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Chemistry
Letters

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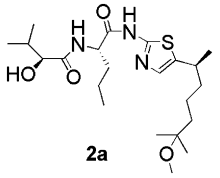
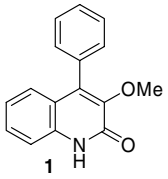
Contents

ARTICLES



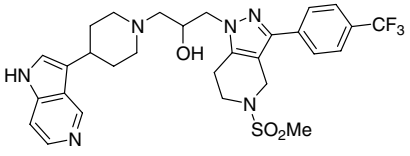
2a

The thiazole-diamide series has been identified as highly potent γ-secretase inhibitors. Several representative compounds showed IC_{50} values of <0.3 nM. The synthesis and SAR, as well as [^{3}H]-**2a**, are described.

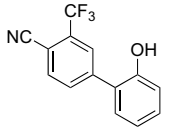


1

Replacement of the methoxy moiety of 3-*O*-methylviridicatin **1** by a thiomethyl dramatically enhances its ability to inhibit TNF-α secretion.

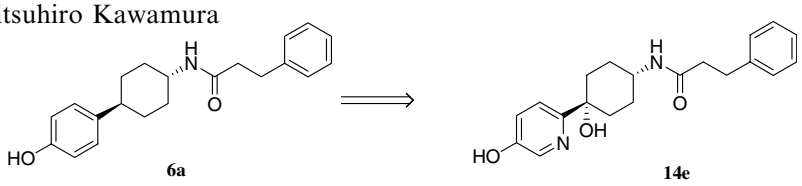


Noncovalent, pyrazole-based cathepsin S inhibitors are reported. Significant improvements in cellular potency were achieved through modification of a 4-(indol-3-yl)piperidine head group.



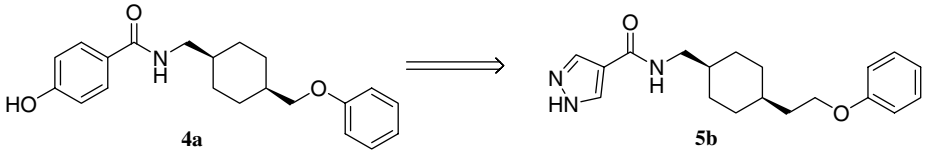
4e Cellular IC_{50} = 0.02 nM

The synthesis and SAR of a series of androgen receptor antagonists is described. The in vivo efficacy of compound **4e** is highlighted.



6a 14e

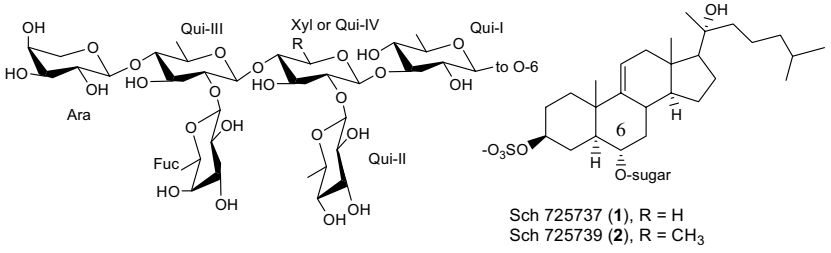
Structure–activity relationship investigation led to *N*-[*cis*-4-hydroxy-4-(5-hydroxypyridin-2-yl)cyclohexyl]-3-phenylpropanamide **14e** as an orally active NR2B-subtype selective *N*-methyl-D-aspartate (NMDA) receptor antagonist with very weak HERG binding (IC_{50} > 30 μM).

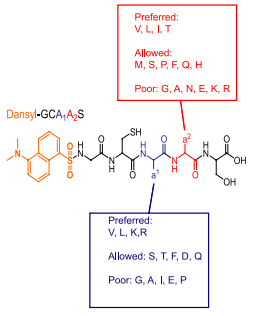


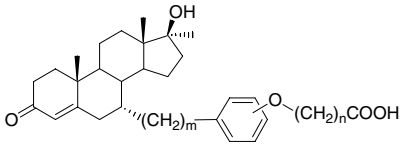
4a 5b

Replacement of the phenol moiety with pyrazole led to a novel potent NMDA-NR2B selective antagonist (**5b**) with an improved metabolic profile. Through this study, a close correlation between reactive metabolites formation and calculated HOMO energies of parent compounds was found.

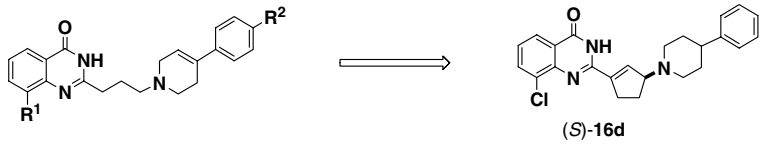
Bioassay-guided fractionation of an active fraction from an extract of a marine starfish, *Novodinia antillensis*, led to the identification of two new saponins, Sch 725737 (**1**) and Sch 725739 (**2**). Compound **1** was identified as the NaV1.8 inhibitor with IC_{50} of ~9 μM.

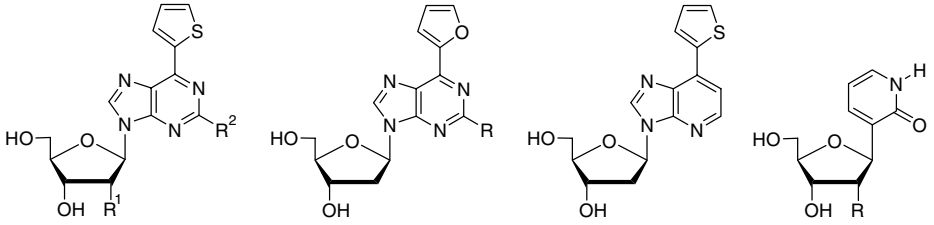


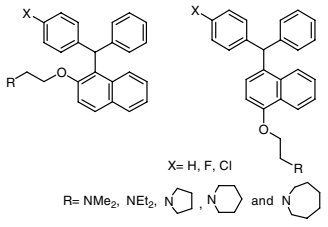


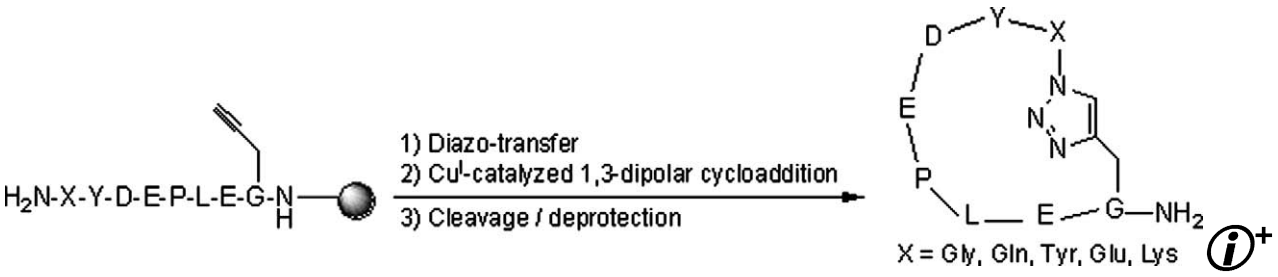


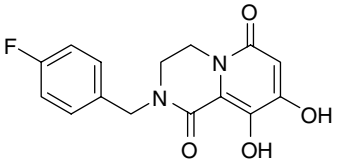
New steroidal compounds were synthesized and showed AR antagonistic activities without agonistic activities in reporter gene assay. SARs of the compounds are also presented in this report.



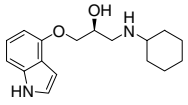








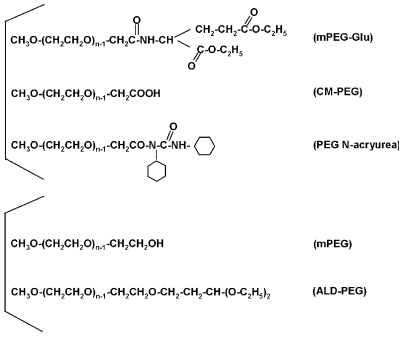
A series of potent novel dihydroxypyridopyrazine-1,6-dione HIV-1 integrase inhibitors was identified. These compounds inhibited the strand transfer process of HIV-1 integrase and viral replication in cells.

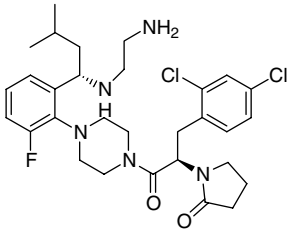


13a Ki = 1.33 nM @ 5-HT$_{1A}$ receptor

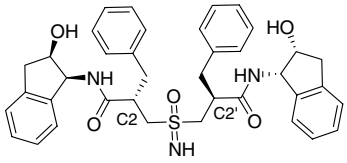
The discovery and synthesis of the 5-HT$_{1A}$ receptor antagonist **13a** is reported.

A clear and powerful purification approach of PEG derivatives was developed on polystyrene-divinylbenzene beads with ethanol/water as eluants and gave the highly pure target products. The novel methods shared the advantages of clearness, reliability and high-performance. The studies suggested that polystyrene-divinylbenzene beads were potent to serve as medium for the purification of PEG derivatives on a preparative scale.

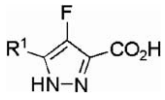




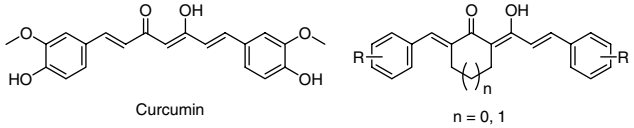
12a: K_i = 0.94 nM, IC_{50} = 21 nM



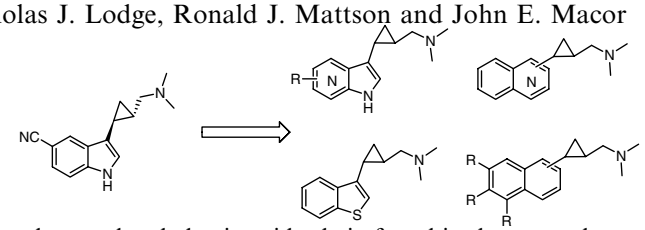
A novel class of sulfoximine-based pseudosymmetric HIV-1 protease inhibitors were designed and synthesized. The most active isomer (2*S*,2′*S*) displays potent activity against HIV-1 protease as well as virus.



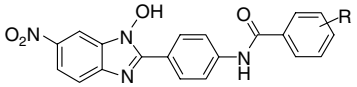
A series of 4-fluoro-5-functionalized pyrazole-3 carboxylic acids were shown to be potent, selective agonists of GPR109a. Improved free fatty acid reduction was observed when compared to niacin.



A number of curcumin analogues were prepared and evaluated for their cytostatic activity. Some of these analogues were found to have significant activity against three representative cancer cell lines.

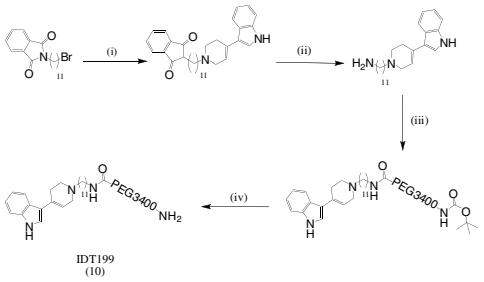


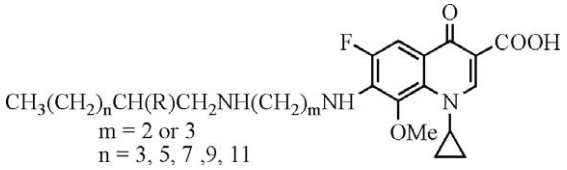
Hybrid molecules containing the cyclopropylmethylamino side chain found in the parent homotryptamine system and an isosteric heteroaryl or naphthyl core were prepared and their binding affinities for the human serotonin transporter determined.



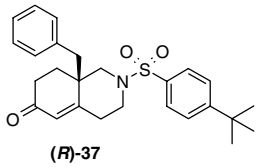
Inhibitors of AraC bacterial transcription factors are shown to limit infections by reducing virulence rather than halting growth of the organisms. This therapeutic approach is intended to prevent infection and minimize the development of bacterial resistance.

(i) 3-(1,2,3,6-Tetrahydro-pyridin-4yl)-1*H*-indole, cesium carbonate, 37.5%; (ii) hydrazine monohydrate, 34.6%; (iii) Boc-NH-PEG-NHS-3400, 100%; (iv) TFA, 100%.



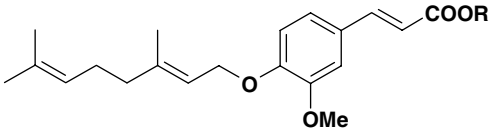


Twelve lipophilic moxifloxacin or gatifloxacin new derivatives were synthetized, seven of them having MIC < 1.25 μg/mL.

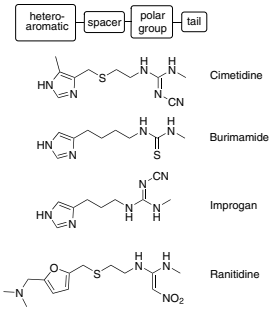


(*R*)-37

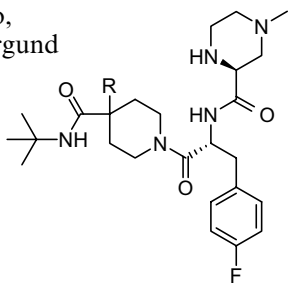
The synthesis and glucocorticoid receptor (GR) binding and functional antagonist activity of a series of substituted 2-azadecalins is reported. (*R*)-**37** was found to be a selective high GR affinity ligand (4 nM) with moderate functional activity (200 nM) in a GR reporter gene assay.



The synthesis of ester derivatives of the title acid and their anti-inflammatory activity are reported.



SAR about the piperidine core in a series of MC4R agonists is described. A number of alkyl substituents that furnish compounds with good affinity and functional potency are reported.



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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