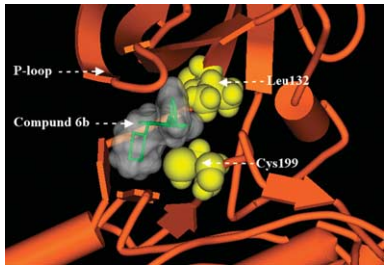
ELSEVIER

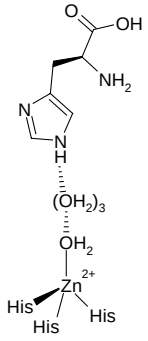
Bioorganic &
Medicinal
Chemistry
Letters

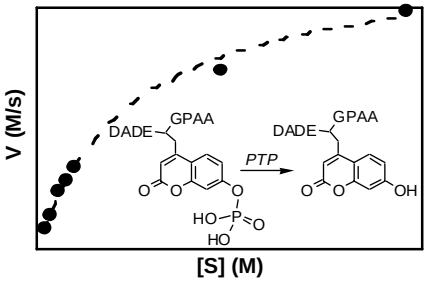
Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 23, 2005

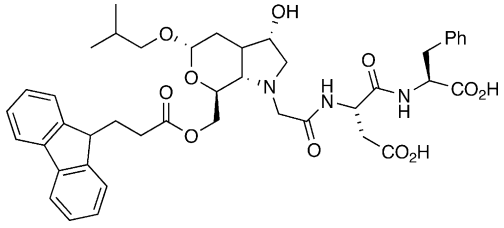
Contents

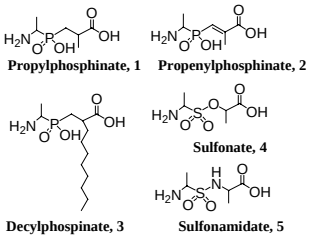
ARTICLES

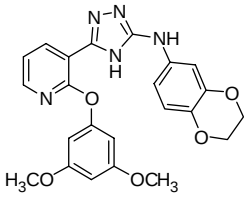




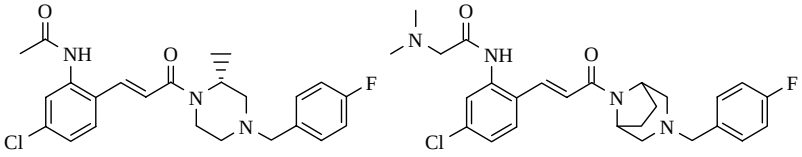






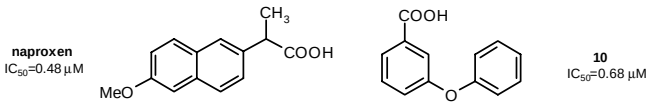


30 EC_{50} = 3.6 nM

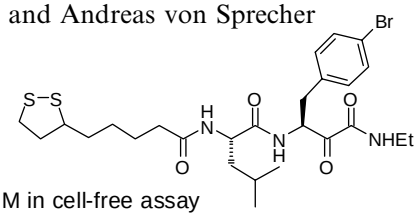


A1B1 **A4B7**

A1B1 and **A4B7** showed oral activity in the mouse collagen induced arthritis.



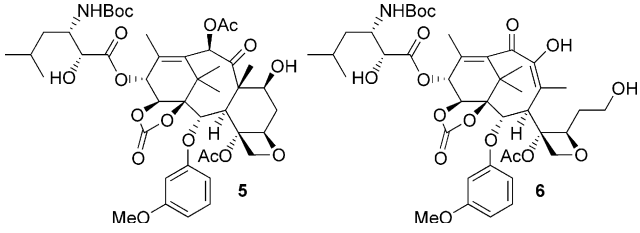
New inhibitors of human recombinant AKR1C3 are reported. Some compounds inhibited the enzyme in submicromolar range.



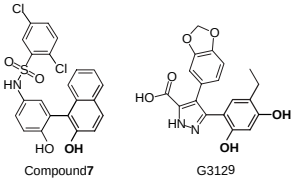
6a, IC_{50} = 25 nM in cell-free assay
IC_{50} = 500 nM in cellular assay

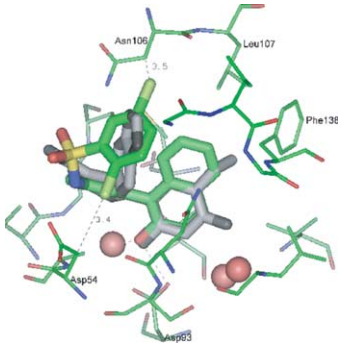
The synthesis of novel α-keto-amide calpain inhibitors bearing a lipoyl residue is reported. They demonstrated an improved activity in muscle cells compared to MDL28170, referring to increased cell membrane permeability.

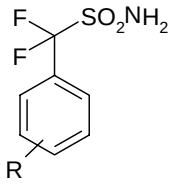
Starting from 10-deacetylbaccatin III, the 2-debenzoyl-2-*m*-methoxybenzoyl analogs of the newer generation taxoids IDN5109 and IDN5390 were synthesized. The biological evaluation of these compounds (**5** and **6**, respectively) showed a general increase of cytotoxicity, as observed in first-generation anticancer taxanes.

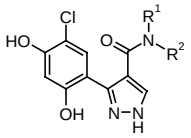


Docking-based virtual screening identified 1-(2-phenol)-2-naphthol compounds as a new class of Hsp90 inhibitors of low to sub-micromolar potency. Here we report the binding affinities and cellular activities of several members of this class. A high resolution crystal structure of the most potent compound reveals its binding mode in the ATP binding site of Hsp90, providing a rationale for the observed activity of the series and suggesting strategies for developing compounds with improved properties.

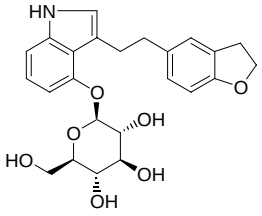




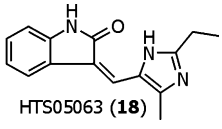




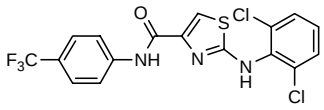
Structure-based drug design using information from X-ray structures of ligands bound to the molecular chaperone Hsp90 has been used to assist in the design of 3-(5-chloro-2,4-dihydroxyphenyl)-pyrazole-4-carboxamides, several of which can make a hydrogen bond to Phe138 of the protein, affording increased binding potency.



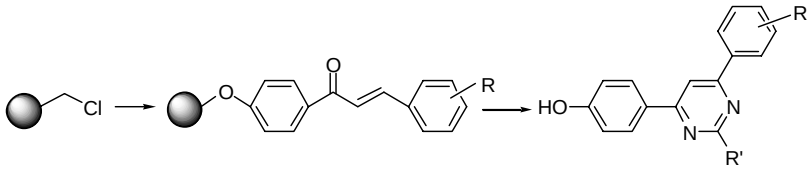
A series of benzo-fused heteroaryl-*O*-glucosides was synthesized and evaluated in SGLT1 and 2 cell-based functional assays. Indole-*O*-glucoside **10a** and benzimidazole-*O*-glucoside **18** exhibited potent in vitro SGLT2 inhibitory activity.



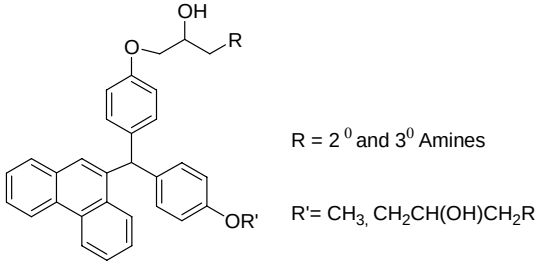
We report here compounds with indolin-2-one scaffold as potent DNA gyrase inhibitors. Using the tools of virtual screening and NMR spectroscopy indolin-2-one analogue HTS05063 (**18**) that inhibits the DNA gyrase supercoiling activity in the low micromolar range was discovered.

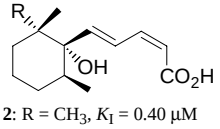


A series of thiazole carboxamides was prepared and evaluated as TRPV1 receptor antagonists. IC50 values of ca. 0.050 mM were achieved in either capsaicin- or acid-mediated calcium influx assays in TRPV1-expressing CHO cells.

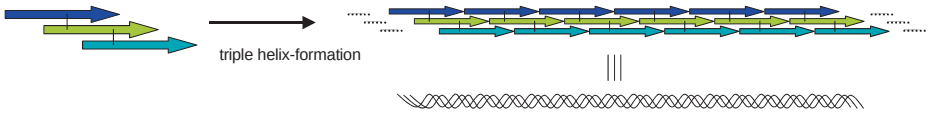


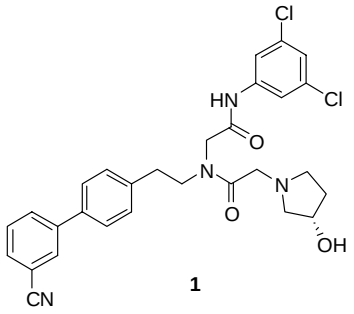
Out of the 20 compounds synthesized, 16 compounds have shown in vitro antimalarial activity against *Plasmodium falciparum* in the range of 0.25–2 μg/mL and 8 compounds have shown antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Ra$, at a concentration of 12.5 μg/mL.



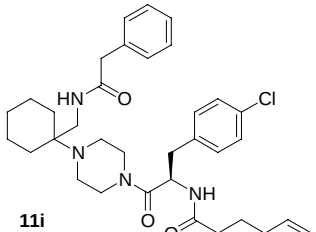


2: R = CH_3, K_I = 0.40 μM
4: R = CHF_2, K_I = 0.41 μM

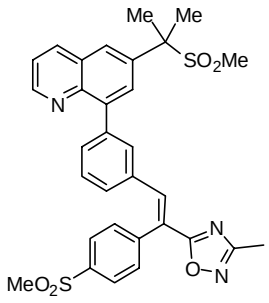




1

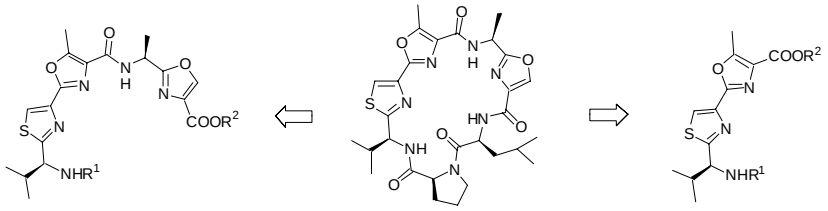


11i
K_i = 16 nM
EC_{50} = 33 nM
E_{max} = 96%



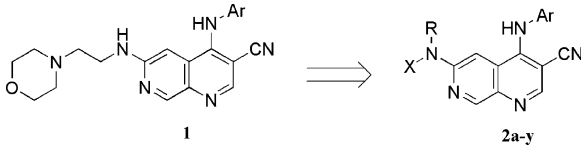
The discovery and SAR of a new series of substituted 8-arylquinoline PDE4 inhibitors are described. From this series of compounds, the development candidate L-454,560 was selected.

L-454,560

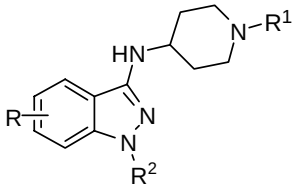


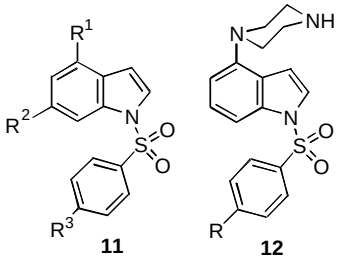
3a-3e Leucamide A (1) 2a-2n

A series of novel 4,2-bisheterocycle tandem derivatives consisting of a methyloxazole and thiazole subunit were synthesized. Many compounds were found to inhibit human influenza A virus. Several analogues exhibited moderate biological activity and could serve as leads for further optimizations for antivirus research.

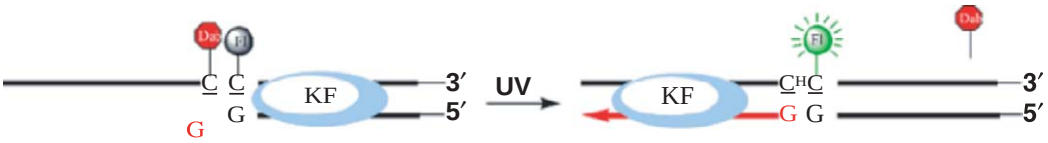


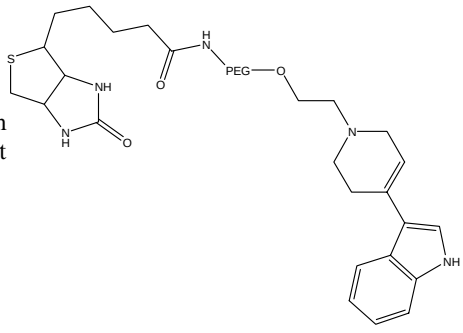
1 2a-y

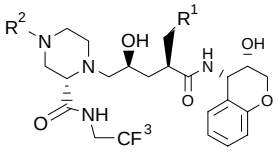


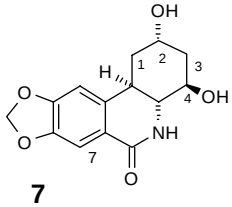


11 12

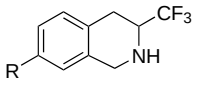




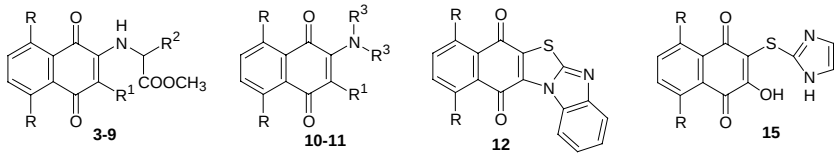




7

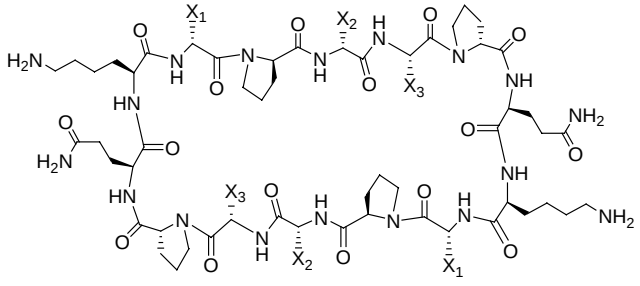


5c, K_i = 0.98 μM

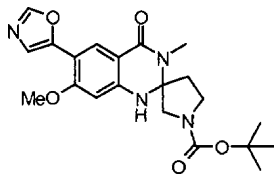


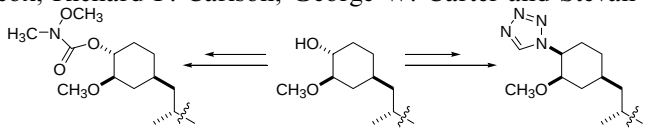
3-9 **10-11** **12** **15**

The synthesis, antifungal, and antibacterial activities of **3**–**15** are described.

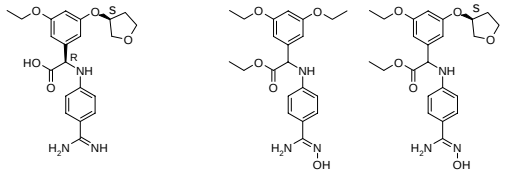


The synthesis and biological activity of a novel series of 7-methoxy-6-oxazol-5-yl-2,3-dihydro-1*H*-quinazolin-4-ones are described. Some of these compounds were found to be potent inhibitors of inosine 5′-monophosphate dehydrogenase type II (IMPDH II).





The synthesis and biological activities of highly efficacious rapamycin analogs **3** and **6** in various autoimmune disease models are reported. A shorter plasma half-life of **3** and **6**, compared to rapamycin, was measured in rats, and a reduced $t_{1/2}$ of **3** versus rapamycin was verified in patients.



We describe the structure-based design and synthesis of nanomolar, orally bioavailable tissue factor/factor VIIa inhibitors which interfere with the coagulation cascade by selective inhibition of the extrinsic pathway.

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.

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X