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Bioorganic & Medicinal Chemistry Letters

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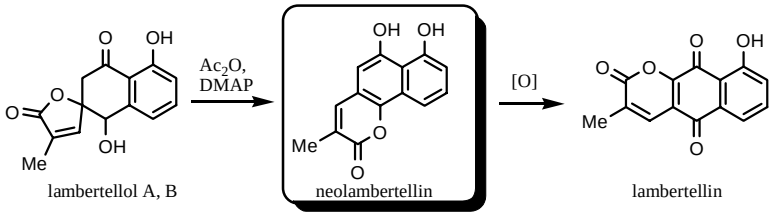
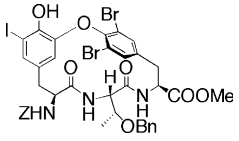
Contents

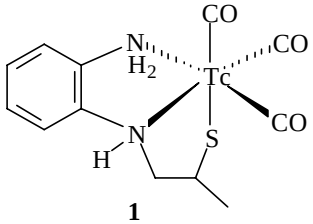
ARTICLES



newly isolated from *L.* sp. 1346



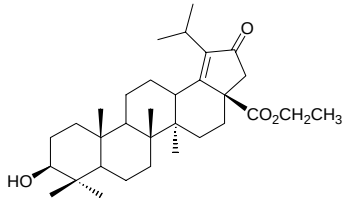
The synthetic eurypamide B analogues possessed effective inhibitory activity against the lipid droplet accumulation in macrophages.

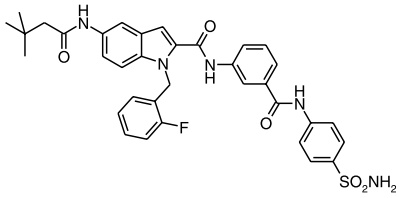


1

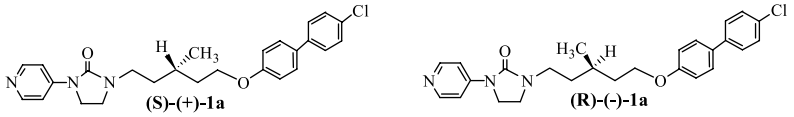
N-(2-Mercapto-propyl)-1,2-phenylenediamine (MPPDA) and *N*-β-aminoethylglycine (AEG) were labelled with $^{99m}Tc(CO)_3^+$ to form the neutral complexes [$^{99m}Tc(CO)_3$(MPPDA)] (**1**) and [$^{99m}Tc(CO)_3$(AEG)], which were analysed by LC–MS. Their biodistribution in mice was studied.

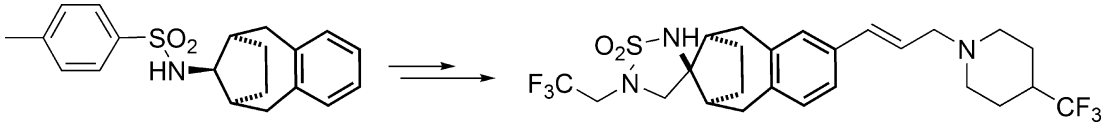
This research is based on intention to prepare and test 3β-hydroxy and 3β,28-dihydroxy analogs of new pro-apoptotic derivatives (betulinines) using selective hydrolysis procedure and strategic-protective groups. The evaluation of cytotoxicity of prepared compounds on several tumor cell lines using an MTT test was our interest. It was found that hydrolysis of acetates in betulinines afforded compounds with higher cytotoxicity in case of 18-lupene-21-ones (e.g., ethyl 3β-hydroxy-21-oxolup-18-en-28-oate), whereas hydrolysis of the 18-lupene-21,22-diones gave less active derivatives.





A novel class of indole-based endothelin-converting enzyme (ECE) inhibitors was identified by high throughput screening. We report systematic optimization of this compound class by means of classical and solid-phase chemistry. Optimized compounds with a bisarylamide side chain at the 2-position of the indole skeleton exhibit low-nanomolar activity on ECE.

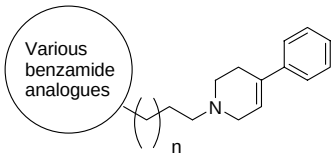


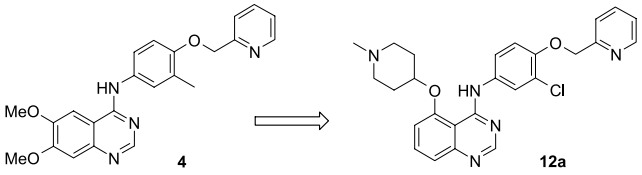


A novel series of *N*-alkyl-substituted cyclic sulfamides were developed from a screening hit.

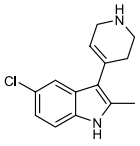
The designed and synthesized anticoagulant activity and structure–activity relationship of a series of low molecular weight peptide inhibitors of Factor Xa, fragment analogues of ATS and GLS, is reported. The newly synthesized peptides have the following structure:

H-X-Pro-Lys-Arg-Lys-Leu-Val-Pro-Y (X=Arg, Lys, Orn or missed and Y=OH, NH_2).

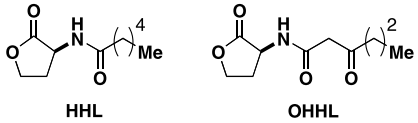




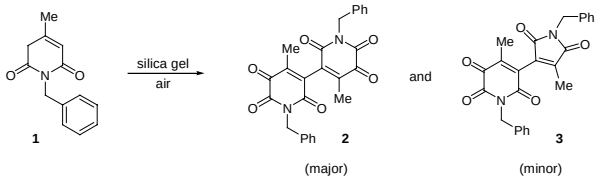
Starting from a 6,7-substituted quinazoline lead **4**, optimisation of 5-substituted quinazolines containing an extended aniline motif led to potent and selective inhibitors of erbB2 receptor tyrosine kinase, and a representative compound **12a** inhibited tumour growth in a mouse xenograft model.

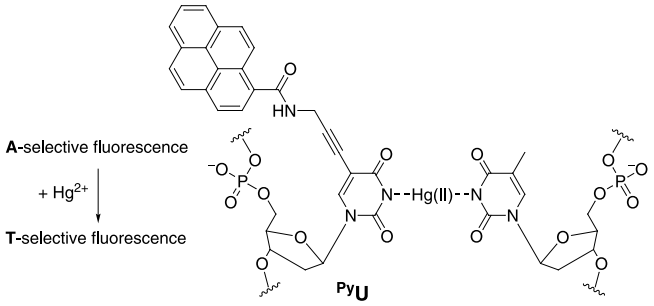


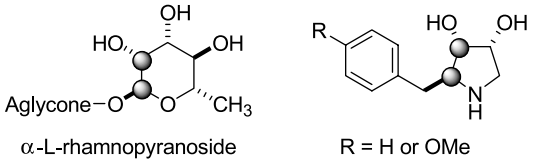
A series of 2-alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles was synthesized and evaluated for their 5-HT$_6$ activity. The most potent agonist in this series was 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole with an IC_{50} = 7.4 nM in ^{3}H-LSD-binding and an EC_{50} = 1.0 nM in a functional assay measuring production of cyclic AMP.

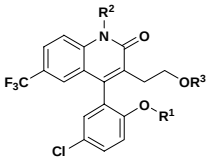


Quorum sensing modulators were synthesized and screened in vivo in the phytopathogen *Erwinia carotovora*. The biological activity of each compound was correlated with its ability to bind *Erwinia* quorum sensing receptor proteins (LuxR homologues) in vitro.



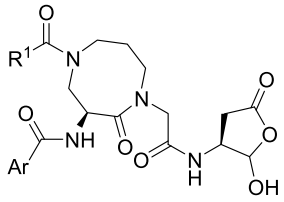




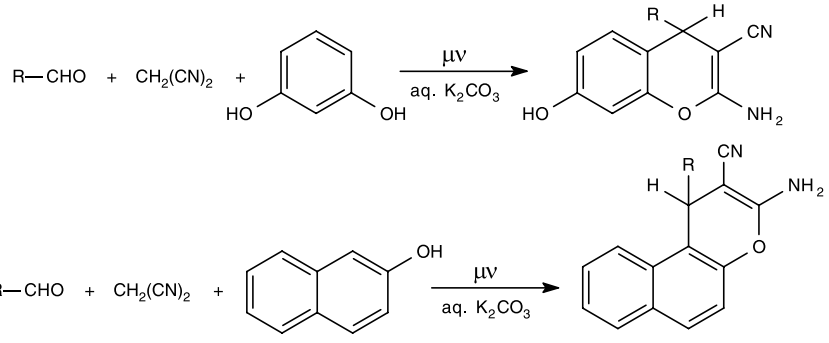


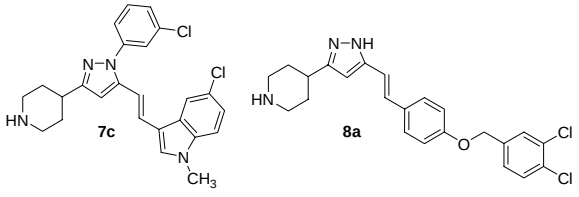
1 = $R^1 = R^2 = R^3 = H$
15 = $R^1 = R^3 = H$, $R^2 = CH_2CN$
17 = $R^1 = R^3 = H$, $R^2 = CH_2CONH_2$
19 = $R^1 = R^3 = H$, R^2 =

Quinolinone **1** is a potent maxi-K potassium channel opener. In an effort to design analogs of **1** with a better inhibitory profile toward the CYP2C9 isozyme, the two acidic sites were chemically modified independently to generate a number of analogs. These analogs were evaluated as maxi-K channel openers in vitro using *Xenopus laevis* oocytes expressing cloned *h*Slo maxi-K channels. Compounds **15**, **17**, and **19** showed potent activity as maxi-K channel openers and were further evaluated for inhibition of the activity of the CYP2C9 isozyme. Compounds **17** and **19** showed diminished inhibitory potency against 2C9 and also against a panel of other more common CYP isozymes.

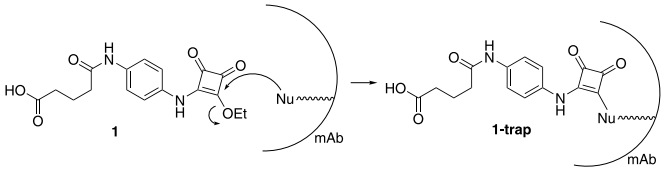


Substituted 2-amino-4*H*-chromenes have been efficiently synthesized in aqueous K_2CO_3 and their in vitro antibacterial activities were evaluated against standard strains of bacteria using Broth Microdilution MIC method.

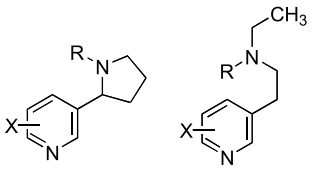




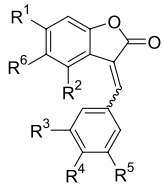
5-[(*E*)-2-Arylvinyl]pyrazoles **7c** and **8a** exhibited potent antibacterial activity against multidrug resistant Gram-positive bacteria with MIC values equivalent to those against susceptible strains.



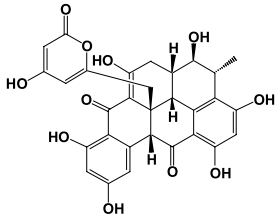
A squaric monoester monoamide motif was employed as an effective reactive immunogen for the discovery of monoclonal antibodies with reactive residue(s) in their combining sites. Two antibodies, 2D4 and 3C8, were uncovered that enhance paraoxon hydrolysis over background. Kinetic analysis of these antibodies was performed and interestingly both undergo a single turnover event due to covalent modification within the antibody combining site. Because antibodies 2D4 and 3C8 result in covalent attachment and thus inactivation of paraoxon, they could be useful probes for investigating paraoxon intoxication.

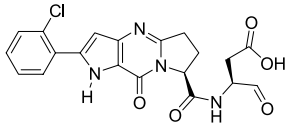


An examination of several 3-(2-aminoethyl)pyridine analogs **2** (with K_i values ranging from 18 to >10,000 nM) and comparison with their structurally related nicotine analogs **1** suggest that the two series likely bind at nicotinic cholinergic receptors in a different fashion.

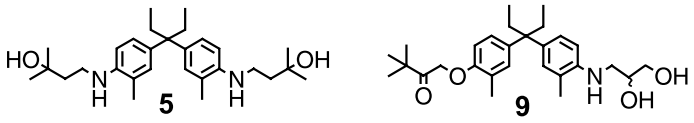


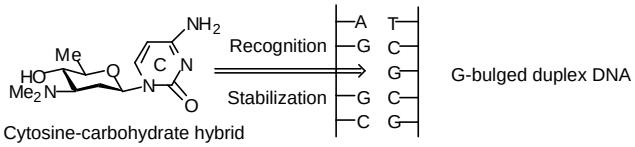
The structure of A-74528 was elucidated by NMR techniques including natural abundance INADEQUATE to be a highly fused polyketide with a side-chain branching site that never appeared before from the nature. The relative configuration was elucidated by the analyses of NOEs and assessment of dihedral angles predicted by QUANTA/CHARMm computations and coupling constants.

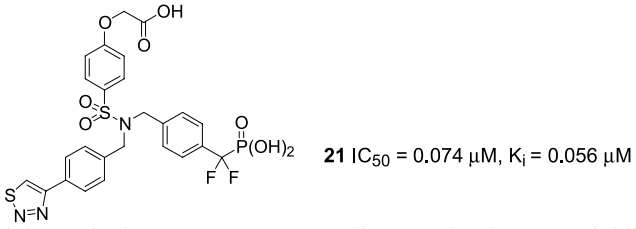




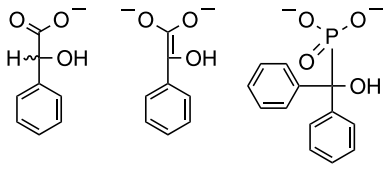
6b, ICE IC_{50}=14 nM



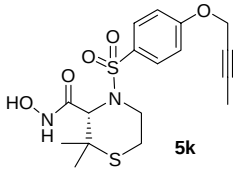




A series of novel sulfonamides containing a single DFMP group were discovered to be potent inhibitors of PTP1B. Investigation of SAR led to the identification of compounds with IC_{50} or K_i values in the low nanomolar range.

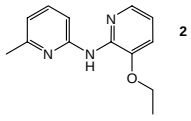


Mandelate racemase has been studied as a paradigm for enzyme-catalyzed abstraction of a proton from carbon acids with relatively high pK_a values. 1,1-Diphenyl-1-hydroxymethylphosphonate is a substrate–intermediate–product analogue and is a modest competitive inhibitor of the enzyme ($K_i = 1.41 \pm 0.09$ mM), suggesting that simultaneous binding of the two phenyl groups obviates mimicry of the *aci*-carboxylate function of the intermediate by the phosphonate group.



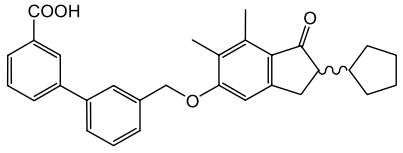
5k

The SAR of a series of potent sulfonamide hydroxamate TACE inhibitors bearing a butynyloxy P1′ group was explored. In particular, compound **5k** has excellent in vitro potency against TACE enzyme and in cells, and oral activity in an in vivo model of TNF-α production and a collagen-induced arthritis model.

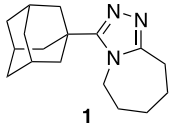


2

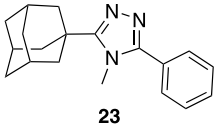
The metabotropic glutamate subtype 5 (mGlu5) receptor has been implicated in a number of CNS disorders. Herein, we report on the discovery, synthesis, and biological evaluation of dipyridyl amines as small molecule mGlu5 antagonists.



The metabotropic glutamate receptor 2 has been implicated in a number of central nervous system disorders. Herein, we report on the discovery, synthesis, and biological evaluation of biphenyl-indanones as potent small molecule mGluR2 allosteric modulators.

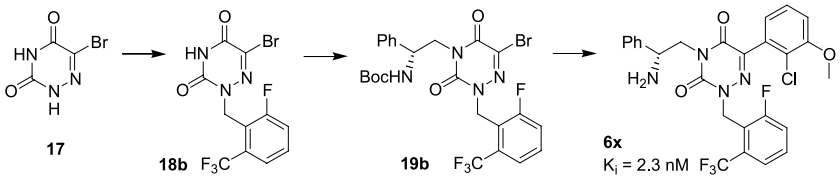


1

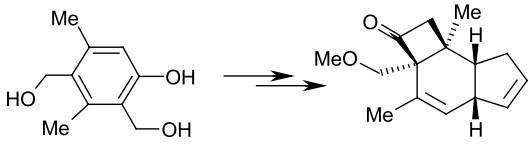


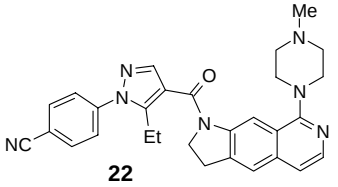
23

The synthesis and biological activity of selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 are reported.

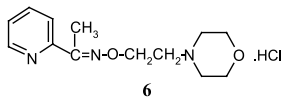


Several efficient synthetic routes for 2-, 4-, and 6-aryl-1,2,4-triazine-3,5-diones were developed. Derivatives were synthesized and studied as gonadotropin-releasing hormone antagonists in an effort to understand structure–activity relationships of the monocyclic compounds.

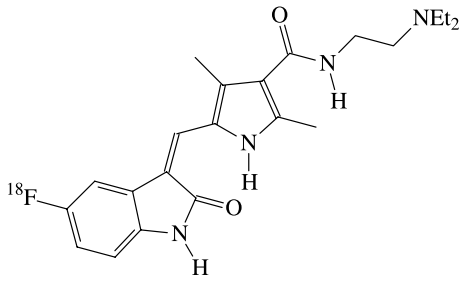




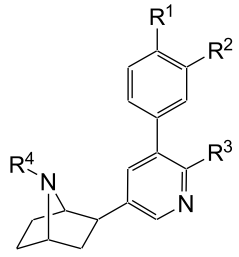
A series of novel 8-piperazinyl-2,3-dihydropyrroloisoquinolines, e.g., compound **22**, was prepared showing high affinity and selectivity for 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors combined with favourable pharmacokinetic properties.

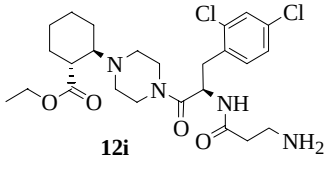


Various oxime ether derivatives of 2-acetylpyridine and 2-acetylfuran series have been synthesised. O-Alkylation of oximes by various alkylaminoethyl halides gave the corresponding oxime ether derivatives. The antiamoebic activities of these compounds were evaluated by microdilution method against *HM1:IMSS* strain of *Entamoeba histolytica*. Four compounds showed lower IC$_{50}$ values than metronidazole. Moreover, compound **6** showed the most promising antiamoebic activity (IC$_{50}$ = 0.5 μM vs IC$_{50}$ = 1.9 μM of metronidazole) in the 2-acetylpyridine series.



[^{18}F]SU11248, [^{18}F]**1**





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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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