

Month 2019 Synthesis and Characterization of Novel 1-Methyl-3-(4-phenyl-4*H*-1,2,4triazol-3-yl)-1*H*-indazole Derivatives

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A series of novel 1-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles was synthesized in three steps from 5-(1-methyl-1*H*-indazol-3-yl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thiones. 5-(1-Methyl-1*H*-indazol-3-yl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thiones were converted into 1-methyl-3-(5-(methylsulfo-nyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles upon methylation followed by treatment with aq. KMnO₄. The reaction of 1-methyl-3-(5-(methylsulfonyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles with Raney nickel resulted in desulphonylation to afford corresponding 1-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazol-3-yl)-1*H*-indazoles. All the new synthesized compounds were characterized by spectral techniques.

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INTRODUCTION

Heterocyclic compounds played significant role in the pharmaceutical, agricultural, biological field, and drug development. Most of the five-membered and sixmembered heterocyclic compounds containing one, two, or three heteroatoms are actively involved in the metabolism of living organisms. Among these sulfurcontaining and nitrogen-containing heterocycles have maintained interest in them and have attracted the researchers over the last decades.

Indazole is nitrogen-containing heterocyclic compound present in several pharmaceutical drugs, such as Granisetron, Lonidamine, and Benzadac. Indazole derivatives show wide spectrum of biological activities, such as anti-inflammatory [1], antimicrobial [2,3], antiproliferative [2], anti-angiogenic [4], and anticonvulsant [5]. Moreover, indazole-containing compounds showed their potential as selective 5-HT4 receptor antagonists [6] and inhibitors of glycogen synthase kinase 3ß [7]. 1.2.4-Triazole derivatives show broad spectrum of pharmacological activities including antibacterial [8-11]. antifungal [12,13], anticonvulsant [14], anti-inflammatory [15], antitumor [16], anticancer [17], and antiviral [17].

In present work, we have synthesized a series of novel 1-methyl-3-(4-phenyl-4H-1,2,4-triazol-3-yl)-1H-indazoles **7a–f** in three steps from 5-(1-methyl-1H-indazol-3-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thiones **4a–f**. 5-(1-Meth-yl-1H-indazol-3-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thiones **4a–f** were converted into 1-methyl-3-(5-(meth-ylsulfonyl)-4-phenyl-4H-1,2,4-triazol-3-yl)-1H-indazoles

6a-f upon methylation followed by treatment with aq. KMnO₄. The reaction of 1-methyl-3-(5-(methy-lsulfonyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles **6a-f** with Raney nickel resulted in desulphonylation to afford corresponding 1-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles **7a-f**.

RESULT AND DISCUSSION

Preparation of 2-(1-methyl-1*H*-indazole-3-carbonyl)-*N*phenylhydrazine-1-carbothioamides **3a–f** was carried out by the reaction of 1-methyl-1*H*-indazole-3-carbohydrazide **1** with substituted phenyl isothiocyanates **2a–f** in isopropyl alcohol [11]. The IR spectrum of compound **3a** showed characteristics bands at 3246, 3197, and 3169 cm⁻¹ (N–H), 1673 cm⁻¹ (C=O), and 1202 cm⁻¹ (C=S). The ¹H NMR spectrum of **3a** showed signals of three N–H protons as singlets at δ 9.48, 9.65, and 10.42 ppm. The ¹³C NMR spectrum of compound **3a** showed carbonyl and thiocarbonyl group signals at δ 181.77 and 161.58 ppm, respectively. The mass spectrum of compound **3a** showed the molecular ion peak at m/z340 (M + H)⁺ (Scheme 1 and Experimental part).

5-(1-Methyl-1*H*-indazol-3-yl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thiones **4a**–**f** were synthesized from the reaction of 2-(1-methyl-1*H*-indazole-3-carbonyl)-*N*-phenylhydrazine-1-carbothioamides **3a**–**f** with 10% aq. NaOH.¹¹ The IR spectrum of compound **4a** showed no signal because of N–H, C=O, and C=S. The ¹H NMR spectrum of **4a** showed proton of S–H as singlet at δ 14.22. The mass



spectrum of compound **4a** showed the molecular ion peak at m/z 322 (M + H)⁺ (Scheme 1 and Experimental part).

The synthesis of 1-methyl-3-(5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles **5a–f** was achieved by treating 5-(1-methyl-1*H*-indazol-3-yl)-4-phenyl-2*H*-1,2,4triazole-3(4*H*)-thiones **4a–f** with methyl iodide and aq. NaOH. The ¹H NMR spectrum of compound **5a** showed three singlet at δ 1.95 (Ar–<u>CH₃</u>), 2.66 (S–<u>CH₃</u>), and 3.79 (N–<u>CH₃</u>) ppm. The ¹³C NMR also showed three signals at δ 14.09 (Ar–<u>CH₃</u>), 17.03 (S–<u>CH₃</u>), and 35.80 (N–<u>CH₃</u>) ppm. The mass spectrum of compound **5a** showed the molecular ion peak at *m/z* 336 (M + H)⁺ (Scheme 1 and Experimental part).

1-Methyl-3-(5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles **5a**–**f** on treatment with aq. KMnO₄ were oxidized to give corresponding 1-methyl-3-(5-(methylsulfonyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*indazoles **6a**–**f**. The IR spectrum of **6a** showed an absorption peak at 1330 and 1151 cm⁻¹ corresponding to SO₂ group. The ¹H NMR spectrum of compound **6a** showed three singlet signal at δ 1.98 (Ar–<u>CH₃</u>), 3.50 (SO₂–<u>CH₃</u>), and 3.81 (N–<u>CH₃</u>). ¹³C NMR also showed three signals at δ 17.14 (Ar–<u>CH₃</u>), 36.08 (SO₂–<u>CH₃</u>), and 43.37 (N–<u>CH₃</u>). The mass spectrum of compound **6a** showed the molecular ion peak at *m*/*z* 368 (M + H)⁺ (Scheme 1 and Experimental part).

Compounds 6a-f on refluxing with Raney Ni in tetrahydrofuran desulphonylation reaction to give corresponding 1-methyl-3-(4-phenyl-4H-1,2,4-triazol-3yl)-1H-indazole derivatives 7a-f. In the IR spectrum of 7a bands at 1330 and 1151 cm⁻¹ corresponding to SO₂ group are absent. The ¹H NMR spectrum of compound 7a showed three singlet signals at δ 1.95 (Ar–CH₃), 3.82 (N–CH₃), and δ 8.81 (triazolyl proton). The ¹³C NMR spectrum showed two signals at δ 17.16 (Ar–CH₃) and 35.78 (N– CH_3). The mass spectrum of compound 7a showed the molecular ion peak at m/z 290 (M + H)⁺ (Scheme 1 and Experimental part).

Structures of all the synthesized novel compounds were confirmed by using IR, ¹H NMR, ¹³C NMR, and LC–MS spectroscopic techniques.

EXPERIMENTAL

All organic solvents were acquired from commercial sources and used as received. The melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on Varian 400 spectrophotometer using

tetramethylsilane as an internal standard and DMSO- d_6 as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Shimadzu (LC–MS) mass spectrometer.

General procedure for the synthesis of 2-(1-methyl-1*H*-indazole-3-carbonyl)-*N*-phenylhydrazine-1-carbothioamides (3a-f). A mixture of compound 1 (0.95 g, 5 mmol) and aryl isothiocyanate 2a-f (5 mmol) in isopropyl alcohol (15 mL) was heated under reflux for 2 h. The progress of reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, a solid product was formed. The formed product was filtered and washed with methanol to afford the pure compound 3a-f.

2-(1-Methyl-1H-indazole-3-carbonyl)-N-(2-methylphenyl) hydrazine-1-carbothioamide (3a). Yield: 1.20 g (71%); White solid; mp: 175–177°C; IR (v_{max}/cm^{-1}): 3246 (N–H), 3197 (N–H), 3169 (N–H), 1673 (C=O), 1202 (C=S); ¹H NMR (400 MHz, DMSO- d_6): δ = 10.42 (s, 1H, –NH); 9.65 (s, 1H, –NH), 9.48 (s, 1H, –NH), 8.18 (d, J = 7.6 Hz, 1H, Ar–H), 7.76 (d, J = 8.4 Hz, 1H, Ar–H), 7.48 (t, J = 7.6 Hz, 1H, Ar–H), 7.31 (t, J = 7.2 Hz, 1H, Ar–H), 7.15–7.19 (m, 4H, Ar–H), 4.15 (s, 3H, N–CH₃), 2.21 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): δ = 181.77, 161.58, 140.63, 138.14, 135.75, 135.55, 129.98, 128.79, 126.62, 126.46, 125.67, 122.61, 122.53, 121.55, 110.41, 36.03, 18.57; MS (LC–MS): m/z 340 (M + H)⁺.

2-(1-Methyl-1H-indazole-3-carbonyl)-N-(3-methylphenyl) hydrazine-1-carbothioamide (3b). Yield: 1.25 g (74%); White solid; mp: 170–172°C; IR (v_{max}/cm^{-1}): 3323 (N–H), 3195 (N–H), 3168 (N–H), 1674 (C=O), 1193 (C=S); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 10.35$ (s, 1H, N–H), 9.70 (s, 2H, N–H), 8.17 (d, J = 8.4 Hz, 1H, Ar–H), 7.77 (d, J = 8.8 Hz, 1H, Ar–H), 7.49 (t, J = 7.2 Hz, 1H, Ar–H), 7.28–7.33 (m, 3H, Ar–H), 7.19 (t, J = 7.6 Hz, 1H, Ar–H), 6.95 (d, J = 7.2 Hz, 2H, Ar–H), 4.16 (s, 3H, N–CH₃), 2.27 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 181.09$, 161.53, 140.66, 139.19, 137.10, 135.44, 127.76, 126.66, 125.46, 122.61, 121.55, 110.45, 36.06, 20.98; MS (LC–MS): m/z 340 (M + H)⁺.

2-(1-Methyl-1H-indazole-3-carbonyl)-N-(4-methylphenyl)

hydrazine-1-carbothioamide (3c). Yield: 1.30 g (77%); White solid; mp: 196–198°C; IR (v_{max}/cm^{-1}): 3241 (N–H), 3195 (N–H), 3159 (N–H), 1661 (C=O), 1201 (C=S); ¹H NMR (400 MHz, DMSO-*d₆*): δ = 10.34 (s, 1H, N–H), 9.67 (s, 2H, N–H), 8.17 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.77 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.49 (t, *J* = 6.9 Hz, 1H, Ar–H), 7.29–7.35 (m, 3H, Ar–H), 7.11 (d, *J* = 8 Hz, 2H, Ar–H), 4.16 (s, 3H, N–CH₃), 2.27 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO-*d₆*): δ = 181.20, 161.60, 140.65, 136.73, 135.45, 133.95, 128.42, 126.66, 125.51, 122.60, 121.51, 110.43, 36.06, 20.56; MS (LC–MS): *m/z* 340 (M + H)⁺. *N*-(2-methoxyphenyl)-2-(1-methyl-1H-indazole-3-carbonyl) hydrazine-1-carbothioamide (3d). Yield: 1.29 g (73%); White solid; mp: 220–222°C; IR (v_{max}/cm^{-1}): 3251 (N–H), 3196 (N–H), 3167 (N–H), 1660 (C=O), 1201 (C=S); ¹H NMR (400 MHz, DMSO-d₆): δ = 9.00–11.00 (b.s., 3H, N–H), 8.17 (m, 2H, Ar–H), 7.78 (d, J = 8.8 Hz, 1H, Ar–H), 7.50 (t, J = 7.6 Hz, 1H, Ar–H), 7.32 (t, J = 7.2 Hz, 1H, Ar–H), 6.90–7.14 (m, 3H, Ar–H), 4.16 (s, 3H, N–CH₃), 3.67 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 168.66, 155.15, 145.88, 139.91, 130.79, 130.11, 129.85, 126.89, 123.95, 122.31, 121.50, 120.97, 120.34, 112.44, 110.30, 55.73, 35.88; MS (LC–MS): m/z 356 (M + H)⁺.

N-(3-methoxyphenyl)-2-(1-methyl-1H-indazole-3-carbonyl) Yield: 1.36 g (77%); hydrazine-1-carbothioamide (3e). White solid; mp: 182–184°C; IR (v_{max}/cm^{-1}) : 3284 (N-H), 3191 (N-H), 3159 (N-H), 1674 (C=O), 1204 (C=S); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 10.35$ (s, 1H, N-H), 9.74 (s, 2H, N-H), 8.17 (d, J = 7.6 Hz, 1H, Ar-H), 7.77 (d, J = 8.8 Hz, 1H, Ar-H), 7.49 (t, J = 7.2 Hz, 1H, Ar-H), 7.31 (t, J = 7.6 Hz, 1H, Ar-H), 7.19–7.22 (m, 2H, Ar–H), 7.09 (d, J = 8 Hz, 1H, Ar-H), 6.70 (dd, J = 8 and 2 Hz, 1H, Ar-H), 4.16 (s, 3H, N-CH₃), 3.73 (s, 3H, O-CH₃); 13 C NMR (100 MHz, DMSO- d_6): $\delta = 180.96$, 158.90, 140.67, 140.43, 135.40, 128.63, 126.68, 122.63, 121.49, 117.38, 110.46, 110.23, 55.08, 36.07; MS (LC-MS): m/z 356 $(M + H)^{+}$.

N-(4-methoxyphenyl)-2-(1-methyl-1H-indazole-3-carbonyl) hydrazine-1-carbothioamide (3f). Yield: 1.26 g (71%); White solid; mp: 184–186°C; IR (v_{max}/cm^{-1}): 3282 (N–H), 3193 (N–H), 3167 (N–H), 1668 (C=O), 1200 (C=S); ¹H NMR (400 MHz, DMSO-d₆): δ = 10.33 (s, 1H, N–H), 9.63 (s, 2H, N–H), 8.17 (d, J = 8.4 Hz, 1H, Ar–H), 7.76 (d, J = 8.4 Hz, 1H, Ar–H), 7.49 (t, J = 7.2 Hz, 1H, Ar–H), 7.29–7.33 (m, 3H, Ar–H), 6.86–6.90 (m, 2H, Ar–H), 4.15 (s, 3H, N–CH₃), 3.73 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 181.43, 161.61, 156.54, 140.65, 135.47, 132.25, 132.17, 127.15, 126.66, 126.15, 122.61, 121.15, 113.66, 113.17, 110.42, 55.21, 36.06; MS (LC–MS): m/z 356 (M + H)⁺.

General procedure for the synthesis of 5-(1-methyl-1*H*-indazol-3-yl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thiones (4a–f). A solution of 10% aq. NaOH (20 mL) and 2-(1methyl-1*H*-indazole-3-carbonyl)-*N*-phenylhydrazine-1-carbothioamides 3a-f (3 mmol) was heated for 1 h at 80°C. The progress of reaction was monitored by TLC. After completion of reaction, contents were cooled to room temperature and poured onto ice-cold water and then acidified with conc. HCl. The product formed was filtered and washed with cold methanol to afford 4a-f.

5-(1-Methyl-1H-indazol-3-yl)-4-o-tolyl-2H-1,2,4-triazole-3(4H)-thione (4a). Yield: 0.60 g (69%); White solid; mp: decompose above 320°C; IR (v_{max}/cm^{-1}): 3069 (C–H), 1590 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆): δ = 14.22 (s, 1H, S-H), 7.98 (d, J = 8.4 Hz, 1H, Ar-H), 7.66 (d, J = 8.4 Hz, 1H, Ar-H), 7.46 (t, J = 8 Hz, 1H, Ar-H), 7.22–7.28 (m, 5H, Ar-H), 3.85 (s, 3H, N-CH₃), 2.37 (s, 3H, Ar-CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 168.04, 145.33, 139.96, 136.07, 134.48, 130.36, 129.62, 129.39, 128.91, 126.94, 126.56, 122.35, 121.55, 120.90, 110.29, 35.91, 17.35;MS (LC-MS): *m/z* 322 (M + H)⁺.

5-(1-Methyl-1H-indazol-3-yl)-4-m-tolyl-2H-1,2,4-triazole-3(4H)-thione (4b). Yield: 0.69 g (72%); White solid; mp: decompose above 300°C; IR (v_{max}/cm^{-1}): 3069 (C–H), 1588 (C=N); ¹H NMR (400 MHz, DMSO- d_6): δ = 14.23 (s, 1H, S–H), 8.01 (d, J = 8.4 Hz, 1H, Ar–H), 7.67 (d, J = 8.8 Hz, 1H, Ar–H), 7.47 (t, J = 8 Hz, 1H, Ar–H), 7.36 (t, J = 8 Hz, 1H, Ar–H), 7.47 (t, J = 8 Hz, 1H, Ar–H), 7.36 (t, J = 8 Hz, 1H, Ar–H), 7.15 (d, J = 8 Hz, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.15 (d, J = 8 Hz, 1H, Ar–H), 3.84(s, 3H, N–CH₃), 2.33 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): δ = 168.57, 145.38, 139.93, 138.08, 134.97, 129.69, 129.09, 128.50, 126.89, 126.83, 125.83, 122.25, 121.80, 120.96, 110.23, 35.91, 20.74; MS (LC–MS): m/z 322 (M + H)⁺.

5-(1-Methyl-1H-indazol-3-yl)-4-p-tolyl-2H-1,2,4-triazole-3(4H)-thione (4c). Yield: 0.73 g (76%); White solid; mp: decompose above 300°C; IR (v_{max}/cm^{-1}): 3069 (C—H), 1590 (C=N); ¹H NMR (400 MHz, DMSO- d_6): δ = 14.22 (s, 1H, S—H), 7.98 (d, J = 8.4 Hz, 1H, Ar—H), 7.66 (d, J = 8.4 Hz, 1H, Ar—H), 7.46 (t, J = 8 Hz, 1H, Ar—H), 7.22–7.28 (m, 5H, Ar—H), 3.85 (s, 3H, N—CH₃), 2.37 (s, 3H, Ar—CH₃); ¹³C NMR (100 MHz, DMSO- d_6): δ = 168.76, 145.45, 139.90, 138.44, 132.52, 129.77, 129.22, 128.44, 126.83, 122.18, 121.84, 120.94, 110.11, 35.90, 20.81; MS (LC–MS): m/z 322 (M + H)⁺.

4-(2-Methoxyphenyl)-5-(1-methyl-1H-indazol-3-yl)-2H-

1,2,4-triazole-3(4H)-thione (4d). Yield: 0.70 g (70%); White solid; mp: decompose above 300°C; IR ($v_{max}/$ cm⁻¹): 3065 (C–H), 1585 (C=N); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 14.17$ (s, 1H, S–H), 8.06 (d, J = 8.4 Hz, 1H, Ar–H), 7.66 (d, J = 8.4 Hz, 1H, Ar–H), 7.45–7.51 (m, 2H, Ar–H), 7.34 (dd, J = 7.6 and 1.6 Hz, 1H, Ar–H), 7.28 (t, J = 8 Hz, 1H, Ar–H), 7.16 (d, J = 8.4 Hz, 1H, Ar–H), 7.07 (t, J = 7.2 Hz, 1H, Ar–H), 3.80 (s, 3H, N–CH₃), 3.56 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 151.07$, 140.71, 135.05, 127.79, 126.75, 125.44, 124.28, 122.76, 122.50, 121.33, 119.79, 111.28, 110.59, 55.76, 36.12; MS (LC–MS): m/z 338 (M + H)⁺.

4-(3-Methoxyphenyl)-5-(1-methyl-1H-indazol-3-yl)-2H-

1,2,4-triazole-3(4H)-thione (4e). Yield: 0.75 g (75%); White solid; mp: 186–188°C; IR (v_{max}/cm^{-1}): 3069 (C–H), 1605 (C=N); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 14.23$ (s, 1H, S–H), 8.01 (d, J = 8.4 Hz, 1H, Ar–H), 7.67 (d, J = 8.4 Hz, 1H, Ar–H), 7.47 (t, J = 7.6 Hz, 1H, Ar–H), 7.38 (t, J = 8 Hz, 1H, Ar–H), 7.27 (t, J = 7.6 Hz, 1H, Ar–H), 7.01–7.07 (m, 2H, Ar—H), 6.92 (d, J = 8 Hz, 1H, Ar—H), 3.86 (s, 3H, N—CH₃), 3.74 (s, 3H, O—CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 168.51$, 159.34, 145.38, 139.96, 136.06, 129.70, 129.47, 126.90, 122.26, 121.86, 120.97, 114.85, 114.64, 110.26, 55.41, 35.95; MS (LC–MS): m/z 338 (M + H)⁺.

4-(4-Methoxyphenyl)-5-(1-methyl-1H-indazol-3-yl)-2H-1,2,4-triazole-3(4H)-thione (4f). Yield: 0.74 g (74%); White solid; mp: 220–222°C; IR (v_{max}/cm^{-1}): 3112 (C-H), 1585 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 14.20 (s, 1H, S-H), 7.99 (d, J = 8.4 Hz, 1H, Ar-H), 7.67 (d, J = 8.4 Hz, 1H, Ar-H), 7.47 (t, J = 7.6 Hz, 1H, Ar-H), 7.25–7.34 (m, 3H, Ar-H), 7.01 (d, J = 8.8 Hz, 1H, Ar-H), 6.85 (d, J = 8.8 Hz, 1H, Ar-H), 3.87 (s, 3H, N-CH₃), 3.81 (s, 3H, O-CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 168.85, 159.42, 145.64, 139.95, 129.92, 129.81, 127.71, 126.89, 122.24, 121.83, 120.97, 119.89, 113.94, 113.88, 110.22, 55.35, 35.94; MS (LC-MS): m/z 338 (M + H)⁺.

General procedure for the synthesis 1-methyl-3-(5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles

(5a-f). Methyl iodide (0.213 g, 1.5 mmol) was added dropwise to a clear solution of 10% aq. NaOH (20 mL) and 5-(1-methyl-1H-indazol-3-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thione **4a-f** (1.5 mmol). The reaction mixture was stirred and heated for 1 h at 50°C. The progress of reaction was monitored by TLC. Upon completion of reaction, the solid product was formed. The formed product was filtered and washed with water followed by methanol to afford the pure **5a-f**.

1-Methyl-3-(5-(methylthio)-4-o-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (5a). Yield: 0.37 g (74%); White solid; mp: 150–152°C; IR (v_{max} /cm⁻¹): 3073 (C–H), 1606 (C=N); ¹H NMR (400 MHz, DMSO- d_6): δ = 8.25 (d, J = 8.4 Hz, 1H, Ar–H), 7.64 (d, J = 8.8 Hz, 1H, Ar–H), 7.42–7.49 (m, 3H, Ar–H), 7.28–7.38 (m, 3H, Ar–H), 3.79 (s, 3H, N–CH₃), 2.66 (s, 3H, S–CH₃), 1.95 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): δ = 152.45, 149.26, 140.03, 135.59, 133.44, 131.01, 130.81, 130.02, 128.11, 127.03, 126.83, 121.99, 121.75, 121.60, 110.09, 35.80, 17.03, 14.09; MS (LC–MS): m/z 336 (M + H)⁺.

1-Methyl-3-(5-(methylthio)-4-m-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (5b). Yield: 0.37 g (75%); White solid; mp: 120–122°C; IR (v_{max} /cm⁻¹): 3070 (C–H), 1604 (C=N); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 8.13$ (d, J = 8 Hz, 1H, Ar–H), 7.62 (d, J = 8.8 Hz, 1H, Ar–H), 7.31–7.45 (m, 3H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.18 (d, J = 8 Hz, 1H, Ar–H), 3.81(s, 3H, N–CH₃), 2.61 (s, 3H, S–CH₃), 2.31 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 152.73$, 149.26, 139.99, 138.81, 134.06, 131.00, 130.24, 128.98, 127.95, 126.74, 124.77, 122.01, 121.87, 121.59, 110.00, 35.73, 20.65, 14.28; MS (LC–MS): m/z 336 (M + H)⁺.

1-Methyl-3-(5-(methylthio)-4-p-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (5c). Yield: 0.38 g (77%); White solid; mp: Month 2019

156–158°C; IR (v_{max}/cm^{-1}): 3076 (C–H), 1609 (C=N); ¹H NMR (400 MHz, DMSO-*d₆*): δ = 8.11 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.62 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.43 (t, *J* = 8 Hz, 1H, Ar–H), 7.21–7.30 (m, 5H, Ar–H), 3.82 (s, 3H, N–CH₃), 2.60 (s, 3H, S–CH₃), 2.35 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO-*d₆*): δ = 152.88, 149.34, 139.97, 136.16, 131.55, 131.04, 129.70, 127.36, 122.03, 126.70, 121.82, 121.55, 109.94, 35.72, 20.73, 14.29; MS (LC–MS): *m/z* 336 (M + H)⁺.

3-(4-(2-Methoxyphenyl)-5-(methylthio)-4H-1,2,4-triazol-3yl)-1-methyl-1H-indazole (5d). Yield: 0.38 g (74%); White solid; mp: 180–182°C; IR (v_{max}/cm^{-1}): 3069 (C–H), 1600 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.19 (d, J = 7.6 Hz, 1H, Ar–H), 7.61 (d, J = 8 Hz, 1H, Ar–H), 7.48–7.53 (m, 1H, Ar–H), 7.41–7.45 (m, 1H, Ar–H), 7.34 (dd, J = 8 and 1.6 Hz, 1H, Ar–H), 7.25 (t, J = 8 Hz, 1H, Ar–H), 7.19 (d, J = 8 Hz, 1H, Ar–H), 7.04 (t, J = 7.6 Hz, 1H, Ar–H), 3.78 (s, 3H, N–CH₃), 3.59 (s, 3H, O–CH₃), 2.59 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 154.72, 152.64, 149.59, 139.84, 131.23, 131.08, 128.85, 126.57, 122.80, 121.72, 121.67, 121.50, 120.44, 112.55, 109.86, 55.67, 35.57, 14.18; MS (LC–MS): m/z 352 (M + H)⁺.

3-(4-(3-Methoxyphenyl)-5-(methylthio)-4H-1,2,4-triazol-3yl)-1-methyl-1H-indazole (5e). Yield: 0.38 g (73%); White solid; 73%; mp: 136–138°C; IR (v_{max}/cm^{-1}): 3067 (C–H), 1601 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.13 (d, J = 8.4 Hz, 1H, Ar–H), 7.63 (d, J = 8.8 Hz, 1H, Ar–H), 7.37–7.45 (m, 2H, Ar–H), 7.24 (t, J = 7.6 Hz, 1H, Ar–H), 7.03–7.09 (m, 2H, Ar–H), 6.94 (d, J = 7.6 Hz, 1H, Ar–H), 3.83 (s, 3H, N–CH₃), 3.72 (s, 3H, O–CH₃), 2.62 (s, 3H, S–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 159.61, 152.70, 149.26, 140.00, 135.18, 131.01, 130.00, 126.72, 122.04, 121.86, 121.58, 119.79, 115.28, 113.58, 109.99, 55.47, 35.74, 14.35; MS (LC–MS): m/z352 (M + H)⁺.

3-3-(4-(4-Methoxyphenyl)-5-(methylthio)-4H-1,2,4-triazol-3yl)-1-methyl-1H-indazole (5f). Yield: 0.36 g (70%); White solid; mp: 204–206°C; IR (v_{max}/cm^{-1}): 3068 (C–H), 1600 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.12 (d, J = 8.4 Hz, 1H, Ar–H), 7.62 (d, J = 8.8 Hz, 1H, Ar–H), 7.43 (t, J = 8 Hz, 1H, Ar–H), 7.28–7.34 (m, 2H, Ar–H), 7.23 (t, J = 8 Hz, 1H, Ar–H), 7.00–7.03 (m, 2H, Ar–H), 3.84 (s, 3H, N–CH₃), 3.79 (s, 3H, O–CH₃), 2.61 (s, 3H, S–CH₃); ¹³C NMR (100 MHz, DMSO-d₆):

$$\begin{split} \delta &= 159.80, \ 153.18, \ 149.58, \ 139.98, \ 131.13, \ 128.98, \\ 126.70, \ 122.05, \ 121.83, \ 121.62, \ 119.92, \ 114.30, \ 113.91, \\ 109.93, \ 55.36, \ 35.72, \ 14.25; \ \text{MS} \ (\text{LC-MS}): \ m/z \ 352 \\ (\text{M} + \text{H})^+. \end{split}$$

General procedure for the synthesis 1-methyl-3-(5-(methylsulfonyl)-4-phenyl-4H-1,2,4-triazol-3-yl)-1H-indazoles (6a-f). A mixture of acetic acid (20 mL), water (10 mL), 1-methyl-3-(5-(methylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-1H-indazole **5a**-f (0.318 g, 0.95 mmol) or **5d**-f (0.333 g, 0.95 mmol), and aq. KMnO₄ (0.150 g,

0.95 mmol) was stirred and heated for 1 h at 50°C. The progress of reaction was monitored by TLC. Upon completion of reaction, contents were cooled to room temperature and poured onto ice-cold water. Thereafter, 3% H₂O₂ was added till color of the reaction mixture disappears. The resulting solid product was filtered and washed with water and methanol to afford pure **6a–c** and **6d–f**, respectively.

*1-Methyl-3-(*5-(*methylsulfonyl*)-4-o-tolyl-4H-1,2,4-triazol-3yl)-1H-indazole (6a). Yield: 0.233 g (67%); White solid; mp: 124–126°C; IR (v_{max}/cm^{-1}): 3029 (C–H), 1557 (C=N), 1330 and 1151 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.28 (d, J = 8.4 Hz, 1H, Ar–H), 7.70 (d, J = 8.8 Hz, 1H, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.41 (d, J = 7.6 Hz, 1H, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.41 (d, J = 7.6 Hz, 1H, Ar–H), 7.33–7.37 (m, 2H, Ar–H), 3.81 (s, 3H, N–CH₃), 3.50 (s, 3H, SO₂–CH₃), 1.98 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 152.57, 150.83, 140.02, 135.98, 132.84, 130.49, 130.41, 129.58, 128.16, 127.08, 126.59, 122.66, 122.34, 121.30, 110.45, 43.37, 36.08, 17.14; MS (LC–MS): *m/z* 368 (M + H)⁺.

1-Methyl-3-(5-(methylsulfonyl)-4-m-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (6b). Yield: 0.243 g (70%); White solid; mp: 170–172°C; IR (v_{max}/cm^{-1}): 3024 (C–H), 1597 (C=N), 1328 and 1147 (SO₂); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 8.22$ (d, J = 8.4 Hz, 1H, Ar–H), 7.69 (d, J = 8.8 Hz, 1H, Ar–H), 7.49 (d, J = 8.4 Hz, 1H, Ar–H), 7.31–7.42 (m, 5H, Ar–H), 3.85 (s, 3H, N–CH₃), 3.46 (s, 3H, SO₂–CH₃), 2.34 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 152.90$, 151.04, 139.93, 138.30, 133.33, 130.74, 129.69, 128.57, 128.48, 126.94, 125.34, 122.51, 122.45, 121.34, 110.29, 43.66, 35.98, 20.70; MS (LC–MS): m/z 368 (M + H)⁺.

1-Methyl-3-(5-(methylsulfonyl)-4-p-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (6c). Yield: 0.247 g (71%); White solid; mp: 222–224°C; IR (v_{max}/cm^{-1}): 3018 (C–H), 1601 (C=N), 1331 and 1142 (SO₂); ¹H NMR (400 MHz, DMSO-*d*₆): $\delta = 8.19$ (d, J = 8.4 Hz, 1H, Ar–H), 7.69 (d, J = 8.4 Hz, 1H, Ar–H), 7.43–7.51 (m, 3H, Ar–H), 7.30–7.32 (m, 3H, Ar–H), 3.86 (s, 3H, N–CH₃); 3.44 (s, 3H, SO₂–CH₃), 2.40 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): $\delta = 152.94$, 151.06, 139.87, 139.64, 130.74, 129.63, 129.20, 127.85, 126.88, 122.37, 121.21, 110.24, 43.52, 35.94, 20.75; MS (LC–MS): *m/z* 368 (M + H)⁺.

3-(4-(2-Methoxyphenyl)-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1H-indazole (6d). Yield: 0.250 g (69%); White solid; mp: 196–198°C; IR (ν_{max}/cm^{-1}): 3012 (C–H), 1605 (C=N), 1321 and 1146 (SO₂); ¹H NMR (400 MHz, DMSO-d6): δ = 8.25 (d, J = 8.4 Hz, 1H, Ar–H), 7.69 (d, J = 8.8 Hz, 1H, Ar–H), 7.48–7.57 (m, 3H, Ar–H), 7.34 (t, J = 8 Hz, 1H, Ar–H), 7.22 (d, J = 8 Hz, 1H, Ar–H), 7.07 (t, J = 7.6 Hz, 1H, Ar–H), 3.83 (s, 3H, N–CH₃), 3.65 (s, 3H, O–CH₃), 3.45 (s, 3H, SO₂–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 154.89.152.80, 151.23, 139.96, 131.81, 129.76, 129.16, 126.99, 122.58, 122.35, 121.33, 120.24, 112.38, 110.40, 55.92, 43.59, 36.02; MS (LC–MS): *m/z* 384 (M + H)⁺.

3-(4-(3-Methoxyphenyl)-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1H-indazole (6e). Yield: 0.261 g (72%); White solid; mp: 160–162°C; IR (v_{max}/cm^{-1}): 3019 (C–H), 1607 (C=N), 1326 and 1151 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.22 (d, J = 8 Hz, 1H, Ar–H), 7.70 (d, J = 8 Hz, 1H, Ar–H), 7.50 (t, J = 7.6 Hz, 1H, Ar–H), 7.42 (d, J = 8 Hz, 1H, Ar–H), 7.33 (t, J = 7.2 Hz, 1H, Ar–H), 7.23 (t, J = 7.6 Hz, 1H, Ar–H), 7.12–7.15 (m, 2H, Ar–H), 3.87 (s, 3H, N–CH₃), 3.75 (s, 3H, O–CH₃), 3.46 (s, 3H, SO₂–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 159.20152.82, 150.99, 139.96, 134.38, 129.69, 129.58, 126.96, 122.46, 121.33, 120.43, 115.69, 114.35, 110.34, 55.50, 43.73, 36.02; MS (LC–MS): m/z 384 (M + H)⁺.

3-(4-(4-Methoxyphenyl)-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1H-indazole (6f). Yield: 0.268 g (74%); White solid; mp: 196–198°C; IR (v_{max}/cm^{-1}): 3020 (C–H), 1597 (C=N), 1323 and 1147 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.20 (d, J = 8.4 Hz, 1H, Ar–H), 7.70 (t, J = 8.4 Hz, 1H, Ar–H), 7.48–7.51 (m, 3H, Ar–H), 7.32 (t, J = 8 Hz, 1H, Ar–H), 7.04 (d, J = 8 Hz, 2H, Ar–H), 3.88 (s, 3H, N–CH₃), 3.82 (s, 3H, O–CH₃), 3.43 (s, 3H, SO₂–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 160.15, 153.13, 151.36, 139.92, 129.78, 129.51, 126.92, 125.88, 122.52, 122.42, 121.33, 113.88, 110.27, 55.42, 43.57, 36.00; MS (LC– MS): m/z 384 (M + H)⁺.

General procedure for the synthesis 1-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles (7a–f). A mixture of Raney Ni (100 *w*/w in 30-mL tetrahydrofuran and 30-mL methanol) and 1-methyl-3-(5-(methylsulfonyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indazoles **6a–f** (0.55 mmol) was heated under reflux for 1 h. The progress of reaction was monitored by TLC. Upon completion of reaction, contents were filtered through Celite bed and filtrate was concentrated to get desired product. The obtained solid was filtered and recrystallized from methanol to afford pure compounds **7a–f**.

1-Methyl-3-(4-o-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole

(7a). Yield: 0.099 g (63%); White solid; mp: 160–162°C; IR (v_{max}/cm^{-1}): 3100 (C–H), 1568 (C=N); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 8.81$ (s, 1H, Ar–H), 8.26 (d, J = 8.4 Hz, 1H, Ar–H), 7.65 (d, J = 8.4 Hz, 1H, Ar–H), 7.40–7.49 (m, 3H, Ar–H), 7.27–7.37 (m, 3H, Ar–H), 3.82 (s, 3H, N–CH₃), 1.95 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 147.55$, 145.05, 140.07, 134.92, 134.36, 131.14, 130.58, 129.47, 127.61, 126.80, 126.67, 121.98, 121.66, 110.08, 35.78, 17.16; MS (LC–MS): m/z 290 (M + H)⁺.

1-Methyl-3-(4-m-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole

(7b). Yield: 0.105 g (67%); White solid; mp: 100–102°C;

IR (v_{max}/cm^{-1}): 3104 (C–H), 1594 (C=N); ¹H NMR (400 MHz, DMSO- d_6): $\delta = 8.88$ (s, 1H, Ar–H), 8.12 (d, J = 8 Hz, 1H, Ar–H), 7.68 (d, J = 8.4 Hz, 1H, Ar–H), 7.47 (t, J = 7.6 Hz, 1H, Ar–H), 7.23–7.38 (m, 5H, Ar–H), 3.92 (s, 3H, N–CH₃), 2.34 (s, 3H, Ar–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 146.99$, 145.24, 140.11, 138.62, 134.60, 131.06, 129.46, 128.72, 126.72, 126.64, 123.38, 122.26, 121.86, 121.54, 110.02, 35.72, 20.64; MS (LC–MS): m/z 290 (M + H)⁺.

1-Methyl-3-(4-p-tolyl-4H-1,2,4-triazol-3-yl)-1H-indazole (7c). Yield: 0.101 g (64%); White solid; mp: 172–176°C; IR (v_{max} /cm⁻¹): 3097 (C—H), 1585 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.85 (s, 1H, Ar—H), 8.09 (d, J = 8 Hz, 1H, Ar—H), 7.68 (d, J = 8.8 Hz, 1H, Ar—H), 7.47 (t, J = 8 Hz, 1H, Ar—H), 7.35 (d, J = 8.4 Hz, 2H, Ar—H), 7.24–7.30 (m, 3H, Ar—H), 3.93 (s, 3H, N—CH₃), 2.36 (s, 3H, Ar—CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 147.06145.38, 140.11, 138.43, 132.21, 131.10, 129.45, 126.74, 126.00, 122.28, 121.87, 121.52, 110.04, 35.75, 20.62; MS (LC–MS): m/z 290 (M + H)⁺.

3-(4-(2-Methoxyphenyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1Hindazole (7d). Yield: 0.110 g (66%); White solid; mp: 120–122°C; IR (v_{max}/cm^{-1}): 3120 (C–H), 1600 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.75 (s, 1H, Ar–H), 8.22 (d, J = 8.4 Hz, 1H, Ar–H), 7.66 (d, J = 8.4 Hz, 1H, Ar–H), 7.40–7.53 (m, 3H, Ar–H), 7.28 (t, J = 8 Hz, 1H, Ar–H), 7.20 (d, J = 8 Hz, 1H, Ar–H), 7.06 (t, J = 7.6 Hz, 1H, Ar–H), 3.85 (s, 3H, N–CH₃), 3.58 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 154.22, 147.71, 145.24, 139.94, 131.34, 130.60, 128.07, 126.56, 123.78, 121.90, 121.71, 121.56, 120.27, 112.38, 109.87, 55.59, 35.57; MS (LC–MS): *m*/z 306 (M + H)⁺.

3-(4-(3-Methoxyphenyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1Hindazole (7e). Yield: 0.115 g (69%); White solid; mp: 156–158°C; IR (v_{max}/cm^{-1}): 3112 (C–H), 1598 (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ = 8.90 (s, 1H, Ar–H), 8.09 (d, J = 8 Hz, 1H, Ar–H), 7.70 (d, J = 8 .8Hz, 1H, Ar–H), 7.47 (t, J = 7.6 Hz, 1H, Ar–H), 7.26 (t, J = 7.6 Hz, 1H, Ar–H), 7.14 (s, 1H, Ar–H), 7.06 (dd, J = 8 and 2 Hz, 1H, Ar–H), 7.00 (d, J = 7.2 Hz, 1H, Ar–H), 3.95 (s, 3H, N–CH₃), 3.76 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ = 159.48, 146.92, 145.25, 140.12, 135.68, 131.03, 129.78, 126.74, 122.29, 121.89, 121.46, 118.32, 114.74, 112.08, 110.08, 55.44, 35.77; MS (LC–MS): m/z 306 (M + H)⁺.

3-(4-(4-Methoxyphenyl)-4H-1,2,4-triazol-3-yl)-1-methyl-1Hindazole (7f). Yield: 0.105 g (63%); White solid; mp: 120–122°C; IR (v_{max} /cm⁻¹): 3112 (C–H), 1600 (C=N). ¹H NMR (400 MHz, DMSO- d_6): $\delta = 8.82$ (s, 1H, Ar–H), 8.11 (d, J = 8 Hz, 1H, Ar–H), 7.68 (d, J = 8.4 Hz, 1H, Ar–H), 7.47 (t, J = 8 Hz, 1H, Ar–H), 7.40 (d, J = 8.8 Hz, 2H, Ar–H), 7.26 (t, J = 8 Hz, 1H, Ar–H), 7.03 (d, J = 8.8 Hz, 2H, Month 2019

Ar–H), 3.93 (s, 3H, N–CH₃), 3.81 (s, 3H, O–CH₃); ¹³C NMR (100 MHz, DMSO- d_6): δ = 159.39, 147.26, 145.51, 140.09, 131.10, 127.67, 127.50, 126.74, 122.23, 121.86, 121.52, 114.08, 110.07, 55.45, 35.80; MS (LC–MS): m/z 306 (M + H)⁺.

CONCLUSION

In conclusion, we have synthesized a series novel 1methyl-3-(4-phenyl-4H-1,2,4-triazol-3-yl)-1H-indazoles from 5-(1-methyl-1H-indazol-3-yl)-4-phenyl-2H-1,2,4triazole-3(4H)-thiones. All synthesized compounds are novel and characterized by using spectral methods.

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