Bioorganic & Medicinal Chemistry Letters 24 (2014) 613–617

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design and synthesis of guanylthiourea derivatives as potential inhibitors of *Plasmodium falciparum* dihydrofolate reductase enzyme

Legesse Adane [a], Shweta Bhagat [a], Minhajul Arfeen [a], Sonam Bhatia [a], Rachada Sirawaraporn [b], Worachart Sirawaraporn [b], Asit K. Chakraborti [a], Prasad V. Bharatam [a,*]

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, Mohali 160062, Punjab, India
[b] Department of Biochemistry, Mahidol University, Bangkok 10400, Thailand

ARTICLE INFO

Article history:
Received 5 September 2013
Revised 22 November 2013
Accepted 2 December 2013
Available online 8 December 2013

Keywords:
Antimalaria
Guanylthiourea
*Pf*DHFR
MESP
Molecular docking

ABSTRACT

A new class of compounds based on S-benzylated guanylthiourea has been designed as potential *Pf*DHFR inhibitors using computer aided methods (molecular electrostatic potential, molecular docking). Several compounds in this class have been synthesized starting from guanylthiourea and alkyl bromides. In vitro studies showed that two compounds from this class are active with the IC_{50} value of 100 μM and 400 nM.

Plasmodium falciparum dihydrofolate reductase (*Pf*DHFR) is one of the validated targets to develop potential therapeutic agents for the treatment of malaria. Inhibition of *Pf*DHFR by typical antifolates such as trimethoprim, cycloguanil and pyrimethamine prevents biosynthesis of thymidine, and consequently interrupts DNA biosynthesis.[1] However, point mutations at amino acid residues such as Ala16, Ile51, Cys59, Ser108 and Ile164 in the active site of wild-type *Pf*DHFR enzyme has resulted in widespread resistance of the parasite to these drugs.[2] Thus, discovery of new potential *Pf*DHFR inhibitors to overcome drug-resistant parasites, is an urgent need.

The known antifolate based *Pf*DHFR inhibitors have 2,4-diaminopyrimidine or 1,3,5-triazine moiety that interact with amino acids in the active site via hydrogen bond and hydrophobic interactions. Molecular modeling studies have shown that potential *Pf*DHFR enzyme inhibitors must fulfill at least three criteria required for chemical and geometrical complementarity of ligands with the active site of the enzyme.[3] These are (i) H-bond donor head group that can form H-bond interaction with Asp54, Ile14 and Leu164, (ii) hydrophobic aromatic tail which occupies the hydrophobic pocket of the active site (Phe58, Met55, Phe116, Pro113, Ile112 and Ser111) to enhance inhibitory activity, and (iii) linker unit between the H-bond donor head groups and hydrophobic aromatic tail to provide flexibility, in order to avoid unfavorable steric clashes with Asn108 in the active site of the mutant *Pf*DHFR enzyme.[3,4]

Dasgupta et al.[5] reported the X-ray crystallographic structures of the wild-type (PDB code: 3DGA) and quadruple mutant (PDB code: 3DG8) *Pf*DHFRs with biguanide based bound ligands (RJF01302 and RJF670). Summerfield et al.[6] suggested, based on the results of crystal structure analysis of *Escherichia coli* DHFR enzyme complexed with amidinoisothiouronium salts (PDB code: 2ANO, 2ANQ) that guanylthiourea (GTU) derivatives can mimic

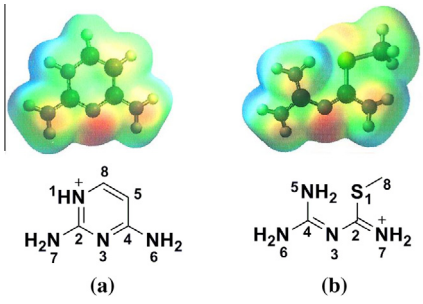
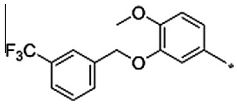
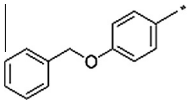
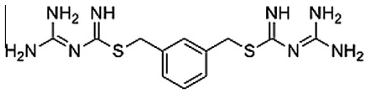
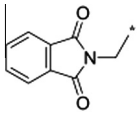
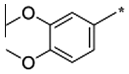
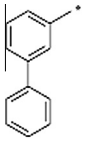
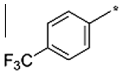
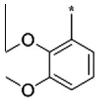
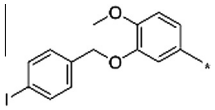
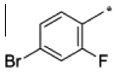
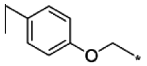
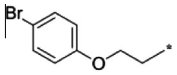
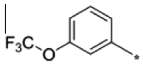
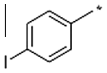
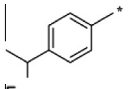
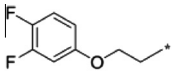
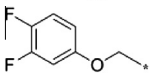


Figure 1. The MESP surfaces of (a) protonated pyrimethamine core and (b) protonated GTU derivative. Red color refers negative potential whereas blue color refers positive potential. All the structures were optimized using B3LYP method and the MESP analysis was generated using SPARTAN software.[10]

* Corresponding author.
E-mail address: pvbharatam@niper.ac.in (P.V. Bharatam).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.12.009

Table 1
The synthesized S-alkylated GTU derivatives (Fig. 3, structure III)

Compounds	R	G_{score}				Yield (%)
		1J3 K	1J3I	3DG8	3DGA	
WR99210	—	−8.708	−8.707	−6.665	−7.837	—
1		−9.075	−8.851	−8.498	−7.327	12.0
2		−8.832	−8.167	−7.514	−6.489	12.0
3		−8.754	−8.430	−8.099	−7.876	90.0
4		−8.620	−8.766	−8.028	−7.031	11.0
5		−8.347	−8.255	−7.102	−6.087	15.0
6		−8.192	−8.041	−7.745	−7.731	54.0
7		−8.160	−7.728	−7.288	−6.319	50.0
8		−8.016	−7.843	−6.673	−6.444	11.5
9		−7.964	−8.271	−6.841	−5.743	57.0
10		−7.878	−7.673	−7.281	−7.026	65.8
11		−7.790	−7.615	−6.750	−6.678	90.0
12		−7.694	−7.932	−6.911	−6.236	40.0
13		−7.651	−7.757	−7.186	−6.975	86.0
14		−7.620	−8.081	−7.540	−7.057	42.0
15		−7.577	−7.467	−6.318	−6.162	72.1
16		−7.526	−7.686	−7.074	−6.344	35.0
17		−7.076	−6.894	−6.414	−6.306	51.0
18		−7.058	−7.528	−6.428	−6.949	48.0