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A Facile Synthesis of New Substituted Thiazol-2-amine Derivatives as Potent Antimicrobial Agent

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Abstract: A facile synthesis of a new thiazol-2-amine derivative as antimicrobial agent and condensation with substituted thiourea compounds to afford the corresponding substituted thiazole derivatives in excellent yields. All the reactions were completed within less reaction time at reflux temperature. According to the result obtained, the compounds 3b, 3d, 3e, 3f, 3g, 3i, 3l, and 3m were found the leader antimicrobial activity with the highest MIC values. The synthesized compound can be considered to develop new antimicrobial drug candidates. Amongst these, many compounds show better antibacterial and antifungal activity. The compounds 3b, 3d, 3e, 3l, and 3m exhibited significant antibacterial activity against *B. subtilis*, *S. aureus*, and *E. coli*. The compounds 3f, 3g, 3i show significant antifungal against fungal strains i.e., *C. albicans*, *A. flavus* and *A. niger*.

Keywords: thiazol-2-amine; antibacterial; antifungal activity.

1. Introduction

In the present global situation, antimicrobial infections created a lot of concern in everyone's mind. The emerging problem of different strains of COVID and their treatment of the drug resistance of different strains created tremendous pressure on humanity. There is an urgent need to develop some promising antimicrobial molecules. Nowadays, the treatment of bacterial infections remains important and has become a challenging problem. To an increasing number of multi-drug resistant microbial pathogens, there is a need to discover new and biologically active molecules. The emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need necessary for new classes of antibacterial agents [1]. The heterocyclic compounds system has found broad applications in drug development to treat hypertension, schizophrenia, HIV, and bacterial [2]. Thiazole and its derivatives are considered thiourea/thiosemicarbazones' cyclic analogs and have been known for good pharmacological profile [3-5]—the research on thiazole nuclei is well known for its medicinal activity. Thiazole scaffold plays a vital role in nature [6]. The thiazole scaffold and its derivatives have been attracted continuing interest over the year because of their various biological activities [6,7]. Recently, researchers have found application in the drug development for the treatment of allergies [8], hypertension [9], inflammation [10], schizophrenia [11], bacterial [12], HIV infections [13,14], hypnotics [15], anti-proliferative

[16], anticancer and antimicrobial [17,18]. Thiazole and its derivatives, thiosemicarbazones, and their bioisosteres (Figure 1), process a remarkable pharmacological profile, whose properties have been extensively studied in medicinal chemistry [19,20].

By considering the above concerns regarding antimicrobial strains and present drugs and the diversified activity of thiazole nuclei, and in continuation of our previous work on different heterocyclic cores to develop as pharmaceutically active targets. In view of these above facts, and as part of our ongoing studies, the above consideration in the continuation of our previous work on heterocyclic compounds like triazoles, thiazoles, and thiazolidonone of pharmaceutical interested as well as antimicrobial agents [21-30]. We report here on the synthesis of some new 2-(benzyl(substituted phenyl)amino)-5-(substituted benzylidene)thiazol-4(5H)-one as antimicrobial agents.

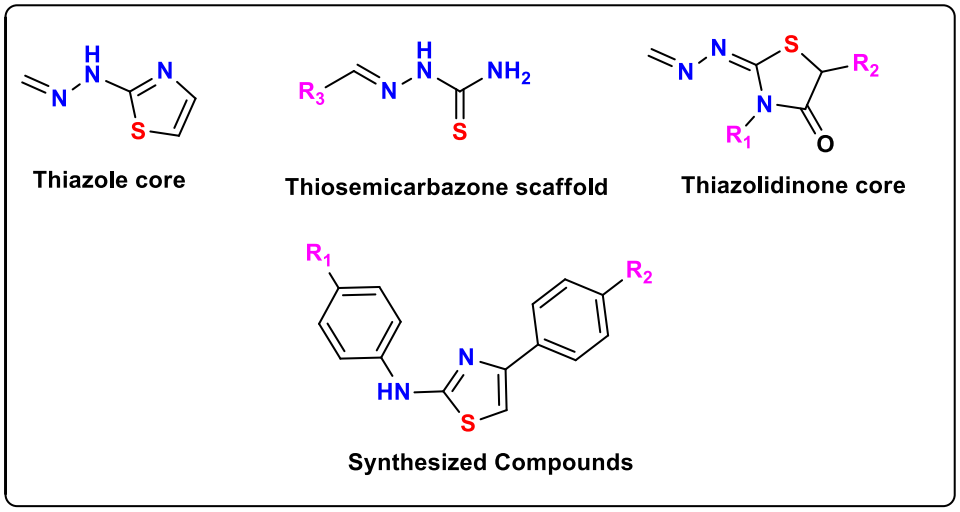


Figure 1. Structures of thiosemicarbazones, thiazole, and synthesized compounds.

2. Materials and Methods

All commercial reagents and chemicals were used without further purification, such as substituted thiourea, substituted α–halo ketone, and used solvent. Melting points were recorded on SRS Optimelt melting point apparatus and are uncorrected. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded on an FT-IR (Bruker). ^{1}H NMR spectra were recorded on a 500 MHz Bruker spectrometer. Chemical shifts are reported as δ ppm units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br), and ^{13}C NMR spectra were recorded on a 125 MHz Bruker spectrometer. Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer. Products were characterized by comparing ^{1}H and ^{13}C NMR spectroscopic data with those available in the literature.

2.1. General procedure of N-(substituted phenyl)-4-(substituted phenyl)thiazol-2-amine (3a-o).

We had to take reaction mixture in a 50 mL round bottom flask; the compound (1a-h) (1 equit.), compound (2a-d) (1 equit.), and potassium carbonate (1 equit.) were added in DMF (1 mL) at reflux temperature, to the stirred reaction mixture for 3-7 h. The progress of the reaction was monitored by TLC (9:1, 10 % n-hexane: ethyl acetate). When completion of the

reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×10 mL) to afford the crude product. The compounds (3a-o) were recrystallized from ethanol and isolated as yellowish solid.

2.1.1. N-(2-nitrophenyl)-4-(p-tolyl)thiazol-2-amine (3a).

Yellow solid. Yield: 94%, mp 140–142 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{13}N_3O_2S$ + H^+] 312.0762, observed 312.0801, ES-MS m/z (%): 322.35. IR νmax/cm–1: 3208 (NH), 1610 (C=C), 1555 (C=N), 1212 (C-S), 1194 (C–N). 1H NMR (500 MHz, DMSO-d6): δ 8.11 (dd, J = 8.9, 1.3 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.54 – 7.46 (m, 2H), 7.31 (dd, J = 7.3, 1.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.21 (ddd, J = 9.2, 7.8, 1.5 Hz, 1H), 2.40 (s, 2H). 13C NMR (125 MHz, DMSO-d6) δ 161.08 (ArC=N), 151.15 (Ar-C), 138.83 (Ar-C), 137.64 (ArC-N), 135.35 (Ar-C), (Ar-C), (C=C), 134.10 (Ar-C), 131.58 (Ar-C), 129.06 (Ar-C), 126.69 (Ar-C), (C=C), 125.79 (Ar-C), (C=C), 120.78 (Ar-C), (C=C), 116.47 (Ar-C), 109.92 (Ar-C), 21.24 (C-CH3)

2.1.2. N-(4-fluorophenyl)-4-(p-tolyl)thiazol-2-amine (3b).

Yellow solid. Yield: 96%, mp 180–182 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{13}FN_2S$ + H+] 285.0817, observed 285.0856 , ES-MS m/z (%): 322.35, IR νmax /cm–1: 3216 (NH), 2822 (CH–Ar), 1583 (C=C), 1454 (C=N), 1016 (C-S), 736 (C–F). 1H NMR (500 MHz, DMSO-d6): δ 9.55 (s, 1H), 7.82 – 7.76 (m, 2H), 7.55 – 7.46 (m, 3H), 7.27 (dq, J = 7.5, 0.9 Hz, 2H), 7.17 – 7.10 (m, 2H). 13C NMR (125 MHz, DMSO-d6) δ = 161.29 (ArC=N), 158.45 (ArC-F)(J = 34 Hz, 2H), 156.43 (Ar-C), 151.18 (ArC-N), 138.83 (Ar-C), 137.78 (Ar-C), 137.76 (Ar-C), 131.58 (Ar-C), (C=C), 129.06 (Ar-C), (C=C), 125.79 (Ar-C), (C=C), 121.04 (Ar-C), (C=C), 120.98 (Ar-C), 116.16 (Ar-C), 116.00 (Ar-C), 109.88 (Ar-C), 21.24 (C-CH3).

2.1.3. N,4-bis(4-nitrophenyl)thiazol-2-amine (3c).

Yellow solid. Yield: 94%, mp 213–215 ºC; (+)ESI-HRMS m/z: calculated for [$C_{15}H_{10}N_4O_4S$ + H+] 343.0456, observed 343.0496, ES-MS m/z (%): 322.35, IR νmax /cm–1: 3217 (NH), 2924 (CH–Ar), 1585 (C=C), 1456 (C=N), 1212 (C-S), 1019 (C–N). 1H NMR (500 MHz, DMSO-*d6*): δ 9.58 (s, 1H), 8.24 – 8.18 (m, 2H), 8.18 – 8.12 (m, 2H), 8.12 – 8.06 (m, 2H), 7.58 – 7.52 (m, 3H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.38 (ArC=N), 151.41 (Ar-C), 147.46 (ArC-N), 144.82 (Ar-C), 142.02 (Ar-C), 137.65 (ArC-N), 126.35 (Ar-C), 125.69 (Ar-C), 124.96 (Ar-C), 118.15 (Ar-C), 109.81 (Ar-C).

2.1.4. N-(2,4-difluorophenyl)-4-(4-nitrophenyl)thiazol-2-amine (3d).

Yellow solid. Yield: 94%, mp 245–247 ºC; (+)ESI-HRMS m/z: calculated for [$C_{15}H_9F_2N_3O_2S$ + H^+] 334.0417, observed 334.0456, IR νmax/cm^{-1}: 3217 (NH), 3020 (CH–Ar), 1559 (C=C), 1464 (C=N), 1150 (C-S), 725 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.62 (s, 1H), 8.24 – 8.18 (m, 2H), 8.13 – 8.06 (m, 2H), 7.55 (s, 1H), 7.43 (dt, J = 7.4, 5.0 Hz, 1H), 7.02 (dtd, J = 15.5, 7.9, 2.7 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 162.90 (ArC=N), 162.80 (Ar-C), 157.62 (ArC-F), 157.56 (Ar-C), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (Ar-C), 154.70 (ArC-F) (J = 26 Hz, 2H), 152.75 (Ar-C), 152.69 (Ar-C), 151.19 (Ar-C), 147.46 (Ar-C), 137.65 (Ar-C), 127.14 (Ar-C), 127.11 (Ar-C), 126.98 (Ar-C), 126.95 (Ar-C), 126.35 (Ar-C), 124.96 (Ar-C), 121.92 (Ar-C), 121.86 (Ar-C), 121.79 (Ar-C), 111.82 (Ar-C), 111.80 (Ar-

C), 111.66 (Ar-C), 111.64 (Ar-C), 109.86 (Ar-C), 104.35 (Ar-C), 104.19 (Ar-C), 104.03 (ArC-S).

2.1.5. 4-(4-nitrophenyl)-N-(3-(trifluoromethyl)phenyl)thiazol-2-amine (3e).

Yellow solid. Yield: 94%, mp 230–232 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{10}F_3N_3O_2S$ + H^+] 366.0479, observed 366.0519, IR νmax/cm^{-1}: 3217 (NH), 3026 (CH–Ar), 1569 (C=C), 1474 (C=N),1160 (C-S), 820 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.58 (s, 1H), 8.24 – 8.18 (m, 2H), 8.13 – 8.06 (m, 2H), 7.60 (t, *J* = 2.2 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.56 (s, 1H), 7.43 (dd, *J* = 10.4, 7.4 Hz, 1H), 7.28 (ddd, *J* = 10.4, 2.2, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.11 (ArC=N), 151.41 (Ar-C), 147.46 (Ar-C), 140.55 (Ar-C) (q, *J* = 2.0 Hz), 137.65 (Ar-C), 131.82 (Ar-C), 131.56(Ar-C), 131.30 (Ar-C), 131.05 (Ar-C), 129.33 (Ar-C) (q, *J* = 1.9 Hz) (Ar-C), 127.28 (Ar-C), 126.35, 125.13 (Ar-C), 124.96 (ArC-F), 122.99 (Ar-C), 120.85 (Ar-C), 120.33 (Ar-C), 119.52 (Ar-C), 119.49 (Ar-C), 119.44 (Ar-C) (d, *J* = 3.8 Hz), 117.41 (Ar-C), 117.36 (d, *J* = 3.8 Hz) (Ar-C), 117.32 (Ar-C), 109.81 (Ar-C).

2.1.6. 4-(4-nitrophenyl)-N-phenylthiazol-2-amine (3f).

Yellow solid. Yield: 94%, mp 170–172 ºC; (+) ESI-HRMS m/z: calculated for [$C_{15}H_{11}N_3O_2S$ + H^+] 298.0606, observed 298.0645, IR νmax/cm^{-1}: 3218 (NH), 3015 (CH–Ar), 1579 (C=C), 1473 (C=N), 1155 (C-S), 825 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.55 (s, 1H), 8.24 – 8.18 (m, 2H), 8.13 – 8.06 (m, 2H), 7.61 – 7.54 (m, 3H), 7.31 – 7.24 (m, 2H), 6.96 (tt, J = 7.0, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.13 (ArC=N), 151.41 (Ar-C), 147.46 (ArC-N), 141.01 (Ar-C), 137.65 (Ar-C), 129.19 (Ar-C), 126.35 (Ar-C), 124.96 (Ar-C), 123.23 (Ar-C), 119.65 (Ar-C), 109.81 (Ar-C).

2.1.7. N,4-bis(4-methoxyphenyl)thiazol-2-amine (3g).

Yellow solid. Yield: 94%, mp 276–278 ºC; (+)ESI-HRMS m/z: calculated for [$C_{17}H_{16}N_2O_2S$ + H^+] 313.0966, observed 313.1005, IR νmax/cm^{-1}: 3220 (NH), 3015 (CH–Ar), 1579 (C=C), 1474 (C=N),1160 (C-S), 725 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.38 (s, 1H), 7.77 – 7.71 (m, 2H), 7.55 – 7.50 (m, 3H), 6.99 – 6.93 (m, 2H), 6.92 – 6.86 (m, 2H), 3.83 (s, 2H), 3.79 (s, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.29 (ArC=N), 159.98 (Ar-C), 155.61 (Ar-C), 151.34 (Ar-C), 138.61 (ArC-N), 127.42 (Ar-C), 127.01 (Ar-C), 121.11 (Ar-C), 114.68 (Ar-C), 114.09 (Ar-C), 109.92 (Ar-C), 55.33 (-OCH_3), 55.32 (-OCH_3).

2.1.8. 4-(4-methoxyphenyl)-N-(p-tolyl)thiazol-2-amine (3h).

Yellow solid. Yield: 94%, mp 180–182 ºC; (+)ESI-HRMS m/z: calculated for [$C_{17}H_{16}N_2OS$ + H^+] 297.1017, observed 297.1056, IR νmax/cm^{-1}: 3222 (NH), 3022 (CH–Ar), 1579 (C=C), 1474 (C=N), 1120 (C-S), 830 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.43 (s, 1H), 7.77 – 7.71 (m, 2H), 7.53 (s, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.13 (m, 2H), 6.92 – 6.86 (m, 2H), 3.83 (s, 2H), 2.35 (s, 1H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.13 (ArC=N), 159.98 (Ar-C), 151.34 (ArC-N), 143.51 (Ar-C), 132.02 (Ar-C), 129.51 (Ar-C), 127.42 (Ar-C), 127.01 (Ar-C), 118.55 (Ar-C), 114.09 (Ar-C), 109.92 (ArC-S), 55.32 (-OCH_3), 20.72 (CH_3).

2.1.9. N-(2,4-difluorophenyl)-4-(4-methoxyphenyl)thiazol-2-amine (3i).

Yellow solid. Yield: 94%, mp 144–146 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{12}F_2N_2OS$ + H^+] 319.0672, observed 319.0876, IR νmax/cm^{-1}: 3217 (NH), 3026 (CH–Ar), 1579 (C=C), 1474 (C=N), 1160 (C-S), 812 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.62 (s, 1H), 7.77 – 7.71 (m, 2H), 7.53 (s, 1H), 7.43 (dt, J = 7.4, 5.0 Hz, 1H), 7.02 (dtd, J = 15.5, 7.9, 2.7 Hz, 2H), 6.92 – 6.86 (m, 2H), 3.83 (s, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 162.90 (ArC=N), 162.80 (Ar-C), 159.98 (ArC-F) (J = 34 Hz, 2H),, 157.62 (Ar-C), 157.56 (ArC-N), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (ArC-F), 154.70 (Ar-C), 152.75 (Ar-C), 152.69 (Ar-C), 151.35 (Ar-C), 127.42 (Ar-C), 127.14 (Ar-C), 127.11 (Ar-C), 127.01 (Ar-C), 126.98 (Ar-C), 126.95 (Ar-C), 121.92 (Ar-C), 121.86 (Ar-C), 121.79 (Ar-C), 114.09 (Ar-C), 111.82 (Ar-C), 111.80 (Ar-C), 111.66 (Ar-C), 111.64 (Ar-C), 109.91 (Ar-C), 104.35 (Ar-C), 104.19 (ArC-S), 104.03 (Ar-C), 55.32 (-OCH_3).

2.1.10. 4-(4-methoxyphenyl)-N-(4-nitrophenyl)thiazol-2-amine (3j).

Yellow solid. Yield: 94%, mp 200–202 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{13}N_3O_3S$ + H^+] 328.0711, observed 328.0750, IR νmax/cm^{-1}: 3211 (NH), 3021 (CH–Ar), 1579 (C=C), 1474 (C=N), 1160 (C-S), 815 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.58 (s, 1H), 8.18 – 8.12 (m, 2H), 7.77 – 7.71 (m, 2H), 7.58 – 7.51 (m, 3H), 6.92 – 6.86 (m, 2H), 3.83 (s, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.37 (Ar-C), 159.98, 151.34 (ArC-N), 144.82 (Ar-C), 142.02 (Ar-C), 127.42 (Ar-C), 127.01 (Ar-C), 125.69 (Ar-C), 118.15 (Ar-C), 114.09 (Ar-C), 109.92 (ArC-S), 55.32 (-OCH_3).

2.1.11. 4-(4-chlorophenyl)-N-(4-methoxyphenyl)thiazol-2-amine (3k).

Yellow solid. Yield: 94%, mp 173–175 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{13}ClN_2OS$ + H^+] 317.0471, observed 317.0510, IR νmax/cm^{-1}: 3227 (NH), 3016 (CH–Ar), 1579 (C=C), 1475 (C=N), 1160 (C-S), 835 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.38 (s, 1H), 7.73 – 7.67 (m, 2H), 7.56 – 7.50 (m, 3H), 7.50 – 7.44 (m, 2H), 6.99 – 6.93 (m, 2H), 3.79 (s, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.29 (ArC=N), 155.61 (Ar-C), 151.58 (ArC-N), 138.61 (Ar-C), 135.12 (Ar-C), 131.88 (Ar-C), 128.39 (Ar-C), 126.92 (Ar-C), 121.11 (Ar-C), 114.68 (Ar-C), 109.83 (ArC-S), 55.32 (-OCH_3).

2.1.12. 4-(4-chlorophenyl)-N-(3-(trifluoromethyl)phenyl)thiazol-2-amine (3l).

Yellow solid. Yield: 94%, mp 162–164 ºC; (+)ESI-HRMS m/z: calculated for [$C_{16}H_{10}ClF_3N_2S$ + H^+] 355.0239, observed 355.0069, IR νmax/cm^{-1}: 3219 (NH), 3023 (CH–Ar), 1569 (C=C), 1454 (C=N), 1160 (C-S), 835 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.58 (s, 1H), 7.73 – 7.67 (m, 2H), 7.62 – 7.51 (m, 3H), 7.48 (s, 1H), 7.46 (s, 1H), 7.43 (dd, J = 10.4, 7.3 Hz, 1H), 7.34 (ddd, J = 10.4, 2.2, 1.3 Hz, 1H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.11 (ArC=N), 151.58 (ArC-N), 140.57 (Ar-C), 140.56 (Ar-C), 140.54 (Ar-C), 140.53 (Ar-C), 135.12 (Ar-C), 131.88 (Ar-C), 131.82 (Ar-C), 131.56 (Ar-C), 131.30 (Ar-C), 131.05 (Ar-C), 129.35 (Ar-C), 129.34 (Ar-C), 129.32 (Ar-C), 129.30 (Ar-C), 128.39 (Ar-C), 127.28 (Ar-C), 126.92 (Ar-C), 125.13 (ArC-F), 122.99 (Ar-C), 120.85 (Ar-C), 120.33 (Ar-C), 119.52 (Ar-C), 119.49 (Ar-C), 119.45 (Ar-C), 119.42 (C=C), 117.41 (Ar-C), 117.38 (Ar-C), 117.35 (Ar-C), 117.32 (Ar-C), 109.83 (ArC-S).

2.1.13. 4-(4-chlorophenyl)-N-(2,4-difluorophenyl)thiazol-2-amine (3m).

Yellow solid. Yield: 94%, mp 122–124 ºC; (+)ESI-HRMS m/z: calculated for [$C_{15}H_9ClF_2N_2S$ + H^+] 323.0177, observed 323.0216, , IR νmax/cm^{-1}: 3230 (NH), 3021 (CH–Ar), 1559 (C=C), 1474 (C=N), 1153 (C-S), 814 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.62 (s, 1H), 7.73 – 7.67 (m, 2H), 7.52 (s, 1H), 7.50 – 7.39 (m, 3H), 7.02 (dtd, J = 15.5, 7.9, 2.7 Hz, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 162.90 (AC=N), 162.81 (Ar-C), 157.62 (ArC-F), 157.56 (Ar-C), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (ArC-F) (J = 42 Hz, 2H),, 154.70 (Ar-C), 152.75 (C-N), 152.69 (Ar-C), 151.58 (Ar-C), 135.12 (Ar-C), 131.88 (Ar-C), 128.39 (Ar-C), 127.14 (Ar-C), 127.11 (Ar-C), 126.98 (Ar-C), 126.92 (Ar-C), 121.92 (Ar-C), 121.86(Ar-C), 121.79 (Ar-C), 111.82 (Ar-C), 111.80 (Ar-C), 111.66 (Ar-C), 111.64 (Ar-C), 109.86 (Ar-C), 104.35 (Ar-C), 104.19 (Ar-C), 104.03 (ArC-S).

2.1.14. 4-(4-chlorophenyl)-N-(4-nitrophenyl)thiazol-2-amine (3n).

Yellow solid. Yield: 94%, mp 235–237 ºC; (+)ESI-HRMS m/z: calculated for [$C_{15}H_{10}ClN_3O_2S$ + H^+] 332.0216, observed 332.0255, IR νmax/cm^{-1}: 3218 (NH), 3024 (CH–Ar), 1579 (C=C), 1464 (C=N),1160 (C-S), 825 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.58 (s, 1H), 8.18 – 8.12 (m, 2H), 7.73 – 7.67 (m, 2H), 7.58 – 7.51 (m, 3H), 7.50 – 7.44 (m, 2H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.35 (ArC=N), 151.58 (ArC-N), 144.82 (Ar-C), 142.02 (Ar-C), 135.12 (ArC-Cl), 131.88 (ArC=C), 128.39 (Ar-C), 126.92 (ArC=C), 125.69 (Ar-C), 118.15 (ArC=C), 109.83 (ArC-S).

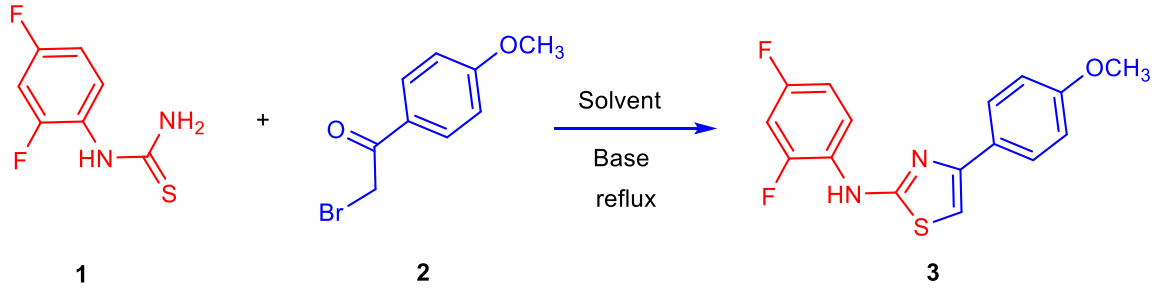
2.1.15. 4-(4-chlorophenyl)-N-phenylthiazol-2-amine (3o).

Yellow solid. Yield: 94%, mp 142–144 ºC; (+)ESI-HRMS m/z: calculated for [$C_{15}H_{11}ClN_2S$ + H^+] 287.0365, observed 287.0404, IR νmax/cm^{-1}: 3217 (NH), 3022 (CH–Ar), 1579 (C=C), 1474 (C=N), 1140 (C-S), 812 (C–N). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.55 (s, 1H), 7.73 – 7.67 (m, 2H), 7.61 – 7.55 (m, 2H), 7.53 (s, 1H), 7.50 – 7.44 (m, 2H), 7.31 – 7.24 (m, 2H), 6.96 (tt, *J* = 7.0, 1.2 Hz, 1H), ^{13}C NMR (125 MHz, DMSO-*d6*) δ 161.13 (ArC-N), 151.58 (ArC-N), 141.01 (Ar-C), 135.12 (Ar-C), 131.88 (Ar-C), 129.19 (Ar-C), 128.39 (Ar-C), 126.92 (Ar-C), 123.23 (Ar-C), 119.65 (Ar-C), 109.83 (ArC-S),

3. Results and Discussion

The synthetic procedures adapted to obtain the target compounds are depicted in (Scheme 1 and 2). We have screened the conditions for the synthesis of N-substituted phenyl thiazole amine. We have synthesized and screened of model reaction of new N-(substituted phenyl)-substituted thiazol-2-amine (3) (Scheme 1, Table 1). The reaction in which the 1-(2,4-difluorophenyl)thiourea (1) (1 mmol) and 2-bromo-1-(4-methoxyphenyl)ethanone (2) (1 mmol), catalyzed by various bases and various solvents, were selected as a model reaction to optimize the reaction condition. The solvents and bases on the condensation reaction, potassium carbonate was found to be the better base, and N,N-dimethylformamide (DMF) was were found to be the best base and solvent for the reaction (Table 1, entry 14); other solvents, including ethanol, toluene, methanol, and acetic acid were less efficient acetic acid (Table 1, entry 1–3, 5-8, 10–13 and 15). The entries from 1 to 13 indicate the lower yields, so we further screened the reaction conditions. Nevertheless, this entire yield was generally low before further optimization. So we have performed further reactions as per (entry 14, Table 1), another

solvent including ethanol, toluene, methanol, and acetic acid less efficient acetic acid (Table 1, entry 1–3, 5-8, 10–13, and 15). Nevertheless, this entire yield was generally low before further optimization.



Scheme 1. Screening of model reaction new N-(2,4-difluorophenyl)-4-(4-methoxyphenyl)thiazol-2-amine (3): Reaction condition: All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent.

DMF gave the corresponding product in 65–95% yield, which was the best among these solvents (Table 1, entries 4, 9, and 14). Sodium acetate and ammonium acetate gave fewer yields with other solvents but gave better yield in combination with methanol as a solvent (Table 1, entries 4 and 9). Also, the effects of different bases were investigated (Table 1, entries 1–15). Potassium carbonate best performance with used solvents and gave better yield (Table 1, entries 11–15). Among these reactions, the same amounts of the solvent, namely 1 mL of DMF turned out to be the best choice with yields of 65%, 80%, and 95% (Table 1, entries 4, 9, and 14). We want to mention that DMF as a solvent with potassium carbonate as a base was the best choice with a yield of 95% and less time (3 h) required to complete the reaction (Table 1, entry 14). Thus we have been decided to carry out the further reactions in DMF with potassium carbonate (Scheme 2, Table 2). As a result, the reaction time was shortened; thermal decomposition was also minimized, at reflux, resulting in higher yields.

Table 1. Screening of base, solvents, reaction time, and yield for the synthesis (3)[a].

Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	Ammonium acetate	Ethanol	8	50
2	Ammonium acetate	Methanol	9	55
3	Ammonium acetate	Acetic acid	9	45
4	Ammonium acetate	DMF	6	65
5	Ammonium acetate	Toluene	9	50
6	Sodium acetate	Ethanol	8	55
7	Sodium acetate	Methanol	9	58
8	Sodium acetate	Acetic acid	9	50
9	Sodium acetate	DMF	4	80
10	Sodium acetate	Toluene	7	60
11	Potassium carbonate	Ethanol	5	55
12	Potassium carbonate	Methanol	6	58
13	Potassium carbonate	Acetic acid	5	60
14	Potassium carbonate	DMF	3	95
15	Potassium carbonate	Toluene	5	60

[a] All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent
[b] Isolated yield.

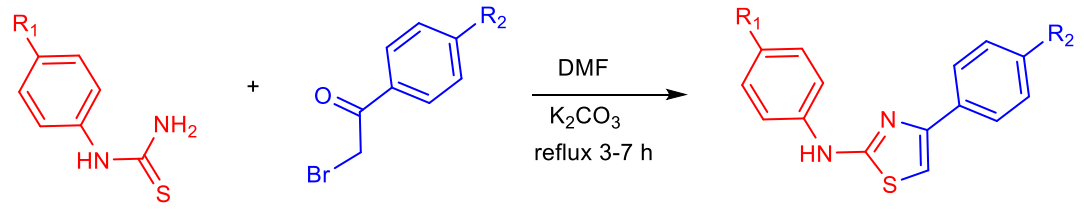
Table 2. Physical data of the synthesized compounds (3a-o)[a].

Compounds	(R^1)	(R^2)	Time (h)	Yield[b] (%)	Melting point (°C)
3a	2-NO_2	4-CH_3	6	94	140-142
3b	4-F	4-CH_3	4	96	180-182
3c	4-NO_2	4-NO_2	6	96	213-215
3d	2-F , 4-F	4-NO_2	3	94	245-247
3e	3-CF_3	4-NO_2	3	96	230-232

Compounds	(R^1)	(R^2)	Time (h)	Yield[b] (%)	Melting point (°C)
3f	H	4-NO_2	5	94	170-172
3g	4-OMe	4-OMe	4	96	276-278
3h	4-Me	4-OMe	4	94	180-182
3i	2-F , 4-F	4-OMe	7	96	144-146
3j	4-NO_2	4-OMe	6	94	200-202
3k	4-OMe	4-Cl	3	92	173-175
3l	3-CF_3	4-Cl	3	94	162-164
3m	2-F , 4-F	4-Cl	5	92	122-124
3n	4-NO_2	4-Cl	6	92	235-237
3o	H	4-Cl	5	92	142-144

[a]Reaction condition (3a-o): Compound (1a-h) (1 mmol), compound (2a-d) (1 mmol), DMF, K_2CO_3 (1 mmol), reflux 3-7 h, reflux

[b]Isolated yield



1a-h **2a-d** **3a-o**

Compounds	(R^1)	(R^2)		(R^1)	(R^2)
3a	2-NO_2	4-CH_3	**3i**	2-F , 4-F	4-OMe
3b	4-F	4-CH_3	**3j**	4-NO_2	4-OMe
3c	4-NO_2	4-NO_2	**3k**	4-OMe	4-Cl
3d	2-F , 4-F	4-NO_2	**3l**	3-CF_3	4-Cl
3e	3-CF_3	4-NO_2	**3m**	2-F , 4-F	4-Cl
3f	H	4-NO_2	**3n**	4-NO_2	4-Cl
3g	4-OMe	4-OMe	**3o**	H	4-Cl
3h	4-Me	4-OMe			

Scheme 2. Synthesis of new N-(substituted phenyl)-substituted thiazol-2-amine (3a-o): **Reaction condition:** Compound (1a-h) (1 mmol), compound (2a-d) (1 mmol), DMF, K_2CO_3 (1 mmol), reflux 3-7 h, reflux. R^1 and R^2 is the substituents on aromatic ring.

3.1. Antimicrobial activity and SAR.

All the newly synthesized compounds (3a-o) were screened for their in-vitro antimicrobial activity against three fungal strains; *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539), and *Aspergillus niger* (NCIM-1196) and two gram-positive bacteria;

Bacillus subtilis (NCIM-2063), *Staphylococcus aureus* (NCIM-2901) and one gram negative bacteria; Escherichia coli (NCIM-2256). The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned [31] by broth dilution method with Ciprofloxacin and Ampicillin as control drugs. At the same time, the antifungal study was carried out by standards agar dilution method, where fluconazole and miconazole were used as control drugs. Methanol was used as solvent control for antibacterial and antifungal testing (Table 3).

Among the series compounds (3b, 3d, 3e, 3i, 3l, 3m), they were found to be the most active molecules, and they are specific towards the gram-positive bacterial, *S. aureus* and *B. subtilis.* Compound (3b) is more active (MIC of 6.5 and 7.0 µg/mL against *B. subtilis* and *S. aureus* respectively) than both standards used in the experiment, while compound (3l and 3m) (MIC of 7.5 and 7.0 µg/mL against *B. subtilis* and MIC of 7.5 and 8.0 µg/mL against *E. coli*). have better activity, but little lower than ciprofloxacin and the comparative level of activity as

ampicillin. The compounds (3d and 3e) have somewhat better activity than both the standard drugs; more importantly, they show better activity against bacterial and fungal strains tested. Compound (3f and 3g) is more active (MIC of 3.5, 8.5, and 7.5 µg/mL against *C. albicans*, *A. flavus*, and *A. niger*, respectively) than both standards used in the experiment, also other compounds have less activity, than Ffluconazole and miconazole. The compounds (3a, 3c, 3f, 3g, 3h) are narrow-spectrum molecules, Remaining compounds of the series (3n, 3j, 3k, and 3o,) have very high MIC values, and therefore they are inactive as antimicrobial agents. It is interesting that bacterium *E. coli* is resistant to all compounds, suggesting that molecules of the series may be inactive against gram-negative bacteria.

3.2. Structure-Activity Relationship (SAR).

The fluoro group is attached to the aromatic ring (R1) shows better antibacterial activity. The compounds such as 3b, 3d, 3e, 3i, 3l, and 3m having fluoro group show electron-withdrawing effect on the benzene ring; for this reason, maybe compounds make more antibacterial active molecules. The compound 3b, 3d, 3e, 3i, 3m shows better activity MIC values 6.5, 10, 09, 20, 7.5 µg/mL respectively against *B. substilis*. The compounds 3b, 3d, 3e, and 3i show better antibacterial activity MIC values 7.0, 12, 15, 7.2, µg/mL, respectively, against *S. aureus.* The hydrogen, methyl, and fluoro group is attached to the aromatic ring shows better antifungal activity.

Table 3. Antimicrobial Minimum Inhibitory Concentration (MIC, µg/mL) the synthesized compounds (3a-o).

Compounds	**MIC Values (µg/mL)[a]**					
	B. substilis	***S. aureus***	***E. coli***	***C. albicans***	***A. flavus***	***A. niger***
3a	75	95	95	95	100	100
3b	**6.5**	**7.0**	85	75	80	75
3c	85	70	90	60	100	80
3d	**10**	**12**	**90**	95	90	100
3e	**09**	**15**	**100**	90	85	100
3f	30	25	95	**3.5**	**8.5**	**7.5**
3g	80	95	100	**4.0**	**7.5**	**6.5**
3h	40	20	75	40	70	85
3i	**20**	**7.2**	**90**	**70**	**75**	**100**
3j	90	95	100	65	60	80
3k	90	95	100	90	85	100
3l	**7.5**	**20**	**7.0**	90	100	90
3m	**7.5**	**85**	**8.0**	75	80	75
3n	60	80	100	95	90	100
3o	90	95	100	90	85	100
Ciprofloxacin	6.30	6.30	4.0	-	-	-
Ampicillin	12.5	12.5	12.5	-	-	-
Fluconazole	-	-	-	10	6.25	6.25
Miconazole	-	-	-	3.25	3.25	3.25

[a]Values are the average of three readings.

The compound 3l shows better antibacterial activity, MIC values 7.5, 20, and 7.0 µg/mL against *B. substilis*, *S. aureus*, and *E. coli*, respectively. The compound 3f shows better antifungal activity MIC values 3.5, 8.5, and 7.5 µg/mL against *C. albicans*, *A. flavus*, and *A. niger*, respectively. The compound 3g shows better antifungal activity MIC values 4.0, 7.5, and 6.5 µg/mL against *C. albicans*, *A. flavus*, and A. *niger*, respectively. The compounds such as 3f, 3g, and 3i having methyl group shows the electron-donating effect on the benzene ring; for this reason, maybe compounds make more antifungal active molecules. Also, the nitro

group is attached to another benzene ring (R2) which shows better antibacterial activity. Also, the methoxy group is attached to another benzene ring (R2) which shows better antifungal activity. We have developed to synthesize substituted thiazole-2-amine derivatives with good yields in the present communications. In summary, we have developed a new methodology for synthesizing thiazole derivatives by coupling substituted 2-bromo ketones and substituted thiourea compounds. At most, the method is a minor modification of the Hantzsch reaction, which is commonly used to prepare aminothiazoles. Efficient and convenient synthesis and investigation of the potent antimicrobial activities of some new N-(substituted phenyl)-4-(substituted phenyl)thiazol-2-amine (3a-o) derivatives. Discovering new structures that could be used as potent antimicrobial agents. The process also exhibits good to excellent yield. This method offers significant advantages such as chief catalyst, mild reaction condition, excellent yield, best conversion, and short reaction time. The compounds 3b, 3d, 3e, 3l, and 3m are exhibited significant antibacterial activity against *B. substilis. S. aureus* and *E. coli*, whereas compounds 3f, 3g, and 3i are displayed significant antifungal activity against fungal strains, i.e., *C. albicans, A. flavus*, and *A. niger*. The synthesis of thiazolone moiety has confirmed our aim is effective for the enhanced antimicrobial activity

4. Conclusions

In summary, we have developed a new methodology for synthesizing thiazole derivatives by coupling substituted 2-bromo ketones and substituted thiourea compounds. This is an efficient and convenient synthesis and investigation of the potent antimicrobial activities of some new N-(substituted phenyl)-4-(substituted phenyl)thiazol-2-amine **(**3a-o) derivatives which are the discovering new structure that can be used as potent antimicrobial agents. The process also exhibits good to excellent yield. This method offers significant advantages such as chief catalyst, mild reaction condition, excellent yield, best conversion, and short reaction time. The compounds 3b, 3d, 3e, 3l, and 3m are exhibited significant antibacterial activity against *B. substilis. S. aureus* and *E. coli*, whereas compounds 3f, 3g, and 3i display significant antifungal activity against fungal strains, i.e., *C. albicans, A. flavus*, and *A. niger*. It also confirmed that the synthesis of thiazolone moiety is effective for enhanced antimicrobial activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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