Bioorganic & Medicinal Chemistry 19 (2011) 5917–5923

Contents lists available at SciVerse ScienceDirect

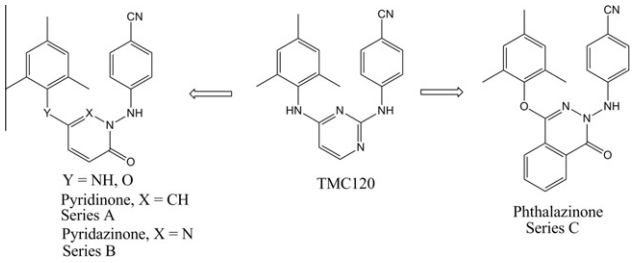
Bioorganic & Medicinal Chemistry

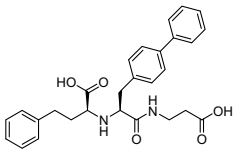
journal homepage: www.elsevier.com/locate/bmc

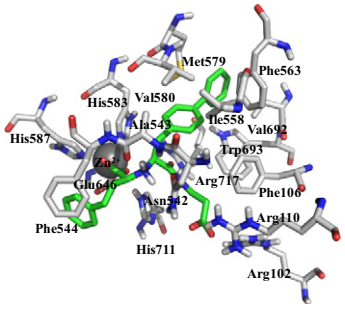
Bioorganic & Medicinal Chemistry Volume 19, Issue 20, 2011

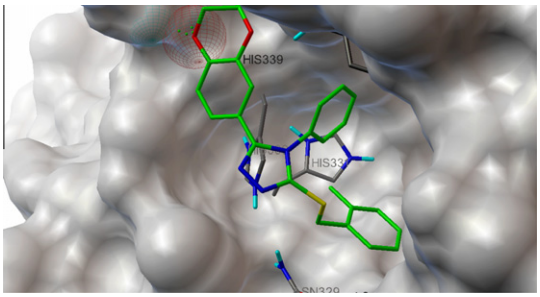
Contents

ARTICLES

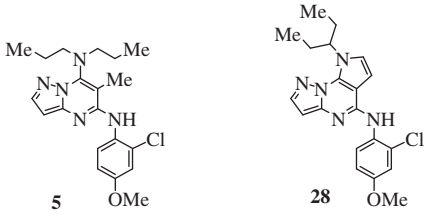


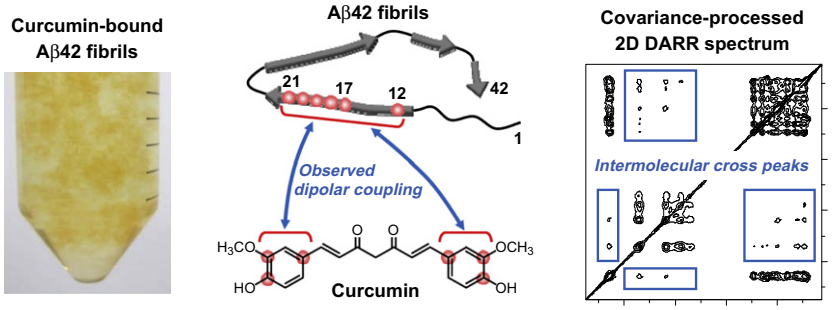


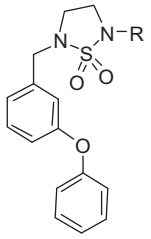




A series of 1,2,4-triazole derivatives containing 1,4-benzodioxan (**5a**–**5q**) have been designed, synthesized, structurally determined, and their biological activities were evaluated as potential MetAP2 inhibitors. All the synthesized compounds were first reported. Among the compounds, compound **5k** showed the most potent biological activity against HEPG2 cancer cell line (IC_{50} = 0.81 μM for HEPG2 and IC_{50} = 0.93 μM for MetAP2), which was comparable to the positive control. Docking simulation by positioning compound **5k** into the MetAP2 structure active site was performed to explore the possible binding model. The results of apoptosis and Western-blot assay demonstrated that compound **5k** possessed good antitumor activity against HEPG2 cancer cell line. Therefore, compound **5k** with potent inhibitory activity in tumor growth inhibition may be a potential antitumor agent against HEPG2 cancer cell.

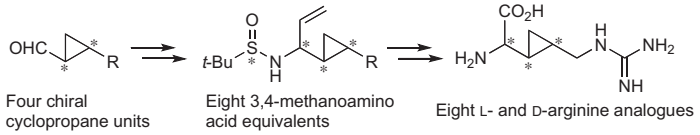


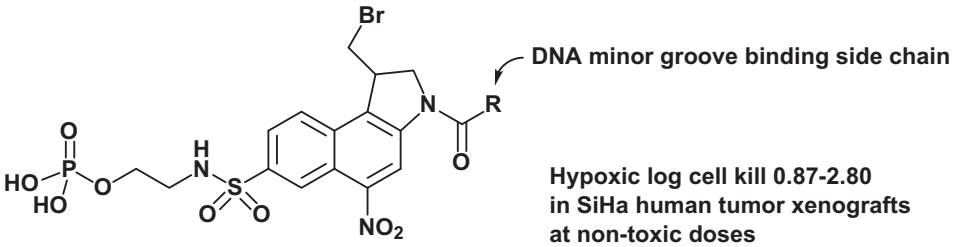




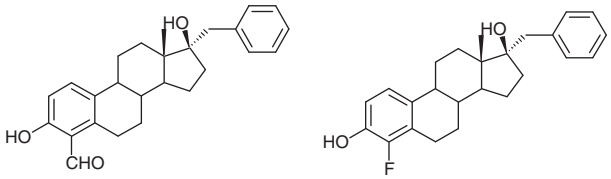
(I) (R=H, ED_{50}: 4 μM TD_{50}: 50 μM)

A new class of compounds that exhibit anti-norovirus activity in a cell-based system and embody in their structure a cyclosulfamide scaffold, has been identified. The structure of the initial hit (compound **2a** (structure (I) where R = H), ED_{50} 4 μM, TD_{50} 50 μM) has been prospected by exploiting multiple points of diversity and generating appropriate structure–activity relationships.



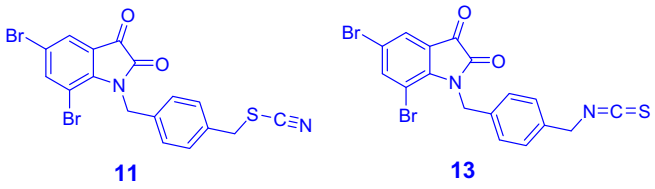


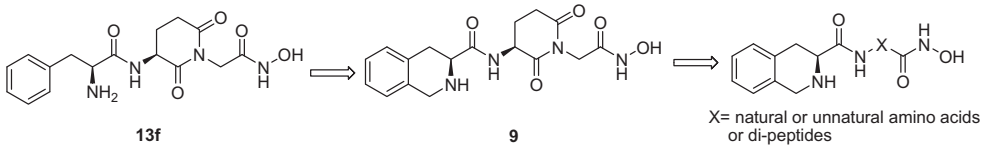
Hypoxic log cell kill 0.87–2.80 in SiHa human tumor xenografts at non-toxic doses.



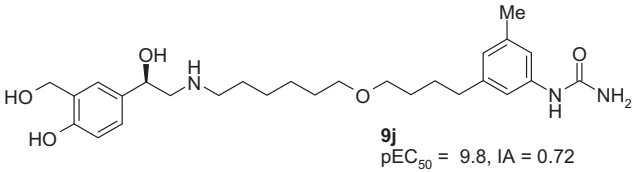
time-dependent STS inhibtor
K_I = 85 nM
k_{inact} = 0.021 min^{-1}

reversible, non-time-dependent,
noncompetitive STS inhibtor
IC_{50} = 40 nM

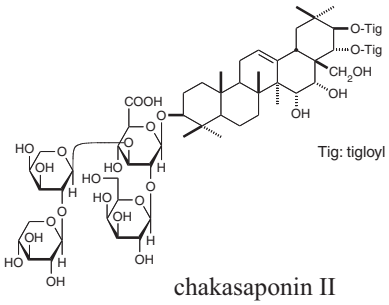




Novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were designed and synthesized as APN inhibitors. Compound **12h** had the best APN inhibition in vitro with the IC_{50} value to 6.28 ± 0.11 μM, which is similar with that of Bestatin (IC_{50} = 5.55 ± 0.01 μM).

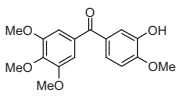


9j
pEC_{50} = 9.8, IA = 0.72

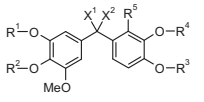


chakasaponin II

The methanolic extract from the flower buds of *Camellia sinensis* showed inhibitory effects on body weight gain and the weight of visceral fats in high-fat diet-fed mice and/or Tsumura Suzuki Obese Diabetic (TSOD) mice. A suppressive effect of the extract on food intake was suggested to contribute to the anti-obesity effect. The *n*-butanol-soluble fraction and a principal constituent, chakasaponin II, inhibited food intake. These inhibitory effects were reduced by pretreatment with a high dose of capsaicin. The *n*-BuOH-soluble fraction and chakasaponin II suppressed mRNA levels of neuropeptide Y in the hypothalamus. Furthermore, chakasaponin II enhanced the release of serotonin (5-HT) from the isolated ilea of mice in vitro.



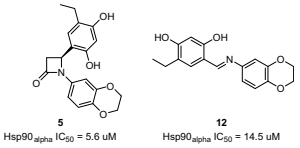
Phenstatin



Some metabolites of phenstatin

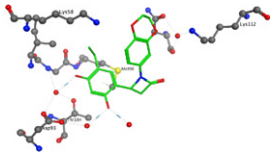
20 $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H$, $X^1,X^2 = O$
23 $R^1 = R^2 = R^3 = Me$, $R^4 = H$, $R^5 = OMe$, $X^1,X^2 = O$
21 $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = H$, $X^1,X^2 = O$
25 $R^1 = R^3 = Me$, $R^2 = R^4 = R^5 = H$, $X^1,X^2 = O$
22 $R^1 = R^3 = Me$, $R^2 = R^4 = H$, $R^5 = OMe$, $X^1,X^2 = O$
24 $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = Me$, $X^1,X^2 = O$
27 $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = X^1 = H$, $X^2 = OH$
26 $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = X^1 = H$, $X^2 = OH$

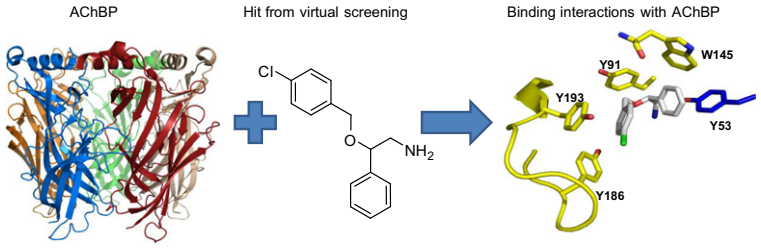
Previous investigations on the incubation of phenstatin with rat and human microsomal fractions revealed the formation of nine main metabolites. The structures of eight of these metabolites have been now confirmed by synthesis and their biological properties have been reported. Eaton's reagent was utilized as a convenient condensing agent, allowing, among others, a simple multigram scale preparation of phenstatin. Synthesized metabolites and related compounds were evaluated for their antiproliferative activity in the NCI-60 cancer cell line panel, and for their effect on microtubule assembly. Metabolite **23** (2′-methoxyphenstatin) exhibited the most potent in vitro cytotoxic activity: inhibition of the growth of K-562, NCI-H322M, NCI-H522, KM12, M14, MDA-MB-435, NCI/ADR-RES, and HS 578T cell lines with GI_{50} values <10 nM. It also showed more significant tubulin polymerization inhibitory activity than parent phenstatin (**3**) (IC_{50} = 3.2 μM vs 15.0 μM) and induced G2/M arrest in murine leukemia DA1-3b cells. The identification of this active metabolite led to the design and synthesis of analogs with potent in vitro cytotoxicity and inhibition of microtubule assembly.

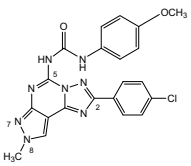


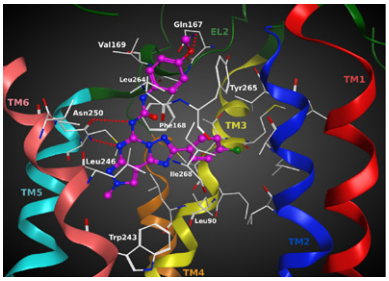
5
$Hsp90_{alpha}$ IC_{50} = 5.6 uM

12
$Hsp90_{alpha}$ IC_{50} = 14.5 uM

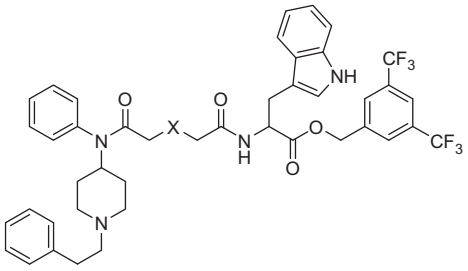


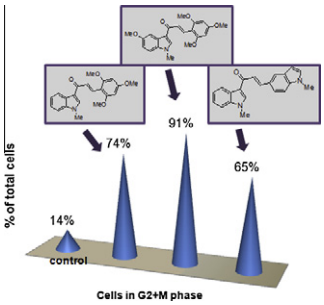


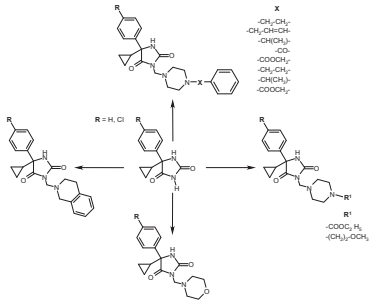




Among the newly synthesized 2-(substituted)phenyl-pyrazolo-triazolo-pyrimidine derivatives bearing optimal substitutions at the C^2-, N^5- and N^8-positions, the compound with a 4-chlorophenyl at C^2, a small methyl group at N^8 and a 4-methoxyphenylcarbamoyl chain at N^5 showed the best hA_3AR profile, as demonstrated by both pharmacological data and molecular modeling investigations.







The library of new *N*-Mannich bases derived from 5-cyclopropyl-5-phenyl- and 5-cyclopropyl-5-(4-chlorophenyl)-imidazolidine-2,4-diones have been synthesized. The in vivo results showed that all of compounds were effective in maximal electroshock test (MES).

*Corresponding author

Supplementary data available via SciVerse ScienceDirect

COVER

The known veterinary anthelmintic and proton ionophore, closantel, was recently discovered to also exhibit potent chitinase inhibition activity and inhibit molting in the parasitic nematode, *Onchocerca volvulus*, the causative agent of the neglected tropical disease onchocerciasis. [C. Gloeckner, A. L. Garner, F. Mersha, Y. Oksov, N. Tricoche, L. M. Eubanks, S. Lustigman, G. F. Kaufmann, K. D. Janda, Repositioning of an existing drug for the neglected tropical disease Onchocerciasis, *Proc. Natl. Acad. Sci., U.S.A.* **2010**, *107*, 3424.]

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 SciVerse Scopus®. Full text available on SciVerse ScienceDirect®

ELSEVIER

ISSN 0968-0896