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Synthesis, characterization and antimicrobial activities of imidazo-[2,1,*b*][1,3,4]-thiadiazoles

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ABSTRACT

*A series of imidazo[2,1-b][1,3,4]-thiadiazoles (**6a-p**) were synthesized by a condensation reaction of 2-amino-5-substituted-[1,3,4]thidiazoles (**5a-b**) with various substituted phenacyl bromides. All structures of the newly synthesized compounds were elucidated by elemental analyses and spectral data. The new compounds were tested for their in vitro antimicrobial activities.*

Key words: Ibuprofen, 4-Methylthiophenyl acetic acid, 2-Amino-thidiazoles, Antimicrobial activity.

INTRODUCTION

Tetramisole [1] is one of the broad spectrum anthelmintic drug, whose discovery led to the search of different condensed imidazo-[2,1-*b*][1,3,4]-thiazole systems [2-5]. Bioisosteric replacement method led to the identification of imidazo[2,1-*b*][1,3,4]thiadiazoles as structurally close to imidazo[2,1-*b*][1,3,4]thiazole systems. This led to the increase in investigation of these heterocycles as new pharmacophores. As a result, a large number of imidazo[2,1-*b*][1,3,4]- thiadiazoles have been reported to possess wide range of biological properties such as antibacterial [6], antifungal [7], anticancer [8], antitubercular [9], anticonvulsant, analgesic [10], and antisecretory [11] activities.

The increasing clinical importance of drug-resistant bacterial pathogens has lent additional urgency to microbiological and antibacterial research. Derivatives of [1,3,4]-thiadiazoles are known to exhibit antibacterial [12,13], antifungal [14], anti-inflammatory [15] and analgesic [16] activities. Most of the known anti-inflammatory drugs show a tendency to exacerbate stomach ulcer and even precipitate these. Ibuprofen [17] is a non-steroidal anti-inflammatory drug much more potent than ibufenac, is used in the treatment of several inflammation diseases with decreased side effects of all the known anti-inflammatory drugs. Ibuprofen containing heterocyclic compounds are found to possess antiinflammatory [18,19], antimicrobial, anticonvulsant [20], analgesic [21] and ulcerogenic [22] activities. It has also been reported that heterocyclic compounds containing 4-thiomethylphenyl moiety possess good anti-inflammatory [23] and antimicrobial [24-26] activities.

In view of the marked bioactivity of these condensed heterocyclic systems and also the biological profiles of heterocycles derived from ibuprofen and 4-thiomethyl phenyl moiety, we thought of designing and synthesizing

some new imidazo-[2,1-*b*][1,3,4]-thiadiazoles (**6**a-p) by replacing the carboxylic acid group of 2-(4-isobutylphenyl)propanoic acid and 4-thiomethylphenyl acetic acid by a imidazothiadiazole nucleus and to evaluate their antibacterial and antifungal activity.

MATERIALS AND METHODS

The melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded ($CDCl_3$/DMSO-d_6 mixture) on a BRUKER AVANCE II - 400 (400 MHz) spectrometer using TMS as an internal standard. LC-Mass spectra were recorded in Agilent Technology. Elemental analysis (CHNS) was performed on the CHNS Elementar Vario EL III. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel plates.

Procedure for the preparation of aroylhydrazides (3)
The mixture of ethyl esters of substituted aromatic acids **2** (0.1 mol) and hydrazine hydrate (0.2 mol) was refluxed in absolute alcohol (50 mL) for 8 h. The excess solvent was then distilled off under reduced pressure and the concentrated solution was quenched in to ice cold water. The solid separated was filtered, washed and dried. The crude product was purified by recrystallization from ethanol.

2-(4-Isobutylphenyl)propionic acid hydrazide, **3a**: Elemental analysis for $C_{13}H_{20}N_2O$ (MW=220) in wt %. Calc. C= 70.87, H= 9.15, N= 12.72, found C= 70.85, H= 9.13, N= 12.70. m.pt 70-71 ^{0}C. yield 85 %, IR (KBr) in cm^{-1}: 3449 (NH, NH_2), 3275 (NH_2), 2972 (C-H), 1695 (CO-NH); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.85 (d, 6H, $2CH_3$, J = 8 Hz), 1.68 (d, 3H, CH_3, J = 8 Hz), 1.80-1.88 (m, lH, CH), 2.45 (d, 2H, CH_2, J = 4 Hz), 4.11 (q, lH, CH, J = 8 Hz), 4.0 (s, 2H, NH_2), 7.5 (br-s, 5H, C_6H_4- and NH); LC-MS (m/z): 220 (M^+);

4-Methylthiophenyl acetic acid hydrazide, **3b**: Elemental analysis for $C_9H_{12}N_2OS$ (MW=196) in wt %. Calcd.: C= 55.09, H= 6.16, N= 14.27, S= 16.34, found C= 55.06, H= 6.15, N= 10.25, S= 15.71. m.pt 136-138 ^{0}C, yield 86 %. IR (KBr) in cm^{-1}: 3344 (NH, NH_2), 3203 (NH_2), 2963 (C-H), 1622 (CO-NH); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.49 (s, 3H, SCH_3), 3.53 (s, 2H,CH_2), 3.82 (br.s, 2H, NH_2), 6.67 (br.s, 1H, NH), 7.18 (d, Ar-H, J = 8.36 Hz), 7.26 (d, Ar-H, J = 8.36 Hz); LC-MS (m/z): 196 (M^+);

Procedure for the preparation of 5-substituted-[1,3,4]thidiazole-2-amine, 5a,b
Acid hydrazide **3 (**0.1 mol) was dissolved in water (100 mL) containing concentrated hydrochloric acid (10 mL). Potassium thiocyanate (0.2 mol) was added to it and the mixture was warmed on a water bath for 5 h. The reaction mixture was cooled. The precipitated solid was filtered, dried and recrystalied from ethanol to get aroyl thiosemicarbazide (177 ^{o}C). The resultant thiosemicarbazide on cyclization with Conc. H_2SO_4 followed by basification with ammonia to afford 5-substituted-[1,3,4]thidiazole-2-amine and it is recrystallised from ethanol.

5-(4-Isobutylphenyl)ethyl-[1,3,4]-thiadiazol-2-amine, **5a:** Elemental analysis for $C_{14}H_{19}N_3S$ (MW= 261) in wt % calc. C= 64.31, H= 7.33, N= 16.08, S=12.27, found C= 64.30, H= 7.31, N= 16.09, S= 12.29. m.pt 198 °C. yield 92 %. IR (KBr) in cm^{-1}: 3274 (NH_2), 3112 (Ar-H), 2952 (C-H), 1619 (C=N). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, J = 8 Hz, 6 H, 2 x CH_3), 1.72 (d, J = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.44 (d, J = 4.0 Hz, 2 H, CH_2), 4.35 (q, J = 8.0 Hz, l H, CH), 5.26 (br-s, 2 H, NH_2), 7.01 (d, J = 8 Hz, 2 H, Ar-H), 7.19 (d, J = 8 Hz, 2 H, Ar-H), - ^{13}C NMR ([D_6] DMSO): δ = 18.34, 18.78, 22.42, 30.28, 37.48, 126.13, 126.32, 128.25, 128.43, 136.20, 139.05, 161.05, 167.15. - LC-MS: *m/z* = 261(M^+).

5-(4-Thiomethylbenzyl)-[1,3,4]-thiadiazol-2-amine, **5b:** Elemental analysis for $C_{10}H_{11}N_3S_2$ (MW= 237) in wt % calc. C= 50.60, H= 4.67, N= 17.70, S= 27.02, found C= 50.56, H= 4.71, N= 17.79, S= 27.05. m.pt. 197-198 °C. yield 88 %. IR (KBr) in cm^{-1}: 3329 (NH_2), 3098 (Ar-H), 2964 (C-H), 1632 (C=N). - ^{1}H-NMR ([D_6] DMSO): δ = 2.49 (s, 3 H, SCH_3), 3.83 (s, 2 H, CH_2), 6.64 (br-s, 2 H, NH_2), 7.18 (d, J = 8.36 Hz, Ar-H), 7.26 (d, J = 8.36 Hz, Ar-H), - ^{13}C NMR ([D_6] DMSO): δ = 16.12, 32.13, 127.51, 128.25, 131.99, 139.21, 152.16, 167.10. - LC-MS: *m/z* = 237 (M^+).

Procedure for the preparation of substituted Imidazolo-[2,1-*b*][1,3,4]-thiadiazole derivatives (6a-p)
A mixtures of 5-substituted-[1,3,4]-thidiazole-2-amines (10 mmol) and appropriate substituted phenacyl bromides (10 mmol) was refluxed in dry ethanol for 24 h. the excess of solvent distilled off and solid hydrobromide that

separated was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized from suitable solvent.

6-Phenyl-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6a**
Elemental analysis for $C_{22}H_{23}N_3S$ (MW=361) in wt % calc.C= 73.09, H= 6.41, N= 11.62, S= 8.87. Found.C= 73.12, H= 6.39, N= 11.68, S= 8.84. IR (KBr) in cm^{-1}: 3101, 3022, 2915, 1631, 1527, 1471 - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.09 (d, *J* = 8 Hz, 2 H, Ar-H), 7.18 (d, *J* = 8 Hz, 2 H, Ar-H), 7.69-7.83 (m, 5 H, Ar-H), 7.95 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.85, 20.86, 27.76, 30.66, 43.33, 45.43, 111.63, 124.26, 124.61, 125.64, 127.34, 127.82, 128.96, 129.13, 138.02, 140.12, 141.05, 143.18, 146.89, 147.03, 171.05.

6-(4-Chlorophenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6b**
Elemental analysis for $C_{22}H_{22}ClN_3S$ (MW= 395) in wt % calc.C= 66.73, H= 5.60, N= 10.61, S= 8.10, Found.C= 66.68, H= 5.63, N= 10.66, S= 8.07, IR (KBr) in cm^{-1}: 3124 (ArC-H), 2959 (C-H), 1578 (C=N), 770 (C-Cl). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.85, 20.86, 27.73, 30.67, 43.35, 45.47, 111.61, 124.34, 124.60, 125.74, 127.72, 129.76, 130.30, 138.68, 140.91, 142.28, 143.96, 147.12, 147.41, 171.26.

6-(4-Nitrophenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6c**
Elemental analysis for $C_{22}H_{22}N_4O_2S$ (MW=406) in wt % calc.C= 65.00, H= 5.46, N= 13.78, S= 7.89. Found.C= 65.06, H= 5.42, N= 13.83, S= 7.84. IR (KBr) in cm^{-1}: 3115 (ArC-H), 2968 (C-H), 1640 (C=N), 1555 (C=C), 1518 (NO_2), 1255 (NO_2). -^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.86, 20.87, 27.74, 30.68, 43.37, 45.48, 111.84, 124.58, 124.94, 125.80, 127.86, 130.04, 131.13, 138.78, 140.88, 142.65, 144.22, 147.47, 148.03, 171.63.

6-(2-Nitrorophenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6d**
Elemental analysis for $C_{22}H_{22}N_4O_2S$ (MW=406). calc.C= 65.00, H= 5.46, N= 13.78, S= 7.89. Found.C= 64.97, H= 5.42, N= 13.83, S= 7.92. IR (KBr) in cm^{-1}: 3095 (ArC-H), 2945 (C-H), 1619 (C=N), 1538 (C=C), 1508 (NO_2), 1272 (NO_2). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.85, 20.86, 27.74, 30.68, 43.36, 45.48, 111.84, 124.58, 124.94, 125.80, 127.86, 130.04, 131.13, 138.78, 140.88, 142.65, 144.22, 147.47, 148.03, 171.58.

6-(4-Fluorophenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6e**
Elemental analysis for $C_{22}H_{22}FN_3S$ (MW=379.49), calc.C= 69.63, H= 5.84, N= 11.07, S= 8.45. Found.C= 69.67, H= 5.78, N= 11.11, S= 8.40. IR (KBr) in cm^{-1}: 3106 (ArC-H), 2947 (C-H), 1600 (C=N), 1540 (C=C), 1221(C-F). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.84, 20.85, 27.72, 30.65, 43.34, 45.44, 111.59, 124.28, 124.55, 125.63, 127.53, 129.60, 130.16, 138.41, 140.58, 141.96, 143.41, 147.02, 147.12, 171.18.

6-(4-Methylphenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6f**
Elemental analysis for $C_{23}H_{25}N_3S$ (MW=375). calc.C= 73.56, H= 6.71, N= 11.19, S= 8.54, Found.C= 73.60, H= 6.68, N= 11.24, S= 8.58. IR (KBr) in cm^{-1}: 3108 (ArC-H), 2950 (C-H), 1567 (C=N). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.84, 20.85, 21.36, 27.72, 30.65, 43.34, 45.44, 111.62, 124.32, 124.67, 125.41, 127.42, 129.27, 130.04, 138.54, 141.08, 141.82, 143.52, 147.16, 147.06, 171.41.

6-(4-Methoxyphenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6g**
Elemental analysis for $C_{23}H_{25}N_3OS$ (MW=391). calc. C= 70.56, H 6.44, N= 10.73, S= 8.19. Found. C= 70.51, H 6.38, N= 10.79, S= 8.25. IR (KBr) in cm^{-1}: 3113 (ArC-H), 22951 (C-H), 1603 (C=N), 1223 (C-O). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). δ = 20.85, 20.86, 27.73, 30.65, 43.34, 45.44, 67.26, 111.62, 124.32, 124.67, 125.41, 127.42, 129.27, 130.04, 138.54, 141.08, 141.82, 143.52, 147.16, 147.06, 171.41.

6-(4-Bromophenyl)-2-(4-isobutylphenyl)ethyl-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6h**
Elemental analysis for $C_{22}H_{22}BrN_3S$ (MW=440). calc.C= 60.00, H= 5.04, N= 9.54, S= 7.28. Found.C= 59.95, H= 5.01, N= 9.59, S= 7.24. IR (KBr) in cm^{-1}: 3112 (ArC-H), 2972 (C-H), 1604 (C=N), 1535 (C=C), 580(C-Br). - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (d, *J* = 8 Hz, 6 H, 2 x CH_3), 1.68 (d, *J* = 8 Hz, 3 H, CH_3), 1.81-1.85 (m, l H, CH), 2.46 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.40 (q, *J* = 8.0 Hz, l H, CH), 7.11 (d, *J* = 8 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.89 (d, *J* = 8 Hz, 2 H, Ar-H), 8.19 (d, *J* = 8 Hz, 2 H, Ar-H), 8.07 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 20.85, 20.86, 27.73, 30.67, 43.35, 45.47, 111.60, 124.32, 124.65, 125.73, 127.70, 129.80, 130.34, 138.72, 140.82, 142.15, 143.88, 147.08, 147.33, 171.25.

6-Phenyl-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6i**
Elemental analysis for $C_{18}H_{15}N_3S_2$ (MW=337) in wt % calc C, 64.06; H, 4.48; N, 12.45; S, 19.00. Found: C, 64.09; H, 4.30; N, 12.62; S, 18.98. IR (KBr) in cm^{-1}: 3079 (ArC-H), 2951 (C-H), 1610 (C=N), 1517 (C=C). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8 Hz, 2 H, Ar-H), 7.69-7.83 (m, 5 H, Ar-H), 8.69 (s, imidazole-proton). 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08;

6-(4-Chlorophenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6j**
Elemental analysis for $C_{18}H_{14}ClN_3S_2$ (371) in wt % calc. C= 58.13, H= 3.79, N= 11.30, S= 17.24, Found. C= 58.17, H= 3.72, N= 11.38, S= 17.20. IR (KBr) in cm^{-1}: 3116 (ArC-H), 2953 (C-H), 1599 (C=N), 752 (C-Cl). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8 Hz, 2 H, Ar-H), 7.57 (d, *J* = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.68 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08;

6-(4-Nitrophenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6k**
Elemental analysis for $C_{18}H_{14}N_4O_2S_2$ (MW=382) in wt % calc C, 56.53; H, 3.69; N, 14.65; S, 16.77. Found: C, 56.60; H, 3.66; N, 14.76; S, 16.79. IR (KBr) in cm^{-1}: 3082 (ArC-H), 2954 (C-H), 1629 (C=N), 1519 (C=C), 1512 (NO_2), 1268 (NO_2). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8 Hz, 2 H, Ar-H), 7.57 (d, *J* = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.70 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08;

6-(2-Nitrophenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6l** Elemental analysis for $C_{18}H_{14}N_4O_2S_2$ (MW=382) in wt % calc. C= 56.53, H= 3.69, N= 14.65, S= 16.77. Found. C= 56.56, H= 3.75, N= 14.60, S= 16.71. IR (KBr) in cm^{-1}: 3115 (ArC-H), 2966 (C-H), 1638 (C=N), 1544 (C=C), 1516 (NO_2), 1262 (NO_2). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8 Hz, 2 H, Ar-H), 7.57 (d, *J* = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.70 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08.

6-(4-Fluorophenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6m.**
Elemental analysis for $C_{18}H_{14}FN_3S_2$ (MW=355) in wt % calc. C, 60.82; H, 3.97; N, 11.82; S, 18.04. Found: C, 60.76; H, 4.05; N, 11.88; S, 18.05. IR (KBr) in cm^{-1}: 3081 (ArC-H), 2947 (C-H), 1633 (C=N), 1532 (C=C), 961 (C-F). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, *J* = 8 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8 Hz, 2 H, Ar-H), 7.57 (d, *J* = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.67 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08.

6-(4-Methylphenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6n**
Elemental analysis for $C_{19}H_{17}N_3S_2$ (MW=351) in wt % calc. C= 64.92, H= 4.87, N= 11.95, S= 18.25, found. C= 64.99, H= 4.81, N= 11.99, S= 18.20. IR (KBr) in cm^{-1}: 3102 (ArC-H), 2948 (C-H), 1560 (C=N). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, J = 8 Hz, 2 H, Ar-H), 7.33 (d, J = 8 Hz, 2 H, Ar-H), 7.57 (d, J = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.67 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08.

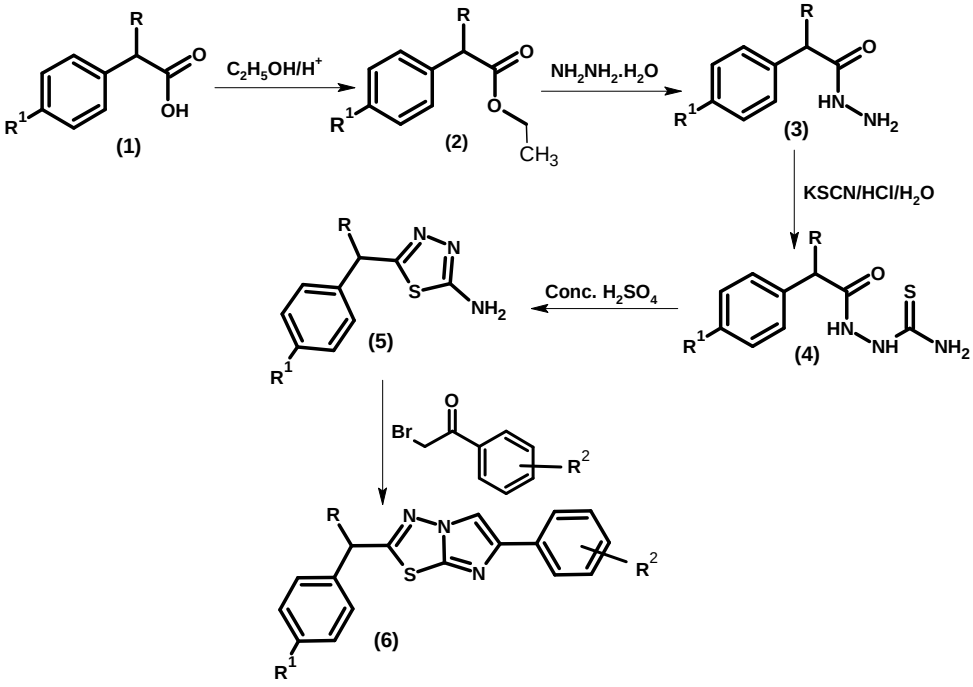
6-(4-Methoxyphenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6o** Elemental analysis for $C_{19}H_{17}N_3OS_2$ (MW=367) in wt % calc. C, 62.10; H, 4.66; N, 11.43; S, 17.45. Found: C, 62.10; H, 4.64; N, 11.44; S, 17.42. IR (KBr) in cm^{-1}: 3091 (ArC-H), 2945 (C-H), 1621 (C=N), 1520 (C=C), 1215 (C-O). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, J = 8 Hz, 2 H, Ar-H), 7.33 (d, J = 8 Hz, 2 H, Ar-H), 7.57 (d, J = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.67 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08.

6-(4-Bromophenyl)-2-(4-methylthiobenzyl)-imidazo-[2,1-*b*][1,3,4]-thiadiazole, **6p** Elemental analysis for $C_{18}H_{14}BrN_3S_2$ (MW=416) in wt % calc. C= 51.92, H= 3.39, N= 10.09, S= 15.40, found. C= 51.86, H= 3.32, N= 10.15, S= 15.47. IR (KBr) in cm^{-1}: 3160 (ArC-H), 2966 (C-H), 1588 (C=N), 1563 (C=C), 568(C-Br). - ^{1}H-NMR ([D_6] DMSO): δ = 2.45 (s, 3 H, SCH_3), 4.39 (s, 2 H, CH_2), 7.25 (d, J = 8 Hz, 2 H, Ar-H), 7.33 (d, J = 8 Hz, 2 H, Ar-H), 7.57 (d, J = 8 Hz, 2 H, Ar-H), 7.78 (d, 2 H, Ar-H), 8.67 (s, imidazole-proton). – ^{13}C-NMR ([D_6] DMSO): δ = 16.13, 32.81, 47.08, 47.36, 66.14, 115.68, 118.02, 127.61, 129.18, 137.24, 138.83, 143.08, 147.94, 163.03, 178.08.

RESULTS AND DISCUSSION

Chemistry

Synthetic strategy of the title compounds is outlined in **Scheme 1.** The acid hydrazides (**3**) were synthesized by the esterification of 2-(4-isobutylphenyl)propanoic acid and 4-methylthiophenyl acetic acid followed by treatment with hydrazine hydrate in absolute alcohol [27, 28]. The resulting acid hydrazides on reaction with potassium thiocyanate in the presence of conc. hydrochloric acid yielded the corresponding thiosemicarbazides (**4**), which on cyclization with conc. H_2SO_4 afforded 2-amino-5-substituted-[1,3,4]thidiazoles (**5**). Condensation of the above aminothidiazols with various substituted phenacyl bromides in acetic acid media yielded imidazothiadiazoles (**6**).



Scheme 1. Synthetic route of the title compounds

The formation of fused imidazo-[2,1-*b*][1,3,4]-thiadiazoles (**6a-p**) was evidenced by their elemental analyses and spectral data. Characterization data of all the newly synthesized compounds are presented in **Table 1**.

Table 1: Characterization data of the compounds, 6a-p

Compound	R	R_1	R_2	Mol. Formula	Mol. Wt.	M.p. (^{0}C)	Yield (%)
6a	CH_3	$CH_2CH(CH_3)_2$	H	$C_{22}H_{23}N_3S$	361	111-113	67
6b	CH_3	$CH_2CH(CH_3)_2$	4-Cl	$C_{22}H_{22}ClN_3S$	395	92-94	78
6c	CH_3	$CH_2CH(CH_3)_2$	4-NO_2	$C_{22}H_{22}N_4O_2S$	406	134-136	69
6d	CH_3	$CH_2CH(CH_3)_2$	2-NO_2	$C_{22}H_{22}N_4O_2S$	406	146-148	82
6e	CH_3	$CH_2CH(CH_3)_2$	4-F	$C_{22}H_{22}FN_3S$	379	98-100	74
6f	CH_3	$CH_2CH(CH_3)_2$	4-CH_3	$C_{23}H_{25}N_3S$	375	81-83	80
6g	CH_3	$CH_2CH(CH_3)_2$	4-OCH_3	$C_{23}H_{25}N_3OS$	391	114-120	65
6h	CH_3	$CH_2CH(CH_3)_2$	4-Br	$C_{22}H_{22}BrN_3S$	439	98-100	82
6i	H	SCH_3	H	$C_{18}H_{15}N_3S_2$	337	131-133	76
6j	H	SCH_3	4-Cl	$C_{18}H_{14}ClN_3S_2$	371	122-124	72
6k	H	SCH_3	4-NO_2	$C_{18}H_{14}N_4O_2S_2$	382	160-162	70
6l	H	SCH_3	2-NO_2	$C_{18}H_{14}N_4O_2S_2$	382	127-129	69
6m	H	SCH_3	4-F	$C_{18}H_{14}FN_3S_2$	355	110-112	84
6n	H	SCH_3	4-CH_3	$C_{19}H_{17}N_3S_2$	351	74-76	79
6o	H	SCH_3	4-OCH_3	$C_{19}H_{17}N_3OS_2$	367	78-80	76
6p	H	SCH_3	4-Br	$C_{18}H_{14}BrN_3S_2$	414	114-116	71

The general IR spectral characters of **5a** and **5b** showed absorption bands ranging from 3,329-3,274 cm^{-1} for NH_2 and 1632-1619 cm^{-1} for C=N moieties. Absence of absorptions bands corresponding to the amide carbonyl group in the region 1760-1705 cm^{-1} and NH-NH_2 in the region 3455-3203 cm^{-1} indicated their formation from the corresponding acid hydrazides. Similarly compounds **6a-p** have showed absorption bands at 1632-1619 cm^{-1} for C=N. The absence of absorption bands of NH_2 group in the region 3,329-3,274 cm^{-1} in the respective IR spectra supported the assigned structures of imidazo-[2,1-*b*][1,3,4]-thiadiazoles.

^{1}H NMR spectrum of 2-amino-5-substituted-[1,3,4]-thiadiazole **5a** showed a down-field D_2O exchangeable broad singlet at δ 5.64 ppm for its NH_2 protons. Two distinct doublets at δ 0.85 (J = 8.0 Hz) and δ 1.68 (J = 8.0 Hz) were also observed for its methyl protons. Isopropyl methyne proton was observed as a multiplet in the region δ 1.80-1.88 and the other methyne proton was observed as a quartet at δ 4.14. Methylene protons were resonated as a doublet at δ 2.45 (J = 4.0 Hz). The aromatic protons appeared as two doublets at δ 6.97 and δ 7.06 with J = 8.0 Hz. Further, LCMS spectrum of **5a** showed the molecular ion peak at m/z = 262, in conformity with its molecular formula, $C_{14}H_{19}N_3S$.

On the other hand, ^{1}H NMR spectrum of **5b** also showed a down-field D_2O exchangeable broad singlet at δ 6.30 corresponding to its NH_2 protons. Two singlets appeared at δ 2.41 and δ 3.83 have been attributed to the SCH_3 and CH_2 protons. The four aromatic protons of 4-metylthiophenyl moiety resonated as two doublets at δ 7.18 and δ 7.20 (J = 8.3 Hz) respectively. Further, LC-MS spectrum of **3b** showed the molecular ion peak at m/z 238, in conformity with its molecular formula, $C_{10}H_{11}N_3S_2$.

In the ^{1}H-NMR spectra of compounds **6a–p**, protons of imidazole CH appeared as a sharp single in the region δ = 7.80 – 8.10 ppm. Also, 2D NMR and ^{13}C-NMR spectra of **6a-p,** the imidazole carbon atom appeared in the region δ = 113.1−114.2 in addition to other characteristic signals of remaining carbon atoms. In the ^{1}H NMR spectra of compounds **6a–p**, protons of imidazole CH appeared as sharp singlets in the region δ 7.80 – 8.10 ppm. Also, 2D NMR and ^{13}C NMR spectra of **6a-p,** the imidazole carbon atom appeared in the region δ 113.1−114.2 in addition to other characteristic signals of remaining carbon atoms.

ANTIMICROBIAL ACTIVITY

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli (*ATTC-*25922)*, *Staphylococcus aureus* (*ATTC-25923*), *Pseudomonas aeruginosa* (*ATTC-27853)* and *Klebsiella pneumonia* (*recultured*) bacterial stains by serial plate dilution method [29, 30]. Serial dilutions of the drug in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37^{o}C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antibacterial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 ^{o}C for an hour. Using a punch, wells were made on these seeds agar plates and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained a 37 ^{o}C for 3-4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard [31, 32]. Zone of inhibition was determined for **6a-p** and results are summarized in **Table 2**. The MIC values were evaluated at concentration range, 1.56-25µg/mL. The figures in the table show the MIC values in µg/mL and the corresponding zone of inhibition in mm.

Table 2: Antibacterial activity of the compounds, 6a-p

Compound	MIC [µg/mL] and zone of inhibition (mm) in parentheses			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
6a	25(<10)	25(<10)	25(<10)	25(<10)
6b	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6c	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6d	25(<10)	25(<10)	25(<10)	25(<10)
6e	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6f	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6g	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6h	25(<10)	25(<10)	25(<10)	25(<10)
6i	25(<10)	25(<10)	25(<10)	25(<10)
6j	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6k	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6l	25(<10)	25(<10)	25(<10)	25(<10)
6m	6.25(16-20)	6.25(16-20)	6.25(16-20)	6.25(16-20)
6n	25(<10)	25(<10)	25(<10)	25(<10)
6o	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6p	25(<10)	25(<10)	25(<10)	25(<10)
Standard (Ciprofloxacin)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

From the antimicrobial activity results, the structure activity relationship can be drawn for test compounds **6a-p**. The variation in antimicrobial activity of the test compounds was explored by varying the substituents at position 2 and 6 of the imidazothiadiazole ring system. Compound (**6b**) containing 2-(4-isobutylphenyl)ethyl moiety at position 2 and 4-chlorophenyl substituent at 6 of the imidazothiadiazole ring exhibited good antibacterial activity against all the bacterial pathogens. When the 4-chlorophenyl group was replaced by 4-fluorophenyl (**6e**), 4-nitrophenyl (**6c**), 4-methylphenyl (**6f**) and 4-methoxyphenyl (**6g**) groups, the activity was found to be decreased, whereas when the 4-chlorophenyl group was replaced by phenyl group (**6a**), 4-bromophenyl (**6h**) and 2-nitrophenyl (**6d**), there was further reduction of activity. Compounds having 4-methylthiobenzyl moiety at position 2 and 4-chlorophenyl (**6j**), 4-fluorophenyl (**6m**) groups at position 6 of the imidazothiadiazole ring showed good antibacterial activity compared to that of the standard used for testing. However, the replacement of above groups with 4-nitrophenyl (**6k**) and 4-methoxyphenyl (**6o**) groups decreased the activity. Whereas, when the 4-chlorophenyl group was replaced by phenyl (**6i**), 4-bromophenyl (**6p**), 2-nitrophenyl (**6l**) and 4-methylphenyl (**6n**) groups, there was further decrease in antibacterial activity.

Antifungal activity

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus (NCIM No. 524), Aspergilus fumigatus (NCIM No. 902), Penicillium maneffei (recultured)* and *Trichophyton mentagrophytes (recultured)* in DMSO by serial plate dilution method [33, 34]. Sabourauds agar media was prepared by dissolving peptone (1g). D glucose (4g) and agar (2g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of sore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plated were dried by placing in an incubator at 37 ^{0}C for 1h. Using a punch wells were made on these seeded agar plates. Minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 ^{0}C for 3-4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with cyclopiroxolamine as standard. Zones of inhibition were determined for **6a-p**. The results are summarized in

Table 3. The MIC values were evaluated at concentration range, 1.56-25µg/mL. The data in the **Table 3** show the MIC values in µg/mL and the corresponding zone of inhibition in mm.

Table 3: Antifungal activity of the compounds, 6a-p

Compound	MIC [µg/mL] and zone of inhibition (mm) in parentheses			
	P. marneffei	*T. mentagrophytes*	*A. flavus*	*A. fumigatus*
6a	25(<10)	25(<10)	25(<10)	25(<10)
6b	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6c	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6d	25(<10)	25(<10)	25(<10)	25(<10)
6e	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
6f	25(<10)	25(<10)	25(<10)	25(<10)
6g	25(<10)	25(<10)	25(<10)	25(<10)
6h	25(<10)	25(<10)	25(<10)	25(<10)
6i	25(<10)	25(<10)	25(<10)	25(<10)
6j	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6k	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6l	25(<10)	25(<10)	25(<10)	25(<10)
6m	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
6n	25(<10)	25(<10)	25(<10)	25(<10)
6o	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
6p	25(<10)	25(<10)	25(<10)	25(<10)
Standard (Ciclopiroxolamine)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

The investigation of antifungal screening data revealed that compounds having the 2-(4-isobutylphenyl)ethyl moiety at position 2 and 4-fluorophenyl (**6e)** moiety at position 6 of the imidazothiadiazole ring exhibited good antifungal activity against all the fungal strains. However**,** the replacement of the above substituents at position 6 by 4-chlorophenyl (**6b**) and 4-nitrophenyl (**6c**) groups reduced their antifungal potency. Further reduction of antifungal activity was observed when phenyl (**6a**), 4-bromophenyl (**6h**), 2-nitrophenyl (**6d**), 4-methylphenyl (**6f**) and 4-methoxyphenyl (**6g**) moieties were substituted at position 6 of the imidazothiadiazole ring Compounds having .4-methylthiobenzyl group at position 2 and 4-fluorophenyl (**6m**) moiety at position 6 were found to possess comparable antifungal activity. The remaining molecules containing 4-chlorophenyl (**6j**), 4-nitrophenyl (**6k**) and 4-methoxyphenyl (**6o**) groups showed lesser degree of activity. Furthermore**,** compounds containing phenyl (**6i**), 2-nitrophenyl (**6l**), 4-bromophenyl (**6p**) and 4-methylphenyl (**6n**) moieties exhibited only marginal antifungal activity.

CONCLUSION

We synthesized a new series of imidazo-[2,1-*b*]-[1,3,4]-thiadiazoles in good yield and evaluated their antibacterial as well as antifungal activity. The screening data revealed that the synthesized compounds exhibited moderate to good activity. The compounds **6b, 6j** and **6m** showed very good bacterial growth inhibition. The good bacterial growth inhibition can be attributed to the presence of 4-chlorophenyl and 4-fluorophenyl substituents at position 6 of the imidazothiadiazole system. On the other hand, compounds **6e** and **6m** containing 2-(4-isobutylphenyl)ethyl/4-methylthiophenyl and 4-fluorophenyl substituents at 2 position and 6 position of imidazothiadiazole system respectively were found to possess good antifungal activity. The observed activity may be attributed to the increased lipophilicity of these molecules due to the presence of fluorine.

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