ELSEVIER

Bioorganic & Medicinal Chemistry Letters

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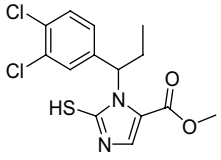
Contents

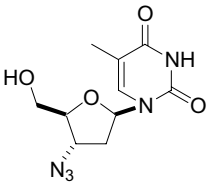
COMMUNICATIONS



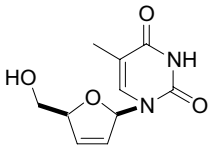
1a

The synthesis and SAR of a new class of CCR2 antagonists based on the lead compound **1a** are described. The optimization of the initial lead delivered nanomolar inhibitors of the MCP-1 induced Ca-flux in human THP-1 cells.

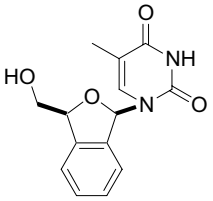
The asymmetric synthesis of isobenzofurane analogues, new potential antiviral agents, is reported. High performance liquid chromatography (HPLC) was the technique chosen to separate the enantiomers. We describe this chiral separation and then determine the enantiomerical excess. The biological results of each tested enantiomer are given.



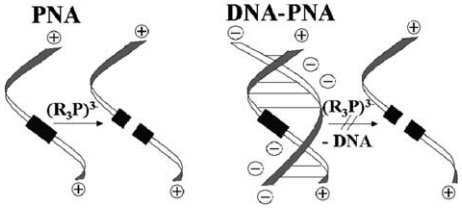
AZT



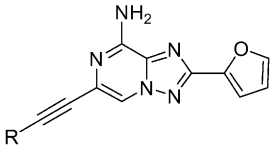
d4T

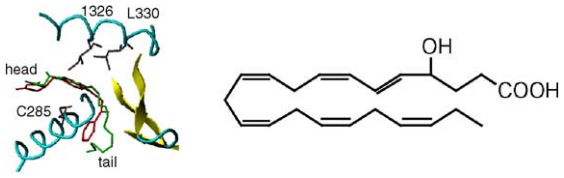


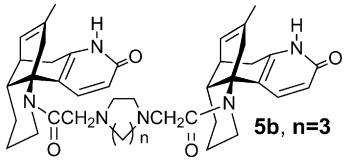
BcF



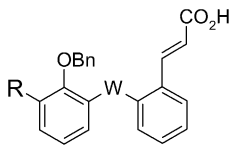
Cleavage of disulfide modified PNA by tris-(carboxyethyl)-phosphine is slowed down 33 times by a complementary DNA.





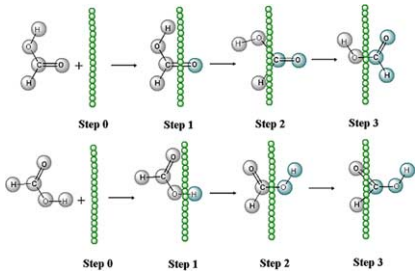


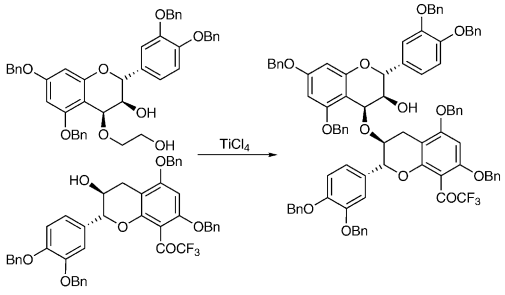
A number of new derivatives of HupB, including bis-HupB, have been synthesized. Among them bis-HupB 5b is 72-fold more potent in inhibition of AChE and 79-fold more selective for AChE versus BChE than HupB.

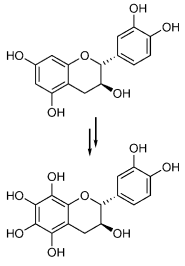


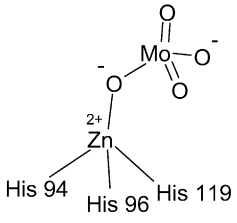
The synthesis, biological activity and the metabolism in vitro of a novel series of EP_3 antagonists have been evaluated. The very potent and selective EP_2 agonist **9** is also reported.

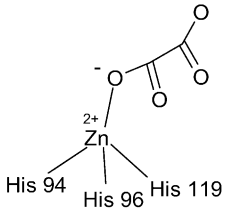
2a R = Me W = $CH_2CH{=}CH$
3a R = Me W = $CH{=}CHCH_2$
9 R = H W = CH=CH



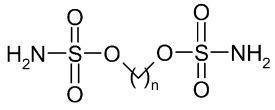




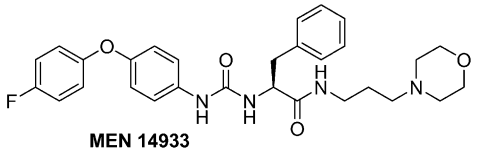




CA IV - oxalate adduct
K_I= 99 nM

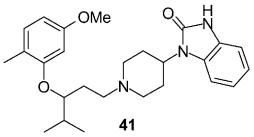


n = 2 - 16



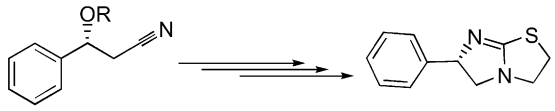
MEN 14933
Ki = 16 nM

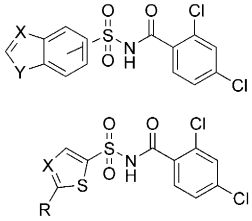
The so-called 'fragment approach' was applied in the search for new leads as selective hNK_2 antagonists. A first round of structural space exploration through the use of bond rigidity as scaffold to support the fragments, afforded **27a** as 200 nM hNK_2 ligand. Further refinement gave **MEN 14933** as a 16 nM hNK_2 ligand, selective versus hNK_1, of a novel class. Conformational analysis was used to study results and plan future work.



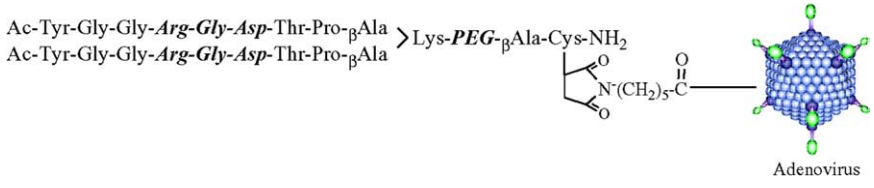
41

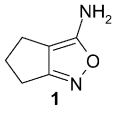
A series of potent and soluble ORL1 agonists was prepared and evaluated. Compound **41** showed antinociceptive properties in mouse formalin paw test (ED_{50} = 1.07 μmol/kg).





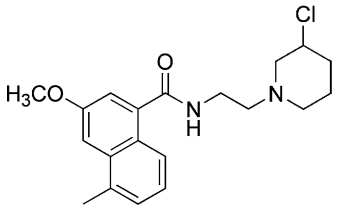
The cytotoxic and oncolytic activity of heterocyclic and fused bicylic sulfonamide analogs is described.





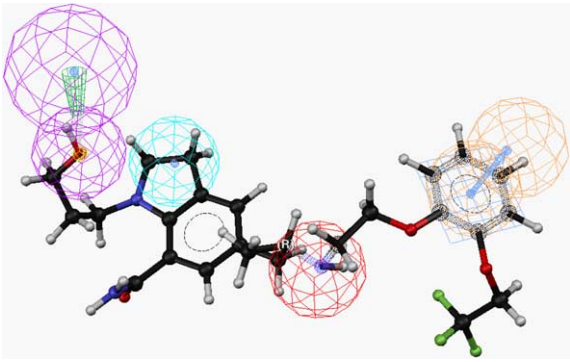
1

The bicyclic amine **1** represents a new lead structure for broad spectrum bactericides. Extensive activity screening as well as toxicity investigations have been carried out for **1** and its derivatives.

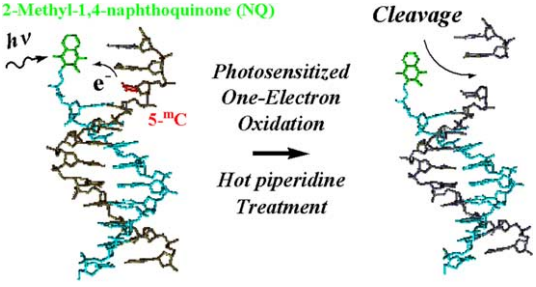


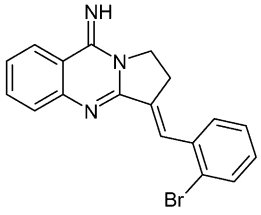
A designed analogue of the left half of azinomycin has been synthesized and unwinds supercoiled DNA.

In this paper three-dimensional pharmacophore hypotheses were built from a training set of 30 α_{1A}-adrenoceptor antagonists. The best pharmacophore is considered to be used in designing new leads for hopefully more active compounds.

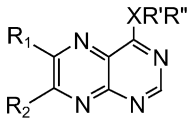


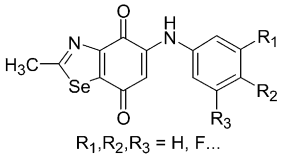
Photosensitized one-electron oxidation of 5-methylcytosine in DNA by 2-methyl-1,4-naphthoquinone, attached to 5′-end of an oligodeoxynucleotide strand, produced 5-formylcytosine and led to selective DNA strand cleavage at the original 5-methylcytosine configuration. This specified photoreaction is useful for positive display of 5-methylcytosine in DNA on a sequencing gel.





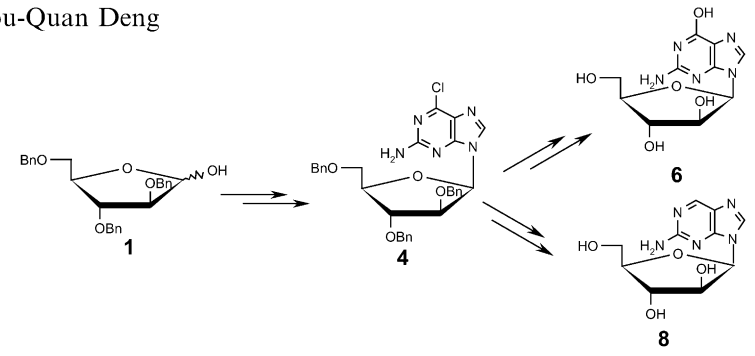
A novel class of CCR3 modulators is described. Optimization led to compound **8b** (K_i: 28 nM), which surprisingly proved to be an agonist.

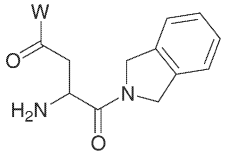




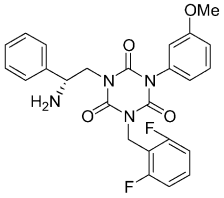
5-Arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles were synthesized and tested for in vitro antifungal activity against pathogenic fungi. Among them, 5-arylamino-4,7-dioxobenzoselenazoles exhibited potent antifungal activity.

A facile method was reported to synthesize 9-β-D-arabianofuranosyl guanine (**6**) and 2-amino-9-(β-D-arabianofuranosyl)purine (**8**) via the key intermediate, 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl-β-D-arabianofuranosyl)purine (**4**), which was stereoselectively prepared using activated molecular sieve as catalyst.

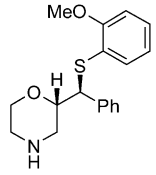




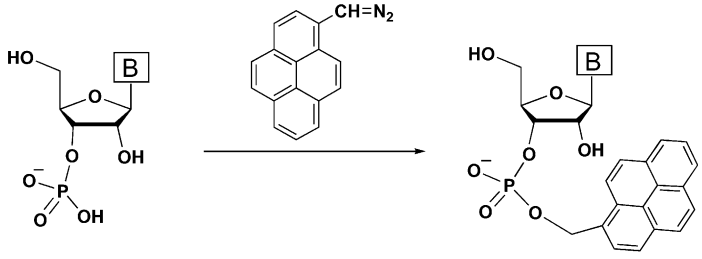
W=1,2,3,4-tetrahydroisoquinoline
W=6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
W=1-(4,4'-difluor-benzhydryl)-piperazine



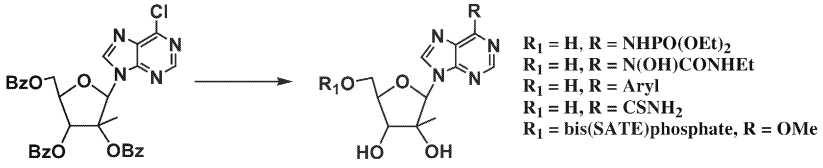
A convenient one-pot synthetic route was developed for the preparation of asymmetric 1,3-dialkyl-1,3,5-triazine-2,4,6-triones from isocyanates, primary amines and *N*-chlorocarbonyl isocyanate. This methodology was applied to the synthesis of a chemical library acting as antagonists of the *h*GnRH receptor.

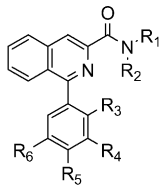


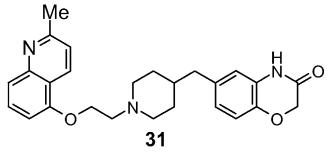
The preparation of novel arylthiomethyl morpholines using a stereochemically versatile route featuring an aldol condensation as the key step is described. Members of this series are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake.

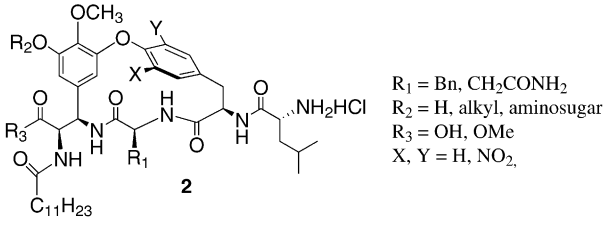


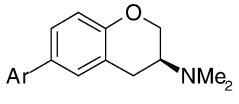
Pyrenyldiazomethane was shown to react quantitatively and selectively at phosphate with 2′-, 3′-, and 5′-nucleotide phosphates incorporating the different nucleic bases.

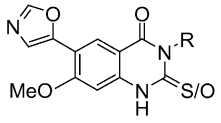




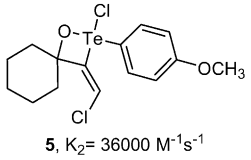






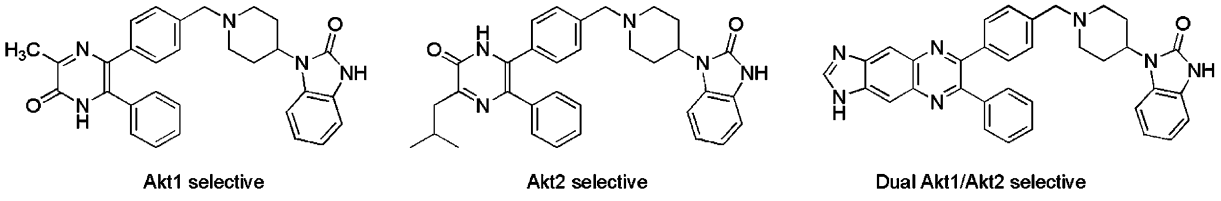


Novel quinazolinethiones and quinazolinediones are reported which exhibit IMPDH II inhibitory activity.

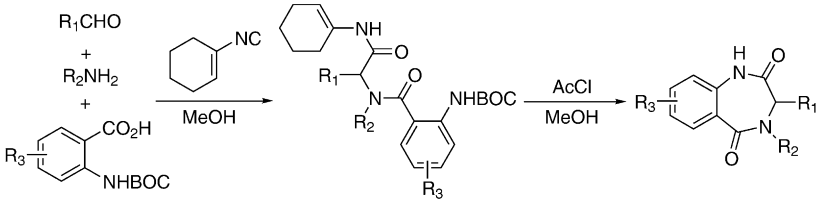


5, K_2= 36000 $M^{-1}s^{-1}$

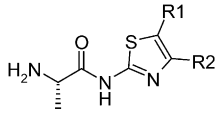
The inhibition of Cathepsin B by a sort of different classes of organotellurium(IV) compounds was described.



Akt1 selective Akt2 selective Dual Akt1/Akt2 selective

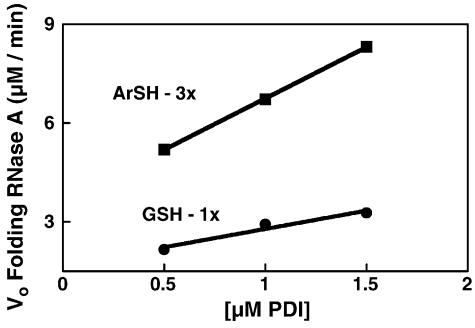


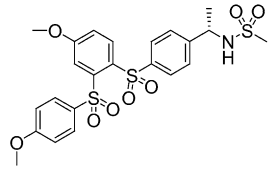
A library of 1,4-benzodiazepine-2,5-diones was screened for binding to the p53-binding domain of HDM2 using Thermofluor®, a miniaturized thermal denaturation assay. The hits obtained were shown to bind to HDM2 in the p53-binding pocket using a fluorescence polarization (FP) peptide displacement assay. The potency of the series was optimized, leading to sub-micromolar antagonists of the p53–HDM2 interaction.



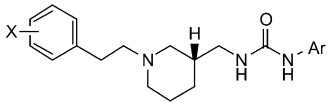
Non-peptidic small molecule SMAC mimetics were designed and synthesized that bind to the BIR3 domain of XIAP using structure-based design. Substituted five-membered heterocycles such as thiazoles and imidazoles were identified that serve as replacements for peptide fragments of the lead.

PDI is an enzyme that acts as a chaperone, shufflase, and oxidase during the folding of disulfide-containing proteins. The ability of aromatic thiols to increase the activity of PDI-catalyzed protein folding over that of the standard thiol glutathione (GSH) was measured. 4–Mercaptobenzoic acid (ArSH) increased the activity of PDI by a factor of three.

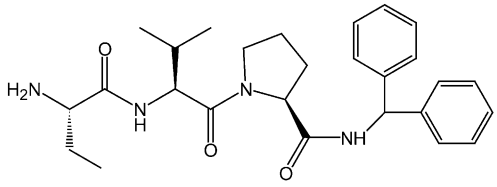




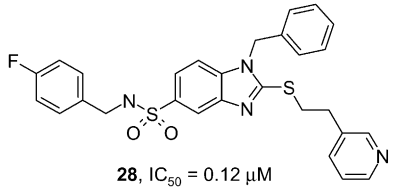
A novel class of cannabinoid CB2 receptor ligands is described. The compounds are nanomolar inhibitors of the CB2 receptor and can show high selectivity over the cannabinoid CB1 receptor. One compound is shown to be a CB2-selective inverse agonist.



The synthesis and structure–activity relationships of *N*-arylalkylpiperidylmethyl ureas as antagonists of the CC chemokine receptor-3 (CCR3) are presented. These compounds displayed potent binding to the receptor as well as functional antagonism of eotaxin-elicited effects on eosinophils.

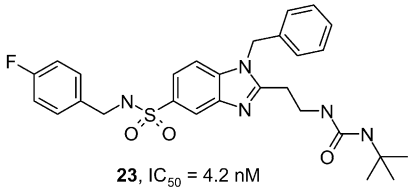


6j (K_i = 24 nM to XIAP BIR3)



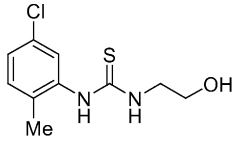
28, IC_{50} = 0.12 μM

A new class of benzimidazole-5-sulfonamides has been identified as nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists. Initial structure–activity relationships are presented resulting in compounds **19** and **28** with submicromolar dual functional activity on human and rat receptors.



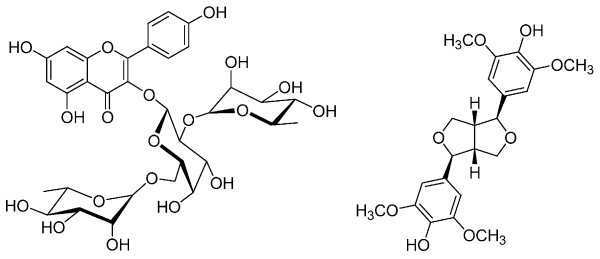
23, IC_{50} = 4.2 nM

The 2-cyclopropyl substituted benzimidazole **2** has been used as a starting point for further optimization of an LHRH antagonist series. SAR studies reveal that a *tert*-butyl urea fragment connected through a simple carbon chain would improve activity. Further modification of the benzylsulfonamide moiety led to the discovery of **23** (IC_{50}: 4.2 nM).

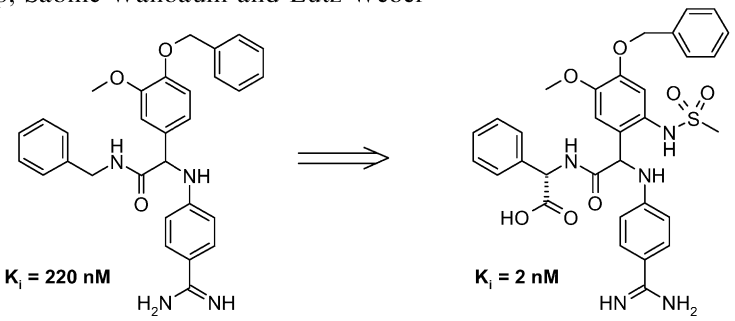


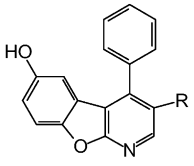
2

Thiourea **2** was identified as a potential HDL-elevating agent from a targeted database search. Structure–activity relationship of its analogs is described.



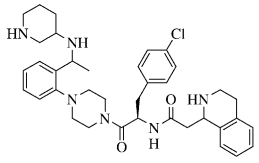
Proof of concept experiments have shown that tissue factor/factor VIIa inhibitors have antithrombotic activity without enhancing bleeding propensity. Starting from lead compounds generated by a biased combinatorial approach, phenylglycine amide tissue factor/factor VIIa inhibitors with low nanomolar affinity and good selectivity against other serine proteases of the coagulation cascade were designed.



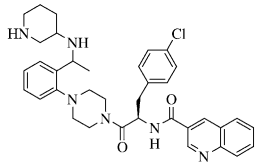


Structural variation of merely one substituent in novel 1-aza-9-oxafluorenes suggests that its hydrogen bond acceptor function might be essential for inhibitory activity and, furthermore, leads to unexpected shifts in the selectivity profile of CDK inhibition.

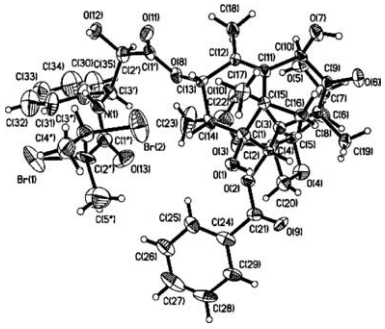
Mismatched bulges in nucleic acid constructs are important in the recognition event between biological molecules. Herein, we report that napthyridine dimer **2** is able to specifically bind G–G mismatches in all nucleic acid constructs comprising of RNA–RNA, RNA–DNA and DNA–DNA duplexes. This binding behavior suggests that the binding process primarily occurs between the guanine base pairs and the napthyridine moiety, and is independent of the tertiary structure of the nucleic acid duplexes.



12e, K_i = 6.3 nM, EC_{50} = 31 nM



12l, K_i = 4.5 nM, IC_{50} = 300 nM



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Non-peptidic small molecules were discovered using structure-based design to mimic SMAC protein believed to trigger apoptosis by abrogating the inhibitory effects of XIAP on caspases. The picture depicts the NMR structure of the SMAC peptide mimetic, compound **20g** bound to BIR3 domain of XIAP indicating the key hydrogen bonds with dotted lines.

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