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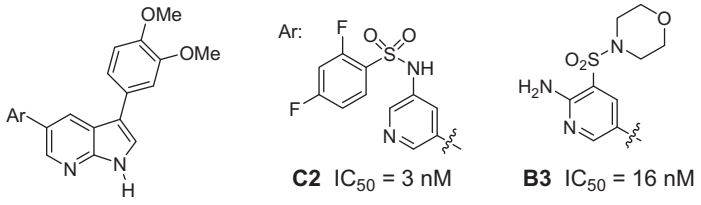
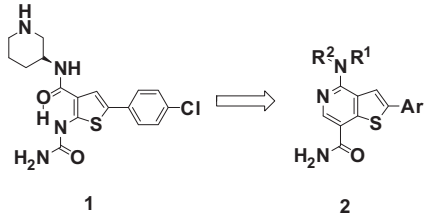
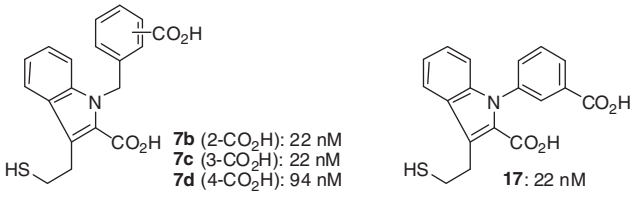
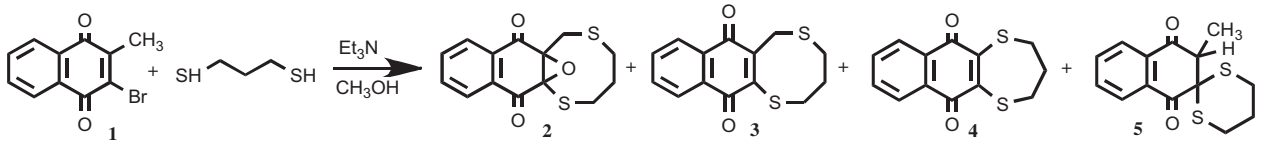
Contents

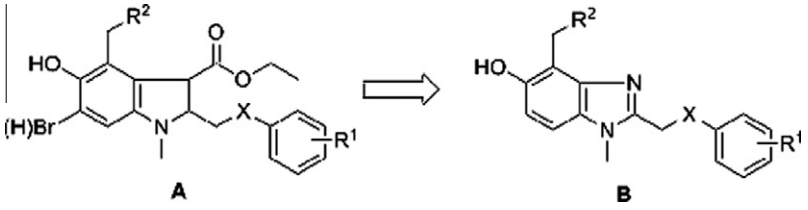


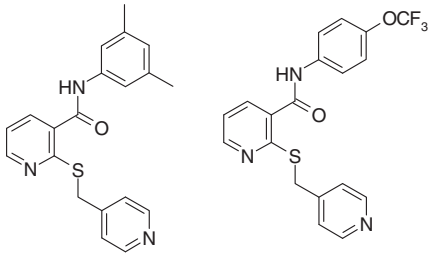


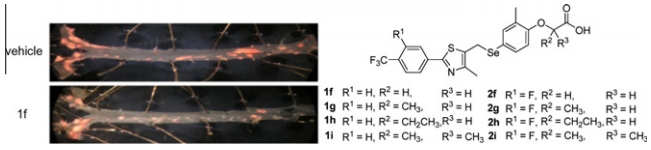
A novel series of CHK1 inhibitors based on thienopyridine template has been designed and synthesized. These inhibitors maintain critical hydrogen bonding with the hinge and conserved water in the ATP binding site. Several compounds show single digit nanomolar CHK1 activities. Compound **70** shows excellent enzymatic activity of 1 nM.

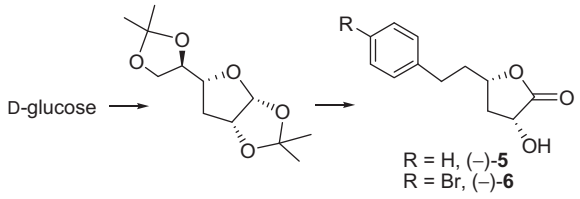


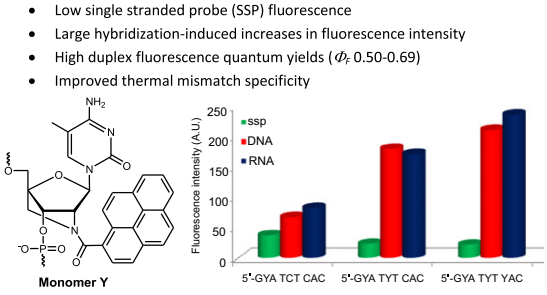


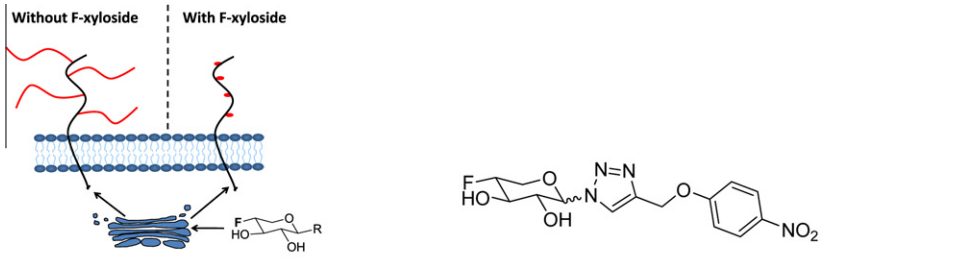




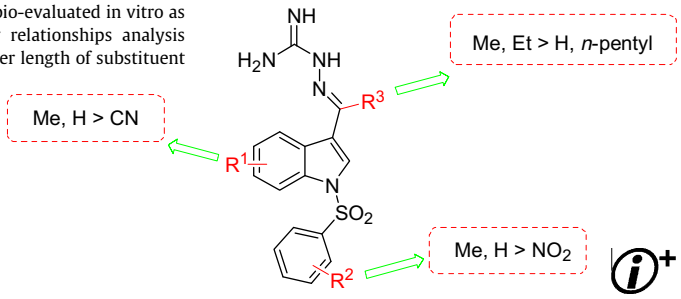


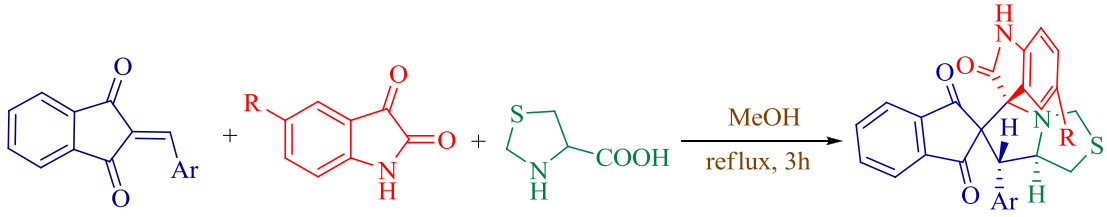


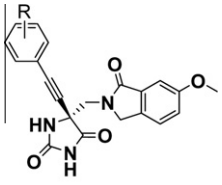




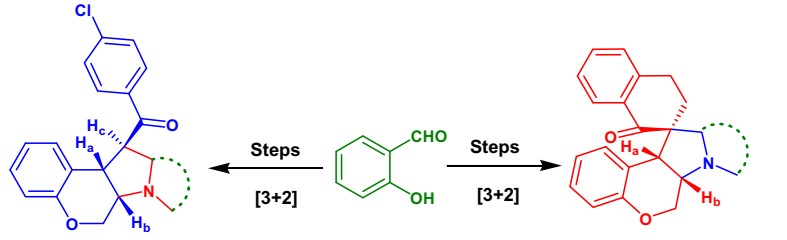
Eighteen Aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles were prepared and bio-evaluated in vitro as antifungal agents against seven phytopathogenic fungi. Preliminary structure–activity relationships analysis demonstrated that introduction of electron-donating substituents R^1 and R^2, and the proper length of substituent R^3 were very important for their antifungal activities.



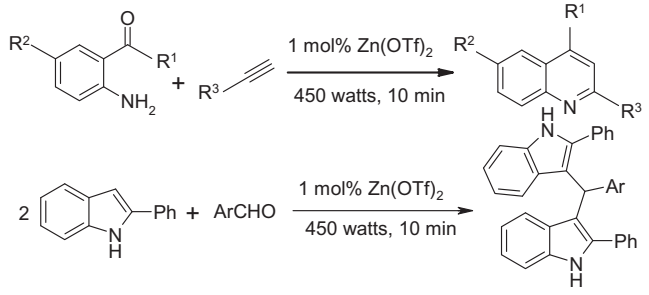


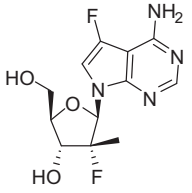


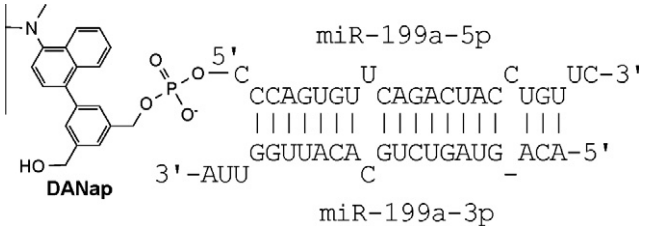
Ki = <1 nM
hWBA = < 250 nM

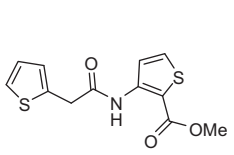


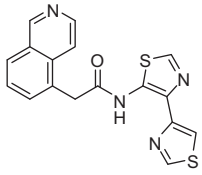
chromeno[3,4-*b*]pyrrole spirochromeno[3,4-*b*]pyrrole

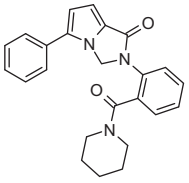




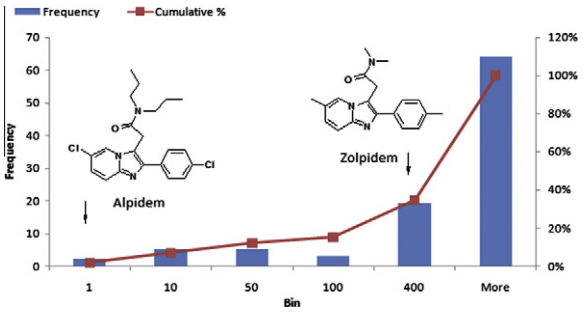


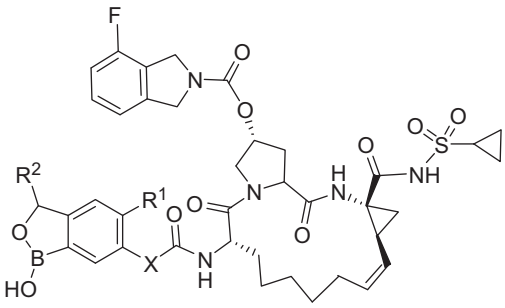


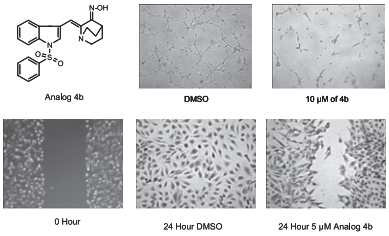


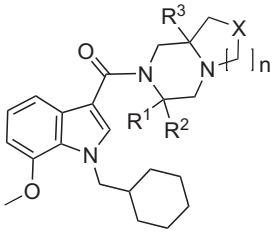


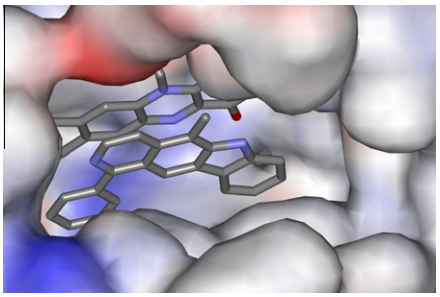
A new lead series was identified in the NPS antagonist field. The compound was prepared following up experimental observations rationalized with computational chemistry techniques and rational design.

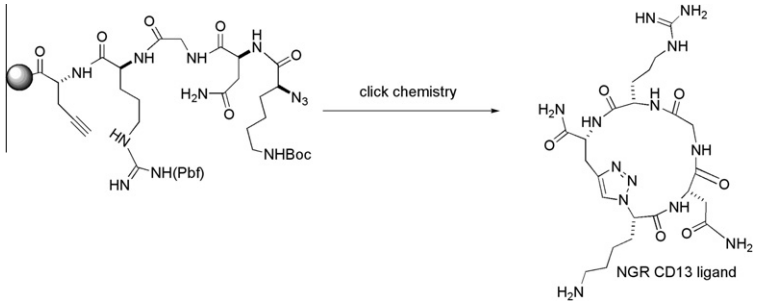


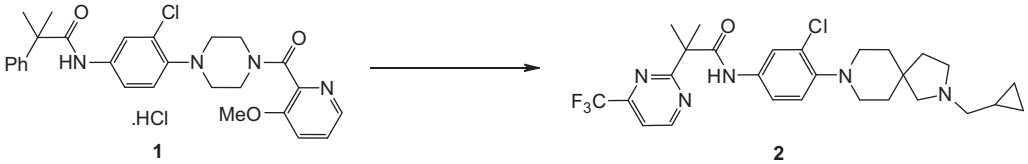








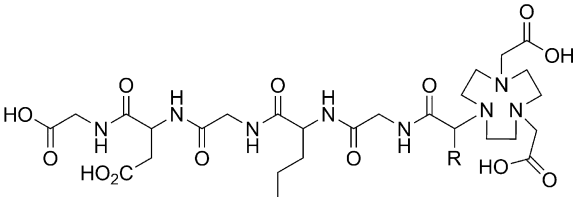




1
hNPY Y2 fpK_i = 7.6
clogP = 4.32
BTB (rat) = 97.1%

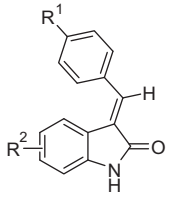
2
hNPY Y2 fpK_i = 6.8
clogP = 4.03
BTB (rat) = 97.2%

The optimisation of diamide **1** to amine **2**, a soluble and selective NPY Y2 receptor antagonist with enhanced CNS exposure is described.

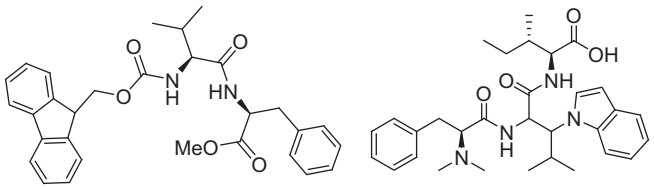


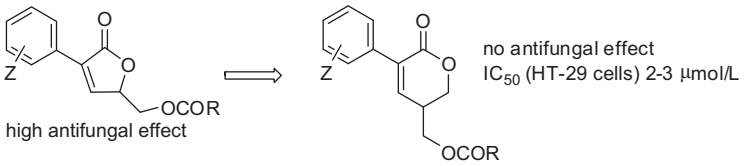
NOTAC6-GRGDG: R=$(CH_2)_3CH_3$
NOTAC8-GRGDG: R=$(CH_2)_5CH_3$
NOTAC10-GRGDG: R=$(CH_2)_7CH_3$

A series of novel 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-ones were synthesized. Some of them displayed potent inhibitory activities against COX-1/2 and 5-LOX in vitro, and strong anti-inflammatory and analgesic activities, and well gastric tolerability in vivo.

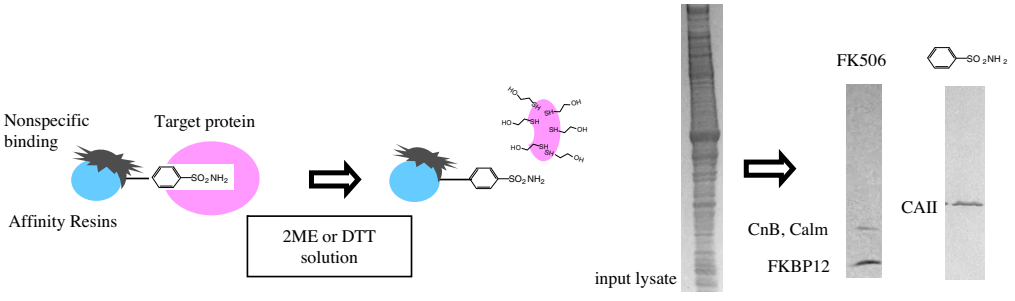


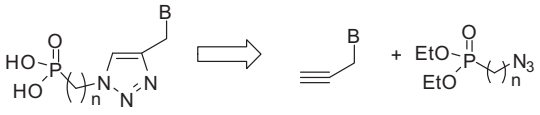
R^1 = NH_2SO_2, CH_3SO_2
R^2 = H, F, Cl, Br, CH_3, NO_2



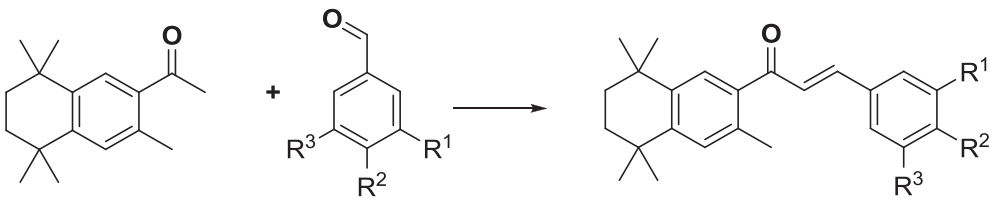


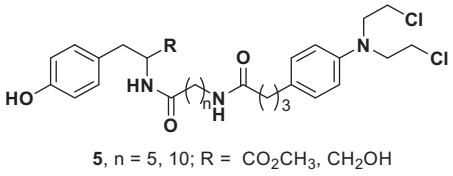
3,5-Disubstituted pyranones analogous to highly antifungally active furanones displayed no antifungal effect. Some of the pyranones, however, possessed cytostatic activity in the micromolar range against several cell lines, including the resistant HT-29 cells.





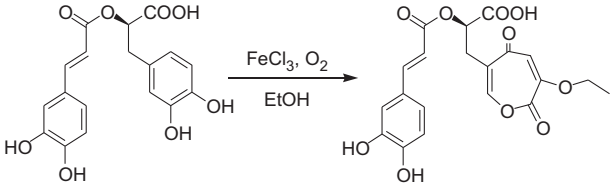
A series of triazoloacyclic nucleoside phosphonates were synthesized and evaluated for their in vitro antiviral activities (HCV and HIV) and cytotoxicities.



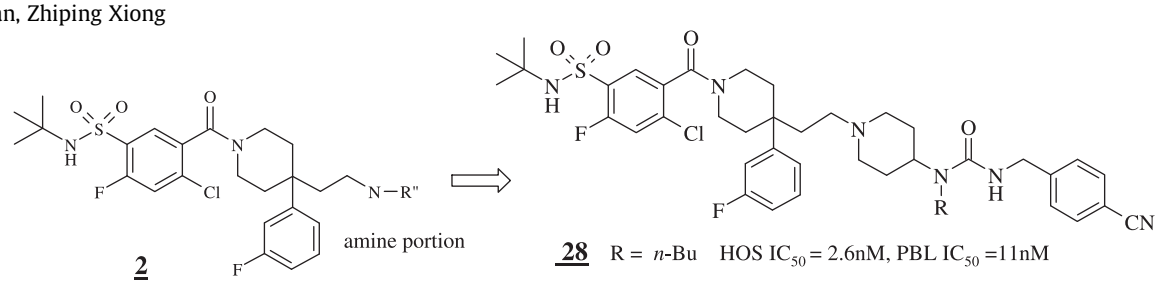


5, n = 5, 10; R = CO_2CH_3, CH_2OH

A series of D- and L-tyrosine-chlorambucil analogs is reported. The novel analogs showed significant in vitro anticancer activity when compared to chlorambucil on breast cancer cell lines. Some of the analogs showed selectivity towards MCF-7 (ER+) breast cancer cells.



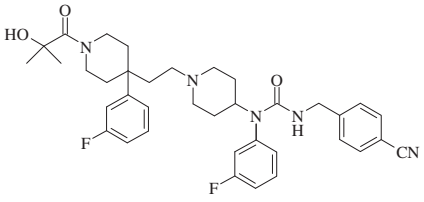
Rosmarinic Acid



2

28 R = *n*-Bu HOS IC_{50} = 2.6nM, PBL IC_{50} =11nM

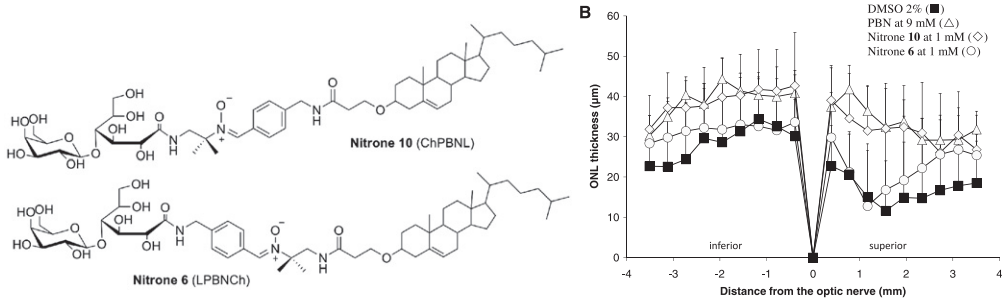
29 R = *m*-Fluorophenyl HOS IC_{50} = 0.4 nM, PBL IC_{50} = 1.7nM

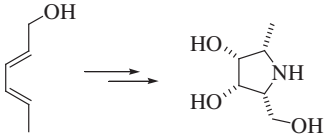


36

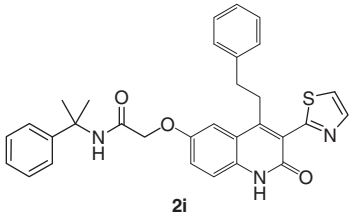
HOS IC_{50}: 8 nM PBL IC_{50}: 8.1 nM

F%: 53 (rat), 45(dog) and 14 (monkey)





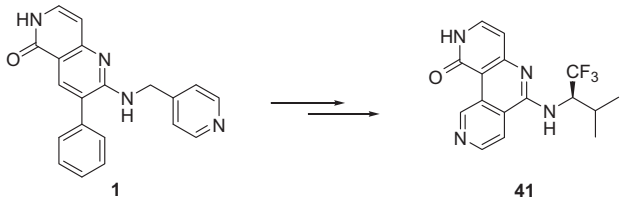
We describe the synthesis of the racemic aminofuranofucitol **3** from sorbic alcohol by nitroso-Diels–Alder as template for the synthesis of GDP-fucose analogues. Evaluation of this pyrrolidine as potent fucosidase and galactosidase inhibitor is discussed.



2i

hA_{2B} cAMP K_i = 5.1 nM

The synthesis and SAR of a novel series of A_{2B} receptor antagonists are reported.

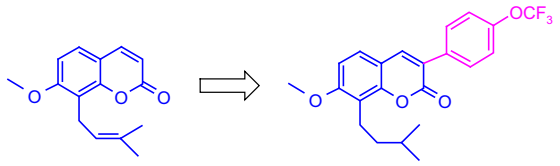


1

JAK2 IC_{50} = 1400 nM
LBE = 0.32

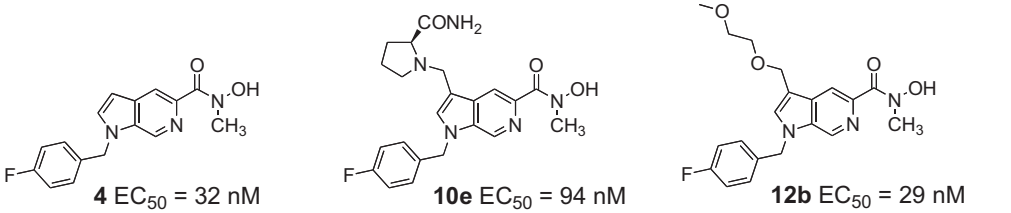
41

JAK2 IC_{50} = 1 nM
In Vivo IC_{50} = 2700 nM
LBE = 0.49



Osthole **8e**

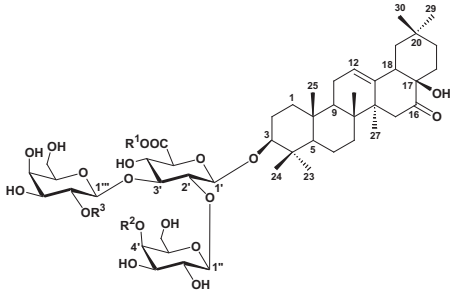
A series of osthole derivatives bearing aryl substituents at 3-position of coumarin, have been prepared and evaluated for their growth inhibitory activity against human breast cancer cell lines MCF-7 and MDA-MB-231. Compound **8e** was found to be the most potent compound with IC_{50} values of 0.24 μM, 0.31 μM against MCF-7 and MDA-MB-231, respectively, which was improved more than 100-folds compared with its parent compound osthole.



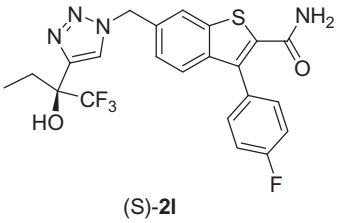
4 EC_{50} = 32 nM
ER (hHEP) = 1.0
LipE = 4.4

10e EC_{50} = 94 nM
ER (hHEP) = 0.36
LipE = 4.9

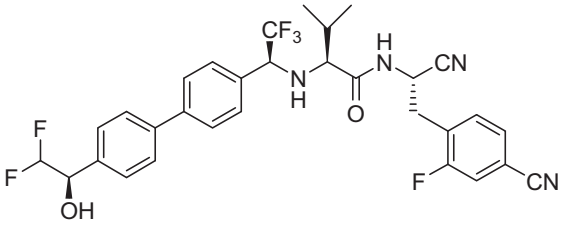
12b EC_{50} = 29 nM
ER (hHEP) = 0.51
LipE = 5.3

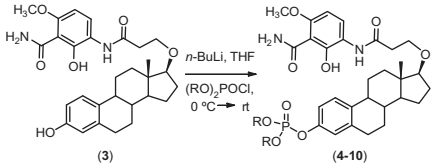


	R^1	R^2	R^3	NO Production, IC_{50} value
3	H	Ac	β-D-Glu	4.96μM
5	CH_3	H	β-D-Xyl	5.19μM



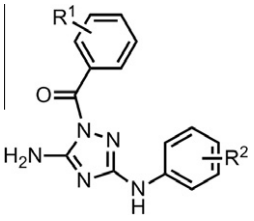
(S)-**2l**
MK-5286

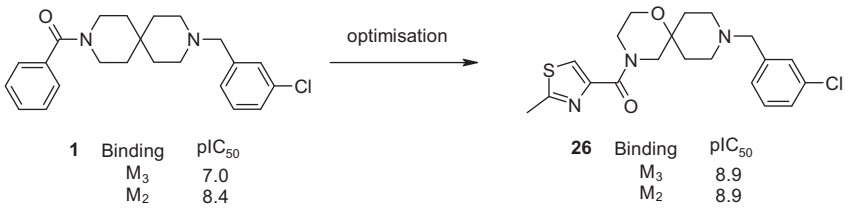




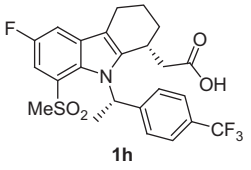
(**3**) (**4-10**)

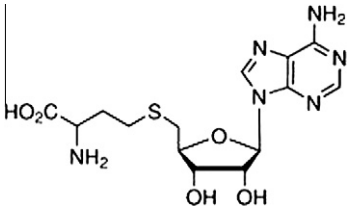
A series of 3-*O*-phosphorylated analogs (**4**–**10**) of a novel bone-targeted estradiol analog (**3**) were synthesized after a thorough study of the reaction of **3** with a selection of phosphoryl chlorides under a variety of reaction conditions. Evaluation of these novel phosphate analogs for affinity for hydroxyapatite revealed that they bind with equal or higher affinity when compared to the bone tissue accumulator, tetracycline.

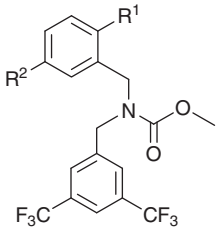




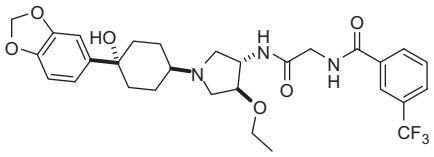
The optimisation of a new series of high potency muscarinic M_3 antagonists, derived from a high throughput screening library hit is described.







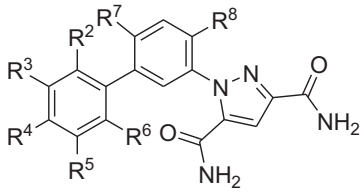
A new class of CETP inhibitors was designed and prepared. These compounds are potent both in vitro and in vivo. The most active compound (**12d**) has shown an ability to raise HDL significantly in transgenic mouse PD model.

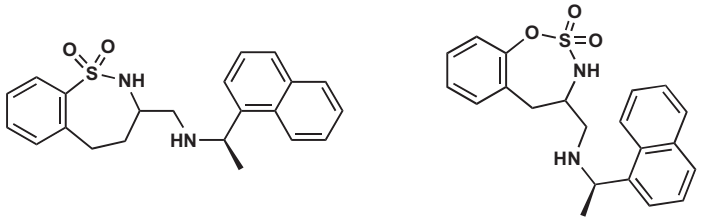


INCB3344

We report the discovery of a novel series of CCR2 antagonists through rational design based on a pharmacophore reported in the literature. SAR studies led to the identification of a potent human and murine CCR2 antagonist INCB3344 with high selectivity and good oral bioavailability in mice.

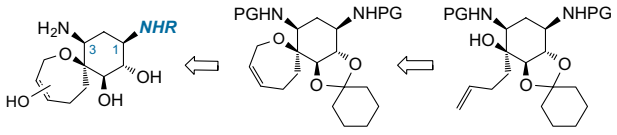
A series of novel low molecular weight biaryl pyrazole dicarboxamides with good in vitro potency and in vivo efficacy were identified as sodium channel blockers. These state dependent sodium channel blockers were synthesized and evaluated for treatment of neuropathic pain. Compound **20** had outstanding efficacy in the Chung rat spinal nerve ligation (SNL) model of neuropathic pain.



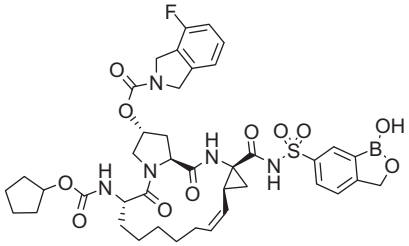


Cyclic sulfonamides and sulfamates as new calcimimetic agents

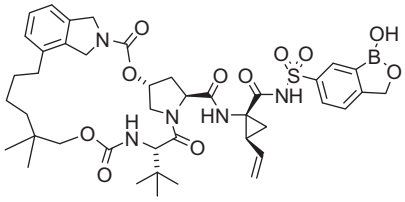
Cyclic sulfonamides and sulfamates as new calcimimetic agents.



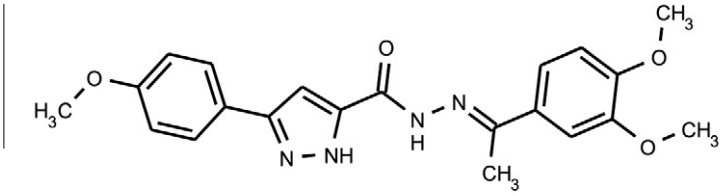
PG= carbamate type protective group



17



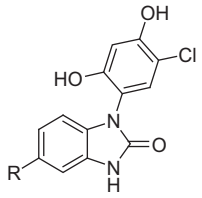
20



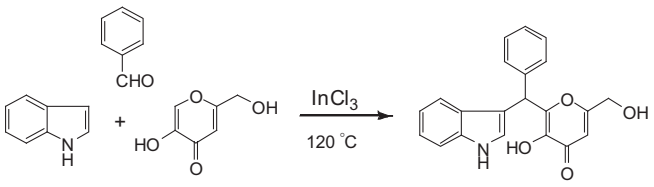
SKI-178

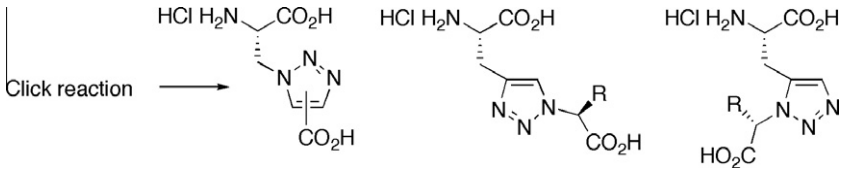
N'-[(1E)-1-(3,4-dimethoxyphenyl)ethylidene]-3-(4-methoxyphenyl)-1H-pyrazole-5-carbohydrazide

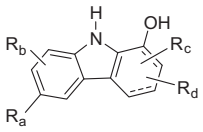
Herein, we report the identification of a novel sphingosine kinase 1-specific small-molecule inhibitor, SKI-178, that is active in vitro and in vivo.

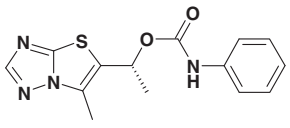


We describe the development of a novel series of *N*-aryl-benzimidazolone HSP90 inhibitors targeting the N-terminal ATP-ase site. SAR development was influenced by structure-based design based around X-ray structures of ligand bound HSP90 complexes. Lead compounds exhibited high binding affinities, ATP-ase inhibition and cellular client protein degradation.



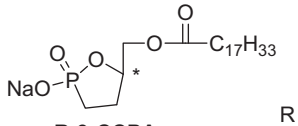






GSK2210875
mGluR5 pIC50 = 7.4
mouse neophobia MED = 5mg/kg p.o.

The identification of the novel orally active mGluR5 antagonist GSK2210875 is described. This MPEP competitive chemotype was identified via HTS and demonstrates intriguing and complex SAR distinct from known mGluR5 ligands. Notably a focus on polar compounds of modest potency but high free brain exposure afforded a compound with oral activity.

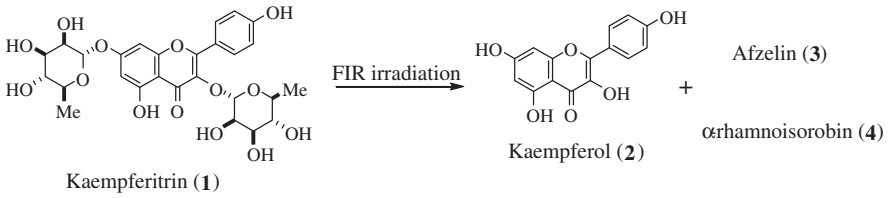


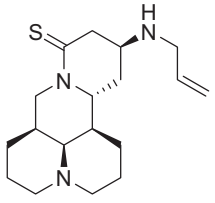
R-3-CCPA
S-3-CCPA

R =R -isomer
S =S -isomer

The first stereochemical synthesis and pharmacological evaluation of 18:1 3CCPA is described.

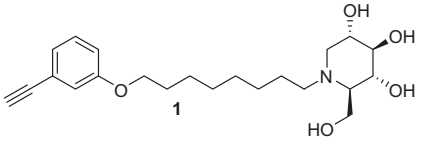
Synthetic inhibitors were used to test the tolerance of the NEU3 active site for modifications of DANA; three potent inhibitors were identified.





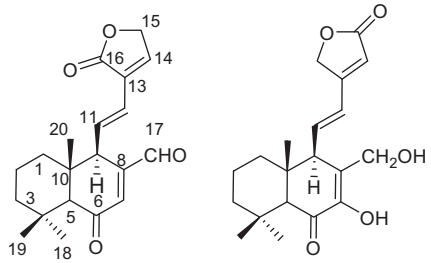
1f

A series of matrine derivatives were synthesized and evaluated for their inhibitory effect on pro-inflammatory cytokines. Compound **1f** was found to be the most potent compound.

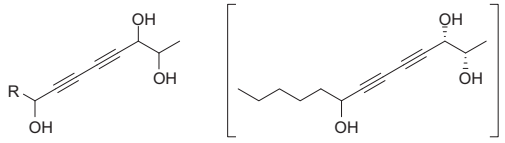


1

The DNJ derivative **1** inhibits lung cancer cell growth, migration and promotes apoptosis



Phytochemical investigation on *Hedychium coronarium* rhizomes yielded two new labdane diterpenes (**1** and **2**) along with 10 known compounds (**3**–**12**). Cytotoxic activity of the isolates were studied against A-549 (human lung carcinoma) SK-N-SH (human neuroblastma), MCF-7 (breast cancer) and HeLa (cervical cancer) cell lines.



We synthesized diyne triols, derivatives of gymnasterkoreayne and evaluated their cancer chemopreventive activities by chemopreventive index (CI) to reveal structure–activity relationship, and discovered more active compounds than natural diynes.

*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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