European Journal of Medicinal Chemistry 44 (2009) 4199–4210

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, spectral and biological evaluation of some new thiazolidinones and thiazoles based on *t*-3-alkyl-r-2,*c*-6-diarylpiperidin-4-ones

G. Aridoss, S. Amirthaganesan, M.S. Kim, J.T. Kim, Yeon Tae Jeong*

Division of Image Science and Information Engineering, Pukyong National University, San 100, Yongdang-Dong, Nam-Gu, Busan 608 739, South Korea

ARTICLE INFO

Article history:
Received 3 March 2009
Received in revised form
9 May 2009
Accepted 15 May 2009
Available online 23 May 2009

Keywords:
2,6-Diarylpiperidin-4-one
Thiazolidinone
Thiazole
Antimycobacterial activity
Antimicrobial activity

ABSTRACT

A stereospecific synthesis of some thiazolidinones and thiazoles was achieved conveniently through certain α-halo keto agents and reactivity of chloroacetyl chloride was successfully enhanced by CsF–Celite + CH_3COONa. NMR studies revealed that the configuration of N–N bond is found to be *anti* with respect to C-3 alkyl group while C=N bond in thiazolidinone is *trans* with respect to N–N bond. Antimycobacterial activity tested against *Mycobacterium tuberculosis* indicated that compounds **19**, **20**, **24**, **29**, **30** and **32** exhibited twofold enhanced potency than Rifampicin. Similarly, antimicrobial screening studies pointed out that compounds **21** and **28** exceptionally noticed promising activities and particularly, **21** against *Staphylococcus aureus* and, **24** and **32** against *Rhizopus* sp. exhibited onefold elevated inhibition potency whereas **21** against *Klebsiella pneumoniae* showed twofold improved potency than Ciprofloxacin and Amphotericin B.

1. Introduction

Tuberculosis (TB) is a chronic life threatening disease caused by slow-growing single infectious agent *Mycobacterium tuberculosis* and kills approximately two million people annually. According to World Health Organization (WHO), one-third of the number of new TB cases (new TB infection develops at a rate of one per second) occurs in Southeast Asia, but the estimated incidence per capita is highest in Africa [1]. The rise in the incidence of tuberculosis worldwide is partly due to poverty and inequity and partly to the HIV/AIDS pandemic, which greatly increase the risk of infectious proceeding to overt disease. Currently, the reemergence of TB infection is further complex by an increase of *M. tuberculosis* strains resistant to first line drugs (MDR-TB) used in conventional antitubercular therapy and is becoming a threat to public health worldwide. Another serious concern, in the context of MDR-TB, is the XDR-TB (extensively drug-resistant tuberculosis), which are strains resistant to first and second line anti-TB drugs. Numerous synthetic molecules with antimycobacterial activity have been reported with known or suspected modes of action right from late 1990s [2–4]. Most of them were identified on the basis of their activity against whole cells.

Though a number of drugs are available for the initial treatment of tuberculosis, the current anti-TB regimen is rather complex and requires longer treatment time. Therefore, a novel class of antimycobacterial is urgently needed with modes of action divergent from those drugs used in current therapy and to shorten the duration for anti-TB therapy.

Thiazolidin-4-ones are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine. Recently, antimicrobial and antimycobacterial activities [5–7] of this framework containing compounds were explored well whereas their 2,3-disubstituted analogues have proved to be predominantly effective non-nucleoside HIV reverse transcriptase inhibitors [8]. Likewise, thiazole and their 2-substituted derivatives were also reported to exhibit diverse biological properties such as antituberculous and antimicrobial activities [9]. Moreover, it has been found in the drug development program for the treatment of inflammation [10] and HIV [11].

In corollary of the interesting biological and pharmaceutical properties and synthetic utility, substantial interest has been demonstrated towards piperidin-4-ones; this substructure containing compounds is widely prevalent in numerous alkaloids and synthetically derived compounds of biological importance [12]. In recent times, our interest has been focused on exploring the reactivity of variously substituted 2,6-diarylpiperidin-4-ones [13] and the generated diverse heterocycles by employing the said synthon were eventually evaluated for their antibacterial, antifungal, analgesic, antipyretic and antimycobacterial profiles [14]. Moreover,

* Corresponding author. Tel.: +82 51 629 6411; fax: +82 51 629 6408.
E-mail address: ytjeong@pknu.ac.kr (Y.T. Jeong).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.05.015

thiosemicarbazones, oximes, oxime ethers or by sulphur and nitrogen containing heterocycles obtained *via* exploring the reactivity of keto group at the 4th position have proved to exert better microbiological activities than their corresponding ketones [15,16].

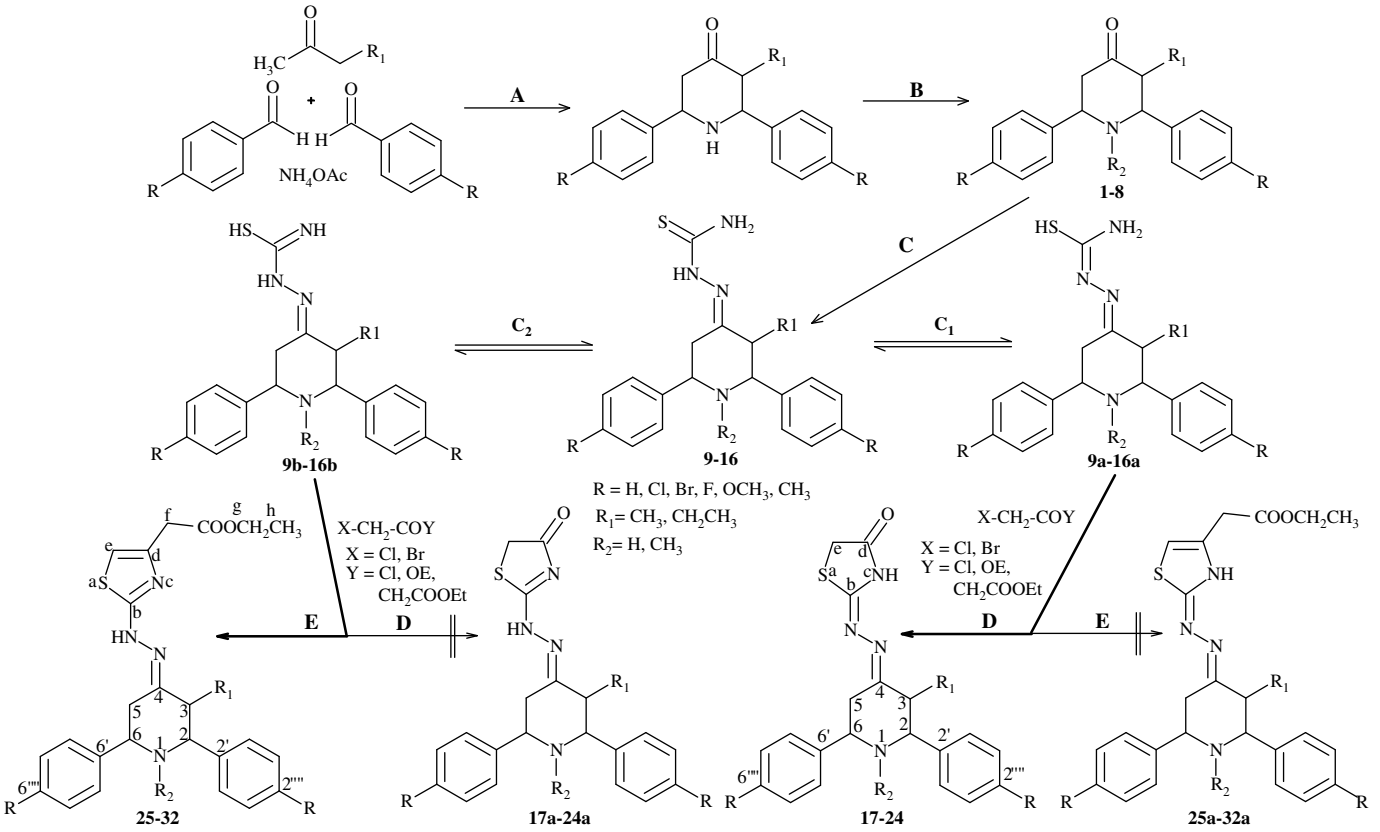
In view of the continued interest in the development of simpler and more convenient synthetic routes for achieving the biologically challenging heterocyclic systems, a simple method is reported herein to synthesize some new piperidone based 1,3-thiazolidin-4-ones and 1,3-thiazoles with good yield in a stereospecific manner by the condensation of easily accessible 3-alkyl-2,6-diarylpiperidin-4-thiosemicarbazones with some α-halocarbonyl compounds as cyclizing reagents. Further, we have found out a suitable α-halocarbonyl compound as a cyclizing reagent for thiazolidinone formation and improved the reactivity of one of the α-halocarbonyl compounds viz., chloroacetyl chloride through CeF–Celite + sodium acetate solid base catalyst using freshly distilled ethanol as solvent. The synthesized compounds are heavily expected to have better biological profiles as thiazolidinone, thiazole and 2,6-diarylpiperidin-4-one bio-labile components are linked together to achieve the target compounds.

2. Chemistry

The synthetic strategy leading to the key intermediate and the target compounds are illustrated in Scheme 1. The key thiosemicarbazone intermediates **9–16** were prepared in excellent yield through two consecutive steps start by condensing suitably substituted benzaldehyde, ketone and ammonium acetate in one pot (afforded piperidones) followed by treatment with thiosemicarbazide in acidic methanol under refluxed condition. The formed thiosemicarbazone can take up two different tautomeric forms (**9–16a** and **b**) as outlined in Scheme 1 (steps C_1 and C_2) and may expect to be stable in solvent. However, the existence of these two forms was confirmed by the reaction of thiosemicarbazones with few cyclizing agents (α-halo keto compounds) such as $ClCH_2COCl$ (CAC), $BrCH_2COCl$ (BAC), $BrCH_2COOEt$ (EBA) and $ClCH_2COCH_2COOEt$ (ECAA) in boiling ethanol. All the synthesized compounds were characterized without ambiguity by analytical and spectral (^1H NMR, ^{13}C NMR, NOESY, HSQC, HMBC, Mass and IR) studies. These studies proved that when cyclization was effected by CAC, BAC and EBA in ethanol, 1,3-thiazolidin-4-ones (**17–24**) were formed exclusively in a stereospecific manner with moderate to good yields (66–85%) without the formation of **17a–24a**. This suggests that enolization (i.e., formation of thioenols **9a–16a** *via* the migration of secondary amino proton) along the path C_1 favors thiozolidinone formation through nucleophilic substitution of halogen by thiolate group which in turn cyclizes by dehydrohalogenation (while using CAC and BAC as reagent) or by loss of a molecule of ethanol (in EBA).

Upon cyclization of **9–16** with ECAA in ethanol, 4-carbethoxymethyl-1,3-thiazoles **25–32** were resulted along the Hantzsch thiazole synthesis and not **25a–32a**. This indicates that the tautomeric form **9b–16b** (through path C_2) favors thiazole synthesis. The aforesaid methods clearly demonstrate that existence of two different tautomeric forms about thioamide group depends upon the nature of cyclizing agent used.

We have investigated in detail about the reactivity of chloroacetyl chloride (CAC), bromoacetyl chloride (BAC) and ethyl bromoacetate (EBA) towards thiosemicarbazone of 2,6-diarylpiperidin-4-ones in ethanol at different catalytic conditions (Method 1: cyclizing agent only; Method 2: cyclizing agent + acetic acid; Method 3: cyclizing agent + acetic acid + sodium acetate;



Scheme 1. Synthesis of compounds **17–32**. Reagents and conditions: (A) i. EtOH/Heat/HCl, ii. NH_3; (B) CH_3I, anhyd. K_2CO_3, dry acetone/Δ; (C) $NH_2NHCSNH_2$, H^+, MeOH/Δ; (D) $ClCH_2COCl$, CsF–Celite/NaOAc, EtOH/Δ or $BrCH_2COCl$, EtOH/Δ or $BrCH_2COOEt$, EtOH/Δ; (E) $ClCH_2COCH_2COOEt$ [or] $ClCH{=}C(OH)CH_2COOEt$ EtOH/Δ.

Method 4: cyclizing agent + sodium acetate; Method 5: cyclzing agent + CeF–Celite + sodium acetate) and also reported the superiority of one over the other on the basis of yield and reaction time.

When cyclization was effected by CAC through Methods 1 to 3, we have achieved the desired products in low yield (24–34%) besides the formation of appreciable quantity of the parent 2,6-diarylpiperidin-4-one (Scheme 2) by C(4)=N cleavage. However, while using sodium acetate as base (Method 4), yield was increased (45–50%) without the formation of parent piperidone. This indicates that the problem seemed to stem from the liberated HCl *in situ* in the reaction that might cause the decomposition of C(4)=N function in products (and not in the thiosemicarbazone function because, its formation from ketone was catalyzed by few drops of con. HCl). Since the CsF adsorbed over Celite was used successfully for the chemoselective esterification of carboxylic acid with alkyl halides [17] and for N-alkylation of different amino compounds [18], we employed CsF–Celite in combination with sodium acetate as catalyst (Method 5) for cyclization. This not only enhanced the yield (66–72%) but also impedes or completely prevents the formation of parent piperidones.

While using EBA as a cyclizing agent, surprisingly the preferred products only yielded (73–80%, Table 1) in all the four methods without the decomposition of formed products (i.e., no piperidone formation). This indicates that C(4)=N function in products may perhaps be stable towards HBr produced *in situ* in the reaction.

In order to recheck this scenario, we have used BAC (contains both chloro and bromo functionalities) in place of EBA but results are different i.e., Methods 2 and 3 end with piperidone formation along with the desired products whereas Methods 1 and 4 exclusively afforded products in good yield (80–85%, Table 1). The aforementioned findings were further confirmed by refluxing the representative compound **17** in ethanol along with few drops of con. HCl or con. HCl/glacial acetic acid mixture as shown in Scheme 2, which afforded the corresponding, piperidone in 21% and 25% respectively.

Therefore, these observations clearly suggest that C(4)=N (in **17**–**24**) is sensitive to HCl or HCl/acetic acid only whereas it is stable in systems containing both HCl and HBr because of the presumed counter ion effect. However, in the case of ECAA, the preferred products only achieved in all the four Methods (1–4) without any degradation. This signifies that loss of conjugation may makes C(4)=N bond more stable in **25**–**32** though HCl is generated *in situ* in the system.

From the obtained results, it is very transparent that use of the reagent without any catalyst (Method 1) is found to be superior over rest of the methods except in using CAC where CsF–Celite + NaOAc was proved to be excellent. Further, on the basis of yield and reaction time, BAC can be used as a surrogate for CAC and EBA in thiazolidinone formation in this series of compounds. The results are reproduced in Table 1.

3. Pharmacology

Antimycobacterial activity of the synthesized compounds **17**–**32** was evaluated against *M. tuberculosis*-H37Rv by radiometric respiratory technique using the BACTEC system [19]. Antibacterial and antifungal activities of the said compounds **17**–**32** were assessed *in vitro* against each three-representative bacterial species viz., *Staphylococcus aureus*, [Gram-positive], *Escherichia coli* and *Klebsiella pneumoniae* [Gram-negative] and fungal species viz., *Candida albicans*, *Aspergillus flavus* and *Rhizopus* sp. by broth microdilution technique as per the guidelines of National Committee for Clinical Laboratory Standards (NCCLS) [20]. The solvent, DMSO used for the preparation of compounds did not show inhibition against the tested organisms.

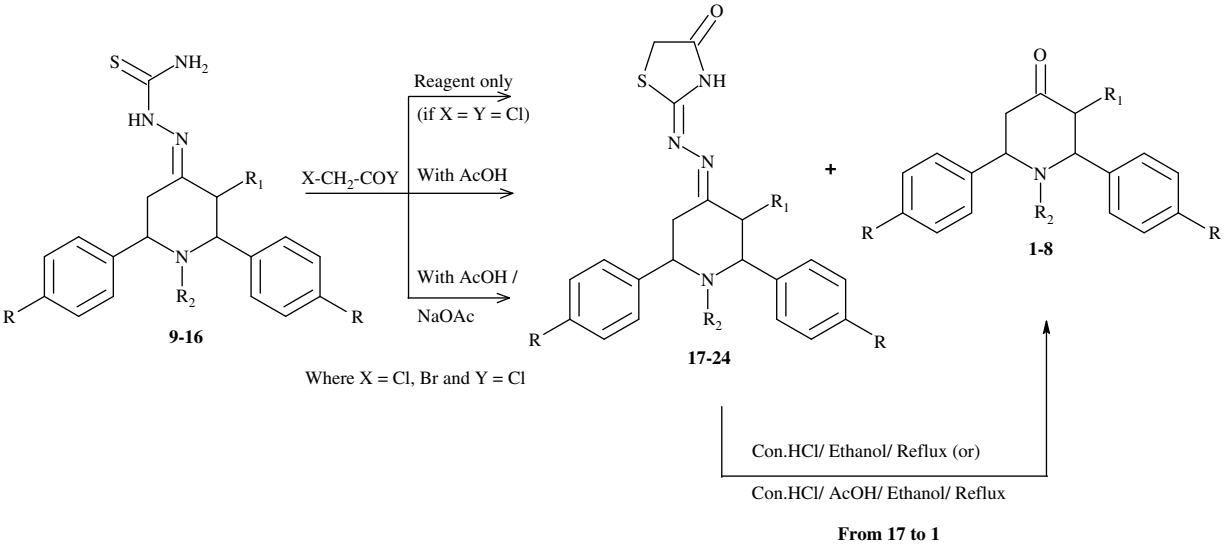
4. Results and discussion

^{1}H and ^{13}C NMR spectra were recorded for all the target compounds whereas for **17** and **27**, IR and mass spectra were also recorded. For comparison, NMR spectra were recorded for the representative key intermediates **9**, **10** and **16**.

4.1. ^{1}H NMR analysis of thiazolidinone derivatives *17–24*

It has been reported earlier that azine formed by 3-methyl-2,6-diphenylpiperidin-4-one [21] exists in a pair of isomers. However, we have achieved exclusively one isomer (evidenced by ^{1}H NMR) in **17**–**24** and exists in s-*trans* (Fig. 1a) form rather than s-*cis* (Fig. 1b) because the latter one is improbable due to the prevailing severe electronic interactions and steric repulsions.

In **9**, **10** and **16**, NH/NH$_2$ signals of thiosemicarbazone moiety appear at 9.19(s)/6.87(d), 8.82(s)/6.48(d) and 8.91(s)/6.69(d) ppm respectively. The position and presence or absence of NH and NH$_2$



Scheme 2. Decomposition of thiazolidinones by different reagents.

Table 1
Synthesis of thiazolidinones (**17**–**24**) and thiazoles (**25**–**32**) using α-halocarbonyl compounds from 3-alkyl-2,6-diarylpiperidin-4-thiosemicarbazones.

Entry	CAC		BAC		EBA		ECAA		Mp (°C)	Molecular formula (Mol. wt.)
	By Method 5		By Method 1		By Method 1		By Method 1			
	RT[a] (h)	Yield[b] (%)	RT (h)	Yield (%)	RT (h)	Yield (%)	RT (h)	Yield (%)		
17	6	72	45 min	85	30 min	80	–	–	188–190	$C_{21}H_{22}N_4OS$ (378.49)
18	6.5	71	1	82	1	75	–	–	84–86	$C_{22}H_{24}N_4OS$ (392.52)
19	6.5	69	1.5	83	1.5	73	–	–	160	$C_{21}H_{20}Cl_2N_4OS$ (447.38)
20	7.0	66	1.5	81	2.0	76	–	–	210–211	$C_{21}H_{20}Br_2N_4OS$ (536.28)
21	7.0	66	1.5	80	2.0	73	–	–	98–100	$C_{21}H_{20}F_2N_4OS$ (414.47)
22	6.0	72	45 min	84	1.5	77	–	–	184	$C_{23}H_{26}N_4O_3S$ (438.54)
23	5.5	70	1	84	1.0	79	–	–	187–188	$C_{23}H_{26}N_4OS$ (406.54)
24	6.0	72	45 min	85	30 min	80	–	–	178–180	$C_{22}H_{24}N_4OS$ (392.52)
25	–	–	–	–	–	–	2.0	90	99–101	$C_{25}H_{28}N_4O_2S$ (448.58)
26	–	–	–	–	–	–	2.5	87	92–93	$C_{26}H_{30}N_4O_2S$ (462.61)
27	–	–	–	–	–	–	2.0	84	84–86	$C_{25}H_{26}Cl_2N_4O_2S$ (517.47)
28	–	–	–	–	–	–	2.5	88	106	$C_{25}H_{26}Br_2N_4O_2S$ (606.37)
29	–	–	–	–	–	–	2.5	85	98–100	$C_{25}H_{26}F_2N_4O_2S$ (484.56)
30	–	–	–	–	–	–	2.0	87	96–98	$C_{27}H_{32}N_4O_4S$ (508.63)
31	–	–	–	–	–	–	2.0	88	88–89	$C_{27}H_{32}N_4O_2S$ (476.63)
32	–	–	–	–	–	–	2.0	90	78–80	$C_{26}H_{30}N_4O_2S$ (462.61)

CAC: chloroacetyl chloride; BAC: bromoacetyl chloride; EBA: ethyl bromoacetate; ECAA: ethyl 4-chloroacetoacetate.
[a] RT: reaction time.
[b] After column chromatography.

signals in the ^{1}H NMR spectrum of final compounds determine the mode of cyclization.

There is a broad and low intense signal with one proton integral at 8.13 ppm for **20** in $CDCl_3$. The same signal is shifted downfield by about 3.65 ppm when recorded in DMSO-d_6 (**17** also shows a broad signal at 11.74 ppm in DMSO-d_6). Therefore it is assigned to amide NH proton (D_2O exchangeable) in thiozolidinone moiety. Further, IR spectra recorded for the representative compound **17** also confirms this by exhibiting three sharp intense bands at 1714, 1632 and 1598 cm^{-1} characteristic for amide carbonyl, C(4)=N and C(b)=N respectively whereas NH of amide and piperidone moiety showed weak broad bands at 3423 and 3161 cm^{-1} respectively.

In all the compounds, the chemical shift value of H-5eq appears significantly in the low field compared to H-5ax (difference is ≈1.3 ppm). Moreover, comparison of piperidine ring protons absorption in thiazolidinone derivatives with their corresponding thiosemicarbazone and parent ketone [22] counter parts indicates that a significant difference is noted only in H-5eq protons (about 0.6/0.8 ppm) while in rest of the protons, the observed difference is minimum. It is apparent from this observation that the configuration of N–N bond in **17**–**24** should be *syn* with respect to C-5 carbon (or *anti* with respect to alkyl group at C-3 position). Further, the magnitude of deshielding in H-5eq confirms that NH proton in thiosemicarbazone should involve in tautomerization to form thioenol isomer as in **9a**–**16a** which upon cyclization, furnished **17**–**24** (where the electron density of the nitrogen adjacent to thiazolidinone ring (C_b=N) is increased due to the existing conjugation). As a result of the suggested configuration, *syn* α C–H bond (C-H5eq) is polarized greatly through the electron pool of N thereby acquires fractional positive charge on the proton (and negative charge on C-5-refer Fig. 2) and in turn deshields remarkably.

Besides, the sharp intense singlet with two protons integral in the region 3.64–3.76 ppm is pertinent to methylene protons of thiazolidinone moiety.

All these observed facts clearly demonstrate that piperidone and thiazolidinone ring systems are linked through azine N–N bond as indicated in Scheme 1 and confirms the proposed structure (**17**–**24**).

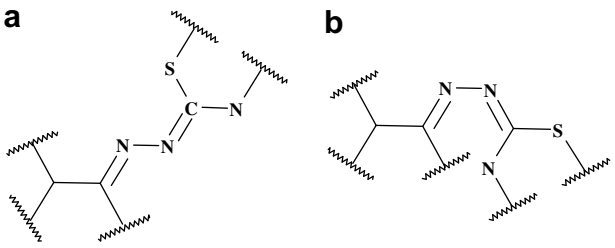
4.2. ^{1}H NMR analysis of thiazole derivatives **25**–**32**

It is obvious that chemical shift values of piperidone ring protons in **25**–**32** do not vary appreciably from their corresponding thiosemicarbazone derivatives. As well, a broad singlet observed at 8.52, 8.48 and 8.61 ppm respectively for **27**, **29** and **32** (in rest of the compounds, absorption due to NH proton could not be identified when recorded in $CDCl_3$) could be assignable to NH proton as it exchanged with D_2O. This clearly envisages that NH of thiosemicarbazone moiety did not involve in thioenol formation through tautomerism, instead amino proton of the same took part in exchange process (as shown in Scheme 1 [**9b**–**16b**]). This is also supported by IR spectra of the representative compound **27** by showing two intense bands at 1732 and 1553 cm^{-1} for ester carbonyl and C(4)=N stretching vibrations respectively. Hence, the final products were obtained through Hantzsch thiazole synthesis upon condensing **9b**–**16b** with ethyl 4-chloroacetoacetate.

However, noticeable deshielding effect on H-5eq protons compared to their corresponding parent ketones [19] suggests that N–NH bond in **25**–**32** also *anti* to the alkyl group at C-3 like N–N bond in **17**–**24**.

Besides the piperidone ring proton signals, the noticed two singlets in the region 6.42–6.47 ppm (for 1H) and 3.56–3.59 ppm (for 2H) of their ^{1}H NMR spectrum (of compounds **25**–**32**) are pertinent to H-e and H-f protons whereas a quartet (for 2H) and triplet (for 3H) in the regions 4.16–4.18 and 1.25–1.27 ppm are respectively due to H-g [CH_2] and H-h [CH_3] protons of ester in thiazole ring system.

The observed magnitude of coupling constants clearly demonstrates that the piperidone ring in both sets of compounds adopts



s-*trans* from s-*cis* form

Fig. 1. Two different isomeric forms of **17**–**32** about azine function.

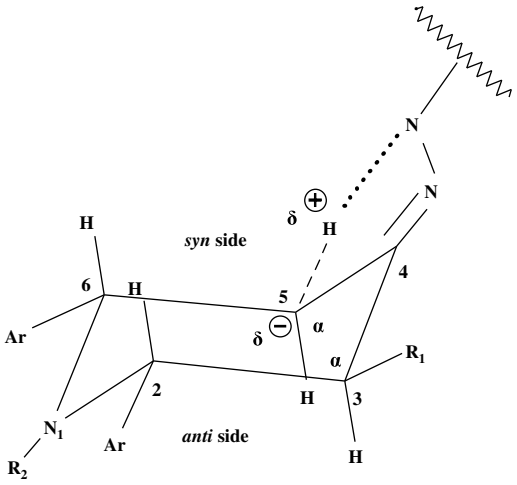


Fig. 2. Electronic interaction in **17**–**32**.

a rigid chair conformation with equatorial orientation of aryl groups at C-2/C-6 and alkyl group at C-3.

4.3. ^{13}C NMR analysis of thiazolidinone derivatives ***17–24***

Though C-5 and C-3 carbons in piperidone ring system are shielded well, the magnitude of shielding is significant at C-5 compared to C-3 carbon. This extent of upfield shift in **17**–**24** is primarily due to the decreased electronegativity of the C═N system compared to the corresponding C═O function in **1**–**8**. Lambert et al. [23] also found the similar trend in six-membered heterocyclic system due to changes in the electronegativity of a function in the ring skeleton. Further, ^{1}H NMR studies revealed that configuration of N–N bond in **17**–**24** is *syn* with respect to C-5 carbon (or *anti* to alkyl group at C-3) and hence polarizes *syn* C-H5e bond as shown in Fig. 2 through electronic interaction. Therefore, C-5 carbon is shielded well compared to C-3.

In addition to the above said resonances, there were also signals in the low field regions 166.9–169.86 and 162.34–162.73 ppm. Earlier reports [21,24] reveal that imine carbon (C-4) showed resonance around 160–163 ppm. Further, our previous studies [13] demonstrate that chemical shift values of C-4 carbon in piperidone system is influenced by the alkyl group at C-3 and/or N-1 and different substituents at 4th position of phenyl groups (i.e., at C-2″″/C-6″″) through electronic and mesomeric effects. On the basis of this, the resonance of C-4 carbon in each of the compounds **17**–**24** is expected to differ by about 1–2 ppm, since they differ by the nature of substituents in the piperidone ring system. Therefore, the absorption frequency in the region 166.9–169.86 ppm only holds good these difference whereas the resonances in the region 162.34–162.73 fail in this respect. Thus, the former and later regions are assigned without ambiguity to C-4 and C-b carbons respectively. Further, two signals in the region 173.5–173.79 and 32.6-32.93 ppm are distinctive for carbonyl (C-d) and methylene carbons (C-e) of thiazolidinone skeleton.

4.4. ^{13}C NMR analysis of thiazole derivatives ***25–32***

Here also the same trend in resonance frequency was noticed for the piperidone ring system. However, the marked upfield shift of C-4 carbon (151.7–153.9) in **25**–**32** compared to **17**–**24** is due to the decreased electronegativity of C(4)═N group by the loss of conjugation. Apart from the piperidone signals, there were four distinctive signals in the low field region and three reasonably intense signals in the high field region characteristic for thiazole moiety. The two closely spaced low intense signals in the region 170.45–170.93 and 169.84–170.23 ppm are respectively due to ester carbonyl and C-b *ipso* carbons. This assignment is also in accordance with the observations of Sarodnick et al. [25] in the substituted thiazole ring system. Similarly, other two low intense signals at ≈144 (143.61–144.49 ppm) and ≈106 ppm (105.69–106.39 ppm) are attributed to other *ipso* carbon C-d and methine carbon C-e respectively. Likewise, the chemical shift values in the high field regions at about 36.99–37.46, 60.89–60.98 and 14.09–14.20 ppm correspond to side chain carbons i.e., C-f, C-g and C-h respectively.

4.5. Two dimensional NMR analysis of compounds ***17*** and ***32***

In order to support the assignments made through one dimensional NMR, two dimensional NMR viz., NOESY, HSQC and HMBC spectra were recorded for the representative compounds **17** and **32** and are displayed in the supplementary files (along with their respective ^{1}H and ^{13}C NMR) while the noticed correlations are given in Tables 2 and 3. The correlations such as C-b/thiazolidinone protons, C-d/thiazolidinone protons and C-4/(3-CH_3/H-5eq) in HMBC spectrum of **17** confirm the respective carbon signals. Similarly, C-d, C-b and COOEt carbonyl signals in **32** were ascertained undoubtedly due to their correlations with H-f/H-e, H-e and H-f/H-g/H-e protons respectively in its HMBC. On the basis of these correlations, the said signals in rest of the compounds were also assigned directly.

4.6. Antimycobacterial activity

Antimycobacterial activity of the compounds was evaluated against *M. tuberculosis*-H37Rv and the observed MICs are presented in Table 4. Isoniazid and Rifampicin were used as standard drugs. It is apparent from the results that none of the compounds showed MIC less than 16 μg/ml. As well, few of the compounds showed comparable activity with Rifampicin but all the compounds were less active than Isoniazid drug. From the obtained results the following SAR has been made. In both series, compounds **17** and **25** with methyl group at C-3 of piperidone system registered the MIC at 64 μg/ml whereas the replacement of methyl by ethyl group completely eliminated the antimycobacterial activity up to a highest concentration (i.e., 256 μg/ml) tested in this study. As is evident from the data (Table 4) that introduction of halogens such as chlorine (**19**) or bromine (**20**) at the *para* position of phenyl groups in thiazolidinone derivative **17** was noteworthy and registered twofold elevated inhibition potency with a lowest MIC of 16 μg/ml whereas the substitution by fluorine (**21**) registered onefold decreased activity than **17**. The above said observations are completely reversed in the case of thiazole series with respect to the said halogens incorporation, i.e., compounds **27** and **28** bearing chlorine and bromine respectively did not show activity even at a maximum concentration of 256 μg/ml whereas fluorine substituted analogue **29** displayed excellent activity at lowest concentration of 16 μg/ml. Instead of electron withdrawing halogens, substitution of electron donating methoxy functionality in **17** and **25** (i.e., compounds **22** and **30** respectively) was also significant in exhibiting moderate to good antimycobacterial activity at MIC 32 and 16 μg/ml respectively. However in both derivatives, methyl group modification (compounds **23** and **31**) in place of methoxy group was not significant as it is evident from the appreciable decrease in activity. A striking observation from this study is that compounds **24** and **32** resulted by methyl group incorporation at the piperidone nitrogen of **17** and **25** respectively displayed promising improvement (MIC at 16 μg/ml i.e., about twofold

Table 2
Correlations in NOESY, HSQC and HMBC spectra of compound **17** [δ (ppm)].

Entry	^{1}H NMR signal	Correlations in NOESY	Correlations in HSQC	Correlations in HMBC
17	0.93 (d, 3H, CH_3 at C-3)	2.62 (st),[a] 3.55 (m),[a] 7.45 (w)[a]	11.94 (CH_3 at C-3)	45.51 (C-3), 69.24 (C-2), 169.74 (C-4)
	2.22 (bt, 1H, H-5ax)	3.61 (m)	37.79 (C-5)	No correlations
	2.62 (m, 1H, H-3ax)	0.93 (m)	45.51 (C-3)	No correlations
	3.55 (d, 1H, H-2ax)	0.93 (m), 3.89 (m), 7.45 (st)	69.24 (C-2)	11.94 (CH_3 at C-3), 61.05 (C-6), 127.87 (*ortho* phenyl carbon), 142.61 (phenyl *ipso* carbon)
	3.61 (dd, 1H, H-5eq)	2.22 (st)	37.79 (C-5)	169.74 (C-4)
	3.74 (s, 2H, thiazolidinone H)	No correlations	32.89 (C-e, i.e., thaizolidinone CH_2)	162.36 (C-b of thaizolidinone imine), 173.42 (C-d of thaizolidinone amide)
	3.89 (dd, 1H, H-6ax)	3.55 (m), 7.43 (m)	61.05 (C-6)	126.70 (*ortho* phenyl carbon)
	7.25 (m, 2H, phenyl *para* protons)	No correlations	127.54, 127.68 (phenyl *para* carbons)	126.70 (phenyl *ortho* carbon)
	7.33 (m, 4H, phenyl *meta* protons)	No correlations	128.34, 128.45 (phenyl *meta* carbons)	127.54, 127.68 (phenyl *para* carbons), 127.89 (phenyl *ortho* carbon), 142.61, 143.56 (phenyl *ipso* carbons)
	7.43, 7.45 (2s, 4H, phenyl *ortho* protons)	3.55 (m), 3.89 (m)	126.70, 127.87 (phenyl *ortho* carbons)	69.24 (C-2), 61.05 (C-6), 127.54, 127.68 (phenyl *para* carbons)

[a] st – strong, w – weak, m – medium.

enhancement) in their inhibitory potency. Therefore, the higher inhibitory activity of compounds **24** and **32** compared to that of corresponding precedents **17** and **25** respectively can be possibly attributed to the lower electronegativity of tertiary nitrogen by the introduced electron releasing methyl group than secondary NH. A comparison of antimycobacterial potency of compounds **17**–**32** calculated against the MIC of Rifampicin is displayed as bar graph in Fig. 3. It is comprehensible from Fig. 3 that compounds **19**, **20**, **24** (in thiazolidinone series), **29**, **30** and **32** (in thiazole series) registered 200% higher antimycobacterial potency while compound **22** (in thiazolidinone series) produced equivalent potency to that of the standard drug, Rifampicin.

4.7. Antimicrobial activity

Antibacterial and antifungal activities of the synthesized compounds (**17**–**32**) were assessed *in vitro* against each three-representative bacterial species viz., *S. aureus*, [Gram-positive], *E. coli* and *K. pneumoniae* [Gram-negative] and fungal species viz., *C. albicans*, *A. flavus* and *Rhizopus* sp. Table 5 displays activity of compounds in terms of minimum inhibitory concentrations (MIC in μg/ml) along with reference drugs, Ciprofloxacin and Amphotericin B respectively for bacteria and fungi. The investigated compounds showed different degrees of antimicrobial activity in relation to the tested microbial species. The extent of antimicrobial activity depended both on the species of microorganism and on the type of functional groups present in the molecule. As the compounds with 3-ethyl group in the piperidone moiety of both thiazolidinone (**18**) and thiazole (**26**) derivatives were almost inactive compared to 3-methyl analogues, we have synthesized the later derivatives only which differs in the substituents at the *para* position of phenyl groups in piperidone nucleus.

4.7.1. Antibacterial activity

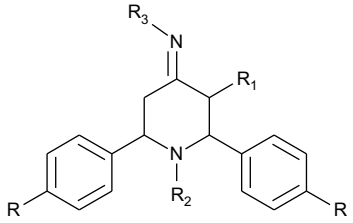
From the obtained results (Table 5), it has been noticed that all the tested compounds exhibited moderate to good antibacterial properties against the tested two Gram-negative and one Gram-positive bacteria except **25**, **31** against *S. aureus*, **18**, **26** against *E. coli* and **18**, **25** and **26** against *K. pneumoniae*. Most of the compounds exhibited significant activity against *S. aureus* as exemplified by compounds **19**–**21**, **28** and **29** with electron withdrawing halogens at the 4th position in phenyl group. Among them, compounds **19**/**20** (with *para* chloro/bromo substituted analogues of **17**) and **21** (with *para* fluoro analogue) produced respectively equivalent and onefold elevated inhibition potency than the reference drug, Ciprofloxacin. Conversely, substitution of electron donating methoxy or methyl functionalities in place of halogens decreased the activity against *S. aureus* appreciably. However, removal of substitution from the

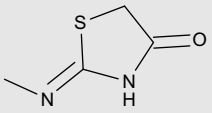
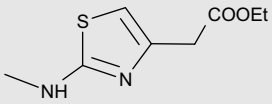
Table 3
Correlations in NOESY, HSQC and HMBC spectra of compound **32** [δ (ppm)].

Entry	^{1}H NMR signal	Correlations in NOESY	Correlations in HSQC	Correlations in HMBC
32	0.87 (d, 3H, CH_3 at C-3)	2.67 (st), 2.89 (m)	12.76 (CH_3 at C-3)	44.82 (C-3), 77.79 (C-2), 152.49 (C-4)
	1.25 (t, 3H, H-h)	4.16 (st)	14.13 (C-h)	60.89 (C-g)
	1.72 (s, 3H, CH_3 at N1)	2.89 (st), 3.19 (st), 7.43 (m)	41.47 (N–CH_3)	69.15 (C-6), 77.79 (C-2)
	2.34 (bt, 1H, H-5ax)	No correlations	36.51 (C-5)	No correlations
	2.67 (m, 1H, H-3ax)	2.89 (m)	44.82 (C-3)	No correlations
	2.75 (dd, 1H, H-5eq)	No correlations	–	No correlations
	2.89 (dd, 1H, H-2ax)	0.87 (w), 1.72 (m), 2.67 (m), 3.19 (w), 7.41, 7.43 (m)	77.79 (C-2)	12.76 (CH_3 at C-3), 41.47 (N–CH_3), 128.08 (phenyl carbon), 142.89 (C-2′ *ipso* carbon)
	3.19 (dd, 1H, H-6ax)	2.89 (m), 7.41, 7.43 (m)	69.15 (C-6)	No correlations
	3.56 (s, 2H, H-f)	6.43 (s), 8.61 (w)	37.38 (C-f)	106.18 (C-e), 143.74 (C-d), 170.46 (C=O)
	4.16 (q, 2H, H-g)	1.25 (st)	60.89 (C-g)	14.13 (C-h), 170.46 (C=O)
	6.43 (s, 1H, Thiazole H)	3.56 (st)	106.18 (Thiazole CH)	37.38 (C-f), 143.74 (C-d), 169.93 (C-b), 170.46 (C=O)
	7.28 (m, 2H, phenyl *para* protons)	No correlations	127.58, 127.61 (phenyl *para* carbons)	126.91 (phenyl *ortho* carbon)
	7.35 (t, 4H, phenyl *meta* protons)	No correlations	128.37, 128.74 (phenyl *meta* carbons)	126.91, 128.01 (phenyl *ortho* carbons), 142.89 (C-2′ *ipso* carbon)
	7.41, 7.43 (2s, 4H, phenyl *ortho* protons)	2.89 (m), 3.19 (m), 1.72 (w)	126.91, 128.08 (phenyl *ortho* carbons)	69.15 (C-6), 77.79 (C-2), 127.58, 127.61 (phenyl *para* carbons),
	8.61 (bs, 1H, NH)	3.56 (w)	–	No correlations

[a] st – strong, w – weak, m – medium.

Table 4
Antimycobacterial activity of compounds **17**–**32** against *M. tuberculosis*-H37Rv (ATCC 27294).



Entry	R_1	R_2	R	R_3		MIC[a] [AP[b]]
						
17	Me	H	H	-do-	–	64 [0.39^{S1}/50^{S2}]
18	Et	H	H	-do-	–	>256
19	Me	H	Cl	-do-	–	16 [1.56^{S1}/200^{S2}]
20	Me	H	Br	-do-	–	16 [1.56^{S1}/200^{S2}]
21	Me	H	F	-do-	–	128 [0.19^{S1}/25^{S2}]
22	Me	H	OMe	-do-	–	32 [0.78^{S1}/100^{S2}]
23	Me	H	Me	-do-	–	64 [0.39^{S1}/50^{S2}]
24	Me	Me	H	-do-	–	16 [1.56^{S1}/200^{S2}]
25	Me	H	H	–	-do-	64 [0.39^{S1}/50^{S2}]
26	Et	H	H	–	-do-	>256
27	Me	H	Cl	–	-do-	>256
28	Me	H	Br	–	-do-	>256
29	Me	H	F	–	-do-	16 [1.56^{S1}/200^{S2}]
30	Me	H	OMe	–	-do-	16 [1.56^{S1}/200^{S2}]
31	Me	H	Me	–	-do-	>256
32	Me	Me	H	–	-do-	16 [1.56^{S1}/200^{S2}]
Isoniazid				–	–	0.25
Rifampicin				–	–	32

^{S1} and ^{S2} – AP compared to Isoniazid and Rifampicin standards respectively.
[a] MIC: minimum inhibitory concentration represented in μg/mL.
[b] Antimycobacterial potency (AP) = MIC of Rifampicin/MIC of test compound × 100.

phenyl groups and inclusion of methyl group at the piperidone nitrogen (compounds **24** and **32**) produced moderate activity against *S. aureus* with a MIC of 16 μg/ml. Against *E. coli*, irrespective of the type of halogens present in the phenyl groups, none of the compounds produced better activity in both series with the exception of **28** (bearing 4-bromo phenyl), which recorded the same MIC (4 μg/ml) with that of the reference standard.

To our surprise, the inhibitory activity of compound **21** against *K. pneumoniae* was especially interesting, exhibiting MIC value about twofold times lower than the reference Ciprofloxacin. Similarly, compounds **20** and **28** exerted onefold lower MIC values than the reference while the remaining compounds produced moderate to no activity against *K. pneumoniae*. The noticed results suggest that the electro-withdrawing property of the 4-substituent in the phenyl ring is important, which is corroborated by elevated activity of compounds with chloro or bromo or fluoro group and decreased activity of compounds with either methyl or methoxy group in the 4-position of phenyl ring. However in thiazole derivatives, only bromine bearing compound seems better than chlorine and fluorine analogues.

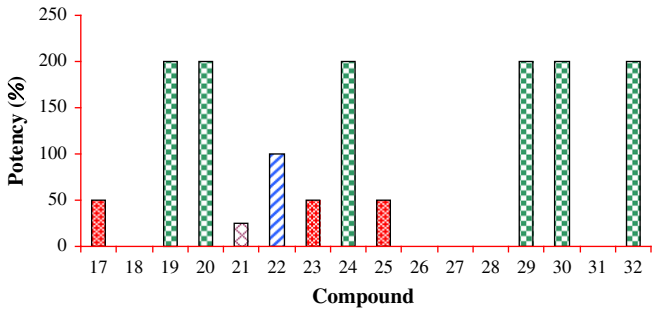


Fig. 3. Comparison of antimycobacterial potency of compounds **17**–**32** with Rifampicin against *M. tuberculosis*-H37Rv.

4.7.2. Antifungal activity

The investigated *in vitro* antifungal screening data has shown that few of the compounds in both the series produced considerable and varied results. It is apparent from Table 5 that compounds with methyl (**17**/**25**) or ethyl (**18**/**26**) group at C-3 failed to exert activity against all the three pathogenic strains at MIC less than 256 μg/ml except **17** against *A. flavus* (for which MIC was noticed at 64 μg/ml). Likewise, incorporation of methoxy (**22** or **30**) or methyl (**23** or **31**) group at the 4th position in phenyl groups of either **17** or **25** also did not show appreciable antifungal activity against the tested organisms. But, instead of methyl or methoxy groups, halogen (particularly, bromine or fluorine) substituted analogues **20**, **21**, **28**, **29** and compounds **24** and **32** obtained by substitution of methyl group at N(1) in **17** or **25** respectively seem better in displaying pronounced inhibitory power. Thus against *C. albicans* and *A. flavus*, compounds **28** and **21** respectively showed equivalent potency in comparison with reference Amphotericin B whilst all other compounds exhibited MIC between 16 and 256 μg/ml. Although compounds **17**, **18** and **25** did not exert antifungal activity against *Rhizopus* sp. up to 256 μg/ml, interestingly, compounds **20**, **21** and **29** exhibited the same potency (MIC: 16 μg/ml) whereas compounds **24** in thiazolidinones and **32** in thiazoles registered

Table 5
In vitro antimicrobial activities (MIC in μg/mL) of compounds **17**–**32** against selected bacterial and fungal strains.

Entry	Thiazolidinone series					
	Minimum inhibitory concentration (MIC[a] in μg/mL)					
	Bacterial strains			Fungal strains		
	S. aureus	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. flavus*	*Rhizopus* sp.
17	64	256	64	>256	64	>256[b]
18	128	>256	>256	256	>256	>256
19	8	128	128	128	128	256
20	8	16	8	64	32	16
21	4	32	4	16	8	16
22	32	32	64	64	128	128
23	64	128	256	>256	128	256
24	16	128	64	64	64	8
Thiazole series						
25	>256	128	>256	>256	256	>256
26	128	>256	>256	>256	>256	256
27	32	64	128	>256	64	128
28	16	4	8	8	32	256
29	16	32	64	128	32	16
30	64	128	256	>256	>256	256
31	>256	128	256	>256	>256	128
32	16	128	32	256	64	8
Cfn[c]	8	4	16	–	–	–
Am B[d]	–	–	–	8	8	16

[a] MIC is the lowest concentration of an antimicrobial agent that will significantly inhibit the visible growth of microorganism after a period of incubation.
[b] No inhibition up to a highest concentration of 256 μg/ml.
[c] Cfn: Ciprofloxacin.
[d] Am B: Amphotericin B.

onefold enhanced potency (MIC: 8 μg/ml) compared to the reference drug. The antifungal screening studies revealed that N(1)-methyl substituted compounds **24** and **32** emerged as potent compounds against *Rhizopus* sp. though they were not effectively inhibited the growth of other two tested fungal strains.

Among the set of series examined for their biological effectiveness, the thiazolidinone bearing compounds elicited better biological response than the corresponding thiazole analogues and particularly the antibacterial potency of the former one is more prominent as revealed from the observed results. It is recognized that the presence of azine function (–C═N–N═C–) is expected to be the key factor in exhibiting better biological activity in thiazolidinone than thiazole because the latter does not have conjugation about the azine function. Moreover, thiazolidin-4-ones were reportedly interfering with the biosynthesis of peptidoglycan (an essential component of the cell wall of both Gram-positive and Gram-negative bacteria) by inhibiting the bacterial enzyme Mur B [26] and hence expressed marked potency.

5. Conclusion

In conclusion, we have reported herewith a stereospecific synthesis of the target compounds **17**–**32** in good yields and are known to exist exclusively in s-*trans* form. As well, reactivity of chloroacetyl chloride towards achieving the desired thiazolidinones was successfully promoted by employing CsF–Celite + sodium acetate combination as catalyst besides finding bromoacetyl chloride as one of the effective choice of cyclizing agents among the three α-halo keto reagents used for thiazolidinone formation. NMR studies proved that the piperidone ring adopts rigid chair conformation with equatorial orientation of alkyl and aryl groups whereas the conformation of N–N bond is found to be *anti* with respect to alkyl group at C-3. Antimycobacterial activity tested against *M. tuberculosis* indicates that compounds **19**, **20**, **24**, **29**, **30** and **32** displayed excellent activity. Likewise, antimicrobial assessment suggested that compounds **21** against *S. aureus*, **20**, **21**, **28** against *K. pneumoniae* and **24** and **32** against *Rhizopus* sp. were remarkably inhibited the growth of the tested organisms at lowest MIC and hence were considered as potent candidates. The structural requirements for the active compound in both series against each strain are represented as schematic diagram in Fig. 4. It is concluded that thaizolidinone derivatives are better than thiazoles in their biological properties.

6. Experimental protocols

6.1. General

The course of the reactions and purity of the products were assessed by performing TLC. Melting points were determined in Electrothermal-9100 (Japan) instrument and are uncorrected. IR spectra were recorded in FT-IR Perkin–Elmer Spectrum GX spectrophotometer and only noteworthy absorption levels (reciprocal centimeters) are listed. All the NMR spectra were recorded on JEOL (Japan) JNM ECP-400 instrument operating at 400 MHz for ^{1}H and 100.6 MHz for completely proton decoupled ^{13}C. $CDCl_3$ and DMSO-d_6 were used as solvent and TMS as internal standard. The chemical shift values were reported in ppm (parts per million) relative to TMS and the spin multiplicities are indicated as follows: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), bt (broad triplet), q (quartet) and m (multiplet) while axial and equatorial are mentioned as 'ax' and 'eq' respectively. Coupling constant (*J*) values are represented in Hertz (Hz). The tubes used for recording NMR spectra are of 5 mm in diameter. Mass spectra were recorded in JEOL, JMS-700 while microanalyses in Heraeus Carlo Erba 1108 CHN analyzer. Purification of the final compounds was done using silica gel (200–400 mesh-60 Å). Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. They were used as received without any further purification.

6.2. Chemistry general procedures

2,6-Diarylpiperidin-4-ones **1**–**7** [27a] were prepared according to the literature procedures.

6.3. Preparation of 1,3-dimethyl-2,6-diphenylpiperidin-4-one (*8*)

A mixture of 3-methyl-2,6-diphenylpiperidin-4-one **1** (1 g, 3.77 mmol), anhydrous potassium carbonate (1 g, 7.5 mmol) and methyl iodide (0.8 g, 5.65 mmol) in acetone (20 ml) was refluxed for 3 h on a water bath. Removal of acetone along with excess of methyl iodide under reduced pressure followed by dilution with water and treatment with aqueous ammonia afforded the corresponding 1,3-dimethyl-2,6-diphenylpiperidin-4-one **8**. This upon recrystallization in hot ethanol gave 0.98 g (93%) of pure compound. Melting point of the pure compound was in good agreement with the literature [27b].

6.4. Preparation of 3-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone (*9*)

3-Methyl-2,6-diphenylpiperidin-4-one **1** (1 g, 3.77 mmol) was completely dissolved in boiling methanol (20 ml). To this, 2–3 drops of con. HCl was added (excess of acid is fatal to the reaction) followed by thiosemicarbazide (0.34 g, 3.77 mmol) and refluxed the contents for 3 h on a water bath. The progress of reaction was monitored by TLC. After the completion of reaction, the contents were brought to room temperature and the separated solids were filtered. Recrystallization of the compound in hot methanol furnished 1.15 g (90%) of pure 3-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone in white crystalline form. Melting point of the pure compound was in

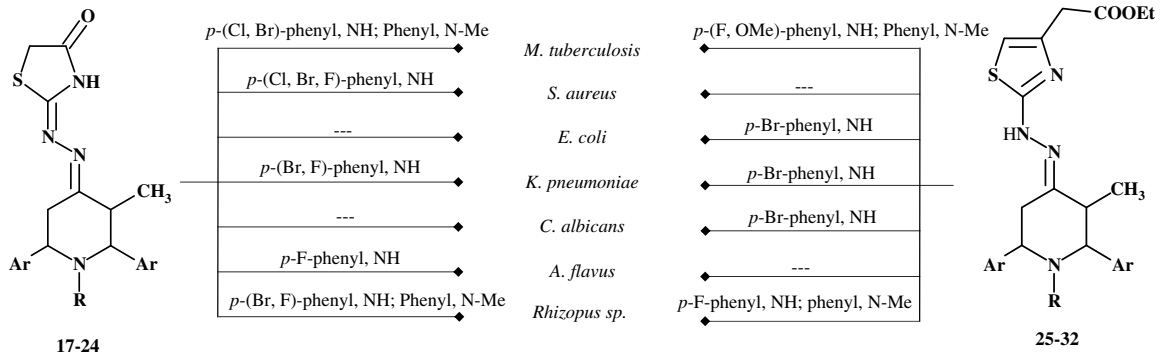


Fig. 4. Comparison of structural requirements for thiazolidinone and thiazole derivatives **17**–**32** towards their antimycobacterial and antimicrobial potencies.

good agreement with the literature [16b]. The rest of the compounds **10**–**16** were prepared in a similar manner.

*6.5. Typical procedure for the synthesis of 2-[3-methyl-2,6-diphenylpiperidin-4-hydrazono]-1,3-thiazolidin-4-one (**17**) by Methods 1–4*

To a boiling solution of 3-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone **9a** (0.4 g, 1.18 mmol) in ethanol (20 ml) along with acetic acid (1 ml – Method 2) or sodium acetate (0.29 g, 3.54 mmol – Method 3) or acetic acid–sodium acetate buffer (1 ml AcOH/0.29 g NaOAc – Method 4) as catalyst or without any catalyst (Method 1), either of the cyclizing agent {$ClCH_2COCl$ [0.13 g (0.1 ml), 1.18 mmol] or $BrCH_2COCl$ [0.19 g (0.1 ml), 1.18 mmol)] or $BrCH_2COOEt$ [0.2 g (0.13 ml) 1.18 mmol]} was added dropwise and refluxed at about 80 °C. Completion of the reaction was ascertained by the pale or intense orange yellow coloration. The contents were then brought to room temperature, poured into water (75 ml) containing sodium bicarbonate and extracted with ethyl acetate (3×25 ml). The combined organic layers were washed with distilled water, brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave the crude mass. Purification of the compound over silica gel using EtOAc:$CHCl_3$ (1:10) or EtOAc:n-hexane (3:10) as eluting solvent afforded the title compound **17** as pale yellow colored resinous mass. Free flowing pale yellow solid (0.38 g, 85% yield while using $BrCH_2COCl$) was obtained upon triturating the residue with n-hexane followed by ether.

*6.6. Typical procedure for the synthesis of 2-[3-methyl-2,6-diphenylpiperidin-4-hydrazono]-1,3-thiazolidin-4-one (**17**) by Method 5*

The solid catalyst CsF–Celite was prepared by stirring an aqueous solution of CsF (Aldrich) and Celite 521 (Fluka) at room temperature for 20 min as reported elsewhere [17,18]. To a well stirred boiling solution of 3-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone **9a** (0.4 g, 1.18 mmol), CsF–Celite (0.27 g, 1.77 mmol) and sodium acetate (0.20 g, 2.36 mmol) in freshly distilled ethanol, chloroacetyl chloride [0.13 g (0.1 ml), 1.18 mmol] was added dropwise. After the completion of reaction, the catalyst was filtered off, washed with ethyl acetate (15 ml). 0.32 g (72% yield) of the title compound **17** was obtained as pale yellow color solid by adopting the above mentioned work-up and purification process: mp 188–190 °C (dec.); IR (KBr) 3423 (amide NH), 3161 (ring NH), 3063, 3030, 2981, 2935, 2796 (weak bands), 1714 (thiazolidinone C═O), 1632 [C(4)═N], 1598 [C(b)═N] (intense bands), 1494, 1455, 1425, 1400, 1376, 1331, 1277, 1259, 1233, 1203, 1101, 1029, 991 (weak bands), 752, 701 (medium intense bands), 529 cm^{-1}. ^1H NMR in $CDCl_3$ (δ ppm): 7.44 (d, 4H, phenyl *ortho* protons), 7.33 (m, 4H, phenyl *meta* protons), 7.25 (m, 2H, phenyl *para* protons), 3.89 (dd, 1H, $J_{6a,5e} = 2.75$, $J_{6a,5a} = 11.53$, H-6ax), 3.74 (s, 2H, thiazolidinone H), 3.61 (dd, 1H, $J_{5a,5e} = 13.55$, H-5eq), 3.55 (d, 1H, $J_{2a,3a} = 10.25$, H-2ax), 2.62 (m, 1H, H-3ax), 2.22 (bt, 1H, H-5ax), 0.93 (d, 3H, $J_{H,Me} = 6.59$, CH_3 at 3); ^1H NMR in DMSO-d_6 (δ ppm): 11.74 (s, 1H, amide NH), 2.50 (s, 1H, NH-merged with solvent signal); ^{13}C NMR (δ ppm): 173.50 (C-d), 169.69 (C-4), 162.47 (C-b), 143.53 (C-6′), 142.59 (C-2′), 128.34, 128.45 (phenyl *meta* carbons), 127.54, 127.68 (phenyl *para* carbons), 126.70, 127.87 (phenyl *ortho* carbons), 69.24 (C-2), 61.05 (C-6), 45.49 (C-3), 37.78 (C-5), 32.91 (C-e), 11.94 (CH_3 at C-3); EI-MS *m*/*z* 378 (26%, M+), 263 (100%), 194 (90%), 167 (13%), 156 (45%), 144 (25%), 128 (36%), 115 (51%), 91 (60%), 77 (40%). Anal. Calcd for $C_{21}H_{22}N_4OS$ (%): C, 66.64; H, 5.86; N, 14.80; Found (%): C, 66.22; H, 5.70; N, 14.69.

Similar procedure was adopted for the synthesis of rest of the compounds **18**–**24** in this series with the same equivalents of respective thiosemicarbazone derivatives and cyclizing agent. NMR spectra of these compounds also recorded using the same solvent system. The given yields of products correspond to bromoacetyl chloride as cyclizing agent because of its superiority over others.

*6.6.1. 2-[3-Ethyl-2,6-diphenylpiperidin-4-hydrazono]-1,3-thiazolidin-4-one (**18**)*

Compound **18** was obtained as yellow color solid from **10a** (0.37 g, 82% yield), mp 84–86 °C (dec.); ^1H NMR (δ ppm): 7.41–7.19 (m, 10H, phenyl protons), 3.89 (dd, 1H, $J_{6a,5e} = 2.56$, $J_{6a,5a} = 11.72$, H-6ax), 3.69 (d [with very small splitting at the peak], 2H, $J = 1.09$, thiazolidinone H), 3.65 (d, 1H, $J_{2a,3a} = 10.25$, H-2ax), 3.57 (dd, 1H, $J_{5a,5e} = 13.36$, H-5eq), 2.48 (m, 1H, H-3ax), 2.21 (bt, 1H, H-5ax), 2.04 (NH at 1), 1.67 (m, 1H, CH_2CH_3 at 3), 1.25 (m, 1H, CH_2CH_3 at 3), 0.88 (t, 3H, $J = 7.32$, CH_2CH_3 at 3); ^{13}C NMR (δ ppm): 173.65 (C-d), 168.24 (C-4), 162.34 (C-b), 143.49 (C-6′), 142.49 (C-2′), 128.74–126.65 (phenyl carbons), 67.49 (C-2), 61.06 (C-6), 52.03 (C-3), 38.12 (C-5), 32.93 (C-e), 19.01 (CH_2CH_3 at C-3), 12.00 (CH_2CH_3 at C-3). Anal. Calcd for $C_{22}H_{24}N_4OS$ (%): C, 67.32; H, 6.16; N, 14.27; Found (%): C, 67.13; H, 6.05; N, 14.18.

*6.6.2. 2-[3-Methyl-2,6-bis(*p*-chlorophenyl)piperidin-4-hydrazono]-1,3-thiazolidin-4-one (**19**)*

Compound **19** was obtained as pale yellow color solid from **11a** (0.37 g, 83% yield), mp 160 °C (dec.); ^1H NMR (δ ppm): 7.39–7.28 (m, 8H, aromatic protons), 3.86 (d, 1H, $J_{6a,5e} = 2.56$, H-6ax), 3.74 (s, 2H, thiazolidinone H), 3.57 (dd, 1H, $J_{5a,5e} = 13.36$, H-5eq), 3.52 (d,

1H, $J_{2a,3a}$ = 10.25, H-2ax), 2.54 (m, 1H, H-3ax), 2.12 (two d [overlapped], 1H, $J_{5a,6a}$ = 12.08, $J_{5a,5e}$ = 13.18, H-5ax], 2.05 (NH at 1), 0.91 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3); ^{13}C NMR (δ ppm): 173.50 (C-d), 166.97 (C-4), 162.73 (C-b), 141.79 (C-6′), 140.79 (C-2′), 132.79 (C-6‴), 132.58 (C-2‴), 128.84–127.67 (aromatic carbons), 67.98 (C-2), 59.98 (C-6), 44.89 (C-3), 37.20 (C-5), 32.62 (C-e), 11.42 (CH_3 at C-3). Anal. Calcd for $C_{21}H_{20}Cl_2N_4OS$ (%): C, 56.38; H, 4.51; N, 12.52; Found (%): C, 56.02; H, 4.42; N, 12.31.

6.6.3. 2-[3-Methyl-2,6-bis(p-bromophenyl)piperidin-4-hydrazono]-1,3-thiazolidin-4-one (**20**)

Compound **20** was obtained as pale yellow color solid from **12a** (0.35 g, 81% yield), mp 210–211 °C (dec.); ^{1}H NMR in $CDCl_3$ (δ ppm): 8.13 (bs, amide NH), 7.49–7.32 (m, 8H, aromatic protons), 3.84 (d, 1H, $J_{6a,5e}$ = 2.56, H-6ax), 3.76 (s, 2H, thiazolidinone H), 3.61 (dd, 1H, $J_{5a,5e}$ = 13.55, H-5eq), 3.52 (d, 1H, $J_{2a,3a}$ = 9.89, H-2ax), 2.54 (m, 1H, H-3ax), 2.09 (two d [overlapped]), 1H, $J_{5a,6a}$ = 11.72, $J_{5a,5e}$ = 13.18, H-5ax), 1.99 (bs, NH at 1), 0.91 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3); ^{1}H NMR in DMSO-d_6 (δ ppm): 11.78 (s, 1H, amide NH); ^{13}C NMR (δ ppm): 173.62 (C-d), 167.34 (C-4), 162.82 (C-b), 142.47 (C-6′), 141.41 (C-2′), 131.28–128.21 (aromatic carbons), 121.21 (C-6‴), 120.96 (C-2‴), 68.28 (C-2), 60.22 (C-6), 45.11 (C-3), 37.38 (C-5), 32.81 (C-e), 11.62 (CH_3 at C-3). Anal. Calcd for $C_{21}H_{20}Br_2N_4OS$ (%): C, 47.03; H, 3.76; N, 10.45; Found (%): C, 47.39; H, 3.89; N, 10.32.

6.6.4. 2-[3-Methyl-2,6-bis(p-fluorophenyl)piperidin-4-hydrazono]-1,3-thiazolidin-4-one (**21**)

Compound **21** was obtained as spongy pale yellow color solid from **13a** (0.35 g, 80% yield), mp 98–100 °C (dec.); ^{1}H NMR (δ ppm): 7.39–6.96 (m, 8H, aromatic protons), 3.86 (dd, 1H, $J_{6a,5e}$ = 2.56, $J_{6a,5a}$ = 11.72, H-6ax), 3.72 (s, 2H, thiazolidinone H), 3.53 (signal was not resolved, 1H, H-5eq), 3.51 (d, 1H, $J_{2a,3a}$ = 09.89, H-2ax), 2.53 (m, 1H, H-3ax), 2.16 (two d [overlapped], 1H, $J_{5a,6a}$ = 12.08, $J_{5a,5e}$ = 13.18, H-5ax), 0.89 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3); ^{13}C NMR (δ ppm): 173.42 (C-d), 169.07 (C-4), 162.76 (C-b), 163.49/163.34 (C-6‴), 161.05/160.89 (C-6‴), 139.27 (C-6′), 138.26 (C-2′), 129.24–115.16 (aromatic carbons), 68.38 (C-2), 60.29 (C-6), 45.66 (C-3), 37.89 (C-5), 32.89 (C-e), 11.85 (CH_3 at C-3). Anal. Calcd for $C_{21}H_{20}F_2N_4OS$ (%): C, 60.85; H, 4.86; N, 13.52; Found (%): C, 60.61; H, 4.94; N, 13.61.

6.6.5. 2-[3-Methyl-2,6-bis(p-methoxyphenyl)piperidin-4-hydrazono]-1,3-thiazolidin-4-one (**22**)

Compound **22** was obtained as pale yellow color solid from **14a** (0.37 g, 84% yield), mp 184 °C (dec.); ^{1}H NMR in $CDCl_3$ (δ ppm): 7.33–6.81 (m, 8H, aromatic protons), 3.84 (1H, merged with *p*-OMe signal, H-6ax), 3.80, 3.75 (s, 6H, OCH_3 at C-2‴/C-6‴), 3.69 (s, 2H, thiazolidinone H), 3.51 (dd, 1H, $J_{5a,5e}$ = 13.55, H-5eq), 3.46 (d, 1H, $J_{2a,3a}$ = 10.25, H-2ax), 2.55 (m, 1H, H-3ax), 2.20 (bt, 1H, H-5ax), 0.89 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3). ^{1}H NMR in DMSO-d_6 (δ ppm): 11.82 (s, amide NH); ^{13}C NMR (δ ppm): 173.53 (C-d), 169.86 (C-4), 162.39 (C-b), 158.98 (C-6‴), 158.85 (C-2‴), 135.83 (C-6′), 134.90 (C-2′), 128.79–113.63 (aromatic carbons), 68.58 (C-2), 60.41 (C-6), 55.18 (OCH_3 at C-2‴/C-6‴), 45.60 (C-3), 37.83 (C-5), 32.90 (C-e), 11.93 (CH_3 at C-3). Anal. Calcd for $C_{23}H_{26}N_4O_3S$ (%): C, 62.99; H, 5.98; N, 12.78; Found (%): C, 63.21; H, 6.11; N, 12.98.

6.6.6. 2-[3-Methyl-2,6-bis(p-methylyphenyl)piperidin-4-hydrazono]-1,3-thiazolidin-4-one (**23**)

Compound **23** was obtained as yellow color solid from **15a** (0.37 g, 84% yield), mp 187–188 °C (dec.); ^{1}H NMR (δ ppm): 7.29–7.06 (m, 8H, aromatic protons), 3.84 (signal was not resolved, 1H, H-6ax), 3.65 (s, 2H, thiazolidinone H), 3.51 (dd, 1H, $J_{5a,5e}$ = 13.55, H-5eq), 3.47 (d, 1H, $J_{2a,3a}$ = 10.25, H-2ax), 2.57 (m, 1H, H-3ax), 2.33, 2.28 (s, 6H, CH_3 at C-2‴/C-6‴), 2.21 (bt, 1H, H-5ax), 0.90 (d, 3H, $J_{H,Me}$ = 6.22, CH_3 at 3); ^{13}C NMR (δ ppm): 173.79 (C-d), 169.66 (C-4), 162.70 (C-b), 140.53 (C-6′), 139.61 (C-2′), 137.11 (C-6‴), 136.94 (C-2‴), 128.99–126.48 (aromatic carbons), 68.87 (C-2), 60.65 (C-6), 45.36 (C-3), 37.68 (C-5), 32.89 (C-e), 21.04, 20.98 (CH_3 at C-2‴/C-6‴), 11.91 (CH_3 at C-3). Anal. Calcd for $C_{23}H_{26}N_4OS$ (%): C, 67.95; H, 6.45; N, 13.78; Found (%): C, 67.66; H, 6.32; N, 13.64.

6.6.7. 2-[1,3-Dimethyl-2,6-diphenylpiperidin-4-hydrazono]-1,3-thiazolidin-4-one (**24**)

Compound **24** was obtained as pale yellow color solid from **16a** (0.38 g, 85% yield), mp 178–180 °C (dec.); ^{1}H NMR (δ ppm): 7.43–7.22 (m, 10H, phenyl protons), 3.71 (d [with mild splitting at the peak], 2H, J = 1.47, thiazolidinone H), 3.46 (dd, 1H, $J_{5a,5e}$ = 13.73, H-5eq), 3.22 (dd, 1H, $J_{6a,5e}$ = 2.93, $J_{6a,5a}$ = 11.72, H-6ax), 2.72 (m, 1H, H-3ax), 2.33 (bt, 1H, H-5ax), 1.69 (s, 3H, N–Me), 0.84 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3); ^{13}C NMR (δ ppm): 173.38 (C-d), 168.85 (C-4), 162.27 (C-b), 144.23 (C-6′), 142.98 (C-2′), 128.76–127.17 (phenyl carbons), 77.75 (C-2), 69.71 (C-6), 45.31 (C-3), 41.42 (N–Me), 38.37 (C-5), 32.89 (C-e), 12.71 (CH_3 at C-3). Anal. Calcd for $C_{22}H_{24}N_4OS$ (%): C, 67.32; H, 6.16; N, 14.27; Found (%): C, 67.01; H, 6.02; N, 14.11.

6.7. Typical procedure for the synthesis of ethyl 2-[3-methyl-2,6-diphenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**25**)

The procedure adopted for the synthesis of thiazolidinones was followed here also with the use of ethyl 4-chloroacetoacetate [0.19 g (0.16 ml), 1.18 mmol] as cyclizing agent. Commencement of the reaction was revealed by change in color of the reaction mixture from colorless to red upon addition of the cyclizing agent. Purification of the compound over silica gel using EtOAc:$CHCl_3$ (0.5:10) or EtOAc:n-hexane (2:10) as eluting solvent afforded the title compound **25** (0.48 g, 90% yield) as dark red color semi-solid from **9b**. Trituration of the residue with ether gave free flowing red color solid: mp 99–101 °C; ^{1}H NMR (δ ppm): 7.48–7.25 (m, 10H, phenyl protons), 6.42 (s, 1H, thiazole H), 4.17 (q, 2H, J = 7.32, H-g), 3.89 (dd, 1H, $J_{6a,5e}$ = 2.38, $J_{6a,5a}$ = 11.53, H-6ax), 3.56 (s, 2H, H-f), 3.52 (d, 1H, $J_{2a,3a}$ = 10.25, H-2ax), 2.99 (dd, 1H, $J_{5a,5e}$ = 13.73, H-5eq), 2.57 (m, 1H, H-3ax), 2.19 (two d (overlapped), 1H, $J_{5a,6a}$ = 12.08, $J_{5a,5e}$ = 13.55, H-5ax), 2.02 (s, NH at 1), 1.26 (t, 3H, J = 7.14, H-h), 0.94 (d, 3H, $J_{H,Me}$ = 6.59, CH_3 at 3); ^{13}C NMR (δ ppm): 170.93 (ester carbonyl), 170.23 (C-b *ipso*), 153.90 (C-4), 143.61 (C-d), 143.22 (C-6′), 142.60 (C-2′), 128.72–126.45 (phenyl carbons), 105.69 (C-e), 69.33 (C-2), 60.91 (C-g), 60.63 (C-6), 44.89 (C-3), 36.99 (C-f), 36.23 (C-5), 14.09 (C-h), 11.99 (CH_3 at C-3). Anal. Calcd for $C_{25}H_{28}N_4O_2S$ (%): C, 66.94; H, 6.29; N, 12.49; Found (%): C, 67.26; H, 6.11; N, 12.24.

The remaining compounds **26**–**32** were also synthesized in a similar fashion.

6.7.1. Ethyl 2-[3-ethyl-2,6-diphenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**26**)

Compound **26** was obtained as brown color solid from **10b** (0.46 g, 87% yield), mp 92–93 °C (dec.); ^{1}H NMR (δ ppm): 7.47–7.23 (m, 10H, phenyl protons), 6.45 (s, 1H, thiazole H), 4.18 (q, 2H, J = 6.96, H-g), 3.88 (dd, 1H, $J_{6a,5e}$ = 2.75, $J_{6a,5a}$ = 11.49, H-6ax), 3.66 (d, 1H, $J_{2a,3a}$ = 10.25, H-2ax), 3.59 (s, 2H, H-f), 2.83 (dd, 1H, $J_{5a,5e}$ = 13.73, H-5eq), 2.46 (m, 1H, H-3ax), 2.19 (bt, 1H, H-5ax), 1.68 (m, 1H, CH_2CH_3 at 3), 1.28 (m, 1H, CH_2CH_3 at 3), 1.27 (t, 3H, J = 7.14, H-h), 0.91 (t, 3H, J = 7.14, CH_2CH_3 at 3); ^{13}C NMR (δ ppm): 170.52 (ester carbonyl), 170.10 (C-b *ipso*), 151.71 (C-4), 144.49 (C-d), 143.11 (C-6′), 142.50 (C-2′), 128.63–126.46 (phenyl carbons), 106.19 (C-e), 67.55 (C-2), 60.94 (C-g), 60.78 (C-6), 51.49 (C-3), 37.43 (C-f), 36.34 (C-5), 19.09 (CH_2CH_3 at 3), 14.16 (C-h), 11.84 (CH_2CH_3 at 3). Anal. Calcd for $C_{26}H_{30}N_4O_2S$ (%): C, 67.50; H, 6.54; N, 12.11; Found (%): C, 67.91; H, 6.32; N, 12.28.

*6.7.2. Ethyl 2-[3-methyl-2,6-bis(*p*-chlorophenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**27**)*

Compound **27** was obtained as shiny and spongy red color solid from **11b** (0.43 g, 84% yield), mp 84–86 °C (dec.); IR (KBr) 3305 (NH), 2976, 2931, 2873, 2815 (weak bands), 1732 (ester C=O), 1553 {C(4)=N} [intense bands], 1489, 1442, 1408, 1369, 1336, 1312, 1260, 1226, 1200, 1152 (weak bands), 1088, 1030, 1013, 829 (medium intense bands), 715, 691, 600, 578 cm^{-1} (weak bands); ^1H NMR (δ ppm): 8.50 (bs, 1H, NH), 7.41–7.26 (m, 8H, aromatic protons), 6.46 (s, 1H, thiazole H), 4.17 (q, 2H, $J = 6.96$, H-g), 3.85 (dd, 1H, $J_{6a,5e} = 2.56$, $J_{6a,5a} = 11.72$, H-6ax), 3.58 (s, 2H, H-f), 3.50 (d, 1H, $J_{2a,3a} = 10.25$, H-2ax), 2.78 (dd, 1H, $J_{5a,5e} = 13.91$, H-5eq), 2.49 (m, 1H, H-3ax), 2.13 [two d (overlapped), 1H, $J_{5a,6a} = 11.70$, $J_{5a,5e} = 13.55$, H-5ax], 1.97 (s, 1H, NH at 1), 1.26 (t, 3H, $J = 7.14$, H-h), 0.93 (d, 3H, $J_{H,Me} = 6.22$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.47 (ester carbonyl), 169.85 (C-b *ipso*), 152.21 (C-4), 144.45 (C-d), 141.49 (C-6′), 140.93 (C-2′), 133.51 (C-2″″/C-6″″), 129.17–127.83 (aromatic carbons), 106.39 (C-e), 68.49 (C-2), 60.97 (C-g), 60.03 (C-6), 44.87 (C-3), 37.39 (C-f), 35.89 (C-5), 14.17 (C-h), 11.91 (CH_3 at 3); EI-MS *m*/*z* 516 (7%, M+), 377 (9%), 331 (67%), 322 (37%), 262 (100%), 254 (72%), 192 (32%), 185 (46%), 165 (30%), 152 (34%), 140 (60%), 115 (36%), 98 (23%), 89 (29%), 71 (29%), 54 (15%). Anal. Calcd for $C_{25}H_{26}Cl_2N_4O_2S$ (%): C, 58.03; H, 5.06; N, 10.83; Found (%): C, 58.31; H, 5.19; N, 10.96.

*6.7.3. Ethyl 2-[3-methyl-2,6-bis(*p*-bromophenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**28**)*

Compound **28** was obtained as shiny and spongy red color solid from **12b** (0.43 g, 88% yield), mp 106 °C (dec.); ^1H NMR (δ ppm): 7.49–7.30 (m, 8H, aromatic protons), 6.46 (s, 1H, thiazole H), 4.17 (q, 2H, $J = 7.14$, H-g), 3.83 (dd, 1H, $J_{6a,5e} = 2.56$, $J_{6a,5a} = 11.72$, H-6ax), 3.58 (s, 2H, H-f), 3.49 (d, 1H, $J_{2a,3a} = 10.25$, H-2ax), 2.79 (dd, 1H, $J_{5a,5e} = 13.91$, H-5eq), 2.49 (m, 1H, H-3ax), 2.12 (bt, 1H, H-5ax), 1.26 (t, 3H, $J = 7.14$, H-h), 0.93 (d, 3H, $J_{H,Me} = 6.59$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.45 (ester carbonyl), 169.87 (C-b *ipso*), 152.16 (C-4), 144.38 (C-d), 141.98 (C-6′), 141.41 (C-2′), 131.81–128.17 (aromatic carbons), 121.63 (C-2″″/C-6″″), 106.37 (C-e), 68.51 (C-2), 60.96 (C-g), 60.04 (C-6), 44.79 (C-3), 37.37 (C-f), 35.85 (C-5), 14.16 (C-h), 11.91 (CH_3 at 3). Anal. Calcd for $C_{25}H_{26}Br_2N_4O_2S$ (%): C, 49.52; H, 4.32; N, 9.24; Found: C, 49.38; H, 4.17; N, 9.16.

*6.7.4. Ethyl 2-[3-methyl-2,6-bis(*p*-fluorophenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**29**)*

Compound **29** was obtained as shiny and spongy red color solid from **13b** (0.44 g, 85% yield), mp 98–100 °C (dec.); ^1H NMR (δ ppm): 8.48 (s, 1H, NH), 7.44–7.02 (m, 8H, aromatic protons), 6.47 (s, 1H, thiazole H), 4.18 (q, 2H, $J = 6.96$, H-g), 3.87 (dd, 1H, $J_{6a,5e} = 2.75$, $J_{6a,5a} = 11.53$, H-6ax), 3.59 (s, 2H, H-f), 3.51 (d, 1H, $J_{2a,3a} = 9.89$, H-2ax), 2.79 (dd, 1H, $J_{5a,5e} = 13.73$, H-5eq), 2.51 (m, 1H, H-3ax), 2.16 (bt, 1H, H-5ax), 2.01 (s, 1H, NH at 1), 1.27 (t, 3H, $J = 7.14$, H-h), 0.93 (d, 3H, $J_{H,Me} = 6.59$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.49 (ester carbonyl), 169.84 (C-b *ipso*), 163.53 (C-6″″), 161.11 (C-2″″), 152.55 (C-4), 144.46 (C-d), 138.81 (C-6′), 138.27 (C-2′), 129.36–115.16 (aromatic carbons), 106.39 (C-e), 68.49 (C-2), 60.98 (C-g), 60.05 (C-6), 45.02 (C-3), 37.41 (C-f), 36.05 (C-5), 14.18 (C-h), 11.92 (CH_3 at 3). Anal. Calcd for $C_{25}H_{26}F_2N_4O_2S$ (%): C, 61.97; H, 5.41; N, 11.56; Found (%): C, 61.78; H, 5.32; N, 11.38.

*6.7.5. Ethyl 2-[3-methyl-2,6-bis(*p*-methoxyphenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**30**)*

Compound **30** was obtained as brown color solid from **14b** (0.44 g, 87% yield), mp 96–98 °C (dec.); ^1H NMR (δ ppm): 7.37–6.87 (m, 8H, aromatic protons), 6.44 (s, 1H, thiazole H), 4.17 (q, 2H, $J = 6.59$, H-g), 3.79 (s, 7H, H-6ax and OCH_3 at C-2″″/C-6″″), 3.57 (s, 2H, H-f), 3.46 (d, 1H, $J_{2a,3a} = 9.52$, H-2ax), 2.78 (signal was not resolved, 1H, H-5eq), 2.51 (m, 1H, H-3ax), 2.16 (bt, 1H, H-5ax), 1.25 (t, 3H, $J = 6.77$, H-h), 0.93 (d, 3H, $J_{H,Me} = 6.22$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.47 (ester carbonyl), 170.12 (C-b *ipso*), 159.04 (C-6″″/C-2″″), 153.55 (C-4), 144.37 (C-d), 135.37 (C-6′), 134.86 (C-2′), 128.78–113.64 (aromatic carbons), 106.15 (C-e), 68.62 (C-2), 60.89 (C-g), 60.08 (C-6), 55.19 (OCH_3 at C-2″″/C-6″″), 44.95 (C-3), 37.37 (C-f), 36.03 (C-5), 14.12 (C-h), 11.98 (CH_3 at 3). Anal. Calcd for $C_{27}H_{32}N_4O_4S$ (%): C, 63.76; H, 6.34; N, 11.02; Found (%): C, 63.42; H, 6.11; N, 10.78.

*6.7.6. Ethyl 2-[3-methyl-2,6-bis(*p*-methylphenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**31**)*

Compound **31** was obtained as red color solid from **15b** (0.46 g, 88% yield), mp 88–89 °C (dec.); ^1H NMR (δ ppm): 7.35–7.13 (m, 8H, aromatic protons), 6.46 (s, 1H, thiazole H), 4.17 (q, 2H, $J = 6.96$, H-g), 3.84 (d, 1H, $J_{6a,5a} = 11.35$, H-6ax), 3.59 (s, 2H, H-f), 3.48 (d, 1H, $J_{2a,3a} = 9.89$, H-2ax), 2.79 (d, 1H, $J_{6a,5a} = 13.69$, H-5eq), 2.54 (m, 1H, H-3ax), 2.34/2.33 (s, 6H, CH_3 at C-2″″/C-6″″), 2.18 (bt, 1H, H-5ax), 1.26 (t, 3H, $J = 6.96$, H-h), 0.93 (d, 3H, $J_{H,Me} = 6.59$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.54 (ester carbonyl), 170.07 (C-b *ipso*), 153.58 (C-4), 140.28 (C-6′), 139.74 (C-2′), 137.39 (C-2″″/C-6″″), 129.32–126.34 (aromatic carbons), 106.29 (C-e), 69.06 (C-2), 60.98 (C-g), 60.49 (C-6), 44.91 (C-3), 37.46 (C-f), 36.06 (C-5), 21.16/21.12 (CH_3 at C-2″″/C-6″″), 14.20 (C-h), 12.06 (CH_3 at 3). Anal. Calcd for $C_{27}H_{32}N_4O_2S$ (%): C, 68.04; H, 6.77; N, 11.75; Found (%): C, 67.65; H, 6.58; N, 11.87.

*6.7.7. Ethyl 2-[1,3-dimethyl-2,6-diphenylpiperidin-4-hydrazino]-1,3-thiazol-4-acetate (**32**)*

Compound **32** was obtained as shiny dark red color solid from **16b** (0.47 g, 90% yield), mp 78–80 °C (dec.); ^1H NMR (δ ppm): δ 8.61 (bs, 1H, NH), 7.41, 7.43 (2s, 4H, phenyl *ortho* protons), 7.41, 7.43 (2s, 4H, phenyl *ortho* protons), 7.35 (t, 4H, phenyl *meta* protons), 6.43 (s, 1H, thiazole H), 4.16 (q, 2H, $J = 6.56$, H-g), 3.56 (s, 2H, H-f), 3.19 (dd, 1H, $J_{6a,5e} = 2.75$, $J_{6a,5a} = 11.89$, H-6ax), 2.89 (d, 1H, $J_{2a,3a} = 10.25$, H-2ax), 2.75 (dd, 1H, $J_{6a,5a} = 13.91$, H-5eq), 2.67 (m, 1H, H-3ax), 2.34 (bt, 1H, H-5ax), 1.72 (s, 3H, N-Me), 1.25 (t, 3H, $J = 7.14$, H-h), 0.87 (d, 3H, $J_{H,Me} = 6.22$, CH_3 at 3); ^{13}C NMR (δ ppm): 170.46 (ester carbonyl), 169.93 (C-b *ipso*), 152.49 (C-4), 143.74 (C-d), 144.42 (C-6′), 142.89 (C-2′), 128.37, 128.74 (phenyl *meta* carbons), 127.58, 127.61 (phenyl *para* carbons), 126.91, 128.08 (phenyl *ortho* carbons), 106.18 (C-e), 77.79 (C-2), 69.15 (C-6), 60.89 (C-g), 44.82 (C-3), 41.47 (N–CH_3), 37.38 (C-f), 36.51 (C-5), 14.13 (C-h), 12.76 (CH_3 at 3). Anal. Calcd for $C_{26}H_{30}N_4O_2S$ (%): C, 67.50; H, 6.54; N, 12.11; Found (%): C, 67.71; H, 6.71; N, 11.88.

*6.8. Decomposition of thiazolidinone (**17**) with con. HCl or con. HCl + acetic acid*

To the boiling solution of 2-[3-methyl-2,6-diphenylpiperidin-4-hydrazono]-1,3-thiazolidin-4-one **17** (0.15 g, 0.39 mmol) in ethanol, con. HCl (0.3 ml or 5 drops because excess of HCl will salt out the product) or con. HCl (0.3 ml or 5 drops) and acetic acid (0.4 ml) were added. The contents were stirred well with reflux. TLC confirmed the decomposition of products into the corresponding 3-methyl-2,6-diphenylpiperidin-4-one (**1**). The reaction mixture was cooled, quenched with aqueous sodium bicarbonate after 13 h because further increase of reaction time had no significance. The reaction mixture was extracted twice with ethyl acetate (2 × 15 ml), washed with water (2 × 15 ml), brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave the crude mass. Purification of the crude product over silica gel using EtOAc:n-hexane (2:10) as eluting solvent afforded compound **1** (0.021 g, 21% while using con. HCl and 0.025 g, 25% while using con. HCl/AcOH) as white crystals. Melting point and NMR spectral data were in good agreement with the reported results [22].

6.9. Biological studies

6.9.1. Antimycobacterial study

Antimycobacterial activity test was done by radiometric respiratory technique using the BACTEC system as described earlier [19]. Isoniazid and Rifampicin were used as standard drugs and DMSO was used as solvent for the preparation of test solution at different concentrations (from 256 to 1 μg/ml).

6.9.2. In vitro antimicrobial study

In vitro antibacterial and antifungal activities were determined by broth microdilution [14,16] in accordance with the methods of the National Committee for Clinical Laboratory Standards (NCCLS) [20]. *S. aureus* as Gram-positive bacterium, *E. coli* and *K. pneumoniae* as Gram-negative bacteria, *C. albicans*, *A. flavus* and *Rhizopus* sp. as fungi were used as test organisms for this study. Ciprofloxacin and Amphotericin B were used as positive controls for bacteria and fungi respectively while DMSO served as negative control. Different concentrations of test compounds (256–1 μg/ml) in DMSO were prepared by twofold serial dilution from the stock solution at 512 μg/ml.

Acknowledgement

This research work was supported by the second stage of BK21 program.

Appendix. Supplementary data

The proposed mechanistic pathways for the formation of fragments encountered in the respective mass spectra of the compounds and their discussion are made. Substituent parameters for hydrazonothiazolidinone and hydrazinothiazole groups on the ring carbon chemical shifts of piperidone framework in **17**–**32** were calculated and discussed. ^{1}H, ^{13}C, NOESY, HSQC and HMBC spectra for the representative compounds **17** and **32** are furnished. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2009.05.015.

References

[1] <http://www.who.int/mediacentre/factsheets/fs104/en/index.html>, March, (2007).
[2] L. Ballell, R.A. Field, K. Duncan, R.J. Young, Antimicrob. Agents Chemother. 49 (2005) 2153.
[3] I. Van Daele, S. van Calenbergh, Exp. Opin. Ther. Pat. 15 (2005) 131.
[4] Y. Zhang, K. Post-Martens, S. Denkin, Drug Discov. Today 11 (2006) 21.
[5] T. de Aquino, A.P. Liesen, R.E.A. da Silva, V.T. Lima, C.S. Carvalho, A.R. de Faria, J.M. de Araújo, J.G. de Lima, A.J. Alves, E.J.T. de Melo, A.J.S. Góes, Bioorg. Med. Chem. 16 (2008) 446.
[6] A. Verma, S.K. Saraf, Eur. J. Med. Chem. 43 (2008) 897.
[7] G. Küçükgüzel, A. Kocatepe, E.D. Clercq, F. Şahin, M. Güllüce, Eur. J. Med. Chem. 41 (2006) 353.
[8] M.L. Barreca, A. Chimirri, L. De Luca, A.M. Monforte, P. Monforte, A. Rao, M. Zappalà, J. Balzarini, E. De Clercq, C. Pannecouque, M. Witvrouw, Bioorg. Med. Chem. Lett. 11 (2001) 1793.
[9] (a) P. Karegoudar, M.S. Karthikeyan, D.J. Prasad, M. Mahalinga, B.S. Holla, N.S. Kumari, Eur. J. Med. Chem. 43 (2008) 261;
(b) M.S. Al-Saadi, S.A. Rostom, H.M. Faidallah, Arch. Pharm. Chem. Life Sci. 341 (2008) 181;
(c) N. Vukovic, S. Sukdolak, S. Solujic, T. Milosevic, Arch. Pharm. Chem. Life Sci. 341 (2008) 491;
(d) M. Shiradkar, G.V. Suresh Kumar, V. Dasari, S. Tatikonda, K.C. Akula, R. Shah, Eur. J. Med. Chem. 42 (2007) 807.
[10] P.K. Sharma, S.N. Sawnhney, A. Gupta, G.B. Singh, S. Bani, Indian J. Chem. 37B (1998) 376.
[11] F.W. Bell, A.S. Cantrell, M. Hogberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordan, M.D. Kinnick, P. Lind, J.M. Morin, R. Noreen, B. Oberg, J.A. Palkowitz, C.A. Parrish, P. Pranc, C. Sahlberg, R.J. Ternansky, R.T. Vasileff, L. Vrang, S.J. West, H. Zhang, X.X. Zhou, J. Med. Chem. 38 (1995) 4929.
[12] (a) S.R. Angle, J.G. Breitenbucher Part J, in: Atta-ur-Rahman (Ed.), Studies in Natural Products Chemistry, Stereoselective Synthesis, vol. 16, Elsevier, New York, 1995, p. 453;
(b) G.V. Grishina, E.L. Gaidarova, N.S. Zefirov, Chem. Heterocycl. Compd. 30 (1994) 1401;
(c) C.-L. Wang, M.A. Wuorola, Org. Prep. Proced. Int. 24 (1992) 585.
[13] (a) G. Aridoss, S. Balasubramanian, P. Parthiban, S. Kabilan, Spectrochim. Acta Part A 68 (2007) 1153;
(b) P. Parthiban, R. Ramachandran, G. Aridoss, S. Kabilan, Magn. Reson. Chem. 46 (2008) 780.
[14] (a) G. Aridoss, S. Balasubramanian, P. Parthiban, S. Kabilan, Eur. J. Med. Chem. 42 (2007) 851;
(b) G. Aridoss, S. Balasubramanian, P. Parthiban, S. Kabilan, Eur. J. Med. Chem. 41 (2006) 268;
(c) G. Aridoss, S. Amirthaganesan, N. Ashok Kumar, J.T. Kim, K.T. Lim, S. Kabilan, Y.T. Jeong, ARKIVOC xv (2008) 133;
(d) G. Aridoss, P. Parthiban, R. Ramachandran, M. Prakash, S. Kabilan, Y.T. Jeong, Eur. J. Med. Chem. 44 (2009) 577;
(e) G. Aridoss, S. Amirthaganesan, N. Ashok Kumar, J.T. Kim, K.T. Lim, S. Kabilan, Y.T. Jeong, Bioorg. Med. Chem. Lett. 18 (2008) 6542.
[15] N. Rameshkumar, A. Veena, R. Ilavarasan, M. Adiraj, P. Shanmugpandiyan, S.K. Sridhar, Biol. Pharm. Bull. (Japan) 26 (2003) 188.
[16] (a) S. Balasubramanian, G. Aridoss, P. Parthiban, C. Ramalingan, S. Kabilan, Biol. Pharm. Bull. (Japan) 29 (2006) 125;
(b) S. Balasubramanian, C. Ramalingan, G. Aridoss, S. Kabilan, Eur. J. Med. Chem. 40 (2005) 694;
(c) P. Parthiban, S. Balasubramanian, G. Aridoss, S. Kabilan, Med. Chem. Res. 14 (8,9) (2005) 523.
[17] J.C. Lee, Y. Choi, Synth. Commun. 28 (1998) 2021.
[18] S. Hayat, A.-U. Rahman, M.I. Choudhary, K.M. Khan, W. Schumann, E. Bayer, Tetrahedron 57 (2001) 9951.
[19] (a) L.B. Heifets, R.C. Good, Current Laboratory Methods for the Diagnoses of Tuberculosis, in: B.R. Bloom (Ed.), Tuberculosis: Pathogenesis, Prevention and Control, ASM Press, Washington DC, 1994, ISBN 1-55581-072-1, pp. 85–108;
(b) A. Mahapatra, S.P.N. Mativandlela, B. Binneman, P.B. Fourie, C.J. Hamilton, J.J.M. Meyer, F. van der Kooy, P. Houghton, N. Lall, Bioorg. Med. Chem. 15 (2007) 7638.
[20] National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, fifth ed. Approved Standard. NCCLS Document M7–A5, National Committee for Clinical Laboratory Standards, Villanova, Pa, 2000.
[21] A. Manimekalai, J. Jayabharathi, L. Rufina, R. Mahendhiran, Indian J. Chem. 42B (2003) 2074.
[22] K. Pandiarajan, R. Sekar, R. Anatharaman, V. Ramalingam, Indian J. Chem. 30B (1991) 490.
[23] J.B. Lambert, D.A. Netael, H.N. Sun, K.K. Lilianstrom, J. Am. Chem. Soc. 98 (1976) 3778.
[24] P. Parthiban, S. Balasubramanian, G. Aridoss, S. Kabilan, Spectrochim. Acta Part A: Mol. Biomol. Spectrosc. 70 (2008) 11.
[25] G. Sarodnick, M. Heydenreich, T. Linker, E. Kleinpeter, Tetrahedron 53 (2003) 6311.
[26] C.J. Andres, J.J. Bronson, S.V. D'Andrea, M.S. Deshpande, P.J. Falk, K.A. Grant-Young, W.E. Harte, H.T. Ho, P.F. Misco, J.G. Robertson, D. Stock, Y. Sun, A.W. Walsh, Bioorg. Med. Chem. Lett. 10 (2000) 715.
[27] (a) C.R. Noller, V. Baliah, J. Am. Chem. Soc. 70 (1948) 3853;
(b) M. Balasubramanian, N. Padma, Tetrahedron 19 (1963) 2135.