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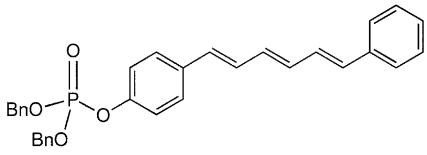
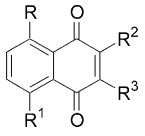
Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 5, 2004

Bioorganic & Medicinal Chemistry Letters

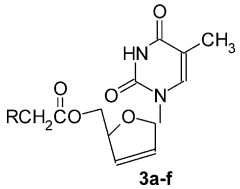
Contents

COMMUNICATIONS

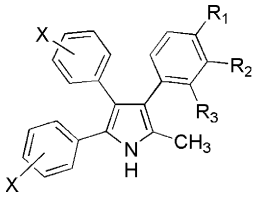




A series of 1,4-naphthoquinone derivatives were synthesized and found active against a number of fungal disease causative species and Walker 256 carcinoma cell lines.

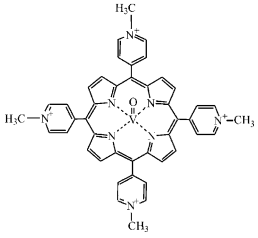


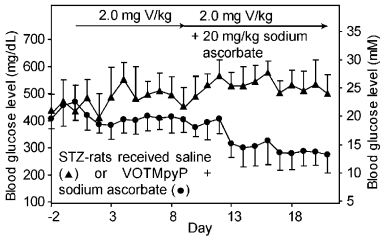
A series of amino acid ester prodrugs of stavudine were synthesized with ciprofloxacin, norfloxacin, isoniazide, pyrazinamide, piperazine and dimethylamino acetic acid in an effort to enhance spectrum of chemotherapeutic properties for the effective treatment of HIV/AIDS.

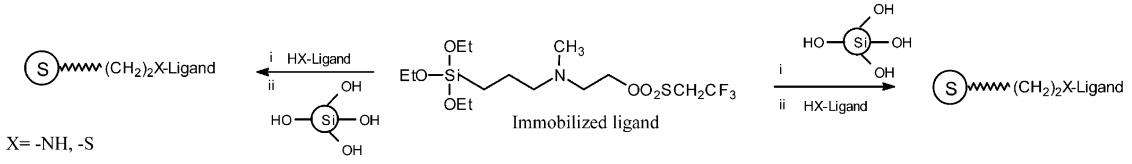


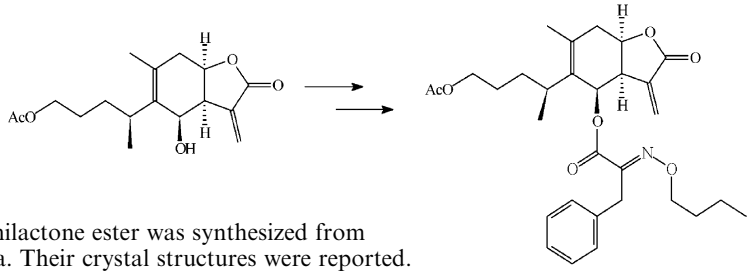
Synthesis and antihyperglycemic activity of various 2-methyl-3,4,5-triaryl-1*H*-pyrroles is described.

VOTMpyP with the $VO(N_4)$ coordination mode, was found to have a potent insulinomimetic activity on the basis of in vitro and in vivo experiments. When the complex was given simultaneously with sodium ascorbate, the high blood glucose levels of type 1 diabetic model STZ-rats were lowered by synergistic effect, probably sustaining the vanadyl state by means of ascorbate distributed in the organs and tissues of animals. This is the first finding on not only the insulinomimetic vanadyl–porphyrin complex but also the occurrence of a synergistic effect of VOTMpyP and sodium ascorbate to lower the high blood glucose levels in diabetic animals.

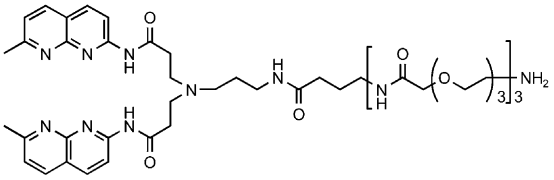




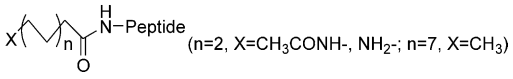




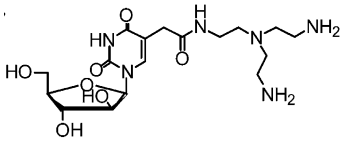
(2-*O*-butyloxime-3-phenyl) propionyl-1-*O*-acetylbritannilactone ester was synthesized from 1-*O*-acetylbritannilactone isolated from *Inula britanni*ca. Their crystal structures were reported. Both compounds inhibited the growth of human HL-60, Bel-7402 cell lines.



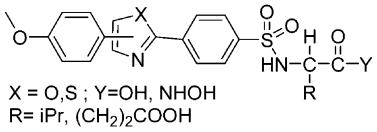
A 27-mer DNA duplex containing a G–G mismatch could be detected at 1 nM concentration by the surface where naphthyridine dimer was immobilized through three poly(ethylene oxide) linker units.



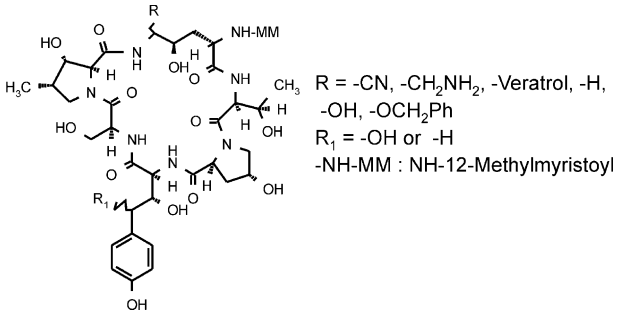
We designed and synthesized novel lipid–peptide hybride compounds with antibacterial activity and characterized the important structural parameters for the activity.

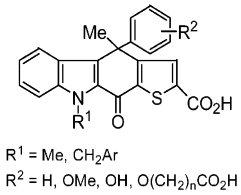


An oligodeoxyribonucleotide (ODN) containing three C5-substituted arabinofuranosyluracils was synthesized by the post-synthetic modification method. The modified ODN could induce RNase H activity and was resistant against nuclease.

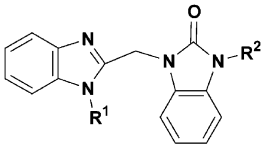


The synthesis and evaluation of thiazolyl- and oxazolylbenzenesulphonamides are described.



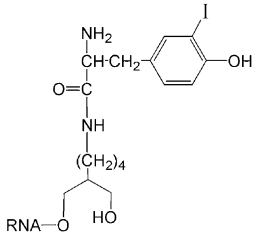


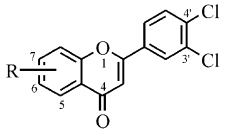
The carbazolothiophene compounds show inhibition against the endothelin-1 induced increase of intracellular calcium ion concentration.



2

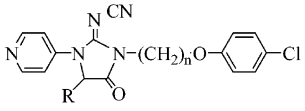
Structure–activity relationships for a series of benzimidazol-2-one-based inhibitors of respiratory syncytial virus are described. These studies focused on structural variation of the benzimidazol-2-one substituent, a vector inaccessible in a series of benzotriazole derivatives on which **2** is based, and revealed a broad tolerance for substituent size and functionality.



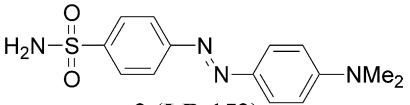


5e : R=7-OMe
6e : R=5-OMe
7e : R=7-OH

A series of chrysin derivatives were prepared from 2,4-, 2,6-dihydroxyacetophenones and 2-hydroxyacetophenone in 2 to 4 steps, respectively. The inhibitory activities of chrysin derivatives were determined by measuring prostaglandin production of RAW 264.7 cells treated with lipopolysaccharide. We found that chrysin derivatives with 3′,4′-dichloro substituents (**5e**, **6e** and **7e**) exhibited the strongest activity among them.

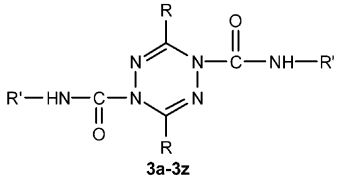


A series of 5-substituted 2-cyanoimino-4-imidazodinone and 2-cyanoimino-4-pyrimidinone derivatives were synthesized and their anticancer cytotoxicity was evaluated in in vitro assay. One of the derivatives, compound **11** exhibited the most potent activity with IC_{50} in the nanomolar range.



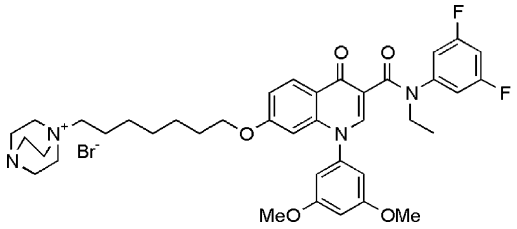
2 (LB-152)

Phenylazo benzenesulfonamide **2** (**LB-152**) was synthesized and evaluated for inhibition of $A\beta_{40}$ aggregation and neurotoxicity.

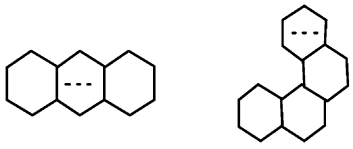


3a-3z

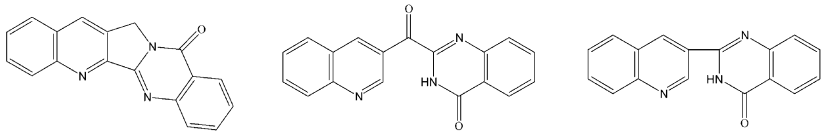
Fifty-five compounds were prepared by the new reactions and their structures were determined by X-ray analysis. Their antitumor activities in vitro were evaluated. The results show *s*-tetrazine derivative especially 1,4-dihydro-*s*-tetrazine is a kind of compound which possesses potential antitumor activities and that warrants further investigation.

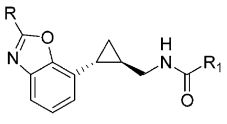


The synthesis, ASBT inhibition and serum cholesterol lowering effect of novel 4-oxo-1-phenyl-1,4-dihydroquinoline derivatives are reported.

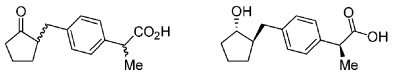


Aromatic stabilities of acenes and helicenes, which are responsible for their biological, environmental and cancerous behavior have been modeled using a newly introduced Sadhana (Sd) and A indices. The results are compared with those obtained from PI (Padmakar-Ivan) index. The regression analysis has shown that excellent results are obtained by considering acenes and helicenes as separate classes of isomeric benzenoid hydrocarbons. Also that out of the three indices used (A, Sd, PI), the A index gave better results.



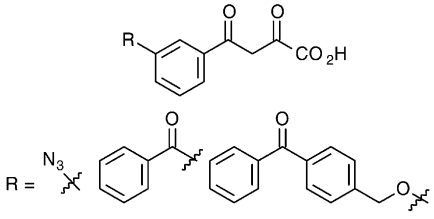


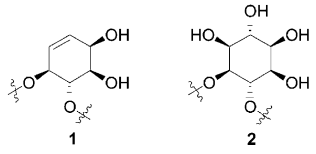
A novel series of benzoxazole derivatives was synthesized and evaluated as melatoninergic ligands. The binding affinity of these compounds for human MT_1 and MT_2 receptors was determined using 2-[^{125}I]-iodomelatonin as the radioligand. The results of the SAR studies in this series led to the identification of compound **28**, which exhibited better MT_1 and MT_2 receptor affinities than melatonin itself. This work also established the benzoxazole nucleus as a melatoninergic pharmacophore, which served as an isosteric replacement to the previously established alkoxyaryl core.



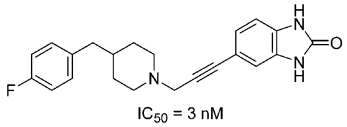
1 : Loxoprofen **5a : (2S,1'R,2'S)-*trans* alcohol**
Active Metabolite

The four *trans*-alcohol metabolites and a mixture of the *cis*-alcohol metabolites of loxoprofen were evaluated for potency and selectivity of inhibition of COX-2 over COX-1. The (2*S*,1′*R*,2′*S*)-*trans*-alcohol metabolite was found to be the most potent inhibitor of COX-2 and to cause a nonselective inhibition of COX-2 and COX-1 in both enzyme and human whole blood assays.

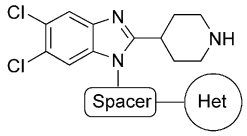


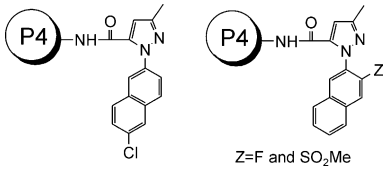


The synthesis, structure, and biological evaluation of oligomers whose structural motifs are based on conduritol-F (**1**) and *muco*-inositol (**2**) are reported.

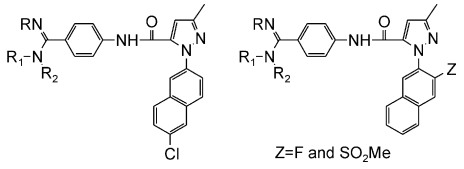


The synthesis and SAR of a variety of benzylpiperidinyl-acetylenes with NR2B receptor selectivity is described.

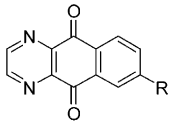




A variety of P4 motifs have been examined for optimization of the 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide-based factor Xa inhibitors. Highly potent factor Xa inhibitors with desired in vitro anticoagulant activity and excellent oral PK profiles have been discovered.

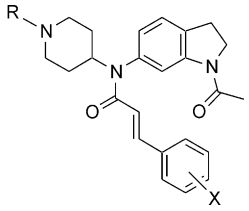


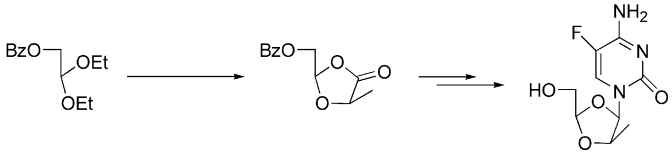
Using *N*,*N*-dialkylated benzamidines as the novel P4 motifs, highly potent and selective factor Xa inhibitors with desired in vitro anticoagulant activity, excellent oral bioavailability and long half-life have been discovered.

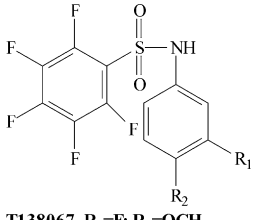


R:-CH_2NR_2
4 Target Compounds

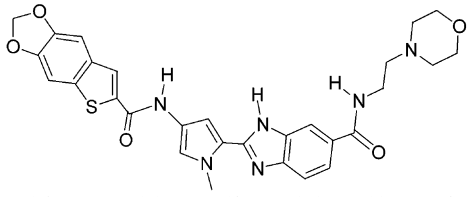
A series of benzo[*g*]quinoxaline-5,10-dione derivatives carrying a 7-dialkylaminomethyl substituent was synthesized and their in vitro cytotoxic activities were evaluated against four human cancer cell lines (HCT-15, SK-OV-3, MD-MB-468 and T-47D). The most active compound **9d** showed cytotoxic activity comparable to that of doxorubicin against HCT-15 cancer cell line.



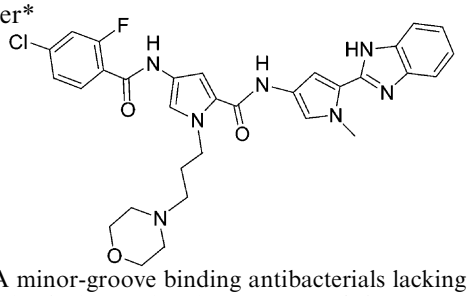


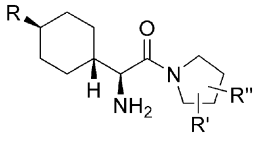


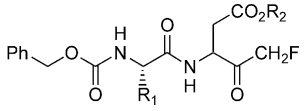
T138067, R_1=F; R_2=OCH_3
[^{11}C]T138067, R_1=F; R_2=O$^{11}CH_3$
[^{18}F]T138067, R_1=^{18}F; R_2=OCH_3

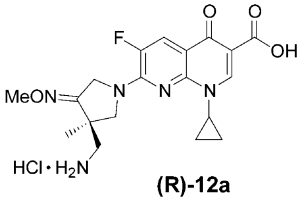


Novel DNA minor-groove binding ligands with a promising antibacterial profile are described. Apart from excellent in vitro potency against multiple Gram-positive bacteria including drug-resistant strains, a small subset of compounds was active against Gram-negative bacteria.

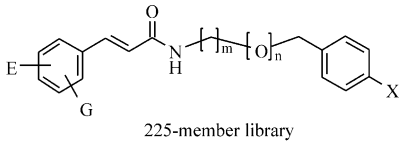






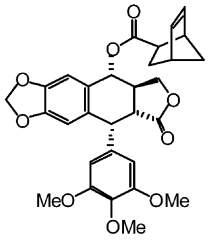


(R)-12a



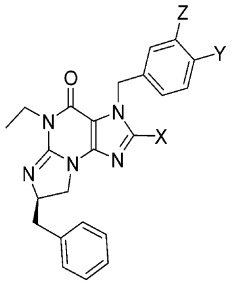
225-member library

E, G = H, OH, alkyl., alkoxy, NO_2, CN, etc.; X = H, Cl, Br; $m = 1, 2, 3$, $n = 0, 1$.

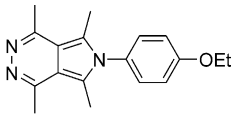


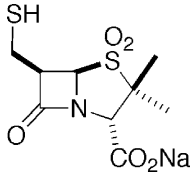
Diverse norbornenecarboxylate esters of podophyllotoxin and diastereoisomers have been prepared through Diels–Alder cycloaddition, by treating their dienophilic acrylates with cyclopentadiene, some of them showing IC_{50} values about 4 nM, that represented an improvement in potency with respect to the natural reference drug.

shogaols

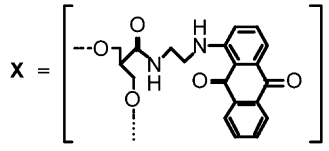


A potent and selective series of phosphodiesterase 5 inhibitors was discovered (PDE5 $IC_{50} = 1.3–11.0$ nM, PDE6/5 = 116–600).

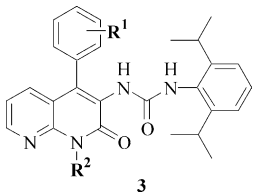




3'-TCTTTTTTTCTT**X**C-5' **GK-302**

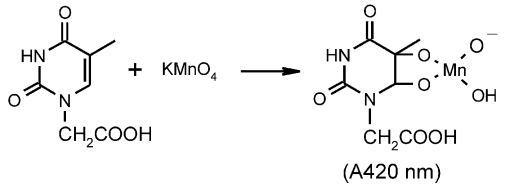


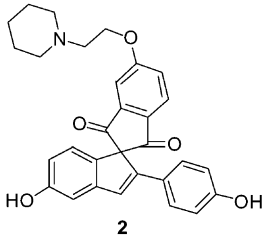
Novel TFO bearing an intercalator forms a stable triplex with a purimidine-gapped polypurine of dsDNA.



3

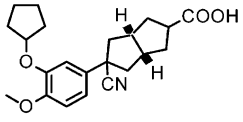
The synthesis and structure–activity relationships of *N*-phenyl-*N*′-[3-(4-phenylnaphthylidinoyl)]urea derivatives **3** as a novel structural class of potent ACAT inhibitors are described.



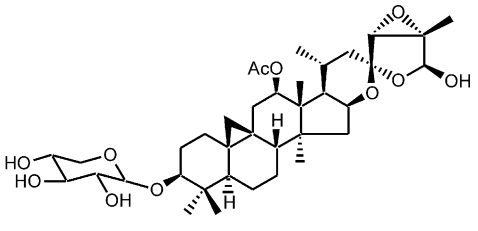


2

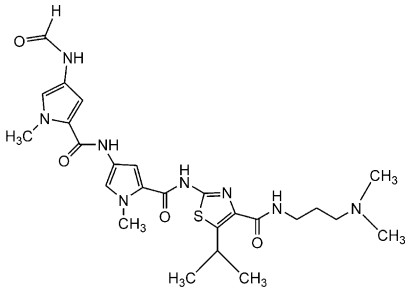
A series of 2-phenylspiroindenediones (e.g., **2**) was prepared. The spiroindenediones were found to be less active than the corresponding spiroindenes as estrogen receptor ligands and failed to demonstrate the receptor subtype selectivity that molecular modeling predicted.



Optimization of the spatial arrangement of the three pharmacophores is attempted using a bicyclo[3.3.0]octane template. Synthesis and biological evaluation is reported.



1 Actein (26S:26R = 3:1)



5

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 htB1 (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htB1 (center) allows for functional selection against thrombin (right).

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