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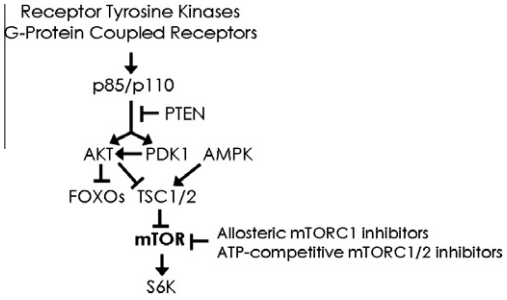
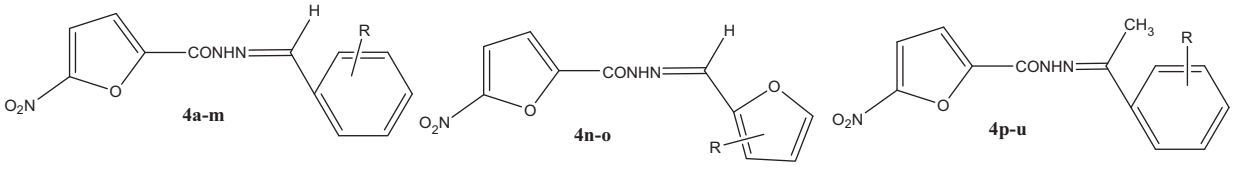
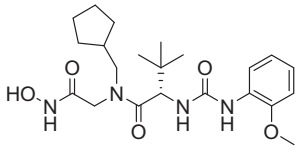
Contents

BMCL DIGEST



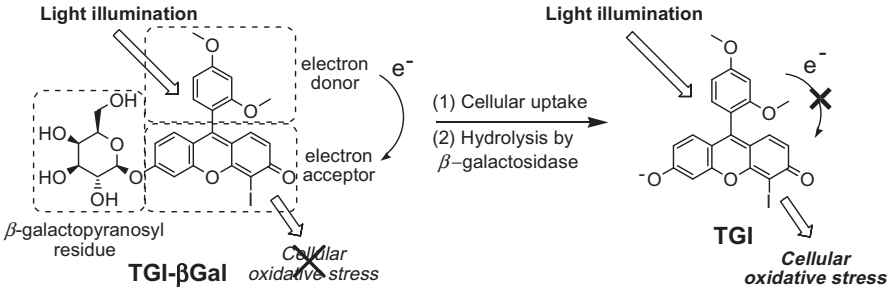
REGULAR ARTICLES



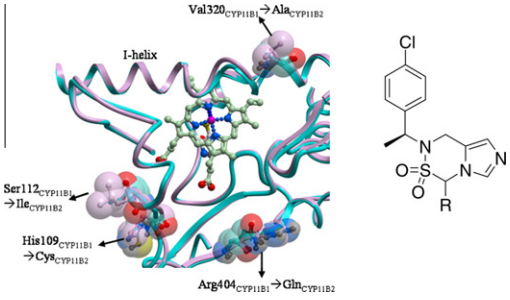


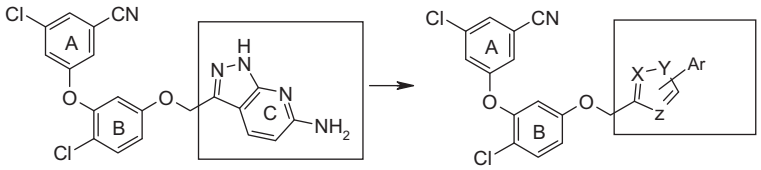
7a

The synthesis and structure–activity relationship studies of peptide deformylase inhibitor **7a** are reported.

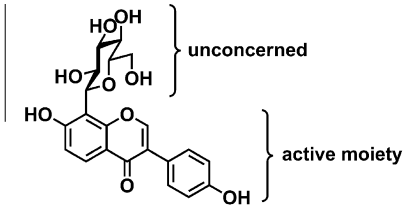


Aldosterone, the final component of the renin–angiotensin–aldosterone system, plays an important role in the pathophysiology of hypertension and congestive heart failure. Aldosterone synthase (CYP11B2) catalyzes the last three steps of aldosterone biosynthesis, and as such appears to be a target for the treatment of these disorders. A sulfonamide–imidazole scaffold has proven to be a potent inhibitor of CYP11B2. Furthermore, this scaffold can achieve high levels of selectivity for CYP11B2 over CYP11B1, a key enzyme in the biosynthesis of cortisol.

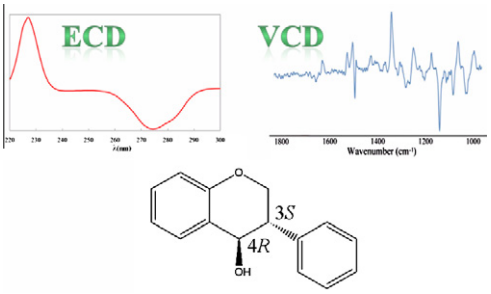




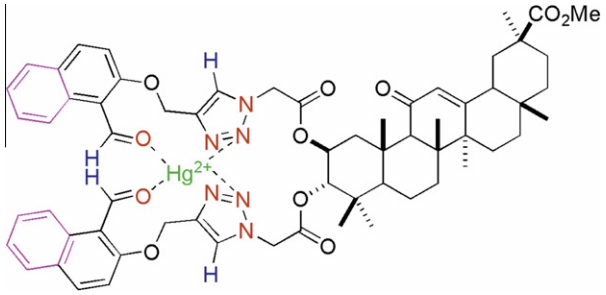
compound **1** (MK-4965)



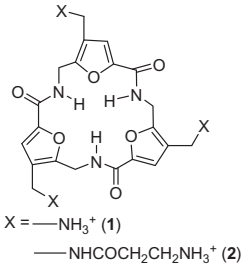
Glucose uptake enhancing activity of Puerarin



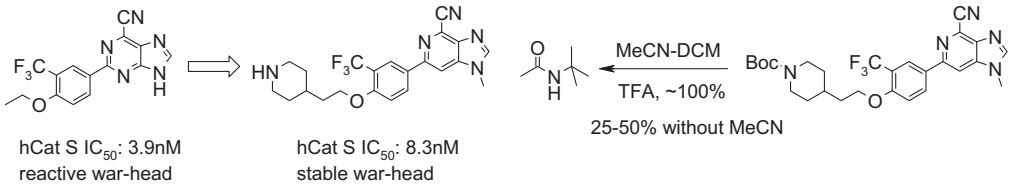
Absolute configurations of isoflavan-4-ol stereoisomers have been studied by ECD, VCD, and the modified Mosher method.

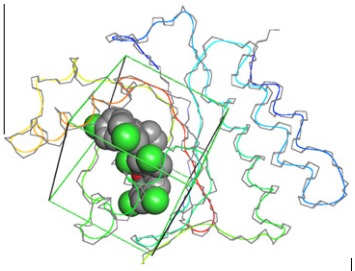


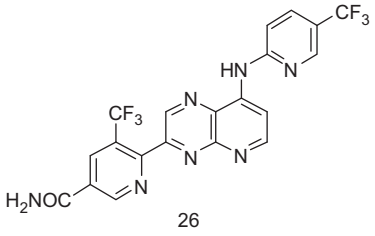
A novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid derived from natural triterpenoid molecules has been synthesized via click chemistry and they showed high selectivity and affinity for Hg^{2+} ion by both the 1,2,3-triazole rings and aldehyde groups.

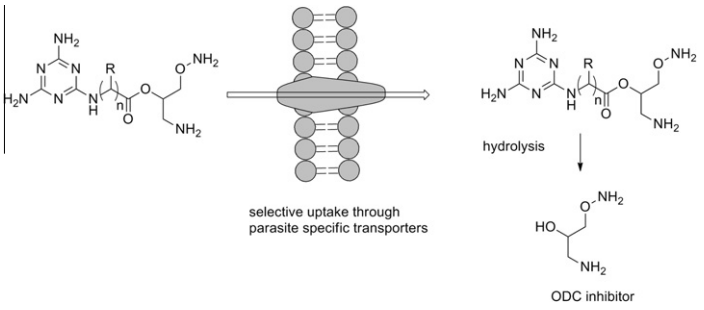


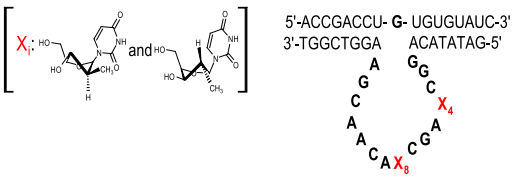
6-Phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile derivatives were identified as selective human cathepsin S inhibitors with a stable thiol trapping nitrile war-head. A novel TFA based Boc deprotection method is also described. This new method uses acetonitrile as a co-solvent to remove *t*-butyl cation related side reactions by an in situ 'Ritter' reaction.





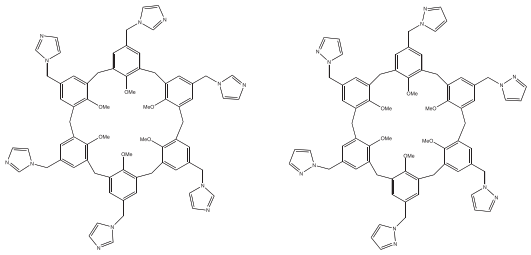




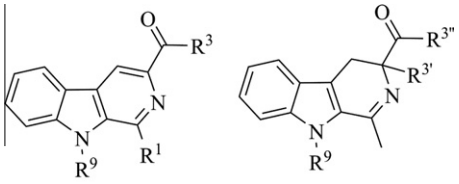


2′-Deoxy-2′-*C*-methyl nucleosides were incorporated at T positions of the catalytic core of a 10-23 DNAzyme directed against estrogen receptor α ARNm. Comparison against DNAzymes modified with LNA-T was also performed.

Synthesis and broad-spectrum anticancer activity of a novel heterocyclic compound **1** containing the title imidazo[4,5-*e*][1,3]diazepine ring system have been reported. The compound shows potent in vitro antitumor activity with low micromolar IC_{50}'s against prostate, lung, breast, and ovarian cancer cell lines tested.

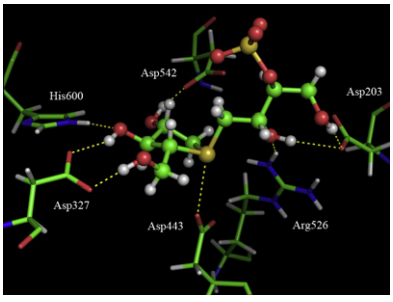


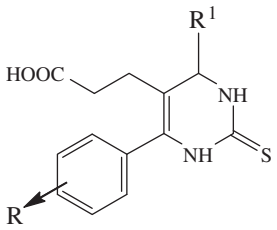
imidazole-calixarene **1** pyrazole-calixarene **2**



15, R^1= -CHO
R^3= -OCH_3
R^9= - H
IC_{50} = 2.9 μM

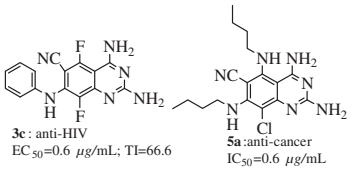
A series of β-carboline derivatives were prepared and evaluated for anti-HIV activity in human CD4+ T cell line CEM-GFP, infected with HIV-1 $NL_{4.3}$. 1-Formyl-β-carboline-3-carboxylic acid methyl ester (**15**) showed IC_{50} of 2.9 μM.





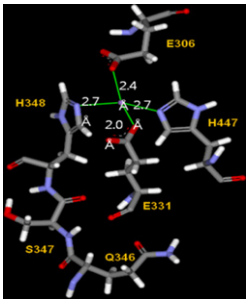
A new series of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives has been synthesized and evaluated for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series show anti-inflammatory activity comparable to diclofenac.

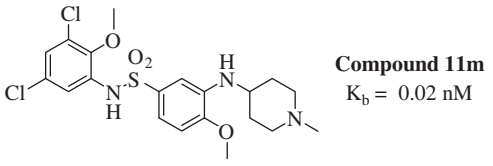
Compound **5** exhibited good binding interactions into the both active site of (a) IN (1QS4) and (b) PR (1HSG). This compound may be dual inhibitor acting against both IN and PR.



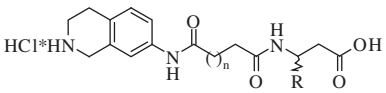
The novel 2,4-diaminoquinazolines **3**–**5** were easily prepared based on the reaction of polyhaloisophthalonitriles with guanidine carbonate. The anticancer and anti-HIV activities of **3**–**5** were evaluated in vitro. Compound 5a was the most potent derivative against the five tumor cell lines with an IC_{50} value lower than 2.5 μg/mL, and **3c** showed the most potent anti-HIV-1 activity with EC_{50} values of 0.6 and 1.6 μg/mL, and TI values of >59.6 and 66.6, respectively.

Based on in silico studies, the residue at position 346 has been proposed to be responsible for the unique substrate specificity of L-arabinose isomerase from *Bacillus licheniformis*.

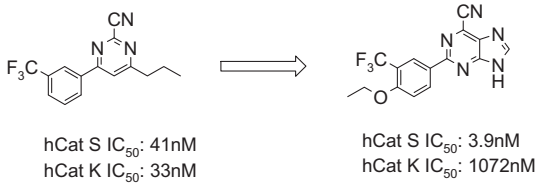




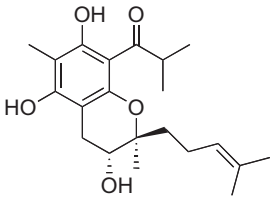
Design, synthesis, SAR and Pharmacokinetic profile of a novel series of Aryl aminosulfonamides as potent 5-HT_6 receptor antagonists is presented. The lead compound was active in animal model of cognition.

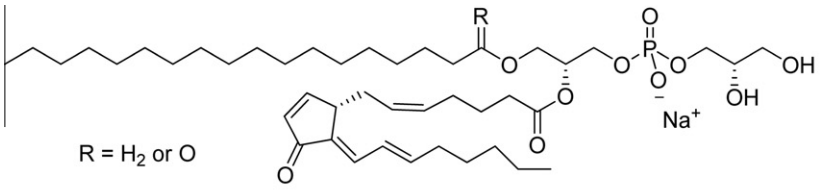


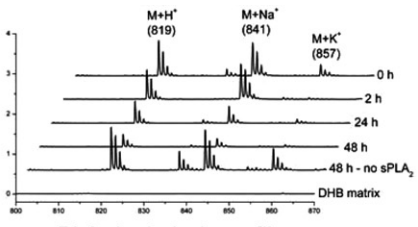
The synthesis of the novel fibrinogen receptor antagonists.

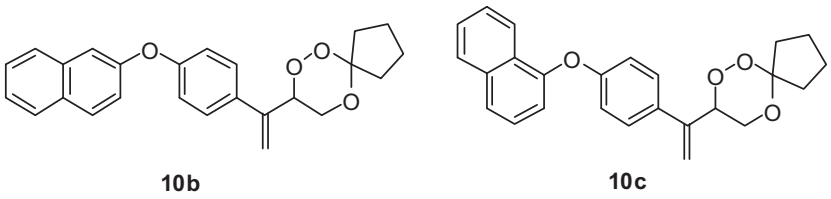


2-Phenyl-9*H*-purine-6-carbonitrile derivatives were designed as selective human cathepsin S inhibitors through P2 optimization and transition state stabilization by an intramolecular H-bond.



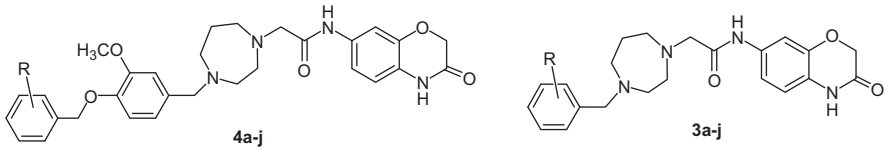






10b **10c**

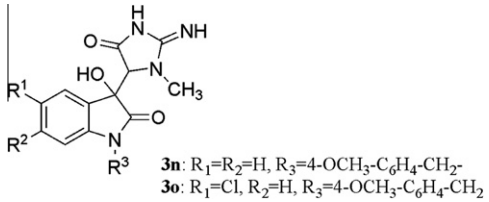
A new series of 6-(4′-aryloxy-phenyl)vinyl-1,2,4-trioxanes **10a**–**d**, **11a**–**d**, and **12a**–**d** have been synthesized and evaluated for their antimalarial activity against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route. Trioxanes **10b** and **10c**, the two most active compounds of the series, provided 100% protection to the infected mice at 48 mg/kg × 4 days.



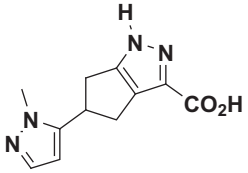
4a-j **3a-j**

Two series of 2-(4-substituted benzyl-1,4-diazepan-1-yl)-*N*-(3,4-dihydro-3-oxo-2*H*-benzo[*b*][1,4]oxazin-7-yl)acetamides (**3a**–**j** and **4a**–**j**) were synthesized and their positive inotropic activity were evaluated by measuring left atrium stroke volume on isolated rabbit heart preparations.

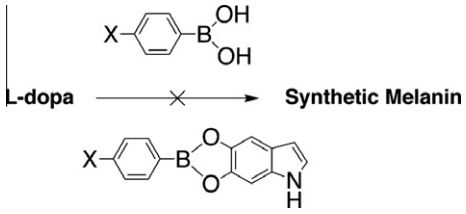
A series of novel 3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one analogs (**3**) have been synthesized under microwave irradiation and conventional heating methods. These analogs were evaluated for their in vitro cytotoxicity against a panel of 57 human tumor cell lines. Compound **3o** had GI_{50} values of 190 nM and 750 nM against A549/ATTC non-small cell lung cancer and LOX IMVI melanoma cell lines, respectively, and both **3n** and **3o** exhibited GI_{50} values ranging from 2 to 5 μM against CCRF-CEM, HL-60(TB), K-562, MOLT-4, and RPMI-8226 leukemia cell lines. These results indicate that *N*-4-methoxybenzyl-3-hydroxy-(2-imino-3-methyl-5-oxo-4-yl)indolin-2-one analogs may be useful leads for anticancer drug development.

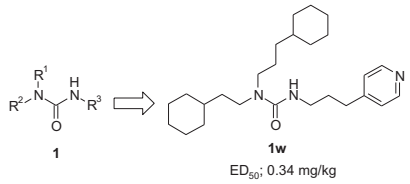


3n: R_1=R_2=H, R_3=4-OCH_3-C_6H_4-CH_2-
3o: R_1=Cl, R_2=H, R_3=4-OCH_3-C_6H_4-CH_2



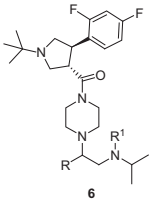
5-Alkyl and aryl-pyrazole-acids have been identified as a new class of selective, small-molecule, agonists of the human orphan G-protein-coupled receptor GPR109a, a high affinity receptor for the HDL-raising drug nicotinic acid.

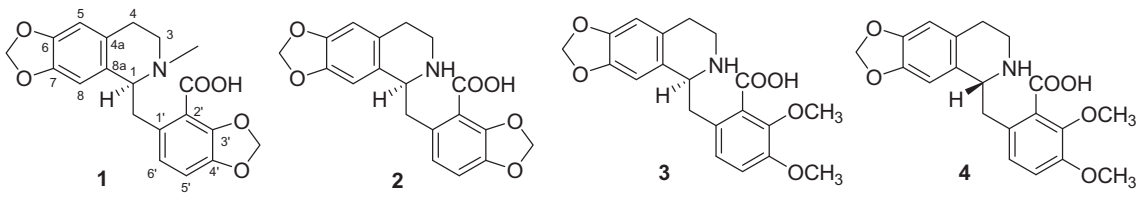




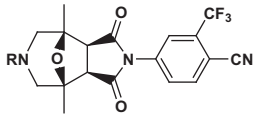
The synthesis of the urea derivatives were performed rapidly in a one-pot manner using a manual synthesizer. Several compounds containing hydrophobic substituents at R^1 and R^2 showed potent inhibitory activities against TNF-α production.

Design, syntheses and structure–activity relationships of piperazine privileged structures containing MC4R agonist compounds **6** were described. The most potent derivatives were low nM MC4R selective full agonists. Several compounds from the series had modest pharmacokinetic properties.

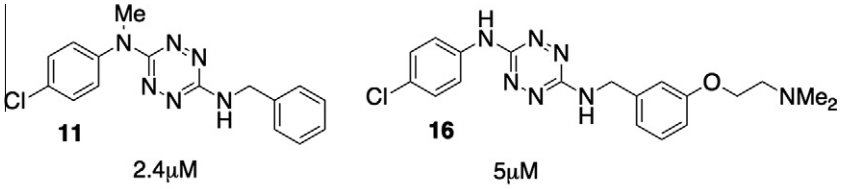


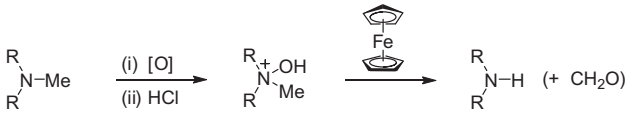


Chemical investigation of the tubers of *Corydalis ternata* resulted in the isolation and characterization of four new benzylisoquinoline alkaloids, *epi*-coryximine (**1**) and coryternatines A–C (**2**–**4**), along with 10 known alkaloids.

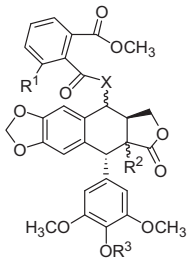


A novel series of 4-[3,5-dioxo-11-oxa-4,9-diazatricyclo[5.3.1.02,6]undec-4-yl]-2-trifluoromethyl-benzonitriles has been synthesized. The ability of these compounds to act as antagonists of the androgen receptor was investigated and several were found to have potent activity in vitro and in vivo.





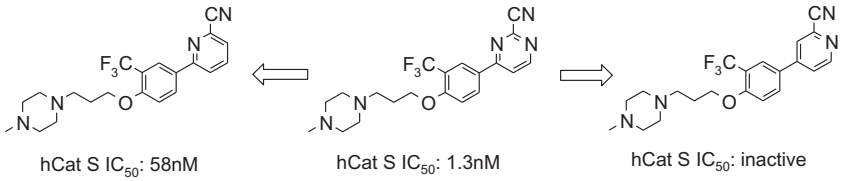
Ferrocene has been found to be a convenient and efficient catalyst for the N-demethylation of a number of opiate and tropane *N*-methyl alkaloids.



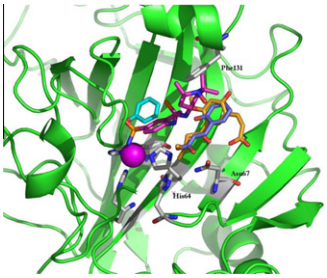
X =O, NH; R^1 = H, NO_2;
R^2 = H, Cl; R^3 = Me, monomethyl phthalate

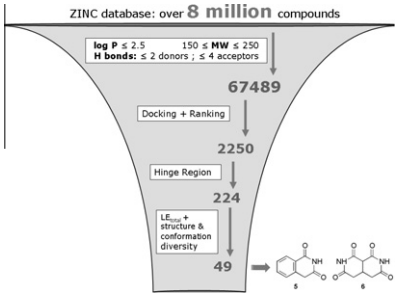
8a-l

Trans-lactone, 4β-substitution, 2β-chlorine substitution, and 4′-methoxy group were the important structural properties of podophyllotoxins for good insecticidal activity.

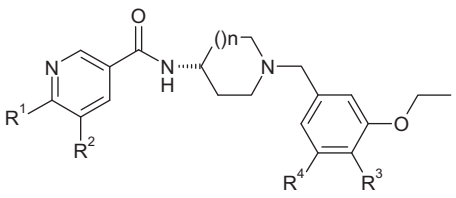


The N3 nitrogen of the pyrimidine-2-carbonitrile based cathepsin cysteine protease inhibitors is critically important. An 'in situ double activation' mechanism was postulated to explain these results. A novel expanded S2 binding pocket for human cathepsin S enzyme was also identified.

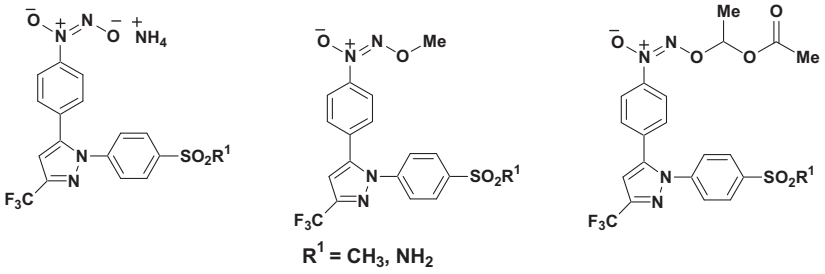


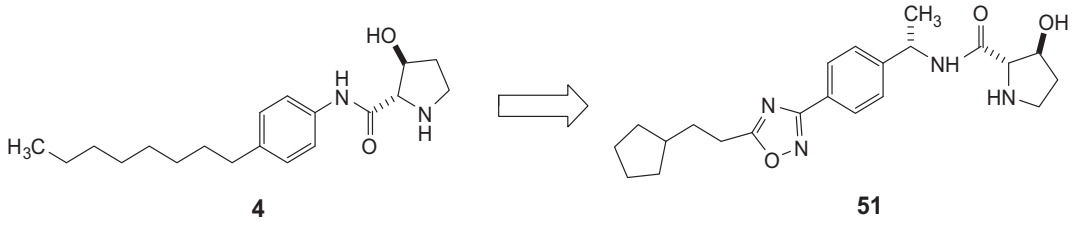


Virtual screening led to the identification of two molecular fragments (**5** and **6**) as NIK inhibitors.

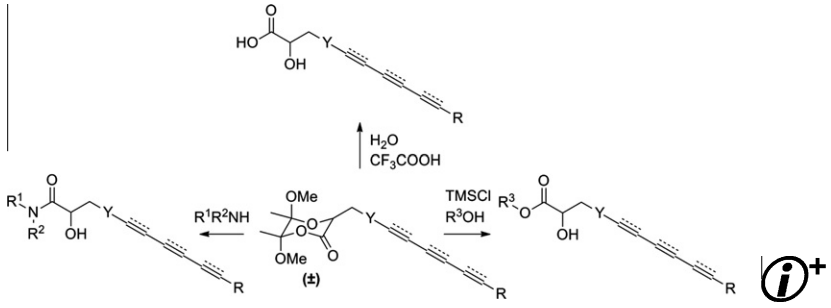


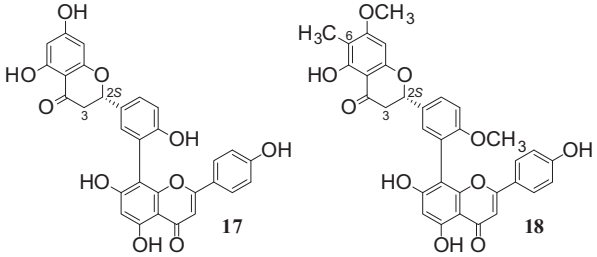
Ki (SST5) = 2.4 - 436 nM



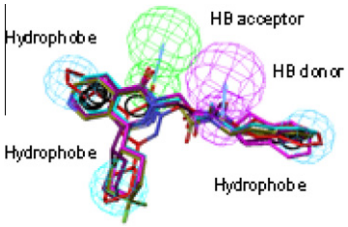


Working off the previously discovered sphingosine kinase-1 (SK1) inhibitor **4**, structural optimization resulted in identification of a new series of analogs exemplified by compound **51** which have improved aqueous solubility and ADME properties while maintain or enhance enzyme potency. The lead **51** has also demonstrated modest oral bioavailability in a rat PK study.

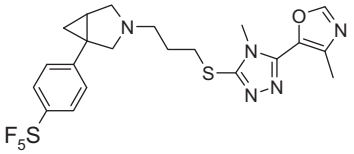




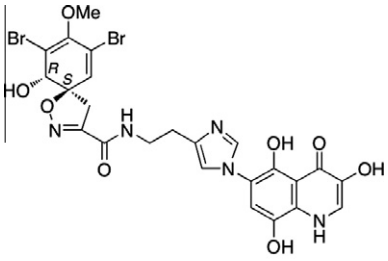
Amentoflavone-type biflavonoids, 2,3-dihydroamentoflavone 17 and 2,3-dihydro-6-methylginkgetin 18 exhibited potent β-secretase (BACE-1) inhibitory effects with IC_{50} values of 0.75 and 0.35 μM, respectively.



The identification of novel α7 nAChR allosteric positive modulators using pharmacophore methods is reported.

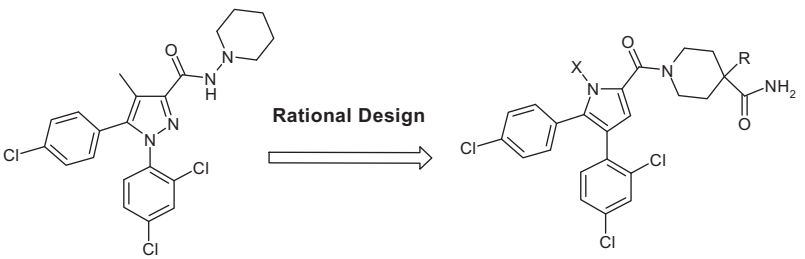


The comparison of selective DA D_3 antagonists with different functional groups is reported.

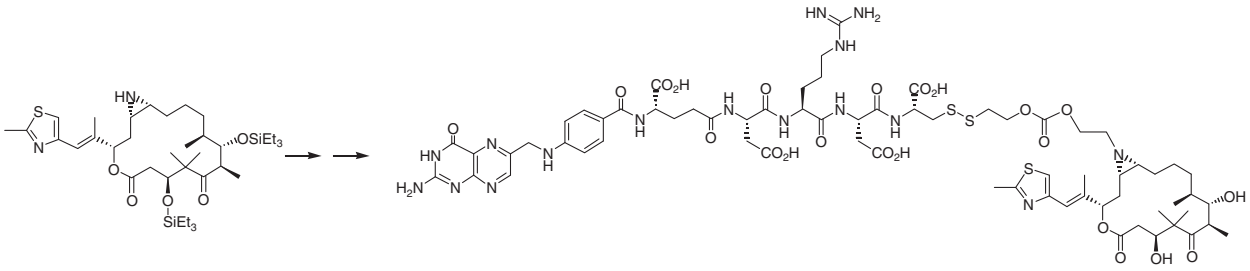


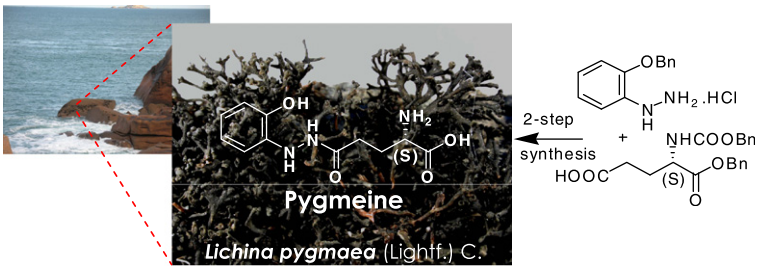
ceratinadin A

A rational design approach around a new pyrrole core with modulation of the topological polar surface area allowed the identification of the potent, selective and peripherally-restricted CB_1 antagonist **11** [X = $-(CH_2)_3NHSO_2Me$; R = (4,4-difluoropiperidyl)] with a IC_{50} (hCB_1) = 1.4 nM.

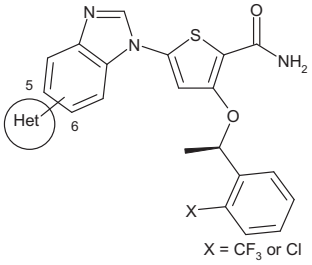


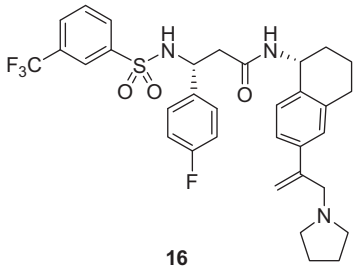
SR141716 (rimonabant) compounds 2 to 11





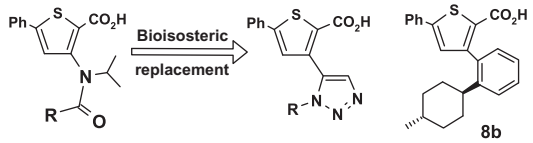
Potent inhibitors of PLK1 with acceptable solubility, mouse iv clearance, and reduced CYP450 inhibition were identified. Drug-like properties were improved using a heteroaryl ring as a functional handle for manipulation of inhibitors' physiochemical and DMPK properties.



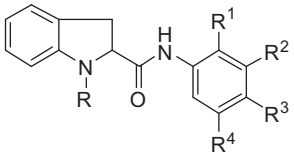


16

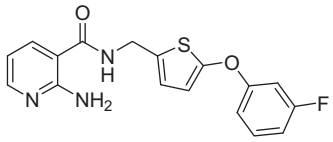
SAR studies led to the discovery of tetralin allylic amines as potent and selective bradykinin B1 receptor antagonists (hB1 IC_{50} = 1.3 nM for compound **16**).



Conformational modeling has been successfully applied to the design of cyclic bioisosteres used to replace a conformationally rigid amide bond in a series of thiophene carboxylate inhibitors of HCV NS5B polymerase. Select compounds were equipotent with the original amide series. Single-point mutant binding studies, in combination with inhibition structure–activity relationships, suggest this new series interacts at the Thumb-II domain of NS5B. Inhibitor binding at the Thumb-II site was ultimately confirmed by solving a crystal structure of **8b** complexed with NS5B.

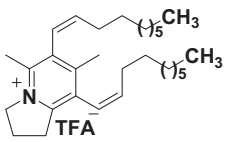


A series of indoline-2-carboxylic acid *N*-(substituted)phenylamide derivatives were synthesized to explore their inhibitory activities of NF-κB and they were also evaluated for cytotoxicity against various cancer cell lines for SAR.



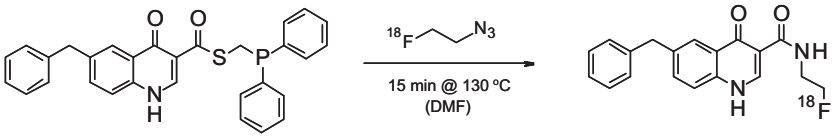
10b MIC = 0.05 μg/ml
(C. albicans)
MIC=0.78μg/ml
(A. fumigatus)

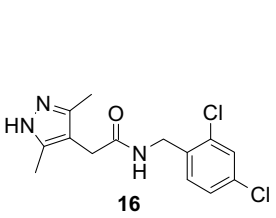
The synthesis of potent antifungal quinoline amide, azaindole amide and pyridine amides and its evaluation are reported.



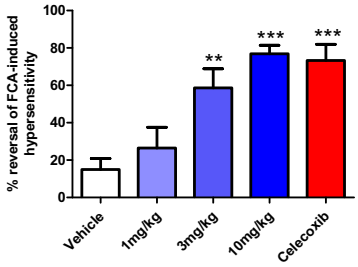
Anibamine

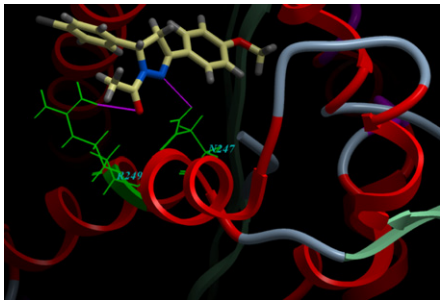
Anibamine produces significant inhibition of prostate cancer cell proliferation at micromolar to submicromolar concentrations and inhibits prostate tumor growth in mice.

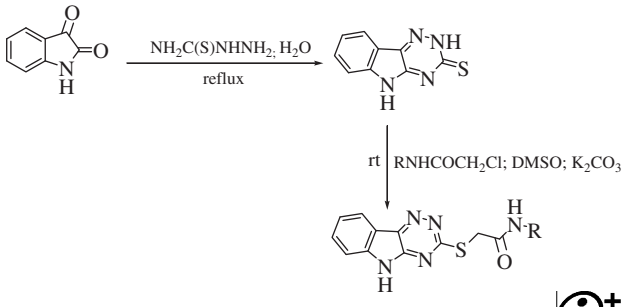


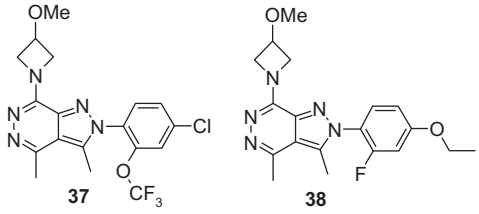


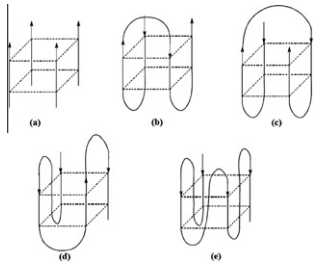
pIC$_{50}$=8.1, MW=312



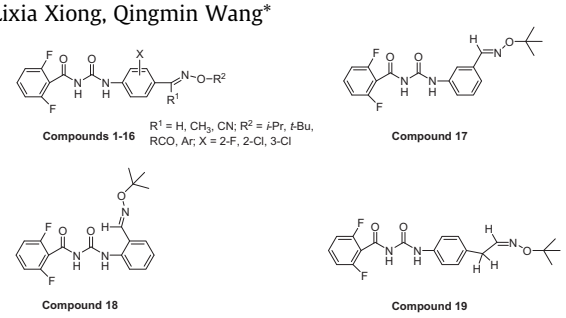




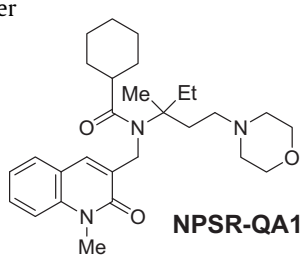




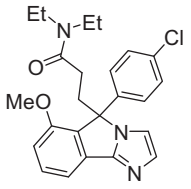
In this study, a series of oligonucleotides with four repeat guanines sequence $d(G_4T_n)_3G_4$ (n = 1–6) were designed and the length of loop affect the polymorphism of G-quadruplex was investigated.



A series of new structural benzoylphenylureas were designed and synthesized and their structure–activity relationships were studied.

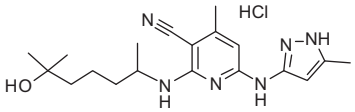


Medicinal chemistry efforts have identified a quinolinone class of potent NPSR antagonists that readily cross the blood–brain barrier. Optimization efforts resulted in the identification of a potent NPSR antagonist which dose-dependently and specifically inhibited ^{125}I-NPS binding in the CNS when administered to rats.



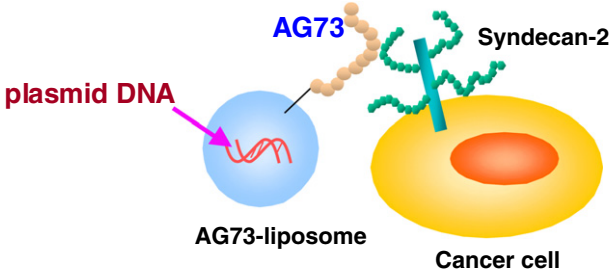
NPSR-PI1

A new structural class of potent antagonists of the Neuropeptide S Receptor (NPSR) is reported. **NPSR-PI1** demonstrates potent in vitro NPSR antagonism and central exposure in vivo.

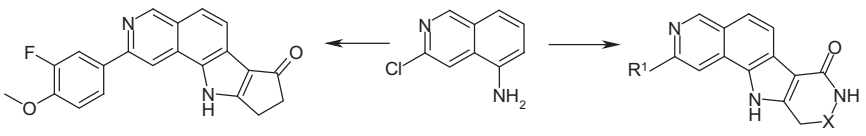


6 K*i* = 1.2 nM

Compound **6** exhibited a potent Aurora A kinase inhibitory activity (K_i = 1.2 nM) and was effective in antitumor mice model at a dose of 30 mg/kg po qd.

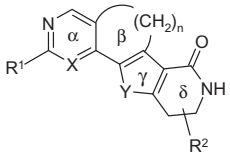


Liposome labeled with AG73, which is a laminin-derived peptide and a ligand for syndecan-2, is found to be a superior non-viral vector for the gene delivery to syndecan-2 overexpressing cancer cells.

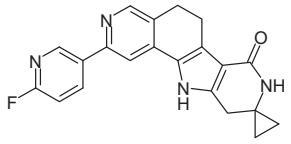


14F

The synthesis and SAR of tetracyclic MK2 inhibitors is reported. Tetracyclic lactams showed good selectivity profiles and potently inhibited TNFα release from hPBMCs. Tetracyclic ketone **14F** was orally bioavailable and inhibited the LPS induced release of TNFα in mice.



X = N, CH; Y = O, NH, NMe
n = 1,2,3



13E

The synthesis and SAR of tetracyclic MK2 inhibitors is reported. Spirocyclopropyl- and spiroazetidine groups attached to the δ-ring produced potent MK2-inhibitors with oral activity in the acute LPS-induced TNFα release model in mice. Compound **13E** showed significant reduction of swelling and histological scores in two chronic arthritis models upon oral administration.

*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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