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

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Received: 18.11.2021; Accepted: 20.12.2021; Published: 14.03.2022

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.

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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 benzyldene)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). 1H 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 13C 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 1H and 13C 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 °C; (+)ESI-HRMS m/z: calculated for [C$_{16}$H$_13$N$_2$O$_5$S + H$^+$] 312.0762, observed 312.0801, ES-MS m/z (%): 322.35. IR vmax/cm$^{-1}$: 3208 (NH), 1610 (C=C), 1555 (C=N), 1212 (C=S), 1194 (C–N). 1H NMR (500 MHz, DMSO-d$_6$): 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-d$_6$) δ 161.08 (ArC=N), 151.15 (Ar-C), 138.83 (Ar-C), 137.64 (Ar-C-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 °C; (+)ESI-HRMS m/z: calculated for [C$_{16}$H$_{14}$FN$_2$S + H$^+$] 285.0817, observed 285.0856, ES-MS m/z (%): 322.35, IR vmax/cm$^{-1}$: 3216 (NH), 2822 (CH–Ar), 1583 (C=C), 1454 (C=N), 1016 (C-S), 736 (C–F). 1H NMR (500 MHz, DMSO-d$_6$): 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-d$_6$) δ = 161.29 (Ar=C=N), 158.45 (Ar-C-F) J = 34 Hz, 2H), 156.43 (Ar-C), 151.18 (Ar-C-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 °C; (+)ESI-HRMS m/z: calculated for [C$_{15}$H$_{10}$N$_2$O$_5$S + H$^+$] 343.0456, observed 343.0496, ES-MS m/z (%): 322.35, IR vmax/cm$^{-1}$: 3217 (NH), 2924 (CH–Ar), 1585 (C=C), 1456 (C=N), 1212 (C-S), 1019 (C–N). 1H NMR (500 MHz, DMSO-d$_6$): 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), 13C NMR (125 MHz, DMSO-d$_6$) δ 161.38 (Ar-C=N), 151.41 (Ar-C), 147.46 (Ar-C-N), 144.82 (Ar-C), 142.02 (Ar-C), 137.65 (Ar-C-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 °C; (+)ESI-HRMS m/z: calculated for [C$_{15}$H$_{12}$F$_2$N$_2$O$_5$S + H$^+$] 334.0417, observed 334.0456, IR vmax/cm$^{-1}$: 3217 (NH), 3020 (CH–Ar), 1559 (C=C), 1464 (C=N), 1150 (C-S), 725 (C–N). 1H NMR (500 MHz, DMSO-d$_6$): 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). 13C NMR (125 MHz, DMSO-d$_6$) δ 162.90 (Ar-C=N), 162.80 (Ar-C), 157.62 (Ar-C-F), 157.56 (Ar-C), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (Ar-C), 154.70 (Ar-C-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).
C), 111.66 (Ar-C), 111.64 (Ar-C), 109.86 (Ar-C), 104.35 (Ar-C), 104.19 (Ar-C), 104.03 (Ar-C).

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\textsubscript{16}H\textsubscript{10}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S + H\textsuperscript{+}] 366.0479, observed 366.0519, IR v\textsubscript{max}/cm\textsuperscript{-1}: 3217 (NH), 3026 (CH–Ar), 1569 (C=C), 1474 (C=N), 1160 (C-S), 820 (C–N). \( ^1\text{H} \text{NMR (500 MHz, DMSO-d6)} \): \( \delta \) 9.58 (s, 1H), 8.24 – 8.18 (m, 2H), 7.83 – 7.80 (m, 1H), 7.58 (t, \( J = 2.2 \) Hz, 1H), 7.59 – 7.53 (m, 1H), 7.56 (s, 1H), 7.43 (dd, \( J = 10.4, 7.4, 7.4 \) Hz, 1H), 7.28 (dd, \( J = 10.4, 2.2, 1.3 \) Hz, 1H).

\( ^{13}\text{C} \text{NMR (125 MHz, DMSO-d6)} \) \( \delta \) 161.13 (Ar-C=N), 157.9 (Ar-C), 147.46 (Ar-C), 140.55 (Ar-C) (q, \( J = 2.0 \) Hz), 137.65 (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 (Ar-C), 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\textsubscript{15}H\textsubscript{11}N\textsubscript{3}O\textsubscript{2}S + H\textsuperscript{+}] 298.0606, observed 298.0645, IR v\textsubscript{max}/cm\textsuperscript{-1}: 3218 (NH), 3015 (CH–Ar), 1579 (C=C), 1473 (C=N), 1155 (C-S), 825 (C–N). \( ^1\text{H} \text{NMR (500 MHz, DMSO-d6)} \): \( \delta \) 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). \( ^{13}\text{C} \text{NMR (125 MHz, DMSO-d6)} \) \( \delta \) 161.13 (Ar-C=N), 151.41 (Ar-C), 147.46 (Ar-C-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\textsubscript{17}H\textsubscript{16}N\textsubscript{3}O\textsubscript{2}S + H\textsuperscript{+}] 313.0966, observed 313.1005, IR v\textsubscript{max}/cm\textsuperscript{-1}: 3220 (NH), 3015 (CH–Ar), 1579 (C=C), 1474 (C=N), 1160 (C-S), 725 (C–N). \( ^1\text{H} \text{NMR (500 MHz, DMSO-d6)} \): \( \delta \) 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), \( ^{13}\text{C} \text{NMR (125 MHz, DMSO-d6)} \) \( \delta \) 161.29 (Ar-C=N), 159.98 (Ar-C), 155.61 (Ar-C), 151.34 (Ar-C), 138.61 (Ar-C-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\textsubscript{3}), 55.32 (-OCH\textsubscript{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\textsubscript{17}H\textsubscript{16}N\textsubscript{2}OS + H\textsuperscript{+}] 297.1017, observed 297.1056, IR v\textsubscript{max}/cm\textsuperscript{-1}: 3222 (NH), 3022 (CH–Ar), 1579 (C=C), 1474 (C=N), 1120 (C-S), 830 (C–N). \( ^1\text{H} \text{NMR (500 MHz, DMSO-d6)} \): \( \delta \) 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), \( ^{13}\text{C} \text{NMR (125 MHz, DMSO-d6)} \) \( \delta \) 161.13 (Ar-C=N), 159.98 (Ar-C), 151.34 (Ar-C-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 (Ar-C-S), 55.32 (-OCH\textsubscript{3}), 20.72 (CH\textsubscript{3}).
2.1.9. N-(2,4-difluorophenyl)-4-(4-methoxyphenyl)thiazol-2-amine (3i).

Yellow solid. Yield: 94%, mp 144–146 °C; (+)ESI-HRMS m/z: calculated for [C_{16}H_{12}F_{2}N_{2}OS + H^+] 319.0672, observed 319.0876, IR vmax/cm^{-1}: 3217 (NH), 3026 (CH–Ar), 1579 (C=C), 1474 (C=N), 1160 (C-S), 812 (C–N). ^1H 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 (dt, J = 15.5, 7.9, 2.7 Hz, 2H), 6.92 – 6.86 (m, 2H), 3.83 (s, 2H). ^13C NMR (125 MHz, DMSO-d6) δ 162.90 (Ar=C=N), 162.80 (Ar-C), 159.98 (Ar-C-F) ( J = 34 Hz, 2H), 157.62 (Ar-C), 157.56 (Ar-C-N), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (Ar-C-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 (Ar-C-S), 104.03 (Ar-C), 55.32 (–OCH3).

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

Yellow solid. Yield: 94%, mp 200–202 °C; (+)ESI-HRMS m/z: calculated for [C_{16}H_{13}N_{2}O_{5}S + H^+] 328.0711, observed 328.0750, IR vmax/cm^{-1}: 3211 (NH), 3021 (CH–Ar), 1579 (C=C), 1474 (C=N), 1160 (C-S), 815 (C–N). ^1H 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). ^13C NMR (125 MHz, DMSO-d6) δ 161.37 (Ar-C), 159.98, 151.34 (Ar-C-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 (Ar-C-S), 55.32 (–OCH3).

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

Yellow solid. Yield: 94%, mp 173–175 °C; (+)ESI-HRMS m/z: calculated for [C_{16}H_{13}ClN_{2}O_{5}S + H^+] 317.0471, observed 317.051, IR vmax/cm^{-1}: 3227 (NH), 3016 (CH–Ar), 1579 (C=C), 1475 (C=N), 1160 (C-S), 835 (C–N). ^1H 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). ^13C NMR (125 MHz, DMSO-d6) δ 161.29 (Ar=C=N), 155.61 (Ar-C), 151.58 (Ar-C-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 (Ar-C-S), 55.32 (–OCH3).

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

Yellow solid. Yield: 94%, mp 162–164 °C; (+)ESI-HRMS m/z: calculated for [C_{16}H_{10}ClF_{3}N_{2}S + H^+] 355.0239, observed 355.0069, IR vmax/cm^{-1}: 3219 (NH), 3023 (CH–Ar), 1569 (C=C), 1454 (C=N), 1160 (C-S), 835 (C–N). ^1H 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). ^13C NMR (125 MHz, DMSO-d6) δ 161.11 (Ar=C=N), 151.58 (Ar-C-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 (Ar-C-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 (Ar-C-S).

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

Yellow solid. Yield: 94%, mp 122–124 °C; (+)ESI-HRMS m/z: calculated for [C₁₅H₁₈Cl₂F₂N₂S + H⁺] 323.0177, observed 323.0216. IR νmax/cm⁻¹: 3230 (NH), 3021 (CH–Ar), 1559 (C=C), 1474 (C=N), 814 (C–N). ¹H 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 (ddt, J = 15.5, 7.9, 2.7 Hz, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ 162.90 (AC=N), 162.81 (Ar-C), 157.62 (Ar-F), 157.56 (Ar-C), 155.61 (Ar-C), 155.54 (Ar-C), 154.77 (Ar-C-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 (Ar-C-S).

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

Yellow solid. Yield: 94%, mp 235–237 °C; (+)ESI-HRMS m/z: calculated for [C₁₅H₁₈ClN₃O₂S + H⁺] 332.0216, observed 332.0255. IR νmax/cm⁻¹: 3237 ºC; (+)ESI-MS: calculated for [C₁₅H₁₈ClN₃S + H⁺] 321.0326, observed 321.0328. ¹H 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), ¹³C NMR (125 MHz, DMSO-d₆) δ 161.35 (ArC=N), 151.58 (ArC-N), 144.82 (Ar-C), 142.02 (Ar-C), 135.12 (Ar-C-Cl), 131.88 (Ar=C), 126.92 (Ar=C), 125.69 (Ar-C), 118.15 (Ar=C), 109.83 (Ar-C-S).

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

Yellow solid. Yield: 94%, mp 142–144 °C; (+)ESI-HRMS m/z: calculated for [C₁₅H₁₈ClN₃S + 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). ¹H 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), ¹³C NMR (125 MHz, DMSO-d₆) δ 161.13 (Ar-C-N), 151.58 (Ar-C-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 (Ar-C-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 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) | Yieldb (%) |
|-------|------------------|---------|----------|------------|
| 1     | Ammonium acetate | Ethanol | 8        | 50         |
| 2     | Ammonium acetate | Methanol| 9        | 55         |
| 3     | Ammonium acetate | Acetic  | 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  | 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  | 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 | (R1) | (R2) | Time (h) | Yieldb (%) | Melting point (°C) |
|-----------|------|------|----------|------------|-------------------|
| 3a        | 2-NO2 | 4-CH3| 6        | 94         | 140-142           |
| 3b        | 4-F   | 4-CH3| 4        | 96         | 180-182           |
| 3c        | 4-NO2 | 4-NO2| 6        | 96         | 213-215           |
| 3d        | 2-F, 4-F | 4-NO2| 3        | 94         | 245-247           |
| 3e        | 3-CF3 | 4-NO2| 3        | 96         | 230-232           |
3o

\[ \text{Compounds} \]

| 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-Cl\(_1\) | 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\(_2\)CO\(_3\) (1 mmol), reflux 3-7 h, reflux
\(^b\)Isolated yield

\[ \text{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\(_2\)CO\(_3\) (1 mmol), reflux 3-7 h, reflux. R}^1 \text{ and R}^2 \text{ 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 fluconazole 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 against B. substilis, S. aureus, and E. coli, 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

| Compounds | MIC Values (μg/mL) | 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        | 4.0    | 3.5         | 8.5       | 7.5     |
| 3g        | 80                | 95          | 100       | 4.0    | 3.5         | 8.5       | 7.5     |
| 3h        | 40                | 20          | 75        | 70     | 75          | 100       |         |
| 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      |         |

*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. subtilis. 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. subtilis. 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.

Funding

This research received no external funding.

Acknowledgments

The authors RBS are thankful to the Principal, Vinayakrao Patil College, Vaijapur, 423701 (MS) India, for providing the laboratory facility.

Conflicts of Interest

The authors declare no conflict of interest.

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