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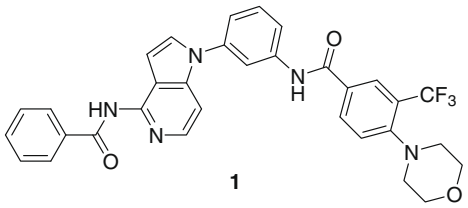
# Bioorganic & Medicinal Chemistry Letters Volume 20, Issue 11, 2010

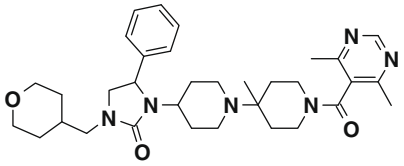
# Contents



**1**

Discovery of a new potent inhibitor of FMS kinase is illustrated. The newly synthesized compound **1** was initially tested at a single concentration of 1μM against 47 different kinases. At this concentration, the% inhibitions of the enzymatic activities of FMS and KDR kinases were 90% and 71%, respectively, while the inhibition in activity was less than 58% for all of the other kinases. In addition, the $IC_{50}$ values for compound **1** against FMS and KDR were 96 and 1058nM, respectively. So, compound **1** was found to be 11 times more selective for FMS kinase than KDR kinase.

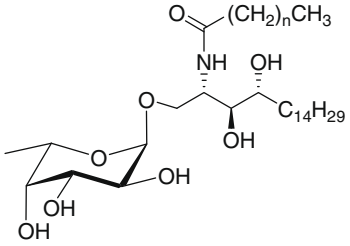




**3**

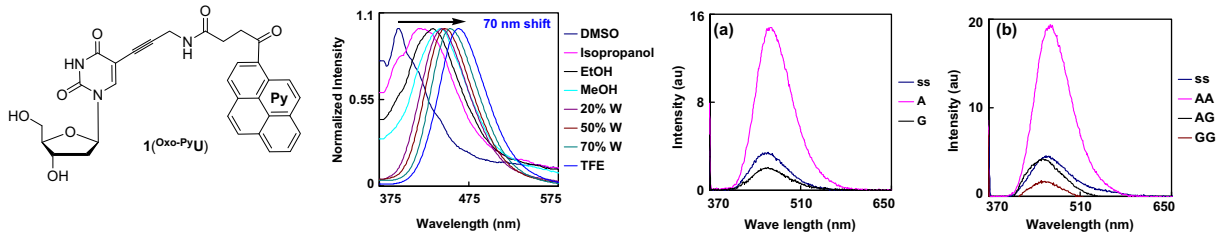
Elaboration of our previously disclosed spiropiperidine template led to the development of a series of novel CCR5 antagonists as represented by analog **3**. Synthetic routes, results of SAR exploration and preliminary lead characterization are described.



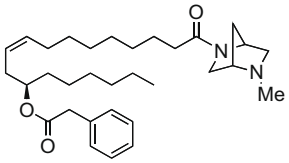


The synthesis of α-L-fucosyl ceramide derivatives and their biological evaluation is described.





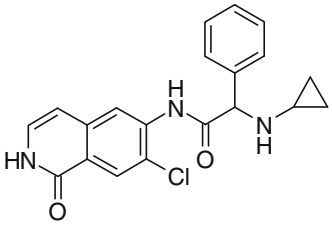

We report the development of new singly and doubly $^{Oxo\text{-}Py}U$ labeled fluorescent oligonucleotide probes for the discrimination of A and consecutive AA bases of target DNA via generation of enhanced fluorescence signal.



**4** CB1R agonist

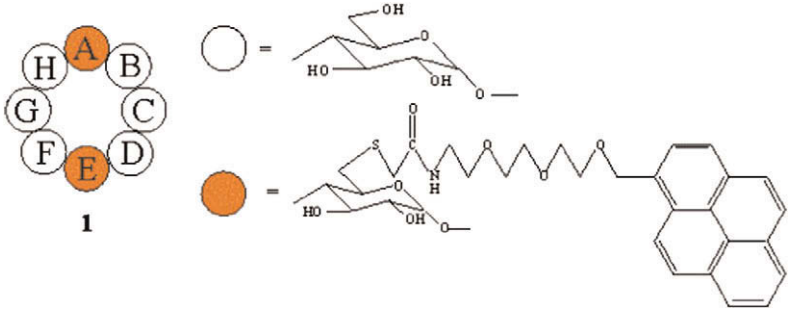
The synthesis of a new cannabinoid receptor (CB1R) agonist, derived from ricinoleic acid and a chiral diazabicycle is reported.





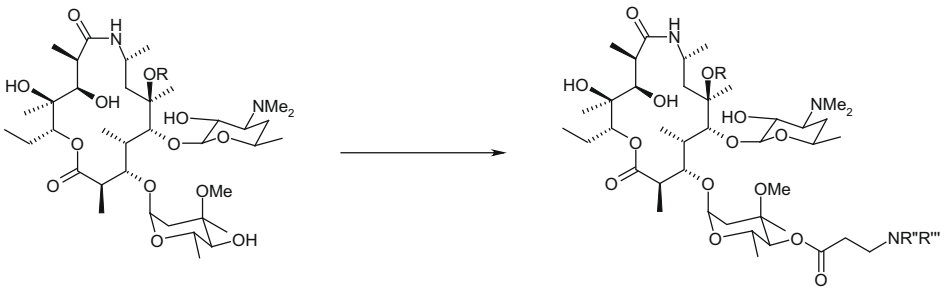
**22**

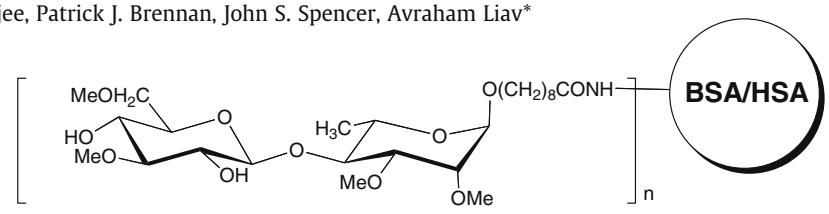




**1**



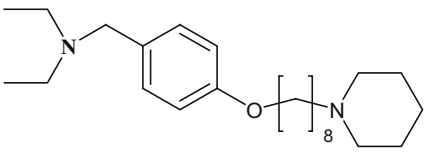





ND-O-BSA, n=32
ND-O-HSA, n=40

The non-reducing disaccharide segment of phenolic glycolipid I from *Mycobacterium leprae*, *O*-(3,6-di-*O*-methyl-β-D-glucopyranosyl)-(1→4)-*O*-2,3-di-*O*-methyl-α-L-rhamnopyranose was synthesized by an improved procedure and efficiently conjugated to bovine/human serum albumin.

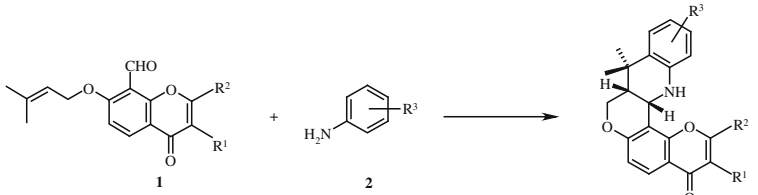





**26** $IC_{50}$=0.092 μM (AChE); $IC_{50}$=0.0073 μM (BChE)

A series of 4-[(diethylamino)methyl]-phenol derivatives were designed, synthesized, and evaluated as cholinesterase inhibitors. Compound **26** was found to be the most potent inhibitor.





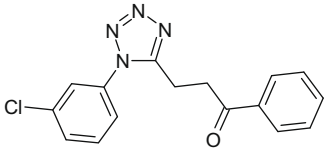

**1**
$R^1$, $R^2$ = H, alkyl, aryl
$R^3$ = H, alkyl, aryl, halo

**2**

**3** *cis*-isomers only

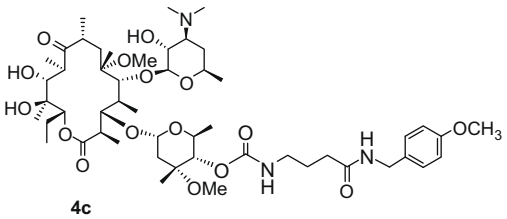
New *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines were synthesized by intramolecular [4+2] imino-Diels–Alder reactions of 2-azadienes derived in situ from aromatic amines and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones. The structures were established by spectroscopic data and further confirmed by X-ray diffraction analysis. These compounds were evaluated for their antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cells.






hHSD1 $IC_{50}$ = 114nM

The synthesis and biological activity of a series of 1,5-substituted 1*H*-tetrazoles that modulate 11β-HSD1 activity is reported.

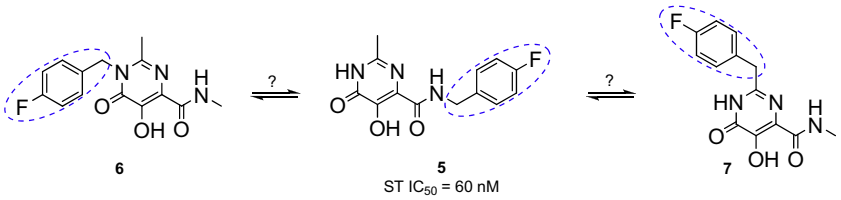


**4c**

MIC = 0.06μg/mL

Novel 4″-*O*-arylalkylcarbamoyl and 4″-*O*-((arylalkylamino)-4-oxo-butyl)carbamoyl clarithromycin derivatives were designed, synthesized and evaluated for their in vitro antibacterial activities. Among them, compound **4c** was the most effective against *Streptococcus pneumoniae* encoded by the *erm* gene.



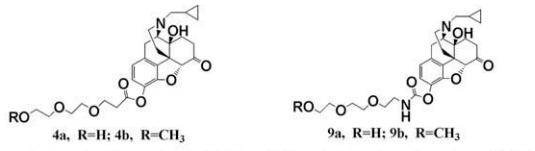


**6** **5** **7**

ST $IC_{50}$ = 60 nM

Would benzyl repositioning of known inhibitor **5** create binding difficulties in **6** and **7**?
Existing docking models say no and a new model says yes.





4a, R=H; 4b, R=$CH_3$

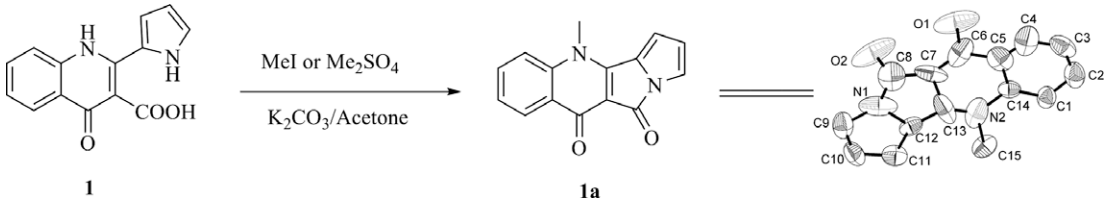
3-*O*-pegylated carboxylate prodrugs of NTX

9a, R=H; 9b, R=$CH_3$

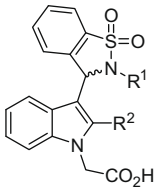
3-*O*-pegylated carbamate prodrugs of NTX

A small library of novel 3-*O*-pegylated carboxylate prodrugs (**4a**–**4b**) and 3-*O*-pegylated carbamate prodrugs (**9a**–**9b**) of naltrexone were synthesized. The goal behind the design of these prodrugs was to investigate their potential for microneedle-enhanced transdermal delivery. All the synthesized 3-*O*-pegylated carboxylate prodrugs (**4a**–**4b**) and 3-*O*-pegylated carbamate prodrugs (**9a**–**9b**) of naltrexone were found to have adequate stability in a transdermal formulation and improved apparent solubility compared to naltrexone. Viscosity effects were postulated to be responsible for the observed non-linearity in the flux-concentration profile of these prodrugs.



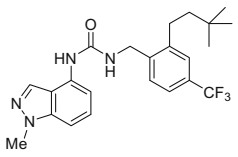


**1** **1a**




CRTh2 (DP2) is a prostaglandin D2 receptor implicated in the recruitment of eosinophils and basophils within the asthmatic lung. Here we report the discovery of a novel series of 3-indolyl sultams that are low nM antagonists of CRTh2. These compounds proved to be selective over the other primary prostaglandin D2 receptor (DP1) as well as the thromboxane A2 receptor (TP).

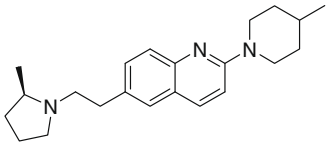





**21** (ABT-116)

The synthesis and SAR of a series of indazole TRPV1 antagonists leading to the identification of ABT-116 are described.

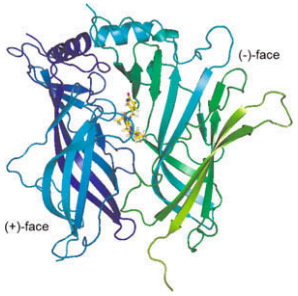




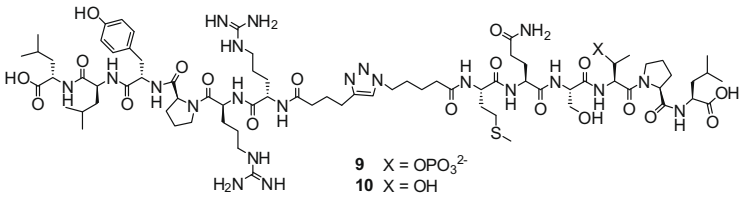

**51**
$H_3$ $pK_i$ = 0.05 nM

A novel series of histamine $H_3$ antagonists containing quinoline core was disclosed. Compound **51** showed 50pM affinity for human histamine $H_3$ in the radio ligand binding assay.

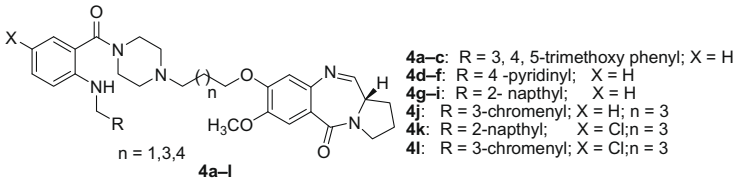




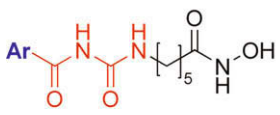

A new series of bis-aromatic ring neonicotinoid analogues (**1a**–**1l**, **2a**–**2c**) were prepared and evaluated for their insecticidal activities. Modeling the ligand–receptor complexes by molecular docking explained the structure–activity relationships observed in vitro.





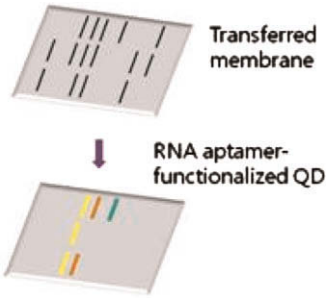



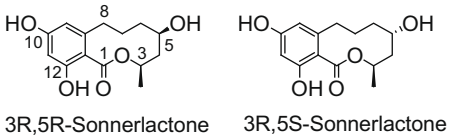


| Compound | Ar | HDAC1 $IC_{50}$ (nM) |
|---|---|---|
| **5b** | Ph | 53 |
| **5g** | 4-Br-Ph | 13 |
| **5i** | 4-I-Ph | 8 |
| **5n** | Naphthalene-2-yl | 6 |
| **19** | 3-$NH_2$-4-Cl-Ph | 11 |



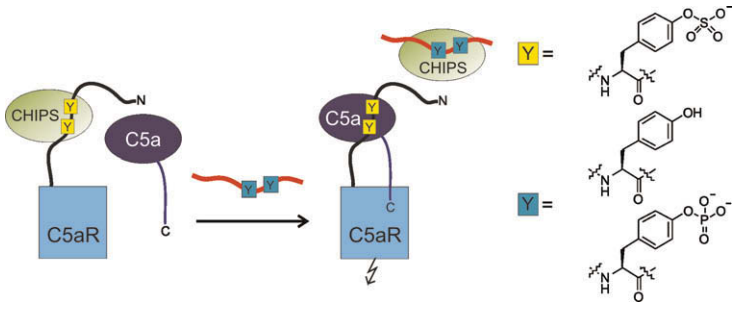




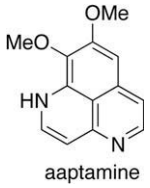

Two new metabolites, 3*R*,5*R*-Sonnerlactone and 3*R*,5*S*-Sonnerlactone, were isolated from the mangrove endophytic fungus Zh6-B1 from the South China Sea. The absolute configuration of 3*R*,5*R*-Sonnerlactone was confirmed by single-crystal X-ray analysis.



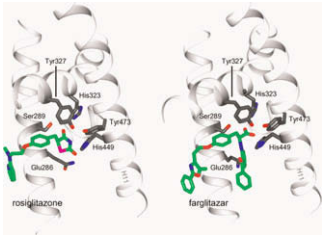




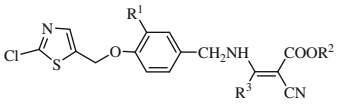




Aaptamine, isoaaptamine, and demethylaaptamine were isolated from the marine sponge *Aaptos suberitoides* as proteasome inhibitors. They inhibited the chymotrypsin-like activity of the proteasome with $IC_{50}$ values of 1.6–4.3 μg/mL.




The large LBP of PPARγ permits different binding systems for typical ligands, and the development of novel ligands of sufficient binding affinity will require adequately hydrophobic pharmacophores.

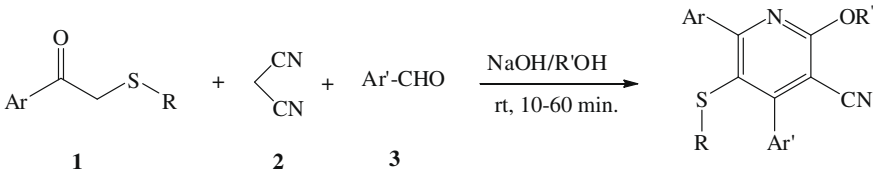





**$R^1$= H 13a-h**
**$R^1$= $OCH_3$ 14a-h**

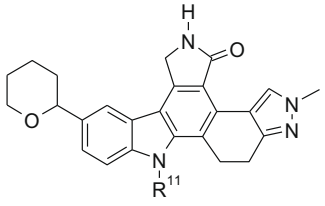
Two series of novel 2-cyano-3-benzylaminoacrylates containing thiazole ring moiety with high Hill inhibitory activities and herbicidal activities were reported.





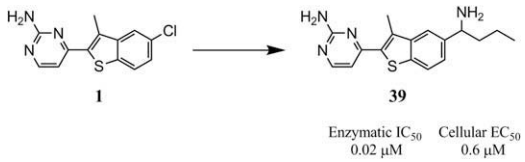

**1** **2** **3** **4/5**





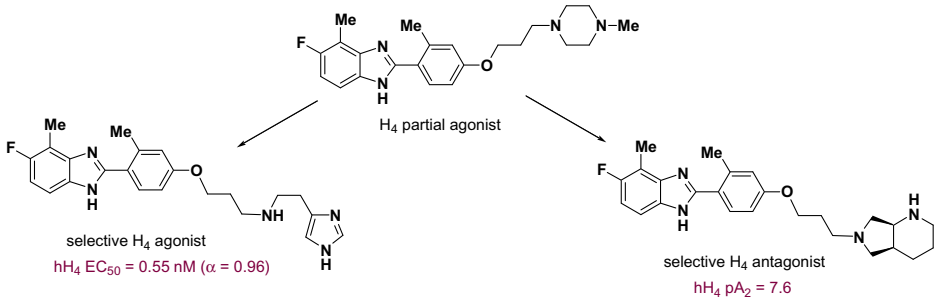

**7f** $R^{11}$ = nBu
**7g** $R^{11}$ = iBu

Structure–activity relationships, X-ray crystallography and oral in vivo anti-tumor activity for a series of 8-THP-DHI dual TIE-2/VEGF-R2 inhibitors are reported.

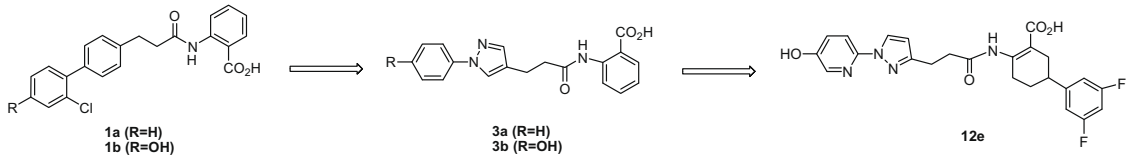



A benzothiophene containing Rho kinase inhibitor was identified in an ultra high-throughput enzymatic assay. SAR studies led to inhibitors with low nM enzymatic $IC_{50}$s, low or sub-μM cellular $EC_{50}$s in a novel label-free assay, and in vivo efficacy in a monkey model of ocular hypertension.



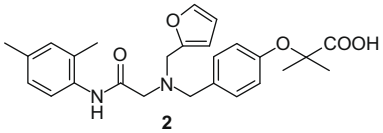




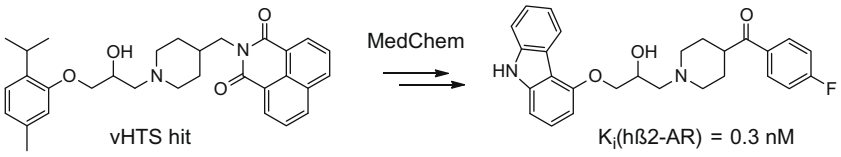




A series of pyrazolyl propionyl cyclohexenamides were discovered as full agonists for the high affinity niacin receptor GPR109A. The structure–activity relationship (SAR) studies were aimed to improve activity on GPR109A, reduce Cytochrome P450 2C8 (CYP2C8) and Cytochrome P450 2C9 (CYP2C9) inhibition, reduce serum shift and improve pharmacokinetic (PK) profiles.

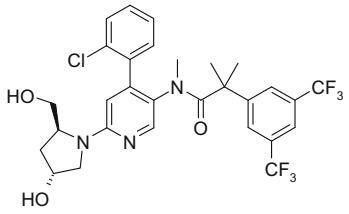





The design, synthesis and pharmacological properties of a novel class of PPARα agonists is described. Compound **2** is a novel, potent and specific glycine amide with oral bioavailability in rodents. The compound is active in vivo and alters plasma lipids in hAPO-A1 transgenic mice after oral administration.



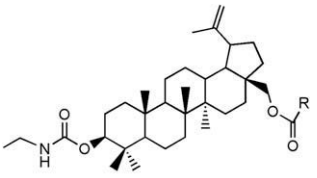



$K_i$ ($hNK_1$) = 0.61 nM
$K_i$ ($hNK_3$) = 1.12 nM

The lead finding activities for a dual $NK_1/NK_3$ receptor antagonist discovery program, resulting in lead compounds with favourable pharmacological and pharmacokinetic properties, are described.

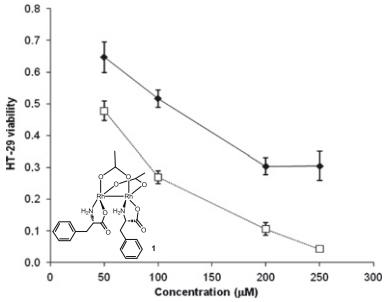




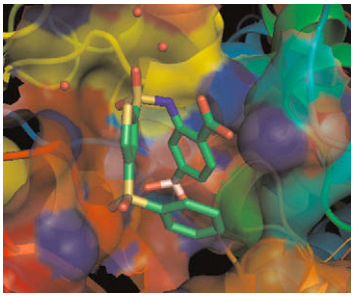

R = $NHC_2H_5$ **(9)**
Me **(11)**

Carbamate derivatives of betulinic acid and betulin were synthesized and tested against fifteen tumor cell lines. The most active compounds **9** (bis(ethylcarbamate)betulin) and **11** (3-*O*-ethylcarbamate of 28-*O*-acetylbetulin) were found to be selectively cytotoxic towards tumor cell lines, inducing apoptosis by activation of caspase 3.

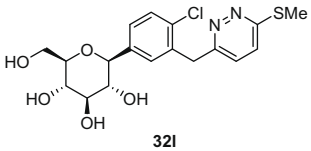





A new rhodium complex ($Rh_2$(*L*-PheAla)$_2$(OAc)$_2$ **1** has demonstrated a stronger anti-proliferative activity than cisplatin, against a human colon adenocarcinoma cell line.



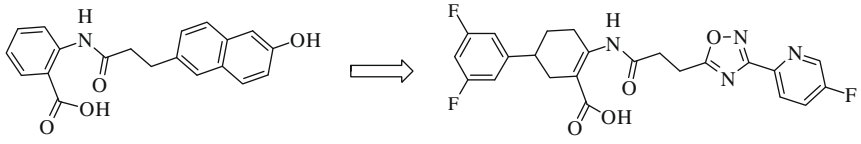




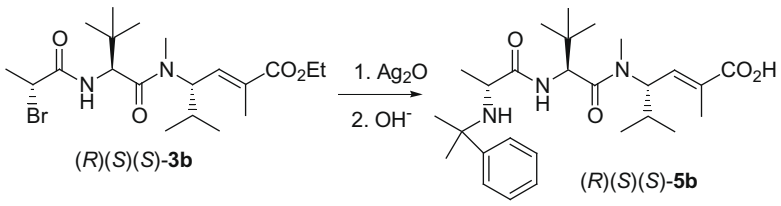

**32l**
(*h*SGLT2 $IC_{50}$ = 13.4 nM)

Novel *C*-aryl glucoside SGLT2 inhibitors containing pyridazine motif were designed and synthesized for biological evaluation. Among various analogs, methylthio-pyridazine **32l** demonstrated the best in vitro inhibitory activity against *h*SGLT2 in this series to date ($IC_{50}$=13. 4nM).



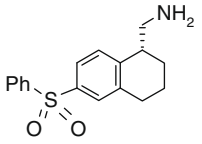




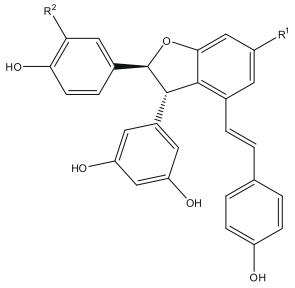




(*R*)(*S*)(*S*)-**3b** (*R*)(*S*)(*S*)-**5b**

A novel class of hemiasterlin analogues has been depicted, through a highly versatile procedure with control of stereochemistry.






| | R$^1$ | R$^2$ |
|---|---|---|
| **scirpusin A** | OH | OH |
| **ε-viniferin glucoside** | OGlc | H |

*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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