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$Pd(PPh_3)_4$ Catalyzed Synthesis of Indazole Derivatives as Potent Anticancer Drug

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Abstract: A series of 3-aryl indazoles and 1-methyl-3-aryl indazole derivatives are prepared with exceptional yields by coupling with several arylboronic acids and methylation by two dissimilar approaches. The as-prepared indazole derivatives (**3a–3j**) and their N-methyl derivatives (**5a–5j**) are evaluated for in vitro anticancer activity against two cancer cell lines, HCT-116 and MDA-MB-231. The results reveal that the indazole derivatives tested display mild to moderate anticancer activities against the cell lines tested.

Keywords: $Pd(PPh_3)_4$; indazole; anticancer activity; HCT-116; MDA-MB-231

1. Introduction

Cancer, a disease of the cell cycles, has remained the largest cause of mortality and morbidity for several decades now. In spite of rapid development in diagnostic and therapeutic protocols, according to the World Health Organization (WHO), cancer holds second place after cardiovascular disease as a cause of death in the world [1]. Among all the available therapeutic methods, chemotherapy still remains a significant option for the treatment of cancer, which has emerged as a new era of molecularly targeted therapeutics [2]. However, the major drawback of successful cancer treatment is the emergence of multi-drug resistance (MDR) in various cancer cell lines due to mutations in the cell, which limit the successful outcomes in most of the cases. Consequently, there is a requirement of novel advances that are exclusively designed to overcome the menace of drug resistance. Thus, the development of novel, potent, and selective anticancer agents is still one of the most significant areas of modern cancer research and turns out to be the main objective of organic and medicinal chemists across the world.

Among the various organic molecules, the nitrogen-containing heterocycles are important building blocks for many bioactive natural products and commercially available drugs. Indazole and its derivatives belong to an enormously important family of nitrogen-containing heterocyclic systems (Figure 1), often allied with a wide range of biological activities [3–7]. Many of indazole derivatives have been reportedly found to possess potent pharmacological activity such as anti-tumor [8,9], anti-platelet [10], antiviral [11], antioxidant [12], anti-spermatogenic activity [13], anti-tubercular [14,15], anti-inflammatory and anti-microbial [16], neuroprotection [17], and COX inhibition activity [18]. Moreover, some indazoles were reported as protein kinase C-B/AKt inhibitors [19], potent IDO1/TDO dual inhibitors [20], and also as 5-HT2, 5-HT3, and 5-HT4 receptor antagonists [21,22].

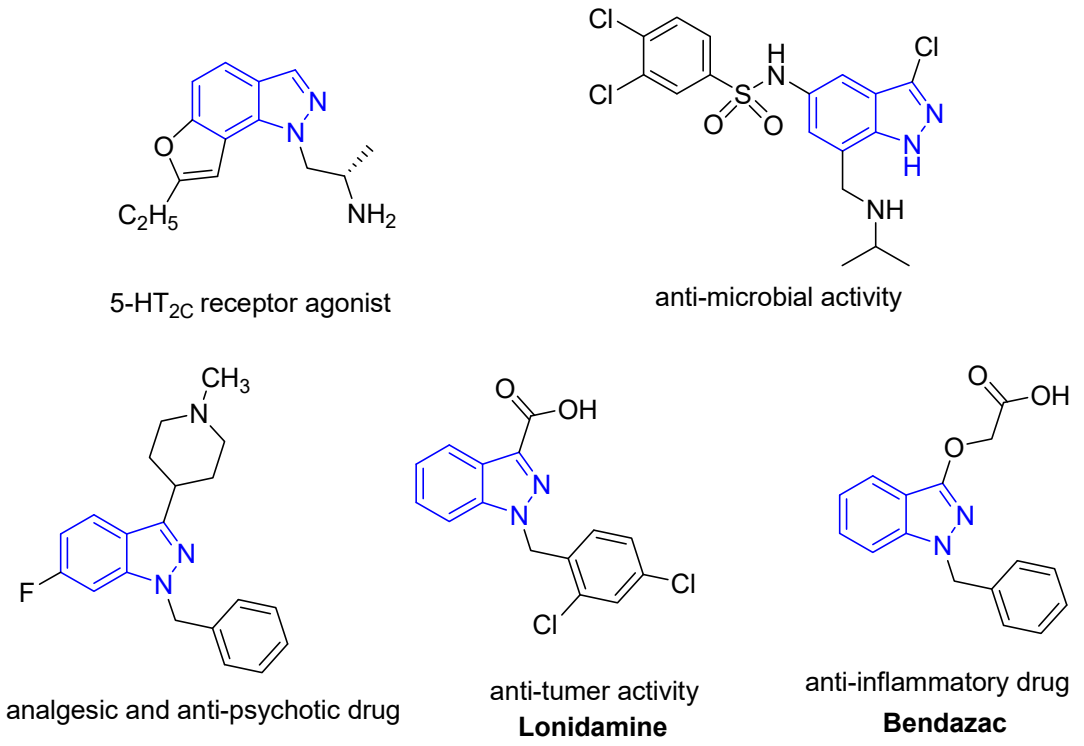


Figure 1. Some biologically active molecules of indazoles.

Furthermore, many of the synthetic and natural indazole based heterocycles with a sundry mechanism of action have been reported as lead anticancer agents [23–25]. Importantly, a number of indazole based anticancer drugs (Figure 2) were used clinically. For example, niraparib has been widely used as an anticancer drug for the treatment of recurrent epithelial ovarian, fallopian tube, breast, and prostate cancer [26], pazopanib [27] and axitinib [28] are tyrosine kinase inhibitors approved by the FDA for renal cell carcinoma; these are some of the present-day anticancer drugs possessing a privileged indazole skeleton. These interesting therapeutic properties of indazole derivatives have made them attractive target molecules in organic synthesis.

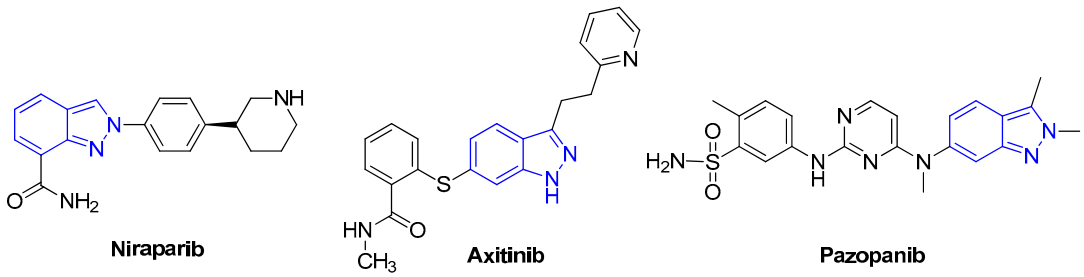
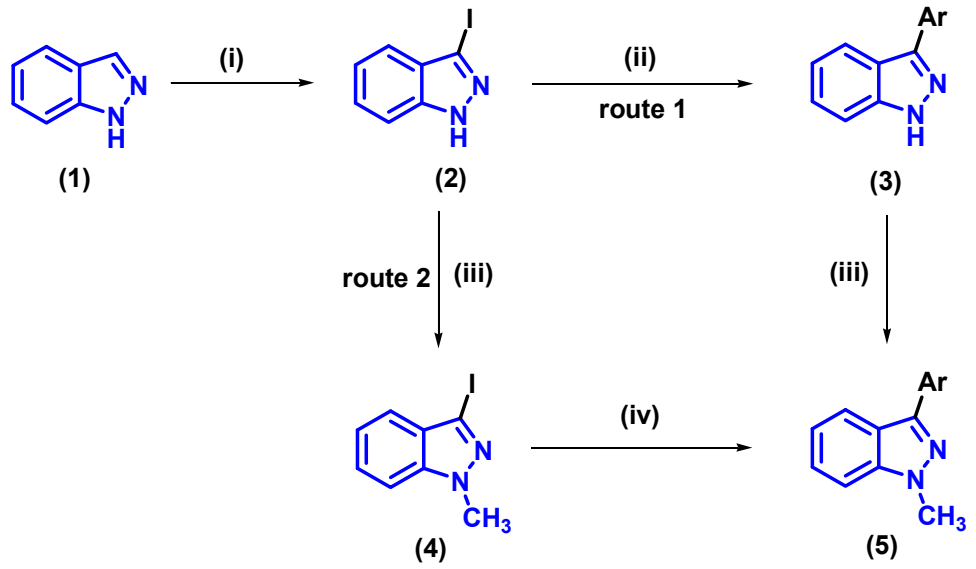


Figure 2. Indazoles containing anticancer drugs.

Considering this wide range of pharmacological activities of indazole scaffolds, various methodologies have been developed by the researchers for the synthesis of these moieties, of which many employed transition metal-based catalytic systems. The various metal catalysts that have been employed are $[Ir(OMe)(COD)]_2$ [29], $[Cp^*RhCl_2]_2$ [30,31], CuCl [32], $[Cp^*CoCl_2]_2$ [33], $Pd(OAc)_2$ [34], $Pd(dba)_2$ [35], ZnBr [36], $FeBr_3$ [37], and $NiCl_2$ [38]. Very recently, our group developed efficient methodologies towards the construction of various heterocyclic compounds using Cu catalyst [39–43]. Inspired by the above facts, and in continuation of our efforts towards the development of new heterocyclic moieties of therapeutic importance [44–46], in the present investigation, we report the synthesis of a series of 3-aryl-1*H*- indazoles and *N*-methyl-3-arylindazoles using $Pd(PPh_3)_4$ catalyst

as shown in Scheme 1. The as-synthesized compounds are characterized using spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS and then later evaluated for their cell growth inhibitory activities (IC_{50}) against HCT-116 and MDA-MB-231 cancer cell lines using the MTT assay method.



Scheme 1. Synthetic route for *N*-methyl-3-aryl indazoles.

Reagents and conditions: (i) KOH, I_2, DMF, 25 °C, 2 h, 77%, (ii) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DMF, 80 °C, 8-12 h, 55-70%, (iii) MeI, KOH, acetone, 0 °C, 10–12 h, 58%–75% (iv) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DMF, 80 °C, 8–12 h, 58%-75%.

2. Experimental

General Information: All the chemicals and reagents are obtained from Sigma-Aldrich(Merck), Karnataka, India; S. D. Fine, Tamilnadu, India, Spectrochem, Mumbai, India, and are utilized without any further purification. Solvents used are dried prior to their use. Reactions are monitored by using precoated (Kieselgel 60 F_{254}, Merck) TLC silica gel plates. Column chromatography is performed using silica gel (60–120 mesh, Merck). Cintex melting point apparatus is used to determine the Melting points. Perkin Elmer 400 FT-IR spectrometer (υ_{max} in cm^{-1}) or a Varian 670-IR FT-IR spectrometer (ATR) is used to record the IR (KBr) spectra. A Bruker DRX-300 (300 MHz FT NMR) or Varian Mercury 500 MHz spectrometer were utilized in recording the ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ and DMSO-d_6. Chemical shifts are presented in δ ppm employing TMS as an internal reference. A Jeol SX-102 spectrometer is used to record the mass spectra.

2.1. Synthesis of 3-iodo-1H-indazole (2)

To a stirred solution of indazole (**1**) (0.2 g, 1.69 mmol) in DMF (10 mL), iodine (0.8 g, 3.38 mmol) was added, followed by addition of KOH pellets (0.3 g, 6.77 mmol) and the whole reaction mixture was stirred for 1 h at room temperature. Then, the mixture was poured into 10% aqueous $NaHSO_3$ and extracted by diethyl ether. Organic layer was washed with water and saturated brine solution, dried over sodium sulphate and subjected to removal of solvent, which yielded a white solid 3-iodo-1*H*-indazole (**2**) (77%); m.p. 90–92 °C; IR (KBr, υ_{max}, cm^{-1}): 3311 (NH str), 3046 (ArCH str), 1650, 1596, 1558 (ArC=C str), 1415 (C=N str), 771 (C-I str); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.5 (s, 1H, NH), 7.52–7.43 (m, 3H, Ar-H), 7.25–7.21 (d, J = 10 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 132.8, 130.7, 128.9, 126.7, 122.0. HRMS: (ESI *m*/*z*) 244.9 $(M + H)^+$.

*2.2. General Procedure for Synthesis of 3-arylindazole (***3a–3j***)*

Under nitrogen atmosphere, to the mixture of 3-iodo indazole (**2**) (0.3 g, 1.2 mmol) and aryl boronic acid (1.8 mmol) in DMF (60 mL), $NaHCO_3$ solution (0.3 g, 3.6 mmol) (2:1 DMF–water) was added. To this reaction mixture, $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol) was added and refluxed at 80 °C for 8–12 h with vigorous stirring. The reaction mixture was then subjected to evaporation under vacuum to obtain a dry product, which was then dissolved in ethyl acetate and washed with saturated brine solution, dried over sodium sulfate, and the solvent ethyl acetate was removed under vacuum to give crude. The crude mixture was purified by silica gel (60–120 mesh) column chromatography using 20% ethyl acetate in hexane as eluent to afford the corresponding 3-aryl-1*H*-indazoles (**3a**–**3j**).

*2.3. General Procedure for Synthesis of N-methyl-3-aryl indazole (***5a–5j***) (Route 1)*

A solution of 3-aryl indazole (**3**) (0.66 mmol) in acetone was cooled to 0 °C, and to it was added KOH (0.05 g, 1.00 mmol). After 15 minutes, at 0 °C, methyl iodide (0.04 mL) is added and stirred for 2 h. The solvent from the reaction mixture was evaporated; the crude solid obtained was dissolved in ethyl acetate and washed with water and brine, dried over sodium sulfate and the solvent removed under vacuum to give a crude compound *N*-methyl-3-aryl indazole. The crude mixture was purified by silica gel (60–120 mesh) column chromatography using 20% ethylacetate in hexane as eluent to afford corresponding N-methyl-3-aryl indazole (**5a**–**5j**).

*2.4. General Procedure for Synthesis of N-methyl-3-aryl indazole (***5a–5j***) (Route 2)*

Under nitrogen atmosphere, to a mixture of *N*-methyl-3-iodoindazole **4** (0.3 g, 1.16 mmol) and aryl boronic acid (1.74 mmol) in DMF, $NaHCO_3$ (0.2 g, 3.4 mmol) in water was added. To this reaction, mixture Pd $(PPh_3)_4$ (0.1 g, 0.1 mmol) was added and refluxed with vigorous stirring for 10–14 h. The solvent of the reaction mixture was then evaporated, and the crude obtained was dissolved in ethyl acetate; the organic phase was washed with brine solution, dried over sodium sulfate, and the solvent was removed under vacuum to give crude compound. The crude mixture is purified by silica gel (60–120 mesh) column chromatography using 30% ethyl acetate in hexane as eluent to afford the respective products N-methyl-3-aryl indazole (**5a**–**5j**).

Spectral Data of Compounds (**3a–3j**) and (**5a–5j**)

3-Phenyl-1H-indazole **(3a):** m.p. 114–116 °C; IR (KBr, υ_{max}, cm^{-1}): 3691 (OH str), 3440 (b,NH str), 2991 (Ar=CH str), 2897 (CH str), 1601, 1545, 1498 (Ar C=C str), 1450 (C=N str), 1233 (N-N str); NMR: ^{1}H (500 MHz, CDCl3): δ = 11.18 (b, 1H), 8.08–8.04 (m, 3H), 7.58 (t, *J* = 7.5, 2H), 7.49–7.46 (m, 1H), 7.43–7.37 (m, 2H), 7.29–7.25 (m, 1H); ^{13}C-NMR: (125 MHz, DMSO): δ = 145.8, 141.7, 133.6, 128.9, 128.2, 127.7, 126.8, 121.4, 121.1, 121.0, 110.2; *m*/*z* (ESI-MS) 195.23 $(M + H)^+$.

3-(Naphthalen-1-yl)-1H-indazole **(3b):** m.p. 136–138 °C; IR (KBr, υ_{max}, cm^{-1}): 3446 (b,NH str), 2929 (Ar=CH str), 1595, 1581, 1506 (ArC=C str), 1418 (C=N str), 1246 (N-N str);NMR: ^{1}H (500 MHz, $CDCl_3$): δ = 12.25 (b, 1H), 8.32–8.31 (m, 1H), 8.01–7.98 (m, 2H), 7.79–7.67 (m, 2H), 7.57–7.52 (m, 2H), 7.48–7.39 (m, 2H), 7.21 (t, *J* = 6.7, 1H), 6.93–6.92 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 143.4, 134.1, 131.9, 131.3, 128.8, 128.2, 128.1, 126.7, 126.4, 126.3, 126.1, 125.4, 121.9, 121.3, 110.9: *m*/*z* (ESI-MS) 245.05 $(M + H)^+$.

3-(4-Fluorophenyl)-1H-indazole **(3c):** m.p. 112–113 °C; IR (KBr, υ_{max}, cm^{-1}): 3406 (NH str), 3078 (ArH str), 2924 (ArH str), 1625, 1563 (ArC=C str), 1440 (C=N str), 1370 (C=N str), 814 (C-F str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (m, 3H, ArH), 7.45 (m, 2H, ArH), 7.25 (m, 1H, ArH); 7.21 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 147.2, 138.5, 130.1, 128.8, 126.2, 124.4, 122.1, 121.7, 113.8; *m*/*z* (ESI-MS) 213.27 $(M + H)^+$.

3-(Pyridin-4-yl)-1H-indazole **(3d):** m.p. 101–103 °C; IR (KBr, υ_{max}, cm^{-1}): 3430 (NH str), 3032 (ArCH str), 1584, 1549, 1491(ArC=C str), 1373 (C=N str), 1211 (N-N str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.62

(m, 4H, Ar-H), 7.62 (d, *J* = 8 Hz, 2H, Ar-H); 7.45 (d, *J* = 9 Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8, 143.6, 138.5, 130.1, 128.8, 126.2, 124.4, 122.1, 121.7, 112.3; *m/z* (ESI-MS) 196.26 $(M + H)^+$.

3-(Pyridin-3-yl)-1H-indazole **(3e):** m.p. 184–186 °C; IR (KBr, υ_{max}, cm^{-1}): 3409 (b, NH str), 3066 (ArCH str), 1589, 1560, 1512(ArC=C str), 1340 (C=N str), 1216 (N-N str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.92 (s, 1H, NH), 9.25 (s, 1H, ArH), 8.65 (d, 1H, *J* = 7.5, Ar-H), 8.42 (d, 1H, *J* = 8.4 Hz, ArH); 8.05 (d, *J* = 7.5 Hz, 1H, Ar-H) 7.22–7.64 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5, 139.6, 139.2, 128.8, 127.5, 126.2, 125.2, 124.4, 124.3, 123.0, 122.6, 122.2; *m/z* (ESI-MS) 196.26 $(M + H)^+$.

3-(4-Methoxyphenyl)-1H-indazole **(3f):** m.p. 85–87 °C; IR (KBr, υ_{max}, cm^{-1}): 3429 (NH str), 3054 (ArH str), 2927 (CH str), 1583, 1487 (ArC=C str), 1438 (C=N str), 1375 (C=N str), 1169 (C-O-C str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H, NH), 8.03 (d, 1H, *J* = 8.0, ArH), 7.85 (dd, 2H, *J* = 10.5, ArH), 7.46 (m, 2H, ArH); 7.22 (m, 1H, ArH), 7.03 (dd, 2H, *J* = 10.4, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 145.7, 141.8, 128.9, 126.6, 126.2, 121.1, 121.1, 114.4, 110.3, 55.3; *m/z* (ESI-MS) 225.31 $(M + H)^+$.

3-(4-(Methylthio)phenyl)-1H-indazole **(3g):** m.p. 123-125 °C; IR (KBr, υ_{max}, cm^{-1}): 3378 (NH str), 3052 (ArH str), 2925 (CH str), 1600, 1521 (ArC=C str), 1346 (C=N str), 1106 (C-S-C str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H, NH), 7.92 (d, 2H, *J* = 7.5, ArH), 7.52 (d, 1H, *J* = 8.4, ArH), 7.38-7.7.51 (m, 4H, ArH); 7.23 (s, 1H, ArH), 2.45 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 145.7, 141.8, 134.7, 129.9, 126.8, 121.4, 121.0, 120.2, 114.2, 112.9, 110.3, 55.3.; *m/z* (ESI-MS) 241.30 $(M + H)^+$.

3-(2-Methoxyphenyl)-1H-indazole **(3h):** m.p. 115–116 °C; IR (KBr, υ_{max}, cm^{-1}): 3325 (b, NH str), 3025 (ArCH str), 2921 (CH str), 1659, 1513, 1437(ArC=C str), 1370 (C=N str), 1212 (N-N str), 1148 (C-O-C str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H, NH), 7.72 (d, 1H, *J* = 7.5 Hz, ArH), 7.52 (d, *J* = 8.5 Hz, 1H, Ar-H) 7.42 (m, 2H, ArH); 7.21 (m, 1H, ArH), 7.09 (m, 1H, ArH), 7.02 (d, 1H, *J* = 10.2 Hz, ArH), 3.8 (s, 3H, OCH_3).^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.3, 143.0, 141.4, 131.4, 129.7, 126.3, 122.2, 122.0, 120.9, 120.5, 111.4, 110.4, 55.4; *m/z* (ESI-MS) 225.30 $(M + H)^+$.

*4-(1H-indazol-3-yl)phenol***(3i):** m.p. 121–123 °C; IR (KBr, υ_{max}, cm^{-1}): 3414 (OH str), 3315 (b,NH str), 2925 (Ar=CH str), 1651, 1560, 1505(ArC=C str), 1414 (C=N str), 1219 (N-N str), 1093 (C-O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.12 (s, 1H, PhOH), 9.62 (s, 1H, NH), 8.01 (d, 1H, *J* = 8.4 Hz, ArH), 7.82 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.49 (d, *J* = 10.2, 1H, ArH), 7.39 (d, *J* = 10.4, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 6.96 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 151.4, 148.6, 138.8, 132.5, 134.8, 128.7, 125.9, 122.1, 113.5, 104.1; *m/z* (ESI-MS) 211.30 $(M + H)^+$.

4-(1H-indazol-3-yl)-N,N-dimethylbenzamide **(3j):** m.p. 116–117 °C; IR (KBr, υ_{max}, cm^{-1}): 3456 (b, NH str), 2933 (Ar=CH str), 2835 (CH str), 1817 (CO str), 1649, 1530, 1488(ArC=C str), 1386(C=N str), 1210 (N-N str); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H, NH), 8.09 (m, 3H, ArH), 7.61 (m, 3H, Ar-H), 7.45 (d, *J* = 10.5 Hz, 1H, ArH); 7.28 (s, 1H, ArH), 3.12 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 145.7, 135.2, 132.2, 130.4, 128.7, 128.6, 128.1, 127.9, 127.3, 126.5, 114.1, 36.4; *m/z* (ESI-MS) 266.35 $(M + H)^+$.

1-Methyl-3-phenyl-1H-indazole **(5a):** m.p. 76–78 °C; IR (KBr, υ_{max}, cm^{-1}): 3429 (NH str), 3054 (ArH str), 2927 (CH str), 1582, 1487 (ArC=C str), 1438 (C=N str), 1375 (C=N str), 1169 (C-O-C str); ^{1}H NMR (400 MHz, DMSO-d6) δ 4.12 (3H, s) 7.24 (1H, t, *J* = 7.6 Hz) 7.38–7.43 (1H, m) 7.46 (1H, t, *J* = 7.6 Hz) 7.52 (2H, t, *J* = 7.6 Hz) 7.70 (1H, d, *J* = 8.3 Hz) 7.98 (2H, d, *J* = 7.3 Hz) 8.07 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d6): δ = 142.4, 141.7, 133.8, 129.4, 128.2, 127.2, 126.7, 121.7, 121.3, 121.1, 110.6, 36.0; *m/z* (ESI-MS) 209.27 $(M + H)^+$.

1-Methyl-3-(naphthalen-1-yl)-1H-indazole **(5b)**: m.p. 137–139 °C; IR (KBr, υ_{max}, cm^{-1}): 3130 (w, Ar=CH str), 2955, 2922, 2863 (CH str), 1625, 1583, 1495(ArC=C str), 1384 (C=N str), 1234 (N-N str), 1157 (C-S-C str); ^{1}H NMR (400 MHz, DMSO-d6) δ 4.20 (3H, s) 7.20 (1H, t, *J* = 7.5 Hz) 7.46–7.69 (5H, m) 7.76 (2H, d, *J* = 7.7 Hz) 8.04 (2H, d, *J* = 8.1 Hz) 8.29 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d6): δ = 142.5, 141.1, 134.2, 131.6, 130.5, 128.8, 128.3, 126.9, 126.8, 126.6, 126.3, 126.1, 123.1, 121.5, 121.0, 110.6, 36.1; *m/z* (ESI-MS) 259.33 $(M + H)^+$.

3-(4-Fluorophenyl)-1-methyl-1H-indazole **(5c):** m.p. 98–100 °C; IR (KBr, υ_{max}, cm^{-1}): 3098 (Ar=CH str), 2935, 2888 (CH str), 1601, 1524, 1480 (ArC=C str), 1354 (C=N str), 1229 (N-N str), 825 (C-F str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (m, 3H, ArH), 7.42 (s, 2H, ArH), 7.21 (m, 3H, ArH), 4.13 (s, 3H,

CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 145.2, 139.1, 136.7, 132.2, 128.9, 128.7, 128.2, 123.4, 119.5, 117.6, 110.5, 35.2; *m/z* (ESI-MS) 227.31 $(M + H)^+$.

1-Methyl-3-(pyridin-4-yl)-1H-indazole **(5d):** m.p. 101–103 °C; IR (KBr, υ_{max},cm^{-1}): 3052(Ar=CH str), 2925 (CH str), 1612, 1508, 1459(ArC=C str), 1390 (C=N str), 1205(N-N str); ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 2H, *J* = 8.5 Hz, ArH), 8.06 (d, 1H, *J* = 8.0 Hz, ArH), 7.92 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.42 (d, *J* = 7.0 Hz, 2H, ArH); 7.26 (m, 1H, ArH), 4.19 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 160.7, 145.7, 135.2, 132.2, 128.7, 128.6, 128.1, 127.9, 126.5, 36.4; *m/z* (ESI-MS) 210.41 $(M + H)^+$.

1-Methyl-3-(pyridin-3-yl)-1H-indazole **(5e):** m.p. 74–76 °C; IR (KBr, υ_{max}, cm^{-1}): 3136 (Ar=CH str), 2949, 2873 (CH str), 1593, 1534(ArC=C str), 1348 (C=N str), 1189 (N-N str); ^1H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 1H, ArH), 8.62 (s, 1H, ArH), 8.36 (dd, 1H, *J* = 7.5 Hz, ArH), 8.02 (d, *J* = 7.0 Hz, 1H, ArH); 7.51 (m, 3H, ArH), 7.32 (s, 1H, ArH). 4.18 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6) δ = 153.6, 149.8, 141.9, 141.8, 137.3, 126.9, 123.7, 122.9, 122.0, 120.5, 110.4, 36.2; *m/z* (ESI-MS) 210.29 $(M + H)^+$.

3-(4-Methoxyphenyl)-1-methyl-1H-indazole **(5f):** m.p. 112–114 °C;IR (KBr, υ_{max}, cm^{-1}): 3098 (Ar=CH str), 2960, 2921, 2872 (CH str), 1607, 1569, 1530(ArC=C str), 1350 (C=N str), 1201 (N-N str), 1164 (C-O-C str); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.90 (d, 2H, *J* = 8.5 Hz, ArH), 7.42 (m, 2H, ArH), 7.23 (m, 1H, ArH); 7.08 (d, *J* = 8.5, 2H, ArH), 4.15 (s, 3H, OCH_3), 3.91 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): ^{13}C- NMR (100 MHz, DMSO-d6) δ = 159.4, 142.4, 141.6, 128.4, 126.6, 126.4, 121.4, 121.3, 121.0, 114.8, 110.5, 55.7, 35.9; *m/z* (ESI-MS) 239.09 $(M + H)^+$.

1-Methyl-3-(4-(methylthio)phenyl)-1H-indazole **(5g):** m.p. 99–101 °C; IR (KBr, υ_{max}, cm^{-1}): 3095 (Ar=CH str), 2956, 2922, 2864 (CH str), 1625, 1582, 1495 (ArC=C str), 1384 (C=N str), 1234 (N-N str), 1157 (C-S-C str); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 1H, ArH), 7.89 (d, 2H, *J* = 8.0 Hz, ArH), 7.41 (m, 4H, ArH), 7.20 (m, 1H, ArH); 4.14 (s, 3H, NCH_3), 2.58 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 160. 6, 145.7, 135.2, 132.2, 131.7, 128.6, 128.1, 127.9, 126.5, 119.7, 55.4, 36.3; *m/z* (ESI-MS) 255.32 $(M + H)^+$.

3-(2-Methoxyphenyl)-1-methyl-1H-indazole **(5h):** m.p. 105–107 °C; IR (KBr, υ_{max}, cm^{-1}): 3053.97b (Ar=CH str), 2955, 2894 (CH str), 1614, 1520, 1459(ArC=C str), 1372 (C=N str), 1278 (N-N str), 1172 (C-O-C str); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.0 Hz, 1H, ArH), 7.78 (d, 1H, *J* = 8.5 Hz, ArH), 7.41 (m, 3H, ArH), 7.05-7.18 (m, 3H, ArH); 4.16 (s, 3H, OCH_3), 3.82 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 143.6, 141.7, 137.6, 132.9, 132.2, 128.9, 128.1, 128.6, 123.3, 120.4, 116.0, 110.5, 55.2, 35.2; *m/z* (ESI-MS) 239.33 $(M + H)^+$.

4-(1-Methylindazol-3-yl)phenol **(5i):** m.p. 241–243 °C; IR (KBr, υ_{max}, cm^{-1}): 3691(OH str), 3439 (NH str), 2991 (Ar=CH str), 2897 (CH str), 1601, 1545, 1498 (ArC=C str), 1449 (C=N str), 1233 (N-N str); ^1H NMR (400 MHz, DMSO-d6) δ 4.06 (3H, s) 6.93 (2H, d, *J* = 8.6 Hz) 7.18 (1H, t, *J* = 7.5 Hz) 7.42 (1H, t, *J* = 7.6 Hz) 7.62 (1H, d, *J* = 8.6 Hz) 7.80 (2H, d, *J* = 8.6 Hz) 8.00 (1H, d, *J* = 8.2 Hz) 9.65 (1H, s); ^{13}C NMR (100 MHz, DMSO-d6) δ = 157.7, 142.8, 141.6, 128.5, 126.5, 124.8, 121.4, 121.2, 120.9, 116.2, 110.3, 35.8; *m/z* (ESI-MS) 225.10 $(M + H)^+$.

N,N-Dimethyl-4-(1-methyl-1H-indazol-3-yl)benzamide **(5j):** m.p. 110–112 °C; IR (KBr, υ_{max}, cm^{-1}): 3054 (Ar=CH str), 2234 (C-NO_2 str), 1679 (CO str), 1583, 1487(ArC=C str), 1375 (C=N str), 1212 (N-N str); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 1H, ArH), 7.57 (d, 2H, *J* = 8.0 Hz, ArH), 7.43 (d, 3H, *J* = 8.4 Hz, ArH), 7.23 (s, 1H, ArH); 4.17 (s, 3H, NCH_3), 3.12 (s, 6H, $N(CH_3)_2$; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 149.6, 147.9, 130.4, 128.7, 127.5, 126.2, 125.6, 124.1, 121.9, 111. 3, 37.2, 36.3; *m/z* (ESI-MS) 280.35 $(M + H)^+$.

2.5. Procedure for Anti-Cancer Activity

The MTT cell proliferation assay method was used to analyze the cell growth on a protocol of 48 h [47]. Human colorectal cancer cell lines (HCT-116 and MDA-MB-231) were procured from the National Centre for Cell Sciences (NCCS), Pune, India, and maintained in DMEM. The cell lines were cultured with DMEM supplemented with 10% FBS, L-glutamine, $NaHCO_3$, and an antibiotic solution containing penicillin (100 U/mL) and streptomycin (100 µg/mL). The exponentially growing cells were seeded at 5×10^3 cells per well into 96-well plates. The culture medium was removed after

24 h incubation at 37 °C and restored with fresh medium containing the candidate compounds in different concentrations. Next, the cells were incubated for another 72 h. Then, 20 mL of MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (5 mg/mL) was added to all wells and incubated for 4 h at 37 °C. The medium containing MTT was discarded, 150 mL of dimethyl sulfoxide (DMSO) was added to each well and the plates agitated until the dark blue crystals (formazan) had completely dissolved; the absorbance was measured using a microplate reader at a wavelength of 570 nm. Each concentration was analyzed in triplicate, and the experiment is repeated three times. The average 50% inhibitory concentration (IC_{50}) is determined from the concentration-response curves according to the inhibition ratio for each concentration.

3. Results and Discussions

3.1. Chemistry

3-substituted indazoles are common components in a variety of biologically potent molecules possessing a pharmaceutical interest in a variety of therapeutic areas [10,48–50]. Hence, the functionalization of indazoles at the C-3 position is of immense interest. With the increasing applications of 3-aryl indazoles in the pharmaceutical industry and inspired by the literature of Suzuki couplings, in the present work, we append the aromatic moieties after iodination at C-3 position of indazole, followed by palladium-catalyzed *C-C* bond formation to obtain 3-aryl-1*H*-indazoles (**3a–3j**). However, the various *N*-methyl-3-aryl-indazoles derivatives (**5a–5j**) are obtained by the *N*-methylation reactions, as given in Scheme 1.

The 3-iodo indazole (**2**) is the key intermediate in this process, which is obtained by the iodination of indazole (**1**) using KOH/I_2 in DMF. Most of the synthesized compounds originated with the Pd-catalyzed aryl coupling reaction of the 3-iodoindazole(**2**) [51] with diverse aromatic boronic acids in dimethylformamide (DMF) which yields 3-aryl-1*H*-indazoles (**3a–3j**). Moreover, the synthesis of *N*-methyl-3-aryl-indazoles derivatives (**5a–5j**) is attempted by two routes (Scheme 1). In **route 1,** the Pd promoted cross-coupling reaction of the 3-iodoindazole [52], with a variety of arylboronic acids under conventional activation producing the consecutive 3-aryl-1*H*-indazoles (**3a–3j**), and yield obtained was 55%–70%, which on methylation with methyl iodide gave the final desired *N*-methyl-3-aryl-indazoles derivatives (**5a–5j**) in 58%–75% yield. However, in **route 2**, the 3-iodo-indazole (**2**) intermediate is first subjected to *N*- methylation using MeI to yield *N*-methyl-3-iodo-indazole intermediate (**4**), which is then reacted with a variety of arylboronic acids to yield *N*-methyl-3-substituted indazoles (**5a–5j**) in good yields. The individual synthetic results such as reaction time, yield, and melting point for the compounds **3a–3j** and **5a–5j** were indicated in Tables 1 and 2**,** respectively. In the synthetic course, during the methylation of 3-substituted indazoles using methyl iodide, yields the *N*-1 methylated product predominantly, and we did not observe any *N*-2 methyl isomer formation in the reaction mixture. It might be due to the reason that the direct methylation of indazoles in the presence of a base generally provides thermodynamically stable *N*-1 methylated products predominantly [53].

Table 1. Details of the series of compounds **3a–3j**.

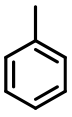
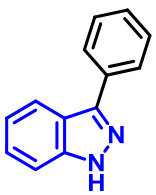
Compound	R-B(OH)$_2$ R =	Product 3a–3j	Time (h)	Yield (%)	M.P. (°C)
3a			12	65	114–116

Table 1. *Cont.*

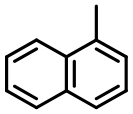
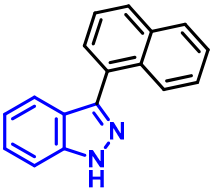
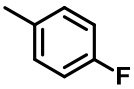
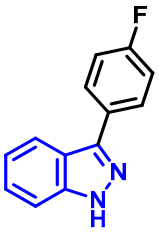
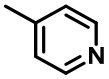
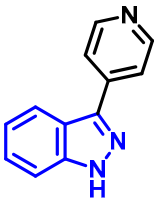
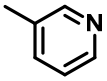
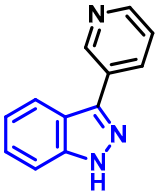
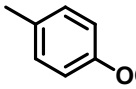
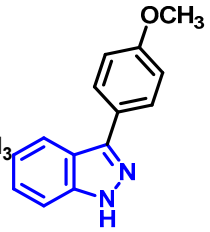
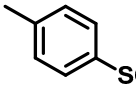
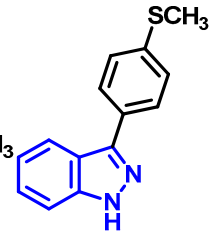
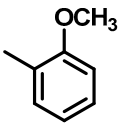
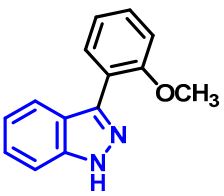
Compound	R-B(OH)$_2$ R =	Product 3a–3j	Time (h)	Yield (%)	M.P. (°C)
3b			10	67	136–138
3c			9	55	112–113
3d			8	63	101–103
3e			8	62	184–186
3f			9	70	85–77
3g			10	70	123–125
3h			9	68	115–116

Table 1. *Cont.*

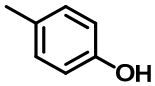
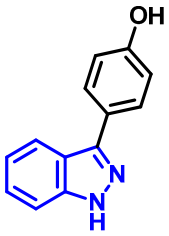
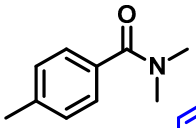
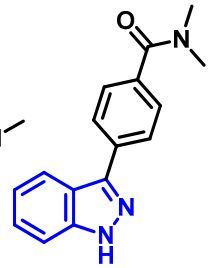
Compound	R-B(OH)$_2$ R =	Product 3a–3j	Time (h)	Yield (%)	M.P. (°C)
3i			8	60	121–123
3j			11	60	116–117

Table 2. Details of the series of compounds **5a–5j.**

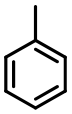
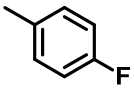
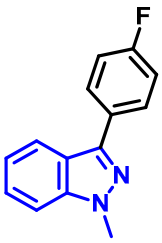
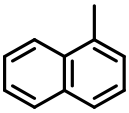
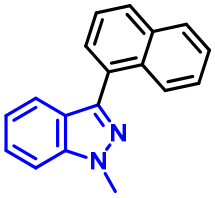
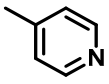
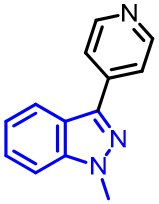
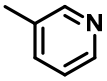
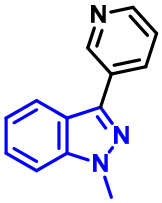
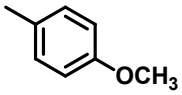
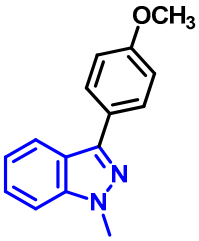
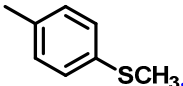
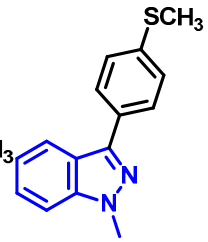
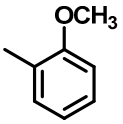
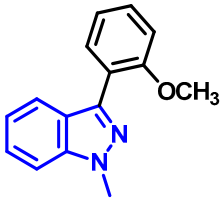
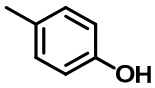
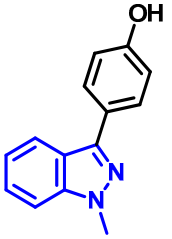
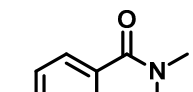
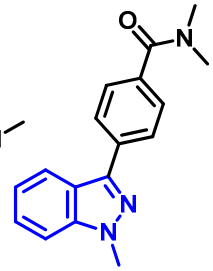
Entry	R-B(OH)$_2$ R =	Product 5a–5j	Time (h)	Yield (%)	M.P. (°C)
5a			12	70	76–78
5c			14	58	98–100
5b			11	72	137–139
5d			10	72	101–103

Table 2. *Cont.*

Entry	R-B(OH)$_2$ R =	Product 5a–5j	Time (h)	Yield (%)	M.P. (°C)
5e			11	70	74–76
5f			10	75	112–114
5g			10	73	99–101
5h			11	72	105–107
5i			10	69	241–243
5j			12	67	110–112

All the spectroscopic and analytical data of the synthesized compounds are in full agreement with the anticipated structures. For example, for the sample **5f,** the appearance of the characteristic peak at 2960 (s), 1164 (s) cm^{-1} is owed to the existence of CH_3, C-O-C groups. The IR stretching bands at 1350 (s) cm^{-1} and 1201 (m) cm^{-1} are because of C=N and due to N-N stretchings, peaks at

1607 (m), 1569 (s) and 1530 (w) cm^{-1} are due to the aromatic Ar-C=C stretching, and peak at 3098 (w) cm^{-1} are because of aromatic =CH stretching which is further confirmed by other spectral analysis. The ^{1}H-NMR spectrum of **5f** displayed signals at chemical shift values δ 3.91 (s, 3H),δ 4.15 (s, 3H), which are assigned to the N-CH_3, O-CH_3 groups, doublet at δ 8.02, 7.90 ppm, multiplet at δ 7.42, 7.23 ppm and another doublet at δ 7.08 ppm assigned for aromatic protons. This spectral data provides strong evidence to assign the structure of the compound (**5f**) as *3-(4-methoxyphenyl)-1-methyl-1H-indazole*, which is further authenticated from its ^{13}C-NMR spectrum, which reveals the existence of 13 different carbons in the compound. The peaks at δ 35.9 and δ 55.7 ppm are allocated to the *N*-CH_3 and *O*-CH_3 carbons, respectively, while the signal at δ 154.9 ppm is attributed to the C_3 carbon of indazole core nuclei. The signals at δ 143-110 ppm are due to the presence of aromatic moiety in the molecule **5f**, i.e., *3-(4-methoxyphenyl)-1-methyl-1H-indazole*. The molecular ion peak at 239.09 $(M + H)^+$ in its mass spectra (ESI) further supports the formation of compound **5f**.

3.2. Cytotoxic Study

Initially, the prepared compounds **3a–3j** are screened for their *in-vitro* anticancer activity against the human colon carcinoma cell line (HCT-116) and the human breast cancer cell line (MDA-MB-231), according to the literature protocol [47]. The cell lines are cultured with DMEM supplemented with 10% FBS, L-glutamine, sodium bicarbonate, and an antibiotic solution containing penicillin (100 U/mL) and streptomycin (100 µg/mL). All cell lines are maintained in culture at 37 °C in an atmosphere of 5% carbon dioxide. The as-synthesized indazoles **3a–3j** are screened for in vitro cytotoxic activity against HCT-116 and MBA-MB-231 cell lines. The anticancer properties of these analogs, i.e., **3a–3j**, are compared with the standard doxorubicin. IC_{50} values of the test compound for 24 h on each cell line are calculated and presented in Table 3.

Table 3. Anticancer activity of compounds **3a–3j.**

Compound	IC_{50} (µg/mL)	
	HCT-116	**MDA-MB-231**
3a	–	–
3b	–	–
3c	92.9 ± 6.5	102.3 ± 13.2
3d	127.6 ± 3.8	117.5 ± 15.0
3e	–	–
3f	109.6 ± 12.3	107.4 ± 10.0
3g	106.6 ± 14	112.2 ± 17.9
3h	93.6 ± 7.2	95 ± 6.8
3i	102 ± 11.1	120.1 ± 7.2
3j	85.3 ± 16.7	87 ± 5.2
Standard *	1.2 ± 0.3	0.3 ± 0.1

"–" indicates IC_{50} value >200 µg/mL; IC_{50} values are reported in micromolar concentrations of the compound to affect 50% inhibition of the tumor cell growth; * doxorubicin is employed as standard.

It is evident from the results that the tested indazole compounds **3c**, **3g**, and **3i** are found to be more potent against the HCT-116 cell line than the MDA-MB-231 cell line. However, the test compound **3j** possesses potent cytotoxic activity against both the cell lines tested, i.e., HCT-116 and MDA-MB-231 at IC_{50} < 87 µg/mL. Very few of the 3-aryl-1-*H*-indazole compounds (**3h** and **3c**) are found to be moderately active against the two cell lines tested. The test compound **3j** showed good activity against the HCT-116 cell line. The test compounds **3c** and **3h** exhibited almost similar activity against the HCT-116 cell line with IC_{50} < 94 µg/mL. The compounds **3h** and **3c** are found to be moderately active against the cell line

MDA-MB-231 with IC_{50} < 96 and IC_{50} < 103 μg/mL, respectively. Unfortunately, the compounds **3a**, **3b,** and **3e** are found to be inactive against the tested two cell lines.

After the screening of the cytotoxic properties of 3-aryl indazoles **3a–3j**, the studies were extended to the evaluation of cytotoxic properties of the final compound i.e., *N*-methyl-3-aryl indazoles **5a–5j** against the cancer cell lines HCT-119 and MDA-MB-231, according to the same literature protocol [47] employed above. The IC_{50} values of the test compounds are compared with the standard doxorubicin and the results of investigation were presented in Table 4. The IC_{50} value of the standard doxorubicin is 1.2 μg/mL against the HCT-116 cell line, 0.3 μg/mL against the MDA-MB-231 cell line. The tested compounds **5a–5j** showed their IC_{50} values in between 54.1–172.4 μg/mL. All the obtained compounds displayed moderate to mild cytotoxic than the standard as evident from their higher IC_{50} values. From the above studies, it can be found that doxorubicin is more potent than the tested compounds; however, the structure related activity study of tested compounds can be used to guide us to develop potent molecules. A graphical illustration for the obtained IC_{50} values for the compounds **3a–3j** and **5a–5j** is given in Figure 3**.**

Table 4. Anticancer activity of compounds **5a–5j.**

Compound	IC_{50} (μg/mL)	
	HCT-116	**MDA-MB-231**
5a	148.8 ± 4.7	172.4 ± 14.2
5b	110.6 ± 5.9	125.7 ± 13.1
5c	63.7 ± 14.0	58.2 ± 14.7
5d	62.3±15.0	81.0±3.4
5e	102 ± 14.0	150.1 ± 7.2
5f	69.0 ± 18.0	80.7 ± 10.5
5g	72.7 ± 20.0	88.5 ± 10.1
5h	90.1 ± 1.5	98.6 ± 18
5i	62.3 ± 6.0	79.0 ± 7.2
5j	79.4 ± 7.4	87.8 ± 6.9
Standard *	1.2 ± 0.3	0.3 ± 0.2

"–" indicates IC50 value >200 μg/mL; IC50 values are reported in micromolar concentrations of the compound to affect 50% inhibition of the tumor cell growth; * doxorubicin is employed as standard.

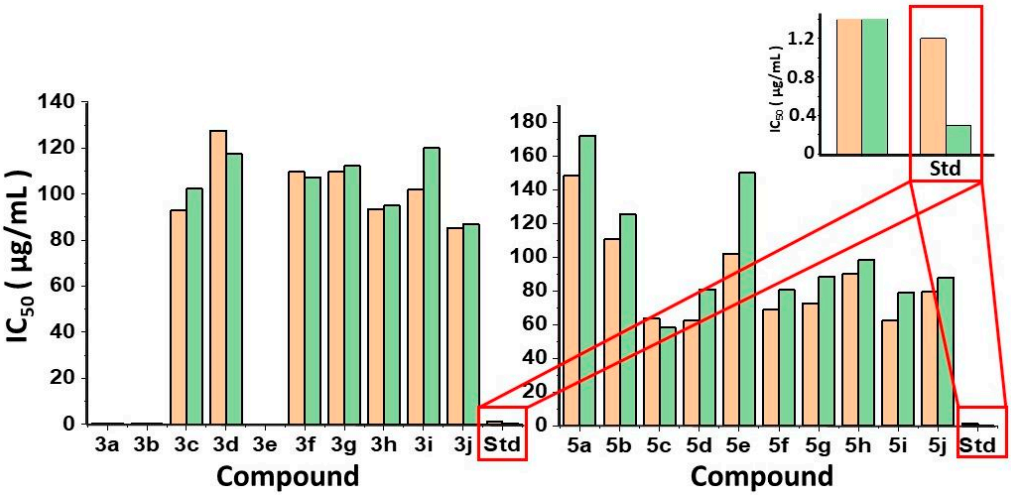


Figure 3. Illustration of the IC_{50} values for the compounds **3(a–ja**; b; c; d; e; f; g; h; i; j) and **5(a–ja**; b; c; d; e; f; g; h; i; j; a; b; c; d; e; f; g; h; i; j).

The result of the present investigation reveals that few of the tested compounds have shown significant decrease in cell viability in two test cell lines. It is evident from the results that the *N*-methyl-3-aryl indazoles (**5a–5j**) are found to be more potent than **3a–3j** against HCT-116 and MDA-MB-231 cell lines. The compounds **5c, 5d**, **5f, 5g,** and **5i** exhibit significant cytotoxic activities against the two cell lines tested. However, the test compound **5c** is found to be more potent against the cell lines HCT116 and MDA-MB-231 with $IC_{50} < 64$ and $IC_{50} < 59$ μg/mL, respectively. The test compounds **5d** and **5i** show potent activity against the cell line HCT-116 with $IC_{50} < 63$ μg/mL. The compounds **5g, 5f** display moderate activity against the HCT-116 cell line with $IC_{50} < 73$ μg/mL. The differential activity among the cell lines may be due to the structure–activity relationship of the molecules. Exponentially growing cells were treated with different concentrations of indazole compounds for 24 h and cell growth inhibition is analyzed through MTT assay.

Structure Activity Relationship (SAR)

The cautious investigation of the relation between structures and anticancer activities data of the test compounds reveals the following assumption about SAR: (i) *N*-methyl-3-aryl indazoles **5a–5j** show higher activity than 3-aryl substituted indazoles derivatives **3a–3j** against the tested cell lines HCT-16 and MDA-MB-231; (ii) additional, slight enhancement of the cytotoxic activity of compounds **5a–5j** over **3a–3j** can be attributed to the presence of the methyl group; (iii) the presence of electron withdrawing fluoro substitution at 4th position of the phenyl ring **5c** is responsible for its superior anti cancer activity. In addition, electron releasing hydroxy group **5i** and *N*,*N*-dimethylamide group **5j** at para position of the phenyl ring exhibited good anti-cancer activity. Hence, from the results of above anticancer activity, it can be concluded that diverse structural requirements are essential for a compound to be active against different cancer targets.

4. Conclusions

In conclusion, a series of 3-aryl-1*H*-indazoles and *N*-methyl-3*H*-indazoles were synthesized successfully using simple reagents. All the synthesized indazoles were screened for their in vitro anti-cancer activities against the cell lines HCT-116 and MDA-MB-231. The results of the cytotoxic studies of the tested compounds reveal that compound **5c** exhibited significant inhibitory effect on the two tested cancer cell lines amongst all the compounds synthesized. Compounds **5i, 5d**, and **3j** also exhibited good cytotoxic activity. Most of the compounds are active against human colon carcinoma cell line (HCT-116) and human breast cancer cell line (MDA-MB-231). However, the prepared compounds are comparatively less potent than commercially available drug doxorubicin (positive control). Nevertheless, we believe that slight structural modification of these active derivatives may yield better prospective anticancer drugs and demand further experimental investigations, especially in the area of anticancer research.

Author Contributions: Conceptualization, H.B.B.; methodology, J.M.R.S.; investigation, S.N.M.B.; carried out the preparation and characterization of Indazole derivatives, S.N.M.B. and R.M.; carried out the interpretation of some part of results, S.F.A., O.A., M.R.S. and H.B.B.; writing—original draft preparation, S.N.M.B.; J.M.R.S.; writing—review and editing, H.B.B.; helped to draft the manuscript, J.M.R.S., S.F.A., O.A., M.R.S. and H.B.B.; supervision, H.B.B. and M.R.H.S.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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