Med Chem Res (2011) 20:274–279
DOI 10.1007/s00044-010-9324-3

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In vitro antimycobacterial activity of novel *N′*-(4-(substituted phenyl amino)-6-(pyridin-2-ylamino)-1,3,5-triazin-2-yl) isonicotinohydrazide

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Received: 16 June 2009 / Accepted: 12 February 2010 / Published online: 25 February 2010

Abstract A variety of *N′*-(4-(substituted phenyl amino)-6-(pyridin-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide, **7a–r** were synthesized by using 2-aminopyridine, isonicotic acid hydrazide and cyanuric chloride, and the structures of these compounds were confirmed by IR and NMR (^{1}H and ^{13}C) spectral analyses. Newly synthesized compounds were tested for their in vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system.

Keywords 2-Aminopyridine · Isonicotic acid hydrazide · s-Triazine · Antibacterial activity

Introduction

In today's scenario, bacterial resistance continues to develop and pose a significant threat both in hospitals, and more recently in the community (Barker 2006). Also, the resistant antibacterial agents for human medicine has been reported by the World Health Organization (WHO). The panel agreed that the list of Critically Important antibacterial agents should be updated regularly as new information becomes available, including data on resistance patterns, new and emerging diseases and the development of new drugs (WHO Report, 2005).

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During the last few years, the potential of s-triazine derivatives in agrochemical and medicinal properties have been subjected to investigation. Literature survey reveals that substituted s-triazine derivatives are associated with a number of pronounced biological activities (Raval and Desai, 2004, Patel *et al.*, 2007; Kumar *et al.*, 2008; Singh *et al.*, 2008). The biological activity is a function of physicochemical properties of the targeted molecule, and this assessment is based on the kinds of chemicals that might fit into an active site (Gubernator and Bohm, 1998; Weiner and William, 1994). In order to randomly explore the novel compounds (Raval and Desai, 2005, 2009; Raval *et al.* 2006, 2008), our idea was to combine, 2-aminopyridine, isonicotic acid hydrazide and s-triazine nucleus, using cyanuric chloride and various amines. As substituted s-triazines derivatives, these compounds remain an attractive proposition, with their significant biological activities and further incorporation with commercial drug viz. isoniazid, enabling access to a wide array of structures with interesting antimycobacterial activity.

Materials and methods

Chemistry

The synthesis of the novel designed compounds is outlined in Scheme 1. Trisubstituted s-triazine derivatives, **7a–r** were easily prepared in one pot by a three-step nucleophilic substitution reaction using 2,4,6-trichloro-1,3,5-triazine, 2-aminopyridine, biologically active isonicotic acid hydrazide and different aromatic amines. All the synthesized compounds were well characterized by spectroscopic data as corroborated by IR, ^{1}H- and ^{13}C- NMR and elemental analyses (Table 1).

Scheme 1 Synthetic route to s-triazine derivatives **7a–r**

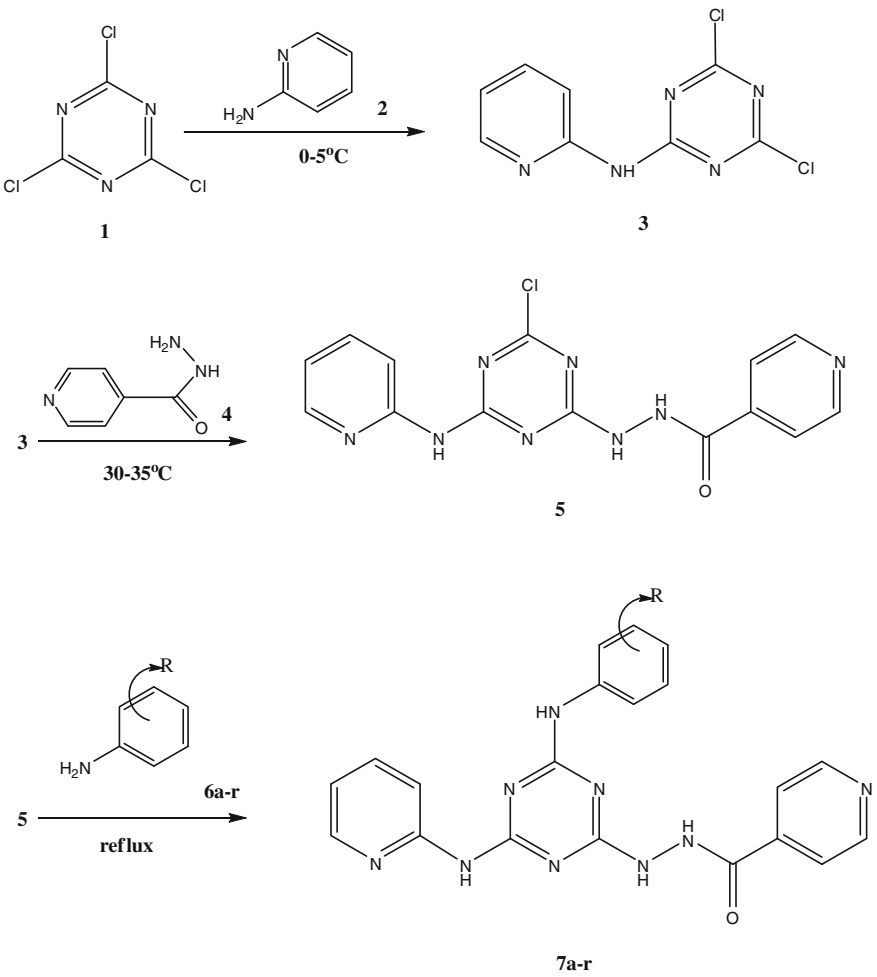

Table 1 Characterization data of **7a–r**

Compd.	R	Melting point (°C)	Yield (%)	Rf value	Anal. Calcd. (found)/%		
					C	H	N
7a	H	222–224	61–63	0.77	60.14 (60.67)	4.29 (4.11)	31.56 (31.29)
7b	2-NO_2	266–267	62–64	0.81	54.05 (54.29)	3.63 (3.77)	31.52 (31.72)
7c	3-NO_2	266–267	61–63	0.82	54.05 (54.12)	3.86 (3.71)	31.52 (31.67)
7d	4-NO_2	268–269	62–63	0.83	54.05 (54.11)	3.86 (3.78)	31.52 (31.77)
7e	2-Cl	248–269	65–67	0.71	55.37 (55.61)	3.72 (3.66)	29.06 (29.21)
7f	3-Cl	242–243	64–65	0.74	58.37 (58.51)	3.72 (3.77)	29.06 (29.34)
7g	4-Cl	241–272	65–67	0.77	58.37 (58.30)	3.72 (3.81)	29.06 (29.27)
7h	2-CH_3	238–239	67–69	0.67	61.01 (61.09)	4.63 (4.49)	30.49 (30.29)
7i	3-CH_3	235–236	68–69	0.69	61.01 (64.11)	4.63 (4.50)	30.49 (30.19)
7j	4-CH_3	237–238	67–69	0.77	61.01 (64.24)	4.63 (4.82)	30.49 (30.47)
7k	2-OCH_3	188–189	76–77	0.72	58.73 (58.81)	4.46 (4.61)	29.35 (29.27)
7l	3-OCH_3	194–197	71–72	0.71	58.73 (58.65)	4.46 (4.66)	29.35 (29.11)
7m	4-OCH_3	201–202	72–74	0.74	58.73 (58.84)	4.46 (5.72)	29.35 (29.29)
7n	2,4-$(Cl)_2$	211–214	67–69	0.69	51.30 (51.42)	3.23 (3.18)	26.92 (26.81)
7o	2,6-$(Cl)_2$	218–220	71–72	0.67	51.30 (51.56)	3.23 (3.29)	26.92 (26.78)
7p	4-SO_2NH_2	277–279	77–79	0.66	50.20 (50.43)	3.79 (3.89)	29.27 (29.11)
7q	2-OH	261–264	64–66	0.68	57.83 (57.77)	4.12 (4.09)	30.35 (30.43)
7r	4-OH	267–269	67–69	0.69	57.83 (57.69)	4.12 (4.19)	30.35 (30.14)

Experimental

All the melting points were taken in open capillaries tube and are uncorrected. The purity of compounds was checked routinely by TLC (0.5-mm thickness) using silica gel, G-coated aluminium, plates (Merck), and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (ν_{max} in cm^{-1}) were recorded on Shimadzu FTIR spectrophotometer using KBr or Nujol technique. ^{1}H- and ^{13}C-NMR spectra were observed on a Bruker's WM 400 FT MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in δ ppm). The elemental analyses (C, H, N) of compounds were performed on Carlo Erba 1108 elemental analyzer.

*N′-(4-(substituted phenylamino)-6-(pyridin-2-ylamino)-1,3,5-triazin-2-yl) isonicotino-hydrazide 7**a–r***

The designated compounds were prepared in one pot by a three-step reaction as follows: The first step consists of nucleophilic substitution(Thruston *et al.*, 1951) of one chlorine atom of cyanuric chloride, **1** in presence of acetone with 2-aminopyridine, **2** to synthesize compound **3** (0–5°C, 0.5–1.0 h). The second step involves further substitution(Thruston *et al.*, 1951) of the second chlorine atom in the presence of acetone with isonicotinic acid hydrazide, **4** to give compound **5** (30–35°C, 3.0–3.5 h). At the third step, the third chlorine atom was substituted (Modha *et al.*, 2001) with various aromatic amines, **6a**–**r** (reflux, 5–6 h) in the presence of aqueous dioxane (Modha *et al.*, 2001) to obtain a series of compounds, **7a**–**r** (Scheme 1). The progress of reaction was monitored by TLC using acetone:toluene (8:2) as eluent. After completion of reaction, the stirring was stopped, and the solution was treated with crushed ice. The product obtained was filtered and dried. The crude products were purified by crystallization from acetone to give the titled compounds. The physical and analytical data of novel compounds are given in Table 1. Their characteristic spectral data are as follows:

*Spectral data of synthesized compounds, **7a–r***

7a: IR (ν_{max} in cm^{-1}): 1670 (>C=O of amide, C=O str), 3340 (NH) and 1325 (CN), 3085 (Aromatic CH str). ^{1}H-NMR δ ppm: 10.19 (s, 1H, CONH–, D_2O exchangeable), 4.11 (s, 1H, NH), 9.24 (s, 1H, NH–Ar), 7.11–8.12 (m, 13H, Ar–H). ^{13}C-NMR δ ppm: 119.1–147.2 (Ar–C), 164.7, 168.1, 176.9 (C=N of s-triazine), 163.27 (CO).

7b: IR (ν_{max} in cm^{-1}): 1672 (>C=O of amide, C=O str), 3345 (NH) and 1327 (CN), 1517, 1371 (NO_2), 3081 (Aromatic CH str). ^{1}H-NMR δ ppm: 10.10 (s, 1H, CONH–, D_2O exchangeable), 4.09 (s, 1H, NH), 9.25 (s, 1H, NH–Ar), 7.21–8.31 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.2–149.3 (Ar–C), 164.8, 168.2, 176.0 (C=N of s-triazine), 163.27 (CO).

7c: IR (ν_{max} in cm^{-1}): 1671 (>C=O of amide, C=O str), 3342 (NH) and 1326 (CN), 1519, 1377 (NO_2), 3084 (Aromatic CH str). ^{1}H-NMR δ ppm: 10.11 (s, 1H, CONH–, D_2O exchangeable), 4.21 (s, 1H, NH), 9.25 (s, 1H, NH–Ar), 7.07–8.29 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.5–147.7 (Ar–C), 165.1, 168.7, 177.2 (C=N of s-triazine), 163.11 (CO).

7d: IR (ν_{max} in cm^{-1}): 1670 (>C=O of amide, C=O str), 3340 (NH) and 1320 (CN), 1519, 1377 (NO_2), 3077 (Aromatic CH str), 1517, 1371 (NO_2, N=O str.). ^{1}H-NMR δ ppm: 10.15 (s, 1H, CONH, D_2O exchangeable), 4.14 (s, 1H, NH), 9.25 (s, 1H, NH–Ar), 7.07–8.29 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 111.7–147.7 (Ar–C), 164.7, 168.7, 176.9 (C=N of s-triazine), 164.77 (CO).

7e: IR (ν_{max} in cm^{-1}): 1675 (>C=O of amide, C=O str), 3310 (NH) and 1325 (CN), 3090 (Aromatic CH str), 835 (C–Cl str). ^{1}H-NMR δ ppm: 10.14 (s, 1H, CONH, D_2O exchangeable), 4.09 (s, 1H, NH), 9.27 (s, 1H, NH–Ar), 7.71–8.91 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 111.9–147.9 (Ar–C), 163.2, 169.9, 176.7 (C=N of s-triazine), 164.5 (CO).

7f: IR (ν_{max} in cm^{-1}): 1676 (>C=O of amide, C=O str), 3315 (NH) and 1320 (CN), 3095 (Aromatic CH str), 830 (C–Cl str). ^{1}H-NMR δ ppm: 10.15 (s, 1H, CONH, D_2O exchangeable), 4.04 (s, 1H, NH), 9.25 (s, 1H, NH–Ar), 7.70–8.90 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 111.9–147.7 (Ar–C), 163.0, 169.7, 176.9 (C=N of s-triazine), 164.0 (CO).

7g: IR (ν_{max} in cm^{-1}): 1677 (>C=O of amide, C=O str), 3319 (NH) and 1327 (CN), 3099 (Aromatic CH str), 837 (C–Cl str). ^{1}H-NMR δ ppm: 10.19 (s, 1H, CONH, D_2O exchangeable), 4.27 (s, 1H, NH), 9.29 (s, 1H, NH–Ar), 7.74–8.92 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 111.7–147.9 (Ar–C), 163.7, 169.9, 176.7 (C=N of s-triazine), 164.9 (CO).

7h: IR (ν_{max} in cm^{-1}): 1672 (>C=O of amide, C=O str), 3315 (NH) and 1327 (CN), 3099 (Aromatic CH str), 832 (C–Cl str). ^{1}H-NMR δ ppm: 10.15 (s, 1H, CONH, D_2O exchangeable), 4.27 (s, 1H, NH), 9.29 (s, 1H, NH–Ar), 7.22–8.59 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 111.7–149.9 (Ar–C), 163.5, 169.7, 176.9 (C=N of s-triazine), 164.9 (CO).

7i: IR (ν_{max} in cm^{-1}): 1674 (>C=O of amide, C=O str), 3322 (NH) and 1322 (CN), 3091 (Aromatic CH str), 1311 (CH_3, C–H bend.). ^{1}H-NMR δ ppm: 10.11 (s, 1H, CONH, D_2O exchangeable), 4.18 (s, 1H, NH), 9.11 (s, 1H, NH–Ar), 7.14–8.14 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.1–147.1 (Ar–C), 160.1, 171.1, 179.1 (C=N of s-triazine), 164.1 (CO).

7j: IR (ν_{max} in cm^{-1}): 1675 (>C=O of amide, C=O str), 3320 (NH) and 1320 (CN), 3089 (Aromatic CH str), 1309

(CH_3, C–H bend.). ^{1}H-NMR δ ppm: 10.18 (s, 1H, CONH, D_2O exchangeable), 4.09 (s, 1H, NH), 9.21 (s, 1H, NH–Ar), 7.94–8.74(m,12H,Ar–H). ^{13}C-NMR δ ppm: 119.1–147.9 (Ar–C), 160.2, 171.7, 179.9 (C=N of s-triazine), 164.2 (CO).

7k: IR (ν_{max} in cm^{-1}): 1684 (>C=O of amide, C=O str), 3325(NH) and 1325(CN), 3092 (Aromatic CH str), 2832 (OCH_3). ^{1}H-NMR δ ppm: 10.22 (s, 1H, CONH, D_2O exchangeable), 3.87 (s, 3H, OCH_3), 4.14 (s, 1H, NH), 9.11 (s, 1H, NH–Ar), 7.80–8.87 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 60.7 (OCH_3), 119.1–147.1 (Ar–C), 162.7, 172.7, 177.9 (C=N of s-triazine), 164.9 (CO).

7l: IR (ν_{max} in cm^{-1}): 1685 (>C=O of amide, C=O str), 3330 (NH) and 1329 (CN), 3099 (Aromatic CH str), 2840 (OCH_3). ^{1}H-NMR δ ppm: 10.27 (s, 1H, CONH, D_2O exchangeable), 3.79 (s, 3H, OCH_3), 4.11 (s, 1H, NH), 9.18 (s, 1H, NH–Ar), 7.77–8.92 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 61.9 (OCH_3), 119.1–147.1 (Ar–C), 162.9, 172.9, 177.9 (C=N of s-triazine), 164.7 (CO).

7m: IR (ν_{max} in cm^{-1}): 1690 (>C=O of amide, C=O str), 3325 (NH) and 1329 (CN), 3092 (Aromatic CH str), 2829 (OCH_3). ^{1}H-NMR δ ppm: 10.24 (s, 1H, CONH, D_2O exchangeable), 3.77 (s, 3H, OCH_3), 4.18 (s, 1H, NH), 9.11 (s, 1H, NH–Ar), 7.72–8.94 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 60.9 (OCH_3), 118.1–149.1 (Ar–C), 162.1, 172.2, 177.7 (C=N of s-triazine), 164.9 (CO).

7n: IR (ν_{max} in cm^{-1}): 1672(>C=O of amide, C=O str), 3311(NH) and 1318(CN), 3087 (Aromatic CH str), 829 (C–Cl str). ^{1}H-NMR δ ppm: 10.11 (s, 1H, CONH, D_2O exchangeable), 4.00 (s, 1H, NH), 9.29 (s, 1H, NH–Ar), 7.71–8.92 (m, 11H, Ar–H). ^{13}C-NMR δ ppm: 112.1–149.2(Ar–C), 163.2, 169.8, 176.9 (C=N of s-triazine), 164.2 (CO).

7o: IR (ν_{max} in cm^{-1}): 1671 (>C=O of amide, C=O str), 3309(NH) and 1311(CN), 3089 (Aromatic CH str), 827(C–Cl str). ^{1}H-NMR δ ppm: 10.10(s, 1H, CONH, D_2O exchangeable), 4.09 (s, 1H, NH), 9.29 (s, 1H, NH–Ar), 7.77–8.98 (m, 11H, Ar–H). ^{13}C-NMR δ ppm: 114.1–146.1 (Ar–C), 163.4, 169.2, 176.5 (C=N of s-triazine), 165.7 (CO).

7p: IR (ν_{max} in cm^{-1}): 1677 (>C=O of amide, C=O str), 3327(NH) and 1327(CN), 3099 (Aromatic CH str), 1140 (SO_2), 3440(NH_2). ^{1}H-NMR δ ppm: 10.11(s, 1H, CONH, D_2O exchangeable), 8.89 (s, 3H, SO_2NH_2), 4.21 (s, 1H, NH), 9.18 (s, 1H, NH–Ar), 7.70–8.77 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.1–148.1 (Ar–C), 161.1, 171.2, 177.9 (C=N of s-triazine), 165.1 (CO).

7q: IR (ν_{max} in cm^{-1}): 1684 (>C=O of amide, C=O str), 3325(NH) and 1325(CN), 3092 (Aromatic CH str), 3560 (OH). ^{1}H-NMR δ ppm: 10.22 (s, 1H, CONH, D_2O exchangeable), 5.29 (s, 1H, OH), 4.12 (s, 1H, NH), 9.11 (s, 1H, NH–Ar), 7.80–8.87 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.1–160.1 (Ar–C), 162.7, 174.1, 179.1 (C=N of s-triazine), 169.1 (CO).

7r: IR (ν_{max} in cm^{-1}): 1683 (>C=O of amide, C=O str), 3329(NH) and 1327(CN), 3097 (Aromatic CH str), 3569 (OH). ^{1}H-NMR δ ppm: 10.21 (s, 1H, CONH, D_2O exchangeable), 5.18 (s, 1H, OH), 4.11 (s, 1H, NH), 9.18 (s, 1H, NH–Ar), 7.82–8.89 (m, 12H, Ar–H). ^{13}C-NMR δ ppm: 119.9–169.9 (Ar–C), 162.1, 174.2, 179.2 (C=N of s-triazine), 169.2 (CO).

Antimycobacterial activity

The primary screening was conducted at concentration of 12.5 or 6.25 mg/ml (or molar equivalent of the highest molecular weight compound in a series of congeners) against *M. tuberculosis H37Rv* (ATCC27294) in BACTEC 12B medium using the BACTEC 460 radiometric system (Collins and Franzblau, 1997; Interleid, 1991). Compounds demonstrating at least 90% inhibition in the primary screen were re-examined at lower concentration (MIC) in broth micro-dilution assay with Almar Blue. The MIC was defined as the lowest concentration inhibiting 99% of the inoculum. Concurrent with the determination of MICs, compounds were tested for cytotoxicity (IC50) in VERO at concentration equal to and greater than the MIC for *M. tuberculosis* H37Rv after 72 h of exposure, viability is assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radioactive Cell proliferation assay. The data are presented in Table 2.

Results and discussion

Chemistry

In this study, a series of 18 new compounds were synthesized. Scheme 1 illustrates the synthetic route for the preparation of target compounds. The purity of the compounds was checked by TLC and elemental analyses; and was characterized by spectral data. The IR spectrum of compounds **7a**–**r** showed absorption peaks between 1670 and 1684 cm^{-1} due to >C=O of amide, 3309–3345 cm^{-1} due to NH and between 1311 and 1329 cm^{-1} due to C=N stretching vibrations. In the ^{1}H-NMR spectra, the signals of the respective protons of the prepared derivatives were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The spectra of all the compounds showed a D_2O-exchangeable broad singlet between δ10.10–10.27 ppm corresponding to CONH proton, and a singlet at 4.00–4.27 δ ppm corresponding to NH proton. The structure was further supported by its ^{13}C-NMR spectra, which showed the signals of respective C=N of s-triazine nucleus at 160.1–165.1, 168.1–174.2 and 176.0–179.2 δ ppm, whereas signal for C=O is found

Table 2 In vitro anti-tubercular activity of s-triazines, **7a–r**

Compd.	Primary screen (12.5 or 6.25 μg/ml)	% Inhibition	Concentration (μM)	Actual MIC (μg/ml)
7a	>12.5	71	0.7110	–
7b	>12.5	67	0.1214	–
7c	>12.5	72	0.1109	–
7d	>12.5	69	0.1211	–
7e	>12.5	80	0.0650	–
7f	>12.5	82	0.0550	–
7g	<6.25	94	0.0250	5.91
7h	>12.5	71	0.1110	–
7i	>12.5	74	0.1218	–
7j	>12.5	77	0.1127	–
7k	6.25	81	0.0677	–
7l	>12.5	83	0.6890	–
7m	<6.25	94	0.0211	4.11
7n	<6.25	92	0.0614	5.92
7o	<6.25	91	0.0311	4.69
7p	<6.25	90	0.0418	6.00
7q	>12.5	71	0.1229	–
7r	>12.5	77	0.1277	–
Isoniazid (0.025–0.05 mg/ml)				

between 163.11 and 169.2 δ ppm. The results of the elemental analysis were within ±0.4% of the theoretical values.

In vitro antimycobacterial activity

All the newly synthesized s-triazine derivatives **7a–r** were tested for their antimycobacterial activity in vitro against *M. tuberculosis H37Rv* using the BACTEC 460 radiometric system. The results are summarized in Table 2 with INH, a standard used for comparison. Among them, the compounds **7g** and **7m–p** produced the highest efficacy and exhibited >90% inhibition at concentrations of 0.0250, 0.0211, 0.0614, 0.0211 and 0.0218 μM, respectively. Thus, the 4-chloro, 4-OCH_3, 2,4-Cl, 2,6-Cl and 4-SO_2NH_2 groups' substitution derivatives displayed relatively higher inhibitory activity, in general. However, the electron-rich groups at para position analogues produced significant increase in inhibitory activity against *M. tuberculosis H37Rv*. On the other hand, analogues with nitro- and methyl group substitution **7b-d**, **7h-j** and phenyl substitution **7a** showed relatively low inhibitory activity against *M. tuberculosis H37Rv*. Instead, (CH_3), (NO_2) and (OH) groups' substitutions at phenyl ring trisubstituted triazine analogues worsen the antimycobacterial activity.

All the newly synthesized compounds **7a–r** were tested for cytotoxicity (IC50) in VERO cells at concentrations of 62.5 mg/ml or 10 times. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radioactive Cell proliferation method. All the active compounds were found to be non-toxic till a level of 62.5 μg/ml. Among the newer derivatives, it is conceivable that derivatives showing antimycobacterial activity can be further modified to exhibit better potency than the standard drugs. The tri-substituted s-triazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of anti-tubercular diseases.

Conclusion

Trisubsituted s-triazine derivatives, **7a–r** were synthesized and characterized for their structure elucidation. Owing to presence of three pharmacologically active nucleus, viz. s-triazine, pyridine and isoniazid in one single molecule, compounds gave good comparable antituberculosis effect. From the given data, it can be concluded that **7g**, **7m**, **7n** and **7o** could be the leading compounds with scope for further development. Concurrently with structural modifications, attempts at improving the solubility and bioavailability of active in vitro compounds are being undertaken. In summary, we have identified a novel series of trisubstituted-1,3,5-triazine, which may develop into the potential class of anti-tubercular agents.

Acknowledgements Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility

(TAACF, USA) as part of a research and development contract with the US National Institute of Allergy and Infectious Diseases. JPR is thankful to Charutar Vidyamandal and SICART, Vallabh Vidyanagar, Gujarat for providing the necessary research and spectral facilities, respectively.

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