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Synthesis, characterization and antibacterial activity of some new thiazole and thiazolidinone derivatives containing phenyl benzoate moiety

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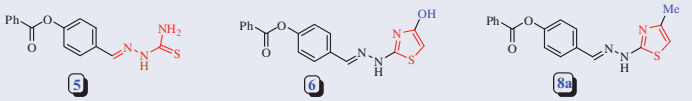
ABSTRACT

4-Formylphenyl benzoate was utilized as a versatile precursor for the construction of new series of heterocyclic scaffolds that contain thiazole and thiazolidin-5-one rings. The antibacterial activity of these scaffolds against two types of bacteria was screened and most of them exhibited good activity. Among the synthesized thiazole derivatives, compounds **5**, **6**, and **8a** showed antibacterial activity close to the standard chemotherapeutic (Ampicillin).

GRAPHICAL ABSTRACT



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KEYWORDS
Antibacterial activity; cyanoacetamide; phenyl benzoate; thiazole; thiazolidine

Introduction

Thiazoles are a class of heterocyclic compounds which merit special attention because of their vital role in the medicinal chemistry. They demonstrated wide spectrum of pharmacological applications such as anticancer,[1] antimicrobial,[2] anti-inflammatory,[3] antitubercular,[4] anti-allergic,[5] anticonvulsant,[6] anti-tumor,[7] antischizophrenic,[8] anti-HIV,[9] tyrosinase inhibitors,[10] anti-trypanosoma cruzi,[11] and antioxidant.[12] Thiazoles are aromatic five-membered heterocyclic compounds that contain sulfur and nitrogen at position 1 and 3, respectively. They are involved in many of the natural products for example, the thiazolium nucleus is a component of vitamin thiamin (B1) and thiamine pyrophosphate (TPP).[13–15] The construction of thiazole ring was first described in the literature by Hantzsch and Weber.[16] Many reports developed these traditional methods for the synthesis of thiazole as the using chemoenzymatic one-pot multicomponent synthesis[17] and application of microwave irradiation in the Hantzsch reaction.[18–20] Thiazole derivatives could be utilized in various chemical reactions such as Knoevenagel reaction[21]. Due to the importance of the core of thiazole and

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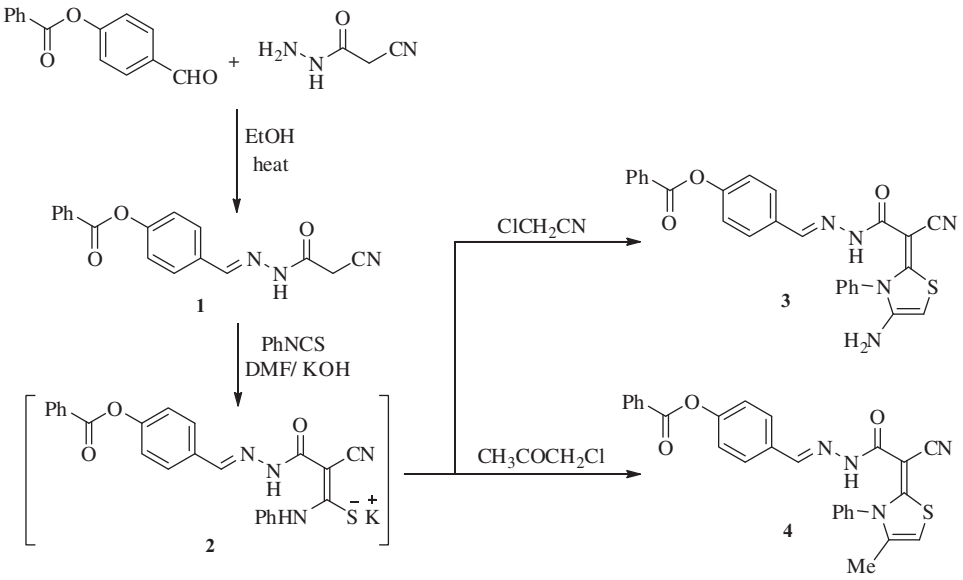
thiazolidinone rings in antimicrobial agents, different compounds incorporating these moieties have been synthesized in our research article to test their antibacterial activity.

Results and discussion

Cyanoacetyl hydrazone **1** was synthesized by refluxing of 4-formylphenyl benzoate[22] with 2-cyanoacetohydrazide[23] in ethanol. Assignment of compound **1** was based on IR, ^{1}H NMR, and elemental analysis. IR spectrum showed characteristic bands at 3199 cm^{-1} for (NH), 2260 cm^{-1} for (CN), and 1733 cm^{-1} for (C=O ester) functions. Then, a base catalyzed addition reaction of cyanoacetyl hydrazone **1** with phenyl isothiocyanate was achieved in DMF to afford the non-isolable intermediate potassium salt **2** which sequently, underwent heterocyclization with chloroacetonitrile and chloroacetone to yield the corresponding thiazole derivatives **3** and **4**, respectively (Scheme 1). Spectral and analytical analyses have been utilized to establish the chemical structures of both **3** and **4**. IR spectra of compound **3** revealed absorption bands at the region 3331–3439 cm^{-1} for (br, NH, NH_2), 2182 cm^{-1} for (CN), 1734 cm^{-1} for ($C{=}O_{(ester)}$). The mass spectrum of **3** showed a molecular ion peak at $m/z = 481$ which was agreed completely with the predicted formula ($C_{26}H_{19}N_5O_3S$). Figure 1 illustrates some decomposition processes of thiazole **3**, fragmentation includes the elimination of an NH_2 group $[M\text{-}16]^+$ followed by the elimination of OH radical to produce the ion at m/z 448. The thiazole ring opening with the following release of an acetylene to produce the ion at m/z 423, which underwent loss HCN and N_2 molecules to give the base peak at m/z 368 with 100% intensity. ^{1}H NMR of compound **4** assigned the appearance of new singlet signals at 1.92, 6.49, and 9.09 ppm characteristic for CH_3, $CH_{(thiazole)}$, and NH protons, respectively.

Into our target to synthesize new thiazole derivatives, six thiazoles **6–9** were resulted *via* a heterocyclization reaction of 4-((2-carbamothioylhydrazono)methyl)phenyl



Scheme 1. Synthesis of thiazole derivatives **3** and **4**.

benzoate (**5**) that was synthesized according to the reported method[24] with α-halo carbonyl compounds and hydrazonyl halides namely; ethyl bromoacetate, bromodiethylmalonate, chloroacetone, phenacylchloride, 2-oxo-2-phenyl-*N*'-*p*-tolylacetohydrazonoyl chloride, and *N*'-(4-methoxyphenyl)-2-oxo-2-phenylacetohydrazonoyl chloride,[25–27] respectively in refluxing commercial ethanol containing anhydrous AcONa (Scheme 2). Assignment of the newly synthesized compounds was based on both spectral and analytical analyses (cf. Experimental section).

To extend our work, we synthesized three thiazolidin-5-one derivatives **10** (**a**–**c**) using the reported method in literature.[28,29] Furthermore, the reactivity of these derivatives as active methylene compounds was tested *via* a Knoevenagel condensation reaction with 4-formylphenyl benzoate in ethyl alcohol containing a catalytic amount of piperidine (three drops) to afford the corresponding arylidine products **11** (**a**–**c**) (Scheme 3). The chemical structures of these products were confirmed using both spectral and analytical analyses. For example, IR spectra of compound **11b** assigned absorptions at 2208 cm^{-1} for (CN), 1714 and 1744 cm^{-1} for ($2C{=}O_{(ester)}$) and 1692 cm^{-1} for ($C{=}O_{(cyclic)}$). ^1H NMR spectrum exhibited two singlet signals at 1.36 and 4.34 ppm assignable to CH_3 and CH_2 protons, respectively. ^{13}C NMR spectrum also confirmed the structure of **11b** through the appearance of signals at 62.31 and 14.22 ppm related to OCH_2 and CH_3 carbons.

Moreover, the reactivity of some known cyanoacetamide thiazole derivatives **12** (**a**–**c**) which were obtained through the synthetic routes reported in literature[30–32] and a new cyanoacetamide derivative **12d** which was prepared by refluxing of 2-amino-6-ethoxybenzothiazole with 3,5-dimethyl-1-cyanoacetyl pyrazole[33] in dioxane was studied toward the Aldol condensation reaction with 4-formylphenyl benzoate to afford arylidine thiazole compounds **13** (**a**–**d**) through refluxing in ethanol with adding few drops of piperidine (3–4 drops) (Scheme 4). Chemical structures of compounds **13** (**a**–**d**) were

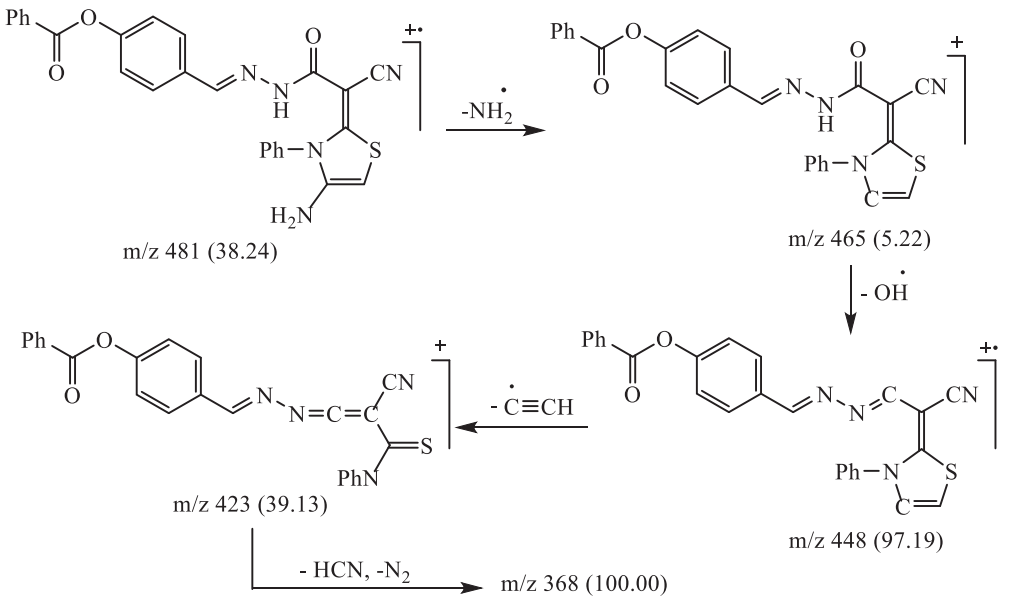
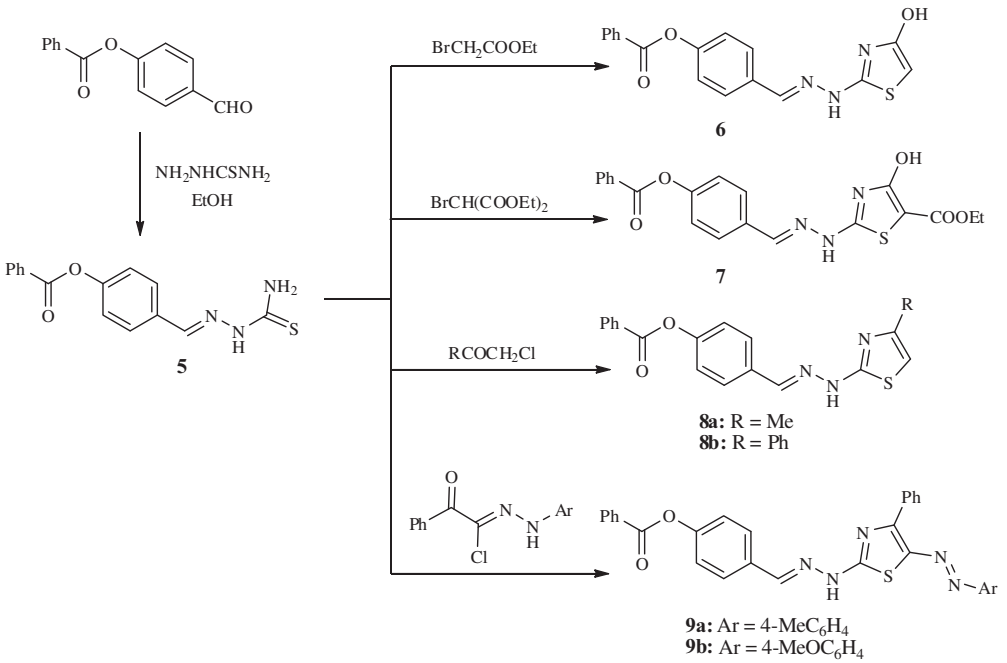
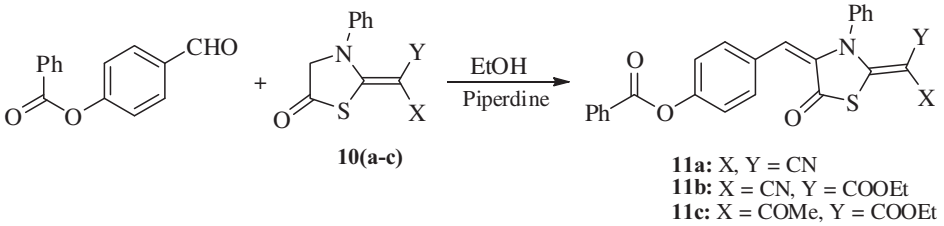


Figure 1. Possible mass fragmentation pattern of compound **3**.



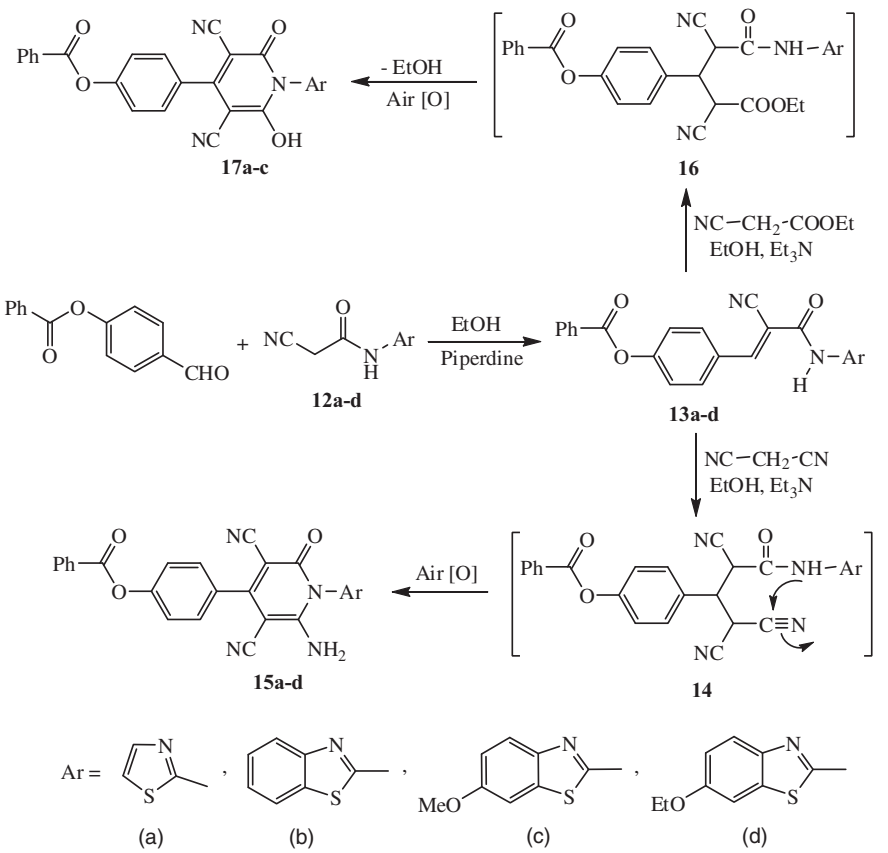
Scheme 2. Synthesis of thiazole derivatives **6**–**9**.



Scheme 3. Synthesis of thiazolidin-5-one derivatives **11** (**a**–**c**).

elucidated using both elemental and spectral analyses. For example, IR of **13c** revealed absorptions at 3226 cm^{-1} for (NH), 2227 cm^{-1} for (CN), and 1730 cm^{-1} for ($C{=}O_{(ester)}$) groups, while ^1H NMR spectrum assigned a singlet signal at 3.80 ppm assignable for (OCH_3) protons.

To further explore the synthetic potentially of compounds **13** (**a**–**d**), the reactivity of **13** (**a**–**d**) towards Michael addition with malononitrile as a possible synthetic route to get pyridinone derivatives **15** (**a**–**d**) was examined. Compounds **15** (**a**–**d**) were achieved by refluxing compounds **13** (**a**–**d**) with malononitrile and TEA in ethyl alcohol to furnish the non-isolable intermediate **14** which then underwent intramolecular heterocyclization to give the corresponding products. In a similar manner, the reaction of compounds **13** (**a**–**c**) with ethyl cyanoacetate and TEA in refluxing EtOH gave the intermediate **16** which underwent an intramolecular heterocyclization to afford pyridinone derivatives **17** (**a**–**c**). Elucidation of the new synthesized derivatives **15** (**a**–**d**) and **17**



Scheme 4. Synthesis of thiazole derivatives **13**–**17**.

(**a**–**c**) was based on elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy (cf. Experimental Section).

Biological activity

All new investigated thiazole derivatives **3**–**17** were subjected to antibacterial screening in vitro against Gram (−ve) (*Escherichia coli*) (MTCC-443) and Gram (+ve) (*Staphylococcus aureus*) (MTCC-96) bacteria and were compared with ampicillin as a standard chemotherapeutic. Then, the results are tabulated in Table 1. Most of the synthesized compounds showed high antibacterial activity against the selected bacteria.

By studying the results of the disc diffusion test that are summarized in Table 1, we found that compounds **3**, **5**, **6**, and **8a** showed potent activity against *S. aureus* bacteria and compounds **6** and **8a** showed excellent activity against *E. coli* bacteria. On the other hand, compounds **4**, **9a**, **9b**, and **13d** showed good activity against *S. aureus* bacteria and compounds **3** and **5** showed good activity against *E. coli*, while all the other tested compounds showed moderate or low activity against the selected bacteria.

According to the above-mentioned results, we may apply the following SARs (structure–activity relationships) and compare between the tested compounds. A comparison of antibacterial activity of compounds with their structures revealed that antibacterial

Table 1. Antibacterial activity of compounds **3**–**17** against *Escherichia coli* and *Staphylococcus aureus* bacteria.

	E. coli (mg/ml)		*S. aureus* (mg/ml)	
Compound no.	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
3	20	76.9	21	87.5
4	16	61.5	20	83.3
5	18	69.2	23	95.8
6	22	84.6	23	95.8
7	NA	–	8	33.3
8a	23	88.5	24	100.0
8b	10	38.5	7	29.2
9a	14	53.8	18	75.0
9b	17	65.4	20	83.3
11a	11	42.3	14	58.3
11b	NA	–	2	8.3
11c	NA	–	2	8.3
13a	7	26.9	15	62.5
13b	13	50.0	15	62.5
13c	3	11.5	5	20.8
13d	5	19.2	17	70.8
15a	9	34.6	10	41.7
15b	NA	–	NA	–
15c	2	7.7	11	45.8
15d	3	11.5	6	25.0
17a	NA	–	NA	–
17b	NA	–	3	12.5
17c	2	7.7	6	25.0
Ampicillin	26	100	24	100

NA: no activity.

Table 2. Minimum inhibitory concentration (μg/ml) of compounds **3**, **4**, **5**, **6**, **8a**, and **9b** against *Escherichia coli* and *Staphylococcus aureus* bacteria.

Compounds	*E. coli*	*S. aureus*
3	500	500
4	375	250
5	250	62.5
6	375	187.5
8a	62.5	46.9
9b	750	375
Ampicillin	125	187.5

activity of the evaluated compounds is related to the attached groups with thiazole derivatives. The presence of amino, hydroxyl, methyl, methoxy, azo, or ethoxy groups incorporated with cyanoacetyl hydrazone or carbamothioyl hydrazone and phenyl benzoate moiety in thiazole derivatives gave significant antibacterial activity against the two bacteria while introducing of electron withdrawing group (phenyl group) instead of electron donating group (methyl group) in compound **8b** decreased the activity as shown in Table 1. Compound **8a** gave the best antibacterial activity against *E. coli* and *S. aureus* bacteria, this may be attributed to the presence of methyl group on the fourth position of thiazole forced to higher activity.

In addition, the minimum inhibitory concentration (MIC) of the most active compounds **3**, **4**, **5**, **6**, **8a**, and **9b** was tested against *E. coli* and *S. aureus* bacteria and the results are reported in Table 2. Most of the tested compounds exhibited high MIC as

shown in Table 2. On the other hand, compound **8a** revealed low MIC (62.5 μg/ml) against *E. coli* and compounds **5** and **8a** exhibited low MIC (62.5, 46.9 μg/ml), respectively against *S. aureus*.

Conclusion

In this paper, we synthesized various series of thiazole derivatives using 4-formylphenyl benzoate as a starting material. The reactivity of some of these thiazoles towards Knoevenagel condensation reaction was studied. All the newly synthesized products were screened against their *in vitro* antibacterial activity, compound **8a** which contains the phenyl benzoate moiety with 4-methylthiazolyl substituent has the highest antibacterial activity. By applying SARs, we found that the presence of electron donating groups (i.e. methyl group in compound **8a**) gave significant antibacterial activities against the two types of bacteria.

Experimental

All melting points were measured in degree Celsius on an electrothermal Gallenkamp (Germany) apparatus. The infrared spectra υ cm^{-1} (KBr) were determined on a Mattson 5000 FTIR Spectrometer (USA). The ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker Avance III spectrophotometer at 400 and 100 MHz, respectively. The mass measurements were recorded on Kratos MS apparatus by EI mode with ionizing voltage 70 eV. Elemental (C, H, and N) analyses were measured on Perkin-Elmer 2400. The results were favorably agree with the calculated values.

Reaction of α-halo derivatives with cyanoacetyl hydrazone 1

General procedure: A 0.005 mole of cyanoacetyl hydrazone **1** (0.49 g), 0.005 mole of phenylisothiocyanate (0.59 ml), and 0.005 mole of KOH (0.28 g) were dissolved in 15 ml DMF, then were stirred overnight. After that, 0.005 mole of α-halo derivatives namely; 2-chloroacetonitrile (0.31 ml) or chloroacetone (0.40 ml) were added drop by drop with stirring for 4 h. After completion of the reaction, the previous mixtures were poured onto ice-water with stirring and the formed precipitates after settling down of the mixtures were filtered off. EtOH was utilized as a recrystallizing solvent to afford compounds **3** and **4**, respectively.

4-((2-(2-(4-Amino-3-phenylthiazol-2(3H)-ylidene)-2-cyanoacetyl)hydrazono)methyl)-phenyl benzoate (3)

Reddish brown powder, m.p. = 214–216 °C, yield 33%. IR (ν_{max}/cm^{-1}): 3331–3439 (br, NH, NH_2), 2182 (CN), 1734 (C=$O_{(ester)}$), 1636 (C=$O_{(amidic)}$), 1600 (C=N). MS *m/z* (%): 481 (M^+) (38.24), 448 (97.19), 424 (26.01), 423 (39.13), 369 (57.92), 368 (100), 104 (30.01), 43 (19.20). Analysis for $C_{26}H_{19}N_5O_3S$ (481.53): Calcd: C = 64.85%; H = 3.98%; N = 14.54%. Found: C = 64.88%; H = 3.11%; N = 14.50%.

4-((2-(2-Cyano-2-(4-methyl-3-phenylthiazol-2(3H)ylidene)acetyl)hydrazono)methyl)phenyl benzoate (4)

Yellow crystals, m.p. = 240–242 °C, yield 67%. IR (ν_{max}/cm^{-1}): 3311 (NH), 2185 (CN), 1738 (C=O$_{(ester)}$), 1640 (C=O$_{(amidic)}$). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.92 (s, 3H, CH_3), 6.49 (s, 1H, CH$_{(thiazole)}$), 7.24 (d, 2H, J = 8.4 Hz, Ar–H), 7.28–7.67 (m, 8H, Ar–H), 7.79 (d, 2H, J = 8.4 Hz, Ar–H), 7.91 (s, 1H, CH=N), 8.20 (d, 2H, J = 7.2 Hz, Ar–H), 9.09 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d6, 100 MHz): δ (ppm) = 26.21 (1C, CH3), 69.71 (1C, C–CN), 96.34 (1C, CH$_{(thiazole)}$), 115,75 (1C, CN), 121.10 (1C), 122.81 (2C), 128.44 (2C), 128.60 (1C), 129.25 (1C), 129.35 (1C), 129.78 (2C), 129.86 (1C), 130.12 (2C), 130.29 (1C), 130.59 (2C), 134.60 (1C), 145.02 (1C, C=N), 151.93 (1C, C–O), 163.45 (1C, C=O$_{(ester)}$), 164.92 (1C, C=O$_{(amidic)}$), 171.30 (1C, S–C–N). Analysis for $C_{27}H_{20}N_4O_3S$ (480.54): Calcd: C = 67.48%; H = 4.20%; N = 11.66%. Found: C = 67.53%; H = 4.18%; N = 11.69%.

Microbiological procedure for the activity study

Materials and method

Each of the compounds was dissolved in DMSO and solution of the concentration 1 mg/ml were prepared separately. Paper discs of Whatman filter paper were prepared with standard size (5 cm) were cut and sterilized in an autoclave. The paper discs soaked in the desired concentration of the complex solution were placed aseptically in the petri dishes containing nutrient agar media (agar 20 g + beef extract 3 g + peptone 5 g) seeded with *S. aureus* and *E. coli*. The petri dishes were incubated at 36 °C and the inhibition zones were recorded after 24 h of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic ampicillin was also recorded using the same procedure as above at the same concentration and solvents. The % activity index for the complex was calculated by the formula as under:

$$\%\ \text{Activity index} = \frac{\text{Zone of inhibition by test compound (diametre)}}{\text{Zone of inhibition by standard (diametre)}} * 100$$

MIC (minimum inhibitory concentration) values for the selected compounds were determined using the previously reported procedure.[34]

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