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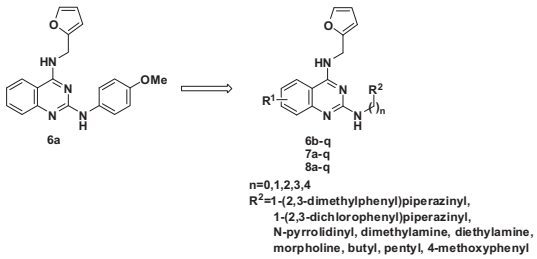
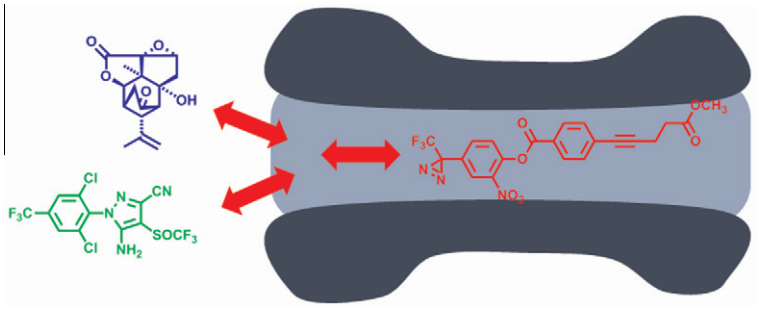
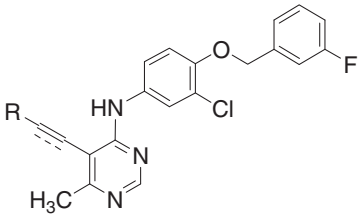
Contents

ARTICLES

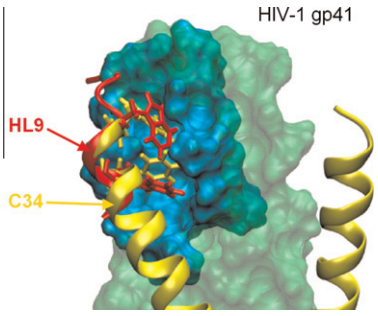


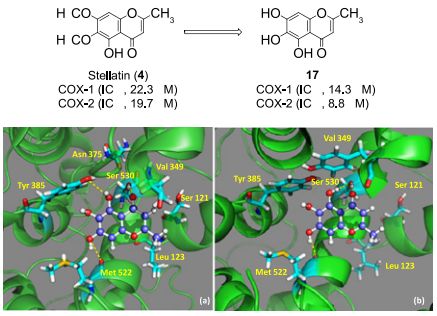
A novel series of 2,4-diaminoquinazoline derivatives were designed, synthesized and biologically evaluated as heat shock protein 90 inhibitors.

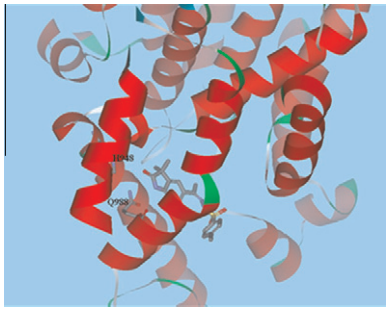


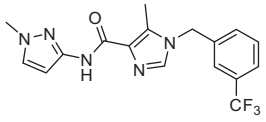


A structure–activity relationship study of 4-anilinopyrimidines for dual EGFR/Her-2 inhibitor has resulted in the identification of 4-anilino-5-alkenyl or 5-alkynyl-6-methylpyrimidine derivatives that have exhibited effective inhibitory activity against both enzymes. The presence of 5-alkenyl or 5-alkynyl moiety with terminal hydrophilic group played important role for inhibition of these enzymes. Selected compounds in the series demonstrated some activity against Her-2 dependent cell line (BT474).

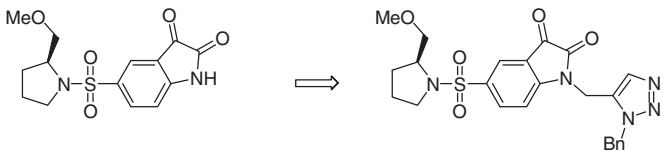




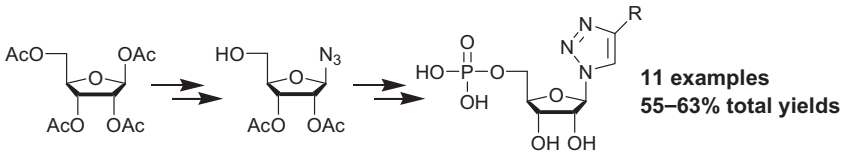


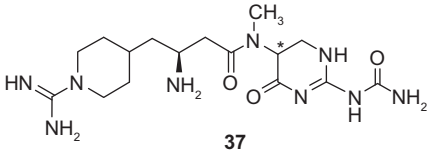


A potent, small molecule inhibitor with a favorable pharmacokinetic profile to allow for sustained SCD inhibition in vivo was identified. Biological evaluation of a SCD inhibitor (**5b**) included in vitro potency at SCD-1 and in vivo modulation of the plasma desaturation index (DI) in rats on a low essential fatty acid (LEFA) diet.



IC_{50} = 120 nM against caspase-3 **IC_{50} = 9 nM against caspase-3**





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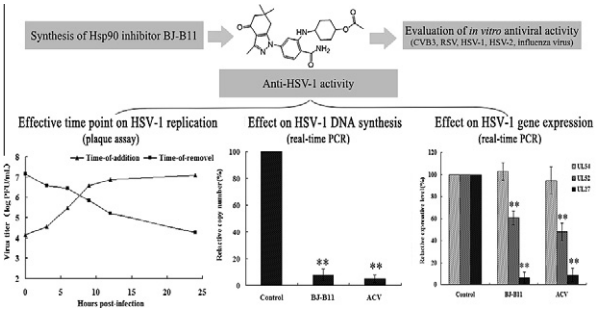
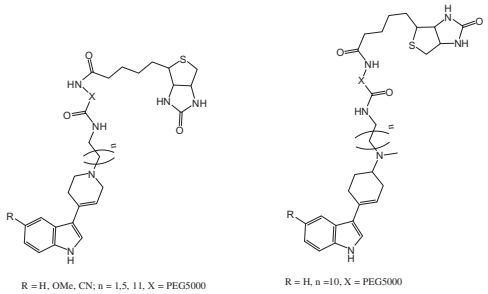
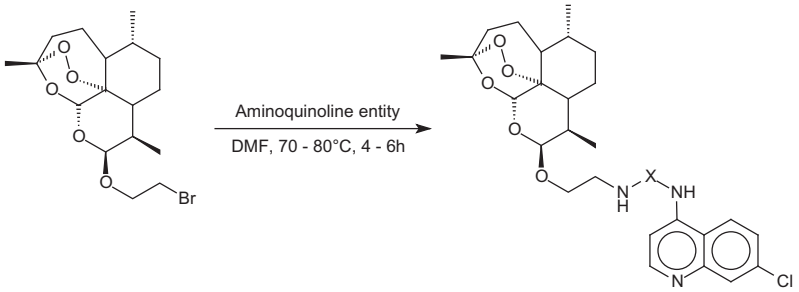
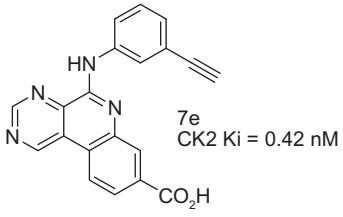
There is an urgent need for the development of novel antimicrobial agents that offer effective treatment against MRSA. Using a new class of dipeptide antibiotic TAN-1057A/B as lead, we designed, synthesized and evaluated analogs of TAN-1057A/B. Several novel dihydropyrimidinone antibiotics demonstrating comparable antibiotic efficacy while possessing favorable selectivity were identified.

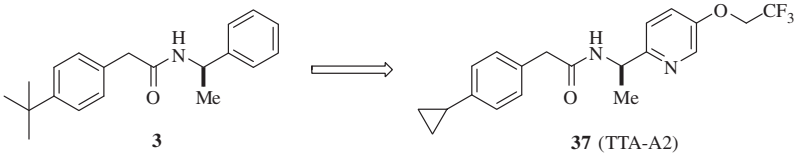


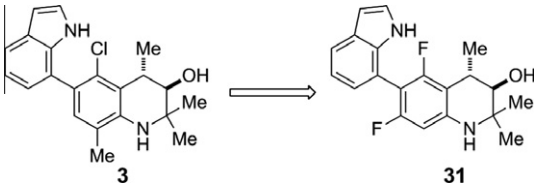


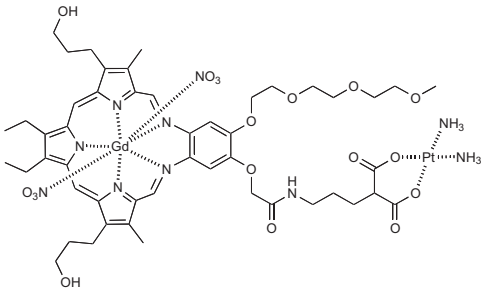


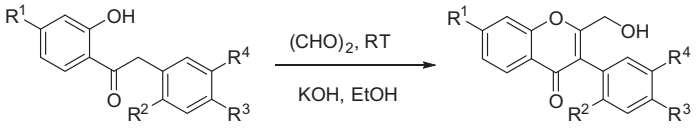
Novel artemisinin-quinoline hybrids were synthesized by connecting dihydroartemisinin via ether and amine bonds to different 4-aminoquinoline entities, and it resulted in compounds with good in vitro antimalarial activity.

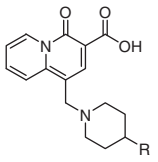




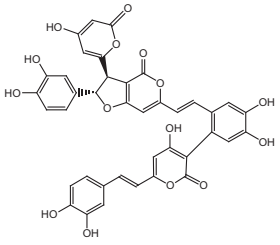




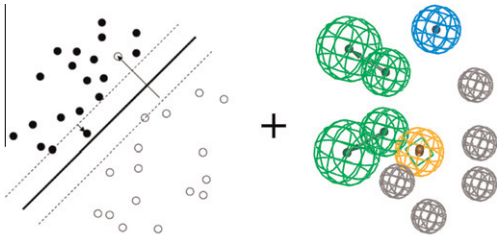




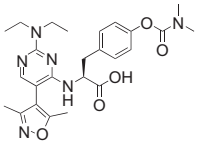
SAR study of the piperidine moiety in a series of quinolizidinone carboxylic acid M_1 positive allosteric modulators was examined.



A new trimeric hispidin derivative, phellinstatin, was isolated from a culture broth of the medicinal fungus *Phellinus linteus* and its structure was established by various spectral analysis. Phellinstatin strongly inhibited *Staphylococcus aureus* enoyl-ACP reductase with an IC_{50} of 6 M and also showed antibacterial activity against *S. aureus* and MRSA.



A multistep VS approach based on SVM and pharmacophore models of mGluR1 antagonists



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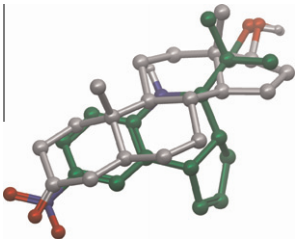
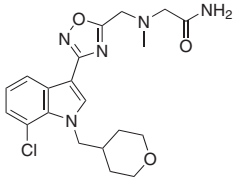
A series of N-(pyrimidin-4-yl)-phenylalanine VLA-4 antagonists is described. Optimization of substituents at the 2 and 5 positions of the pyrimidine ring gave **14**, a very potent VLA-4 inhibitor which is orally active in a sheep asthma model.



We report design and synthesis of tricyclic tetrahydroquinolines by a four-point pharmacophore method as new SARMs. This compound has a decreased virilizing effect with retention of the anabolic effect as compared with DHT in vivo.



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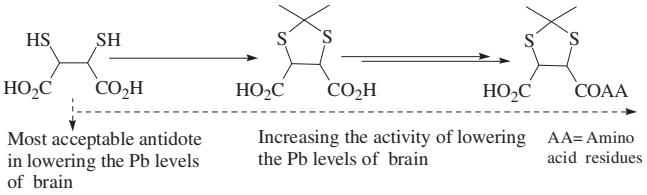
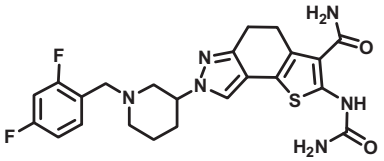
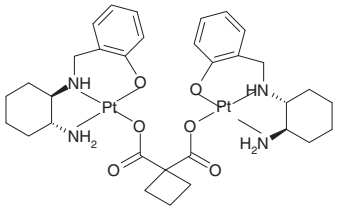




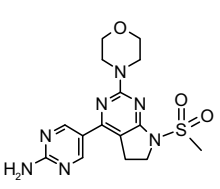
2t

IKK-β inhibitors characterized by a dihydrothieno [2,3-*e*] indazole core are reported. Compound **2t** was efficacious in a mouse model of LPS-stimulated TNF-α production.

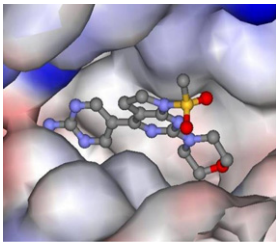


D4

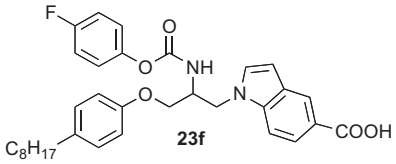
Novel dinuclear platinum(II) complexes were designed, prepared and biologically evaluated. Results indicated that compound **D4** showed better antitumor activity than carboplatin against two selected human cell lines.



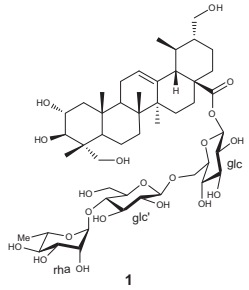
CH5132799

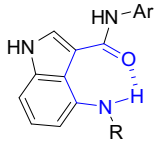


An orally available, potent class I PI3K inhibitor, CH5132799, was discovered by structure-based drug design.

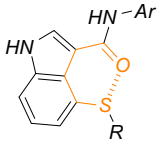


Phytochemical investigation resulted in isolation of one new ursane-type triterpene glycoside, asiaticoside G (**1**) and nine known compounds from the leaves of *Centella asiatica*. The anti-inflammatory activities of the isolated compounds were investigated on lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. Asiaticoside G (**1**) potently inhibited the production of nitric oxide and tumor necrosis factor-α with inhibition rates of 77.3% and 69.0%, respectively, at the concentration of 100 μM.

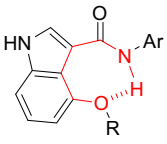




pseudo 7-membered ring
KDR 25% inhi.@10μM

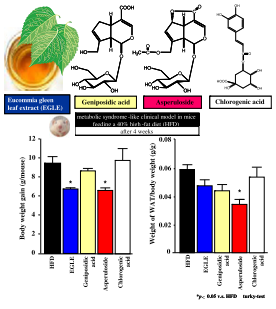


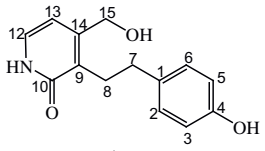
pseudo 6-membered ring
KDR 92% inhi.@10μM



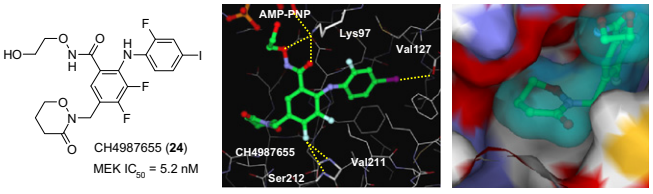
pseudo 7-membered ring
KDR 4% inhi.@10μM

Ar = -3-CF_3-Ph
R = -CH_2-4-Py



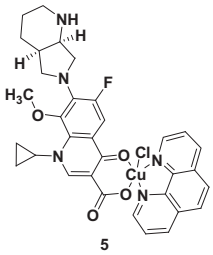


1



Novel allosteric MEK inhibitor CH4987655 (**24**) possessing unique 3-oxo-[1,2]oxazinane substructure was designed and synthesized. CH4987655 shows slow dissociation from the target enzyme and high metabolic stability together with strong oral antitumor efficacy.

Novel moxifloxacin–copper complexes were synthesized, characterized and screened for anti-proliferative and apoptosis-inducing activity against hormone dependent (MCF-7 and T47D) and hormone independent (MDA-MB-231 and BT-20) breast cancer cell lines and was compared against non-tumorigenic breast epithelial cell line (MCF-10A). The results indicated that copper conjugate **2** and its nitrogen adducts **3**–**5** exert significant growth inhibition of cancer cell lines and apoptosis-induction, compared to parent moxifloxacin (**1**) without any significant effect on non-tumorigenic MCF-10A cells. Interestingly, compound **5** was found to be very active against multiple cell lines.



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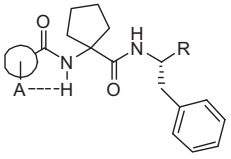
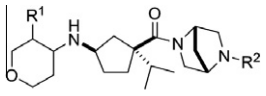
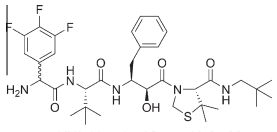




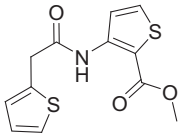
R^1 = H, OMe, F
R^2 = COR^3, $COOR^3$, $CONHR^3$

This report describes the design and synthesis of a series of CCR2 antagonists incorporating non-aryl/heteroaryl RHS motifs and a 2.2.1 ring system.



KNI-10774a, IC_{50} = 13.2 nM

The SAR of a series of tri-substituted thiophene JNK3 inhibitors is described. By optimizing both the N-aryl acetamide region of the inhibitor and the 4-position of the thiophene we obtained single digit nanomolar compounds, such as **47**, which demonstrated an in vivo effect on JNK activity when dosed orally in our kainic acid mouse model as measured by phospho-*c*-jun reduction.



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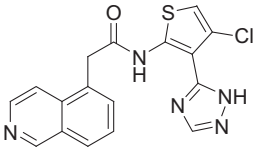
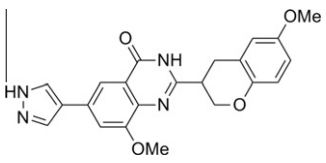
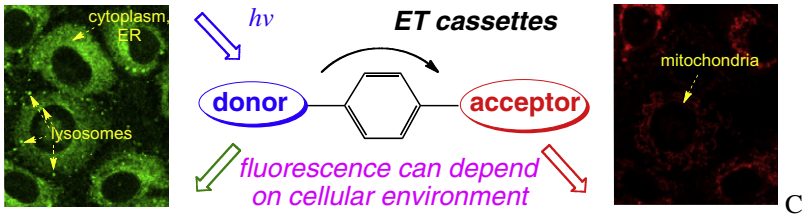
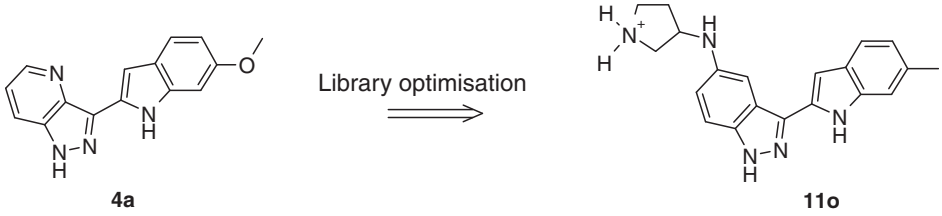
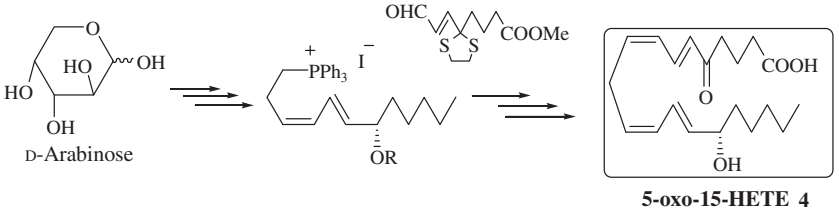


47

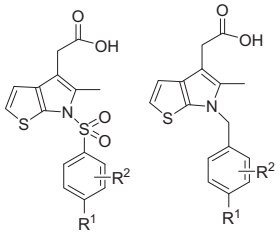


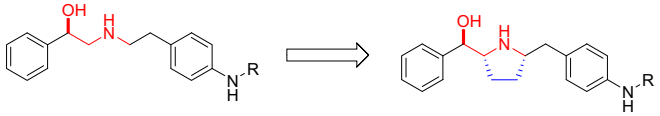




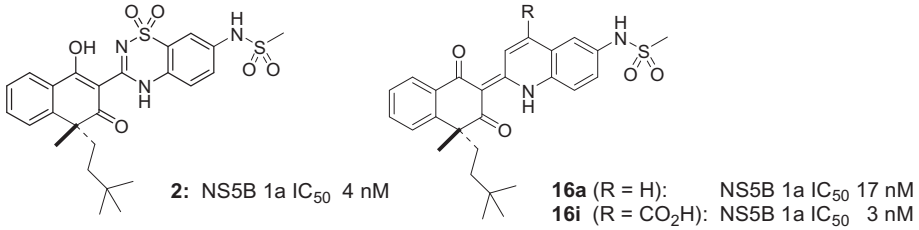


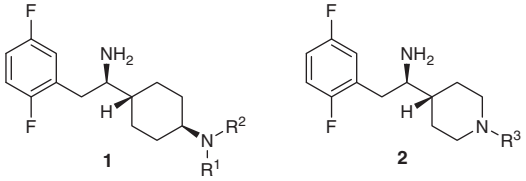
The first total synthesis of 6(*E*),8(*Z*),11(*Z*),13(*E*) 5-oxo-15-HETE **4** was accomplished. The synthetic material was evaluated in the calcium mobilization assay and compared with 5-oxo-ETE the natural ligand for the OXE receptor.



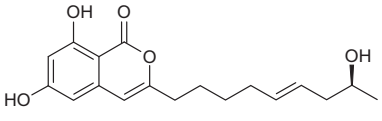


A novel class of human β_3-adrenergic receptor agonists was designed in effort to improve selectivity and metabolic stability versus previous disclosed β_3-AR agonists. As observed, many of the β_3-AR agonists seem to need the acyclic ethanolamine core for agonist activity. We have synthesized derivatives that constrained this moiety by introduction of a pyrrolidine. This unique modification maintains human β_3 functional potency with improved selectivity versus ancillary targets and also eliminates the possibility of the same oxidative metabolites formed from cleavage of the N–C bond of the ethanolamine. Compound **39** exhibited excellent functional β_3 agonist potency across species with good pharmacokinetic properties in rat, dog, and rhesus monkeys. Early de-risking of this novel pyrrolidine core (**44**) via full AMES study supports further research into various new β_3-AR agonists containing the pyrrolidine moiety.



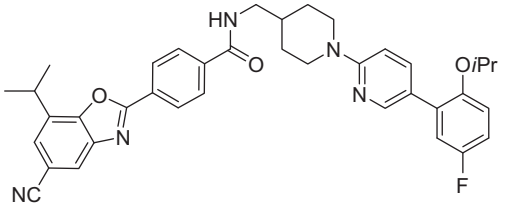


A novel series of 4-substituted-[(1*R*)-1-amino-2-(2,5-difluorophenyl)ethyl]cyclohexanes **1** and piperidines **2** were prepared and evaluated for inhibition of dipeptidyl dipeptidase IV (DPP-4) for treatment of type 2 diabetes.

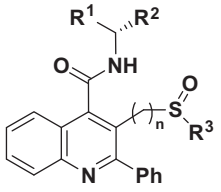


1

A new isocoumarin named fusariumin (**1**), together with two known resorcylic macrolides aigialomycin D (**2**) and pochonin N (**3**), has been isolated from the cultures of *Fusarium* sp., an endophytic fungus from *Melia azedarach*. The isolates displayed significant growth inhibitory activity against the brine shrimp (*Artemia salina*).



Compound **11v** was the first in its series found to be a potent inhibitor of CETP (IC_{50} = 16 nM), with robust in vivo efficacy (ΔHDLc = 24 mg/dL) and absent of any potentially liable aniline-containing substructures.



Synthesis and SAR of a series of C3-alkylsulfoxide substituted quinolines as potent NK3 receptor antagonists are reported. These compounds have excellent NK3 functional activity, good selectivity and drug-like properties. Several key compounds have good in vitro/in vivo DMPK characteristics, and are active in a gerbil locomotor activity model.

OTHER CONTENTS

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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