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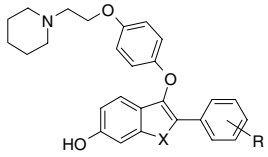
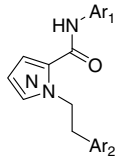
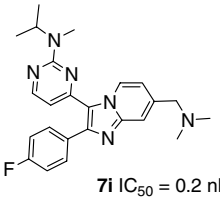
Contents

ARTICLES



SAR studies are described, which led to the discovery of novel SERMs for the treatment of uterine fibroids.

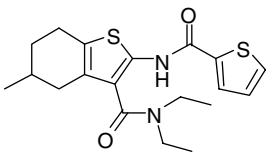




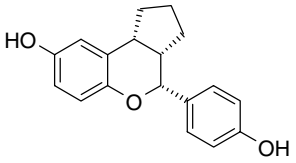
7i IC_{50} = 0.2 nM

Diaryl imidazo[1,2-*a*]pyridine derivatives bearing *N*-alkyl amino substituents have been synthesized and evaluated as highly potent Et-PKG inhibitor and efficacious anticoccidial agents.

We have identified and synthesized a series of thiophene containing inhibitors of kinesin spindle protein. SAR studies led to the synthesis of **33**, which was co-crystallized with KSP and determined to bind to an allosteric pocket previously described for other known KSP inhibitors.



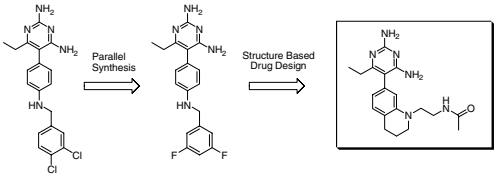
33

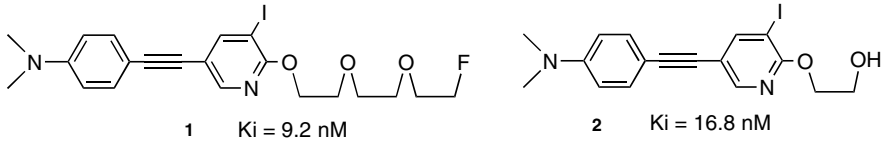


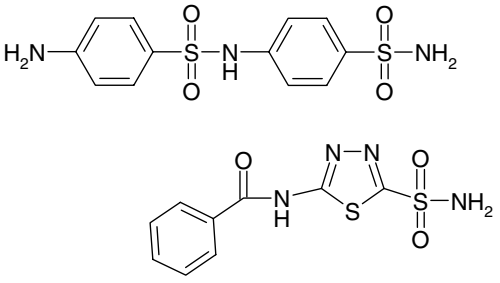
SERBA, **5b**

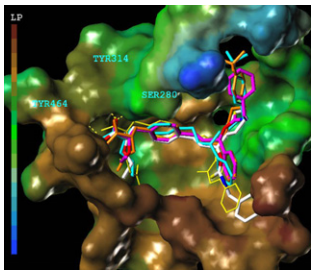
Structure–activity relationship studies that lead to the discovery of benzopyran **5b** are reported.

Novel 2,4-diaminopyrimidine-based small molecule renin inhibitors are disclosed. Through high throughput screening, parallel synthesis, X-ray crystallography, and structure based drug design, we have developed the first non-chiral, non-peptidic, small molecular template to possess moderate potency against renin. The designed compounds consist of a novel 6-ethyl-5-(1,2,3,4-tetrahydro-quinolin-7-yl)pyrimidine-2,4-diamine ring system that exhibit moderate potency (IC_{50}: 91–650 nM) against renin while remaining 'Rule-of-five' compliant.

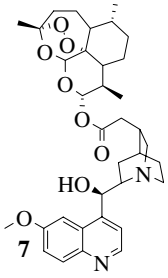


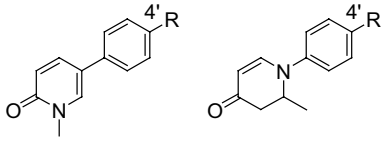




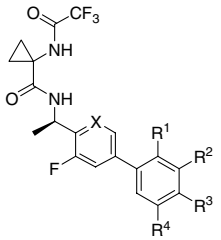


The artemisinin–quinine hybrid **7** was synthesised and shown to have potent activity against the 3D7 and drug-resistant FcB1 strains of *Plasmodium falciparum* in culture. Its activity was superior to that of artemisinin alone, quinine alone, or a 1:1 mixture of artemisinin and quinine.

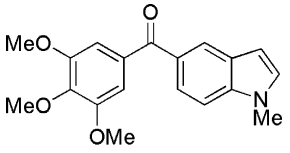




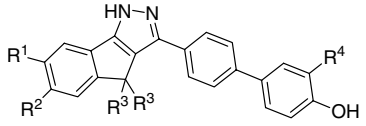
4′-Substituted bicyclic pyridones were prepared and evaluated for non-steroidal inhibition of type 1 and 2 steroid 5α-reductase (SR). SAR for 4′-substituents were determined and compared to SAR derived from a known class of SR inhibitor.

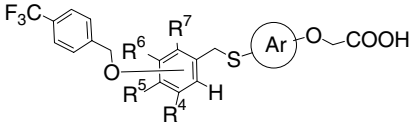


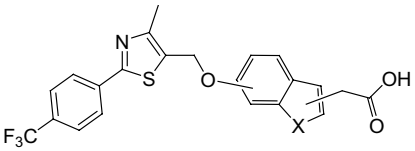
SAR study of the biphenyl region of cyclopropanecarboxamide derived bradykinin B_1 antagonists was examined.



8b: IC_{50} = 9.2-26 nM

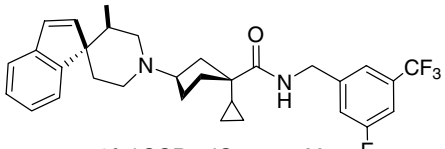






X = O, N, S

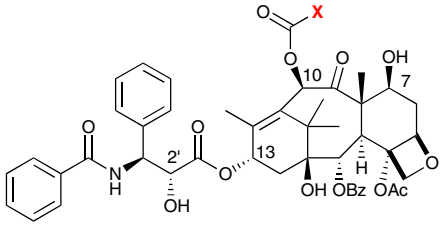
The synthesis and structure–activity relationships of a series of novel and selective benzothiophene, benzofuran and indole-based peroxisome proliferator-activated receptor δ agonists.



6f, *h*CCR2 IC_{50} = 2 nM
*m*CCR2 IC_{50} = 8 nM

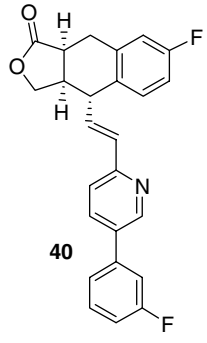
A series of low molecular weight antagonists of both the human and murine CC chemokine receptor 2, containing a 1-alkyl-3-(3-methyl-4-spiroindenylpiperidine)-substituted cyclopentanecarboxamide, is described.

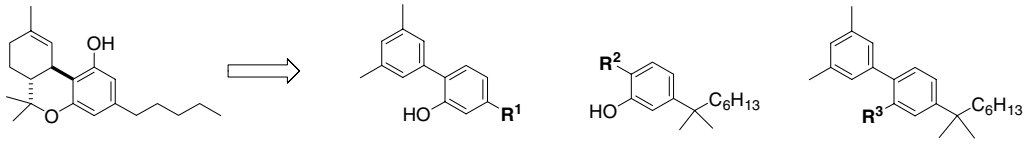
A series of paclitaxel C-10 carbamates was synthesized and evaluated in a bi-directional permeability assay in comparison with paclitaxel and the blood–brain barrier-permeable C-10 ester derivative, TX-67.



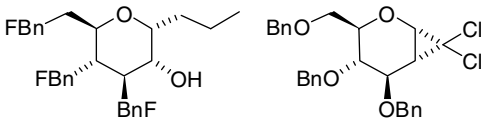
X = CH_3, **Paclitaxel**
X = CH_2CH_2COOH, **TX-67**
X = $NHCH_2COOH$, **CNDR-3**

The synthesis and biological activity of a novel series of thrombin receptor antagonists is described. This series of compounds showed excellent in vitro and in vivo potency. The most potent compound (40) had an IC50 of 7.6 nM and showed robust inhibition of platelet aggregation in a cynomolgus monkey model after oral administration.



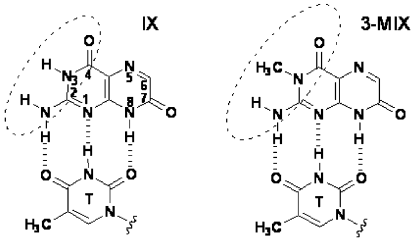


A series of novel-substituted biaryl cannabinoid mimetics was synthesized and their biological activity determined.



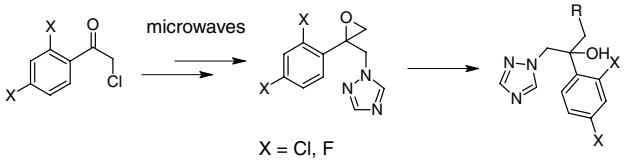
HeLa, GI_{50} = 5.6 μM HOS, GI_{50} = 1.6 μM

Fifty-two *C*-glycosides were synthesized and their in-vitro antiproliferative activity against human cervical carcinoma (HeLa) and osteosarcoma (HOS) screened, showing significant activity.

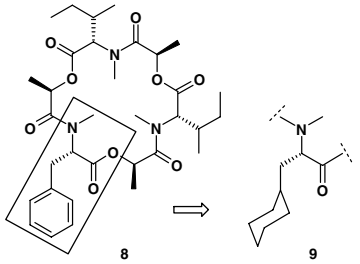


Introducing a methyl group to isoxanthopterin (**IX**), both selectivity and binding affinity for T against C are achieved by 3-methyl isoxanthopterin (**3-MIX**).

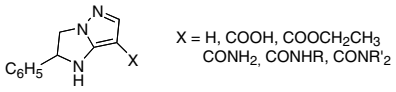
A series of fluconazole analogues **5**–**20** incorporating azaindole and indole moieties were prepared using oxirane intermediates synthesized under microwave irradiation. All of the compounds were evaluated in vitro against two clinically important fungi, *Candida albicans* and *Aspergillus fumigatus*. Four 2,4-dichlorophenyl derivatives **6**, **13**, **14** and **18** exerted high antifungal activity against *C. albicans* with MIC_{80} values 3- to 28-fold lower than that of fluconazole.



Cyclohexadepsipeptides (CHDPs) with cyclohexylmethyl side chains represent novel enniatins with in vivo activity against the parasitic nematode *Haemonchus contortus* Rudolphi in sheep. It was found that the replacement of benzylic by cyclohexylmethyl side chains on the enniatin skeleton can increase anthelmintic efficacy. Here we report on a simple total synthesis of the precursors for this type of CHDPs and efficient chemical transformation of the benzylic into the corresponding cyclohexylmethyl side chains.

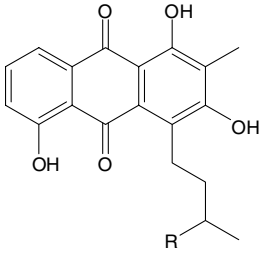


Chemical transformation of the MePhe containing enniatin **8** into the *(S)*-MeCha containing CHDP **9**.

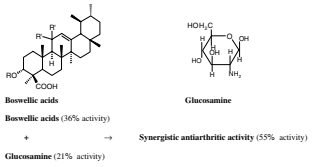


We report here the synthesis of title compounds and their evaluation on neutrophil activation and recruitment.

Two novel anthraquinones, lupinacidins A (**1**) and B (**2**), have been isolated from the culture broth of an endophytic actinomycete. Lupinacidins showed significant inhibitory effects on invasion of murine colon 26-L5 carcinoma cells.

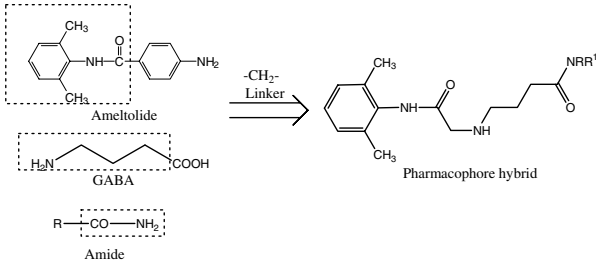


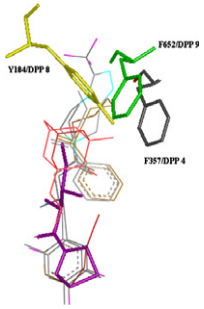
1 R=Me
2 R=H



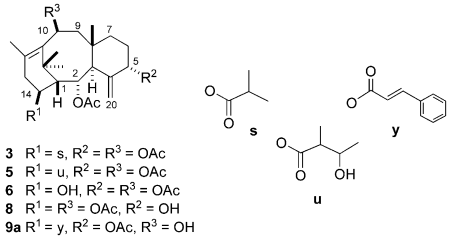
Leukotriene inhibiting boswellic acids and glucosamine individually are known for their anti-arthritic potential in preclinical and clinical studies. A combination of both displayed significant synergism in chronic inflammation, whereas in acute inflammation it was almost insignificant.

A series of pharmacophoric hybrids of ameltolide-γ-aminobutyric acid (GABA)-amides was designed, synthesized, and evaluated for their anticonvulsant and neurotoxic properties. Compound 4-(2-(2,6-dimethylaminophenylamino)-2-oxoethylamino)-*N*-(2,6-dimethylphenyl) butanamide (**7**) emerged as the most potent derivative effective in all the three animal models of seizure with no neurotoxicity at the anticonvulsant dose.

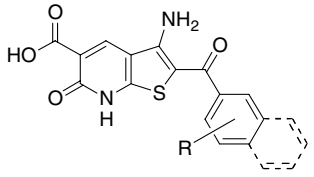


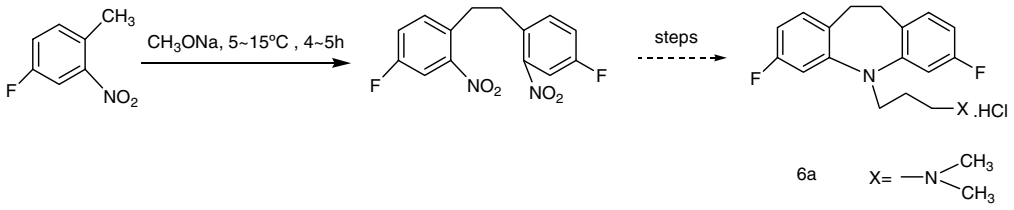


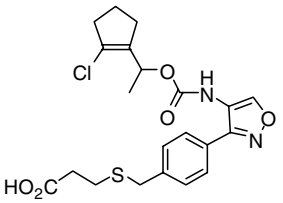
New taxoids bearing a bulky acyloxy group at C-2, C-5, C-7, C-9, C-10, and C-14 were obtained by chemical and bio- transformations of taxuyunnanine C and its analogs. In them, compounds **3**, **5**, **6**, **8**, and **9a** have significant effects of the accumulation of calcein in MDR 2780AD. Since compounds **6** and **8** have no cytotoxic activity, they are desirable compounds as MDR cancer reversal agent. Since compounds **3**, **5**, and **9a** have moderate cytotoxic activity, they are expected to be lead compounds of new-type anticancer agents.



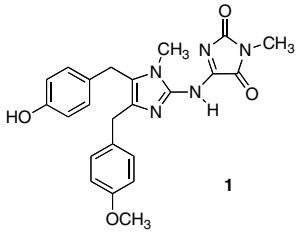
3 R^1 = s, R^2 = R^3 = OAc
5 R^1 = u, R^2 = R^3 = OAc
6 R^1 = OH, R^2 = R^3 = OAc
8 R^1 = R^3 = OAc, R^2 = OH
9a R^1 = y, R^2 = OAc, R^3 = OH





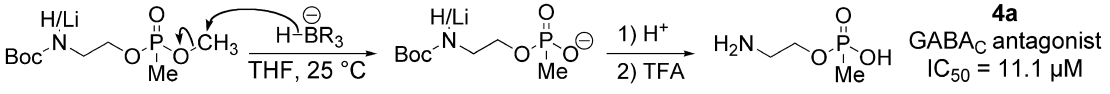


A series of isoxazole derivatives were synthesized and their antagonistic activities against LPA stimulation on both LPA_1/CHO cells and rHSC cells were evaluated. Among them, 3-(4-{4-[1-(2-chloro-cyclopent-1-enyl)-ethoxycarbonylamino]-isoxazol-3-yl}-benzylsulfanyl)-propionic acid (**34**) showed the most potent activities.

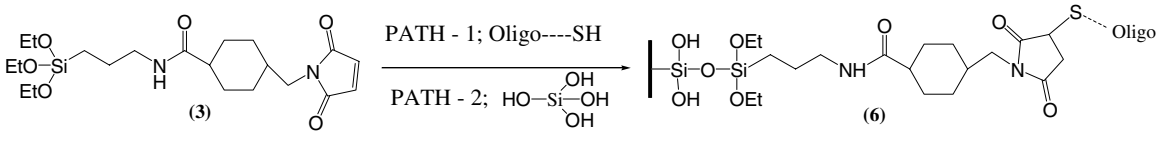


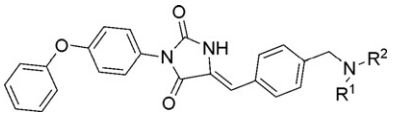
1

The syntheses of deletion analogues and thiazole analogues of naamidine A (**1**) are reported, together with data indicating inhibition of EGF- and IL3-dependent mitogenesis.

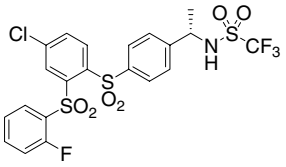


Lithium trialkylborohydrides were found to mono-dealkylate dialkylphosphonates rapidly (rate of cleavage Me, Bn > 1°). The reaction was applied to the synthesis of a new $GABA_C$ antagonist, 2-aminoethyl methylphosphonate (**4a**).

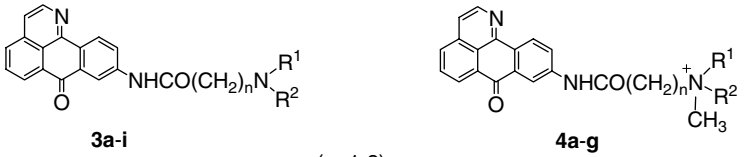




We report here new chemical series acting as antagonists of melanin-concentrating hormone receptor 1 (MCHR-1). Synthesis and structure–activity relationships are described leading to the identification of compounds with optimized in vitro pharmacological and in vitro ADME profiles. In vivo activity has been demonstrated in animal models of food intake and depression.



Optimization of triaryl bis-sulfone cannabinoid ligands is described. Formation of the trifluoromethane sulfonamide moiety gives compounds that are highly potent and selective for CB2 with improved plasma levels.

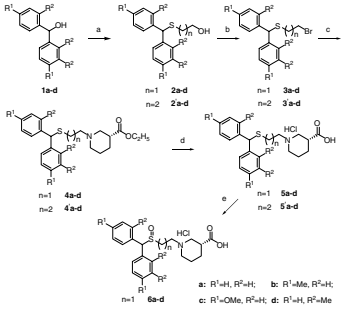


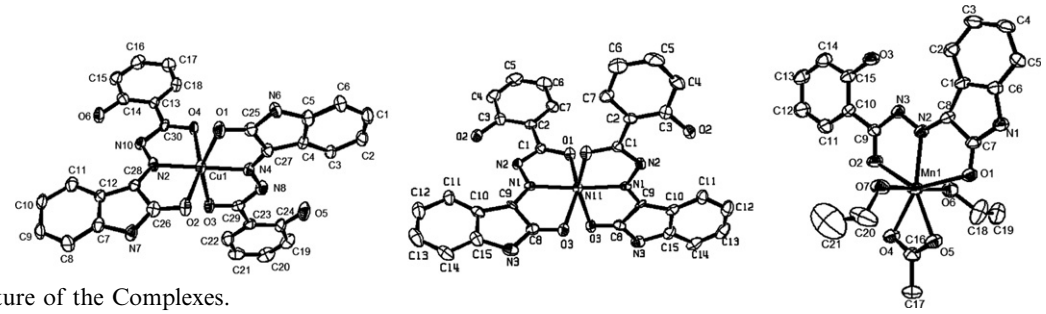
3a-i **4a-g**

(n=1-3)

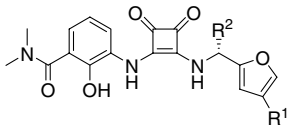
$\left(-N\begin{matrix}R^1\\R^2\end{matrix}= -N\square,\ N(CH_3)_2,\ -NEt_2,\ -NH(CH_2)_2N(CH_3)_2,\ -NH(CH_2)_2OH\right)$

The synthesis of the novel uptake inhibitor **6a** (IC_{50} = 0.92 μm) is reported.





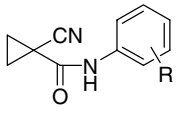
Crystal Structure of the Complexes.

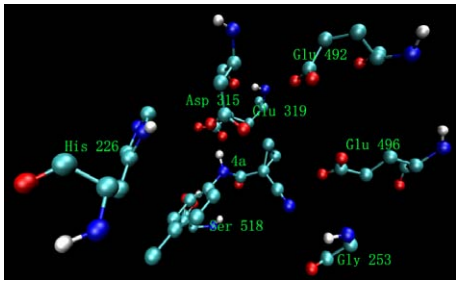


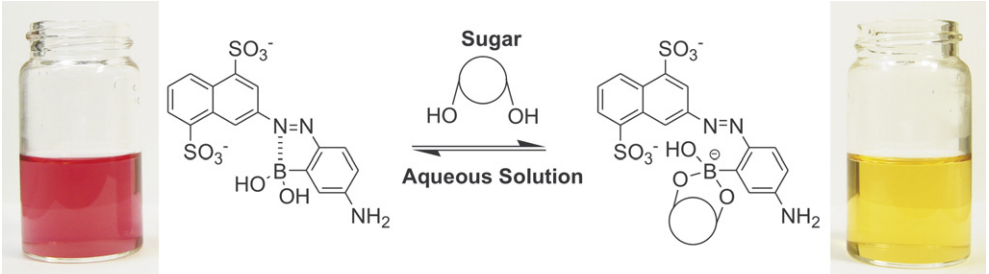
16 R^1 = iPr, R^2 = Et

The discovery and synthesis of the potent CXCR2 and CXCR1 dual antagonist **16** is described.

1-Cycan-1-cycloproprane derivatives against KARI were synthesized.

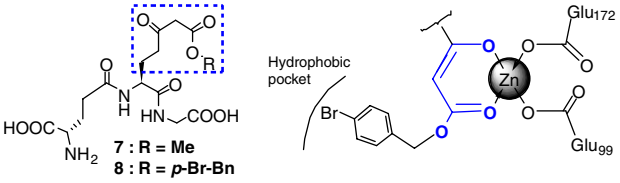






λ_{max} = 521 nm

λ_{max} = 398 nm



The known affinity of ethyl acetoacetate (ACC) toward divalent zinc prompted us to attempt its employment as a chelating moiety in the design of glyoxalase-I inhibitors. A practical synthetic route was developed to incorporate this pharmacophore into the side chain of glutamic acid, with flexibility to allow incorporation of additional functionality at the end-stage of the synthesis. Herein, the details of this synthetic approach as well as the evaluation of the resultant β-keto ester compounds are 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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