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Bioorganic & Medicinal Chemistry Letters

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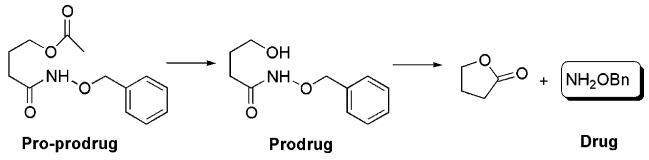
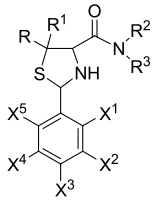
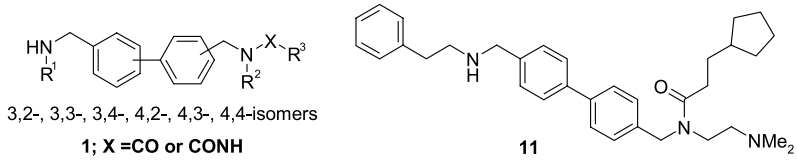
Contents

ARTICLES

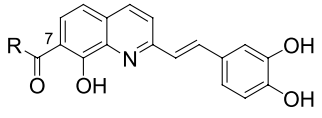


The synthesis and reactivity of hydroxy hydroxamates as models for a prodrug form of hydroxylamine are described. γ-Hydroxy hydroxamates were found to enable hydroxylamine release via lactonisation. Hydroxamates were found to undergo esterase catalysed hydrolysis.

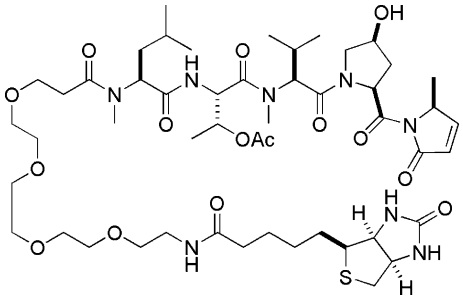


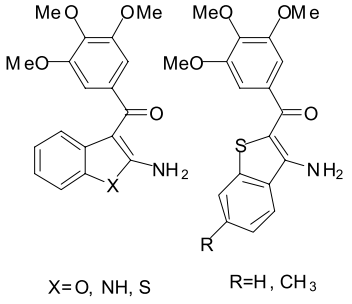


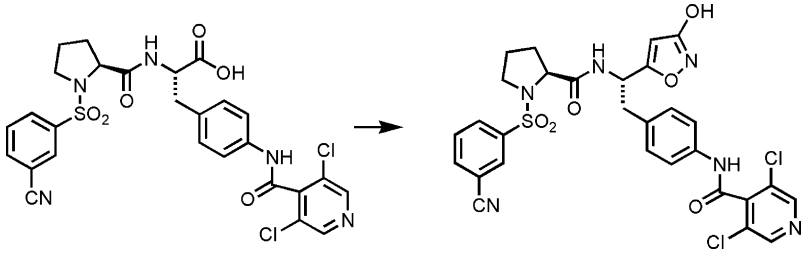
A series of biphenylmethylamines with affinity for the 5-ht$_{5A}$ receptor was identified by high-throughput screening of array **1**, synthesised by high-throughput solid-phase chemistry. Compound **11** was identified as the most potent and selective 5-ht$_{5A}$ receptor antagonist from this series.

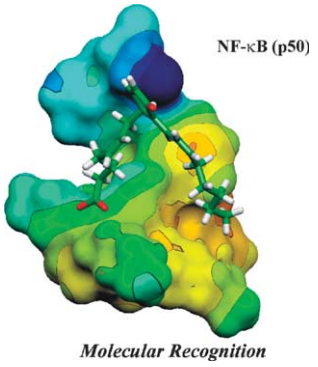


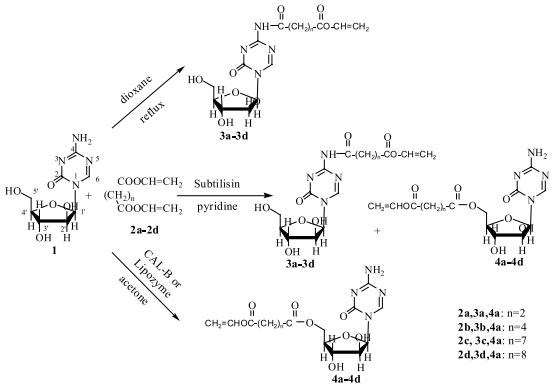
Novel variants of HIV-1 replication inhibitors of the styrylquinoline class harboring aroyl/acyl group at the C-7 position have been synthesized. In sharp contrast with styrylquinolines bearing a carboxylic acid group at C-7, these compounds proved to be inactive toward HIV-1 integrase in in vitro assays.

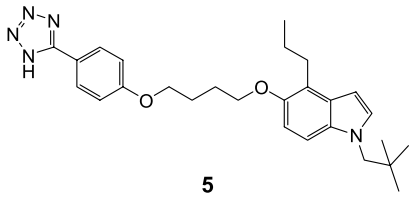












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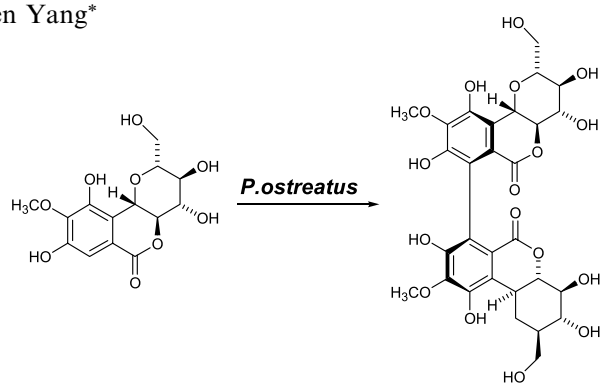
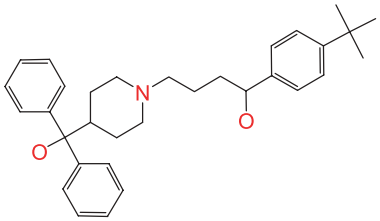
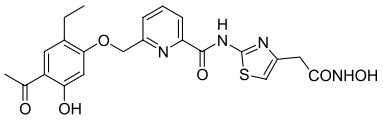
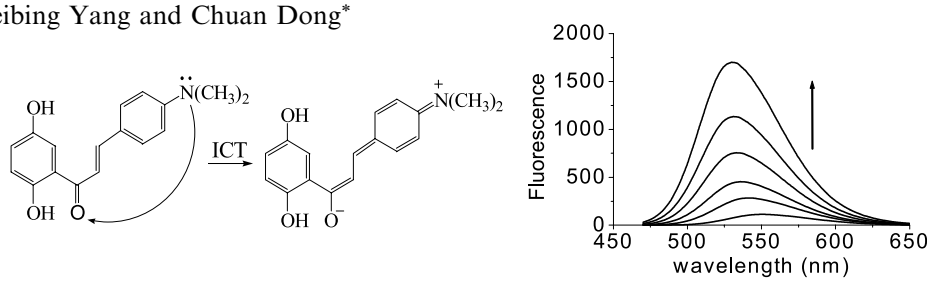




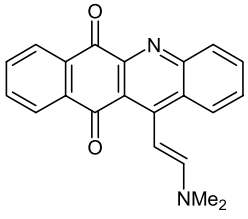
(terfenadine, a typical substrate of CYP3A4)



HTS and the following synthesis of a series of compounds led us to the discovery of hydroxamic acid analogs as potent dual inhibitors of phosphodiesterase (PDE)-1 and -5. Some of them showed the expected potent vasodilatory effects with a rising level of cGMP.

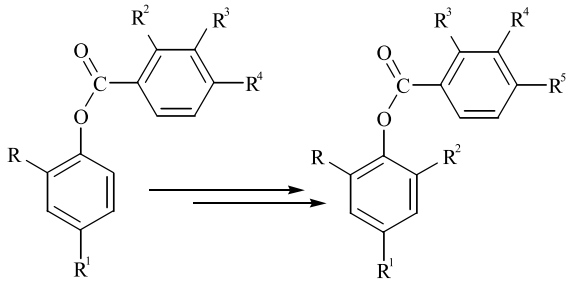


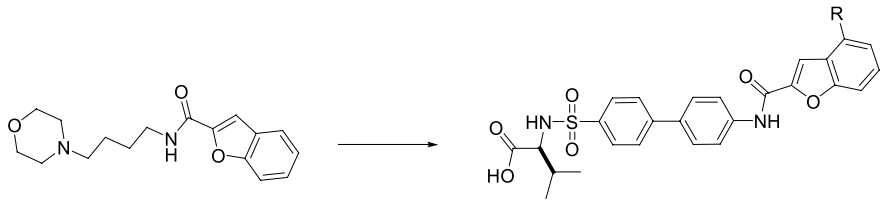
Intramolecular charge transfer fluorescence probe 4′-dimethylamino-2,5-dihydroxychalcone binding to human serum albumin exhibited dramatic enhancement of fluorescence intensity with accompanying blue shift of the emission maximum.



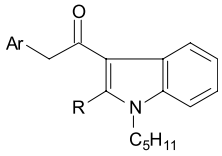
A range of heteroarylenamines were prepared and evaluated against *Mycobacterium tuberculosis* $H_{37}Rv$ (Mtb). Cell-based studies indicate that the compounds exhibit activity via a novel mechanism of action compared to current front-line therapies.

Benzoylation of (hydroxy phenyl) phenyl methanone **2a**–**g** to benzoyl phenyl benzoates **4a**–**g** was achieved in good yield. All the newly synthesized compounds were evaluated for their phospholipase A_2 [E.C. 3.1.1.4] and hyaluronidase [E.C. 3.2.1.35] enzyme inhibitory activity in snake venom as source and their structure–activity relationship with respect to different groups is reported for the first time.



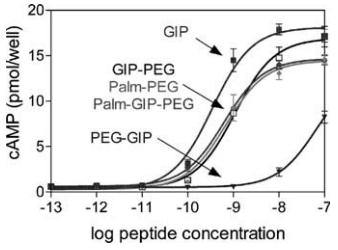


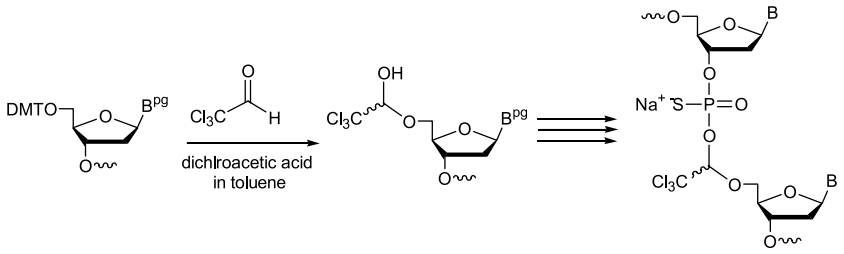
A potent, selective series of MMP-13 inhibitors has been derived from a weak inhibitor that did not bear a zinc chelator.



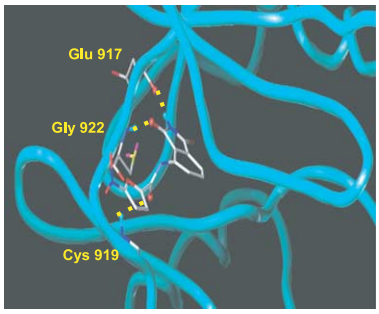
The synthesis and pharmacology of 30 1-pentyl-3-arylacetylindoles (R = H and CH_3) are described. Two of these compounds are highly efficacious and selective ligands for the CB_1 receptor.

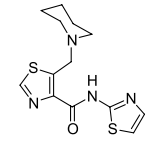
Potent and DPPIV-stable PEGylated GIP peptides are reported.





The presence of chloral in dichloroacetic acid leads to the formation of trichloroacetaldehyde modified oligonucleotides.

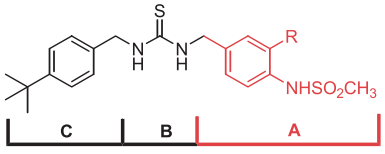


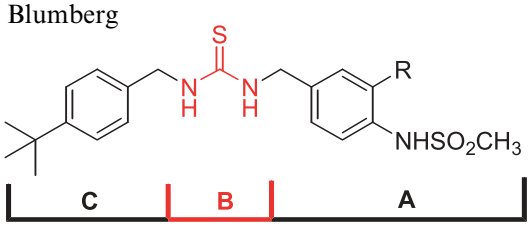


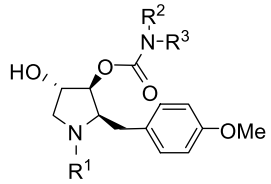
TCAT

9b IC_{50} 10 nM for *Ec*MetAP1
75 nM for *Sc*MetAP1

Systematic SAR studies on the thiazole ring 5-substituent of TCAT inhibitors of *Ec*MetAP1 and *Sc*MetAP1 revealed that the introduction of a β-alkoxy or an amino group enhanced the inhibitory activity significantly.







Solid-phase synthesis of a library based on the natural product anisomycin is described. The resulting library was tested against a panel of bacterial and fungal targets, and active compounds were identified in a *Staphylococcus aureus* whole-cell assay and an efflux-deficient fungal whole-cell assay.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Amerliorating transthyretin amyloidogenesis by native state kinetic stabilization mediated by small molecule binding. Small molecule binding to the amyloidogenic protein transthyretin kinetically stabilizes the native tetrameric state, preventing dissociation to folded monomers that misfold and misassemble into toxic intermediates, amorphous aggregates, and amyloid fibrils. The Kelly laboratory has developed several structurally distinct inhibitor families, depicted in the background, that are undergoing pharmacological evaluation. Created by Steven M. Johnson, graduate student in Professor Jeffery W. Kelly's laboratory, Department of Chemistry, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.

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