European Journal of Medicinal Chemistry 46 (2011) 4354–4365

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and studies of novel 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-*s*-triazines as potential antimicrobial, antimycobacterial and anticancer agents

Rahul V. Patel [a], Premlata Kumari [a,*], Dhanji P. Rajani [b], Kishor H. Chikhalia [c]

[a] Department of Applied Chemistry, S.V. National Institute of Technology, Surat 395 007, Gujarat, India
[b] Microcare Laboratory, Surat 395 001, Gujarat, India
[c] Department of Chemistry, School of Science, Gujarat University, Ahmedabad 380 009, Gujarat, India

ARTICLE INFO

Article history:
Received 31 May 2011
Received in revised form
1 July 2011
Accepted 4 July 2011
Available online 8 July 2011

Keywords:
2,4,6-Trichloro-1,3,5-triazine
4-Hydroxyquinoline
Piperazine
Antimicrobial activity
Antimycobacterial activity
Anticancer activity

ABSTRACT

A series of novel *s*-triazine analogs were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectroscopy and elemental analysis. Preliminary screening of target compounds against eight bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Proteus vulgaris*, *Shigella flexneria*), four fungi (*Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus clavatus*, *Candida albicans*) and *Mycobacterium tuberculosis* H37Rv indicated that **5d**, **5h**, **5n**, **5p**, **5q**, **5r**, **5s**, **5t** and **5u** were the most active compounds among twenty one studied. Thus, they were further subjected to *in vitro* biological evaluation against human prostate cancer cell line (DU-145) and the results indicate that two compounds **5n** and **5s** were markedly active.

1. Introduction

Control of deadly infectious diseases is seriously threatened by multidrug emergence and dissemination of resistant pathogenic microbes. The issue is of serious consideration in the developing countries. Patients with AIDS are immune suppressed, and very susceptible to the opportunistic microbial infections [1]. On the other hand, *Mycobacterium tuberculosis* remains a leading infectious cause of death in the world today, with an estimated two million deaths each year. Due to the quiescent form of *M. tuberculosis* strains, many of the currently available antimycobacterial drugs have become ineffective by the imminent exigency of multidrug-resistant [2–4]. The WHO has estimated that, according to the stop TB partnership's global plan to stop TB, 2006–2015, 1.3 million MDR-TB cases will need to be treated in the 27 high MDR-TB burden countries between 2010 and 2015. In 2008, there were an estimated 8.9–9.9 million incident cases of TB, 9.6–13.3 million prevalent cases of TB, 1.1–1.7 million deaths from TB among HIV-negative people and an additional 0.45–0.62 million TB deaths among HIV-positive people [5]. The continual emergence of multidrug resistance to clinically available drugs has lent additional urgency to develop new antimicrobial agents likely to be unaffected by existing resistance mechanisms.

In chemotherapeutic point of view, the search for a molecule having multiple targets has always been a very attractive strategy for medicinal chemists. Since the fluorine containing compounds often show significant biological activity profiles being their superior metabolic stability and the lipophilicity [6], we are interested to have 4-amino-2-trifluoromethyl-benzonitrile substitution to the *s*-triazine core. Moreover, 4-amino-2-trifluoromethyl-benzonitrile is also a useful pharmacophore found in the anti prostate cancer drug bicalutamide as a structural unit [7]. Therefore, in the present study an attempt has been made to identify the efficacy of the newly synthesized compounds against DU-145 prostate cancer cell line. In addition, some piperazine substituted analogs were also found to display activity against prostate cancer cell line DU-145 [8–10].

As a part of our ongoing research aiming the synthesis of novel biologically active *s*-triazine derivatives [11–13], herein we report the synthesis and pharmacological activities of novel 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl /piperidinyl)-*s*-triazines. 1,3,5-Triazine nucleus has gathered an

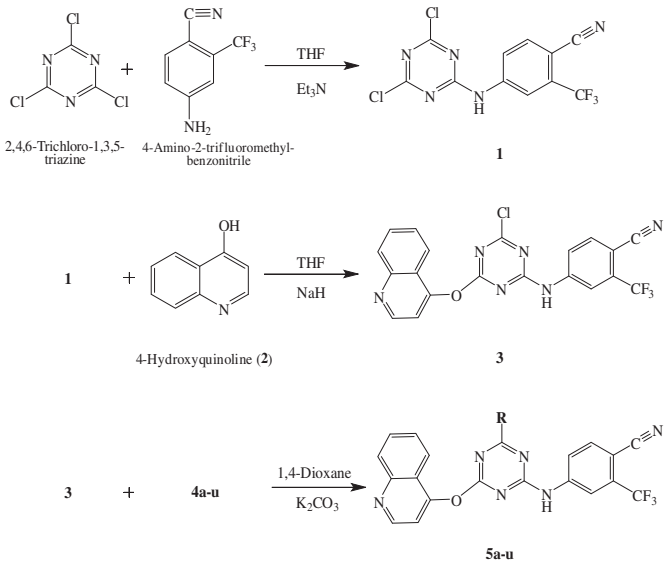
* Corresponding author. Tel.: +91 9904003863.
E-mail address: premlatakumari1@gmail.com (P. Kumari).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.07.006

immense attention among chemists due to its diverse biological activities such as antimicrobial [14–16], anticancer [17], antimalarial [18] and antiviral [19] activities. Profound medicinal applications associated with piperazine heterocycle render them as useful structural units in drug research [20–24]. Recent studies have confirmed that several *s*-triazine derivatives bearing morpholine, piperidine and some piperazine moieties are effective against *M. tuberculosis* H37R_V strain [25], while the piperazine–quinoline combination is found in the structure of many well known antimicrobial drugs like ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, enrofloxacin etc. Prompted by these observations it was contemplated to envisage the combination of above mentioned biolabile components of significant activities in a compact system to identify new candidates that may be value in designing new biologically active agents.

2. Chemistry

Synthesis of intermediates and target compounds was accomplished according to the steps illustrated in Schemes 1 and 2. The first step comprises formation of intermediate **1** in very good yield by the nucleophilic displacement of one chlorine atom of *s*-triazine ring by 4-amino-2-trifluoromethyl-benzonitrile. Compound **1** displayed an absorption band at 2223 cm^{-1} confirming the presence of a C≡N group, and a strong band near 3282 cm^{-1} further confirmed the presence of an –NH group. The synthesis of disubstituted *s*-triazine intermediate **3** was achieved in 80% of yield by the reaction between 4-(4,6-dichloro-1,3,5-triazin-2-ylamino)-2-trifluoromethyl-benzonitrile (**1**) and 4-hydroxyquinoline in the presence of 60% NaH at 45–50 °C. A characteristic band appeared at 1256 cm^{-1} corresponded to the C–O–C linkage in the IR spectra of compound **3**. Subsequent coupling of the so formed compound **3** with the desired piperazines and piperidines under basic conditions in 1,4-dioxane solvent at 70–80 °C formed the corresponding 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-*s*-triazines (**5a**–**u**). This reaction proceeded in good yields and is general for different substituted piperazines and piperidines. The correct synthesis of **5a**–**u** was confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR [26] spectral analysis and the purity was ascertained by elemental analysis.



Scheme 1. Synthetic route of novel s-triazine derivatives **5a**–**u**.

3. Results and discussion

3.1. Pharmacology

3.1.1. Antimicrobial activity

Investigation on antibacterial screening data (Table 1) revealed that some of the compounds showed a good deal of activity against all the mentioned bacteria. Final *s*-triazinyl derivatives with piperazine moiety bearing halogen substituent in the form of single chlorine atom (**5c** and **5p**) displayed promising activity against *Klebsiella pneumoniae* at 12.5 μg/mL of MIC, 26 mm and 25 mm of zone of inhibition, respectively. The said compound (**5p**) was found to exhibit good activity against *Proteus vulgaris* at the low MIC value of 6.25 μg/mL and inhibition zone of 24 mm. Compound **5d** with substitution of two chlorine atoms at the 2nd and 3rd position of the phenyl ring of the piperazine base displayed strong inhibitory action against both of the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus cereus* at 6.25 μg/mL of MIC and 28 mm of growth inhibitory diameter. In addition, the same compound (**5d**) was also appeared with substantial activity against *K. pneumoniae*, *Salmonella typhi* and *Shigella flexneria* at 12.5 μg/mL of MIC and 24–25 mm of inhibition zones. Final *s*-triazine derivatives (**5q**, **5r**) with single fluorine atom substitution at the 2nd and 4th position of the piperazinyl phenyl ring, respectively, indicated remarkable activity against *B. cereus* at 6.25 μg/mL of MIC and 27 mm and 26 mm of inhibition zone, respectively. Furthermore, compound **5q** showed appreciable activity at 12.5 μg/mL of MIC against *Escherichia coli* and *K. pneumoniae* by exhibiting 26 mm of inhibition zone, whereas, potently inhibited *P. vulgaris* at 6.25 μg/mL of MIC and 25 mm of inhibitory zone. Final derivative (**5s**) with highly electronegative trifluoromethyl group at the 3rd position of phenyl ring of piperazine moiety was found to contribute excellent activity against six bacteria (*S. aureus*, *B. cereus*, *E. coli*, *Pseudomonas aeruginosa*, *S. typhi* and *S. flexneria*) among eight studied at the MIC level 6.25 and 12.5 μg/mL and 25–28 mm of inhibition zones. Compound **5n** with functionalization of two methyl groups at the 3rd and 5th position of the piperidine ring displayed excellent activity at 6.25 μg/mL of MIC against *S. aureus* and *P. vulgaris* as well as against *E. coli*, *S. typhi* and *S. flexneria* at 12.5 μg/mL of MIC. This compound indicated 25–27 mm of growth inhibitory zones against the above mentioned bacterial strains. Final derivative (**5h**) bearing piperazine ring with the aliphatic acetyl linkage appeared with good inhibitory potential toward *E. coli* at 12.5 μg/mL of MIC and 24 mm of inhibition zone as well as against *P. vulgaris* at 6.25 μg/mL of MIC and 27 mm of inhibition zone. Final *s*-triazine derivatives with methoxy functional group(s) in the form of 2,3,4-trimethoxy benzyl piperazine (**5t**) and single methoxy group functionalization at the 4th position of the phenyl ring of piperazine base (**5u**) displayed strong inhibitory potential against *B. cereus* and *P. aeruginosa* at 6.25 μg/mL of MIC and 26–28 mm of inhibitory zones as well as against *E. coli* and *S. flexneria* at 12.5 μg/mL of MIC and 23–26 mm of growth inhibitory diameter. Moreover, compound **5t** was able to indicate highest inhibition of *S. aureus* at 6.25 μg/mL of MIC and 28 mm of inhibition zone as well as inhibition of *K. pneumoniae*, *S. typhi* and *P. vulgaris* at 12.5 μg/mL of MIC and 23–26 mm of inhibition zones.

The antifungal results (Table 2) revealed that, the synthesized compounds showed variable degree of inhibition against the tested fungi. Final halogen(s) substituted *s*-triazine derivatives **5d** and **5p** displayed higher inhibitory effect against *Aspergillus fumigatus* at 25 μg/mL of MIC, 25 mm and 26 mm of inhibition zones, respectively. Compound **5h** with acetyl linkage to the piperazine ring exhibited substantial activity against *Aspergillus clavatus* at 12.5 μg/mL of MIC and 27 mm of inhibition zone. Derivative (**5q**) bearing fluorine atom at the 2nd position of phenyl