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Chemistry
Letters

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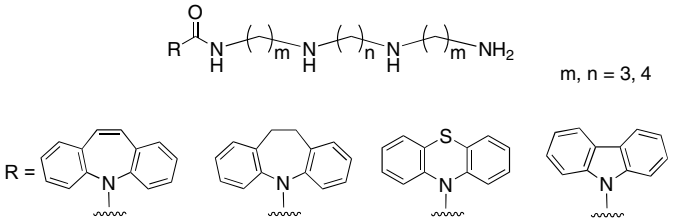
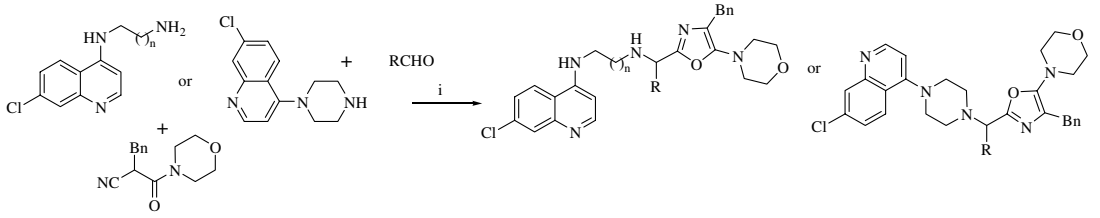
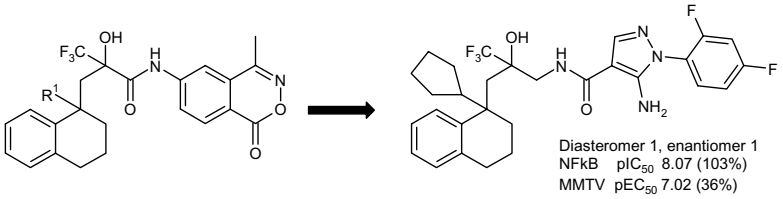
Contents

ARTICLES

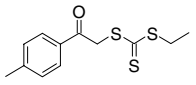




The synthesis and biological activity of a new series of 4-aminoquinoline-containing 2,4,5-trisubstituted aminoxazoles is described.



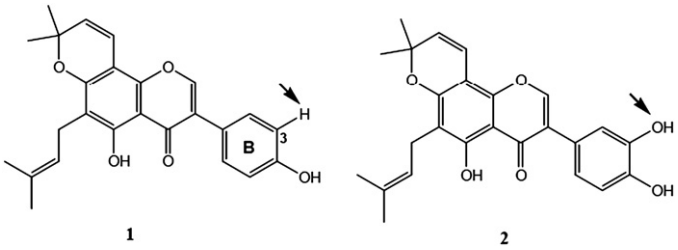
Based on a modelling and iterative approach, a potent dissociated glucocorticoid agonist was discovered where the benzoxazinone is replaced with an aryl pyrazole.



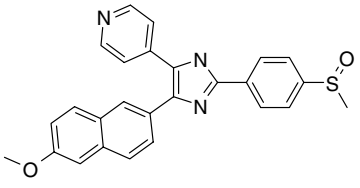
1c pIC_{50} = 6.2 (Biochemical HDAC assay)

Trithiocarbonates are described as a new class of head groups for HDAC inhibition with biochemical and cellular activity.

Pomiferin (**2**) was isolated from the fruits of *Maclura pomifera* as a potential histone deacetylase inhibitor. Its structure was determined by spectral and chemical methods. It inhibited histone deacetylase derived from PC-3 cell lines with GI_{50} values ranging from 3.78 μM. Further structure–activity relationships of position 3 on ring B from aromatic ring will be reported in due course.



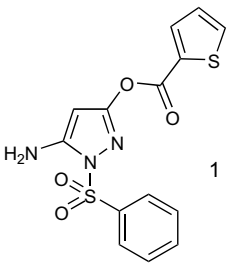
1 **2**



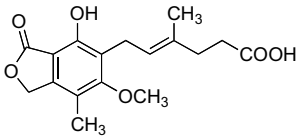
5 IC_{50} 250 nM

The synthesis and in-depth evaluation of compound **5**, an inhibitor (IC_{50} = 250 nM) of Tie2 kinase, is described.

Substituted pyrazole esters were identified as hits in a high throughput screen (HTS) of the NIH Molecular Libraries Small Molecule Repository (MLSMR) to identify inhibitors of the enzyme cathepsin B. Members of this class, along with functional group analogs, were synthesized in an effort to define the structural requirements for activity. Analog characterization was hampered by the need to include a reducing agent such as dithiothreitol (DTT) or cysteine in the assay, highlighting the caution required in interpreting biological data gathered in the presence of such nucleophiles. Despite the confounding effects of DTT and cysteine, our studies demonstrate that the pyrazole **1** acts as alternative substrate for cathepsin B, rather than as an inhibitor.



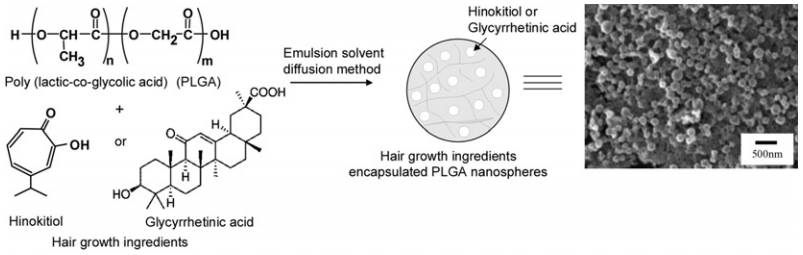
1

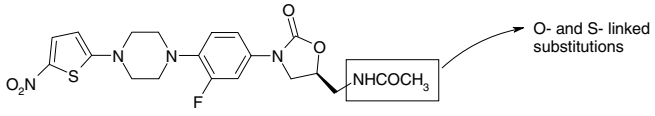


Mycophenolic acid (**1**)

Mycophenolic acid (**1**), known as an inhibitor of inosine monophosphate dehydrogenase (IMPDH), was found to inhibit the differentiation of 3T3-L1 pre-adipocytes into mature adipocytes. Although the effect of **1** could be attributed to inhibition of IMPDH, we identified **1** as a latent agonist of PPARγ. This is the first report that molecular target of **1** except IMPDH was found.

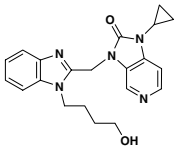
The permeation of hair growing ingredients encapsulated in PLGA nanosphere having about 200 nm in mean particle size to the follicles of extracted human skin, and their effects on the fur growth of C3H mice, was evaluated. The PLGA nanospheres are useful carriers to deliver hair growing ingredients to follicles.



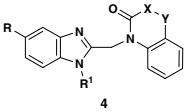


1 (RBx 8700)

Novel oxazolidinone derivatives of the lead compound RBx 8700 containing methylene oxygen- and methylene sulfur-linked substituents at C5-position were synthesized and their biological activity reported.

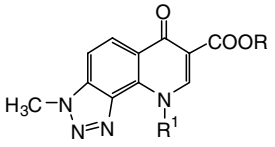


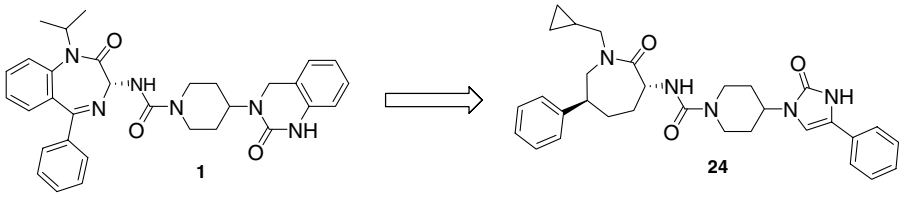
BMS-433771 (1)



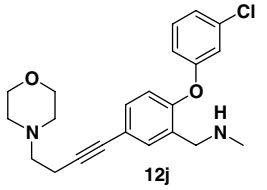
4

The effect of structural variation of the benzimidazol-2-one ring of RSV fusion inhibitors related to BMS-433771 (**1**) was examined in conjunction with side chain modifications and the introduction of an aminomethyl substituent at the 5-position of the core benzimidazole moiety. Replacement of the benzimidazol-2-one moiety with benzoxazole, oxindole, quinoline-2-one, quinazolin-2,4-dione and benzothiazine derivatives provided a series of potent RSV fusion inhibitors **4**. However, the intrinsic potency of 6,6-fused ring systems was generally less than that of comparably substituted 5,6-fused heterocycles of the type found in BMS-433771 (**1**). The introduction of an aminomethyl substituent to the benzimidazole ring enhanced antiviral activity in the 6,6-fused ring systems.





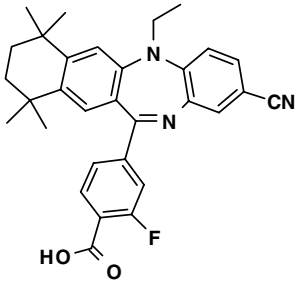
A series of (3*R*)-amino-(6*S*)-phenyl caprolactams were identified as benzodiazepine replacements for an early lead structure **1**. The syntheses and SAR studies leading to the discovery of **24** are described.

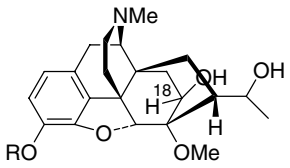


H_3 K_i =3.0 nM
SERT K_i=7.3 nM

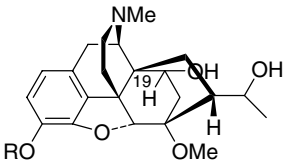
Novel benzyl amines are potent histamine H_3 antagonists and serotonin reuptake inhibitors.

A series of diazepinylbenzoic acid derivatives were synthesized and tested in the inhibition assay of the transactivation of RXR. Oral treatment of cyano derivatives showed anti-diabetic and anti-obesity effects in KK-A^y mice.

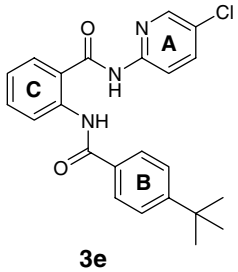




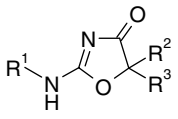
Partial mu opioid agonists



Full mu opioid agonists

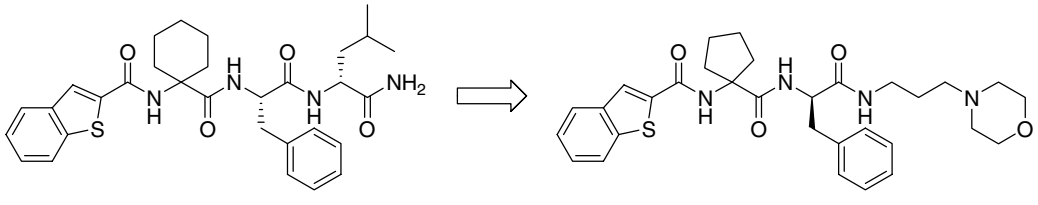


3e



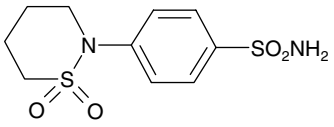
1

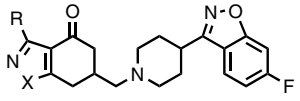
Compounds of general formula **1** were found to be potent inhibitors of 11β-HSD1. Synthesis, structure–activity relationship and metabolic stability of these compounds are reported.



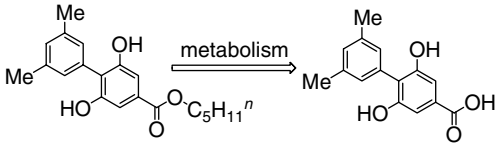
1 pKi = 7.15 (hNK_2) **43** pKi = 9.2 (hNK_2)

In the search for a novel class of hNK2 antagonists, compound **1** was identified from a tripeptide library. Subsequent optimization of binding affinity and physicochemical properties afforded **43**, subnanomolar hNK2 antagonist.



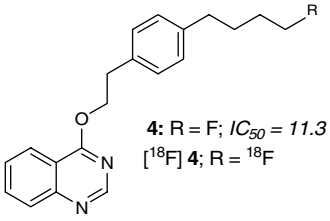


X = NH, NCH_3, O
R = H, CH_3

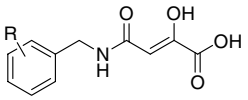


active soft CB-ligand inactive product

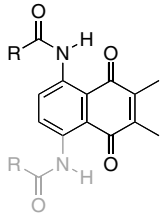
Several quinazoline derivatives based on fenazaquin were synthesized as highly potent MC-I inhibitors. One of these (shown above) was radiolabeled using ^{18}F and was shown to have rapid uptake and retention in the heart.



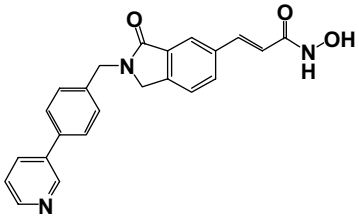
4: R = F; *IC_{50} = 11.3 nM*
[^{18}F] **4**; R = ^{18}F



SAR study of benzyl amide-ketoacid based chemotype yielded highly active inhibitors of the HIV-integrase.

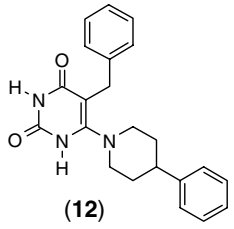


Peri-amide-substituted naphthoquinones were synthesized and their reduction potentials, N–H IR and N–H ^{1}H NMR absorptions were recorded.

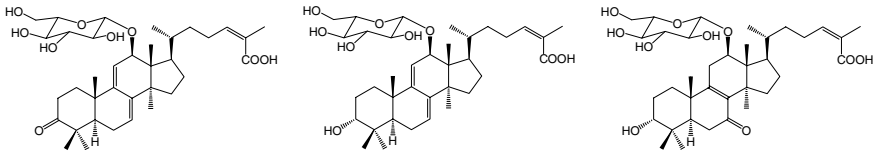


We designed and synthesized hydroxamic acid derivatives bearing a 4-(3-pyridyl)phenyl group as a cap structure, and found that they exhibit potent histone deacetylase (HDAC) inhibitory activity.

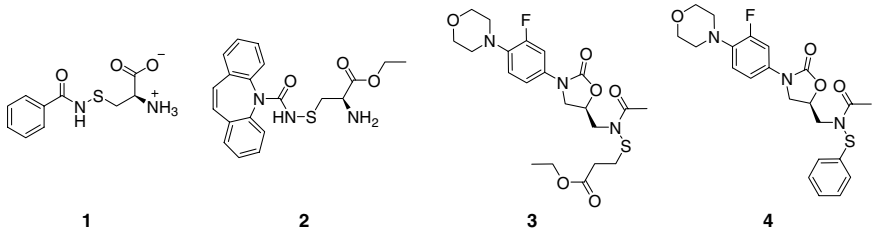
A virtual screening approach followed by lead optimization led to a series of compounds, exemplified by **12**, that were potent, selective GR antagonists.



(**12**)

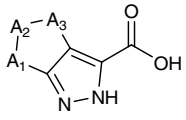


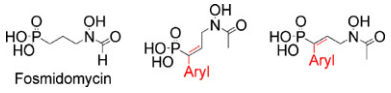
New triterpene glucosides, oligoporins A–C, protecting DNA from Fenton reaction, were isolated from the methanolic extract of the fruiting bodies of *Oligoporus tephroleucus*. Their structures were established by spectroscopic methods. These compounds significantly exhibited protective effect to plasmid DNA damage by hydroxyl radical (OH) generated from the Fenton reaction with hydrogen peroxide and ferrous.

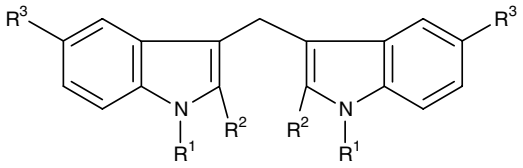


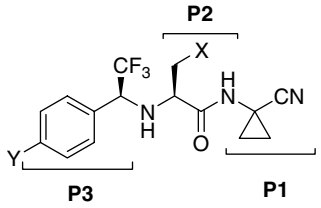
The objective of this report is to introduce the novel concept of utilizing sulfenamides as prodrugs for compounds containing an NH-acidic functionality, particularly weakly acidic amide-type functionalities.

A strategy for lead identification of new agonists of GPR109a is described. Early compound triage led us to focus on a series of pyrazole acid derivatives. Further elaboration of these compounds provided a series of 5,5-fused pyrazoles to be used as lead compounds for further optimization.

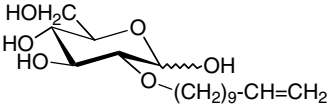






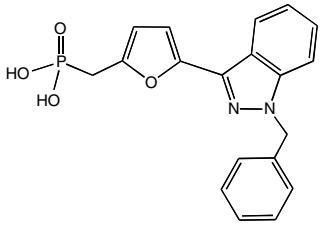


The Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Qué., Canada H9H 3L1.

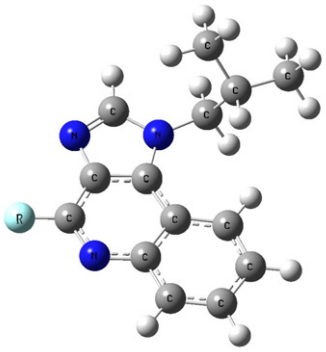


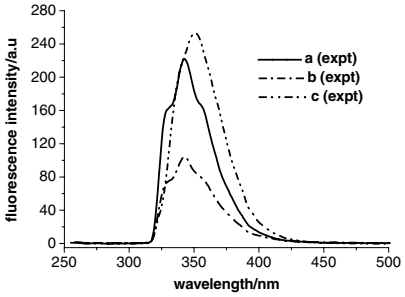
Ki (PfHT) = 2 ± 0.3 μM
Ki (GLUT1) > O.5 mM

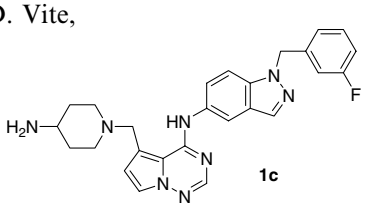
The synthesis and testing of a phosphonate analogue of the soluble guanylate cyclase (sGC) activator YC-1 is described. With enhanced aqueous solubility, the effects of this analogue on sGC are reported.

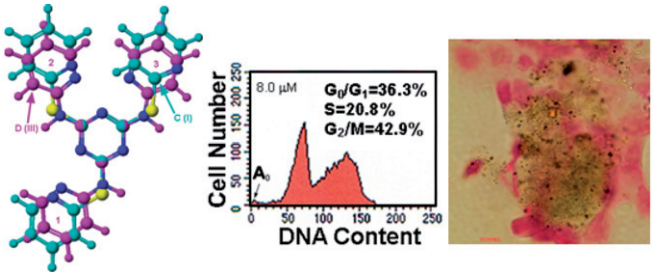


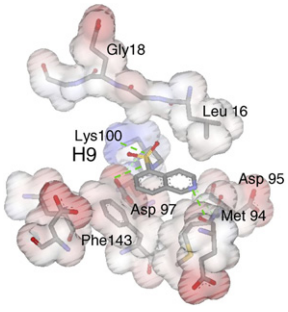
YC-1 phosphonate analogue **5**

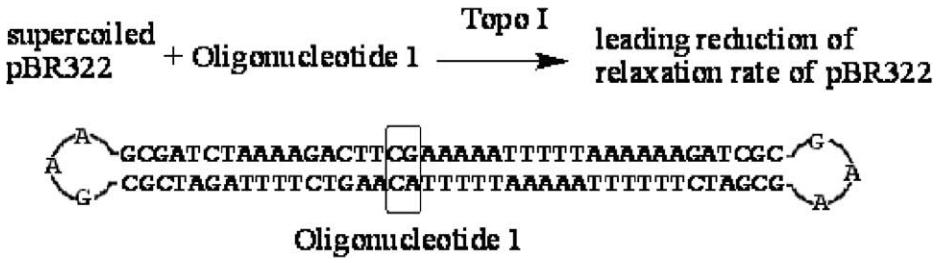




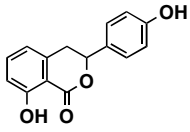




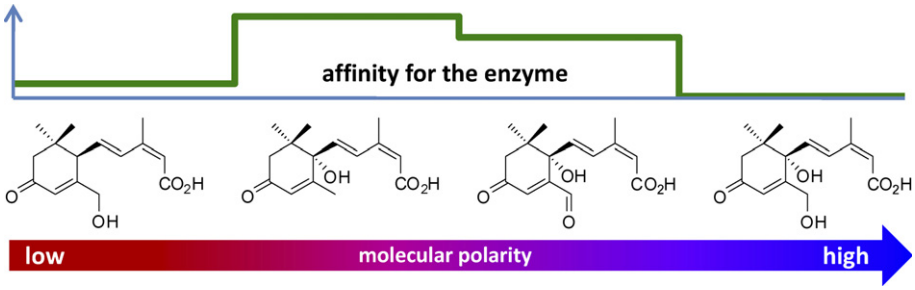


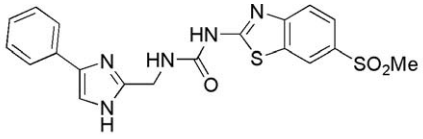


Two 3-phenyldihydroisocoumarins (hydrangenol and phyllodulcin), a 3-phenylisocoumarin (thunberginol A), and a stilbene (hydrangeaic acid) from the processed leaves of *Hydrangea macrophylla* var. *thunbergii* (Hydrangeae Dulcis Folium) promoted adipogenesis of 3T3-L1 cells. Hydrangenol, a principal constituent, significantly increased the amount of adiponectin released into the medium and mRNA levels of adiponectin, peroxisome proliferator-activated receptor γ2 (PPARγ2), and glucose transporter 4 (GLUT4), while it decreased the expression of interleukin 6 (IL-6) mRNA. Furthermore, hydrangenol significantly lowered blood glucose and free fatty acid levels 2 weeks after its administration at a dose of 200 mg/kg/d in KK-A^y mice.



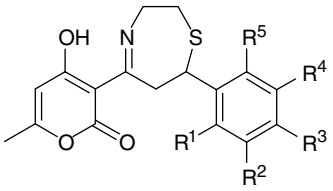
hydrangenol



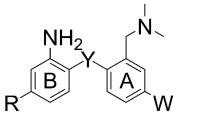


Streptococcus pneumoniae FabK IC_{50} 0.14 μM
MIC 0.5 μg/mL

We discovered the phenylimidazole derivative as a novel inhibitor of bacterial enoyl-ACP reductase (FabK). It selectively exhibited strong FabK-inhibitory activity and good antibacterial activities against *Streptococcus pneumoniae*.



The discovery and SAR studies of 5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-7-phenyl-(*E*)-2,3,6,7-tetrahydro-1,4-thiazepines as a novel series of apoptosis inducers is reported.



R = Me, F, Cl or CN
Y = O or S
W = H, F or Cl

The synthesis of highly potent fluorinated SERT tracers is 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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