ELSEVIER

Bioorganic & Medicinal Chemistry Letters

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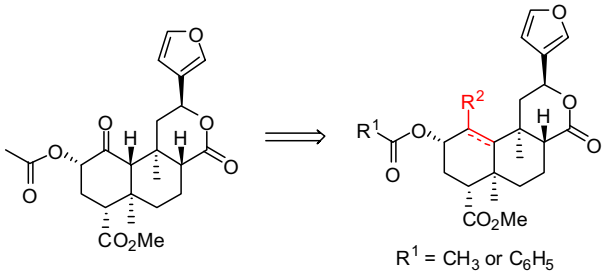
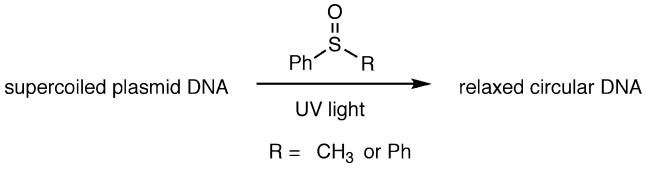
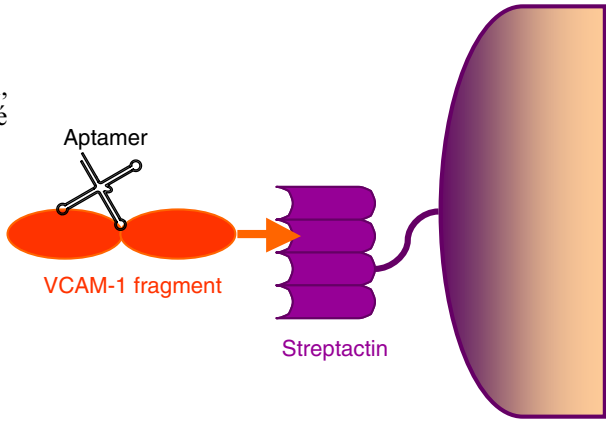
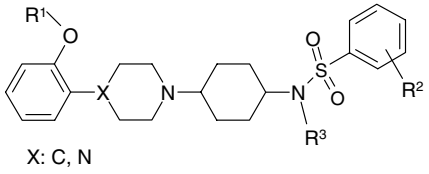
Contents

ARTICLES

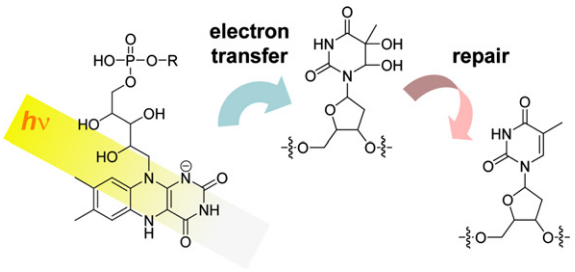


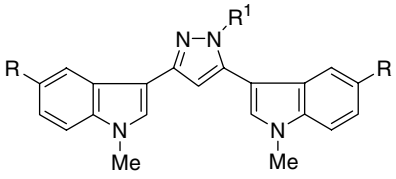




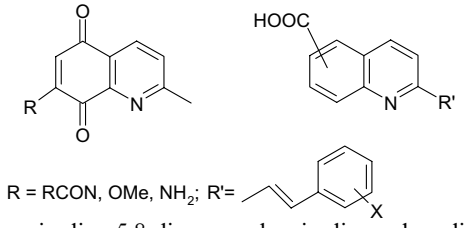


A series of aminocyclohexylsulfonamides that show selectivity to human $\alpha_{1a/1d}$ adrenergic receptors and are stable against human liver microsomal metabolism were developed. These compounds have potential for the treatment of BPH/LUTS.

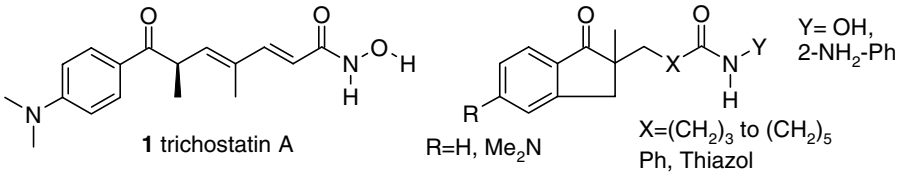




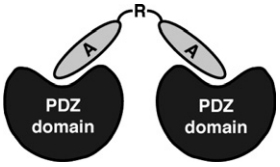
The synthesis and antitumor activity of novel 3,5-bis(3′-indolyl)pyrazole derivatives are reported.



The structure–activity relationships of new quinoline-5,8-diones and quinolinecarboxylic acids exhibiting antiproliferative activity were investigated.

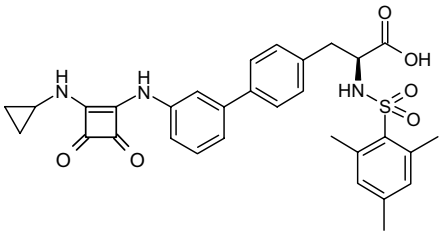


Hybrids of known histone deacetylases inhibitors (HDI) based on indanones were synthesized. Several alkylated indanones were obtained as hydroxamic acid and aminobenzamides derivatives and evaluated for their antiproliferative activity towards non small lung cancer cell line H661.

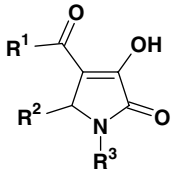


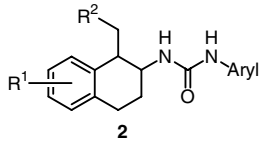
The design, synthesis, and thermodynamic binding evaluation of homobivalent peptides capable of binding two PDZ domain proteins is presented.

Vitronectin receptor ($\alpha_V\beta_3$) antagonists have been implicated as a possible new treatment of restenosis following balloon angioplasty. In this work we investigate a series of novel arginine mimetic scaffolds leading to new insight of the $\alpha_V\beta_3$/ligand interaction. Squaric acid amide **10** is a subnanomolar $\alpha_V\beta_3$ antagonist with improved potency on human smooth muscle cell migration.



10: $\alpha_V\beta_3$: 0,5 nM; SMC: 10 nM

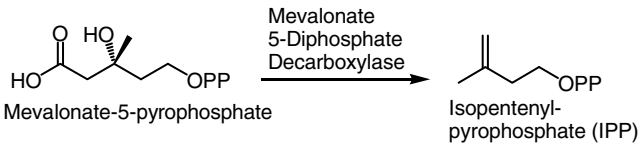




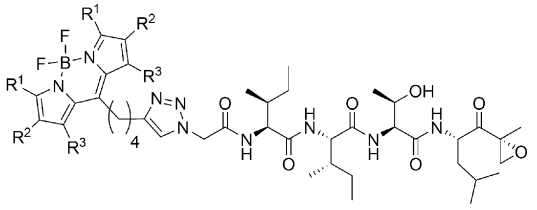
2

Aryl = 5-isoquinolinyl or 2-hydroxy-8-naphthyl

The synthesis and biological activity of a series of aminotetralin-derived heteroaryl urea TRPV1 antagonists is reported.

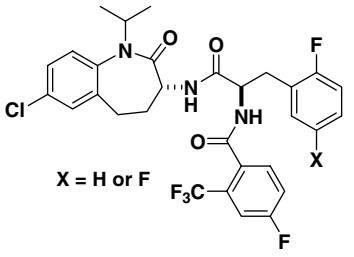


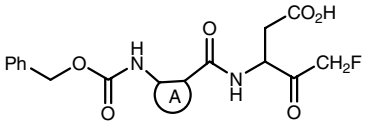
Mevalonate 5-diphosphate decarboxylase plays an important role in regulating cholesterol biosynthesis, which was studied through incubation with various synthetic substrate analogs and characterization of mutated enzymes.



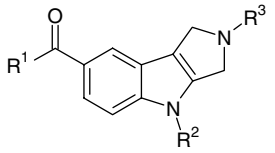
The synthesis of three acetylene functionalized BODIPY dyes is described. These dyes are used to synthesize a panel of fluorescent epoxomicin derived proteasome probes.

A series of benzazepinones were synthesized and evaluated as $hNa_v1.7$ sodium channel blockers. Several compounds from this series displayed good oral bioavailability and exposure and were efficacious in a rat model of neuropathic pain.

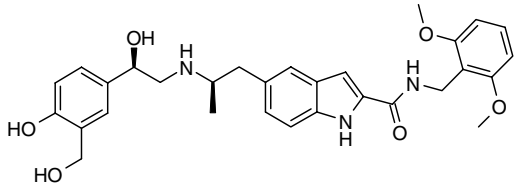




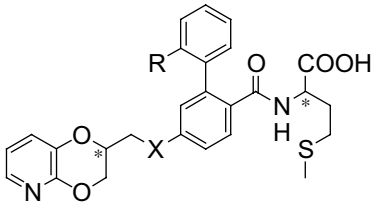
The synthesis and biological evaluation of a group of peptidomimetic 2-(*Z*-amino)benzamide-aspartyl fluoromethylketones and related compounds as caspase inhibitors are reported.



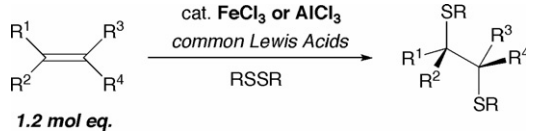
The preparation and evaluation of a novel class of CB2 agonists based on a 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole moiety are reported.

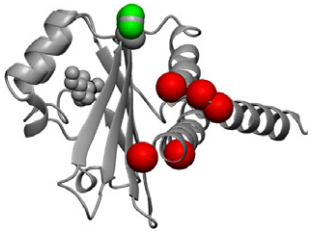


The design and profile of a series of indole containing long acting β_2-adrenoceptor agonists is described. Evaluation of these analogues using an in vitro guinea pig trachea tissue model demonstrates that analogues within this series have salmeterol-like duration of action with potential for long duration of action in humans.

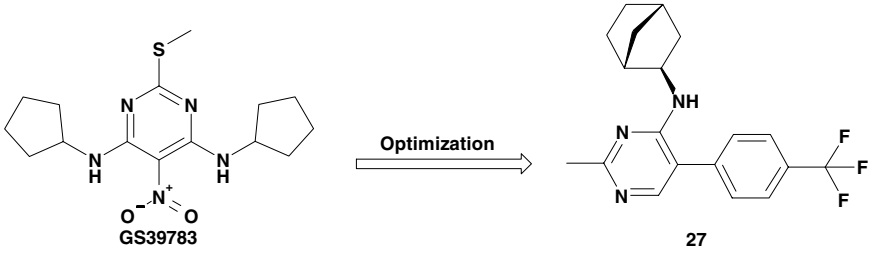


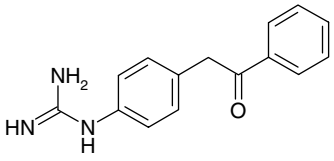
1-4	R = Me	X = O
5-8	= OMe	= O
9-12	= Me	= NHCO
13-16	= OMe	= NHCO





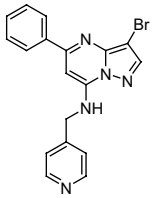
The anomalous ability of xylose to bind to the *Escherichia coli* quorum-sensing receptor protein SdiA is reported.



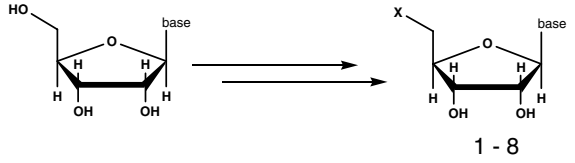


We have investigated the conformation of a uPA inhibitor in different crystalline environments. The crystal structures of the urokinase-type plasminogen activator in complex with GPPE and GPPE-picrate were determined.

Pyrazolo[1,5-*a*]pyrimidine **9** emerged as a key template for further optimization toward the identification of CDK inhibitors.

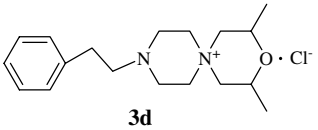


9 CDK2 IC_{50} = 0.029 uM



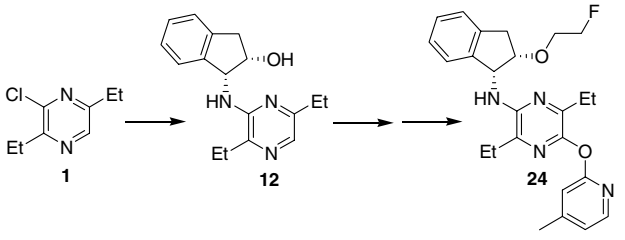
Compound	Base	X
1	adenine	$-SCH_2CH_2COOH$
2	adenine	$-SCH_2CH_2CONH_2$
3	adenine	$-SCH_2CH_2COOC_2H_5$
4	1,3-dideazaadenine	$-SCH_2CH_2COOH$
5	1,3-dideazaadenine	$-SCH_2CH_2CONH_2$
6	1,3-dideazaadenine	$-SCH_2CH_2COOC_2H_5$
7	6-nitro-1,3-dideazaadenine	$-SCH_2-CH=CH_2$
8	6-nitro-8-ethyl-1,3-dideazaadenine	$-SCH_2-CH=CH_2$

All the newly synthesized compounds are structurally analogous to SAH molecule and have shown good antifungal and antibacterial activity.

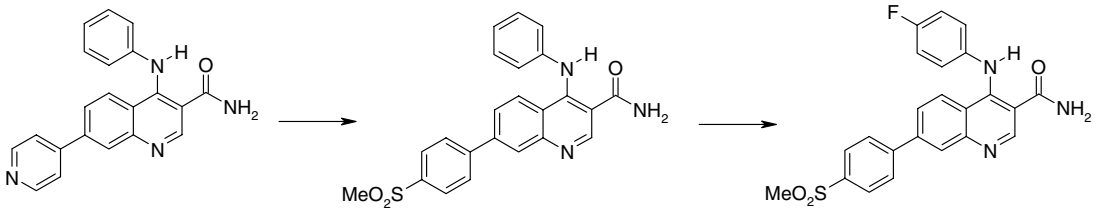


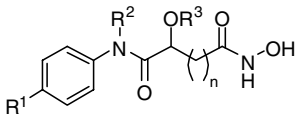
3d

65% inhibition in acetic acid writhing test at dose of 31 μmol/kg;
LD_{50} = 1.55 mmol/kg, ip.

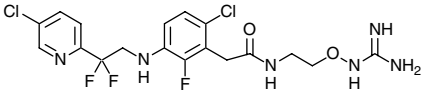


hCRF1 Ki = 11 ± 1 nM



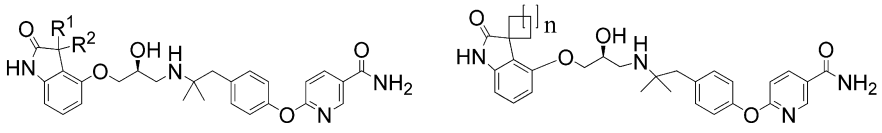


The synthesis of a series of ω-alkoxy ethers analogues of suberoylanilide hydroxamic acid, and their HDAC inhibitory and antiproliferative activity on human cell lines are reported.

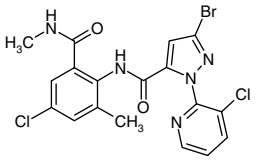


Ki (thrombin) = 1.8 nM

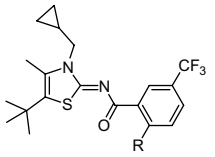
2-(2-Chloro-6-fluorophenyl)acetamides having 2,2-difluoro-2-aryl/heteroaryl-ethylamine P3 and oxyguanidine P1 substituents are potent thrombin inhibitors (K_i = 0.9–33.9 nM). 2-(5-Chloro-pyridin-2-yl)-2,2-difluoroethylamine was the best P3 substituent, yielding the most potent inhibitor (K_i = 0.7 nM). Replacing the P3 heteroaryl group with a phenyl ring or replacing the difluoro substitution with dimethyl or cyclopropyl groups in the linker reduced the affinity for thrombin significantly. The aminopyridine P1s also provided an increase in potency.



The synthesis and biological evaluation of a series of oxindole β_3 adrenergic receptor agonists is described. A modulation of rat atrial tachycardia was observed with substitution at the 3-position of the oxindole moiety.

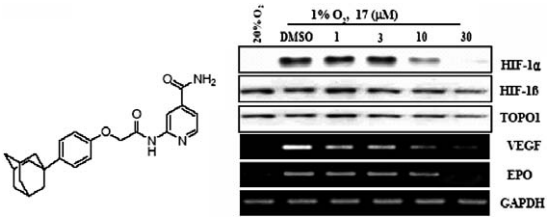


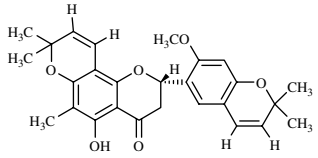
This paper describes the discovery of Rynaxypyr™, the first member from a novel class of anthranilic diamides, with exceptional activity against insects of the order Lepidoptera. Rynaxypyr™ has been found to exhibit its action by release of intracellular Ca^{2+} stores mediated by the ryanodine receptor. A comparison of *Heliothis virescens* (*Hv*) ryanodine receptor activity is made versus insecticidal potency on a series of Lepidoptera, including *Hv*. Remarkably high differential receptor selectivity is also demonstrated between insect and mammalian cell lines in support of the low mammalian toxicity.



R = H : **4-9** CB_2 IC_{50} = 13 nM F = 52%
R = OMe : **4-27** CB_2 IC_{50} = 1.2 nM

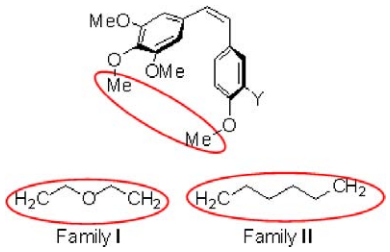
Compounds **4-9** and **4-27** had high affinities for the human CB_2 receptor (CB_2 IC_{50} = 13 nM and 1.2 nM) and a high selectivity for CB_2 (CB_1 IC_{50}/CB_2 IC_{50} = 270 and 1600). Furthermore, compound **4-9** had good oral bioavailability (F = 52%, 3 mg/kg).



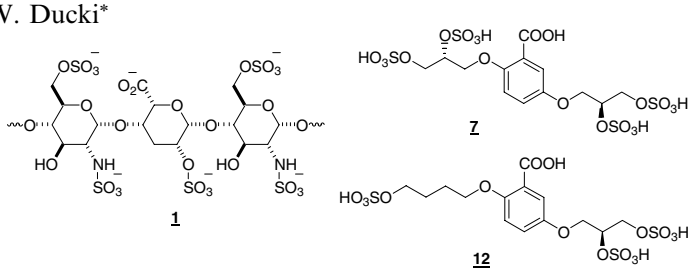


(1)

From *Lespedeza virgata* (Thunb.) DC. five known and one new (1) flavonoids were isolated. This new compound when tested in superoxide anion scavenging assay exerted the highest antioxidant activity (IC_{50} = 0.14 mg/ml).

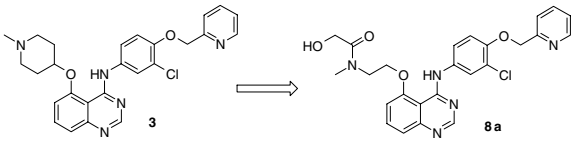


The activity as inhibitors of tubulin polymerization of macrocyclic analogues of combretastatins is reported.

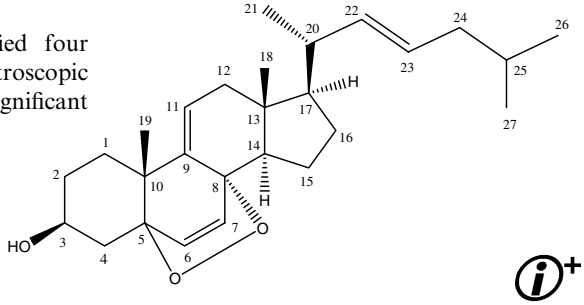


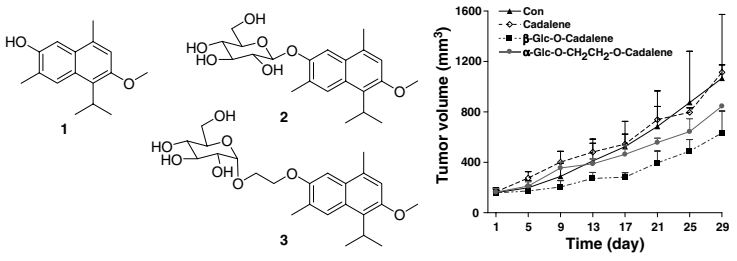
The synthesis of simple, non-sugar glycosaminoglycan (GAG) mimics has been achieved and the analogues evaluated for their ability to inhibit the activation of the MET receptor by hepatocyte growth factor/scatter factor (HGF/SF).

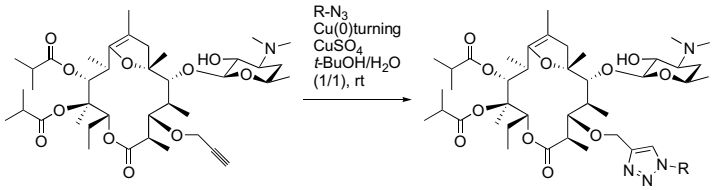
Neutral 5-substituted 4-anilinoquinazolines addressed high in vivo clearance and phospholipidosis associated with previous basic compounds such as **3**, and a representative compound **8a** inhibited tumor growth in a mouse xenograft model when co-administered with the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT).



From the fungus *Stereum hirsutum* have been isolated and identified four epidioxysterols. Their structures were elucidated on the basis of spectroscopic analysis and chemical reactions. Epidioxysterols were found to show significant activity against *Mycobacterium tuberculosis*.

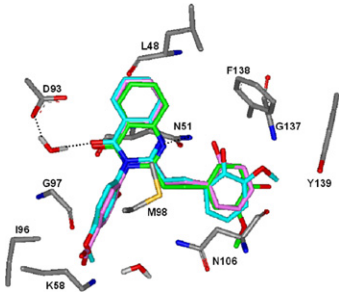


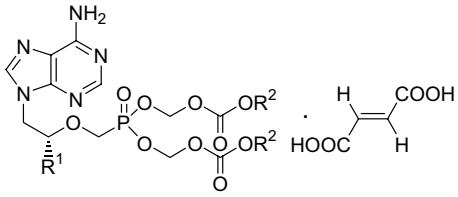




One of 10 kinds of triazole compounds, the adamantyl-triazole product **5b**, was produced as a potential lead of new antibiotic for use against MRSA and VRE strains, using click methodology.

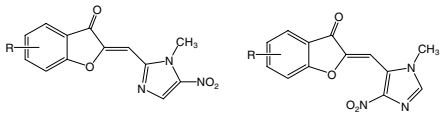
A novel class of 3-phenyl-2-styryl-3H-quinazolin-4-one Hsp90 inhibitors with in vitro anti-tumor activity is identified by structure-based virtual screening of a chemical database with docking simulations in the N-terminal ATP-binding site, in vitro ATPase assay using yeast Hsp90, and cell-based Her2 degradation assay in a consecutive fashion.





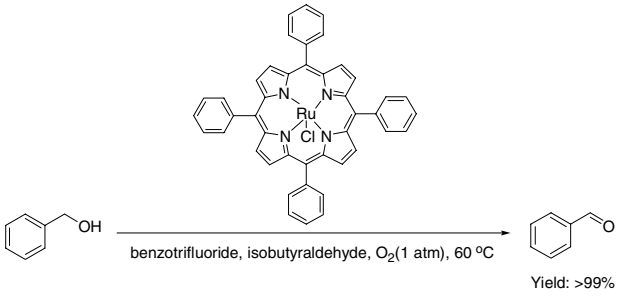
A series of new acyclic nucleotide analogues were synthesized and tested for in vitro antiviral activity against HIV/HBV. Most of tested compounds exhibited potent antiviral activity.

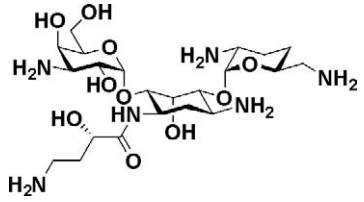
Synthesis, biological evaluation, and QSAR analysis of a novel class of (Z)-2-(nitroimidazolylmethylene)-3(2H)-benzofuranone derivatives (**11a**–**p** and **12a**–**m**) as antibacterial agents are described.

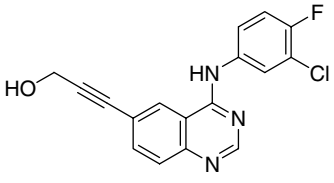


11a-p **12a-m**

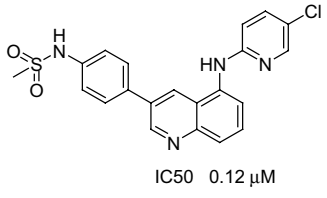
R = H, 5-Cl, 5-Me, 5-OMe, 5-Br, 5-I, 5-NO_2, 6-Cl, 6-Me, 6-OMe, 7-Cl, 7-Me, 7-OMe, 6,7-$(OMe)_2$, 6-OH, 4,6-$(OH)_2$



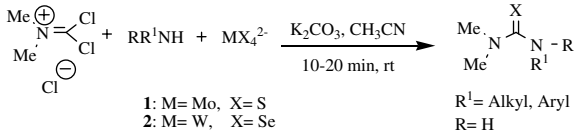




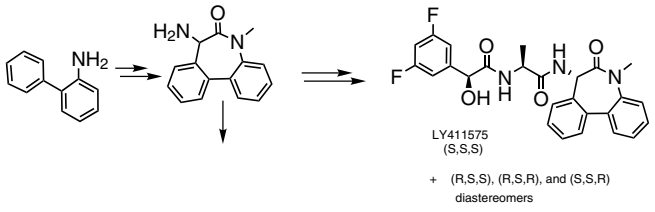
IC_{50} 14 nM for in vitro EGFR kinase inhibition.



A novel series of c-Jun N-terminal kinase (JNK) inhibitors based on 3,5-disubstituted quinolines are reported.



A facile, one-pot synthesis of thio and selenourea derivatives is reported. Some of the derivatives showed potent inhibitory activity against urease (jack bean) in the nanomolar range.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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