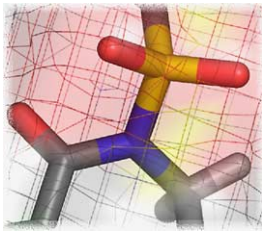
ELSEVIER

Bioorganic &
Medicinal
Chemistry

Bioorganic & Medicinal Chemistry Vol. 13, No. 3, 2005

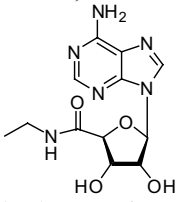
Contents

REVIEW



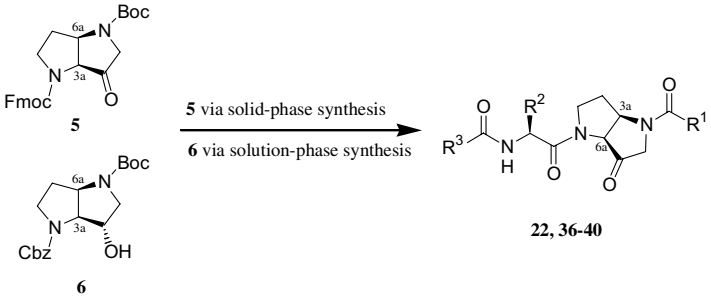
Kenner's safety-catch linker evolved over the years into a unique and versatile tool in various chemistry associated disciplines. An overview about linker construct variations, activation methods, applications and technical aspects is given.

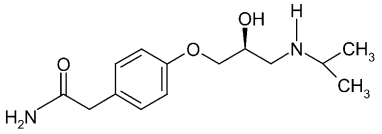
ARTICLES



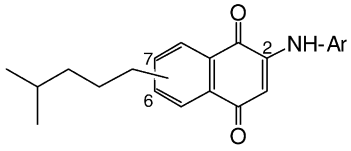
The RDF descriptors have been applied to the study of the A_{2B} agonist effect of adenosine analogues reported with this activity. A model able to describe more than 70% of the variance in the experimental activity was developed with the use of the mentioned approach. In contrast, none of the eleven different approaches was able to explain more than 47% of the variance in the mentioned property.

Fmoc-protected 5,5-bicyclic intermediates **5** and **6** were prepared through an intramolecular cyclisation of *anti*-epoxide **17**. Building block **5** was utilised in a solid phase synthesis and building block **6** in solution syntheses of potent peptidomimetic inhibitors of a range of CAC1 cysteinyl proteinases. Compound **22** was evaluated in vitro as a low nanomolar and selective inhibitor of human cathepsin K that exhibited sub-micromolar activity in a cell-based human osteoclast assay of bone resorption.



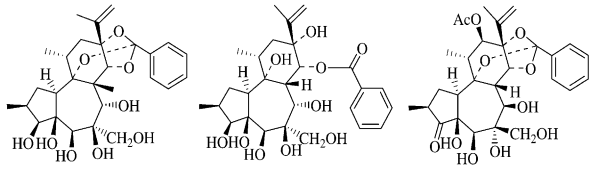


Enantioselective synthesis of (*S*)-atenolol has been described here. The chiral source used is the Jacobsen catalyst (*R*,*R*) (salen Co(III)OAc) complex for the resolution of terminal epoxide.

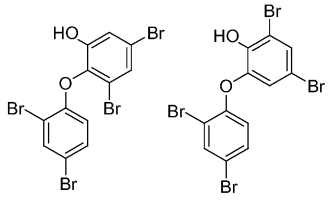


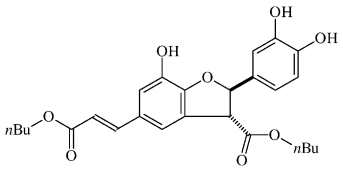
Several 6(7)-alkyl-2-(alkyl/arylamino)-1,4-naphthoquinones (NQ) have been prepared and evaluated as cytotoxics. Those with *p*-oxyarylamino substituents were the most potent compounds, showing GI_{50} under μM level.

Twelve highly oxygenated novel daphnane-type diterpenoids genkwanines A–L (**1**–**12**), together with four known diterpenes (**13**–**16**), were isolated from the bud of *Daphne genkwa*, a well-known TCM. The inhibitory activity against endothelium cell HMEC proliferation and cytotoxic activities against two tumor cell lines were assessed for all the compounds **1**–**16**, and found to be significant and structure related.

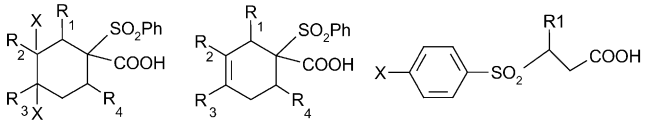


1 **9** **12**



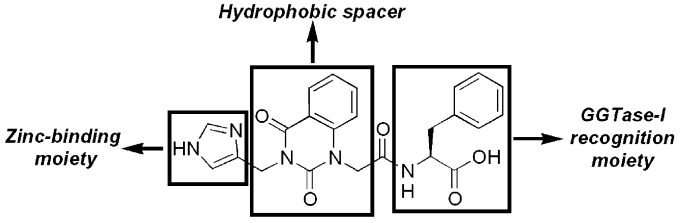


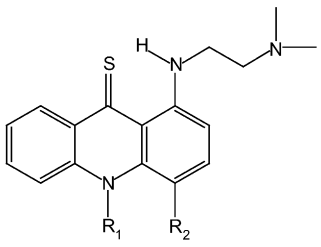
A synthetic dihydrobenzofuran lignan showed a high activity against chloroquine-resistant *Plasmodium falciparum* (strain K1) (IC_{50} 0.43 μg/mL) and *Leishmania donovani* (axenic amastigotes) (IC_{50} 0.12 μg/mL), which was confirmed in an infected macrophage assay (IC_{50} 0.19 μg/mL).

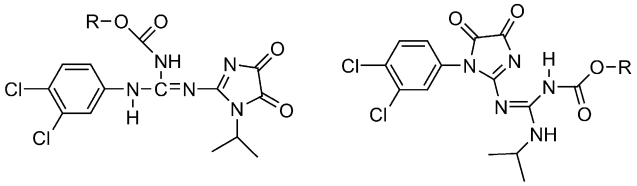


A structure-taste study of arylsulfonyl(cyclo)alkanecarboxylic acids is reported.

Using a benzoyleneurea scaffold as a mimetic for the central dipeptide (AA), CAAX peptidomimetic inhibitors that selectively block the activity of PGGTase-I over PFTase were synthesized. In this series, compound **6c** containing a L-phenylalanine moiety displayed the highest inhibition activity against PGGTase-I (IC_{50} = 170 nM). These PGGTase-I inhibitors represent novel and promising leads for the development of potent inhibitors of mammalian PGGTase-I as antitumor agents.

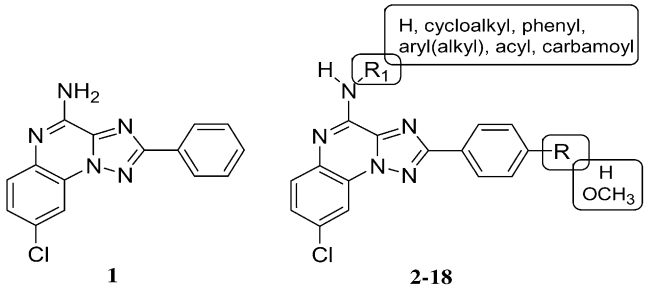




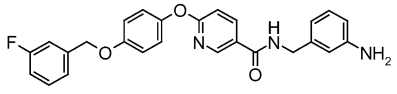


R = CH_2CH_3, $C(CH_3)_3$, $CH_2CH(CH_3)_2$

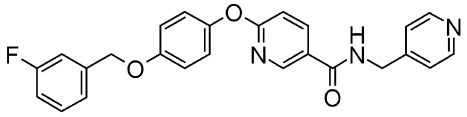
The synthesis and bA_1, bA_{2A}, and hA_3 adenosine receptor binding affinity of some 2-phenyl-1,2,4-triazolo[1,5-*a*]-quinoxaline derivatives **2–18** bearing different substituents on either the 4-amino moiety (acyl or carbamoyl groups) or the 2-phenyl ring (4-OCH_3) of previously reported 8-chloro-2-phenyl-1,2,4-triazolo[1,5-*a*]quinoxalin-4-amine (**1**), are described. Structure–activity relationships have been explained analyzing the three-dimensional structure of the antagonist-A_3 receptor models obtained by molecular docking simulation.



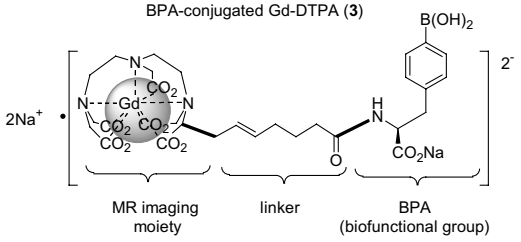
1 **2-18**

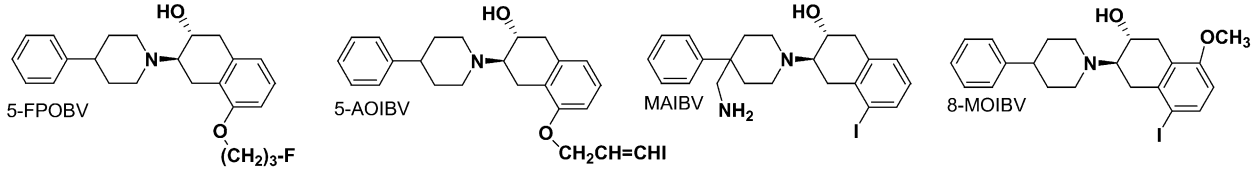


A series of 6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinamide derivatives were prepared, and their inhibitory activities against the reverse and forward modes of the sodium–calcium exchanger were evaluated. The structure–activity relationships for these compounds are discussed, and the results of a QSAR study are presented.

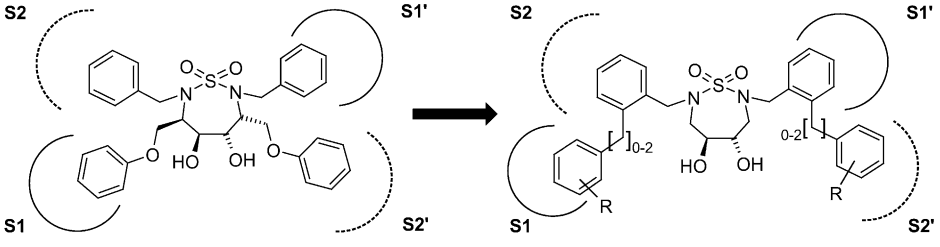


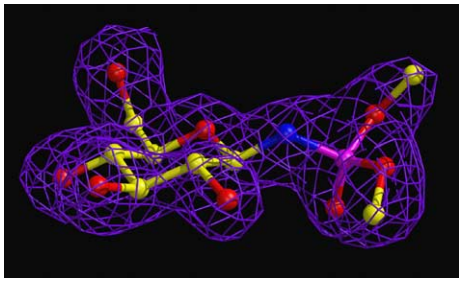
A series of benzyloxyphenyl derivatives were prepared, and their inhibitory activities against the reverse and forward modes of the sodium–calcium exchanger (NCX) were evaluated. The structure–activity relationships of these compounds are discussed. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(pyridin-4-ylmethyl)nicotinamide was further evaluated for its effects in a heart failure model.



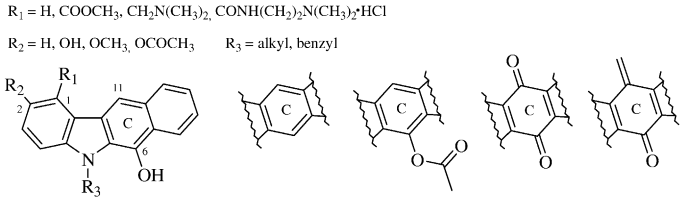


Four sets of enantiomeric derivatives of benzovesamicol were synthesized and their binding affinities for the VAChT determined in vitro. The high affinity of the fluorinated (5-FPOBV) and the iodinated (5-AOIBV) derivatives make them potential PET or SPECT radiotracers.

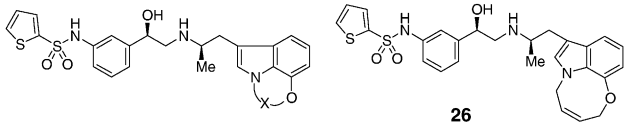




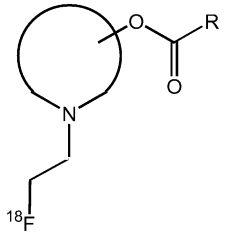
β-D-Glucopyranosyl bismethoxyphosphoramidate, a glucosyl phosphate analogue, was tested for inhibition of and binding to glycogen phosphorylase b. The structural basis of inhibition is presented by analysing the crystal structure of the enzyme in complex with the inhibitor at 1.83 Å resolution.



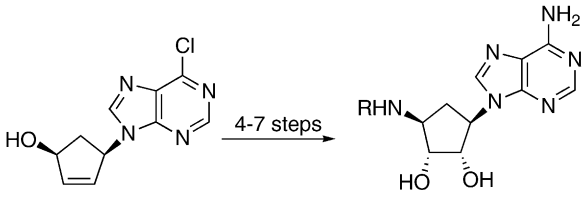
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→2)]-β-D-Gal*p*-1→OMp
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-1→OMp
β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→2)]-β-D-Gal*p*-(1→6)
-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→2)]
-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-[α-L-Ara*f*-(1→3)]-β-D-Gal*p*-(1→6)-β-D-Gal*p*-1→OMp



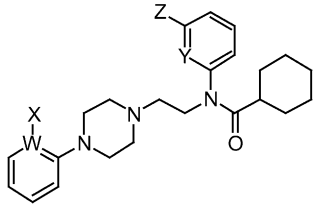
The synthesis and biological evaluation of a series of 1,7-cyclized indole-based human β_3-adrenergic receptor (AR) agonists are described. SAR studies showed that the size of the 1,7-linker portion significantly affected subtype selectivity for the β_3-AR. An unsaturated eight-membered ring analogue **26** exhibited potent agonistic activity and extremely high selectivity for human β_3-AR.



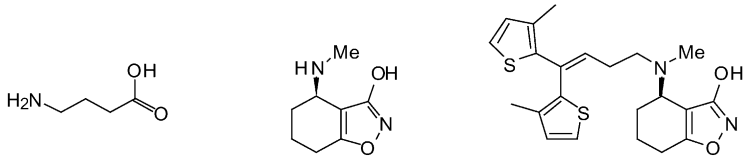
A series of ^{18}F-labeled PMP analogs was evaluated in vivo as AChE substrates for PET imaging.



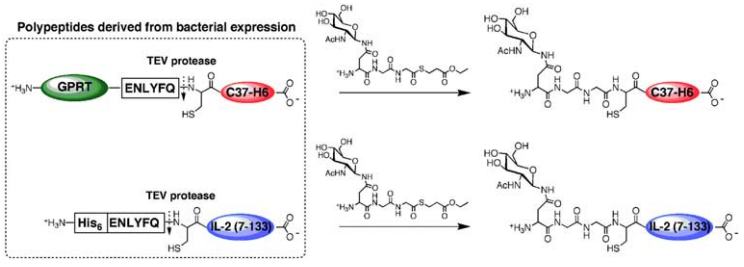
3, R = Ac
4, R = CHO
5, R = CH_3



W	X	Y	Z
C	OMe	NO	H
C	OMe	NO	Cl
N	O	N	H



GABA (*R*)-*N*-Me-*exo*-THPO (**5**) (*R*)-**28d**



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

A safety pin ensures reliable connection as long as it is properly closed. Likewise *N*-acyl-sulfonamides can be used to link molecules, temporarily. Unlocking the safety-catch by controlled activation transforms the inert constructs into reactive species. These resulting *N*-acyl-*N*-alkyl-sulfonamide anchors depicted in the background possess attractive applicability in bioorganic and medicinal chemistry. [Heidler, P.; Link, A. *Bioorg. Med. Chem.* **2005**, *13*, 585–599].
© 2005 A. Link. Published by Elsevier Ltd.

SCIENCE DIRECT™

Full text of this journal is available, on-line from **ScienceDirect**. Visit **www.sciencedirect.com** for more information.

CONTENTS Direct

This journal is part of **ContentsDirect**, the ***free*** alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: **http://contentsdirect.elsevier.com**

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0968-0896