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Synthesis, characterization and in vitro biological evaluation of some new 1,3,5-triazine-chalcone hybrid molecules as *Mycobacterium tuberculosis* H37Rv inhibitors

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ABSTRACT

A novel series of 1,3,5-triazine-chalcone hybrid molecules (4a-ii) have been synthesized and evaluated in vitro for *Mycobacterium tuberculosis* H37Rv inhibitory potency using Alamar blue assay and the activity expressed as the minimum inhibitory concentration (MIC) in µg/mL. The antitubercular activity screening data revealed that the compound 4z demonstrated comparatively the most potent inhibitory activity, with MIC value 3.125 µg/mL. It is noteworthy that the compounds 4e, 4p and 4bb also showed appreciable inhibitory activity with MIC value 6.25 µg/mL. Most of the compounds displayed significantly promising activity and their structure-activity relationships were also discussed. This could be the remarkable starting point to develop new lead molecules with potential antitubercular activity.

1. Introduction

Tuberculosis (TB) remains a major global health problem. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320000 deaths among HIV-positive people) [1]. It is caused by several species of Mycobacteria including *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. leprae* and *M. avium* that are intracellular, Gram-positive, non-motile, and rod-shaped obligate aerobic pathogens of higher vertebrates [2]. Although this disease can be cured with the current therapy, the treatments require six to nine months of time period that is too long, and accompanied by significant toxicity [3]. These factors make patient compliance to therapy very difficult, and this noncompliance frequently selects for drug-resistant TB bacteria [4]. An increasing occurrence of deaths due to tuberculosis and the known drawbacks of the current existing drugs including the emergence of multi drug-resistant strains have led to a renewed interest in the discovery of new antitubercular agents with novel modes of actions [5]. The topical researches focused on new synthetic products that have shown a useful way to obtain a potentially rich source of drug candidates [6-9].

In recent past, 2,4,6-trisubstituted-1,3,5-triazine scaffolds were discovered as a potent inhibitors of *Mycobacterium tuberculosis* (Mtb) 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 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],

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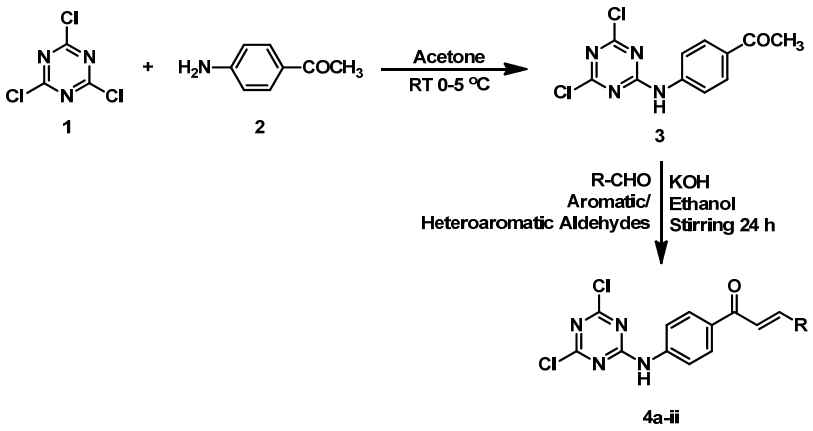

Scheme 1

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]. Similarly, chalcones (α,β-unsatured ketones) captivated significant attention in drug discovery chemistry. Chalcones (α,β-unsatured ketones) have gained huge significance as these compounds exhibit several biological activities, such as antimicrobial [68], antiviral [69], antioxidant [70], radical inhibitor [71], antitumor [72], carbonic anhydrase inhibitor [73], xanthine oxidase inhibitor [74], antibacterial [75], plant growth regulator [76], free radical scavenger [77], anti-inflammatory [78] and analgesic [79].

As a part of our on-going research in systematic investigation of synthesizing some novel bioactive compounds in relation to their Mtb H37Rv inhibitory activity, we prepared a series of some novel 1,3,5-triazine-chalcone hybrid molecules (**4a-ii**) [80]. However, we have found that 1,3,5-triazine-chalcone hybrid molecules (**4a-ii**) have the considerable potential to act as a new class of Mtb H37Rv inhibitors, 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-chalcone hybrid molecules (**4a-ii**) synthesized in the present study were earlier not reported to possess any inhibitory activity against Mtb H37Rv strain.

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 DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The electronspray 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-chalcone hybrid molecules (4a-ii)

The reaction sequence intended for the preparation of title compounds (**4a-ii**) is shown in Scheme 1, and their physical properties are depicted in Table 1. The chief intermediate in the present study 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino) phenyl)ethanone (**3**) was prepared by reaction between cyanuric chloride i.e. 2,4,6-trichloro-1,3,5-triazine (**1**) and 4-aminoacetophenone (**2**) [10]. Further, successive base catalyzed Claisen-Schmidt condensation of the compound **3** with appropriate substituted aromatic/heteroaromatic aldehydes in the presence of 100% potassium hydroxide solution in ethanol afforded a series of 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(substituted)-2-propen-1-ones (**4a-ii**) in good yield. 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. Eventually all the spectra of the new products (**4a-ii**) are in keeping with the predictable structures.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(phenyl)-2-propen-1-one (**4a**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3155 (N–H), 3031 (C–H, aromatic), 2884 (C–H, aliphatic), 1688 (C=O), 1645 (C=C, aliphatic), 1513 (C=C, aromatic), 689 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.13-7.74 (m, 9H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.01 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.74 (s, 1H, NH). ESI-MS (*m/z*): 372 [M+H]$^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-methylphenyl)-2-propen-1-one (4b): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3152 (N–H), 3022 (C–H, aromatic), 2881 (C–H, aliphatic), 1689 (C=O), 1623 (C=C, aliphatic), 1501 (C=C, aromatic), 688 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 3H, CH_3), 7.43-8.04 (m, 8H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.01 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.74 (s, 1H, NH). ESI-MS (*m/z*): 386 [M+H]$^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-methylphenyl)-2-propen-1-one (**4c**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3027 (C–H, aromatic), 2777 (C–H, aliphatic), 1703 (C=O), 1603 (C=C, aliphatic), 1450 (C=C, aromatic), 688 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H, CH_3), 7.38-8.05 (m, 8H, Ar-H), 7.73 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.04 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.69 (s, 1H, NH). ESI-MS (*m/z*): 386 [M+H]$^+$.

Table 1. Physical characterization and *Mycobacterium tuberculosis* H37Rv inhibitory activity data of 1,3,5-triaizne-chalcone hybrids (**4a-ii**) and standard drugs.

Compound	R	Molecular formula	Molecular weight (g)	M.p. (°C)	Yield (%) [a]	% Elemental analysis of C, H, N [b]						MIC [c] (μg/mL)
						Calculated			Found			
						C	H	N	C	H	N	
4a	Phenyl	$C_{18}H_{12}Cl_2N_4O$	371	177	81	58.24	3.26	15.09	58.21	3.21	15.05	50
4b	2-MeC_6H_4	$C_{19}H_{14}Cl_2N_4O$	385	165	79	59.24	3.66	14.54	59.22	3.62	14.52	25
4c	3-MeC_6H_4	$C_{19}H_{14}Cl_2N_4O$	385	181	88	59.24	3.66	14.54	59.25	3.61	14.53	100
4d	4-MeC_6H_4	$C_{19}H_{14}Cl_2N_4O$	385	144	75	59.24	3.66	14.54	59.22	3.64	14.51	50
4e	2-OMeC_6H_4	$C_{19}H_{14}Cl_2N_4O_2$	401	152	91	56.87	3.52	13.96	56.82	3.51	13.95	6.25
4f	3-OMeC_6H_4	$C_{19}H_{14}Cl_2N_4O_2$	401	166	78	56.87	3.52	13.96	56.83	3.51	13.91	25
4g	4-OMeC_6H_4	$C_{19}H_{14}Cl_2N_4O_2$	401	171	74	56.87	3.52	13.96	56.84	3.56	13.96	50
4h	3-OHC_6H_4	$C_{18}H_{12}Cl_2N_4O_2$	387	118	77	55.83	3.12	14.47	55.85	3.11	14.42	50
4i	4-OHC_6H_4	$C_{18}H_{12}Cl_2N_4O_2$	387	129	88	55.83	3.12	14.47	55.83	3.11	14.45	100
4j	3,5-diOHC_6H_3	$C_{18}H_{12}Cl_2N_4O_3$	403	147	85	53.62	3.00	13.89	53.61	3.02	13.81	50
4k	4,5-diOHC_6H_3	$C_{18}H_{12}Cl_2N_4O_3$	403	154	84	53.62	3.00	13.89	53.61	3.04	13.82	50
4l	2-Me,5-OHC_6H_3	$C_{19}H_{14}Cl_2N_4O_2$	401	169	85	56.87	3.52	13.96	56.86	3.51	13.93	25
4m	2-$NH_2C_6H_4$	$C_{18}H_{13}Cl_2N_5O$	386	179	83	55.97	3.39	18.13	55.95	3.31	18.11	50
4n	3-$NH_2C_6H_4$	$C_{18}H_{13}Cl_2N_5O$	386	122	81	55.97	3.39	18.13	55.94	3.32	18.12	100
4o	4-$NH_2C_6H_4$	$C_{18}H_{13}Cl_2N_5O$	386	139	74	55.97	3.39	18.13	55.93	3.35	18.14	100
4p	2-$NO_2C_6H_4$	$C_{18}H_{11}Cl_2N_5O_3$	416	111	84	51.94	2.66	16.83	51.95	2.62	16.82	6.25
4q	3-$NO_2C_6H_4$	$C_{18}H_{11}Cl_2N_5O_3$	416	177	87	51.94	2.66	16.83	51.92	2.65	16.85	25
4r	4-$NO_2C_6H_4$	$C_{18}H_{11}Cl_2N_5O_3$	416	174	74	51.94	2.66	16.83	51.93	2.62	16.81	50
4s	2-ClC_6H_4	$C_{18}H_{11}Cl_3N_4O$	405	168	95	53.29	2.73	13.81	53.21	2.71	13.82	12.5
4t	3-ClC_6H_4	$C_{18}H_{11}Cl_3N_4O$	405	151	77	53.29	2.73	13.81	53.22	2.74	13.81	100
4u	4-ClC_6H_4	$C_{18}H_{11}Cl_3N_4O$	405	146	81	53.29	2.73	13.81	53.23	2.71	13.84	25
4v	2,4-diClC_6H_3	$C_{18}H_{10}Cl_4N_4O$	440	194	92	49.12	2.29	12.73	49.11	2.25	12.71	50
4w	2-FC_6H_4	$C_{18}H_{11}Cl_2FN_4O$	389	112	97	55.55	2.85	14.39	55.53	2.82	14.35	50
4x	3-FC_6H_4	$C_{18}H_{11}Cl_2FN_4O$	389	150	92	55.55	2.85	14.39	55.52	2.84	14.35	50
4y	4-FC_6H_4	$C_{18}H_{11}Cl_2FN_4O$	389	130	88	55.55	2.85	14.39	55.51	2.81	14.32	25
4z	2,4-diFC_6H_3	$C_{18}H_{10}Cl_2F_2N_4O$	407	110	84	53.09	2.48	13.76	53.01	2.42	13.72	3.125
4aa	Furan-2yl	$C_{16}H_{10}Cl_2N_4O_2$	361	138	93	53.21	2.79	15.51	53.22	2.75	15.50	25
4bb	Thiophen-3-yl	$C_{16}H_{10}Cl_2N_4OS$	377	119	82	50.94	2.67	14.85	50.97	2.65	14.82	6.25
4cc	Pyrrol-2yl	$C_{16}H_{11}Cl_2N_5O$	360	122	85	66.25	3.42	11.89	66.22	3.41	11.86	25
4dd	Pyridin-2-yl	$C_{17}H_{11}Cl_2N_5O$	372	138	77	54.86	2.98	18.82	54.82	2.96	18.88	25
4ee	Pyridin-3-yl	$C_{17}H_{11}Cl_2N_5O$	372	165	75	54.86	2.98	18.82	54.81	2.95	18.89	100
4ff	Pyridin-4-yl	$C_{17}H_{11}Cl_2N_5O$	372	201	83	54.86	2.98	18.82	54.85	2.92	18.81	50
4gg	Naphthalen-2-yl	$C_{22}H_{14}Cl_2N_4O$	421	119	87	62.72	3.35	13.30	62.71	3.32	13.32	100
4hh	Naphthalen-3-yl	$C_{22}H_{14}Cl_2N_4O$	421	147	78	62.72	3.35	13.30	62.72	3.31	13.33	100
4ii	Anthracen-9-yl	$C_{26}H_{16}Cl_2N_4O$	471	199	87	66.25	3.42	11.89	66.22	3.40	11.85	100
Ethambutol												3.125
Pyrazinamide												3.125
Streptomycin												6.25

[a] Crystallization solvent is ethanol.
[b] Elemental analysis of C, H, and N were within ±0.4% of theoretical value.
[c] *Mycobacterium tuberculosis* H37Rv.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methylphenyl)-2-propen-1-one (**4d**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3015 (C–H, aromatic), 2762 (C–H, aliphatic), 1705 (C=O), 1601 (C=C, aliphatic), 1440 (C=C, aromatic), 685 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.39 (s, 3H, CH_3), 7.31-7.66 (m, 8H, Ar-H), 7.73 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.02 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.62 (s, 1H, NH). ESI-MS (*m/z*): 386 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-methoxyphenyl)-2-propen-1-one (**4e**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3027 (C–H, aromatic), 2975 (C–H, aliphatic), 1700 (C=O), 1603 (C=C, aliphatic), 1417 (C=C, aromatic), 713 (C–Cl), 1171 (C–O–C), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.86 (s, 3H, OCH_3), 7.20-8.05 (m, 8H, Ar-H), 7.48 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.05 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.66 (s, 1H, NH). ESI-MS (*m/z*): 402 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-methoxyphenyl)-2-propen-1-one (**4f**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3027 (C–H, aromatic), 2977 (C–H, aliphatic), 1700 (C=O), 1605 (C=C, aliphatic), 1457 (C=C, aromatic), 687 (C–Cl), 1171 (C–O–C), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.88 (s, 3H, OCH_3), 7.12-8.21 (m, 8H, Ar-H), 7.71 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.65 (s, 1H, NH). ESI-MS (*m/z*): 402 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**4g**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3021 (C–H, aromatic), 2970 (C–H, aliphatic), 1690 (C=O), 1602 (C=C, aliphatic), 1455 (C=C, aromatic), 677 (C–Cl), 1170 (C–O–C), 1055 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.86 (s, 3H, OCH_3), 7.12-7.92 (m, 8H, Ar-H), 7.71 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.05 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.75 (s, 1H, NH). ESI-MS (*m/z*): 402 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-hydroxyphenyl)-2-propen-1-one (**4h**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3445 (O–H), 3124 (N–H), 3015 (C–H, aromatic), 2984 (C–H, aliphatic), 1689 (C=O), 1606 (C=C, aliphatic), 1415 (C=C, aromatic), 676 (C–Cl), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.36-8.01 (m, 8H, Ar-H), 7.67 (d, *J* = 15.6 Hz, 1H, HC=CH (H-α)), 8.18 (d, *J* = 15.6 Hz, 1H, HC=CH (H-β)), 9.85 (s, 1H, NH), 12.32 (s, 1H, OH). ESI-MS (*m/z*): 388 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-hydroxyphenyl)-2-propen-1-one (**4i**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3444 (O–H), 3124 (N–H), 3019 (C–H, aromatic), 2982 (C–H, aliphatic), 1684 (C=O), 1602 (C=C, aliphatic), 1412 (C=C, aromatic), 671 (C–Cl), 1055 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.16-7.62 (m, 8H, Ar-H), 7.68 (d, *J* = 15.6 Hz, 1H, HC=CH (H-α)), 8.14 (d, *J* = 15.6 Hz, 1H, HC=CH (H-β)), 9.82 (s, 1H, NH), 12.31 (s, 1H, OH). ESI-MS (*m/z*): 388 $[M+H]^+$.

(E)-1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3,5-dihydroxyphenyl)-2-propen-1-one (**4j**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3440 (O–H), 3122 (N–H), 3027 (C–H, aromatic), 2890 (C–H, aliphatic), 1700 (C=O), 1605 (C=C, aliphatic), 1511 (C=C, aromatic), 688 (C–Cl), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.21-8.02 (m, 7H, Ar-H), 7.79 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 8.03 (d, *J* = 15.3 Hz, 1H,

HC=CH (H-β)), 9.89 (s, 1H, NH), 11.52 (s, 2H, OH). ESI-MS (*m/z*): 404 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4,5-dihydroxyphenyl)-2-propen-1-one (**4k**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3395 (O–H), 3127 (N–H), 3017 (C–H, aromatic), 2989 (C–H, aliphatic), 1686 (C=O), 1615 (C=C, aliphatic), 1545 (C=C, aromatic), 689 (C–Cl), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.55-8.03 (m, 7H, Ar-H), 7.83 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 8.08 (d, *J* = 15.3 Hz, 1H, HC=CH (H-β)), 9.58 (s, 1H, OH), 9.87 (s, 1H, NH), 10.57 (s, 1H, OH). ESI-MS (*m/z*): 404 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-methyl-5-hydroxyphenyl)-2-propen-1-one (**4l**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3440 (O–H), 3122 (N–H), 3021 (C–H, aromatic), 2975 (C–H, aliphatic), 1690 (C=O), 1641 (C=C, aliphatic), 1486 (C=C, aromatic), 678 (C–Cl), 1054 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.47 (s, 3H, CH_3), 7.62-8.01 (m, 7H, Ar-H), 7.81 (d, *J* = 15.3 Hz, 1H, HC=CH (H-α)), 8.08 (d, *J* = 15.3 Hz, 1H, HC=CH (H-β)), 9.01 (s, 1H, NH), 10.52 (s, 1H, OH). ESI-MS (*m/z*): 402 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-aminophenyl)-2-propen-1-one (**4m**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3367 (NH_2), 3117 (N–H), 2978 (C–H, aromatic), 2763 (C–H, aliphatic), 1693 (C=O), 1597 (C=C, aliphatic), 1413 (C=C, aromatic), 688 (C–Cl), 1296 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.74-8.11 (m, 8H, Ar-H), 7.58 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.65 (s, 1H, NH), 10.51 (s, 2H, Ar-NH_2). ESI-MS (*m/z*): 387 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-aminophenyl)-2-propen-1-one (**4n**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3367 (NH_2), 3117 (N–H), 2978 (C–H, aromatic), 2763 (C–H, aliphatic), 1693 (C=O), 1597 (C=C, aliphatic), 1413 (C=C, aromatic), 688 (C–Cl) , 1290 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.72 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.74-8.11 (m, 8H, Ar-H), 8.01 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.67 (s, 1H, NH), 10.54 (s, 2H, Ar-NH_2). ESI-MS (*m/z*): 387 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-aminophenyl)-2-propen-1-one (**4o**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3362 (NH_2), 3115 (N–H), 2979 (C–H, aromatic), 2761 (C–H, aliphatic), 1690 (C=O), 1590 (C=C, aliphatic), 1410 (C=C, aromatic), 684 (C–Cl), 1290 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.71 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.77-8.14 (m, 8H, Ar-H), 8.12 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.65 (s, 1H, NH), 10.52 (s, 2H, Ar-NH_2). ESI-MS (*m/z*): 387 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-nitrophenyl)-2-propen-1-one (**4p**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3024 (C–H, aromatic), 2776 (C–H, aliphatic), 1700 (C=O), 1604 (C=C, aliphatic), 1414 (C=C, aromatic), 688 (C–Cl), 1529 (N=O), 1291 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.86-8.18 (m, 8H, Ar-H), 8.05 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.35 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.72 (s, 1H, NH). ESI-MS (*m/z*): 417 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-nitrophenyl)-2-propen-1-one (**4q**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3115 (N–H), 3026 (C–H, aromatic), 2775 (C–H, aliphatic), 1700 (C=O), 1599 (C=C, aliphatic), 1412 (C=C, aromatic), 688 (C–Cl), 1522 (N=O), 1290 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.55-8.39 (m, 8H, Ar-H), 7.86 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.73 (s, 1H, NH). ESI-MS (*m/z*): 417 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-nitrophenyl)-2-propen-1-one (**4r**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3205 (N–H), 3016 (C–H, aromatic), 2895 (C–H, aliphatic), 1710 (C=O), 1589 (C=C, aliphatic), 1442 (C=C, aromatic), 680 (C–Cl), 1520 (N=O), 1287 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.54-8.29 (m, 8H, Ar-H), 7.83 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.07 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.23 (s, 1H, NH). ESI-MS (*m/z*): 417 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-chlorophenyl)-2-propen-1-one (**4s**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3027 (C–H, aromatic), 2893 (C–H, aliphatic), 1689 (C=O), 1597 (C=C, aliphatic), 1450 (C=C, aromatic), 688 (C–Cl), 786 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.60 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.62-8.24 (m, 8H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.65 (s, 1H, NH). ESI-MS (*m/z*): 406 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-chlorophenyl)-2-propen-1-one (**4t**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3121 (N–H), 3025 (C–H, aromatic), 2891 (C–H, aliphatic), 1686 (C=O), 1594 (C=C, aliphatic), 1451 (C=C, aromatic), 786 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.45 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.62-7.74 (m, 8H, Ar-H), 7.79 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.65 (s, 1H, NH). ESI-MS (*m/z*): 406 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-chlorophenyl)-2-propen-1-one (**4u**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3126 (N–H), 3023 (C–H, aromatic), 2883 (C–H, aliphatic), 1690 (C=O), 1588 (C=C, aliphatic), 1442 (C=C, aromatic), 681 (C–Cl), 785 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.61 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.67-7.82 (m, 8H, Ar-H), 7.87 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.63 (s, 1H, NH). ESI-MS (*m/z*): 406 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2,4-dichlorophenyl)-2-propen-1-one (**4v**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3124 (N–H), 3018 (C–H, aromatic), 2891 (C–H, aliphatic), 1689 (C=O), 1641 (C=C, aliphatic), 1485 (C=C, aromatic), 691 (C–Cl), 786 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.65-8.23 (m, 7H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.69 (s, 1H, NH). ESI-MS (*m/z*): 441 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2-fluorophenyl)-2-propen-1-one (**4w**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3117 (N–H), 3017 (C–H, aromatic), 2977 (C–H, aliphatic), 1693 (C=O), 1605 (C=C, aliphatic), 1415 (C=C, aromatic), 688 (C–Cl), 1116 (C–F). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.36-8.03 (m, 8H, Ar-H), 7.55 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.82 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.68 (s, 1H, NH). ESI-MS (*m/z*): 390 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(3-fluorophenyl)-2-propen-1-one (**4x**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3112 (N–H), 3011 (C–H, aromatic), 2974 (C–H, aliphatic), 1690 (C=O), 1602 (C=C, aliphatic), 1412 (C=C, aromatic), 680 (C–Cl), 1011 (C–F). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.16-7.73 (m, 8H, Ar-H), 7.75 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.81 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.78 (s, 1H, NH). ESI-MS (*m/z*): 390 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(4-fluorophenyl)-2-propen-1-one (**4y**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3114 (N–H), 3212 (C–H, aromatic), 2975 (C–H, aliphatic), 1694 (C=O), 1602 (C=C, aliphatic), 1412 (C=C, aromatic), 1106 (C–F), 685 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.22-7.63 (m, 8H, Ar-H), 7.65 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.82 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.77 (s, 1H, NH). ESI-MS (*m/z*): 390 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(2,4-difluorophenyl)-2-propen-1-one (**4z**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3021 (C–H, aromatic), 2884 (C–H, aliphatic), 1693 (C=O), 1605 (C=C, aliphatic), 1415 (C=C, aromatic), 688 (C–Cl), 1114 (C–F). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.39-8.31 (m, 7H, Ar-H), 7.76 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.08 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.69 (s, 1H, NH). ESI-MS (*m/z*): 408 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(furan-2-yl)-2-propen-1-one (**4aa**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3420 (N–H), 3062 (C–H, aromatic), 3030 (C–H, aliphatic), 1671(C=O), 1591 (C=C, aliphatic), 1453 (C=C, aromatic), 696 (C–Cl), 1155 (C–O–C), 1053 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.74 (s, 1H, Ar-H), 6.21 (m, 1H, Ar-H), 7.16-7.50 (m, 5H, Ar-H), 7.62 (d, *J* =

16 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 9.73 (s, 1H, NH). ESI-MS (*m/z*): 362 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(thiophen-3-yl)-2-propen-1-one (**4bb**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3430 (N–H), 3019 (C–H, aromatic), 2973 (C–H, aliphatic), 1689 (C=O), 1599 (C=C, aliphatic), 1414 (C=C, aromatic), 688 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.68 (s, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 7.12 (s, 1H, Ar-H), 7.33-7.58 (m, 4H, Ar-H), 7.76 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.02 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.68 (s, 1H, NH). ESI-MS (*m/z*): 378 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(pyrrol-2-yl)-2-propen-1-one (**4cc**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3144 (N–H), 3052 (N–H), 3017 (C–H, aromatic), 2973 (C–H, aliphatic), 1695 (C=O), 1615 (C=C, aliphatic), 1414 (C=C, aromatic), 678 (C–Cl), 1308 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.46 (s, 1H, Ar-H), 7.44 (m, 1H, Ar-H), 7.55-7.61 (m, 5H, Ar-H), 7.76 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.03 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.64 (s, 1H, NH), 10.55 (s, 1H, NH). ESI-MS (*m/z*): 361 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(pyridin-2-yl)-2-propen-1-one (**4dd**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3019 (C–H, aromatic), 2931 (C–H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C–Cl), 1308 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.98 (d, *J* = 16 Hz, 1H, HC=CH (H-α)), 7.13-7.69 (m, 8H, Ar-H), 7.78 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 9.60 (s, 1H, NH). ESI-MS (*m/z*): 373 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(pyridin-3-yl)-2-propen-1-one (**4ee**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3122 (N–H), 3011 (C–H, aromatic), 2922 (C–H, aliphatic), 1679 (C=O), 1609 (C=C, aliphatic), 1422 (C=C, aromatic), 1308 (C–N), 681 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.22 (d, *J* = 16 Hz, 1H, HC=CH (H-α)), 7.23-7.59 (m, 8H, Ar-H), 7.68 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 9.58 (s, 1H, NH). ESI-MS (*m/z*): 373 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(pyridin-4-yl)-2-propen-1-one (**4ff**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3019 (C–H, aromatic), 2931 (C–H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C–Cl), 1308 (C–N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.98 (d, *J* = 16 Hz, 1H, HC=CH (H-α)), 7.13-7.69 (m, 8H, Ar-H), 7.78 (d, *J* = 16 Hz, 1H, HC=CH (H-β)), 9.60 (s, 1H, NH). ESI-MS (*m/z*): 373 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(naphthalen-2-yl)-2-propen-1-one (**4gg**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3102 (N–H), 3015 (C–H, aromatic), 2926 (C–H, aliphatic), 1684 (C=O), 1602 (C=C, aliphatic), 1416 (C=C, aromatic), 682 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.62-7.83 (m, 11H, Ar-H), 7.87 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.16 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.70 (s, 1H, NH). ESI-MS (*m/z*): 422 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(naphthalen-3-yl)-2-propen-1-one (**4hh**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3115 (N–H), 3019 (C–H, aromatic), 2931 (C–H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.62-8.33 (m, 11H, Ar-H), 7.89 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.26 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.71 (s, 1H, NH). ESI-MS (*m/z*): 422 $[M+H]^+$.

(E)-1-(4-(4,6-Dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(anthracen-9-yl)-2-propen-1-one (**4ii**): Colour: Light yellow crystals. FT-IR (KBr, ν_{max}, cm^{-1}): 3127 (N–H), 3019 (C–H, aromatic), 2931 (C–H, aliphatic), 1689 (C=O), 1604 (C=C, aliphatic), 1417 (C=C, aromatic), 688 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.98-7.41 (m, 13H, Ar-H), 7.59 (d, *J* = 15.6 Hz, 1H, HC=CH (H-α)), 8.06 (d, *J* = 15.6 Hz, 1H, HC=CH (H-β)), 9.75 (s, 1H, NH). ESI-MS (*m/z*): 472 $[M+H]^+$.

2.3. Mycobacterium tuberculosis H37Rv *inhibitory activity*

The *Mycobacterium tuberculosis* inhibitory activity of 1,3,5-triazine-chalcone hybrid molecules **4a-ii** were assessed against Mtb H37Rv strain using micro plate Alamar Blue assay (MABA) [81]. 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 Alamar 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. The results of Mtb H37Rv inhibitory activity studies are given in Table 1.

3. Results and discussion

3.1. Synthesis

The IR spectrum of all the compounds **4a-ii** exhibited the characteristic absorptions at various frequencies correspondingly at 3310-3110 and 1640-1715 cm^{-1} suggesting the presence of a secondary amine group and α,β-unsaturated carbonyl group respectively. In the ^{1}H NMR spectra of 1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino) phenyl)-3-(substituted)-2-propen-1-ones (**4a-ii**), a singlet integrating for one proton characteristic of the secondary amine NH group was observed in between δ 9.2-9.4 ppm as a broad signal. As seen in case of compound **4a**, the IR spectrum of **4a** exhibited characteristic –C=C– (aliphatic) and –C=C– (aromatic) stretching bands at frequencies 1645 and 1513 cm^{-1}, respectively. The other IR absorptions at various frequencies correspondingly at 3155 and 1688 cm^{-1} suggesting the presence of a secondary amino group and α,β-unsaturatedketone group, respectively. The 400 MHz ^{1}H NMR spectrum of the compound **4a** in DMSO-d_6 as solvent with TMS as an internal standard exhibited characteristic peaks of H_α and H_β protons of α,β-unsaturated ketone bridge appeared as two doublets, one doublet at δ 7.78 ppm (H_α, *J* = 15.2 Hz) and the other one at δ 8.01 ppm (H_β, *J* = 15.2 Hz). The large *J* value 15.2 Hz of both the protons clearly reveals the *trans* geometry at the double bond. The distinguishing peak of NH proton appears as one singlet δ 9.74 ppm. The ESI mass spectrum (positive ion mode) of **4a** revealed a $(M+H)^+$ ion at *m/z* 372. Based on the above spectral information the structure of the compound **4a** was confirmed as (*Z*)-1-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino)phenyl)-3-(phenyl)-2-propen-1-one [82-84].

3.2. Mycobacterium tuberculosis H37RV *inhibitory activity*

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized 1,3,5-triazine-chalcone hybrid molecules (**4a-ii**) is illustrated in (Table 1). The antitubercular activity screening data revealed that the compound **4z** demonstrated comparatively the most potent inhibitory activity, with MIC value 3.125 µg/mL. It is interesting to note that the compounds **4e**, **4p** and **4bb** also showed appreciable inhibitory activity with MIC value 6.25 µg/mL. Compound **4s** was also showed satisfactory inhibitory activity with MIC value 12.5 µg/mL. The other compounds such as **4b**, **4f**, **4l**, **4q**, **4u**, **4y**, **4aa**, **4cc** and **4dd** showed moderate level of activity with MIC 25 µg/mL.

The compounds **4a**, **4d**, **4g**, **4h**, **4j**, **4k**, **4m**, **4r**, **4v**, **4w**, **4x** and **4ff** exhibited comparatively reasonable inhibitory activity with MIC value 50 µg/mL. Correspondingly, the compounds **4c**, **4i**, **4n**, **4o**, **4t**, **4ee**, **4gg**, **4hh** and **4ii** exhibited comparatively poor inhibitory activity with MIC value 100 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 direct revision into the Structure-Activity Relationship (SAR) of these compounds clearly exhibited the intrinsic property of *Mycobacterium tuberculosis* (H37Rv) inhibitory activity associated with the basic skeleton consisting of 1,3,5-triazine and α,β-unsaturatedketone moieties [85] with MIC values range 100-3.125 µg/mL. It is noteworthy that the observed inhibitory activity of 1,3,5-triazine-chalcone hybrid molecules **4a-ii** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/ heteroaromatic aldehyde from which the corresponding 1,3,5-triazine-chalcone hybrid molecules **4a-ii** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The aromatic/heteroaromatic aldehydes derived chalcone derivatives of 1,3,5-triazine, as seen in the case of compounds followed its activity order as **4bb** (Thiophen-3-yl, MIC: 6.25 µg/mL) > **4aa** (Furan-2yl, MIC: 25 µg/mL), **4cc** (Pyrrol-2yl, MIC: 25 µg/mL), **4dd** (Pyridin-2-yl, MIC: 25 µg/mL) > **4a** (Phenyl, MIC: 50 µg/mL), **4ff** (Pyridin-4-yl, MIC: 50 µg/mL) > **4ee** (Pyridin-3-yl, MIC: 100 µg/mL), **4gg** (Naphthalen-2-yl, MIC: 100 µg/mL), **4hh** (Naphthalen-3-yl, MIC: 100 µg/mL), **4ii** (Anthracen-9-yl, MIC: 100 µg/mL), respectively. The compounds **4z** (2,4-diFC_6H_3, MIC: 3.125 µg/mL) > **4s** (2-ClC_6H_4, MIC: 12.5 µg/mL) > **4u** (4-ClC_6H_4, MIC: 25 µg/mL), **4y** (4-FC_6H_4, MIC: 25 µg/mL) > **4v** (2,4-diClC_6H_3, MIC: 50 µg/mL), **4w** (2-FC_6H_4, MIC: 50 µg/mL), **4x** (3-FC_6H_4, MIC: 50 µg/mL) > **4t** (3-ClC_6H_4, MIC: 100 µg/mL) displayed better inhibitory potency indicating the significance of halogen substituents on the phenyl ring of 1,3,5-traizine-chalcone motif. It is also reported that the compounds substituted with electron releasing or activating groups was found to be biologically relevant and the activity order was **4e** (2-$OMeC_6H_4$, MIC: 6.25 µg/mL) > **4b** (2-MeC_6H_4, MIC: 25 µg/mL), **4f** (3-$OMeC_6H_4$, MIC: 25 µg/mL), **4l** (2-Me,5-OHC_6H_3, MIC: 25 µg/mL) > **4d** (4-MeC_6H_4, MIC: 50 µg/mL), **4g** (4-$OMeC_6H_4$, MIC: 50 µg/mL), **4h** (3-OHC_6H_4, MIC: 50 µg/mL), **4j** (3,5-diOHC_6H_3, MIC: 50 µg/mL), **4k** (4,5-diOHC_6H_3, MIC: 50 µg/mL), **4m** (2-$NH_2C_6H_4$, MIC: 50 µg/mL) > **4c** (3-MeC_6H_4, MIC: 100 µg/mL), **4i** (4-OHC_6H_4, MIC: 100 µg/mL), **4n** (3-$NH_2C_6H_4$, MIC: 100 µg/mL), **4o** (4-$NH_2C_6H_4$, MIC: 100 µg/mL), respectively. The compounds substituted with electron withdrawing or deactivating nitro group was found to be biologically relevant and the activity order was, **4p** (2-$NO_2C_6H_4$, MIC: 6.25 µg/mL) > **4q** (3-$NO_2C_6H_4$, MIC: 25 µg/mL) > **4r** (4-$NO_2C_6H_4$, MIC: 50 µg/mL), respectively. It is reported 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 **4l** (2-Me,5-OHC_6H_3, MIC: 25 µg/mL) > **4h** (3-OHC_6H_4, MIC: 50 µg/mL), **4j** (3,5-diOHC_6H_3, MIC: 50 µg/mL), **4k** (4,5-diOHC_6H_3, MIC: 50 µg/mL) > **4i** (4-OHC_6H_4, MIC: 100 µg/mL), respectively.

4. Conclusion

A series of new class of *Mycobacterium tuberculosis* H37Rv inhibitors is reported, the synthesis of which is characterized by conventional methods. During this study we have identified a number of 1,3,5-triazine-chalcone hybrid molecules (**4a-ii**) empowered with significant *Mycobacterium tuberculosis* H37Rv inhibitory properties. Structure activity relationship studies revealed that substitution at position 3 of α,β-unsaturated ketone further substitution is important to modulate the activity. Further studies determining the *in vivo* antitubercular activity of these compounds are under progress.

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