POC-1

Synthesis of Novel Pyrimidine Derivatives as Potential Anticancer Agents

Makarem M. Korraa, Azza T. Taher, Hala B. El-Nassan, Eman A.El-Khouly

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University.
Kasr El Aini St. Cairo, 11562 Egypt

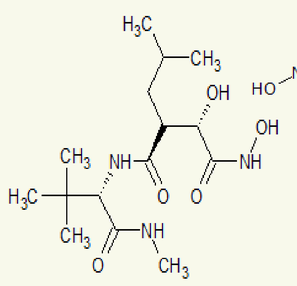
Introduction

Collagenase-**II** (MMP-8) represent one of the subtypes of Matrix metalloproteinases (MMPs) which are a superfamily of zinc- and calcium-dependent endopeptidases that are responsible for hydrolysis of the peptide bond[1]. Over-regulation of their activity, however, results in uncontrolled degradation of the extracellular matrix in diseases such as cancer[2] (tumor growth, invasion and metastasis), arthritis[3] and multiple sclerosis[4].

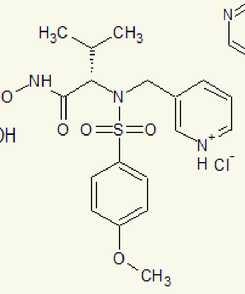
Consequently, there has been significant interest in the development of drugs to control the over-regulation of MMP production. Some orally active MMP inhibitors are currently under clinical investigation for the treatment of cancer and/or arthritis. Representative examples include succinamides (Marimastat) **1 [5-7]**, linear sulfonamides (CGS-27023A) **2 [8]**, heterocyclic sulfonamides (Prinomastat) **3 [9-10]**, and biphenylbutanoic acid derivatives (BAY-129566) **4 [11]**.

Recently, a novel class of barbituriatic acid derivatives (RO200-1770) **5** was identified as inhibitors of collagenases type 2 (MMP-8) **[12].**

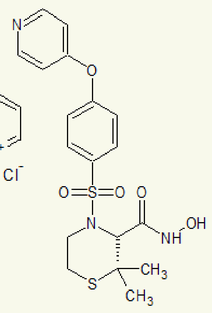
Structures of MMP Inhibitors



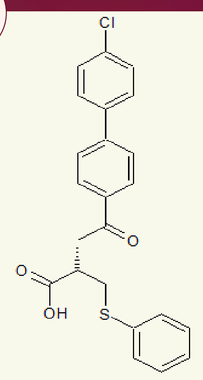
Marimastat
1



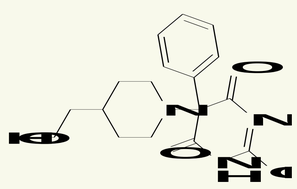
CGS-27023A
2



Prinomastat
3



BAY-129566
4



RO200-1770
5

Docking Study

All the target compounds were subjected to docking study to explore their affinity and binding mode to MMP-8. The docking study was performed using MOE-2008. The 3D structure of MMP-8 complexed with Compound **5** was obtained from the protein data bank (PDB entry: 1JJ9) **[12]** The vicinity where compound **5** is situated was considered as the active site of MMP-8 and compound **I** was considered as lead structure. We performed 30 docking iteration for each ligand, and the top-scoring configuration of each of the ligand-enzyme complexes was selected on energetic grounds. Two important H-bonds between compound **I** and the amino acid residues Ala161 and Leu160,Co-ordinate bond with Zn^{2+} ion and Hydrophobic interactions with aminoacid residues His197,His201 and His207 were observed.

Figures (1-3) showed interaction of Lead compound or Synthetized compounds with active site of MMP-8.

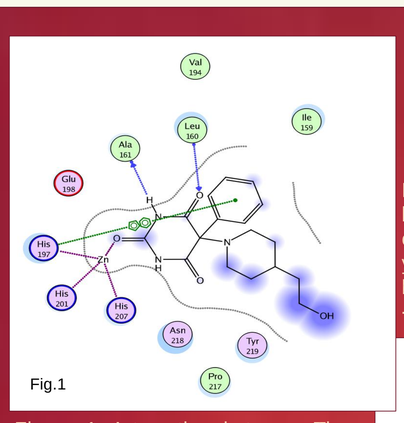


Fig.1

Figure 1. Interaction between The lead compound 5 and binding site of MMP-8 with E-score:-10.4135 (rmsd:1.3486).

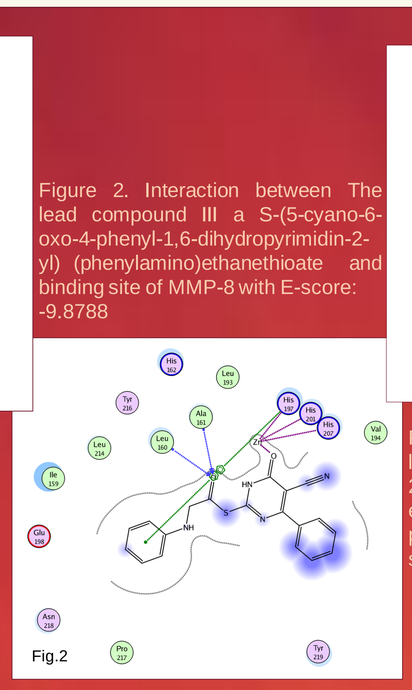


Fig.2

Figure 2. Interaction between The lead compound **III** a S-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl) (phenylamino)ethanethioate and binding site of MMP-8 with E-score: -9.8788

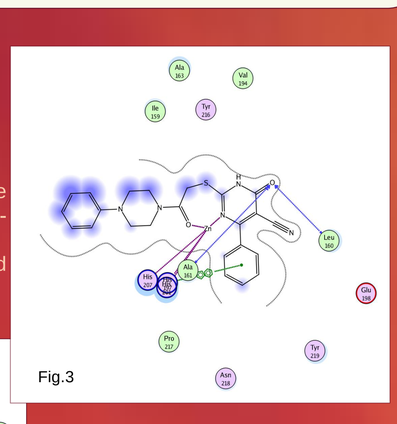


Fig.3

Figure 3. Interaction between The lead compound IV c 6-Oxo-2-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethylsulfanyl]-4-phenyl-1,6-dihydro-pyrimidine-5-carbonitrile and binding site of MMP-8 with E-score:-11.0322

Conclusion

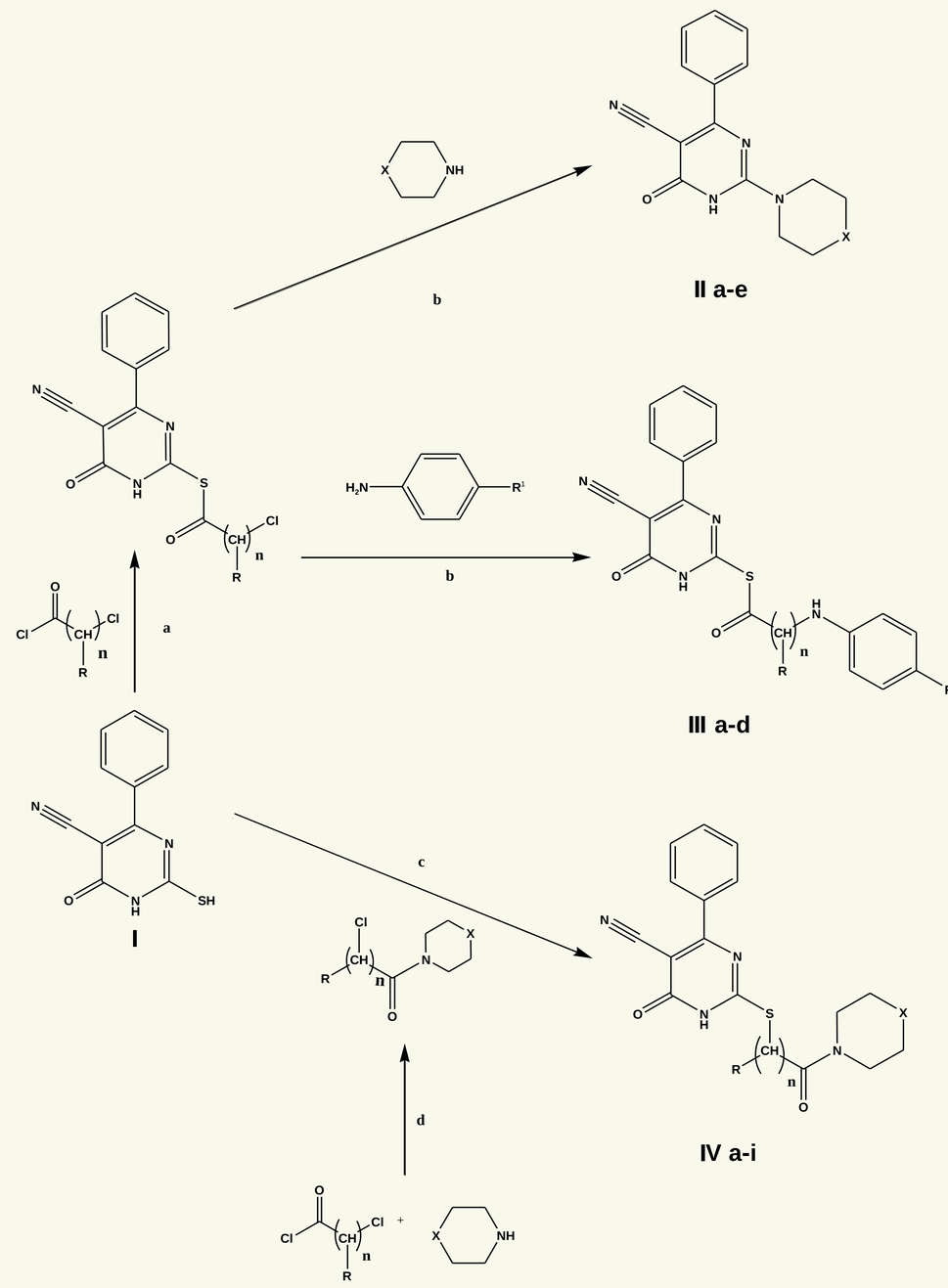
The docking study revealed that almost all of the proposed target compounds bind to Zn^{2+} ion, Ala161, and Leu160 in MMP-8 with higher or comparable binding energy score than the lead compound **I** and thus showed promising activity as MMP-8 inhibitors. Accordingly, these compounds were synthesized hoping that they have potential anticancer activity.

Research Objectives

We were encouraged to prepare a novel series of S-acylated **III a-d** and S-alkylated **IV a-i** pyrimidine derivatives as inhibitors of MMP-8. All the target compounds were subjected to docking study to explore their affinity and binding mode to MMP-8. We also aim to study the effect of the length of spacer and the bulkiness of aryl groups on the anticancer activity.

The synthesis of the target compounds is outlined in **Scheme 1**

Scheme I



Scheme 1. Reagents: a) dry benzene ,dry DMF, anhydrous K_2CO_3
b) dry benzene ,dry DMF,TMA
c) dry benzene
d) dry DMF, anhydrous K_2CO_3

References

[1]. Woessner, J. F.; Nagase, H. Matrix Metalloproteinases and TIMPS; Oxford University Press: Oxford,2000.
[2]. Nelson,A. R.; Fingleton, B.; Rothemberg, M. L.; Matrisian, L. M. J. Clin. Oncol. 2000, 18, 1135.
[3]. Clark, I. M.; Rowan, A. D.; Cawston, T. E. Expert Opin. Anti-Inflammatory Immunomodulatory Invest. Drugs 2000, 2, 16
[4]. Leppert, D.; Lindberg, R. L. P.; Kappos, L.; Leib, S. L. Brain Res. Rev. 2001, 36, 249.
[5] Cherney, R. J.; Wang, L.; Meyer, D. T.; Xue, C.-B.; Arner, E. C.; Copeland, R. A.; Covington, M. B.; Hardman, K. D.; Wasserman, Z. R.; Jaffee, B. D.; Decicco, C. P. Macrocyclic hydroxamate inhibitors of matrix metalloproteinases and TNF-a production. Biorg. Med. Chem. Lett. 1999, 9, 1279-1284.
[6] Steward, W. P. Marimastat (BB2516): current status of development. Cancer Chemother. Pharmacol. 1999, 43, S56-60.
[7] Rhomberg, W. Marimastat (British Biotech plc.). Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs 1999, 1, 507-524.
[8] MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V. S.; Parker, D. T. Discovery of CGS 27023A, a nonpeptidic, potent, and orally active stromelysin inhibitor that blocks cartilage degradation in rabbits. J. Med. Chem. 1997, 40, 2525-2532.
[9] Pikul, S.; McDow-Dunaway, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; McPhail, M. V.; Snider, C. E.; Taiwo, Y. O.; Rydel, T.; Dunaway, C. M.; Gu, F.; Mieling, G. E. Discovery of potent, achiral matrix metalloproteinase inhibitors. J. Med. Chem. 1998, 41, 3568
[10] Shalinsky, D. R.; Brekken, J.; Zou, H.; McDermott, C. D.; Forsyth, P.; Edwards, D.; Margosiak, S.; Bender, S.; Truitt, G.; Wood, A.; Varki, N. M.; Appelt, K. Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. Ann. N. Y. Acad. Sci. 1999, 878, 236-270.
[11]Rowinsky, E. K.; Humphrey, R.; Hammond, L. A.; Aylesworth, C.; Smetzer, L.; Hidalgo, M.; Morrow, M.; Smith, L.; Garner, A.; Sorensen, J. M.; Von Hoff, D. D.; Eckhardt, S. G. Phase I and pharmacologic study of the specific matrix metalloproteinase inhibitor BAY 12-9566 on a protracted oral daily dosing schedule in patients with solid malignancies. J.Clin. Oncol. 2000, 18, 178-186.
[12] Brandstetter, H.; Grams, F.; Glitz, D.; Lang, A.; Huber, R.; Bode, W.; Krell, H.; Engh, R. A. J. Biol. Chem. 2001, 276, 17405.