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Research Article

Synthesis and Antimicrobial Activity of Some New Barbituric Acid Derivatives Containing Thiazole Moiety from Sulfadiazine

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Abstract

A new series of barbituric acid derivatives w prepared and characterized by Fourier-transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance (^{1}H-NMR) and nuclear magnetic resonance (^{13}C-NMR). The antimicrobial studies of synthesized compounds were screened for antibacterial activity against three different types of bacteria (*Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*), and against two types of fungi (*Candida albicans* and *Aspergillus flavus*). In this research, a reaction of sulfadiazine with chloroacetylchloride gave 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide [A] which was reacted with thiourea, and with K_2CO_3 to give thiazole derivative [B]. The last compound (thiaole derivative) was reacted with chloroacetyl chloride in basic medium to form compound [R]. 5,5-Diethyl barbituric acid and 5-phenyl,5-ethyl barbituric acid were treated with formaldehyde to give 1,3-bis(hydroxyl methyl)barbituric acids derivatives [B_1-B_2]. Finally, the compound [R] reacted with 1,3-bis(hydroxyl methyl) barbituric acids derivatives via Williamson reaction to form new barbituric acid derivatives [RB_1-RB_2]. By the reaction of 5,5-diethyl barbituric acid with 5-phenyl,5-ethyl barbituric acid, new compounds of barbituric acids derivatives [RB_3] and [RB_4] were obtained. The biological applications of the synthesized compounds showed a greater effect in antimicrobial activities from the starting material (sulfadiazine).

Keywords: Sulfadiazine; Thiazole; Barbituric acid; Antimicrobial activity

Introduction

Sulfadiazine is one of the antibiotic drugs that belong to the sulfonamide group; it has been utilized in veterinary and human therapy over 60 years [1]. Also, it is utilized for the treatment of urinary tract infections (UTIs) [2], and in clinic as a topical agent either alone or in combination with other compounds in the treatment of wound and burn infections [3]. Thiazoles are a group of heterocyclic compounds that possess a wide variety of biological activities and their utility as medicaments is very much established [4]. The applications of thiazoles were found in drug development for the treatment of inflammation, bacterial, allergies, HIV infections hypertension, schizophrenia, hypnotics and in the treatment of pain [5]. Barbituric acid, or pyrimidine-2,4,6-(1H,3H,5H)-trione,H_3BA, that contains five hetero atoms (three O and two N) is commonly known as barbiturates [6]. It was prepared by Adolf Von Baeyer in 1864 from a combination of the urea and malonic acid [7]. Barbituric acid has been extensively utilized in

biological and medical studiws for many years, the best known of which is their sedative activity in the central nervous system [8]. They are a favour in medicinal chemistry as anticonvulsants, sedatives, hypnotics and anxiolytic agents [9].

Experimental

All reagents and solvents were purchased from commercial sources and used without purification. Melting points (m.p.) were recorded using Electro thermal melting point apparatus (UK). Fourier-transform infrared spectra were recorded using Shimadzu FTIR-8400S infrared spectrophotometer by KBr disc (Kufa University). Proton nuclear magnetic resonance (^{1}H-NMR) and nuclear magnetic resonance (^{13}C-NMR) were recorded by Bruker spectrometer, operating at (400MHZ for ^{1}HNMR and 75 MHZ for ^{13}C NMR) with DMSO-d_6 as a solvent (Abu Ali Center Lab, Mashhad, Iran). Thin layer chromatography (TLC) was performed on aluminum plates and coated with a layer of (0.25 mm) silica gel; compounds were detected by iodine vapor. Autoclave was used to sterilize agar media, supplied by Prestige Medical-England. Incubator was used to maintain different temperatures required for the growth of organism, supplied by Memert-Germany.

Synthesis of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl) acetamide[A] [10]

To a stirred mixture of sulfadiazine (0.01 mol) and triethylamine (1.67 mL) in dimethylformamide (DMF) as solvent, chloroacetyl chloride (0.01 mol) was added drop-wise by micropipette. After the addition was completed, the mixture was stirred for 3 h without heating. Finally, the solvent was evaporated, and the precipitate was filtered, dried and washed with distilled water-ether to give compound [A]. The crystalline precipitates were re-crystallized with ethanol. Yield: Pale yellow, 87 %; m.p. = 220 – 222 °C; retardation factor (R_f) = 0.75; the TLC for the reaction was completed by using benzene : methanol = 4 : 1.

Synthesis of 4-(2-aminothiazol-4-ylamino)-N-(pyrimidin-2-yl)benzene sulfonamide [B] [11]

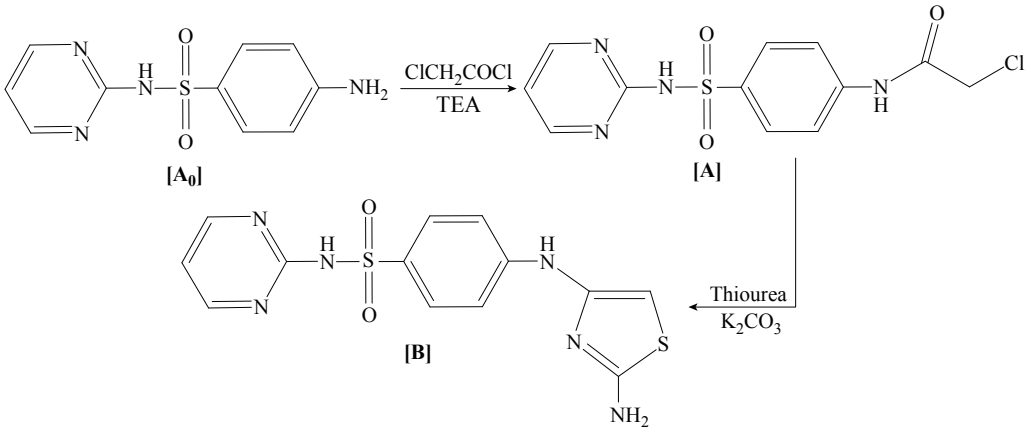
A mixture of [A] (0.01 mol), thiourea (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in absolute ethanol (25 mL) was heated under reflux on water bath for 12 h. The excess of ethanol was removed by distillation and the residue was treated with 5% sodium carbonate solution to remove acid impurities. The yellow precipitate was filtered, washed with water several times and dried at 50 °C. Finally, the product was crystallized from ethanol. Yield: 78%; m.p.=178 – 180 °C; R_f = 0.58; benzene : methanol = 4 : 1 (Scheme 1).

2-chloro-N-(4-(4-(N-pyrimidin-2-ylsulfamoyl) phenylamino)thiazol-2-yl)acetamide[R] [12]

Preparation method of compound [R] was the same as preparation method of compound [A] in step 1: 0.01 mol of compound [B] and 0.01 mol of triethylamine in DMF; 0.01mol of chloroacetyl chloride was added drop-wise to the mixture. The reaction mixture was stirred for 4 h without heating. The product obtained after the evaporation of the solvent was filtered, washed with ether and re-crystallized with ethanol. Yield: Dark brown, 65%; m.p. = 211– 213 °C; R_f= 0.7; TLC for the reaction was completed by using benzene : methanol = 4 : 1.

Synthesis of 1,3-bis(hydroxyl methyl) barbituric acids derivatives [B_1]-[B_2] [13]

5,5-diethyl barbituric acid and 5-phenyl,5-ethyl



Scheme 1 Preparation of thiazole derivative [B].

barbituric acid (0.01 mol) was dissolved in ethanol (20 mL) and distilled water (10 mL). To this solution, formaldehyde (0.02 mol) was added. The mixture was refluxed at 60 – 70 °C for 12 h. The solvent was evaporated; the solid precipitate was suspended in water (10 mL), and extracted with chloroform to give 5,5-diethyl-1,3-bis(hydroxylmethyl)pyrimidine-2,4,6(1H,3H,5H)-trione [B_1] and 5-ethyl-5-phenyl-1,3-bis(hydroxylmethyl)-pyrimidine-2,4,6(1H,3H,5H) trione [B_2]. Yield: White, 85% and 87%; m.p. = 93 – 95 and 163 - 165 °C; R_f = 0.7 and 0.65, respectively.

Synthesis of barbituric acids derivative [RB_1]-[RB_2] [14]

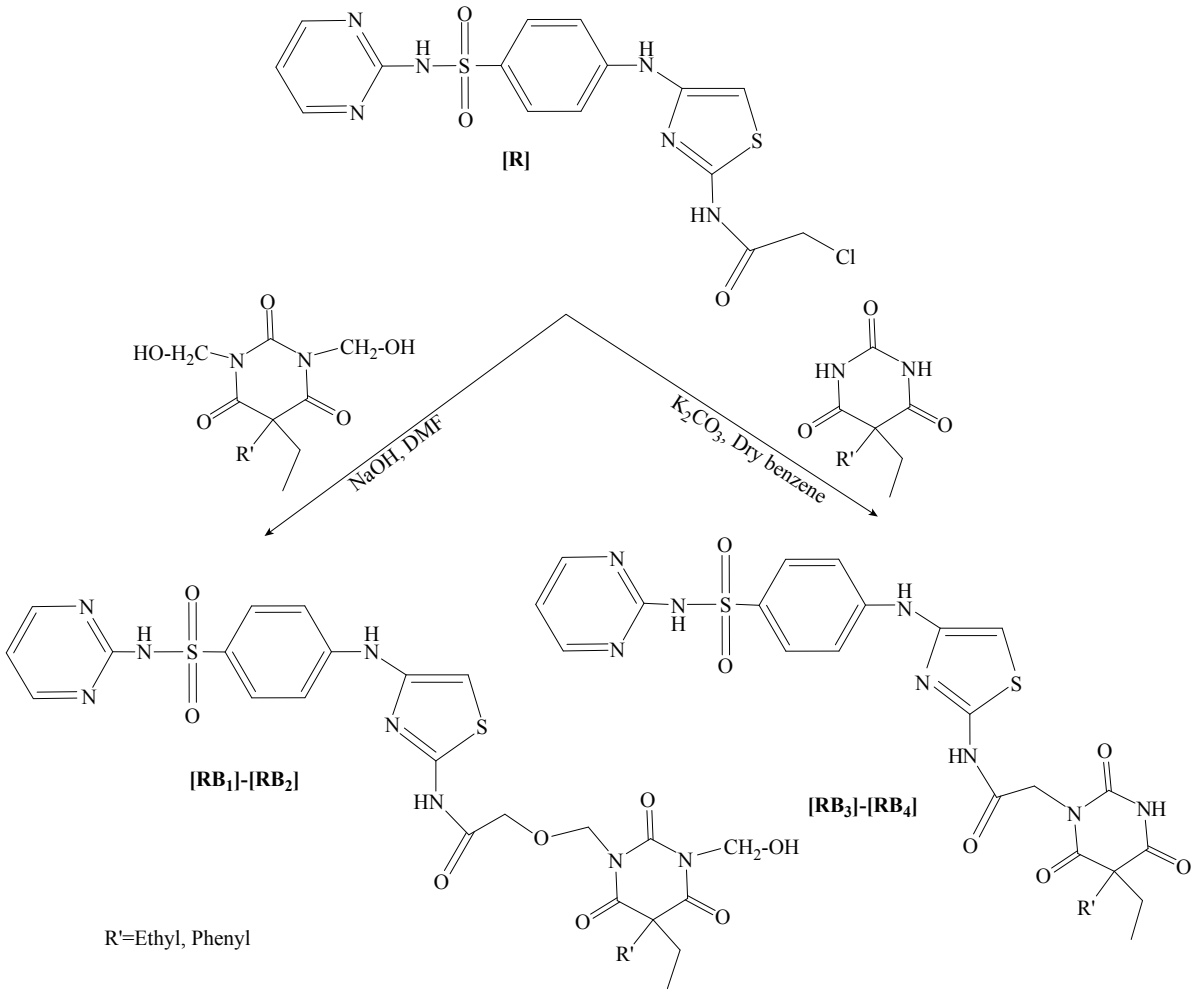
0.01 mol of compounds [R] in 15 mL DMF was added drop wise to the stirred suspension of 0.01 mol [B_1]-[B_2] respectively and 0.01 mol NaOH in 15 mL DMF. The mixture was refluxed for 5 h. Then, the reaction mixture was diluted with water (40 mL), andthen extracted with ether (2×20 mL). The combined organic layers were washed successively with water (30 mL), filtered and evaporated to dryness to give compounds [RB_1]-[RB_2] (Table 1).

Synthesis of barbituric acids derivative [RB_3]-[RB_4] [15]

To a solution of 5,5-diethylbarbituric acid and 5-ethyl-5-phenyl barbituric acid (0.01 mol), respectively, 15 mL of dry benzene and 0.01 mol compound [R] and 0.01 mol potassium carbonate

Table 1 Some physical properties of barbituric acids derivative

Composition	General formula	Color	Yield (%)	M.P. (°C)	R_f
RB_1	$C_{26}H_{32}N_8O_8S_2$	Pale yellow	76	170-172	0.62
RB_2	$C_{30}H_{32}N_8O_8S_2$	Pale yellow	69	280-282	0.71
RB_3	$C_{24}H_{27}N_8O_6S_2$	Light brown	72	237-239	0.65
RB_4	$C_{28}H_{27}N_8O_6S_2$	Light brown	64	163-165	0.62



Scheme 2 Preparation of barbituric acid derivatives [RB_1]-[RB_4].

was added. The mixture was refluxed for 4-5 h with stirring. The residue obtained was treated with ice-cold water (5 mL), filtered, dried in oven and recrystallized (Table 1, Scheme 2).

Test of biological activity

Bacterial suspension was prepared from used bacteria and compared with McFarland tube 1.5×10^8 cell/mL which refers to the sensitivity prepared and the number of bacteria cultivated. Bacterial suspension was spread on Muller Hinton Agar homogeneously (0.1 mL) to cover the whole medium. Afterwards, three holes were made in the paten dish by the cork piercing to diameter of 6 mm at the concentration used. Diluted solutions of 0,03 and 0.06 mg/mL were prepared for each compound at pH 7. Then, the concentrated solutions prepared from chemical compounds were put in holes to reveal their effectiveness of biological activity. The paten dish was incubated at temperature 37 °C for 24 h. Finally, the diameter of inhibition zone for each disc was measured by the ruler to determine the effectiveness of each compound and compare it with the standard limits of sensitivity of the same species of bacteria against antibiotics [16].

To examine the antifungal activity, 0,03 and 0.06 mg/mL of synthesized compounds were dissolved in 5 mL dimethyl sulfoxide as solvent, and evaluated in vitro employing the filter paper disc method against *Candida albicans* and *Aspergillus flavus* by measuring inhibition zone in millimetre [17].

Results and Discussion

In this research, a series of new barbituric acid derivatives [RB_1]-[RB_4] containing thiazole moiety were synthesized from sulfa drug. Sulfadiazine is the starting material for this research, it was converted to 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl) acetamide [A] by the reaction with chloroacetyl chloride and triethylamine in DMF as solvent. The synthesized compound [A] was characterized by sodium fusion test and the result was positive**.** The chlorine element was identified using saturated solution of $AgNO_3$ reagent; white precipitate was observed, which was due to the presence of chlorine in compound [A]. FTIR spectrum showed the disappearance of one absorption band at 3425 cm^{-1} which was due to the stretching vibrations of -NH_2 group of sulfadiazine, the remaining of the band at 3381 cm^{-1} which was due to the N-H group of amide, the absorption band at 3080 cm^{-1} which was attributed to the -CH_2 group, the absorption band at 1670 cm^{-1} due to the stretching band of C=O amide group, and the absorption band at 665 cm^{-1} due to the stretching band of C-Cl group. All these changes in absorption bands are good evidence to the formation of compound [A].

The compound 4-(2-aminothiazol-4-ylamino)-N-(pyrimidin-2-yl) benzene sulfonamide [B] was prepared by the reaction of [A] with thiourea and anhydrous potassium carbonate (Scheme 1). The structure of 4-(2-aminothiazol-4-ylamino)-N-(pyrimidin-2-yl) benzene sulfonamide [B]was confirmed by FTIR, ^{1}H-NMR and ^{13}C-NMR.

The FTIR spectrum of [B] showed absorption of the band at 3394-3358 cm^{-1} due to the NH_2 group and absence of the band at 665 cm^{-1} due to C–Cl for compound [A]. The appearance of stretching vibration band at 3275 cm^{-1} was due to the -NH group. FTIR showed absorption peaks at 1543 cm^{-1} (C=C thiazole), 1583 cm^{-1} (C=C aromatic), 1622 cm^{-1} (C=N thiazole) and 1662 cm^{-1}(C=N pyrimidine).

^{1}H-NMR spectrum (DMSO-d_6, δ ppm) of [B]: 7.25 (s, 2H, NH_2), 5.33 (s, 1H, C-5 thiazole), 7.46-7.71 (m, 4H, Ar-H), 11.48 (s, 1H, NH-SO_2), and 10.46 (s, 1H, NH).

^{13}C-NMR spectrum (DMSO-d_6, δ ppm) of [B]: 160.5 (C-NH_2), 109.7 (C-5 thiazole), 139.6 (C-1 thiazole), 112.3-133.4 (C-aromatic ring), 164.7 (N=C–N pyrimidine), and 157.7(C–N pyrimidine).

Compound [R] was synthesized by treatment of 4-(2-aminothiazol-4-ylamino)-N-(pyrimidin-2-yl) benzene sulfonamide [B] with chloro acetyl chloride using triethylamine as a base triethylamine in DMF.

FTIR spectrum (KBr, cm^{-1}) of [R] showed appearance of absorption bands at 3404 cm^{-1} of stretching vibration of rhe NH group, and absorption bands at 2924 and 657 cm^{-1} of stretching vibrations of -CH_2 and C-Cl groups, respectively. Absorption band at 1674 cm^{-1} was due to the stretching vibration of C=O amide group. FTIR showed absorption peaks at 1543 cm^{-1} for C=C thiazole, and at 1593 cm^{1} for C=C aromatic.

^{1}H-NMR spectrum (DMSO-d_6, δ ppm) of [R]: 8.52 (s, 1H, NH amide), 4.37 (s, 2H,CH_2–Cl), 5.33 (s, 1H, C-5 thiazole), 7.39-7.73 (m, 4H, Ar-H), 12.47 (s,1H, NH-SO_2), and 11.36 (s, 1H, NH).

^{13}C-NMR spectrum (DMSO-d_6, δ ppm) of [R]:

164.0 (C=O amide), 43.6 (CH_2-Cl), 161.5 (C-NH_2), 107.1 (C-5 thiazole), 140.3 (C-1 thiazole), 111.5-133.4 (C aromatic ring), 164.6 (N=C–N pyrimidine), and 157.6 (C–N pyrimidine).

1,3-bis(hydroxyl methyl) barbituric acid derivatives [B_1]-[B_2] were prepared from the reaction of 5,5-diethyl barbituric acid and 5-phenyl,5-ethyl barbituric acid with formaldehyde. According to the FTIR spectrum for [B_1] , H-bonding of the OH)band was a broad peak at 3452 cm^{-1}. The absorption band at 1674 cm^{-1} was due to the -C=O amide group, and the absorption bands at 1714 and 1766 cm^{-1} was due to the stretching vibration for -C=O barbituric acid. And for compound [B2], the H-bonding of OH band was at 3464 cm^{-1}; the C=O group of amide was shown at 1635 cm^{-1}. Also, absorption band was at 1724 cm^{-1} for -C=O barbituric acid.

Williamson etherification of 2-chloro-N-(4-(4-(N-pyrimidin-2 ylsulfamoyl)phenyl- amino)thiazol-2-yl)acetamide [R] with [B_1]-[B_2] in DMF as solvent and the presence of NaOH offered [RB_1]-[RB_2] in very good yields, while the compounds [RB_3]-[RB_4] were prepared from the reaction of intermediates [R] with 5,5-diethylbarbituric acid and 5-ethyl-5-phenyl barbituric acid.

[RB_1]: 2-((5,5-diethyl-3-(hydroxymethyl)-2,4,6-trioxotetrahydropyrimidin-1(2H)yl)methoxy)-N-(4-(4-(N-pyrimidin-2-ylsulfamoyl)phenylamino)thiazol-2-yl)acetamide.

FTIR spectrum (KBr, cm^{-1}) of [RB_1]: 1668 (υ(C=O) amide), 3412 (υ(O-H), 1712, 1689 (υ(2(C=O)) barbituric), 1595 (υ(C=C) aromatic), 1548 (υ(C=C) thiazole), 2968 and 2929 (υ(C–H) aromatic and (CH_2-O)), 2831(υ(C–H) aliphatic), 1363 and 1134(υ(SO_2)), 1255 and 1232 (υ(C–O) and (C–O–C)), 1051 (υ(C–O) and (C–O-H)).

^{1}H-NMR spectrum (DMSO-d6, δ ppm) of [RB_1]: 1.67 (q, 4H, CH_2 barbituric acid), 0.64 (t, 6H, CH_3 barbituric acid), 5.45 (s, 2H, O-CH_2-N), 5.31 (s, 2H, N-CH_2), 4.24 (s, 2H, $COCH_2$), 8.49 (s,1H, NH amide), 7.32-7.70 (m, 4H, Ar-H), 5.68 (s, 1H, C-5 thiazole), 10.93 (s, 1H, NH), and 11.36 (s, 1H, NH pyrimidine).

[RB_2]: 2-((5-ethyl-3-(hydroxymethyl)-2,4,6-trioxo-5-phenyltetrahydropyrimidin-1(2H)-yl)methoxy)-N-(4-(4-(N-pyrimidin-2-ylsulfamoyl)phenylamino) thiazol-2-yl) acetamide.

FTIR spectrum (KBr, cm^{-1}) of [RB_2]: 1668 (υ(C=O) amide), 3323 (υ(O-H)), 1710 and 1691 (υ(2(C=O)) barbituric), 1629 (υ(C=N) thiazole), 1589 (υ(C=C) aromatic), 1548 (υ(C=C) thiazole), 3059, 2964 and 2927 (υ(C–H) aromatic and (CH_2-O)), 3190 (υ(C–H) and (HC=N) pyrimidine), 2854 (υ(C–H) aliphatic), 1363 and 1134 (υ(SO_2)), 1263 and 1238 (υ(C–O) and (C–O–C)), and 1097 (υ(C–O) amd (C–O-H)).

^{1}H-NMR spectrum (DMSO-d6, δ ppm) of [RB_2]: 1.74 (q, 4H, CH_2 barbituric acid), 0.72 (t, 6H, CH_3 barbituric acid), 5.35 (s, 2H, O-CH_2-N), 5.21 (s, 2H, N-CH_2), 4.11 (s, 2H, $COCH_2$), 8.45 (s,1H, NH amide), 7.22-7.65 (m, 4H, Ar-H), 5.63 (s, 1H, C-5 thiazole), 10.83 (s, 1H, NH), and 11.23 (s, 1H, NH pyrimidine).

[RB_3]: 2-(5,5-diethyl-2,4,6-trioxotetrahydropyrimidin-1(2H)-yl)-N-(4-(4-(N-pyrimidin-2-ylsulfamoyl)phenylamino)thiazol-2-yl)acetamide,

FTIR spectrum (KBr, cm^{-1}) of [RB_3]: 1678 (υ(C=O) amide), 3404 (υ(N-H)), 1762 and 1712 (υ(2(C=O)) barbituric), 1629 (υ(C=C) thiazole), 1585 (υ(C=C) aromatic), 1537 (υ(C=C) thiazole), 3080, 2974 and 2933 (υ(C–H) aromatic and (CH_2-O)), 3170 (υ(C–H) and (HC=N) pyrimidine), 2862 (υ(C–H) aliphatic), 1375 and 1153 (υ(SO_2)), 1240 (υ(C–O) and (C–O–C)), and 1091 (υ(C–O) and (C–O-H)).

^{1}H-NMR spectrum (DMSO-d6, δ ppm) of [RB_3]: 1.82 (q, 4H, CH_2 barbituric acid), 0.74 (t, 6H, CH_3 barbituric acid), 4.98 (s, 2H, O-CH_2-N), 4.70 (s, 2H, N-CH_2), 4.29 (s, 2H, $COCH_2$), 8.48 (s,1H, NH Amide),7.01-7.95 (m, 4H, Ar-H), 5.52 (s, 1H, C-5 thiazole), 10.71 (s, 1H, NH), and 11.55 (s, 1H, NH pyrimidine).

[RB_4]: 2-(5-ethyl-2,4,6-trioxo-5-phenyltetrahydropyrimidin-1(2H)-yl)-N-(4-(4-(N pyrimidin-2-ylsulfamoyl)phenylamino)thiazol-2-yl) acetamide

FTIR spectrum (KBr, cm^{-1}) of [RB_4]: 1670 (υ(C=O) amide), 3406 (υ(N-H)), 1710, Overlap (υ(2(C=O)) barbituric), 1625 (υ(C=C) thiazole), 1591 (υ(C=C) aromatic), 1543 (υ(C=C) thiazole), 3062, 2962 and 2927 (υ(C–H) aromatic and (CH_2-O)), 3099 (υ(C–H) and (HC=N) pyrimidine), 2854 (υ(C–H) aliphatic), 1355 and 1141 (υ(SO_2)), 1253 and 1228 (υ(C–O) and (C–O–C)), and 1087 (υ(C–O) and (C–O-H)).

^{1}H-NMR spectrum (DMSO-d6, δ ppm) of [RB_4]: 1.79 (q, 4H, CH_2 barbituric acid), 0.78 (t, 6H, CH_3 barbituric acid), 5.24 (s, 2H, O-CH_2-N), 5.01 (s, 2H, N-CH_2), 4.16 (s, 2H, $COCH_2$), 8.67 (s,1H, NH amide), 7.20-7.85 (m, 4H, Ar-H), 5.25 (s, 1H, C-5 thiazole), 10.75 (s, 1H, NH), and 11.52 (s, 1H, NH pyrimidine).

Antimicrobial activity

Antibacterial activity of the synthesized compounds was tested against three types of bacteria, *Staphylococcus aureus* as a gram-positive bacterium, *Escherichia coli* and *Pseudomonas aeruginosa* as gram-negative bacteria by using Muller Hinton Agar medium. The prepared compounds [B], [R], [RB_1], [RB_2], [RB_3] and [RB_4] were measured for zone of inhibition around each disc. Solvent control (DMSO) did not inhibit bacteria or fungi. The test results are presented in Table 2 and Fig. 1, which showed that [B] and [R] exhibited high antibacterial active against *S. aureous*, *P. aeruginosa* and *E. coli* at 0.03 and 0.06 mg/mL. Compound [RB_1] exhibited high antibacterial active against *P.* aeruginosa, and it was moderately active against *E. coli* whereas inactive against *S.*

Table 2 Antibacterial activity of some synthesized compounds

Sample		Inhibition zone diameter (mm/mg sample)					
		S. aureus		*P. aeruginosa*		*E. coli*	
		0.03	0.06	0.03	0.06	0.03	0.06
[B]		20	28	20	25	20	20
[R]		28	30	25	28	22	28
[RB_1]		--	--	20	20	11	12
[RB_2]		--	20	11	15	15	15
[RB_3]		20	28	--	--	17	20
[RB_4]		18	20	--	20	--	20
Antibiotics	Gentamicin	31		28		22	
	Penicillin	32		20		23	
	Control : DMSO	0		0		0	

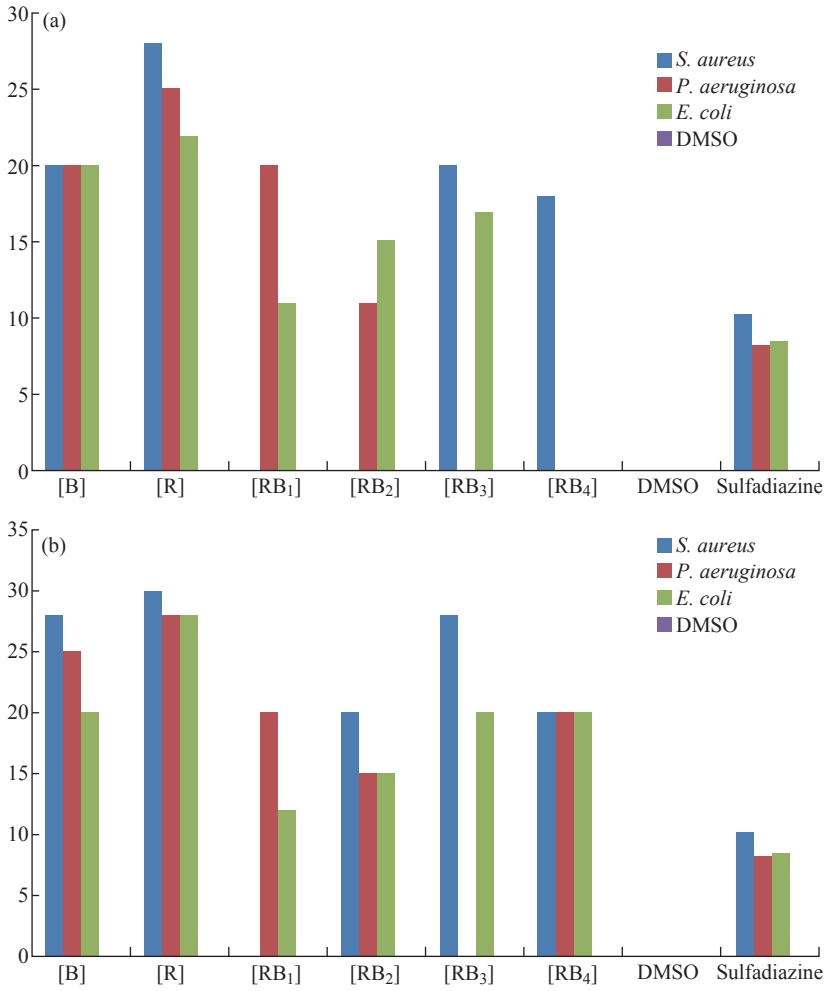


Fig. 1 Antibacterial activity of some synthesized compounds at **(a)** 0.03 mg/mL and **(b)** 0.06 mg/mL.

aureous for both concentrations. [RB_2] exhibited moderate antibacterial activity against *P. aeruginosa* and *E. coli*, while it exhibited high antibacterial activity against *S. aureous* at 0.06 mg/mL and inactive at 0.03 mg/mL. Compound [RB_3] exhibited high antibacterial activity against *S. aureous*, and *E. coli*, while it exhibited inactivity against *P. aeruginos.*

Finally, compound [RB_4] exhibited high antibacterial activity against *S. aureous*, high antibacterial activity against *P. aeruginosa* and *E. coli* at 0.06 mg/mL, and inactivity against *S. aureous* at 0.06 mg/mL.

Antifungal activity of the synthesized compounds was tested against two types of fungi, *Candida albicans* and *Aspergillus flavus* by using potato dextrose agar (PDA) medium. The test results are presented in Table 3 and Fig. 2. Compounds [B], [R], [RB_1], [RB_3]

Table 3 Antifungal activity of some synthesized compounds

Sample		Inhibition zone diameter (mm/mg sample)			
		Candida alicans		*Aspergillus flavus*	
		0.03	0.06	0.03	0.06
	[B]	22	25	--	--
	[R]	30	30	--	15
	[RB_1]	20	28	15	--
	[RB_2]	--	--	15	15
	[RB_3]	23	30	25	15
	[RB_4]	25	28	20	--
Antifungal	Fluconazole	22		16	
	Voriconazole	28		--	
	Nystatin	--		13	
	Control : DMSO	0		0	

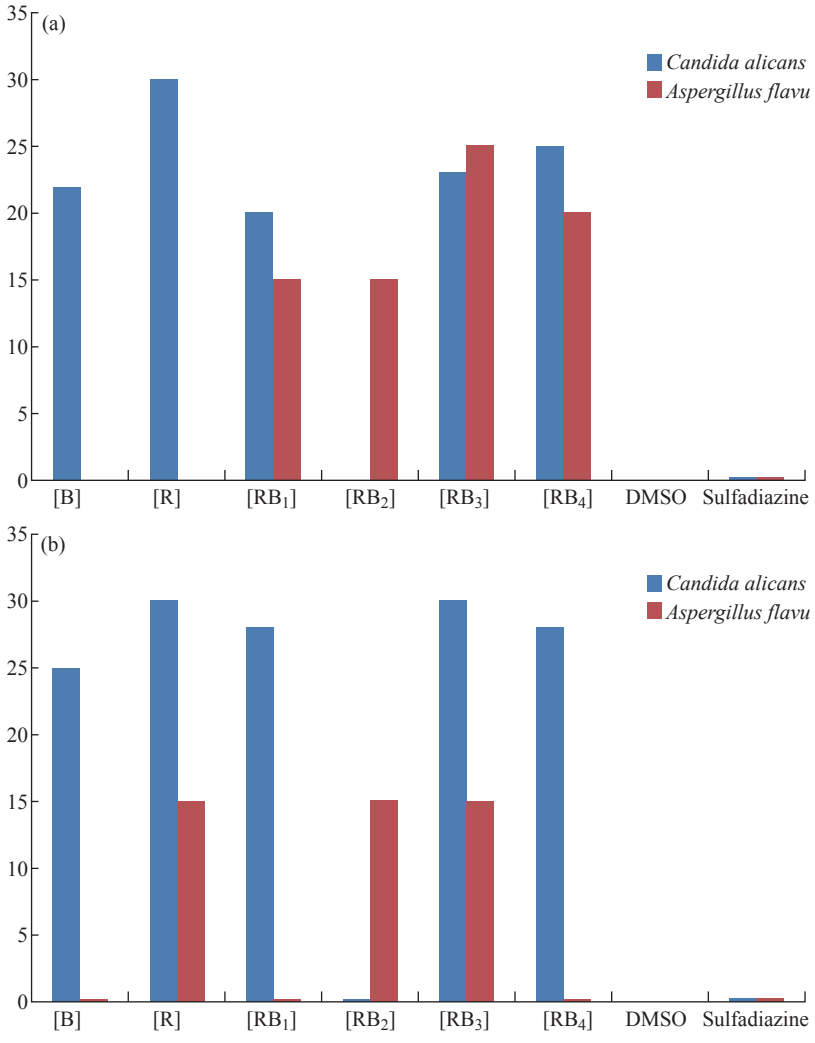


Fig. 2 Antifungal activity of some synthesized compounds at **(a)** 0.03 mg/mL and **(b)** 0.06 mg/mL.

and [RB_4] exhibited high antifungal activity against *Candida albicans*, while compound RB_3 was inactive against the same fungus at 0.03 and 0.06 mg/mL.

To *Aspergillus flavus*, compound [B] was inactive at 0.03 and 0.06 mg/mL, while compound [R] exhibited moderate antifungal activity at 0.06 mg/mL and inactivity at 0.03 mg/mL. Compound [RB_1] was moderately active at 0.03 mg/mL and inactive at 0.06 mg/mL. [RB_2] was moderately active at 0.03 and 0.06 mg/mL. Compound [RB_3] was highly active at 0.03 mg/mL, while it was moderately active at 0.06 mg/mL. Compound [RB_4] was highly active at 0.03 mg/mL whereas inactive at 0.06 mg/mL.

FTIR spectra for some compounds are presented in Fig. 3-6; ^{1}H-NMR and ^{13}C-NMR spectra for some compounds are presented in Fig. 7-12; and antimicrobial activities for some compounds are shown in Fig. 13 and 14.

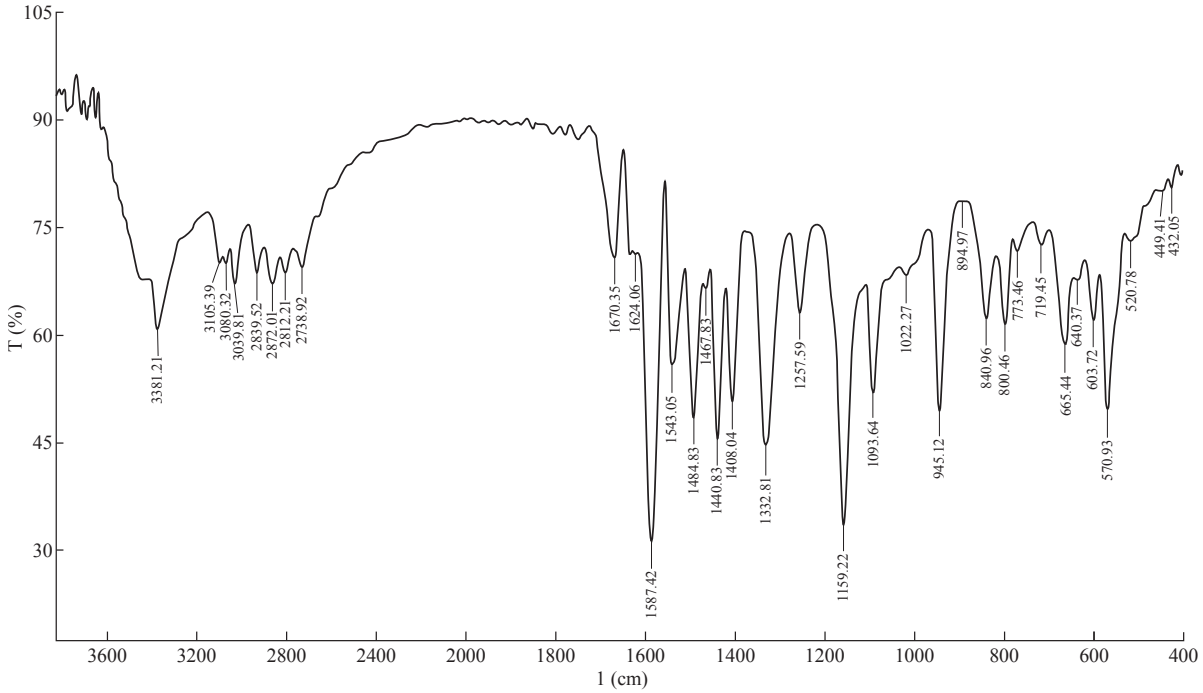


Fig. 3 FTIR spectrum of compound [A].

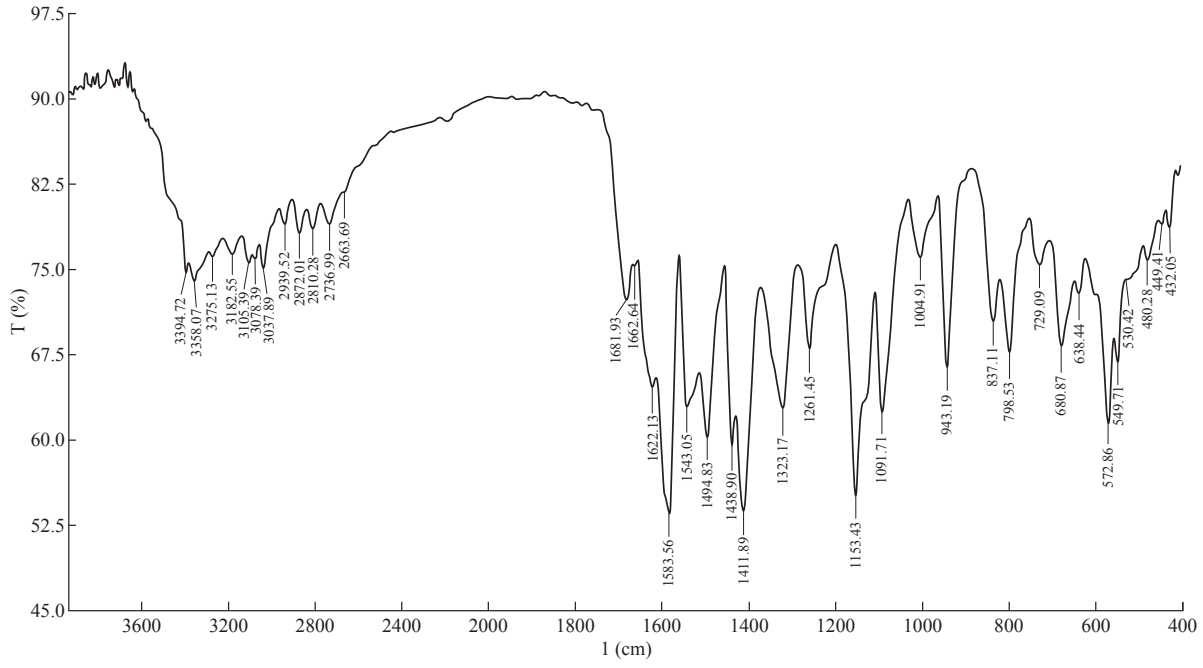


Fig. 4 FTIR spectrum of compound [B].

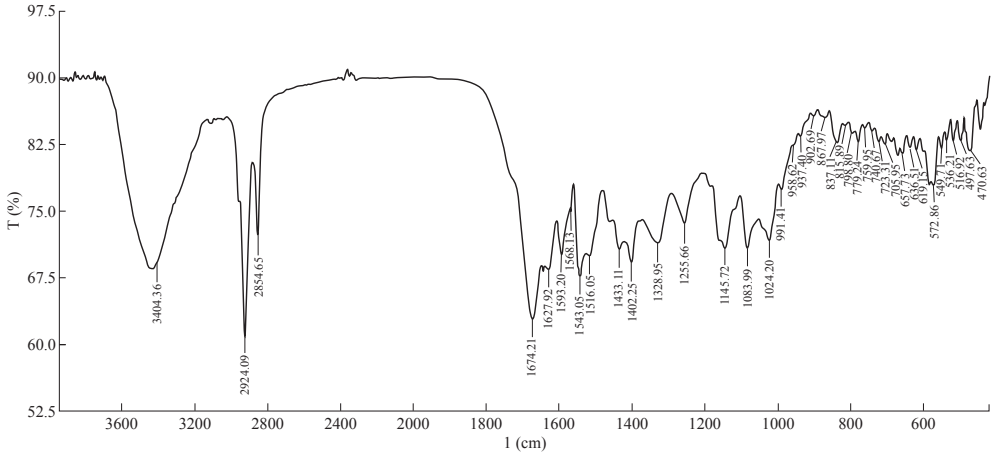


Fig. 5 FTIR spectrum of compound [R].

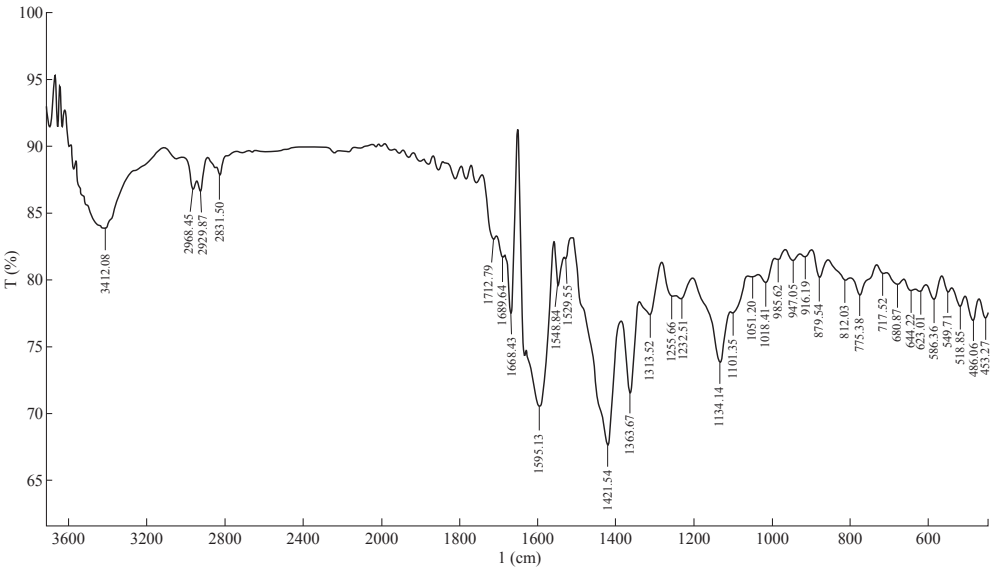


Fig. 6 FTIR spectrum of compound [RB_1].

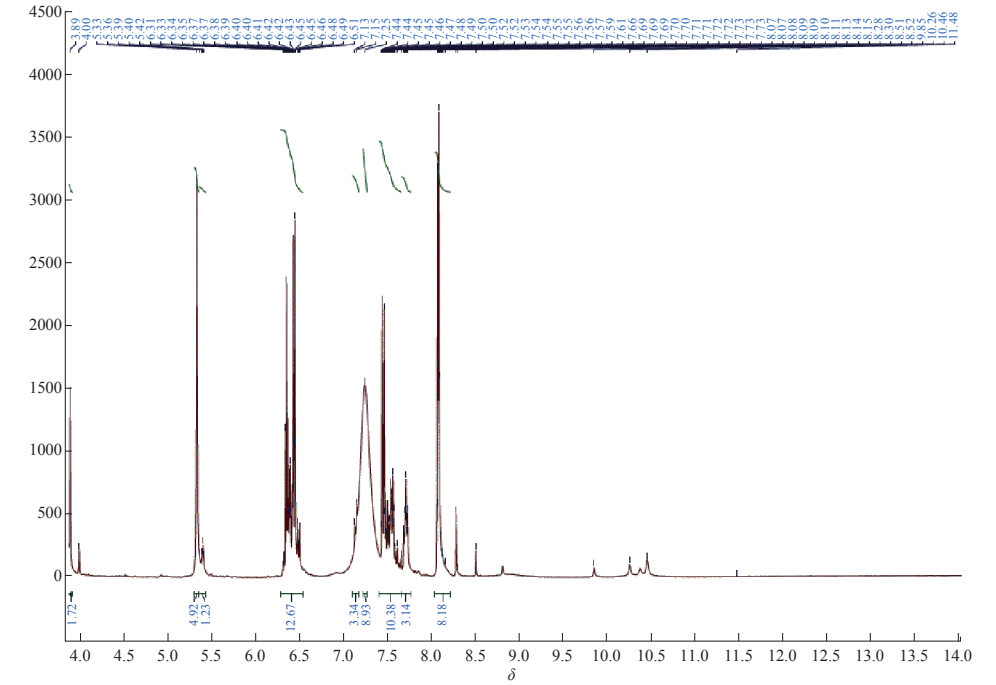


Fig. 7 ^{1}H-NMR spectrum of compound [B].

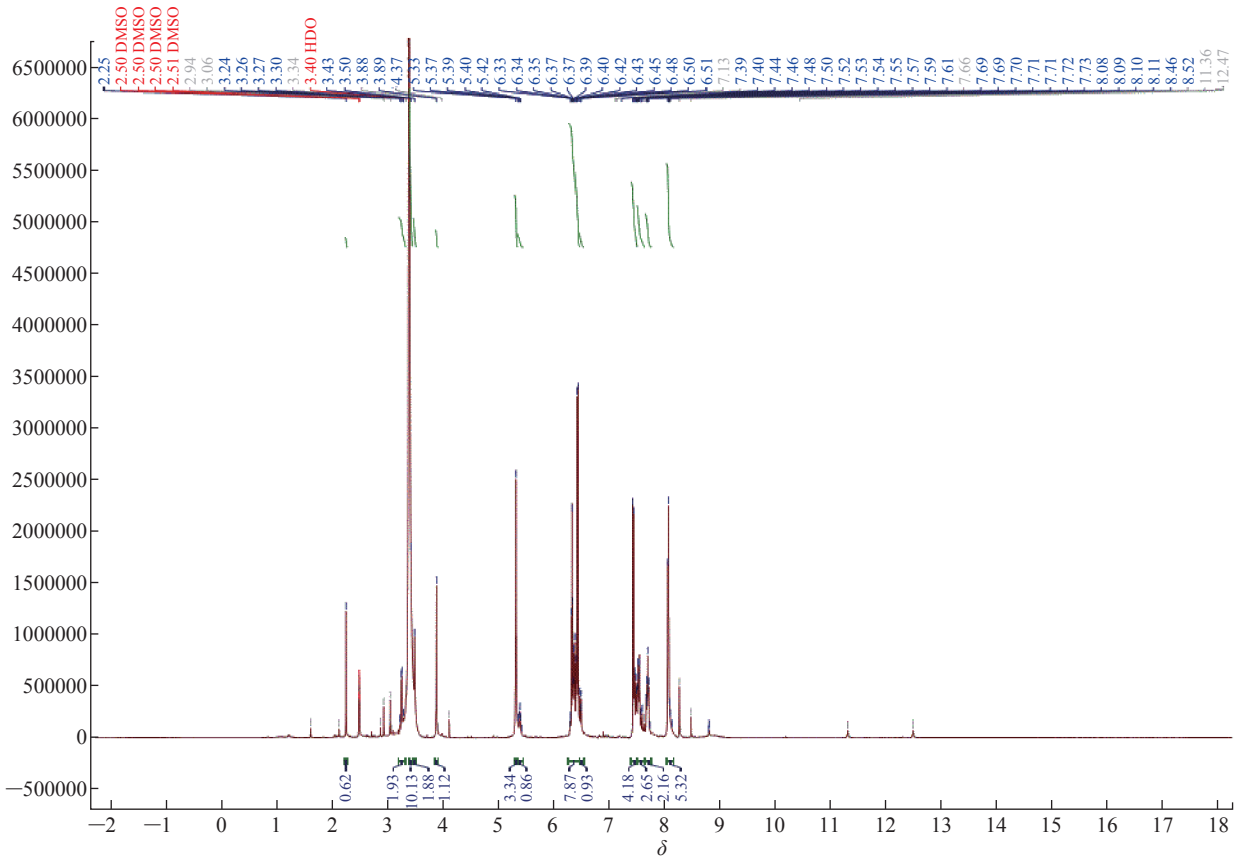


Fig. 8 ^{1}H-NMR spectrum of compound [R].

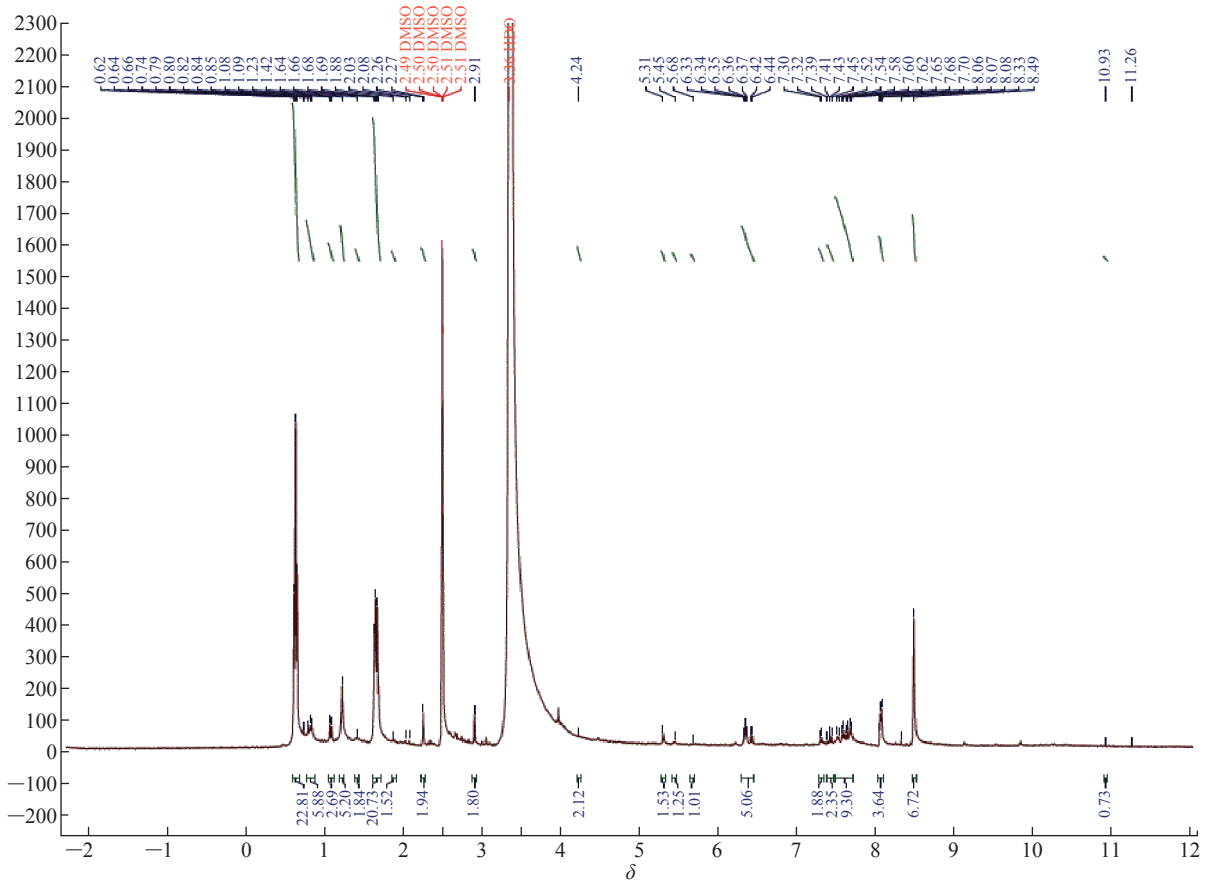


Fig. 9 ^{1}H-NMR spectrum of compound [RB_1].

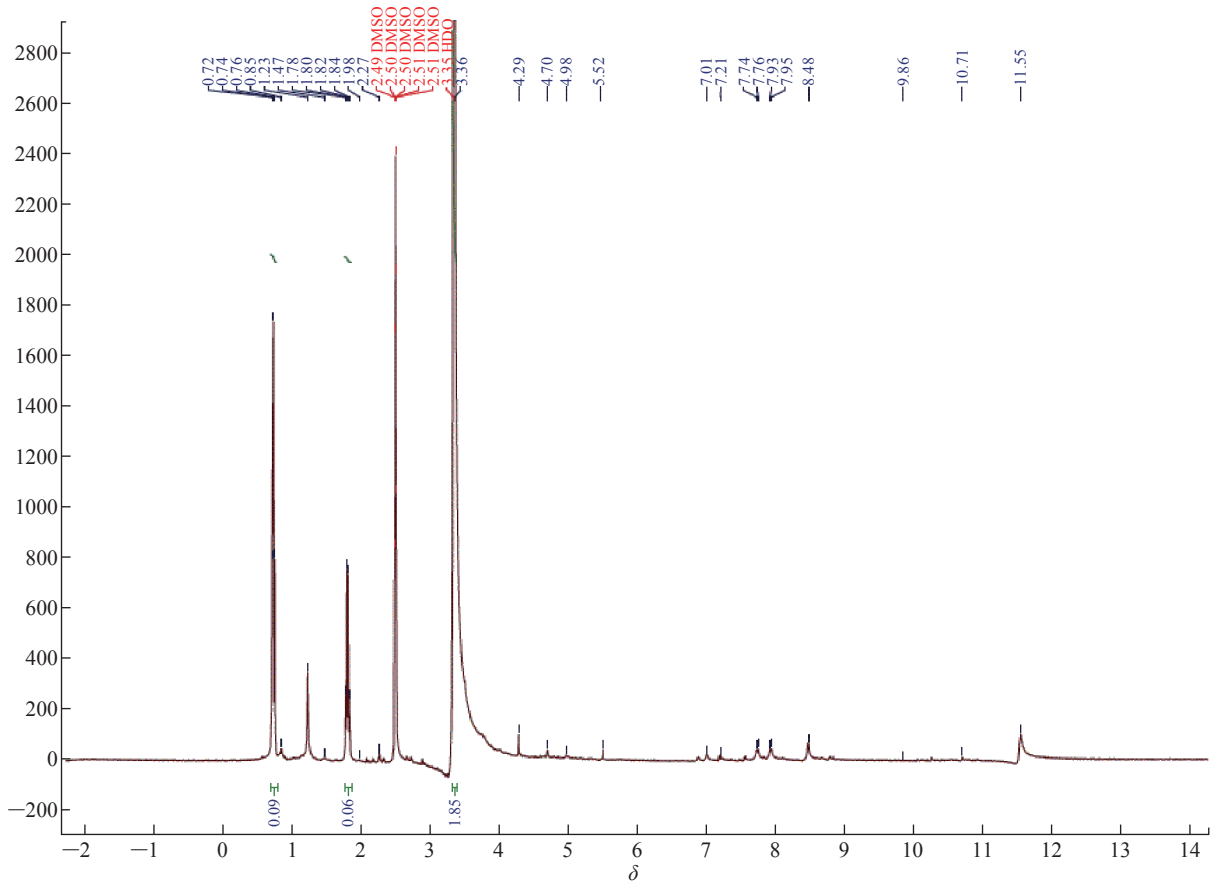


Fig. 10 ^{1}H-NMR spectrum of compound [RB_3].

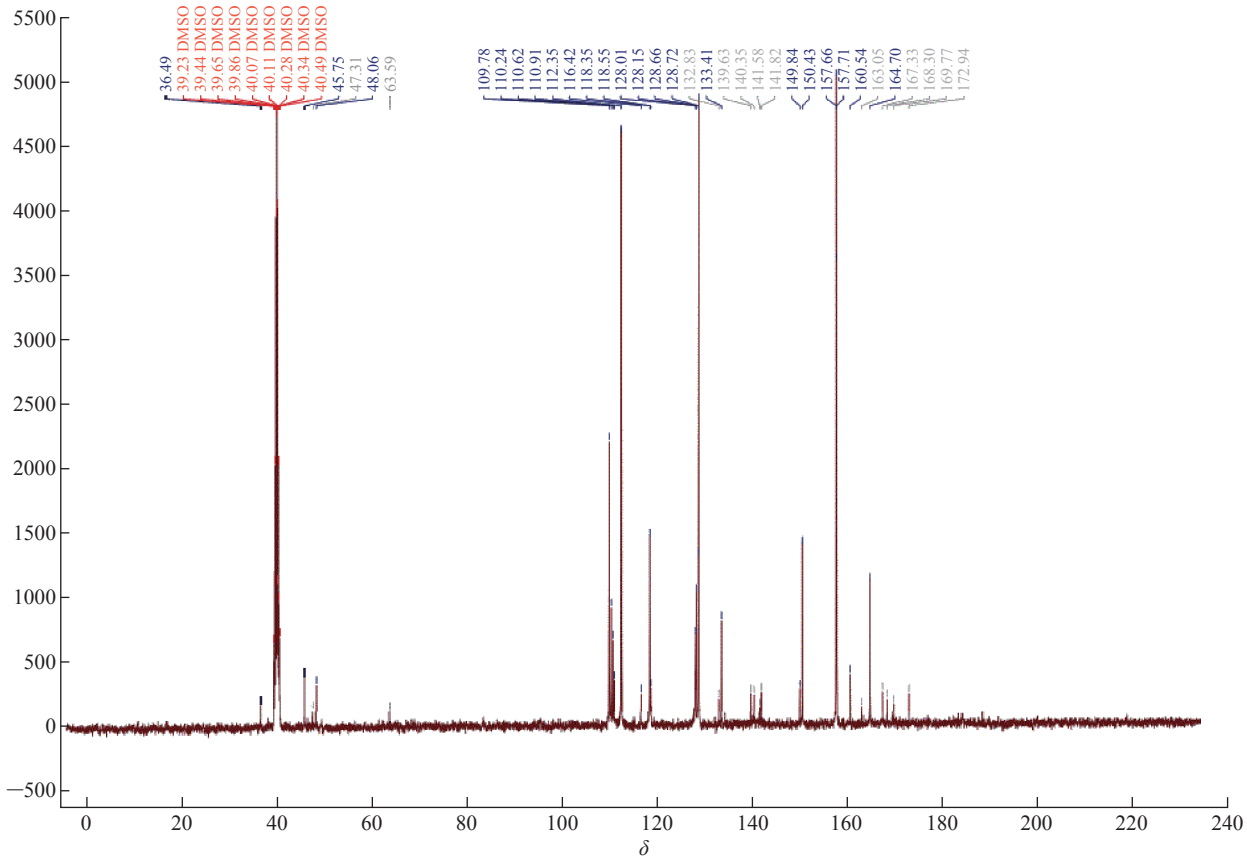


Fig. 11 ^{13}C-NMR spectrum of compound [B].

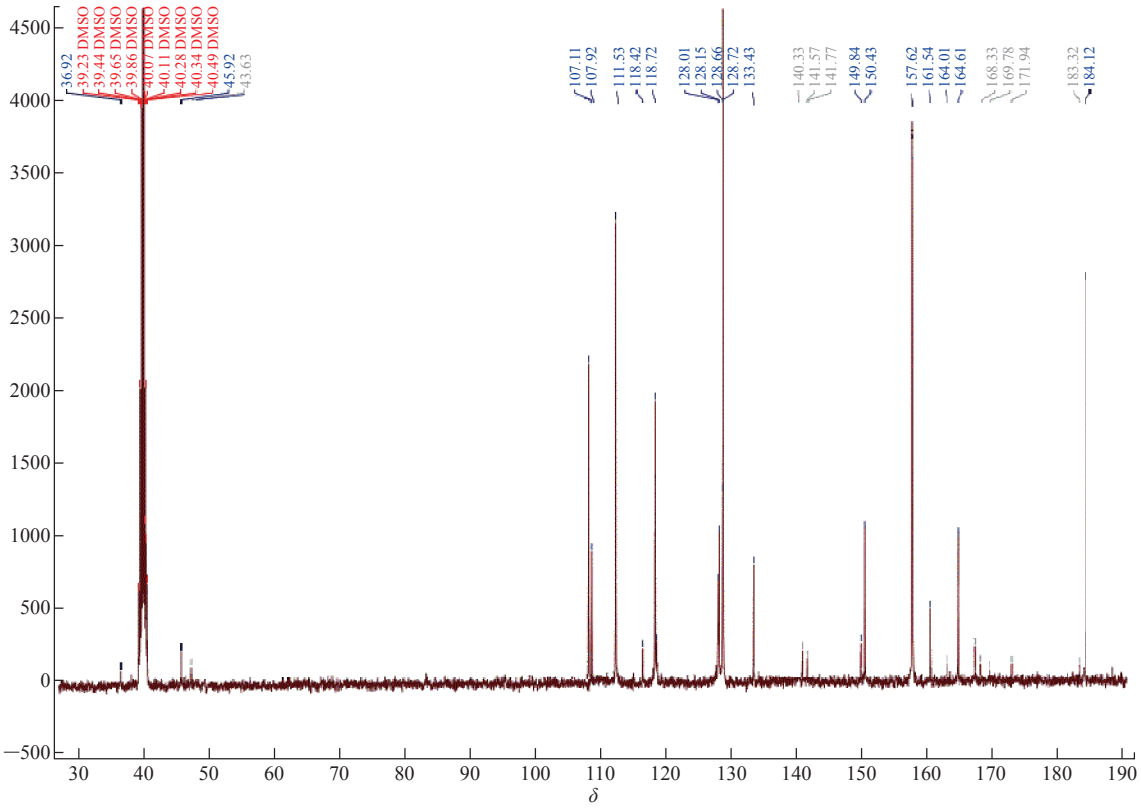


Fig. 12 ^{13}C-NMR spectrum of compound [R].

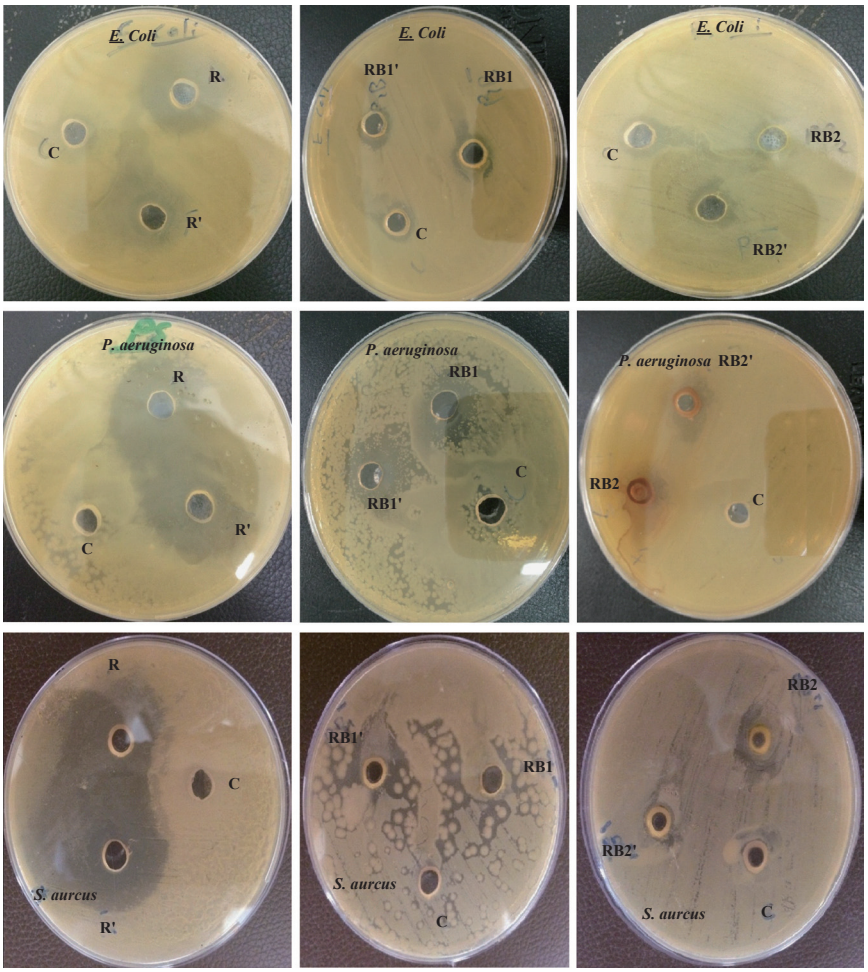


Fig. 13 Antibacterial activity of compounds [R], [RB_1] and [RB_2].

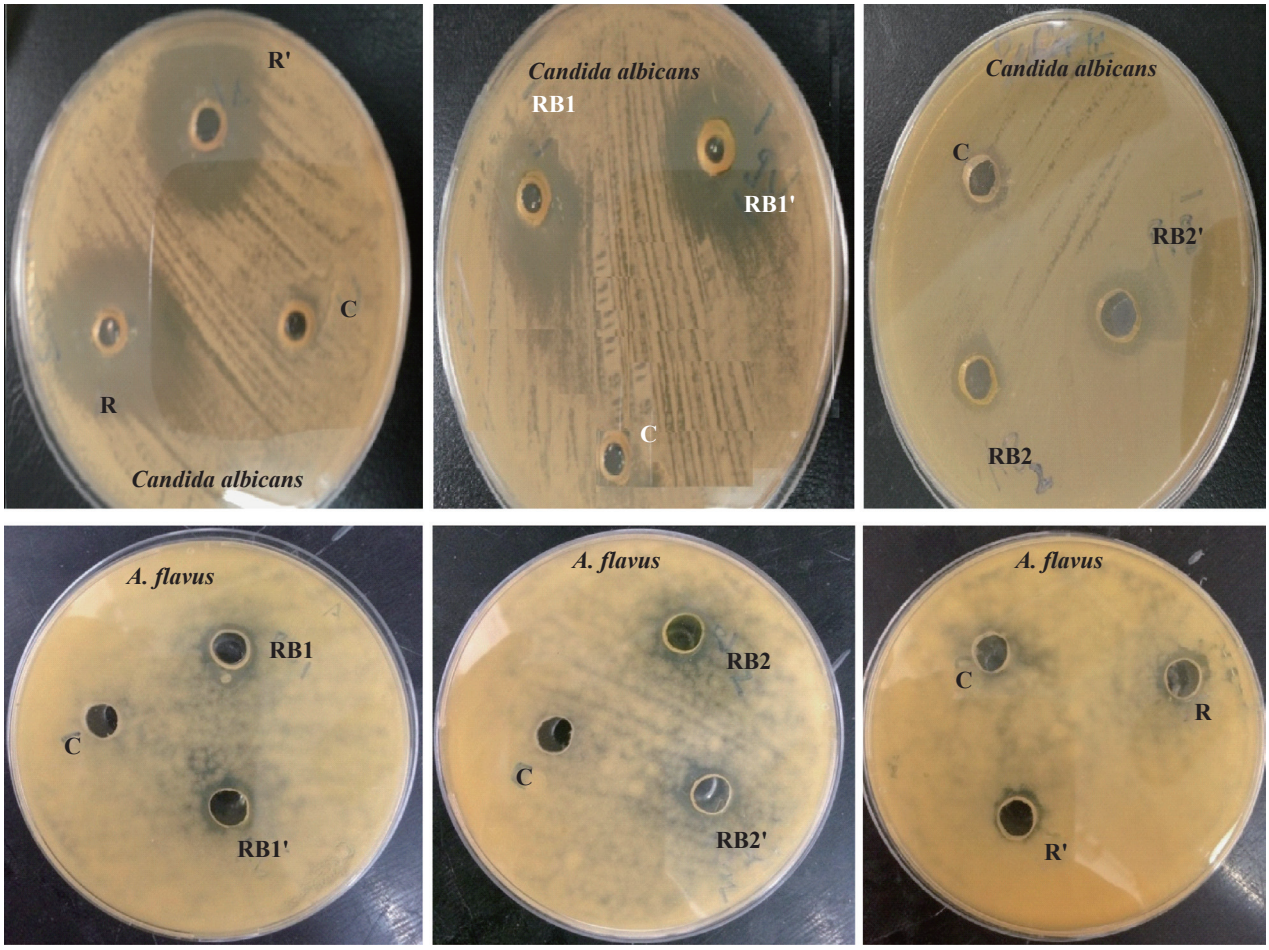


Fig. 14 Antifungal activity of compounds [R], [RB_1] and [RB_2].

Conclusions

This research involved the synthesis of some new barbituric acid derivatives and the study of antimicrobial activity of the prepared compounds. FTIR, ^{1}H-NMR and ^{13}C-NMR techniques confirmed formation of these derivatives. Antifungal activities of the synthesized compounds were observed against two types of fungi, *Candida albicans* and *Aspergillus flavus* using PDA medium. Some of the synthesized compounds were shown to be highly active at 0.03 mg/mL whereas moderately active at 0.06 mg/mL.

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Conflict of Interests

The authors declare that no competing interest exists.

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