Bioorganic & Medicinal Chemistry Letters 20 (2010) 1315–1323

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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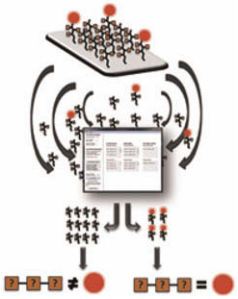
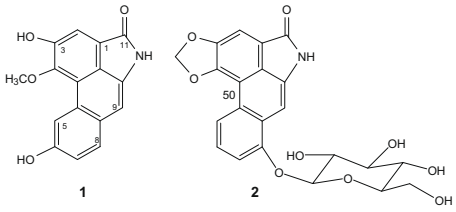
Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 4, 2010

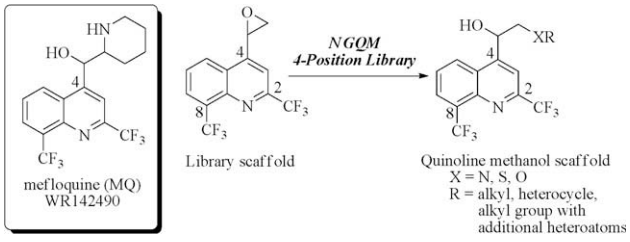
Contents

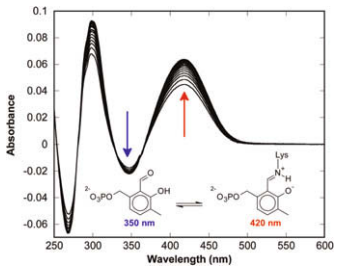
ARTICLES



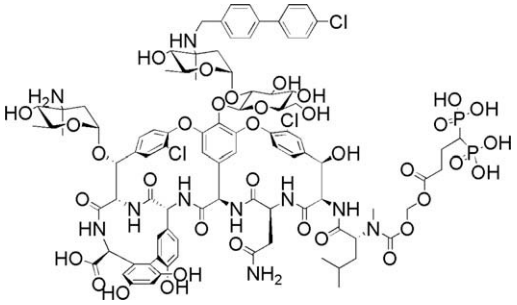


Two novel substituted phenanthrene compounds, SCH 546909 (**1**), and another glycoside (**2**) were isolated from the methanolic extract of the Chinese plant *Aristolochia manshuriensis*. The structures of **1** and **2** were established by NMR. They were identified as inhibitors of the CDK2 enzyme. Compound **1** was found to be a potent inhibitor of the CDK2 enzyme with an IC_{50} of 140 nM, whereas compound **2** was found to be less active with an IC_{50} of >10 μM.

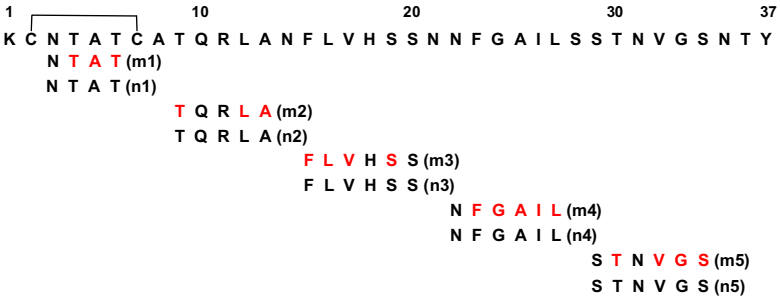


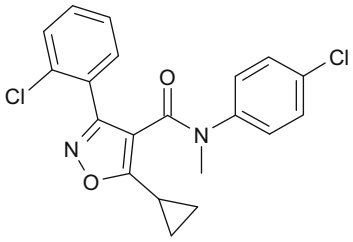


Formation of aspartate aminotransferase internal aldimine with 1-deaza-pyridoxal 5́-phosphate. The free cofactor analogue, λ_{max} ~350 nm, displays a bathochromic shift upon formation of the internal aldimine, λ_{max} ~420 nm. The internal aldimine with pyridoxal 5́-phosphate absorbs at ~430 nm.

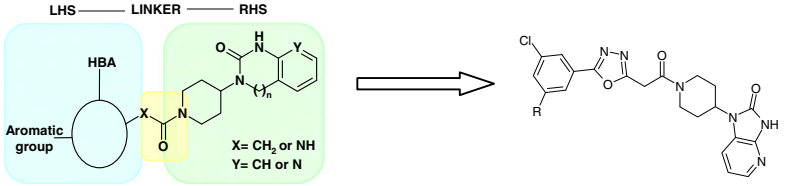


The syntheses and in vitro characterization of bisphosphonated vancomycin and oritavancin prodrugs are reported.

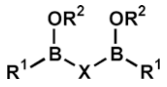


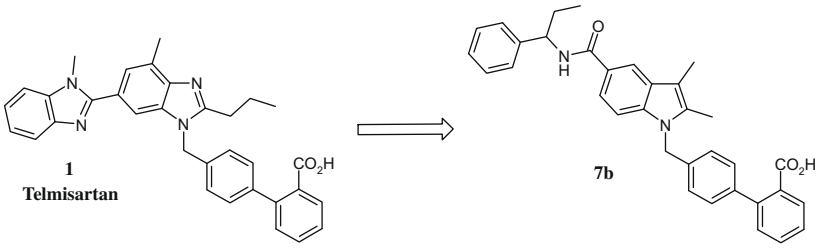


61: pEC_{50} (hTGR5) = 8.4

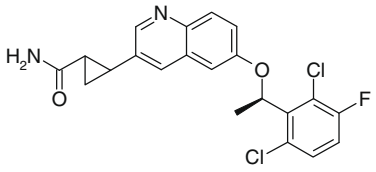


Using a pharmacophore model, based on known CGRP receptor antagonists, a novel series of oxadiazole CGRP receptor antagonists has been identified and the subsequent optimisation to enhance both potency and bioavailability is presented.

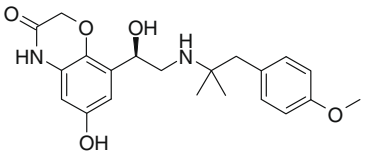




Starting from the structure of Telmisartan, a new series of potent and selective PPARγ modulators was identified. The synthesis, in vitro and in vivo evaluation of the most potent compounds are reported and the X-ray structure of compound **7b** bound to the PPARγ ligand binding domain is described.

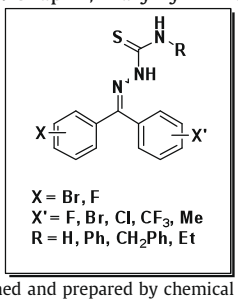


c-Met IC_{50} = 9.3 nM
MKN45 IC_{50} = 93 nM

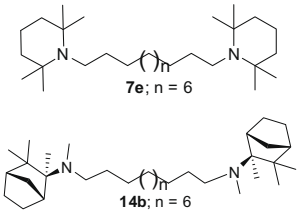


(R)-**4p**

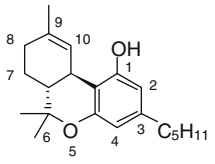
The discovery of the β_2-adrenoceptor agonist (*R*)-**4p** designated olodaterol is described. The preclinical profile of the compound suggests a bronchoprotective effect over 24 h in humans.



A variety of benzophenone thiosemicarbazone analogs have been designed and prepared by chemical synthesis. A sub-set of these compounds demonstrated potent inhibition of cathepsin L with minimal inhibition of cathepsin B.

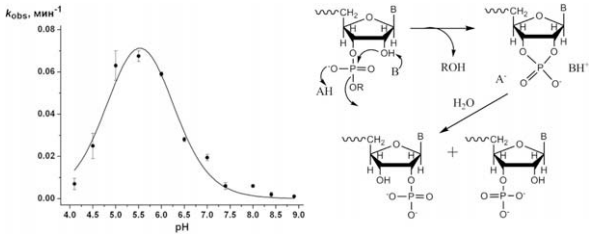


Compounds **7e** and **14b** demonstrated high potency in decreasing nicotine-evoked [^{3}H]dopamine release from rat striatal slices (IC_{50} = 2.2 and 46 nM, respectively). Such bis-tertiary amino analogs may provide a new strategy for the design of drugable ligands that have high inhibitory potency against nAChRs mediating nicotine-evoked dopamine release in striatum, which have been suggested to be target receptors of interest in the development of potential smoking cessation therapies.

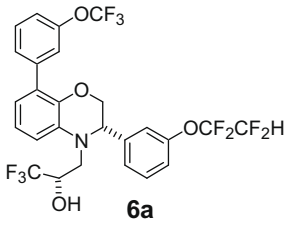


1, Δ9-THC

Modification of Δ9-THC (**1**) utilizing the C-1 triflate intermediates was investigated. The resulting compounds indicate that these modifications can lead to potent and selective CB_2 ligands.

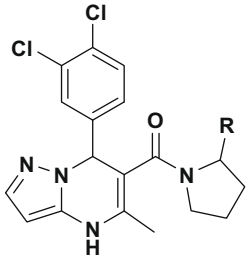


RNA hydrolysis in the presence of HSA and rHSA proceeds via 2′,3′-cyclophosphate intermediates in accordance with a general acid–base mechanism of catalysis.



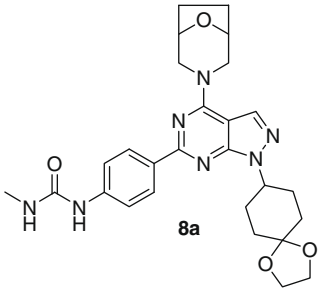
6a

2,3-Dihydro-3,8-diphenylbenzo[1,4]oxazine **6a** is a potent inhibitor (IC_{50} = 26 nM) of cholesteryl ester transfer protein (CETP). It possesses a favorable pharmacokinetic profile and long human liver microsome stability ($t_{1/2}$ = 62 min). It increases HDL-C in animal model studies. The SAR of this series is discussed herein.

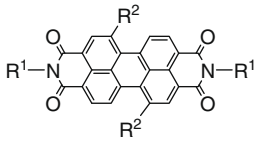


Design and synthesis of pyrazolodihydropyrimidines as K_V1.5 blockers led to the discovery of **7d** as a potent and selective antagonist. This compound showed atrial selective prolongation of effective refractory period in rabbits and was selected for clinical development.

Combination of a 1-cyclohexyl ketal group with a 2,6-ethylene bridged morpholine in the 4-position and a ureidophenyl group in the 6-positon of the pyrazolopyrimidine resulted in compound **8a**, that selectively suppressed key mTOR biomarkers in vivo for at least 8 h following oral administration and showed excellent activity in a tumor xenograft model.

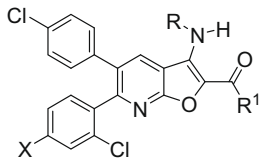


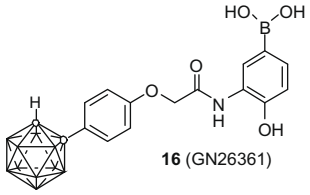
8a



R^1 = $(CH_2)_6NH_3^+$; Spermine
R^2 = $O(CH_2)_3NH_3^+$; OMe ; Br

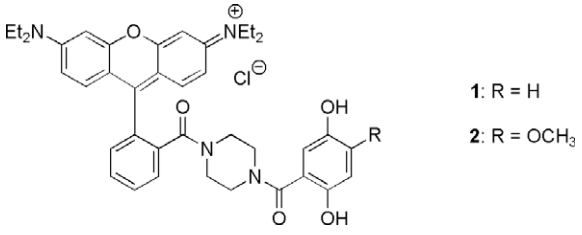
Fluorescent perylenediimide probes modified with 2, 4, 6, or 8 ammonium groups were synthesized and their binding to the antithrombotic drug heparin was studied by fluorescence spectroscopy in solution.





16 (GN26361)

Compound **16** (GN25361) was found to be a potent inhibitor against HIF-1α accumulation under hypoxic condition without affecting the mRNA expression level of HIF-1α.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

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ISSN 0960-894X