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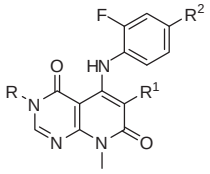
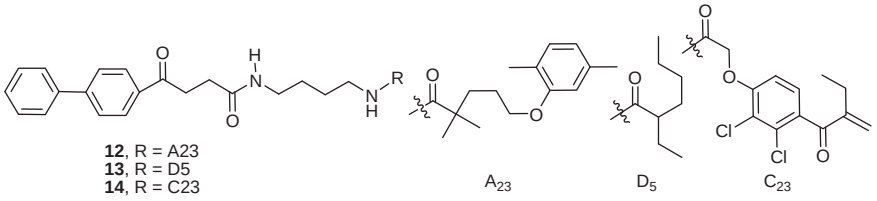
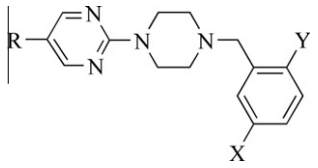
Contents

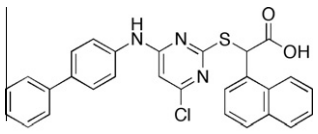
ARTICLES



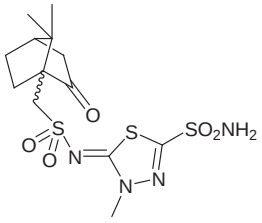
A series of potent 8-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione inhibitors of MEK kinase was designed and synthesized. Structural properties and biological activities are described.



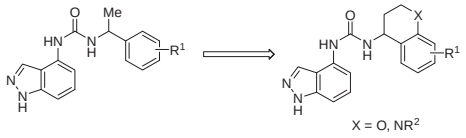




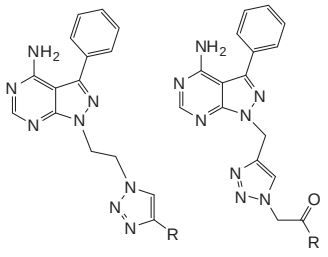
Compound **16**
IC_{50} mPGES-1 = 0.94 μM
IC_{50} 5-LO = 0.1 μM (in PMNL)



16 (1'R): Ki(CA I)= 5246 nM, Ki(CA II) = 1773 nM; Ki(CA VA)= 5.9 nM, Ki(CA VB)= 7.8 nM

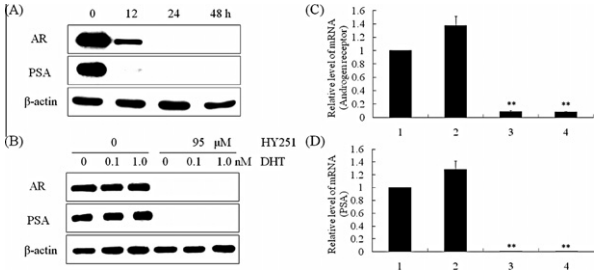


X = O, NR^2

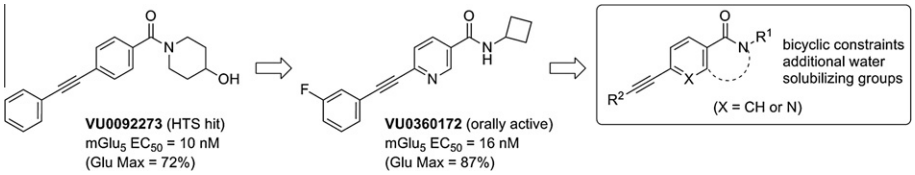


R =alkyl, aryl, orheteroaryl

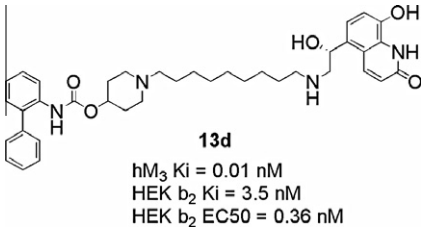
The synthesis, Src kinase inhibitory potencies, and anticancer activities of two classes of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates are reported.

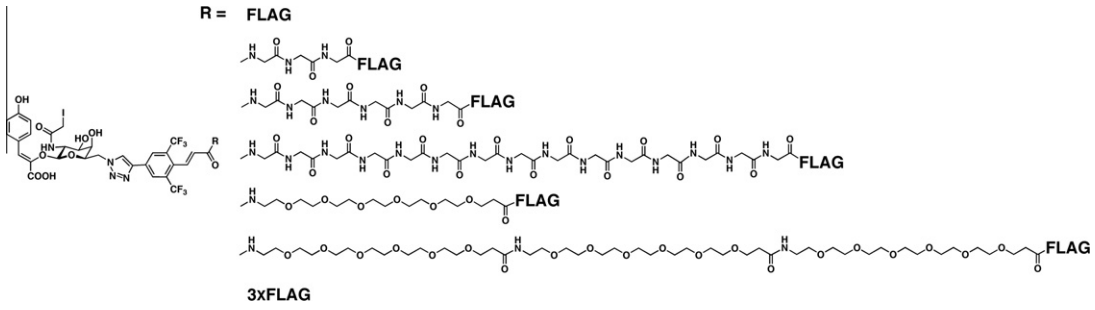


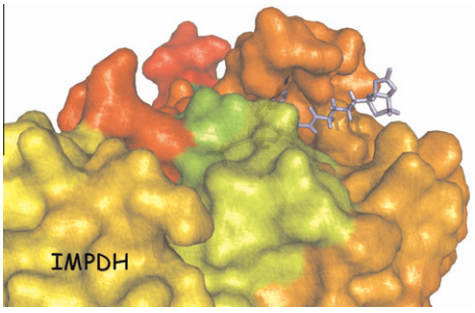
Effect of HY251, a novel decahydrocyclopenta[a]indene tetraol, on down-regulation of *AR* and *PSA* gene.

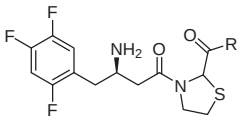


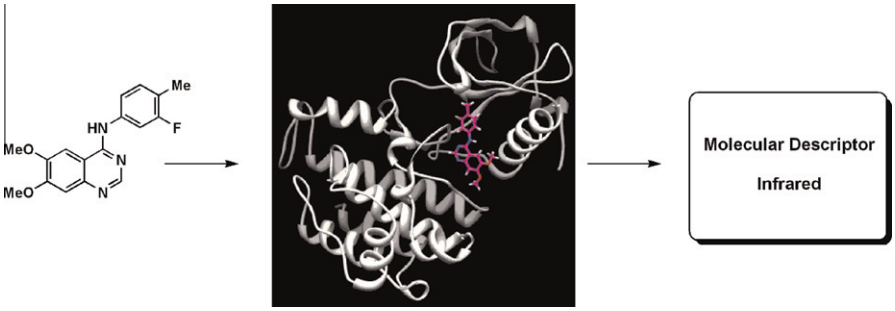
This Letter describes the hit-to-lead progression and SAR of a series of biphenyl acetylene compounds derived from an HTS screening campaign targeting the $mGlu_5$ receptor. 'Molecular switches' were identified that modulated modes of pharmacology, and several compounds within this series were shown to be efficacious in reversal of amphetamine induced hyperlocomotion in rats after ip dosing, a preclinical model that shows similar positive effects with known antipsychotic agents.

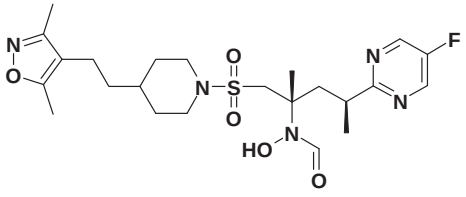




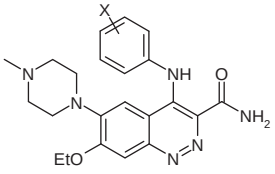


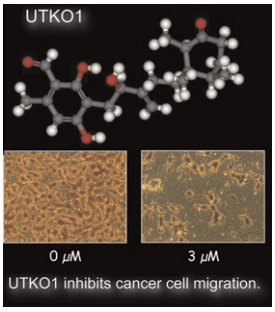


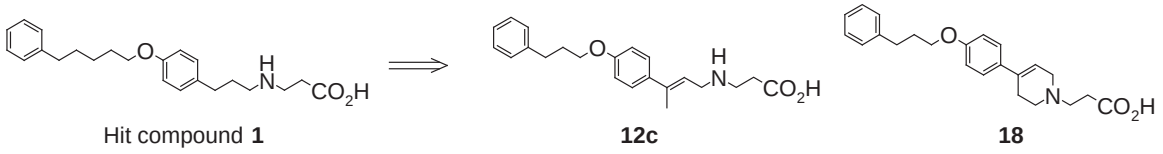




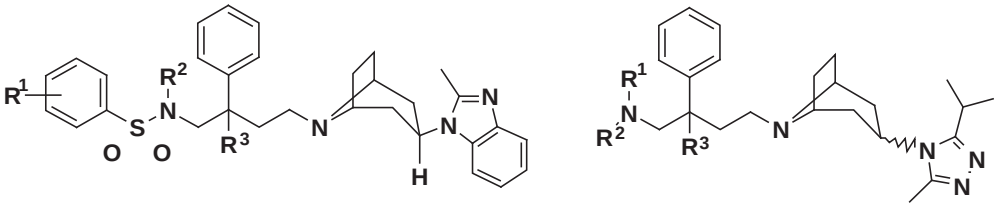
ADAM-TS4 IC_{50} = 0.69 nM
MMP-13 IC_{50} = >8100 nM

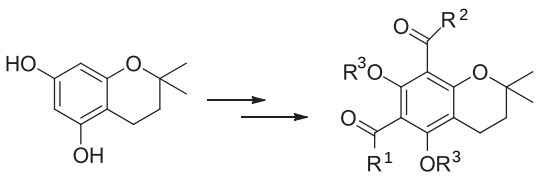


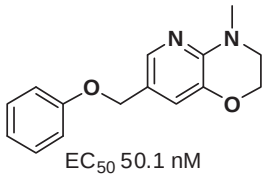




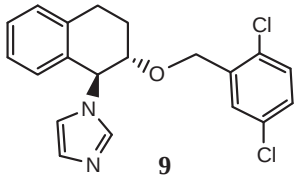
Structure–activity relationship of sphingosine-1-phosphate receptor agonist was examined. Novel S1P agonists with cinnamyl scaffold or 1,2,5,6-tetrahydropyridine scaffold were identified.







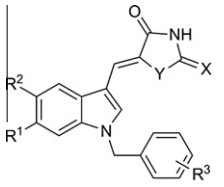
Positive allosteric modulators of $mGlu_5$ are described.



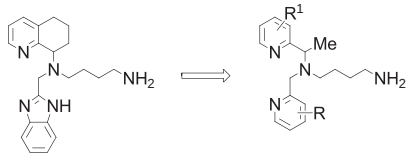
9

A novel series of aryloxy tetrahydronaphthyl and cyclohexyl azoles were synthesized as antileishmanials. Among all, compound **9** was identified as the most potent analogue with both in vitro and in vivo activity against *Leishmania donovani*.

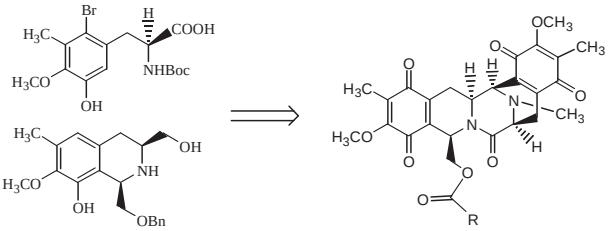
A series of novel substituted (*Z*)-5-((1-benzyl-1*H*-indol-3-yl)methylene) imidazolidin-2,4-diones (**3a**–**f**) and (*Z*)-5-((1-benzyl-1*H*-indol-3-yl)methylene)-2-iminothiazolidin-4-ones (**3g**–**o**) have been synthesized and evaluated for in vitro cytotoxicity against a panel of 60 human tumor cell lines. Compound **3i** exhibits potent growth inhibition against melanoma UACC-257 (GI_{50} = 13.3 nM) and ovarian OVCAR-8 (GI_{50} = 19.5 nM) cancer cells and significant cytotoxicity (LC_{50} = 308 and 851 nM, respectively) against the same cell lines within this series of compounds. A second analog, **3a**, had GI_{50} values of 307 and 557 nM against SK-MEL-2 melanoma and A498 renal cancer cell lines, and exhibited GI_{50} values ranging from 0.30 to 6 μM against 98% of the cancer cell lines in the 60-cell panel.

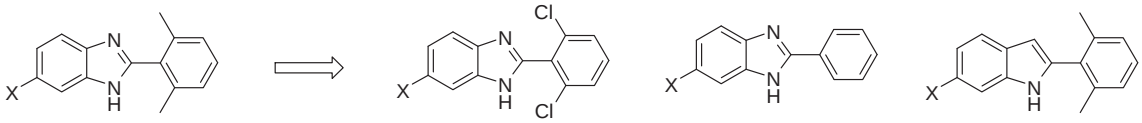


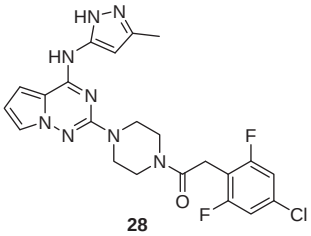
3a: X= O, Y=NH, R^1=-$COOCH_3$, R^2=H, R^3=*p*-CN
3i: X=NH, Y=S, R^1=H, R^2= Cl, R^3= *p*-F



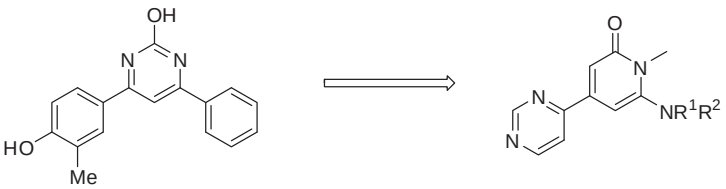
A novel series of CXCR4 antagonists were identified based on the substantial redesign of AMD070. These compounds possessed potent anti-HIV-1 activity and showed excellent pharmacokinetics in rat and dog.





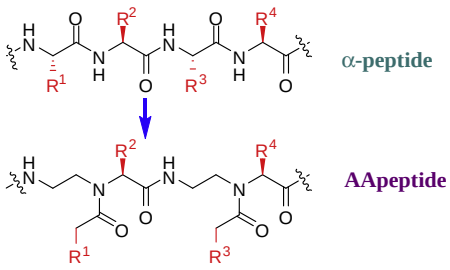


28
JAK2 IC_{50} = 1 nM
JAK3 IC_{50} / JAK2 IC_{50} = 67
SET2 IC_{50} = 80 nM

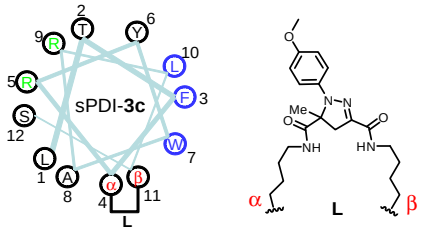


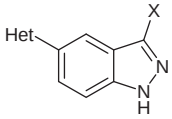
1 **2**

The synthesis and structure–activity relationships for a novel series of 6-amino-4-(pyrimidin-4-yl)pyridones derived from a high throughput screening hit are discussed. Optimization of lead matter afforded compounds with good potency, selectivity and central nervous system (CNS) exposure.

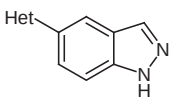


A new class of oligomeric peptidomimics were described and synthesized.

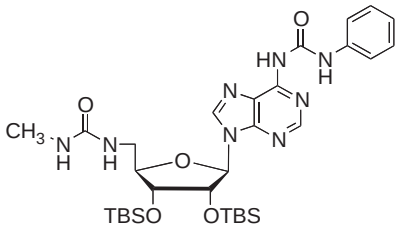


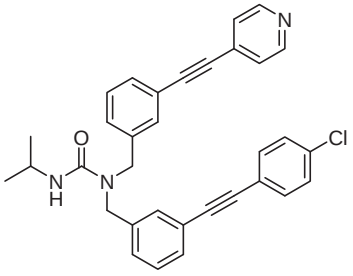


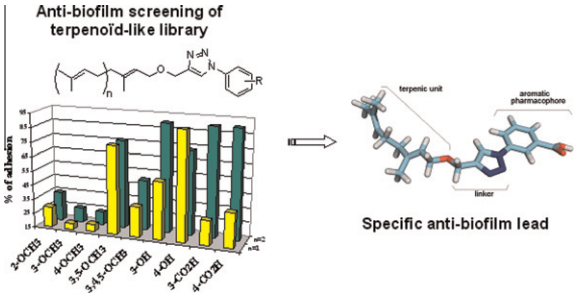
We report the synthesis and biological evaluation of 5-substituted indazoles and amino indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing [2+3] cycloaddition reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for numerous kinases such as Rock2, Gsk3β, Aurora2 and Jak2.

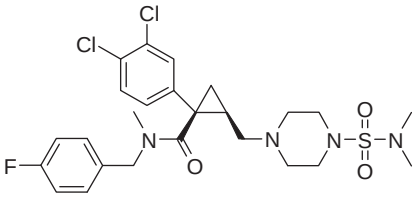


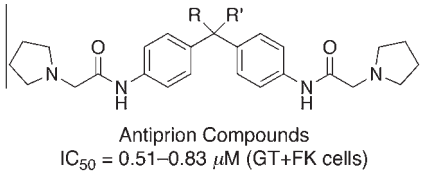
We report the synthesis and biological evaluation of 5-substituted indazoles as kinase inhibitors. The compounds were synthesized in a parallel synthesis fashion from readily available starting materials employing heterocycle forming and multicomponent reactions and were evaluated against a panel of kinase assays. Potent inhibitors were identified for Gsk3β, Rock2, and Egfr.



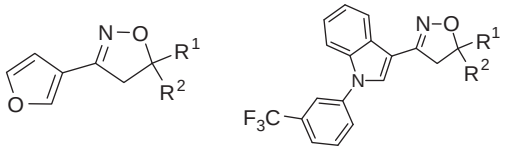




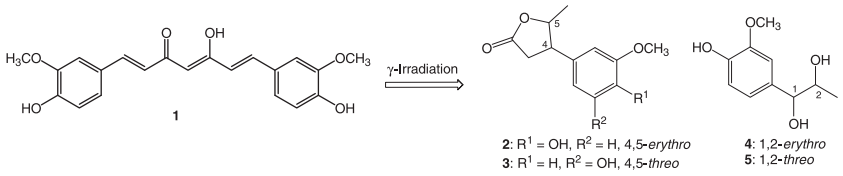


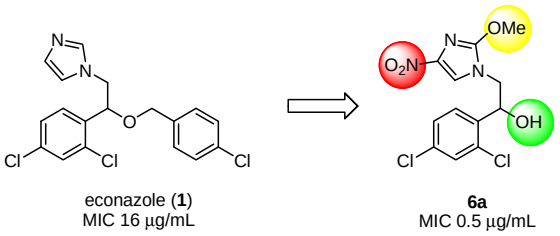


A series of GN8 derivatives were synthesized, and their antiprion activity was tested in TSE-infected mouse neuronal cells. GN8 derivatives bearing substituents at the benzylic position exhibited an improved antiprion activity with the IC_{50} values of 0.51–0.83 μM.

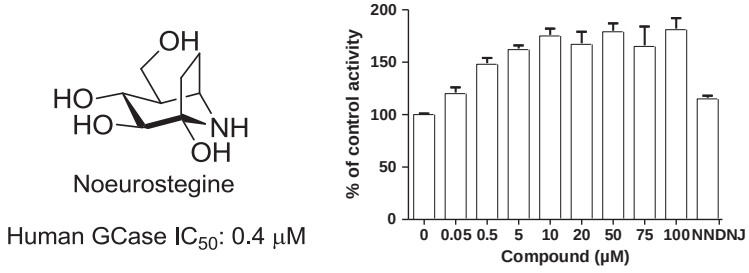


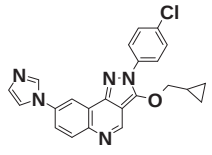
Two series of novel furan and indole compounds were synthesized and probed for inhibition of macrophage migration inhibitory factor (MIF) activity. Several compounds from both series inhibited the activity of MIF at levels equal to or significantly better than ISO-1 (an early MIF inhibitor). The majority of the compounds that robustly inhibited the spontaneous secretion/release/recognition of MIF from freshly isolated human peripheral blood mononuclear cells were from the furan series (compounds **5**, **9**, **13**, **15**, and **16**). In contrast, compounds that markedly inhibited the MIF-induced production of pro-inflammatory cytokines were predominantly from the indole series (compounds **26**, **29**, and **32**).





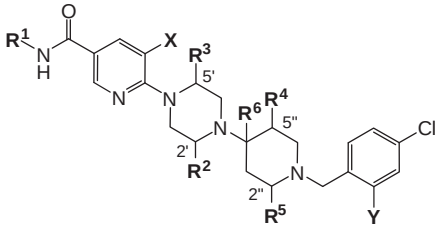
Econazole-derived nitroimidazoles were designed and synthesized as antitubercular agents.





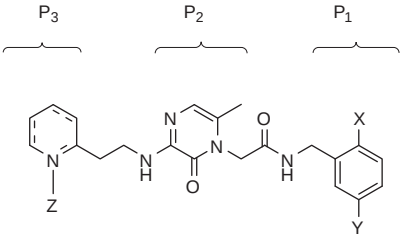
19

A novel series of agonists at the benzodiazepine binding site of the $GABA_A$ receptor based on CGS-9896 was identified. SAR work and efforts to increase metabolic stabilities are described which led to the identification of potent agonists such as **19** with selectivities either for α2- or α1-containing $GABA_A$ receptors.



The structure–human CXCR3 binding affinity relationship of a series of pyridyl–piperazinyl-piperidine derivatives was explored.

A series of 3-aminopyrazinone P2 thrombin inhibitors bearing non-charged groups (X, Y) at the P1 benzylamino position was optimized with respect to functional potency, in vivo efficacy and oral bioavailability by manipulation of polarity at the P3 pyridine position (Z = H, piperidine; Z = O, pyridine-*N*-oxide).



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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