International Journal of Organic Chemistry, 2015, 5, 15-28
Published Online March 2015 in SciRes. http://www.scirp.org/journal/ijoc
http://dx.doi.org/10.4236/ijoc.2015.51003

Synthesis, Spectroscopic Characterization and Antimicrobial Activity of Some New 2-Substituted Imidazole Derivatives

Asmaa S. Salman, Anhar Abdel-Aziem, Marwa J. S. Alkubbat

Department of Chemistry, Faculty of Science, Al-Azhar University, Girls' Branch, Nasr City, Cairo, Egypt
Email: salman_2007_ok@yahoo.com

Received 15 January 2015; accepted 1 March 2015; published 9 March 2015

Abstract

The reaction of imidazole-2-thione derivative 1 with 2-chloro-*N*-*p*-tolylacetamide afforded the corresponding 2-(1*H*-imidazol-2-ylthio)-*N*-*p*-tolylacetamide 2. Reaction compound 2 with different reagents such as *p*-chlorobenzaldehyde and *p*-chlorophenyl diazonium chloride afforded the corresponding arylidene derivative 3 and hydrazone derivative 6. Reactions of 2 with carbon disulfide in dimethylformamide (DMF) in one equivalent potassium hydroxide afforded intermediate potassium sulphide salt 8, which treatment with dilute hydrochloric acid and phenacyl bromide afforded the corresponding 2-[*p*-tolylcarbamoyl]ethanedithioic acid 9 and 3-[benzo-ylmethylthio]-*N*-*p*-tolyl-3-thioxo-propaneamide 10. While the reaction 2 with carbon disulphide in the presence of two equivalent potassium hydroxide in DMF gave non-isolated potassium salt 11, which was allowed to react with halogenated compounds namely ethyl chloroacetate and methyl iodide afforded the corresponding 3, 3-bis[(ethoxycarbonyl)methylthio]-*N*-*p*-tolylacrylamide 12 and 3,3-bis-(methylthio)-*N*-*p*-tolylacrylamide 13 respectively. Reaction 2 with phenyl isothiocyanate in basic DMF yielded the intermediate potassium sulphide salt 18. Acidification 18 with dilute hydrochloric acid afforded the corresponding thiocarbamoyl derivative 19. Treatment of intermediate 18 with methyl iodide, phenacyl bromide and ethylchloroacetate afforded the 3-anilino-3-(methylthio)-*N*-*p*-tolylacrylamide 20, 2-(1,3-thiazol-2(3*H*)-ylidene)-*N*-*p*-tolylacetamide 21 and 2-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-*N*-*p*-tolylacetamide 22 respectively. The structure of the newly synthesized compounds has been confirmed by elemental analysis and spectra data. Synthesized compounds 2, 3, 6, 13, 15a, 15b, 17, 20, 21, 22 and 23 were screened for their antibacterial activities *in vitro* against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative (*Pseudomonas aeuroginosa* and *Escherichia coli*) and antifungal activities against (*Aspergillus fumigates*, *Syncephalastrum racemosum*, *Geotrichum candidum* and *Candida albicans*).

How to cite this paper: Salman, A.S., Abdel-Aziem, A. and Alkubbat, M.J.S. (2015) Synthesis, Spectroscopic Characterization and Antimicrobial Activity of Some New 2-Substituted Imidazole Derivatives. *International Journal of Organic Chemistry*, **5**, 15-28. http://dx.doi.org/10.4236/ijoc.2015.51003

Keywords

Imidazole-2-Thione, *α*-Oxoketen Dithioacetals, Thiocarbamyl, Thiazole, Antibacterial, Antifungal

1. Introduction

Aromatic heterocycles are valuable synthetic templates for the preparation of new compounds with specific biological, pharmaceutical and material properties. The pursuit of these properties requires efficient synthetic routes that allow rapid construction of diverse aromatic heterocycles with defined substitution patterns. Therefore, *α*-oxoketen dithioacetals and thiocarbamyl as the organic synthetic intermediates have been widely used in the formation of alicyclic, aromatic and heterocyclic compounds [1]-[4]. In view of the above and in continuation of our studies on the synthesis of heterocyclic compounds exhibiting biological activity, we report here the synthesis of some novel heterocycles compounds incorporating imidazole moiety from *α*-oxoketen dithioacetals and thiocarbamyl.

2. Material and Methods

2.1. Experiment

All melting points were determined in open glass capillaries on a Gallen kamp 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 (90 MHz) spectrometer using TMS as an internal standard and dimethyl sulphoxide (DMSO-d6) as a solvent. Chemical shifts were expressed in δ (ppm) values and mass spectra were determined on Finnigan Incos 500 (70 ev). Elemental analyses were determined using a Parkin-Elmer 240C Microanalyzer. The microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University.

2.1.1. 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacetamide 2

A mixture of **1** (0.01 mol) and 2-chloro-*N*-*p*-tolylacetamide (0.01 mol) in DMF (25 ml) contain few drop of triethylamine was heated under reflux for 6 h. 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 ethanol to give **2** as pall yellow crystals. Yield: 70%. M.p.: 156˚C - 158˚C; IR (K Br) cm^{-1}: 3246 (NH), 1683 (C=O), 3041, 2931 (CH), 1600 (C=N); 1H-NMR (DMSO-d6) 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.

2.1.2. 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-3-(4-chlorophenyl)-*N*-*p*-tolylacrylamide 3

A mixture of **2** (0.01 mol) and *p*-chlorobenzaldehyde (0.01 mol) in ethanol (30 ml) containing few drop of piperidine (0.5 ml) was refluxed for 3h. The reaction mixture was left to cool then poured onto ice water contain few drops of HCl and the obtained solid was recrystallized from ethanol to give **3** as white crystals. Yield: 60%. M.p.: 170˚C - 171˚C; IR (KBr) cm^{-1}: 3247 (NH), 1687 (C=O), 3046, 2951 (CH); 1H-NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 10.31 (s, 1H, NH), 7.09 - 7.47 (m, 23H, Ar-H and =CH); MS *m/z* (%): 632 (M^+, 11.24), 548 (23.22), 520 (398.33), 430 (23.22), 386 (27.34), 309 (24.34), 80 (100); Anal. Calcd. for $C_{37}H_{27}Cl_2N_3OS$ (632.60): C, 70.25; H, 4.30; Cl, 11.21; N, 6.64; S, 5.07. Found: C, 70.00; H, 4.00; Cl, 11.00; N, 6.44; S, 5.00.

2.1.3. 5-(4-Chlorophenyl)-4-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolyl-1*H*-pyrazole-3-amine 4

A mixture of **3** (0.01 mol) and hydrazine hydrate (0.01 mol) in 30 ml absolute ethanol was added few drops of glacial acetic and refluxed for 8 - 10 h. After completion of the reaction, excess of solvent was distilled off; the separated solid was filtered, washed with water, and recrystallized from methanol to give **4** as yellow crystals.

Yield: 55%. M.p.:138˚C - 140˚C; IR (KBr) cm^{-1}: 2922, 3054 (CH), 3437 (NH); 1H-NMR (DMSO-d6) δ ppm: 1.74 (s, 3H, CH_3), 7.17 - 7.49 (m, 23H, Ar-H and NH), 9.40 (s, 1H, NH); MS *m/z* (%): 644 (M^+, 11.02), 630 (12.44), 558 (9.13), 537 (5.98), 511 (8.03), 483 (6.61), 464 (12.76), 405 (17.64), 333 (9.29), 388 (9.49), 233 (100); Anal. Calcd. for $C_{37}H_{27}Cl_2N_5S$ (644.61): C, 68.94; H, 4.22; Cl, 11.00; N, 10.86; S, 4.97. Found: C, 68.64; H, 4.00; Cl, 10.99; N, 10.66; S, 4.67.

2.1.4. 5-(4-Chlorophenyl)-4-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ythio]-1-phenyl-*N*-*p*-tolyl-1*H*-pyrazol-3-amine 5

A mixture of **3** (0.01 mol), phenyl hydrazine (0.01 mol), glacial acetic acid (20 ml) and few drop of HCl was refluxed for 8 - 10 h. The reaction mixture was then left to cool at room temperature, and poured onto ice cold water (100 ml). The solid product was collected by filtration and recrystallized from acetic acid to give **5** as grey crystals. Yield: 60%. M.p.: 290˚C - 292˚C; IR (KBr) cm^{-1}: 3426 (NH), 3048, 2926 (CH), 1594 (C=N); 1H-NMR (DMSO- d6) δ ppm: 1.90 (s, 3H, CH_3), 7.13 - 7.48 (m, 27H, Ar-H), 13.03 (s, 1H, NH); MS *m/z* (%): 720 (M^+, 8.26), 628 (7.05), 554 (6.68), 538 (7.90), 615 (8.51), 512 (8.26), 423 (6.93), 266 (11.42); Anal. Calcd. for $C_{43}H_{31}Cl_2N_5S$ (720.71):C, 71.66; H, 4.34; Cl, 9.84; N, 9.72; S, 4.45. Found: C, 71.36; H, 4.04; Cl, 9.54; N, 9.42; S, 4.25.

2.1.5. 2-[2-(4-Chlorophenyl)hydrazono]-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacetamide 6

To a cold solution of **2** (0.01 mol) in pyridine (30 ml) was added with continuous stirring 4-chloro phenyl-diazonium salt (0.01 mol) [prepared by adding sodium nitrite (0.02 mol) in water (8 ml) to a cold solution of the *p*-chloroaniline in the appropriate amount of hydrochloric acid]. The reaction mixture was stirred at room temperature for 2 h, and the solid products, so formed, were collected by filtration and recrystallized from benzene to give **6** as red crystals. Yield: 67%. M.p.:118˚C - 120˚C; IR (KBr, cm^{-1}): 3259, 3136 (NH), 1604 (C=N), 1686 (C=O); 1H-NMR ((DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 7.09 - 7.47 (m, 22H, Ar-H), 8.58(s, 1H, NH), 10.32(s, 1H, NH); MS *m/z* (%): 648 (M^+, 40.12), 543(43.83), 471(45.68), 442 (33.33), 362 (33.95), 367 (33.95), 287 (55.02), 211 (35.80), 196 (54.94), 77 (100); Anal. Calcd. for: $C_{36}H_{27}Cl_2N_5OS$(648.60): C, 66.66; H, 4.20; Cl, 10.93; N, 10.80; S, 4.94. Found: C, 66.36; H, 4.0 0; Cl, 10.73; N 10.50; S, 4.74.

2.1.6. 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-2-[*p*-tolylcarbamoyl] ethanedithioicacid 9

To suspension of finely powdered potassium hydroxide (0.01 mol) in dry DMF (20 ml) at 0˚C, the acetamide derivative **2** (0.01 mol) was added, the resulted mixture was cooled at 10˚C in an ice bath, then carbon disulfide (0.01 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h. Then hydrochloric acid (2 M, 20 ml) was added drop wise and stirring continued for additional 1 h. Then, the reaction mixture was poured into ice water. The solid product that formed was filtered off, dried, and recrystallized from the ethanol to give **9** as yellow crystals. Yield: 75%. M.p.: 222˚C - 224˚C; IR (KBr, cm^{-1}: 3231 (NH), 1682 (CO), 3043, 2855 (CH), 1271 (C=S); MS *m/z* (%): 587 (M^+ +1, 4.08), 586 (M^+, 4.53), 553 (3.18), 520 (5.47), 480 (3.35), 415 (3.46), 233 (100), 221 (3.80), 77 (96.65); Anal. Calcd. for $C_{31}H_{24}ClN_3OS_3$ (586.19): C, 63.52; H, 4.13; Cl, 6.05; N, 7.17; S, 16.41. Found: C, 63.32; H, 4.00; Cl, 6.00; N, 7.00; S, 16.21.

2.1.7. 3-[Benzoylmethylthio]-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolyl-3-thioxo-propaneamide 10

To suspension of finely powdered potassium hydroxide (0.01 mol) in dry DMF (20 ml) at 0˚C, the acetamide derivative **2** (0.01 mol) was added, the resulted mixture was cooled at 10˚C in an ice bath, then carbon disulfide (0.01 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h. Then cooled again to 0˚C, phenacyl bromide (0.01 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h. Then poured into crushed ice, the resulting precipitate was filtrated off, dried and recrystallized from ethanol to give **10** as yellow crystals. Yield: 80%. M.p.: 146˚C - 148˚C; IR (KBr, cm^{-1}): 3416 (NH), 1762, 1686 (CO), 1280 (C=S), 1600 (C=N), 3052, 2967, 2913 (CH); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 4.57 (s, H, CH), 7.10 - 8.02 (m, 23H, Ar-H), 10.31 (s, 1H, NH); Anal. Calcd. For $C_{39}H_{30}ClN_3O_2S_3$ (704.32): C, 66.51;

H, 4.29; Cl, 5.03; N, 5.97; S, 13.66. Found: C, 66.31; H, 4.09; Cl, 5.00; N, 5.77; S, 13.46.

2.1.8. 3,3-Bis[(ethoxycarbonyl)methylthio]-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacrylamide 12

To suspension of finely powdered of potassium hydroxide (0.02 mol) in dry DMF(20 ml) at 0˚C the acetamide derivative **2** (0.01 mol) was added, the resulted mixture was cooled at 10˚C in an ice bath, then carbon disulfide (0.01 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h. Then cooled again to 0˚C, ethyl chloroacetate (0.02 mol) was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for 6 h. Then poured into crushed ice, the resulting precipitate was filtrated off, dried and recrystallized from benzene to give **12** as yellow crystals. Yield: 65%. M.p.: 120˚C - 122˚C; IR (KBr, cm^{-1}): 3252 (NH), 1736, 1685 (CO), 3049, 2980, 2925 (CH); 1H-NMR (DMSO-d6) δ ppm: 1.13 - 1.23 (m, 6H, 2-CH_2 –$\underline{CH_3}$), 4.33 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 4.04 - 4.153 (m, 4H, $\underline{2CH_2}$-CH_3), 2.24 (s, 3H, CH_3), 7.09 - 7.51 (m, 18H, Ar-H), 10.32 (s, 1H, NH); Anal. Calcd. for $C_{39}H_{36}ClN_3O_5S_3$ (758.37): C, 61.77; H, 4.78; Cl, 4.67; N, 5.54; S, 12.68. Found:C, 61.67; H, 4.58; Cl, 4.47; N, 5.34; S, 12.38.

2.1.9. 3,3-Bis(methylthio)-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacrylamide 13

Compound **13** was synthesized as mentioned above in synthesis of **12** but using methyl iodide (0.02 mol) instead of ethyl chloroacetate, the resulting product was recrystallized from ethanol to give **13** as yellow crystals. Yield: 60%. M.p.: 166˚C - 168˚C; IR (KBr, cm^{-1}): 3438 (NH), 1674 (CO), 3050, 2919 (CH); 1H-NMR (DMSO-d6) δ ppm 2.21 (s, 3H, CH_3), 7.18 - 7.68 (m, 19H, Ar-H and NH), 2.28 (s, 6H, $2SCH_3$); MS *m/z* (%): 614 (M^+, 20.64), 611(16.71), 568 (13.154), 506 (19.41), 415 (13.27), 315 (14.74), 252 (15.48), 206 (17.44), 237 (15.97), 75 (100); Anal. Calcd. for $C_{33}H_{28}ClN_3OS_3$(614.24): C, 64.53; H, 4.59; Cl, 5.77; N, 6.84; S, 15.66. Found: C, 64.23; H, 4.39; Cl, 5.57; N, 6.64; S, 15.36.

2.1.10. 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-3,3-dihydrazino-*N*-*p*-tolylacrylamide 14

A mixture of compound **13** (0.01 mol) and hydrazine hydrate (80%, 0.02 mol) was heated under reflux for 4 h, then left to cool. The obtained solid product was triturated with ethanol (10 ml), filtered off, washed with ethanol, dried and recrystallized from butanol afford compound **14** as white crystals. Yield: 60%. M.p.: 210˚C - 213˚C; IR(KBr, cm^{-1}): 3297, 3269, 3196, 3126 (NH_2, NH), 1682 (CO), 3061, 2959 (CH); 1H-NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 7.09 - 7.56 (m, 19H, Ar-H and NH), 10.33 (s, 1H, NH), 10.51 (s.1H, NH), 4.84 (s, 2H, NH_2), 4.89 (s, 2H, NH_2); MS *m/z* (%): 582 (M^+, 66.04), 517 (13.21), 470 (50.94), 444 (61.32), 397 (100), 381 (58.49), 321 (24.53); Anal. Calcd. for $C_{31}H_{28}ClN_7OS$ (582.11): C, 63.96; H, 4.85; Cl, 6.09; N, 16.84; S, 5.51. Found: C, 63.66; H, 4.65; Cl, 6.00; N, 16.64; S, 5.41.

2.1.11. Reaction of 3,3-Bis(methylthio)-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacrylamide 13 with Amines

A mixture of **13 (**0.01 mol) suitable amine such as *o*-phenylenediamine, *o*-aminophenol and/or p-chloroaniline (0.01 mol) in DMF (25 ml) was heated under reflux for 6 h. 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 appropriate solvent.

2-(*1H*-Benzimidazol-2-yl)-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacetamide 15a

White powder. Yield: 65%. M.p.: 238˚C - 240˚C (ethanol and DMF); IR (KBr, cm^{-1}): 3245, 3188 (NH); 3055, 2924, 2865 (CH), 1659 (CO), 1607 (C=N); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 7.09 - 7.53 (m, 22H, Ar-H); 7.95 (s, 1H, NH), 10.30 (s, 1H, NH), 4.61(s, 1H, CH); MS *m/z* (%): 626 (M^+, 29.10), 491 (212.31), 424 (29.10), 391 (31.97), 379 (35.25), 328 (26.64), 75 (100); Anal. Calcd. for $C_{37}H_{28}ClN_5OS$(626.17): C, 70.97; H, 4.51; Cl, 5.66; N, 11.18; S, 5.12. Found: C, 70.67; H, 4.21; Cl, 5.46; N, 11.08; S, 5.02.

2-(1,3-Benzoxazol-2-yl)-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacetamide 15b

Pale grey crystals. Yield: 55%. M.p.:176˚C - 178˚C (ethanol); IR (KBr, cm^{-1}) 3246 (NH); 1687 (CO), 1600

(C=N), 3048, 2922, 2864 (CH); 1H-NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 7.09 - 7.47 (m, 22H, Ar-H); 10.43 (s, 1H, NH), 4.16 (s, 1H, CH); MS *m/z* (%): 627 (M^+, 11.96), 611 (11.52), 516 (10.49), 492 (8.57), 405 (8.86), 330 (9.16), 264 (10.34), 173 (10.49), 77 (100); Anal. Calcd. for $C_{37}H_{27}Cl\ N_4O_2S$ (627.15):C, 70.86; H, 4.34; Cl, 5.65; N, 8.93; S, 5.11. Found: C, 70.66; H, 4.04; Cl, 5.45; N, 8.73; S, 5.00.

2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-3-(4-chlorophenylamino]-3-(methylthio)-*N*-*p*-tolylacrylamide 16

White powder. Yield: 65%. M.p.: 190˚C - 192˚C (ethanol); IR (KBr, cm^{-1}) 3246, 3191 (NH); 1687 (CO), 1599 (C=N); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 7.09 - 7.62 (m, 23H, Ar-H and NH); 10.29 (brs, 1H, NH); MS *m/z* (%): 693 (M^+, 53.29), 631 (43.13) 622 (40.72), 607 (40.72), 471 (35.93), 330 (53.89), 234 (35.93), 257 (51.51), 272 (34.13), 77 (100); Anal. Calcd. for $C_{38}H_{30}Cl_2N_4OS_2$ (693.70): C, 65.79; H, 4.36; Cl, 10.22; N, 8.08; S, 9.24. Found: C, 65.59; H, 4.26; Cl, 10.02; N, 8.00; S, 9.04.

2.1.12. 4-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-3-(*p*-tolylamino)-5-(methylthio)-1*H*-pyrrole-2-carboxylic Acid 17

A mixture of compound **13** (0.01 mol) and glycine (0.01 mol) in ethanol (30 ml) containing triethylamine (5 drops) was heated under reflux for 8 h. The formed solid product was filtered off, dried and recrystallized from ethanol to give **17** as a yellow powder. Yield: 62%. M.p.: 180˚C - 182˚C; IR (KBr, cm^{-1}): 3436 (OH), 3247, 3184 (NH); 1773 (CO), 1607 (C=N); 1HNMR ((DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 2.29 (s, 3H, SCH_3), 7.09 - 7.47 (m, 20H, Ar-H and 2NH); 13.29 (s, 1H, OH); MS *m/z* (%): 623 (M^+, 7.89), 579 (13.92), 575 (21.87), 516 (10.93), 480 (19.28), 470 (14.12), 390 (12.33), 293 (15.52), 261 (13.12), 214 (24.25), 77 (100); Anal. Calcd. for $C_{34}H_{27}ClN_4O_2S_2$ (623.18): C, 65.53; H, 4.37; Cl, 5.69; N, 8.99; S, 10.29. Found: C, 65.23; H, 4.17; Cl, 5.49; N, 8.79; S, 10.09.

2.1.13. 3-Anilino-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolyl-3-thioxopropan 19

To a stirred solution of powdered potassium hydroxide (0.02 mol) in DMF (20 ml), compound **2** (0.02 mol) was added. After stirring for 30 min, phenyl isothiocyanate (0.02 mol) was added to the resulting mixture, stirring was continued for 6 h, and then poured over crushed ice containing hydrochloric acid. The solid product that formed was filtered off, washed with water, dried and recrystallized from ethanol to give **19** as yellow crystals. Yield: 64%. M.p.: 186˚C - 188˚C; IR (KBr, cm^{-1}): 3246, 3191 (NH), 3084, 2925 (CH), 1656 (C=O), 1606 (C=N), 1238 (C=S); 1H-NMR(DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 10.40 (s, 1H, NH), 10.20 (s, 1H, NH), 7.05 - 7.59 (m, 23H, Ar-H), 4.12 (s, 1H, CH); MS *m/z* (%): 645 (M^+, 23), 629 (22.03), 612 (23), 554 (18.32), 521 (20.91), 512 (23), 526 (18.12), 316 (22.65), 300 (187.12), 224 (29.21), 192 (20.21), 80 (100); Anal. Calcd. for $C_{37}H_{29}ClN_4OS_2$ (645.23): C, 68.87; H, 4.53; Cl, 5.49; N, 8.68; S, 9.94. Found: C, 68.67; H, 4.23; Cl, 5.29 N, 8.48; S, 9.64.

2.1.14. 3-Anilino-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-3-(methylthio)-*N*-*p*-tolylacrylamide 20

To a stirred solution of potassium hydroxide (0.01 mol) in DMF (20 ml) was added compound **2** (0.01mol). After the mixture was stirred for 30 min, phenyl isothiocyanate (0.01 mol) was added to the resulting mixture. Stirring was continued for 6 h, and then methyl iodide (0.01 mol) was added and stirring was continued for 6 h. The reaction mixture was poured onto ice-cold water. The solid product that formed was collected by filtration, dried and recrystallized from ethanol to give compound **20** as yellow crystals. Yield: 62%. M.p.: 234˚C - 236˚C; IR (KBr, cm^{-1}): 3246, 3191 (NH), 1656 (C=O), 1604 (C=N), 3086, 2874(CH); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 2.54 (s, 3H, SCH_3), 10.30 (s, 1H, NH), 10.38 (s, 1H, NH), 7.03 - 7.70 (m, 23H, Ar-H); MS *m/z* (%): 659 (M^+, 44.26), 597 (63.93), 476 (27.87), 433 (56.84), 366 (51.64), 328 (63.93), 296 (42.62), 73 (100); Anal. Calcd. for $C_{38}\ H_{31}ClN_4OS_2$(659.26): C, 69.23; H, 4.74; Cl, 5.38; N, 8.50; S, 9.73. Found: C, 69.03; H, 4.54; Cl, 5.08; N, 8.30; S, 9.53.

2.1.15. 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-2-(3,4-diphenyl-thiazol-2(3*H*)-ylidene)-*N*-*p*-tolylacetamide 21 and 2-[1-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-2-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-*N*-*p*-tolylacetamide 22

To a cold suspension of powdered potassium hydroxide (0.01 mol) in DMF (20 ml) was added compound **2**

(0.01 mol) and phenyl isothiocyanate (0.01 mol). The reaction mixture was stirred at room temperature for 6 h, and then treated with phenacyl bromide and/or ethyl chloroacetate (0.01 mol) and the stirring was continued at room temperature for further 10 h. The reaction mixture was poured into 50 ml of cold water. The result solid products were collected by filtration and recrystallized from a mixture of ethanol/DMF (1:1) to give compounds **21** and **22.**

21: Yellow powder. Yield: 65%. M.p.: 240˚C - 242˚C; IR (KBr, cm^{-1}): 3248 (NH), 1659 (C=O), 3056, 2937, 2871 (CH), 1604 (C=N); 1H-NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 10.40 (s, 1H, NH), 7.05 - 7.59 (m, 29 H, Ar-H and H-5 thiazoline); MS *m/z* (%):745 (M^+, 43.29), 695 (40.24), 577 (41.40), 450 (39.63), 421 (36.59), 313 (43.29), 217 (50.00), 172 (46.34), 111 (100). Anal. Calcd. for $C_{45}H_{33}Cl\ N_4OS_2$ (745.35): C, 72.51; H, 4.46; Cl, 4.76; N, 7.52; S, 8.60. Found: C, 72.31; H, 4.26; Cl, 4.46; N, 7.32; S, 8.50.

22: Pale grey crystals. Yield: 62%. M.p.: 228˚C - 230˚C; IR (KBr, cm^{-1}): 3245 (NH), 3084, 2929, 2873 (CH), 1726, 1657 (C=O); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 10.41 (s, 1H, NH), 7.06 - 7.60 (m, 23H, Ar-H), 4.13 (s, 2H, CH_2); MS *m/z* (%): 670 (M^+-CH_3, 12.66), 654 (10.97), 594 (19.83), 503 (14.77), 475 (12.24), 348 (10.97), 139 (14.98), 125 (18.35), 55 (100). Anal. Calcd. for $C_{39}H_{29}ClN_4O_2S_2$ (685.25): C, 68.36; H, 4.27; Cl, 5.17; N, 8.18; S, 9.36. Found: C, 68.06; H, 4.07; Cl, 5.00; N, 8.00; S, 9.16.

2.1.16. 2-[5-Benzylidene-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene]-2-[1-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-2-ylthio]-*N*-*p*-tolylacetamide 23

To a well-stirred solution of compound **22** (0.01 mol) in DMF (20 ml), piperidine (0.2 ml) and benzaldehyde (0.01 mol) were added. The reaction mixture was stirred at 80˚C for 3 h. The separated crystals was filtered, dried and recrystallized from ethanol to give **23** as white crystals. Yield: 60%. M.p.: 252˚C - 254˚C; IR (KBr, cm^{-1}): 3249 (NH), 3090, 2997 (CH), 1657, 1734 (C=O); 1H-NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, CH_3), 10.53 (s, 1H, NH), 7.03 - 7.70 (m, 29H, Ar-H and =CH); MS *m/z* (%):773 (M^+, 6.72), 723 (77.3), 707 (57.14), 570 (50.42), 479 (54), 388 (100), 372 (58.82) Anal. Calcd. for $C_{46}H_{33}ClN_4O_2S_2$ (773.36): C, 71.44; H, 4.30; Cl, 4.58; N, 7.24; S, 8.29. Found: C, 71.24; H, 4.00; Cl, 4.28; N, 7.04; S, 8.09.

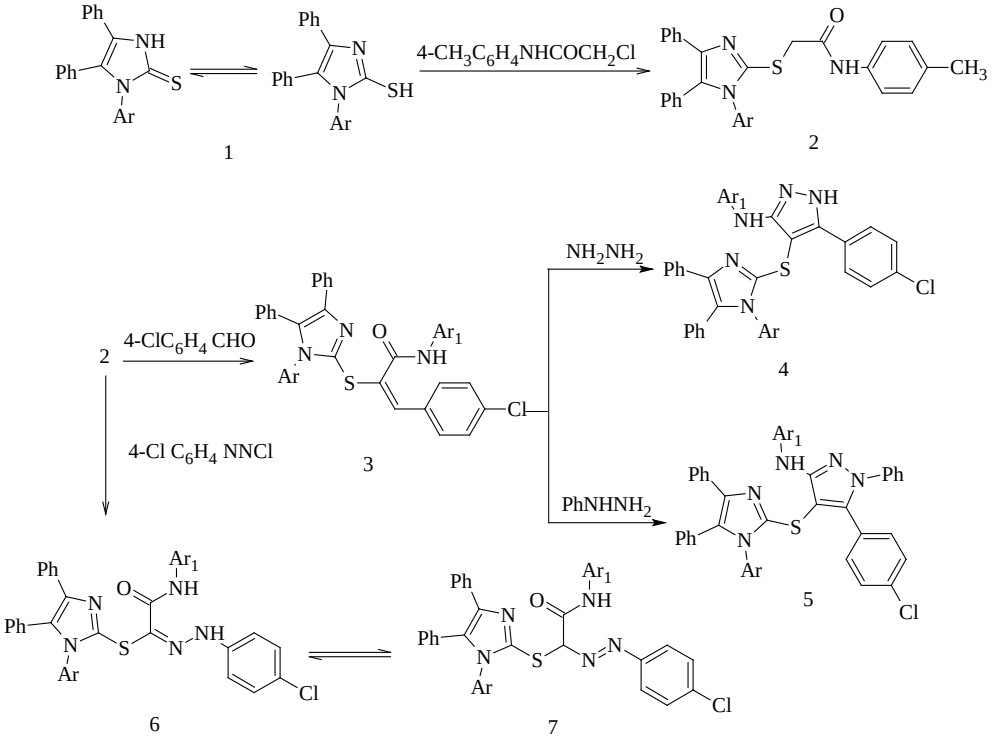
2.2. Antimicrobial Assays

Synthesized compounds **2, 3, 6, 13, 15a, 15b, 17, 20, 21, 22** and **23** 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* (RCMB 010043) and *Escherichia coli* (RCMB 010052) and against four species of fungi, namely *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotrichum candidum* (RCMB 05097) and *Candida albicans* (RCMB 05036). The antibacterial and antifungal activities were determined by means of inhibition % ± standard deviation at a concentration of 100 µg/ ml of tested samples [5]-[7]. Optical densities of antimicrobial were measured after 24 hours at 37˚C to bacteria and measured after 48 hours at 28˚C 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.

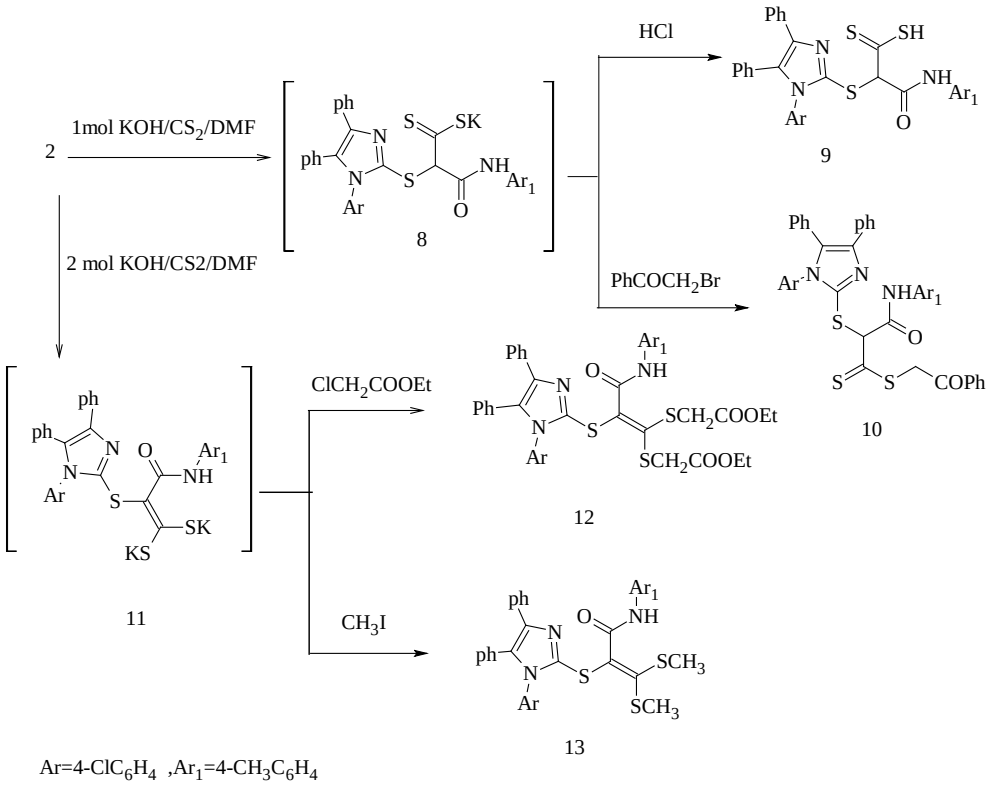
3. Results and Discussion

3.1. Chemistry

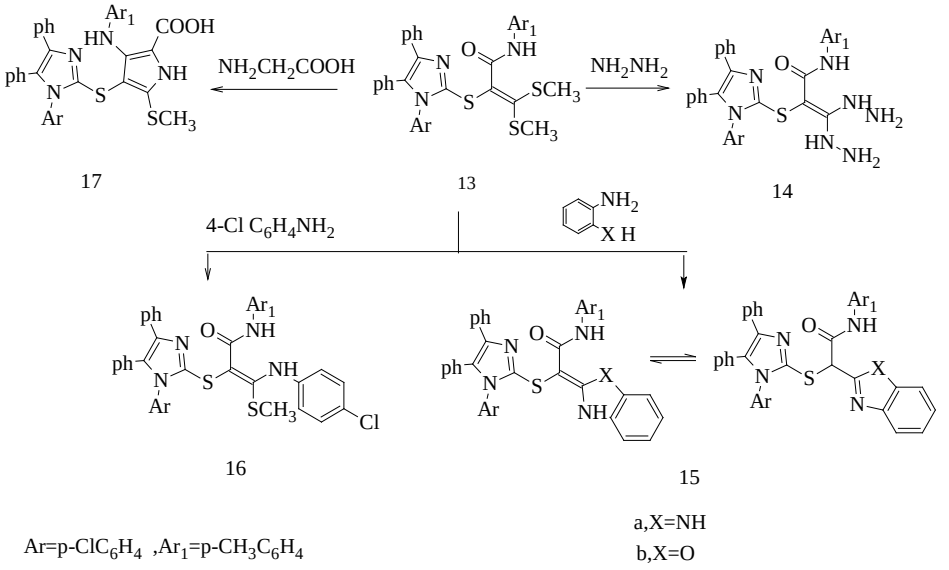
The synthetic procedures adopted to obtain the target compounds are depicted in **Schemes 1-4**. *S*-Alkylation of 1-(4-chlorophenyl)-4,5-diphenyl-*1H*-imiazole-2-thione **1** with 2-chloro-*N*-*p*-tolylacetamide afforded the corresponding 2-(1*H*-imidazol-2-ylthio)-*N*-*p*-tolylacetamide derivative **2**. The assignment of structure **2** was based on both elemental analysis and spectral data. 1H-NMR spectrum of **2** in (DMSO-d6) revealed signals at 2.24 ppm corresponding to CH_3 group and a single at 4.11 ppm for CH_2 group. Moreover, mass spectrum showed a molecular ion peak at *m/z* 510 corresponding to a molecular formula $C_{30}H_{24}ClN_3OS$. Further evidence for the structure of compound **2** was obtained through studying their chemical reactivity via some chemical reactions. Thus, interaction of compound **2** with *p*-chlorobenzaldehyde yielded the arylidene derivative **3** (**Scheme 1**). 1H-NMR spectrum in (DMSO-d6) of **3** show the disappearance of CH_2 protons observed with the respective starting precursors **2** at δ 4.11 ppm, and the appearance multiple signals in the region at δ 6.41 - 7.27 ppm corresponding to



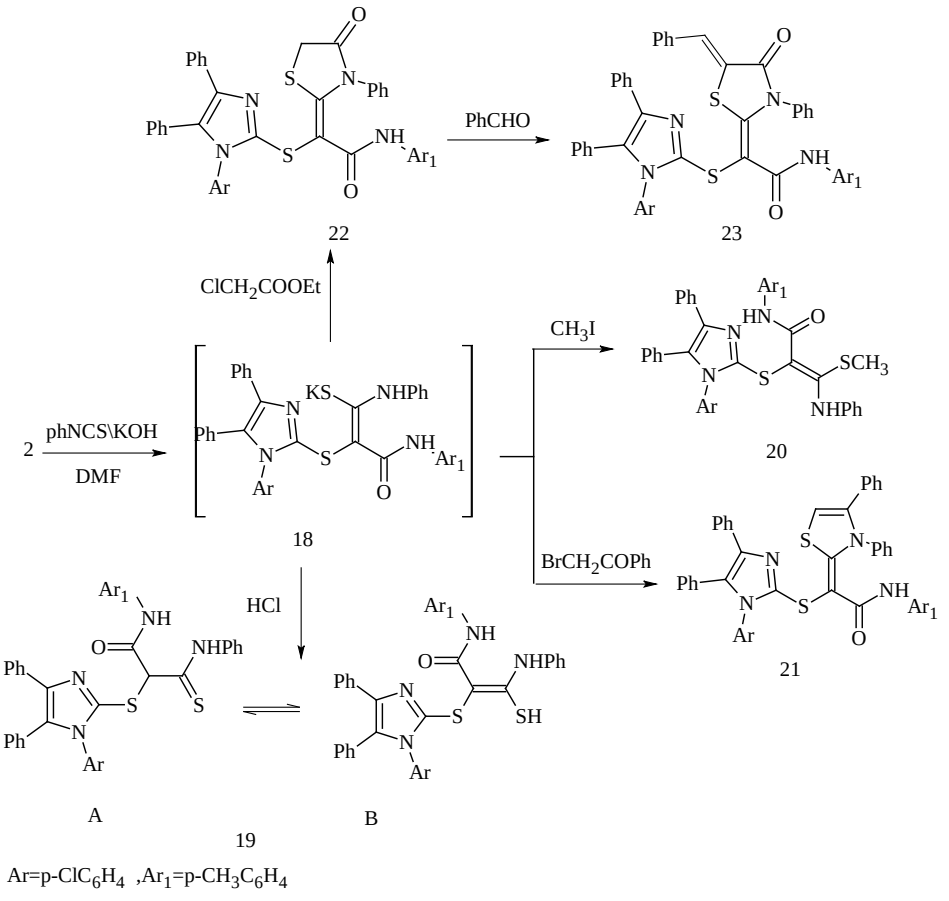
Scheme 1. Formation of compounds 2-6.



Scheme 2. Formation of compounds 8-13.



Scheme 3. Formation of compounds 14-17.



Scheme 4. Formation of compounds 18-22.

the aromatic protons together with 1H benzylidene C=CH proton. Mass spectrum of **3** showed a molecular ion peak at *m/z* 632 corresponding to the molecular formula $C_{37}H_{27}Cl_2N_3OS$ (see experimental section).

Reaction of arylidene derivatives **3** with hydrazine hydrate in ethanol [8] and few drop of acetic acid gave the

corresponding 1*H*-pyrazol-3-amine derivative **4**. While, reaction **3** with phenyl hydrazine in the presence of acetic acid and few drops of hydrochloric acid [9] afforded the corresponding 1-phenyl-1*H*-pyrazol-3-amine **5.** The structure of the pyrazole derivatives **4** and **5** were established on the basis of analytical and spectral data. The IR spectrum of **4** showed the disappearance of absorption band of C=O group and appearance of new absorption band of NH at 3238 cm^{-1}. Mass spectrum of **4** showed a molecular ion peak at *m/z* 644 corresponding to the molecular formula $C_{37}H_{27}Cl_2N_5S$.

Diazotization of *p*-chloroaniline followed by coupling with active methylene group in compound **2** in pyridine yielded the hydrazone form **6** rather than the azo form **7** based on spectral data [10]. The 1H-NMR spectrum of compound **6** recorded in (DMSO-d6) revealed a signal at δ 8.58 ppm, which could be attributed to hydrazone NH group (**Scheme 1**).

Reaction of compound **2** with carbon disulphide and one equivalent potassium hydroxide in dimethylformamide (DMF) gave non-isolated intermediate potassium salt **8**. Treatment of the non-isolable potassium salts **8** with dilute hydrochloric acid [11] afforded the corresponding 2-(1*H*-imidazol-2-ylthio)-2-(*p*-tolylcarbamoyl) ethanedithioic acid **9**. The assignment of structure **9** was based on both elemental analysis and spectral data. The IR spectrum displayed absorptions band at 3231 cm^{-1} (NH) and 1271 cm^{-1} (C=S). The mass spectrum showed the molecular ion peak at *m/z* 586 corresponding to the molecular formula $C_{31}H_{24}ClN_3OS_3$. On the other hand, treatment of intermediate salt **8** with phenacyl bromide [12] to give the corresponding 3-[benzoylmethylthio]-2-[1*H*-imidazol-2-ylthio]-*N*-*p*-tolyl-3-thioxo-propaneamide derivatives **10**. The 1H-NMR spectra of **10** in (DMSO-d6) revealed a single at δ 4.39 ppm and δ 4.57 ppm assigned to the CH_2 and CH protons respectively (**Scheme 2**).

While the reaction **2** with carbon disulphide in the presence of two equivalent potassium hydroxide in DMF to give non-isolated potassium salt **11**, which was allowed to react with halogenated compounds namely ethylchloroacetate [13] and methyl iodide [14] afforded the corresponding 3,3-bis[(ethoxycarbonyl)methylthio]-*N*- *p*-tolylacrylamide **12** and 3,3-bis-(methylthio)-*N*-*p*-tolylacrylamide **13** respectively. We suggest a mechanism for the formation of **12** in which the intermediate **I** is obtained first, then elimination of potassium chloride (**Figure 1**).

The structure of synthesis compound **12** and **13** ware elucidated on the basis of the elemental analysis and spectral data. For example, 1H-NMR spectra in (DMSO-d6) of **12** displayed two multiple at 1.13 - 1.23 and 4.04 - 4.13 for ethoxy protons of two carboethoxy group and two single at 4.33 and 4.37 ppm for two methylene protons. On the other hand, 1H-NMR spectrum (DMSO-d6) of **13** showed single signal at δ 2.28 ppm for 6 protons of two similar methyl protons. The mass spectrum of compound **13** showed a molecular ion peak at *m/z* 614 corresponding to a molecular formula $C_{33}H_{28}ClN_3OS_3$ (**Scheme 2**).

Moreover, condensation of **13** with hydrazine hydrate afforded the corresponding 3, 3-dihydrazino-*N*-*p*-tolylacrylamide derivative **14**. The structure of **14** was identified as the reaction product on the basis of its elemental analysis and spectral data. The 1H-NMR spectrum of **14** showed a multiple signals in the region at δ 7.09 - 7.56 ppm corresponding to the aromatic protons together with the NH proton, two single signals at δ 4.84 ppm and 4.89 corresponding to the two NH_2 protons, and another two single signals at δ 10.33 and δ 10.51 ppm assignable to two NH protons. Mass spectrum of **14** showed a molecular ion peak at *m/z* 582 corresponding to a molecular formula $C_{31}H_{28}ClN_7OS$. In addition, the condensation of **13** with suitable amine namely *o*-phenylenediamine, and *o*-aminophenol [15] in refluxing absolute ethanol to afford the corresponding 2-(1*H*-benzimidazol-2-yl)- and 2-(1,3-benzoxazol-2-yl)-*N*-*p*-tolylacetamide **15a, b** respectively (**Scheme 3**). The structures of compounds **15a, b** were established and confirmed by their elemental analysis and spectral data (see experimental section). The formation of **15 a, b** were assumed to proceed through nucleophilic attack of the two -NH2 group in *o*-phenylenediamine,or NH,OH groups in *o*-aminophenol to the ethylenic double bond in the compound **13** followed by elimination of two moles of methyl mercaptan (**Figure 2**).

S,*S*-acetals **13** was converted to corresponding *S*,*N*-acetals by reacting with appropriate primary. Thus, reaction of **13** with p-chloroaniline afforded ketene *N*,*S*-acetals **16** (**Scheme 3**). The assignment of the structure of **16** was based on spectral data. The IR spectrum of **16** showed absorption bands at 3246, 3191 cm^{-1} for two NH. Its 1H-NMR spectrum (DMSO-d6) of **16** showed single signal at δ 2.39 ppm for SCH_3 protons, δ 7.09 - 7.62 ppm corresponding to the aromatic protons together with the NH proton and single signals at δ 10.29 ppm assignable to NH. The mass spectrum of **16** showed a molecular ion peak at *m/z* 693 corresponding to the molecular formula $C_{38}H_{30}Cl_2N_4OS_2$.

Furthermore, the reaction of **13** with Glycine in ethanol containing triethylamine [16] afforded the corresponding 1*H*-pyrrole-2-carboxylic acid derivatives **17** (**Scheme 3**). The assignment of the structure of **17** was

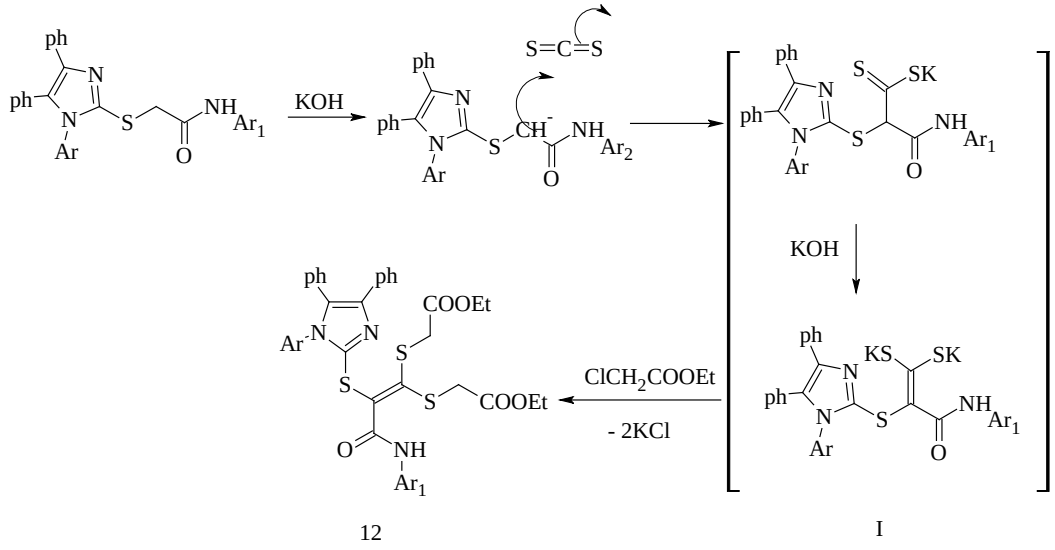


Figure 1. Proposed mechanism formation of 3,3-bis[(ethoxycarbonyl)methylthio]-*N*-*p*-tolylacrylamide derivatives 12.

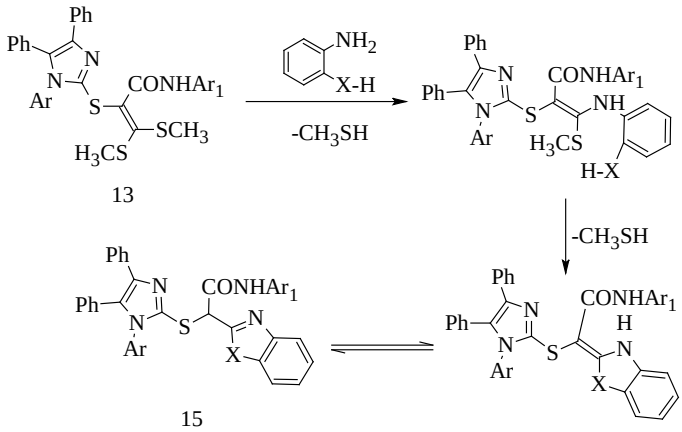


Figure 2. The proposed mechanism formation 15a, b.

based on spectral data. The IR spectrum of **17** showed absorption bands at 3436 cm^{-1} (OH) and 3247, 3184 cm^{-1} (NH). Its 1H-NMR spectrum (DMSO-d6) single signal at δ 2.29 ppm for SCH_3 protons, δ 7.09 - 7.47 ppm corresponding to the aromatic protons together with the 2NH protons. The mass spectrum of **17** showed a molecular ion peak at *m/z* 623 corresponding to the molecular formula $C_{34}H_{27}ClN_4O_2S_2$.

2-(1*H*-imidazol-2-ylthio)-*N*-*p*-tolylacetamide **2** was utilized as a key intermediate for the synthesis of thiocarbamoyl derivative **19** via its reaction with phenyl isothiocyanate. Thus, reaction **2** with phenyl isothiocyanate in DMF in the presence of an equimolar amount of potassium hydroxide yielded the non-isolable intermediate potassium sulphide salt **18.** Acidification of the potassium salt **18** with dilute hydrochloric acid afforded the corresponding thiocarbamoyl derivative **19**, which can exist in two tautomeric thione-thiol forms A and B (**Scheme 4**). Assignment of the product **19** was based on elemental analysis and spectral data. 1H-NMR spectrum displayed multiple signals at δ 7.05 - 7.59 ppm for aromatic protons and two single signals at δ 10.40 and 10.20 ppm assignable to two NH protons. Mass spectrum showed a molecular ion peak at *m/z* 645 corresponding to a molecular formula $C_{37}H_{29}ClN_4OS_2$.

Treatment of the non-isolable potassium sulfide salt **18** with methyl iodide [17] afforded the ketene N, S-acetal **20**. The structure of **20** was established on the basis of its elemental analysis and spectral data. Its IR spectrum showed absorption bands at 3246, 3191 cm^{-1} due to two NH groups. On addition 1H NMR spectrum (DMSO-d6) displayed single signal at δ 2.54 ppm for SCH_3. The mass spectrum showed a molecular ion peak at

m/z 659 corresponding to a molecular formula $C_{38}H_{31}ClN_4OS_2$ (**Scheme 4**).

On the other hand, reaction of **18** with phenacyl bromide and ethyl chloroacetate [18] afforded 2-(3, 4-diphenyl-1,3-thiazol-2(3*H*)-ylidene)- and 2-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-*N*-*p*-tolylacetamide **21** and **22** respectively. The structures of compounds **21** and **22** were established and confirmed by their elemental analysis and spectral data. The 1H-NMR spectrum of **21** showed a multiple signals in the region at δ 7.05 - 7.59 ppm corresponding to the aromatic protons together with the H-**5** protons of the thiazole ring and a single signal at δ 10.40 ppm for NH proton. Mass spectrum of **21** revealed a molecular ion peak at *m/z* 745 corresponding to a molecular formula $C_{45}H_{33}ClN_4OS_2$. The IR spectrum of **22** showed absorption bands at 1726 cm^{-1} due to CO of thiazolidinone ring. The 1H-NMR spectrum of **22** showed a single signal equivalent to two protons at δ 4.13 ppm which represent the CH_2 protons of the thiazolidinone ring. The Claisene Schmidt condensation of thiazolidin-5-one **22** with benzaldehyde [19] in DMF and in the presence of a catalytic amount of piperidine afforded arylidene derivatives **23** (**Scheme 4**). The structures of latter products were confirmed based on elemental analysis and spectral data (see experimental section).

3.2. Antimicrobial Activity

Synthesized compounds **2**, **3, 6, 13, 15a, 15b, 17, 20, 21, 22 and 23** were evaluated for antibacterial and antifungal activities.

3.2.1. Antibacterial Activity

Synthesized compounds **2**, **3, 6, 13, 15a, 15b, 17, 20, 21, 22 and 23** were screened for their antibacterial activities *in vitro* against Gram-positive namely *Staphylococcus aureus* (RCMB 0100010) and *Bacillus subtilis* (RCMB 010067) and Gram- negative *Pseudomonas aeuroginosa* (RCMB 010043) 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 bacteria rather than the Gram-negative bacteria. Compounds **3, 13** and **15a** exhibited excellent antibacterial activity against the tested organisms while compounds **15b**, **17, 20, 21** and **23** showed moderate antibacterial activity against the tested organisms and compound **2, 6** and **22** showed weak antibacterial activity against the tested organisms. In addition, all test compounds were found to be inactive against *Pseudomonas aeuroginosa* (RCMB 010043).

3.2.2. Antifungal Activity

The newly synthesized compounds **2, 3, 6, 13, 15a, 15b, 17, 20, 21, 22 and 23** were screened for their antifungal activities *in vitro* against, *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotrichum candidum* (RCMB 05097) and *Candida albicans* (RCMB 05036). Amphotericin B was used as standards to evaluate the potency of the tested compounds. The inhibitory effects of the synthetic compounds against these organisms are given in **Table 2**, **Figure 4**.

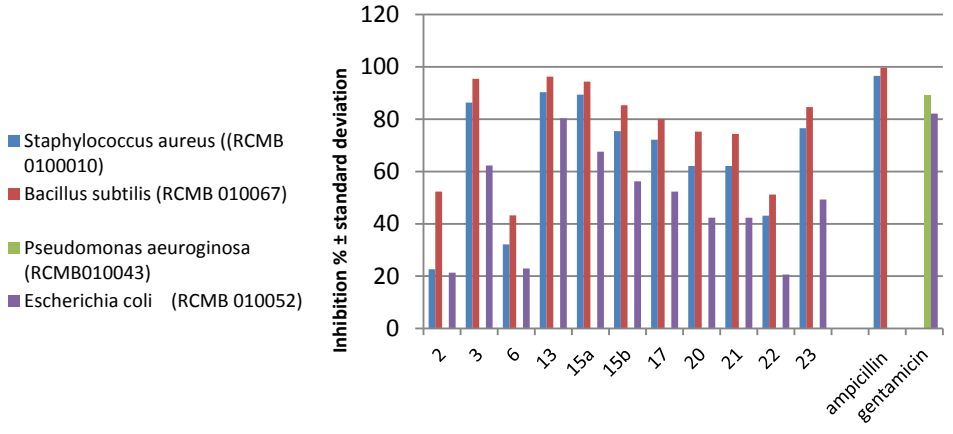


Figure 3. Graphical representation of the antibacterial activity of tested compounds compared to ampicillin and gentamicin.

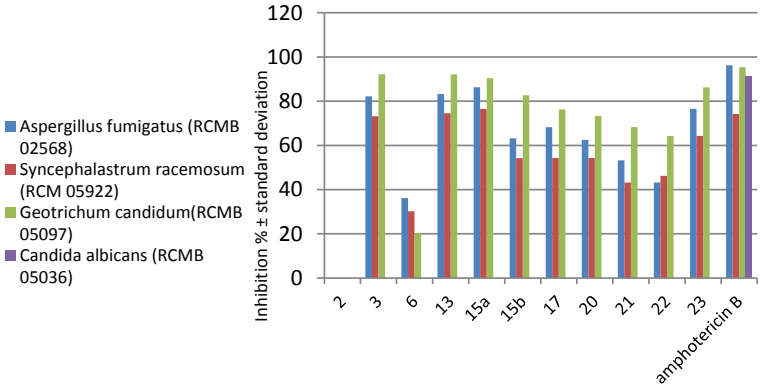


Figure 4. Graphical representation of the antifungal activity of tested compounds compared to amphotericin B.

Table 1. Antibacterial evaluation of the some synthesized compounds.

Comp. No.	Inhibition % ± standard deviation			
	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus ((RCMB 0100010)	*Bacillus subtilis* (RCMB 010067)	*Pseudomonas aeuroginosa* (RCMB 010043)	*Escherichia coli* (RCMB 010052)
2	22.63 ± 0.25	52.31 ± 0.37	NA	21.36 ± 0.44
3	86.32 ± 0.44	95.41 ± 0.25	NA	62.31 ± 0.25
6	32.12 ± 0.63	43.25 ± 0.42	NA	22.96 ± 0.16
13	90.31 ± 0.43	96.25 ± 0.53	NA	80.36 ± 0.33
15a	89.35 ± 0.15	94.32 ± 0.42	NA	67.58 ± 0.53
15b	75.44 ± 0.44	85.34 ± 0.58	NA	56.23 ± 0.19
17	72.13 ± 0.44	80.12 ± 0.63	NA	52.34 ± 0.25
20	62.14 ± 0.44	75.24 ± 0.63	NA	42.36 ± 0.25
21	62.14 ± 043	74.32 ± 0.53	NA	42.32 ± 0.25
22	43.12 ± 0.44	51.21 ± 0.25	NA	20.63 ± 0.33
23	76.52 ± 0.2	84.63 ± 0.3	NA	49.32 ± 0.3
Reference drugs				
Ampicillin	96.52 ± 0.2	99.65 ± 0.3		
Gentamicin			89.23 ± 0.1	82.14 ± 0.3

Table 2. Antifungal evaluation of the some synthesized compounds.

Comp. No.	Inhibition % ± standard deviation			
	Aspergillus fumigatus (RCMB 02568)	*Syncephalastrum racemosum* (RCMB 05922)	*Geotrichum candidum* (RCMB 05097)	*Candida albicans* (RCMB 05036)
2	NA	NA	NA	NA
3	82.21 ± 0.53	73.21 ± 0.44	92.14 ± 0.58	NA
6	36.21 ± 0.44	30.21 ± 0.37	20.36 ± 0.25	NA
13	83.25 ± 0.25	74.52 ± 0.25	92.13 ± 0.38	NA
15a	86.32 ± 0.33	76.52 ± 0.25	90.43 ± 0.34	NA
15b	63.22 ± 0.34	54.25 ± 0.25	82.68 ± 0.58	NA
17	68.23 ± 0.39	54.32 ± 0.58	76.24 ± 0.58	NA
20	62.52 ± 0.39	54.32 ± 0.16	73.25 ± 0.58	NA
21	53.21 ± 0.58	43.20 ± 25	68.30 ± 0.35	NA
22	43.25 ± 0.25	46.24 ± 0.58	64.25 ± 0.17	NA
23	76.52 ± 0.25	64.31 ± 0.44	86.23 ± 0.63	NA
Amphotericin B	96.25 ± 0.1	74.25 ± 0.2	95.36 ± 0.2	91.29 ± 0.1

Compounds **13, 15a** exhibited excellent antifunger activity, which is better than the amphotericin B against *Syncephalastrum racemosum* (RCMB 05922), while its strong antifunger activity against *Aspergillus fumigatus* (RCMB 02568) and *Geotrichum candidum* (RCMB 05097) is comparable to amphotericin B. The compounds **3, 15b, 17, 20, 21, 22 and 23** showed strong moderate activity against *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922) and *Geotrichum candidum* (RCMB 05097) compared to amphotericin B against. While the compounds **6** weak antifungal activity against *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotrichum candidum* (RCMB 05097). On the other hand, compound **2** inactive against all organism. Furthermore, all test compounds were found to be inactive against *Candida albicans* (RCMB 05036).

4. Conclusion

In this paper, we report the synthesis of 2-(1*H*-imidazol-2-ylthio)-*N*-*p*-tolylacetamide **2**. The active methylene moiety of compound **2** was allowed to react with CS_2 and/or phenyl isothiocyanate in dimethylformamide in the presence of potassium hydroxide and yielded the non-isolable intermediate potassium sulphide salt **8, 11** and **18**, which is used as intermediate to synthesis series of novel substituted imidazole derivatives in good yield. Synthesized compounds **2, 3, 6, 13, 15a, 15b, 17, 20, 21, 22 and 23** were evaluated for antibacterial and antifungal activities. Most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria. Compound **13** exhibited excellent antibacterial activity against *Staphylococcus aureus* (RCMB 0100010), *Bacillus subtilis* (RCMB 010067) *and Escherichia coli* (RCMB 010052). Compounds **13, 15a** exhibited excellent antifunger activity, which is better than the amphotericin B against *Syncephalastrum racemosum* (RCMB 05922).

References

[1] Dieter, R.K. (1986) *α*-Oxo Ketene Dithioacetals and Related Compounds: Versatile Three-Carbon Synthons**.** *Tetrahedron*, **42**, 3029-3096. http://dx.doi.org/10.1016/S0040-4020(01)87376-2

[2] Junjappa, H., Ila, H. and Asokan, C.V. (1990) *α*-Oxoketene-S,S-, N,S- and N,N-acetals: Versatile Intermediates in Organic Synthesis. *Tetrahedron*, **46**, 5423-5506. http://dx.doi.org/10.1016/S0040-4020(01)87748-6

[3] Khali, M.A., Sayed, S.M. and Raslan, M.A. (2012) Reactivity of 2-Cyano-*N*-(4-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1*H*-pyrazol-5-yl)acetamide: A Facile Synthesis of Pyrazole, Thiazole, 1,3,4-Thiadiazole and Polysubstituted Thiophene Derivatives. *American Journal of Organic Chemistry*, **2**, 161-170. http://dx.doi.org/10.5923/j.ajoc.20120206.06

[4] Abdelhamid, A.O and Afifi, M.A. (2010) Synthesis of Some New Thiazoles and Pyrazolo[1,5-*a*]pyrimidines Containing an Antipyrine Moiety. *Synthetic Communications*, **40**, 1539-1550. http://dx.doi.org/10.1080/00397910903100726

[5] Kaya, E.G., Ozbilge, H. and Albayrak, S. (2009) Determination of Effect of Gentamicin against *Staphylococcus aureus* by Using Microbroth Kinetic System. *Ankem Derg*, **23**, 110-114.

[6] Sofy, A.R., Hmed, A.A., Sharaf, A.M. and El-Dougdoug, K.A. (2014) Structural Changes of Pathogenic Multiple Drug Resistance Bacteria Treated with *T. vulgaris* Aqueous Extract. *Nature and Science*, **12**, 83-88.

[7] Caldeira, E.M., Osório, A., Oberosler, E.L., Vaitsman, D.S., Alviano, D.S. and Nojima, M.D.G. (2013) Antimicrobial and Fluoride Release Capacity of Orthodontic Bonding Materials. *Journal of Applied Oral Science*, **21**, 327-334. http://dx.doi.org/10.1590/1678-775720130010

[8] Shabaan, M., Taher, A. and Osman, E.O. (2011) Synthesis of Novel 3,4-Dihydroquinoxalin-2(1*H*)-one Derivatives. *European Journal of Chemistry*, **3**, 365-371.

[9] Voskiene, A., Mickevicius, V. and Mikulskiene, G. (2007) Synthesis and Structural Characerization of Products Condensation 4-Carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinones with Hydrazines. *ARKIVOC*: *Archive for Organic Chemistry*, **2007**, 303-314.http://dx.doi.org/10.3998/ark.5550190.0008.f29

[10] Mohare, R.M., Fleit, D.H. and Sakka, O.K. (2011) Novel Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor Activity. *Molecules*, **16**, 16-27. http://dx.doi.org/10.3390/molecules16010016

[11] El-Bayouki, K.A., Basyounia, W.M., Mohamed, Y.A., Aly, M.M. and Abbas, S.Y. (2011) Novel 4(3*H*)-Quinazolinones Containing Biologically Active Thiazole, Pyridinone and Chromene of Expected Antitumor and Antifungal Activities. *European Journal of Chemistry*, **2**, 455-462. http://dx.doi.org/10.5155/eurjchem.2.4.455-462.171

[12] Elgemeie, G.H., Elghandour, A.H., Ali, H.A. and Hussein, A.M. (2002) Novel 2-Thioxohydantoin Ketene Dithioacetals:

Versatile Intermediates for Synthesis of Methylsulfanylimidazo[4,5-*c*]pyrazole and Methylsulfanylpyrrolo[1, 2-*c*]imidazoles. *Synthetic Communications*, **32**, 2245-2253. http://dx.doi.org/10.1081/SCC-120005435

[13] Wang, Y., Dong, D., Yang, Y., Huang, J., Ouyang, Y. and Liu, Q. (2007) A Facile and Convenient One-Pot Synthesis of Polysubstituted Thiophenes from 1, 3-Dicarbonyl Compounds in Water. *Tetrahedron*, **63**, 2724-2728. http://dx.doi.org/10.1016/j.tet.2006.12.090

[14] Khalil, A.M., Berghot, M.A. and Goudal, M.A. (2009) Synthesis and Antibacterial Activity of Some New Heterocycles Incorporating Phthalazine. *European Journal of Medicinal Chemistry*, **44**, 4448-4454. http://dx.doi.org/10.1016/j.ejmech.2009.06.003

[15] Elgemeie, G.H., Elghandour, A.H. and Abd Elaziz, G.W. (2003) Novel Synthesis of Heterocyclic Ketene N,N-, N,O-, and N,S-Acetals Using Cyanoketene Dithioacetals. *Synthetic Communications*, **33**, 1659-1664. http://dx.doi.org/10.1081/SCC-120018927

[16] Sommena, G.L., Comelb, A. and Kirsch, G. (2005) An Easy Access to Variously Substituted Pyrroles Starting from Ketene Dithioacetals. *Synthetic Communications*, **35**, 693-699. http://dx.doi.org/10.1081/SCC-200050365

[17] Bondock, S., Rabie, R., Etman, H.A. and Fadda, A. (2008) Synthesis and Antimicrobial Activity of Some New Heterocycles Incorporating Antipyrine Moiety. *European Journal of Medicinal Chemistry*, **43**, 2122-2129. http://dx.doi.org/10.1016/j.ejmech.2007.12.009

[18] Bondock, S., Fadaly, W. and Metwally, M.A. (2010) Synthesis and Antimicrobial Activity of Some New Thiazole, Thiophene and Pyrazole Derivatives Containing Benzothiazole Moiety. *European Journal of Medicinal Chemistry*, **45**, 3692-3701. http://dx.doi.org/10.1016/j.ejmech.2010.05.018

[19] Rao, R.M., Reddy, G.N. and Sreeramulu, J. (2011) Synthesis of Some New Pyrazolo-Pyrazole Derivatives Containing Indoles with Antimicrobial Activity. *Der Pharma Chemica*, **3**, 301-309.