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Synthesis and Antitumor Evaluation of Novel 5-Bromo Indole-Aryl Keto Hydrazide-Hydrazone Analogues

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A wide variety of indole, substituted benzaldehyde linked keto hydrazide-hydrazone analogues were designed, synthesized and evaluated for their cytotoxicity against eight human cancer cell lines HeLa, A549, MCF-7, K562, HEK293, HT29, SF295 and HL60. All these synthesized compounds showed potent antitumor activities on the above eight human cancer cell lines. Among them, **6a** and **6h** compounds exhibited potent antitumor activity on HL 60 and A549 cancer cell lines with IC_{50} value of 3.913 and 4.838 µM than the standard drug cisplatin with IC_{50} values of 27 and 36 µM, respectively.

Keywords: 5-Bromo indole, Keto hydrazide-hydrazones, Lung cancer, Bone marrow cancer, MTT assay.

INTRODUCTION

Heterocycles by far are the largest classical division of organic chemistry and are of immense importance. Synthesis of such heterocyclic compounds are pharmaceutical important and a foremost task of chemists due to its vast pharmacological and industrial applications. A large number of heterocyclic systems with different hetero moieties act as good anticancer agents in cancer chemotherapy and showed potent anticancer activities against a panel of human cancer cell lines [1-10].

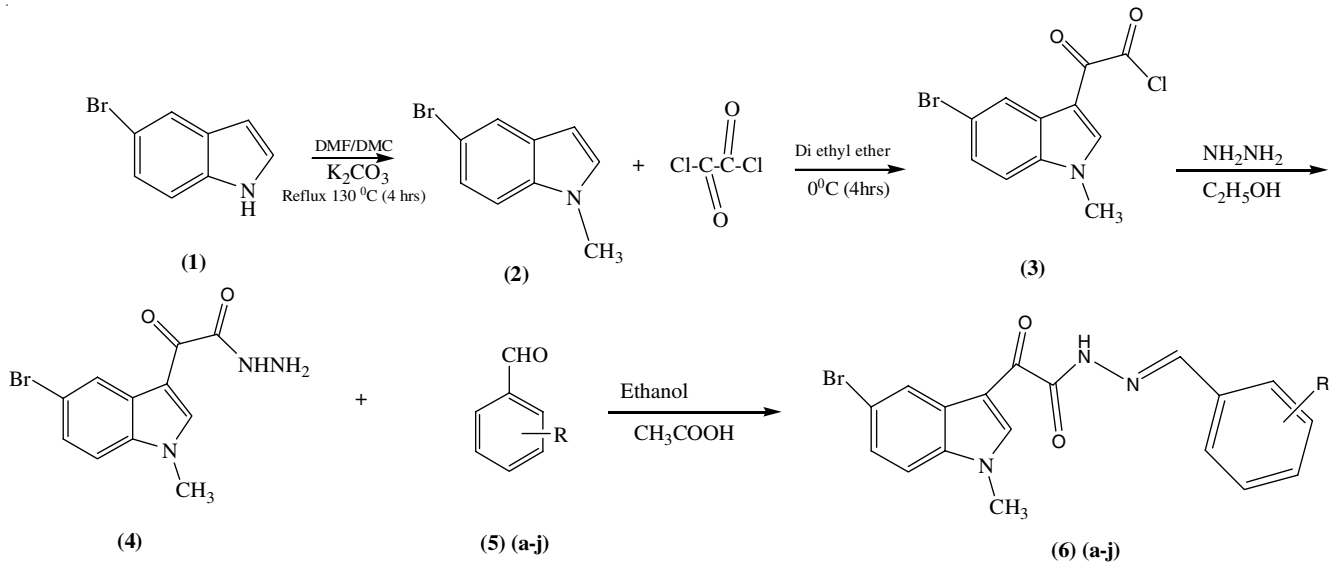
From these heterocyclic compounds, indole fused aryl aldehyde compounds constitute an important class of compounds for new drug development, in order to discover an effective indole hydrazide-hydrazone derivatives against human cancer cell lines. Previously indole-hydrazide-hydrazone derivatives shows antimicrobial [11-17], antifungal [18], anticonvulsant [19], anti-inflammatory, antiplatelet [20-24] and antituberculosis activities [25-28]. But these series of indole fused aryl aldehydes analogues shows potent antitumor [29-33] activity on anticancer [34-36] human cell lines.

Similarly, hydrazide-hydrazone (-CO-NH-N=CH-) moiety was also evaluated for different biological activities including antitubercular, antimicrobial, antimalarial, anticonvulsant, anti-inflammatory, antileishmanial and antitumour activities.

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. Micro analysis was done on Perkin-Elmer model 240 analyzer and the values were found within ± 0.4 % of the theoretical values. ^{1}H NMR spectra were recorded on BRUKER-400 Ultra Shield ™ 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.

General procedure: The synthesis of novel indole-aryl fused keto hydrazide-hydrazone analogues were shown in **Scheme-I**. 5-Bromo indole (**1**) on methylation with DMC, K_2CO_3 at 130 °C in DMF as solvent over a period of 4 h gave 5-bromo-N-methyl indole (**2**). The compound **2** treated with oxalyl chloride at 0 °C in diethyl ether as solvent for 6 h then afforded 5-bromo-N-methyl indolyl mono oxolyl chloride (**3**). This mono oxolyl chloride (**3**) was refluxed with hydrazine hydrate with ethanol over 6 h gave 5-bromo N-methyl indolyl keto-3-carbohydrazide (**4**). Finally, this keto carbohydrazide (**4**) refluxed with different aryl aldehydes (**5a-i**) in ethanol and glacial acetic acid over 6 h afforded new indole-aryl fused keto hydrazide-hydrazone derivatives (**6a-i**) with good yields.



5a: R = *o*-NO_2 **5f:** R = *o*-OH **6a:** R = *o*-NO_2 **6f:** R = *o*-OH
5b: R = *o*-Cl **5g:** R = *m*-OH **6b:** R = *o*-Cl **6g:** R = *m*-OH
5c: R = *p*-F **5h:** R = H **6c:** R = *p*-F **6h:** R = H
5d: R = *p*-OH **5i:** R = *p*-$N(CH_3)_2$ **6d:** R = *p*-OH **6i:** R = *p*-$N(CH_3)_2$
5e: R = *p*-CH_3 **5j:** R = *m*-Br **6e:** R = *p*-CH_3 **6j:** R = *m*-Br

Scheme-I: Schematic representation for the synthesis of novel keto hydrazide-hydrazones

Synthesis of (E)-N'-(2-nitrobenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2 oxoaceto hydrazide (6a): 500 mg (1.7 mmol, 1.0 eq) of 2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (**4**) was dissolved in 3 mL of acetic acid, to this 179 mg (1.7 mmol, 1 eq) of *o*-nitro benzaldehyde was added and stir for 6 h at 90 °C. Later the reaction mass was neutralized with a cold $NaHCO_3$ solution, filtered and recrystallize from ethanol then afforded **6a**. m.p. = 328-330 °C; m.w. = 429; IR (KBr, ν_{max}, cm^{-1}) = 3195, 1666, 1527, 1344, 1197, 980, 790; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) = 8.17 (s, 1H CH) 8.15 (brs, 1H NH); 7.64-7.83 (m, 4H Ar-H); 7.23-7.42 (m, 4H Ar-H); 4.04 (s, 3H CH_3); ESI-MS: 429 $(M+H)^+$.

Synthesis of (E)-N'-(2-chlorobenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6b): The compound **6b** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq. *o*-chloro benzaldehyde **5b** then gave **6b**. m.p. = 325-327 °C; m.w. = 418; IR (KBr, ν_{max}, cm^{-1}) = 3193, 1662, 1550, 1371, 1236, 959, 792; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) = 8.62 (s, 1H CH) 8.40 (brs, 1H NH); 7.66-8.06 (m, 4H Ar-H); 7.25-7.51 (m, 4H Ar-H); 3.75 (s, 3H CH_3); ESI-MS: 418 $(M+H)^+$.

Synthesis of (E)-N'-(4-fluorobenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoaceto hydrazide (6c): The compound **6c** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *p*-fluoro benzaldehyde **5c** then given **6c**. m.p. = 320-322 °C; m.w. = 402; IR (KBr, ν_{max}, cm^{-1}) = 3248, 1667, 1510, 1372, 1238, 977, 792; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) = 8.28 (s, 1H CH), 8.05 (brs, 1H NH); 7.77-7.86 (m, 4H Ar-H); 7.27-7.46 (m, 4H Ar-H); 4.09 (s, 3H CH_3); ESI-MS: 402 $(M+H)^+$.

Synthesis of (E)-N'-(4-hydroxybenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6d): The compound **6d** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *p*-hydroxy benzaldehyde **5d** then gave **6d**. m.p. = 332-334 °C; m.p. = 400; IR (KBr, ν_{max}, cm^{-1}) = 3246, 1665, 1513, 1373, 1241, 979, 791; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) = 8.28 (s, 1H CH) 8.05 (brs, 1H NH); 7.77-7.86 (m, 4H Ar-H); 7.27-7.46 (m, 4H Ar-H) 4.09 (s, 3H CH_3); ESI-MS:400 $(M+H)^+$.

Synthesis of (E)-N'-(4-methylbenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6e): The compound **6e** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *p*-methyl benzaldehyde **5e** then afforded **6e**. m.p. = 320-321 °C; m.w. = 398; IR (KBr, ν_{max}, cm^{-1}) = 3202, 1664, 1546, 1370, 1235, 975, 788; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm) = 8.23 (s, 1H CH) 8.02 (brs, 1H NH); 7.61-7.85 (m, 4H Ar-H); 7.38-7.46 (m, 4H Ar-H) 3.81 (s, 3H CH_3); ESI-MS: 398 $(M+H)^+$.

Synthesis of (E)-N'-(2-hydroxybenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6f): The compound **6f** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *o*-hydroxy benzaldehyde **5f** then afforded **6f**. m.p. = 326-328 °C; m.w. = 402; IR (KBr, ν_{max}, cm^{-1}) = 3038, 1660, 1559, 1372, 1225, 758; ^{1}H NMR (DMSO-d_6, 400 MHz δ ppm) = 8.16 (s, 1H, CH) 7.95 (brs, 1H NH); 7.41-7.84 (m, 4H Ar-H); 6.84-7.33 (m, 4H Ar-H) 3.81 (s, 3H CH_3); ESI-MS: 400 $(M+H)^+$.

Synthesis of (E)-N'-(3-hydroxybenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6g): The compound **6g** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *m*-hydroxy benzaldehyde **5g** then gave **6g**. m.p. = 333-335 °C; m.w. = 402; IR (KBr, ν_{max},

cm^{-1}) = 3238, 1648, 1540, 1372, 1234, 792; ^{1}H NMR (DMSO-d_6, 400 MHz δ ppm) = 8.18 (s, 1H CH) 7.97 (brs, 1H NH); 7.43-7.85 (m, 4H Ar-H); 7.09-7.40 (m, 4H Ar-H) 3.82 (s, 3H CH_3); ESI-MS: 400 $(M+H)^+$.

Synthesis of (E)-N'-benzylidene-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6h): The compound **6h** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq benzaldehyde **5h** then afforded **6h**. m.p. = 327-329 °C; m.w. = 384; IR (KBr, ν_{max}, cm^{-1}) = 3212, 1663, 1554, 1328, 1240, 794; ^{1}H NMR (DMSO-d_6, 400 MHz δ ppm) = 8.23 (s, 1H CH) 8.01 (brs, 1H NH); 7.71-7.80 (m, 4H Ar-H); 7.23-7.67 (m, 4H Ar-H) 3.82 (s, 3H CH_3); ESI-MS: 384 ESI-MS: 400 $(M+H)^+$.

Synthesis of (E)-N'-(4-(dimethylamino)benzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6i): The compound **6i** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq N,N-dimethyl benzaldehyde **5i** then gave **6i**. m.p. = 335-337 °C; m.w. = 427; IR (KBr, ν_{max}, cm^{-1}) = 3205, 1605, 1524, 1368, 1249, 791; ^{1}H NMR (DMSO-d_6, 400 MHz δ ppm) = 8.12 (s, 1H CH) 7.92 (brs, 1H NH); 7.52-7.85 (m, 4H Ar-H); 6.79-7.45 (m, 4H Ar-H) 4.04 (s, 3H CH_3), 3.62-3.81 (s, 3H CH_3), 3.01-3.37 (s, 3H CH_3); ESI-MS: ESI-MS:400 $(M+H)^+$.

Synthesis of (E)-N'-(3-bromobenzylidene)-2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (6j): The compound **6e** was prepared by following the method described for the preparation of the compound **6a**, employing 500 mg, 1.0 eq. **4** with 1.7 mmol, 1.0 eq *m*-bromo benzaldehyde (**5j**) then afforded **6j**. m.p. = 312-314 °C; m.w. = 463; IR (KBr, ν_{max}, cm^{-1}) = 3197, 1654, 1576, 1331, 1236, 785; ^{1}H NMR (DMSO-d_6 400 MHz, δ ppm) = 8.24 (s, 1H CH) 8.03 (brs, 1H NH); 7.82-7.96 (m, 4H Ar-H); 7.52-7.79 (m, 4H Ar-H) 3.82 (s, 3H CH_3); ESI-MS: 461 $(M+H)^+$.

Detection method

***in vitro* cytotoxicity assay:** Cytotoxicity activities against human cancer cell lines of these synthesized compounds were tested by method of MTT assay. These compounds were dissolved in dimethyl sulphoxide and diluted in culture media prior to the application. Different dilutions of each compound were tested (0.1 to 100 μM) with an incubation period of not more than 48 h. 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 anticancer potency of these hydrazide hydrazones compounds (**6a-j**) indicated by IC_{50} values (50 % inhibitory concentration) were calculated by compared to the standard drug cisplatin. From plotted absorbance data for the dose-response curves. Statistical analysis was performed using SPSS software version 16.0. IC_{50} values (μM) are expressed as the mean ± SD of five independent experiments. Human cancer cell lines were used, HeLa (cervical cancer cell line), A549 (alveolar adenocarcinoma cell line), SF295 (glioblastoma-multiforme cell line), HT-29 (colorectal adenocarcinoma), MCF-7 (breast cancer), K562 (chronic myelogenous leukemia cell line) HEK 293 (normal embryonic kidney cell line) and HL60 (acute myelogenous leukemia) obtained from the Cell Bank of the Nexcelom Sciences (NCI 60). All cell lines were maintained in Eagle's minimal essential medium (MEM) with 5 % of Fetal bovine serum (FBS), gentamicin 50 μg/mL. Cultures were maintained in 75 cm^2 culture flasks at 37°C, 5 % CO_2 and 100 % relative humidity and media was changed at least twice a week.

RESULTS AND DISCUSSION

***in vitro* Cytotoxicity:** The synthesized 10 analogues were screened for their anticancer activity against the selected human cancer cell lines such as cervical (HeLa), alveolar (A549), breast (MCF-7), chronic myelogenous leukemia (K562), colorectal (HT29), glioblastomamultiforme (SF295) and acute myelogenous leukemia (HL60) as per reported protocol. The anticancer activities of tested compounds ranged between 3.913-57.06 μM (Table-1). Compound **6a** show potent cytotoxicity against four cell lines with IC_{50} values 7.433 μM (HeLa), 4.291 μM (MCF-7), 5.43 μM (HT29) and 3.913 μM (HL60) whereas compound **6b** shows potent anticancer activity against six cell lines with IC_{50} values 9.053 μM (HeLa), 12.419 μM (A549), 9.71 μM (MCF-7) 11.94 μM (K562), 8.11 μM (SF295), 7.791 μM (HL60). The compounds **6c, 6f** and **6g** showed good anticancer activities against

TABLE-1
BIOLOGICAL ACTIVITY OF 5-BROMO INDOLE ARYL KETO HYDRAZIDE HYDRAZONE DERIVATIVES WITH STANDARD ANTICANCER DRUG CISPLATIN

Compd.	HeLa	A549	MCF-7	K562	HEK293	HT29	SF295	HL60
6a	7.433±0.233	10.8010±0.922	4.291±0.502	16.930±0.280	23.714±0.973	5.43±0.591	17.610±0.331	3.913±0.758
6b	9.053±0.312	12.4190±0.119	9.710±0.910	11.940±0.741	26.560±0.418	9.31±0.484	8.110±0.702	7.791±0.159
6c	14.711±0.481	45.3300±0.293	5.420±0.240	15.410±0.854	29.440±0.261	14.51±0.751	14.490±0.229	26.040±0.449
6d	23.827±0.829	57.0600±0.720	14.600±0.590	27.900±0.300	18.140±0.917	7.59±0.638	11.054±0.471	32.590±0.592
6e	49.041±0.492	38.2990±0.450	21.110±0.284	12.380±0.318	15.040±0.611	19.38±0.119	11.621±0.641	25.530±0.628
6f	19.115±0.731	15.7390±0.710	7.990±0.222	16.590±0.769	12.990±0.594	19.66±0.420	17.940±0.300	15.038±0.749
6g	9.822±0.491	18.4233±0.381	9.800±0.601	22.500±0.999	25.610±0.731	21.29±0.711	15.820±0.550	19.580±0.495
6h	11.193±0.559	4.8380±0.521	15.730±0.109	26.480±0.428	27.550±0.817	17.44±0.351	12.740±0.181	24.920±0.285
6i	11.361±0.391	8.3000±0.441	19.390±0.841	25.190±0.316	32.680±0.666	14.99±0.109	19.280±0.460	14.060±0.388
6j	11.094±0.694	13.7000±0.803	24.700±0.733	17.370±0.449	44.100±0.269	21.77±0.177	23.050±0.704	19.390±0.571
Cisplatin	13.000±0.650	36.0000±0.154	15.000±0.639	28.072±0.881	19.520±0.397	9.05±0.731	14.455±0.770	27.281±0.418

where, HeLa - Human Cervical cancer cell line; A549 - Human alveolar adenocarcinoma cell line; MCF-7 - Human breast adenocarcinoma cell line; K562 - Human chronic myelogenous leukemia cell line; HEK 293 - Human normal embryonic kidney cell line; HT29 - Human colorectal adenocarcinoma; SF295 - Human glioblastoma-multiforme; HL60 - Human acute myelogenous leukemia.

breast cancer cell line with IC_{50} value of 5.42, 7.99 and 9.8 μM, respectively. The compound **6d** showed better anticancer activity among the colorectal adeno carcinoma HET29 cancer cell line with IC_{50} value of 7.59 μM. While the compound **6e** exhibited good anticancer activities against chronic leukemia cancer cell line with IC_{50} values of 12.38 μM, whereas the compound **6j** shows the potent anticancer activity on **A549** with IC_{50} value of 13.7μM. Among them, **6a** and **6h** compounds exhibited potent antitumor activity on HL60 and A549 cancer cell lines with IC_{50} value of 3.913 μM and 4.838 μM than the standard drug cisplatin with IC_{50} values of 27 and 36 μM, respectively. These two compounds may be identified as promising drug lead compounds. Almost, the total derivatives showed potent anticancer activities against particular human cancer cell lines. The compound **6e** showed less antitumor activities against all the cell lines.

Conclusion

All the synthesized hydrazide-hydrazone derivatives were evaluated for their cytotoxicity against eight human cancer cell lines HeLa, A549, MCF-7, K562, HT29, SF295, HL60. Among them, **6a** and **6h** compounds exhibited potent antitumor activity on HL60 and A549 cancer cell lines with IC_{50} value of 3.913 μM and 4.838 μM than the standard drug cisplatin with IC_{50} values of 27 μM and 36 μM, respectively. These two compounds may be identified as promising drug lead compounds.

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