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Synthesis, Charectertisation and Antitubercular Evaluation of Pyarzoline Clubbed Thiazole Hybrids

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Abstract:

In our previous work, we have synthesised novel isoxazole conjugated pyrazoline derivatives by reacting isoxazolyl chalcones (1-15) with thiosemicarbazide in glacial acetic acid. From these compounds, 15 isoxazole conjugated pyrazoline carbothioamides were synthesised, compounds 24 and 25 are selected for further optimisation. In continuation to this work, pyrazoline-clubbed thiazole hybrids were synthesied by using potential antimycobacterial isoxazole conjugated pyrazoline carbothioamides – 24 and 25. The pyrazoline-1-carbothioamides- 24 (3-(isoxazol-5-yl)-5-(3,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide) and 25 (3-(isoxazol-5-yl)-5-(2,3,4-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide) were further optimized and synthesized eight more compounds (24a-24d, 25a-25d) which have a substituted thiazole ring. These compounds are purified by recrystallisation and charecterised by FT IR, ^{1}H NMR and Mass spectra. Compound 24a have shown potent antimycobacterial activity.

Keywords: Thiazole;FTIR; NMR; Mass; antitubercular activity; *Mycobacterium tuberculosis* H37Rv; MABA assay.

Introduction

Tuberculosis (TB) caused by the bacteria Mycobacterium tuberculosis (Mtb), is one of the world's most serious problems today. According to WHO forecasts, TB killed 1.4 million people in 2019, including 208,000 HIV-infected patients. The main factor guiding Mtb's supremacy over humans is its ability to dwell inside its host. It is highly skilled at eluding the host's developed immune defences against it and can exhibit transitions between the active and latent stages of the sickness. Rifampicin-resistant (RR-TB) and multidrug-resistant (MDR-TB) tuberculosis were detected in 206,030 cases globally in 2019. The number of cases reported in 2018 was 186,883, which is a 10% increase (1).

The field of medicinal chemistry has recently seen the emergence of a potential method known as molecular hybridization. This technique enables the synthesis of molecules by combining two or more heterocyclic scaffolds. The topic of drug resistance has been addressed by the use of this technique, which has been essential in the generation of potent molecules against a variety of infectious illnesses and malignancies. It is important to note that the conjugation of numerous heterocycles has been shown to have a synergistic impact on the biological activity of drugs that have recently been synthesized.

A great amount of research in the field of medicinal chemistry has been directed toward pyrazoline and thiazole derivatives because of the strong biological activity that they possess.

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Only few of the research that have shed light on the amazing antibacterial potential of these compounds (2-5). In addition, the effectiveness of these substances as antifungal agents has been shown in a number of studies (6-8). Moreover, the cytotoxic (10-13) , anticancer (14-16) and antitubercular activities (17-21) of these compounds have been demonstrated.

Our research efforts in medicinal chemistry have been oriented towards a pioneering synthesis and evaluation of pyrazoline clubbed thiazole hybrids. The purpose of this strategic endeavor was to encourage the development of powerful lead compounds that selectively target tuberculosis. We used a strategy that was founded on the utilization of molecular hybridization principles, with the objective of developing novel molecules that exhibited increased bioactivity against these essential therapeutic targets.

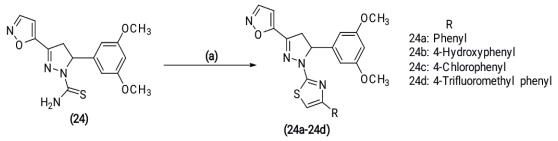
Materials and methods

General

Isoxazole-3-carbaldehyde, 4-Trifluoromethoxy acetophenone, thiosemicarbazide and substituted phenacyl bromides were purchased from Aldrich, Mumbai and remaining chemicals were obtained from local supplier-National Scientific, India. Pre-coated silica gel 60 F254 (Merck, Mumbai) and iodine crystals were purchased by silica gel-G for TLC. On a melting point device, melting points were determined in open tube capillaries and stated in °C without being adjusted. The (Shimadzu) KBr pellet technique was used to record infrared spectra. Inter standard (TMS) was used to record NMR (^1H, ^{13}C) data in $CDCl_3$ and chemical shifts are provided in units. Mass spectra was recorded on Agilent LC-MS instrument.

Synthesis of thiazole derivatives (24a - 24d) of 5 - (3, 5 - dimethoxyphenyl) -3-(isoxazol-5-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (24):

Compound 24 (1 mmol) was dissolved in 20-30 mL of ethanol and stirred at 30°C. Subsequently, the solution was refluxed (100-130°C) for 45 minutes to 1 hour in the presence of different phenacyl bromides (1 mmol). The progress of the reaction was monitored using TLC. When the reaction was completed, the reaction mixture was cooled to room temperature where we observed the formation of an impure precipitate. Further, the precipitate was filtered using a Buchner funnel and dried in a desiccator. The dried product was purified using recrystallization either by methanol or ethanol as the recrystallizing solvent to get the pure crystals of target compounds (24a-24d) (22). (Scheme 1)



Scheme 1: Synthesis of compounds 24a-24d. (a) Phenacyl bromides, ethanol, refluxed for 45 min to 1 h.

Table 1 outlines the reaction parameters, in-

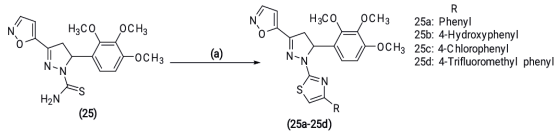
Table 1. Reaction conditions employed for the synthesis of the compounds (24a-24d)

S.No	Compound code	Reactants and Solvent	Temperature (°C)	Time (min)	Recrystallizing solvent	Yield (%)
1	**24a**	Compound **24** (1 mmol) + Phenacyl bromide; 25 mL ethanol	100	45	Methanol	71
2	**24b**	Compound **24** (1 mmol) + 4-Hydroxy phenacyl bromide; 20 mL ethanol	120	45	Methanol	61
3	**24c**	Compound **24** (1 mmol) + 4-Chlorophenacyl bromide; 25 mL ethanol	115	50	Ethanol	81
4	**24d**	Compound **24** (1 mmol) + 4-Trifluorophenacyl bromide; 30 mL ethanol	130	60	Ethanol	79

volved reagents, and the choice of recrystallization solvents applied in the production of the specified compounds, namely compounds-24a, 24b, 24c, and 24d.

Synthesis of thiazole derivatives (25a - 25d) of 3 - (isoxazol - 5 - yl) - 5 - (2,3,4 - trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (25):

Compound 25 (1 mmol) was dissolved in ethanol (20-30 mL) and stirred at 30°C. Following this, the solution was refluxed within a temperature range of 100-130°C for a duration of 45 minutes to 1 hour, employing various phenacyl bromides (1 mmol) as reactants. The progression of the reaction was traced by TLC analysis. Upon completion of the reaction, the reaction mixture was cooled to room temperature, resulting in the formation of an impure precipitate. This precipitate was isolated through filtration using a Buchner funnel and subsequently dried within a desiccator. The dried product underwent purification via recrystallization, utilizing either methanol or ethanol as the recrystallizing solvent, yielding pure crystals of the targeted compounds (25a-25d) (22). (Scheme 2)



Scheme 2: Synthesis of compounds 25a-25d. (a) Phenacyl bromides, ethanol, Reflux for 45 min to 1 h.

Table 2. Reaction conditions employed for the synthesis of the compounds **(25a-25d)**

S.No	Compound code	Reactants and Solvent	Temperature (°C)	Time (min)	Recrystallizing solvent	Yield (%)
1	**25a**	Compound **25** (1 mmol) + Phenacyl bromide; 20 mL ethanol	115	45	Ethanol	64
2	**25b**	Compound **25** (1 mmol) + 4-Hydroxy phenacyl bromide; 20 mL ethanol	110	60	Methanol	72
3	**25c**	Compound **25** (1 mmol) + 4-Chlorophenacyl bromide; 30 mL ethanol	115	45	Ethanol	82
4	**25d**	Compound **25** (1 mmol) + 4-Trifluorophenacyl bromide; 25 mL ethanol	130	50	Ethanol	80

Table 2 outlines the reaction conditions, reagents, and recrystallization solvent used for the synthesis of target compounds compounds-25a, 25b, 25c, and 25d.

5-(5-(3,5-dimethoxyphenyl)-1-(4-phenylthiazol-2-yl)-4,5-dihydro-1H-pyrazol-3-yl) isoxazole (24a): Yield 71%; m.p. 218-220 °C; FT-IR (KBr, cm^{-1}): 1548 (C=C), 1586 (C=N); 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.22-8.62(10H, Ar-H); 5.27 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 3.81 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12Hz), 3.19 (1H, H_A, dd, J_{AX} = 3.6Hz, dd, J_{AB}=16Hz), 2.48 (6H, 2x-OCH_3), 2.12 (3H, -OCH_3); Mass Analysis (m/z, %): 463.52 (M+1, 99.66); Anal. Calcd for: $C_{24}H_{22}N_4O_4S$: C, 60.26; H, 4.67; N, 11.71; Found: C, 60.72; H, 4.96; N, 11.91.

4-(2-(5-(3,5-dimethoxyphenyl)-3-(isoxazol-5-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)phenol (24b): Yield 61%; **m.p**. 256-258°C; FT-IR (KBr, cm^{-1}): 1533 (C=C), 1579 (C=N); 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.12-8.71 (11H, Ar-H); 5.26 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 5.10 (1H, Ar-OH), 3.74 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12 Hz), 3.14 (1H, H_A, dd, J_{AX} = 3.6 Hz, dd, J_{AB}=16Hz), 2.37 (6H, 2x-OCH_3); Mass Analysis (m/z, %): 449.50 (M+1, 99.41); Anal. Calcd for: $C_{24}H_{20}N_4O_4S$: C, 61.66; H, 4.52;

N, 12.53; Found: C, 61.84; H, 4.57; N, 12.75.

5-(1-(4-(4-chlorophenyl) thiazol-2-yl)-5-(3,5-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)isoxazole (24c) : Yield 81%; m.p. 193-195°C; FT-IR (KBr, cm^{-1}): 1546 (C=C), 1589 (C=N) 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.25-8.69 (11H, Ar-H); 5.29 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 3.84 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12Hz), 3.18 (1H, H_A, dd, J_{AX}= 3.6Hz, dd, J_{AB}=16Hz), 2.32 (6H, 2x-OCH_3) ; Mass Analysis (m/z, %): 466.94 (M+1, 99.66), 468.94 (M+2, 33.35); Anal. Calcd for: $C_{23}H_{19}ClN_4O_3S$: C, 59.22; H, 4.16; N, 12.12; Found: C, 59.39; H, 4.33; N, 12.20.

5-(5-(3,5-dimethoxyphenyl)-1-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)isoxazole (24d): Yield 79%; m.p. 176-178°C; FT-IR (KBr, cm^{-1}): 1548 (C=C), 1591 (C=N); 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.28-8.91 (11H, Ar-H), 5.29 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12 Hz), 3.84 (1H, H_B, dd, J_{AB} = 16 Hz, dd, J_{BX}= 12 Hz), 3.23 (1H, H_A, dd, J_{AX} = 3.6 Hz, dd, J_{AB}=16 Hz), 2.35 (6H, 2x-OCH_3); Mass Analysis (m/z, %): 501.50 (M+1, 99.35); Anal. Calcd for: $C_{24}H_{19}F_3N_4O_3S$: C, 57.66; H, 3.86; N, 11.28; Found: C, 57.85; H, 3.91; N, 11.33.

5-(1-(4-phenylthiazol-2-yl)-5-(2,3,4-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) isoxazole (25a): Yield 64%; m.p. 292-294°C ; FT-IR (KBr, cm^{-1}): 1559 (C=C), 1588 (C=N); 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.20-8.63(10H, Ar-H), 5.27 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 3.84 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12Hz), 3.13 (1H, H_A, dd, J_{AX} = 3.6Hz, dd, J_{AB}=16Hz), 2.42 (3H, -OCH_3), 2.34 (6H, 2x-OCH_3); Mass Analysis (m/z, %): 463.14 (M+1, 99.32); Anal. Calcd for: $C_{24}H_{22}N_4O_4S$: C, 62.42; H, 4.82; N, 12.18; Found: C, 62.69; H, 4.85; N, 12.25.

4-(2-(3-(isoxazol-5-yl)-5-(2,3,4-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)phenol (25b): Yield 72%; m.p. 266-268°C; FT-IR (KBr, cm^{-1}): 1535 (C=C), 1581 (C=N), 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.22-8.75 (9H, Ar-H); 5.29 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 5.12 (1H, Ar-OH), 3.68 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12 Hz), 3.16 (1H, H_A, dd, J_{AX} = 3.6 Hz, dd, J_{AB}=16Hz), 2.32 (6H, 2x-OCH_3), 2.39 (3H, -OCH_3); Mass Analysis (m/z, %): 479.13 (M+1, 99.41); Anal. Calcd for: $C_{24}H_{22}N_4O_5S$: C, 60.31; H, 4.68; N, 11.83; Found: C, 60.36; H, 4.73; N, 11.96.

5-(1-(4-(4-chlorophenyl)thiazol-2-yl)-5-(2,3,4-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)isoxazole (25c) : Yield 82%; m.p. 178-180°C; FT-IR (KBr, cm^{-1}): 1548 (C=C), 1585 (C=N), 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.28-8.77(9H, Ar-H); 5.27 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 3.86 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12Hz), 3.19 (1H, H_A, dd, J_{AX} = 3.6Hz, dd, J_{AB}=16Hz), 2.41 (3H, -OCH_3), 2.35 (6H, 2x-OCH_3); Mass Analysis (m/z, %): 497.10 (M+1, 99.71), 499.10 (M+2, 33.27); Anal. Calcd for: $C_{24}H_{21}ClN_4O_4S$: C, 58.10; H, 4.28; N, 11.29; Found: C, 58.22; H, 4.36; N, 11.35.

5-(1-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)-5-(2,3,4-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)isoxazole (25d) : Yield 80%; m.p. 158-160°C; FT-IR (KBr, cm^{-1}): 1550 (C=C), 1583 (C=N); 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.33-8.85 (9H, Ar-H); 5.31 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12 Hz), 3.86 (1H, H_B, dd, J_{AB} = 16 Hz, dd, J_{BX}= 12 Hz), 3.26 (1H, H_A, dd, J_{AX} = 3.6 Hz, dd, J_{AB}=16 Hz), 2.43 (3H, -OCH_3), 2.38 (6H, 2x-OCH_3); Mass Analysis (m/z, %): 531.12 (M+1, 99.35); Anal. Calcd for: $C_{25}H_{21}F_3N_4O_4S$: C, 56.63; H, 3.41; N, 10.61; Found: C, 56.71; H, 3.45; N, 10.79.

In vitro antitubercular activity

The antitubercular activity of the target compounds was performed by the use of Microplate Alamar Blue Assay (MABA).

Principle of MABA assay

The MABA assay is an essential method used to assess how effective compounds are against *Mycobacterium tuberculosis*, the bacterium responsible for tuberculosis. First introduced by Franzblau *et al*., (1998), this assay

works by evaluating the bacteria's metabolic activity to gauge their viability when exposed to different compounds (23). Essentially, the MABA starts by introducing the test compound to cultures of *Mycobacterium tuberculosis*. Then, a dye called Alamar Blue is added to these cultures. Alamar Blue is a dye that changes color from blue to pink when it encounters bacteria that are actively metabolizing. The effectiveness of the compound in fighting tuberculosis is measured by its ability to hinder the growth and metabolic activity of the bacteria. Consequently, the change in color shown by the Alamar Blue dye acts as a measurable indicator, showing how much the bacterial metabolic activity has reduced and giving us an idea of how well the compound works in inhibiting *Mycobacterium tuberculosis*. (23)

Protocol for the MABA assay of the compounds

Target isoxazole linked 1-carbothioamido-4,5-dihydro-1H-pyrazoles were tested for their antimycobacterial activity against the *M. tuberculosis* H37Rv strain. All medications' minimum inhibitory concentrations (MICs), or the lowest concentration of the medicine that inhibits 99% of the bacteria present at the start of the experiment, were calculated using a broth dilution test. All of the substances under study had their MICs measured and compared to those of Isoniazid. Middlebrook 7H9 broth with 10% albumin-dextrose-catalase and 0.2% glycerol was used to dilute the culture to 105 cfu mL-1 after it had been thawed. All of the working compounds were dissolved in DMSO and then diluted twice in broth to reach the required concentration. After that, 0.05 mL of standardised culture was introduced into each U-tube and the cultures were grown at 37°C for 21 days. U-tubes were used to track development, with isoniazid serving as a "positive control" and untreated inoculum serving as a "negative control" (24-26)

Results and discussion on the synthesis and characterization of pyrazoline clubbed thiazole hybrids

The synthesis of the target pyrazoline-clubbed thiazole hybrids 24a-24d and 25a-25d are represented in Schemes-1 and 2 respectively. Additionally, the melting point, percentage yield, spectral characterization and elemental analysis data are provided for all the eight compounds. All the eight compounds were synthesized by refluxing pyrazoline-1-carbothioamides (24 and 25) with different kinds of phenacyl bromides in the presence of ethanol as solvent. The yield of the eight compounds was ranging between 61-85%.

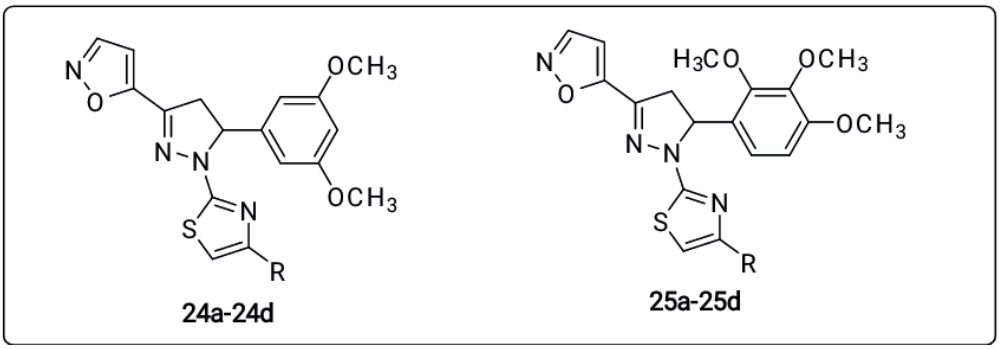
In the FT-IR spectrum of target compounds 24a-24d and 25a-25d, the disappearance of absorption band at 3369 cm^{-1} and the appearance of strong absorption bands corresponding to C=N and C=C confirmed the formation of pyrazoline clubbed thiazole hybrids. Further, the 1H NMR spectrum showed signals of pyrazoline scaffold as doublet of doublets at chemical shift values-5.26-5.35 (1H, Hx, dd, J_{AX} = 3.6Hz, dd, J_{BX}=12Hz), 3.74-3.88 (1H, H_B, dd, J_{AB} = 16Hz, dd, J_{BX}= 12Hz) and 3.16-3.29 (1H, H_A, dd, J_{AX} = 3.6Hz, dd, J_{AB}=16Hz) ppm respectively. Additional peaks pertaining to aromatic protons were seen in between 6-9 ppm. The M+1 peak in their mass spectrum confirmed the molecular weight whereas the elemental analysis data is agreement with the chemical composition of the expected structures.

To contextualize our findings, we compared our results with existing literature. Our synthesis approach aligns with methodologies utilized in prior studies (4,27). However, our spectral characterization, particularly the FT-IR and 1H NMR profiles, exhibit distinctive signals and patterns not reported previously, signifying unique structural attributes (28). Notably, the disappearance of the 3369 cm^{-1} band in our hybrids resonates with observations made by Hawaiz *et al*., (2014) in similar compound formations (29). These deviations warrant further investigation into the potential implications for biological activities and structural modifications.

Antitubercular activity

The pyrazole-1-carbothioamides 24 and 25 had shown highest antitubercular activity among the target compounds 16-30. Based on their efficient activity of the two compounds 24

Table 3. Antitubercular activity of pyrazoline clubbed thiazole hybrids (24a-24d and 25a-25d) (expressed as MIC in µg/mL)



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S.No	Compound code	R	*M. tuberculosis* H37Rv
1	**24a**	Phenyl	0.1
2	**24b**	4-Hydroxyphenyl	1
3	**24c**	4-Chlorophenyl	0.5
4	**24d**	4-Trifluoromethyl phenyl	0.5
5	**25a**	Phenyl	0.25
6	**25b**	4-Hydroxyphenyl	0.25
7	**25c**	4-Chlorophenyl	0.5
8	**25d**	4-Trifluoromethyl phenyl	1
9	**Isoniazid**	-	0.25

and 25, we further optimized and synthesized eight more compounds (24a-24d, 25a-25d) which have a substituted thiazole ring conjugated with the pyrazoline scaffold in order to improve their antitubercular potency. The activity was performed using the same protocol discussed by other researchers (30-32) i.e MABA assay and the positive control used in the study was isoniazid. The results of antitubercular activity of the pyrazoline conjugated thiazoles (24a-24d, 25a-25d) are summarized in Table 3.

The synthesized eight new compounds (24a-24d, 25a-25d) were evaluated for antitubercular activity using isoniazid as a positive control. Among the four compounds in 24a-24d, the activity of compound 24a is same as compared to 24. The compounds 24b, 24c and 24d had reduced activity than 24 with an MIC value of 0.1 µg/mL, 0.5 µg/mL and 0.5 µg/mL respectively. The above results suggest that the conversion of pyrazoline carbothioamide to pyrazoline conjugated thiazole is not a much useful strategy to enhance the antitubercular potency. However, the retaining of the activity of compound 24a with MIC value 0.1 µg/mL is interesting and this compound may be explored further by substituting the phenyl ring on the ortho, meta and para-positions with groups other than -OH, -Cl and -CF_3.

The compounds 25a and 25b had shown same antitubercular potency as that of the compound 25 with an MIC of 0.25 µg/mL whereas the compounds 25c and 25d had an antitubercular potency of 0.5 and 1 µg/mL which

is less than the lead compound 25. This shows that the modification of compound 25 to 25c and 25d is not a much useful strategy for increasing the antitubercular potency of the synthesized pyrazoline conjugated thiazole derivatives. However, the similar potency of the derivatives 25a and 25b indicates that the phenyl ring on the thiazole scaffold can be incorporated with other kinds of small polar substituents that may have marginal effect on improving the activity.

In assessing the antitubercular efficacy of the synthesized pyrazoline-conjugated thiazole derivatives, our study revealed noteworthy comparisons to existing literature. According to Dawood et al., (2023), a similar strategy employing pyrazoline-thiazole derivatives demonstrated varied outcomes in contrast to our findings. Within our synthesized compounds, 24a manifested sustained potency akin to the lead compound 24, suggesting promising potential (Dawood et al., 2023). However, the conversion of pyrazoline carbothioamide to pyrazoline-conjugated thiazole, as explored in compounds 24b, 24c and 24d, resulted in decreased antitubercular activity compared to compound 24, diverging from the expected enhancement strategy (Dawood et al., 2023).

Regarding compounds 25a-25d, comparative findings from Bhandare et al., (2022) align with our observations to a certain extent. Both our study and study of Bhandare et al., (2022) research reported analogous antitubercular potency for compounds 25a and 25b, maintaining equivalence to compound 25. However, the alteration from compounds 25a and 25b to 25c and 25d within our synthesized derivatives led to reduced antitubercular efficacy (33).

Our results suggest potential avenues for further exploration. Specifically, the sustenance of activity in compound 24a proposes an avenue for future investigation by substituting the phenyl ring at various positions with alternate groups, as proposed by Sever et al., (2019). Sever et al.'s work indicated that diversifying substituents on the phenyl ring might yield improvements in the antitubercular properties of pyrazoline-thiazole derivatives (10).

Conclusion

A novel series of pyrazoline-clubbed thiazole hybrids were synthesied by using potential antimycobacterial isoxazole conjugated pyrazoline carbothioamides – 24 and 25 of our previous work. Among 8 compounds (24a, 24b,24c and 24d) synthesised by thiazole linking, 24a exhibited potent antimycobacterial agent bearing phenyl subtituent at 4th position of thiazole ring with an MIC at 0.1 µg/mL which is better than Isoniazid. Further studies are underway to know about the possible mode of action of the optimised compound.

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