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Synthesis and anticancer evaluation of indazole-aryl hydrazide-hydrazone derivatives

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Abstract: A new series of hydrazide-hydrazones linked between indazole and substituted benzaldehydes were designed, synthesized and evaluated for their cytotoxicity against four human cancer cell lines (HeLa, MDA-MB-231, MCF-7 and A549). Among the synthesized compounds 10a, 10e, and 10h showed promising cytotoxicity specifically on some of the tested cell lines with IC_{50} values of 2.1 (HeLa), 2.37 (MCF-7) and 1.39 (MCF-7) respectively. The compound 10a exhibited its potent activity especially on HeLa cell line. Further, the compound 10e was identified as a promising drug lead which showed promising cytotoxicity with IC_{50} value of 1.39 μM towards MCF-7 breast cancer cell line as compared with standard drug doxorubicin (IC_{50} value 0.54 μM). While all these new compounds showed no cytotoxicity on the normal human embryonic kidney cell line, HEK-293.

Introduction

The chemistry of nitrogen heterocyclic compounds has attracted more attention during recent years, due to their reactivity and novel biological activities. Most of the fused heterocyclic systems exhibit excellent anti-tumor activities and also act as potent anti-tumor agents in cancer chemotherapy[1–14]. Indazole was a heterocyclic aromatic compound and it was a fusion of both benzene and pyrazole compounds. Different indazole derivatives were screened a broad spectrum of potent biological activities which include anti-tumor[15–17], antimicrobial[18,19], anti-depressant[20], anti-platelet[21], anti-emetic[22], anti-spermatogenic[23], anti-HIV[24–26], anti-inflammatory[27–29], anticataract[30], anti-analgesic and anti-pyretic[31] activities. N-Acyl hydrazones of indazole derivatives were evaluated for their micromolar inhibitory activities against Mur D and Mur C enzymes from *Escherichia coli*[32].

Similarly, the functional group hydrazide-hydrazone (-CO-NH-N=CH-) was also evaluated for different pharmaceutical activities including anti-tumor[33–36], anti-malarial[37], anti-convulsant[38], anti-inflammatory[39], anti-tubercular[40], antileishmanial[41] and antimicrobial[42] activities. The anticancer drugs such as ionidamine 1, indole-indazolyl hydrazide-hydrazone 2 and pyrimidine fused indazole-3-amine 3 as shown in Fig. 1.

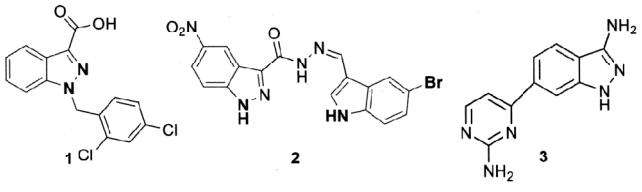


Fig. 1. Structures of ionidamine, indole-indazolyl hydrazide-hydrazone and pyrimidine fused indazole-3-amine.

In continuation of our research work, we designed and synthesized a variety of 5-nitro indazole-aryl fused hydrazide-hydrazone derivatives and screened their anti-tumor activities against cervical (HeLa), breast (MDA-MB-231, MCF-7) and lung (A549) cancer cell lines.

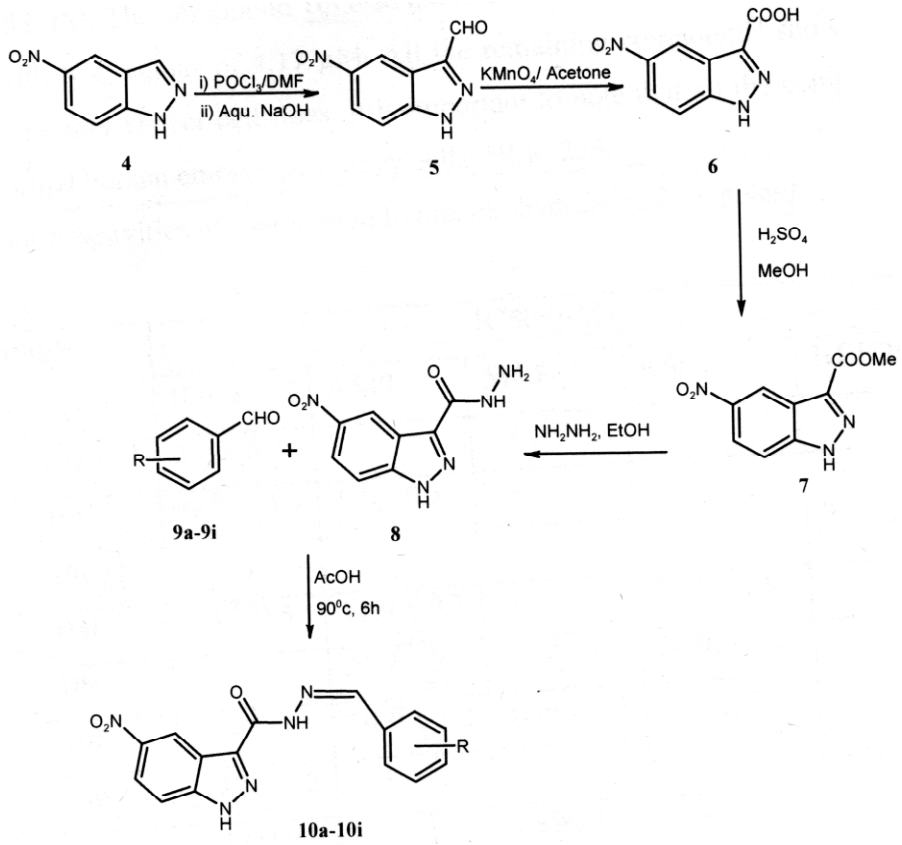
Results and discussion

Synthesis:

The synthesis of indazole-aryl fused hydrazide-hydrazone derivatives were shown in Scheme 1. Vilsmeier-Haack reaction of 5-nitro indazole 4 gave 5-nitro indazole-3-aldehyde 5. This aldehyde 5 undergo oxidation with $KMnO_4$ in acetone at room temperature over 6 h gave 5-nitro indazole-3-carboxylic acid 6. The compound 6 was refluxed with methanol and catalytic amount of conc. H_2SO_4 over a period of 6 h then yield 7, which was reacted with hydrazine hydrate in ethanol solvent by refluxing for 8 h then gave the acid hydrazide 8 with good yield. Finally, the acid hydrazide was condensed with different aryl aldehydes 9a-9i in glacial acetic acid at 90°C over 6 h time period then afforded indazole-aryl fused hydrazide-hydrazone derivatives 10a-10i with good yields.

Biological evaluation – In vitro cytotoxicity:

The synthesized ten derivatives were screened for their anticancer activity against the selected five human cancer cell lines such as cervical (HeLa), breast (MDA-MB-231 and MCF-7), lung (A549) and kidney (HEK-293) as per reported protocol and shown by IC_{50} in μM. The anticancer activities of tested compounds ranged between 0.37–32.7 μM (Table 1). Among them, the compound 10d showed potent anticancer activity against HeLa cell line with IC_{50} value of 0.37 μM. The compounds 10a and 10g exhibited potent anticancer activity especially on cervical cancer cell line HeLa with IC_{50} value of 2.1 μM and 3.19 μM respectively then these compounds act as potent drug leads in cancer chemotherapy. The compounds 10e, 10f and 10h showed good anticancer activities against breast cancer cell line with IC_{50}



where, 9a, R = H, 9b, R = *o*-NO_2, 9c, R = *p*-F, 9d, R = *o*-Cl, 9e, R = *p*-$N(CH_3)_2$, 9f, R = *o*-OH, 9g, R = *m*-OH, 9h, R = *p*-OH, 9i, R = *p*-CH_3, 10a, R = H, 10b, R = *o*-NO_2, 10c, R = *p*-F, 10d, R = *o*-Cl, 10e, R = *p*-$N(CH_3)_2$, 10f, R = *o*-OH, 10g, R = *m*-OH, 10h, R = *p*-OH, 10i, R = *p*-CH_3

Scheme 1. Schematic representation for the synthesis of novel hydrazide-hydrazones.

Table 1. Anticancer activities of synthesized hydrazide-hydrazone derivatives

Sample	IC_{50} (μM)				
	HeLa	A549	MCF-7	K562	HEK-293
10a	2.1 ± 0.7	–	–	–	–
10b	16.3 ± 0.9	6.1 ± 0.5	–	–	–
10c	–	–	–	–	–
10d	0.37 ± 0.5	11.9 ± 0.7	–	32.7 ± 1.9	–
10e	–	21.7 ± 2.3	2.37 ± 1.9	26.9 ± 1.5	–
10f	–	10.9 ± 1.2	5.39 ± 1.3	13.6 ± 1.3	–
10g	3.19 ± 1.2	–	–	–	–
10h	4.17 ± 0.9	–	1.39 ± 0.9	–	–
10i	23.7 ± 1.9	5.32 ± 1.3	26.7 ± 1.8	–	–
Doxorubicin (Standard)	0.5 ± 0.2	0.69 ± 0.5	0.54 ± 0.3	0.71 ± 0.45	

where, A549–Human alveolar adenocarcinoma cell line, HeLa–Human Cervical cancer cell line, MCF-7–Human breast adenocarcinoma cell line, K562–Human chronic myelogenous leukemia cell line, HEK-293–Human normal embryonic kidney cell line.

value of 2.37 μM, 5.39 μM and 1.39 μM respectively. While the compounds 10b and 10i exhibited anticancer activities against lung cancer cell line with IC_{50} values of 6.1 μM and 5.32 μM. The compound 10i also exhibited anticancer activity against cervical cancer cell line HeLa with IC_{50} values of 4.17 μM. All the remaining compounds showed less anticancer activities among the four cancer cell lines. It is important to note that all the compounds showed no activity on the normal human embryonic kidney cells, HEK-293.

Experimental

All the chemicals, reagents and solvents were purchased from Avra Pvt. Ltd. and Sigma-Aldrich. Purity of the compounds was checked by TLC on silica gel plates and spots were visualized by exposure to ultra violet light. ^{1}H NMR spectra were recorded on Bruker-400 Ultra Shield^{TM} Spectrometer. Chemical shifts (δ) are expressed in ppm using DMSO-d_6 solvent and tetra methyl saline (TMS) as internal standard. The physical constants and spectral data of the synthesized compounds are presented.

Synthesis of 5-nitro-N′-[(Z)-phenylmethylidene]-1H-indazole-3-carbohydrazide (10a):

5-Nitro-1*H*-indazole-3-carbohydrazide (8, 500 mg, 2.26 mmol, 1.0 eq.) was dissolved in 3 mL glacial acetic acid. To this reaction mixture 2.26 mmol, 1.0 eq. benzaldehyde 9a was added and heated at 90°C for 6 h. Later the reaction mass was neutralized with a cold $NaHCO_3$ solution. Now the compound was filtered and dried. The dry compound was purified through recrystallization process by using 99% ethanol solvent and then gave 10a. Pale brown color solid. Yield: 83%, m.p. 115–117°C; IR (KBr): 3328, 1741, 1669, 1547, 1389, 1132, 950, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (NH, brs), 11.24 (NH, brs), 8.14 (1H, s), 7.99 (1H, s), 7.68–7.65 (3H, m), 7.43–7.41 (4H, m) ppm; ESI-MS: 310 $(M+H)^+$.

Synthesis of 5-nitro-N′-[(Z)-(2-nitrophenyl) methylidene]-1H-indazole-3-carbohydrazide (10b):

This compound 10b was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *o*-nitro benzaldehyde 9b then give 10b. Yellowish brown color solid. Yield: 81%, m.p. 150–152°C; IR (KBr): 3303, 1745, 1671, 1565, 1340, 1266, 1117, 930, 835, 731 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (NH, brs), 11.53 (NH, brs), 8.55 (1H, s), 8.34 (1H, s), 8.08–8.01 (2H, m), 7.82–7.76 (2H, m), 7.68–7.62 (2H, m) ppm; ESI-MS: 355 $(M+H)^+$.

Synthesis of N′-[(Z)-(4-fluorophenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10c):

This compound 10c was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *p*-fluoro benzaldehyde 9c then give 10c. Dark brown color solid. Yield: 78%, m.p. 142–144°C; IR (KBr): 3310, 1740, 1676, 1544, 1378, 1225, 1145, 934, 832, 769 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (NH, brs), 11.25 (NH, brs), 8.72 (1H, s), 8.15 (1H, s), 7.98–7.94 (1H, m), 7.75–7.70 (1H, m), 7.38–7.24 (4H, m) ppm; ESI-MS: 328 $(M+H)^+$.

Synthesis of N′-[(Z)-(2-chlorophenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10d):

This compound 10d was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *o*-chloro benzaldehyde 9d then afforded 10d. Pale brown color solid. Yield: 84%, m.p. 112–114°C; IR (KBr): 3368, 1740, 1671, 1556, 1392, 1286, 932, 794 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.80 (NH, brs), 11.49 (NH, brs), 8.99 (1H, s), 8.55 (1H, s), 8.38 (1H, s), 7.96–7.94 (2H, m), 7.52–7.39 (3H, m) ppm; ESI-MS: 344 $(M+H)^+$.

Synthesis of N′-{(Z)-[4-(dimethylamino) phenyl]-methylidene}-5-nitro-1H-indazole-3-carbo hydrazide (10e):

This compound 10e was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *p*-N,N-dimethyl amino benzaldehyde 9e then afforded 10e. Yellowish dark brown color solid. Yield: 87%, m.p. 142–144°C; IR (KBr): 3310, 1742, 1678, 1519, 1428, 956, 810, 736 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.03 (NH, brs), 10.93 (NH, brs), 8.50 (1H, s), 7.99 (1H, s), 7.85 (1H, s), 7.66–7.64 (1H, d, *J* 8.4 Hz), 7.49–7.44 (2H, m), 6.78–6.71 (2H, m), 3.00 (3H, s), 2.96 (3H, s) ppm; ESI-MS: 353 $(M+H)^+$.

Synthesis of N′-[(Z)-(2-hydroxyphenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10f):

This compound 10f was prepared following the method described for the preparation of the compound 11a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *o*-hydroxy benzaldehyde 9f then give 10f. Pale brown color solid. Yield: 79%, m.p. 165–167°C; IR (KBr): 3457, 1674, 1555, 1485, 1391, 945, 853 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.21 (NH, brs), 9.01 (1H, s), 8.34 (1H, s), 8.27 (1H, s), 7.50–7.48 (1H, s), 7.29–7.20 (1H, m), 6.99–6.83 (3H, m) ppm; ESI-MS: 326 $(M+H)^+$.

Synthesis of N′-[(Z)-(3-hydroxyphenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10g):

This compound 10g was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *m*-hydroxy benzaldehyde 9g then afforded 10g. Pale brown color solid. Yield: 82%, m.p. 182–184°C; IR (KBr): 3455, 1743, 1648, 1549, 1414, 1318, 942, 874 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.33 (NH, brs), 11.17 (NH, brs), 8.05 (1H, s), 7.89 (1H, s), 7.24–7.19 (2H, m), 7.13 (1H, s), 7.08 (1H, s), 7.05–7.02 (1H, s), 6.81–6.79 (1H, d, *J* 8 Hz) ppm; ESI-MS: 326 $(M+H)^+$.

Synthesis of N′-[(Z)-(4-hydroxyphenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10h):

This compound 10h was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *p*-hydroxy benzaldehyde 9h then give 10h. Yellowish brown color solid. Yield: 83%, m.p. 183–185°C; IR (KBr): 3462, 1691, 1548, 1261, 962, 823 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.13 (NH, brs), 11.02 (NH, brs), 9.86 (OH, brs), 8.03 (1H, s), 7.88 (1H, s), 7.70–7.68 (1H, d, *J* 8.4 Hz), 7.51–7.46 (2H, t), 6.87–6.79 (3H, m) ppm; ESI-MS: 326 $(M+H)^+$.

Synthesis of N′-[(Z)-(4-methylphenyl) methylidene]-5-nitro-1H-indazole-3-carbohydrazide (10i):

This compound 10i was prepared following the method described for the preparation of the compound 10a, employing 500 mg, 1.0 eq. 8 with 2.26 mmol, 1.0 eq. *p*-methyl benzaldehyde 9i then gave 10i. Dark brown color solid. Yield: 76%, m.p. 123–125°C; IR (KBr): 3456, 1742, 1648, 1549, 1426, 1368, 966, 810 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.28 (NH, brs), 11.16 (NH, brs), 8.67 (1H,

s), 7.95 (1H, s), 7.78–7.76 (1H, d, *J* 8 Hz), 7.57–7.53 (2H, m), 7.33–7.23 (3H, m) ppm; ESI-MS: 324 $(M+H)^+$.

In vitro cytotoxicity assay:

Cytotoxicity of the synthesized compounds was assessed on the basis of measurement of the *in vitro* growth in the 96-well microtitre plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals by a previously described method (Mosmann 1983). Cell lines for testing *in vitro* cytotoxicity included HeLa derived from human cervical cancer cells (ATCC No. CCL-2), A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26), MCF-7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) and HEK-293 derived from normal human embryonic kidney cells (ATCC No. CRL-1573) were obtained from American Type Culture Collection, Manassas, VA, USA. All tumour cell lines were maintained in a modified DMEM medium supplemented with 10% fetal bovine serum, along with 1% non-essential amino acids except L-glutamine, 0.2% sodium hydrogen carbonate, 1% sodium pyruvate and 1% antibiotic mixture (10000 units penicillin and 10 mg of streptomycin per mL). The cells were washed and re-suspended in the above medium and then 100 mL of this suspension was seeded into a 96-well bottom plate. The cells were kept at 37ºC in a humidified incubator (Model 2406 Shellab CO_2 incubator, Sheldon, Cornelius, OR) under a 5% CO_2 atmosphere. After incubation for 24 h, the cells were treated for 2 days with the test compounds at concentrations ranging from 0.1–100 mM in DMSO and were assayed at the end of the second day. After incubation for 48 h, the cells were subjected to the MTT colorimetric assay (5 mg mL^{-1}). The effects of the different test compounds on the viability of the tumour cell lines were measured at 540 nm using a multimode reader (Infinite® M200Pro, Tecan, Switzerland). Doxorubicin was used as positive control for comparison purpose and 1% DMSO as a vehicle control. In order to account for the toxicity of DMSO, the values obtained for the DMSO control were subtracted from those of the test compounds. Dose-response curves were plotted for the test compounds and controls after correction by subtracting the background absorbance from that of the blanks. The antitumor potency of the compounds indicated by IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose-response curves. Statistical analysis was performed using GraphPad PRISM software version 3.0 (GraphPad Software, Inc, La Jolla, CA, USA). IC_{50} values (in μM) are expressed as the mean ± S.D of four independent experiments. All experimental data were compared using Student's t-test. In all comparisons, $p < 0.05$ was considered statistically significant.

Conclusion

All the synthesized hydrazide-hydrazone derivatives were evaluated for their cytotoxicity against four human cancer cell lines (HeLa, MDA-MB-231, MCF-7 and A549). Among the synthesized compounds, 10a, 10e, and 10h showed promising cytotoxicity specifically on some of the tested cell lines with IC_{50} values of 2.1 (HeLa), 2.37 (MCF-7) and 1.39 (MCF-7) respectively. The compound 10a exhibited its potent activity especially on HeLa cell line. Further, the compound 10e was identified as a promising drug lead which showed promising cytotoxicity with IC_{50} value of 1.39 μM towards MCF-7 breast cancer cell line as compared to the standard drug doxorubicin (IC_{50} value 0.54 μM).

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