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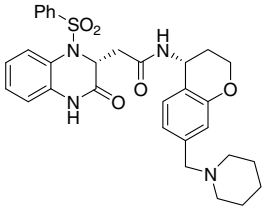
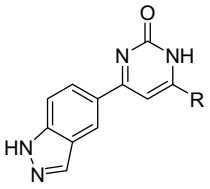
Contents

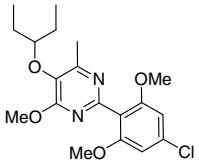
ARTICLES



Novel dihydroquinoxalinone acetamides containing bicyclic aminotetralins or chromans were found to be potent Bradykinin B1 receptor antagonists.

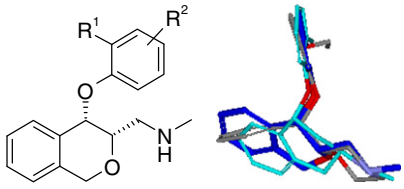


A series of 4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1*H*)-ones were identified by HTS as inhibitors of CDC7. Molecular modeling and medicinal chemistry techniques were employed to explore the SAR for this series with a focus on removing potential metabolic liabilities and improving cellular potency.

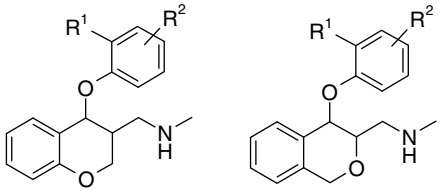


12b, CRF-1 $K_i = 9$ nM

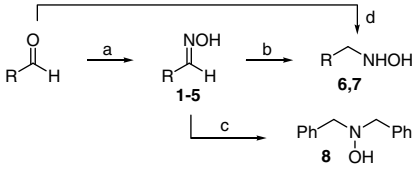
The design, synthesis, and structure–activity relationship studies of a novel series of CRF-1 receptor antagonists, the 2-arylpyrimidines, are described. The effects of substitution on the aromatic ring and the pyrimidine core on CRF-1 receptor binding were investigated. A number of compounds with K_i values below 10 nM and lipophilicity in a minimally acceptable range for a CNS drug (*c*Log $P < 5$) were discovered.



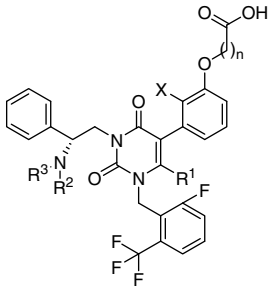
A series of chiral ring-constrained norepinephrine reuptake inhibitors equivalent to atomoxetine in potency, selectivity, and inhibition of CYP2D6 but more stable to oxidative metabolism.

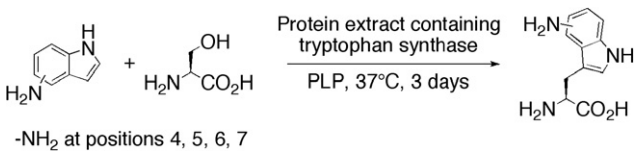


A series of heterocyclic ring-constrained norepinephrine reuptake inhibitors have activities as racemates equivalent to atomoxetine (IC_{50}'s < 10 nM).

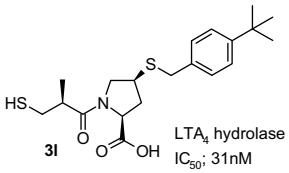


Hydrolysis of DNA is of increasing importance in biotechnology and medicine. In this Letter, we present the DNA-cleavage potential of metal-free hydroxylamines and oximes as new members of nucleic acid cleavage agents.

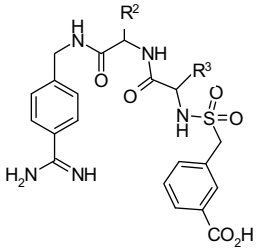




A one-pot biotransformation for the generation of a series of L-aminotryptophans using tryptophan synthase-containing bacterial cell free extract is reported. The extract can be freeze-dried and stored without appreciable loss of activity.

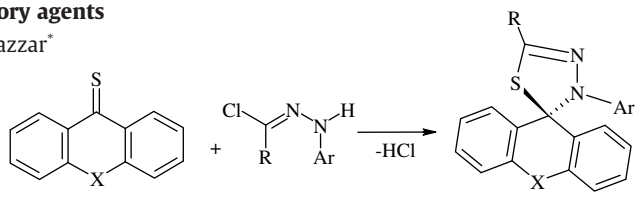


Synthesis and leukotriene A_4 (LTA_4) hydrolase inhibitory activity of *N*-mercaptoacylproline and (4*R*)-*N*-mercaptoacylthiazolidine-4-carboxylic acid derivatives are reported. An *N*-mercaptoacyl group, (2*S*)-3-mercapto-2-methylpropionyl group, was effective for both scaffolds. Additional introduction of a substituent, such as 4-*tert*-butyl benzylthio, with (*S*)-configuration at the C_4 position of proline yielded potent LTA_4 hydrolase inhibitors.



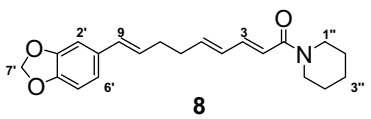
12b R^2=Gln, R^3=Ile
12d R^2=Gln, R^3=Thr
12e R^2=Met, R^3=Thr
12f R^2=Met, R^3=Ile

We succeeded in target hopping in the serine protease family using crystal structures of human FVIIa/TF in complex with peptide mimetic inhibitors.



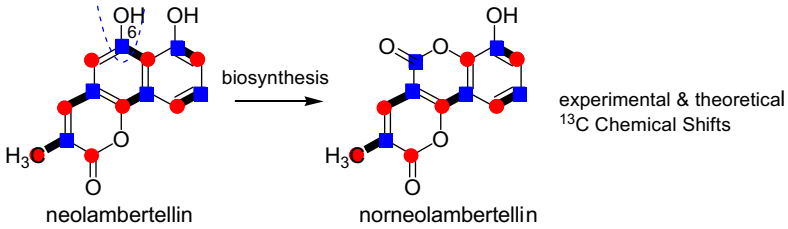
4a,b **5a-g** **6a-g , X = S** **7a-g , X = O**

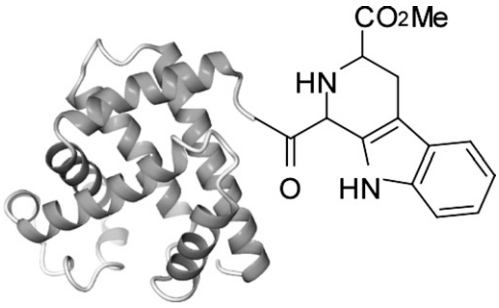
The 1,3-dipolar cycloaddition of nitrile imines to 9*H*-thioxanthone-9-thione and 9*H*-xanthone-9-thione afforded novel *spiro*-thioxanthene-9′,2-[1,3,4]thiadiazoles **6a**–**g** and *spiro*-xanthene-9′,2-[1,3,4]thiadiazoles **7a**–**g** in good yields. Some of the newly synthesized compounds were tested for anti-inflammatory and analgesic activities comparable to ibuprofen. Compounds **6a**,**d**,**e** and **7a**,**d**,**e** showed significant activity compared to standard drug. The toxicity studies revealed that neither death nor other behavioral or toxicological changes were observed on rats up to a dose as high as 200 mg/kg.



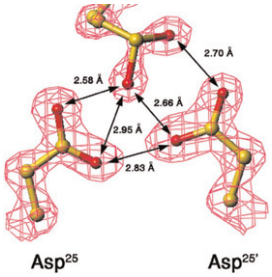
8

Eight alkamides **1**–**8** were isolated from EtOH extracts of the fruits of *Piper longum* and *nigrum*. Among the tested alkamide derivatives **1**–**8**, dehydropipernonaline (**8**) showed the most inhibition of the direct binding between sICAM-1 and LFA-1 of THP-1 cells in a dose-dependent manner, with an IC_{50} value of 6.0 μg/mL.

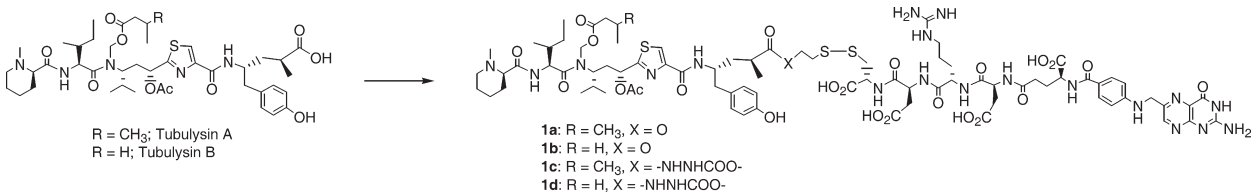


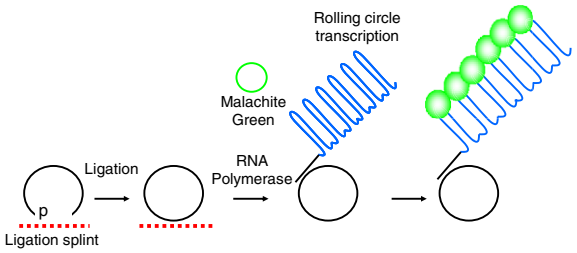


This work describes the methodology for the N-terminal modification of proteins by the Pictet–Spengler reaction.

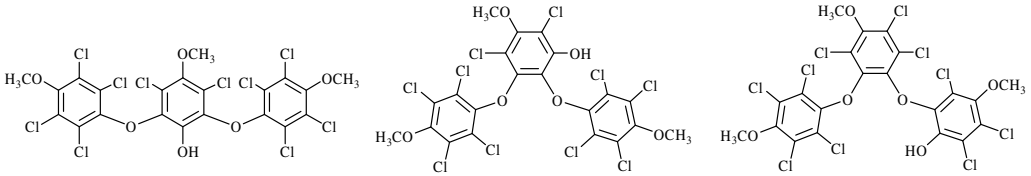


Crystal structure of HIV-1 protease with its ketomethylene isostere inhibitor is reported.



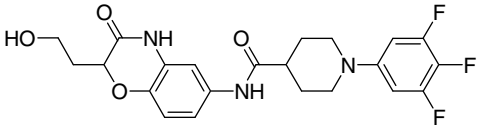


We demonstrate a fluorescence generation of tandem repeats of a malachite green (MG) RNA aptamer using rolling circle transcription.

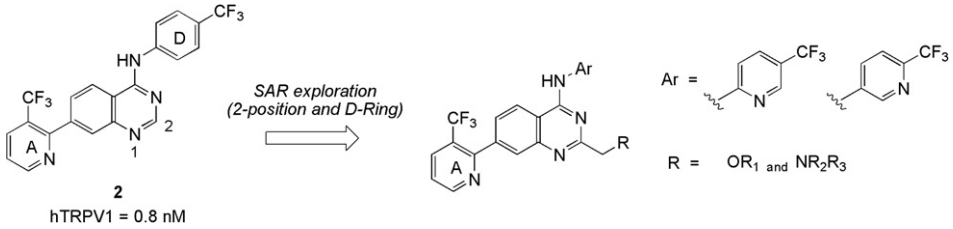


Chlorophellin A **Chlorophellin B** **Chlorophellin C**

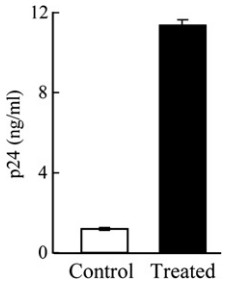
Polychlorinated compounds with PPAR-γ agonistic effect have been isolated together with the known compound, drosophilin A, from the methanolic extract of the fruiting body of the fungus *Phellinus ribis*. Chemical structures were assigned on the basis of NMR and mass spectrometric analyses. Chlorophellin C of compounds exhibited the most potent PPAR-γ agonistic effect and was comparable to rosiglitazone.



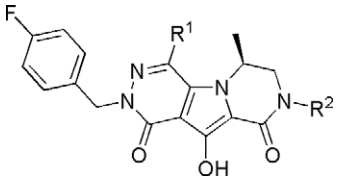
A series of piperidine carboxamides were developed as potent antagonists of the transient receptor potential receptor vanilloid 1 (TRPV1), an emerging target for the treatment of pain. A focused library of polar head groups led to the identification of a benzoxazinone amide that afforded good potency in cell-based assays. Synthesis and a QSAR model will be presented.

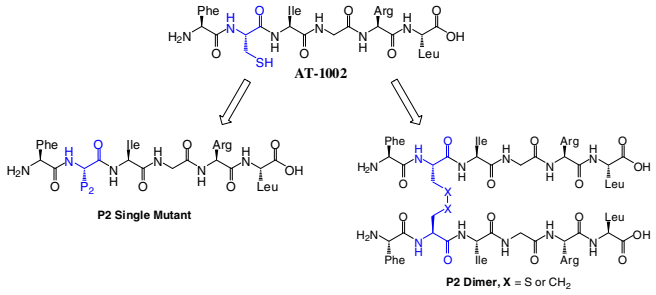


2
hTRPV1 = 0.8 nM

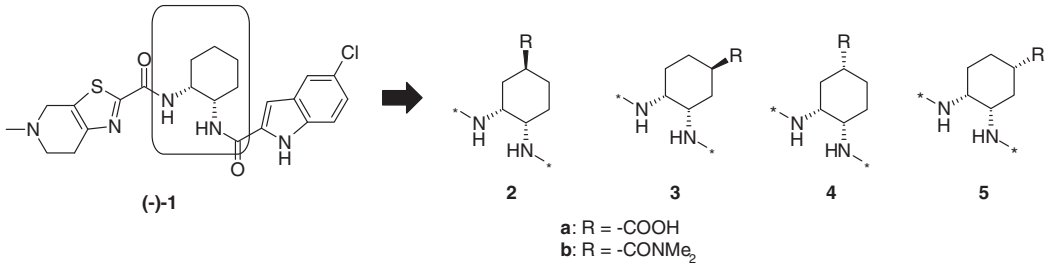


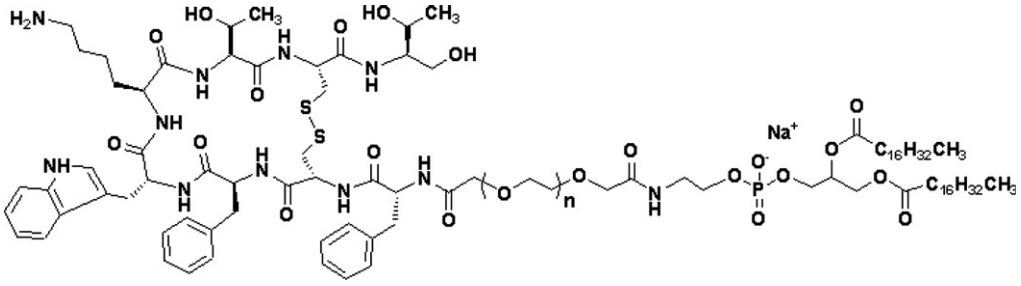
A good correlation between fifty-percent inhibitory concentration of hybrid liposomes (HL) on the growth of MOLT-4 cells chronically infected with human immunodeficiency virus and the membrane fluidity of HL was obtained.



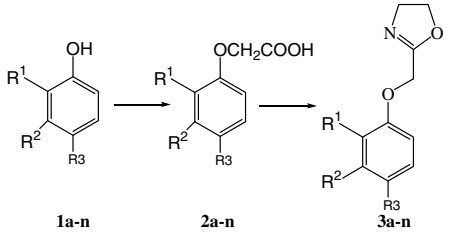


The structure–activity relationship of a permeability modulating peptide **AT-1002** was elaborated with the specific goal to replace P2 cysteine amino acid. We report herein, the discovery of peptides that exhibit reversible permeability enhancement properties with increased stability profile.



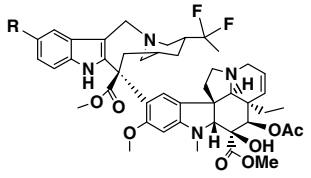


Chemical structure of Octreotide-PEG-DSPE.



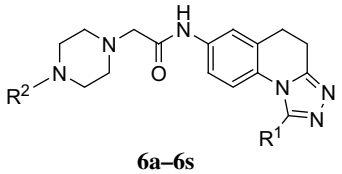
1a-n **2a-n** **3a-n**

A series of potential biologically active 2-aryloxy methyl oxazolines **3a**–**n**, have been synthesized from substituted hydroxybenzenes **1a**–**n** with good chemical yield and screened for their anti-inflammatory, ulcerogenic, cyclooxygenase activities and also for their acute toxicity.



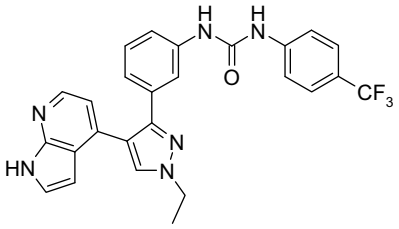
2-50

A series of novel C-12′ substituted vinflunine derivatives have been synthesized. Several compounds in this series possess comparable in vitro cytotoxic potency against A549 cell lines.



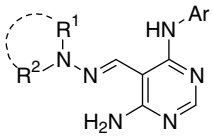
6a–6s

A series of *N*-(4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-7-yl)-2-(piperazin-1-yl)acetamide derivatives were synthesized and their positive inotropic activity was evaluated by measuring left atrium stroke volume on isolated rabbit heart preparations.

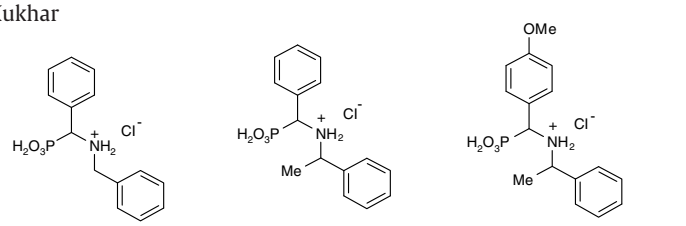


6h

We have identified the title compound **6h** as a novel, potent, and selective B-Raf kinase inhibitor using knowledge-based design.



Members of a novel class of 4-amino-6-arylamino-pyrimidine-5-carbaldehyde hydrazones were identified as potent dual ErbB-2/EGFR kinase inhibitors using concept-guided design approach.

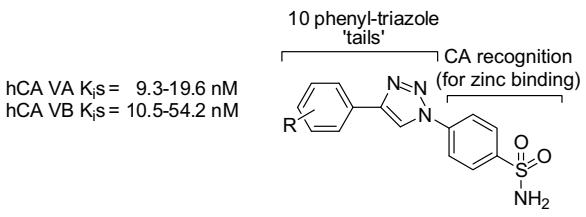


1a (*R*) IC_{50} =5.0 nM
1b (*S*) IC_{50} =198 nM

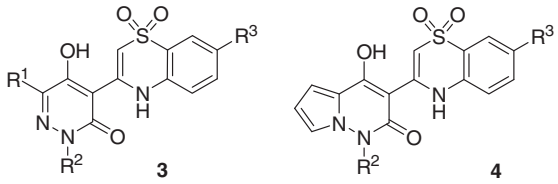
2a (*1R2S*) IC_{50} =1210 nM
2b (*1S2R*) IC_{50} = 26 nM

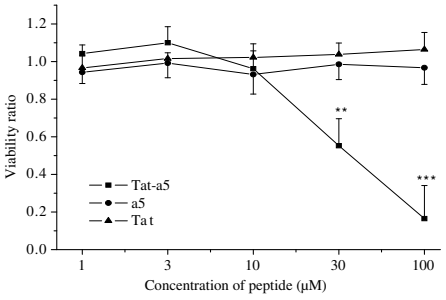
3a (*1R2S*) IC_{50} =1070 nM
3b (*1S2R*) IC_{50} = 18 nM

The evaluation of inhibitory activity of enantiomerically pure α-(*N*-benzylamino)benzylphosphonic acids toward human prostatic acid phosphatase is reported. The enantioselectivity has been explained using a molecular docking approach.

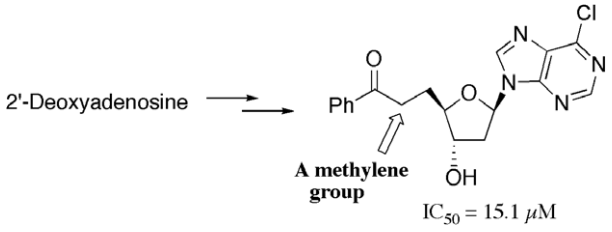


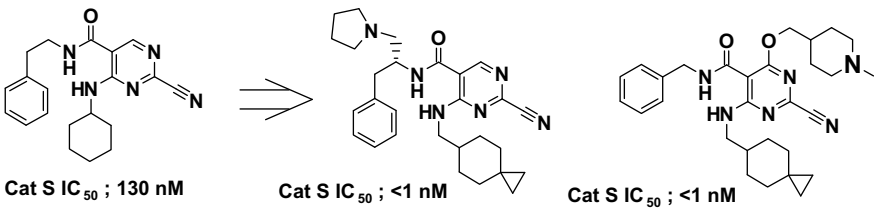
This paper describes the synthesis of and mitochondrial carbonic anhydrase inhibition for a novel library of benzenesulfonamides with variously substituted 4-phenyl-1,2,3-triazole 'tail' moieties.

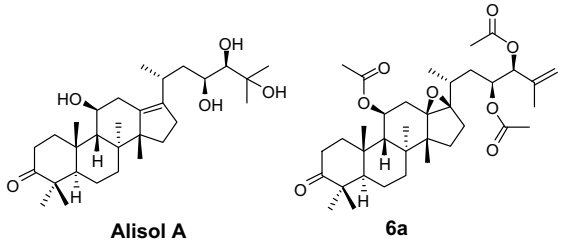




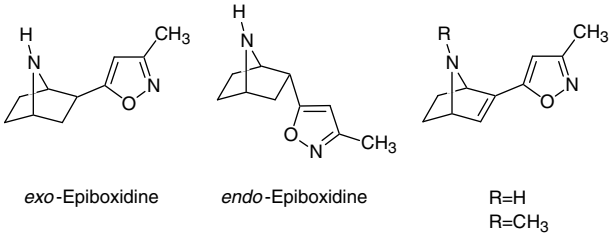
KAQIRAMECNILGRKKRRQRRR (**Tat-a5**)HIV-Tat (49–57): RKKRRQRRR (**Tat**)Cyclin B (285–296): KAQIRAMECNIL (**a5**).



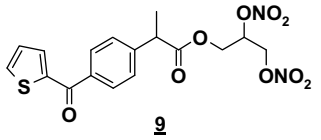




A series of alisol A derivatives were synthesized and assayed for their anti-HBV activities in vitro. The most active compound **6a** showed IC_{50} of 0.024 and 0.028 mM to HBsAg and HBeAg, respectively, with CC_{50} > 2.6 mM, resulting remarkable selective indices (SI_{HBsAg} > 108, SI_{HBeAg} > 93).

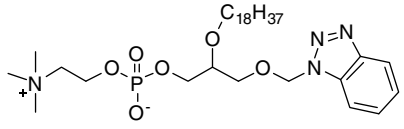


An efficient Stille coupling-based synthesis of epiboxidine and unsaturated analogues is reported. The compounds were assayed for their binding affinity at neuronal α4β2 and α7 nicotinic acetylcholine receptors.

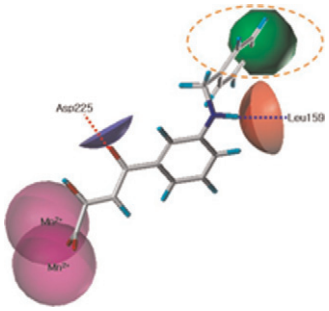


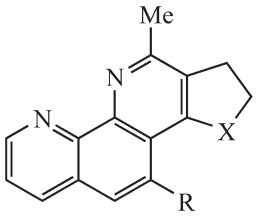
Compound **9** :
PC3 cell growth inhibition at 10μM :
- 52 % after 24h incubation time
- 0 % after 72h incubation time

A study of the action mechanism of new NO-donating profens on prostatic cancer cell lines is reported.

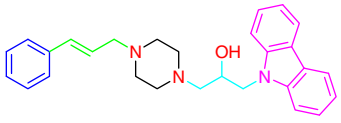


The parallel synthesis of a series of alkyl ether phospholipids is reported. Compound **17** showed good inhibition of *L. donovani* growth.



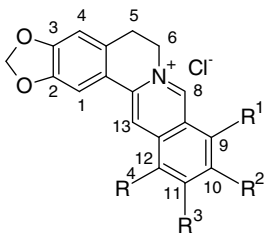


A novel series of 1,10-phenanthrolines derivatives were designed and prepared. All compounds showed potent antiplasmodial activities in vitro against both sensitive an chloroquine-resistant lines and also potent antigametocytal activity.

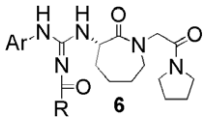


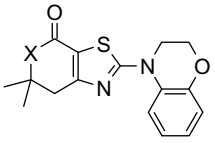
Incentrom A (1)

Pharmacophore and structure–activity relationship of Incentrom A that inhibits the chromosome segregation process in yeast were established. A series of Incentrom A analogs were synthesized and tested for the anti-yeast activity.



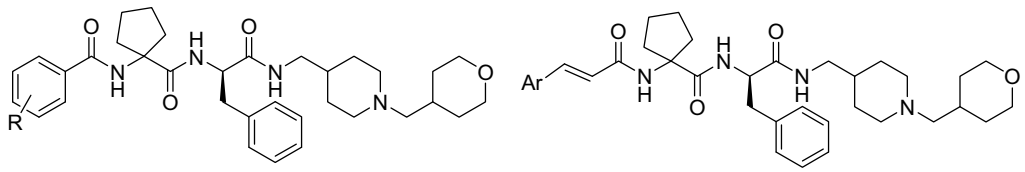
R^1-R^4 = H, OH, OCH_3, OC_2H_5, OC_3H_7 etc.



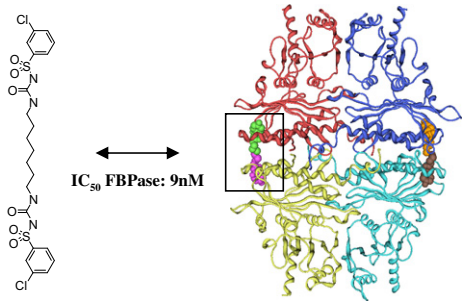


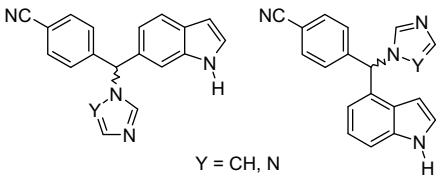
3 X=CH_2
4 X=NH

The SAR and pharmacokinetic profiles of a series of multi-isoform PI3K inhibitors based on a 3,4-dihydro-2H-benzo[1,4]oxazine scaffold are disclosed.

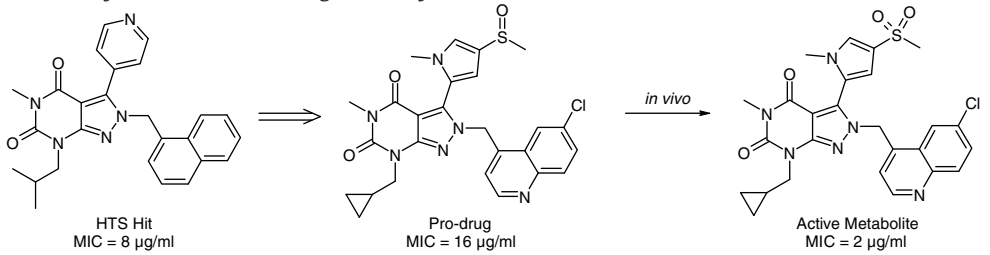


Starting from an in-house prepared library of capped dipeptides, we have identified a series of molecules with subnanomolar binding affinity for the hNK_2 receptor containing a dipeptide cyclopentanglycine-D-phenyl alanine as a core and C- and N-terminal capping groups. Here we report how we were able to manipulate the N-terminal capping group to obtain significant in vivo activity after iv and id administration.

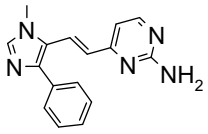




Two new series of benzonitrile derivatives on position 6 or 4 of the indole ring were successfully synthesized via a Leimgruber–Batcho reaction. The target compounds were further evaluated as aromatase inhibitors.

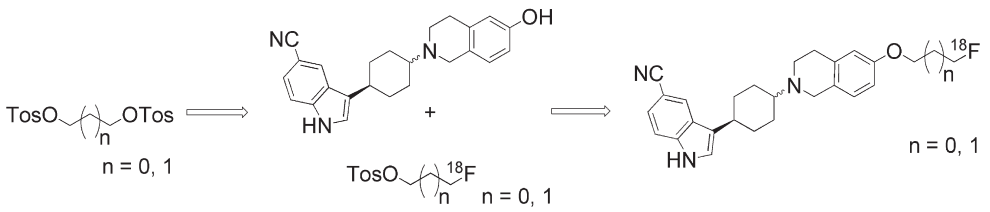


To achieve high bioavailability towards the design of *Helicobacter pylori* antibacterial drugs, a pro-drug approach was implemented wherein a sulfoxide moiety is oxidized in vivo to the more potent sulfone.



pTie-2 Cell IC_{50} = 340 nM

The discovery and SAR of a novel class of imidazole-alkene-pyrimidine kinase inhibitors, which inhibit Tie-2 in vitro and in cells is reported. These compounds are lead-like with low molecular weight and good physical properties, and are orally bioavailable.



*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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