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Design, Synthesis of Some New Thio-Substituted Imidazole and Their Biological Activity

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Abstract In an attempt to find a new class of antimicrobial and antioxidant agents, a two new series of S-alkyl-imidazolidin-4-one(**3a,b-5**) and S-alkyl-imidazole **13a-d,15a-e**,**16**,**17a,b** and **25a-d** were prepared. Their antioxidant potential were evaluated using DPPH (1,1-diphenyl-2-picrylhydrazyl) radical method in vitro. Their antibacterial screening against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeuroginosa* and *Escherichia coli* and antifungal activity against *Aspergillus fumigates*, *Syncephalastrum racemosum*, *Geotrichum candidum* and *Candida albicans* were also evaluated, most of the compounds showed to potent and significant results when compared to the respective standards. Structures of the newly synthesized compounds were established by elemental analysis and spectral data.

Keywords Imidazolidine-2-thione, Imidazole-2-thione,1,3-Thiazolidinone, Benzimidazole, Acid hydrazide,1,3-Oxadiazole, Antioxidant, Antibacterial, Antifungal

1. Introduction

In general, imidazoles is important family of heterocyclic compounds with a broad interest due to their bioactive properties [1], such as antimicrobial [2-5], antitumor [6, 7], anti- HIV [8], anticonvulsant [9], antitubercular [10], antiprotonzoal [11] and anti-inflammatory [12]. Imidazole ring is also present in some of the clinically used drug structures (asetomidate, cimetidine, omeprazole, lansoprazole, azomycine, azomycine, flumazenil, thyroliberin, methimazole, pilocarpine and etomidate) acting as a pharmacophoric group or a substituent [13]. On other hand, imidazole-2-thione and 2-thioxo-imidazolidin -4-one are present in compounds that have anti-inflammatory [14], antivirala activity [15], antibacterial, antifungal, antioxidant [16, 17], anticancer [18] and anti- proliferative [19]. In view of the important biological properties of the imidazole ring we planned to synthesize some new 2-thio-substituted-imidazoles and imidazolidine derivatives bearing side chains with different structures, as such derivatives could possess interesting and useful biological properties.

2. Experiment

2.1. General

All melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr discs. 1H-NMR spectra were recorded on a Varian EM-390 (90MHz) spectrometer using TMS as an internal standard and DMSO-d6 as a solvent. Chemical shifts were expressed in δ (ppm) values. Mass spectra were determined on Finnigan Incos500 (70 ev). Elemental analyses were determined using a Parkin-Elmer 240 C. Microanalyzer. The microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University.

2.2. Chemistry

2.2.1. 2-(Benzylthio)-3-(4-chlorophenyl)-5,5-diphenyl-imidazolidin-4-one 3a

A mixture of **1** (0.01 mol) and benzyl chloride (0.01 mol) in ethanol (20 ml) was refluxed in the presence of few drop of TEA for 6 h. The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol to gives **3a** as white needles Yield: 75%. m.p.176-178°C. IR (KBr, cm^{-1}): 3029, 2933 (CH), 1731 (CO),1598(C= N).1H-NM R (DMSO-*d6*) δ ppm: 4.38(s,2H,CH_2),7.11-7.47(m,19H,Ar-H).MS,m/z % ,468 (M^+, 5.79), 363 (1.02),209 (0.58), 302(22.3), 91(100).Anal. Calcd. for $C_{28}H_{21}ClN_2OS$ (468.99):C,71.71; H, 4.51; Cl, 7.56 ; N, 5.97; S,6.84. Found: C, 71.51; H, 4.31; Cl, 7.36 ; N, 5.67; S,6.64.

2.2.2. 2-(Methylthio)-3-(4-chlorophenyl)-5,5-diphenyl-imidazolidin- 4-one 3b

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To a solution of compound **1** (0.01 mol) in ethanol (20 ml) and sodium hydroxide (0.01mol in water 2 ml), methyl iodide (0.01mol) was added drop wise. After stirring for 3 h at room temperature (20–23°C), solid products was filtered off washed with water, and recrystallized from ethanol to give **3b** as white plates. Yield: 70%.m.p.186-189°C. (KBr, $_x$ cm^{-1}): 3054,2918(CH), 1690(CO).1H-NMR (DMSO- *d6*) δ ppm: 2.59(s,3H,CH_3), 7.18-7.47 (m,14H, Ar-H).MS, m /z %, 392(M^+,0.50),3.77(26.57).376(100),361(2.15), 233 (85.24), 111(58.26).Anal. Calcd. for $C_{22}H_{17}ClN_2OS$(392.90): C, 67.25; H,4.36 ;Cl,9.02; N,7.13; S,8.16.Found: C, 67.05; H, 4.26 ; Cl,9.00; N,7.00; S, 8.00.

2.2.3. Ethyl [3-(4-chlorophenyl)-4-oxo-5,5-diphenyl-imidazolidin -2-ylthio]acetate 4

A mixture of **1** (0.01 mol), ethyl chloroacetate (0.012 mol), and anhydrous K_2CO_3 (0.01 mol) in 40 ml of dry acetone was refluxed on a water bath for 15 h., then poured into cold water. Solid obtained was filtered off, washed with cold water and rerystallized from ethanol to give **4** as pink needles. Yield 50% .m.p.128-130 ℃ . IR (KBr,cm^{-1}) 1741, 1676(2C=O),3055,2984,2918(CH). 1H-NMR(DMSO- *d6*) δ ppm:1.18 (t,3H, *J*=7.1 Hz,CH_2-$\underline{CH_3}$), 4.12(q,2H, *J*=7.1 Hz, $\underline{CH_2}CH_3$),4.04(s, 2H, CH_2), 7.16-7.50 (m, 14H, Ar-H). MS, m/z%, 464 (M^+, 28.87) , 434(58), 420 (56.70), 352 (96.91), 342 (59.79) 204 (100). Anal. Calcd.for $C_{25}H_{21}ClN_2O_3S$ (464.96): C,64.58; H,4.55; Cl, 7.62; N, 6.02; S,6.90. Found: C, 64.38; H, 4.45; Cl,7.42; N, 6.00 ; S,6.60.

2.2.4. 2-(Benzoylmethylthio)-3-(4-chlorophenyl)-5,5-di-pheny- l-imidazolidin-4-one 5

To a mixture of **1** (0.01 mol) and phenacyl bromide (0.01 mol) in ethanol (30 ml) was added few drops of TEA. The reaction mixture was refluxed for 6h.The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol to give **5** as yellow plates.Yield: 80%. m.p.196-197℃. IR (KBr, cm^{-1}): 1693, 1671(C=O), 3057, 2906 (CH).1H-NMR (DMSO-*d6*)δ ppm: 4.10(s,2H,CH_2),7.14-7.72 (m,17H, Ar-H), 8.03 (d, 2H, J= 8.7 Hz, Ar-H).MS, m/z %, 497 (M^+,8.82), 420 (8.82), 363 (9.39), 352 (14.94), 77(100). Anal. Calcd. for $C_{29}H_{21}$ Cl N_2O_2S(497.01): C,70.08; H,4.26;Cl, 7.13; N,5.64; S, 6.45. Found:C, 69.00; H,4.16;Cl ,7.03 ; N,5.54; S, 6.25.

2.2.5. 3-(4-Chlorophenyl)-2- (3-oxo-1,3- diphenylprop -1-en-2-ylthio)-5,5-diphenyl- imidazolidin-4-one 6

A mixture of **5** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (30 ml) containing few drops of piperidine (0.5 ml) was refluxed for 3h. The reaction mixture was left to cooled then poured onto ice water containing few drops of HCl and the obtained solid was crystallized from ethanol to gives **6** as yellow granules.Yield:55%.m.p.260-262℃. IR (KBr,cm^{-1}): 3056, 2920, 2853(CH), 1696, 1663 (C=O).1H-NMR (DMSO-d6) δ ppm:7.09-7.84(m,25H, Ar-H and =CH). Anal.Calcd. for $C_{36}H_{25}Cl\ N_2O_2S$ (585.11): C,73.90; H,4.31; Cl,6.06; N,4.79; S,5.48.Found: C,73.60; H,4.11; Cl,6.00; N, 4.59; S,5.28.

2.2.6. Methyl 2-[3-(4-chlorophenyl)-4-oxo-5,5-diphenyl-imidazolidin-2-ylthio]-3-oxo-3-phenyl-propane-dithio ate 8 and Ethyl [2-(3-(4-chlorophenyl)-4-oxo-5, 5-diphenyl- imidazolidin-2-ylthio)-3-oxo-3-phenyl -propane dithioyl) acetate 9

To a cold suspension of KOH (0.01 mol) in dry DMF (25 ml), compound **5** (0.01mol) was added and then carbon disulphide (0.01mol) was added slowly drop wise under stirring over a period of 15 min while the temperature of the mixture was maintained at 5–10℃. The mixture was stirred at room temperature for 12 h, then cooled again to 0℃, methyl iodide (0.01mol) or ethyl chloroacetate (0.01mol) was added drops wise over a period of 10 min. The reaction mixture was stirred for 6 h. at room temperature and then poured into ice cold-water. The resulting precipitate was filtered off, dried and crystallized from proper solvent.

8: Yellow crystals. Yield 60%. m.p. 210-212℃ (DMF-ethanol); IR(KBr,cm^{-1}):3058, 2923, 2851 (CH), 1735,1695 (C=O),1260(C=S);1H-NMR (DMSO-*d*6) δ ppm:4.32 (s,1H, CH), 2.07(s,3H,CH_3);7.13-7.58 (m,19H, Ar-H).Anal. Calcd. for $C_{31}H_{23}ClN_2O_2S_3$(587.17):C,63.41; H,3.95; Cl, 6.04; N , 4.77; S, 16.38. Found: C,63.21; H, 3.65; Cl,6.00; N,4.57; S, 16.18.

9: Yellow plates. Yield 65%. m.p.140-142^{o}C (benzene). IR (KBr,cm^{-1}): 3059, 2980, 2924 (CH),1695,1741,1633 (C= O), 1291(C=S).1H-NMR(DMSO-*d*6)δ ppm:4.51(s,1H,CH), 4.04 (s,2H,CH_2);1.16(t,3H, *J* = 7.1 Hz , CH_2 CH_3) ; 4.10 (q, 2H, *J* =7.1 Hz, $\underline{CH_2}CH_3$); 7.13- 7.59 (m,17H, Ar-H),8.03 (d, 2H, Ar-H).Anal.Calcd. for $C_{34}H_{27}ClN_2O_4S_3$ (659.24): C, 61.94; H, 4.13; Cl,5.38; N,4.25; S,14.59. Found:C,61.64; H, 4.00; Cl, 5.28; N,4.05; S,14.29.

2.2.7. 2-[1-(3-(4-Chlorophenyl)-4-oxo-5,5-diphenyl -imidazolidin-2-ylthio)-2-oxo-2-phenylethylidene]-3-phenyl-1,3- thiazolidin-4-one (11)

To a stirred suspension of finely powdered KOH (0.01 mol) in dry DMF (10 ml),compound **5** (0.01 mol) was added, and then phenyl isothiocyanate (0.01mol) was added slowly. After complete addition, the mixture was stirred at room temperature for 12 h, then ethyl chloroacetate (0.01 mol) was added to the mixture.The reaction mixture was stirred for 6 h.,then poured into crushed ice. The resulting precipitate was filtrated off, dried and recrystallized from ethanol to give **11** as yellow crystals. Yield 63%. m.p.123- 126℃. IR (KBr cm^{-1}): 1728, 1663,1632 (C=O), 3057, 2979, 2925(CH). 1H-NMR (DMSO-*d*6) δ ppm: 4.04 (s,2H, CH_2), 7.16-7.58 (m,24H, Ar-H). Anal. Calcd. for $C_{38}H_{26}ClN_3O_3S_2$ (672.21): C,67.90;H,3.90; Cl,5.27; N, 6.25 ; S,9.54. Found: C, 67.60; H,3.70; Cl,5.07; N,6.05; S,9.24 .

2.2.8. 2-[5-Amino-4-(*1H*-benzoimidazol-2-yl)-3- phenyl -thiophen-2-ylthio]-3-(4-chlorophenyl)-5,5-diphenyl-i midazolidin-4-one 12

To a solution of compound **5** (0.01 mol) in absolute ethanol (25 ml) containing morpholine (0.2 ml), 2-(1*H*-benzimidazol-2-yl)acetonitrile (0.01mol) and elemental sulfur (0.01 mol) were added. The reaction mixture was refluxed for 4 h, then cooled, poured onto ice cold water and neutralized by dilute HCl. The solid so formed was collected by filtration and crystallized from ethanol to give compound **12**as brown granules.Yield 65%. m.p.350-352℃. IR(KBr,cm^{-1}):3245,3145,3130(NH,NH_2), 1695(C=O), 3045, 2907 (CH).1H-NMR (DMSO-*d*6) δ ppm: 4.81 (s, 2H,NH_2), 13.03 (s,1H,NH), 7.13-7.58 (m,23H, Ar-H). Anal. Calcd.for $C_{38}H_{26}ClN_5OS_2$(668.23):C,68.30; H,3.92; Cl, 5.31; N,10.48; S, 9.60.Found: C,68.00; H,3.62; C, 5.11; N,10.28; S ,9.40

2.2.9. General procedure for synthesis of 1-(4-substituted phenyl)-4,5-diphenyl-S-alkyl-imidazole13a-d and 15a-e

A mixture of **2a,b** (0.01 mol) and respective halo compounds (0.01 mol) in ethanol (50 ml) was refluxed in the presence of few drops of TEA for 6-8 h. the solid product separated from the hot mixture was filtered off, washed with water and recrystallized from the proper solvent.

2-(Benzylthio)-1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole 13a

White crystals. Yield: 55%. m.p.180-182°C (ethanol-DMF).IR(KBr,cm^{-1}):3030,2927(CH),1592(C=N).1H- NMR (DMSO-*d*6) δ ppm:4.38 (s,2H, CH_2),7.10-7.49(m,19H, Ar-H). MS, m/z %, 453(M^+, 18.49) , 452(16.63), 417(20.45), 362 (2.17), 302(100),304 (34.77) ,91 (52.89). Anal Calcd. for $C_{28}H_{21}ClN_2S$ (452.99): C,74.24;H,4.67; Cl,7.83; N, 6.18; S, 7.08. Found: C,74.01;H,4.37;Cl,7.53; N,6.08; S, 6.81.

2-(Benzythio)-1-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole 13b

Yellow powder. Yield: 75 %. m.p.160-162°C (ethanol-DMF).IR(KBr,cm^{-1}): 3063,2917(CH),1592(C=N).1H-NMR (DMSO-*d*6) δ ppm:4.40(s,2H,CH_2),6.63-8.18(m,19H,Ar-H) MS, m/z %,464 (M^++1, 27.22),463 (M^+,77.39), 430 (43.38), 372(5.79),309 (43.34),91(100).Anal. Calcd. for $C_{28}H_{21}N_3O_2S$: (463.55) C,72.55; H,4.57; N,9.06; S,6.92.Found: C,72.25; H, 4.37; N,9.00; S,6.62.

2-[1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazol-2-ylthio]acetonitrile 13c

Pal brown granules.Yield:60%. m.p 190-192°C (ethanol). IR(KBr,cm^{-1}): 2246(CN), 3026, 2988, 2862(CH),1599 (C=N). 1H-NMR (DMSO-*d*6) δ ppm:4.28(s,2H, CH_2),7.19-7.51(m,14H, Ar-H). MS, m/z % :401(M^+,38.96), 361 (3.58) , 303 (100),103 (16.42),79 (86.37).Anal. Calcd. for $C_{23}H_{16}ClN_3S$ (401.91):C, 68.73; H, 4.01; Cl, 8.82; N,10.46; S, 7.98. Found:C,68.53;H,3.89; Cl, 8.55; N,10.16.S,7.96

2-[4,5-Diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio]-acetonitrile 13d

Yellow plates. Yield 61%. m.p. 176-178°C (ethanol-DMF). IR (KBr, cm^{-1}):2240 (CN), 3073, 2973, 2921 (CH), 1594 (C=N).1H-NMR (DMSO-*d*6) δ ppm: 4.29(s, 2H,CH_2), 6.62- 8.27(m,14H,Ar-H). MS, m/z %, 412 (M^+, 49.12), 413 (M^++1,14.81),372 (15.46),314 (100),76 (28.30). Anal. Calcd. for $C_{23}H_{16}N_4O_2S$(412.46).C,66.97; H,3.91; N,13.58; S,7.77. Found: C, 66.67; H,3.61; N,13.32; S,7.57.

1-[1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazol-2-ylthio]propan-2-one 15a

Pale yellow granules.Yield:70%.m.p.181-183°C (ethanol). IR(KBr,cm^{-1}):1711(C=O), 3049, 2974, 2947 (CH). 1H-NMR (DMSO- *d*6) δ ppm: 2.30(s,3H, $COCH_3$), 4.17(s,2H,S CH_2),7.18-7.50 (m,14H, Ar-H).M.S,m/z %:418 (M^+, 52.25) , 383(46.85),292(50.45), 264 (66.67), 153 (45.05), 77 (40.54), 54 (100). Anal.Calcd. for: $C_{24}H_{19}ClN_2OS$ (418.93):C,68.81; H, 4.57;Cl,8.46; N,6.69;S,7.65.Found: C,68.51; H,4.27;Cl, 8.26 ; N,6.39; S,7.35.

1-[4,5-Diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio] propan-2-one 15b

Yellow crystals. Yield: 65%. m.p.150-152°C (ethanol–DMF). IR (KBr, cm^{-1}):1680 (C=O), 3062, 2950, 2915, 2859 (CH).1H-NMR (DMSO-d6) δ ppm:2.30 (s,3H,$COCH_3$), 4.20 (s, 2H, SCH_2), 6.63-8.16 (m,14H, Ar-H). MS, m/z%: 430 (M^+ +1, 15.36), 429 (M^+,48.06),386 (100), 372 (2.29), 340 (20.31),314(34.42),76 (27.29). Anal. Calcd. for: $C_{24}H_{19}N_3O_3S$ (429.49): C,67.12; H,4.46; N, 9.78; S,7.47. Found: C, 67.02 ; H,4.16; N,9.48; S,7.17.

2-[Benzoylmethylthio]-1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole 15c

White plates. Yield: 75%. m.p. 216-218°C (ethanol). IR(KBr, cm^{-1}): 1691(C=O),3055, 2952(CH);1H-NMR (DMSO -*d*6) δ ppm:4.81(s,2H,SCH_2),7.13–8.06 (m,19H, Ar-H), MS, m/z %: 481(M^+,35.85), 366 (38.9), 293 (32.70), 264(49.06), 76(37.74),63.95(100). Anal. Calcd. for: $C_{29}H_{21}ClN_2OS$(481.0): C,72.41; H,4.40; Cl,7.37; N,5.82; S,6.67. Found: C,72.11; H,4.10; Cl, 7.17; N, 5.52;S,6.37.

2-[(Benzoylmethyl)thio]-4,5-diphenyl-1-(4-nitrophenyl)-1H-imidazole 15d

Yellow crystals.Yield:72%. m.p.170-174°C (ethanol). IR (KBr,cm^{-1}):1683(C=O),3062,2988(CH). 1H-NMR (DMSO-*d*6) δ ppm: 4.84(s,2H,SCH_2), 6.90–8.24(m,19H, Ar-H).MS, m/z %, 492 (M^++1,16.67), 491(M^+,47.37), 461 (55.62), 432 (47.37), 419(48.25), 369(50.88), 292 (50), 225 (100). Anal. Calcd. for:$C_{29}H_{21}N_3O_3S$(491.561): C,70.86; H,4.31; N, 8.55; S ,6.52.Found:C,70.56; H,4.01; N,8.25;S,6.22.

2-[4,5-Diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio] acetamide 15e

Yellow brownish needles. Yield: 65%. m.p.160-163°C (ethanol). IR(KBr,cm^{-1}):1676(C=O),3439,3379(NH_2), 3058, 2918(CH).1H-NMR (DMSO-*d*6) δ ppm:3.93 (s,2H,SCH_2), 6.64-8.27(m,16H,Ar-H and NH_2).M.S, m/z %:430 (M^+, 43.78),414(26.73), 369(30.41),362 (32.35),250 (26.73), 152 (8.76),8 (100). Anal. Calcd. For: $C_{23}H_{18}N_4O_3S$ (430.48):C, 64.17; H,4.21; N,13.01; S,7.45. Found: C,64.00; H,4.00; N, 13.00 ; S,7.15.

2.2.10. 1-(4-Chlorophenyl)-2-(methylthio)-4,5-diphenyl-1H-imidazole 16

To a solution of compound **2a** (0.01mol) in ethanol (20ml) and sodium hydroxide (0.01mol in water 2 ml), dimethyl sulfate (0.01mol) was added drop wise. The reaction mixture was refluxed for 6 h. The reaction mixture was left to cool, the crude solid was filtered off,washed with water, and recrystallized from ethanol to give **16** as pale yellow powder. Yield 67%. m.p.190-193°C. IR (KBr, cm^{-1}): 3055, 2920(CH), 1594(C=N).1H-NMR (DMSO-*d*6) δ ppm: 2.61 (s, 3H, CH_3),7.14-7.48 (m, 14H, Ar-H). MS, m/z %, 377 (M+, 40.60), 376 (28.97), 375 (100), 341(1.92), 302 (24.65), 265.9(3.50),192(66.4).Anal.Calcd.for:$C_{22}H_{17}ClN_2S$(376.90): C,70.11; H,4.55; Cl, 9.41; N,7.43; S,8.51.Found:C,70.00; H, 4.25; Cl,9.21; N,7.13; S,8.31.

2.2.11. General procedure for synthesis of ethyl [4,5-diphenyl-1-(4-substituted phenyl)-*1H*-imidazol-2-ylthio] acetate 17a,b

A mixture of **2a,b** (0.01 mol) and ethyl chloroacetate (0.01mol)in 15ml ethanol containing few drops of TEA was refluxed for 6 h. The reaction mixture was left to cool, the crude solid was filtered off, washed with water and recrystallized from ethanol.

Ethyl (1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-2-ylthio) acetate 17a

White crystals.Yield:55%. m.p.128-130°C (ethanol). IR (KBr,cm^{-1}):1740(C=O), 3054,2920(CH). 1H-NMR(DMSO-*d*6) δ ppm:1.17(t,3H, *J*=7.1 Hz, $CH_2\underline{CH_3}$);4.02 (s,2H,CH_2); 4.11 (q, 2H, *J*=7.1 Hz,$\underline{CH_2}CH_3$);7.17-7.49 (m,14H,Ar-H). MS, m/z %,448 (M^+,100),449 (M^++1,31.63), 422.9 (0.69), 375 (55.44), 362(5.22). Anal. Calcd. for: $C_{25}H_{21}ClN_2O_2S$ (448.96): C,66.88; H,4.71; Cl,7.90; N,6.24; S,7.14. Found : C, 66.58;H,4.31; Cl,7.60; N, 6.00; S,7.00.

Ethyl (4,5-diphenyl-1-(4-nitrophenyl)- 1H-imidazol-2-ylthio) acetate 17b

Yellow powder .Yield:50 %.m.p.144-146°C (ethanol); IR (KBr, cm^{-1}): 1734(C=O), 3074, 2982, 2926(CH); 1H-NMR (DMSO-d6) δ ppm:1.18(t,3H, *J*=7.1 Hz CH_2 CH_3);4.06 (s, 2H, CH_2) ; 4.13(q, 2H, *J*=7.1Hz, $\underline{CH_2}CH_3$);7.21–8.28(m, 14H,Ar-H).MS, m/z %,459 (M^+,94.15),430 (1.76), 414 (8.35) , 413 (1.53), 372 (6.28), 86 (100), Anal. Calcd. for: $C_{25}H_{21}N_3O_4S$(459.51):C,65.34;H,4.61;N,9.14;S,6.98. Found: C, 65.04; H,4.31; N, 9.00 ; S,6.68.

2.2.12. 2-(4,5-Diphenyl-1-(4-nitrophenyl)-1*H*-imidazol-2-ylthio)acetohydrazide 18

A mixture of compound **17b** (0.01 mol) and hydrazine hydrate (10 ml, 85%) in ethanol (20 ml) was stirred well and refluxed for 6 h. The reaction mixture was cooled and the crude product was collected by filtration, washed with water and recrystallized from ethanol to give **18** as yellow plates. Yield: 60%.m.p. 254 - 258°C. IR(KBr, cm^{-1}): 1664(C=O), 3394,3331,3231(NH,NH_2),3055,2923(CH);1616(C=N).1H-NMR (DMSO - *d*6) δ ppm:6.41 - 7.43 (m,14,Ar-H), 12.80(s,1H,NH), 5.34(s,2H,NH_2), 3.85(s,2H,CH_2). MS, m/z%, 443 (M^+-2, 81.42), 398 (60.03),323 (71.68), 292 (72.57),92 (100). Anal.Calcd for $C_{23}H_{19}N_5O_3S$(445.49): C,62.01; H, 4.30;N,15.72;S,7.20. Found: C,61.89; H,4.00;N, 15.52;S, 7.00.

2.2.13. 2-[4,5-Diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio]-N'-benzylidene-acetohydrazide 19

A mixture of acid hydrazide **18** (0.01 mol) and benzaldehyde (0.01 mol) in absolute ethanol (30 ml) was heated under reflux for 4 h in presence of TEA (0.2 ml). Reaction mixture was then poured into ice cold water and filtered off and recrystallized from DMF to give **19** as white plates Yield: 65% .m.p. 288-290 ℃. IR (KBr, cm^{-1}): 1658(C=O), 3226 (NH),3049,2920 (CH).1H-NMR(DMSO-*d*6) δ ppm: 5.01 (s, 2H,CH_2),6.32–6.44(m,3H,Ar-H and CH= C), 6.76- 6.82 (m, 2H,Ar-H),7.13-7.38 (m,15H, Ar-H),12.00(s, 1H, NH). Anal. Calcd. for $C_{30}H_{23}N_5O_3S$ (533.60): C,67.53; H, 4.34; N,13.12; S,6.01.Found: C,67.33; H,4.24;N, 13.00;S , 5.89 .

2.2.14. 1-[2-(4,5-Diphpenyl-1-(4-nitrophenyl)-1*H*-imidazol-2-ylthio)acetyl]-4-phenyl-thiosemicarbazide 20

A mixture of acid hydrazide **18** (0.01mol) and phenyl isothiocyanate (0.01mol) was refluxed in ethanol for 4h. The reaction mixture was left to cooled, the crude solid was filtered off,washed twice with cold ethanol, dried and recrystallized from ethanol to give **20** as white powder. Yield 62%. m.p.158-160℃. IR (KBr,cm^{-1}):3428,3212 (NH), 3052, 2923(CH), 1664 (C=O),1251(C=S).1H-NMR (DMSO- *d*6) δ ppm:4.17(s,2H,CH_2),12.96 (s,1H,NH), 12.80 (s, 1H, NH),12.48(s,1H, NH), 6.42-7.83(m,19H, Ar-H).Anal.Calcd. for $C_{30}H_{24}N_6O_3S_2$(580.68):C,62.05;H,4.17;N,14.47;S, 11.04. Found: C,61.99 ;H ,4.00; N,14.27; S,11.0 .

2.2.15. 2-(4,5-Diphpenyl-1-(4-nitrophenyl)-1*H*-imidazol-2-ylthio)-N'-(4-oxo-3-phenyl-thiazolidin-2-ylidene)-acetohydrazide 21

To a suspension of thiosemicarbazide derivatives **20** (0.01mol) in glacial acetic acid (5 ml), anhydrous sodium acetate (0.02 mol) and chloroacetic acid (0.02 mol) were added. The reaction mixture was refluxed for 4 h then cooled, diluted with water and allowed to stand overnight. The product was filtered off and recrystallised from ethanol to give **21** as white plates. Yield: 55%. m.p.139-140℃. IR (KBr, cm^{-1}):3374(NH), 1724, 1671(C= O).1H-NMR (DMSO - *d*6) δ ppm: 4.33(s,2H,CH_2),4.50 (s, 2H, CH_2), 11.18 (s,1H, NH), 6.43-7.62(m,19 H, Ar-H). Anal. Calcd for $C_{32}H_{24}N_6O_4S_2$(620.70):C,61.92;H,3.90;N,13.54;S,10.33. Found:C, 61.62; H, 3.70; N, 13.34; S,10.13.

2.2.16. 5-[4,5-Diphenyl-1-(4-nitrophenyl)-1*H*-imidazol - 2-ylthio)methyl]-1,3,4-oxadiazole-2*(* 3*H*)thione 22

A solution of acid hydrazide **18** (0.01 mol) in pyridine (50 ml) and carbon disulphide (0.02 mol) was refluxed on water

bath for 7h.The reaction mixture was allowed to cooled and then acidified with dilute hydrochloric acid. The solid obtained was collected by filtration, washed with water,and recrystallized from ethanol to give **22** as white granules. m.p. 278-280°C. IR (KBr, cm^{-1}):3430 (NH), 3053, 2919(CH), 1623(C=N). 1H-NMR(DMSO-*d*6):δ ppm:12.79 (s, 1H,NH), 6.41(d,2H, J= 8.4,Ar-H),6.79 (d.2H, J= 8.4, Ar- H), 7.14-7.34 (m, 10H, Ar-H),5.19 (s,2H,CH_2).Anal.Calcd for $C_{24}H_{17}N_5O_3S_2$ (487.55): C,59.12; H,3.51; N ,14.36; S, 13.15. Found: C, 59.00; H,3.31;N ,14.06 ;S,13.00 .

2.2.17. General procedure for Synthesis of *N*-chloro-acetamide derivatives 24a-c

Chloroacetyl chloride (0.05 mol) was added drops wise over one hour to a solution of suitable aryl amine and /or appropriate sulfa drug (0.05 mol) in ethanol / DMF (50 ml, 1:1) contain few drops of TEA. Then the solution was left to stirring overnight. The resulting precipitates was filtered off and washed with ethanol and used in second step.

2.2.18. General procedure for synthesis of 2-(1*H*-imidaz-ol-2-ylthio)-*N*-substituted acetamide derivatives 25a-e

A mixture of **2a,b** (0.01 mol) and *N*-chloroarylacetamide derivatives **24 a-c** (0.01 mol) in DMF (25 ml) contain few drops of TEA was heated under reflux for 6h. The reaction mixture was left to cool and then poured to ice cooled water (100 ml). The solid product that formed was filtered off, dried well and recrystallized from suitable solvent.

2-[1-(4-Chlorophenyl)-4,5-diphenyl-*1H*-imidazol-2-ylthio]-*N*-*p*-tolyl-acetamide 25a

Pall yellow powder. Yield: 70%. m.p.158-160°C (ethanol). IR (KBr, cm^{-1}):3246 (NH),1683 (C=O),3041, 2931(CH), 1600(C=N).1H-NMR(DMSO-*d*6) δ ppm: 4.11 (s, 2H, CH_2), 2.24(s, 3H, CH_3), 10.36 (s,1H, NH), 7.09 -7.47(m,18H, Ar-H). MS, m/z %, 510 (M^+, 26.25), 404 (17.60), 375(27.06), 362(8.612), 193 (100), 147 (10.5). Anal. Calcd. for:$C_{30}H_{24}ClN_3OS$(510.05):C,70.64; H, 4.74; Cl, 6.95; N,8.24; S,6.29 .Found C,70.44; H,4.54; Cl, 6.65; N,8.04; S,6.09 .

2- [4,5-Diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio]-N-p-tolyl-acetamide (25b)

White needles. Yield: 75%. m.p.168-170°C (ethanol-DMF). IR(KBr,cm^{-1}): 3246(NH),1684(C=O),1599(C=N). 1H-NMR (DMSO- *d*6) δ ppm: 4.10(s, 2H, CH_2), 2.24 (s, 3H, CH_3), 10.31(s,1H, NH),7.09-7.47(m,18H, Ar-H). MS, m/z %, 518(M^+-2,40.80), 474 (19.54), 459(10.92), 399 (37.93), 385(32.76),342(100), 306(24.71), 148(12.64),134 (14.94). Anal. Calcd. for:$C_{30}H_{24}N_4O_3S$(520.603):C, 69.21; H,4.65; N,10.76;S,6.16.Found:C,69.00; H,4.45; N,10.46; S,6.00.

N-(4-Aminosulfonylphenyl)-2-[1-(4-chlorophenyl)-4.5-diphenyl-1H- imidazol-2-ylthio]acetamide (25c)

White granules. Yield: 60%. m.p.> 360°C (ethanol). IR(KBr, cm^{-1}): 1670 (C=O),1593(C=N),3330,3250,3150 (NH,NH_2),3048,2913(CH).1H-NMR (DMSO-*d* 6) δ ppm: 4.11(s,2H,CH_2),13.04(s,1H, NH),7.12-7.48(m,20H, Ar-H and NH_2).MS, m/z %, 575 (M^+,63.06), 559 (51.35), 523 (49.55), 383(100), 362 (29.73), 212(49.55). Anal. Calcd. for $C_{29}H_{23}ClN_4O_3S_2$ (575.10):C, 60.56; H,4.03; Cl, 6.16; N, 9.74; S, 11.15. Found: C,60.26; H,4.00; Cl,6.00 ; N , 9.53; S, 11.00.

N-(4-Aaminosulfonylphenyl)-2-(4.5-diphenyl-1-(4-nitrophenyl)-1H-imidazol-2-ylthio)acetamide (25d)

White plates. Yield: 68%. m.p.280-282°C (ethanol); IR (KBr,cm^{-1}): 1668(C=O),1594(C=N),3375, 3292, 3140 (NH,NH_2),3056,2913(CH).1H-NMR(DMSO-*d*6) δ ppm: 4.12 (s,2H, CH_2), 13.16 (s,1H, NH),6.91-8.21(m, 20H, Ar-H and NH_2).M.S, m/z % ,585(M+, 48.65),523 (84.68), 504(73.87), 448(59.46), 372(66.67), 214(61.26), 143 (100). Anal. Calcd. for $C_{29}H_{23}N_5O_5S_2$(585.65): C, 59.47; H, 3.96; N,11.96; S,10.95.Found: C,59.27; H,3.66; N, 11.73; S, 10.65 .

2-[4,5-Diphenyl-1-(4-nitrophenyl)-1*H*-imidazol-2-ylthio]-*N*-[4-(pyrimidin-2-ylsulfamoyl)-phenyl]-acetamide 25e

Gray powder.Yield:55%.m.p.238-240°C (ethanol). IR (KBr, cm^{-1}):1659(C=O), 3061,2966(CH),3238,3181(NH). 1H-NMR (DMSO-*d*6) δ ppm: 4.13 (s,2H, CH_2), 10.83 (s, 1H,NH),11.60(s, 1H,NH), 7.13- 7.48 (m, 21H, Ar-H and pyrimidine). MS, m/z %, 663(M^+,17.76),584 (18.07) , 569 (22.74),506(21.18),429 (35.20), 371 (20.56), 291 (21.81), 276(16.82),248(17.13), 57(100). Anal. Calcd. for $C_{33}H_{25}N_7O_5S_2$(663.72):C,59.72;H,3.80; N,14.77; S;9.66. Found: C, 59.52; H,3.60; N,14.67; S;9.46.

2.3. Biological Evaluation

2.3.1. Antimicrobial Assays

Synthesized compounds **4,5,11,13a,15e,17a,25c and 25e** were screened for their antimicrobial activities *in vitro* against two species of Gram-positive bacteria, namely *Staphylococcus aureus*(RCMB 0100010) and *Bacillus subtilis* (RCMB 010067), two Gram-negative bacteria, namely *Pseudomonas aeuroginosa* (RCMB010043) and *Escherichia coli* (RCMB 010052) and against four species of fungi, namely *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922),*Geotrichum candidum* (RCMB05097) and *Candida albicans* (RCMB 05036).The antibacterial and antifungal activity were determined by means of inhibition % ± standard deviation at a concentration of 100 µg/ ml of tested samples[20-22]. Optical densities of antimicrobial were measured after 24 hours at 37℃ to bacteria and measured after 48 hours at 28℃ to fungal using a multidetection microplate reader at the Regional Center for Mycology and Biotechnology (Sun Rise-Tecan, USA at 600 nm) Al-Azhar University. Ampicillin, gentamicin and Amphotericin B were used as references to evaluate the potency of the tested compounds under the same conditions.

2.3.2. DPPH Antioxidant Assay

The free radical scavenging activity of the synthesis compounds **1,2, 3b, 4, 5, 13c, 15a, 15c, 16** and **20**were evaluated by 1,1-diphenyl-2-picrylhydrazil (DPPH) according to the previously reported method [23]. Briefly, an 0.1 m M solution of DPPH in methanol was prepared, and 1 ml of this solution was added to 3ml of the solutions of all compound in methanol at different concentrations (5,10, 20, 40 µg / ml).The mixtures were shaken vigorously and allowed to stand at room temperature for 30 min. Then their absorbance were measured at 517 nm using a UV-VIS spectrophotometer (Genesys 10 UV: Thermo Electron Corporation). Ascorbic acid was used as the reference. Lower absorbance values of reaction mixture indicate higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated by using the following formula :

DPPH scavenging effect (% inhibition) = [A_c-A_s/A_c x100]

Where A_c is the absorbance of the control (blank, without test sample) and A_s is the absorbance of the test samples. IC_{50} value is the concentration of the compound required to inhibit 50% of DPPH• production

3. Results and Discussion

3.1. Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1- 4.The starting compounds 3-(4-chlorophenyl)-5,5-diphenyl-2-thioxoimidazol- idin-4-one **1** and 1-(4-substituted phenyl)-4,5-diphenyl-1*H*- imidazole-2-thione **2a,b** were prepared according to the previously reported procedure [24].Alkylation of 5,5-diphenyl-2-thioxoimidazolidin-4-one **1** with benzyl chloride and methyl iodide afforded 2-benzylthio- and 2-methylthio-3-(4-chlorophenyl)-5,5-diphenyl-imidazolidin-4-one **3a,b** respectively. The structures of **3a,b** was supported on the basis of elemental analyses and spectral data. The 1H-NMR spectra of **3a** in (DMSO-*d*6) revealed a singlet at δ 4.38 ppm assigned to the SCH_2 protons**.** Its mass spectrum showed a molecular ion peak at m/z 468.99 corresponding to a molecular formula $C_{28}H_{21}ClN_2OS$.

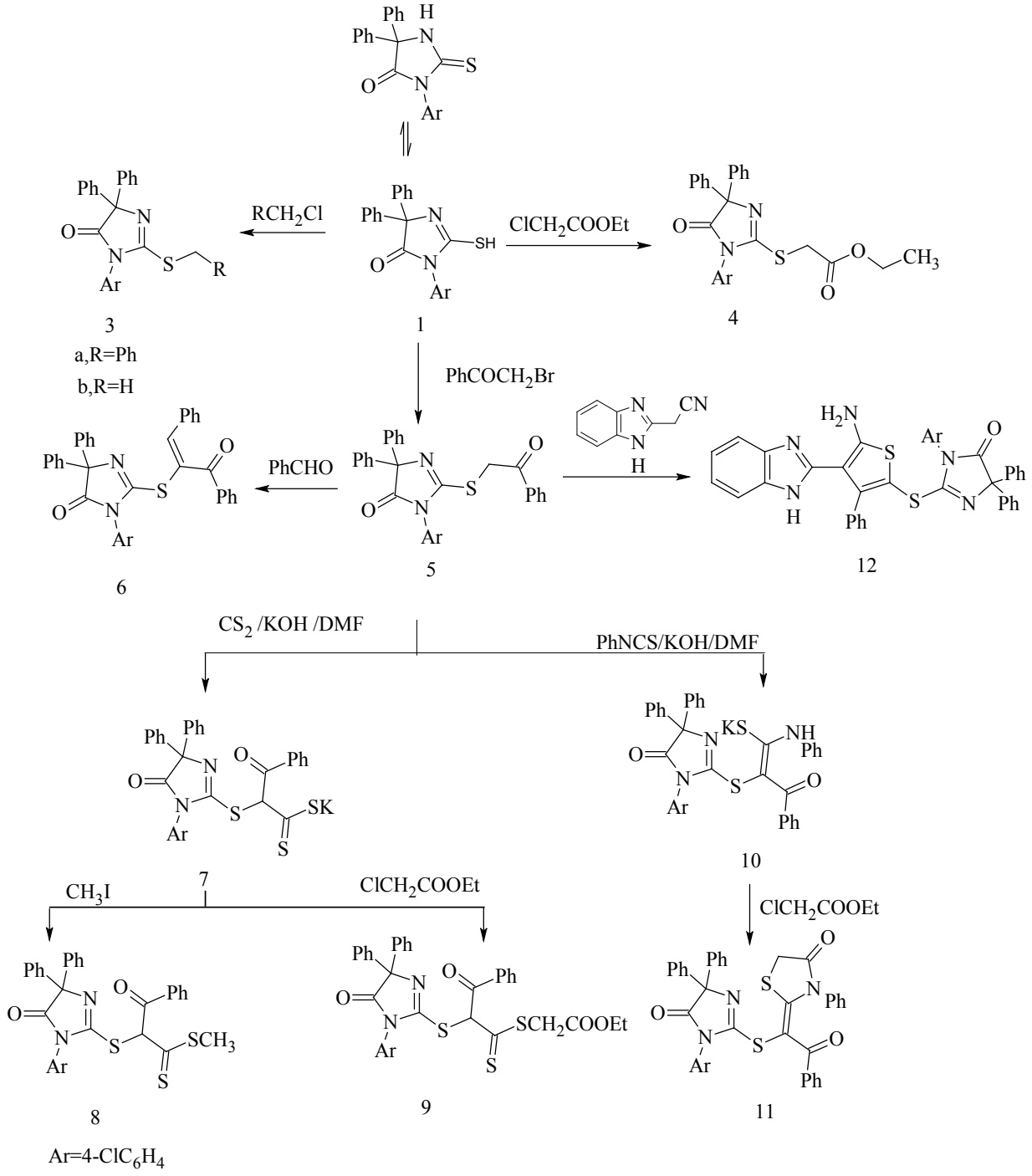
Imidazolidin-4-one derivative **1** was treated with ethyl chloroacetate in dry acetone containing anhydrous K_2CO_3 afforded ethyl [3-(4-chlorophenyl)-4-oxo-5,5-diphenyl-imidazolidin-2-ylthio]acetate **4.** IR spectra of **4** showed a characteristic absorption bands at 1741 for carbonyl group .The 1H NMR spectra of **4** in (DMSO-*d*6) showed a triplet at δ 1.18 ppm, quartet at δ 4.12 ppm corresponds to CH_2CH_3 group and singlet at δ 4.04 ppm corresponds to CH_2 protons. In addition, mass spectrum of **4** showed a molecular ion peak at m/z 464 corresponding to a molecular formula $C_{25}H_{21}ClN_2O_3S$ **(Scheme 1).**

Reaction **1** with phenacyl bromide in the presence of catalytic amount of triethylamine (TEA) in ethanol [25] afforded the corresponding 2-(benzoylmethylthio)-5,5-di-phenyl-imidazolidin-4-one **5.** Compound **5**was used as a key for synthesis of different heterocyclic compounds via treatment with different reagents. Thus, reaction of imidazolidin-4-one **5** derivative with benzaldehyde in the presence of piperidine [26] to yield the arylidine derivatives **6**. 1H-NMR spectrum of **6** in (DMSO-*d*6) show the disappearance of CH_2 protons observed in starting **5** at δ 4.10 ppm and the appearance multiplet signals at δ 7.09-7.84 ppm corresponding to the aromatic protons together with C=CH proton.

On the other hand, reaction of compound **5** with carbon disulphide in basic dimethylformamide (DMF) gave non-isolated potassium monothiolate derivatives **7**. Alkylation of compound **7** by using methyl iodide and ethyl chloroacetate [27] give methyl dithioate derivative **8** and ethyl (3-phenyl-propanedithioyl)acetate derivative **9**.Structures **8** and **9** were established by the correct analyses and spectroscopic data (see Experimental Section).

Treatment of compound **5** with phenyl isothiocyanate in basic DMF give non-isolated potassium salt **10** and then adduct ethyl chloroacetate [28] cycloalkylation occurred to afford the 1,3-thiazolidin-4-one derivative **11**.The formation of thiazoldin-4-one **11** may be rationalized through the first S-alkylation, then cyclisation to give **11**.The structure of the isolated product **11** was elucidated on the basis of their spectral data. The IR spectrum of exhibits bands at 1728 cm^{-1} to thiazolidinone CO. The 1H-NMR spectra revealed a thiazolidinone CH_2 signal at δ 4.04.

Furthermore, compound **5** undergoes Gewald reaction via treatment with elemental sulfur and 2-(1H-benzimidazol-2-yl) acetonitrile in absolute ethanol and DMF (2:1) containing a catalytic amount of morpholine [29] afforded the corresponding 2-[3-phenyl-thiophen-2-ylthio]-5,5-diphenyl- imidazolidin-4-one derivative **12 (Scheme 1).** Structure of **12** was confirmed on the basis of analytical and spectral data. The IR spectra showed the disappearance of CN group and showed an absorption bands at 3245, 3145, 3130 cm^{-1} corresponding to the NH_2, NH groups .1H-NMR spectra showed NH_2 and NH protons appeared at δ 4.81 and δ13.03 ppm respectively as s singlet signals. Mechanism for the formation of **12** in which the intermediate **I** is obtained first, then cyclization to give **12** (**Figure 1).** Several alkylated derivatives were obtained from 1-(4-substituted phenyl)- 4,5-diphenyl-1H-imidazole- 2-thione **2a,b**. Thus, upon treatment of **2a,b** with benzyl chloride, chloroacetonitrile, chloroacetone, phenacyl bromide and chloroacetamide in the presence of catalytic amount of TEA in ethanol [30] afforded the corresponding S-alkylated derivatives **13 a-d** and **15a-e** respectively **(Scheme 2).** The structures of new compounds were supported on the basis of elemental analyses and spectral data. For example, IR spectra of compounds **13c,d** revealed absorption bands for CN at 2246,2240 cm^{-1} and characteristic absorption band at 1711,1680,1691,1683,1676 cm^{-1} for the C=O confirming the structure of **15 a-e**.



Scheme 1. Synthesis of compounds 3-12

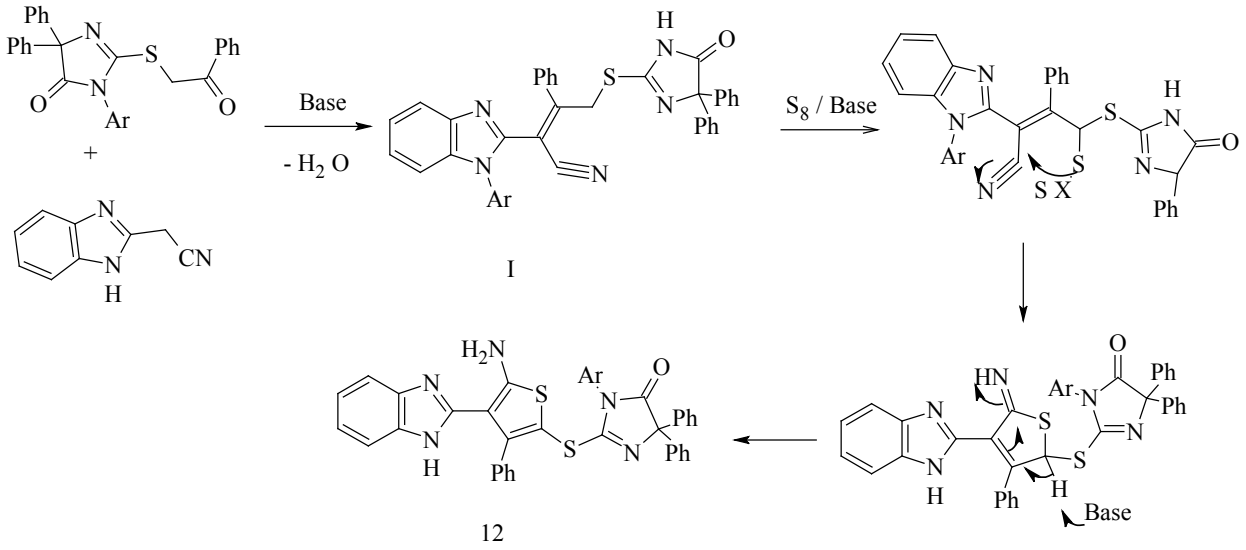
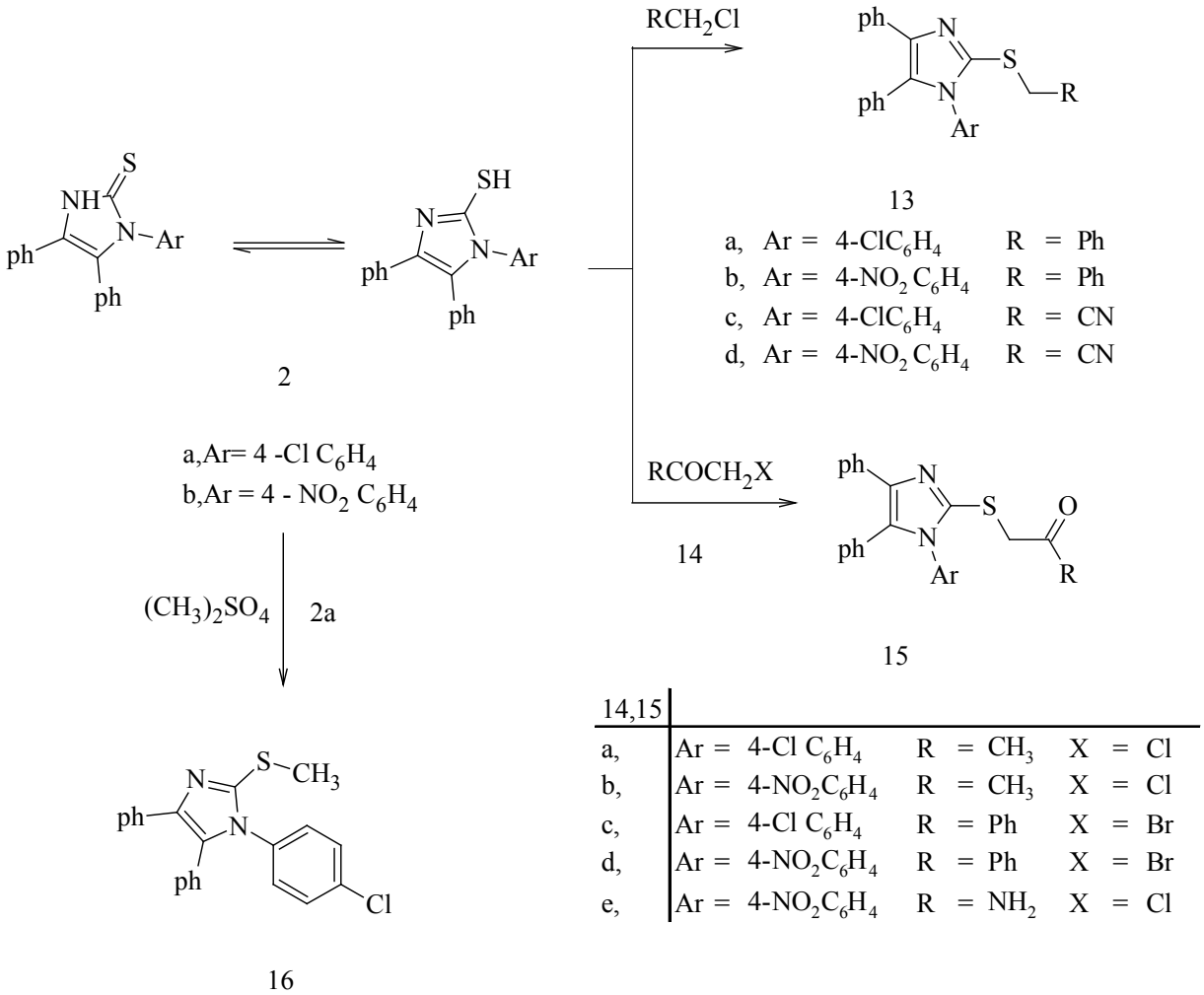


Figure 1. The proposed mechanism formation 2(3- phenyl -thiophen-2-ylthio]-imidazolidin-4-one 12



Scheme 2. Synthesis of Compounds 13-16

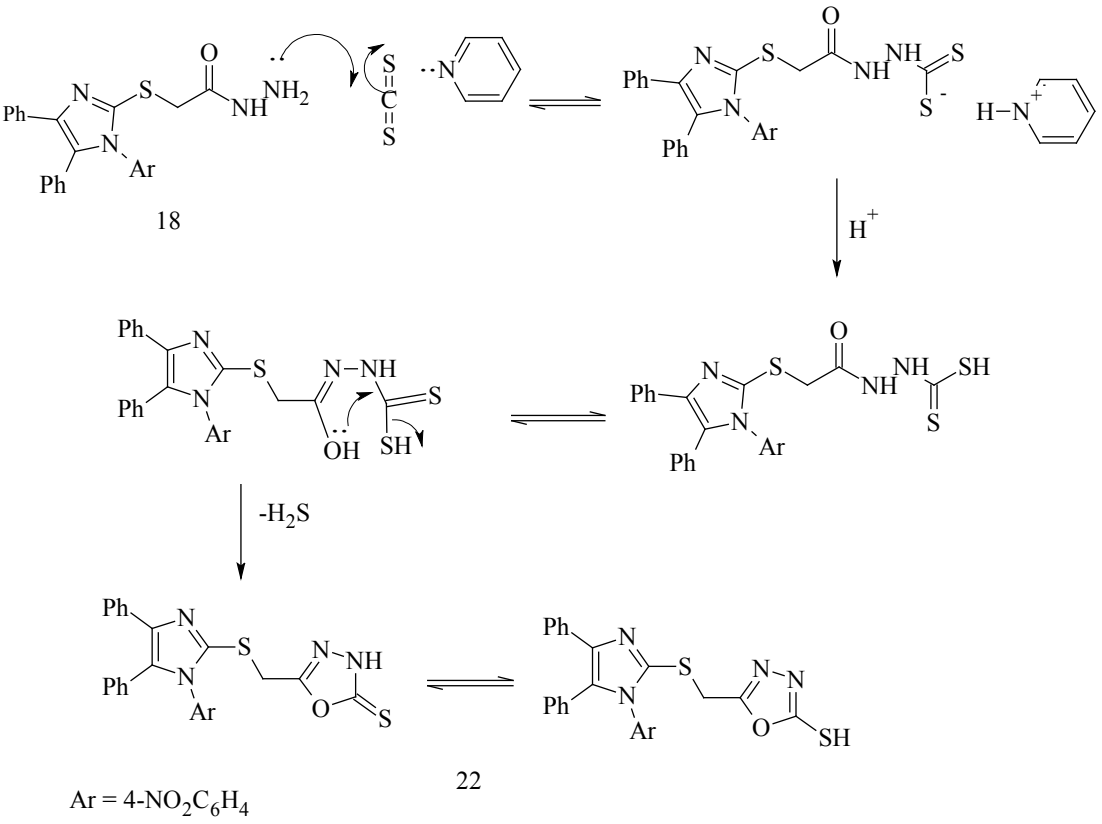


Figure 2. The proposed mechanism formation 1,3,4-oxadiazole-2-thione derivative 22

On the other hand, reaction of 1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole-2-thione **2a** with dimethyl sulphate in the presence of sodium methoxide to yield 1-(4-chlorophenyl)-2-(methylthio)-4,5-diphenyl-1*H*-imidazole **16.** 1*H*-

NMR spectrum of **16** displayed the following signals at δ 2.61 corresponding to the SCH_3 group (see Experimental Section).

Reaction of imidazole-2-thione **2a,b** with ethyl chloroacetate in ethanol in the presence of TEA [31] led to the formation of ethyl (4,5-diphenyl -1-(4-substituted phenyl)-1*H*-imidazol-2-ylthio) acetate **17a,b (Scheme 3)**. Structures of compounds **17,b** was elucidated with elemental analysis and spectral data. IR spectra of **17b** showed a characteristic absorption bands at 1734 cm^{-1} for the ester carbonyl group. The 1H-NMR spectra (DMSO-*d6*) of **17b** revealed the presence of triplet and quartet signal at δ 1.18 and 4.13 ppm attributed to CH_3CH_2 of ethyl ester. In addition, mass spectrum of **17b** showed a molecular ion peak at m/z 459 corresponding to a molecular formula $C_{25}H_{21}N_3O_4S$.

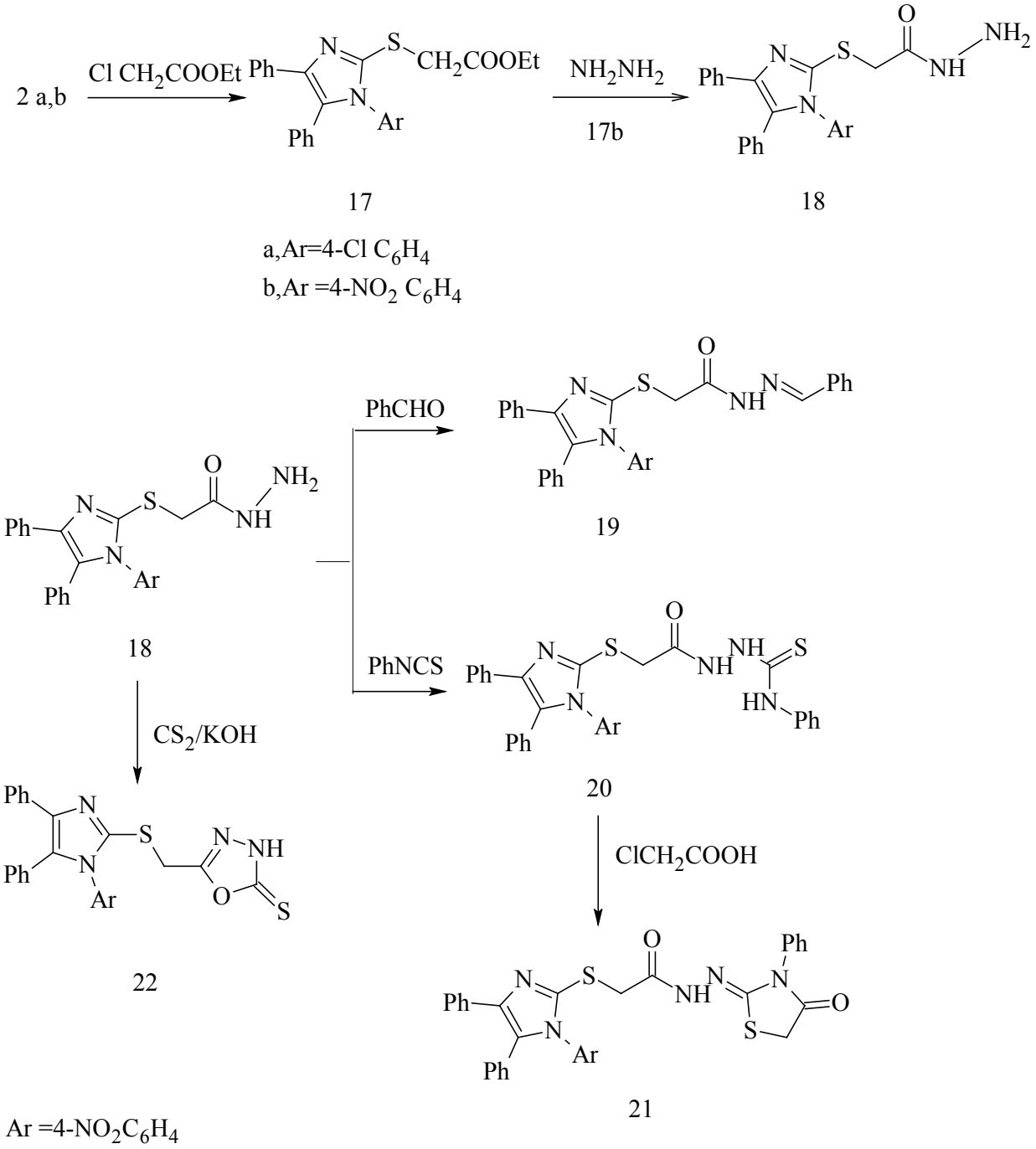
Reaction of ethyl (1*H*-imidazol-2-ylthio)acetate **17b** with hydrazine hydrate [32] gives the (1*H*-imidazol-2-ylthio] acetohydrazide derivative**18**.1H-NMR spectrum of **18** in (DMSO-*d6*) revealed new signals at 5.34 ppm corresponding to NH_2 proton, a singlet at 12.80 ppm for NH proton. Moreover, IR spectrum showed an NH and NH_2 stretching band at 3394,3331,3231 cm^{-1} and a carbonyl absorption band at 1664 cm^{-1}.

Compound **18** showed interesting reactivity toward a variety of chemical reagents. Thus, acid hydrazide**18** reacted with benzaldehyde [33] to afford the corresponding arylidine derivative **19**. The 1H-NMR spectrum of the **19** showed singlet at δ 12.00 ppm for NH proton and a multiplet signals in the region at δ 6.32- 6.44 ppm corresponding to the aromatic protons together with the =CH olefinic proton in addition to the disappearance of the NH_2 signal originally present in acid hydrazide **18**.

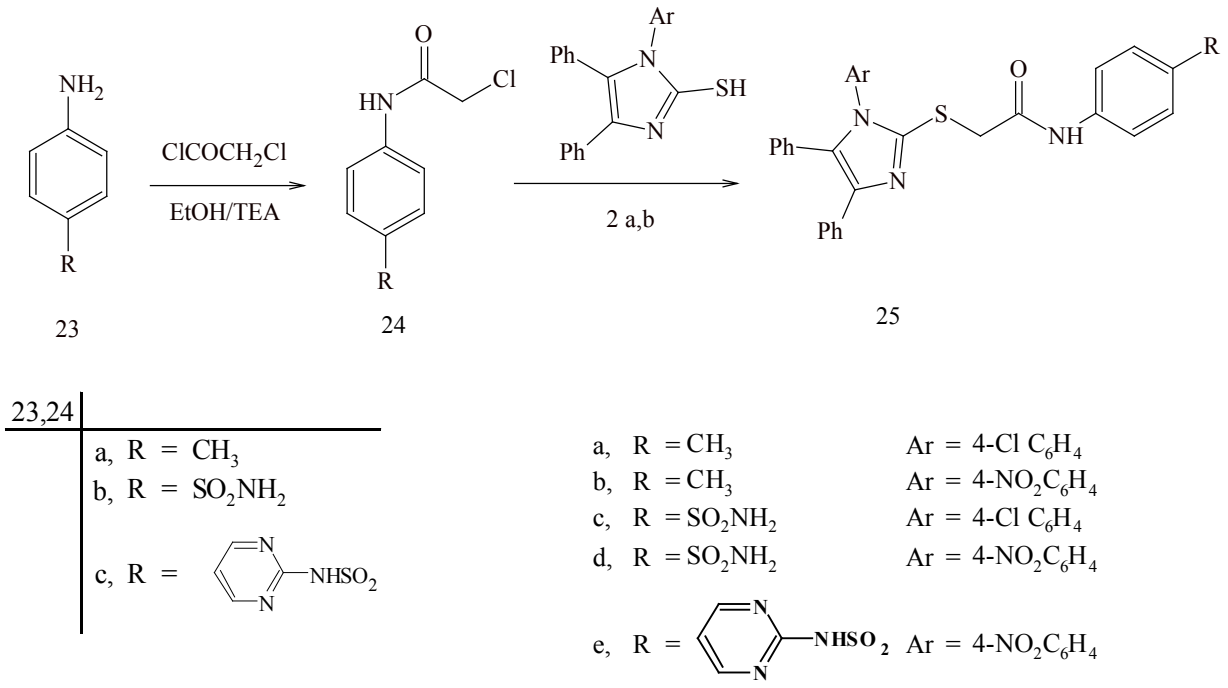
Condensation of **17** with phenyl isothiocyanate [34] in boilng ethanol afforded the corresponding phenyl thiosemicarbazide derivatives **20**. 1H-NMR spectrum of compound compound **20** showed three signals at δ 12.48, 12.80, 12.96 ppm which were accounted f or three NH protons. N'-(3- phenyl-thiazolidin-2-ylidene)acetohydrazide derivative **21** was obtained by reaction of phenyl thiosemicarbazide derivative **20** with chloroacetic acid and anhydrous sodium acetate in glacial acetic acid [35].The structure of **21** was elucidated by microanalysis and spectral data.IR spectra of **21** showed absorption band at 3374 cm^{-1} corresponding to NH group and two bands at 1724,1671cm^{-1} assigned to 2 C=O.1H-NMR revealed two singlet signals at δ 4.33, 4.50 ppm corresponding to protons of $2CH_2$ groups and signals at δ 11.18 ppm assigned to NH proton. The preparation of the 1,3,4-oxadiazole-2-thione derivative **22** was achieved by reaction of compound **18** with carbon disulphide under strong basic conditions followed by acidification[36,37] with dil.HCl **(Scheme 3).** The reaction proceeds via nucleophilic addition followed by 1,5-cyclisation to give **22 (Figure 2).**

2-(1*H*-Imidazol-2-ylthio)-*N*-substituted acetamide

derivatives **25a-e** were prepared by *S*-alkylation of 1-(4-substi- tuted phenyl)-4,5-diphenyl-*1H*-imidazole-2-thiole **2a,b** with 2-chloro-*N*-substituted acetamide derivatives [38. 39] **24a-c**. The intermediate **24a-c** were prepared by the reaction of *p*-toluidine, 4-amino-benzenesulfonamide,4-amino-*N*-(pyrimidin-2-yl) benzenesulfonamide **23a-c** with 2-chloro acetylchloride in the presence TEA [40,41] **(Scheme 4).**



Scheme 3. Synthesis of Compounds 17-22



Scheme 4. Synthesis of compounds 24a-c and 25-e

3.2. Biological Activity

3.2.1. Antimicrobial Activity

Synthesized **4, 5, 11, 13a, 15e, 17a, 25c and 25e** were evaluated for antibacterial and antifungal activity

Antibacterial Activity

Synthesized compounds **4,5,11,13a,15e,17a,25c and 25e** were screened for their antibacterial acti- vities *in vitro* against Gram-positive *Staphylococcus aureus(RCMB 0100010)* and *Bacillus subtilis (RCMB 010067)* and Gram-negative *Pseudomonas aeuroginosa* (RCMB010043) and *Escherichia coli*(RCMB 010052) Ampicillin and gentamicin were used as references to evaluate the potency of the tested compounds.The inhibitory effects of the synthetic compounds against these organisms are given in **Table 1, Figure 3**.

In general, most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria. All test compounds were found to be inactive against *Pseudomonas aeuroginosa* (RCMB 010043).

Compounds **17a 25c** and **25e** exhibited excellent activity against *Staphylococcus aureus* (RCMB 0100010) and *Bacillus subtilis* (RCMB 010067) compared with the standards ampicillin.While compounds **4,5,11, 13a and 15e** showed moderate to weak activity against *Staphylococcus aureus* (RCMB 0100010) and *Bacillus subtilis* (RCMB 010067) compared with the standards ampicillin. On other hand, compounds **17a** and **25e** strong activities against *Escherichia coli* (RCMB 010052) compared with the standards gentamicin. While compounds **4**, **5, 11, 13a, 15e** and **25c** moderate to week activity against *Escherichia coli* (RCMB 010052) compared with the standards gentamicin.

Antifungal Activity

The newly synthesized compounds **4, 5, 11**, **13a, 15e, 17a, 25c and 25e** were screened for their antifungal activities *in vitro* against *Aspergillus fumigatus (RCMB02568*), *Syncephalastrum racemosum (RCMB05922*), *Geotrichum candidum (RCMB05097*) and *Candida albicans (RCMB 05036*). The inhibitory effects of the synthetic compounds against these organisms are given in **Table 2, Figure 4.**

Compound **11, 25c** and, **25e** showed strong activities against *Aspergillus fumigatus (RCMB02568*) , *Syncephalastrum racemosum (RCMB05922*) and *Geotrichum candidum (RCMB05097*) comparable to *Amphotericin B*. On the other hand compounds **4, 5 13a, 15e**, and **17a** showed moderate to weak activities against *Aspergillus fumigatus (RCMB02568*), *Syncephalastrum racemosum* (RCMB05922) and *Geotrichum candidum* (RCMB05097) comparable to *Amphotericin B* .Furthermore, all test compound were found to be inactive against Candida albicans (RCMB 05036)

In vitro Antioxidant Activity-DPPH radical method

In general the principle of DPPH method is based on nitrogen centered stable free radical DPPH has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine (non radical). The change in the absorbance

produced in this reaction has been used to measure antioxidant property. [42-43]. The free radical-scavenging activity of the synthesized molecules was measured in terms of hydrogen donating or radical scavenging ability using the stable radical DPPH. The reduction capacity of DPPH radical which is induced by antioxidant was determine by the decrease in its absorbance at 517nm. It is visually noticeable as a change in colour from purple to yellow. This was expressed as the inhibition percentage.

The antioxidant activity of the newly synthesized compounds **1,2,3b,4,5,13c,15a,15c, 16** and **20** were evaluated by DPPH method. The results are shown in **Table 3 and figure 5 and 6**. The data in Table 3 showed clearly that compounds **2** and **20** have high activity while compound **11,3b** and **5** showed weak activities. On the other hand, compounds **4,13c,15a,15c** and **16** showed no activities.

4. Conclusions

Novel series of 2-thio-substituted- imidazoles and imidazolidine were synthesis. Screening for some selected compounds was carried for their potential antibacterial, antifungal and antioxidant activity using DPPH free radical scavenging method. Compound **25e** exhibited excellent activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* compared with the standards drugs. **25e** showed strong activities against *Aspergillus fumigatus*, *Geotrichum candidum* comparable to *Amphotericin B*. compound **2** and **20** showed good DPPH scavenging activity.

Table 1. Antibacterial evaluation of the same synthesized compo

comp. No.	inhibition % ±Standard deviation			
	Gram positive bacteria		Gram negative e bacteria	
	Staphylococcus aureus (RCMB 0100010)	Bacillus subtilis (RCMB 010067)	Pseudomonas aeuroginosa (RCMB010043)	Escherichia coli (RCMB 010052)
4	60.21±1.3	71.20±0.21	NA	43.21±1.4
5	34.25±0.28	51.63±1.2	NA	32.14±0.63
11	64.21±0.63	79.23±0.82	NA	57.32±0.92
13a	13.25±0.24	16.13±0.32	NA	9.32±0.46
15e	34.12±0.32	43.21±0.16	NA	18.31±0.44
17a	80.12±0.63	84.32±0.18	NA	63.21±0.34
25c	90.32±0.44	93.23±0.21	NA	56.35±0.58
25e	93.24±0.25	96.25±0.32	NA	80.32±0.14
Reference drugs				
Ampicillin	96.52±0.2	99.65±0.3		
Gentamicin			89.23±0.1	82.14±0.3

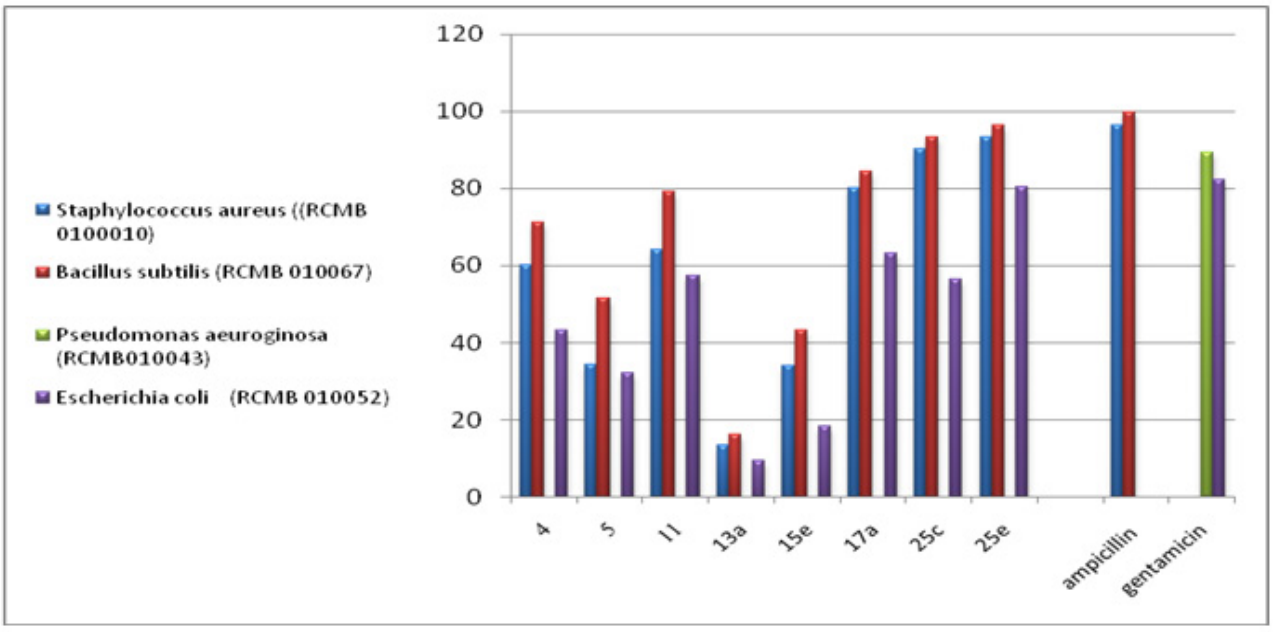


Figure 3. Graphical Representation of Antibacterial Activity of Some Synthesis Compounds

Table 2. Antifungal evaluation of the same synthesized compounds

Comp. No.	Inhibition % ± standard deviation			
	Aspergillus fumigatus (RCMB02568)	*Syncephalastrum racemosum (RCMB05922)*	*Geotrichum candidum(RCMB05097)*	*Candida albicans (RCMB 05036)*
4	63.25±0.28	52.41±0.58	73.84±0.28	NA
5	*52.41±1.2*	*43.21±0.63*	*61.20±0.28*	NA
11	*73.25±1.3*	*64.85±0.64*	*81.35±0.29*	NA
13a	11.63±0.58	9.25±0.44	15.63±0.25	NA
15e	22.36±0.44	16.25±0.44	29.31±0.58	NA
17a	63.25±0.19	60.11±0.44	70.32±0.52	NA
25c	78.32±0.44	62.34±0.58	84.31±0.38	NA
25e	90.32±0.44	68.25±0.58	93.21±0.37	NA
	Reference drugs			
Amphotericin B	96.25±0.1	74.25±0.2	95.36±0.2	91.29±0.1

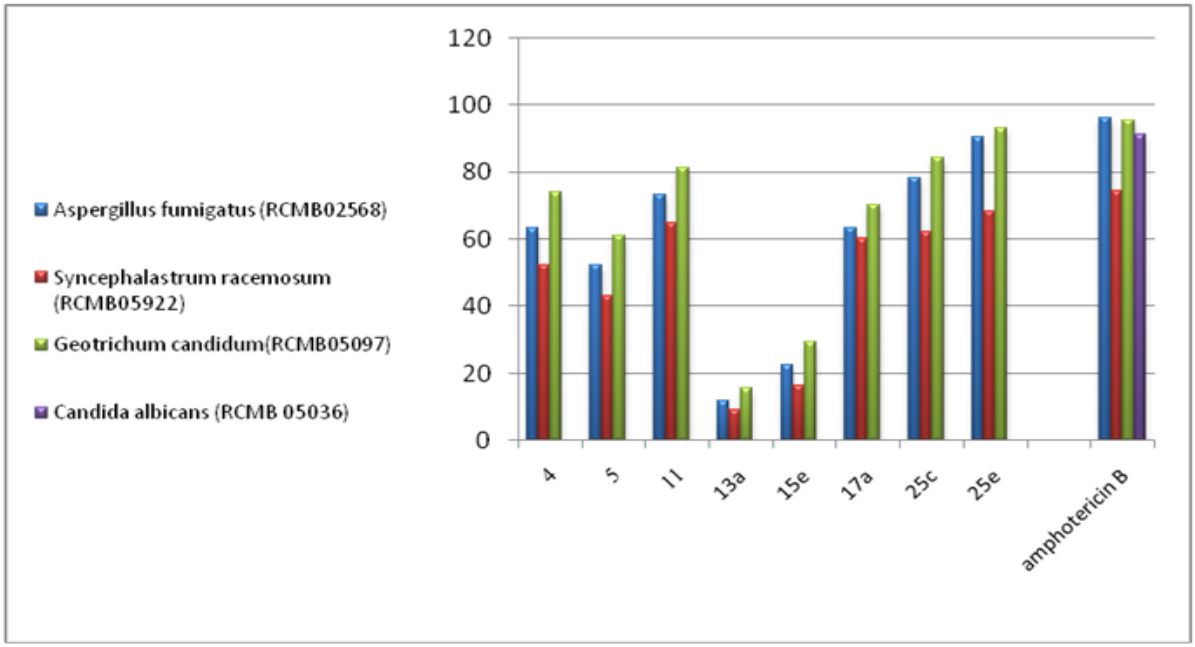


Figure 4. Graphical Representation of Antifungal Activity of Some Synthesis Compounds

Table 3. The in vitro antioxidant activity of some synthesis compounds in DPPH method

Comp.No.	Sample conc. (µg/ml)				IC_{50} µg./ml
	5 µg/ml	10µg/ml	20µg/ml	40µg/ml	
	(%) Inhibition				
1	1.93	18.84	28.21	41.58	62.22
2	12.19	28.11	49.79	67.58	20.24
3b	6.21	13.37	25.79	37.47	67.52
4	-	-	-	-	-
5	2.46	17.58	26.42	38.84	96.4
13c	-	-	-	-	
15a	-	-	-	-	
15c	-	-	-	-	
16	-	-	-	-	
20	23.85	42.63	56.32	71.37	15.38
Ascorbic acid	11.78	17.49	70.94	92.48	14.21

(–) Showed no scavenging activity

IC_{50} value is the concentration of the compound required to inhibit 50% of DPPH• production

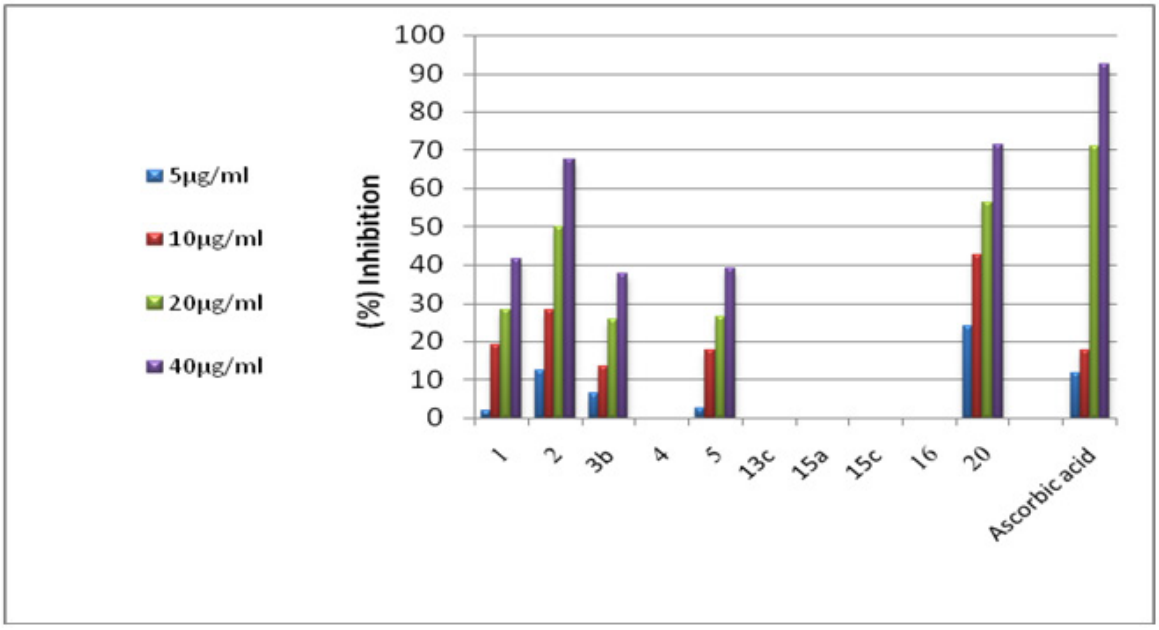


Figure 5. Radical Scavenging Potential of The Synthesis Compounds By DPPH Method at Different Concentration

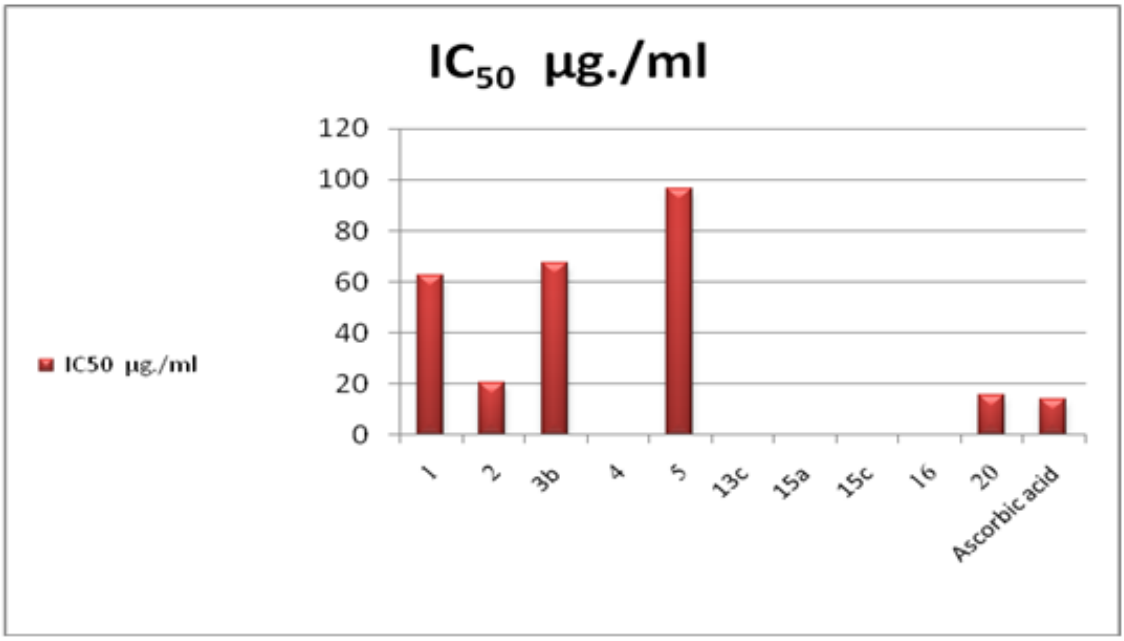


Figure 6. IC_{50} Value of The Newly Synthesized Compounds

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