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Chemistry
Letters

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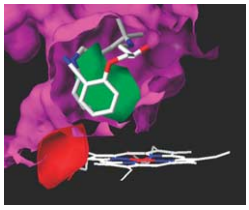
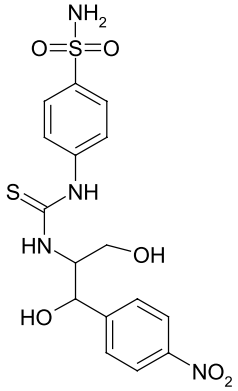
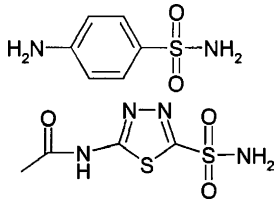
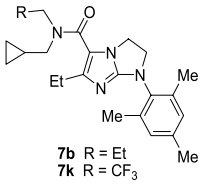
Contents

ARTICLES



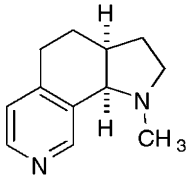




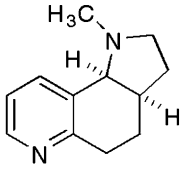


The synthesis and SAR of constrained dihydroimidazoimidazoles, and behavioral activity of compounds **7b** (K_i 42 nM) and **7k** (K_i 41 nM) in a mouse canopy model of anxiety, are reported.

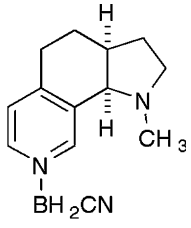
The rigid nicotine analog ACME and its *N*-cyanoborane conjugate ACME-B are selective partial agonists of rat α7 nicotinic receptors expressed in *Xenopus* oocytes, with no significant activation of either α3β4 or α4β2 receptors. ACME-B is both more potent and efficacious than ACME.



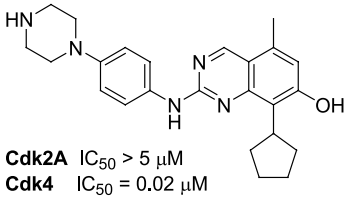
1
ACME

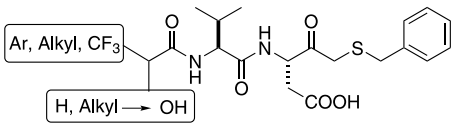


2
BCME

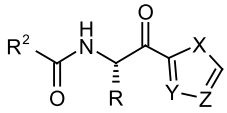


3
ACME-B

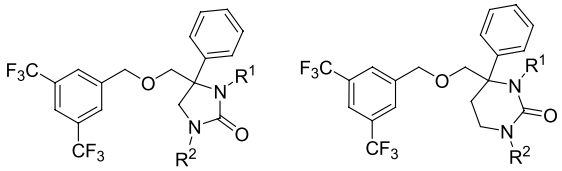




The evolution of capped valine aspartyl ketones as caspase 3 inhibitors is described in terms of the effect of hydrogen bonding and lipophilic interactions on potency and selectivity.

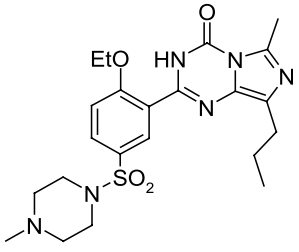


Ketoheterocyclic inhibitors of cathepsin K have been disclosed. SAR of potency enhancing P^2–P^3 groups coupled with ketoheterocyclic warheads to provide cathepsin K inhibitors have been described. In addition, a novel route to access α-ketothiazoles using a key thioamide functionality has been disclosed. The mild method employed allows for the presence of diverse functional groups, such as amide and carbamate functionalities, commonly found in protease inhibitors that have peptidomimetic scaffolds. This new method should provide a quick entry into functionally diverse protease inhibitors.

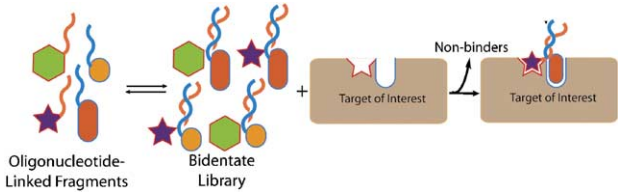


2 **3**

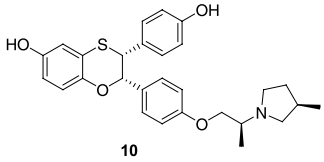
Several different heterocyclic systems were compared as PDE5 inhibitor scaffolds. In addition to the known 3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-ones and pyrazolopyrimidinones, isomeric imidazo[1,5-*a*][1,3,5]triazin-4(3*H*)-ones (e.g., **30**) were also shown to be potent and selective PDE inhibitor scaffolds with in vivo activity. SAR trends were elucidated for sulfonamide derivatives with generality across different scaffolds.



30, IC_{50}=10nM

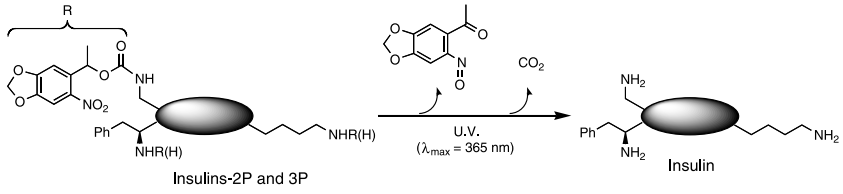


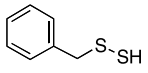
A library of bidentate fragments linked through an oligonucleotide duplex was tested for protein binding. Thermal denaturation experiments showed that the melting temperature, thus stability, of the bidentate binding ligand increased from 59 to 71°C in the presence of protein.



10

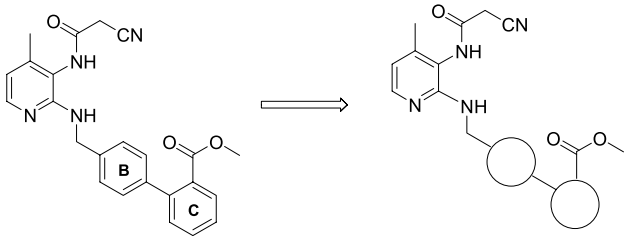
An optimized side chain for dihydrobenzoxathiin SERAMs was discovered and attached to four dihydrobenzoxathiin platforms. The novel SERAMs show exceptional estrogen antagonist activity in uterine tissue and an MCF-7 breast cancer cell assay.

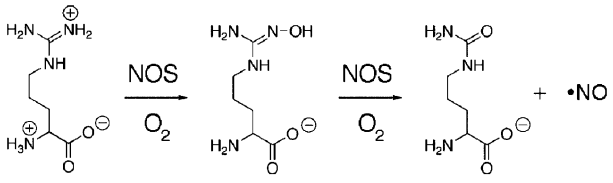




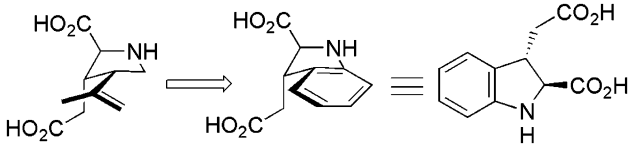
Hydropersulfides (RS_xSH) have been implecated as important intermediates in cell-killing by the anticancer natural products leinamycin and varacin. Here experiments with synthetic benzyl hydrodisulfide (BnSSH) provide direct evidence that persulfides readily decompose to yield cytotoxic reactive oxygen species under physiologically relevant conditions.

An SAR analysis of 2,3-diaminopyridine bradykinin B_1 antagonists was carried out and revealed that either of the aromatic rings comprising the biphenyl region could be effectively replaced with non-aromatic carbo- or heterocyclic rings.



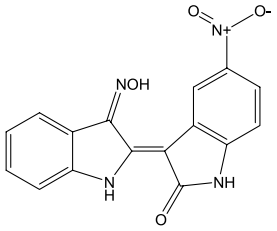


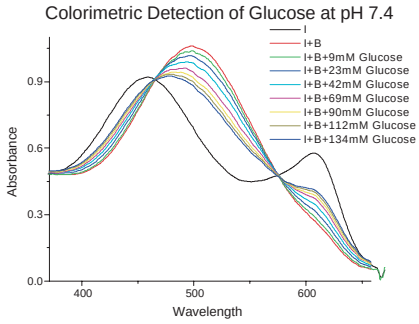
Synthetic N^{δ}-methyl-L-arginine and commercially available L-canavanine were evaluated as alternate substrates of inducible nitric oxide synthase.

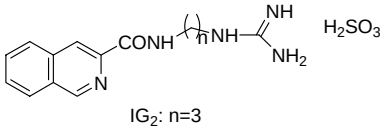


Conformationally constrained, indole/indoline-based analogues based on the well-known glutamate receptor agonist kainic acid were designed and synthesized. Screening for ionotropic glutamate receptor activity showed these compounds to be kainate receptor antagonists, rather than agonists.

A novel indirubin analog, indirubin-5-nitro-3′-monoxime, inhibited cell proliferation against various human cancer cells. Additional studies indicate that the mechanism of action of this analog against human lung cancer cells might be to arrest cell cycle progression at G_2/M phase and induce apoptosis via p53- and mitochondria-dependent pathways.







IG_2: n=3

Synthesis and biological evaluation of a series of isoquinoline derivatives are described. The compound IG_2 bearing guanidinium group-terminated side chain can block the HIV-1 Tat–TAR RNA interaction and exhibit the antiviral potency.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Schematic of a bidentate biotin ligand binding two adjacent biotin sites on the tetrameric SA. Subunits (red, cyan, blue, and pink) binding biotin (green) through an amine-modified (yellow) DNA duplex. PDB code: streptavidin (1SWG). NDB code: duplex DNA (BDL084). [Sprinz, K. I.; Tagore, D. M.; Hamilton, A. D. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3908.]

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