Synthesis of novel indole-benzimidazole derivatives

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2-Methylindole-3-acetic acid and its 5-methoxy derivative were prepared from the respective phenylhydrazines and levulinic acid. Indole-3-carboxylic acid was obtained from indole, dimethylformamide and trifluoroacetic acid. These indole carboxylic acids were then condensed with substituted *o*-phenylenediamines under high temperature conditions in the presence of polyphosphoric acid as a catalyst to give the combined indole-benzimidazoles.

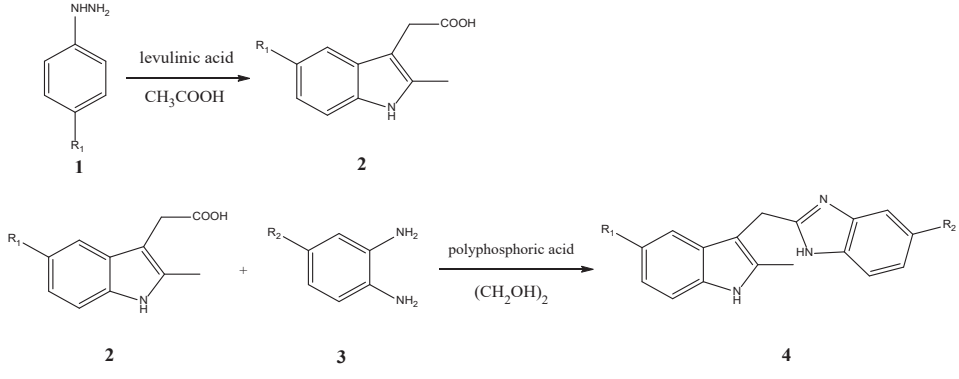
Keywords: 2-methylindole-3-acetic acid, indole-3-carboxylic acid, substituted *o*-phenylenediamines, indole-benzimidazoles

Indoles and their derivatives are common heterocyclic compounds in nature. The indole ring system is an important structural component of many drugs.[1] Indole derivatives are used as neuroprotective agents affecting oxidative stress,[2] potent opioid receptor agonists,[3] highly functionalised pharmacophores[4] and potent PPAR-c binding agents with potential application for the treatment of osteoporosis.[5] Drugs containing an indole ring are used for the treatment of peripheral neuropathy and neurodegenerative diseases,[6] as glucokinase activators,[7] in the cytotoxic antibiotic CC-1065 and prodrugs,[8] and as PPAR delta activators for the treatment of cardiovascular diseases and dyestuffs.[9]

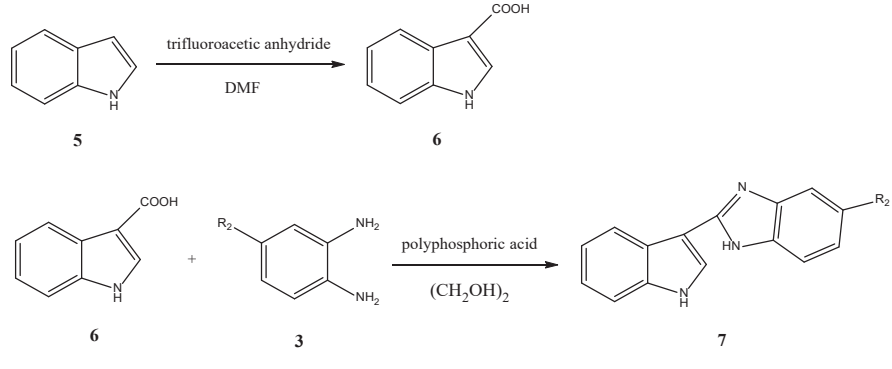
Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest.[10] Substituted benzimidazole derivatives have found applications in diverse therapeutic areas, including antiulcer, antihypertensive,[11] antiviral, antifungal, anticancer[7,12] and antihistamine drugs.[13]

Results and discussion

We have developed an efficient method for the synthesis of linked indole-benzimidazole derivatives which involves the combination of either 2-methylindole-3-acetic acid (**2** R = H), its 5-methoxy derivatives (**2** R = OMe) or indole-3-carboxylic acid (**6**) with the easily accessible substituted *o*-phenylenediamines (**3**) in the presence of a high boiling point solvent containing polyphosphoric acid as a catalyst. In the initial experiments 2-methylindole-3-acetic acid (**2** R = H) was synthesised from phenylhydrazine (**1** R = H) and levulinic acid and reacted with *o*-phenylenediamine (**3** R = H) in a normal solvent such as ethanol, methanol or DMF but without success. Only a low yield was obtained when the reaction was carried out in a solvent with a higher boiling point. However, when polyphosphoric acid was used as a catalyst in ethylene glycol as a solvent, compound **4a** was obtained in 86% yield. On the basis of this result, we have synthesised a series of substituted indole-benzimidazole derivatives (**4b**–**4f**, **7a**–**7c**) from compounds **2** and **6** in a single-step process. The results are summarised in Table 1.



Scheme 1



Scheme 2

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Table 1 Substituted indole-benzimidazole derivatives

Compound	R_1	R_2	Yield (%)
4a	–H	–H	86
4b	–H	$-CH_3$	87
4c	–H	$-COOCH_2CH_3$	83
4d	$-OCH_3$	–H	78
4e	$-OCH_3$	$-CH_3$	62
4f	$-OCH_3$	$-COOCH_2CH_3$	72
7a		–H	79
7b		$-CH_3$	62
7c		$-COOCH_2CH_3$	61

Conclusion

In conclusion, we have synthesised a series of new indole-benzimidazole derivatives in a two-step process. The method has the advantages of shorter reaction times, good yields and easy workup.

Experimental

Reagents were purchased from commercial suppliers and used as received. TLC analysis was performed using silica gel plates and using ultraviolet light (254 nm) or vanillin solution for visualisation. Melting points were taken on an Electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were determined on a 500 MHz Bruker spectrometer. Mass spectra were determined on a XEVO G2-XS spectrometer. Infrared spectra were determined on a Bruker EQUINOXX55 infrared spectrometer.

Preparation of compound **2**

Compound **1** (10 mmol) was dissolved in acetic acid (30 mL), and levulinic acid (15 mmol) was added to the stirred solution which was then refluxed for 4 h. After cooling to room temperature, the mixture was poured into water (200 mL) and then the solution was treated with 30% sodium hydroxide to slight acidity (pH = 5–6). The precipitated solid was filtered off, recrystallised from ethanol and dried *in vacuo* to give compound **2**.

2-Methylindole-3-acetic acid (**2a**): Yellow solid, yield 78%, m.p. 200–203 °C (199–200 °C[14]); ^{1}H NMR (500 MHz, $CDCl_3$), δ 2.31 (3H, s, CH_3), 3.65 (2H, s, CH_2), 6.97 (1H, t, *J* = 7.5 Hz, ArH), 7.12 (1H, t, *J* = 7.5 Hz, ArH), 7.23 (1H, d, *J* = 6.0 Hz, ArH), 7.33 (1H, d, *J* =6.0 Hz, ArH), 10.83 (1H, s, COOH), 12.15 (1H, s, NH); IR (ν_{max} cm^{-1}): 1504, 1518, 1565, 1624, 1769, 2935, 3001, 3535; HRMS *m/z* 190.0824 (calcd 190.0823 for $C_{11}H_{11}NO_2$ [M + H]$^+$).

5-Methoxy-2-methylindole-3-acetic acid (**2b**): Red brown solid, yield 74%, m.p. 161–163 °C (161–162 °C[15]); ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.31 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 3.70 (2H, s, CH_2), 7.19 (1H, d, *J* = 7.5 Hz, ArH), 7.23 (1H, d, *J* = 7.5 Hz, ArH), 7.56 (1H, s, *J* = 7.5 Hz, ArH), 10.80 (1H, s, COOH), 12.21 (1H, s, NH); IR (ν_{max} cm^{-1}): 1092, 1581, 1602, 1604, 1671, 1773, 2926, 3072, 3232; HRMS *m/z* 220.0923 (calcd 220.0929 for $C_{12}H_{13}NO_3$ [M + H]$^+$).

Preparation of compound **4**

Compound **3** (10 mmol) was dissolved in ethylene glycol (50 mL) and then compound **2** (10 mmol) and a small amount of polyphosphoric acid were added to the stirred solution which was then refluxed for several hours (the reaction was monitored by TLC). On completion of the reaction, the mixture was poured into ice water. The solution was treated with 30% sodium hydroxide to slight alkalinity (pH = 9). The precipitated solid was filtered off, recrystallised from ethanol and dried *in vacuo* to give compound **4**.

2-((2-Methyl-1H-indole-3-yl) methyl)-1H-benzimidazole (**4a**): Khaki solid, yield 86%, m.p. 215–218 °C; ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.31 (3H, s, CH_3), 3.87 (2H, s CH_2), 7.01 (1H, t, *J* = 7.5 Hz, ArH), 7.16 (1H, t, *J* = 7.5 Hz, ArH), 7.45 (2H, t, *J* = 5.0 Hz, ArH), 7.50 (2H, d, *J* = 5.0 Hz, ArH), 7.86 (1H, d, *J* = 7.5 Hz, ArH), 8.03 (1H, d, *J* = 7.5 Hz, ArH), 11.75 (1H, s, NH), 12.85 (1H, s, NH); IR (ν_{max} cm^{-1}): 1504, 1580, 1610, 1622, 1638, 1660, 1669, 2874, 3242, 3431; HRMS *m/z* 262.1302 (calcd 262.1300 for $C_{17}H_{15}N_3$ [M + H]$^+$).

5-Methyl-2-((2-methyl-1H-indole-3-yl) methyl)-1H-benzimidazole (**4b**): Brown solid, yield 87%, m.p. 246–248 °C; ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.31 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.84 (2H, s, CH_2), 7.05 (1H, t, *J* = 7.5 Hz, ArH), 7.17 (1H, t, *J* = 7.5 Hz, ArH), 7.48 (1H, d, *J* = 4.5 Hz, ArH), 7.53 (1H, d, *J* = 4.5 Hz, ArH), 7.60 (2H, d, *J* = 7.5 Hz, ArH), 8.13 (1H, s, ArH), 11.76 (1H, s, NH), 12.91 (1H, s, NH); IR (ν_{max} cm^{-1}): 1505, 1520, 1545, 1610, 1640, 1650, 1672, 2860, 2910, 3371, 3420; HRMS *m/z* 276.1451 (calcd 276.1456 for $C_{18}H_{17}N_3$ [M + H]$^+$).

2-((2-Methyl-1H-indole-3-yl) methyl)-1H-benzimidazole-5-ethyl formate (**4c**): Dark brown solid, yield 83%, m.p. 198–201 °C, ^{1}H NMR (500 MHz, DMSO-d_6), δ 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 2.30 (3H, s, CH_3), 3.84 (2H, s, CH_2), 4.30 (2H, m, CH_2), 7.06 (1H, t, *J* = 7.5 Hz, ArH), 7.19 (1H, t, *J* = 7.5 Hz, ArH), 7.45 (1H, d, *J* = 8.0 Hz, ArH), 7.56 (1H, d, *J* = 8.0 Hz, ArH), 7.61 (2H, d, *J* = 7.5 Hz, ArH), 8.12 (1H, s, ArH), 11.71 (1H, s, NH), 12.84 (1H, s, NH); IR (ν_{max} cm^{-1}): 1217, 1530, 1539, 1585, 1593, 1606, 1651, 1652, 1780, 2899, 2969, 3296, 3476; HRMS *m/z* 334.1509 (calcd 334.1511 for $C_{20}H_{19}N_3O_2$ [M + H]$^+$).

2-((5-Methoxy-2-methyl-1H-indole-3-yl) methyl)-1H-benzimidazole (**4d**): Sandy brown solid, yield 78%, m.p. 205–206 °C, ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.31 (3H, s, CH_3), 3.42 (3H, s, OCH_3), 3.82 (2H, s, CH_2), 6.90 (1H, d, *J* = 7.5 Hz, ArH), 7.12 (1H, d, *J* = 7.5 Hz, ArH), 7.45 (2H, t, *J* = 5.0 Hz, ArH), 7.50 (1H, d, *J* = 5.0 Hz, ArH), 8.12 (1H, s, *J* = 7.5 Hz, ArH), 8.03 (1H, d, *J* = 7.5 Hz, ArH), 11.79 (1H, s, NH), 12.88 (1H, s, NH); IR (ν_{max} cm^{-1}): 1100, 1515, 1540, 1554, 1590, 1620, 1671, 1680, 2840, 2910, 3301, 3395; HRMS *m/z* 292.1408 (calcd 292.1405 for $C_{18}H_{17}N_3O$ [M + H]$^+$).

5-Methyl-2-((5-methoxy-2-methyl-1H-indole-3-yl)methyl)-1H-benzimidazole (**4e**): Dark brown solid, yield 62%, m.p. 231–234 °C, ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.31 (3H, s, CH_3), 2.40 (3H, s, CH_3), 3.42 (3H, s, OCH_3), 3.82 (2H, s CH_2), 7.06 (1H, t, *J* = 7.5 Hz, ArH), 7.16 (1H, t, *J* = 7.5 Hz, ArH), 7.51 (1H, d, *J* = 5.0 Hz, ArH), 7.56 (1H, d, *J* = 5.0 Hz, ArH), 7.65 (2H, d, *J* = 7.5 Hz, ArH), 7.99 (1H, s, ArH), 11.63 (1H, s, NH), 12.78 (1H, s, NH); IR (ν_{max} cm^{-1}): 1110, 1520, 1537, 1560, 1582, 1610, 1670, 1685, 2850, 2905, 2925, 3310, 3290; HRMS *m/z* 306.1556 (calcd 306.1562 for $C_{19}H_{19}N_3O$ [M + H]$^+$).

2-((5-Methoxy-2-methyl-1H-indole-3-yl)methyl)-1H-benzimidazole-5-ethyl formate (**4f**): Brown solid, yield 72%, m.p. 229–230 °C, ^{1}H NMR (500 MHz, DMSO-d_6), δ 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 2.29 (3H, s, CH_3), 3.42 (3H, s, OCH_3), 3.85 (2H, s, CH_2), 4.28 (2H, m, CH_2), 7.01 (1H, t, *J* = 7.5 Hz, ArH), 7.21 (1H, t, *J* = 7.5 Hz, ArH), 7.46 (1H, d, *J* = 4.0 Hz, ArH), 7.57 (1H, d, *J* = 4.0 Hz, ArH), 7.70 (2H, d, *J* = 7.5 Hz, ArH), 8.13 (1H, s, ArH), 11.45 (1H, s, NH), 12.77 (1H, s, NH); IR (ν_{max} cm^{-1}): 1105, 1200, 1515, 1526, 1572, 1600, 1615, 1660, 1675, 1750, 2860, 2900, 2930, 3315, 3340; HRMS *m/z* 364.1620 (calcd 364.1616 for $C_{21}H_{21}N_3O_3$ [M + H]$^+$).

Preparation of indole-3-carboxylic acid (**6**)

Indole (2.34 g, 20 mmol) was dissolved in DMF (10 mL) and then trifluoroacetic anhydride (4.2 mL, 30 mmol) was added dropwise at 0 °C. After stirring at room temperature for 3 h, water was added and the resulting pink solid was filtered. The collected solid was treated with 20% NaOH (40 mL, 0.2 mol) at 50 °C overnight. After cooling to room temperature, the solution was extracted with Et_2O. The aqueous phase was acidified with concentrated HCl and the product was obtained by filtration. Compound **6** indole-3-carboxylic acid was obtained as a light yellow solid, yield 77%, m.p. 194–196 °C (194–196 °C[16]); ^{1}H NMR (500 MHz, DMSO-d_6), δ 7.12 (2H, t, *J* = 5.0 Hz, ArH), 7.48 (1H, d, *J* = 7.5 Hz, ArH), 7.95 (1H, d, *J* = 7.5 Hz, ArH), 8.13 (1H, s, ArH), 11.68 (1H, s, COOH), 11.79 (1H, s, NH); IR (ν_{max} cm^{-1}): 1513, 1554, 1613, 1682, 1776, 3019, 3376; HRMS *m/z* 162.0511 (calcd 162.0510 for $C_9H_7NO_2$ [M + H]$^+$).

Preparation of compound **7**

Compound **3** (10 mmol) was dissolved in ethylene glycol (50 mL) and then compound **6** (10 mmol) and a small amount of polyphosphoric

acid were added to the stirred solution which was then refluxed for several hours (the reaction was monitored by TLC). On completion of the reaction, the mixture was poured into ice water. The solution was treated with 30% sodium hydroxide to slight alkalinity (pH = 9). The precipitated solid was filtered, recrystallised from ethanol and dried *in vacuo* to give compound **7**.

2-(1H-Indole-3-yl)-1H-benzimidazole (**7a**): Yellow solid, yield 79%, m.p. 224–226 °C (226–228 °C[17]), ^{1}H NMR (500 MHz, DMSO-d_6), δ 7.28 (2H, t, *J* = 7.5 Hz, ArH), 7.34 (2H, t, *J* = 7.5 Hz, ArH), 7.47 (1H, d, *J* = 7.5 Hz, ArH), 7.52 (1H, d, *J* = 7.5 Hz, ArH), 7.81 (2H, d, *J* = 4.0 Hz, ArH), 8.03 (1H, s, ArH), 12.41 (1H, s, NH);. IR (ν_{max} (cm^{-1}): 1482, 1500, 1526, 1605, 1617, 3405, 3426;. HRMS *m/z* 234.0984 (calcd 234.0987 for $C_{15}H_{11}N_3$ [M + H]$^+$).

2-(1H-Indole-3-yl)-5-methyl-1H-benzimidazole (**7b**): Dark brown solid, yield 62%, m.p. 215–217 °C (214–216 °C[17]), ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.38 (3H, s, CH_3), 7.12 (1H, d, *J* = 7.5 Hz, ArH), 7.34 (2H, t, *J* = 4.0 Hz, ArH), 7.54 (1H, d, *J* = 7.5 Hz, ArH), 7.56 (1H, s, ArH), 7.72 (2H, d, *J* = 4.0 Hz, ArH), 8.12 (1H, s, ArH), 12.46 (1H, s, NH); IR (ν_{max} cm^{-1}): 1490, 1500, 1580, 1605, 1620, 1670, 1680, 2950, 3300, 3380; HRMS *m/z* 248.1146 (calcd 248.1143 for $C_{16}H_{13}N_3$ [M + H]$^+$).

2-(1H-Indole-3-yl)-1H-benzimidazole-5-ethyl formate (**7c**): Dark brown solid, yield 61%, m.p. 220–221 °C, ^{1}H NMR (500 MHz, DMSO-d_6), δ 1.31 (3H, t, *J* = 7.5 Hz, CH_3), 4.25 (2H, m, CH_2), 7.11 (1H, d, *J* = 7.5 Hz, ArH), 7.34 (2H, t, *J* = 4.0 Hz, ArH), 7.56 (1H, d, *J* = 7.5 Hz, ArH), 7.62 (1H, s, ArH), 7.71 (2H, d, *J* = 4.0 Hz, ArH), 8.16 (1H, s, ArH), 12.36 (1H, s, NH); IR (ν_{max} cm^{-1}): 1119, 1482, 1486, 1540, 1576, 1670, 1672, 1675, 1736, 2974, 3287, 3412; HRMS *m/z* 306.1201 (calcd 306.1198 for $C_{18}H_{15}N_3O_2$ [M + H]$^+$).

Received 25 May 2016; accepted 22 July 2016
Paper 1604116 doi: 10.3184/174751916X14737735069962
Published online: 27 September 2016

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