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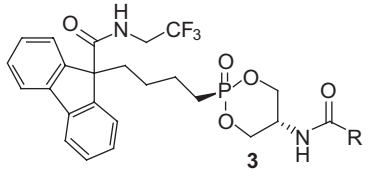
Chemistry
Letters

Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 20, 2004

Contents

COMMUNICATIONS



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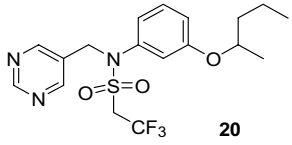

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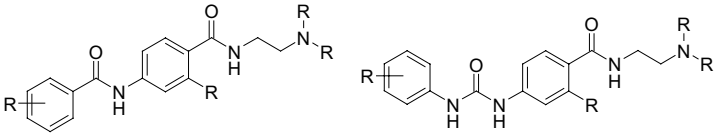
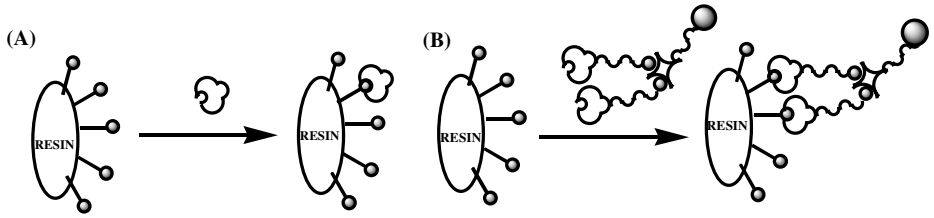
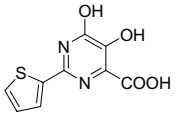
Pyrimidine methyl anilines as potent and selective mGlu2 potentiators are described. Findings from the structure–activity-relationship investigations are discussed.

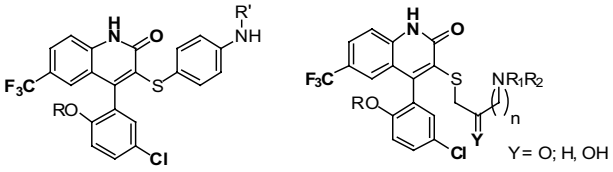


Synthesis, in vitro biological evaluation and structure–activity relationships of novel hMCH1R-antagonists are disclosed. The nature of the amine side chains could be varied considerably in contrast to the central benzamide scaffold and aromatic substituents.

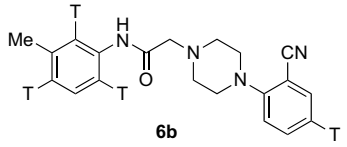




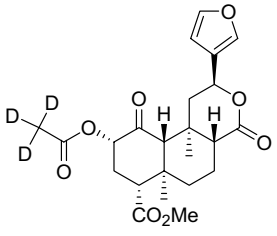
The discovery of a simple 2-thienyl substituted 5,6-dihydroxypyrimidine-4-carboxylic acid active-site inhibitor of the HCV NS5B polymerase inhibitor is reported. Structure–activity relationships that led to an understanding of the pharmacophore around the pyrimidine ring is also described.



A series Maxi-K openers for the treatment of erectile dysfunction based on the 3-thio-quinolinine core is described. Significant levels of channel opening (up to 550% of control) are seen in transfected oocytes. Functional activity in rabbit corpus cavemosum tissue strips confirms the potential to effect therapy for ED, the effect being maximal for the 3-amino-2-hydroxy thiol side chain.



6b



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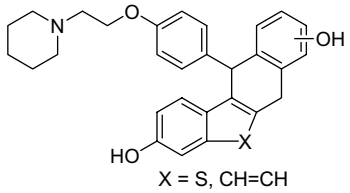
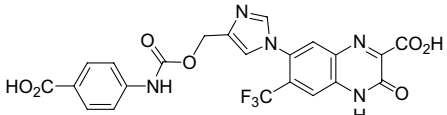
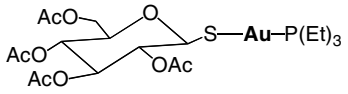


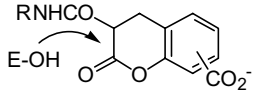
The synthesis and biological evaluation of two series of conformationally restricted SERMs are disclosed. In each series (benzothiophene or naphthalene), the ligand side chain is constrained to adopt a defined orientation. The orientation of the side chain has a significant impact on functional activity.

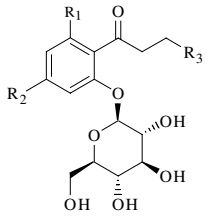


KRP-199

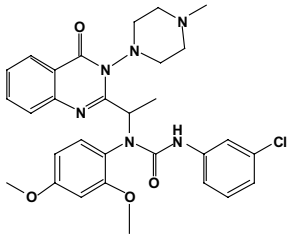
We describe the synthesis, physicochemical and biological properties of a novel series of 7-imidazolyl-6-trifluoromethyl quinoxalinecarboxylic acids with a substituted phenyl group. Among them, compound **9k (KRP-199)** was found to possess high potency and selectivity for the AMPA-R and to exhibit good neuroprotective effects in vivo, and also showed good physicochemical properties by introduced trifluoromethyl group at the C-6 position.





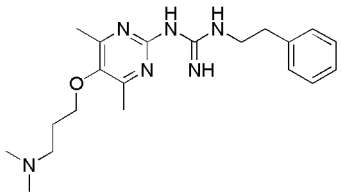


A series of glucose conjugates was synthesized and tested for inhibition of SGLT1 and SGLT2.

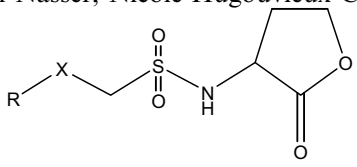


The discovery of a series of quinazolinone-based fungal efflux pump inhibitors by high-throughput screening for potentiation of fluconazole in *C. albicans* is described. Attempts to improve the aqueous solubility of screening hits led to the discovery of an analog with greatly improved physical properties and activity against clinically-relevant *Candida* spp.

Structure–activity relationships of a novel series of fungal efflux pump inhibitors with respect to potentiation of the activity of fluconazole against strains of *Candida albicans* and *Candida glabrata* over-expressing ABC-type efflux pumps are systematically explored.

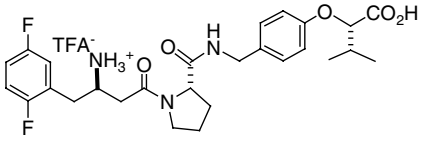


An SAR study on a high-throughput screening lead for HCV-IRES translation inhibition led to the identification of low μM inhibitors.



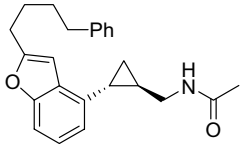
R = alkyl- or phenylalkyl- X = CH_2 or C=O

A series of 11 *N*-sulfonyl homoserine lactones has been synthesised. Some of them were found to competitively inhibit the action of 3-oxohexanoyl-L-homoserine lactone, the natural inducer of bioluminescence in the bacterium *Vibrio fischeri*. Molecular modeling suggests a possible explanation based on the prevention of structural rearrangements necessary for the formation of the active dimer of LuxR.



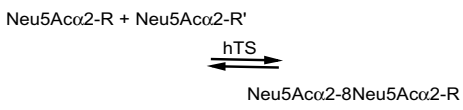
37, DPP-IV IC_{50} = 0.48 nM

In-house screening of the Merck sample collection identified proline derived homophenylalanine **3** as a DPP-IV inhibitor with modest potency (DPP-IV $IC_{50} = 1.9\mu M$). Optimization of **3** led to compound **37**, which is among the most potent and selective DPP-IV inhibitors discovered to date.

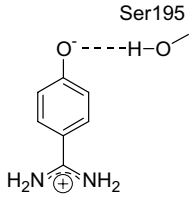


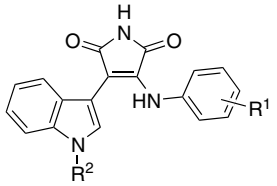
3a

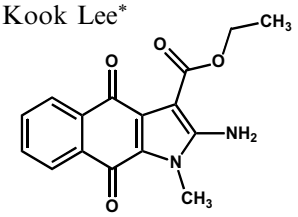
N-{2-[2-(4-Phenylbutyl)benzofuran-4-yl]cyclopropylmethyl}acetamide **3a** was synthesized as an orally bioavailable agonist at MT_1 and MT_2 melatonin receptors with significantly low vasoconstrictive activity.

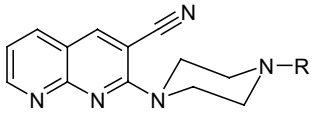


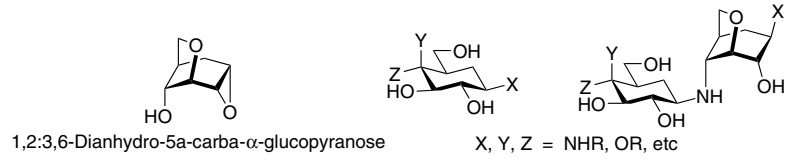
Human blood *trans*-sialidase able to form and split α2-8 disialic bond in gangliosides.



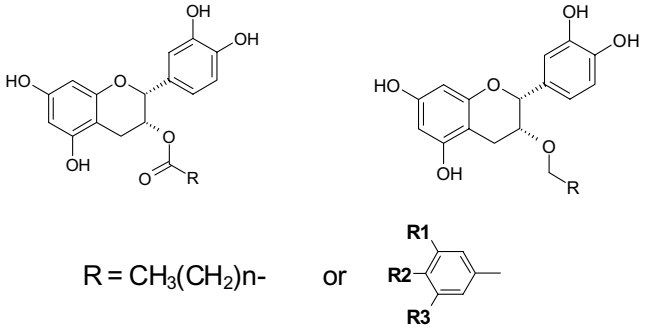


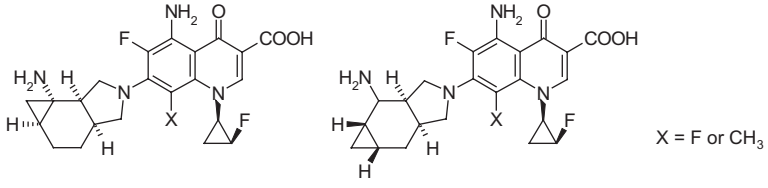




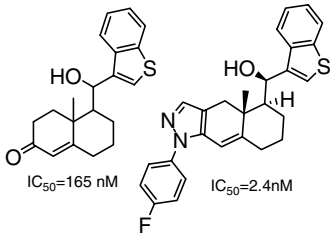


We report the synthesis and anticancer effects of 3-*O*-acyl and alkyl-(−)-epicatechin derivatives.

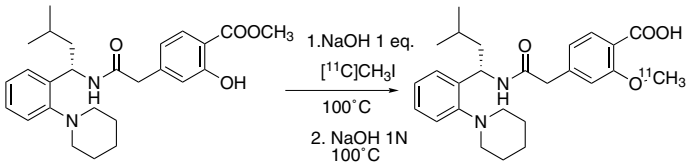


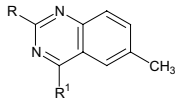


New quinolone compounds were synthesized and evaluated their antibacterial activity and enzyme selectivity.



A novel class of phenylpyrazole fused Wieland–Miescher ketone derivatives are high affinity, receptor specific, selective modulators of glucocorticoid receptor (GR) function.

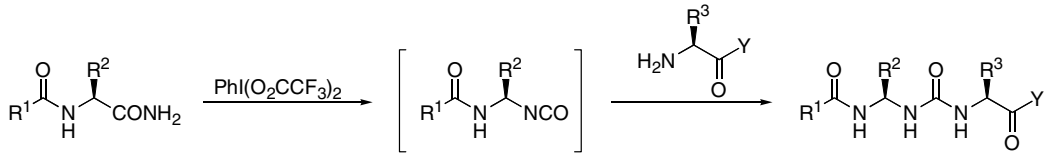




(Compound 6)

6a R = Ph ; R^1 = *p*-Me_2N-Ph
6b R = Ph ; R^1 = *p*-MeO-Ph
6c R =  ; R^1 = Ph
6d R =  ; R^1 = *p*-Me_2N-Ph
6e R =  ; R^1 = *p*-MeO-Ph

Aromatase is a target of pharmaceutical interest for the treatment of estrogen-dependent cancers. Azole derivatives such as letrozole or anastrozole have been developed for aromatase inhibition and are used for the treatment of breast tumors. In this paper, four 4-triazolylflavans were synthesized and were found to exhibit moderate to high inhibitory potency against aromatase.



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 htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].

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