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Synthesis and in vitro antimycobacterial activities of novel 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone

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The difficulty in managing tuberculosis includes the prolonged duration of the treatment, the emergence of drug resistance, and coinfection with HIV/AIDS. Tuberculosis control requires new drugs that act on novel drug targets to help in combating resistant forms of *Mycobacterium tuberculosis* and reduce the treatment duration. For this purpose, 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone derivatives were synthesized and their structures were elucidated by elemental analyses, IR, and ^{1}H-NMR. The in vitro antimycobacterial activities of synthesized compounds **5a-l** were determined by the agar proportion method against *Mycobacterium tuberculosis* H37Rv. Among the target compounds, **5b** and **5f** exhibited the best antimycobacterial activity, with a MIC value of 5 μg/mL.

Key Words: 3(2H)-Pyridazinone, acetophenone hydrazone, antimycobacterial activity, antitubercular drugs

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Introduction

Tuberculosis (TB) is a deadly disease caused by mycobacterial infection, and *Mycobacterium tuberculosis* is the major pathogen for TB in humans.[1] On an annual basis, active cases of TB account for 1.7 million deaths around the world. There are about 2 billion individuals worldwide who are currently infected with *M. tuberculosis*, the causative agent for TB, but most never develop the active form of the disease.[2,3]

The resurgence in the disease is caused by an inadequate and extended chemotherapy that relies on drugs developed in the mid-twentieth century.[4] The associated poor patient compliance and emergence of drug resistant forms of TB, coupled with a strong epidemiological coexistence with HIV/AIDS, highlights the fundamental need for new, more effective drugs to treat the disease.[5,6]

The past 20 years have seen the worldwide appearance of multidrug-resistant (MDR) TB, followed by extensively drug-resistant (XDR) TB, and, most recently, strains that are resistant to all antituberculosis drugs. MDR tuberculosis is caused by *M. tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin, and XDR tuberculosis by mycobacteria resistant to rifampicin and INH, any fluoroquinolone, and 1 of the 3 injectable drugs, capreomycin, kanamycin, and amikacin. Drug resistance severely threatens tuberculosis control, since it raises the possibility of a return to an era in which drugs are no longer effective.[7–9]

Consequently, although efficacious anti-TB drugs are available, TB is still a serious global threat to public health, and a continued search is imperative for new antimycobacterial agents and therapeutic regimens.

Hydrazone derivatives are a considerable pharmacophore group for antimicrobial activity.[10] Many researchers have synthesized these compounds as target structures and evaluated their biological activities. Hydrazones have been reported to possess, among others, antibacterial,[11–14] antifungal,[11–14] antitubercular,[11,15–21] antiviral[22,23] and antimalarial[24,25] activities. In this context, we synthesized new 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone **5a-l** in order to investigate their in vitro antimycobacterial activities by using the agar proportion method against *M. tuberculosis* H37Rv.

Experimental

Chemistry

Materials

The fine chemicals and all solvents used in this study were purchased from Merck and Aldrich Chemical Co.

Melting points of the compounds were determined on an Electrothermal 9200 melting point apparatus and the values given are uncorrected. The IR spectra of the compounds were recorded on a Bruker Vector 22 IR (Opus Spectroscopic Software Version 2.0) spectrophotometer as KBr disks. Elemental analyses were performed with a LECO 932 CHNS analyzer, and ^{1}H-NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) on a Varian Mercury 400 MHz FT-NMR spectrometer at the Central Laboratory of the Faculty of Pharmacy, Ankara University, Ankara, Turkey.

General procedure for synthesis of 6-substituted-3(*2H*)-pyridazinone-2-acetyl-2-(substituted-/nonsubstituted acetophenone) hydrazone derivatives 5a-l

A mixture of 6-substituted-3(2*H*)-pyridazinone-2-yl-acetohydrazide derivatives **4a-c** (0.01 mol) and ap-

propriately substituted acetophenone (0.01 mol) was refluxed in 15 mL of ethanol for 6 h. The mixture was then poured into ice-water. The precipitate formed was recrystallized from ethanol.

6-(4-phenylpiperazine)-3(2*H*)-pyridazinone-2-acetyl-2-acetophenonehydrazone (compound 5a)

Yield 61%. Mp 234-235 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H, N-H, exchangeable with D_2O), 7.70-7.67 (d, 1H, pyridazinone H_5), 7.66-6.94 (m, 10H, aromatic protons), 6.84-6.81 (d, 1H, pyridazinone H_4), 5.04 and 4.66 (s, s, 2H, CH_2), 3.39-3.37 (t, 4H, piperazine a+a' protons), 3.29-3.27 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1705 (C=O, hydrazone), 1662 (C=O, 3(2*H*)-pyridazinone), 3216 (N-H). Anal. Calcd. for $C_{24}H_{26}N_6O_2$: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.13; H, 6.30; N, 19.37.

6-(4-phenylpiperazine)-3(2*H*)-pyridazinone-2-acetyl-2-(4-bromoacetophenone) hydrazone (compound 5b)

Yield 73%. Mp 243-244 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.67 (s, 1H, NH), 7.72-7.69 (d, 1H, pyridazinone H_5), 7.67-6.88 (m, 9H, aromatic protons), 6.80-6.77 (d, 1H, pyridazinone H_4), 5.02 and 4.63 (s, s, 2H, CH_2), 3.36-3.34 (t, 4H, piperazine a+a' protons), 3.28-3.25 (t, 4H, piperazine b+b' protons), 2.22 (s, 3H, CH_3). FT-IR (KBr): υ 1703 (C=O, hydrazone), 1666 (C=O, 3(2*H*)-pyridazinone), 3217 (N-H). Anal. Calcd. for $C_{24}H_{25}BrN_6O_2$: C, 56.59; H, 4.95; N, 16.50. Found: C, 56.81; H, 5.05; N, 16.69.

6-(4-phenylpiperazine)-3(2*H*)-pyridazinone-2-acetyl-2-(4-chloroacetophenone) hydrazone (compound 5c)

Yield 67%. Mp 252-253 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.69 (s, 1H, NH), 7.73-7.70 (d, 1H, pyridazinone H_5), 7.68-6.91 (m, 9H, aromatic protons), 6.83-6.79 (d, 1H, pyridazinone H_4), 5.06 and 4.68 (s, s, 2H, CH_2), 3.36-3.34 (t, 4H, piperazine a+a' protons), 3.28-3.24 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1706 (C=O, hydrazone), 1665 (C=O, 3(2*H*)-pyridazinone), 3214 (N-H). Anal. Calcd. for $C_{24}H_{25}ClN_6O_2$: C, 62.00; H, 5.42; N, 18.08. Found: C, 62.07; H, 5.54; N, 17.96.

6-(4-phenylpiperazine)-3(2*H*)-pyridazinone-2-acetyl-2-(4-fluoroacetophenone) hydrazone (compound 5d)

Yield 81%. Mp 262-263 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.70 (s, 1H, NH), 7.76-7.74 (d, 1H, pyridazinone H_5), 7.67-6.89 (m, 9H, aromatic protons), 6.82-6.80 (d, 1H, pyridazinone H_4), 5.05 and 4.66 (s, s, 2H, CH_2), 3.39-3.37 (t, 4H, piperazine a+a' protons), 3.29-3.27 (t, 4H, piperazine b+b' protons), 2.24 (s, 3H, CH_3). FT-IR (KBr): υ 1704 (C=O, hydrazone), 1668 (C=O, 3(2*H*)-pyridazinone), 3215 (N-H). Anal. Calcd. for $C_{24}H_{25}FN_6O_2$: C, 64.27; H, 5.62; N, 18.74. Found: C, 64.14; H, 5.74; N, 18.77.

6-[4-(4-fluorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-acetophenone hydrazone (compound 5e)

Yield 80%. Mp 271-272 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.73 (s, 1H, NH), 7.77-7.75 (d, 1H, pyridazinone H_5), 7.72-6.96 (m, 9H, aromatic protons), 6.85-6.83 (d, 1H, pyridazinone H_4), 5.07 and 4.70 (s, s, 2H, CH_2), 3.39-3.37 (t, 4H, piperazine a+a' protons), 3.30-3.28 (t, 4H, piperazine b+b' protons), 2.21 (s, 3H, CH_3). FT-IR (KBr): υ 1705 (C=O, hydrazone), 1666 (C=O, 3(2*H*)-pyridazinone), 3213 (N-H). Anal. Calcd. for $C_{24}H_{25}FN_6O_2$: C, 64.27; H, 5.62; N, 18.74. Found: C, 64.04; H, 5.33; N, 18.81.

6-[4-(4-fluorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-bromoacetophenone) hydrazone (compound 5f)

Yield 62%. Mp 248-249 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.80 (s, 1H, NH), 7.79-7.76 (d, 1H, pyridazinone H_5), 7.70-6.95 (m, 8H, aromatic protons), 6.86-6.84 (d, 1H, pyridazinone H_4), 5.07 and 4.70 (s, s, 2H, CH_2), 3.40-3.38 (t, 4H, piperazine a+a' protons), 3.30-3.28 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1705 (C=O, hydrazone), 1663 (C=O, 3(2*H*)-pyridazinone), 3216 (N-H). Anal. Calcd. for $C_{24}H_{24}BrFN_6O_2$: C, 54.66; H, 4.59; N, 15.94. Found: C, 54.82; H, 4.48; N, 16.12.

6-[4-(4-fluorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-chloroacetophenone) hydrazone (compound 5g)

Yield 50%. Mp 229-230 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.82 (s, 1H, NH), 7.77-7.75 (d, 1H, pyridazinone H_5), 7.79-6.72 (m, 8H, aromatic protons), 6.99-6.97 (d, 1H, pyridazinone H_4), 5.10 and 4.80 (s, s, 2H, CH_2), 3.42-3.39 (t, 4H, piperazine a+a' protons), 3.31-3.29 (t, 4H, piperazine b+b' protons), 2.24 (s, 3H, CH_3). FT-IR (KBr): υ 1704 (C=O, hydrazone), 1665 (C=O, 3(2*H*)-pyridazinone), 3214 (N-H). Anal. Calcd. for $C_{24}H_{24}Cl\,FN_6O_2$: C, 59.69; H, 5.01; N, 17.40. Found: C, 59.81; H, 5.16; N, 17.26.

6-[4-(4-fluorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-fluoroacetophenone) hydrazone (compound 5h)

Yield 40%. Mp 241-242 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.79 (s, 1H, NH), 7.75-7.72 (d, 1H, pyridazinone H_5), 7.68-6.90 (m, 8H, aromatic protons), 6.85-6.83 (d, 1H, pyridazinone H_4), 5.07 and 4.70 (s, s, 2H, CH_2), 3.39-3.37 (t, 4H, piperazine a+a' protons), 3.29-3.27 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1706 (C=O, hydrazone), 1662 (C=O, 3(2*H*)-pyridazinone), 3216 (N-H). Anal. Calcd. for $C_{24}H_{24}F_2N_6O_2$: C, 61.79; H, 5.19; N, 18.02. Found: C, 61.51; H, 5.36; N, 17.93.

6-[4-(4-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-acetophenone hydrazone (compound 5i)

Yield 56%. Mp 280-281 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.72 (s, 1H, NH), 7.73-7.70 (d, 1H, pyridazinone H_4), 7.67-6.90 (m, 9H, aromatic protons), 6.82-6.80 (d, 1H, pyridazinone H_4), 5.05 and 4.70 (s, s, 2H, CH_2), 3.37-3.35 (t, 4H, piperazine a+a' protons), 3.27-3.25 (t, 4H, piperazine b+b' protons), 2.22 (s, 3H, CH_3). FT-IR (KBr): υ 1706 (C=O, hydrazone), 1664 (C=O, 3(2*H*)-pyridazinone), 3218 (N-H). Anal. Calcd. for $C_{24}H_{25}ClN_6O_2$: C, 62.00; H, 5.42; N, 18.08. Found: C, 62.17; H, 5.56; N, 17.98.

6-[4-(4-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-bromoacetophenone)hydrazone (compound 5j)

Yield 48%. Mp 231-232 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.70 (s, 1H, NH), 7.77-7.75 (d, 1H, pyridazinone H_4), 7.65-6.90 (m, 8H, aromatic protons), 6.80-6.79 (d, 1H, pyridazinone H_4), 5.07 and 4.70 (s, s, 2H, CH_2), 3.38-3.36 (t, 4H, piperazine a+a' protons), 3.28-3.26 (t, 4H, piperazine b+b' protons), 2.24 (s, 3H, CH_3). FT-IR (KBr): υ 1704 (C=O, hydrazone), 1663 (C=O, 3(2*H*)-pyridazinone), 3212 (N-H). Anal. Calcd. for $C_{24}H_{24}BrClN_6O_2$: C, 53.00; H, 4.45; N, 15.45. Found: C, 53.08; H, 4.40; N, 15.35.

6-[4-(4-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-chloroacetophenone) hydrazone (compound 5k)

Yield 73%. Mp 237-238 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.72 (s, 1H, NH), 7.75-7.73 (d, 1H,

pyridazinone H_5), 7.69-6.92 (m, 8H, aromatic protons), 6.82-6.80 (d, 1H, pyridazinone H_4), 5.09 and 4.72 (s, s, 2H, CH_2), 3.37-3.35 (t, 4H, piperazine a+a' protons), 3.29-3.27 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1707 (C=O, hydrazone), 1666 (C=O, 3(2*H*)-pyridazinone), 3214 (N-H). Anal. Calcd. for $C_{24}H_{24}Cl_2N_6O_2$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.96; H, 5.01; N, 16.59.

6-[4-(4-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-(4-fluoroacetophenone) hydrazone (compound 5l)

Yield 45%. Mp 245-246 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.68 (s, 1H, NH), 7.76-7.74 (d, 1H, pyridazinone H_4), 7.67-6.90 (m, 8H, aromatic protons), 6.78-6.75 (d, 1H, pyridazinone H_4), 5.06 and 4.68 (s, s, 2H, CH_2), 3.36-3.34 (t, 4H, piperazine a+a' protons), 3.28-3.26 (t, 4H, piperazine b+b' protons), 2.23 (s, 3H, CH_3). FT-IR (KBr): υ 1704 (C=O, hydrazone), 1664 (C=O, 3(2*H*)-pyridazinone), 3213 (N-H). Anal. Calcd. for $C_{24}H_{24}ClFN_6O_2$: C, 59.69; H, 5.01; N, 17.40. Found: C, 59.82; H, 5.18; N, 17.14.

Biological activity

Agar proportion method

The minimum inhibitory concentration (MIC) values of each synthesized compound, **5a-l**, were tested by agar dilution in duplicate as recommended by the Clinical Laboratory Standards Institute (CLSI).[26,27] Positive and negative growth controls were run in each assay. INH and ethambutol (EMB) were used as control agents. H37Rv was used as the standard strain. Stock solutions of synthesized compounds **5a-l** and reference compounds were prepared in DMSO/H_2O (50%) at a concentration of 1000 μg/mL. These solutions were filtered through a 0.22-μm membrane filter (Millipore, USA). Middlebrook 7H10 agar medium (Difco) was supplemented with oleic acid-albumin-dextrose-catalase (OADC, BBL^{TM}). Synthesized compounds **5a-l** and control agents were added to obtain an appropriate final concentration in the medium. The final concentrations of INH and ethambutol were 0.2-1 μg/mL and 1 μg/mL, respectively. Synthesized compounds **5a-l** were prepared at final concentrations of 2.5, 5, 10, 20, and 40 μg/mL. Agar without any references and synthesized compounds **5a-l** were used as a positive growth control, and 3 mL of prepared medium was dispensed into sterile tubes. The DMSO concentration in the final solutions was not above 1% for antimycobacterial activity.

Inoculum preparation

H_{37}Rv was maintained in Lowenstein-Jensen medium. A culture suspension was prepared by subculturing in Middlebrook 7H9 broth (Difco) supplemented with 10% OADC at 37 °C for 7-10 days, until a density corresponding to 10^{-2} to 10^{-4} dilutions were obtained from McFarland standard No. 1. Then 0.1 mL of the diluted suspension was inoculated onto the control and the other tubes with **5a-l** in different concentrations. The tubes were incubated at 37 °C in an atmosphere of 5% CO_2 for 3 weeks. The MIC values were defined as the lowest concentration that inhibited more than 90% of the bacterial growth, and the results of INH and EMB were interpreted according to the CLSI. The MIC was considered the lowest concentration that showed no visible colonies in all dilutions.

Results and discussion

Chemistry

The synthetic route of the synthesized compounds is given in the Figure. Reaction of 3,6-dichloropyridazine with arylpiperazines afforded 3-chloro-6-substitutedpyridazine derivatives **1a-c**. The physical and spectral properties of 3-chloro-6-substitutedpyridazines **1a-c** were in accordance with the literature.[28,29] Hydrolysis of compounds **1a-c** was carried out upon heating in glacial acetic acid to afford 6-substituted-3(2*H*)-pyridazinone derivatives **2a-c**. Compounds **2a-c** were made to react with ethyl bromoacetate to afford the ethyl 6-substituted-3(2*H*)-pyridazinone-2-ylacetate derivatives **3a-c**, from which the 6-substituted-3(2*H*)-pyridazinone-2-yl acetohydrazide derivatives **4a-c** were obtained by treatment with hydrazine hydrate (99%). The compounds synthesized, **2a-c**, **3a-c**, and **4a-c**, reported previously by us, were synthesized in this study as earlier reported. IR and ^{1}H-NMR spectral data of these compounds were in accordance with the data reported in our previous study.[30–34]

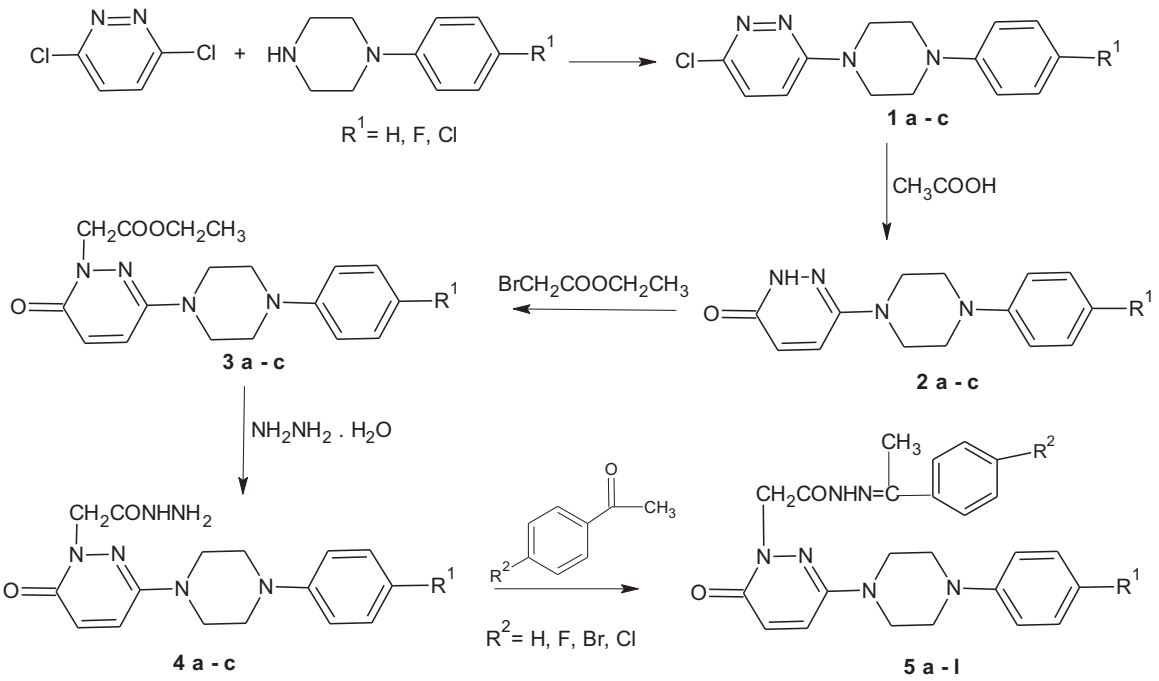


Figure. Synthetic route of the synthesized compounds.

By the reaction of 3(2*H*)-pyridazinone-2-yl acetohydrazides **4a-c** with substituted acetophenone in ethanol, 12 new final compounds, **5a-l**, were synthesized. All of the newly synthesized compounds, **5a-l**, were identified by IR and ^{1}H-NMR spectra and confirmed by elemental analysis.

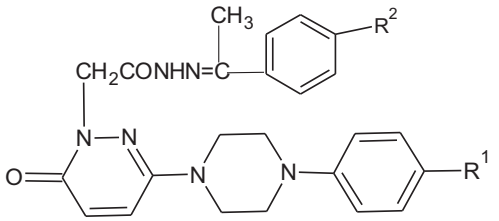
The elemental analysis data for each compound were in good agreement with the empirical formula proposed. In the IR spectra, newly synthesized compounds **5a-l** exhibited characteristic υ (C=O) bands at 1703-1707 and 1662-1668 cm^{-1} for acetyl side chains and pyridazinone rings, respectively. The υ (N—H) stretching bands were centered at 3212-3218 cm^{-1}.

The ^{1}H-NMR spectral data of compounds **5a-l** are presented in the Experimental Section. The ^{1}H-NMR spectra of all complexes were consistent with their corresponding protons as chemical shift values and numbers of hydrogen.

Antimycobacterial activity test

The literature survey on functional groups that could be considered as pharmacophores for antitubercular activities revealed that the hydrazone moiety is common among most of the antitubercular agents.[10,35] For this purpose, a series of 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazones, **5a-l**, were tested in vitro against *M. tuberculosis* H37Rv, which is susceptible to INH and EMB. The MIC was determined using the agar proportion method in Middlebrook 7H10 medium.

Table. In vitro antimycobacterial activity of 6-Substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone **5a-l**.



5 a - l

Compound	R^1	R^2	MIC (μg/mL)*
5a	H	H	20
5b	H	Br	5
5c	H	Cl	40
5d	H	F	20
5e	F	H	20
5f	F	Br	5
5g	F	Cl	N/A
5h	F	F	N/A
5i	Cl	H	N/A
5j	Cl	Br	40
5k	Cl	Cl	40
5l	Cl	F	N/A
INH			0.2
EMB			1

*Compounds regarded as not active (N/A) if no inhibition was observed at 40 μg/mL.

The MIC values of synthesized compounds **5a-l** and reference compounds INH and EMB are given in the Table. Comparison of the activities of synthesized compounds **5a-l** indicated that compounds **5b** and **5f**, with a 4-bromoacetophenonehydrazone substituent, were the most potent compounds, with MIC values of 5 μg/mL. Among the synthesized compounds, **5a**, **5d**, and **5e**, bearing a nonsubstituted or 4-fluoroacetophenonehydrazone, exhibited inhibitory effects with MIC values of 20 μg/mL. The other synthesized compounds, **5c**, **5j**, and **5k**, were found to be the least active compounds against *M. tuberculosis* H37Rv, with MIC values of 40 μg/mL. As shown in the Table, **5g, 5h, 5i**, and **5l** did not seem to have antimycobacterial activity.

The newly synthesized compounds derived from 4-bromoacetophenone hydrazone, **5b** and **5f**, were found to be more active than the other acetophenone hydrazone compounds. This finding is consistent with the data reported in the literature, of a hydrazone analog with derived substituted benzaldehyde.[10,17,35] In the literature, it was also reported that the aryl ring with electron-withdrawing substituents enhanced the activity, especially the bromo substituent, and with electron-donating substituents/properties, activity decreased.[36–38] In conclusion, 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(substituted/nonsubstituted acetophenone) hydrazone derivatives **5b** and **5f** seem to have the potential to be used as antimycobacterial agents, but further in vitro and in vivo experiments are required to verify their antimycobacterial activities.

References

1. Tripathi, R. P.; Tewari, N.; Diwivedi, N.; Tivari, V. K. *Med. Res. Rev.* **2005**, *25*, 93-131.
2. Arcus, V. L.; Lott, J. S.; Johnston, J. M.; Baker, E. N. *Drug Discov. Today* **2006**, *11*, 28-35.
3. Umesiri, F. E.; Sanki, A. K.; Boucau, J.; Ronning, D. R.; Sucheck, S. J. *Med. Res. Rev.* **2010**, *30*, 290-326.
4. Haydel, S. E. *Pharmaceuticals* **2010**, *3*, 2268-2290.
5. Toossi, Z. *J. Infect. Dis.* **2003**, *188*, 1146-1155.
6. Kranzer, K.; Houben, R. M.; Glynn, J. R.; Bekker, L. G.; Wood, R.; Lawn, S. D. *Lancet Infect. Dis.* **2010**, *10*, 93-102.
7. Logu, A. D.; Onnis, V.; Saddi, B.; Congiu, C.; Schivo, M. L.; Cocco, M. T. *J. Antimicrob. Chemoth.* **2002**, *49*, 275-282.
8. Takahashi, K.; Hasegawa, Y.; Abe, T.; Yamamoto, T.; Nakashima, K.; Imaizumi, K.; Shimokata, K. *Tuberculosis* **2008**, *88*, 52-57.
9. Caminero, J. A.; Sotgiu, G.; Zumla, A.; Migliori, G. B. *Lancet Infect. Dis.* **2010**, *10*, 621-629.
10. Rollas, S.; Küçükgüzel, S. G. *Molecules* **2007**, *12*, 1910-1939.
11. Küçükgüzel, S. G.; Mazi, A.; Şahin, F.; Öztürk, S.; Stables, J. *Eur. J. Med. Chem.* **2003**, *38*, 1005-1013.
12. Özkay, Y.; Tunalı, Y.; Karaca, H.; Işıkdağ, İ. *Eur. J. Med. Chem.* **2010**, *45*, 3293-3298.
13. Ajani, O. O.; Obafemi, C. A.; Nwinyi, O. C.; Akinpelu, D. A. *Bioorg. Med. Chem.* **2010**, *18*, 214-221.
14. Salgın-Gökşen, U.; Gökhan-Kelekçi, N.; Göktaş, O.; Köysal, Y.; Kılıç, E.; Işık, S.; Aktay, G.; Ozalp, M. *Bioorg. Med. Chem.* **2007**, *15*, 5738-5751.

15. Sriram, D.; Yogeeswari, P.; Madhu, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4502-4505.
16. Maccari, R.; Ottaná, R.; Vigorita, M. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2509-2513.
17. Sriram, D.; Yogeeswari, P.; Devakaram, R. V. *Bioorg. Med. Chem.* **2006**, *14*, 3113-3118.
18. Koçyiğit-Kaymakçıoğlu, B.; Oruç, E.; Unsalan, S.; Kandemirli, F.; Shvets, N.; Rollas, S.; Anatholy, D. *Eur. J. Med. Chem.* **2006**, *41*, 1253-1261.
19. Imramovský, A.; Polanc, S.; Vinsová, J.; Kocevar, M.; Jampílek, J.; Reckova, Z.; Kaustová, J. *Bioorg. Med. Chem.* **2007**, *15*, 2551-2559.
20. Turan-Zitouni, G.; Özdemir, A.; Kapancıklı, Z. A.; Benkli, K.; Chevallet, P.; Akalin G. *Eur. J. Med. Chem.* **2008**, *43*, 981-985.
21. Pavan, F. R.; Maia, P. I.; Liete, S. R. A.; Deflon, V. M.; Batista, A. A.; Sato, D. N.; Franzbau, S. G.; Liete, C. Q. F. *Eur. J. Med. Chem.* **2010**, *45*, 1898-1905.
22. Abdel-Aal, M. T.; El-Sayed, W. A; El-Ashry, E. H. *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 656-663.
23. El-Sabbagh, O. I.; Rady, H. M. *Eur. J. Med. Chem.* **2009**, *44*, 3680-3686.
24. Walcourt, A.; Loyevsky, M.; Lovejoy, D. B.; Gordeuk, V. R.; Richardson, D. R. *Int. J. Biochem. Cell B* **2004**, *36*, 401-407.
25. Gemma, S.; Kukreja, G.; Fattorusso, C.; Persico, M.; Romano, M. P.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, E.; Basilico, N.; Taramelli, D.; Yardley, V.; Butini, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5384-5388.
26. National Committee for Clinical Laboratory Standards. *Susceptibility Testing of Mycobacteria, Nocardia, and Other Aerobic Actinomycetes*:;*pproved Standard NCCLS Document M24-A*. Wayne, Pennsylvania, 2003.
27. Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS). *Antimycobacterial Susceptibility Testing for M. tuberculosis: Tentative Standard NCCLS Document M24-T*. Villanova, Pennsylvania, 2002.
28. Boissier, J. R.; Ratouis, R.; Dumont, C. *J. Med. Chem.* **1963**, *6*, 541-544.
29. Elvio, B.; Paravicini, F.; Emilio, T. *Farmaco Ed. Sci.* **1969**, *24*, 919-929.
30. Gökçe, M.; Doğruer, D. S.; Şahin, M. F. *Il Farmaco* **2001**, *56*, 233-237.
31. Şahin, M. F.; Badıçoğlu, B.; Gökçe, M.; Küpeli, E.; Yeşilada, E. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 445-452.
32. Dündar, Y.; Gökçe, M.; Küpeli, E.; Şahin, M. F. *Arzneim-Forsch Drug Res.* **2007**, *57*, 777-781.
33. Yelken, G. *6-Sübstitüe-3(2H)-Piridazinon 2-il Asetohidrazit Türevi Bileşiklerin Sentezi Antibakteriyel ve Antifungal Aktivetelerinin İncelenmesi*. Gazi University, Institute of Health Science, Ankara, Turkey, 2008.
34. Gökçe, M.; Utku, S.; Küpeli, E.;*ur. J. Med. Chem.* **2009**, *44*, 3760-3764.
35. Sriram, D.; Yogeeswari, P.; Madhu, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 876-878.
36. Sriram, D.; Yogeeswari P.; Reddy, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2113-2116.
37. Ali, M. A.; Shaharyar, M. *Bioorg. Med. Chem.* **2007**, *15*, 1896-1902.
38. Fassihi, A; Azadpour, Z; Delbari, N.; Saghaie, L.; Memarian, H. R.; Sabet, R.; Alborzi, A.; Miri, R.; Pourabbas, B.; Mardaneh, J.; Mousavi, P.; Moeinifard, B.; Sadeghi-aliabadi, H. *Eur. J. Med. Chem.* **2009**, *44*, 3253-3258.