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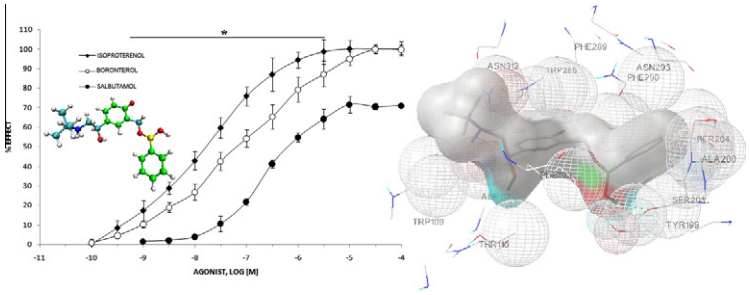
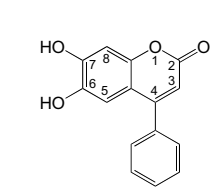
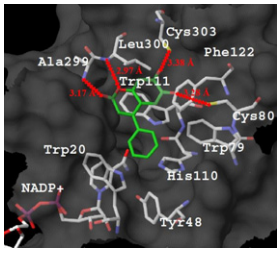
Contents

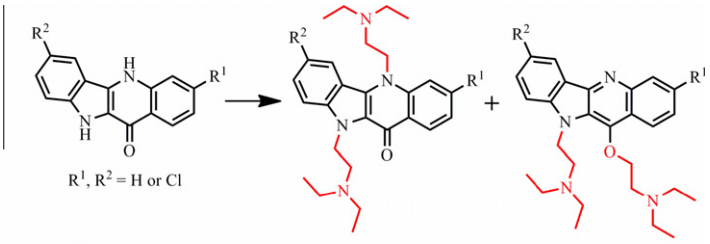
ARTICLES





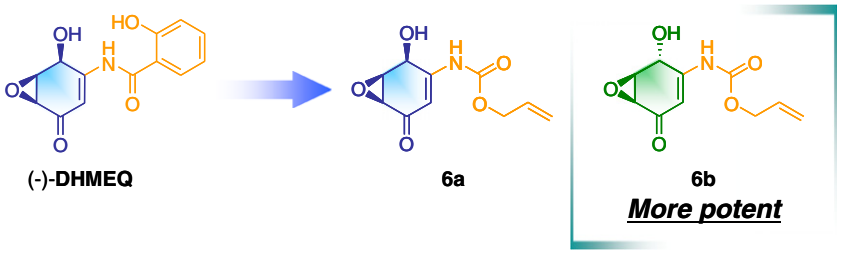
6,7-Dihydroxy-4-phenylcoumarin





Quindolones
IC_{50} (*P.f.*W2): 8500 - 10000 nM

Quindolones derivatives
IC_{50} (*P.f.* W2): 51 - 539 nM

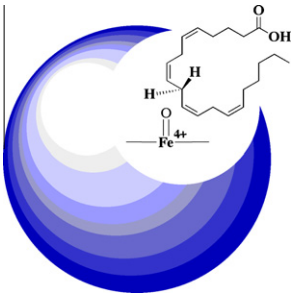


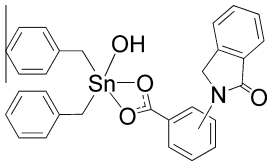
(-)-DHMEQ

6a

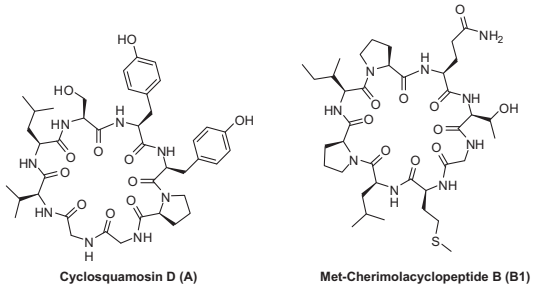
6b

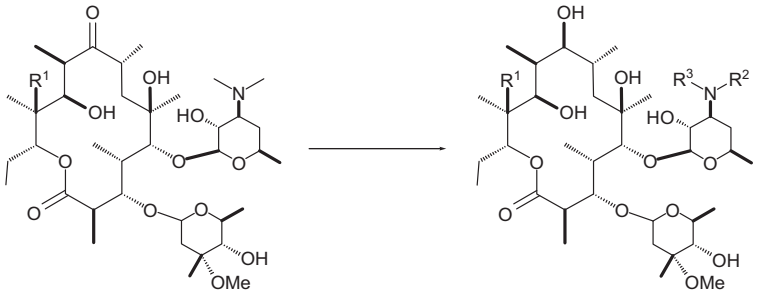
More potent

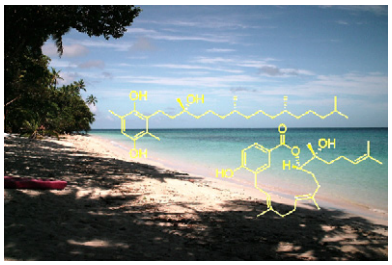


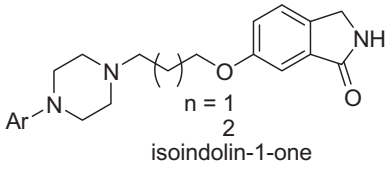


Synthesis of organotin complexes $Sn(OH)(bz)_2L$ (bz = benzyl, HL = 2-, 3-, or 4-(1-oxo-1*H*-2,3-dihydroisoindol-2-yl)benzoic acid) and the evaluation of their antifungal and antibacterial activity is reported.

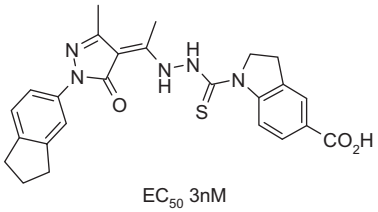




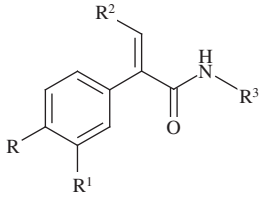




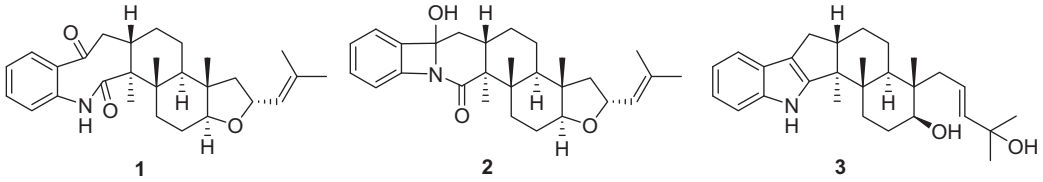
A series of 6-alkoxyisoindolin-1-ones are presented as potential antipsychotics. The in vitro pharmacological profile includes D_2 partial agonism (30–55%), 5-HT_{1A} partial agonism (60–90%), and 5-HT_{2A} antagonism. Selected compounds in this series displayed good in vivo activity and potency.

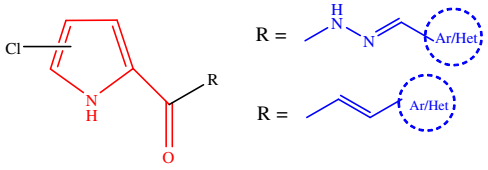


Novel series of carbohydrazides as small molecule TPO receptor agonists are reported.

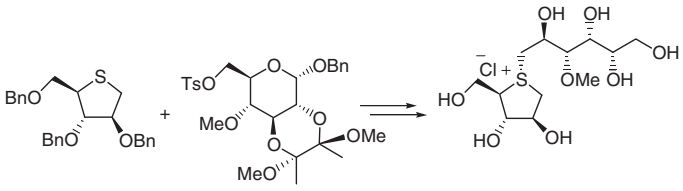


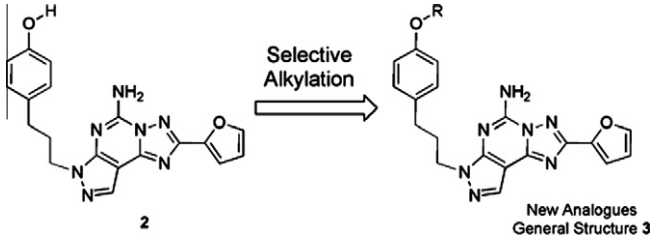
The phenylacetamide **1** represents the archtypical glucokinase activator (GKA) in which only the *R*-isomer is active. In order to probe whether the chiral center could be replaced, we prepared a series of olefins **2** and show in the present work that these compounds represent a new class of GKAs. Surprisingly, the SAR of the new series paralleled that of the saturated derivatives with the exception that there was greater tolerance for larger alkyl and cycloalkyl groups at R^2 region in comparison to the phenylacetamides. In normal Wistar rats, the 2,3-disubstituted acrylamide analog **10** was well absorbed and demonstrated robust glucose lowering effects.

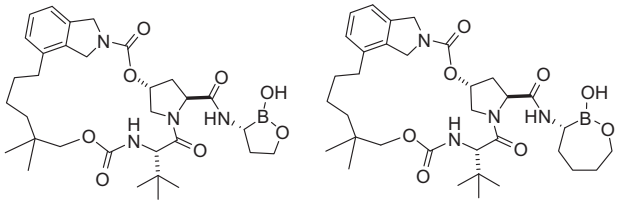




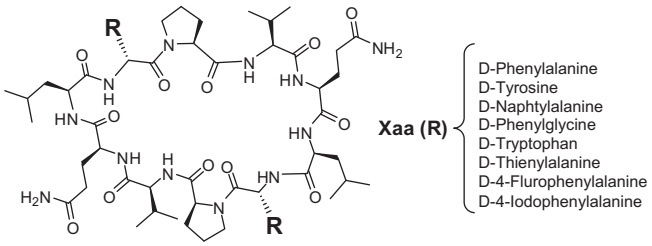
In an attempt to identify new potential lead as antimicrobial agent, 31 novel chloropyrrole derivatives of aroyl hydrazones and chalcones incorporating common pharmacophore of pyoluteorin derivatives were synthesized.



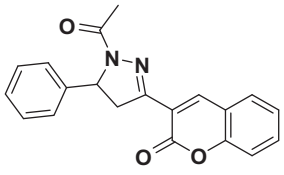




9a **9e**

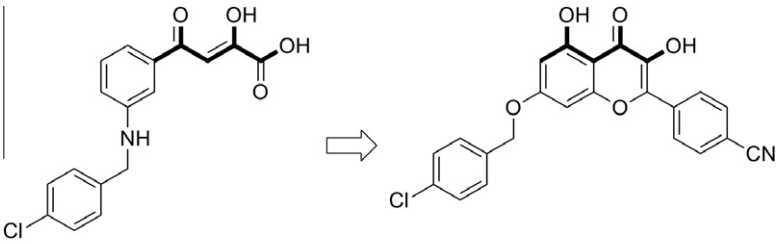


Gln-GS



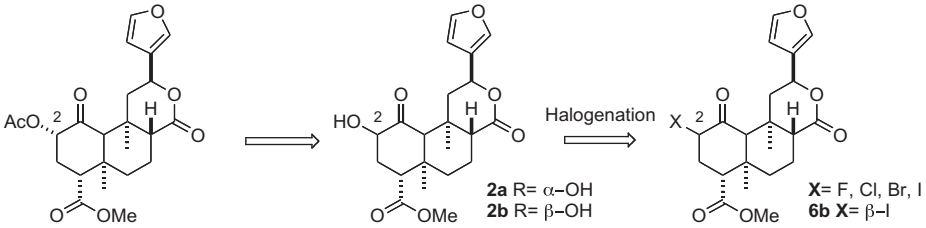
3d

Novel coumarin derivatives containing 4,5-dihydropyrazole moiety as potential telomerase inhibitors were synthesized. The bioassay tests showed that compound **3d** exhibited potentially high activity against human gastric cancer cell SGC-7901 with the IC_{50} value was 2.69 ± 0.60 μg/mL.

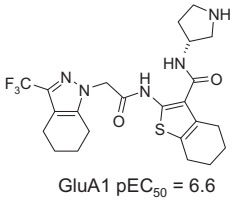


Aryl diketo acid (ADK)
(EC_{50} = 0.82 μM)

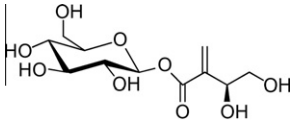
7-*O*-arylmethylgalangin
(EC_{50} = 0.9 μM)



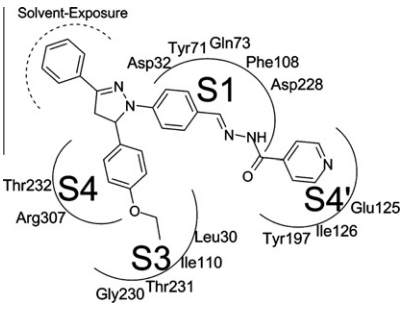
We have carried out the synthesis and biological evaluation of C-2 halogenation analogs of salvinorin A. KOPR binding and functional studies reveal β isomer in general binds better than α isomer and affinity to the kappa receptor increases with atomic radius (I > Br > Cl > F) with the exception of iodinated analog **6b**, which is a partial agonist with E_{max} of 46% of U50,488H.

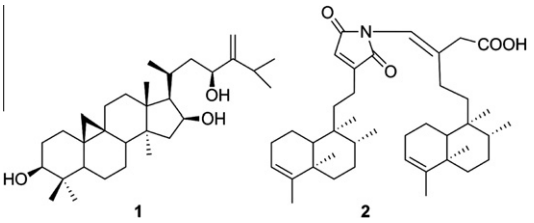


Starting from an HTS hit, the evolution of lead compound **22**, a positive allosteric modulator of the AMPA receptor is described using structure based drug design.

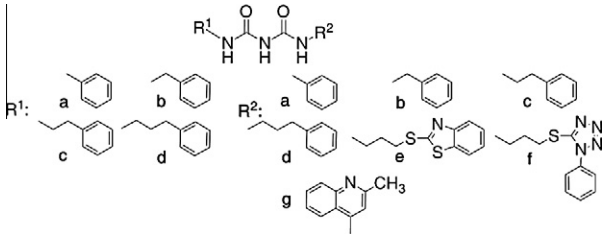


Twenty compounds identified via in silico were tested in BACE-1 FRET assays and methylthiazoletetrazolium (MTT) cytotoxicity experiment. Two compounds: **2** and **15** demonstrated IC_{50} values of 0.53 and 9.4 μM in addition to low toxic effect to the neuroblastoma cells.

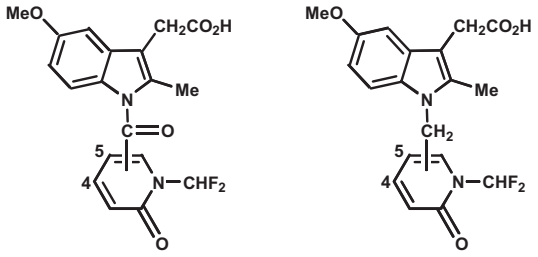


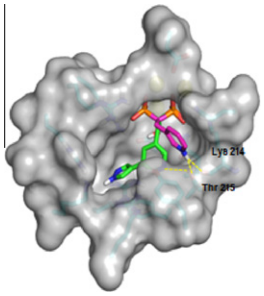


Two new compounds named Longitriol (**1**) and Longimide A (**2**) together with previously known Longimide B (**3**) were isolated from the leaves of *Polyalthia longifolia* var. *pendula*. Compounds **1** and **2** were tested in vitro against four human cancer cell lines and found to be most active against cervical carcinoma cell lines with IC_{50} value of 10.03 and 4.12 μg/mL, respectively.

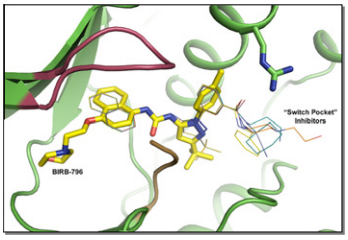


Design, synthesis and cytotoxicity of several biurets substituted at N and N′ with different combination of R^1 and R^2 groups on human breast cancer T47D cell line are described.



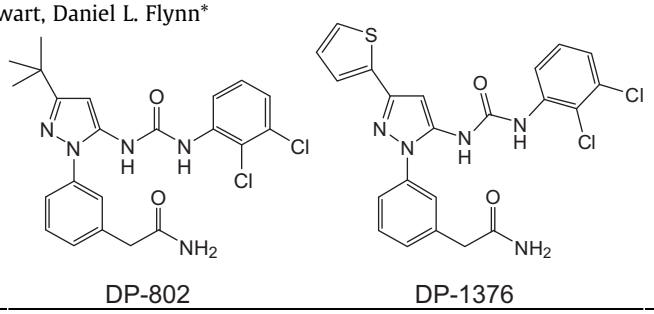


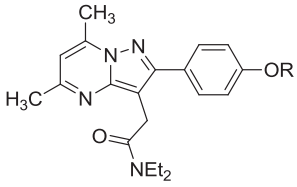
A structure-based approach was pursued in designing novel bisphosphonate active site inhibitors of the human farnesyl pyrophosphate synthase (hFPPS) that compete for binding with both IPP and risedronate.



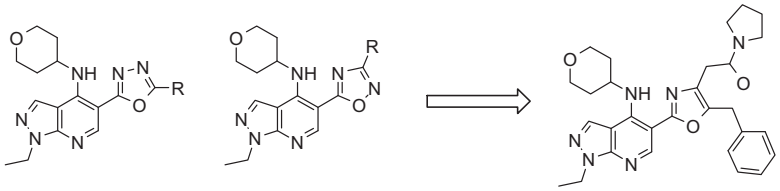
Herein we describe the identification and characterization of a class of molecules that are believed to extend into a region of p38 known as the 'switch pocket'. Although these molecules lack a canonical hinge binding motif, they show K_i values as low as 100 nM against p38α. It is also clear that molecules that interact with this region of the protein demonstrate different binding kinetics than a canonical ATP mimetic, as well as a wide range of kinome profiles. Thus, the switch pocket presents new opportunities for kinome selectivity which could result in unique biochemical responses and offer new opportunities in the field of kinase drug discovery.

Switch control pocket inhibitors of p38-*alpha* kinase are described. X-ray crystallography reveals a unique mode of binding to the switch control pocket residues arginine 67 or arginine 70.

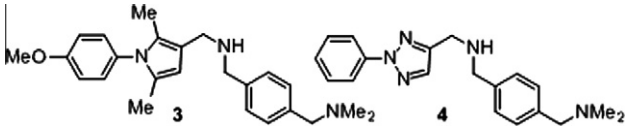




The synthesis of pyrazolo[1,5-*a*]pyrimidine acetamides, in vitro receptor binding and their ability to increase pregnenolone biosynthesis is reported.

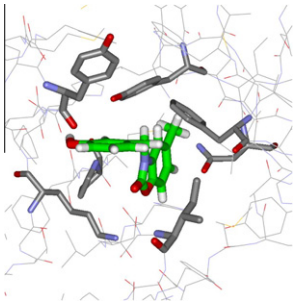


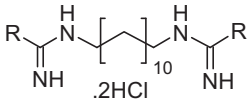
Several series of pyrazolo[3,4-b]pyridine-5-heterocycles have been identified as potent inhibitors of PDE4B. Molecular modelling and X-ray crystallography on early analogues **7a**–**f** and **10a**–**f** led to the design of pyrazolo[3,4-b]pyridine-5-oxazole **16**, which shows sub-nM potency against PDE4B. The crystal structure of **16** bound to PDE4B is also described.



Pyrrole- and 1,2,3-triazole-based 2,3-oxidosqualene cyclase (OSC) inhibitors **3** and **4** were discovered by conducting a virtual screening, a docking study based on the crystallographic structure of OSC, and biological assays. A preliminary structure–activity-relationship study of **3** was also conducted.

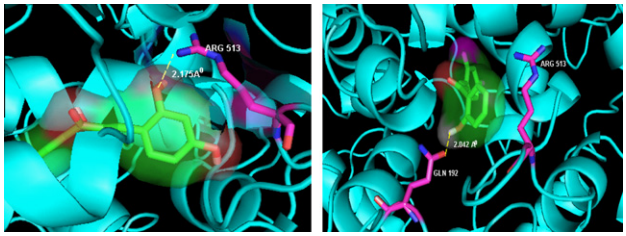
Substituted benzoxazol-2-ones are reported as antagonists of the signaling by macrophage migration inhibitory factor (MIF). One of the potent analogues is shown to attenuate MIF-dependent ERK1/2 phosphorylation in human synovial fibroblasts.

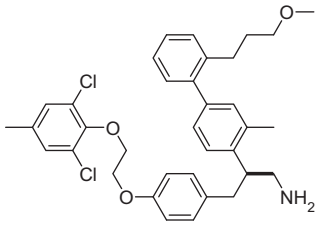




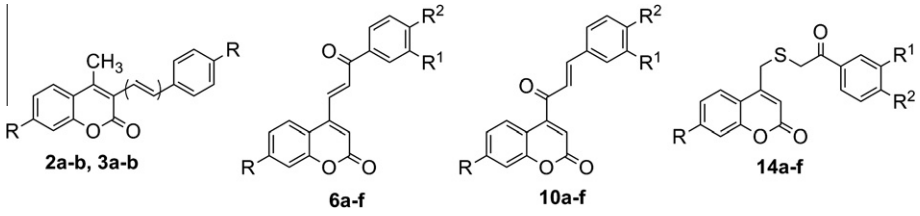
The antimalarial potencies and the RSA of bis-*N*-alkylamidines and a new series of reverse-benzamidine derivatives are reported.

A series of hydroxyl- and fluoro-substituted 2′-hydroxychalcones have been synthesized as garcinol analogs and structurally characterized. The compounds were evaluated for their SOD activities and molecular docking studies were performed on them in COX-2 protein cavity. The fluorinated compounds were found to be more potent than their hydroxyl counterparts indicating the influence of metabolically stable C–F bonds towards bioavailability. The difluoro derivatives were found to be most effective against human pancreatic BxPC-3 cancer cells which possess up-regulated COX-2 expression as well as against a human breast cancer BT-20 cells with triple negative phenotype.

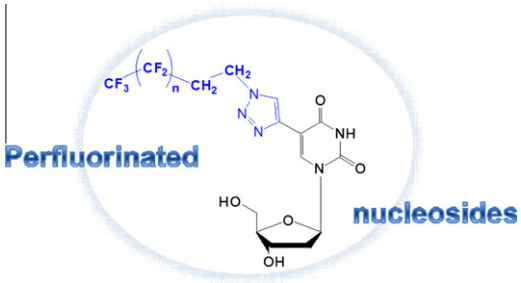




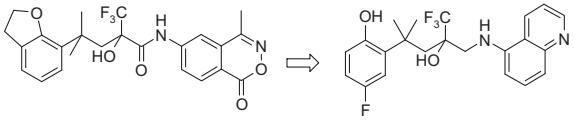
The discovery and SAR of a series of potent renin inhibitors possessing a novel biaryl scaffold are described herein. Molecular modeling revealed that the cyclopropylamide spacer present in our lead compound can be replaced by a simple, substituted aromatic ring such as a toluene. The resulting compounds exhibit subnanomolar renin IC_{50} and good oral bioavailability in rats.



Novel coumarin-based Cdc25 phosphatases inhibitors.



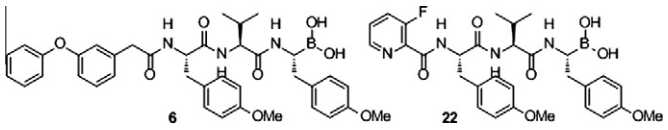
Novel synthesized perfluoroalkyltriazole-appended nucleosides exhibit anticancer activities against several cancer cell lines.



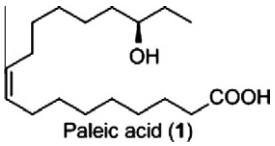
GR pIC_{50} 7.7
PR pIC_{50} 7.7
TR(HeLa) pIC_{50} 8.2 (75% eff.)
TA(HeLa) pEC_{50} 7.9 (43% eff.)

GR pIC_{50} 9.0
PR pIC_{50} < 6.0
TR(HeLa) pIC_{50} 8.2 (84% eff.)
TA(HeLa) pEC_{50} 7.1 (50% eff.)

The dissociated glucocorticoid receptor (GR) agonist ZK 216348 (**1**) is rendered GR-selective by replacing the methylbenzoxazine moiety with quinolines. Compounds were shown to be efficacious in vitro in reporter gene and cell assays, along with reduced activity in a transactivation assay, hinting at an improved therapeutic window over corticosteroids.



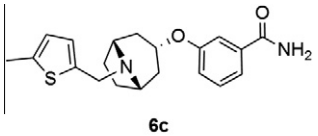
The structure–activity relationship of the boronic acid derivatives of tyropeptin, a proteasome inhibitor, was studied. Among 41 derivatives, 3-phenoxyphenylacetamide **6** and 3-fluoro picolinamide **22** displayed the most potent inhibitory activity toward chymotryptic activity of proteasome and cytotoxicity, respectively.



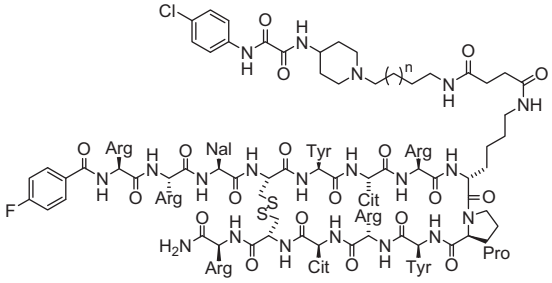
Paleic acid (**1**)

A synthetic route to paleic acid **1**, antibicrobial agent effective against *Mannheimia haemolytica* and *Pasteurella multocida*, has been established. The procedure was also applied to the preparation of structurally related analogs, which were used in structure–activity relationship studies for antibacterial activity.

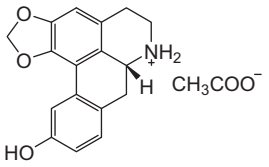
Discovery and SAR studies of a novel series of potent and selective kappa opioid receptor antagonists containing an 8-azabicylo[3.2.1]octane core is described. Analog **6c** was shown to successfully inhibit kappa agonist-induced rat diuresis in vivo.


6c

κ GTPγS IC_{50} = 20 nM
μ GTPγS IC_{50} = 722 nM
δ GTPγS IC_{50} = 8310 nM

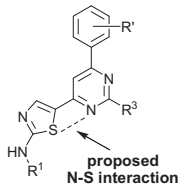


SAR studies of CD4 mimics and their conjugation with a CXCR4 antagonist are reported.

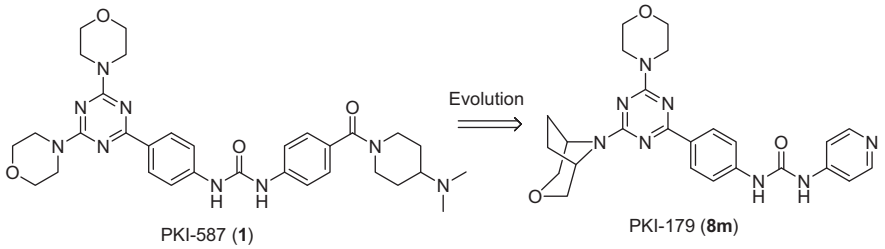


(6a*R*)-normecambroline
IC_{50} = 4.0 μM (HeLa)

A new aporphine alkaloid, (6a*R*)-normecambroline (**1**), was identified from the bark of *Neolitsea dealbata*. This compound inhibited selectively against HeLa cells with an IC_{50} of 4.0 μM.

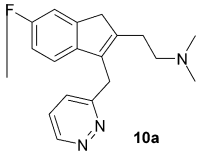


An intramolecular nitrogen–sulfur nonbonding interaction has been used in the design of a novel series of 2-aminothiazol-5-yl-pyrimidines as p38α MAP kinase inhibitors.



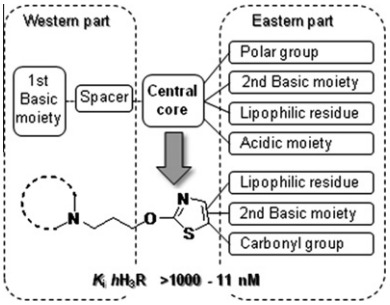
PKI-587 (**1**)
IV efficacious PI3K inhibitor

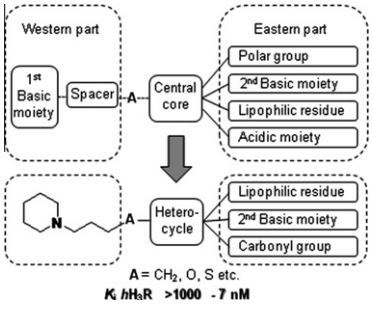
PKI-179 (**8m**)
Orally efficacious PI3K inhibitor

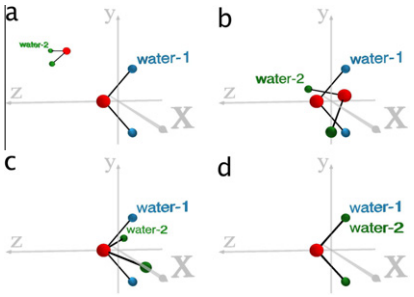


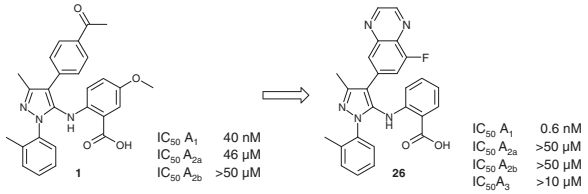
10a

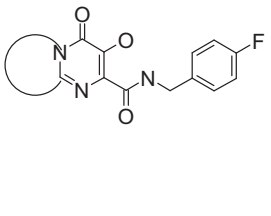
Several indenes with high affinity for the H_1 receptor and appropriate selectivity versus off-targets were assessed for metabolism profile and in vivo properties. Compound **10a** displayed a diversified metabolism profile, showed equivalent efficacy in a rat EEG/EMG model to a previously identified clinical candidate, and a potentially superior pharmacokinetic profile as determined from a human microdose study.



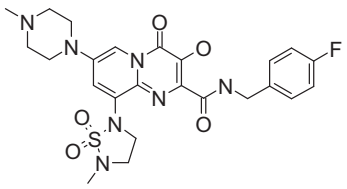






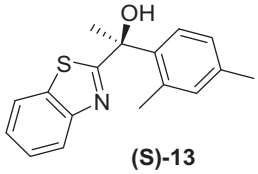


scaffold A to I



48

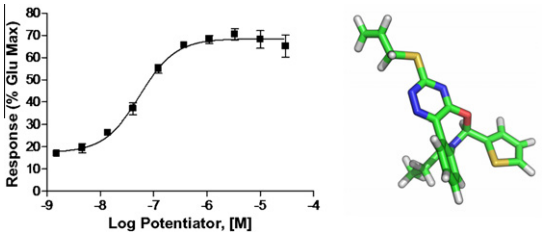
EC_{50} 3nM



(S)-13

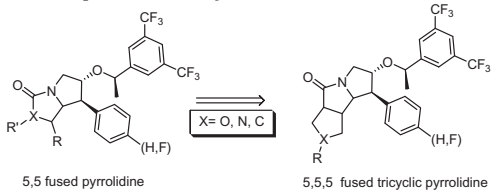
pEC_{50} 8.0 ± 0.1, %Eff. 83 ± 5

1-(Benzothiazol-2-yl)-1-(4-chlorophenyl)ethanol (**1**) was identified as a positive allosteric modulator (PAM) of the CaSR in a functional cell-based assay. This compound belongs to a class of compounds that is structurally distinct from other known positive allosteric modulators e.g., the phenylalkylamines cinacalcet, a modified analog (**13**) potentially suppressed parathyroid hormone (PTH) release in rats, consistent with its profile as a PAM of CaSRs.



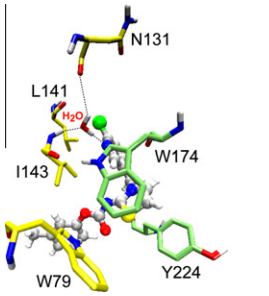
Positive allosteric modulation of the metabotropic glutamate receptor subtype 5 was studied by conducting a comparative molecular field analysis on 118 benzoxazepine derivatives. The model with the best predictive ability retained significant cross-validated correlation coefficients of q^2 = 0.58 (r^2 = 0.81) yielding a standard error of 0.20 in pEC_{50} for this class of compounds. The subsequent contour maps highlight the structural features pertinent to the bioactivity values of benzoxazepines.

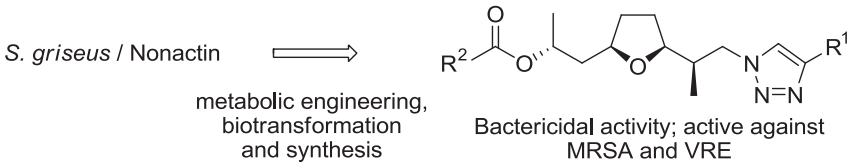
Previously, we had disclosed a novel class of hNK_1 antagonists based on the 5,5-fused pyrrolidine core. These compounds displayed subnanomolar hNK_1 affinity along with good efficacy in a gerbil foot-tapping (GFT) model, but unfortunately they had low to moderate functional antagonist (IP-1) activity. To elaborate on the SAR of this class of hNK_1 compounds and to improve functional activity, we have designed and synthesized a new class of hNK_1 antagonist with a third fused ring. Compared to the 5,5-fused pyrrolidine class, these 5,5,5-fused tricyclic hNK_1 antagonists maintain subnanomolar hNK_1 binding affinity with highly improved functional IP-1 activity (<10% SP remaining). A fused tricyclic methyl, hydroxyl geminally substituted pyrrolizinone (compound **20**) had excellent functional IP (<2% SP remaining), hNK_1 binding affinity, off-target selectivity, pharmacokinetic profile and in vivo activity. Complete inhibition of agonist activity was observed at both 0 and 24 h in the gerbil foot-tapping model with an ID_{50} of 0.02 mpk at both 0 and 24 h, respectively.

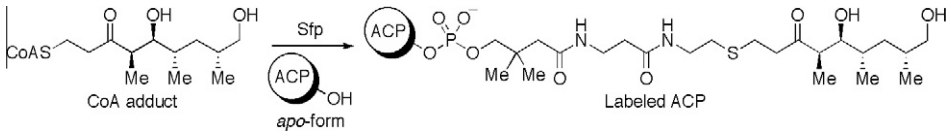


5,5 fused pyrrolidine

5,5,5 fused tricyclic pyrrolidine







(**a**: R^1= R^2= H, **b**: R^1= CH_3, R^2= H, **c**: R^1= R^2= CH_3, **d**: R^1= C_2H_5, R^2= H)

4-Bromo-3,4-dimethyl-1-phenyl-2-phospholene 1-oxide (**3c**) was first synthesized from 3,4-dimethyl-1-phenyl-2-phospholene 1-oxide (**2c**) by a bromo-radical substitution reaction occurred at C-4 position by NBS and AIBN. The novel phospha sugar analogue exerted high anti-proliferative effect on U937 cells evaluated by MTT in vitro methods and was much more efficient than that of Gleevec®, which is known as a molecule targeting chemotherapeutical agent.

*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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