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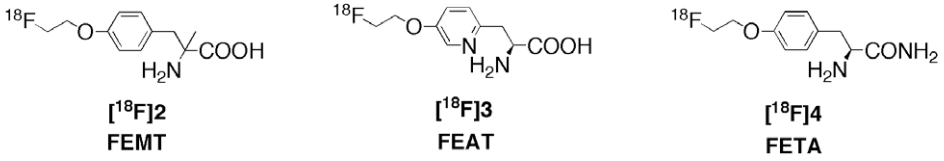
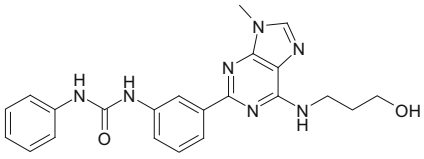
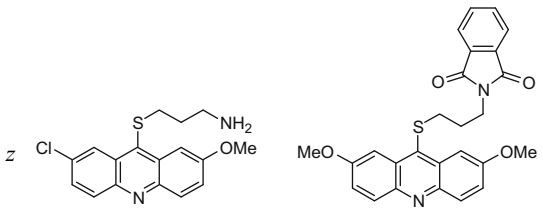
Contents



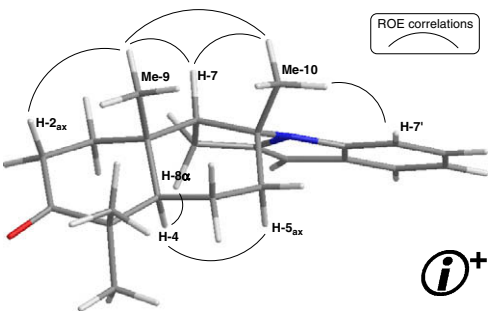
Synthesis and in vitro evaluation of three new fluoroalkyl tyrosine derivatives as PET imaging agents are reported.

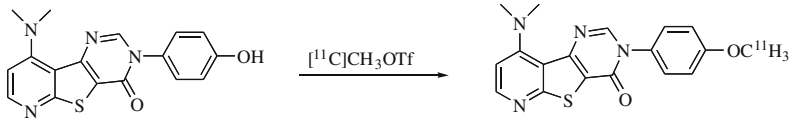


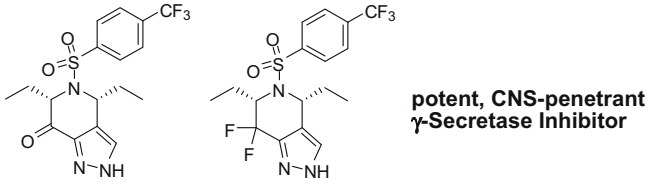
A structure–activity relationship study of a screening hit has led to the identification of bisarylureas as potent inhibitors of *Streptococcus agalactiae* Stk1. As this target has been directly linked to bacterial virulence, these inhibitors can be considered as a promising step towards antivirulence drugs.

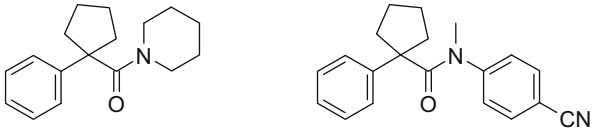


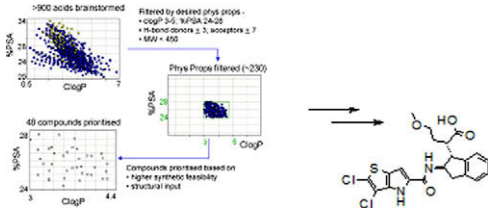
In continuation of our study on medicinal plants of Cameroon, stem barks of *Polyalthia suaveolens* were phytochemically studied. This investigation yielded a new indolosesquiterpene alkaloid, named polysin (**1**) and four hitherto known alkaloids (**2**–**5**). Polysin (**1**) appeared as a competitive reversible inhibitor (K_i = 10 μM) of phosphofructo kinase (PFK) of *Trypanosoma brucei* with respect to fructose-6-phosphate (K_i/K_M = 0.05) and could be used in the design of new trypanocidal drugs. The other isolated compounds (**2**–**5**) also exhibited interesting inhibitory effects on selected glycolytic enzymes (PFK, glyceraldehyde-3-phosphate dehydrogenase and aldolase).



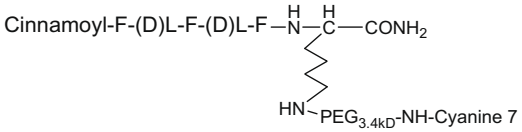








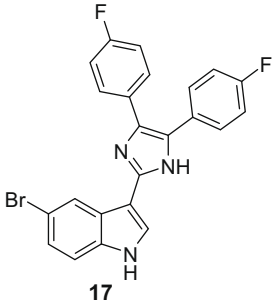
A series of carboxylic acid glycogen phosphorylase inhibitors, which have potential as oral antidiabetic agents, is described. Defining and applying simple physicochemical design criteria was used to assess the opportunity and to focus synthetic efforts on compounds with the greatest probability of success. The study led to compound **17**, which exhibits a good balance of properties including potent inhibition of recombinant human liver glycogen phosphorylase in vitro, a good DMPK profile including excellent bioavailability and low clearance and good in vivo activity in a glucagon challenge model of diabetes in Zucker rats.



9

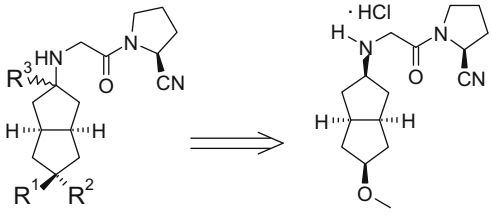
A series of Cyanine 7 labeled neutrophil-specific agents were developed for noninvasive near infrared fluorescence imaging.

Compound **17** [3-(4,5-bis(4-fluorophenyl)-1*H*-imidazol-2-yl)-5-bromo-1*H*-indole] was identified as a potent antimicrobial derivative with MIC of 1 μg/mL against methicillin-resistant *Staphylococcus aureus*.

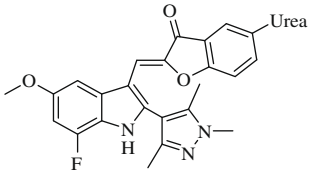


17

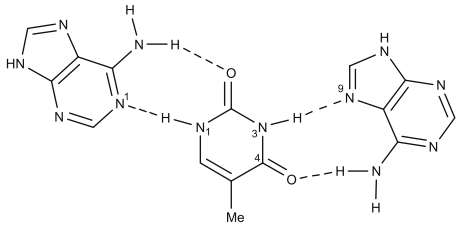
A series of novel bicyclo[3.3.0]octane derivatives have been synthesized and found to be dipeptidyl peptidase 4 (DPP-4) inhibitors. Compounds **10a** and **10b** demonstrate good efficacies in oral glucose tolerance tests.



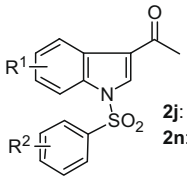
10b



A series of 5-ureidobenzofuran-3-one indoles as potent inhibitors of PI3K-α and mTOR has been developed. In the MDA-MB-361 breast cancer model, the lead compound shrank the tumor size remarkably when dosed at 25 mg/kg iv on days 1, 5, and 9.



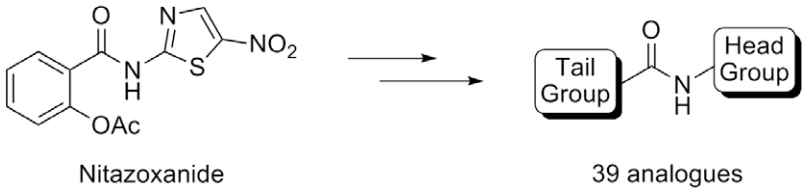
The first known complex of the titled DNA bases was prepared by co-crystallization and studied by X-ray diffraction.



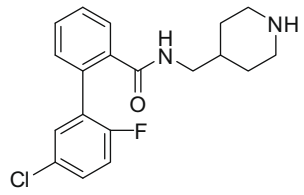
2a-u

2j: R^1 = 6-Me, R^2 = H. TI >555.55,CC_{50} >200 μg/mL, EC_{50} = 0.36 μg/mL
2n: R^1 = 6-Me, R^2 = 4-Et.TI = 791.85,CC_{50} >102.94 μg/mL, EC_{50} = 0.13 μg/mL

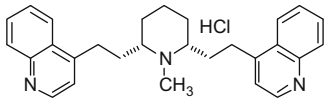
It demonstrated that introduction of the acetyl group at the 3-position of *N*-arylsulfonyl-6-methylindoles could generally lead to the more potent analogs.



Biaryl amides were discovered as novel and subtype selective M_1 agonists. The identification, synthesis, and initial SAR that led to the discovery of compound **3j** are described.



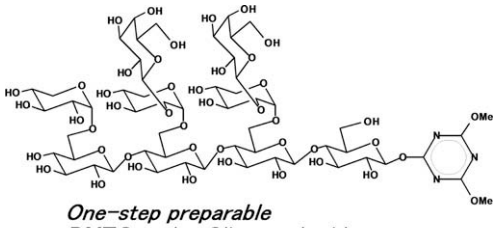
3j, M_1 pEC_{50} = 8.0
> 100-fold selective over M_2 - M_5



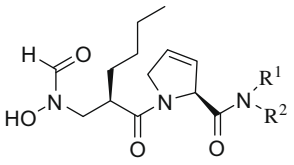
Quinlobelane•HCl
VMAT2[^{3}H]-DA uptakein hibition
$K_{i=}$ 51±5nM

Replacing the phenyl rings of the VMAT2 inhibitor, lobelane with pyridyl, quinolyl and indolyl rings affords analogues with improved water solubility. The synthetic studies reported herein underscore the paucity of hydrogenation methods that offer selectivity between different classes of heteroaromatic lobelane analogues. Quinolyl rings were found to be the only replacement for the phenyl rings in lobelane that resulted in retention of VMAT2-inhibitory properties.

Two kinds of 4,6-dimethoxy-1,3,5-triazine (DMT) oligoxyloglucans have been synthesized via one-step procedure starting from the corresponding unprotected oligoxyloglucans in water to study action of endo-β-1,4-D-glucanase III from *Trichoderma reesei*.

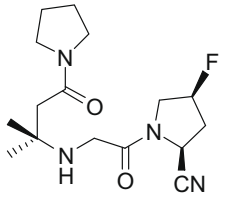


One-step preparable
DMT Complex Oligosaccharide



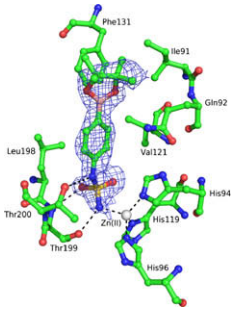
1a~1r

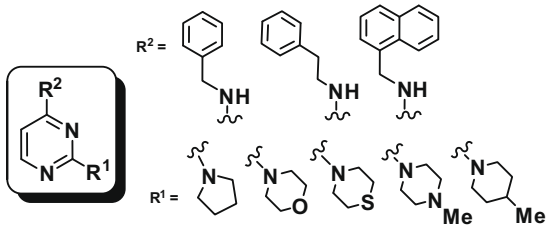
Design and synthesis of 2,5-dihydropyrrole formyl hydroxyamino derivatives as novel peptide deformylase inhibitors and their antibacterial activities against susceptible and resistant Gram-positive bacterial strains have been reported.

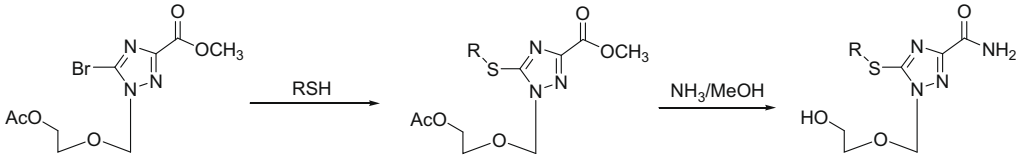


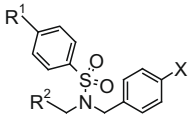
12a

DPP-IV IC_{50} = 15 nM

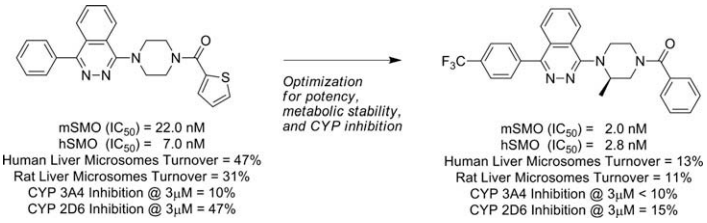


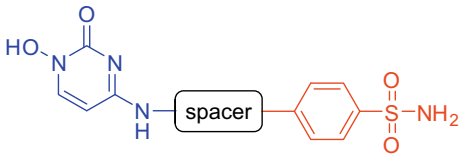






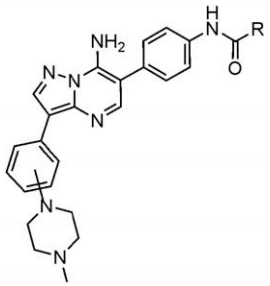
The discovery of a novel series of CXCR3 antagonists is described. Starting from an HTS positive, iterative optimization gave potent compounds (IC_{50} 15 nM in a chemotaxis assay). The strategy employed to improve the metabolic stability of these derivatives is described.



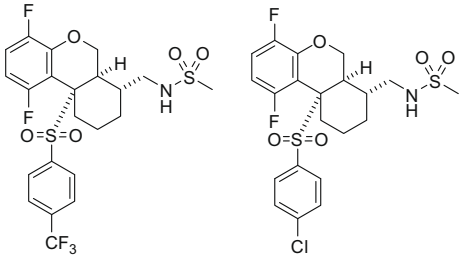


1: K_I (CAII) = 31nM

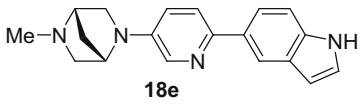
K_I (CAIX) = 3.4nM



The preparation of pyrazolo[1,5*a*]pyrimidines and their evaluation as inhibitors of lymphocyte-specific kinase (Lck) both in vitro and in vivo is described.



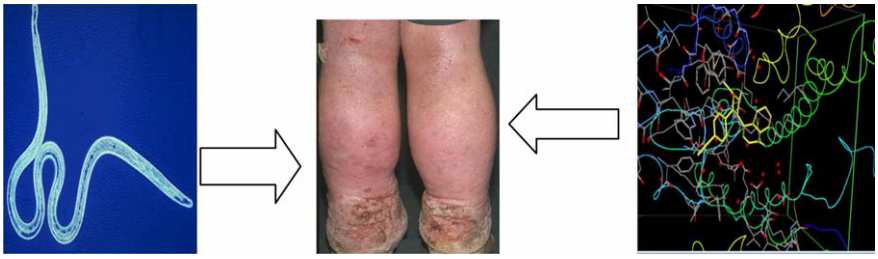
15a IC_{50} = 13 nM **17a** IC_{50} = 2.5 nM

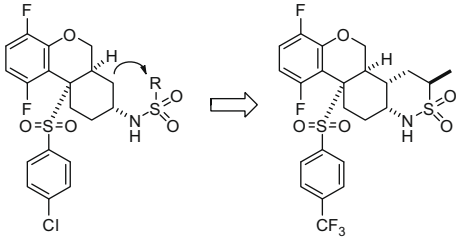


18e

A series of biaryl substituted 2,5-diazabicyclo[2.2.1]heptanes were synthesized as potent and selective α7 NNR agonists. Among them, compound **18e** shows a α7 binding affinity of 0.2 nM.

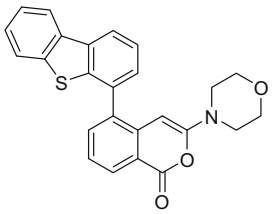
In the present investigation novel series of 4-substituted-1-(8-hydroxy-quinolin-5-yl)-azetidin-2-ones are synthesized, screened for in vitro anti-filarial activity against *Brugia malayi*. *In silico molecular* docking analysis of title compounds performed in to the active site of enzyme glutathione-*S*-transferases.

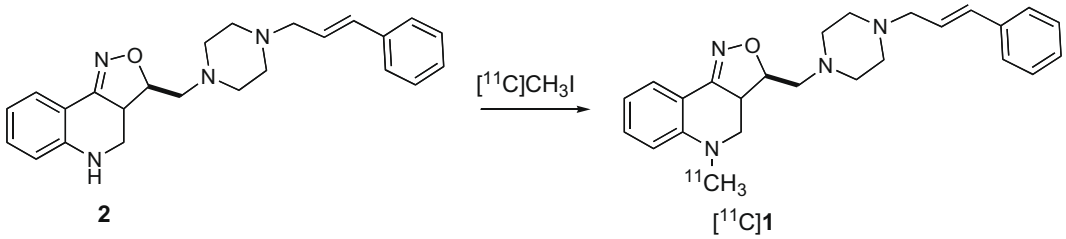


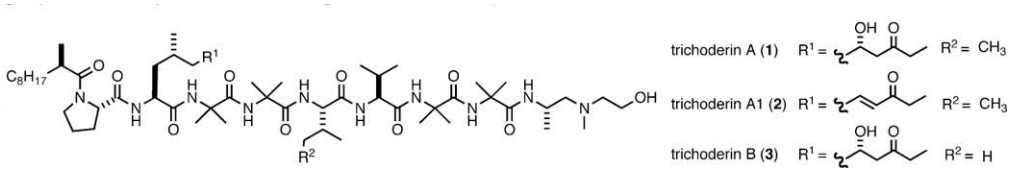


1b (R = CF_3: IC_{50} = 27 nM) **2a** (IC_{50} = 1.6 nM)

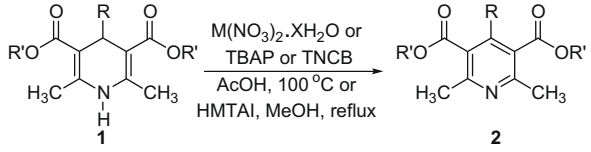
Replacement of the core heterocycle of a defined series of chromen-4-one DNA-PK inhibitors by the isomeric chromen-2-one (coumarin) and isochromen-1-one (isocoumarin) scaffolds was investigated. Structure-activity relationships for DNA-PK inhibition were broadly consistent, albeit with a reduction of potency compared with the parent chromenone.





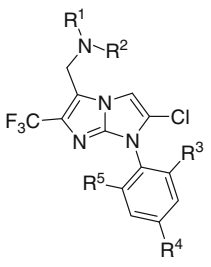


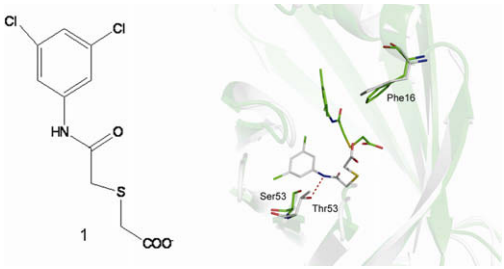
Three new aminolipopeptides, designated trichoderins A (**1**), A1 (**2**), and B (**3**), were isolated from a culture of marine sponge-derived fungus of *Trichoderma* sp. as anti-dormant mycobacterial substances.



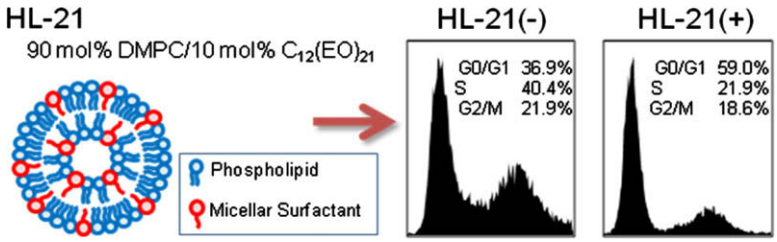
Facile aromatization of various 1,4-dihydropyridines was investigated using metal nitrates, TBAP, TNCB and HMTAI as oxidants. Efficient conversion of nifedipine-d_3 to dehydronifedipine-d_3 as an internal standard.

A novel series of [6-chloro-2-trifluoromethyl-7-aryl-7*H*-imidazo[1,2-*a*]imidazol-3-ylmethyl]-dialkylamines was discovered as potent CRF_1R antagonists. The optimization of binding affinity in the series by the parallel reaction approach is discussed herein.

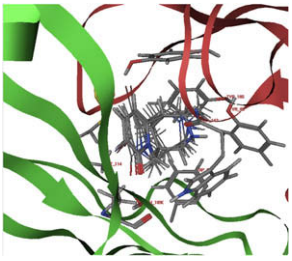




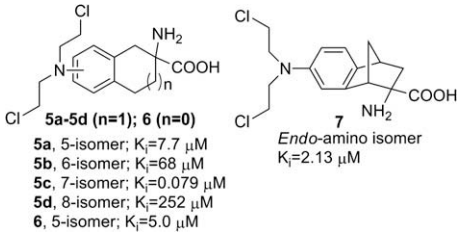
Compound **1** was identified as an inhibitor of human FABP4 with an IC_{50} of 13.5 μM and it showed a selectivity more than 144-fold over human FABP3.



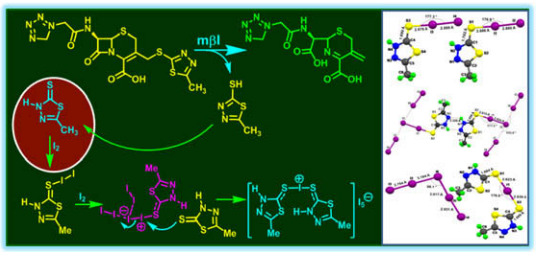
Hybrid liposomes composed of 90 mol % L-α-dimyristoylphosphatidylcholine (DMPC) and 10 mol % polyoxyethylene(21)dodecyl ether ($C_{12}(EO)_{21}$) specifically accumulated and induced cell cycle arrest in human cholangiocarcinoma cells.



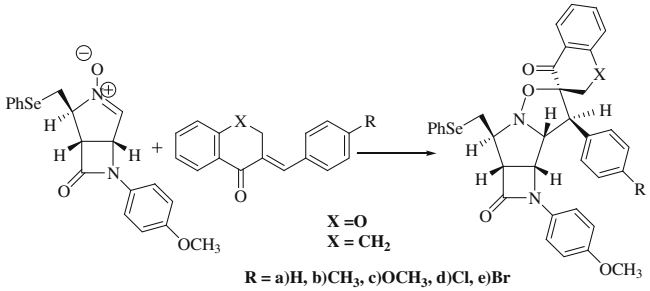
Cytisine and several derivatives docked into an acetylcholine binding protein of *Lymnaea stagnalis* (Ls-AChBP), taken as a model of the agonist binding site of neuronal nicotinic acetylcholine receptor (nAChR). A strong correlation was found between the docking energies and experimental pIC_{50} values.

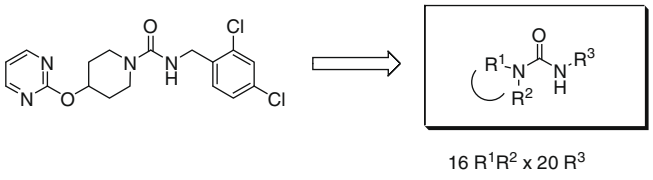


Placing the mustard moiety at C-7 of the tetralin ring (**5c**) affords greatest affinity for the System LAT1 transporter; the more conformationally restrained analogs (**6** and **7**) of DL-2-NAM-7 had lower affinity than **5c**.

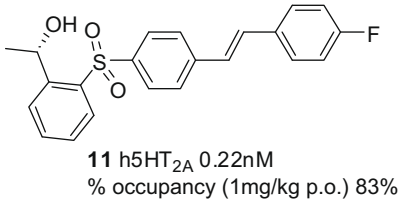


This study provides the first experimental evidence that the heterocyclic side chains present in cephalosporins not only inhibits peroxidase-catalyzed iodination reactions, but also reacts with iodine to produce stable charge-transfer complexes. The peroxidase inhibition and reactivity toward iodine must be taken into account while designing new antibiotics based on cephalosporins as these activities may adversely affect the thyroid activity.

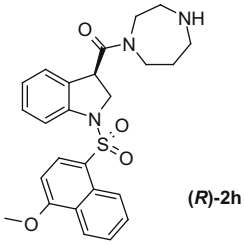




Rapid exploration of multi-dimensional SAR around a series of trisubstituted urea inhibitors of sEH was accomplished using a focused library approach.

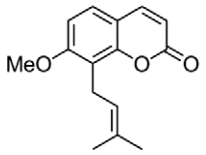


Herein is described the development of a non-basic series of aryl sulfones as 5-HT$_{2A}$ receptor antagonists with excellent receptor occupancy on oral dosing *in vivo*.



(*R*)-2h

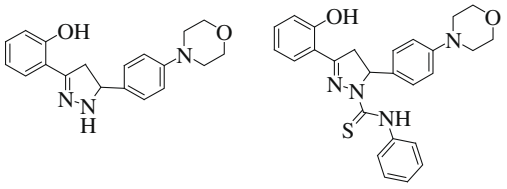
We report the identification and SAR around *N*-(2-aminoalkyl)-1-(arylsulfonyl)indoline-3-carboxamides—a novel chemotype of 5-HT$_6$ antagonists.



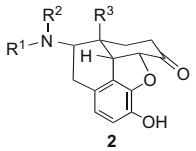
osthol (**1**)
IC_{50}=1.6 μM

Inhibitior for Rev-export from the crude drug Cnidii Monnieris Fructus

Prenylcoumarin osthol (**1**) was disclosed as the new Rev-export inhibitor from Cnidii Monnieris Fructus. Both prenyl residue and carbonyl conjugated double bond were revealed to play an important role in the biological potency of **1**.

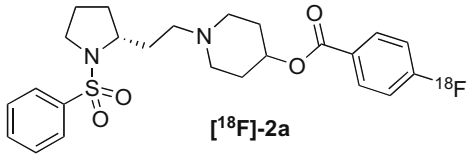


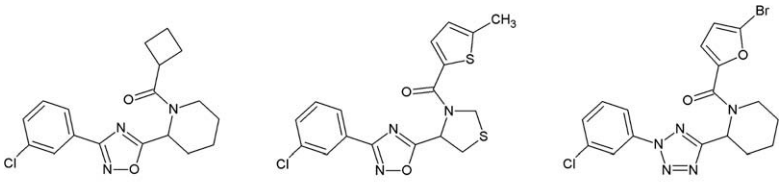
In search for a new analgesic and anti-inflammatory agent with improved potency, we designed and synthesized a series of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenols **6**(**a**–**g**) and its *N*-phenylpyrazol-1-carbothioamide **7**(**a**–**g**) by Claisan–Schmidt condensation followed by the reaction of hydrazine hydrate. All the synthesized compounds were assayed for their in vivo analgesic and anti-inflammatory activities. All the compounds synthesized showed the potential to demonstrate analgesic and anti-inflammatory activity, of particular interest compounds **6a**, **6b**, **6g**, **7a**, **7d** and **7g** were found comparable to Diclofenac.



2

Novel 15–16 nornaltrexone derivatives **2** were synthesized using a double decarboxylation reaction as the key reaction to examine the Beckett–Casy model.

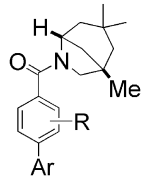




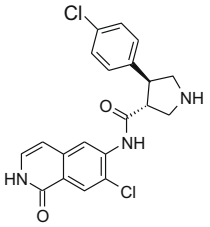
3
rmGluR5 pK$_i$ = 6.69
SILE = 3.91
LELP = 3.80

9a
rmGluR5 pK$_i$ = 7.08
SILE = 3.79
LELP = 5.70

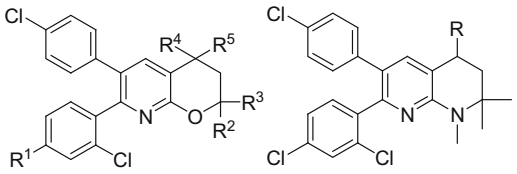
17a
rmGluR5 pK$_i$ = 7.31
SILE = 3.78
LELP = 4.31

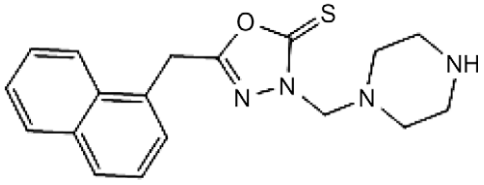


A series of biaryl amides containing an azabicyclo[3.2.1]octane amine headpiece were synthesized and evaluated as mixed arginine vasopressin (AVP) receptor antagonists.

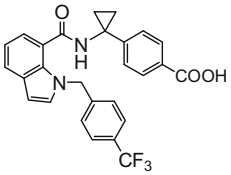


32

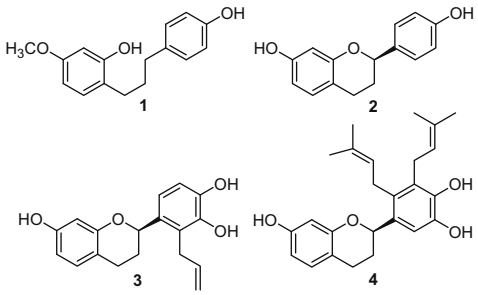




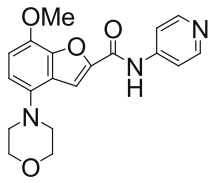
A series of oxadiazole and triazolothiadiazole derivatives were synthesized and evaluated their mushroom tyrosinase inhibitory activities. Compound **5** exhibited highest tyrosinase inhibitory activity with IC_{50} value of 0.87 ± 0.16 μM.



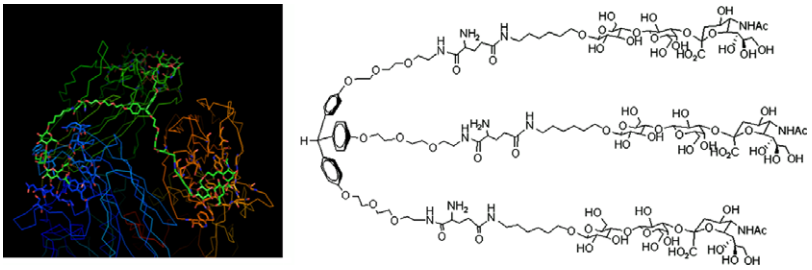
MF-766
EP_4 *K*i = 0.23 nM
EP_4 functional IC_{50} = 1.3 nM
In vivo AIA ED_{100} = 0.025 mg/kg/day



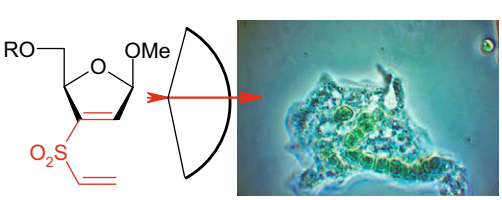
Four estrogenic compounds, broussonin A (**1**), tupichinol C (**2**), kazinol U (**3**), and (+)-(2*R*) kazinol I (**4**) were identified from *Broussonetia kazinoki*.



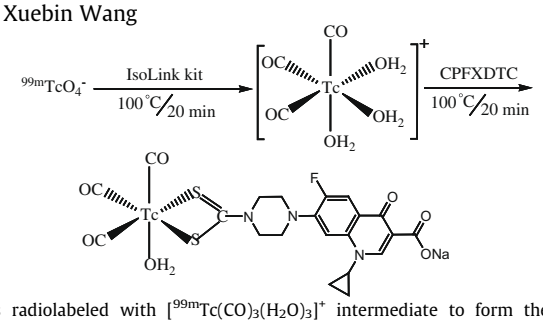
The discovery of a novel series of A_{2A} antagonists is described. A selected compound was shown to be able to induce anti-parkinsonian effects in MPTP-treated common marmosets.



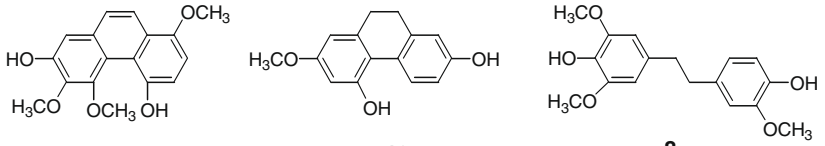
A trivalent anti-influenza reagent with sialyllactose at the terminals shows ~85% inhibition against influenza virus infection in an assay with MDCK cells at the concentration of 400 μM.



Divinyl sulfone-modified carbohydrates have been synthesized for the first time by reacting carbohydrate epoxides with thioethanol and one of the modified divinyl sulfones initiated significant cell death in *Entamoeba* species.



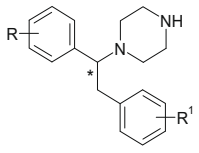
The ciprofloxacin dithiocarbamate (CPFXDTC) was radiolabeled with $[^{99m}Tc(CO)_3(H_2O)_3]^+$ intermediate to form the $^{99m}Tc(CO)_3$–CPFXDTC complex in high yield. The biodistribution and SPECT imaging studies reveal its good biological features as an infection imaging agent.



1 **12** **8**

A new phenanthrene, 3,4,8-trimethoxyphenanthrene-2,5-diol (**1**), along with nine known phenanthrenes and three known bibenzyls was isolated from *Dendrobium nobile*. All of the isolates were evaluated for their potential to inhibit the LPS-induced NO production in murine macrophage RAW 264.7 cells.

New *N*-(1,2-diphenylethyl)piperazines **6** are disclosed as dual serotonin and noradrenaline reuptake inhibitors (SNRI). Piperazine (−)-**6a** was identified as a potent and selective dual SNRI with improved metabolic stability and reduced ion channel activity when compared to previous examples.



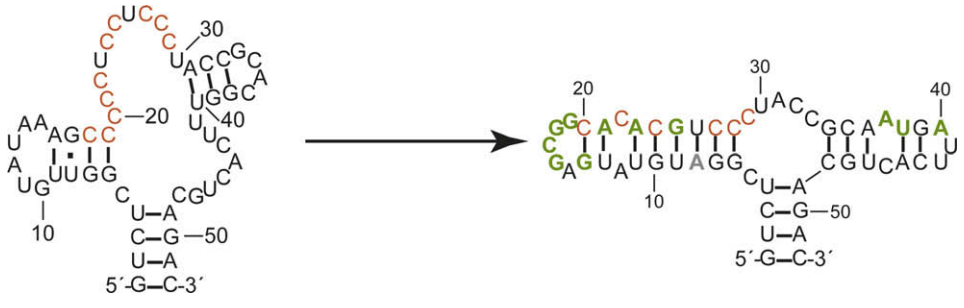
6a-t

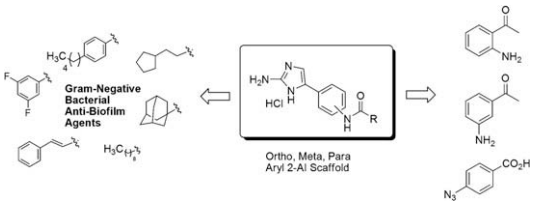
e.g. (-)-**6a**: R = H; R^1 = 2-OMe

SRI, K_i = 2 nM
NRI, K_i = 12 nM
DRI, K_i = 2940 nM

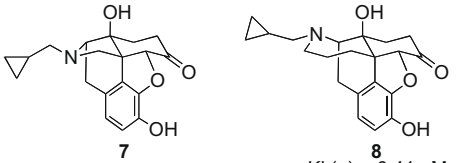
HLM, $T_{1/2}$ > 120 min
CYP2D6-i, IC_{50} = >30,000 nM
K^+ hERG, IC_{50} = 22,900 nM
Na^+ TTX-S, IC_{50} = 5400 nM

R = H; 2-F; 3-F; 4-F * = *RS*, *R* or *S*
R^1 = OMe; OnPr; OiPr; OcPr; OCH_2cPr; $OCHF_2$; OCF_3; 2,3-OCH_2CH_2-

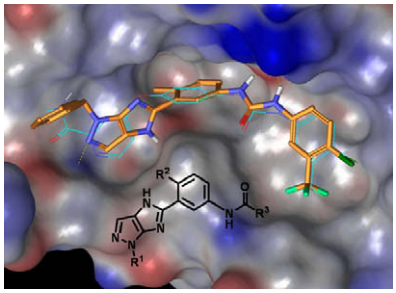




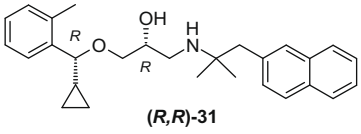
The synthesis and biofilm inhibitory activity of a 30-member aryl amide 2-aminoimidazole library against the three biofilm forming Gram-negative bacteria *Escherichia coli*, *Psuedomonas aeruginosa*, and *Acinetobacter baumannii* is presented. The most active compound identified inhibits the formation of *E. coli* biofilms with an IC_{50} of 5.2 μM and was observed to be non-toxic to planktonic growth, demonstrating that analogues based on an aryl framework are viable options as biofilm inhibitors within the 2-aminoimidazole family.



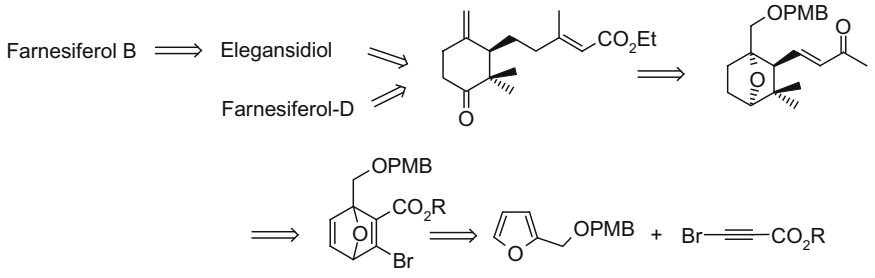
Novel naltrexone derivatives **7** and **8** were synthesized to examine the Beckett–Casy model.

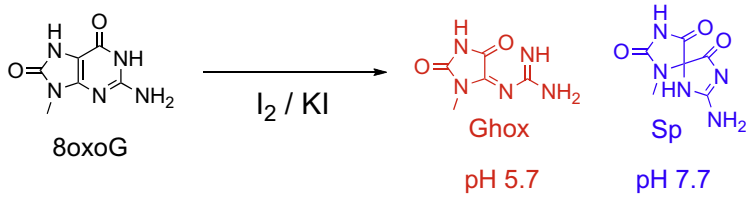


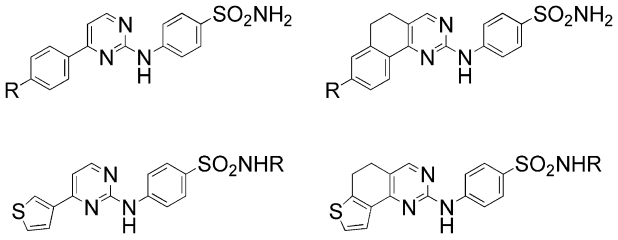
A series 1,4-dihydropyrazolo[4,3-*d*]imidazole phenyl derivatives and their antiproliferative activities against A375P human melanoma cell line and WM3629 cell line were described.



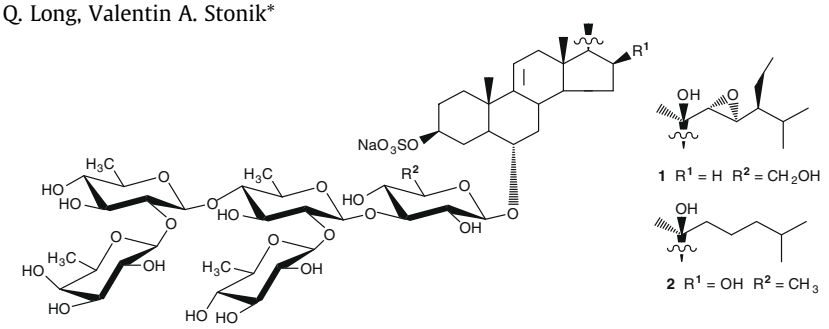
The discovery of an orally available and short-acting calcium-sensing receptor antagonist (*R*,*R*)-**31** is reported.

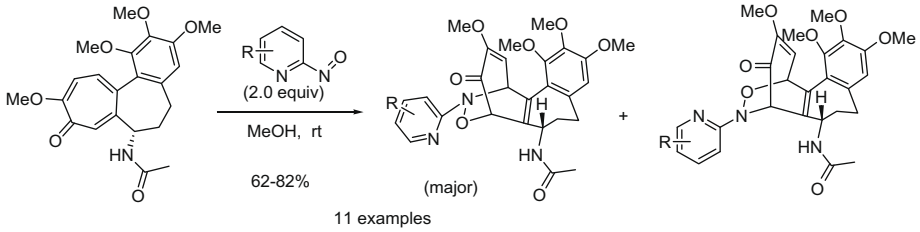






A series of anilinopyrimidines and their tricyclic analogues were synthesized and evaluated as IKKβ inhibitors.





OTHER CONTENT

*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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