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A FACILE SYNTHESIS AND IN VITRO BIOLOGICAL EVALUATION OF A SERIES OF SUBSTITUTED BENZOFURANS AS ANTITUBERCULAR AGENTS

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ABSTRACT

We have prepared a series of some benzofuran substituted chalcones (2a-d) and their heterocyclic analogs such as isoxazolines (3a-d), pyrimidines (4a-d), pyrazolines (5a-d), benzodiazepines (6a-d) and benzothiazepines (7a-d) respectively, have been synthesised via ultrasound-promoted irradiation (20 kHz) and characterized by using physical and spectral analytical data. Further these compounds were evaluated for their in vitro antitubercular activity using Alamar blue assay.

KEYWORDS: Chalcone, Isoxazoline, Pyrimidine, Pyrazoline, Benzodiazepine, Benzothiazepine.

1. INTRODUCTION

Benzofuran and its derivatives have attracted the attention of chemists since the earl 1960s mainly because of the broad spectrum of biological properties exhibited by this class of compounds.[1] The enormous amount of research work that has been conducted in the pharmaceutical laboratories on these compounds during the last few decades derives its inspiration from the discovery of clinically used coronary vasodilators such as Amiodarone and Benziodarone.[2]

Heterocyclic compounds are of immense importance due to their wide spectrum of bioactive properties. These compounds have attracted the attention of chemists and biologists due to their varied nature of potential pharmacological activities.[3] Since the compounds containing heteroatoms such as oxygen, nitrogen and sulfur were reported to possess diverse biological and pharmacological activities[4], as the most important study in the present research work focused on the synthesis of some novel benzofuran linked chalcones and their heterocyclic derivatives[6-9] by conventional condensation reactions.[10-11] These compounds were further purified by chromatographic methods and identified by physical and spectral analytical data were reporting for the first time.

The utilization of high intensity ultrasound offers a facile, versatile synthetic tool for organic compounds that are often unavailable by conventional methods. The primary physical phenomena associated with ultrasound that are relevant to materials synthesis are cavitation and nebulization. Acoustic cavitation (the formation, growth, and implosive collapse of bubbles in a liquid) creates extreme conditions inside the collapsing bubble and serves as the origin of most sonochemical phenomena in liquids or liquid-solid slurries. Nebulization (the creation of mist from ultrasound passing through a liquid and impinging on a liquid-gas interface) is the basis for ultrasonic spray pyrolysis with subsequent reactions occurring in the heated droplets of the mist. Cavitation-induced sonochemistry provides a unique interaction between energy and matter, with hot spots inside the bubbles of ˜5000 K, pressures of ˜1000 bar, heating and cooling rates of >1010K s-1; these extraordinary conditions permit access to a range of chemical reaction space normally not accessible, which allows for the synthesis of a wide variety of unusual chemical structures.[12]

2. MATERIALS AND METHODS

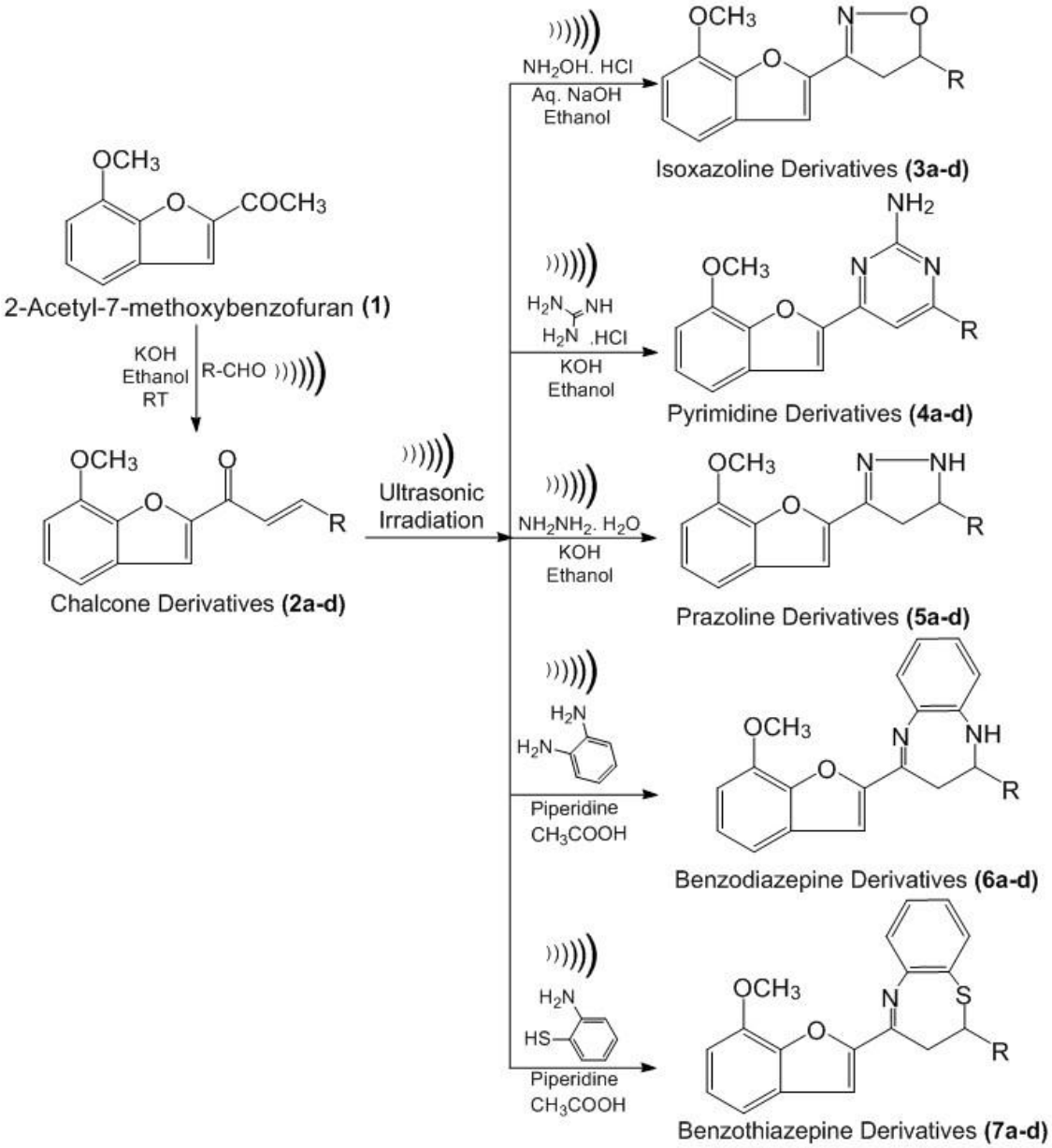
2.1. Instrumentation

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. Ultrasonication based synthesis was carried out using Model LeelaSonic-500, 500W instrument.

2.2. Synthesis

The convention organic reaction sequence planned for the preparation of title compounds is shown in **Scheme 1**, and their physical and spectroscopic data has been analysed. The ultrasound prompted organic reactions[3-10] sequence planned for the preparation of title compounds is shown in **Scheme 1**, and their physical and spectroscopic properties are depicted in **Table 1-6**.

Scheme 1. Reactions and reagents for the synthesis of titled compounds

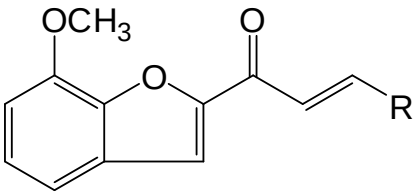


General procedure for the synthesis of Chalcones (2a-d)

Chalcones were prepared via Ultrasound (US)-promoted Claisen-Schmidt[11] condensation reaction between 2-acetyl-7-methoxylbenzofuran (1) and appropriate aromatic aldehydes (a:

Benzaldehyde, b: 3-Methoxybenzaldehyde, c: 3-Hydroxybenzaldehyde and d: 3-Fluorobenzaldehyde) in the presence of 15% potassium hydroxide solution in ethanol were subjected to US (20 kHz) irradiation at room temperature for 1 h afforded to give corresponding 1-(7-Methoxybenzofuran-2-yl)-3-(substituted)prop-2-en-1-ones (2a-d) in good yield.

Table 1: Physical and spectral characterization data of Chalcones 2a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{0}C)	Yield (%)	FT-IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm)
2a	C_6H_5	$C_{18}H_{14}O_3$	278	170	75	Chalcone 1621 (C=O) 1506 (C=C)	Chalcone Hα (7.3) Hβ (6.9)
2b	3-OMeC_6H_4	$C_{19}H_{16}O_4$	308	210	55	Chalcone 1617 (C=O) 1510 (C=C)	Chalcone Hα (7.3) Hβ (6.8)
2c	3-OHC_6H_4	$C_{18}H_{14}O_4$	294	196	67	Chalcone 1633 (C=O) 1527 (C=C)	Chalcone Hα (7.5) Hβ (6.9)
2d	3-FC_6H_4	$C_{18}H_{13}FO_3$	296	175	74	Chalcone 1645 (C=O) 1537 (C=C)	Chalcone Hα (7.7) Hβ (7.2)

Physical and spectral characterization of Chalcone (2a)

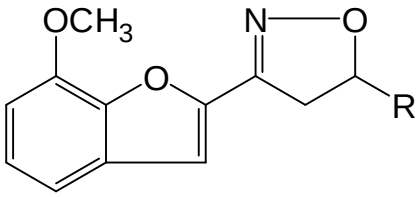
The titled compound 2a was analyzed for molecular formula $C_{18}H_{14}O_3$, m.p. 170 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm) spectra of 2a showed characteristic peaks (Table 1). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 2a was confirmed as 1-(7-methoxybenzofuran-2-yl)-3-(phenyl)prop-2-en-1-one. All the compounds synthesized in the present study (2a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 1).

General procedure for the synthesis of Isoxazolines (3a-d)

Isoxazolines were prepared by subsequent condensation reaction of chalcone derivatives (2a-d) and hydroxylamine hydrochloride with catalytic amount of 20% sodium hydroxide in

ethanol was taken in a round bottomed flask and subjected to US (20 kHz) irradiation for 2 h. Then reaction mixture was kept at room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by recrystallization from ethanol to give corresponding 3-(7-Methoxybenzofuran-2-yl)-5-substituted-4,5-dihydroisoxazoles (3a-d) in good yield.

Table 2: Physical and spectral characterization data of Isoxazolines 3a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{0}C)	Yield (%)	FT-IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm)
3a	C_6H_5	$C_{18}H_{15}NO_3$	293	182	77	Isoxazoline ring 1650 (C=N-O) 1230 (C-O-N)	Isoxazoline ring Ar-CH_2 (3.8, 3.2) Ar-CH (6.2)
3b	3-OMeC_6H_4	$C_{19}H_{17}NO_4$	323	194	61	Isoxazoline ring 1653 (C=N-O) 1232 (C-O-N)	Isoxazoline ring Ar-CH_2 (3.9, 3.2) Ar-CH (6.2)
3c	3-OHC_6H_4	$C_{18}H_{15}NO_4$	309	164	54	Isoxazoline ring 1651 (C=N-O). 1231 (C-O-N)	Isoxazoline ring Ar-CH_2 (3.9, 3.2) Ar-CH (6.2)
3d	3-FC_6H_4	$C_{18}H_{14}FNO_3$	311	122	81	Isoxazoline ring 1652 (C=N-O) 1231 (C-O-N)	Isoxazoline ring Ar-CH_2 (3.8, 3.2) Ar-CH (6.1)

Physical and spectral characterization of isoxazoline (3a)

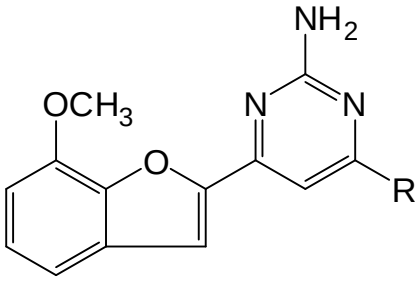
The titled compound 3a was analyzed for molecular formula $C_{18}H_{15}NO_3$, m.p. 182 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) spectra of 3a showed characteristic peaks (Table 2). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 3a was confirmed as 3-(7-methoxybenzofuran-2-yl)-5-phenyl-4,5-dihydroisoxazole (3a). All the compounds synthesized in the present study (3a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 2).

General procedure for the synthesis of Pyrimidines (4a-d)

Pyrimidines were prepared by subsequent condensation reaction of chalcone derivatives (2a-d) and guanidine hydrochloride with catalytic amount of 20% potassium hydroxide in ethanol was taken in a round bottomed flask and subjected to US (20 kHz) irradiation for 3 h. Then

reaction mixture was kept at room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by recrystallization from ethanol to give corresponding 4-(7-Methoxybenzofuran-2-yl)-6-substituted-pyrimidin-2-amines (4a-d) in good yield.

Table 3: Physical and spectral characterization data of Pyrimidines 4a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{o}C)	Yield (%)	FT-IR (KBr, ν_{max},cm^{-1})	^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm)
4a	C_6H_5	$C_{19}H_{15}N_3O_2$	317	155	81	Pyrimidine ring 1621 (C=N)	Pyrimidine ring Ar-CH (5.95)
4b	3-OMeC_6H_4	$C_{20}H_{17}N_3O_3$	347	188	51	Pyrimidine ring 1620 (C=N)	Pyrimidine ring Ar-CH (5.94)
4c	3-OHC_6H_4	$C_{19}H_{15}N_3O_3$	333	194	49	Pyrimidine ring 1624 (C=N)	Pyrimidine ring Ar-CH (5.97)
4d	3-FC_6H_4	$C_{19}H_{14}FN_3O_2$	335	167	65	Pyrimidine ring 1624 (C=N)	Pyrimidine ring Ar-CH (5.91)

Physical and spectral characterization of pyrimidine (4a)

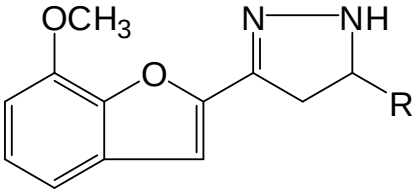
The titled compound 4a was analyzed for molecular formula $C_{19}H_{15}N_3O_2$, m.p. 155 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) spectra of 4a showed characteristic peaks (Table 3). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 4a was confirmed as 4-(7-methoxybenzofuran-2-yl)-6- phenyl-pyrimidin-2-amine (4a). All the compounds synthesized in the present study (4a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 3).

General procedure for the synthesis of Pyrazolines (5a-d)

Pyrazolines were prepared by subsequent condensation reaction of chalcone derivatives (2a-d) and guanidine hydrochloride with catalytic amount of 100% potassium hydroxide in ethanol was taken in a round bottomed flask and subjected to US (20 kHz) irradiation for 2 h. Then reaction mixture was kept at room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by

recrystallization from ethanol to give corresponding 3-(7-Methoxybenzofuran-2-yl)-5-substituted -4,5-dihydro-1H-pyrazoles (5a-d) in good yield.

Table 4: Physical and spectral characterization data of Pyrazolines 5a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{0}C)	Yield (%)	FT-IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm)
5a	C_6H_5	$C_{18}H_{16}N_2O_2$	292	233	67	Pyrazoline ring 1630 (C=N) 3241 (-NH-)	Pyrazoline ring Ar-CH_2 (3.8, 3.1) Ar-CH (5.9)
5b	3-OMeC_6H_4	$C_{19}H_{18}N_2O_3$	322	214	54	Pyrazoline ring 1621 (C=N) 3214 (-NH-)	Pyrazoline ring Ar-CH_2 (3.6, 3.4) Ar-CH (5.7)
5c	3-OHC_6H_4	$C_{18}H_{16}N_2O_3$	308	241	66	Pyrazoline ring 1622 (C=N) 3227 (-NH-)	Pyrazoline ring Ar-CH_2 (3.4, 3.8) Ar-CH (5.9)
5d	3-FC_6H_4	$C_{18}H_{15}FN_2O_2$	310	244	61	Pyrazoline ring 1621 (C=N) 3219 (-NH-)	Pyrazoline ring Ar-CH_2 (3.6, 3.3) Ar-CH (5.9)

Physical and spectral characterization of pyrazoline (5a)

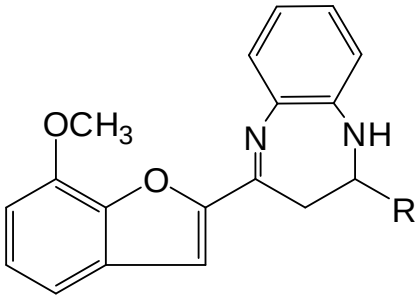
The titled compound 5a was analyzed for molecular formula $C_{18}H_{16}N_2O_2$, m.p. 233 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm) spectra of 5a showed characteristic peaks (Table 4). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 5a was confirmed as 3-(7-methoxybenzofuran-2-yl)-5- phenyl -4,5-dihydro-1H-pyrazole (5a). All the compounds synthesized in the present study (5a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 4).

General procedure for the synthesis of Benzodiazepines (6a-d)

Benzodiazepines were prepared by subsequent condensation reaction of chalcone derivatives (2a-d) and ortho-phenylenediamine with catalytic amount of acetic acid and piperidine in methanol was taken in a round bottomed flask and subjected to US (20 kHz) irradiation for 4 h. Then reaction mixture was cooled to room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by

recrystallization from ethanol to give corresponding4-(7-Methoxybenzofuran-2-yl)-2-substituted-2,3-dihydro-1H benzo[b] [1,4]diazepines (6a-d) in good yield.

Table 5: Physical and spectral characterization data of Benzodiazepines 6a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{o}C)	Yield (%)	FT-IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm)
6a	C_6H_5	$C_{24}H_{20}N_2O_2$	363	210	71	Benzodiazepine ring 1630 (C=N) 3243 (-NH-)	Benzodiazepine ring Ar-CH_2 (3.7, 3.4) Ar-CH (5.4)
6b	3-OMeC_6H_4	$C_{25}H_{22}N_2O_3$	398	199	66	Benzodiazepine ring 1622 (C=N) 3214 (-NH-)	Benzodiazepine ring Ar-CH_2 (3.7, 3.3) Ar-CH (5.4)
6c	3-OHC_6H_4	$C_{24}H_{20}N_2O_3$	384	157	57	Benzodiazepine ring 1627 (C=N) 3217 (-NH-)	Benzodiazepine ring Ar-CH_2 (3.8, 3.2) Ar-CH (5.6)
6d	3-FC_6H_4	$C_{24}H_{19}FN_2O_2$	386	188	89	Benzodiazepine ring 1622 (C=N) 3117 (-NH-)	Benzodiazepine ring Ar-CH_2 (3.3, 3.8) Ar-CH (5.6)

Physical and spectral characterization of benzodiazepine (6a)

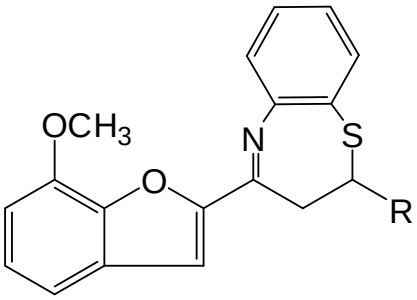
The titled compound 6a was analyzed for molecular formula $C_{24}H_{20}N_2O_2$, m.p. 210 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) spectra of 6a showed characteristic peaks (Table 5). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 6a was confirmed as 4-(7-Methoxybenzofuran-2-yl)-2-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (6a). All the compounds synthesized in the present study (6a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 5).

General procedure for the synthesis of Benzothiazepines (7a-d)

Benzothiazepines were prepared by subsequent condensation reaction of chalcone derivatives (2a-d) and ortho-aminothiophenol with catalytic amount of acetic acid and piperidine in methanol was taken in a round bottomed flask and subjected to US (20 kHz) irradiation for 4

h. Then reaction mixture was kept at room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by recrystallization from ethanol to give corresponding 4-(7-methoxybenzofuran-2-yl)-2-substituted-2,3-dihydrobenzo[b][1,4] thiazepine (7a-d) in good yield.

Table 6: Physical and spectral characterization data of Benzothiazepines 7a-d.



Code	R	Molecular Formula	MW (g)	M.p. (^{0}C)	Yield (%)	FT-IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm)
7a	C_6H_5	$C_{24}H_{19}NO_2S$	385	115	67	Benzothiazepine ring 781 (C-S) 3240 (-NH-)	Benzothiazepine ring Ar-CH_2 (3.4, 3.2) Ar-CH (6.2)
7b	3-$OMeC_6H_4$	$C_{25}H_{21}NO_3S$	415	146	64	Benzothiazepine ring 784 (C-S) 3188 (-NH-)	Benzothiazepine ring Ar-CH_2 (3.4, 3.2) Ar-CH (6.3)
7c	3-OHC_6H_4	$C_{24}H_{19}NO_3S$	401	137	51	Benzothiazepine ring 786 (C-S) 3333 (-NH-)	Benzothiazepine ring Ar-CH_2 (3.4, 3.2) Ar-CH (6.1)
7d	3-FC_6H_4	$C_{24}H_{18}FNO_2S$	403	157	67	Benzothiazepine ring 781 (C-S) 3222 (-NH-)	Benzothiazepine ring Ar-CH_2 (3.4, 3.2) Ar-CH (6.0)

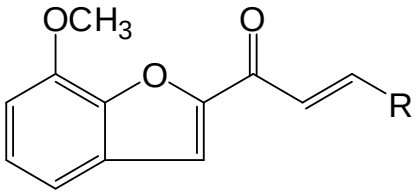
Physical and spectral characterization of benzothiazepine (7a)

The titled compound 7a was analyzed for molecular formula $C_{24}H_{19}NO_2S$, m.p. 115 ^{0}C. The FT-IR (KBr, ν_{max}, cm^{-1}) and ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) spectra of 7a showed characteristic peaks (Table 1). The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the 7a was confirmed as 4-(7-methoxybenzofuran-2-yl)-2- phenyl-2,3-dihydrobenzo[b][1,4]thiazepine (7a). All the compounds synthesized in the present study (7a-d) were characterized based on the above mentioned physical and spectroscopic methods (Table 6).

3. In vitro antitubercular activity

The *Mycobacterium tuberculosis* H37Rv inhibitory activity of a series of some chalcones (2a-d) and their heterocyclic analogs such as isoxazolines (3a-d), pyrimidines (4a-d), pyrazolines (5a-d), benzodiazepines (6a-d) and benzothiazepines (7a-d) was assessed by using micro plate Alamar Blue assay (MABA) described by Maria et al.[13] 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 **Tables 7-12 & Figures 1-6**.

Table 7: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of chalcones (2a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
2a	C_6H_5	100
2b	3-$OMeC_6H_4$	25
2c	3-OHC_6H_4	100
2d	3-FC_6H_4	6.25
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

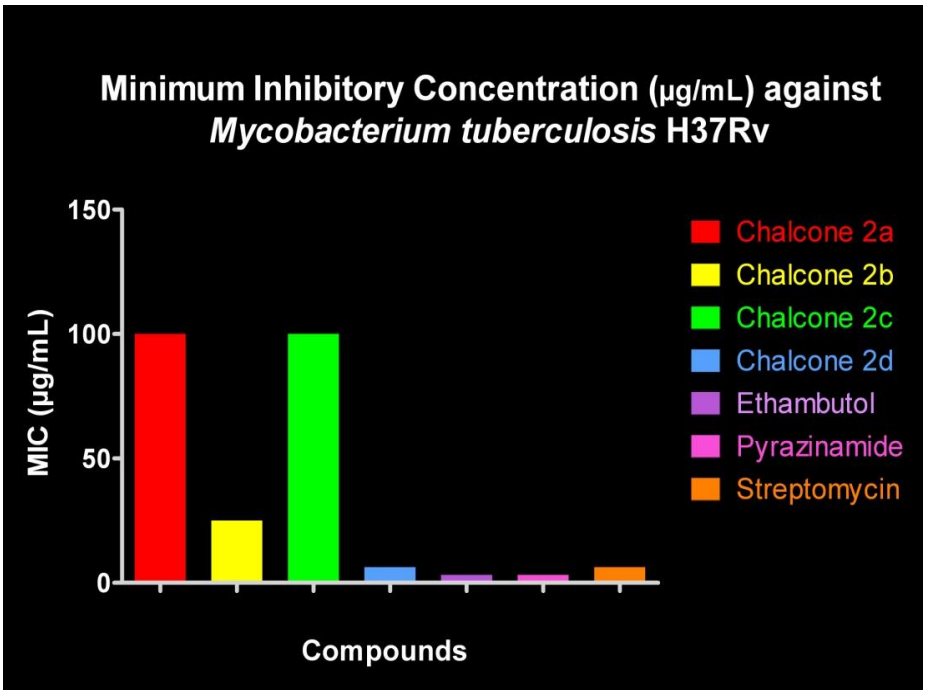


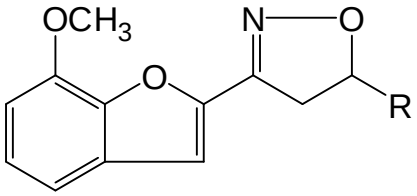
Figure 1: ***Mycobacterium tuberculosis*** **H37Rv inhibitory activity data of chalcones (2a-d).**

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **chalcones 2a-d** is illustrated in (**Table 7 & Figure 1**). The antitubercular activity screening data revealed that the compound **2d** demonstrated comparatively the most potent inhibitory activity, with MIC value **6.25 µg/mL**. It is interesting to note that the compound **2b** also showed appreciable inhibitory activity with MIC value **25 µg/mL**. The other compounds such as **2a** and **2c** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **chalcone** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-chalcone** hybrid molecules **2a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-chalcone** hybrid molecules **2a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and

mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **2d (3-FC_6H_4, 6.25 µg/mL)**.

Table 8: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of isoxazolines (3a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
3a	C_6H_5	50
3b	3-$OMeC_6H_4$	100
3c	3-OHC_6H_4	100
3d	3-FC_6H_4	25
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

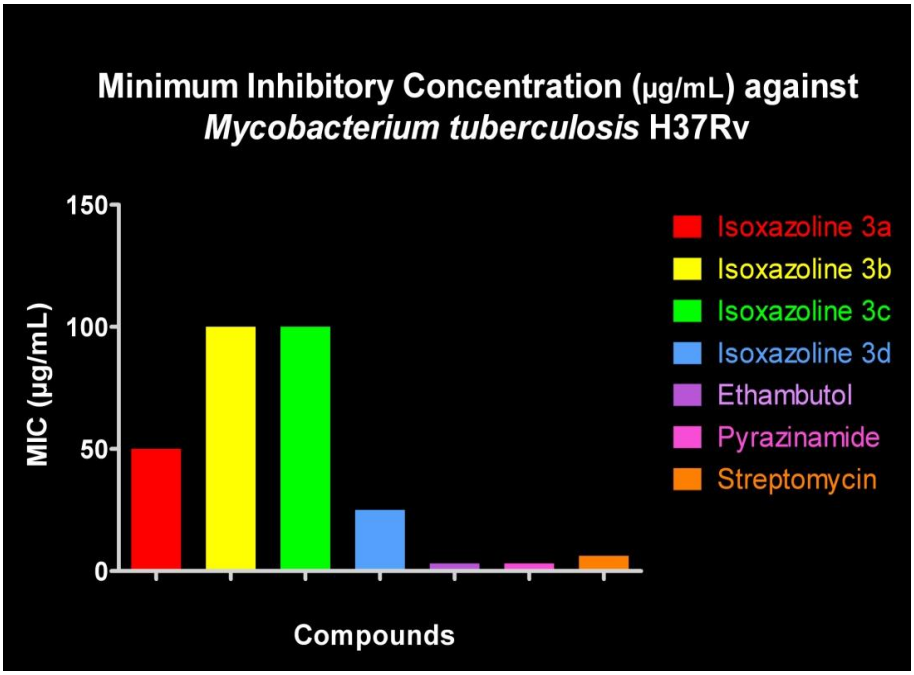


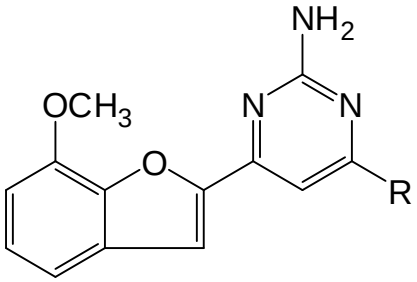
Figure 2: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of isoxazolines (3a-d).

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **isoxazolines 3a-d** is illustrated in (**Table 8 & Figure 2**). The antitubercular

activity screening data revealed that the compound **3d** demonstrated comparatively the most potent inhibitory activity, with MIC value **25 µg/mL**. It is interesting to note that the compound **3a** also showed appreciable inhibitory activity with MIC value **50 µg/mL**. The other compounds such as **3b** and **3c** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **isoxazoline** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-isoxazoline** hybrid molecules **3a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-isoxazoline** hybrid molecules **3a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **3d (3-FC_6H_4, 25 µg/mL)**.

Table 9: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of pyrimidines (4a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
4a	C_6H_5	100
4b	3-$OMeC_6H_4$	50
4c	3-OHC_6H_4	50
4d	3-FC_6H_4	12.5
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

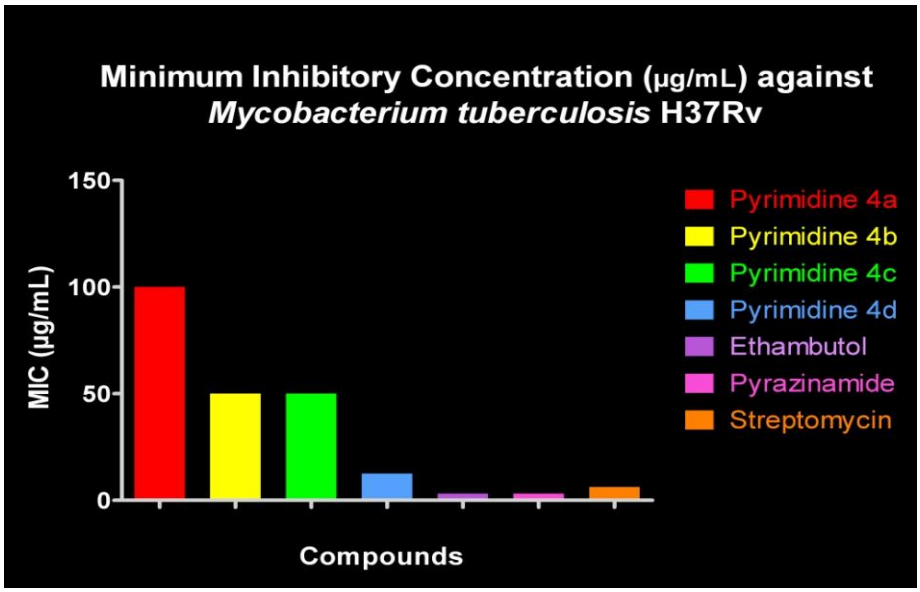
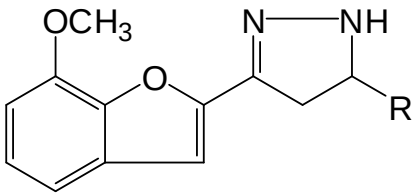


Figure 3: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of pyrimidines (4a-d).

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **pyrimidines 4a-d** is illustrated in (**Table 9 & Figure 3**). The antitubercular activity screening data revealed that the compound **4d** demonstrated comparatively the most potent inhibitory activity, with MIC value **12.5 µg/mL**. It is interesting to note that the compounds **4b and 4c** also showed appreciable inhibitory activity with MIC value **50 µg/mL**. The other compound **4a** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **pyrimidine** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-pyrimidine** hybrid molecules **4a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-pyrimidine** hybrid molecules **4a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **4d (3-FC_6H_4, 12.5 µg/mL)**.

Table 10: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of pyrazolines (5a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
5a	C_6H_5	100
5b	3-$OMeC_6H_4$	50
5c	3-OHC_6H_4	100
5d	3-FC_6H_4	25
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

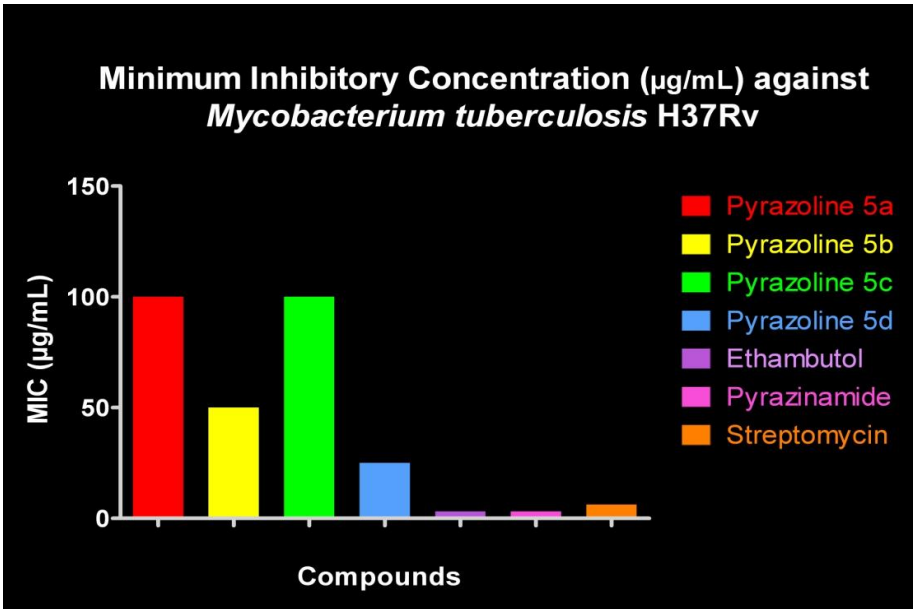


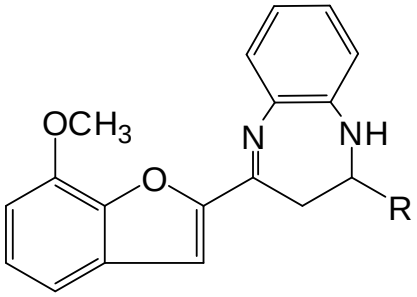
Figure 4: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of pyrazolines (5a-d).

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **pyrazolines 5a-d** is illustrated in (**Table 10 & Figure 4**). The antitubercular activity screening data revealed that the compound **5d** demonstrated comparatively the most potent inhibitory activity, with MIC value **25 µg/mL**. It is interesting to note that the compound **5b** also showed appreciable inhibitory activity with MIC value **50 µg/mL**. The other compounds **5a and 5c** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **pyrazoline** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-pyrazoline** hybrid molecules **5a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-pyrazoline** hybrid molecules **5a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **5d (3-FC_6H_4, 25 µg/mL)**.

Table 11: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of benzodiazepines (6a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
6a	C_6H_5	100
6b	3-$OMeC_6H_4$	100
6c	3-OHC_6H_4	100
6d	3-FC_6H_4	50
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

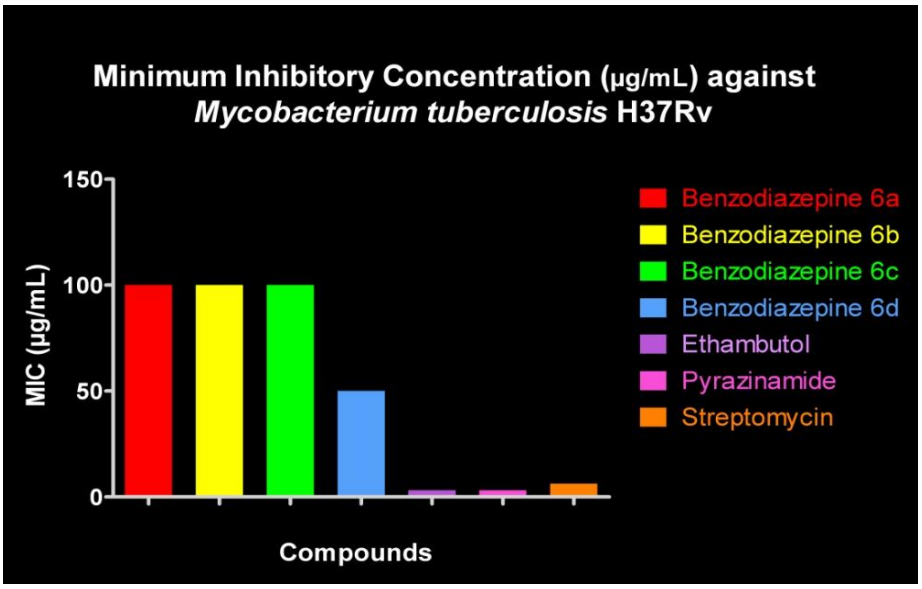
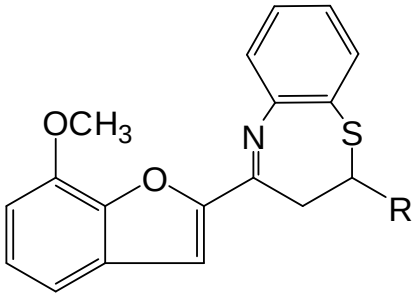


Figure 5: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of benzodiazepines (6a-d).

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **benzodiazepines 6a-d** is illustrated in (**Table 11 & Figure 5**). The antitubercular activity screening data revealed that the compound **6d** demonstrated comparatively the most potent inhibitory activity, with MIC value **50 µg/mL**. The other compounds **6a, 6b and 6c** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **benzodiazepine** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-benzodiazepine** hybrid molecules **6a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-benzodiazepine** hybrid molecules **6a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **6d (3-FC$_6$H$_4$, 50 µg/mL)**.

Table 12: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of benzothiazepines (7a-d).



Compound Code	R	Minimum Inhibitory Concentration (MIC) in (µg/mL) against *Mycobacterium tuberculosis* H37Rv
7a	C_6H_5	100
7b	3-$OMeC_6H_4$	50
7c	3-OHC_6H_4	100
7d	3-FC_6H_4	6.25
Ethambutol	-	3.125
Pyrazinamide	-	3.125
Streptomycin	-	6.25

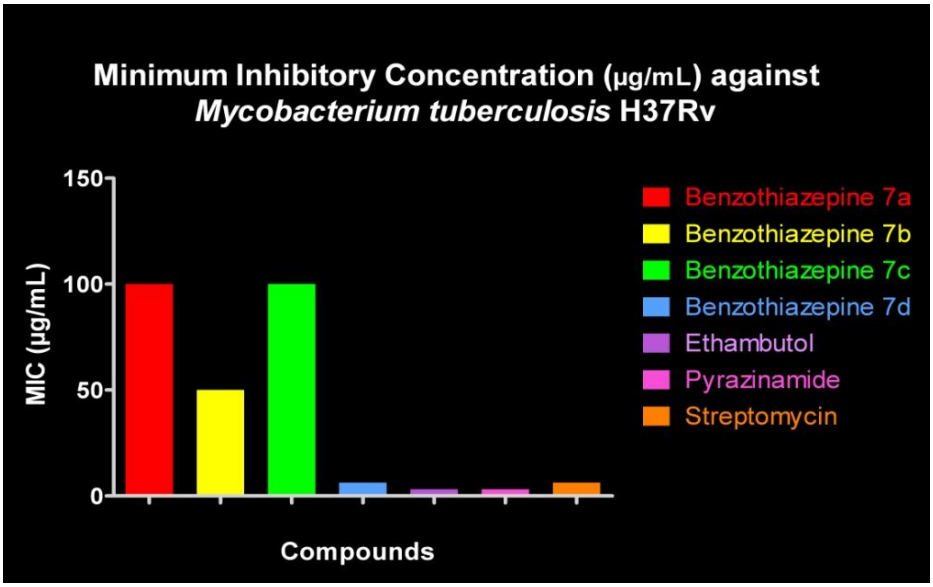


Figure 6: *Mycobacterium tuberculosis* H37Rv inhibitory activity data of benzothiazepines (7a-d).

The results of *in vitro Mycobacterium tuberculosis* (H37Rv) inhibitory activity of the synthesized **benzothiazepines 7a-d** is illustrated in (**Table 12 & Figure 6**). The antitubercular activity screening data revealed that the compound **7d** demonstrated comparatively the most potent inhibitory activity, with MIC value **6.25 µg/mL**. It is interesting to note that the compound **7b** also showed appreciable inhibitory activity with

MIC value **50 µg/mL**. The other compounds **7a and 7c** showed deprived level of activity with MIC **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 quick look 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 **benzofuran** and **benzothiazepine** moieties with MIC values range **100-3.125** µg/mL. It is noteworthy that the observed inhibitory activity of **benzofuran-benzothiazepine** hybrid molecules **7a-d** against *Mycobacterium tuberculosis* (H37Rv) revealed the importance of the type of substituted aromatic/heteroaromatic aldehyde from which the corresponding **benzofuran-benzothiazepine** hybrid molecules **7a-d** were obtained, which in some cases was enhanced by the influence of some substituents and decreased by some other substituents. The compound substituted with inductively electron withdrawing and mesomericaly electron releasing substituent was found to be biologically relevant as seen in case of compound **7d (3-FC$_6$H$_4$, 6.25 µg/mL)**, this observation possibly be the extraordinary opening position to develop a series of some new benzothiazepines consisting of benzofuran moiety as potential antitubercular agents.

4. REFERENCES

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