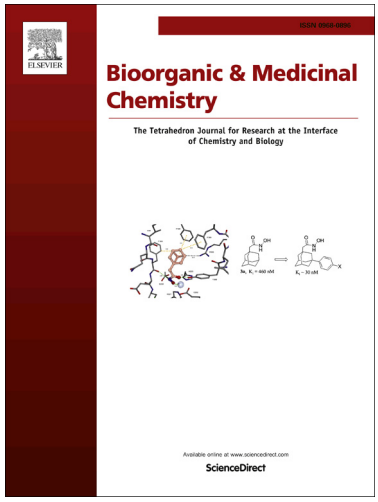
Accepted Manuscript



Design and synthesis of new barbituric- and thiobarbituric acid derivatives as potent urease inhibitors: structure activity relationship and molecular modeling studies

Abdul Rauf, Sohail Shahzad, Marek Bajda, Muhammad Yar, Faiz Ahmed, Nazar Hussain, Muhammad Nadeem Akhtar, Ajmal Khan, Jakub Jończyk

PII: S0968-0896(15)00448-4
DOI: http://dx.doi.org/10.1016/j.bmc.2015.05.038
Reference: BMC 12334

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 18 April 2015
Revised Date: 23 May 2015
Accepted Date: 25 May 2015

Please cite this article as: Rauf, A., Shahzad, S., Bajda, M., Yar, M., Ahmed, F., Hussain, N., Akhtar, M.N., Khan, A., Jończyk, J., Design and synthesis of new barbituric- and thiobarbituric acid derivatives as potent urease inhibitors: structure activity relationship and molecular modeling studies, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.05.038

Design and synthesis of new barbituric- and thiobarbituric acid derivatives as potent urease inhibitors: structure activity relationship and molecular modeling studies

Abdul Rauf[a,*], Sohail Shahzad[a,b], Marek Bajda[c], Muhammad Yar[b,*], Faiz Ahmed[a], Nazar Hussain[a], Muhammad Nadeem Akhtar[d], Ajmal Khan[e], Jakub Jończyk[c]

[a]*Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan*

[b]*Interdisciplinary Research Center in Biomedical Materials, COMSATS Institute of Information Technology, Lahore,54000, Pakistan*

[c]*Department of Physicochemical Drug Analysis, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Cracow, Poland*

[d]*Faculty of Industrial Sciences & Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak 26300, Kuantan Pahang, Malaysia*

[e]*H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan*

*Correspondence Address:

E-mail addresses: lecorganic@yahoo.com (A Rauf); drmyar@ciitlahore.edu.pk (M. Yar)

Abstract:

In this study 36 new compounds were synthesized by condensing barbituric acid or thiobarbituric acid and respective anilines (bearing different substituents) in the presence of triethyl orthoformate in good yields. *In vitro* urease inhibition studies against jack bean urease revealed that barbituric acid derived compounds **(1-9** and **19-27)** were found to exhibit low to moderate activity however thiobarbituric acid derived compounds **(10-18** and **28-36)** showed significant inhibition activity at low micro-molar concentrations. Among the synthesized compounds, compounds (**15**), (**12**), (**10**), (**36**), (**16**) and (**35**) showed excellent urease inhibition with IC_{50} values 8.53±0.027, 8.93±0.027, 12.96±0.13, 15±0.098, 18.9±0.027 and 19.7±0.63 μM, respectively, even better than the reference compound thiourea (IC_{50} = 21±0.011). The compound (**11**) exhibited comparable activity to the standard with IC_{50} value 21.83±0.19 μM. *In silico* molecular docking studies for