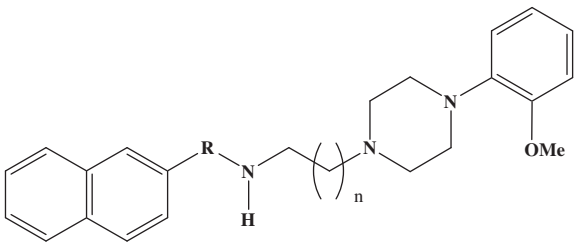


This communication describes the design and in vitro biological evaluation of novel generation 5 PAMAM dendrimers conjugated with riboflavin as a targeting ligand.

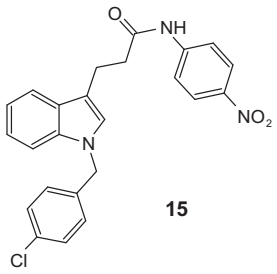


12-26

We report herein the synthesis of novel 7-(4-alkoxyimino-3-aminomethyl-3-methylpiperidin-1-yl) fluoroquinolone derivatives **12–26**. All of the title compounds have good potency in inhibiting the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* including MRSE (MIC: 0.125–4 μg/mL).

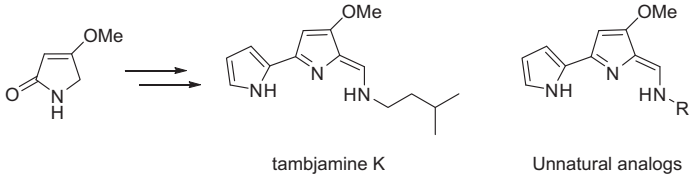


A series of piperazine-alkyl-naphthamides (R = CO or SO_2; *n* = 1–5) was prepared and tested for their affinity for 5-HT_{1A}, α_{2A}, D4.2, D3 and D2L receptors. Homology and sulphonamide/carboxamide isosteric replacement differentially affect the binding affinity for these receptors.

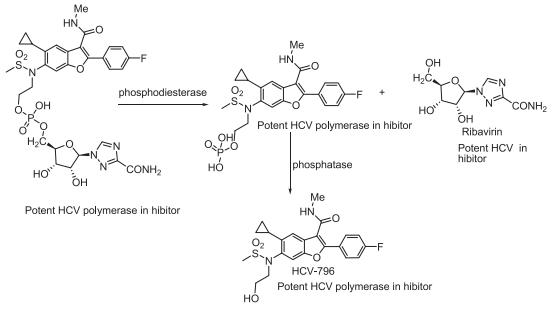


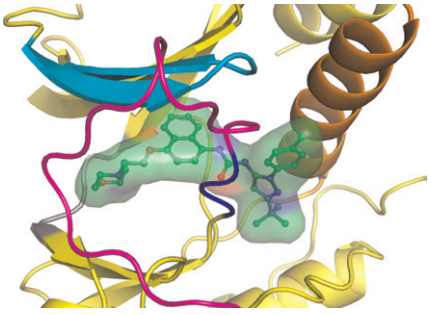
15

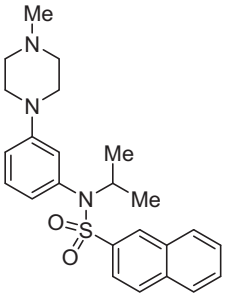
N-Aryl-3-(indol-3-yl)propanamides were synthesized and their immunosuppressive activities were evaluated. Compound **15** exhibited a significant inhibitory activity on murine splenocytes proliferation assay in vitro and on mice delayed-type hypersensitivity (DTH) assay in vivo.

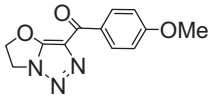


The first total synthesis of tambjamine K and a library of unnatural analogs is reported. Unnatural analogs were shown to be more potent in viability, proliferation, and invasion assays than the natural product in multiple cancer cell lines, with minimal to no cytotoxicity on non-transformed cell lines.



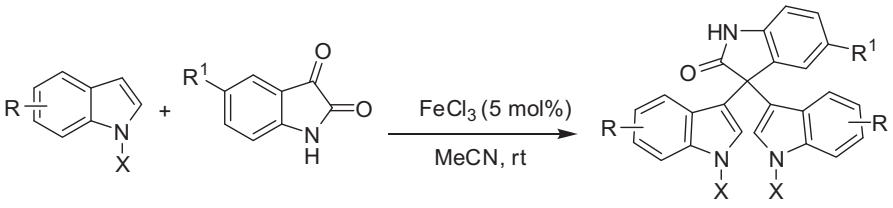




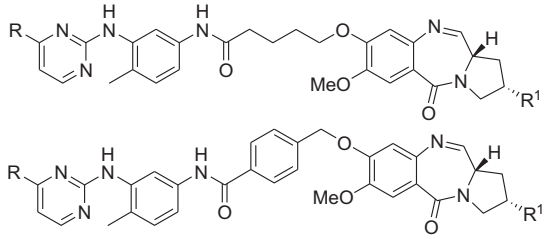


6j IC_{50} = 1.9 μg/mL

A series of heterocycle-fused 1,2,3-triazoles were easily prepared by the 1,3-dipolar cycloaddition in a one-pot reaction and evaluated in vitro against a panel of human tumor cell lines. 1,3-Oxazoheterocycle fused 1,2,3-triazoles were more potent against the tumor cell lines. 4-Methoxyphenyl substituted 1,3-oxazoheterocycle fused 1,2,3-triazole **6j** was found to be the most potent derivative with IC_{50} values lower than 1.9 μg/mL against A431 cell line.

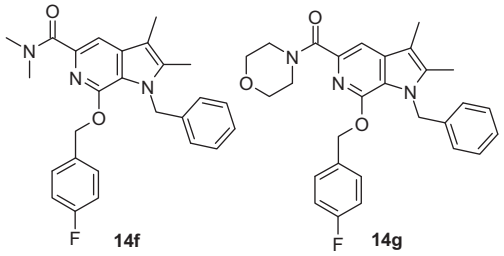


4a-p

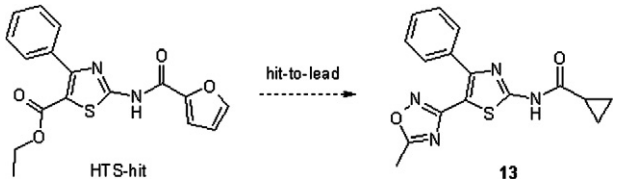


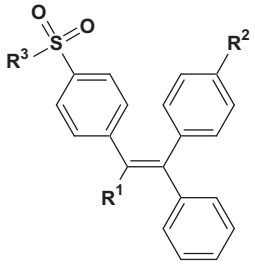
4a: R = 3-pyridyl; R^1 = H
4b: R = 3,4,5-trimethoxyphenyl; R^1 = F
4c: R = 3,4,5-trimethoxyphenyl; R^1 = H

5a: R = 3-pyridyl; R^1 = H
5b: R = 3-pyridyl; R^1 = F

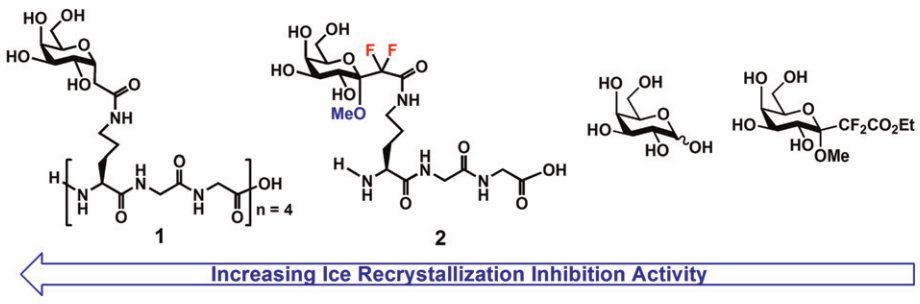


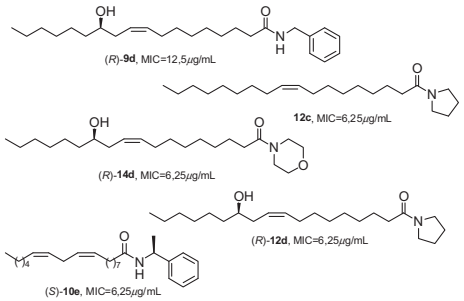
The synthesis of the potent acid pump antagonists **14f** and **14g** (IC_{50} = 28 and 29 nM) is reported.

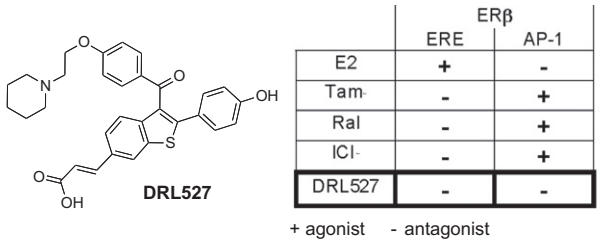


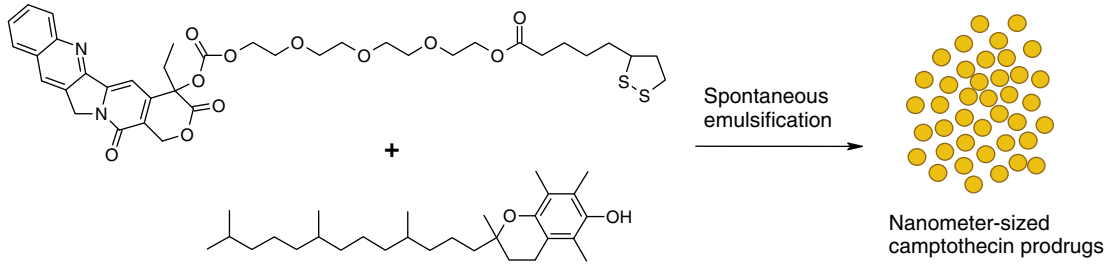


R^1 = Et, R^2 = O*CH_3, R^3 = CH_3
R^1 = *n*-Bu, R^2 = O*CH_3, R^3 = CH_3
R^1 = *n*-Bu, R^2 = OCH_2CH_2*F, R^3 = CH_3
R^1 = Et, R^2 = H, R^3 = *CH_3
R^1 = *n*-Bu, R^2 = H, R^3 = *CH_3
R^1 = CH_2CH_2*F, R^2 = H, R^3 = CH_3
*Indicates position suitable for labelling with a [^{11}C] or [^{18}F] radionuclide

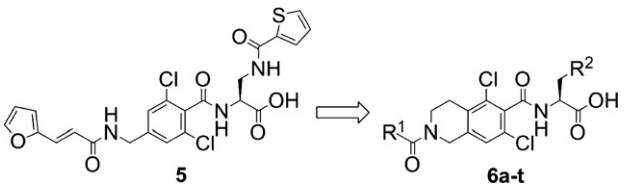




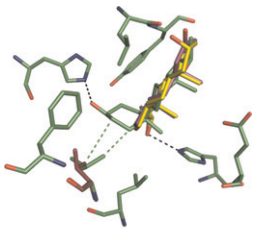




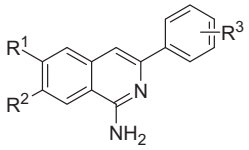
Nanometer-sized camptothecin prodrugs were prepared from camptothecin prodrug molecules and α-tocopherol by using spontaneous emulsification.

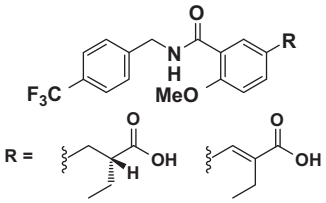


The discovery of a novel series of tetrahydroisoquinoline (THIQ) derivatives as potent and orally bioavailable LFA-1/ICAM-1 antagonists is described.

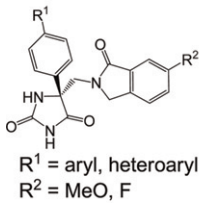


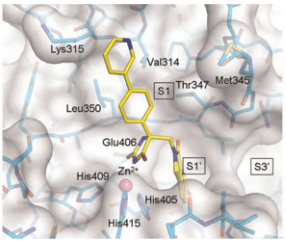
Structure of AKR1C1



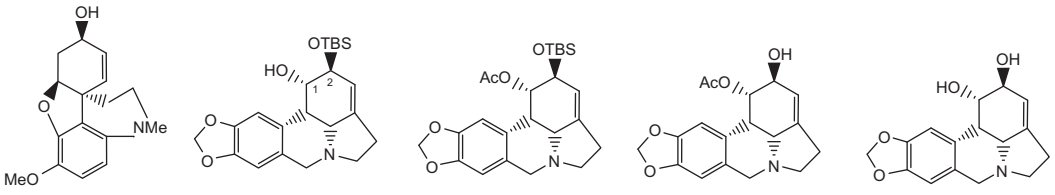


Screening of our library of peroxisome proliferator-activated receptor (PPAR) agonists yielded several phenylpropanoic acid-derived γ-secretase inhibitors (GSIs).



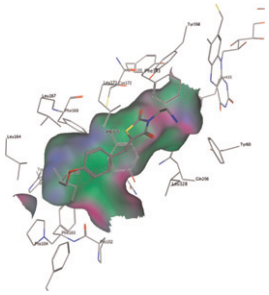


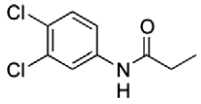
A series of biaryl substituted hydantoin TACE inhibitors is disclosed. Many compounds in this series exhibit sub-nanomolar TACE activities and good rat PK.

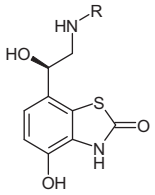


Galanthamine **4** Analog **26** Analog **27** Analog **28** Lycorine **25**

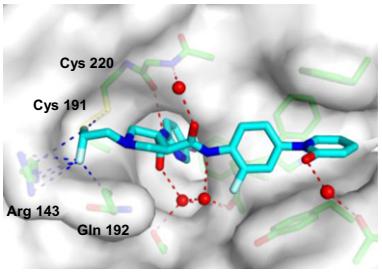
The synthesis of differentially functionalized analogs of the Amaryllidaceae alkaloid lycorine, accessed via a concise chemoselective silylation strategy, is described uncovering two of the most potent inhibitors of acetylcholinesterase (AChE) identified to date in this series. Important elements of this novel pharmacophore were elucidated through structure–activity relationship (SAR) studies.

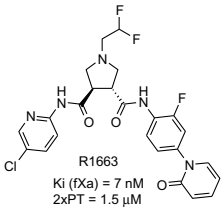


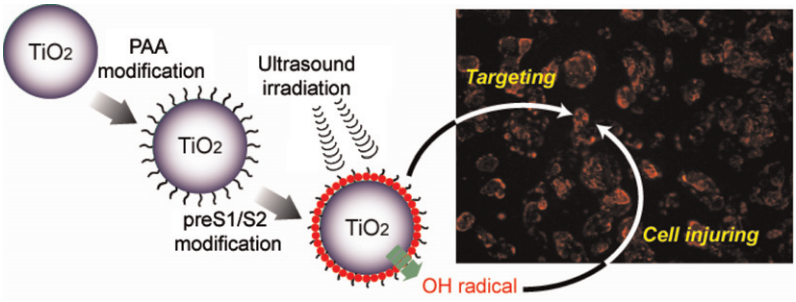


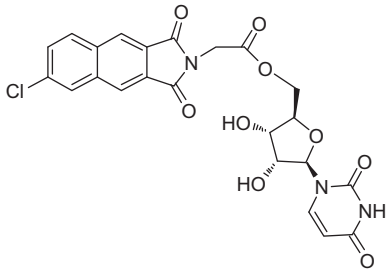


THLE LC_{50} bucket	# Cmpds Toxic@10μM (Total: 155)	# Cmpds Clean@10μM (Total: 57)
<10μM	8	0
10-25μM	7	3
25-50μM	20	0
50-100μM	19	3
>100μM	101	51

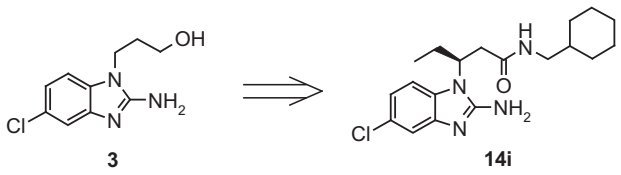


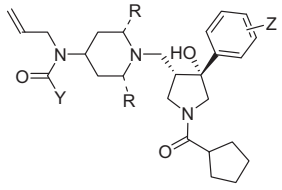


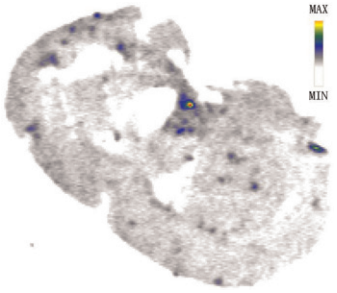


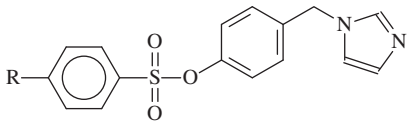


The synthesis and fluorescence properties of new highly fluorescent nucleosides are reported.









R=various substituted sulfonyl derivatives, e.g., CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, CF_3, F and Ph

We report the synthesis and evaluation of a series of potent inhibitors of P450$_{17\alpha}$.

*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