ELSEVIER

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Medicinal
Chemistry
Letters

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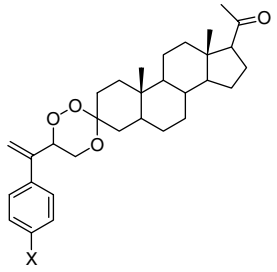
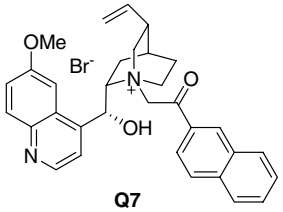
Contents

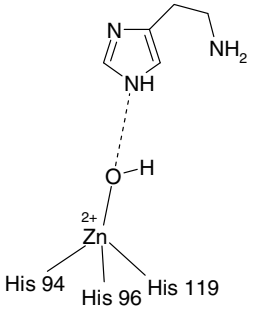
ARTICLES

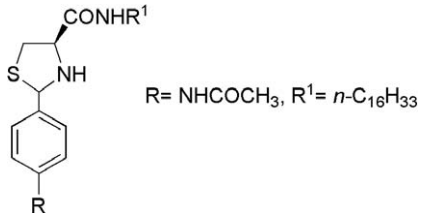


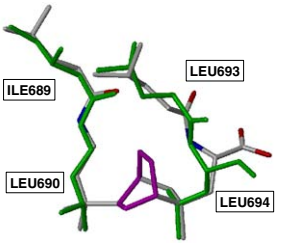
Several representative amphiphilic cationic quinine-derivatives have been synthesized and evaluated against methicillin- resistant *Staphylococcus aureus*. This is the first reported antibacterial activity of this class of compounds. In vitro the minimal inhibitory concentration values of the best compound **Q7** ranged from 0.4 to 1.6 μg/mL (MBC < 3.2 μg/mL).

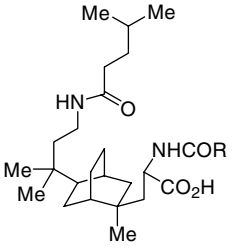


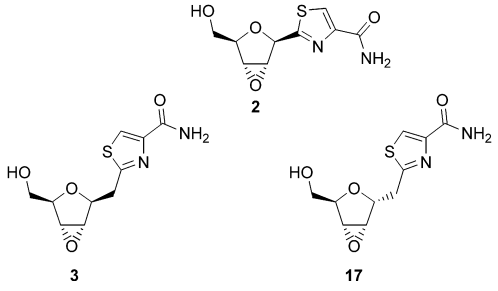
Q7

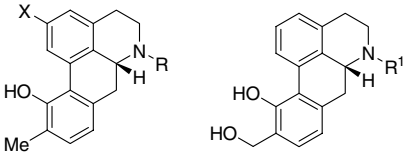






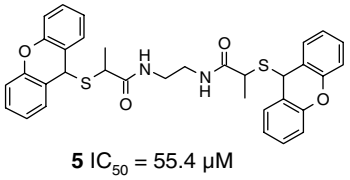


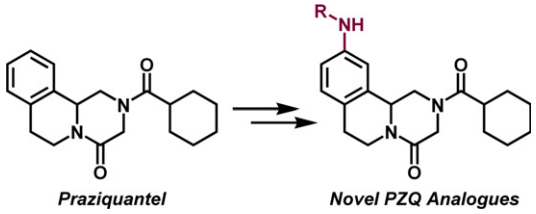


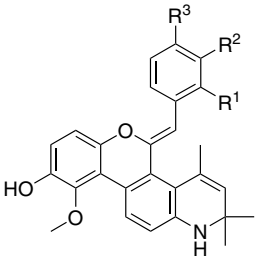


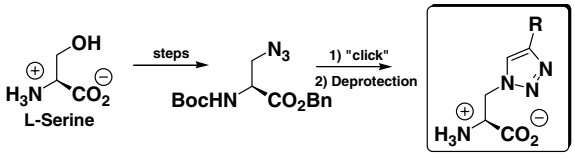
2 X = H, R = Me
3 X = OMe, R = Me
4 X = OMe, R = *n*-Pr

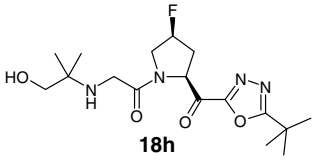
5 R^1 = Me
6 R^1 = *n*-Pr







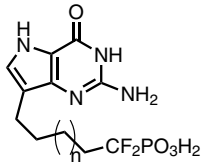




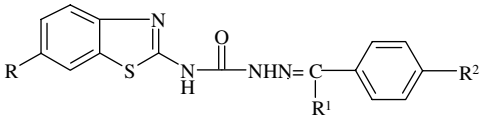
18h

Compound **18h** showed excellent inhibitory activity against DPPIV, good selectivity over DPPII and DPPVIII, and showed good PK, PD profile.

DFPP-DG is a very potent PNP inhibitor with apparent inhibition constants of 4.4 and 8.1 nM versus calf-spleen and human erythrocyte PNPs, respectively. One of its analogues, ***homo*-DFPP-DG**, is even more potent versus human enzyme, with an apparent inhibition constant of 5.3 nM.

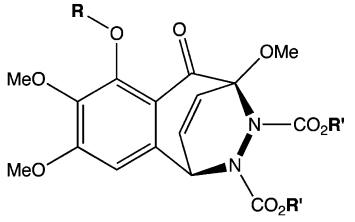


DFPP-DG n=1
***homo*-DFPP-DG** n=2



(1-15)

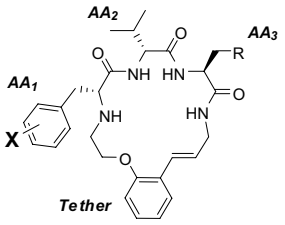
A series of 1,3-benzothiazol-2-yl semicarbazones (**1**–**15**) were prepared in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. All the synthesized compounds were in good agreement with elemental and spectral data. Majority of the compounds were active in MES screen. Selected compounds were checked for their lipophilic character.



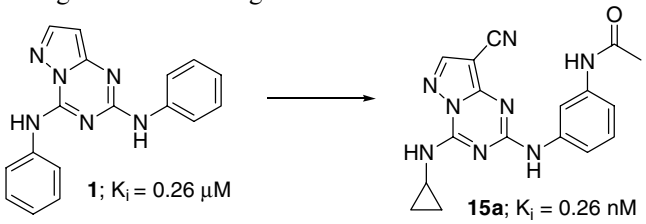
R = -OH, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2(CH_2)_2CH_3$ -$CH_2C_6H_5$, -CH_2*p*F-C_6H_4, -CH_2*o*F-C_6H_4, -CH_2*p*Cl-C_6H_4 -CH_2*p*OMe-C_6H_4

R' = -CH_3, -CH_2CH_3, -$CH_2CH(CH_3)_2$

The synthesis and protozoocidal evaluation of a series of endocyclic hydrazines based on benzotropolone ethers is described.

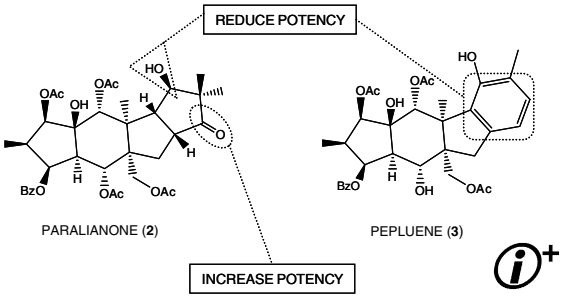


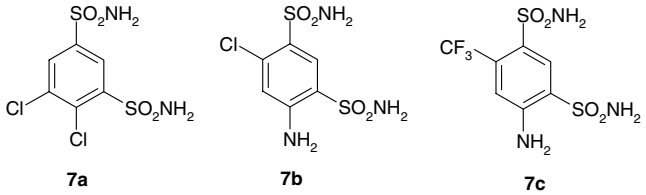
New macrocylic peptidomimetics bearing novel unnatural amino acids are reported as potent motilin antagonist.

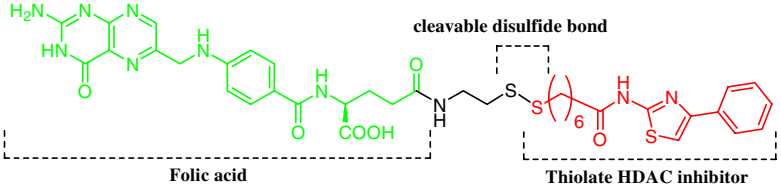


Structure-guided modifications to a series of pyrazolo[1,5-a][1,3,5]triazine derivatives provided pM inhibitors of protein kinase CK2 with low μM cytotoxic activity in cell-based assays with prostate and colon cancer cell lines.

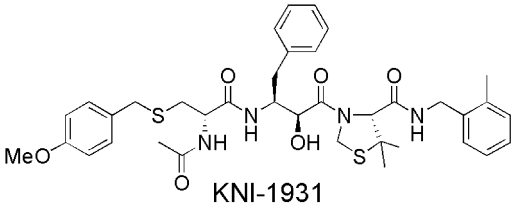
The isolation and structural characterization of paraliane and pepluane diterpenes are described. Preliminary pharmacological tests let us to draw structure–activity relationships on this incoming class of promising anti-inflammatory agents.

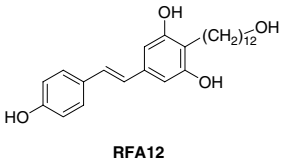




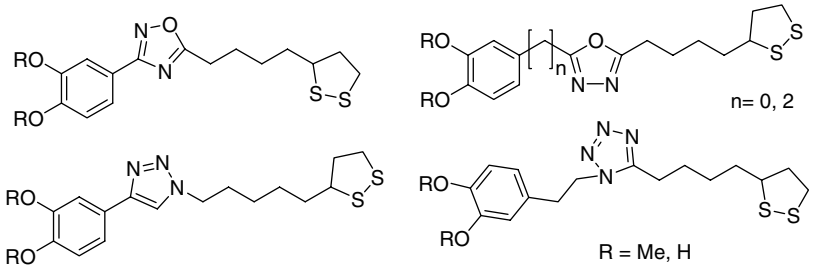


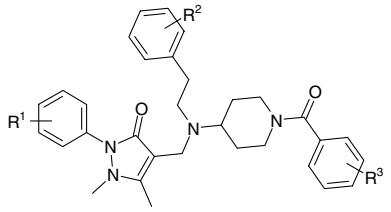
Aiming to develop selective anticancer drugs, we designed and synthesized three disulfides bearing a folic acid moiety as candidate folate receptor (FR)-targeted prodrugs of thiolate histone deacetylase inhibitors. One of the folate conjugates showed growth-inhibitory activity toward folate receptor-positive MCF-7 breast cancer cells.

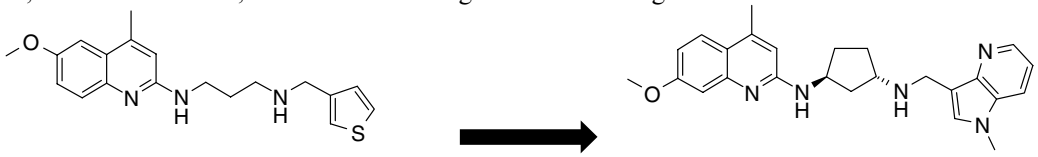


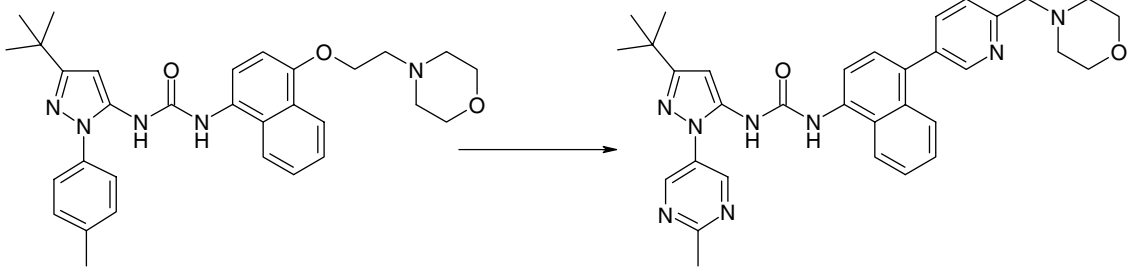


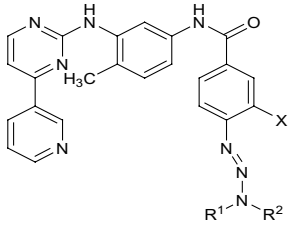
Synthesis of resveratrol fatty alcohols (RFAs), a new class of molecules acting simultaneously on neuroprotection and neuroregeneration is described. RFAs represent an innovative approach for the treatment of different neuropathies.

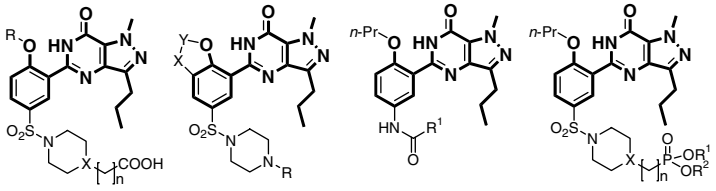


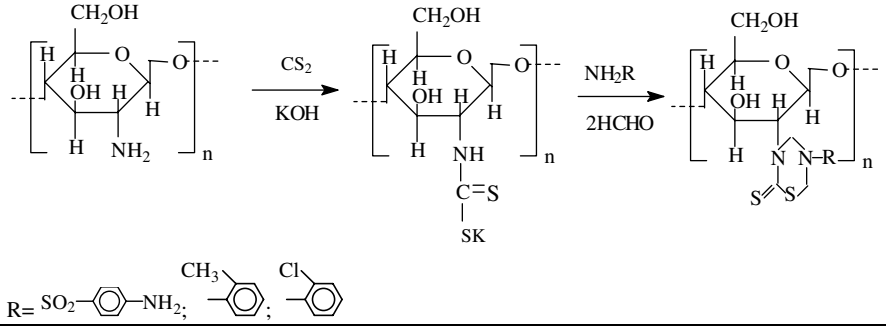


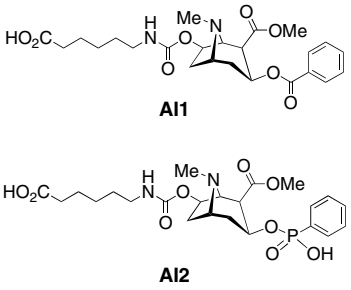


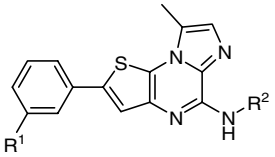


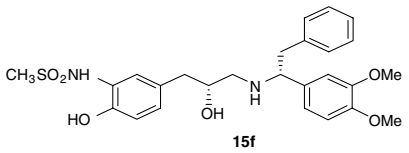








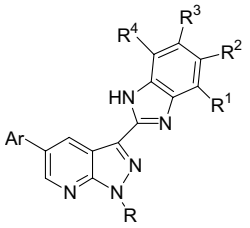




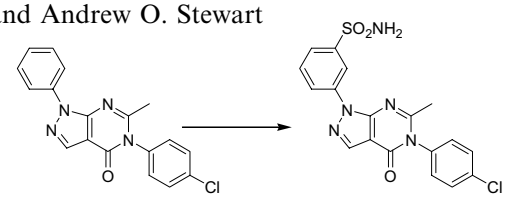
15f

Utilization of N-substituted-4-hydroxy-3-methylsulfonanilidoethanolamines **1** as selective β_3 agonists is complicated by their propensity to undergo metabolic oxidative N-dealkylation, generating 0.01–2% of a very potent α_1 adrenergic agonist **2**. A summary of the SAR for this hepatic microsomal conversion precedes presentation of strategies to maintain the advantages of chemotype **1** while mitigating the consequences of N-dealkylation. This effort led to the identification of 4-hydroxy-3-methylsulfonanilidopropanolamines **15** for which the SAR for the unique stereochemical requirements for binding to the β adrenergic receptors culminated in the identification of the potent, selective β_3 agonist **15f**.

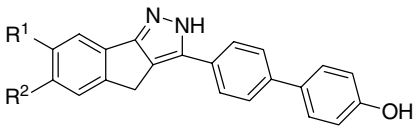
A series of 3,5-disubstituted pyrazolo[3,4-*b*]pyridine cyclin-dependent kinase (CDK) inhibitors was synthesized. These compounds showed potent and selective CDK inhibitory activities and inhibited in vitro cellular proliferation in cultured human tumor cells. Selected compounds were evaluated in an in vivo tumor xenograft model. The synthesis and biological evaluation of these pyrazolo[3,4-*b*]pyridines and related compounds are reported.



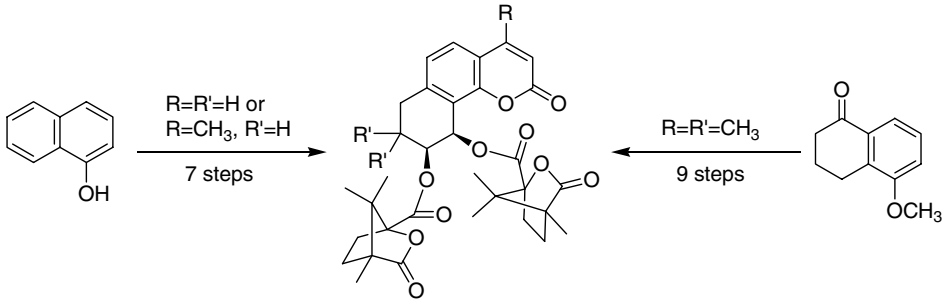
Hit to lead study of a series of novel and subtype-selective mGluR1 antagonists was discussed. Early ADME evaluation was key to guiding the SAR and generating orally bioavailable lead molecule.

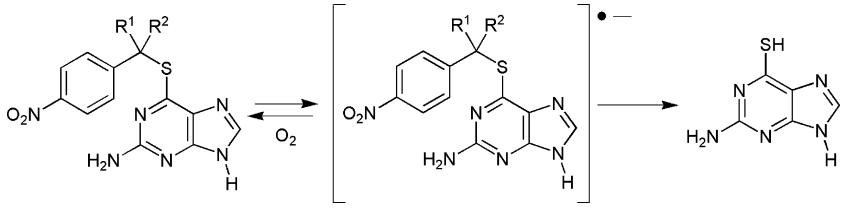


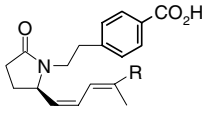
Keywords: mGluR1 antagonist, Hit to Lead, ADME



A series of potent tricyclicpyrazole-based Chk1 inhibitors were synthesized and their biological activities were evaluated.

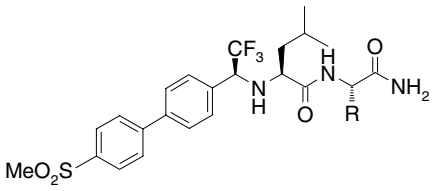


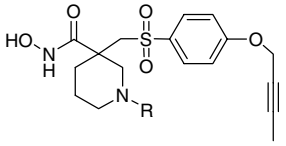




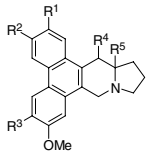
1b

Many of the reported inhibitors of cathepsin K rely on an electrophilic functionality to interact with the nucleophilic cysteine residue found in the catalytic site of this class of enzymes. We report a novel series of cathepsin K inhibitors where a nitrile electrophile has been replaced with an α-substituted amide. Introduction of the benzyl substituent resulted in a 24-fold increase in potency over the unsubstituted amides. This series of compounds also showed excellent selectivity against the cathepsins B, L, and S. Mechanistic studies show that these compounds are slowly processed substrates of Cat K.



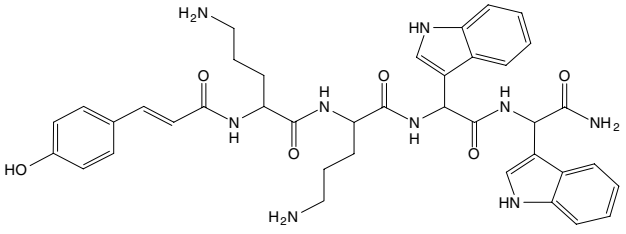


Structure-based methods were used to design β-sulfone 3,3-piperidine hydroxamates as TACE inhibitors with the aim of improving selectivity for TACE versus MMP-13. Several compounds in this series were synthesized and evaluated in enzymatic and cell-based assays. These analogs exhibit excellent in vitro potency against isolated TACE enzyme and show good selectivity for TACE over the related metalloproteases MMP-2, -13, and -14.

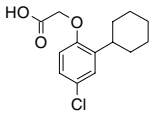


Compounds	R^1	R^2	R^3	R^4	R^5	N^{10}
DCB-3500	OMe	OMe	OMe	H	H (*S*)	–
DCB-3501	OMe	OMe	OMe	OH (*R*)	H (*S*)	–
DCB-3503	OMe	OMe	OMe	OH (*S*)	H (*S*)	–
DCB-3506	OMe	OH	OMe	OH (*S*)	H (*S*)	–
PA-2 (Tylophoridicine E)	H	OH	OMe	OH (*S*)	H (*S*)	–
PA-3 (Tylophoridicine C)	H	OMe	OH	OH (*S*)	H (*S*)	N^+–O^-
PA-4 (Tylophoridicine F)	H	OMe	OMe	OH (*R*)	H (*S*)	N^+–O^-
PA-5 [(*R*)-(+)-Deoxytylophorinidine]	H	OMe	OH	H	H (*R*)	–
PA-6 (Tylophorinine)	H	OMe	OMe	OH (*R*)	H (*S*)	–
PA-7 (Tylophorinidine)	H	OMe	OH	OH (*S*)	H (*S*)	–

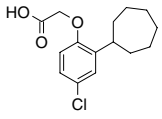
Structure–activity relationships were explored based on a series of phenanthroindolizidine alkaloids synthesized or isolated. DCB-3503 and PA-7 (tylophorinidine) were determined to be the most active compounds against HepG2 tumor growth both in vitro and in vivo.



High throughput screening identified a phenoxyacetic acid scaffold **3** as a novel CRTh2 receptor antagonist chemotype. Optimisation furnished compound **6b**, which showed functional potency for inhibition of human eosinophil shape change and oral bioavailability in the rat.



3



6b

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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