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Bioorganic & Medicinal Chemistry Letters

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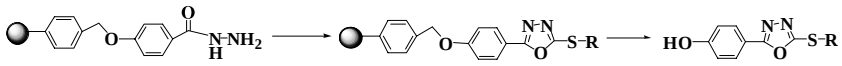
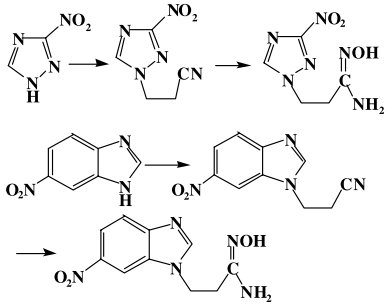
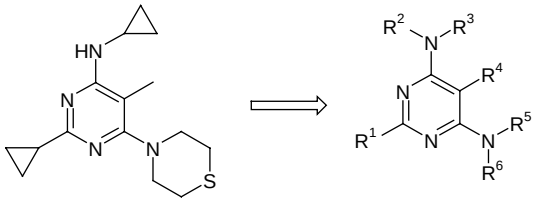
Contents

ARTICLES

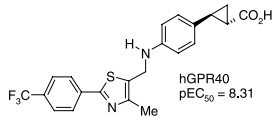


Solid-phase synthesis of 2,5-disubstituted 1,3,4-oxadiazoles has been developed.

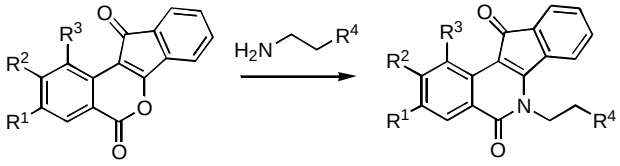




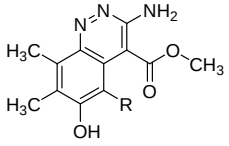
The synthesis and SAR around 4,6-diaminopyrimidine derivatives as dual M3 antagonists and PDE4 inhibitors are reported.



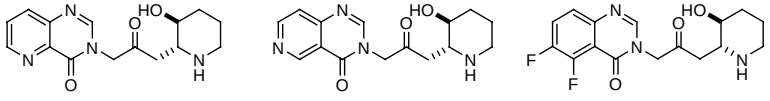
The first report on the identification and structure–activity relationships of a novel series of GPR40 agonists based on a 3-(4-{[*N*-alkyl]amino}phenyl)propanoic acid template is described. Structural modifications to the original screening hit yielded compounds with a 100-fold increase in potency at the human GPR40 receptor and pEC_{50}s in the low nanomolar range. The carboxylic acid moiety is not critical for activity but typically elicits an agonistic response higher than those observed with carboxamide replacements. These compounds may prove useful in unraveling the therapeutic potential of this receptor for the treatment of Type 2 diabetes.

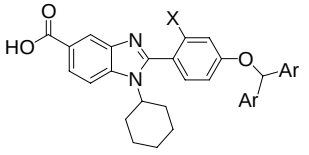


A one-pot, two-step synthesis of indenopyrans and their conversion to indenoisoquinoline topoisomerase I inhibitors are reported.

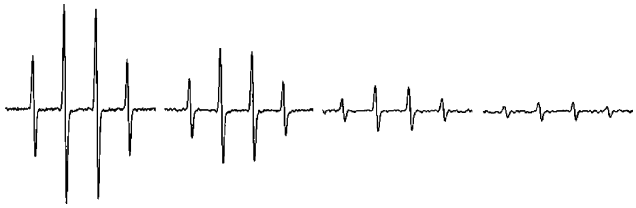


6-Hydroxycinnolines and cyclohexa-2,5-diene-1,4-dione derivatives were synthesized and tested for in vitro antifungal activity against *Candida* species and *Aspergillus niger*. Among them, 2-amino-7,8-dimethyl-6-hydroxycinnolines exhibited potent antifungal activity.



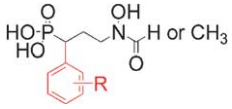


A series of 1-cycloalkyl-2-phenyl-1*H*-benzimidazole-5-carboxylic acid derivatives was synthesized and evaluated for their ability to inhibit HCV NS5B polymerase and subgenomic HCV RNA replication in the replicon cells.



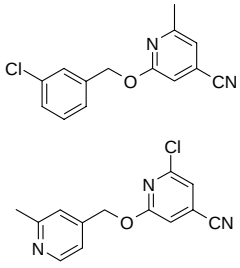
Control **0.03 mg/mL** **0.06 mg/mL** **0.12 mg/mL**

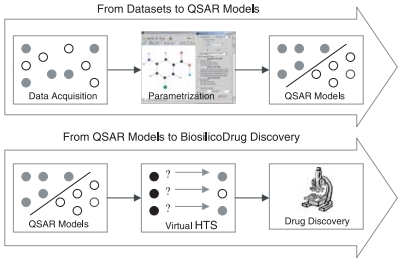
Novel chitin derivative was prepared by chemical modification. Aminoethyl-chitin (AEC) exhibited free radical scavenging effects against DPPH, hydroxyl, superoxide, and peroxyl radicals. Especially, AEC was more active against hydroxyl radical.

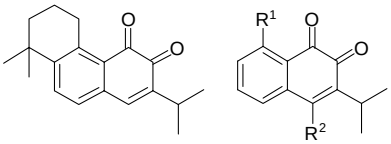


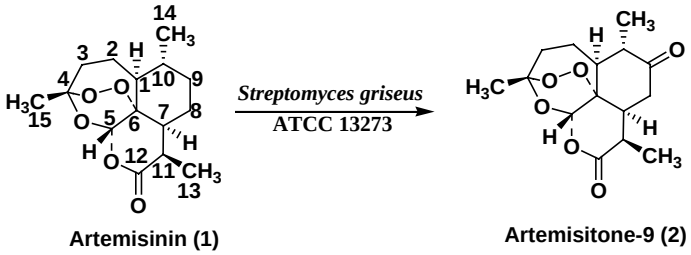
A series of α-substituted fosmidomycin analogues was synthesized and evaluated for DOXP reductoisomerase inhibition and *Plasmodium falciparum* growth inhibition. In the latter assay, most analogues proved superior to fosmidomycin.

The optimisation of a chemically unstable HTS hit led to mGluR5 antagonists with high affinity for the allosteric MPEP binding site and anxiolytic-like activity in vivo.

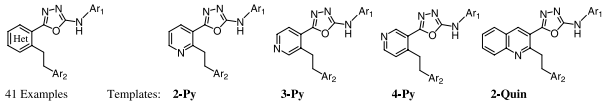




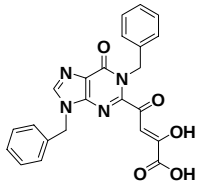


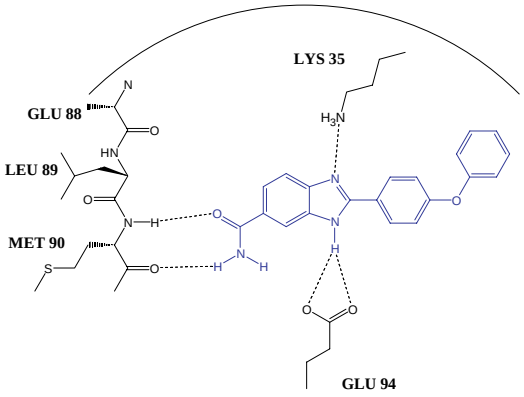


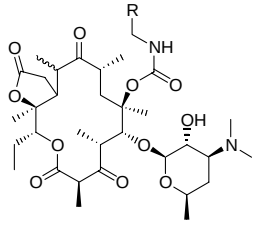
Artemisinin (**1**) was regioselectively converted to artemisitone-9 (**2**) and three other oxidative metabolites by *Streptomyces griseus* **ATCC 13273.**

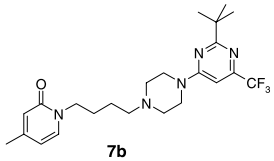


We have developed a series of novel potent ((pyridin-4-yl)ethyl)pyridine derivatives active against kinases VEGFR-1 and -2. Both specific and dual ATP-competitive inhibitors of VEGFR-2 were identified. Kinase selectivity could be controlled by varying the arylamino substituent at the 1,3,4-oxadiazole ring. Most specific molecules displayed >10-fold selectivity for VEGFR-2 over VEGFR-1. Compound activities in both in vitro and cell-based assays (IC_{50} < 100 nM) were similar to those of reported clinical and development candidates, including PTK787 (Vatalanib). High permeability of the active compounds across Caco-2 cell monolayer ($>30 \times 10^{-5}$ cm/min) is indicative of their potential for intestinal absorption upon oral administration.









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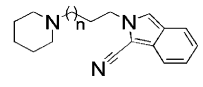
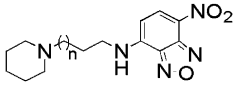
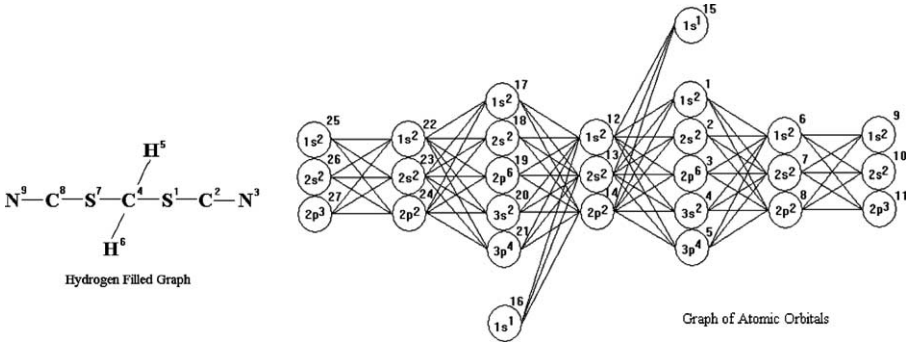
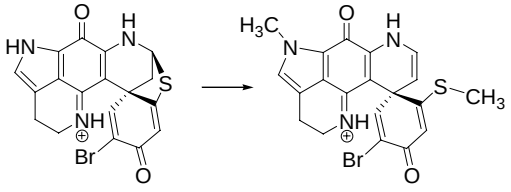


n = 1-4



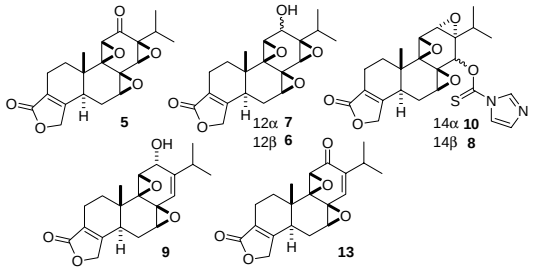
n = 2, 3



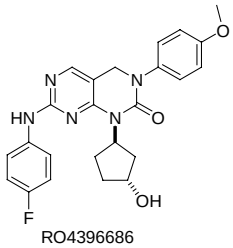


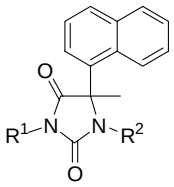
Semi-synthetic routes to the enzyme inhibitory and potently anti-proliferative marine natural products discorhabdins P and U were developed by one-step methylation reactions of discorhabdins C and B, respectively. Two novel semi-synthetic derivatives of discorhabdin U were also prepared, one of which (**6**) exhibited significant anti-proliferative activity.

The semisynthesis and SAR study of C-ring modified cytotoxic triptolide analogues were reported.

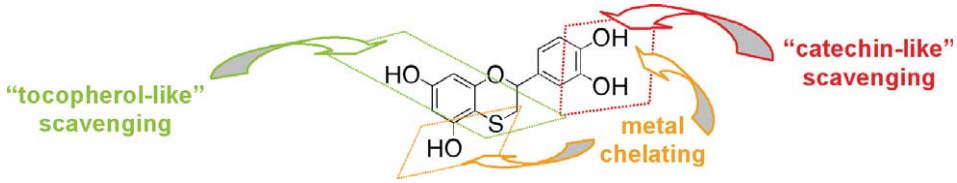


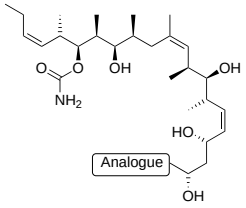
The biological evaluation of RO4396686, an inhibitor of the key pro-angiogenic kinases KDR, FGFR, and PDGFR is reported.



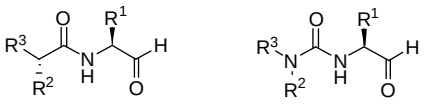


1,3,5,5-Tetrasubstituted 2,4-imidazolinedione (hydantoin) derivatives were evaluated as Ftase inhibitors. Potent Ftase inhibitors without thiol or peptide were obtained in three steps.

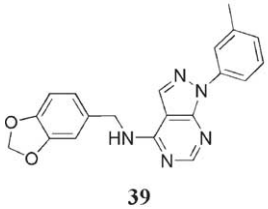


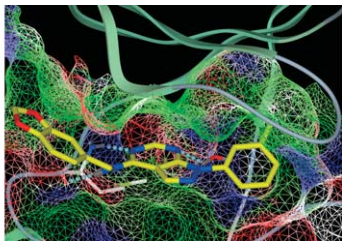


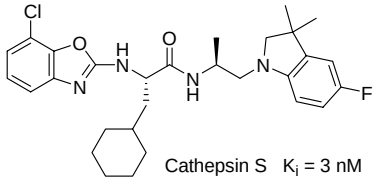
A collection of seven new 23,24-dihydrodiscodermolide analogues have been synthesized with modifications to the lactone ring, some of which show antiproliferative activities similar to discodermolide.

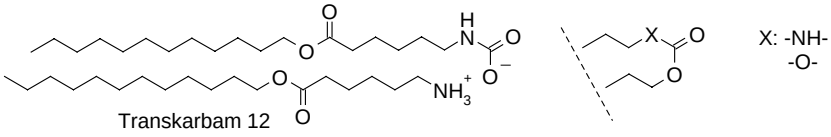


A series of peptide aldehyde derivatives in which the P_2 chiral carbon has been replaced with a nitrogen atom were synthesized as urea-based peptidomimetic inhibitors of μ-calpain.

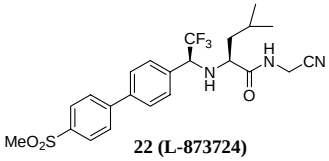




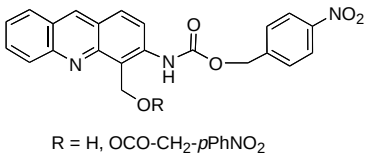




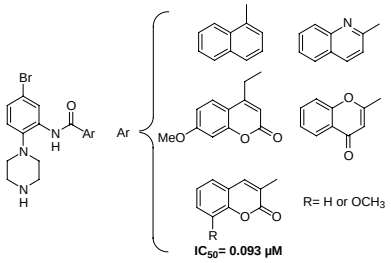
Series of carbamic and carbonic acid esters has been prepared as analogues of transkarbam 12 and their transdermal penetration-enhancing activity has been evaluated in vitro.

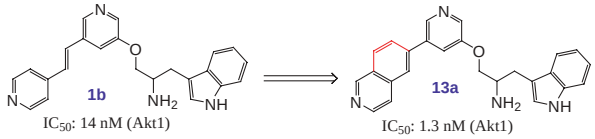


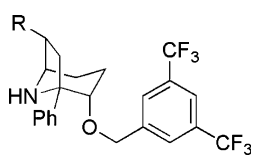
Based on our previous study with trifluoroethylamine as a P2–P3 amide isostere of cathepsin K inhibitor, further optimization led to identification of compound **22** (L-873724) as a potent and selective non-basic cathepsin K inhibitor.



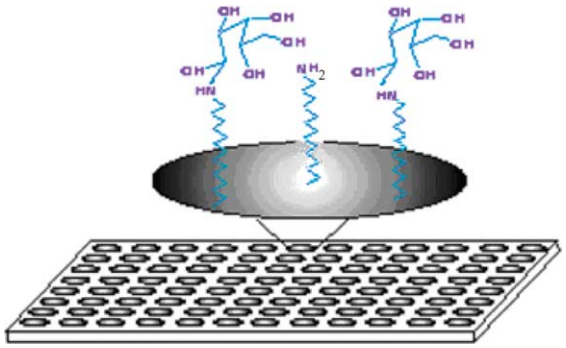
R = H, OCO-CH_2-*p*$PhNO_2$

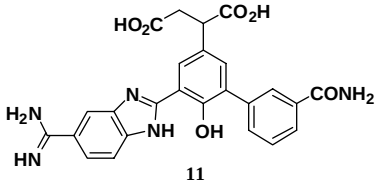






1-Phenyl-8-azabicyclo[3.2.1]octane ethers are NK_1 receptor antagonists. Substitution at the 6-*exo*-position leads to high affinity NK_1 antagonists with a prolonged duration of action in vivo. Incorporation of an α-methyl substituent in the pendent benzyl ether side chain gave compounds with increased selectivity over the hERG channel.

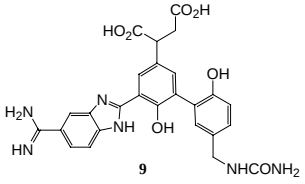




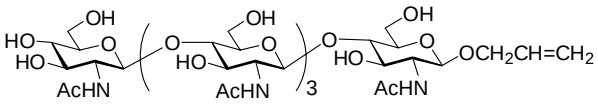
11

Plasma kallikrein is a serine protease that is involved in pathways of inflammation, complement fixation, coagulation, and fibrinolysis. Herein, we describe the SAR and structural binding modes of a series of inhibitors of plasma kallikrein as well as the pharmacokinetics of a lead analog **11** in rat.

Highly selective and potent factor VIIa–tissue factor (fVIIa·TF) complex inhibitors were generated through structure-based design. The pharmacokinetic properties of an optimized analog (**9**) were characterized in several preclinical species, demonstrating pharmacokinetic characteristics suitable for once-a-day dosing in humans. Analog **9** inhibited platelet and fibrin deposition in a dose-dependent manner after intravenous administration in a baboon thrombosis model, and a pharmacodynamic concentration–response model was developed to describe the platelet deposition data. Results for heparin and enoxaparin (Lovenox®) in the baboon model are also presented.



9



A quantitative Structure–activity relationship study (QSAR) on a set of carbonic anhydrase inhibitors is presented using first-order valence connectivity index ($^1\chi^v$). The inhibitory activity against three isozymes CAI, CAII (cystolic forms), and CAIV (membrane bound form), some of which are involved in important physiological processes, were considered for this purpose. All the three activities were well modeled by $^1\chi^v$ in multi-parametric regression containing indicator parameters. The results are critically discussed on the basis of variety of statistical analyses.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Crystal structures of **19** bound to the allosteric site of KSP. Protein shown in solid ribbon. Green patch indicates location of a hydrophobic region in the binding site. [Fraley, M. E.; Garbaccio, R. M.; Arrington, K. L.; Hoffman, W. F.; Tasber, E. S.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Fernandes, C.; Schaber, M. D.; Lobell, R. B.; Tao, W.; South, V. J.; Yan, Y.; Kuo, L. C.; Prueksaritanont, T.; Shu, C.; Torrent, M.; Heimbrook, D. C.; Kohl, N. E.; Huber, H. E.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 1775.]

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