Synthesis, heterocyclization and anti-tumour activity evaluation of some benzimidazole derivatives

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Methylbenzimidazole 1 is converted to imidazole acrylic acid 3 via cyclo condensation with chloral followed by hydrolysis. Compound 3 also obtained from the reaction of *o*-phenylenediamine with maleic anhydride. Treatment of 1 with SeO_2 yielded the oxidized product 4 (Aldehyde 4) which undergoes Wittig reaction using ester and Ph_3P to furnish the acrylates 5. Compound 5 is also obtained by cyclocondensation of *o*-phenylenediamine and the corresponding maleate. Cyclization of 3 using Ac_2O provides pyrroloimidazole 6. Imidazole 6 undergoes several transformations using HCl, ammonium hydroxide in neutral medium, *o*-phenylene diamine/HCl to provide acrylic acid 3, amide 7 and/or bicompound 8 respectively. Anilide 9 is obtained as a result of condensation of 3 with amines. Ester 5 undergoes 1,4-addition to benzimidazole ring to give the corresponding anilino derivative 10. Pyridazine cyclization is acheived by treatment of 5 with NH_2OH in acidic medium. *In vitro* cytotoxicity is evaluated using SRB (sulphorhodamine-B) assay against two human cell lines, breast and liver carcinoma cell lines. The results show that compound 11 has strong activity against all cell lines tested.

Keywords: Active methylene, benzimidazoles, cytotoxicity activity, hydrazines, lactambenzimidazole.

IMIDAZOLES act as an interesting class of five-membered nitrogen heterocyclic system that contain 1,3-dinitrogen atom because of their wide range of pharmacological applications, such as angiotensin inhibitors[1,2], anti-inflammatory[3] and antimicrobial activities[4–7]. Imidazole derivatives show highly cytotoxicity activity, which represent as new candidates in cancer treatment[8] and play a great role in biochemical transformations[9]. Potency and high applicability of the imidazole pharmacophore are attributed to its hydrogen bond donor–acceptor capability as well as its high affinity for metals present in many protein active sites[10]. Derivatives of imidazoles have been reported to possess antimicrobial, anti-mycobacterial, anthelmintic, anti-inflammatory and insecticidal properties[11–13]. Many studies showed that azole heterocycles such as imidazole and triazole are useful pharmacophores for anti-mycobacterial activity[14–18].

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All melting points reported are uncorrected. IR spectra was run on a pyeunicam sp3-100 infrared spectrophotometer using KBr disc technique. ^{1}H NMR spectra were recorded on a Varian 5 M–250 MHz spectrometer using DMSO as a solvent. Elemental analysis was carried out using elemental analyser model at 240°C.

β-(2-Benzimidazolyl)acrylic acid (3) – Method A: A mixture of *o*-phenylenediamine (0.01 mol), maleic anhydride (0.01 mol) and DMF (50 ml) was stirred at room temperature for one hour. The solid that separated upon dilution with water was crystallized from acetic acid.

Method B: To a solution of 2-methylbenzimidazole (0.01 mol) in (20 ml) anhydrous toluene, 0.3–0.5 g anhydrous zinc chloride (4 g) and chloral (0.01 mol; 9.6 ml in 20 ml toluene) were added. The mixture was heated for 3 h on a water bath at 90–95°C and then, cooled, filtered and washed with ethanol. The mixture was treated with (80 ml) ethanol and (100 ml, 25%) sodium hydroxide, heated gently and then cooled in ice. The mixture was boiled for 2–3 h and cooled again, ethanol was removed by vacuum distillation during cooling and then (50–60 ml) conc. HC1 was added. The hydrochloride of *β*-(2-benzimidazolyl)acrylic acid was formed (soluble in water). The unreacted substances were filtered out, and the filtrate was neutralized by 10% sodium hydroxide to obtain the free acid which was crystallized from acetic acid.

(**1**): A pale yellow crystal with yield = 70%, m.p. = 197–198°C, IR (KBr): revealed peaks at 3250–3850 cm^{-1}, 3350 cm^{-1} and 1715 cm^{-1} for OH, NH and C=O groups respectively. ^{1}HNMR (DMSO-d_6): 4.8 (2H, *dd* –CH=CH–), 8.20–8.33 (4H, *m*, ar.), 11.0–12.5 (1H, *s*, NH), 12.80 (1H, *s*, –COOH). Anal. Calc. for $C_{10}H_8N_2O_2$ (188.2): %C; 63.82, %H; 4.28, %N; 14.89 and found: %C; 63.70, %H; 4.22, %N; 14.75.

Methyl or ethyl-*β*(-2-benzimidazolyl) acrylate esters (**5a**, **b**) – Method A: A mixture of *o*-phenylenediamine (0.01 mol), dimethyl or diethylmaleate (0.01 mol) and few drops of piperidine were fused at 120°C (oil bath) for 3 h. The solid product was extracted by benzene after cooling and was crystallized from the proper solvent.

Method A: Treatment of 2-methylbenzimidazole (0.01 mol) by SeO_2 (1.5 g), gives 2-formylbenzimidazole, which was added to methoxy and ethoxy carbonyl methylene triphenyl phosphorus yield (0.01 mol) in (15 ml) benzene and the mixture was refluxed for 5 h, cooled and 50 ml (10%) HC1 was added. The solid obtained was crystallized from benzene.

(**5a**): A yellowish crystal yield = 80%, m.p. = 116–118°C, IR (KBr): 3350 (NH) cyclic, 1750 (C=O), 1630 (C=N cyclic). ^{1}HNMR (DMSO-d_6): 3.83 (3H, *s*, OCH_3), 4.9 (2H, *dd*, –CH=CH–), 8.32–8.43 (4H, *m*, ar.), 12.93 (1H, br(*s*), NH). Anal. Calc. for $C_{11}H_{10}N_2O_2$ (202.21): %C; 65.34, %H; 4.98, %N; 13.85 and found: %C; 65.24, %H; 4.88, %N; 13.80.

(**5b**): A colourless crystal with yield = 80%, m.p. = 118–121°C, IR (KBr): 3350 (NH) cyclic, 1750

(C=O), 1630 (C=N cyclic). ^{1}HNMR (DMSO-d_6): 1.36 (3H, *t*, CH_3), 4.2 (2H, *q*, CH_3), 4.9 (*dd*, 2H, –CH=CH–), 8.32–8.43 (4H, *m*, ar.), 12.93 (br(*s*), 1H, NH). Anal. Calc. for $C_{12}H_{12}N_2O_2$ (216.24): %C; 66.65, %H; 5.59, %N; 12.96 and found: %C; 66.58, %H; 5.52, %N; 12.88.

Benzimidazo[l,5 a]3-pyrrolin-2-one (**6**): A mixture of β-(2-benzimidazolyl)acrylic acid (**1**) (0.01 mol) in (20 ml) benzene and (10 ml) acetic anhydride was refluxed for 1 h. The solid product separated after evaporation and cooling was crystallized from benzene, A brown crystal with yield = 85%, m.p. = 235–237°C, IR (KBr): 1710 (C=O) lactam, 1640 (C=N) cyclic, 1630 (C=C) conj. ^{1}HNMR (DMSO-d_6): 4.81–5.14 (2H, *dd*, –CH=CH) cyclic, 8.23–8.38 (4H, *m*, ar.). Anal. Calc. for $C_{10}H_6N_2O$ (170.17): %C; 70.58, %H; 3.55, %N; 16.46 and found: %C; 70.50, %H; 3.45, %N; 16.40.

Methyl-α-arylamino-β-(2-benzimidazolyl)propionate (**7a–b**): A mixture of lactame (**6**) (0.01 mol) and ammonium hydroxide and/or aniline (0.1 mol) in ethanol was refluxed for 3 h. The solid product was crystallized from ethanol.

(**7a**): A pale yellow crystal with yield = 90%, m.p. = 160–162°C, IR (KBr): 3370 (NH) cyclic, 3250 (NH) amide, 1700–1680 (C=O) amide. ^{1}H NMR (DMSO-d_6): 5.2 (1H, *s*, CONH), 4.9 (2H, *dd*, –CH=CH–), 7.31–7.42 (4H, *m*, ar.), 10.71 (1H, br(*s*), NH). Calc. for $C_{10}H_9N_3O$ (187.07): %C; 64.16, %H; 4.85, %N; 22.45 and Found: %C; 64.11, %H; 4.75, %N; 22.33.

(**7b**): A yellow crystal with yield = 88%, m.p. = 165–166°C, IR (KBr): 3370 (NH) cyclic, 3250 (NH) amide, 1700–1680 (C=O) amide. ^{1}H NMR (DMSO-d_6): 5.39 (br, 1H, CONH), 4.89 (2H, *dd*, –CH=CH–), 7.31–7.42 (4H, *m*, ar.), 7.5–7.63 (5H, *m*, ar.), 10.11 (1H, br(*s*), NH). Calc. for $C_{16}H_{13}N_3O$ (263.29): %C; 72.99, %H; 4.98, %N; 15.96 and found: %C; 72.80, %H; 4.89, %N; 15.90.

(*E*)-1,2-*bis*(1H-benzo[*d*]imidazol-2-yl)ethene (**8**): A mixture of compound (7) (0.01 mol) and *o*-phenylenediamine (0.1 mol) in dil HCl (3–4 drops) in ethanol was refluxed for 3 h. The solid product was crystallized from ethanol. A brownish crystal with yield = 80%, m.p. = 152–154°C, IR (KBr): 3350 (NH) cyclic, 3250 (NH) amide and 1630 (C=N) cyclic. ^{1}H NMR (DMSO-d_6): 4.8 (2H, *dd*, –CH=CH–), 7.22–7.5 (8H, *m*, ar.). Calc. for $C_{16}H_{12}N_4$ (260.29): %C; 73.83, %H; 4.65, %N; 21.52 and found: %C; 73.75, %H; 4.60, %N; 21.44.

Synthesis of anilide (benzimidazole acrylamide derivatives) (**9a–c**): A mixture of acid **3** (0.01 mol) and appropriate amine (0.01 mol) in ethanol (20 ml) was refluxed for 2 h. The solid product obtained upon cooling was separated by filtration and crystallized from butanol to give (**9a–c**) respectively.

(**9a**): A colourless crystal with yield = 80%, m.p. = 145–147°C, IR (KBr): 3370 (NH) cyclic, 3250 (NH) amide, 1700–1680 (C=O) amide, 1630 (C=N) cyclic. ^{1}H NMR (DMSO-d_6): 4.8 (2H, *dd*, –CH=CH–), 7.22–7.5 (4H, *m*, ar.), 7.82–8.25 (4H, *m*, ar.), 10.22 (1H, br(*s*), NH). Calc. for $C_{16}H_{12}N_4O_3$ (308.27): %C; 62.33, %H; 3.92, %N; 18.17 and found: %C; 62.21, %H; 3.80, %N; 18.05.

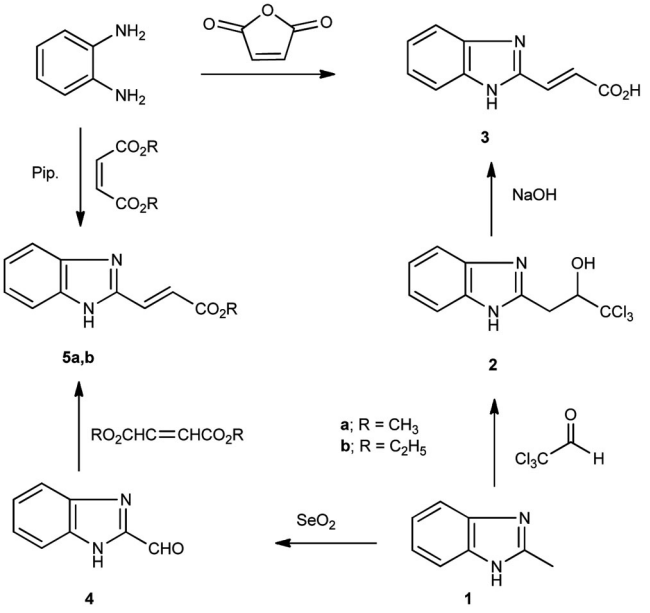
(**9b**): A white yellow crystal with yield = 80%, m.p. = 142–144°C, ^{1}HNMR (DMSO-d_6): 2.34 (3H, *s*, CH_3), 4.8 (2H, *dd*, –CH=CH–), 7.22–7.5 (4H, *m*, ar.), 7.17 (4H, *m*, ar.), 10.22 (1H, br(*s*), NH). Calc. for $C_{17}H_{15}N_3O$ (277.32): %C; 73.63, %H; 5.45, %N; 15.15 and found: %C; 73.55, %H; 5.39, %N; 15.10.

(**9c**): A white yellow crystal with yield = 80%, m.p. = 140–141°C, ^{1}HNMR (DMSO-d_6): 4.34 (2H, *s*, CH_2), 4.8 (2H, *dd*, –CH=CH–), 7.22–7.5 (4H, *m*, ar.), 7.23 (4H, *m*, ar.), 8.02 (1H, br(*s*), NH). Calc. for $C_{17}H_{15}N_3O$ (277.32): %C; 73.63, %H; 5.45, %N; 15.15 and found: %C; 73.50, %H; 5.37, %N; 15.05.

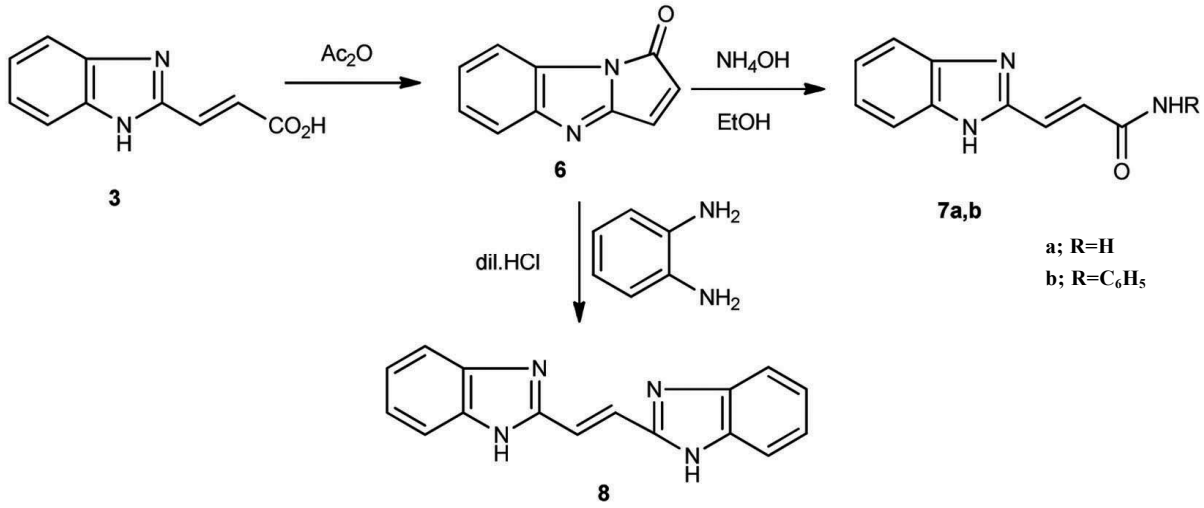
α-Arylamino-β-(2-benzilmidazolyl) propionic acid (**10a–d**): A mixture of (5**a** or **b**) (0.01 mol) and the appropriate amine (0.01 mol) namely aniline, 2,4-di methyl aniline, *p*-toluidine and benzylamine respectively, in butanol was refluxed for 4 h. The solid products were crystallized from ethanol.

(**10a**): A pale yellow crystal with yield = 80%, m.p. = 130–132°C, IR (KBr): 3370–2880 (OH carboxylic), 3280 (NH), 1720 (C=O), 1630 (C=N) cyclic. ^{1}H NMR (DMSO-d_6): 2.8 (2H, *d*, CH_2), 3.8 (1H, *t*, H), 6.7–7.2 (5H, *m*, ar.), 4.3 (1H, br(*s*), NH), 7.2–7.5 (4H, *m*, ar.), 11.2–12.7 (1H, *s*, COOH). Calc. $C_{16}H_{15}N_3O_2$ for (281.31): %C; 68.31, %H; 5.37, %N; 14.94 and found: %C; 68.22, %H; 5.30, %N; 14.86.

(**10b**): A yellow crystal with yield = 80%, m.p. = 122–123°C, ^{1}HNMR (DMSO-d_6): 2.1 (3H, *s*, CH_3), 2.3 (3H, *s*, CH_3), 2.8 (2H, *d*, CH_2), 3.8 (1H, *t*, CH), 6.4–6.8 (3H, *m*, ar.), 4.3 (1H, br(*s*), NH), 7.2–7.5 (4H, *m*, ar.), 11.2–12.7 (1H, *s*, COOH). Calc. for $C_{18}H_{19}N_3O_2$ (310.14): %C;



Scheme 1. Synthetic routes of benimidazoles **1–5**.



Scheme 2. Synthetic approaches of benimidazole **3**, **7a**, **b** and **8** by ring opening of **6**.

69.88, %H; 6.19, %N; 11.34 and found: %C; 69.80 %H; 6.11, %N; 11.28.

(**10c**): A yellowish crystal with yield = 80%, m.p. = 120–122°C, ^{1}H NMR (DMSO-d_6): 2.34 (3H, *s*, CH_3), 2.8 (2H, *d*, CH_2), 3.8 (1H, *t*, CH), 6.4–7 (4H, *m*, ar.), 4.3 (br(*s*), 1H, NH), 7.2–7.5 (4H, *m*, ar.), 11.2–12.7 (1H, *s*, COOH). Calc. for $C_{17}H_{17}N_3O_2$ (295.34): %C; 69.14, %H; 5.80, %N; 14.23 and found: %C; 69.08, %H; 5.77, %N; 14.11.

(**10d**): A yellowish brown crystal with yield = 80%, m.p. = 125–126°C, ^{1}HNMR (DMSO-d_6): 3.8 (3H, *s*, CH_2), 2.8 (2H, *d*, CH_2), 3.8 (1H, *t*, CH), 7.2–7.3 (5H, *m*, ar.), 4.3 (1H, br(*s*), NH), 7.2–7.5 (4H, *m*, ar.), 11.2–12.7 (1H, *s*, COOH). Calc. for $C_{17}H_{17}N_3O_2$ (277.32): %C; 69.14, %H; 5.80, %N; 14.23 and found: %C; 69.05, %H; 5.77, %N; 14.12.

Benzimidazo[**l**, **6a**]-2H-pyridazine-3-one (**11**): A mixture of methyl or ethyl β-(2-benzimidazolyl)acrylate (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in acetic acid was refluxed for 3 h. The solid product was recrystallized from butanol. A colourless crystal with yield = 80%, m.p. = 190–191°C, IR (KBr): 3330 (NH) cyclic, 1670 (C=O), 1630 (C=N), 1610 (C=C) conj. ^{1}H NMR (DMSO-d_6): 7.88 (2H, *m*, ar.), 8.23–8.41 (4H, *m*, ar.), 12.89 (1H, br(*s*), NH). Calc. for $C_{10}H_7N_3O$ (185.18): %C; 64.86, %H; 3.81, %N; 22.69 and found: %C; 64.70, %H; 3.72, %N; 22.55.

SRB assay of cytotoxic activity: It was carried out according to the previously reported work[19] using human tumour cell lines, breast carcinoma cell line (MCF7) and liver carcinoma cell line (HEPG2). Cell lines were obtained from National Cancer Institute, Cairo, Egypt.

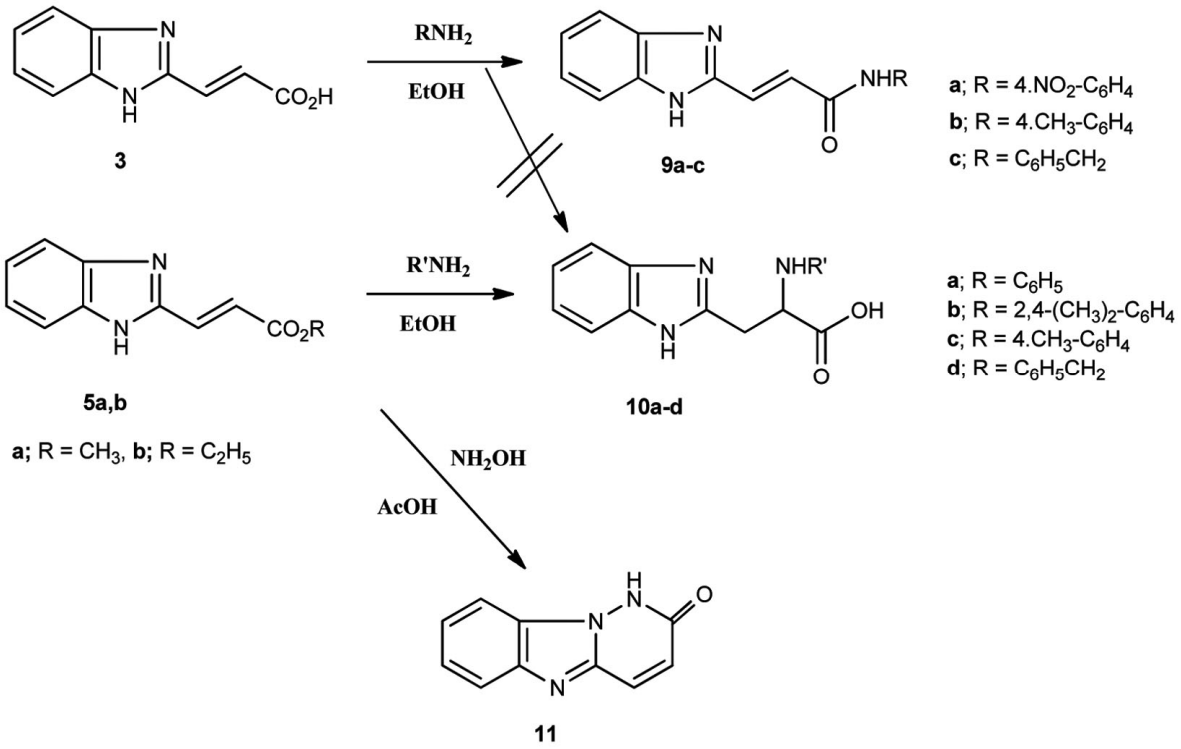
Benzimidazole acrylic acid seemed to be of suitable functionality for further heteroannelation using simple available laboratory reagent, providing imidazole derivative of potential biological activities.

Methylimidazole with its activated methyl group was reacted with chloral hydrate to give the acrylic derivative **3** presumably via the non-isolable aldol intermediate **2**, that undergo basic hydrolysis (Scheme 1). Compound **3** was also obtained as a result of condensation reaction between *o*-phenylenediamine and maleic anhydride (Scheme 1). Structure of compound **3** was confirmed from spectral data, thus its IR revealed peaks at 3250–3850 cm^{-1}, 3350 cm^{-1} and 1715 cm^{-1} for OH, NH and C=O groups respectively. Also ^{1}H NMR displayed the trans-protons of CH=CH as doublet at 4.8 ppm, aromatic protons at 8.33 as multiplet while the deshielded NH and COOH protons were confirmed at 11–12.5 ppm and 12.8 ppm respectively.

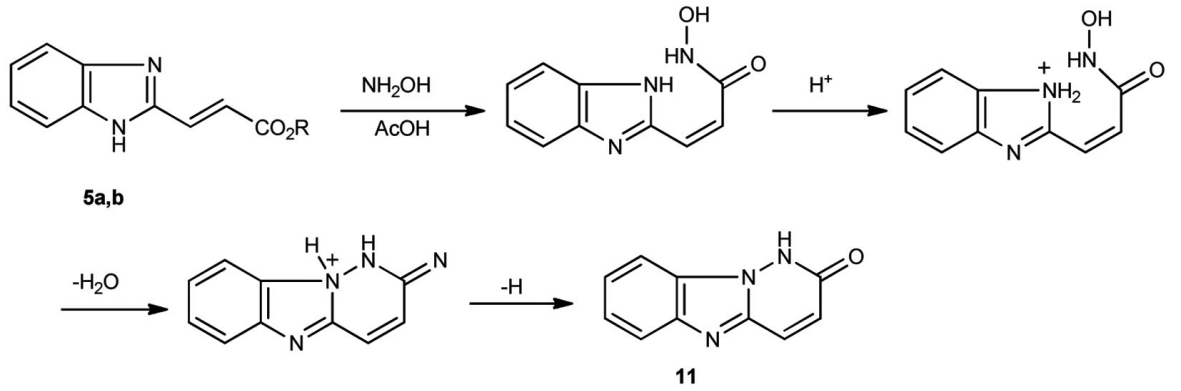
The aldehyde **4** and corresponding ester under witting reaction afforded the ester **5**, which in turn was obtained from the nucleophilic attack of amino group of *o*-phenylenediamine to the electrophilic carbon of maleiate (Scheme 1). Structure of compound **5a** was elucidated from analytical in addition to IR and ^{1}H NMR. Thus, IR spectrum showed NH, C=O and C=N absorption bands at 3350 cm^{-1}, 1750 cm^{-1} and/or 1630 cm^{-1} for C=N. ^{1}H NMR spectrum of **5a** showed the methoxy protons as a singlet at 3.83 ppm, olefenic protons as double doublet at 4.9 ppm, aromatic protons at 8.32–8.43 ppm as multiplet in addition to NH at 12.93 ppm. ^{1}H NMR spectrum of **5b** showed the ethoxy protons as 1.36 (3H, *t*, CH_3), 4.2 (2H, *q*, CH_3) (Scheme 1).

Upon refluxing of **3** with AC_2O as acylating agent resulted in pyrrole cyclization affording the condensed pyrroloimidazole (**6**) (Scheme 2). The structure of compound **6** was confirmed from the absence of OH absorption band in IR spectrum in addition to the disappearance of cyclic NH in IR and ^{1}H NMR.

The behaviour of **6** towards nucleophilic reagent was examined; thus ammonolysis of **6** using ammonium



Scheme 3. Synthetic approaches of benzimidazoles **9**–**11**.



Scheme 4. Mechanistic route of preparation of compound **11**.

Table 1. IC_{50} value of compound 11 against breast and liver carcinoma cell lines

Name of cell line	IC_{50} value (μg/ml)
MCF7	30.1
HEPG2	3.31

hydroxide and aniline resulted in ring cleavage affording imidazole derivative **7** which was confirmed from the presence of NH in IR and ^{1}H NMR. Treatment of compound **6** with *o*-phenylenediamine leads to ring opening followed by intramolecular cyclodehydration affording benzimidazole derivative **8**. The structure of biscompound **8** was confirmed from ^{1}H NMR spectrum which showed the olefenic protons as double doublet at 4.9 ppm in addition to the deshielded NH protons at 11.9 ppm (Scheme 2).

The attack of nucleophilic nitrogen of amines to the electrophilic carbon of carboxylic group of **3** provided the anilide derivative **9** and none of the addition products **10** were obtained.

Structure of compound **9** was elucidated from analytical in addition to IR and ^{1}H NMR. Thus, IR spectrum showed 3370 (NH) cyclic, 3250 (NH) amide, 1700–1680 (C=O) amide, 1630 (C=N) cyclic, ^{1}HNMR (DMSO-d_6): 4.8 (2H, *dd*, –CH=CH–), 7.22–7.5 (4H, *m*, ar.), 7.82–8.25 (4H, *m*, ar.), 10.22 (1H, br(*s*), NH) (Scheme 3).

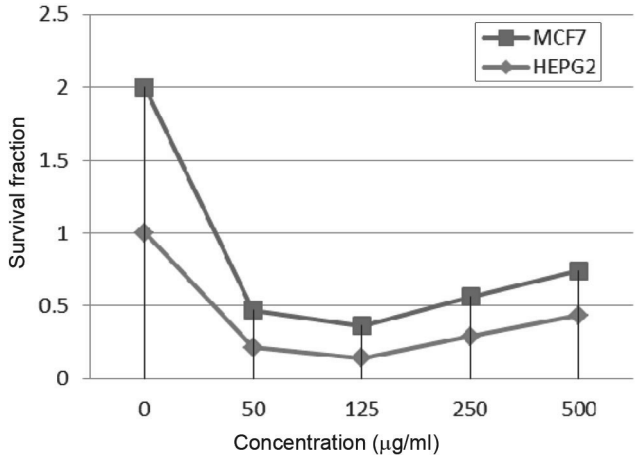


Figure 1. Percentage of survival fraction of breast and liver carcinoma cell lines against concentration (μg/ml) compound **11**.

The anilides of type **10** was obtained through 1,4-addition of the aromatic amines to the imidazole derivative 5 (Scheme 3). The α-amino acid structure of **10** was elucidated from spectral analysis, thus IR spectrum showed NH around 3340 cm^{-1}, C=O in the region of 1760–1770 cm^{-1}. ^1H NMR of the same compound provided (CH_2–CH–) structure as doublet at 1.3 ppm, triplet at 1.4 ppm in addition to aliphatic NH as a broad signal at 4.3 ppm. The benzimidazole derivative **11** was obtained as a result of attack of hydroxyl amine to the ester carbonyl carbon followed by intramolecular cyclodehydration. The pyridone structure **11** was shown from the carbonyl absorption at 1670 cm^{-1} and NH at 3390 cm^{-1}. Also ^1H NMR of **11** displayed NH signal at 12.89 pm as a broad signal (Schemes 3 and 4).

The potential cytotoxicity activity of compound **11** was tested against two human cell lines (MCF7 breast carcinoma cell line and HEPG2 liver carcinoma cell line) by SRB method. The results of antitumour activity showed that compound **11** has strong activity against all cell lines tested. The antitumour activity of compound **11** is summarized in Figure 1 and Table 1. The IC_{50} values of compound **11** against each cell lines were 30.1 μg/ml and 3.31 μg/ml for MCF7 and HEPG2 respectively.

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