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The Recent Outstanding Medicinal Activity of 2-(Aryl/Heteroaryl)Thiazolidine-4-One Derivatives as Antituberculous Agents

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Abstract

Indeed, the scaffold of thiazolidin-4-one (4-oxo-thiazolidine) has garnered significant interest in the medicinal chemistry due to its versatility and diverse biological activities, including potential applications in anti-tuberculosis (anti-TB) drug discovery. Its structural properties enable modifications, facilitating the development of various small molecules with desirable pharmacological properties. The review outlines the various medical uses, (anti-TB properties), of thiazolidin-4-derived compounds over the past two decades, highlighting promising candidates such as **53a**, **53b**, and **53d**, which have demonstrated MICs (0.05-0.2) µg/ml against the strain of *M. TB* H37Rv, along with compound 108 exhibiting a MIC of 0.36 mM. Additionally, compounds **55b, 56, 54k** and **54i** have shown full effectiveness against Mycobacterium TB (*H37Ra)*, with MIC (0.031-0.125) µg/ml. Acidomycin has exhibited high activity against MDR and XDR as a various strains. This review also explores SAR of the tested compounds and their potential targets.

Keywords: medicinal activity;Anti-TB activity; Thiazolidin-4-ones; Anti-cancer; SAR

1. Introduction

Tuberculosis (TB) is actually a chronic disease, not an acute one, caused primarily by Mycobacterium TB. Additionally, more than 1.3 million people died from TB in 2022 (including 167,000 people infected with HIV). Moreover, globally, tuberculosis is the second most important killer infectious disease after Covid-19 (above HIV and AIDS) [1–6].

According to the World TB Report, TB has caused approximately 1.2 million human deaths among HIV-negative individuals and an additional 251,000 human deaths among HIV-infected persons. Although there's been a slight decrease compared to the data in the 2018 report [7], the coexistence of HIV and TB can worsen the disease process, impacting both TB and the viral infection [8].

The official global estimates indicate that more than 10 million people are confirmed to have TB each year [6], amounting to more than 130 patients per 100,000 population. Additionally, TB is indeed considered one of the most drug-resistant diseases, posing a severe threat to humanity. The global report for 2019 [6] showed that 500,000 people were infected with TB resistant to the drug rifampicin, comprising 78% of cases. Furthermore, 3.4% of human cases of TB and 18% of vial-treated cases are multidrug- or rifampicin-resistant (RR-TB) [6].

It's fascinating how modern organic compounds are being investigated for various therapeutic purposes like anti-cancer, anti-inflammatory, analgesic, and antimicrobial activities, aligning with the versatile nature of peptides in medical research. This broad approach opens up numerous potential applications [9-22].

The development and optimization of TB drugs and molecular targets is crucial for various reasons: to reduce the duration of treatment, target different TB strains (MDR and XDR).

The discussed compounds effectively control latent TB, without antagonizing other anti-TB drugs, and are compatible with various anti-HIV therapies [23]. The approach involves discovering a variety of newly synthesized compounds by building upon previously known derivatives with high biological activity. Over the last decade, there has been significant interest among researchers in molecules with small structural sizes containing five-membered heterocyclic moieties for designing therapeutic agents, including the thiazolidine-4-one model. Thiazolidine-4 is characterized by a pentagonal ring with (S / N / CO) at positions 1, 3, and 4, respectively (Figure 1).

Thiazolidine-4-one derivatives are already distinguished compounds with significant biological effects in the fields of medicinal and pharmaceutical chemistry. They exhibit diverse biological activities as documented in various biological journals. For instance, they function as anticancer agents against various cancer cells [24-27] and demonstrate potent antimicrobial activity [28-32], anti-inflammatory [33, 34], antiviral [35], anti-Toxoplasma gondii [36, 37], and antitrypanosomal activities [38].

It's noted that some derivatives of thiazolidine-4-one are already available on the global market, including ralitoline (an

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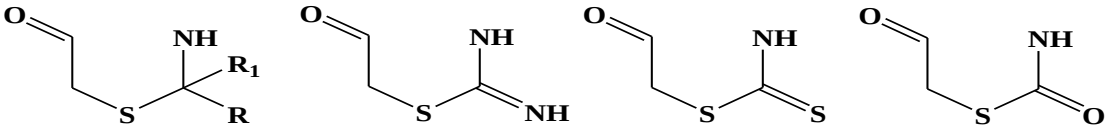
anticonvulsant), etozoline (a diuretic), and pioglitazone (a hypoglycemic agent). Thiazolidinedione-4 demonstrates diverse effects through various molecular targets, (PPARγ, ALR2, COX-2 and PI3K-γ). This versatility in molecular targets contributes to the broad spectrum of biological activities exhibited by thiazolidin-4-ones [39].



R, R1=Alk, Ar, Het.

Figure 1; Structures of the 4-oxo-thiazolidine derivatives.

Indeed, thiazolidine-4-ones exert their effects through various molecular targets, including MEK, Pim 1- 3, PTP1B and MurD ligase, among others. These diverse molecular targets contribute to the increased efficiency of 4-oxo-thiazolidine, making it very promising and scalable drug candidates in multiple therapeutic areas [40, 41].

Previous information on thiazolidine-4 derivatives regarding their potent anti-TB properties was very diverse and also incomplete [42-45]. In addition, data on thiazolidin-4-ones (4-oxo-thiazolidines) and the study of their biological activity as potent anti-TB agents are either very scarce or, on the other hand, distinctly absent from current reviews [40, 41, 47-49]. However, highlighting the last two decades, researchers have observed that there is a very clear increase in the biological effect of 4-oxo-thiazolidine derivatives as anti-TB compounds, and the results have shown that some 4-oxo-thiazolidine derivatives have promising potential. This study aims to collect, analyze, and then organize all information about their biological activity and their various anti-TB effects of thiazolidines and their derivatives as reported (2000 – 2020). This effort seeks to provide a comprehensive understanding of the potential of thiazolidine-4 in combating TB.

2. The general medicinal properties of the 4-oxo-thiazolidine

The 4-oxo-thiazolidine moiety has several medicinal properties and is known for its diverse biological activities, including antibacterial, antifungal, antiviral, anti-inflammatory, antitumor, and antidiabetic effects. These properties make it a promising scaffold for the development of novel therapeutic agents.

Many medical discoveries and academic research have been conducted on the compound 4-thiazolidinone and other heterocyclic compounds based on it. It has been found that these various precursors have a diverse and very promising biological and medical effect, which has already been proven to work with high efficiency as anti-inflammatory and anti-inflammatory agents. Oncology, antimicrobial, antidiabetic, and antibacterial [50-52], 1960s, which showed that there was a rapid growth in the number of scientific papers in the medical field [53], many reviews and also many different patents covering various 4-thiazolidinone derivatives [54-59].

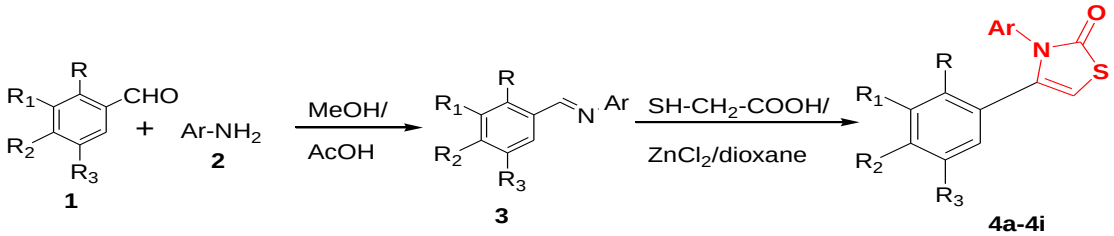
3. Medicinal properties of the 2-alkyl 4-oxo-thiazolidine, as anti-TB.

3.1. 2, 3-Diarylthiazolidin-4-one derivatives

Hetaryl substitutes containing in particular 1, 3-thiazolidine-4-one derivatives with various heterocyclic moieties such as imidazole [60], thiazole [61, 62], benzimidazole [63], acridine [64], 4(3H)-Quinazolinone [65], triazine derivatives, pyridine [66], or diazine have demonstrated potent antibacterial [67-69]. Most of the mentioned 2, 3-diaryl-(1, 3) - 4-oxo-thiazolidine derivatives have very diverse medical uses in human therapeutic terms (as promising potential drugs), including various strains of the antimicrobial, human antitumor properties and anti-HIV virus.

Additionally, they have effects on CNS, such as anticonvulsant and hypnotic effects [70–73].

Moreover, these derivatives was identified and have been shown to have an effective role as potent inhibitors of the bacterial enzyme Mur B, and indeed it has been proven that Mur B is essential in the process of peptidoglycan biosynthesis. Suggesting their potential as antibacterial agents. Laboratory tests have shown promising antibacterial activity for certain derivatives, highlighting their potential in combating bacterial infections [74].



Scheme 1; Synthesis of the 2, 3-diaryl-(1, 3) - 4-oxo-thiazolidine (4a–4i).

Table 1; the inhibition zone (diameter, mm)

No.	Ar -	- R	- R_1	- R_2	- R_3	*E. coli*	*B. subtillis*	*S. typhi*
3-a	Antipyrine	H	OCH_3	OH	I	20	17	21
3-b	2,6-Dichlorophenyl	H	OCH_3	OH	I	27	22	14
3-c	1,2,4-Triazole	H	OCH_3	OH	I	20	19	19
3d	Antipyrine	H	OCH_3	OH	Br	15	20	18
3e	2,6-Dichlorophenyl	H	OCH_3	OH	Br	23	22	16
3-f	1, 2, 4 - Triazole	H	OCH_3	OH	Br	21	16	18
3-g	Antipyrine	OH	I	H	I	14	18	17
3-h	2,6-Dichlorophenyl	OH	I	H	I	19	16	22
3-I	1,2,4-Triazole	OH	I	H	I	18	20	21
4-a	Antipyrine	H	OCH_3	OH	I	14	18	20
4-b	2,6-Dichlorophenyl	H	OCH_3	OH	I	21	19	14
4-c	1, 2, 4 - Triazole	H	OCH_3	OH	I	20	18	19
4-d	Antipyrine	H	OCH_3	OH	Br	13	20	23
4-e	2,6-Dichlorophenyl	H	OCH_3	OH	Br	21	23	13
4-f	1, 2, 4 - Triazole	H	OCH_3	OH	Br	15	17	24
4-g	Antipyrine	OH	I	H	I	27	24	25
4-h	2,6-Dichlorophenyl	OH	I	H	I	19	16	15
4-i	1, 2, 4 - Triazole	OH	I	H	I	25	23	21
	Tetracycline					**30**	**25**	**28**

The compounds have recently been biologically tested for antibacterial against (E. coli, B. subtilis and S. typhi), for example, at concentrations ranging from (50 to 100) µg/ml [75].

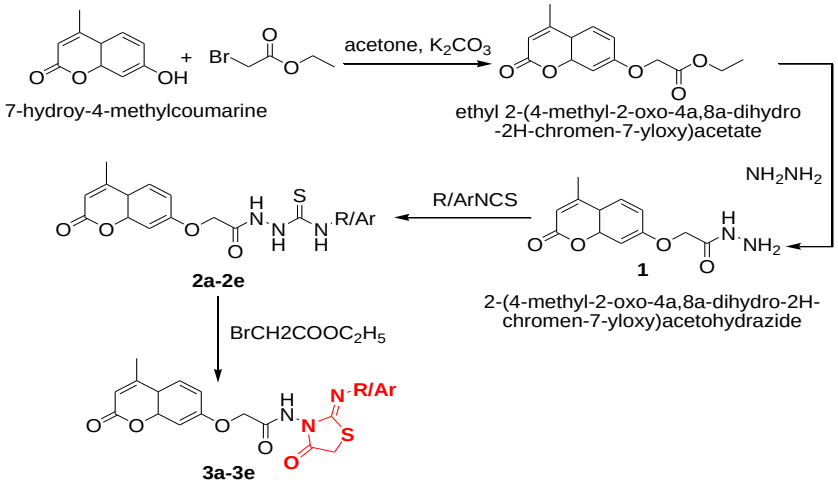
All the compounds were found to have significant activity against bacteria, with a (MIC, 50 µg/mL), comparable to the drug known as tetracycline, which served as the popular standard drug. In addition, the variation of inhibition of some of the tested compounds was demonstrated, as shown in (Table 1).

It has also been discovered that modern compounds have very promising antibacterial against various bacterial strains, were also tested using (ADM method, 50 - 100 µg/ml).

All compounds demonstrated a good activity against the bacteria, with MIC (50 µg/mL), compared to the standard drug, tetracycline. Moreover, the degree of inhibition among the biologically tested compounds exhibited significant variation, indicating differing levels of effectiveness against the tested bacterial strains, as outlined in (Table 1).

Thiosemicarbazides (Aminothiourea) It was noted that it has promising scavenging activity against DPPH radicals and galphenoxyls compared to 4-thiazolidinone. In fact, some thiosemicarbazides have shown activity similar to or even superior to ascorbic acid. Furthermore, in tests of antifungal assay against many fungus, thiosemicarbazides have showed promising results [76].

The 2-alkyl thiazolidin-4-ones encompass a range of derivatives with varied alkyl, aryl and heteryl moieties, which have demonstrated anti-TB activity. These derivatives constitute a diverse class of compounds with potential therapeutic benefits against TB. The study conducted by Subhedar et al. [77] highlights the preparation and is followed by a detailed study as anti - TB of 2,3-diaryl-(4-oxo-thiazolidine) derivatives. The composites were synthesized by Subhedar et al. [77] by reaction with thioglycolic acid. Among the evaluated derivatives, compounds (1a-1e), (Figure 2), exhibited promising as anti-TB agent (M. TB and M. bovis), with IC50 (2.2 - 8.9) µg/ml. Additionally, they showed selectivity towards dormant M. TB strains, but did not display significant as antibacterial agents. Anju et al. [78] further modified these derivatives through Mannich reaction the (4-oxo-thiazolidine) moiety at active center (position 5).

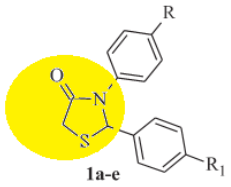


R/Ar: 3a – methyl; 3b – ethyl; 3c – phenyl; 3d – p-tolyl; 3e – p- methoxyphenyl.

Scheme 2; Synthesis of derivatives (3a-3e and 2a-2e)

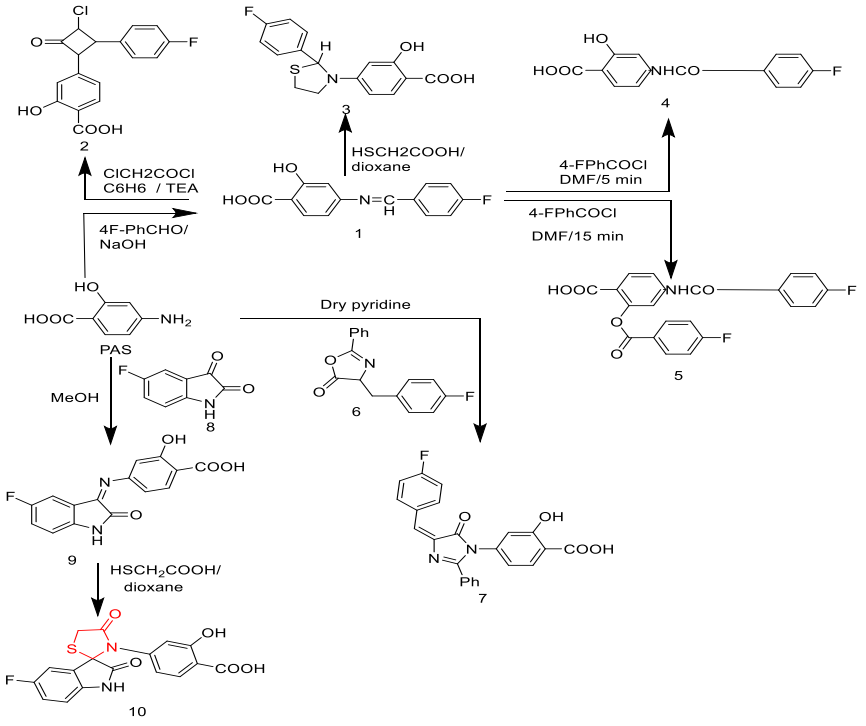
The mentioned derivatives have been assessed for their high efficacy against M. TB H37Rv.

In addition, these derivatives numbered (2 – 10) are synthesized by reacting various amino acids with salicylic acid (PAS) to close the ring. These reactions involved subjecting the Schiff base of PAS to cyclization occurs, resulting in the formation of an azetidinone moiety 2, (4-oxo-thiazolidine) 3 and a spiro-fluoroindolothiazoline-dione 10. In addition, the reaction between PAS, p-Fluorobenzoyl chloride and 5-oxazolinon led to obtaining various derivatives Nos. 4, 5 and 7. Some of these compounds exhibited significant inhibition against Mycobacterium strains, with favorable log P values, indicating potential as antitubercular agents, as observed in (Tables 2 and 3) [79].



1a: R=OCH_3, R1=H; 1b: R=H, R1=Cl; 1c: R=H, R1= OCH3; 1d: R=H, R1=F; 1e: R=H, R1=Br.

Figure 2; The general structures of 2, 3-diaryl (4-oxo-thiazolidine) (1a-1e).



Scheme 3; the general procedure for Synthesis of p-amino salicylic acids **(2- 10)**.

Table 2; Anti-TB screening results for compounds **1-10 (first level)**

Compound	MIC (µg/mL)[a]	GI[b]
1	< 6.25	95 %
2	< 6.25	96 %
3	< 6.25	98 %
4	< 6.25	98 %
5	< 6.25	98 %
7	< 6.25	94 %
9	< 6.25	94 %
10	< 6.25	98 %

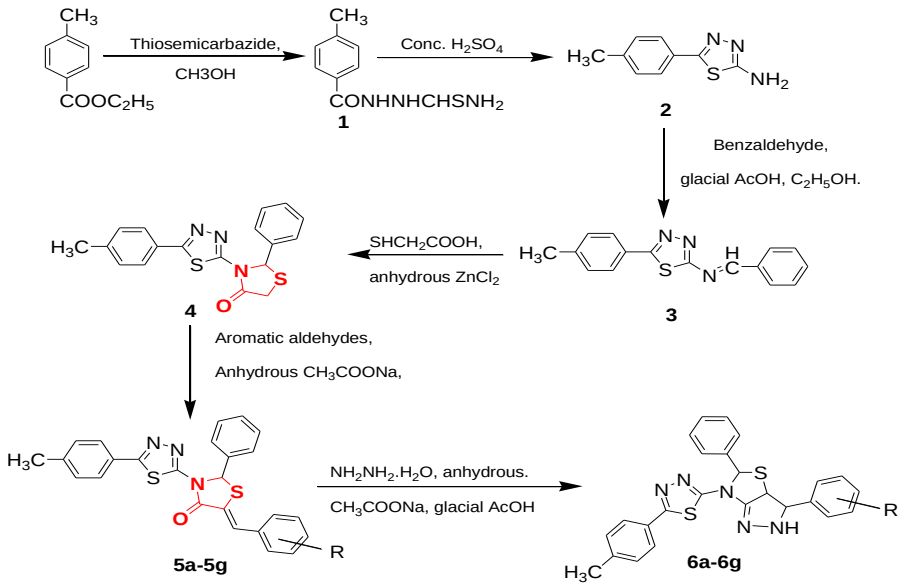
a= MIC of Rifampicin: 0.125–0.25 µg/mL versus *M. TB* H37Rv.
b= H37Rv strains of *M. TB*.

Table 3: Anti-TB screening results for compounds **1-10 (second level)**

Compound	MIC (µg/mL)[a]	IC_{50} (µg/mL)[a]	SI (IC_{50}/MIC)	log p[b]
3	< 6.25	29	4.64	2.82
4	< 6.25	27	4.32	2.17
5	< 4.25	14	3.29	4.2
10	< 6.25	27	4.32	1.93

a = MABA assay; b = Calculated log *P*.

The synthesis involves reacting the analogues of 1, 3, 4-thiadiazol-2-yl) - (4-oxo-thiazolidine) moiety (5a-g) in the presence of hydrazine hydrate to produce compounds 6a-g. On the other hand, all compounds were evaluated for their biological activity as antimicrobial as well as anti-TB. Some of the tested compounds showed significant biological activities, such as antimicrobial and anti-TB, and it is worth noting that they proved to be superior to standard drugs. This indicates their potential as promising therapeutic agents against various microbial infections and TB (Tables 4 and 5). [80].



(5a, 6a), R=4-Cl; (5b, 6b), R=4-NO2; (5c, 6c), R= 4-N (CH3)2; (5d, 6d), R= 3-NO2; (5e, 6e), R= 4-OCH3; (5f, 6f), R= 3, 4, 5-(OCH3)3; (5g, 6g), R= 4-Br.

Scheme 4; Synthesis of compounds (**6a–g**).

Based on the information provided, it seems that compound 2 (Figure 3) displayed weak anti-mycobacterial activity with a MIC of 25 µg/ml. However, when the coumarin moiety was substituted at position 2 instead of the aryl group of the thiazolidinedi-4-one ring (as shown in Fig. 4), it did not enhance the antimycobacterial activity. Out of the 15 compounds tested, only three compounds (3a-3c) give a good anti-TB (MIC, 25 µg/ml). It appears that these three compounds were more effective against mycobacteria compared to compound 2 and its coumarin derivative [81].

The anti-TB activities were evaluated against the M. TB H37Rv, by using the assay in type Microplate Alamar Blue, (MABA). Compound 4, which is 2-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-1, 3-thiazolidin-4-one (as shown in Figure 4), demonstrated slightly better anti-TB activity against M. TB H37Rv compared to other compounds tested in the study [82]. Compound 4 displayed significant inhibition of mycobacterial growth, achieving 99% inhibition at 12.5 µg/ml.

Makki et al. [83] it was reported in 2013 that the moiety of 4-fluoro-phenyl was replaced from position no. 3 to position no. 2 of the 4-oxo-thiazolidine ring, 5 (Figure 4). This change in the chemical structure led to a significant improvement in the biological effect (equivalent to 2-fold), with an MIC (6.25 µg/ml), against M. TB, which is compared to the original derivative (4) [84].The newly synthesized series comprises 12 compounds of 3-phenyl-2-(4-(tetrazolo [1, 5-a] quinoline-4-ylmethoxy) phenyl) thiazolidinedi-4-ones. Among these, derivatives 6a-6c, (Figure 5), displayed promising anti-TB activity against M. bovis (BCG), with MIC values of 9.13, 7.09, and 3.80 µg/ml, respectively, it is superior to pyrazinamide (called an anti-infective drug), used as a reference, (MIC 20 µg/ml). On the other hand, derivative 6c also showed a MIC (20.34 µg/ml), against M. TB.Conversely, replacing the aryl group at position 2 with an alkyl carboxy group did not enhance antibacterial activity, as observed with compounds 7 and 8 (depicted in Figure 6), both showing an MIC of 25 µg/ml against M. TB (H37Ra) [85]. Thiazolidin-4-ones (4-oxo-thiazolidine) incorporating sulfamethoxazole (as depicted in (Figure 7) exhibited significantly better ant-TB activity. It is worth noting that the five-digit derivatives, (9a-9e), showed significant activity against M. bovis, IC90 values (0.058 - 0.22 µg/ml), and against M. TB (H37Ra), with IC90 values (0.43 to 5.31 µg/ml) [86]. Among them, compound 9e, at position 2 of thiazolidinedi-4-one, is replaced by a 2, 6-difluorophenyl group and the activity is obviously increased, IC90 (0.058, 0.43 µg/ml), against (BCG and H37Ra), respectively.

Table 4; Antimicrobial screening results for compounds **6a–g** (MIC lg/ml).

Comp no. 6	*B. subtilis*	*B. thuringiensis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*B. fabae*	*F. oxysporam*
a	3.125	6.25	12.5	6.25	3.125	12.5	6.25
b	3.125	3.125	6.25	12.5	12.5	25	25
c	25	25	50	25	12.5	12.5	25
d	6.25	6.25	12.5	12.5	25	50	25
e	12.5	25	25	50	3.125	3.125	6.25
f	12.5	12.5	12.5	50	3.125	3.125	3.125
g	3.125	3.125	3.125	3.125	25	12.5	25
Streptomycin	3.125	6.25	6.25	6.25	NA[a]	NA[a]	NA[a]
Treflu can	NA[a]	NA[a]	NA[a]	NA[a]	3.125	3.125	3.125

[a] Not Active. [b] *B. subtilis* (MTCC No: 1133), *B. thuringiensis* (MTCC No: 4714), *E. coli* (MTCC No: 443), and *P.aeruginosa* (MTCC No: 2297). [c] *C. albicans* (MTCC No: 183), *B. fabae* (ATCC No: 14862) and *F. oxysporam* (MTCC No: 7392).

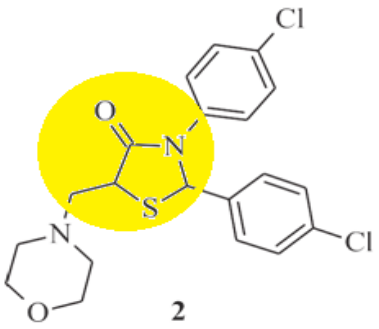


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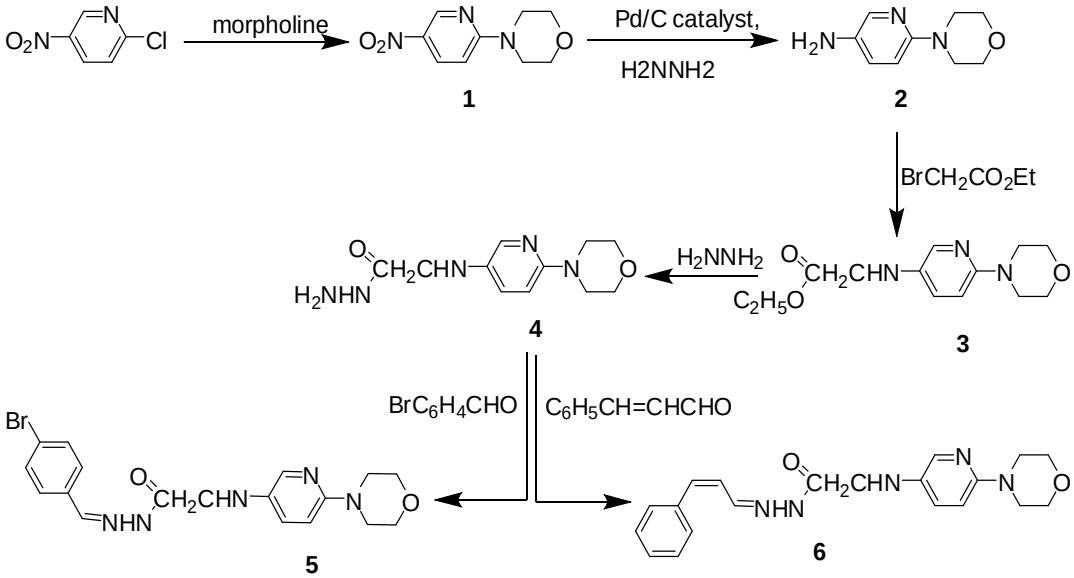
Figure 3; the structure of derivative **2**.

Table 5; Anti-TB screening results for compounds (**6a–6g),** (MIC lg/ml).

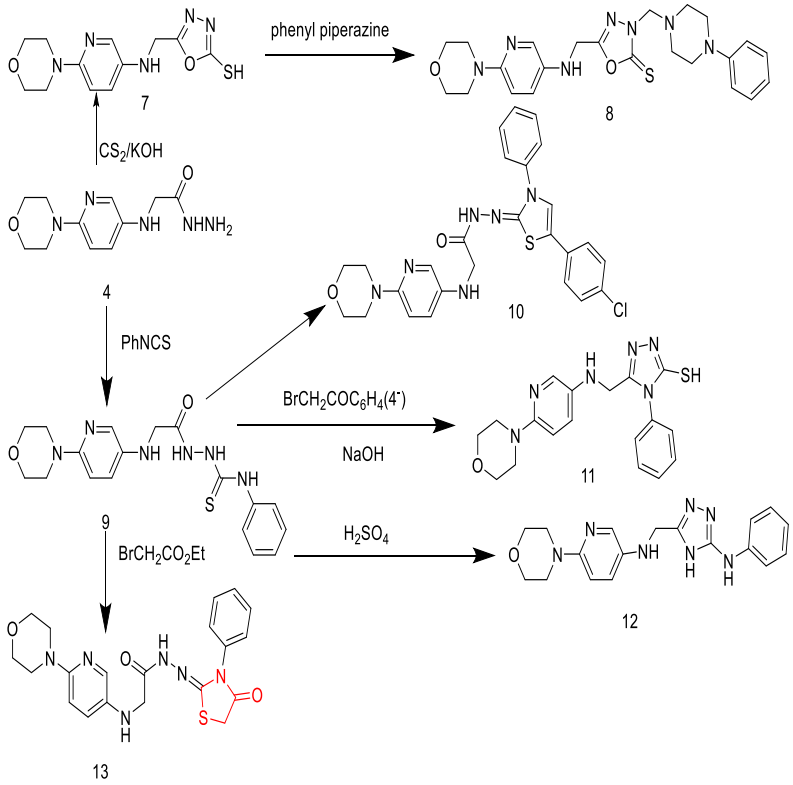
No.	Compounds	MIC (lg/ml) $H_{37}Rv$
1	6a	= 6.25
2	6b	= 3.125
3	6c	= 25
4	6d	> 6.25
5	6e	> 25
6	6f	= 25

The synthesis of acetohydrazide analogue (compound 4) involved several steps. It started with the conversion of 6-morpholin-4-ylpyridin-3-amine (compound 2) to the ester (compound 3), which was then transformed into Schiff bases (compounds 5 and 6). Moreover, in 2013 [87], a carbamide compound (9) was obtained by Bektaş et al., when hydrazine was reacted with phenyl isothiocyanate, which suggests that the reaction involved the formation of a thiocarbonyl group. It is likely that the hydrazide reacted with phenylisothiocyanate through a nucleophilic addition-elimination mechanism, resulting in the formation of carbothiamide. Compound 9 can be further modified to obtain different derivatives. Treatment of compound 9 with NaOH leads to the formation of a 1, 2, 4-triazole derivative (compound 11). This indicates that there was a reaction involving the replacement of the sulfur atom in compound 9 with an oxygen atom from NaOH, resulting in the formation of a triazole ring. Moreover, reacting the last derivative (9), with strong acid (H2SO4) leads to formation of a 1, 3, 4-thiadiazole derivative (compound 12). This suggests that there was a reaction involving cyclization and elimination reactions under acidic conditions, leading to the formation of a thiadiazole ring. These reactions indicate that compound 9 can serve as a versatile intermediate for synthesizing different derivatives by modifying its functional groups through appropriate reagents and conditions. It would be interesting to investigate the properties and activities of these derivatives in relevant applications or biological assays.

The cyclocondensation reaction of the last derivative (9), with 4-chloro-phenacyl bromide and / or ethyl bromoacetate yielded a derivative of the 1,3-thiazole moiety (compound 10) or a 1,3-thiazolidine derivative (compound 13), respectively. The novel derivatives were then screened for their antimicrobial and antiurease activities. Some of these compounds showed activity against M. smegmatis, as well as against C. albicans and S. cerevisiae, albeit in high concentrations. Compound 10 showed the highest efficacy, showing enzyme inhibitory activity with an IC50 at 2.37 ± 0.19 μM, (Tables 6 and 7), [87].



Scheme 5; Synthetic pathway for the preparation of compounds (**1–6**)



Scheme 6; Synthetic route for preparing compounds (**7-13**).

Table 6; Study of the antimicrobial effect of the new 11 analogues **(3-13,** lg/ml)

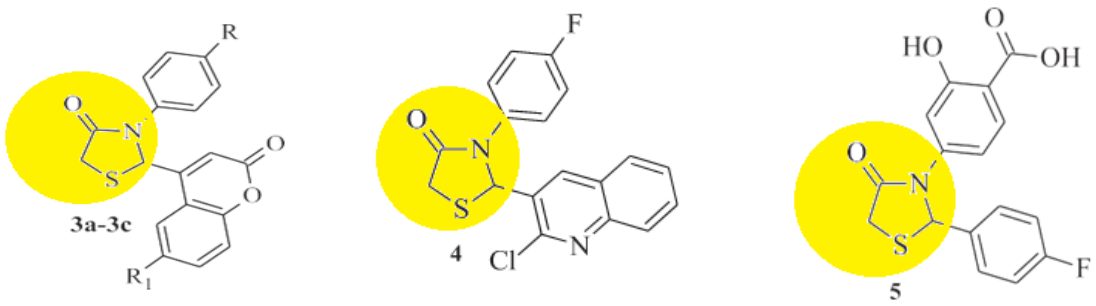
Comp. no	(MIC and Microorganisms)								
	Ec	**Yp**	**Pa**	**Ef**	**Sa**	**Bc**	**Ms**	**Ca**	**Sc**
3	–	–	–	–	–	–	125	1,000	1,000
4	–	–	–	–	–	–	125	500	1,000
5	–	–	–	–	–	–	31.3	1,000	1,000
6	–	–	–	–	–	–	–	500	1,000
7	–	–	–	–	–	–	–	500	1,000
8	62.5	62.5	62.5	31.3	31.3	62.5	125	1,000	1,000
9	–	–	–	–	–	–	125	1,000	1,000
10	–	–	–	–	–	–	–	500	1,000
11	–	–	–	–	–	–	125	500	1,000
12	–	–	500	–	–	–	15.6	500	1,000
13	–	–	–	–	–	–	–	500	1,000
Amp.	8	32	>128	2	2	<1	4	<8	<8
Str.							4		
Flu.								<8	<8

Ec*: Escherichia coli* ATCC 25922, Yp: *Yersinia pseudo-TB* ATCC 911, Pa: *Pseudomonas aeruginosa* ATCC 43288, Ef: *Enterococcus faecalis* ATCC 29212, Sa: *Staphylococcus aureus* ATCC 25923, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC 607,Ca: *Candida albicans* ATCC 60193, Sc: *S. cerevisiae* RSKK 251, Amp.: Ampicillin, Str.: Streptomisin, Flu.: Fluconazole

Table 7; The urease inhibitory activity of morpholin derivatives

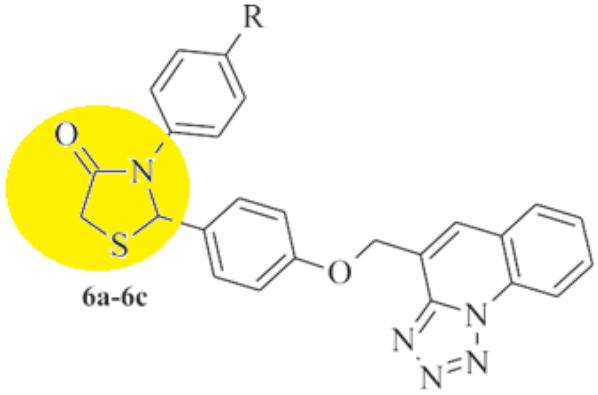
Compounds	IC_{50} (lM)[a]
3.	13.23 ± 2.25
4.	7.92 ± 1.43
5.	6.87 ± 0.06
6.	8.29 ± 2.30
7.	7.01 ± 0.68
8.	4.99 ± 0.59
9.	8.07 ± 1.25
10.	2.37 ± 0.19
11.	4.77 ± 0.92
12.	6.05 ± 1.19
13.	4.46 ± 0.22

[a] Mean ±SD



3a: R= H, R_1= CH_3; **3b**: R= OCH_3, R_1= CH_3; **3c**: R=Cl, R_1= OCH_3.

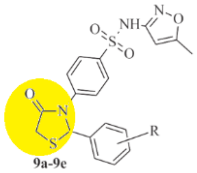
Figure 4; The structures of novel derivatives [(**3a-3c**), (**4**) and (**5**)].



6a: R= H; **6b**: R= 4-C_2H_5O; **6c**: R=4-NO_2.

Figure 5; The structure of the thiazolidin-4-ones (**6a, 6b** and **6c**).

Figure 6; The structures of derivatives (**7** and **8**).



9a: R= 4-F; **9b**: R= 4-Cl; **9c**: R=4-CF_3; **9d**: R= 2, 6-diCl; **9e**: R=2, 6-diF.

Figure 7; The general Structures of sulfa-methoxazole incorporated (4-oxo-thiazolidine) moiety.

It's promising that the sulfamethoxazole-thiazolidinedi-4 hybrids demonstrated reduced effect against human cancer cell lines (MCF-7, HCT116, and A549), suggesting their potential for therapeutic application, as determined by the MTT assay. This indicates their potential for further development as antitubercular agents with reduced harmful effects on normal cells.

3.2. 3-Carboxamide (4-oxo-thiazolidines).

In 2012, Sharma et al. They succeeded in synthesizing phenothiazine derivatives, initiating the process with thioglycolic acid as outlined in reference [88]. The study evaluated 38 analogues against M. TB H37Rv, with a focus on exploring their potential as TB-agents. While the compounds showed weak activity against fungi overall, compound 10 exhibited the most significant inhibition against M. TB, with a growth inhibition of 75% at a concentration of 50 µg/ml. Additionally, compounds 11 and 12, which are 5-arylidene moiety, showed inhibition rates of 83% and 82%, respectively, at the same concentration. Samandiyah et al. synthesized a series of thiazolidinedi-4-one (20 carboxamide derivatives), with potential implications for further research, as shown in Figure 9 [89].

On the other hand, the substitution of the phenothiazine with a 6-nitro-indazole, as observed in analogues (13a-13j and 14a-14j), led to a notable enhancement in the anti-TB activity compared to Sharma et al.'s compounds. These compounds exhibited (MICs) ranging from 1.25 to 7.50 µg/ml, with compounds 13h-13j and 14h-14j containing nitro groups showing the highest activity (shown in red in (Figures 8 and 9). Notably, analogues (14c, 14d, 14e, 14f, 14h, 14i, and 14j) displayed activity levels similar to the reference drugs isoniazid (at 1.25 µg/ml) and rifampicin (at 2.50 µg/ml), as outlined in (Table 8) [88]. Furthermore, the (SAR) analysis reveals that compounds containing chloro- and bromo derivatives demonstrate notably higher anti-TB activity compared to unsubstituted derivatives in the phenyl moiety. Furthermore, the analysis highlights that the anti-TB activity of the tested compounds is contingent upon the presence of an electron-withdrawing substituent. This suggests that compounds with such substituents exhibit enhanced activity against TB.

Samandiyah et al. [90] expanded their research by modifying the active derivatives (14a-14j) with a 5-nitro -1, 3-thiazole moiety (highlighted in red color, Figure 10), [90], resulting in 10 new derivatives named 15a-15j. These newly synthesized compounds exhibited anti-TB activity within a low concentration range of 2.50 to 12.50 µg/ml against M. TB H37Rv, as detailed in (Table 8).

Moreover, the study of SAR, indicated a promising effect on the anti-TB activity of the derivatives due to the electron-withdrawing substituents. Similar to (13a-13j), (14a-14j), and 15a-15j) showed the following activity: NO2 > Cl > Br > H. This suggests that compounds with nitro groups exhibited the highest activity, followed by those with chloro, bromo, and unsubstituted phenyl rings.

3.3. 2-Aryl-3-amino-(4-oxo-thiazolidine) derivatives

Among (4-oxo-thiazolidine) highlighted in red in (Figure 11), the analogues (22) and (23a-23c) demonstrated promising anti-TB. It appears that the other derivatives did not exhibit significant activity in this context [91, 92].

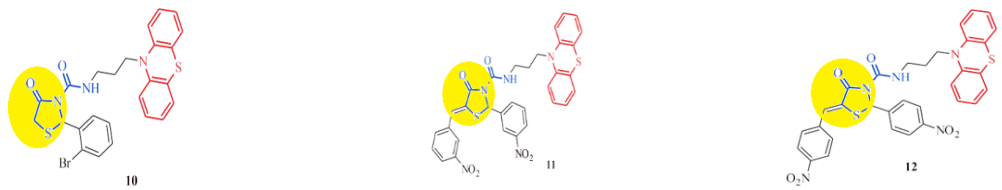
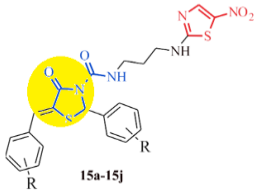


Figure 8; The structure derivatives of (**10-12**).

13a, 14a: R= H; **13b, 14b**: R= 4-Cl; **13c, 14c**: R= 3-Cl; **13d, 14d**: R= 2-Cl; **13e, 14e**: R= 4-Br; **13f, 14f**: R= 3-Br; **13g, 14g**: R= 2-Br; **13h, 14h**: R= 4-NO_2; **13i, 14i**: R= 3-NO_2; **13j, 14j**: R= 2-NO_2.

Figure 9; The structure derivatives of (**13a-13j, 14a-14j**).



15a: R= H; **15b**: R= 4-Cl; **15c**: R= 3-Cl; **15d**: R= 2-Cl; **15e**: R= 4-Br; **15f**: R= 3-Br; **15g**: R= 2-Br; **15h**: R= 4-NO_2; **15i:** R= 3-NO_2; **15j**: R= 2-NO_2.

Figure 10; The structure derivatives of (**15a-15j**).

Table 8; Anti-TB activity of (13a-13j, 14a-14j and 15a- 15j) against *M. TB*.

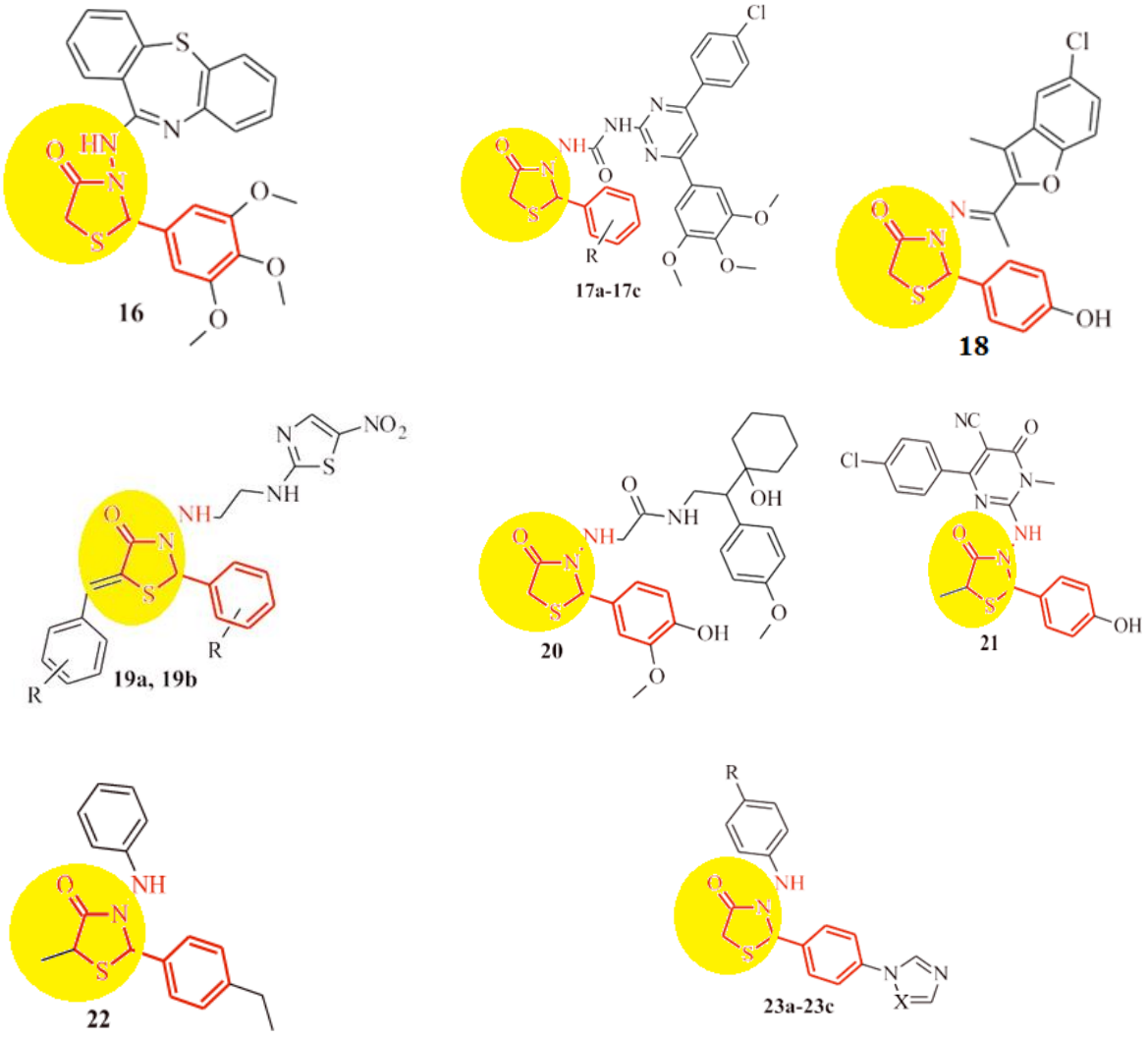
Compound	R	MIC, mg/mL	Compound	R	MIC, mg/mL
13a	H	7.50	14g	2-Br	4.25
13b	4-Cl	4.75	14h	4-NO_2	1.50
13c	3-Cl	4.50	14i	3-NO_2	1.75
13d	2-Cl	4.25	14j	2-NO_2	2.25
13e	4-Br	5.25	15a	H	12.50
13f	3-Br	4.50	15b	4-Cl	2.50
13g	2-Br	4.75	15c	3-Cl	2.75
13h	4-NO_2	4.25	15d	2-Cl	2.50
13i	3-NO_2	4.25	15e	4-Br	2.75
13j	2-NO_2	3.75	15f	3-Br	2.75
14a	H	6.25	15g	2-Br	6.25
14b	4-Cl	3.25	15h	4-NO_2	2.50
14c	3-Cl	1.50	15i	3-NO_2	2.50
14d	2-Cl	2.25	15j	2-NO_2	2.75
14e	4-Br	2.50	isoniazid	-	1.25
14f	3-Br	1.25	rifampicin	-	2.50

Compounds, (16), (17a - 17c), (18), and (19a, 19b) demonstrated weak-activity against M. TB H37Rv. Compound 16, featuring a dibenzothiazepine substituent, exhibited a MIC of 125 µg/ml, while derivatives 17a-17c, containing substituted pyrimidine fragments, showed a MIC of 100 µg/ml, rendering them practically inactive [93, 94]. In addition, 4-oxo-thiazolidine derivatives (18, 19a, and 19b) demonstrated limited activity as anti-TB, MIC (25 µg/ml), against M. TB, as reported in references [95, 96].

Derivative 20 demonstrated significant inhibition of mycobacterial growth, achieving 99% inhibition at 16 µg/ml [97].

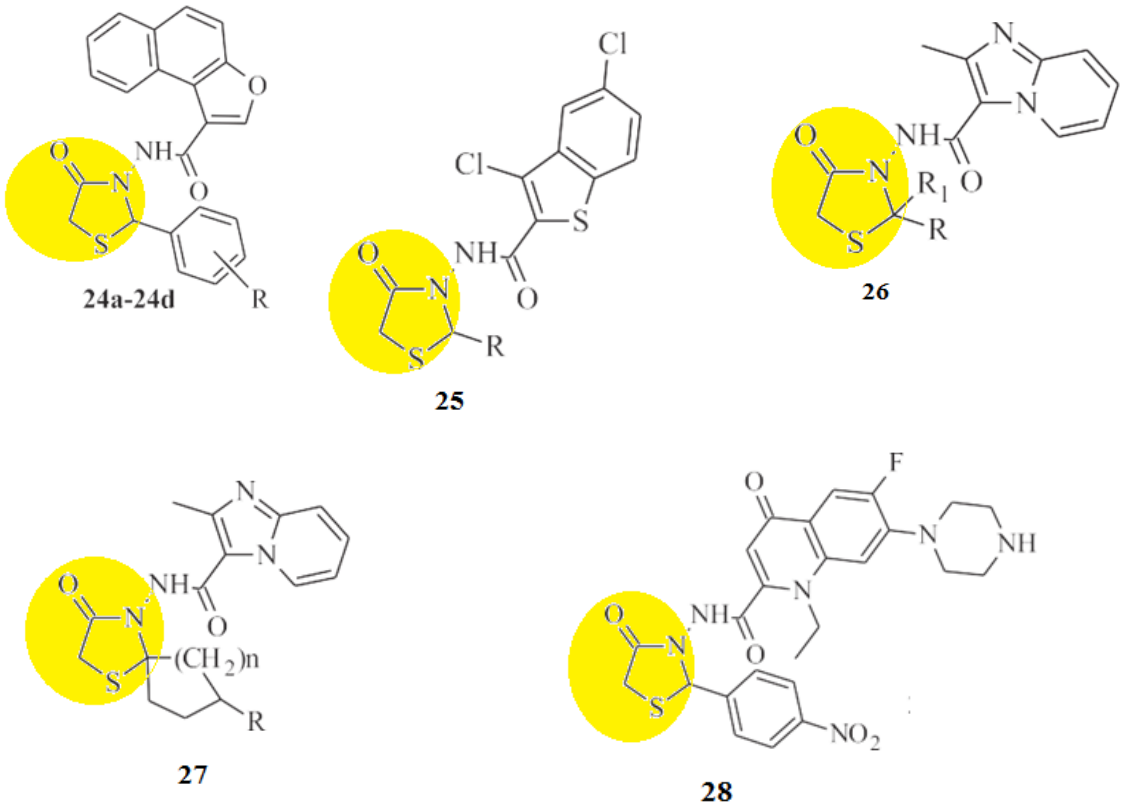
Compound 21, exhibited a lower level of inhibition, with only 44% inhibition of mycobacterial of M. TB at 12.5 µg/ml [98]. Compound 22 exhibited slightly enhanced activity by inhibiting fungal growth at of 12.5 µg/ml, as reported in reference [91]. The new derivatives (23a-23c) exhibited a good activity as anti-TB, with MIC (14.27-14.74) mM [92]. However, when analyzing the activity as anti-TB of 4-oxo-thiazolidine, connected with acyl group in heterocyclic moieties, a weak effect is observed (Figure 12).

For instance, compounds 24a-24d demonstrated anti-TB activity, MIC (50 µg/ml), which assessed against M. TB by using the assay (MABA), as indicated in reference [99]. Additionally, several compounds based on compound 25 were derived by Narut et al., for their anti-TB activity, considering various physicochemical descriptors. This study could offer insights for designing more potent anti-TB analogs of thiazolidinedione, as highlighted in reference [100].



17a: R= 2-NO_2; **17b**: R= 4-CH_3O; **17c**: R= 2-OH; **19a**: R= 2-Cl; **19b**: R= 4-NO_2; **23a**: R= CH_3, X=CH; **23b**: R= H, X=N; **23c**: R= H, X=CH.

Figure 11; The derivatives (**17a, 17b, 17c, 19a, 19b, 23a, 23b** and **23c**)



24a: R= 2-OH; **24b**: R= 4-OH; **24c**: R= 3-NO_2; **24d**: R= 4-NO_2; **26**: R, R_1= CH_3, C_2H_5; **27**: R= H, CH_3, C_2H_5, n = 1, 2.

Figure 12; The structures of (**24a, 24b, 24c, 24d, 26** and **27**).

From the information provided, it seems that derivatives 26 and 27 were ineffective against M. TB at 6.25 µg/ml [101]. However, analogue no. 28 exhibited a good biological effect, against M. smegmatis with an MIC of 16.28 mM compared to another derivative in the same group [102].

In addition, Dhumal et al. [103] 10 compounds containing (4-oxo-thiazolidine) moiety were synthesized. All compounds which was synthesized in reference [103] were evaluated for potential biological effect, against M. TB and M. bovis. On the other hand, the compounds [103], showed moderate biological effect, against Mycobacterium species, while the results of compound 29 showed that it had inhibition rates of 71% and 62% at a concentration of 30 µg/ml against M. TB (H37Ra) and M. bovis (BCG) respectively. Notably, compound 29 showed the highest activity among all compounds tested in the series (Figure 13).

Dighe et al. [104] conducted a modification of compound 29 by substituting the pyrazine moiety at position 2 of the thiazole with an isatin derivatives. This alteration led to an enhancement in anti-TB biological activity. Additionally, (30a-30d) were identified as having a potential promising as antibacterial, with MIC values ranging from 0.78 to 6.25 mM. These compounds feature a substituent with (Cl / F) in the phenyl moiety. Notably, the most active compound was the (derivative 30c), with an MIC of 0.78 mM. Kucukguzil et al. They obtained two active derivatives, (31 and 32), (Figure 14), which indeed showed distinct and diverse inhibition of M. TB growth in the initial screening. Compound 31 achieved 90% inhibition, while compound 32 exhibited 98% inhibition at a concentration of 6.25 µg/ml [105]. In a study conducted by Güzel et al. [106], Compounds 33a-33f were identified, all showing significant growth inhibition of M. TB H37Rv at a test concentration of 6.25 µg/ml. Specifically, compounds 33a, 33d, and 33e exhibited 99% inhibition, while compounds 33b, 33c, and 33f showed 98% inhibition (Fig. 14). One crucial observation is that all these compounds underwent substitution by 2-phenyl at p-position of the thiazolidine-4-ones with (33a, 33d, 33b, 33e, 33c and 33f). Ilango et al. [107], a remarkable series of thiazolidin-4-one (4-oxo-thiazolidine) derivatives were synthesized, designated as (34a-34f), and evaluated for their anti-TB biological effect against M. TB. Furthermore, new results indicated: the analogues (34a-34f), have activity ranged from 0.79 to 9.7 µg/ml. Among these derivatives, the most promising compound, 34f, exhibited a MIC of 0.79 µg/ml, which is close to the MIC of the reference drug isoniazid (0.56 µg/ml).

3.4. 2-Aryl/alkyl-3-isonicotinoylamino- (4-oxo-thiazolidine) moiety

Furthermore, isonicotinoyl-amino moiety, highlighted in blue color, (Figure 15). Additionally, pyrazinoylamino moiety,

highlighted in red color, (Figure 15), into position 3 of (4-oxo-thiazolidine) moiety, holds the potential to enhance anti-TB activity. This is due to the fact that these parts are components of isoniazid and pyrazinamide, respectively, two of the most widely used anti-TB drugs. Incorporating these elements into new compounds may improve efficacy against TB. Bhat reported the (derivative 35, Figure 15) as a compound with antimycobacterial activity that is 2-fold derivatives better than the reference drug against M. smegmatis. The MIC for compound 35 was reported to be 12.5 µg/ml [108]. Apologies for the oversight. The corrected MIC value for compound 35 was reported as 6 µg/ml.

In addition, some newly analogues of compound 35, which prepared by [108],

Bhat et al. in 2000 [108], substituted ethyl, heptyl, or nonyl groups at position 2 of the (4-oxo-thiazolidine) moiety, which did not give sufficient biological effect as antibacterial, MIC (25 - 100) µg/ml. Chitre et al. [109] synthesized a many analogues of pyrazine-2-carbohydrazide derivatives. The novel 23 analogues were tested against M. TB and M. bovis, in type (H37Ra and BCG), respectively. It's noteworthy that Chitre et al. [109] discovered a positive relationship between presence of a chloro atom in position 4 in the phenyl moiety and an increase in biological effect. Furthermore, compound 36 exhibited increased activity against M. bovis (BCG), demonstrating an MIC of 8.48 µg/ml.

The antimycobacterial activity of derivatives (37a-37e), (Table 9), was compared to the alkyl analogue 35, showing promising results [110]. Compound 37a, with an unsubstituted phenyl ring, exhibited no activity. However, derivatives with hydroxyl (R-OH) or methoxy (R-OCH3) groups on the phenyl moiety (compounds 37b, 37c, 37f) displayed enhanced antimycobacterial activity, with MIC (0.31 - 1.25) µg/ml.

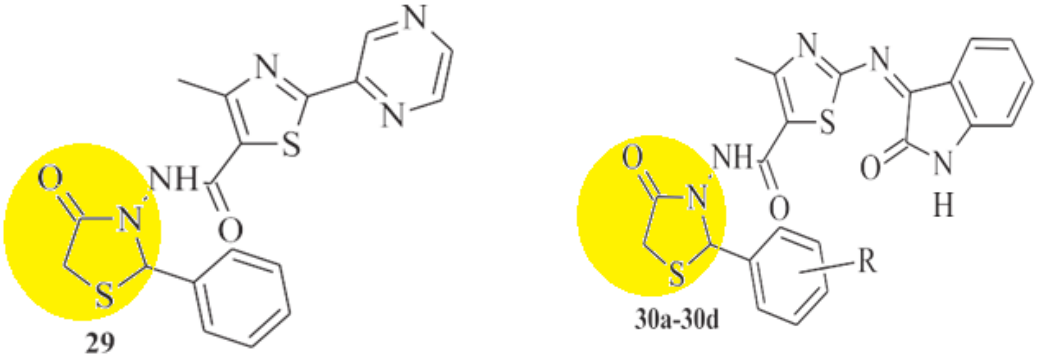
On the other hand, the investigated (37d, 37e), with the nitro and dimethylamino substitutions, have slightly lower biological activity compared to other compounds, MIC (3.12 and 5.0 µg/ml), respectively.

The biological screening of compound 37c showed significant antibacterial biological activity with an MIC (0.31) µg/ml, while compound 37b showed respectable activity with an MIC (0.62) µg/ml. These values compare with isoniazid and rifampicin drugs, (MIC 0.2 µg/ml and 1.0 µg/ml), respectively. However, replacing benzene moiety with a furan-2yl (analogue 38) resulted in a slight decrease in antibacterial activity (MIC of 1.25 µg/ml) [110].

Patel et al. screened a compounds, including 2-heteroaryl analogues (38-40) and 4-oxo-thiazolidine derivatives (compounds 41a, 41b) (Table 10), for their antimycobacterial activity [111]. In screening the compounds which prepared in [111], the compounds (most of them) showed a similar area of inhibition to the growth of M. TB and this was compared to the drug isoniazid, at (20 µg/ml).

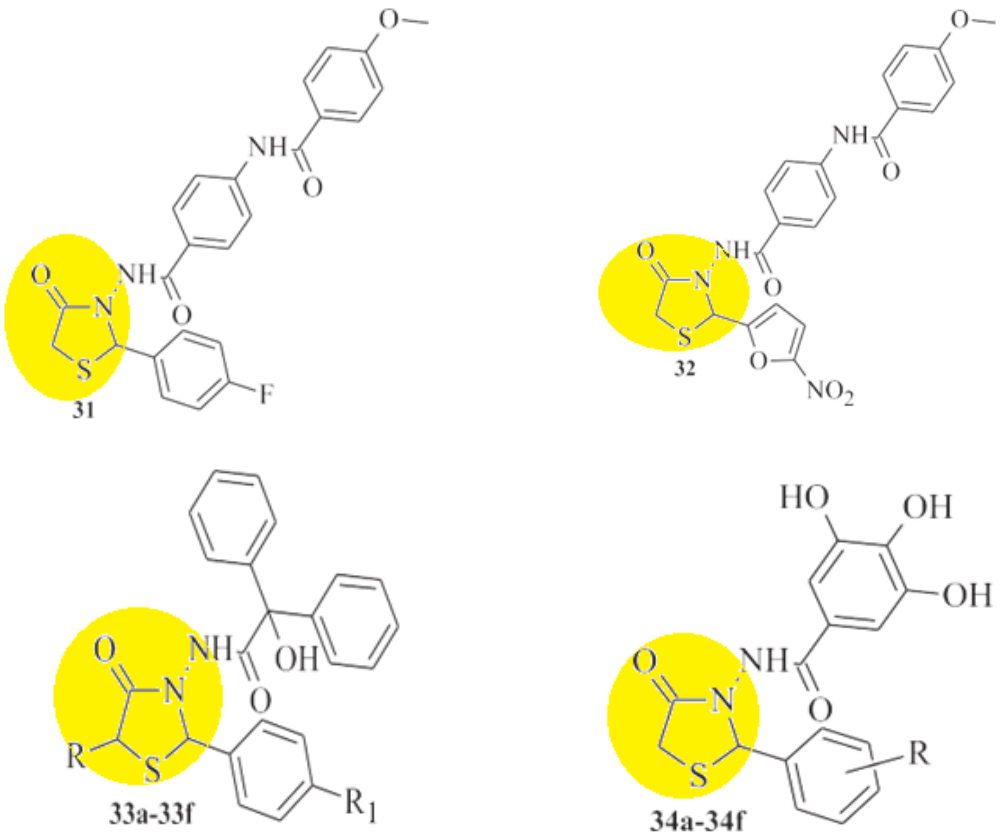
Subhedar et al. [112] a variety of tetrazoloquinoline hybrids (thiazolidine-4-based) were synthesized by a one-pot reaction, cyclocondensation, using [DBUH] [OAc], yielding a pure product with a high percentage. They then screened all the hybrid compounds for their biological antibacterial activity against M. TB and M. bovis, in type (H37Ra and BCG), respectively.

Six different compounds of thiazolidin-4-ones combined derivatives of tetrazoloquinoline with an iso nicotinoylamino acid moiety (derivatives from 42a to 42f) showed a good biological effect, against both M. TB and M. bovis, (in type (H37Ra and BCG), respectively (Figure 15). The most active analogues showed MIC (0.99 - 13.55 mM) against M. TB and (0.14 - 8.43 mM) against M. bovis (Table 3). In addition, the promising compounds showed low toxicity against different three cancer cell lines in type (MCF-7, A549, and HCT116).



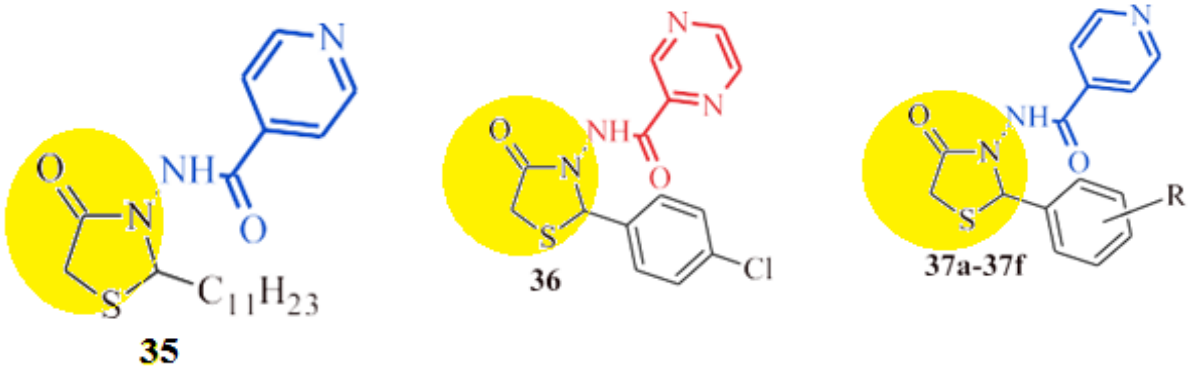
30a: R= 2-F; **30b**: R= 4-F; **30c**: R= 2-Cl; **30d**: R= 4-Cl

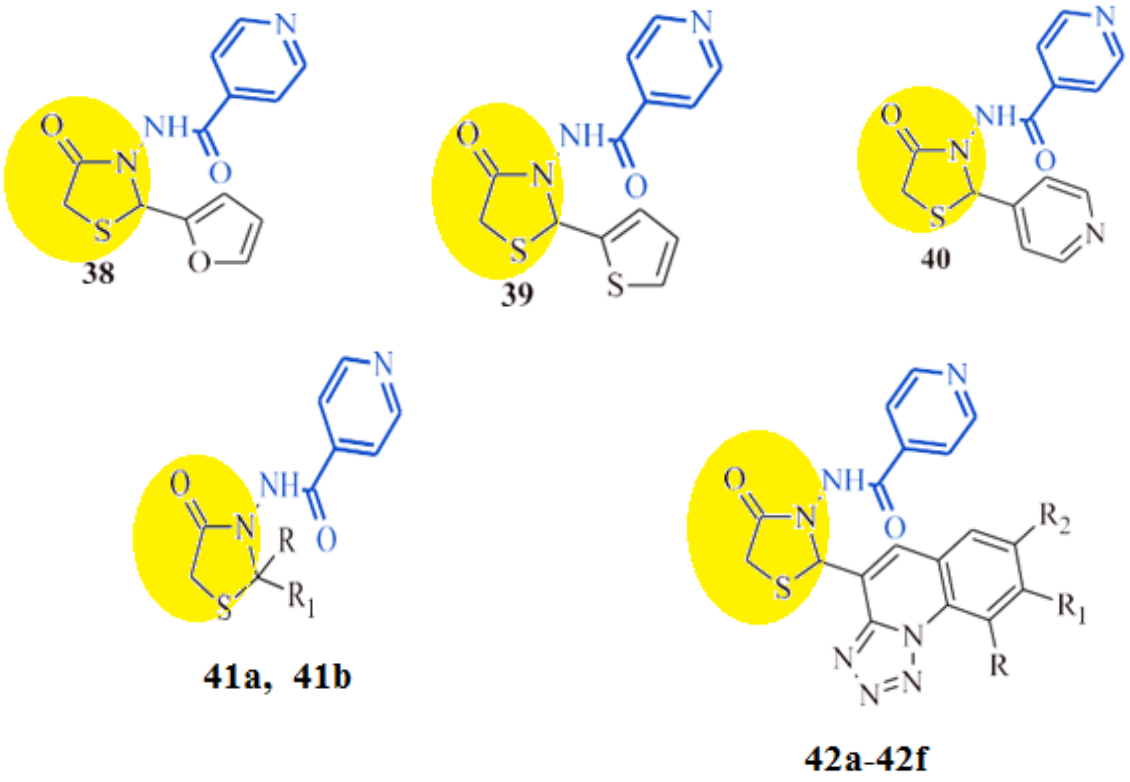
Figure 13; The structures of (**29, 30a, 30b, 30c** and **30d**).



33a: R= H, R_1= 4- Cl; **33b**: R= H, R_1= 4- CN; **33c**: R= H, R_1= 4- $OCH_2C_6H_5$; **33d**: R= CH_3, R_1= 4-Cl; **33e**: R= CH_3, R_1= 4- CN; **33f**: R= CH_3, R_1= 4- $OCH_2C_6H_5$; **34a**: R= H; **34b**: R= 2-OH; **34c**: R= 2-OH, 3-CH_3O; **34d**: R= 3-OH; **34e**: R, = 4-OH; **34f**: R= 2-Cl.

Figure 14; The structures of analougs [**(31), (32), (33a-33f)** and **(34a-34f)**].





37a: R= H; **37b**: R= 2-OH; **37c**: R= 4-OH, 3-OCH_3; **37d**: R= 4- NO_2; **37e**: R= 4$(CH_3)_2N$; **37f**: R= 4-OCH_3; **41a**: R= CH_3, R_1= C_6H_5; **41b**: R= C_6H_5, R_1= C_6H_5; **42a**: R, R_1, R_2= H; **42b**: R=CH_3, R_1, R_2= H; **42c**: R, R_2= H, R_1=CH_3 ; **42d**: R, R_1= H, R_2=CH_3; **42e**: R, R_2= H, R_1=OCH_3; **42f**: R, R_1= H, R_2=OCH_3.

Figure 15; The structures of derivatives (**41a, 41b** and **42a-42f**).

3.5. Indole incorporated (4-oxo-thiazolidine) moiety

Analogues moiety of the (4-oxo-thiazolidine) ring, with moieties thiazole (and / or) indole were assayed against M. TB [113]. Additionally, two analogues (43a and 43b) exhibited weak activity as anti-mycobacterial agent (MIC of 50 µg/ml, Figure 16). However, replacing the aryl moiety in the thiazole group with a coumarin (compound 44) resulted in a slight increase in antimycobacterial activity, showing 80% growth inhibition (12.5 µg/ml) [114]. Further modifications were made to optimize the antitubercular activity of these compounds.

Table 9; Anti-TB activity of the novel compounds **37a-37f** against *M. TB.*

Compound (37)	**R**	**MIC,** µg/ml
a	H	Resistant
b	$-^2OH$	0.62
c	$-^4OH$, $-^3OCH_3$	0.31
d	4-NO_2	3.12
e	$-^4N(CH_3)_2$	5.0
f	$-^4OCH_3$	1.25
isoniazid	-	0.2
rifampicin	-	1.0

Table 10; Antitubercular activity of the novel **42**(**a-f**).

Compound (42)	***M. TB* H37Ra MIC, mM**	***M. bovis BCG*** **MIC, mM**
a	13.55	0.43
b	1.77	0.51
c	2.61	0.30
d	2.14	8.43
e	1.66	0.36
f	0.99	0.14
rifampicin	0.024	0.021

Indole-incorporated thiazolidine derivatives, highlighted in blue in (Figure 16), revealed antimycobacterial activity upon replacing the thiazole moiety in a position 3 of (4-oxo-thiazolidine) moiety with a group of the iso-nicotinoyl amino group, this could be an interesting finding for this interesting area of the research. Compound 46 exhibited a zone of inhibition of 35 mm, compared to 31 mm for isoniazid, albeit at a concentration of 20 μg/ml [111].

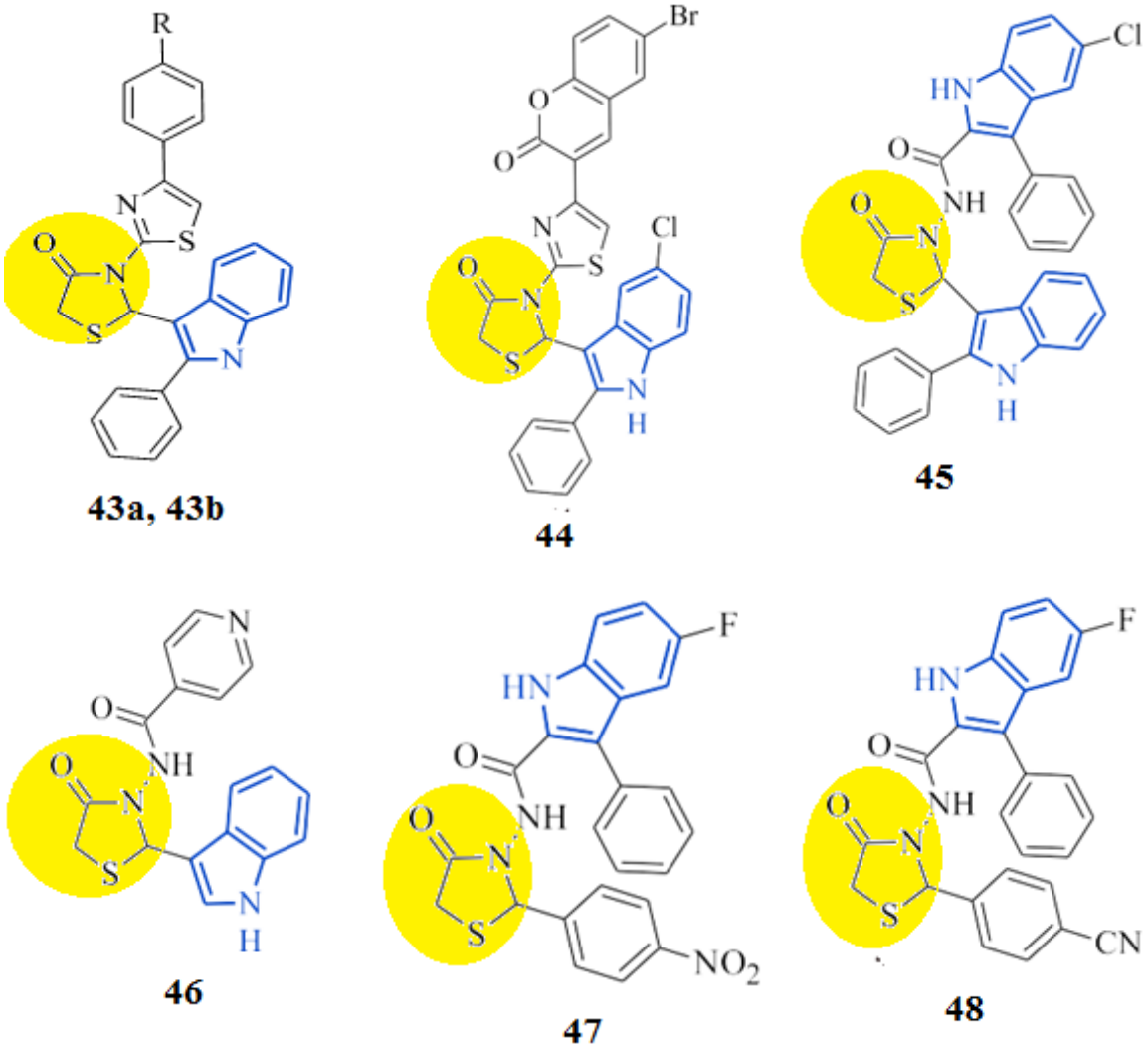
Modification at the position 3 of investigated (4-oxo-thiazolidine) moiety by a group of 2-indoleylamino enhances its biological activity slightly. Moreover, derivative 45 showed high biological effect against M. TB, MIC (12.5 μg/ml), and on the other hand, derivatives (47 and 48), showed an MIC (6.25 μg/ml) against the same bacterial strain (M. TB) [115, 116]. Furthermore, when the indole moitey was incorporated as various spiro analogous of thiazolidine-4-one (Figure 17), compounds (49, 50 and 51) completely inhibited mycobacterial growth by up to (90% - 95%) at a concentration of 12.5 μg/ml, While compound 52 gives a higher biological response than its precursor, giving 98% inhibition (6.25 μg/ml) [117].

3.6. 2-Aryl-3-heteryl-(4-oxo-thiazolidine) moiety

As reported by Dadlani et al. in 2004 [118], adding a thiadiazole nucleus to the thiazolidine-4-ones at active position, (number 3), (53a-53d) leads to the formation of new compounds that are characterized by having moderate and good biological activity (Figure 18) [108]. In addition, the biological results for analogues (53a - 53b), showed clear effect against M. TB with an MIC (12.5 μg/ml). Therefore, we can conclude that replacing one of the (4-hydroxy / 4-methyl groups), in the phenyl moiety with a substitution via 4-methoxy moiety, give a slightly increased effect, with an MIC (6.25 μg/ml), for compound 53c. In addition, the addition of the second methoxy group in the phenyl moiety to give the analogue no. 53d, results in significantly enhanced biological activity as antibacterial, with an MIC (1.6 μg/ml), similar to, (or better than), the MIC values of the reference drugs isoniazid and ciprofloxacin, (1.6 μg/ml and 3.12 μg/ml), respectively.

Moreover, modification in the 1, 3, 4-thiadiazole moiety in active position 3 at the (4-oxo-thiazolidine) moiety (derivatives 54a-54l) leads to improved biological antibacterial effect against M. TB [119].

Distinctive results were recorded for all analogues (54a-54l), (Table 11), with biological effect better or equal to the reference drugs, as it was found that their effect ranged from MIC (from 1.6 to 6.25 μg/ml), (Table 4). The two analogues (54k and 54l), were much more effective against M. TB H37Rv when compared to the reference drugs called (pyrazinamide and streptomycin). In 2011, the previously described modifications were implemented by El Bialy et al. [120].



43a: R=H; **43b**: R=Cl.

Figure 16; The structures of the derivatives (**43a, 43b, 44, 45, 46, 47** and **48**).

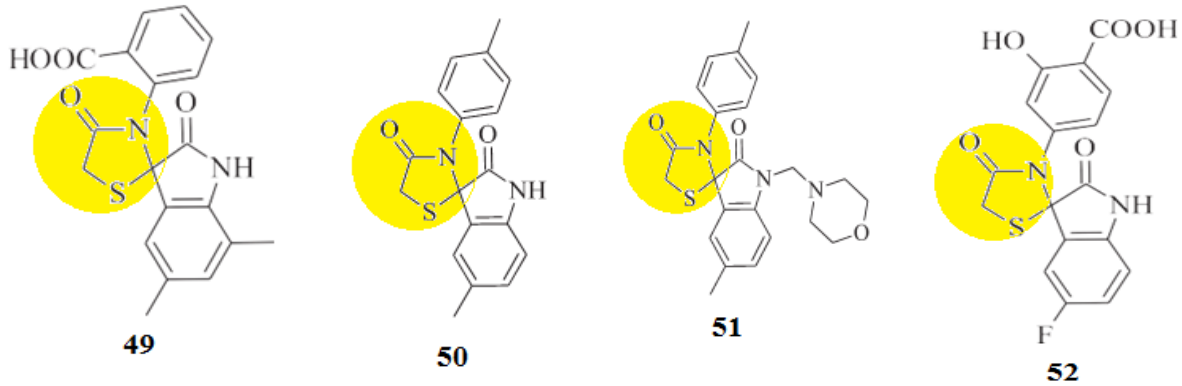
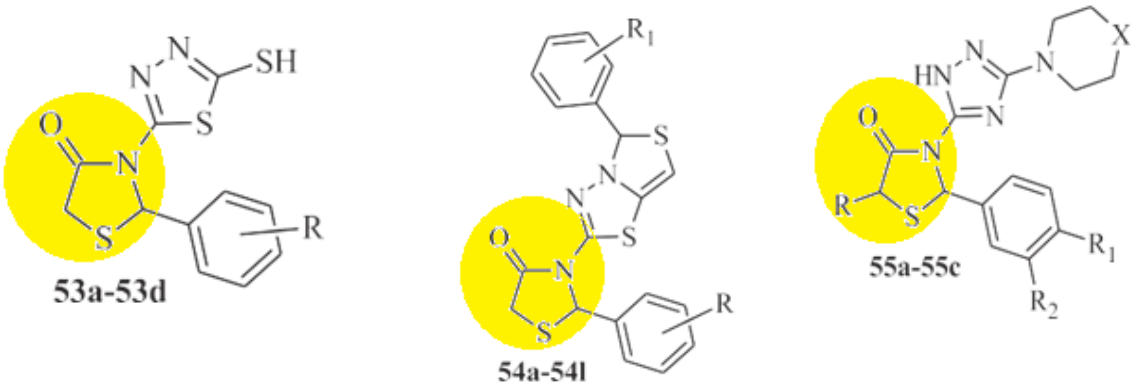


Figure 17; The structures of (**49-52**)



53a: R= 4-OH; **53b**: R= 4-CH_3; **53c**: R= 4-OCH_3; **53d**: R= 3, 4- diOCH_3; **54a**: R= R_1= H; **54b**: R= H, R_1= 4-CH_3; **54c**: R= H, R_1= 4-OH; **54d**:R=H, R_1=4-N$(CH_3)_2$; **54e**: R= 2-Cl, R_1= H; **54f**: R= 4-Cl, R_1= H; **54g**: R= 2-CH_3, R_1= 4-CH_3; **54h**: R= 2-OH, R_1= 4-OH; **54i**: R=2-OH_3, R_1=4-N$(CH_3)_2$; **54j**: R=4-OH_3, R_1=4-N$(CH_3)_2$; **54k**: R= R_1= 4-OH; **54l**: R= R_1= 4-CH_3; **55a**: R= H, R_1=R_2 = OCH_2O, X=O; **55b**: R= H, R_1= R_2 = OCH_2O, X=NCH_3; **55c**: R= R_1=CH_3, R_2 = H, X=NCH_3.

Figure 18; The structures of (**53a-53d, 54a-54i**, and **55a-55c**)

Table 11; Anti-TB activity of compounds (**54a-54i**) against *M. TB*.

Compound (54)	**R**	**R_1**	**MIC,** μg/ml
a	-H	H	= 6.25
b	-H	-$^4CH_3$	= 6.25
c	-H	-^{4}OH	= 6.25
d	-H	-^{4}N$(CH_3)_2$	= 6.25
e	-^{2}Cl	-H	= 3.12
f	-^{4}Cl	-H	= 3.12
g	-$^2CH_3$	-$^4CH_3$	= 3.12
h	-^{2}OH	-^{4}OH	= 3.12
i	-$^2OCH_3$	-^{4}N$(CH_3)_2$	= 3.12
j	-$^4OCH_3$	-^{4}N$(CH_3)_2$	= 3.12
k	-^{4}OH	-^{4}OH	= 1.6
l	-$^4CH_3$	-$^4CH_3$	= 1.6
pyrazinamide	-	-	= 3.12
streptomycin	-	-	= 6.25

That's an interesting finding! Modifying the 1,2,4-triazole in the active position 3 of the thiazolidine-4-ones seems to have led to promising derivatives with good biological potential, particularly as antibacterial and antifungal agents. Compound 55b, in particular, appears to be a standout with strong activity against both Candida albicans and Aspergillus fumigatus strains. It would be intriguing to see how these compounds could be further developed for potential therapeutic use [120].

3.7. Other thiazolidin-4-ones

In 2005 it was discovered by Srivastava et al [121]. They discovered a group of synonyms of spiro thiazolidin-4-ones, then after proving their structures by various chemical methods, then the novel synonyms of spiro thiazolidin-4-ones (4-oxo-thiazolidine) tested against M. TB [121]. It was clear from the results that this type of compound appears biologically promising, so compound 56 showed a high inhibition of 94% (12.5 μg/ml) (Figure 19). In addition, the rest of the derivatives showed a higher rate of inhibition than before analogues, ranging from 96-97% at a higher concentration of 25 mg/ml [122]. The obtained compounds (prepared in reference [121]) were subjected to various docking studies on the M. TB enzyme DprE1, a potential target of M. TB. These docking studies aim to determine the structural requirements of these compounds.

This is done in order to ensure effective inhibition of the enzyme. Thus measuring the extent of potential antibacterial activity.The prepared compounds showed anti-TB activity with MIC values (6.25 – 50) µg/ml. Moreover, docking studies have shown that the chemical interactions of the hydrophobic of aromatic and nitro groups are very important for the inactivation of the DprE1 enzyme, indicating a mechanism needed to understand its potential action.

Bockman et al. [123] reported interesting results regarding the acidomycin (Figure 19). The authors observed that acidomycin displayed potent and have a good activity against of M. TB, including drug-sensitive and multidrug-resistant strains, with MIC values ranging from 0.096 to 6.2 mM. Furthermore, it exhibited selectivity against Mycobacterium spp. as it did not show activity against Gram-positive and Gram-negative bacterial strains [123].

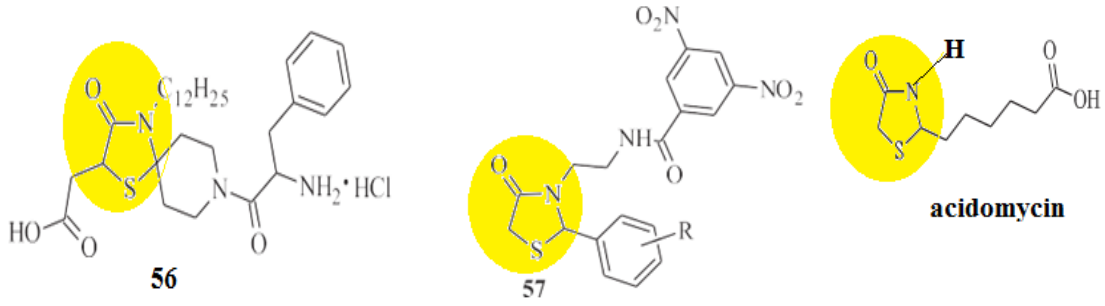


Figure 19; The structures of compound **56**, **57** and acidomycin.

4. Conclusion

This review highlights the promising anti-mycobacterial activities of 4-oxo-thiazolidine analogues, showcasing their good potential as novel antit-TB agents. Through extensive screening tests and molecular research, these compounds have demonstrated superior activity compared to reference drugs, suggesting the possibility of targeting new molecular pathways in TB treatment. Moreover, derivatives 53a, 53b and 53d have shown to be very promising as anti-tuberculosis agents. In addition, compounds 55b, 56, 54k and 54i showed complete activity against M. tuberculosis (H37Ra), with MIC (0.031-0.125) mg/mL. µg/ml

5. References

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