Bioorganic & Medicinal Chemistry 18 (2010) 463–476

Contents lists available at ScienceDirect

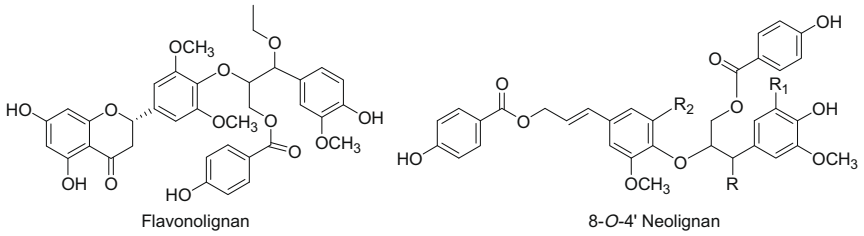
Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

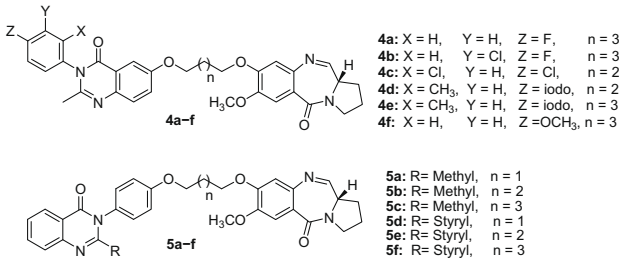
Bioorganic & Medicinal Chemistry Volume 18, Issue 2, 2010

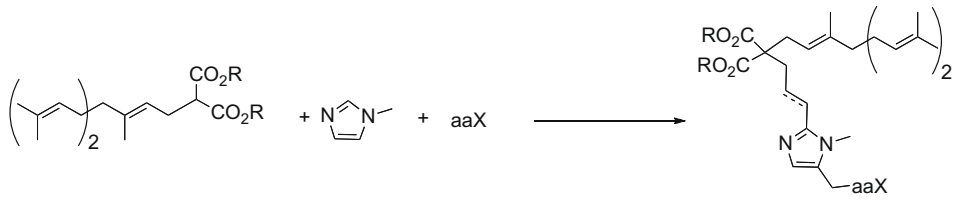
Contents

ARTICLES

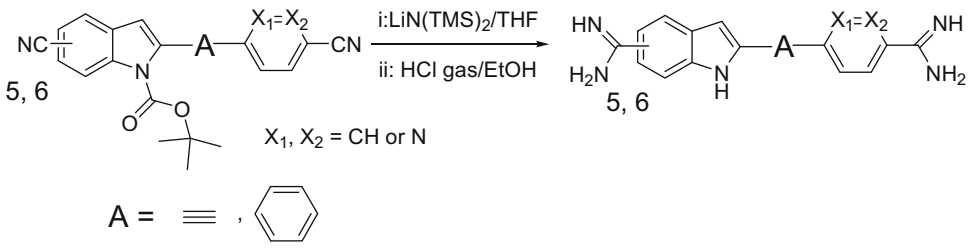


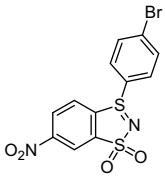
Three new flavonlignans (**1**–**3**) and five new 8-*O*-4′ neolignan derivatives (**4**–**8**) were isolated from the EtOAc extract of *Calamus quiquesetinervius*.



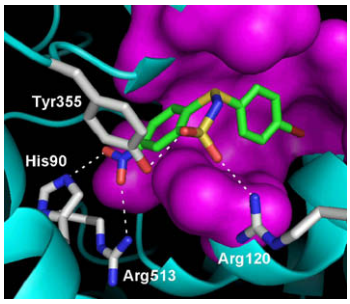


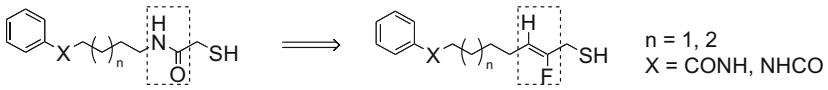
New FPP analogues were synthesized. The most active derivative was coupled to aaX motif through the imidazole ring affording new FTase inhibitors active against *Plasmodium falciparum* and *Trypanosoma brucei*.

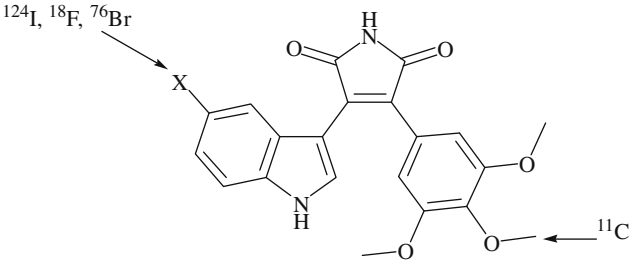




1

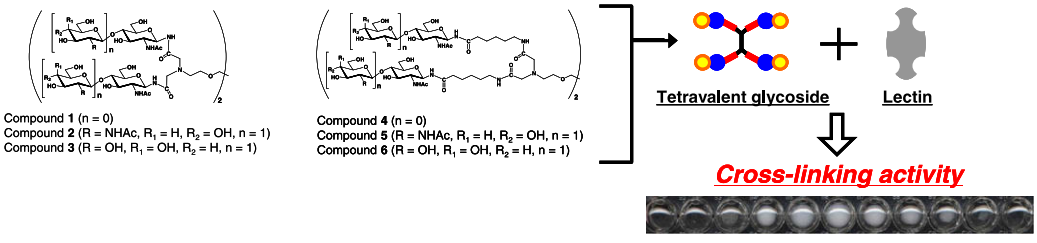


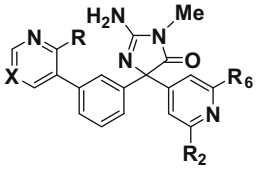




X = H, F, Br, I

New 3-aryl-4-indolylmaleimide derivatives were synthesized and evaluated as potential PET biomarkers for monitoring angiogenic processes.

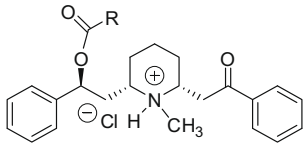




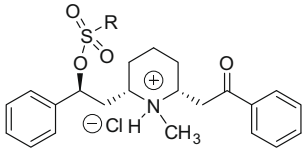
R_2, R_6 = Me, Et, i-Pr
R = H, F
X = C, N

Steric substituents close to the BACE1 Pro_{70}/BACE2 Lys_{86} mutation has generated a conflict between the ligand and the BACE2 enzyme backbone, thus resulting in highly selective BACE1 inhibitors.

A series of carboxylate and sulfonate esters of lobeline have been synthesized. The sulfonate esters exhibited high affinity (K_i = 5–17 nM), at α4β2* nicotinic receptors, but were less active as inhibitors of neurotransmitter transporters. The carboxylate esters had lower affinity at α4β2* nicotinic receptors (0.06–19.3 μM) and moderate affinity and selectivity at neurotransmitter transporters.

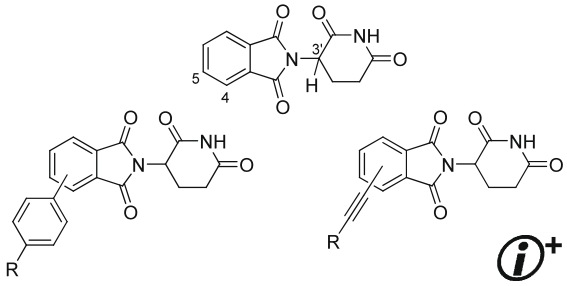


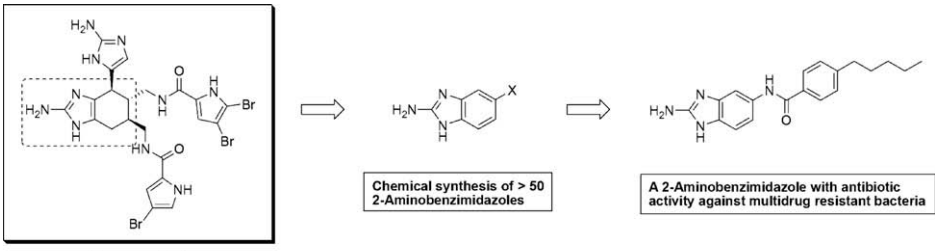
4: R=*p*-methoxyphenyl
α7*: K_i=18.4 μM; α4β2*: K_i=19.3 μM
DAT: K_i=3.8 μM; SERT: K_i= 2.04 μM
VMAT2: K_i=2.98 μM



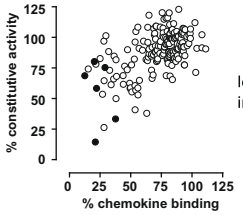
11: R=*p*-toluyl
α7*: K_i=18.0 μM; α4β2*: K_i=5 nM
DAT: K_i=29.1 μM; SERT: K_i= 16.2 μM
VMAT2: K_i=10.8 μM

Thalidomide analogues containing either a phenyl or alkyne tether were prepared using cross coupling reactions. Several analogues were far more efficient in the inhibition of the expression of the Tumour Necrosis Factor (TNF) monitored through a novel reporter system. Several derivatives showed increased cytotoxicity due to induction of an apoptotic response.



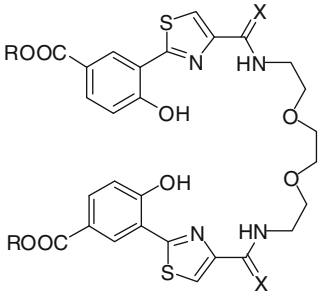


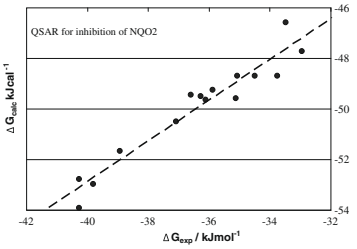
Bromoageliferin



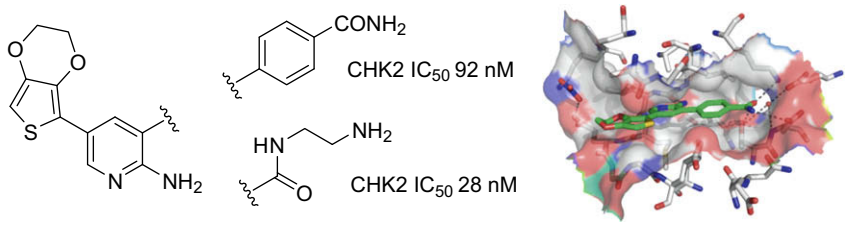
Identification of nonpeptidergic ligands for US28 that inhibit constitutive signaling and/or chemokine binding

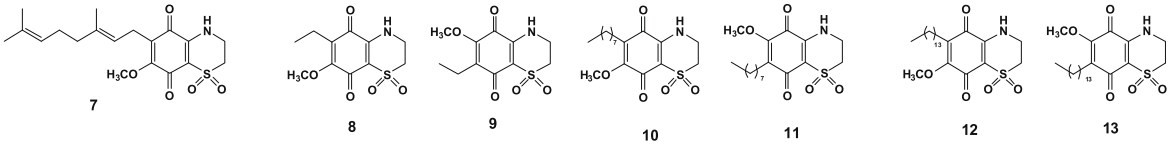
Bis-2-(2-hydroxy-phenyl)-thiazole-4-carboxamides or -thiocarboxamides (BHPTCs) are efficient bis-tridentate iron chelators with promising biological properties: lipophilic dithioamide BHPTC (R = CH_3, X = S) displayed in vitro an antiproliferative activity on several cancerous cell lines when hydrophilic diamide BHPTC (R = H, X = O) proved to be as efficient and less toxic as deferoxamine (DFO) when tested for its cytoprotective activity against iron overload.



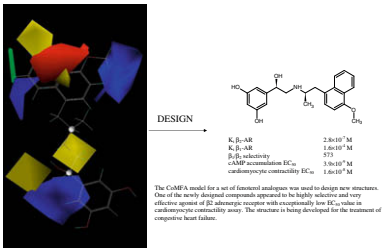


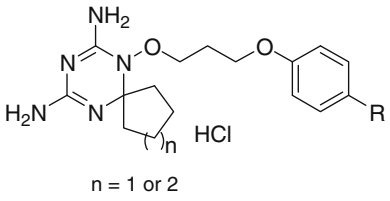
A series of 5-, 8-substituted triazoloacridin-6-ones have been synthesized and biologically evaluated as novel inhibitors of the quinone oxidoreductases, NQO1 and NQO2. Molecular modeling provides insights into their structure–activity behaviour and selectivity.



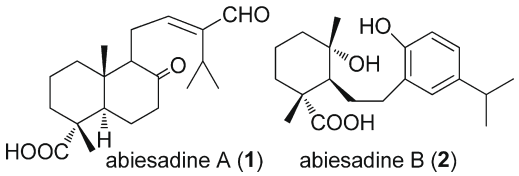


Structurally simplified analogues (**8**–**13**) of aplidinone A (**7**) have been synthesized. Compound **11** is a potent pro-apoptotic agent which also inhibits the TNFα-induced NF-κB activation in human leukemia T cells.

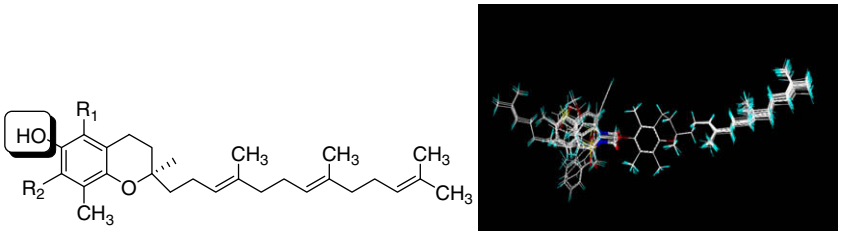


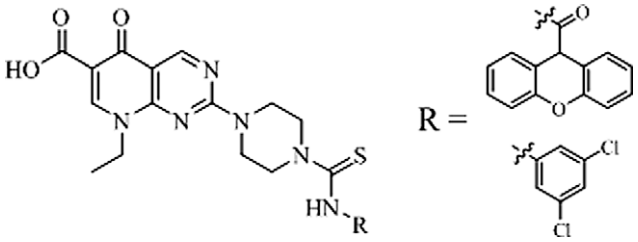


Antifolate agents with *para* substitution R on phenyl ring according to Craig plot were prepared and investigated in vitro for DHFR inhibitory activity and antiproliferative activity against A549 cancer cells.

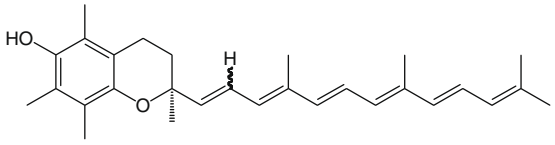


Twenty-five new diterpenes, abiesadines A–Y (**1**–**25**) were isolated from the aerial parts of *Abies georgei* together with 29 known ones (**26**–**54**).

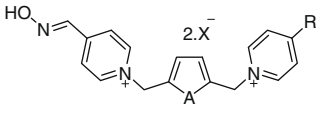




Pipemidic acid analogs were the most potent among our previously identified non-lipid small molecule inhibitors of the anticancer target enzyme, autotaxin.

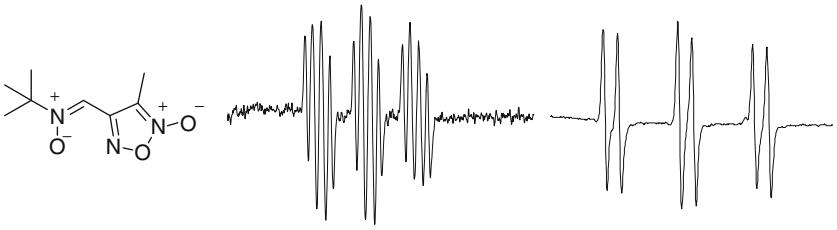


Peroxidation sensitive fluorescent Vitamin E

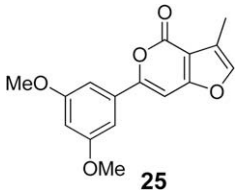


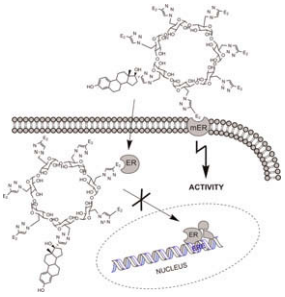
R = $CONH_2$; A = S (52% reactivation and k_r 0.0417 min^{-1} for EeAChE)
R = CHNOH; A = O (52% reactivation and k_r 0.0423 min^{-1} for EeAChE)

A reactivation potency of new series of bisquaternary pyridinium oximes with heteroaromatic linkers (thiophene, furan, isoxazole) for paraoxon-inhibited electric eel AChE and recombinant human AChE is reported. Compounds bearing thiophene and furan linker showed comparable reactivation potency to trimedoxime and obidoxime at 10^{-5} M.

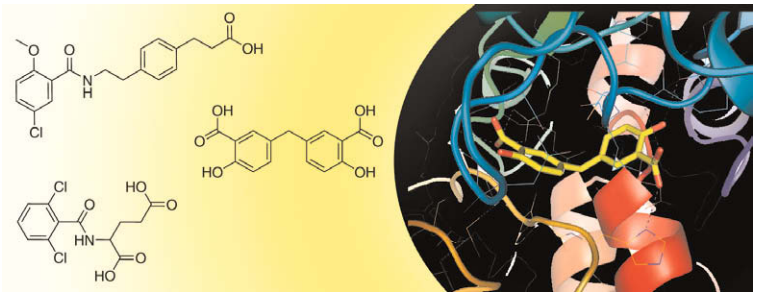


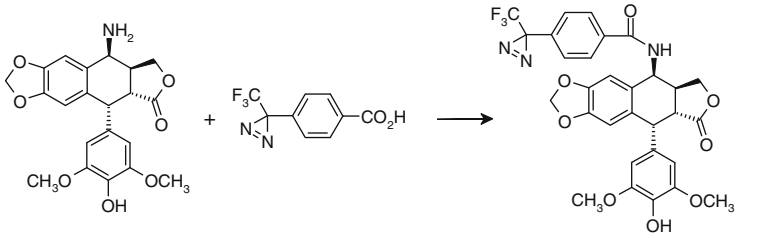
A new series of heteroaryl nitrones bearing furoxanyl and thiadiazolyl moieties were evaluated for their free radical-trapping properties.



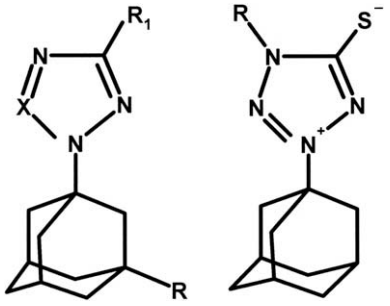


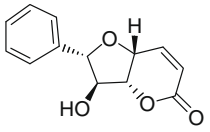
The first small molecules reported with biochemical selectivity towards an individual DNMT enzyme were discovered by virtual screening and experimental characterization.





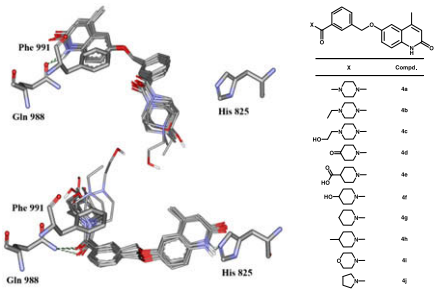
Photoaffinity etoposide probe
useful for labeling topoisomerase II

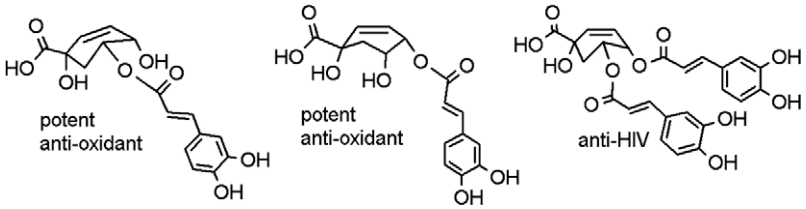


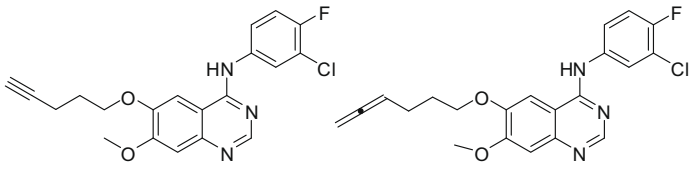


(-)-Altholactone

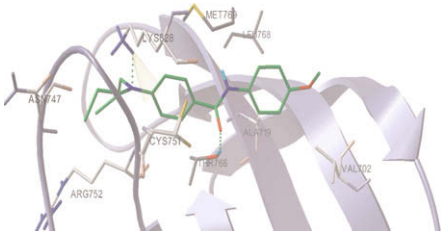
A comparative study of the apoptotic activities of a related group of styryllactones and the potential of one of them, (−)-altholactone, to act synergistically with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) are discussed.



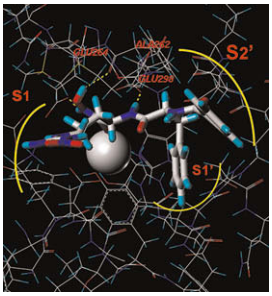


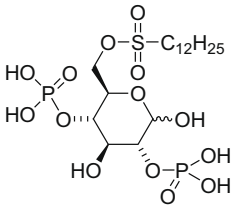


Of all the studied compounds, compounds **5b** and **5t** exhibited the most potent EGFR and HER-2 inhibitory activity. Docking simulation was performed to position compounds **5b** and **5t** into the EGFR active site to determine the probable binding model. Antiproliferative assay results indicated that some of the benzoic nitrogen mustard derivatives possessed high antiproliferative activity against MCF-7. In particular, compounds **5b** and **5t** with potent inhibitory activity in tumor growth inhibition may function as potential antitumor agents.

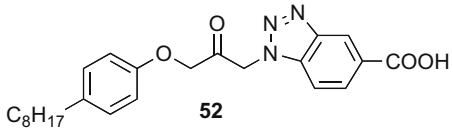


A series of bi- or tri-peptide analogues with the scaffold L-argnine were designed, synthesized and evaluated for their inhibitory activities against APN and metalloproteinase-2 (MMP-2). All of the compounds exhibited higher selectivity. Within this series, compound **C6** and **C7** (IC_{50} = 4.2 and 4.3 μM) showed comparable APN inhibitory activities with the positive control bestatin (IC_{50} = 3.8 μM).

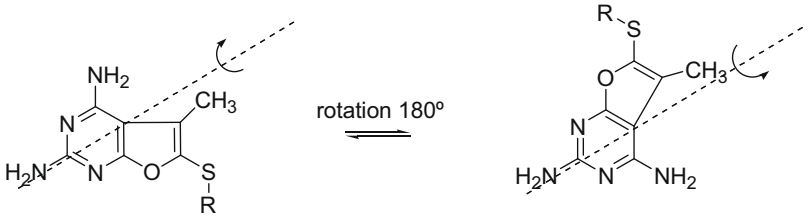


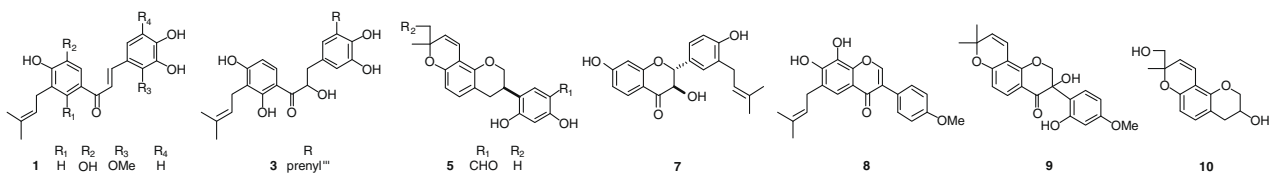


A carbohydrate-derived analogue of potent and selective acid sphingomyelinase inhibitor phosphatidylinositol-3,5-bisphosphate was synthesized. This compound is more potent and as selective as its parent compound.

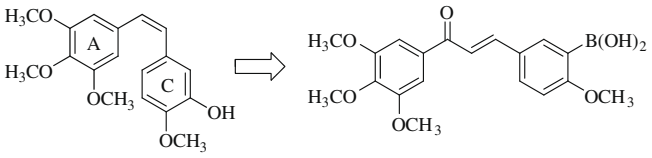


52





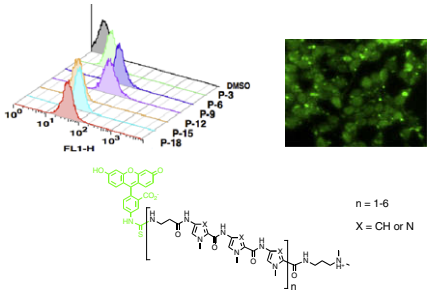
Bioassay-guided fractionation of the EtOH extract of licorice (*Glycyrrhiza glabra* roots), using a GAL-4-PPAR-γ chimera assay method, resulted in the isolation of 39 phenolics, including 10 new compounds (**1**–**10**).



Combretastatin A-4 (CA-4) **4**

Boronic acid chalcone analogs of combretastatin A-4 were designed and synthesized. The cytotoxicity study identified that the boronic acid chalcone **4** was potent towards 16 human cancer cell lines with GI_{50} values in the range of 10–200 nM, and another three cell lines with GI_{50} values below 10 nM.

In order to investigate the influence of molecular size and pyrrole (Py)/imidazole (Im) content on the cell permeability of Py–Im-polyamide-fluorescein conjugates we systematically designed the Py-polyamides and Im-polyamides. Flow cytometric analysis revealed that Py-polyamides, even those with large molecular size, **P-15** and **P-18**, showed good cellular uptake, but Im-polyamides showed very poor uptake. Fluorescence microscopy revealed that conjugate **P-6** exhibited nuclear localization, while **P-18** showed less nuclear stain but intracellular localization, suggesting that increased molecular size is one of the determinants in reducing nuclear access. Furthermore, results for hairpin polyamide conjugates **H-1**, **H-2**, and **H-3** containing different Py/Im content indicated that cellular uptake increases as the Im residue is reduced. It appears that Py–Im-polyamide has general properties regardless of whether they have a linear or a hairpin structure.



*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (http://www.pymol.org). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, *102*, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, *61*(6), 355–360].

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

ELSEVIER

ISSN 0968-0896