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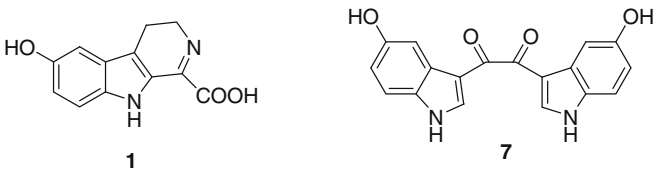
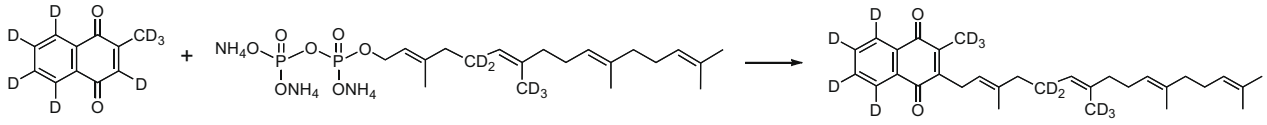
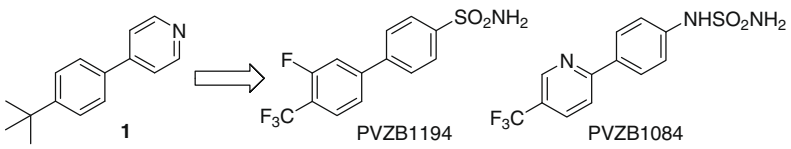
Contents

ARTICLES

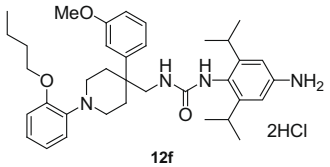


Isolation and structure elucidation of new compound **1** and isocitrate lyase inhibitory activity of compounds **1**–**7** are described.

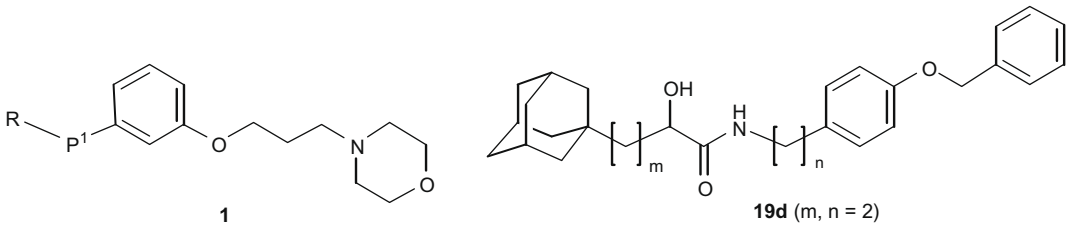




Synthesis of 4-(4-*tert*-butylphenyl)pyridine (**1**) analogues as KSP inhibitor, SAR, cytotoxicity and mitotic arrest in HeLa cells are described. Distinct KSP distribution by different chemotypes of KSP inhibitor is also reported.

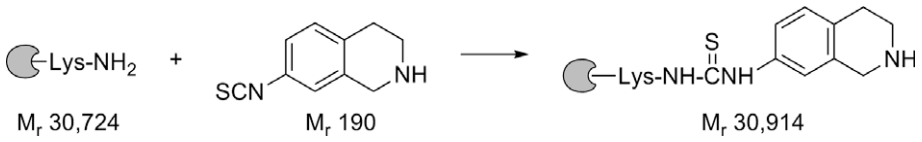


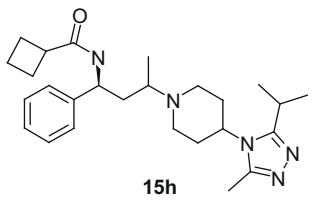
12f



1 **19d** (m, n = 2)

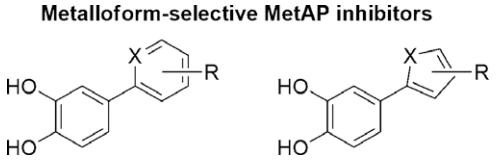
Inhibition of soluble epoxide hydrolase (sEH) has been proposed as a promising new pharmaceutical target for diseases involving hypertension and vascular inflammation. We evaluated a number of non-urea primary pharmacophores based on the test scaffold **1** (P^1 = NHCONH) which led to the discovery of hydroxyamide analog **19d** as a novel and potent sEH inhibitor.

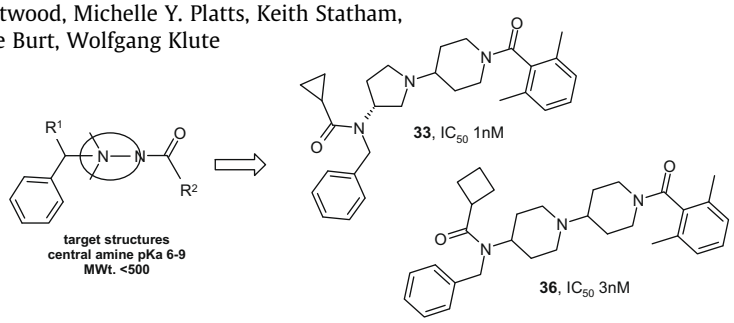


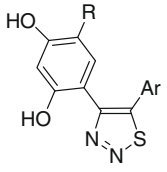


15h

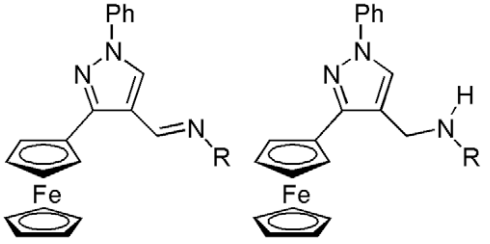
The development of a new class of CCR5 antagonist replacing the tropane core of maraviroc by piperidine with a branched *N*-substituent is described. Compound **15h** shows good whole cell antiviral activity together with microsomal stability and only weak activity at the hERG ion channel.



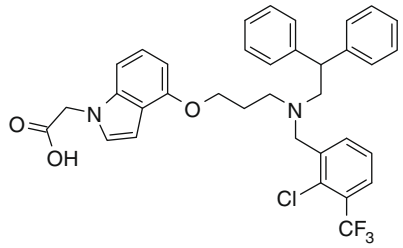




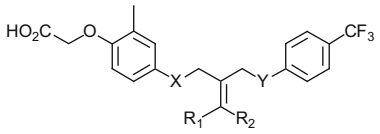
The synthesis and in vitro binding of the thiadiazole inhibitors of Hsp90 with K_ds up to 5 nM.



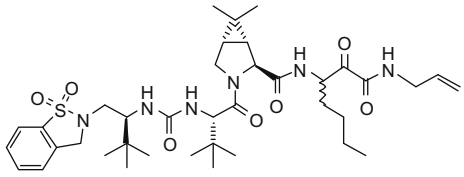
Nine imines and the corresponding amines were synthesized and screened for their in vitro antimicrobial activity against 11 bacteria and three fungal/yeast strains. One of amines (R = *tert*-butyl) showed the higher activity in comparison with widely used tetracycline.



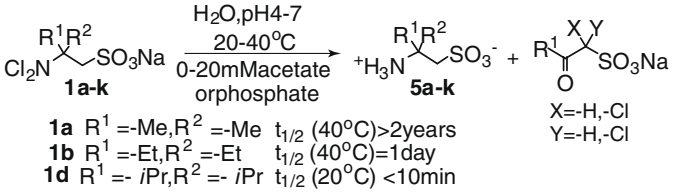
A novel series of 1H-indol-1-yl tertiary amine LXR agonists has been designed. This manuscript will describe optimization of this series of LXR agonists using a structure-based design strategy. In addition, the SAR of this novel series and a crystal structure of a selected ligand bound to the LXRα LBD will be disclosed.



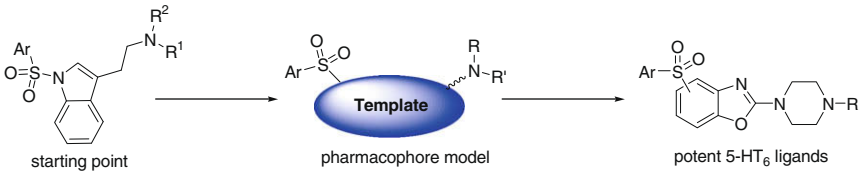
Synthesis and SAR of potent and selective PPARδ agonists is described.



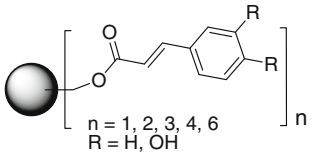
K_i* = 5 nM
EC_{90} = 80 nM
HNE/HCV = 6100



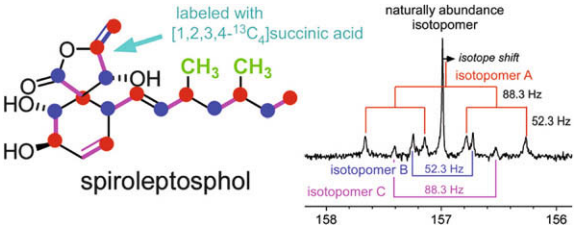
The structure–stability relationship (SSR) of alkyl and cycloalkyl β-substitutions on *N,N*-dichlorotaurines reveals order-of-magnitude changes in their aqueous (pH 4–7, 20–40 °C) stabilities. Stieglitz rearrangement is one of the mechanisms of decomposition and produces β-ketosulfonic acids and chlorinated derivatives thereof.

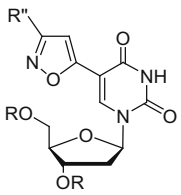


Identification and detailed SAR of a novel series of benzoxazole derivatives as potent 5-HT$_6$ ligands are reported.

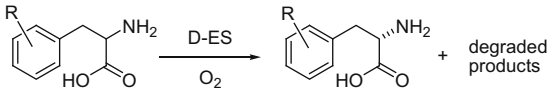


Novel cinnamoyl and caffeoyl clusters were synthesized by multiple Cu(I)-catalyzed [1,3]-dipolar cycloadditions and their anti-5-lipoxygenase inhibitory activity was tested. Caffeoyl cluster showed an improved 5-lipoxygenase inhibitory activity compared to caffeic acid, with caffeoyl trimer **16** and tetramer **19** showing the best 5-lipoxygenase inhibitory activity.

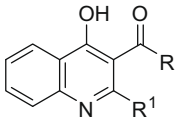




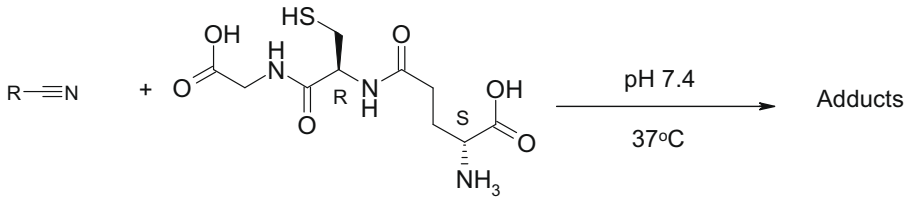
Novel nucleosides were designed and synthesized by [3+2] cycloaddition, and showed moderate antiviral activities. The nucleosides were tested against 12 different viruses.



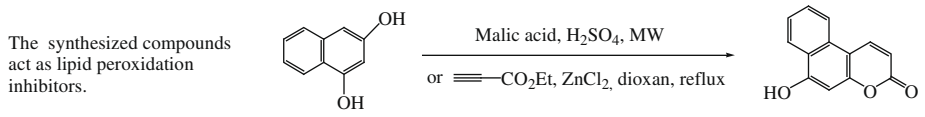
The bacterium *Aeromonas* sp. (CGMCC 2226) can enantioselectively scavenge D-isomer, making L-AADs in high ee. Eleven L-AADs were produced in high ee from corresponding racemates.

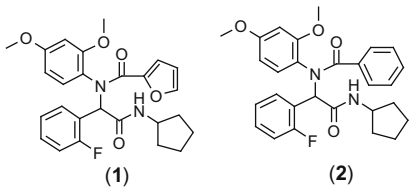


1 ($R = OC_2H_5$; $R^1 = CH_3$)
2 ($R = OH$; $R^1 = CH_3$)
3 ($R = OC_2H_5$; $R^1 = C_5H_{11}$)
4 ($R = OH$, $R^1 = C_5H_{11}$)
5 ($R = OC_2H_5$; $R^1 = C_{10}H_{21}$)
6 ($R = OH$; $R^1 = C_{10}H_{21}$)
7 ($R = OC_2H_5$; $R^1 = C_{15}H_{31}$)
8 ($R = OH$; $R^1 = C_{15}H_{31}$)

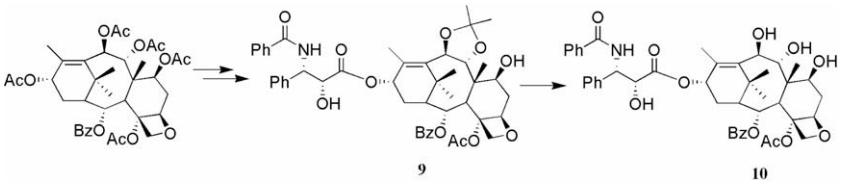


The reactivity of various nitriles towards glutathione has been used as an *in-vitro* risk assessment tool. This method provides a level of ranking for analogues and benchmarking against a marketed drug.

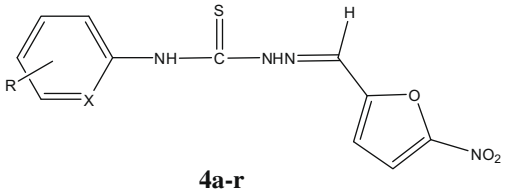




A novel series of small molecule C5a antagonists is reported.

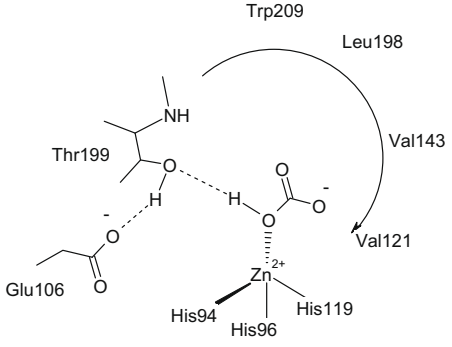


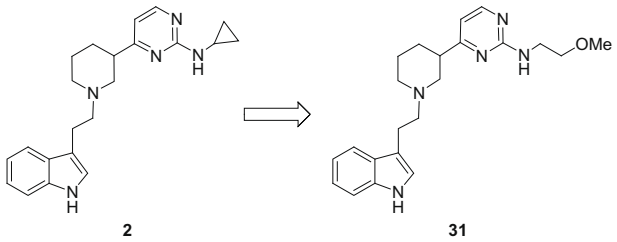
1-Deoxy-9α-dihydrotaxane analogs **9** and **10** were semi-synthesized from 1-deoxybaccatin VI, isolated from *Taxus mairei*, and tested for cytotoxic activity. Taxane **9** is 10-fold less cytotoxic than paclitaxel, while **10** is equally active. In the tubulin polymerization assay (ED_{50} values), **10** is 4-fold less effective than paclitaxel, but 3-fold superior to **9**. These observations can be explained by analysis of the corresponding taxane/β-tubulin complexes.



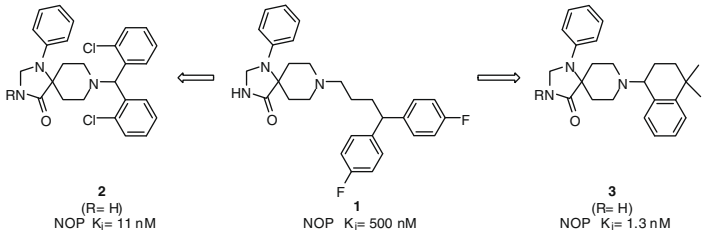
4a-r

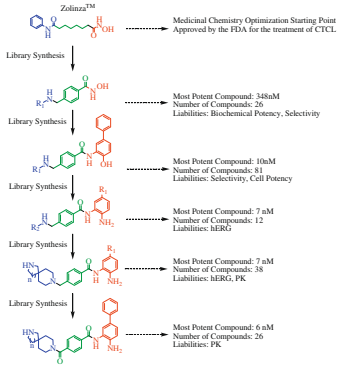
Eighteen 5-nitrofuran-2-yl derivatives were prepared and tested for their in vitro activity against tubercular and various non-tubercular mycobacterium species in log-phase and 6-week-starved cultures.

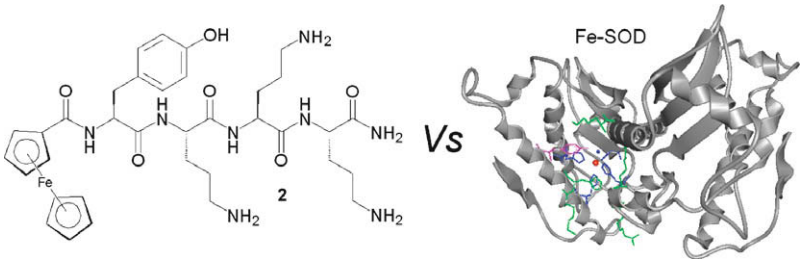




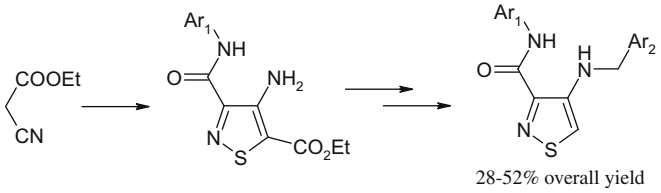
A series of N-8 substituted analogs based upon the spiropiperidine core of the original lead compound **1** was synthesized. This lead has been elaborated to compounds to give compounds **2** and **3** (R = H) that exhibited high NOP binding affinity as well as selectivity against other known opioid receptors. These two series have been further functionalized at the amido nitrogen. The synthesis and structure–activity relationship (SAR) of these and related compounds are discussed.



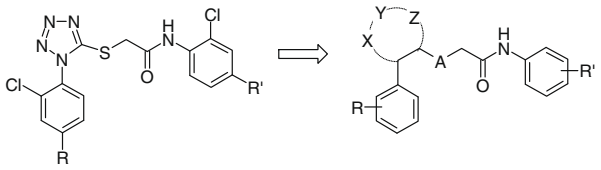




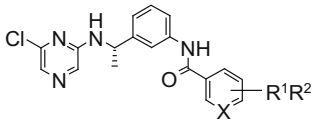
C-terminal amidated cationic ferrocenoyl peptide bioconjugates Fc-Orn-Orn-Orn (**1**), Fc-Tyr-Orn-Orn-Orn (**2**) were synthesised and evaluated as superoxide dismutase mimics and for their ability to inhibit peroxynitrite-mediated tyrosine nitration.



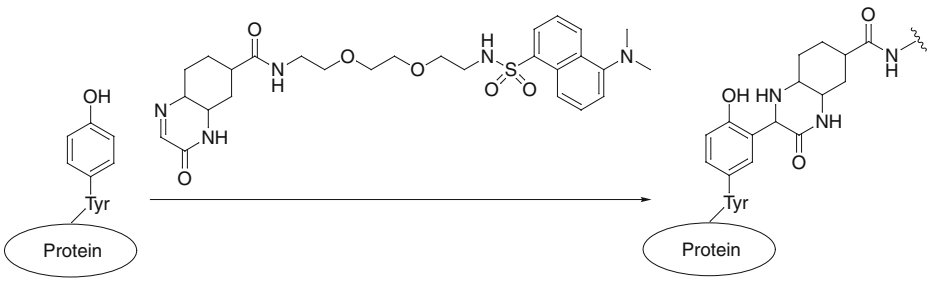
Novel derivatives of isothiazoles are described as potent ATP-competitive inhibitors of vascular endothelial growth factor receptors I and II (VEGFR-1/2). Several derivatives featuring bulky meta-substituents in the amide portion of the molecule displayed both good potency (27–41 nM) and 4- to 8-fold specificity for VEGFR-2 versus VEGFR-1.

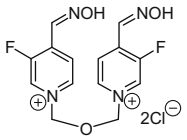


Different acyclic, cyclic and heterocyclic tetrazole replacements were investigated in order to evaluate the conformational and electronic contribution of the linker in the binding of the tetrazolylacetanilides inhibitors in the NNRTI pocket.



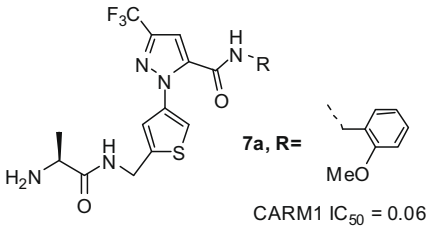
A novel series of 2-(α-methylbenzylamino) pyrazines have been synthesized and shown to be potent inhibitors of the FMS tyrosine receptor kinase.



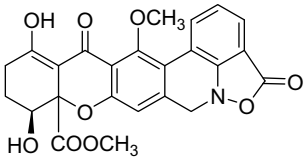


We have designed and synthesized the fluorinated oxime derivatives, which quantum mechanical calculations suggest should have a greater lipophilicity and BBB permeability than their non-fluorinated analogs.

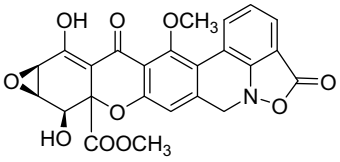
A series of *N*-benzyl-1-heteroaryl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamides targeting co-activator associated arginine methyltransferase 1 (CARM1) have been designed and synthesized. The potency of these inhibitors was influenced by the nature of the heteroaryl fragment with the thiophene analogues being superior to thiazole, pyridine, isoindoline and benzofuran based.



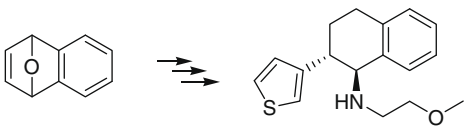
CARM1 IC_{50} = 0.06 μM



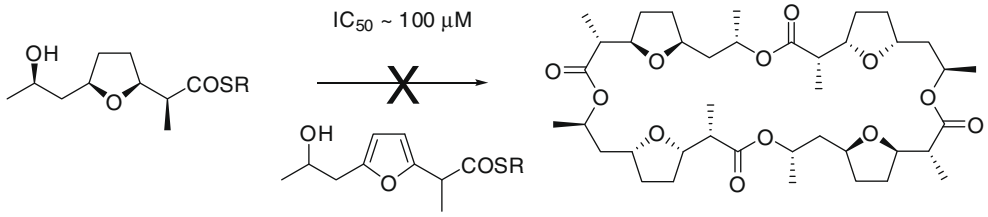
Parnafungin C

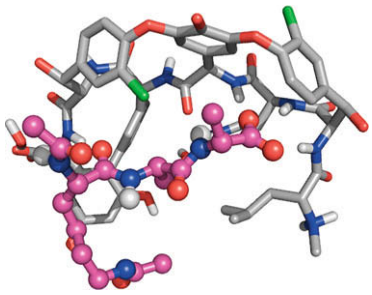


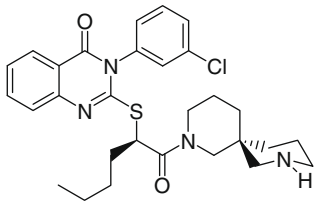
Parnafungin D



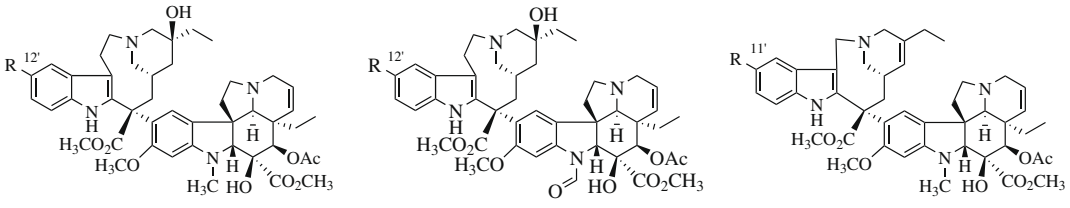
5.2a





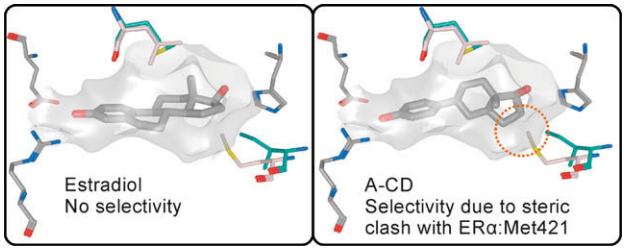


38

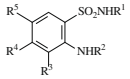


Vinblastine **Vincristine** **Vinorelbine**

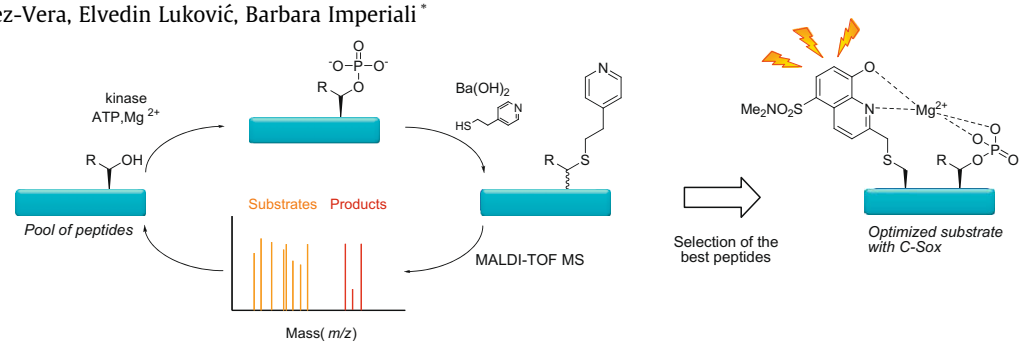
The development of selective iodination conditions for the dimeric vinca alkaloids vinblastine, vincristine, and semisynthetic derivative vinorelbine led to the preparation of new analogues of these important antitumor agents.

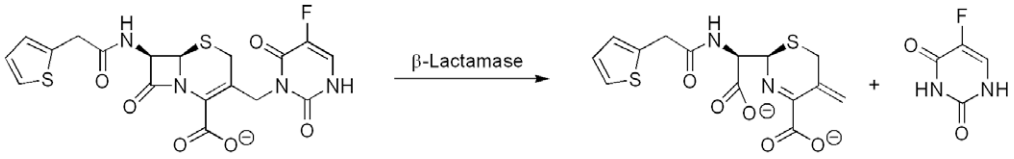


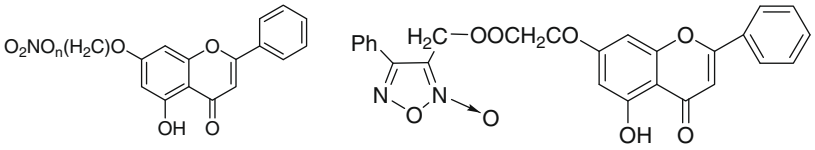
IDRA21 is one of the most potent cognitive enhancers. We have demonstrated that in vivo IDRA21 (**1**) was quickly hydrolyzed to 2-amino-5-chlobenzensulfonamide that posses in vitro a biological activity similar to that of IDRA21 itself. Taking 2-amino-5-chlobenzensulfonamide as the lead compound, a novel class of AMPAR positive allosteric modulators has been prepared.



compd	R1	R2	R3	R4	R5
2	-H	-H	-H	-H	-Cl
3	-CH_3	-H	-H	-H	-Cl
4	-CH_2CH_3	-H	-H	-H	-Cl
5	-$CH_2CH_2CH_3$	-H	-H	-H	-Cl
6	-H	-CH_3	-H	-H	-Cl
7	-H	-CH_2CH_3	-H	-H	-Cl
8	-H	-$CH_2CH_2CH_3$	-H	-H	-Cl
9	-H	-$CHCH_3CH_3$	-H	-H	-Cl
10	-H	-H	-H	-H	-H
11	-H	-H	-H	-Cl	-H
12	-H	-H	-H	-Cl	-Cl
13	-H	-H	-H	-OCH_3	-H
14	-H	-H	-H	-H	-NO_2
15	-H	-H	-H	-Cl	-SO_2NH_2
16	-H	-H	-CH_3	-H	-H







Two types of new chrysin derivatives were prepared by coupling NO donors of alkyl nitrate and furazan derivatives. These compounds were tested in human umbilical vein endothelial cells and all the compounds exhibited cell proliferation. Notable effects of promoting angiogenesis were observed for all the modified compounds using chick chorioallantoic membrane (CAM) assay.

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ⓘ+ 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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