European Journal of Medicinal Chemistry 109 (2016) 187–198

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Identification of β-Amino alcohol grafted 1,4,5 trisubstituted 1,2,3-triazoles as potent antimalarial agents

Nalmala Devender [a], Sarika Gunjan [b, f], Stuti Chhabra [c], Kartikey Singh [a], Venkata Reddy Pasam [a], Sanjeev K. Shukla [d, ***], Abhisheak Sharma [e], Swati Jaiswal [e], Sunil Kumar Singh [b], Yogesh Kumar [c], Jawahar Lal [e], Arun Kumar Trivedi [c], Renu Tripathi [b, f, **], Rama Pati Tripathi [a, f, *]

[a] Medicinal and Process Chemistry Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India
[b] Parasitology Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India
[c] Biochemistry Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India
[d] Sophisticated Analytical Instrument Facility Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India
[e] Pharmacokinetics & Metabolism Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India
[f] Academy of Scientific and Innovative Research (AcSIR), New Delhi 110001, India

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form
6 December 2015
Accepted 20 December 2015
Available online 23 December 2015

Keywords:
β-aminoalcohol
Antiplasmodial
Antimalarial
Pharmacokinetics
p53 protein upregulation

ABSTRACT

In a quest to discover new drugs, we have synthesized a series of novel β-amino alcohol grafted 1,2,3-triazoles and screened them for their *in vitro* antiplasmodial and *in vivo* antimalarial activity. Among them, compounds **16** and **25** showed potent activity against chloroquine-sensitive (*Pf*3D7) strain with IC_{50} of 0.87 and 0.3 μM respectively, while compounds **7** and **13** exhibited better activity *in vitro* than the reference drug against chloroquine-resistance strain (*Pf*K1) with IC_{50} of 0.5 μM each. Compound **25** showed 86.8% *in vivo* antimalarial efficacy with favorable pharmacokinetic parameters. Mechanistic studies divulged that potent compounds significantly boosted p53 protein levels to exhibit the antimalarial activity.

© 2015 Elsevier Masson SAS. All rights reserved.

1. Introduction

Malaria caused mainly by *Plasmodium falciparum* claims millions of lives annually despite the availability of an arsenal of drugs belonging to mainly six classes: aminoquinolines, arylaminoalcohols, artemisinins, antifolates, antibiotics and inhibitors of the respiratory chain [1–3]. The current drugs for prophylaxis and treatment of malaria are scarce and development of resistance to chloroquine and many other antimalarial drugs including the recently reported artemisinins limits the utility of these drugs in certain areas [4–6]. Due to the drawbacks associated with the existing drugs and the absence of any viable vaccine, a massive effort has been made to identify new antimalarial leads acting through a novel mechanism [7]. An intensive research in this area to discern the molecular and cellular features of the parasite and new interventions to curtail this disease is noticed today. It has been perceived that several anticancer compounds exhibit potent antimalarial activity such as nutlin-3, combretastatin A-4 (CA-4), 1,5-disubstituted 1,2,3-triazoles (Fig. 1), and microtubule inhibitors trifluralin and vinblastine [8]. Recently several 1,2,3-triazole hybrids have been reported with potent anticancer, antimalarial, antidiabetic, antitubercular, antifungal and antiinflammatory activities [9–12].

The history of anticancer compounds as useful antimalarial agents dates back to 1913, when the nature of cancer and malaria therapy with quinine was commented on by J. Beard [13]. However, no serious attention was paid to the practicality of anticancer agents as new brand of antimalarials. Quite recently a new report

* Corresponding author. Medicinal and Process Chemistry Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India.
** Corresponding author. Parasitology Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India.
*** Corresponding author. NMR Facility, Sophisticated Analytical Instrument Facility Division, CSIR- Central Drug Research Institute (CSIR-CDRI), Lucknow 226031, India.
E-mail addresses: skshukla@cdri.res.in (S.K. Shukla), renu_tripathi@cdri.res.in (R. Tripathi), rpt.cdri@gmail.com, rp_tripathi@cdri.res.in (R.P. Tripathi).

http://dx.doi.org/10.1016/j.ejmech.2015.12.038
0223-5234/© 2015 Elsevier Masson SAS. All rights reserved.

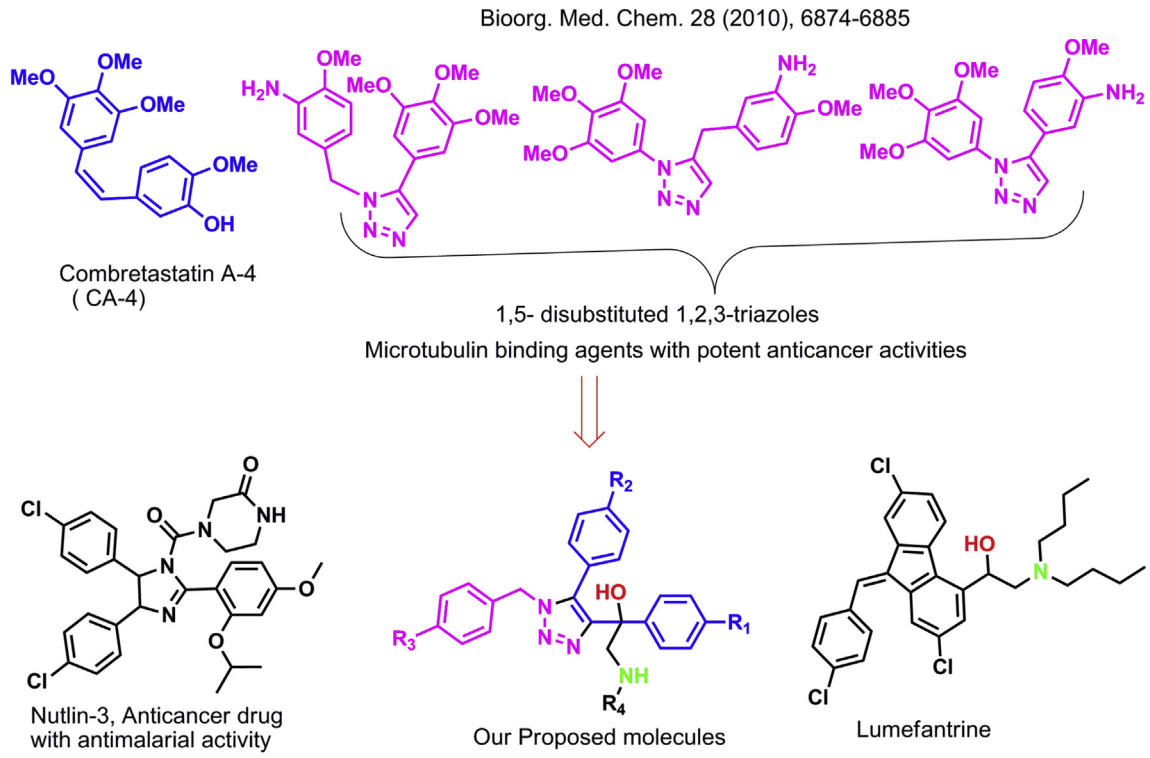

Fig. 1. Representative anticancer and antimalarial agents and our proposed molecules.

by Kaushansky et al. [8], has revealed that liver cells, the cells first infected by *Plasmodium* parasites post mosquito bite, actually behave similarly to cancer cells and therefore with the aid of cancer drugs, the liver can become a hostile environment for the malaria parasite. They have also demonstrated that suppression of host p53 is critical for parasite survival in malaria infection. Nutlin-3, an anticancer drug interferes with p53 suppression and thereby exhibit antimalarial activity *in vitro* and *in vivo* through the elevation of host p53 protein levels, and also decreases parasite burden in the uninfected liver cells. On the other hand, many arylamino alcohols were reported as potent antimalarial agents such as lumefantrine (Fig. 1), quinine, mefloquine and halofantrine; but the complete mechanism of action for this type of antimalarial was poorly delineated besides heam binding studies [14]. Keeping in view these facts and in a continuation of our efforts on drug discovery program for new chemical entities with novel mechanism [15,16], we have synthesized β-amino alcohol grafted 1,4,5-trisubstituted 1,2,3-triazoles, previously identified as having anticancer properties [17,20] and evaluated them for *in vitro* antiplasmodial activity against chloroquine sensitive (3D7) and resistant (K1) strains of *P. falciparum*. *In vivo* antimalarial efficacy of most the potent (*in vitro*) antimalarial compounds was also determined against *Plasmodium yoelii nigeriensis* in Swiss mice by oral administration. Further, we have also studied *in vivo* pharmacokinetic profile and p53 protein upregulation in MCF-7 cells to reveal the pathway for activity exhibited by our novel inhibitors. This upregulation and activation of p53 may also be attributed to apoptosis inducing ability of these compounds via ROS generation and p38 activation leading to DNA damage as shown in our previous report [17].

2. Results and discussion

2.1. Chemistry

Synthesis of the target compounds (Scheme 1) commenced with the readily accessible 1,3 diphenyl propenones (chalcones, **1a**-**1g**), which were prepared by the condensation of appropriate aromatic aldehyde and acetophenones as reported earlier [18,19]. These chalcones on [3 + 2] cycloaddition reaction with benzylazides (**2a** or **2b**) separately in the presence of tetrabutylammonium hydrogensulfate (TBAHS) as a catalyst in DMF at 100 °C led to the formation of 1-substituted-4-benzoyl-5-aryl-*1H*-1,2,3-triazoles (**3a**-**3h**) in 60–74% yields as described in our previously reported protocol [20]. These triazolyl methanones (**3a-3h**) on reaction with trimethylsulfoxonium ylide (generated *in situ* by the reaction of equimolar amounts of trimethylsulfoxonium iodide and potassium *tert*-butoxide) in DMSO at room temperature gave the respective crude 1-benzyl-5-phenyl-4-(2-phenyl oxiran-2-yl)-1*H*-1,2,3-triazoles (**4a-4h**) with 70–88% yields. These triazolyl oxiranes were unstable for long periods, hence the next step of nucleophilic ring opening was carried out immediately with various substituted anilines in the presence of potassium carbonate as a base in DMSO and water (1:1, v/v) at 60–80 °C to give the desired 1-benzyl-5-phenyl-1*H*-1,2,3-triazol-4-yl-2-arylamino-substituted phenyl ethanols (**5-28**) as racemic compounds in 60–78% yields. Structures of all the synthesized compounds were established by their ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry (HRMS).

2.2. Biological evaluation

2.2.1. In vitro antiplasmodial activity

All the final compounds (**5-28)** were screened for *in vitro* antiplasmodial activity against chloroquine (CQ) sensitive (3D7) and

Download English Version:

https://daneshyari.com/en/article/1395237

Download Persian Version:

https://daneshyari.com/article/1395237

Daneshyari.com