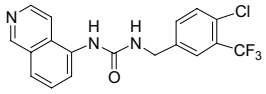
ELSEVIER

Bioorganic &
Medicinal
Chemistry
Letters

Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 12, 2004

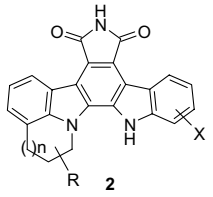
Contents

COMMUNICATIONS



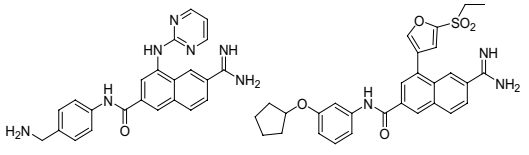
7k

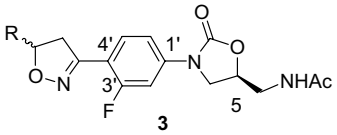
N-Isoquinolin-5-yl-*N*′-aralkyl-ureas and -amides were developed as potent ligands of human vanilloid receptor 1. *N*-Isoquinolin-5-yl-*N*′-(4-chloro-3-trifluoromethylbenzyl)urea **7k** exhibited subnanomolar binding affinity and upon capsaicin challenge, behaved as a full functional antagonist at low nanomolar concentrations.



2

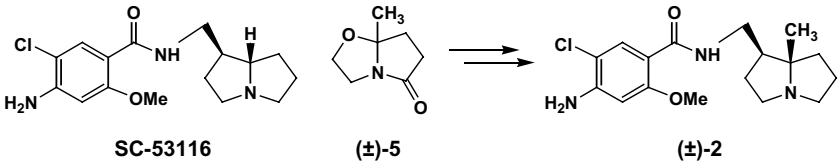
A novel series of 1,7-annulated indolocarbazoles was synthesized and their D1/CDK4 inhibitory and antiproliferative activity were evaluated.



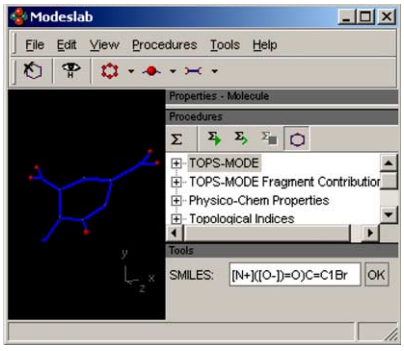


3

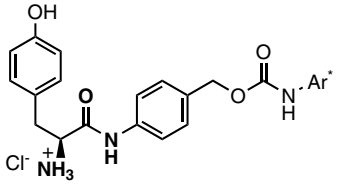
A series of oxazolidinone antibacterial agents containing a 5-substituted isoxazol-3-yl moiety were synthesized via a nitrile oxide [3+2] dipolar cycloaddition reaction. These compounds were screened against a panel of susceptible and resistant Gram-positive organisms. Several analogs from this series were comparable to or more potent than linezolid in vitro.



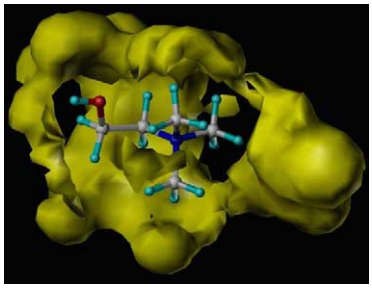
Pyrrolizidine (±)-**2**, the bridgehead-methyl analog of **SC-53116**, was prepared and evaluated for 5-HT_4 agonism activity in the rat tunica muscularis (TMM) mucosae assay. Compound (±)-**2** has an EC_{50} of 449 nM in the TMM assay, as compared to 23 nM for **SC-53116**, and 66 nM for the racemate of **SC-53116**.

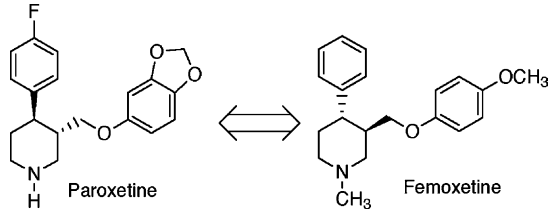


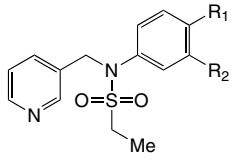
The TOPological Sub-Structural Molecular Design (TOPS-MODE) approach has been applied to the study of the adenosine kinase inhibitory activity of pyrrolo[2,3-*d*]pyrimidine nucleoside analogues. A model is able to describe around 77% of the variance in the experimental activity of 32 analogues of these compounds was developed with the use of the mentioned approach.



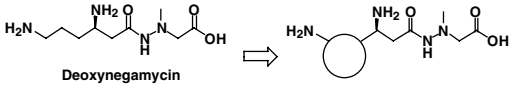
The viability of a three-component enzyme activated image contrast system was demonstrated using a family of tyrosine–chromophore conjugates linked by an inert spacer.



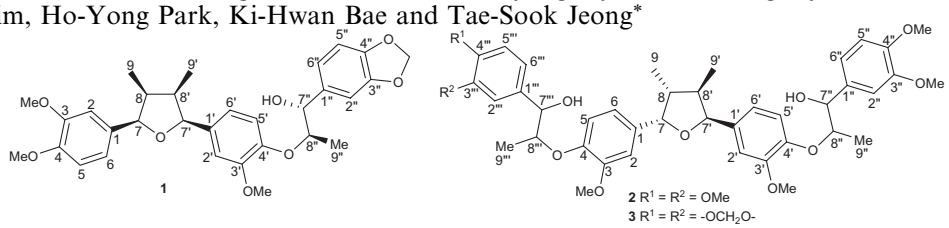




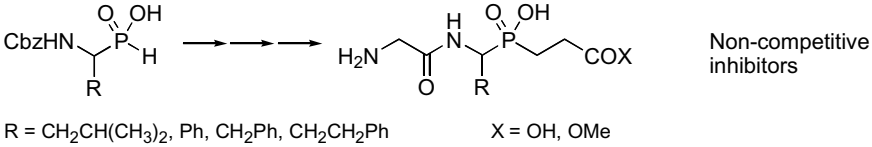
The structure–activity relationship of a subtype selective mGlu2 potentiator, LY181837 is explored.



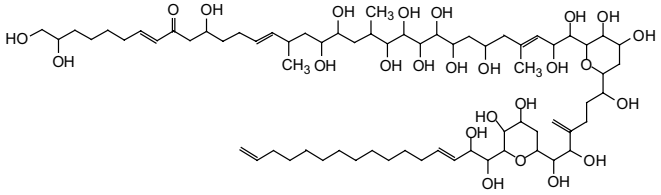
Methods were developed to synthesize a number of conformationally restricted β-amino acids. Incorporation of these β-amino acids into deoxynegamycin template has resulted in structurally novel and conformationally restricted analogs. These analogs were evaluated in whole cell assays and as inhibitors of cell-free protein synthesis to assess their antibacterial properties.



Compounds **1**–**3** isolated from the methanolic extracts of *Saururus chinensis* root inhibited hACAT-1 and hACAT-2 activities. The EtOAc-soluble fraction, which contained compounds **1**–**3**, of methanol extracts of *S. chinensis* exhibited strong cholesterol-lowering effect in high cholesterol-fed mice.

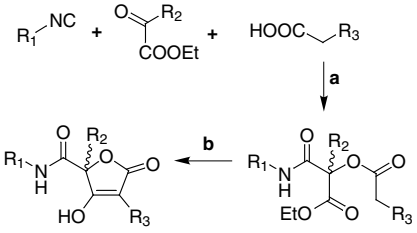


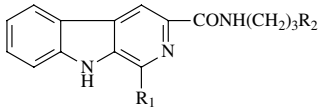
Phosphinic tripeptides were designed and synthesised as transition state analogue inhibitors of cathepsin C. Surprisingly, they revealed noncompetitive mode of binding with different kinetics for *C*-terminal acids comparing to the corresponding esters.



Lingshuiol (**1**)

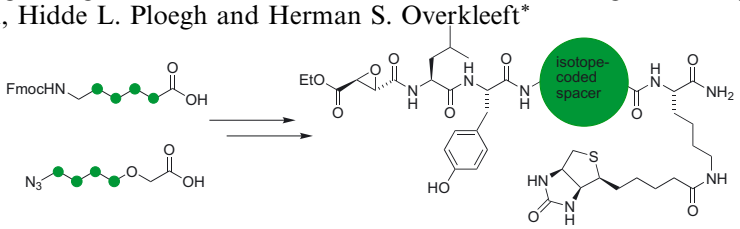
A novel polyhydroxy compound with a linear carbon-chain, lingshuiol (**1**), had been isolated from the cultured marine dinoflagellate *Amphidinium* sp. It possessed powerful cytotoxic activity against A-549 and HL-60 with the IC_{50} of 0.21 and 0.23 μM, respectively.



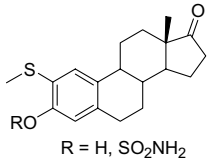


R_1 = H, CH_3
R_2 = NH_2, NHC(=NH)NH_2

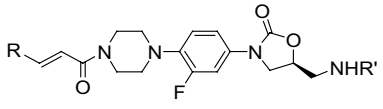
Four new β-carboline derivatives were synthesized and their effects on Tat–TAR interaction as well as to HIV-1 in MT4 cells were evaluated. Furthermore, capillary electrophoresis was used to study the binding specificity of compound **6** to TAR RNA in inhibiting the Tat–TAR interaction.



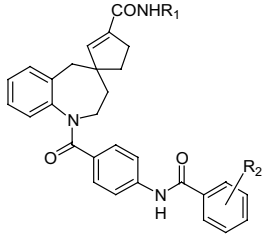
The synthesis of two new deuterium-containing spacers and their incorporation into quantitative functional proteomics tools, aimed at the cathepsin family of cysteine proteases is described. It is shown that the labeling pattern of these isotope-coded probes is not altered, as compared to the parent compound.



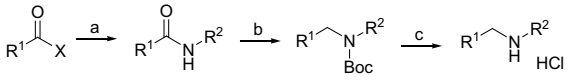
A flexible, direct, high yielding synthesis of 2-alkylsulfanyl estrogens has been developed. 2-Methylsulfanyl estradiol (2-MeSE2) and its 3-*O*-sulfamate derivative display a similar anti-proliferative activity to 2-methoxyestradiol (2-MeOE2).



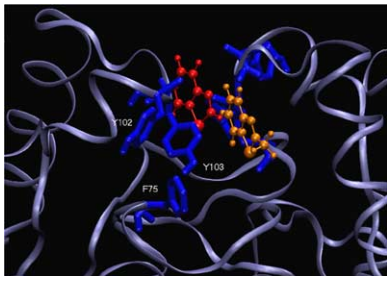
A number of substituted piperazinyl oxazolidinone derivatives have been synthesized and their antibacterial activities were evaluated. A systematic SAR was carried out to get highly potent analog of oxazolidinone.

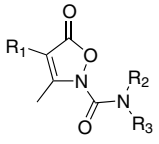


A series of spirobenzazepines have been synthesized and evaluated as selective V_{1a} and V_{1a}/V_2 dual vasopressin receptor antagonists.

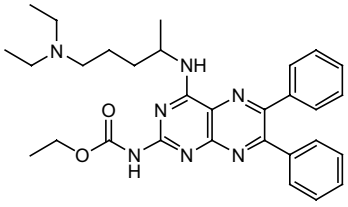


Collections of secondary amines for compound library generation can be efficiently prepared by amide reduction using BH_3–THF or Red-Al followed by brief methanolysis, trapping with di-*tert*-butyl dicarbonate, and deprotection with HCl. The sequence requires no chromatography or distillation and provides multi-gram quantities of pure HCl salts in a short time.

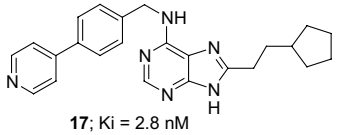




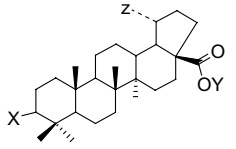
A series of (5-(2*H*)-isoxazolonyl ureas were developed as nanomolar inhibitors of hormone-sensitive lipase, an enzyme of potential importance in the treatment of diabetes.



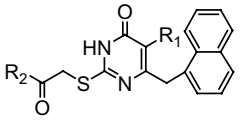
The preparation of a new 2-carbamoyl pteridine, its activity data against FtsZ from *M. tuberculosis* (Mtb), and in vitro antibacterial data against Mtb strain H37Ra are presented.



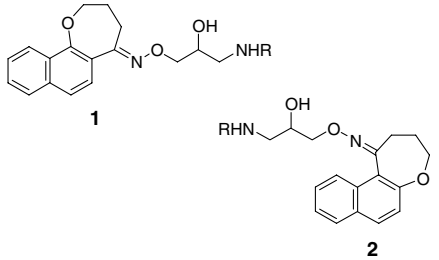
17; Ki = 2.8 nM

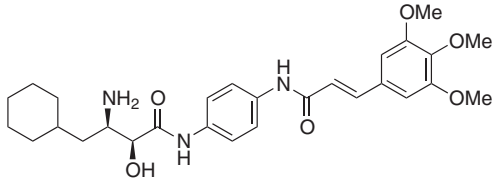


X = -OCO-R^1/-N=CH-R^2/=N-NH-R^3/-NH-NH-R^4;
Y = $COCH=CH_2$; Z = $CH(=CH_2)CH_3$/$CH(CH_3)_2$

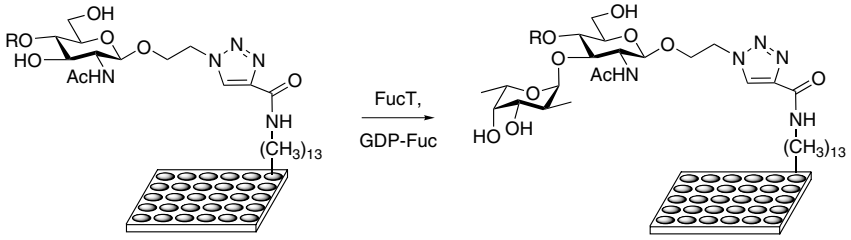


R_1= Me, Et, iPr
R_2= Ph, (4'-Me)Ph, (4'-OMe)Ph, (4'-F)Ph, (4'-Cl)Ph, Me, OMe, OEt

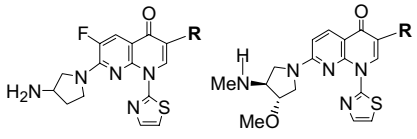




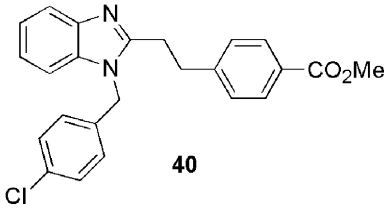
The rational design and synthesis of β-amino-α-hydroxy amide derivatives as reversible inhibitors of methionine aminopeptidase-2 (MetAP2) with anti-proliferative activity against human umbilical vein endothelial cells (HUVECs) is described.



Inhibitors to fucosyltransferase were screened in a high-throughput manner using a noncovalent carbohydrate microarray strategy and four nanomolar inhibitors were identified.



The synthesis and SARs of various 3-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines as antitumor agents are reported. The series of novel 3-substituted analogs showed good cytotoxic activity against murine P388 leukemia while antibacterial activity of these 3-substituents was significantly less than 3-carboxy group, implying the discrepancy between antitumor SARs and antibacterial SARs.



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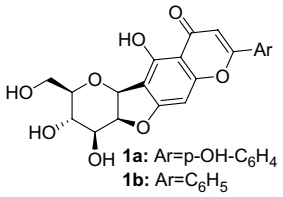
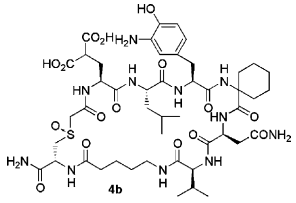
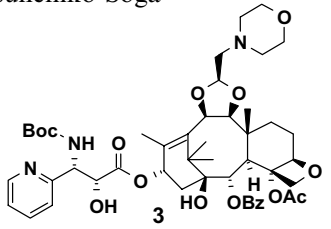


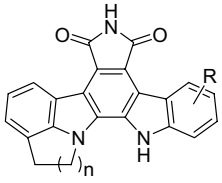
The first total synthesis of structurally unique flavonoids **1a** and **1b** is described. These compounds showed very strong anti-inflammatory effect against delayed hypersensitivity in a mouse model.



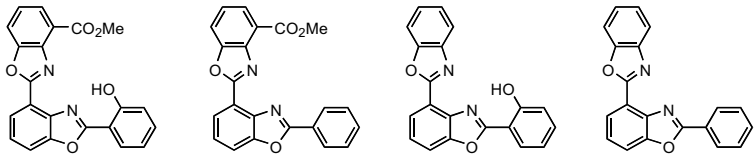
The synthesis of orthogonally protected L-3-aminotyrosine suitable for solid phase peptide synthesis and its first use for the preparation of a series of nonphosphorylated Grb2-SH2 domain antagonists were reported. The 3-aminotyrosine containing sulfoxide-cyclized hexapeptide **4b** exhibited potent Grb2-SH2 domain binding affinity ($IC_{50} = 50$ nM), with only six residues free of phosphotyrosine or phosphotyrosine mimics.



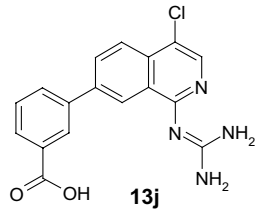
To improve the metabolic stability of **3**, new taxane analogues were synthesized. Most of the synthetic compounds maintained antitumor activity and were scarcely metabolized by human liver microsomes. And some compounds exhibited potent antitumor effects against B16 melanoma BL6 in vivo by both iv and po administration similarly to **3**.



A series of novel 1,7-annulated indolocarbazoles was prepared and evaluated for kinase inhibitory activity.

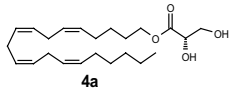


Three new analogs of UK-1 have been synthesized and their efficacies as topoisomerase II inhibitors have been determined. Results show that UK-1 and two of these analogs are catalytic inhibitors of topo II and identifies a critical structural motif necessary for enzyme inhibition.



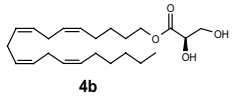
13j

A series of 1-isoquinolinylguanidines are selective inhibitors of uPA. Compound **13j** (UK-356,202) combines excellent potency and selectivity, and has been selected as a candidate for clinical evaluation.



4a

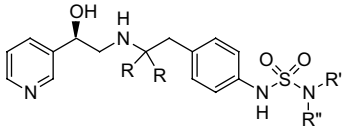
E_{max} (%basal±SE) 278 ± 21
-log EC_{50} ± SE 4.4 ± 0.2



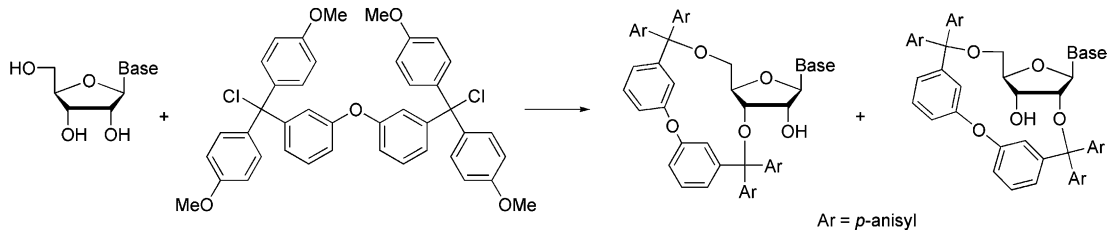
4b

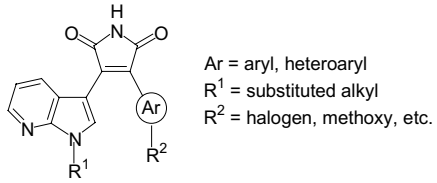
E_{max} (%basal±SE) 301 ± 8
-log EC_{50} ± SE 4.6 ± 0.1

Novel derivatives of arachidonyl alcohol were synthesized and evaluated for their CB1 receptor activity by [^{35}S]GTP$_\gamma$S assay using rat cerebellar membranes.

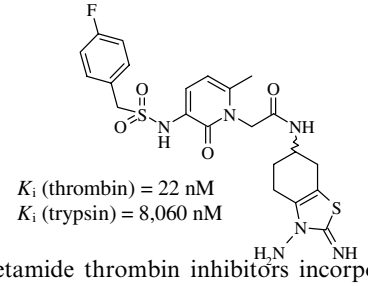


A series of sulfamide-based analogs related to L-796568 were prepared and evaluated for their biological activity at the human β_3-adrenergic receptor (AR). This modification allows for a significant reduction in molecular weight, while maintaining single-digit nanomolar potencies at the β_3-AR and high selectivities versus the β_1- or β_2-AR.

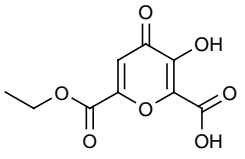




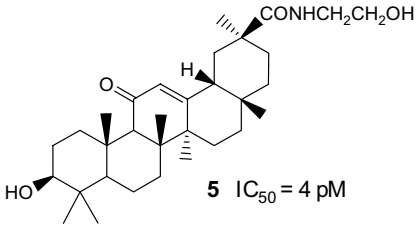
A novel series of 3-(7-azaindolyl)-4-(aryl/heteroaryl)maleimides was identified as potent GSK-3β inhibitors with excellent selectivity over PKC-βII (>300-fold), as well as a broad panel of other protein kinases. The compounds were effective in a cell-based functional assay.



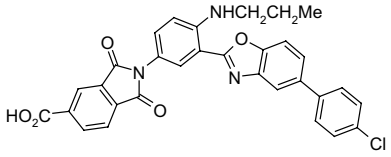
The optimization of 3-amino-2-pyridinone acetamide thrombin inhibitors incorporating weakly basic heterobicyclic P_1-arginine side-chain mimetics is described.



The monoethyl ester of meconic acid was discovered as novel inhibitor of HCV NS5B RNA dependent RNA polymerase. SAR around this molecule will be presented to provide an improved basis for structure-based ligand design.

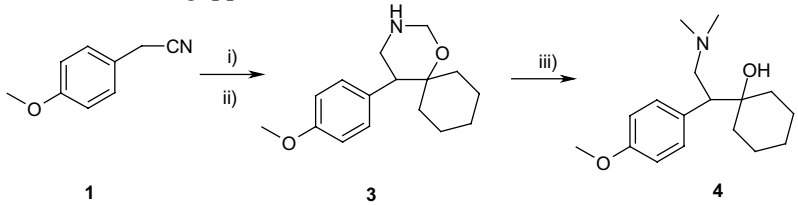


The discovery of a novel potent selective inhibitor of 11β-HSD2 from a series of amides using 18β-glycyrrhetinic acid as a template is described.



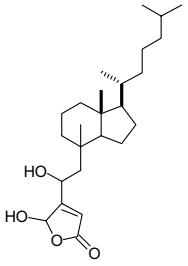
A novel class of 2,3-dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acids are described as inhibitors of the *endo*-β-glucuronidase heparanase. Several of the compounds display potent heparanase inhibitory activity (IC_{50} 200–500 nM).

Dynamin 1 GTPase contains a pleckstrin homology (PH) domain that interacts with lipids. We report a series of simple lipid-like molecules that display moderate inhibitory activity. Inhibitory activity is linked to chain length and quaternarization of the terminal amine. A change in the counterion, Cl versus Br or I, had little effect on potency. However, introduction of a hydrophobic collar proximal to the charged site was beneficial to dynamin GTPase inhibitory action.

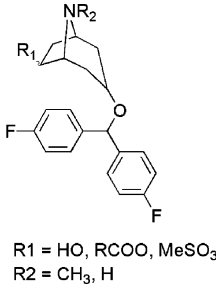


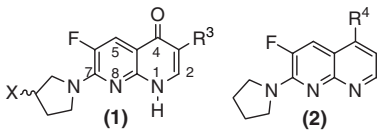
A novel synthetic method was developed for the synthesis of venlafaxine using inexpensive reagents. An improvement in the method, in the yield was achieved for the conversion of the venlafaxine. This is an improved version, simple and efficient method for the large-scale synthesis of venlafaxine.

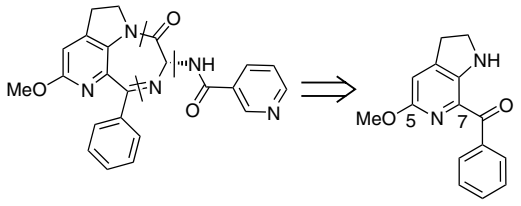
QSAR study on the tumor-associated transmembrane carbonic anhydrase IX (CA IX) isoenzyme has been made using a large pool of distance-based topological indices: W, Sz, PI, $^{0}\chi$, $^{1}\chi$, $^{2}\chi$, $^{0}\chi^{v}$, $^{1}\chi^{v}$, and $^{2}\chi^{v}$. A combined set of 32 aromatic and heterocyclic compounds, including the six clinically used derivatives: acetazolamide, methazolamide, ethoxyzolamide, dichlorophenamide, dorzolamide, and brinzolamide are used for this purpose. The results have shown that the inhibition of the tumor-associated isoenzyme IX with aromatic and heterocyclic sulfonamides can be modeled excellently in multiparametric regression after introduction of indicator parameters. The predictive power of the models is discussed using probable error of correlation (PE), variance-inflation factor (VIF), and cross-validation parameters: PRESS, SSY, r^{2}_{cv}, S_{PRESS}, and PSE. This is the first report on QSAR study on inhibition of tumor-associated isoenzyme IX.

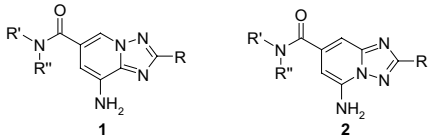


Potent dysidiolide analogs were synthesized by structural hybridization of dysidiolide and vitamin D_3. These analogs exhibited strong inhibitory activity toward dual-specificity phosphatase Cdc25A (IC_{50}=0.44–0.89 μM).

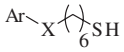






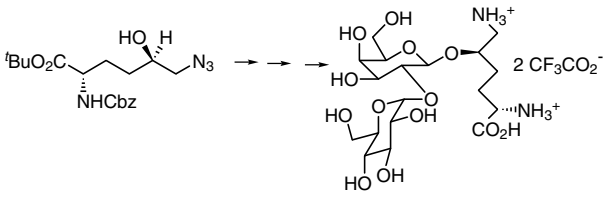


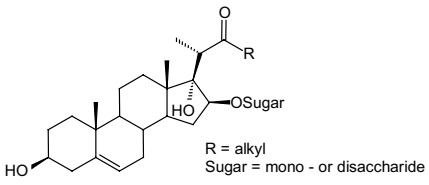
The hydrogen bond donor and acceptor strengths of two arrays of isomeric triazolopyridines derivatives **1** and **2** was analysed and compared to their affinities towards adenosine receptor subtypes.



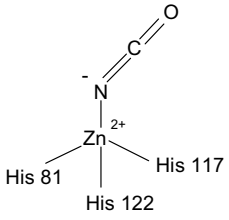
6 : Ar = Ph, X = -NHCO-
17: Ar = 3-biphenyl, X = -NHCO-
21: Ar = 3-quinoline, X = -NHCO-
24: Ar = 2-naphthalene, X = -CONH-
25: Ar = 2-benzofuran, X = -CONH-

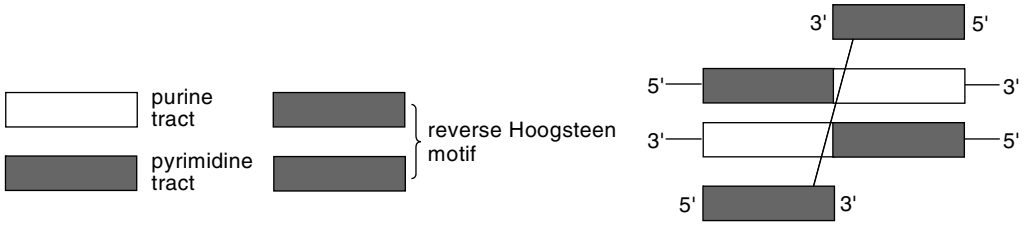
A series of thiol-based SAHA analogues was designed and synthesized. Compound **6**, in which the hydroxamic acid of SAHA was replaced by a thiol, was found to be as potent as SAHA, and optimization of this series led to the identification of HDAC inhibitors (**17**, **21**, **24**, and **25**) more potent than SAHA.

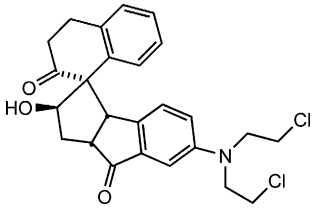




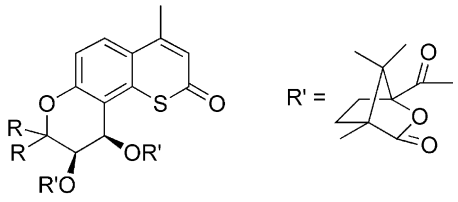
A number of analogues of a potent antitumor saponin OSW-1 were synthesized and tested for cytotoxicity.



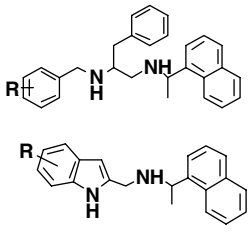


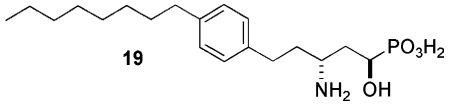


A spirocyclic agent equipped with alkylative functionality was prepared and demonstrated its ability to alkylate specific bulged sequences in a hairpin oligonucleotide substrate.

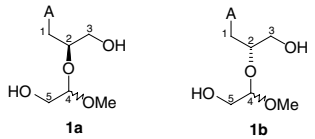


9a: R = CH_3
b: R = H





The in vitro and in vivo properties of **19** support a connection between S1P receptor agonism and immunosuppressive efficacy.



A new synthesis of chiral acyclic nucleoside and nucleotide analogues starting from D(−)- or L(+)-riboses was proposed. Antiviral properties of the synthesized compounds towards a pox virus family were evaluated.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by ***Indraneel Ghosh,*** *Department of Chemistry, University of Arizona.* The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].

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ISSN 0960-894X