Scientific paper

Synthesis and Antimycobacterial Activity of Various 1-(8-Quinolinyloxy)-3-piperazinyl(piperidinyl)-5-(4-cyano-3-trifluoromethylphenylamino)-*s*-triazines

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Abstract

This study presents the synthesis of novel 1-(8-quinolinyloxy)-3-piperazinyl(piperidinyl)-5-(4-cyano-3-trifluoromethylphenyl amino)-*s*-triazines. The synthetic route to final piperazinyl *s*-triazines consists of two nucleophilic substitution reactions of 4-amino-2-trifluoromethylbenzonitrile and 8-hydroxyquinoline with 2,4,6-trichloro-1,3,5-triazine resulting in 2,4-disubstituted-6-chloro-1,3,5-triazine derivatives to introduce the piperazinyl or piperidinyl functionality. The structures of the compounds were elucidated with the aid of IR, ^{1}H NMR, ^{19}F NMR, mass spectroscopy and elemental analysis. The title compounds were then investigated for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv strain by using BACTEC MGIT and Lowenstein–Jensen MIC method. Compound 4-[4-(3,5-dimethylpiperidin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (**5n**) was the most potent one among the tested compounds. It was as potent as ethambutol to inhibit *M. tuberculosis* H37Rv completely (99%) at the minimum inhibitory concentration (MIC) of 3.12 μg/mL. Compounds **5p**, **5s** and **5u** have shown equal potency to that of pyrazinamide at the minimum inhibitory concentration (MIC) of 6.25 mg/mL to inhibit (99%) *M. tuberculosis* H37Rv.

Keywords: 2,4,6-Trichloro-1,3,5-triazine, 8-hydroxyquinoline, 4-amino-2-trifluoromethylbenzonitrile, piperazine, antimycobacterial activity.

1. Introduction

With an estimated 2 million deaths each year due to the quiescent form of mycobacterium tuberculosis strains, many of the currently available antimycobacterial drugs have become ineffective, by the imminent exigency of multidrug-resistancy (MDR).[1–3] 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. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. 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 (classified as HIV deaths in the International Statistical Classification of Diseases), with best estimates of 9.4 million, 11.1 million, 1.3 million and 0.52 million, respectively.[4] This clearly underscores the need of developing novel biologically active agents for more effective tuberculosis treatment. Owing to the continual emergence of MDR to clinically available drugs, evolution of new drugs that specifically target the quiescent bacilli may have a thoughtful impact on the treatment of TB in shorter time.

As a part of our continuous efforts towards the development of new and efficient biologically active *s*-triazinyl agents,[5–8] we have synthesized some novel 1-(8-quinolinyloxy)-3-piperazinyl(piperidinyl)-5-(4-cyano-3-trifluoromethylphenyl amino)-*s*-triazines. The advent of 1,3,5-triazines, associated with diverse biological activities such as antimicrobial,[9,10] antiprotozoal,[11] anticancer,[12] antimalarial[13] and antiviral[14] activity, accelerated the rate of progress of 1,3,5-triazine derivatives. In addition, heterocyclic scaffolds containing ring nitrogen atoms are well known to contribute to good antimicrobial activity.[15,16] Likewise, 4-amino-2-trifluoromethylbenzonitrile is also a useful pharmacophore found in the anticancer drug bicalutamide as a structural unit.[17] Fluorine has played a pivotal role in novel drug discovery for modulating physical and biological properties of the molecules. Due to its higher electronegativity, incorporation of fluorine atom(s) within the molecule can enhance their biopotency, bioavailability, metabolic stability and lipophilicity. Trifluoromethylation is one of the most significant strategies to improve pharmacological activities of the molecule due to its high lipophilicity, thereby enhancing *in vivo* uptake and transport of the candidate;[18] therefore, we are interested to have 4-amino-2-trifluoromethylbenzonitrile substitution to the *s*-triazine core. A literature survey revealed that piperazines and substituted piperazines are an important family of heterocyclic compounds attracting significant interest in medicinal chemistry.[19–22] Recently several *s*-triazine derivatives bearing morpholine, piperidine and some piperazine moieties were reported to possess potent antimycobacterial activity.[23] The favorable antimycobacterial properties of 8-hydroxyquinoline prompted us to combine this structural component with the *s*-triazine nucleus.[24–27] Moreover, piperazine-quinoline combination is often found in many well known antibacterial drugs, like ciprofloxacin, norfloxacin etc. After this initial literature survey, it was observed that till now enough efforts have not been invested in the combination of these three moieties into a single scaffold and into identification of new candidates that may be useful in designing new, potent, selective and less toxic antimycobacterial agents. This approach of merging such pharmacophores may achieve the important medical accomplishment of minimizing the probability of resistance formation.

2. Experimental Section

2. 1. Materials

2,4,6-Trichloro-1,3,5-triazine and 8-hydroxyquinoline were purchased from Sigma Aldrich Chemicals Pvt. Ltd., Mumbai, India. 4-Amino-2-trifluoromethylbenzonitrile was a gift from Ramdev Chemicals Pvt. Ltd., Boisar, India. Acetone, tetrahydrofuran and 1,4-dioxane of HPLC grade were purchased from Rankem, Surat, India. The TLC plates (silica gel 60 F254) were obtained from Merck, Germany. Substituted piperazine derivatives were gifts from Dr. Prem's Molecules Pvt. Ltd., Vadodara, India, Modepro India Pvt. Ltd., Mumbai, India, Trichem Pvt. Ltd., Mumbai, India, Siddharth Interchem Pvt. Ltd., Ankleshwar, India and Mahrshee Laboratories, Bharuch, India, Trichem Pvt. Ltd., Mumbai, India.

2. 2. Methods

Melting points were determined in open capillaries on a Veego electronic apparatus VMP–D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (4000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400–S FT–IR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. Thin layer chromatography was performed on object glass slides (2 × 7.5 cm) coated with silica gel–G and spots were visualized under UV irradiation. ^1H NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India Pvt. Ltd., Mumbai, India) using DMSO as a solvent and TMS as internal standard with ^1H resonant frequency of 400 MHz. ^{19}F NMR spectra were obtained on the same spectrometer using $CDCl_3$ as a solvent and $CFCl_3$ as an external standard, positive for downfield shift with ^{19}F resonant frequency of 400 MHz. The ^1H NMR and ^{19}F NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si) and $CFCl_3$ and were performed at centre for excellence, Vapi, India. The splitting patterns are designated as follows; s, singlet; br s, broad singlet; d, doublet; m, multiplet. The mass spectra were recorded on Jeol SX–102 (EI) model and were performed at CDRI, Lucknow. Elemental analyses (C, H, N) were performed using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany).

2. 3. Synthesis

4-[4,6-Dichloro-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (**1**).

To a stirred solution of 2,4,6-trichloro-1,3,5-triazine (10 g, 54 mmol) in anhydrous THF (150 mL) 4-amino-2-trifluoromethylbenzonitrile (10.09 g, 54 mmol) was drop wise added at 0–5 °C. The resulting reaction mixture was stirred at this temperature for 2 h. Then triethylamine (5.48 g, 54 mmol) was added and stirring was continued for another 5 h. The reaction mixture was then treated with crushed ice, followed by neutralization with dilute HCl, and filtered, dried, and recrystallized from acetone to afford **1**. Yield: 90%; mp 259.5 °C dec. IR (KBr) ν 2223 (CN) cm^{-1}.

4-[4-Chloro-6-(quinoline-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (**3**).

To a stirred solution of 8-hydroxyquinoline (8 g, 55 mmol) in anhydrous THF (150 mL) 60% NaH (1.32 g, 55 mmol) was added at room temperature during 1 h and **1**

(18.41 g, 55 mmol) was then added to the mixture. Stirring was continued for another 16 h at 45 °C. Progress of the reaction was monitored by TLC using toluene:acetone (95:5 v/v) as eluent. The mixture was treated with crushed ice, filtered and dried to afford **3**.[28,29] Yield: 82%; mp 267.7 °C dec. IR (KBr) ν 2223 (CN), 1255 (C–O–C) cm^{-1}.

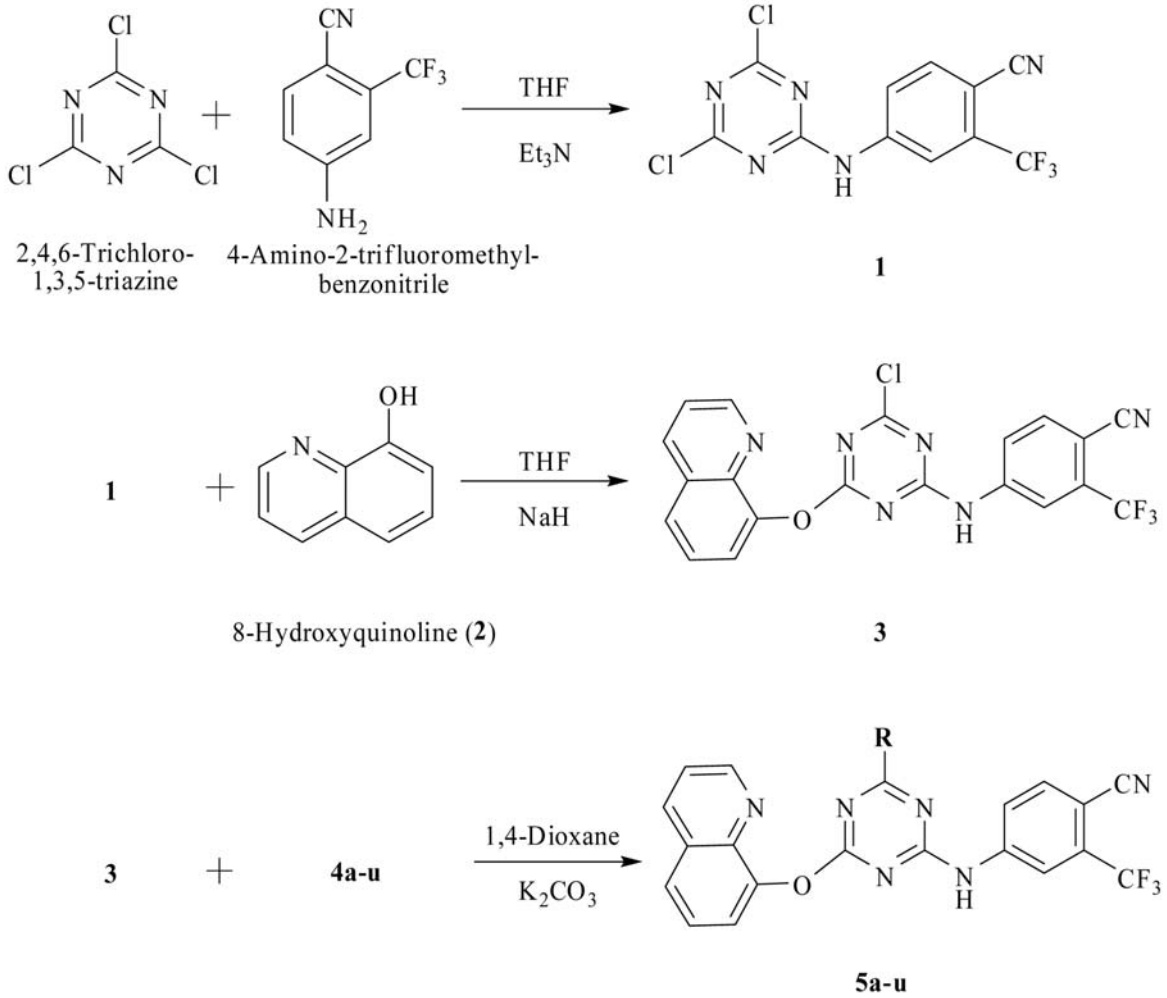
2. 3. 1. General Procedure for Preparation of Compounds 5a–u

To a solution of **3** (10 mmol) in 1,4-dioxane (30 mL), the respective substituted piperazine derivative (10 mmol) was added and the reaction mixture was refluxed for 8–16 h. Potassium carbonate (10 mmol) was used for neutralization of the reaction mixture. Progress of the reaction was monitored by TLC using toluene:acetone (98:2 v/v) as eluent. The mixture was then treated with crushed ice and neutralized by dilute HCl. The precipitate thus obtained was filtered off, dried and recrystallized from THF to afford the desired compounds **5a**–**u**.

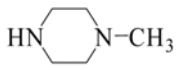
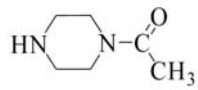
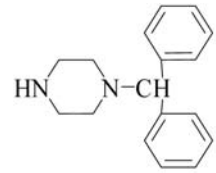
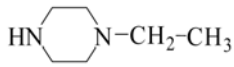
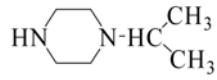
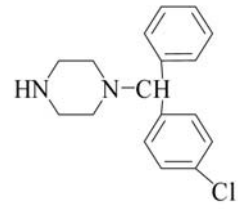
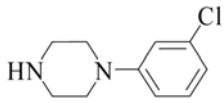
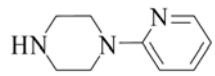
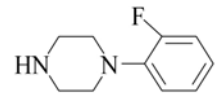
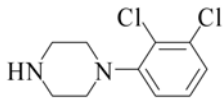
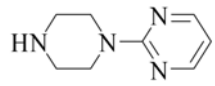
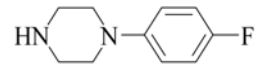
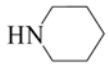
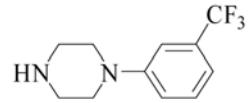
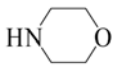
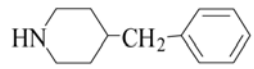
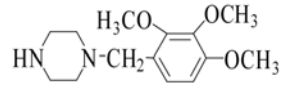
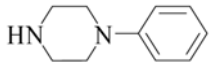
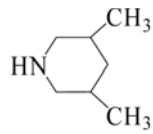
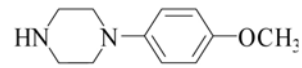
Where, **4a**–**u**, **R =** piperazine and piperidine derivatives

4-[4-(4-Methylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5a). Yield: 78%; mp 273–275 °C; IR (KBr) ν 3290 (NH), 2221 (CN), 1255 (C–O–C), 814 (*s*-triazine C–N str.) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 1H, NH), 7.55–7.62 (m, 3H, quinoline), 7.15–7.45 (m, 6H, Ar-H), 3.84 (br s, 8H, piperazine), 2.40 (s, 3H, CH_3). EMI-MS (*m/z*): 507.63 (M^+). Anal. Calcd for $C_{25}H_{21}F_3N_8O$ (506.48 g mol^{-1}): C, 59.28; H, 4.18; N, 22.12. Found: C, 59.27; H, 4.19; N, 22.10.

4-[4-(4-Ethylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5b). Yield: 83%; mp 247–248 °C; IR (KBr) ν 3288 (NH), 2223 (CN), 1255 (C–O–C), 811 (*s*-triazine C–N str.) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H, NH), 7.56–7.63 (m, 3H, quinoline), 7.22–7.54 (m, 6H, Ar-H), 3.82 (br s, 8H, piperazine), 2.40 (q, J = 7.3 Hz, 2H, CH_2), 2.13 (t, J = 6.8 Hz, 3H, CH_3). EMI-MS (*m/z*): 521.93 (M^+). Anal. Calcd for $C_{26}H_{23}F_3N_8O$ (520.51 g mol^{-1}): C, 59.99; H, 4.45; N, 21.53. Found: C, 59.97; H, 4.44; N, 21.53.



Scheme 1 Synthesis of compounds **5a–u**

No.	Structure	No.	Structure	No.	Structure
4a		**4h**		**4o**	
4b		**4i**		**4p**	
4c		**4j**		**4q**	
4d		**4k**		**4r**	
4e		**4l**		**4s**	
4f		**4m**		**4t**	
4g		**4n**		**4u**	

4-[4-[4-(3-Chlorophenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5c). Yield: 79%; mp 262–264 °C; IR (KBr) ν 3304 (NH), 2220 (CN), 1257 (C–O–C), 813 (*s*-triazine C–N str.), 754 (C–Cl) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H, NH), 7.71–7.78 (m, 3H, quinoline), 7.13–7.40 (m, 10H, Ar-H), 3.85 (br s, 8H, piperazine). EMI-MS (*m/z*): 604.16 (M^+). Anal. Calcd for $C_{30}H_{22}ClF_3N_8O$ (603.00 g mol^{-1}): C, 59.76; H, 3.68; N, 18.58. Found: C, 59.75; H, 3.66; N, 18.59.

4-[4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5d). Yield: 71%; mp >300 °C; IR (KBr) ν 3278 (NH), 2221 (CN), 1255 (C–O–C), 806 (*s*-triazine C–N str.), 754 (C–Cl) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H, NH), 7.53–7.59 (m, 3H, quinoline), 7.23–7.45 (m, 9H, Ar-H), 3.83 (br s, 8H, piperazine). EMI-MS (*m/z*): 638.73 (M^+). Anal. Calcd for $C_{30}H_{21}C_{12}F_3N_8O$ (637.44 g mol^{-1}): C, 56.53; H 3.32; N, 17.58. Found: C, 56.51; H, 3.31; N, 17.57.

4-[4-Piperidin-1-yl-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5e). Yield: 80%; mp 288–289 °C; IR (KBr) ν 3289 (NH), 2224 (CN), 1256 (C–O–C), 817 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H, NH), 7.64–7.69 (m, 3H, quinoline), 7.22–7.39 (m, 6H, Ar-H), 3.91 (t, J = 4.7 Hz, 4H, piperidine), 3.70 (t, J = 5.9 Hz, 6H, piperidine). EMI-MS (*m/z*): 492.30 (M^+). Anal. Calcd for $C_{25}H_{20}F_3N_7O$ (491.47 g mol^{-1}): C, 61.10; H, 4.10; N, 19.95. Found: C, 61.11; H, 4.09; N, 19.93.

4-[4-Morpholin-4-yl-6-(quinolin-8-yloxy)-1,3,5-tria-

zin-2-ylamino]-2-trifluoromethylbenzonitrile (5f). Yield: 90%; mp 275–276 °C; IR (KBr) ν 3282 (NH), 2221 (CN), 1375 (morpholine C–O–C str.), 1258 (C–O–C), 812 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 1H, NH), 7.56–7.62 (m, 3H, quinoline), 7.15–7.45 (m, 6H, Ar-H), 3.83 (t, *J* = 6.9 Hz, 4H, morpholine), 3.85 (t, *J* = 7.1 Hz, 4H, morpholine). EMI-MS (*m/z*): 494.69 (M^+). Anal. Calcd for $C_{24}H_{18}F_3N_7O_2$ (493.44 g mol^{-1}): C, 58.42; H, 3.68; N, 19.87. Found: C, 58.40; H, 3.69; N, 19.85.

4-[4-(4-Phenylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5g). Yield: 81%; mp 256–259 °C; IR (KBr) ν 3290 (NH), 2225 (CN), 1256 (C–O–C), 815 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 1H, NH), 7.57–7.60 (m, 3H, quinoline), 7.09–7.39 (m, 11H, Ar-H), 3.89 (br s, 8H, piperazine). EMI-MS (*m/z*): 569.77 (M^+). Anal. Calcd for $C_{30}H_{23}F_3N_8O$ (568.55 g mol^{-1}): C, 63.38; H, 4.08; N, 19.71. Found: C, 63.38; H, 4.06; N, 19.70.

4-[4-(4-Acetylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5h). Yield: 84%; mp 238–240 °C; IR (KBr) ν 3296 (NH), 2223 (CN), 1700 (C=O), 1475 (CH_3), 1255 (C–O–C), 819 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H, NH), 7.60–7.66 (m, 3H, quinoline), 7.13–7.30 (m, 6H, Ar-H), 3.85 (br s, 8H, piperazine), 2.39 (s, 3H, CH_3). EMI-MS (*m/z*): 535.60 (M^+). Anal. Calcd for $C_{26}H_{21}F_3N_8O_2$ (534.49 g mol^{-1}): C, 58.43; H, 3.96; N, 20.96. Found: C, 58.41; H, 3.95; N, 20.95.

4-[4-(4-Isopropylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2- trifluoromethylbenzonitrile (5i). Yield: 67%; mp 287–288 °C; IR (KBr) ν 3293 (NH), 2222 (CN), 1380 (isopropyl), 1257 (C–O–C), 819 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H, NH), 7.67–7.70 (m, 3H, quinoline), 7.12–7.42 (m, 6H, Ar-H), 3.79 (br s, 8H, piperazine), 2.44 (q, *J* = 7.6 Hz, 1H, CH), 2.40 (d, *J* = 6.5 Hz, 6H, CH_3). EMI-MS (*m/z*): 535.89 (M^+). Anal. Calcd for $C_{27}H_{25}F_3N_8O$ (534.54 g mol^{-1}): C, 60.67; H, 4.71; N, 20.96. Found: C, 60.68; H, 4.69; N, 20.96.

4-[4-(4-Pyridin-2-ylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5j). Yield: 80%; mp 291–292 °C; IR (KBr) ν 3299 (NH), 2223 (CN), 1256 (C–O–C), 806 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 1H, NH), 7.60–7.64 (m, 4H, 3H of quinoline and 1H of pyridyl), 7.19–7.35 (m, 9H, Ar-H), 3.84 (br s, 8H, piperazine). EMI-MS (*m/z*): 570.47 (M^+). Anal. Calcd for $C_{29}H_{22}F_3N_9O$ (569.54 g mol^{-1}): C, 61.16; H, 3.89; N, 22.13. Found: C, 61.17; H, 3.89; N, 22.15.

4-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5k). Yield: 85%; mp 283–284 °C; IR (KBr) ν 3284 (NH), 2218 (CN), 1255 (C–O–C), 806 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H, NH), 7.98–8.05 (m, 5H, 3H of quinoline and 2H of pyrimidyl), 7.27–7.35 (m, 7H, Ar-H), 3.84 (br s, 8H, piperazine). EMI-MS (*m/z*): 571.55 (M^+). Anal. Calcd for $C_{28}H_{21}F_3N_{10}O$ (570.53 g mol^{-1}): C, 58.95; H, 3.71; N, 24.55. Found: C, 58.93; H, 3.70; N, 24.56.

4-[4-(4-Benzylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5l). Yield: 69%; mp 268–270 °C; IR (KBr) ν 3283 (NH), 2221 (CN), 1255 (C–O–C), 806 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H, NH), 7.69–7.71 (m, 3H, quinoline), 7.24–7.52 (m, 11H, Ar-H), 3.85 (br s, 8H, piperazine), 2.40 (s, 2H, CH_2). EMI-MS (*m/z*): 583.78 (M^+). Anal. Calcd for $C_{31}H_{25}F_3N_8O$ (582.58 g mol^{-1}): C, 63.91; H, 4.33; N, 19.23. Found: C, 63.88; H, 4.39; N, 19.17.

4-[4-(4-Benzylpiperidin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5m). Yield: 72%; mp 287 °C; IR (KBr) ν 3275 (NH), 2222 (CN), 1257 (C–O–C), 816 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H, NH), 7.97–8.03 (m, 3H, quinoline), 7.22–7.34 (m, 11H, Ar-H), 3.85 (t, *J* = 6.7 Hz, 4H, piperidine), 3.49 (t, *J* = 8.6 Hz, 4H, piperidine), 2.44 (s, 2H, CH_2), 1.91 (t, *J* = 7.2 Hz, 1H, CH, piperidine). EMI-MS (*m/z*): 582.41 (M^+). Anal. Calcd for $C_{32}H_{26}F_3N_7O$ (581.59 g mol^{-1}): C, 66.08; H, 4.51; N, 16.86. Found: C, 66.02; H, 4.48; N, 16.89.

4-[4-(3,5-Dimethylpiperidin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5n). Yield: 81%; mp 289–291 °C; IR (KBr) ν 3288 (NH), 2225 (CN), 1257 (C–O–C), 808 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H, NH), 7.99–8.04 (m, 3H, quinoline), 7.21–7.57 (m, 6H, Ar-H), 3.80–3.86 (m, 4H, piperidine), 2.30 (br s, 2H, CH_2, piperidine), 1.88 (q, *J* = 8.1 Hz, 2H, piperidine), 1.29 (d, *J* = 6.8 Hz, 6H, 2 × CH_3). EMI-MS (*m/z*): 520.87 (M^+). Anal. Calcd for $C_{27}H_{24}F_3N_7O$ (519.52 g mol^{-1}): C, 62.42; H, 4.66; N, 18.87. Found: C, 62.46; H, 4.63; N, 18.85.

4-[4-(4-Benzhydrylpiperazin-1-yl)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5o). Yield: 74%; mp 277–278 °C; IR (KBr) ν 3290 (NH), 2224 (CN), 1256 (C–O–C), 811 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H, NH), 7.59–7.65 (m, 3H, quinoline), 7.21–7.44 (m, 16H, Ar-H), 3.75 (br s, 8H, piperazine), 2.29 (s, 1H, CH). EMI-MS (*m/z*): 659.51 (M^+). Anal. Calcd for $C_{37}H_{29}F_3N_8O$ (658.67 g mol^{-1}): C, 67.47; H, 4.44; N, 17.01. Found: C, 67.45; H, 4.48; N, 17.05.

4-[4-{4-[(4-Chlorophenyl)-phenylmethyl]-piperazin-1-yl}-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5p). Yield: 76%; mp 269–271 °C; IR (KBr) ν 3294 (NH), 2223 (CN), 1257 (C–O–C), 811 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 1H, NH), 7.82–7.89 (m, 3H, quinoline), 7.11–7.71 (m, 15H, Ar-H), 3.84 (br s, 8H, piperazine), 2.41 (s, 1H, CH). EMI-MS (*m/z*): 694.37 (M^+). Anal. Calcd for $C_{37}H_{28}ClF_3N_8O$ (693.12 g mol^{-1}): C, 64.12; H, 4.07; N, 16.17. Found: C, 64.15; H, 4.03; N, 16.21.

4-[4-[4-(2-Fluorophenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5q). Yield: 77%; mp 275–277 °C; IR (KBr) ν 3292 (NH), 2224 (CN), 1255 (C–O–C), 814 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H, NH), 7.77–7.80 (m, 3H, quinoline), 7.17–7.44 (m, 10H, Ar-H), 3.83 (br s, 8H, piperazine). ^{19}F NMR (400 MHz, $CDCl_3$) δ –122.2 (s, 1F, CF). EMI-MS (*m/z*): 587.69 (M^+). Anal. Calcd for $C_{30}H_{22}F_4N_8O$ (586.54 g mol^{-1}): C, 61.43; H, 3.78; N, 19.10. Found: C, 61.41; H, 3.72; N, 19.06.

4-[4-[4-(4-Fluorophenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5r). Yield: 75%; mp 292–293 °C; IR (KBr) ν 3290 (NH), 2221 (CN), 1255 (C–O–C), 812 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H, NH), 7.82–7.92 (m, 3H, quinoline), 7.09–7.39 (m, 10H, Ar-H), 3.80 (br s, 8H, piperazine). ^{19}F NMR (400 MHz, $CDCl_3$) δ –117.4 (s, 1F, CF). EMI-MS (*m/z*): 587.39 (M^+). Anal. Calcd for $C_{30}H_{22}F_4N_8O$ (586.54 g mol^{-1}): C, 61.43; H, 3.78; N, 19.10. Found: C, 61.45; H, 3.75; N, 19.08.

4-{4-(Quinolin-8-yloxy)-6-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-1,3,5-triazin-2-ylamino}-2-trifluoromethylbenzonitrile (5s). Yield: 60%; mp >300 °C; IR (KBr) ν 3286 (NH), 2220 (CN), 1255 (C–O–C), 812 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H, NH), 7.83–7.88 (m, 3H, quinoline), 7.11–7.67 (m, 10H, Ar-H), 3.76 (br s, 8H, piperazine). ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.8, –63.5 (s, 6F, 2 × CF_3). EMI-MS (*m/z*): 637.64 (M^+). Anal. Calcd for $C_{31}H_{22}F_6N_8O$ (636.55 g mol^{-1}): C, 58.49; H, 3.48; N, 17.60. Found: C, 58.53; H, 3.44; N, 17.57.

4-{4-(Quinolin-8-yloxy)-6-[4-(2,3,4-trimethoxybenzyl)-piperazin-1-yl]-1,3,5-triazin-2-ylamino}-2-trifluoromethylbenzonitrile (5t). Yield: 85%; mp 281–282 °C; IR (KBr) ν 3297 (NH), 2223 (CN), 1475 (CH_2), 1257 (C–O–C), 810 (*s*-triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.82 (s, 1H, NH), 7.69–7.72 (m, 3H, quinoline), 7.11–7.73 (m, 10H, Ar-H), 3.88 (br s, 8H, piperazine), 2.56 (s, 9H, OCH_3). EMI-MS (*m/z*): 673.62 (M^+). Anal. Calcd for $C_{34}H_{31}F_3N_8O_4$ (672.66 g mol^{-1}): C, 60.71; H, 4.65; N, 16.66. Found: C, 60.68; H, 4.67; N, 16.69.

4-[4-[4-(4-Methoxyphenyl)-piperazin-1-yl]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-ylamino]-2-trifluoromethylbenzonitrile (5u). Yield: 88%; mp 270–272 °C; IR (KBr) ν 3290 (NH), 2218 (CN), 1255 (C–O–C), 814 (*s*–triazine C–N str.) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H, NH), 7.81–7.90 (m, 3H, quinoline), 7.17–7.47 (m, 10H, Ar-H), 3.81 (br s, 8H, piperazine), 2.45 (s, 3H, OCH_3). EMI-MS (*m/z*): 599.67 (M^+). Anal. Calcd for $C_{31}H_{25}F_3N_8O_2$ (598.58 g mol^{-1}): C, 62.20; H, 4.21; N, 18.72. Found: C, 62.22; H, 4.19; N, 18.67.

2. 4. In vitro Evaluation of Antimycobacterial Activity

The preliminary antimycobacterial assessment for the final synthesized compounds was carried out using BACTEC MGIT method. The Mycobacterial Growth Indicator Tubes (MGIT) containing 4 mL of modified Middlebrook 7H9 Broth Base were numbered as per the title compounds to be tested for antimycobacterial efficacy by means of various concentrations prepared. The suspension was allowed to stand for 20 min and the tubes were centrifuged at 3000 rpm for 15 min. After that, prepared suspension of 10^4 to 10^7 CFU/mL of H37 R_V *M. tuberculosis* strain was added in the medium to be incubated and 0.1 mL of egg-based medium (L. J.) was also added. The MGIT tubes were then tightly recapped, mixed well and incubated in the BACTEC MGIT instrument at 37 °C until positivity is observed. The readings were measured daily starting from the second day of incubation. Positive cultures were usually detected within 10 days. For reading the actual results the MGIT tubes were removed from incubator and placed on the UV light next to a positive control tube and an uninoculated tube (negative control). Bright fluorescence detected by the corresponding MGIT tube was noticed in the form of bright orange color in the bottom of the tube and also an orange reflection on the meniscus.[30] The primary screening was conducted at concentration of 6.25 μg/mL against *M. tuberculosis* H37 Rv in BACTEC MGIT system. Compounds demonstrating 99% inhibition in the primary screen were described as most potent compounds. All the other compounds to be tested were re-examined for their actual MIC by using Lowenstein–Jensen MIC method. The MIC was defined as the lowest concentration inhibiting 99% of the inoculum. Compounds displaying 99% inhibition in the primary screen (MIC, 6.25 μg/mL) were not further evaluated.

The secondary antimycobacterial screening for test compounds was obtained for *M. tuberculosis* H37 Rv, by using L. J. (Lowenstein and Jensen) MIC method[31,32] for the measurement of MIC, and is defined as the lowest concentration of drug, which inhibits ≥ 99% of bacterial

population present at the beginning of the assay. Stock solutions of primary 1000, 500, 250, and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, 3.12, 1.56 μg/mL dilutions of each test compound in DMSO (dimethyl sulfoxide) were added in the liquid L. J. medium and then media were sterilized by inspissation method. A culture of *M. tuberculosis* H37 Rv growing on L. J. medium was harvested in 0.85% saline in bijou bottles. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37 Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12 days, 22 days and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37 Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. The standard strain *M. tuberculosis* H37Rv was tested with known drugs rifampicin, isoniazid, ethambutol and pyrazinamide.

3. Results and Discussion

3. 1. Chemistry

Synthesis of intermediates and target compounds was accomplished according to the steps illustrated in Scheme 1. The first step comprises formation of intermediate **1** in good yield by the nucleophilic displacement of one chlorine atom of *s*-triazine ring by 4-amino-2-trifluoromethylbenzonitrile. The synthesis of disubstituted *s*-triazine intermediate **3** was achieved in 81% yield by the reaction between 4-(4,6-dichloro-1,3,5-triazin-2-ylamino)-2-trifluoromethylbenzonitrile (**1**) and 8-hydroxyquinoline in the presence of 60% NaH at 45–50 °C. Subsequent coupling of the so formed compound with the desired piperazines and piperidines under basic conditions in 1,4-dioxane at 70–80 °C formed the corresponding 1-(8-quinolinyloxy)-3-piperazinyl(piperidinyl)-5-(4-cyano-3-trifluoromethylphenylamino)-*s*-triazines. This reaction proceeded in good yields and is general for different substituted piperazines and piperidines. A C_3N_3 stretching in the *s*-triazine ring was observed at 806–820 cm^{-1}. Compound **1** displayed an absorption band at 2218–2225 cm^{-1} confirming the presence of a cyano group, and a strong band near 3250–3297 cm^{-1} due to the presence of an NH group. Moreover, a characteristic band appeared at 1255 cm^{-1} corresponding to the C–O–C linkage, while disappearance of the OH peak at 3610 cm^{-1}, belonging to the 8-hydroxyquinoline, indicated the formation of intermediate **3**. Absence of a C–Cl stretching band at 700–760 cm^{-1} confirmed the formation of the final products by the condensation of piperazines to *s*-triazine ring as all the chlorine atoms of *s*-triazine ring were substituted by 4-amino-2-trifluoromethylbenzonitrile, 8-hydroxyquinoline and piperazines or piperidines. The synthesis of **5a**–**u** was confirmed on the basis of NMR spectra. The piperazine proton gave a signal at 3.75–3.88 ppm, the NH group at 8.80–8.87 ppm, the proton of the quinoline moiety resonated at 7.53–7.78 ppm and the proton atoms belonging to the piperidine moiety resonated in the region 1.29–2.44 ppm. ^{19}F NMR spectral data have been interpreted based on literature data reported.[33] ^{19}F NMR spectra for the analogue **5f** and **5g** confirmed the presence of fluorine atom on the *ortho* and *para* positions of the phenyl ring, respectively, by giving the corresponding peaks at around –122.2 and –117.4 ppm, whereas another fluorine NMR spectra obtained for the compound **5h** gave two peaks at –62.8 and –63.1 ppm corresponding to two trifluoromethyl functional groups. Proposed structure of newly synthesized analogues has been assigned on the basis of correct mass spectra analysis., i.e. mass spectrum of compound **5e** revealed a molecular ion peak at *m/z* = 492.3 (M^+) corresponding to the molecular formula $C_{25}H_{20}F_3N_7O$. All of the novel compounds gave C, H and N analyses within 0.10 percent points from the theoretical values.

3. 2. Pharmacology

In vitro antimycobacterial activities of compounds **5a**–**u** were assessed against *M. tuberculosis* H37Rv strain. The preliminary results observed from BACTEC MGIT method along with the measurement of the potency of the standard drugs for comparison purpose, presented in Table 1 indicated that final *s*-triazines **5n** (bearing two methyl functional groups attached to the position 3 and 5 of the piperidine moiety), **5p** and **5s** (bearing halogenated phenyl piperazine bases) as well as compound **5u** (bearing a methoxy group at the *para* position of the phenyl ring of piperazine base) exhibited highest inhibition (99%) at a constant concentration level (6.25 μg/mL) against *M. tuberculosis* H37Rv. These compounds were considered to be most potent analogues among all the final compounds tested. The primary BACTEC MGIT bioassay results obtained have driven us to examine the potency (MIC) of the remaining compounds as well as the compounds tested earlier against *M. tuberculosis* H37Rv. The secondary biological screening was performed using Lowenstein–Jensen MIC method and the results revealed that final *s*-triazinyl compound **5n** was the most potent compound to inhibit *M. tuberculosis* H37Rv completely (99%) at the MIC of 3.12 μg/mL. Compounds **5d** (containing two chlorines at the phenyl ring of piperazine base) and **5t** (bearing three methoxy groups at the phenyl ring of benzyl piperazine moiety bridged to s-triazine core) showed good inhibition effect with the MIC of 12.5 μg/mL, while compounds **5c**, **5q** and **5r** (incorporating mono halo (Cl or F) substituted phenyl ring of piperazine entity) demonstrated 25 μg/mL of MIC against *M. tuberculosis* H37Rv. Final *s*-triazine derivatives **5h** and **5i** (bearing acetyl and isopropyl linkage to the nitrogen of piperazine base condensed to the nucleus) appeared with good activity at MIC level 50 μg/mL and 62.5 μg/mL, res-

Table 1. Antimycobacterial activity of newly synthesized compounds

Entry	R	BACTEC Method		L. J. MIC Method	
		MIC (μg/mL)	% Inhibition	MIC (μg/mL)	% Inhibition
5a	*N*-Methylpiperazine	>6.25	–	250	97
5b	*N*-Ethylpiperazine	>6.25	–	200	98
5c	1-(3-Chlorophenyl)piperazine	>6.25	–	25	98
5d	1-(2,3-Dichlorophenyl)piperazine	>6.25	–	12.5	99
5e	Piperidine	>6.25	–	200	96
5f	Morpholine	>6.25	–	100	98
5g	*N*-Phenylpiperazine	>6.25	–	500	96
5h	*N*-Acetylpiperazine	>6.25	–	62.5	98
5i	*N*-Isopropylpiperazine	>6.25	–	50	98
5j	1-(2-Pyridyl)piperazine	>6.25	–	250	97
5k	1-(2-Pyrimidyl)piperazine	>6.25	–	200	96
5l	*N*-Benzylpiperazine	>6.25	–	200	95
5m	4-Benzylpiperidine	>6.25	–	200	97
5n	3,5-Dimethylpiperidine	6.25	99	3.12	99
5o	*N*-Benzhydryl piperazine	>6.25	–	100	97
5p	4-Chlorobenzhydrylpiperazine	6.25	99	6.25	99
5q	2-Fluorophenylpiperazine	>6.25	–	25	99
5r	4-Fluorophenylpiperazine	>6.25	–	25	99
5s	3-Trifluoromethylphenylpiperazine	6.25	99	6.25	99
5t	2,3,4-Trimethoxylbenzylpiperazine	>6.25	–	12.5	99
5u	1-(4-Methoxyphenyl)piperazine	6.25	99	6.25	99
	Isoniazid	0.20	99		
	Refampicin	0.25	99		
	Ethambutol	3.12	99		
	Pyrazinamide	6.25	99		

Each value is the mean of two independent experiments

pectively. Final morpholine-bearing compound **5f** as well as compound **5o** (with *N*-benzhydrylpiperazine substituent) displayed moderate inhibition of *M. tuberculosis* H37Rv at the MIC level of 100 μg/mL, whereas remaining derivatives were found to exert higher MIC at 250–500 μg/mL.

4. Conclusions

From the bioassay it is clear that the introduction of appropriate substituent on the *s*-triazine ring would lead to the more bioactive compounds. It can be stated that the variation of antimicrobial activity may be associated with the nature of tested microorganisms and is due to the chemical structure of the tested compounds. Bioassay results revealed that 6 out of the 21 tested compounds displayed excellent *in vitro* antimycobacterial inhibitory effects, whereas compound **5n** possessed most potent activity in the bioassay. Collectively, compounds **5d**, **5n**, **5p**, **5s**, **5t** and **5u** could be considered to possess higher potency identified in this study as the higher potency observed with the final compounds containing halogen(s) (Cl or F) or methoxy group(s) functionality. Therefore, it was concluded that there exists ample scope for further study in this class of compounds in order to discover varied biological profiles such as anticancer activity or anti-HIV activity. The study is currently under investigation and the results will be published in due course.

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Povzetek

Predstavljamo sintezo novih 1-(8-kinoliniloksi)-3-piperazinil(piperidinil)-5-(4-ciano-3-trifluorometilfenil amino)-*s*-triazinov. Sintezna pot do končnih piperazinil *s*-triazinov je sestavljena iz dveh nukleofilnih substitucij 4-amino-2-trifluorometilbenzonitrila in 8-hidroksikinolina z 2,4,6-trikloro-1,3,5-triazinom pri čemer z uvedbo piperazinilnega oz. piperidinilnega fragmenta nastanejo 2,4-disubstituirani-6-kloro-1,3,5-triazinski derivati. Strukture novih spojin smo ugotovili s pomočjo IR, ^{1}H NMR, ^{19}F NMR, masne spektroskopije in elementne analize. Pripravljenim spojinam smo z uporabo metod BACTEC MGIT in Lowenstein-Jensen MIC *in vitro* določili antimikobakterijsko aktivnost proti *Mycobacterium tuberculosis* sevu H37Rv. Spojina 4-[4-(3,5-dimetilpiperidin-1-il)-6-(kinolin-8-iloksi)-1,3,5-triazin-2-ilamino]-2-trifluorometilbenzonitril (**5n**) se je izkazala kot najbolj učinkovita izmed vseh testiranih spojin. Pri inhibiciji *M. tuberculosis* H37Rv se je s popolno inhibicijo (99%) izkazala tako učinkovita kot etambutol, minimalna koncentracija inhibicije (MIC) je bila izmerjena 3.12 μg/mL. Spojine **5p**, **5s** in **5u** so pokazale enako učinkovitost kot pirazinamid z MIC vrednostjo 6.25 mg/mL in s popolno inhibicijo (99%) *M. tuberculosis* H37Rv.