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Synthesis, antimicrobial and antitubercular activity of some cyclohexenone and indazole derivatives

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The series of compounds 6-carbethoxy-5-aryl-3-(3,5-dibromo-4-methoxy phenyl)-2-cyclohexenones **2a-j** are obtained from the (*2E*)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones **1a-j** by Michael addition of ethyl acetoacetate, followed by internal Claisen condensation. Reaction of **2a-j** with hydrazine hydrate afforded the corresponding 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-3*H*-indazol-3-ones **3a-j**. The constitution of all the synthesized compounds have been established by elemental analyses, IR, ^{1}H NMR and mass spectral data. All the compounds have been screened for their antimicrobial activities and compounds **2a-j** have been tested for antitubercular activity.

Keywords: Cyclohexenones, indazoles, antimicrobial activity, antitubercular activity

Research in the field of antimicrobial and antitubercular agents is of significant interest for medicinal chemists aiming towards the discovery of new agents having potential activity, broader spectrum and safer therapeutic profiles than the currently available ones. The primary aim was to synthesize different cyclohexenone and indazole derivatives conjugated with well-known pharmacophoric moieties of potential antimicrobial activity, as for example, chalcone.

Several reports have pointed out the value of chlacones as antimicrobial and antitubercular agents, some of them from this laboratory[1-3]. On the other hand, the antimicrobial and antitubercular activity of cyclohexenone and indazole rings substituted with a wide variety of functionalities has also been reported from this laboratory[4-6].

Taking these considerations into account, molecular conjugation of the chalcone moiety with two or more active counterparts has been designed and synthesized with the hope of producing novel cyclohexenone and indazole derivatives that may possess good antibacterial and antitubercular activity.

Cyclohexenone and indazole derivatives exhibit a variety of pharmacological properties like anticancer[6], antitumor[7], antiasthametic[8], antipyretic[9], antiviral[10] and tyrosine kinases inhibitor[11] activity. Keeping this in the view, herein is reported the synthesis of some cyclohexenone **2a-j** and indazole **3a-j** derivatives to study their biopotentiality.

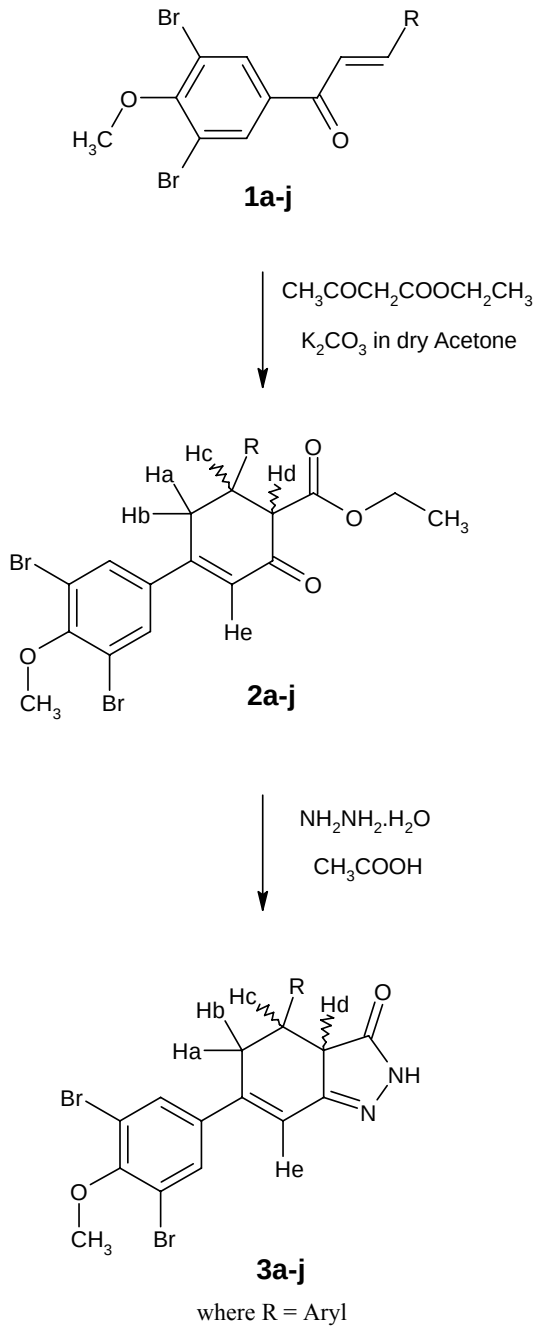
The reaction of different arylaldehydes with 3,5-dibromo-4-methoxy acetophenone in the presence of catalytic amount of 40% KOH (0.5 mL) afforded (*2E*)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones[12] **1a-j**. Michael addition of **1a-j** with ethyl acetoacetate in presence of K_2CO_3 followed by internal Claisen condensation gives 6-carbethoxy-5-aryl-3-(3, 5-dibromo-4-methoxyphenyl)-2-cyclohexenones[4] **2a-j**. Reaction of **2a-j** with hydrazine hydrate yielded the corresponding 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-3*H*-indazol-3-one[4] **3a-j** (**Scheme I**).

The structure of the synthesized compounds were assigned on the basis of elemental analyses, ^{1}H NMR, IR and mass spectral data. All the compounds were screened for antimicrobial activity against different strains of bacteria and fungi and compounds **2a-j** screened for antitubercular activity towards *Mycobacterium tuberculosis*.

Results and Discussion

Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), U.S.A.



Scheme I

Primary screening of the compounds for anti-tubercular activity has been conducted at 6.25μg/mL against *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294, in BACTEC 12B medium using the ALAMAR radiometric system.

The antitubercular activity data were compared with that of standard drug Rifampin at 0.25 μg/mL concentration, which showed 98% inhibition (**Table I**).

Antimicrobial activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against varieties of bacterial strains such as *Bacillus megaterium* ATCC 14518, *Bacillus substilis* ATCC 23857, *Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 29213, and fungi *Aspergillus niger* ATCC 9029 at 40 μg/mL concentration. Standard drugs like Ampicillin, Amoxicillin, Norfloxacin, Benzyl penicillin and Greseofulvin were used for comparison purposes (**Table I**).

The compounds were evaluated and screened following the reported protocol[13]. From the activity data, it is observed that compounds **2d** and **2g** show moderate activity against *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294. Compounds **2d, 2i, 3c, 3d** and **3i** were found to be active against *Bacillus megaterium*. Among the compounds **3i** is found to be more potent, while **2f, 3b** and **3g** were moderately active against *Bacillus megaterium* ATCC 14518. In the series **2e** is potent and rest of the compounds are moderately active against *Bacillus substilis* ATCC 23857. Against *Escherichia coli* ATCC 25922 strain compound **2h** is highly active as compared to others, while compounds **2e, 2j** and **3e** were moderately active. Compounds **3a** and **3e** are highly active, while compounds **2d** and **3h** were moderately active against *Proteus vulgaris* ATCC 29213. Compounds **2h, 2i** and **3e** were highly active while compounds **2f, 3c, 3d** and **3i** were moderately active against *Aspergillus niger* ATCC 9029 as compared to the standard drugs.

Experimental Section

Melting points were determined in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer in KBr disc and the most important absorption bands (cm^{-1}) are listed. ^1H NMR spectra were recorded on Bruker Avance II spectrometer (300 MHz) using TMS as an internal standard with chemical shifts given in δ (ppm). Mass spectra were determined using direct inlet probe on a GCMS-QP2010 instrument. Elemental analyses were performed on a Carlo Erba EA 1108 elemental analyzer. The results of elemental analyses (CHN) were within ±0.4% of the theoretical values. Thin layer chromatography were performed by using silica gel G (E. Merck) plates to assess the

Table I — Antimicrobial screening results of compounds **2a-j** and **3a-j**

Compd	R	% Inhibition Antitubercular activity	Zones of inhibition in mm				
			Antibacterial activity				Antifungal activity
			B. mega	*B. substilis*	*E. coli*	*P. vulgaris*	*A. niger*
2a	C_6H_5-	15	08	11	12	10	08
2b	3-Br-C_6H_4-	00	12	12	14	12	10
2c	2-Cl-C_6H_4-	22	06	10	16	10	10
2d	4-Cl-C_6H_4-	39	18	10	12	14	08
2e	4-$N(CH_3)_2$-C_6H_4-	07	13	20	18	11	10
2f	4-OCH_3-C_6H_4-	03	17	05	10	09	16
2g	3,4-$(OCH_3)_2$-C_6H_3-	45	15	12	10	12	12
2h	2-NO_2-C_6H_4-	08	05	09	21	08	20
2i	3-NO_2-C_6H_4-	01	18	14	12	10	22
2j	4-NH_2-C_6H_4-	00	14	11	20	13	12
3a	C_6H_5-	-	12	10	10	16	10
3b	3-Br-C_6H_4-	-	17	10	12	14	14
3c	2-Cl-C_6H_4-	-	19	17	14	10	16
3d	4-Cl-C_6H_4-	-	18	16	13	10	18
3e	4-$N(CH_3)_2$-C_6H_4-	-	11	12	18	17	20
3f	4-OCH_3-C_6H_4-	-	12	11	16	12	12
3g	3,4-$(OCH_3)_2$-C_6H_3-	-	17	10	12	09	08
3h	2-NO_2-C_6H_4-	-	13	13	14	14	05
3i	3-NO_2-C_6H_4-	-	20	10	10	11	16
3j	4-NH_2-C_6H_4-	-	14	09	10	10	14
Ampicillin	-	-	20	24	22	21	-
Amoxicillin	-	-	21	24	25	25	-
Norfloxacin	-	-	18	17	24	25	-
Benzyl penicillin	-	-	20	18	18	15	-
Greseofulvin	-	-	-	-	-	-	24
Rifampin	-	98	-	-	-	-	-

progress of reactions and homogeneity of the synthesized compounds. Visualization was accomplished either in UV chamber or by exposure to iodine vapour.

General procedure for the preparation of (2*E*)-1-(3,5-dibromo-4-methoxy- phenyl)-3-aryl-prop-2-en-1-ones, 1a-j: A mixture of 3,5-dibromo-4-methoxy-acetophenone (3.08 g, 0.01 mole) and different substituted arylaldehyde (0.01 mole) in methanol (25 mL) was stirred at RT for 24 hr, in the presence of catalytic amount of 40% KOH. The resulting solution was poured into crushed ice. The solid separated was filtered, dried and purified by recrystallization from ethanol.

General procedure for the preparation of 6-carbethoxy-5-aryl-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenones, 2a-j: A solution of (*2E*)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones **1a-j** (0.01 mole) and ethyl acetoacetate (0.02 mole) in dry acetone (20 mL) containing catalytic amount of anhydrous K_2CO_3 (0.04 mole) was stirred at RT for 5 hr. The reaction mixture was filtered and excess of solvent was removed under vacuum to get the solid product, which was purified by recrystallization from dioxane.

6-Carbethoxy-5-phenyl-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2a: Yield 68%, m.p. 115-17°C. IR (KBr): 3063 (C=C-H), 2922 (C-C-H), 1723 (C=O ester), 1672 (C=O cyclic), 1522 (C=C), 1269 (C-O-C), 590 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.22-1.26 (3H, t, *J* = 6.7 Hz, -CH_2-C*H*$_3$), 2.53-2.57 (2H, m, Ha and Hb), 3.91 (3H, s, OCH_3), 3.95-4.01 (2H, q, -C*H*$_2$-CH_3), 4.11-4.13 (1H, d, *J* = 8.1 Hz, -Hd), 4.41-4.43 (1H, m, -Hc), 6.02 (1H, s, -He), 7.25-7.45 (7H, m, Ar-H). Anal. Calcd for $C_{22}H_{20}Br_2O_4$ (508.19): C, 51.99; H, 3.97. Found: C, 51.93; H, 4.03%. MS (EI): *m/z* 509.

6-Carbethoxy-5-(3-bromophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2b: Yield 70%, m.p. 202-04°C. IR (KBr): 3031 (C=C-H), 2945 (C-C-H), 1738 (C=O ester), 1683 (C=O cyclic), 1536 (C=C), 1252 (C-O-C), 559 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.24-1.28 (3H, t, J = 6.6 Hz, -CH_2-CH_3), 2.40-2.44 (2H, m, Ha and Hb), 3.95 (3H, s, OCH_3), 3.97-4.01 (2H, q, -CH_2-CH_3), 4.01-4.03 (1H, d, J = 8.3 Hz, -Hd), 4.07-4.09 (1H, m, -Hc), 6.11 (1H, s, -He), 6.67-6.98 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{19}Br_3O_4$ (587.09): C, 45.01; H, 3.26. Found: C, 44.98; H, 3.34%. MS (EI): *m/z* 588 (M+2) 560.

6-Carbethoxy-5-(2-chlorophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2c: Yield 66%, m.p. 112-13°C. IR (KBr): 3042 (C=C-H), 2926 (C-C-H), 1729 (C=O ester), 1673 (C=O cyclic), 1523 (C=C), 1235 (C-O-C), 568 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.21-1.25 (3H, t, J = 6.9 Hz, -CH_2-CH_3), 2.24-2.28 (2H, m, Ha and Hb), 3.83 (3H, s, OCH_3), 3.86-3.92 (2H, q, -CH_2-CH_3), 3.92-3.94 (1H, d, J = 8.0 Hz, -Hd), 3.96-3.98 (1H, m, -Hc), 6.02 (1H, s, -He), 7.02-7.26 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{19}Br_2ClO_4$ (542.64): C, 48.69; H, 3.53. Found: C, 48.62; H, 3.50%. MS (EI): *m/z* 543 (M+1) 544.

6-Carbethoxy-5-(4-chlorophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2d: Yield 68%, m.p. 103-05°C. IR (KBr): 3028 (C=C-H), 2915 (C-C-H), 1723 (C=O ester), 1669 (C=O cyclic), 1546 (C=C), 1226 (C-O-C), 545 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.17-1.19 (3H, t, J = 6.9 Hz, -CH_2-CH_3), 2.11-2.19 (2H, m, Ha and Hb), 3.78 (3H, s, OCH_3), 3.82-3.84 (1H, d, J = 8.3 Hz, -Hd), 4.00-4.06 (2H, q, -CH_2-CH_3), 3.88-3.90 (1H, m, -Hc), 6.13 (1H, s, -He), 6.89-7.13 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{19}Br_2ClO_4$ (542.64): C, 48.69; H, 3.53. Found: C, 48.64; H, 3.46%. MS (EI): *m/z* 543 (M+1) 544.

6-Carbethoxy-5-(4-N,N-dimethylphenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2e: Yield 62%, m.p. 126-28°C. IR (KBr): 3015 (C=C-H), 2938 (C-C-H), 1741 (C=O ester), 1666 (C=O cyclic), 1524 (C=C), 1188 (C-O-C), 535 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.01-1.05 (3H, t, J = 6.5 Hz, -CH_2-CH_3), 2.08-2.14 (2H, m, Ha and Hb), 2.95 (6H, s, -$N(CH_3)_2$), 3.77-3.79 (1H, d, J = 7.9 Hz, -Hd), 3.83-3.85 (1H, m, -Hc), 3.90 (3H, s, OCH_3), 3.96-4.02 (2H, q, -CH_2-CH_3), 6.28 (1H, s, -He), 7.03-7.45 (6H, m, Ar-H). Anal. Calcd for $C_{24}H_{25}Br_2NO_4$ (551.26): C, 52.29; H, 4.57; N, 2.54. Found: C, 52.23; H, 4.63; N, 2.51%. MS (EI): *m/z* 552.

6-Carbethoxy-5-(4-methoxyphenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2f: Yield 76%, m.p. 134-36°C. IR (KBr): 3024 (C=C-H), 2912 (C-C-H), 1736 (C=O ester), 1674 (C=O cyclic), 1515 (C=C), 1172 (C-O-C), 548 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.09-1.15 (3H, t, J = 6.8 Hz, -CH_2-CH_3), 2.24-2.26 (2H, m, Ha and Hb), 3.55-3.57 (1H, d, J = 8.0 Hz, -Hd), 3.77-3.79 (1H, m, -Hc), 3.95 (3H, s, -OCH_3), 3.99 (3H, s, OCH_3), 4.11-4.15 (2H, q, -CH_2-CH_3), 6.28 (1H, s, -He), 6.94-7.32 (6H, m, Ar-H). Anal. Calcd for $C_{23}H_{22}Br_2O_5$ (538.22): C, 51.33; H, 4.12. Found: C, 51.25; H, 4.14%. MS (EI): *m/z* 539 (M+2) 541.

6-Carbethoxy-5-(3,4-dimethoxyphenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2g: Yield 82%, m.p. 222-24°C. IR (KBr): 3028 (C=C-H), 2908 (C-C-H), 1722 (C=O ester), 1669 (C=O cyclic), 1526 (C=C), 1153 (C-O-C), 568 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.20-1.24 (3H, t, J = 6.8 Hz, -CH_2-CH_3), 2.34-2.38 (2H, m, Ha and Hb), 3.63-3.65 (1H, d, J = 8.1 Hz, -Hd), 3.85-3.87 (1H, m, -Hc), 3.94 (3H, s, -OCH_3), 3.99 (6H, s, OCH_3), 4.18-4.20 (2H, q, -CH_2-CH_3), 6.34 (1H, s, -He), 6.96-7.20 (5H, m, Ar-H). Anal. Calcd for $C_{24}H_{24}Br_2O_6$ (568.25): C, 50.73; H, 4.26. Found: C, 50.69; H, 4.25%. MS (EI): *m/z* 569.

6-Carbethoxy-5-(2-nitrophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2h: Yield 72%, m.p. 168-70°C. IR (KBr): 3042 (C=C-H), 2914 (C-C-H), 1731 (C=O ester), 1673 (C=O cyclic), 1534 (C=C), 1126 (C-O-C), 552 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.15-1.17 (3H, t, J = 6.5 Hz, -CH_2-CH_3), 2.46-2.50 (2H, m, Ha and Hb), 3.47-3.49 (1H, d, J = 8.3 Hz, -Hd), 3.72-3.74 (1H, m, -Hc), 3.82 (3H, s, -OCH_3), 3.90-3.94 (2H, q, -CH_2-CH_3), 6.27 (1H, s, -He), 7.23-7.49 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{19}Br_2NO_6$ (553.19): C, 47.77; H, 3.46; N, 2.53. Found: C, 47.72; H, 3.49; N, 2.52%. MS (EI): *m/z* 554 (M+1) 555.

6-Carbethoxy-5-(3-nitrophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2i: Yield 66%, m.p. 134-36°C. IR (KBr): 3025 (C=C-H), 2937 (C-C-H), 1737 (C=O ester), 1679 (C=O cyclic), 1522 (C=C), 1114 (C-O-C), 521 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.21-1.25 (3H, t, J = 6.9 Hz, -CH_2-CH_3), 2.33-2.39 (2H, m, Ha and Hb), 3.40-3.42 (1H, d, J = 7.8 Hz, -Hd), 3.57-3.59 (1H, m, -Hc), 3.78 (3H, s, -OCH_3), 3.93-3.99 (2H, q, -CH_2-CH_3), 6.32 (1H, s, -He), 7.10-7.26 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{19}Br_2NO_6$ (553.19): C, 47.77; H, 3.46; N, 2.53. Found: C, 47.74; H, 3.46; N, 2.44%. MS (EI): *m/z* 554.

6-Carbethoxy-5-(4-aminophenyl)-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenone, 2j: Yield 69%,

m.p. 156-58°C. IR (KBr): 3031 (C=C-H), 2912 (C-C-H), 1717 (C=O ester), 1661 (C=O cyclic), 1534 (C=C), 1120 (C-O-C), 556 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 1.12-1.16 (3H, t, *J* = 6.8 Hz, $-CH_2-CH_3$), 2.01-2.05 (2H, m, Ha and Hb), 3.27-3.29 (1H, d, *J* = 8.2 Hz, -Hd), 3.40-3.42 (1H, m, -Hc), 3.88 (3H, s, $-OCH_3$), 4.11-4.13 (2H, q, $-CH_2-CH_3$), 6.53 (1H, s, -He), 6.86-7.15 (6H, m, Ar-H), 8.45 (2H, bs, $-NH_2$). Anal. Calcd for $C_{22}H_{21}Br_2NO_4$ (523.21): C, 50.50; H, 4.05; N, 2.68. Found: C, 50.46; H, 4.01; N, 2.72%. MS (EI): *m/z* 524.

General procedure for the preparation of 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-3*H*-indazol-3-ones, 3a-j: A mixture of 6-carbethoxy-5-aryl-3-(3,5-dibromo-4-methoxyphenyl)-2-cyclohexenones **2a-j** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol (25 mL) containing glacial acetic acid (1 mL) as a catalyst was refluxed over a water bath for 6 hr. The solid separated upon cooling was filtered, dried and purified by recrystallization from dioxane.

6-(3,5-Dibromo-4-methoxyphenyl)-4-phenyl-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3a: Yield 63%, m.p. 220-22°C. IR (KBr): 3456 (N-H), 3058 (C=C-H), 2962 (C-C-H), 1669 (C=O), 1648 (C=N), 1518 (C=C), 1210 (C-O-C), 534 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.46-2.50 (2H, m, Ha and Hb), 3.97 (3H, s, $-OCH_3$), 6.52-6.54 (1H, d, *J* = 5.0 Hz, -Hd), 6.83-6.85 (1H, m, -Hc), 7.02 (1H, s, -He), 7.09-7.48 (7H, m, Ar-H), 10.03 (1H, bs, -NH). Anal. Calcd for $C_{20}H_{16}Br_2N_2O_2$ (476.16): C, 50.45; H, 3.39; N, 5.88. Found: C, 50.37; H, 3.44; N, 5.85%. MS (EI): *m/z* 477.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(3-bromophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3b: Yield 65%, m.p. 186-88°C. IR (KBr): 3442 (N-H), 3035 (C=C-H), 2918 (C-C-H), 1653 (C=O), 1635 (C=N), 1524 (C=C), 1169 (C-O-C), 556 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.30-2.34 (2H, m, Ha and Hb), 3.83 (3H, s, $-OCH_3$), 6.40-6.44 (1H, d, *J* = 4.6 Hz, -Hd), 6.68-6.70 (1H, m, -Hc), 6.88 (1H, s, -He), 6.99-7.56 (6H, m, Ar-H), 9.76 (1H, bs, -NH). Anal. Calcd for $C_{20}H_{15}Br_3N_2O_2$ (555.05): C, 43.28; H, 2.72; N, 5.05. Found: C, 43.26; H, 2.79; N, 5.01%. MS (EI): *m/z* 555 (M+2) 557.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(2-chlorophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3c: Yield 76%, m.p. 152-54°C. IR (KBr): 3434 (N-H), 3018 (C=C-H), 2945 (C-C-H), 1668 (C=O), 1642 (C=N), 1513 (C=C), 1143 (C-O-C), 568 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.17-2.21 (2H, m, Ha and Hb), 3.92 (3H, s, $-OCH_3$), 6.08-6.11 (1H, d, *J* = 4.2 Hz, -Hd), 6.50-6.52 (1H, m, -Hc), 7.09 (1H, bs, -NH), 7.18-7.46 (7H, m, Ar-H + -He). Anal. Calcd for $C_{20}H_{15}Br_2ClN_2O_2$ (510.60): C, 47.04; H, 2.96; N, 5.49. Found: C, 46.99; H, 2.99; N, 5.47%. MS (EI): *m/z* 511 (M+1) 512.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(4-chlorophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3d: Yield 83%, m.p. 190-92°C. IR (KBr): 3412 (N-H), 3026 (C=C-H), 2931 (C-C-H), 1671 (C=O), 1644 (C=N), 1538 (C=C), 1120 (C-O-C), 496 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.31-2.33 (2H, m, Ha and Hb), 3.83 (3H, s, $-OCH_3$), 6.41-6.43 (1H, d, *J* = 4.3 Hz, -Hd), 6.68-6.70 (1H, m, -Hc), 6.92 (1H, s, -He), 7.02-7.47 (6H, m, Ar-H), 8.26 (1H, bs, -NH). Anal. Calcd for $C_{20}H_{15}Br_2ClN_2O_2$ (510.60): C, 47.04; H, 2.96; N, 5.49. Found: C, 46.96; H, 3.04; N, 5.43%. MS (EI): *m/z* 511.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(4-N,N-dimethylphenyl)-2,3a,4,5-tetra-hydro-3*H*-indazol-3-one, 3e: Yield 58%, m.p. 148-50°C. IR (KBr): 3448 (N-H), 3051 (C=C-H), 2928 (C-C-H), 1662 (C=O), 1652 (C=N), 1511 (C=C), 1106 (C-O-C), 568 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.10-2.13 (2H, m, Ha and Hb), 2.95 (6H, s, $-N(CH_3)_2$), 3.66 (3H, s, $-OCH_3$), 6.18-6.20 (1H, d, *J* = 4.4 Hz, -Hd), 6.24-6.27 (1H, m, -Hc), 6.99 (1H, s, -He), 7.12 (1H, bs, -NH), 7.14-7.59 (6H, m, Ar-H). Anal. Calcd for $C_{22}H_{21}Br_2N_3O_2$ (519.22): C, 50.89; H, 4.08; N, 8.09. Found: C, 50.83; H, 4.12; N, 8.03%. MS (EI): *m/z* 520 (M+2) 522.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(4-methoxyphenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3f: Yield 83%, m.p. 190-92°C. IR (KBr): 3448 (N-H), 3016 (C=C-H), 2958 (C-C-H), 1656 (C=O), 1646 (C=N), 1520 (C=C), 1132 (C-O-C), 538 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.40-2.44 (2H, m, Ha and Hb), 3.94 (6H, s, $-OCH_3$), 6.20-6.22 (1H, d, *J* = 4.7 Hz, -Hd), 6.47-6.49 (1H, m, -Hc), 6.74 (1H, s, -He), 7.12-7.55 (6H, m, Ar-H), 10.12 (1H, bs, -NH). Anal. Calcd for $C_{21}H_{18}Br_2N_2O_3$ (506.18): C, 49.83; H, 3.58; N, 5.53. Found: C, 49.79; H, 3.66; N, 5.48%. MS (EI): *m/z* 507.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(3,4-dimethoxyphenyl)-2,3a,4,5-tetra- hydro-3*H*-indazol-3-one, 3g: Yield 62%, m.p. 120-22°C. IR (KBr): 3435 (N-H), 3022 (C=C-H), 2934 (C-C-H), 1667 (C=O), 1640 (C=N), 1531 (C=C), 1096 (C-O-C), 547 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.20-2.26 (2H, m, Ha and Hb), 3.96 (3H, s, $-OCH_3$), 4.01 (6H, s, $-OCH_3$), 6.08-6.10 (1H, d, *J* = 4.3 Hz, -Hd), 6.20-6.23 (1H, m, -Hc), 6.55 (1H, s, -He), 6.96-7.26 (5H, m, Ar-H), 9.53

(1H, bs, -NH). Anal. Calcd for $C_{22}H_{20}Br_2N_2O_4$ (536.21): C, 49.28; H, 3.76; N, 5.22. Found: C, 49.23; H, 3.81; N, 5.19%. MS (EI): *m/z* 537.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(2-nitrophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3h: Yield 73%, m.p. 134-36°C. IR (KBr): 3458 (N-H), 3041 (C=C-H), 2962 (C-C-H), 1659 (C=O), 1632 (C=N), 1513 (C=C), 1123 (C-O-C), 565 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.34-2.38 (2H, m, Ha and Hb), 3.91 (3H, s, $-OCH_3$), 6.21-6.24 (1H, d, J = 4.4 Hz, -Hd), 6.34-6.36 (1H, m, -Hc), 6.82 (1H, s, -He), 6.93 (1H, bs, -NH), 7.11-7.46 (6H, m, Ar-H). Anal. Calcd for $C_{20}H_{15}Br_2N_3O_4$ (521.15): C, 46.09; H, 2.90; N, 8.06. Found: C, 46.05; H, 2.86; N, 8.10%. MS (EI): *m/z* 522 (M+1) 523.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(3-nitrophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3i: Yield 76%, m.p. 165-67°C. IR (KBr): 3424 (N-H), 3010 (C=C-H), 2946 (C-C-H), 1675 (C=O), 1641 (C=N), 1524 (C=C), 1118 (C-O-C), 543 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.30-2.34 (2H, m, Ha and Hb), 3.93 (3H, s, $-OCH_3$), 6.17-6.20 (1H, d, J = 4.5 Hz, -Hd), 6.26-6.28 (1H, m, -Hc), 6.86 (1H, s, -He), 6.97 (1H, bs, -NH), 7.05-7.39 (6H, m, Ar-H). Anal. Calcd for $C_{20}H_{15}Br_2N_3O_4$ (521.15): C, 46.09; H, 2.90; N, 8.06. Found: C, 46.04; H, 2.82; N, 8.12%. MS (EI): *m/z* 522 (M+1) 523.

6-(3,5-Dibromo-4-methoxyphenyl)-4-(4-aminophenyl)-2,3a,4,5-tetrahydro-3*H*-indazol-3-one, 3j: Yield 58%, m.p. 98-100°C. IR (KBr): 3456 (N-H), 3024 (C=C-H), 2923 (C-C-H), 1649 (C=O), 1632 (C=N), 1498 (C=C), 1089 (C-O-C), 512 cm^{-1} (C-Br); ^1H NMR ($CDCl_3$): δ 2.15-2.21 (2H, m, Ha and Hb), 3.85 (3H, s, $-OCH_3$), 5.97-5.99 (1H, d, J = 4.6 Hz, -Hd), 6.03-6.05 (1H, m, -Hc), 6.30 (1H, s, -He), 7.12 (1H, bs, -NH), 7.20-7.59 (6H, m, Ar-H), 9.53 (2H, bs, $-NH_2$). Anal. Calcd for $C_{20}H_{17}Br_2N_3O_2$ (491.17): C, 48.91; H, 3.49; N, 8.56. Found: C, 48.87; H, 3.55; N, 8.51%. MS (EI): *m/z* 492.

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