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Chemistry
Letters

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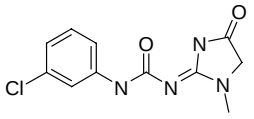
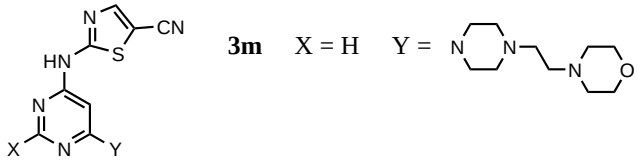
Contents

ARTICLES

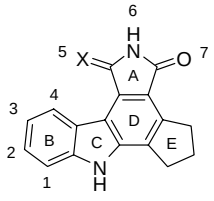


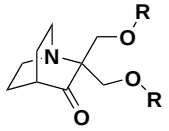
Structure–activity relationship of the mGluR5 antagonist fenobam is reported.

Pyrimidino-thiazolyl carbonitriles were prepared that are potent VEGFR-2 (KDR) kinase inhibitors. The modification of lead structures resulted in **3m** which exhibited the best overall profile in KDR inhibitory activity, iv/po pharmacokinetics, and reduced hERG affinity.

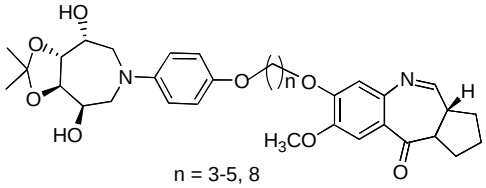


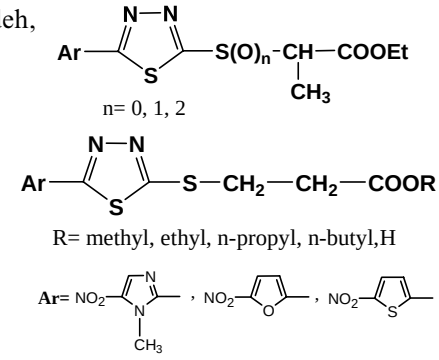
A series of novel pyrrolocarbazole lactams was identified as potent PARP-1 inhibitors in vitro and in a PC12 cellular NAD^+ depletion assay. The SAR trends of substituents at the 3-position, as well as the effect of blocking the indole or lactam NH-groups of the template by methylation or formylation, are discussed in relation to molecular modeling studies.

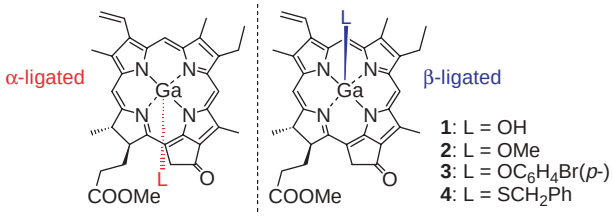


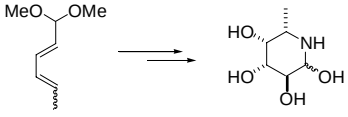


Several 2,2-disubstituted quinuclidinone analogs were prepared and evaluated as anti-proliferative agents.

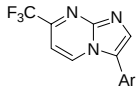




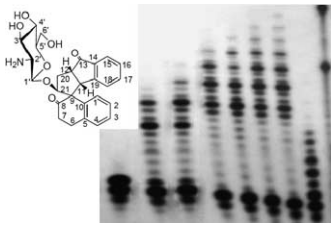




The L-*fuco*-nojirimycin was synthesised starting from asymmetric hetero-Diels–Alder reaction with chiral D-ribose nitroso-dienophiles. It appears as a very potent α-L-fucosidase inhibitor (K_i = 1 nM).

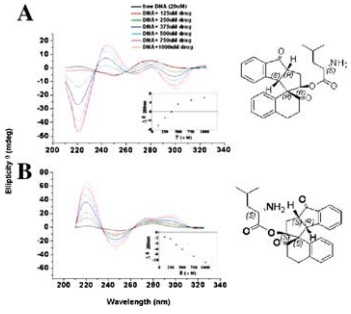


Imidazo[1,2-*a*]pyrimidines are $GABA_A$ receptor benzodiazepine binding site ligands which can exhibit functional selectivity for the α_3 subtype over the α_1 subtype. SAR studies to optimize this functional selectivity are described.

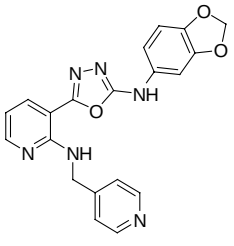


The designed chiral spirocyclic helical compounds have been found to have strong stimulation effect on DNA triplet repeat strand slippage synthesis. Their stimulation activities on DNA strand slippage show that they may bind to or induce the formation of a bulge or related structure during in vitro replication of DNA triplet repeats.

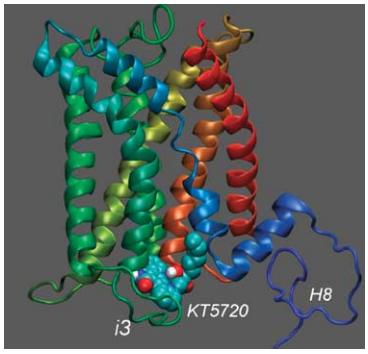
Synthesis of chiral spirocyclic helical compounds containing leucine that mimic the core of DNA bulge binder NCSi-gb has been described. The interaction between the compounds and DNA was studied by circular dichroism (CD). The results suggested that the two synthetic diastereoisomers **7** and **8** specifically targeted the bulge site of DNA and induced conformational change of bulged DNA greatly.

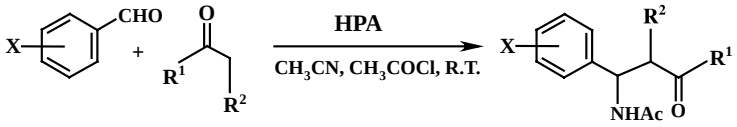


The synthesis, SAR studies, and pharmacokinetic properties of oxadiazole based tubulin inhibitor class are reported. This class of compounds binds to the colchicine site on tubulin and has antimitotic activity with nanomolar potency against tumor cell lines including cells with MDR phenotype.

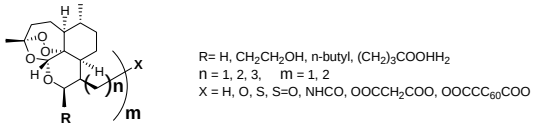


EC_{50} (MDR cell line) = 7.8 nM

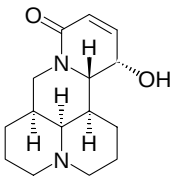




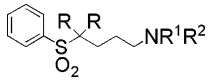
A new and important catalytic activity of HPAs (cheap, commercially available, noncorrosive, and environmentally benign compounds) has been studied for the synthesis of β-acetamido ketones in excellent yields under mild reaction conditions.



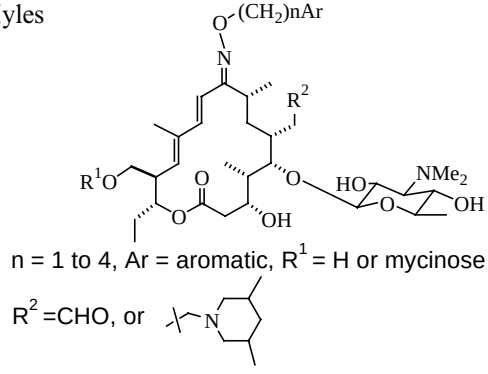
Nonacetal-type derivatives of artemisinin and their novel dimers were synthesized and some of them showed potent in vivo antiangiogenic activity on chorioallantoic membrane higher than or comparable to those of fumagillin and thalidomide.

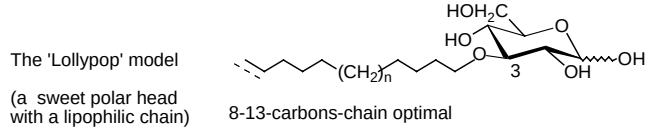


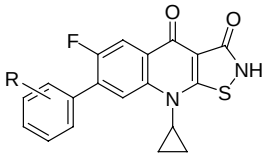
(+)-12α-Hydroxysophocarpine, a new quinolizidine alkaloid was isolated from the roots of *Sophora flavescens*, together with 10 known quinolizidine alkaloids. (+)-Oxysophocarpine, (−)-sophocarpine, (+)-lehmannine and (−)-13,14-dehydrosophoridine showed significant anti-HBV activity in vitro.



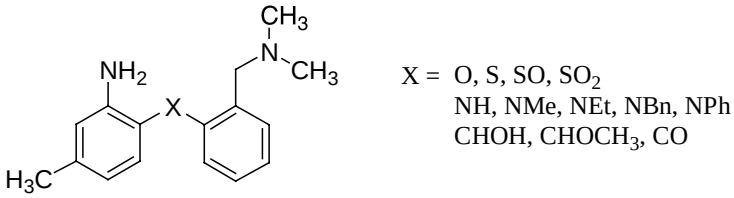
A novel series of 5-HT$_7$ receptor ligands has been identified and evaluated, providing compounds showing a broad spectrum of functional activities and good selectivity over selected receptors and ion channels.



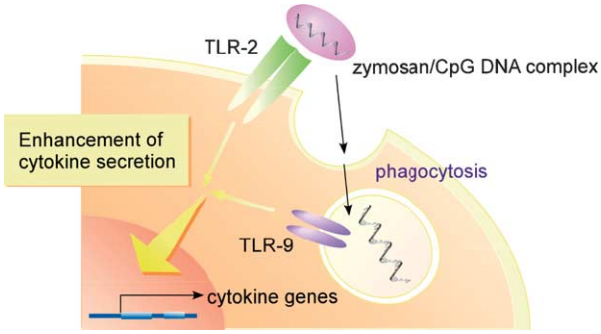


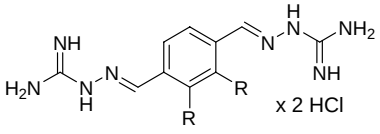


We describe a novel series of isothiazoloquinolones that demonstrate strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* and low cytotoxic activity against a human cell line.

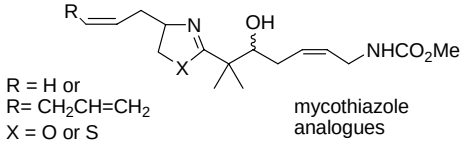


A series of diphenylsulfide derivatives was prepared and their binding affinities for monoamine transporters (SERT, DAT, and NET) are reported.

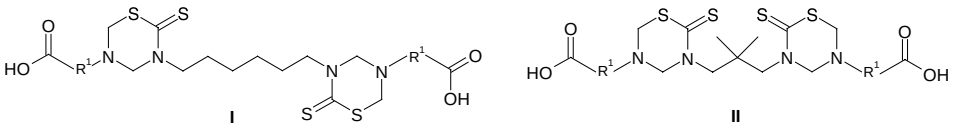




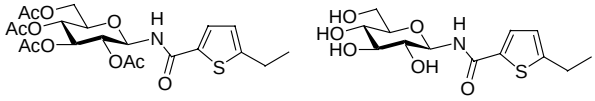
A homologous series of bis-guanylhydrazone compounds decorated with hydrophobic functionalities bind and neutralize lipopolysaccharide (LPS) with a potency comparable to that of polymyxin B, a peptide antibiotic known to sequester LPS.



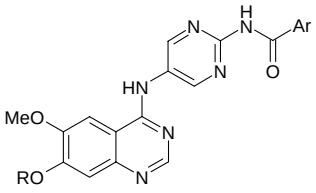
New structurally mycothiazole analogues were synthesized and evaluated against HCT-15 colon tumor cells and L_4 larvae of *Nippostrongylus brasiliensis*.



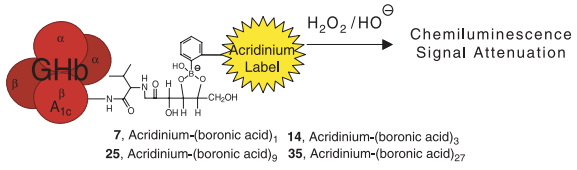
The potent in vitro anti-trypanosomal activity of alkyl-linked bis tetrahydro (2*H*) 1,3,5 thiadiazine 2-thiones (THTT) **I** and **II** is reported.

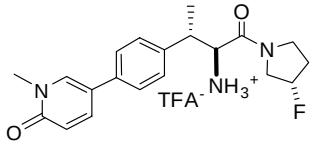


Per-O-acetylated-*N*-glucosyl-thiophene-2-carboxamides showed significant inhibition of both serum and bFGF stimulated uptake of [^{3}H]thymidine, when compared to the unprotected analogues.



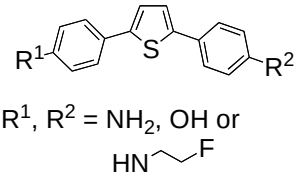
The discovery, optimisation and subsequent structural determination of a novel class of Aurora kinase inhibitors are described.



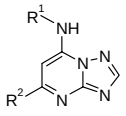


9, DPP-IV IC_{50} = 34 nM

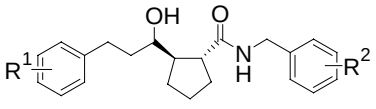
anti-Substituted biaryl β-methylphenylalanine derived amides have been shown to be potent DPP-4 inhibitors exhibiting excellent selectivity over both DPP8 and DPP9. The optimized compound **9** exhibited good pharmacokinetic profiles in three preclinical species.



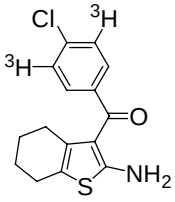
Synthesis and SAR of novel 2,5-diphenylthiophene derivatives as Aβ plaque imaging agents are reported. The inhibition constant (K_i) of potent compounds ranges from 3.9 to 10 nM.



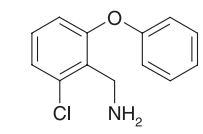
Crystallographic and modelling data, in conjunction with a medicinal chemistry template-hopping approach, led to the identification of a series of novel and potent inhibitors of human cyclin-dependent kinase 2 (CDK2), with selectivity over glycogen synthase kinase-3β (GSK-3β). One example had a CDK2 IC_{50} of 120 nM and showed selectivity over GSK-3β of 167-fold.



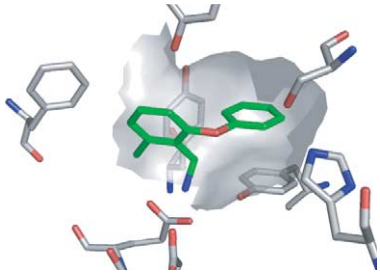
Novel cyclopentane-based 3-phenyl-1-hydroxypropyl compounds were evaluated for inhibitory activity against the peripheral nerve and sodium channel $Na_V1.7$ and off-target activity against the cardiac potassium channel hERG.

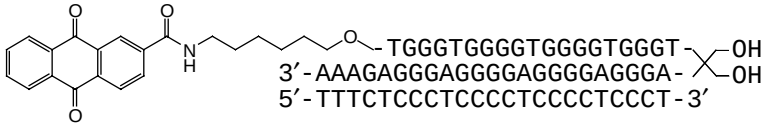


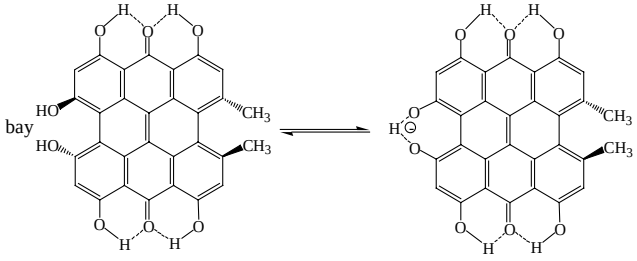
A virtual screening approach for S1-binding fragments of dipeptidyl peptidase IV using FlexX-Pharm docking confirmed substructures of known inhibitors and identified novel fragments with activities in the micromolar range suitable as starting points for structure-based design.



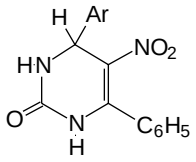
IC_{50} (DPP-IV) = 37 μM





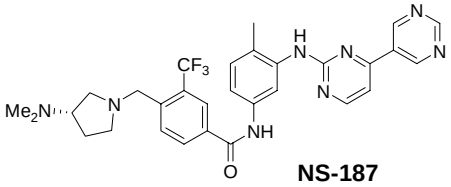


By means of time-dependent density functional theory calculations, it is revealed that the anion of hypericin, derived from proton dissociation in the bay region, is responsible for the photosensitive features of the pigment.



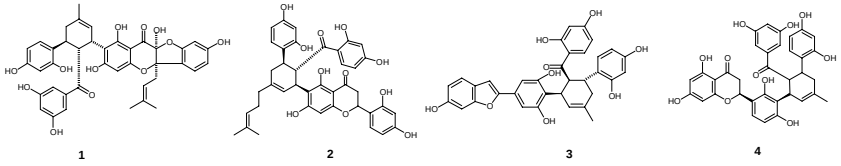
Ar = C_6H_5, 4-HOC_6H_4, 3-FC_6H_4, 3-$O_2NC_6H_4$, 3-Py, 2-Th

The antiarrhythmic activity of title compounds toward two types of experimental rat arrhythmia has been studied.



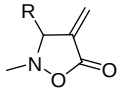
NS-187

A series of 3-substituted benzamide derivatives of STI-571 (imatinib mesylate) was prepared and evaluated for antiproliferative activity against the Bcr-Abl-positive leukemia cell line K562. Several 3-halogenated and 3-trifluoromethylated compounds, including NS-187, showed excellent potency.



1 **2** **3** **4**

An organic layer prepared from the Chinese crude drug 'Sang-Bai-Pi' (*Morus* root bark) was studied in order to identify the inhibitory compounds for protein tyrosine phosphatase 1B (PTP1B). Bioassay-guided fractionation resulted in the isolation of sanggenon C (**1**), sanggenon G (**2**), mulberrofuran C (**3**), and kuwanon L (**4**) as PTP1B inhibitors, along with moracin O (**5**) and moracin P (**6**). Compounds **1**–**4** inhibited PTP1B with IC_{50} values ranging from 1.6 ± 0.3 μM to 16.9 ± 1.1 μM.



R = alkyl, aryl

A series of 4-methylideneisoxazolidin-5-ones was synthesized and their cytostatic activity against L-1210, HL-60, and NALM-6 leukemia cell lines was evaluated. The most potent analogues had $IC_{50} < 1$ μM.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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