Synthesis, Characterization and Spectral Studies of Various Newer 4-Benzyloxy-1*H*-indole-2-carboxylic Acid (Arylidene)-hydrazides

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4-Benzyloxyindole-2-carboxylic acid hydrazide reacts with aromatic and heterocyclic aldehydes in alcoholic medium in refluxing conditions to give 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazides, important synthetic intermediates for the synthesis of a newer class of pharmacologically active compounds. We describe here the synthesis of various 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazides by conventional as well as microwave irradiation techniques. The structures of these compounds have been confirmed by spectroscopic techniques (FTIR, NMR and MS). Some of the interesting features of the electron impact mass spectral fragmentation pattern of these compounds are also discussed.

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The Indole nucleus is an important element of many pharmacologically active compounds. It has been investigated as a starting material for the synthesis of hallucinogenic compounds *i.e*., psychochemical like bufotenin, psilocin and dimethyltryptamine and various organic natural products as well as a precursor in alkaloid [1]. Some N-methylindole-3-hydrazones have shown antihypertensive activity in spontaneously hypertensive rat [2]. Most of the 3-substituted indole acetic acid derivatives such as its hydrazide and corresponding pyridazinone derivatives are found to possess antimicrobial activity [3]. Hydrazone derivatives of indole-2-carboxylic acid hydrazide are useful as psychopharmacological agents and as monoamineoxidase (MAO) inhibitor [4]. From the synthetic point of view, hydrazones are important synthons for several transformations [5] and their synthesis from various precursors is well documented [6]. Keeping in view their biological and synthetic utility, much attention has been paid to develop new methodologies for the construction of this structural framework [7]. In the present course, we have synthesized newer 4-benzyloxyindole-2-carboxylic acid hydrazide (**1**) and 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazide (**2**-**10**) using new eco-friendly microwave irradiation technique as well as conventional heating methods. All the above compounds were characterized by spectral analysis.

Hydrazinolysis of 4-benzyloxyindole-2-carboxylic acid hydrazide from corresponding methyl ester was carried out by conventional method as well as by microwave technique. The conventional method involved the refluxing of mixture of corresponding ester and excess of hydrazine hydrate for 16 hours while in the case of the microwave technique, a

Scheme 1

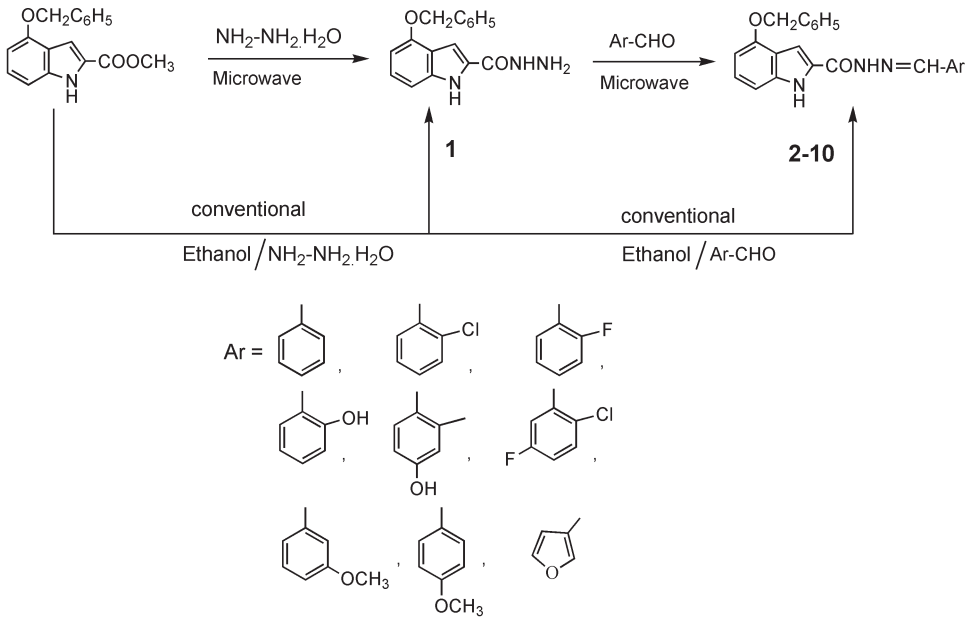
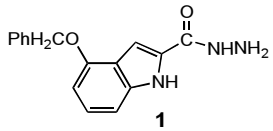
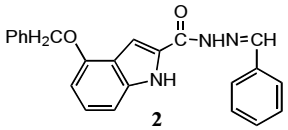
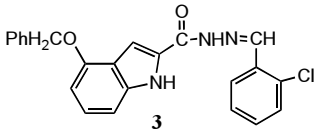
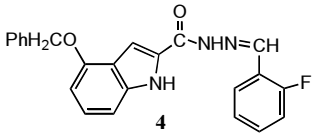
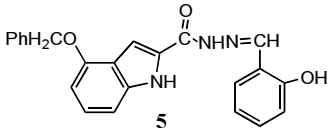
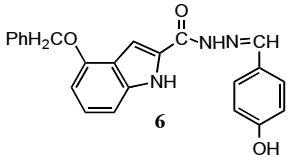
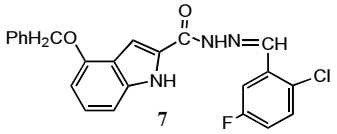
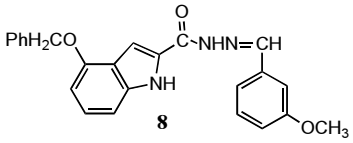
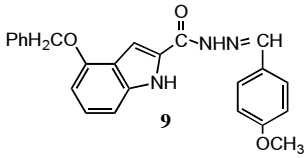
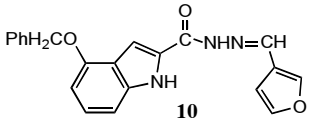


Table 1

Synthesis of 4-Benzyloxy-1*H*-indole-2-carboxylic Acid (Arylidene)-hydrazide

Product	Time		Yield of the product (%)	
	MW (min)	Conventional (hr)	MW	Conventional
 **1**	10	16	86	50
 **2**	10	8	86	55
 **3**	6	7	90	40
 **4**	5	6	85	30
 **5**	6	8	85	30
 **6**	5	10	88	35
 **7**	3	8	87	45
 **8**	10	14	85	40
 **9**	10	12	89	33
 **10**	10	16	86	40

mixture of ester and hydrazine hydrate (1:1 molar ratio) was irradiated with microwaves for 10 minutes in the absence of any solvent, catalyst and solid support. The results of the two approaches (conventional and microwave technique) are summarized in Table 1 (product **1**).

Various newer 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazide (**2**-**10**) were also prepared by the condensation of **1** with different aromatic aldehydes under microwave irradiations and conventional methods. They are prepared in conventional method by refluxing **1** with the different aldehydes in alcohol and in microwave irradiation technique without any solvent. The overall yield of products obtained using the microwave irradiation technique is in the range of 85-90% as compared to the conventional methods where the yields were 30-55%. The reaction time is 3-10 minutes by microwave irradiation as compared to conventional methods of 6-16 hours (Scheme 1).

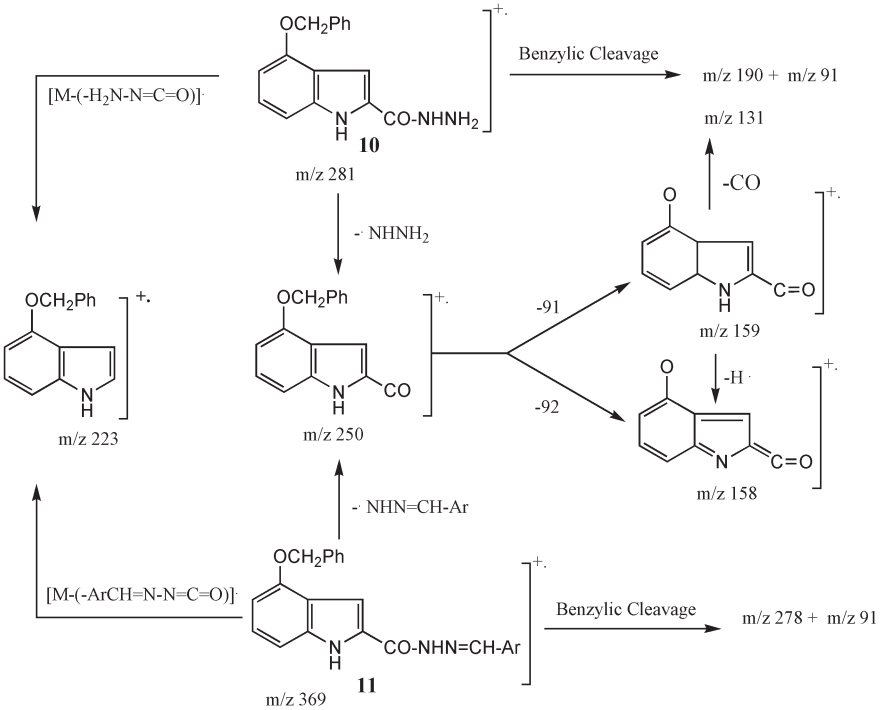
Spectral Analysis.

The IR spectrum of 4-benzyloxyindole-2-carboxylic acid hydrazide showed absorption bands at 1629 and 1100 cm^{-1} corresponding to C=O and C-N stretching vibrations. Two bands at 3302 and 3225 cm^{-1} appeared due to the presence of $–NH_2$ and –NH groups. The corresponding 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazides showed similar spectra except that bands due to the NH_2 group, instead of bands at 1565-1555 cm^{-1} due to C=N stretching, were observed.

The ^1H NMR spectrum of 4-benzyloxyindole-2-carboxylic acid hydrazide displayed a singlet at δ 9.8 ppm due to the NHCO proton. Presence of later was further supported by the appearance of a peak at 161.6 in its ^{13}C NMR spectrum. Another broad singlet at 4.2 (2H) corresponded to NH_2 protons while a singlet at 10.5 resonated due to indole NH proton. Benzylic CH_2 protons appeared at 5.2 in its ^1H NMR spectrum while as a sharp singlet at 69.5 ppm in its ^{13}C NMR spectrum. Eight benzenoid protons and one indolic CH proton appeared as multiplet at 7.0-7.8 ppm. Similar pattern for the proton resonances was also observed in the ^1H NMR spectrum of hydrazones. In addition, a singlet corresponding to N=CH proton appeared at δ 7.9-8.7 depending upon the substituent in the phenyl ring of the aldehyde molecule. Also, broad singlet at 4.2 ppm corresponding to the $–NH_2$ protons in the spectrum of **10** was not observed in those of hydrazones.

In the EI mass spectra of 4-benzyloxyindole-2-carboxylic acid hydrazides and all the 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazides, molecular ion peaks were distinct. Fragment ion peak at m/z 250 could be attributed to the loss of $NHNH_2$ and NHN=CH-Ar radicals from the molecular ions of hydrazide and 4-benzyloxy-1*H*-indole-2-carboxylic acid (arylidene)-hydrazide respectively. The formation of fragment ion at m/z 223 can be rationalized by the loss of neutral isocyanate (H_2N-N=C=O or ArCH=N-N=C=O) from molecular ion as depicted in Scheme 2. The fragment ion peak at

Scheme 2



m/z 158 could arise due to the loss of benzylic and H radical (either in concerted or stepwise manner) from the fragment ion having m/z value of 250 (Scheme 2). In addition, benzylic cleavage in the molecular ion gave rise to peaks at m/z [M-91] as also m/z 91 due to characteristic tropylium cation. The ion m/z 131 is obtained due to the loss of CO from that of m/z 159.

In conclusion, we described the microwave-assisted synthesis of newer 4-benzyloxyindole-2-carboxylic acid hydrazide and various newer 4-benzyloxy-1*H*-indole-2-carboxylicacid (arylidene)-hydrazide were prepared using the same technique. Spectral properties and mass spectral fragmentation pattern of these hydrazides and hydrazones were also discussed.

EXPERIMENTAL

4-Benzyloxyindole-2-carboxylic Acid Hydrazide (**1**).

4-Benzyloxyindole-2-carboxylic acid methyl ester (10 mmol) was dissolved in 99% hydrazine hydrate (10 mmol) in a conical flask and was placed in a domestic microwave oven. After irradiating at 450 watt for 10 minutes, the solid product was washed with the ethanol to give the 4-benzyloxyindole-2-carboxylic acid hydrazide **1** (86 %); mp: 248-250 °C. IR (KBr) = 3316 & 3282 (-NH_2), 3120, 2929, 1637 (CO), 1230, 1097, 759, 732 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.5 (s, 1H, indole NH, exchangeable), 9.8 (s, 1H, -NHCO, exchangeable), 7.0-7.8 (m, 8 x Ar-H, 1 x indole CH), 5.25(s, 2H, -OCH_2), 4.2 (bs, 2H, -NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.55 (-OCH_2), 100.10 (C-7), 101.09 (C-5), 106.07 (C-3), 118.89 (C-8), 124.58 (C-6), 128.03 (C-2'/6'), 128.24 (C-4'), 128.88 (C-3'/5'), 129.55 (C-2), 137.81 (C-1'), 138.22 (C-9), 152.99 (C-4), 161.60 (CO); EI-MS: m/z (%) = 281 (51), $[C_{16}H_{15}N_3O_2]^+$, 250 (20), 223 (12), 190 (40), 159 (20), 131 (18), 91 (100), 76 (8), 65 (16), 51 (8).

General Procedure for the Synthesis of 4-Benzyloxy-1H-indole-2-carboxylic Acid (Arylidene)-hydrazide.

Carboxylic acid hydrazide (5 mmol) was mixed with aldehyde (5 mmol) in a glass tube and the mixture was irradiated with microwaves for the time period specified in Table 1 at a power setting of 100 Watts. The reaction was monitored by TLC. After completion of the reaction, the solid product was recrystallized from the ethanol to give the pure hydrazones.

4-Benzyloxy-1*H*-indole-2-carboxylicacidbenzylidene-hydrazide (**2**).

This compound has a mp of 216-218 °C, IR (KBr): 3445, 3178, 3029, 1628, 1526, 1510, 1360, 1258, 1241, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.9 (s, 1H, N=CH), 6.9-7.7 (m, 13 x Ar-H, 1 x indole CH), 5.2 (s,-OCH_2). EIMS: m/z (%) = 369 (98) $[C_{23}H_{19}N_3O_2]^+$, 278 (98), 250 (22), 223 (12),159 (22) 158 (36), 130 (29), 103 (12), 91 (100) ,65 (8).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-2-Chlorobenzylidene)-hydrazide (**3**).

This compound has a mp of 220-222 °C, IR (KBr) = 3436, 1633, 1556, 1433, 1263, 758 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H, NH indole exchangeable), 10.5 (s, 1H, CONH, exchangeable), 8.5 (s, 1H, N=CH), 7.0-7.8 (m, 12 x Ar-H, 1 x indole CH), 5.1 (s, 2H, CH_2). EIMS: m/z (%) = 403 (84) $[C_{23}H_{18}N_3O_2Cl]^+$, 367 (8), 312 (100), 276 (8), 250 (24), 235 (10), 223 (12) 158 (44), 131 (25), 91 (100), 65 (22).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-2-Fluoro-benzylidene)-hydrazide (**4**).

This compound has a mp of 188-190 °C, IR (KBr) = 3422, 3298, 3070, 2970, 1634, 1560, 1364, 1245, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H, NH indole, exchangeable), 11.0 (s, 1H, CONH, exchangeable), 8.7 (s, 1H, N=CH), 7.1-7.8 (m, 12 x Ar-H, 1 x indole CH), 5.2 (s, 2H, CH_2); EIMS: m/z (%) = 387 (84) $[C_{23}H_{18}N_3O_2F]^+$, 296 (100), 281 (10), 250 (22), 223 (12), 158 (38), 131 (22), 91 (84), 65 (12).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-2-Hydroxy-benzylidene)-hydrazide (**5**).

This compound has a mp of 250-252 °C, IR (KBr): 3298, 3250, 3064, 2966, 1651, 1622, 1560, 1360, 1258, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H, OH), 11.2 (s, 1H, NH indole exchangeable), 10.8 (s, 1H, CONH, exchangeable), 8.4 (s, 1H, N=CH) 7.0-7.7 (m, 12 x Ar-H, 1 x indole CH), 5.12 (s, 2H, CH_2); MS: m/z (%) = 385 (82) $[C_{23}H_{19}N_3O_3]^+$, 294 (12), 250 (22), 223 (8),160 (84), 131 (22), 91 (100), 65 (18).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (4-Hydraoxy-benzylidene)-hydrazide (**6**).

This compound has a mp of 260-262 °C; IR (KBr) = 3304, 3259, 3064, 2936, 1614, 1544, 1382, 1254, 761 cm-1; ^1H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H, OH), 11.0 (s, 1H, NH indole, exchangeable), 10.8 (s, 1H, CONH, exchangeable), 8.4 (s, 1H, N=CH), 7.0-7.8 (m, 12 x Ar-H, 1 x indole CH), 5.1 (s, 2H, CH_2); MS: m/z (%) = 385 (40) $[C_{23}H_{19}N_3O_3]^+$, 294 (38), 250 (8), 223 (8), 158 (22), 136 (18), 91 (100), 65 (18).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-2-Chloro-5-fluoro-benzylidene)-hydrazide (**7**).

This compound has a mp of 186-188 °C; IR (KBr) = 3474, 3295, 2964, 1644, 1544, 1382, 1254, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.5 (s, 1H, NH indole, exchangeable), 9.8 (s, 1H, CONH, exchangeable), 8.5 (s, 1H, N=CH), 7.0-7.8 (m, 11 x Ar-H, 1 x indole CH), 5.1 (s, CH_2). MS: m/z (%) = 421 (12) $[C_{23}H_{17}N_3O_2\ FCl]^+$, 158 (8), 131(16), 91 (100).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-3-Methoxy-benzylidene)-hydrazide (**8**).

This compound has a mp of 178-180 °C; IR (KBr): 3308, 3238, 3052, 2992, 1631, 1547, 1365, 1272, 1171, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.7 (s, 1H, CONH, exchangeable), 7.9 (s, 1H, N=CH), 6.9-7.8 (m, 12 x Ar-H, 1 x indole CH), 5.1 (s, 2H, CH_2); MS: m/z (%) = 399 (100) $[C_{24}H_{21}N_3O_3]^+$, 308 (84), 294 (38), 250 (22), 223 (12), 158 (22), 131 (18), 91 (78), 65 (20).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid (-4-Methoxy-benzylidene)-hydrazide (**9**).

This compound has a mp of 210-212 °C; IR (KBr): 3308, 3238, 3052, 2992, 1631, 1547, 1365, 1272, 1171, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.2 (s, 1H, NH indole, exchangeable), 10.8 (s, 1H, CONH, exchangeable), 8.3 (s, 1H, N=CH), 7.1-7.8 (m, 12 x Ar-H, 1 x indole CH), 5.1 (s, 2H, CH_2); EIMS: m/z (%) = 399 (100) $[C_{24}H_{21}N_3O_3]^+$, 308 (86), 294 (38), 250 (12), 223 (8), 158 (22), 136 (18), 91 (100), 65 (20).

4-Benzyloxy-1*H*-indole-2-carboxylic Acid Furan-3-ylmethylene-hydrazide (**10**).

This compound has a mp of 180-182 °C; IR (KBr) = 3448, 3179, 3035, 1628, 1578, 1512, 1357, 1266, 1240, 1160, 1064, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.3 (s, 1H, NH indole, exchangeable), 10.8 (s, 1H, CONH, exchangeable), 8.5 (s, 1H, N=CH), 6.5-7.7 (m, 8 x Ar-H, 1 x indole CH, 3 x furan CH), 5.12 (s, 2H, CH_2); MS: m/z (%) = 359 (82) $[C_{21}H_{17}N_3O_3]^+$, 268 (60) $[M-91]^+$, 250 (22), 223 (12), 159 (22), 131 (22), 91 (100), 65 (16).

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