Bioorganic & Medicinal Chemistry Letters 25 (2015) 3867–3872

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological evaluation of phaitanthrin congeners as anti-mycobacterial agents

Ahmed Kamal [a,c,*], B. V. Subba Reddy [b,*], B. Sridevi [a,b,c], A. Ravikumar [a,c], A. Venkateswarlu [b], G. Sravanthi [c], J. Padma Sridevi [d], P. Yogeeswari [d], D. Sriram [d]

[a] Medicinal Chemistry and Pharmacology, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India
[c] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Hyderabad 500 037, India
[d] Department of Pharmacy, Birla Institute of Technology & Science-Pilani, Hyderabad 500078, India

ARTICLE INFO

Article history:
Received 28 April 2015
Revised 13 July 2015
Accepted 18 July 2015
Available online 26 July 2015

Keywords:
Tryptanthrin
Indolo[2,1-*b*]quinazoline-6,12-dione
MDR-TB
Enoyl-acyl carrier protein reductase (InhA)
In silico molecular docking study

ABSTRACT

Natural alkaloid, tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) and its analogues are found to exhibit potent anti-tubercular activity against MDR-TB. A novel class of indolo[2,1-*b*]quinazolinones have been synthesized to evaluate their anti-mycobacterial activity. Enoyl-acyl carrier protein reductase (InhA) of *Mycobacterium tuberculosis* is one of the key enzymes and has been validated as an effective anti-microbial target. In silico molecular docking study demonstrates that the synthesized compounds exhibit high affinity for the *M. tuberculosis* drug target InhA. Phaitanthrin is a natural product, which belongs to a family of tryptanthrin and exhibits structural similarity except at position 6. Phaitanthrin derivatives are prepared by modifying the keto functionality of tryptanthrin. These phaitanthrin congeners are found to display promising anti-tubercular activity.

Tuberculosis (TB), which is acknowledged as a global health catastrophe, is a chronic bacterial infection caused by *Mycobacterium tuberculosis*. Most infections in humans result in asymptomatic, latent infection and about one in ten latent infections eventually progresses to active disease.[1] Hence, the discovery of new drugs is very much in need to combat tuberculosis. Multidrug resistant (MDR) and extensively drug resistant (XDR) TB strains are of concern for human society, the solution for growing emergence of resistance in the pathogen is the development of new affordable drugs with high potency and low toxicity.

Indolo[2,1-*b*]quinazoline-6-12-dione or tryptanthrin is a versatile lead for designing the potential drugs with diverse medical functions. Tryptanthrin is a potent and structurally useful alkaloid isolated from the natural sources such as *Phaius mishmensis* and *Isatis*, *Calanthe*, *Wrightia*, *Couroupota* and *Strobilanthes* species.[2–7] In particular the orchid *Phaius mishmensis* was reported to be a rich source of tryptanthrin based compounds and all those shown in Figure 1, have been isolated from this plant.[8] Tryptanthrin consists of both quinazoline and indole core structures and showed a variety of intriguing biological properties such as antibacterial, antifungal, antiprotozoal and antiparasitic activities.[9–12] Although systematic synthesis and structure–activity relationship studies for anti-tubercular, COX inhibitory and cytotoxic activity have led several promising candidates for further development, none of them has yet been successfully launched for clinical usage.[13] Structure of tryptanthrin is comparatively simple, lacking asymmetric centres, it has a fairly low molecular weight and has a structure which differs significantly from all previously established anti-tubercular agents. Tryptanthrin proved rather more potent against *M tb* H37Rv (1 mg/L) and *M. avium* (4 mg/L) than against *M. smegmatis* (6 mg/L) and exhibit same potency as that of well-known anti-tubercular agents such as INH, streptomycin and ethambutol. One significant implication of this is that tryptanthrin can be proposed to be operating by a molecular mechanism different than that employed by most of the existing anti-tubercular agents and might be useful in cases where existing agents would fail to cure patients.[14]

The natural alkaloid, tryptanthrin represents a potential lead for new tuberculosis drugs since tryptanthrin and its synthetic analogues possess potent in vitro activity against *Mycobacterium tuberculosis* (*Mtb*). When tryptanthrin is tested against a panel of multidrug-resistant strains of *M. tuberculosis*, it shows more potency (MICs of 0.5–1 μg/mL) than isoniazid (MICs 4–16 μg/mL).[15] Though tryptanthrin and its analogues are active against MDR-TB, their cellular target is unknown. Therefore,

* Corresponding authors. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail address: ahmedkamal@iict.res.in (A. Kamal).

http://dx.doi.org/10.1016/j.bmcl.2015.07.057
0960-894X/

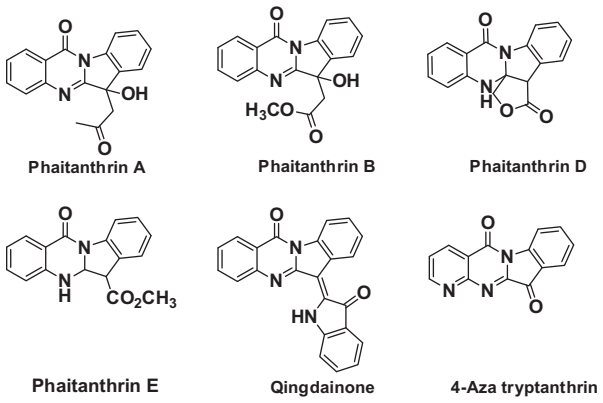


Figure 1. Tryptanthrin derivatives isolated from natural sources.

tryptanthrin is an important class of structural motif for the development of new drugs for the treatment of tuberculosis.[16] As a part of our interest on chemical and pharmacological studies of natural alkaloids, we have been interested in compounds possessing the tryptanthrin skeleton due to their fascinating biological activities.

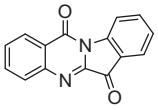
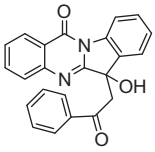
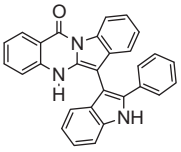
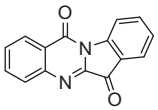
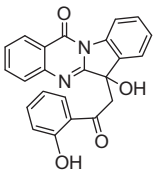
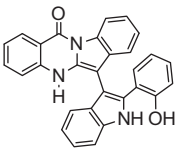
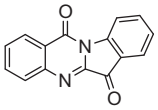
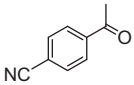
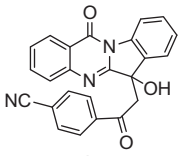
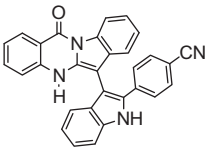
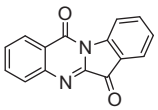
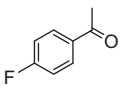
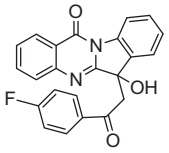
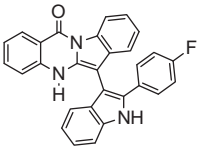
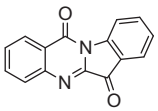
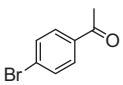
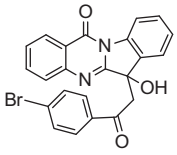
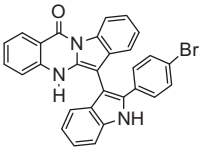
We designed and synthesized a new series of tryptanthrin based molecules in which the keto group at position 6 of the indolo[2,1-*b*]quinazoline core was replaced by other functional groups. In this manuscript we report the synthesis and activity studies performed.

In this endeavor, we designed and synthesized a series of novel anti-tubercular agents, based on indolo[2,1-*b*]quinazoline-6, 12-dione (Table 1) and 11*H*-indeno[1,2-*b*]quinoxalin-11-one (Table 2) derived natural products.[17–21]

The synthesis of indolo[2,1-*b*]quinazoline-6,12-dione is shown in Scheme 1. Accordingly, treatment of isatin (**1**) with isatoic anhydride (**2**) in the presence of *N*-ethyl piperidine and diisopropylcarbodiimide (DIC) in dry pyridine at 100 °C afforded the desired product **3** in 93% yield. Aldol condensation of **3** with ketones in the presence of dimethyl amine furnished the β-hydroxyketones (**4a**–**k**). Finally, the condensation of **4a**–**k** with phenylhydrazine in glacial acetic acid at 80 °C afforded the corresponding indole derivatives (**5a**–**j**).

Next, we prepared a new series of spiroindenoquinoxalines in good yields through a condensation of β-hydroxyketones (**9a**–**c**) with phenylhydrazine under acidic conditions (Scheme 2). Accordingly, treatment of *o*-phenylenediamine with ninhydrin in the presence of acetic acid in ethanol gave the 11*H*-indeno[1,2-*b*] quinoxalin-11-one **8**, which was then subjected to aldol condensation with aryl ketones in the presence of dimethyl amine to afford the β-hydroxyketones (**9a**–**c**). Upon treatment of β-hydroxyketone with phenylhydrazine in the presence of catalytic amount of HCl in

Table 1
Synthesis of indolo[2,1-*b*]quinazoline analogues (**4a**–**4k**) and (**5a**–**5j**)

Entry	Tryptanthrin	Ketone	Hydroxyketone **4**	Yield (%)	Indoloquinazoline product **5**	Yield (%)
1			 **4a**	92	 **5a**	88
2			 **4b**	90	 **5b**	86
3			 **4c**	84	 **5c**	92
4			 **4d**	80	 **5d**	85
5			 **4e**	91	 **5e**	84