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Synthesis, characterization and in vitro biological evaluation of some new 1,3,5-triazine-*bis*-azomethine hybrid molecules as potential antitubercular agents

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ABSTRACT

A series of 1,3,5-triazine-bis-azomethinehybrid molecules (4a-p and 5a-p) were synthesized and tested against *Mycobacterium tuberculosis* H37Rv strain. Preparation of the titled compounds was achieved by reaction of *N*-(4-aminobenzylidene)-4-methoxy-6-methyl-1,3,5-triazin-2-amine (3) with aromatic/heteroaromatic aldehydes (4a-p)and ketones (5a-p). Among the compounds tested, (4d) was identified as the most active *in vitro* with MIC value 3.125 µg/mL against *Mycobacterium tuberculosis* H37Rv.

1. Introduction

Tuberculosis (TB) remains a serious public health problem, worsened by an increased frequency of multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) launched the Global Project on Anti-Tuberculosis Drug Resistance Surveillance to measure the prevalence of drug resistance. Data from the global reports on resistance to anti-tuberculosis (anti-TB) drugs have shown that drug resistance still presents worldwide and that MDR-TB is present in almost all the world. However, a number of new chemical entities have been discovered recently with significant antitubercular activity, so far no new drug has entered into the market since 1960s. To overcome this rapid development of drug resistance, there is a critical need to discover and develop new drugs, acting through a novel mode of action for the efficient chemotherapy of tuberculosis [1,2].

Triazines are a class of organic nitrogen-containing six-membered heterocyclic compounds known for a long period of time. They can structurally exist as three isomers varied with their position of nitrogen atoms on the benzene ring, and are referred to as 1,2,3-triazine, 1,2,4-triazineand 1,3,5-triazine. In particular, considerable attention has been devoted to the development of 1,3,5-triazine derivatives in comparison with 1,2,3-triazine and 1,2,4-triazine derivatives, due to their variety of applications in different fields [3,4]. 1,3,5-Triazines can also be called as symmetric or *s*-triazines. The chemistry of this group of compounds has been studied intensively since past two centuries due to their wide spread applications in the pharmaceutical, textile, plastic and rubber industries and are used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents. In recent times, several studies have been carried out on the antitumor activity of 1,3,5-triazines. Some of these analogues, hexamethylmelamine, almitrine and irsogladine are clinically used as anticancer agents. Baker triazines(4,6-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazine based analogs) are becoming increasingly important as pharmaceuticals. Baker triazine antifol had been undergoing clinical trials as a drug candidate in cancer chemotherapy [5-8]. Although 1,3,5-triazines are well known in the context of anticancer drugs, this ring is also found in the drug used in the chemotherapy of malaria, as seen in case of cycloguanil [9]. Recently, 2,4,6-trisubstituted-1,3,5-triazine scaffolds were discovered as a potent inhibitors of *Mycobacterium tuberculosis* H37Rv [10]. Currently 1,3,5-triazine derivatives have been found to possess wide range of biological activities, such as adenosine receptor antagonist [11], antiamoebic [12], anticancer [13], antileishmanial [14], antimalarial [15], antimicrobial [16], antiviral [17], antitubercular [18], carbonic anhydrase inhibitor [19], cathepsin B inhibitor [20], cholesteryl ester transfer protein inhibitor [21], corticotropin-releasing

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factor ligand [22], CRF_1 PET imaging agent [23], cytosolic phospholipase $A_{2\alpha}$ inhibitor [24], dipeptidyl peptidase IV inhibitor [25], bacterial enzyme DNA helicase inhibitor [26], dual PI3/mTOR inhibitor [27], glucocerebrosidase inhibitor [28], α-glucosidase inhibitor [29], growth factor inhibitor [30], human gonadotropin-releasing hormone receptor antagonist [31], 5-HT_7 receptor antagonist [32], inosine monophosphate dehydrogenase inhibitor [33], mTOR kinase inhibitor [34], voltage-gated sodium channel Na_v 1.7 antagonist [35], neuronal voltage-gated sodium channel blocker [36], phosphodiesterase type 4 inhibitor [37], protein kinase CK2 inhibitor [38], ROCK inhibitor [39], β-secretase inhibitor [40], sorbitol dehydrogenase inhibitor [41], tryptophan hydroxylase inhibitor [42] and VLA-4 integrin antagonist [43]. Similarly, azomethine moiety has gained a great importance, since it has been found to possess several biological activities, such as antimicrobial [44-47], antiviral [48,49], antioxidant [50], radical inhibitor [51], antitumor [52,53], carbonic anhydrase inhibitor [54], xanthine oxidase inhibitor [55], antibacterial [56-59], plant growth regulator [60], free radical scavenger [61], trypsin inhibitor [62], inhibitor of cartilage matrix degeneration [63], 5-HT_6 antagonist [64], anti-inflammatory [65] and analgesic [66,67].

As a part of our ongoing research activities in systematic investigation of synthesizing some novel bioactive compounds in relation to their antitubercular activity against *Mycobacterium tuberculosis* H37Rv, we prepared various 1,3,5-triazine-*bis*-azomethine hybrid molecules (**4a-p** and **5a-p**). However, we have found that 1,3,5-triazine-bis-azomethine hybrid molecules (**4a-p** and **5a-p**) have the considerable potential to act as a new class of antitubercular agents, which can be obtained with the efficient methods in organic synthesis (Scheme 1).The novelty of this work is that none of the 1,3,5-triazine-*bis*-azomethine hybrid molecules (**4a-p** and **5a-p**) synthesized in the present study were earlier not reported to possess any antitubercular activity against *Mycobacterium tuberculosis* H37Rv.

2. Experimental

2.1. Instrumentation

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The FT-IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker 400 MHz. spectrometer in MeOD-$d_4$using TMS as internal standard and chemical shifts are expressed in δ ppm. The Electron spray Ionisation mass spectra (ESI-MS) were recorded on an Agilent 6100 QQQ mass spectrometer (positive ion mode). The UV-Vis absorption spectra of the compounds were recorded on a Hitachi U-1600 spectrophotometer.

2.2. General procedure for the synthesis of 1,3,5-triazine-bis-azomethine hybrid compounds (4a-4p and 5a-5p)

The reaction sequence intended for the preparation of title compounds (**4a-p** and **5a-p**) is shown in Scheme 1. The chief intermediate in the present study *N*-(4-aminobenzylidene)-4-methoxy-6-methyl-1,3,5-triazin-2-amine (**3**) was prepared by reaction between 4-methoxy-6-methyl-1,3,5-triazine-2-amine (**1**) and 4-aminobenzaldehyde (**2**). Further, successive acid catalysed condensation of the (**3**) with appropriate substituted aromatic/heteroaromatic aldehydes and ketones in absolute ethanol under reflux afforded a series of 1,3,5-triazine-*bis*-azomethine hybrid molecules (**4a-p** and **5a-p**) in good yield.

4-Methoxy-6-methyl-N-(4-(benzylideneamino)benzylidene)-1,3,5-triazin-2-amine (**4a**): Colour: Cream. Yield: 89%. M.p.: 233-235 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.65 (C–H), 1659.57 (C=N), 1249.98 (C–N), 1163.43 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.51 (m, 1H, Ar-H), 7.67 (d, *J* = 7.2 Hz, 4H, Ar-H), 7.93 (d, *J* = 7.2 Hz, 4H, Ar-H), 8.15 (s 1H N=CH), 9.45 (s, 1H, N=CH). ESI-MS (*m/z*): 332 [M+H]$^+$. Anal. calcd. for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.85; H, 5.13; N, 21.11%.

4-Methoxy-6-methyl-N-(4-(4-methylbenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4b**): Colour: Cream. Yield: 77%. M.p.: 215-217 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.79 (C–H), 1659.95 (C=N), 1248.82 (C–N), 1163.80 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.39 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.76 (d, *J* = 8.2 Hz, 4H, Ar-H), 8.25 (s 1H N=CH), 9.85 (s, 1H, N=CH). ESI-MS (*m/z*): 346 [M+H]$^+$. Anal. calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.52; H, 5.53; N, 20.27%.

4-Methoxy-6-methyl-N-(4-(4-dimethylaminobenzylidene amino)benzylidene)-1,3,5-triazin-2-amine (**4c**): Colour: Cream. Yield: 81%. M.p.: 245-247 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2953.94 (C–H), 1659.91 (C=N), 1232.68 (C–N), 1164.84 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.00 (s, 6H, CH_3), 3.94 (s, 3H, OCH_3), 6.72 (d, *J* = 2.3 Hz, 4H, Ar-H), 7.73 (d, *J* = 8.2 Hz, 4H, Ar-H), 8.35 (s 1H N=CH), 9.94 (s, 1H, N=CH). ESI-MS (*m/z*): 375 [M+H]$^+$. Anal. calcd. for $C_{21}H_{22}N_6O$: C, 67.36; H, 5.92; N, 22.44. Found: C, 67.34; H, 5.91; N, 22.43%.

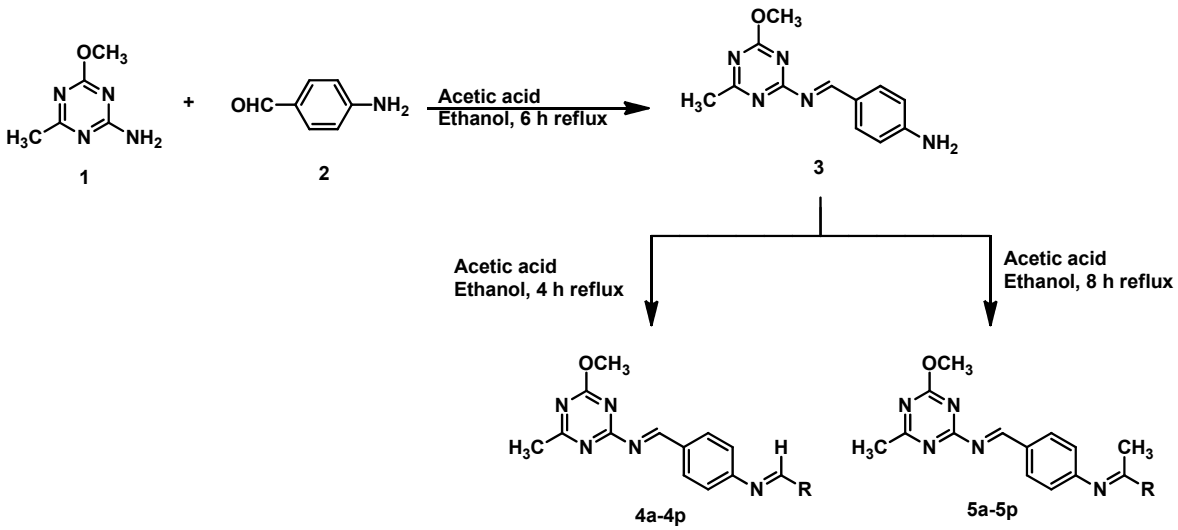
4-Methoxy-6-methyl-N-(4-(3,4,5-trimethoxybenzylidene amino)benzylidene)-1,3,5-triazin-2-amine (**4d**): Colour: Cream. Yield: 72%. M.p.: 253-255 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3010.93 (C–H), 1684.96 (C=N), 1234.08 (C–N), 1128.44 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 6H, OCH_3), 3.88 (s, 6H, OCH_3), 7.43-7.52 (m, 6H, Ar-H), 8.05 (s 1H N=CH), 8.73 (s, 1H, N=CH). ESI-MS (*m/z*): 422 [M+H]$^+$. Anal.c alcd. for $C_{22}H_{23}N_5O_4$: C, 62.70; H, 5.50; N, 16.62. Found: C, 62.72; H, 5.54; N, 16.61%.

4-Methoxy-6-methyl-N-(4-(3-ethoxy-4-hydroxybenzylidene amino)benzylidene)-1,3,5-triazin-2-amine (**4e**): Colour: Cream. Yield: 66%. M.p.: 232-234 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3321.68 (O–H), 2955.87 (C–H), 1659.91 (C=N), 1249.53 (C–N), 1163.85 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.40 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.96 (s, 1H, Ar-H), 7.39-7.54 (m, 6H, Ar-H), 7.92 (s, 1H, OH), 8.25 (s 1H N=CH), 8.42 (s, 1H, N=CH). ESI-MS (*m/z*): 392 [M+H]$^+$. Anal. calcd. for $C_{21}H_{21}N_5O_3$: C, 64.44; H, 5.41; N, 17.89. Found: C, 64.42; H, 5.45; N, 17.83%.

4-Methoxy-6-methyl-N-(4-(3-nitrobenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4f**): Colour: Cream. Yield: 75%. M.p.: 223-225 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2957.03 (C–H), 1659.81 (C=N), 1461.77 (NO_2, asymmetric str.), 1310.19 (NO_2, symmetric str.), 1250.85 (C–N), 1189.22 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.97-8.34 (m, 7H, Ar-H), 8.71 (s, 1H, Ar-H), 8.22 (s 1H N=CH), 9.87 (s, 1H, N=CH). ESI-MS (*m/z*): 377 [M+H]$^+$. Anal. calcd. for $C_{19}H_{16}N_6O_3$: C, 60.63; H, 4.28; N, 22.33. Found: C, 60.61; H, 4.23; N, 22.31%.

4-Methoxy-6-methyl-N-(4-(4-chlorobenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4g**): Colour: Cream. Yield: 84%. M.p.: 231-233 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2982.89 (C–H), 1684.01 (C=N), 1254.61 (C–N), 1129.09 (C–O), 809.56 (C–Cl). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.54 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.88 (d, *J* = 8.2 Hz, 4H, Ar-H), 8.41 (s 1H N=CH), 9.87 (s, 1H, N=CH). ESI-MS (*m/z*): 366 [M+H]$^+$. Anal. calcd. for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.41; N, 19.14. Found: C, 62.31; H, 4.44; N, 19.12%.

4-Methoxy-6-methyl-N-(4-(2,4-dichlorobenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4h**): Colour: Cream. Yield: 92%. M.p.: 205-207 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2956.71 (C–H), 1659.70 (C=N), 1250.40 (C–N), 1163.89 (C–O), 807.12 (C–S). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.67-7.93 (m, 6H, Ar-H), 8.15 (s, 1H, Ar-H), 8.55 (s 1H N=CH), 9.94 (s, 1H, N=CH). ESI-MS (*m/z*): 401 [M+H]$^+$. Anal. calcd. for $C_{19}H_{15}Cl_2N_5O$: C, 57.01; H, 3.78; N, 17.50. Found: C, 57.03; H, 3.72; N, 17.54%.



Scheme 1

4-Methoxy-6-methyl-N-(4-(3-bromobenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4i**): Colour: Cream. Yield: 87%. M.p.: 216-218 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2994.14 (C–H), 1686.51 (C=N), 1260.80 (C–N), 1260.80 (C–O), 749.40 (C–Br). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.65-7.88 (m, 7H, Ar-H), 8.01 (s, 1H, Ar-H), 8.23 (s 1H N=CH), 9.92 (s, 1H, N=CH). ESI-MS (*m/z*): 411 [M+H]$^+$. Anal. calcd. for $C_{19}H_{16}BrN_5O$: C, 55.62; H, 3.93; N, 17.07. Found: C, 55.65; H, 3.91; N, 17.02%.

4-Methoxy-6-methyl-N-(4-(4-bromobenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4j**): Colour: Cream. Yield: 64%. M.p.: 220-222 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2975.58 (C–H), 1679.96 (C=N), 1279.05 (C–N), 1177.39 (C–O), 757.48 (C–Br). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.73 (d, *J* = 8.1 Hz, 4H, Ar-H), 7.79 (d, *J* = 8.1 Hz, 4H, Ar-H), 8.11 (s 1H N=CH), 8.88 (s, 1H, N=CH). ESI-MS (*m/z*): 411 [M+H]$^+$. Anal. calcd. for $C_{19}H_{16}BrN_5O$: C, 55.62; H, 3.93; N, 17.07. Found: C, 55.61; H, 3.96; N, 17.09%.

4-Methoxy-6-methyl-N-(4-(2-hydroxy-3-bromo-5-chloro benzylideneamino)benzylidene)-1,3,5-triazin-2-amine (**4k**): Colour: Cream. Yield: 73%. M.p.: 241-243 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3322.10 (O–H), 2924.07 (C–H), 1657.51 (C=N), 1281.21 (C–N), 1205.89 (C–O), 816.21 (C–Cl), 749.40 (C–Br). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.08 (s, 1H, OH), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.33 (s 1H N=CH), 9.94 (s, 1H, N=CH). ESI-MS (*m/z*): 461 [M+H]$^+$. Anal. calcd. for $C_{19}H_{15}BrClN_5O_2$: C, 49.53; H, 3.28; N, 15.20. Found: C, 49.55; H, 3.29; N, 15.22%.

4-Methoxy-6-methyl-N-(4-(4-allyloxybenzylideneamino) benzylidene)-1,3,5-triazin-2-amine (**4l**): Colour: Cream. Yield: 79%. M.p.: 236-238 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.65 (C–H), 1659.57 (C=N), 1249.98 (C–N), 1163.43 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 5.26 (s, 2H, CH_2), 5.88 (s, 1H, CH_2), 7.23 (d, *J* = 8.7 Hz, 4H, Ar-H), 7.86 (d, *J* = 8.7 Hz, 4H, Ar-H), 8.15 (s 1H N=CH), 8.92 (s, 1H, N=CH). ESI-MS (*m/z*): 388 [M+H]$^+$. Anal. calcd. for $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08. Found: C, 68.23; H, 5.42; N, 18.06%.

4-Methoxy-6-methyl-N-(4-(pyrrol-2-yl-methyleneamino) benzylidene)-1,3,5-triazin-2-amine (**4m**): Colour: Cream. Yield: 91%. M.p.: 249-251 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3144.78 (N–H), 2955.65 (C–H), 1659.21(C=N), 1249.56 (C–N), 1163.55 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.60-7.01 (m, 7H, Ar-H), 8.30 (s, 1H, NH), 8.15 (s 1H N=CH), 8.45 (s, 1H, N=CH). ESI-MS (*m/z*): 321 [M+H]$^+$. Anal. calcd. for $C_{17}H_{16}N_6O$: C, 63.74; H, 5.03; N, 26.23. Found: C, 63.72; H, 5.05; N, 26.21%.

4-Methoxy-6-methyl-N-(4-(pyridine-3-yl-methyleneamino) benzylidene)-1,3,5-triazin-2-amine (**4n**): Colour: Cream. Yield: 88%. M.p.: 197-199 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2924.18 (C–H), 1660.42 (C=N), 1251.47 (C–N), 1164.38 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.32-7.93 (m, 7H, Ar-H), 8.01 (s, 1H, Ar-H), 8.15 (s 1H N=CH), 9.93 (s, 1H, N=CH). ESI-MS (*m/z*): 333 [M+H]$^+$. Anal. calcd. for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 65.01; H, 4.82; N, 25.27%.

4-Methoxy-6-methyl-N-(4-(indol-3-yl-methyleneamino) benzylidene)-1,3,5-triazin-2-amine (**4o**): Colour: Cream. Yield: 80%. M.p.: 203-205 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3167.96 (N–H), 2979.84 (C–H), 1635.12 (C=N), 1243.50 (C–N), 1149.64 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3), 8.25 (s 1H N=CH), 9.94 (s, 1H, N=CH).9.40 (s, 3H, OCH_3), 7.15-7.35 (m, 7H, Ar-H), 7.51 (s, 1H, Ar-H), 8.14 (d, *J* = 7.2 Hz, 2H, Ar-H). ESI-MS (*m/z*): 371 [M+H]$^+$. Anal. calcd. for $C_{21}H_{18}N_6O$: C, 68.09; H, 4.90; N, 22.69. Found: C, 68.06; H, 4.92; N, 22.66%.

4-Methoxy-6-methyl-N-(4-(anthracen-9-yl-methyleneamino) benzylidene)-1,3,5-triazin-2-amine (**4p**): Colour: Cream. Yield: 71%. M.p.: 217-219 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2857.74 (C–H), 1668.63 (C=N), 1250.47 (C–N), 1163.98 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.66 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.76 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.08 (d, *J* = 8.0 Hz, 4H, Ar-H), 8.39 (d, *J* = 8.0 Hz, 4H, Ar-H), 8.59 (s, 1H, Ar-H), 8.33 (s 1H N=CH), 9.85 (s, 1H, N=CH). ESI-MS (*m/z*): 432 [M+H]$^+$. Anal. calcd. for $C_{27}H_{21}N_5O$: C, 75.16; H, 4.91; N, 16.23. Found: C, 75.15; H, 4.90; N, 16.27%.

4-Methoxy-6-methyl-N-(4-(1-(phenyl)ethylideneamino) benzylidene)-1,3,5-triazin-2-amine (**5a**): Colour: Cream. Yield: 63%. M.p.: 210-212 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2957.65 (C–H), 1661.63 (C=N), 1250.62 (C–N), 1164.44 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.94 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.51 (m, 5H, Ar-H), 7.66-8.05 (m, 4H, Ar-H), 8.31 (s 1H N=CH). ESI-MS (*m/z*): 346 [M+H]$^+$. Anal. calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.52; H, 5.51; N, 20.25%.

4-Methoxy-6-methyl-N-(4-(1-(4-methylphenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5b**): Colour: Cream. Yield: 61%. M.p.: 199-201 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.72 (C–H), 1660.23 (C=N), 1249.51 (C–N), 1163.80 (C–O). ^{1}H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.99 (s, 3H, CH_3), 2.30 (s, 3H,

CH_3), 2.38 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.279 (d, *J* = 8.1 Hz, 4H, Ar-H), 7.82 (d, *J* = 8.1 Hz, 4H, Ar-H), 8.15 (s 1H N=CH). ESI-MS (*m/z*): 360 $[M+H]^+$. Anal. calcd. for $C_{21}H_{21}N_5O$: C, 70.17; H, 5.89; N, 19.48. Found: C, 70.14; H, 5.82; N, 19.47%.

4-Methoxy-6-methyl-N-(4-(1-(3-methoxyphenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5c**): Colour: Cream. Yield: 88%. M.p.: 205-207 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.46 (C–H), 1660.25 (C=N), 1248.98 (C–N), 1163.33 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.30 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.94 (s, 6H, OCH_3), 7.26-7.53 (m, 7H, Ar-H), 7.51 (s, 1H, Ar-H), 8.10 (s 1H N=CH). ESI-MS (*m/z*): 376 $[M+H]^+$. Anal. calcd. for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.12; H, 5.63; N, 18.62%.

4-Methoxy-6-methyl-N-(4-(1-(4-methoxyphenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5d**): Colour: Cream. Yield: 71%. M.p.: 211-213 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.79 (C–H), 1659.83 (C=N), 1249.65 (C–N), 1163.72 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 6H, OCH_3), 7.19 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.97 (d, *J* = 8.2 Hz, 4H, Ar-H), 8.12 (s 1H N=CH). ESI-MS (*m/z*): 376 $[M+H]^+$. Anal. calcd. for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.15; H, 5.63; N, 18.62%.

4-Methoxy-6-methyl-N-(4-(1-(2-hydroxyphenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5e**): Colour: Cream. Yield: 72%. M.p.: 226-228 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3322.98 (O–H), 2957.05 (C–H), 1661.33 (C=N), 1250.54 (C–N), 1164.39 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.97 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.92-7.97 (m, 8H, Ar-H), 8.21 (s 1H N=CH), 10.85 (s, 1H, OH). ESI-MS (*m/z*): 362 $[M+H]^+$. Anal. calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.42; H, 5.32; N, 19.35%.

4-Methoxy-6-methyl-N-(4-(1-(4-hydroxyphenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5f**): Colour: Cream. Yield: 82%. M.p.: 213-215 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3323.61 (O–H), 2956.52 (C–H), 1660.80 (C=N), 1250.54 (C–N), 1164.36 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.94 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.80 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.82 (d, *J* = 8.0 Hz, 4H, Ar-H), 8.01 (s, 1H, OH), 8.31 (s 1H N=CH). ESI-MS (*m/z*): 362 $[M+H]^+$. Anal. calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.42; H, 5.32; N, 19.31%.

4-Methoxy-6-methyl-N-(4-(1-(2,4-dihydroxyphenyl) ethylide neamino)benzylidene)-1,3,5-triazin-2-amine (**5g**): Colour: Cream. Yield: 69%. M.p.: 202-204 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3337.82 (O–H), 2957.21 (C–H), 1660.34 (C=N), 1250.54 (C–N), 1164.06 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.56 (m, 5H, Ar-H), 6.62 (m, 1H, Ar-H), 7.57 (m, 1H, Ar-H), 8.14 (s 1H N=CH), 11.01 (s, 1H, OH), 11.15 (s, 1H, OH). ESI-MS (*m/z*): 378 $[M+H]^+$. Anal.calcd. for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.62; H, 5.08; N, 18.52%.

4-Methoxy-6-methyl-N-(4-(1-(2,5-dihydroxyphenyl) ethylide neamino)benzylidene)-1,3,5-triazin-2-amine (**5h**): Colour: Cream. Yield: 83%. M.p.: 206-208 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3412.64 (O–H), 2955.64 (C–H), 1658.10 (C=N), 1251.82 (C–N), 1164.84 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.74-6.80 (m, 6H, Ar-H), 7.58 (m, 1H, Ar-H), 8.21 (s 1H N=CH), 10.25 (s, 1H, OH), 10.23 (s, 1H, OH). ESI-MS (*m/z*): 378 $[M+H]^+$. Anal. calcd. for $C_{20}H_{19}N_5O_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.61; H, 5.05; N, 18.58%.

4-Methoxy-6-methyl-N-(4-(1-(2-hydroxy-5-methyl-phenyl) ethylideneamino)benzylidene)-1,3,5-triazin-2-amine (**5i**): Colour: Cream. Yield: 67%. M.p.: 214-216 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3322.98 (O–H), 2956.63 (C–H), 1660.86 (C=N), 1250.04 (C–N), 1164.08 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 6H, 2×CH_3), 3.94 (s, 3H, OCH_3), 7.45-7.62 (m, 7H, Ar-H), 7.91 (s, 1H, OH), 8.33 (s 1H N=CH). ESI-MS (*m/z*): 376 $[M+H]^+$. Anal. calcd. for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.13; H, 5.62; N, 18.63%.

4-Methoxy-6-methyl-N-(4-(1-(6-hydroxy-5-methyl-phenyl) ethylideneamino)benzylidene)-1,3,5-triazin-2-amine (**5j**): Colour: Cream. Yield: 79%. M.p.: 194-196 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3323.91 (O–H), 2956.20 (C–H), 1659.77 (C=N), 1249.85 (C–N), 1163.95 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.19 (s, 6H, 2×CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.73-8.13 (m, 7H, Ar-H), 8.32 (s 1H N=CH), 12.31 (s, 1H, OH). ESI-MS (*m/z*): 376 $[M+H]^+$. Anal. calcd. for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.14; H, 5.62; N, 18.69%.

4-Methoxy-6-methyl-N-(4-(1-(3-nitrophenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5k**): Colour: Cream. Yield: 81%. M.p.: 199-201 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2957.43 (C–H), 1691.88 (C=N), 1527.48 (NO_2, asymmetric str.), 1346.04 (NO_2, symmetric str.), 1250.71 (C–N), 1164.29 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.45-7.62 (m, 7H, Ar-H), 7.91 (s, 1H, OH), 8.44 (s 1H N=CH). ESI-MS (*m/z*): 391 $[M+H]^+$. Anal. calcd. for $C_{20}H_{18}N_6O_3$: C, 61.53; H, 4.65; N, 21.53. Found: C, 61.52; H, 4.63; N, 21.51%.

4-Methoxy-6-methyl-N-(4-(1-(4-nitrophenyl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5l**): Colour: Cream. Yield: 86%. M.p.: 195-197 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2957.42 (C–H), 1693.14 (C=N), 1528.47 (NO_2, asymmetric str.), 1345.00 (NO_2, symmetric str.), 1260.16 (C–N), 1164.25 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.73 (d, *J* = 8.2 Hz, 4H, Ar-H), 7.62 (d, *J* = 8.2 Hz, 4H, Ar-H), 8.11 (s 1H N=CH). ESI-MS (*m/z*): 391 $[M+H]^+$. Anal. calcd. for $C_{20}H_{18}N_6O_3$: C, 61.53; H, 4.65; N, 21.53. Found: C, 61.55; H, 4.62; N, 21.59%.

4-Methoxy-6-methyl-N-(4-(1-(thiophen-2-yl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5m**): Colour: Cream. Yield: 61%. M.p.: 237-239 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2956.83 (C–H), 1660.40 (C=N), 1250.03 (C–N), 1164.07 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.01 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.45 (m, 6H, Ar-H), 7.82 (s, 1H, Ar-H), 8.08 (s 1H N=CH). ESI-MS (*m/z*): 352 $[M+H]^+$. Anal. calcd. for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93. Found: C, 61.57; H, 4.85; N, 19.91%.

4-Methoxy-6-methyl-N-(4-(1-(pyridin-3-yl)ethylideneamino) benzylidene)-1,3,5-triazin-2-amine (**5n**): Colour: Cream. Yield: 75%. M.p.: 225-227 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2955.91 (C–H), 1659.39 (C=N), 1249.97 (C–N), 1163.71 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.97 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.45-8.17 (m, 8H, Ar-H), 8.39 (s 1H N=CH). ESI-MS (*m/z*): 347 $[M+H]^+$. Anal. calcd. for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.87; H, 5.21; N, 24.22%.

4-Methoxy-6-methyl-N-(4-(1-(naphthalen-2-yl)ethylidene amino)benzylidene)-1,3,5-triazin-2-amine (**5o**): Colour: Cream. Yield: 70%. M.p.: 221-223 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2957.08 (C–H), 1661.40 (C=N), 1265.26 (C–N), 1164.29 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 1.94 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.33-8.17 (m, 11H, Ar-H), 8.22 (s 1H N=CH). ESI-MS (*m/z*): 396 $[M+H]^+$. Anal. calcd. for $C_{24}H_{21}N_5O$: C, 72.89; H, 5.35; N, 17.71. Found: C, 72.85; H, 5.32; N, 17.76%.

4-Methoxy-6-methyl-N-(4-(1-(fluoren-2-yl)ethylideneamino) benzylidene)-1,3,5-triazin-2-amine (**5p**): Colour: Cream. Yield: 69%. M.p.: 256-258 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2998.79 (C–H), 1675.75 (C=N), 1266.83 (C–N), 1158.45 (C–O). ^1H NMR (400 MHz, MeOD-d_4, δ, ppm): 2.35 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 7.33 (m, 1H, Ar-H), 7.35-7.47 (m, 2H, Ar-H), 7.94-8.22 (m, 4H, Ar-H), 8.27 (m, 4H, Ar-H), 8.29 (s 1H N=CH). ESI-MS (*m/z*): 434 $[M+H]^+$. Anal. calcd. for $C_{27}H_{23}N_5O$: C, 74.81; H, 5.35; N, 16.16. Found: C, 74.83; H, 5.37; N, 16.15%.

2.3. Antitubercular activity

The antitubercular activity of 1,3,5-triazine-*bis*-azomethine hybrid molecules (**4a-p** and **5a-p**) were assessed against *Mycobacterium tuberculosis* H37RV strain using micro plate Alamar Blue assay (MABA) [68]. This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly,

200 µL of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µL of the Middle brook 7H9 broth and serial dilution of compounds was made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this time, 25 µL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration, which prevented the color change from blue to pink.

3. Results and discussion

3.1. Synthesis

All the newly synthesized compounds were characterized by CHN elemental analysis and spectroscopic methods such as FT-IR, ^{1}H NMR, and LC mass spectral analysis. A mixture of 4-methoxy-6-methyl-N-(4-aminobenzylidene)-1,3,5-triazin-2-amine (**3**) (0.005 mol) and benzaldehyde (0.005 mol) was stirred in ethanol (15 mL) for 10 min and then catalytic amount of acetic acid (0.5 mL) was added to it. The mixture was kept under reflux for 4 h. Then the precipitated compound **4a** was filtered under vacuum and washed with water, purified by column chromatography and crystallized from ethanol. The IR spectrum of the compound **4a** exhibited the absorption frequency at 1659.57 (C=N) cm^{-1} suggesting the presence of a characteristic -C=N- stretching band. The 400 MHz ^{1}H NMR spectrum of the compound **4a** in MeOD-d_4 as solvent with TMS as an internal standard exhibited characteristic peaks of (N=CH) protons as two singlets, one singlet at δ 8.15 ppm and the other one at δ 9.45 ppm respectively. The ESI mass spectrum (positive ion mode) of **4a** revealed a $(M+H)^+$ ion at *m/z* 332 which is consistent with its molecular formula. Similarly, a mixture of 4-methoxy-6-methyl-*N*-(4-aminobenzylidene)-1,3,5-triazin-2-amine (**3**) (0.005 mol) and acetophenone (0.005 mol) was stirred in ethanol (20 mL) for 5 min and then catalytic amount of acetic acid (1 mL) was added to it. The mixture was kept under reflux for 8 h. Then the precipitated compound **5a** was filtered under vacuum and washed with water, purified by column chromatography and crystallized from ethanol. The IR spectrum of the compound **5a** exhibited the characteristic absorption frequency at 1661.63 (C=N) cm^{-1} suggesting the presence of a characteristic -C=N- stretching band. The 400 MHz ^{1}H NMR spectrum of the compound **5a** in MeOD-d_4 as solvent with TMS as an internal standard exhibited characteristic peak of (N=CH) proton as singlet at δ 8.31 ppm. The ESI mass spectrum (positive ion mode) of **5a** revealed a $(M+H)^+$ ion at *m/z* 346 which is consistent with its molecular formula. Eventually all the spectra of the new products (**4b**-**p** and **5b**-**p**) are in keeping with the predictable structures.

3.2. Antitubercular activity

The antitubercular activity screening data revealed that the compound **4d** demonstrated comparatively the most potent inhibitory activity, with MIC value 3.125 µg/mL. It is interesting to note that the compounds **4k** and **5h** also showed appreciable inhibitory activity with MIC value 6.25 µg/mL. Compounds **4g**-**i**, **5b**, **5c** and **5l** were also showed satisfactory inhibitory activity with MIC value 12.5 µg/mL. The other compounds such as **4b**, **4c**, **4e**, **4j**, **4l**, **4m**, **5e**, **5f**, **5g**, **5k** and **5m** showed moderate level of activity with MIC 25 µg/mL. The compounds **4a**, **4f**, **4n**, **4o**, **4p**, **5a**, **5d**, **5i**, **5j**, **5n**, **5o** and **5p** exhibited comparatively less inhibitory activity with MIC value 50 µg/mL in comparison with the standard drugs (Ethambutol, MIC: 3.125 µg/mL; Pyrazinamide, MIC: 3.125 µg/mL and Streptomycin, MIC: 6.25 µg/mL). A straight look into the SAR (Structure-Activity Relationship) of these compounds clearly exhibited the intrinsic phenomenon of *Mycobacterium tuberculosis* (H37Rv) inhibitory activity associated with the basic skeleton consisting of 1,3,5-triazine and *bis*-azomethine moieties with MIC values range 50-3.125 µg/mL. It is remarkable that the observed inhibitory property of 1,3,5-triazine-bis-azomethine hybrid molecules(**4a**-**p** and **5a**-**p**) against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the nature of substituted aromatic/hetero aromatic aldehyde or ketone from which the corresponding 1,3,5-triazine-bis-azomethine hybrid molecules (**4a**-**p** and **5a**-**p**) were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The aromatic/heteroaromatic aldehyde or ketone (acetophenone) derived *bis*-azomethine analogs of 1,3,5-triazine, as seen in the case of compounds **4n**-**p**, **5a** and **5n**-**p** containing pyridine-3-yl, indol-3-yl, anthracen-9-yl, naphthalen-2-yl and fluoren-2-yl ring structure showed moderate MIC value 50 µg/mL. The compounds **4m** (derived from pyrrole-2-carboxaldehyde) and **5m** (derived from 2-acetylthiophene) displayed better inhibitory potency with MIC 25 µg/mL indicating the significance of five membered heterocyclic ring towards its observed antitubercular activity. This observation indicates substituted phenyl ring is suitable rather than ring replacement towards improved activity against *Mycobacterium tuberculosis* (H37Rv). The compounds having halogen substituents either at *meta* or *para* positions significantly enhanced the activity with MIC value 25-6.25 µg/mL as seen in case of compounds **4g**-**j**. It is also reported that the compounds substituted with electron releasing groups was found to be biologically relevant and the activity order was (**4d** (3,4,5-triOCH$_3$, MIC: 3.125 µg/mL) > **5b** (4-CH$_3$, MIC: 12.5 µg/mL), **5c** (3-OCH$_3$, MIC: 12.5 µg/mL) > **4b** (4-CH$_3$, 25 µg/mL), **4c** (N(CH$_3$), MIC: 25 µg/mL)), respectively. It is important that considerable activity was observed when the hydroxyl groups are substituted at different positions on the phenyl ring as seen in the case of compounds **4k**, **5h**, **4e** and **5e**-**5g** and the order of activity was **4k** (2-OH,3-Br,5-Cl, MIC : 6.25 µg/mL), **5h** (2,5-diOH, MIC : 6.25 µg/mL) > **4e** (3-OC$_2$H$_5$,4-OH, MIC: 25 µg/mL), **5e** (2-OH, MIC: 25 µg/mL), **5f** (4-OH, MIC: 25 µg/mL), **5g** (2,4-diOH, MIC: 25 µg/mL) respectively. The compounds **5i** (MIC: 50 µg/mL) and **5j** (MIC: 50 µg/mL) having the methyl group substitution on the phenyl ring at position 5 along with the hydroxyl group substitution at 6 (**5j**) and 2 (**5i**) positions, respectively showed poorer level of inhibitory activity when compared with that of the compounds (**5e**-**h**) possessing only hydroxyl group substitution [69-72].

4. Conclusion

A series of new class of 1,3,5-triazine-*bis*-azomethine hybrid molecules (**4a**-**p** and **5a**-**p**) is reported, the synthesis and characterization of which is achieved by conventional methods. During this study, we have identified a number of 1,3,5-triazine-bis-azomethine hybrid molecules (**4a**-**p** and **5a**-**p**) empowered with significant antitubercular activity against *Mycobacterium tuberculosis* H37Rv. Structure activity relationship studies revealed that molecular hybridization of 1,3,5-triazine and *bis*-azomethine moieties were vital for the initiation and retaining the inhibitory activity. Further studies determining the *in vivo* antitubercular activity of these compounds is under progress.

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