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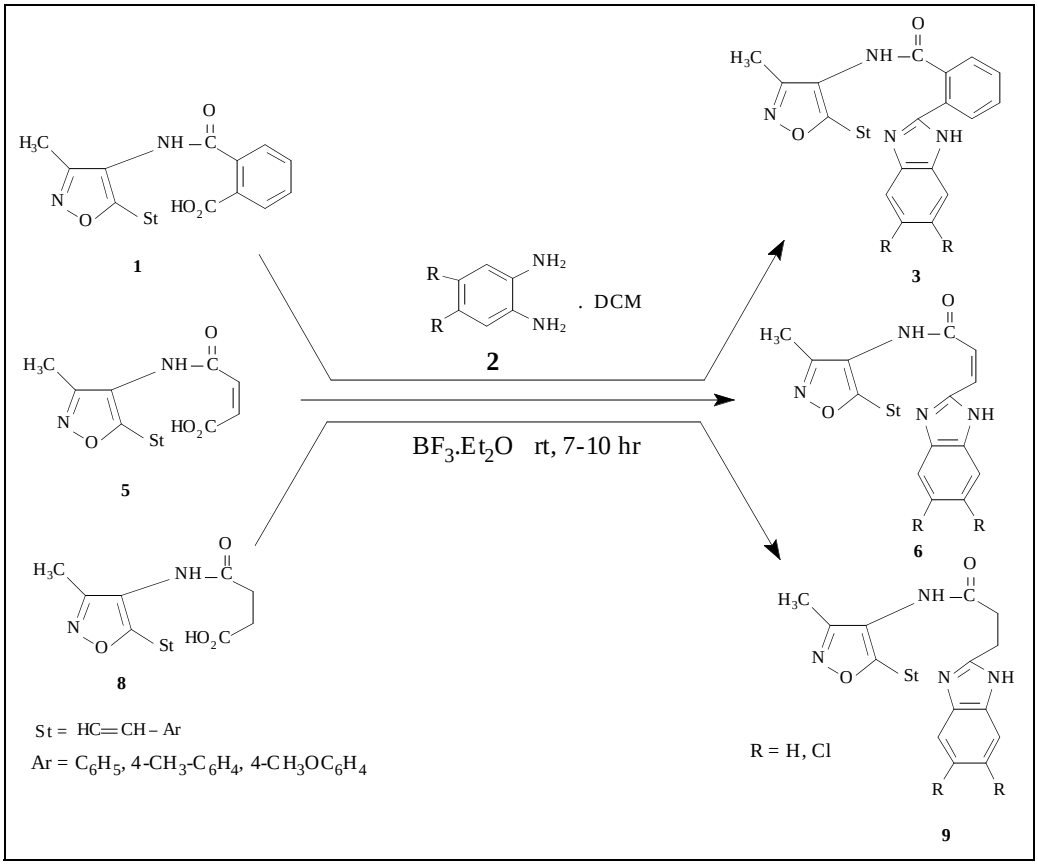

Benzimidazoles **3, 6** and **9** have been synthesized selectively in excellent yields by cyclocondensation of β-(3-methyl-5-styryl-4-isoxazolyl amido) benzoic acids, acrylic acids and propionic acids with 1,2-phenylene diamines by employing BF_3·Et_2O as the catalyst. When the same reaction was carried out in pyridine it resulted in mixture of products in each case (**3 & 4, 6 & 7** and **9 & 10**). Other methods tried by using polyphosphoric acid, HCl, TFA also led to mixtures of **3 & 4, 6 & 7** and **9 & 10** in each case, similar to that of pyridine reaction.

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INTRODUCTION

Benzimidazole is an important nucleus that has been extensively used in medicinal chemistry, notable examples being the antihistaminic astemizole and the antiulcerative omeprazole [1]. Benzimidazoles are also known for their anti-inflammatory [2], antibiotic [3], antihelmintic [4], anticancer [5] and antiviral activities [6]. In recent years benzimidazoles have been reported to act as topoisomerase I inhibitors [7], selective neuro-peptide "Y Y 1" receptor antagonists [8], angiotensin II (A II) inhibitors [9], potential antitumor agents [10], smooth muscle cell proliferation inhibitors [11], and in diverse areas of chemistry [12].

Isoxazoles have been found to posses marked biological effects as CAN stimulants [13], anti-inflammatory and analgesic [14], antimicrobial [15], antitumor [16], in chemotherapy [17] and found to possess vasodilating effect [18] similar to that of nifedipine.

Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity was produced [19-20]. The chemistry of these linked biheterocycles has been a fascinating field of investigation in medicinal chemistry as they have been found to exhibit enhanced biological profile [21]. In view of this, we undertook the synthesis of isoxazolyl substituted benzimidazoles.

A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of substituted benzimidazoles [22]. However, these methods suffer drawback with regard to yields and involvement of multi steps and some other factors. Therefore the introduction of new efficient methods is still in demand.

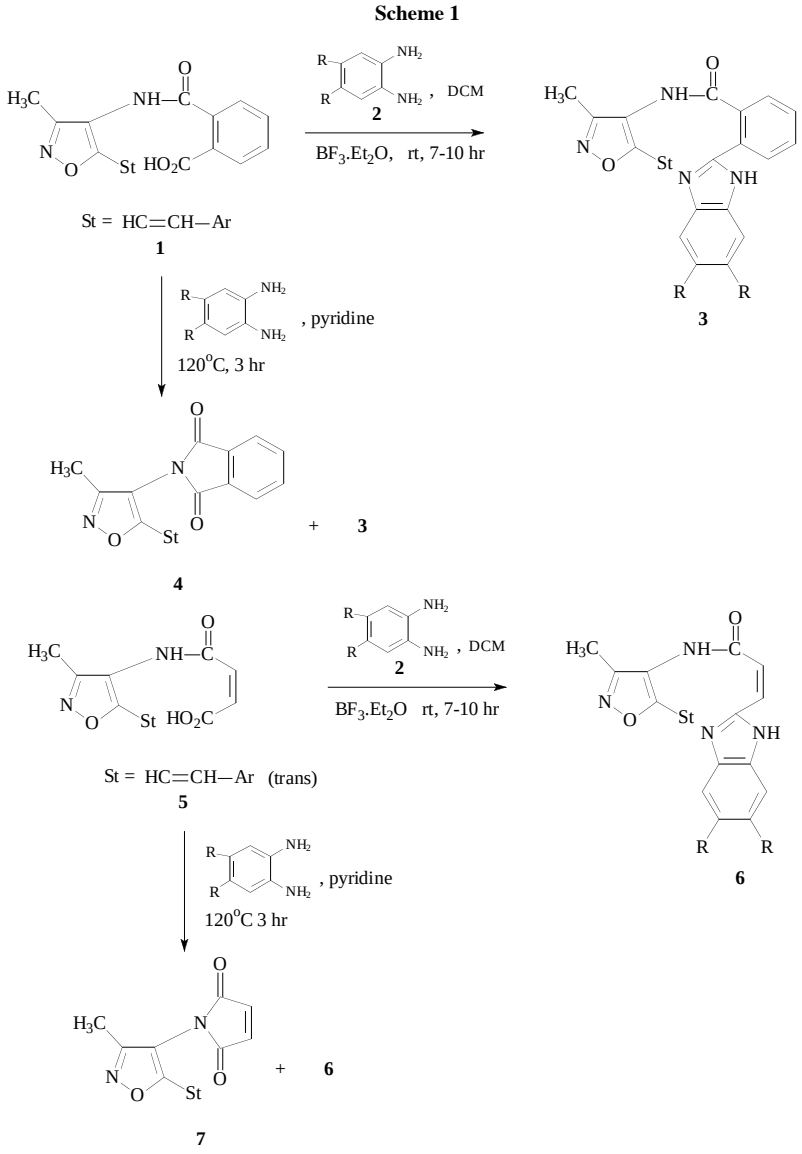
As a sequel to our work on development of new methodologies for the synthesis of substituted isoxazoles [23], we now report a selective synthesis of isoxazolyl substituted benzimidazoles in presence of $BF_3{\cdot}Et_2O$.

RESULTS AND DISCUSSION

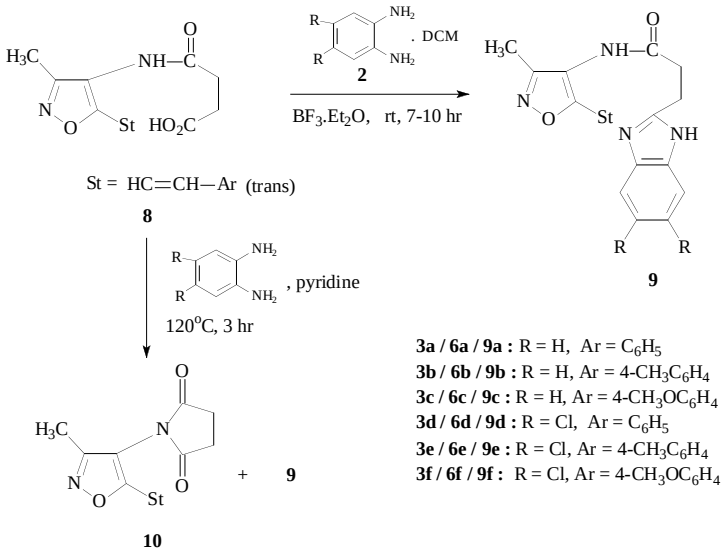
The required starting materials *viz*., phthalic monoamide **1**, maleic monoamide **5** and succinic monoamide **8** have been prepared by grinding the 4-amino-3-methyl-5-substituted styrylisoxazole [24] with phthalic anhydride, maleic anhydride and succinic anhydride separately in a mortar for 2 h. The reaction was monitored with TLC. It was extracted with $NaHCO_3$ solution. The clear filtrate on neutralization gave the corresponding products phthalic mono amide **1**, maleic monoamide **5** and succinic monoamide **8**, which were characterized by spectral data [25].

In a typical case, a mixture of 1 equiv. of phthalic monoamide **1** or maleic monoamide **5** or succinic monoamide **8** and 1 equiv. of 1,2-phenylene diamine **2** in dichloromethane were stirred for 15 min. at room temp., then $BF_3{\cdot}Et_2O$ in dichloromethane was added to it dropwise and reaction mixture was stirred at room temperature for 10 hr. After the usual process, 2-isoxazolyl substituted benzimidazole **3, 6** and **9**, respectively, was obtained as sole product in each case, in excellent yield (80-95%) (Scheme 1).

Scheme 1



Scheme 1 (continued)



The reaction was extended to phthalic monoamides **1** (Ar = 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$), maleic monoamides **5** (Ar = 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$), succinic monoamides **8** (Ar = 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$) which are reacted with 1,2-phenylenediamines **2** (R = H, Cl) to afford the corresponding 2-isoxazolyl substituted benzimidazoles **3, 6** and **9** respectively, in excellent yields (Table 1).

When the same reaction was carried out in pyridine at 120 °C, cyclodehydration to imide [25] (**4, 7, 10**) as well as cyclocondensation with 1,2-phenylene diamines took place resulting in the formation of mixture of products **3 & 4, 6 & 7** and **9 & 10** (40:60 ratio) (Scheme-1). In this context, we envisaged that, exclusive formation of desired 2-isoxazole substituted benzimidazoles could be achieved

Scheme 2

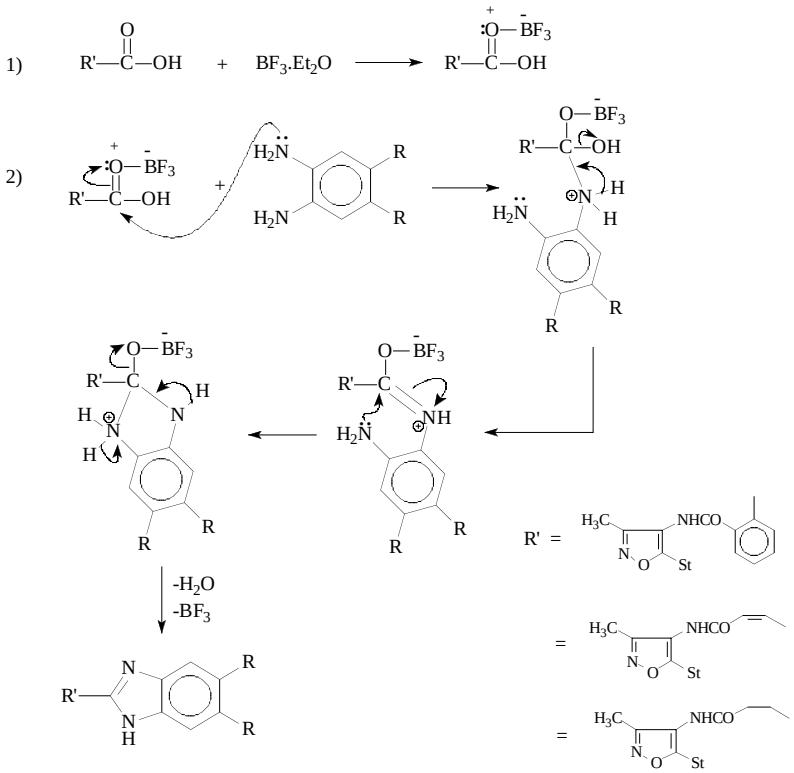


Table 1

Synthesis of Benzimidazoles Catalysed by Pyridine and $BF_3 \cdot Et_2O$

Compd No.	Ar	R	m.p. (°C)[a]	Pyridine[c]		$BF_3.Et_2O$	
				Reaction time (hr)	Yield (%)[b]	Reaction time (hr)	Yield (%)[b]
3a	C_6H_5	H	181-183	14	35	10	82
3b	4-$CH_3C_6H_4$	H	172-174	12	42	8	87
3c	4-$CH_3OC_6H_4$	H	169-170	12	40	8	94
3d	C_6H_5	Cl	191-193	15	30	9	89
3e	4-$CH_3C_6H_4$	Cl	197-199	16	36	8	94
3f	4-$CH_3OC_6H_4$	Cl	203-204	13	41	7	95
6a	C_6H_5	H	178-179	13	37	9	89
6b	4-$CH_3C_6H_4$	H	165-166	12	41	8	80
6c	4-$CH_3OC_6H_4$	H	175-176	11	40	7	91
6d	C_6H_5	Cl	188-190	14	32	10	83
6e	4-$CH_3C_6H_4$	Cl	194-196	13	42	9	92
6f	4-$CH_3OC_6H_4$	Cl	208-210	11	43	7	94
9a	C_6H_5	H	155-158	12	36	10	85
9b	4-$CH_3C_6H_4$	H	142-144	13	42	9	90
9c	4-$CH_3OC_6H_4$	H	149-151	12	44	8	95
9d	C_6H_5	Cl	185-187	14	38	9	81
9e	4-$CH_3C_6H_4$	Cl	200-202	12	40	8	89
9f	4-$CH_3OC_6H_4$	Cl	213-215	14	45	8	92

[a] All of the products were characterized by ^{1}H NMR, IR and mass spectral and elemental analysis data. [b] Isolated yields after column chromatography. [c] Yields of **4, 7** and **10** are in nearly 40%.

by using only $BF_3 \cdot Et_2O$. Other methods tried by using polyphosphoric acid, HCl and TFA also led to the mixture of two products in each case.

So, selective intermolecular cyclocondensation has been achieved by utilizing $BF_3 \cdot Et_2O$ only. Moreover, $BF_3 \cdot Et_2O$ is an efficient catalyst and tolerant towards chloro, methyl and methoxy groups on the aromatic ring. We have successfully demonstrated the usage of $BF_3 \cdot Et_2O$ as selective cyclocondensation catalyst, by avoiding the intramolecular cyclodehydration of the substrate itself. A single selective and desired product has been achieved in excellent yields.

EXPERIMENTAL

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin Elmer spectrum BX series FT-IR spectrometer. ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethylsilane as internal standard and mass spectra on Jeol JMC D-300 spectrometer. The silicagel (0.040 x 0.063 mm) used for column chromatography was purchased from Merck. Elemental analyses (C, H and N) were carried out on Carlo Erba 106 and Perkin Elmer model 240 analysers.

General procedure for synthesis of isoxzolyl substituted phthalic monoamides (1b, c) maleic monoamides (5b, c) and succinic monamides (8b, c). 4-Amino-3-methyl-5-substituted styrylisoxazole (10 mmol) and phthalic anhydride / maleic anhydride / succinic anhydride (10 mmol) were mixed well in a mortar and ground for 2 hrs at room temperature. The mixture was kept at room temperature for another 2 hrs for the completion of reaction. The resulting solid was extracted with aqueous bicarbonate solution. The clear filtrate on acidification gave the crude solid, which was recrystallized from absolute ethanol to afford isoxazolyl substituted phthalic monoamides, maleic monoamides and succinic monoamides respectively in excellent yields.

2-[({3-Methyl-5-[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}amino)carbonyl]benzoic acid (1b). This compound was obtained as colourless crystals, yield 82%; mp. 182-184°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, isoxazole-CH_3), 2.53 (s, 3H, CH_3), 6.80 (d, J=12 Hz, 1H, CH=CH), 7.04 (d, J=12 Hz, 1H, CH=CH), 7.22-7.85 (m, 8H, Ar-H), 9.21 (bs, 1H, NHCO, D_2O exchangeable), 11.60 (bs, 1H, COOH, D_2O exchangeable); MS (EI) *m/z* 362 (M^+); IR (KBr): cm^{-1} 1692, 1712 (C=O), 3055 (OH), 3179 (NH). *Anal*. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.61, H, 4.97; N, 7.73%; found: C, 69.55; H, 4.99; N, 7.69%.

2-[({5-[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}amino)carbonyl]benzoic acid (1c). This compound was obtained as colourless crystals, yield 88%; m.p. 175-178°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, isoxazole-CH_3), 3.70 (s, 3H, OCH_3), 6.77 (d, J=12 Hz, 1H, CH=CH), 6.92 (d, J=12 Hz, 1H, CH=CH), 7.20-7.75 (m, 8H, Ar-H), 9.90 (bs, 1H, NHCO, D_2O exchangeable), 11.22 (bs, 1H, COOH, D_2O exchangeable); MS (EI) *m/z* 378 (M^+), IR (KBr): cm^{-1} 1685, 1723 (C=O), 2990 (OH), 3220 (NH). *Anal*. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.76; N, 7.40%; found: C, 66.61; H, 4.79; N, 7.34%.

4-({3-Methyl-5-[(*E*}-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}amino)-4-oxo-2-butenoic acid (5b). This compound was obtained pale yellow colour crystals, yield 79%; m.p. 184-185°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H, isoxazole – CH_3), 2.45 (s, 3H, CH_3), 6.30 (d, J=12 Hz, 1H, CH=CH), 6.65 (d, J=12 Hz, 1H, CH=CH), 7.02-7.76 (m, 4H, Ar-H & 2H, CH=CH), 10.21 (bs, 1H, NHCO, D_2O exchangeable), 11.44 (s, 1H, COOH, D_2O exchangeable); MS (EI) *m/z* 312 (M^+); IR (KBr): cm^{-1} 1652, 1705 (C=O), 3059 (OH), 3272 (NH). *Anal.*

Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.12; N, 8.97%; found: C, 65.31; H, 5.17; N, 8.94%.

4-({5-[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}amino)-4-oxo-2-butenoic acid (5c). This compound was obtained as pale yellow colour crystals, yield 74%; m.p. 152-154°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, isoxazole-CH_3), 3.60 (s, 3H, OCH_3), 6.45 (d, J=12 Hz, 1H, CH=CH), 6.71 (d, J=12 Hz, 1H, CH=CH), 6.90-7.76 (m, 4H, Ar-H & 2H, CH=CH), 10.67 (bs, 1H, NHCO, D_2O exchangeable), 11.80 (s, 1H, COOH, D_2O exchangeble), MS (EI) *m/z* 328 (M^+); IR (KBr): cm^{-1} 1675, 1712 (C=O), 3110 (OH), 3315 (NH). *Anal*. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.87; N, 8.53%; found: C, 62.24; H, 4.82; N, 8.50%.

4-({3-Methyl-5-[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolylamino)-4-oxobutanoic acid (8b). This compound was obtained as colourless crystals, yield 72%; m.p. 121-124°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, isoxazole –CH_3), 2.31 (s, 3H, CH_3), 2.73 (m, 4H, CH_2-CH_2), 6.70 (d, J=12 Hz, 1H, CH=CH), 6.90 (d, J=12 Hz, 1H, CH=CH), 7.25-7.88 (m, 4H, Ar-H), 9.92 (bs, 1H, NHCO, D_2O exchangeable), 11.32 (s, 1H, COOH, D_2O exchangeable); MS (EI) *m/z* 314 (M^+); IR (KBr): cm^{-1} 1670, 1715 (C=O), 3035 (OH), 3257 (NH). *Anal*. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.73; N, 8.91%; found: C, 64.91; H, 5.70; N, 8.94%.

4-({5-[(*E*)-2-(3-Methoxyphenyl)-1-ethenyl]]-3-methyl-4-isoxazolyl}amino)-4-oxobutanoic acid (8c). This compound was obtained as colourless crystals, yield 78%; m.p. 112-116°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, isoxazole-CH_3), 2.62 (m, 4H, CH_2-CH_2), 3.65 (s, 3H, OCH_3), 6.80 (d, J=12 Hz, 1H, CH=CH), 7.03 (d, J=12 Hz, 1H, CH=CH), 7.25-7.78 (m, 4H, Ar-H), 10.32 (bs, 1H, NHCO, D_2O exchangeable) 11.65 (s, 1H, COOH, D_2O exchangeble): MS (EI) *m/z* 330 (M^+): IR (KBr): cm^{-1} 1681, 1710 (C=O), 3010 (OH), 3325 (NH). *Anal*. Calcd. For $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.45; N, 8.58%; found: C, 61.74; H, 5.49; N, 8.59%.

General procedure for synthesis of isoxazolyl substituted phthalimide (4), maleimide (7) and succinimides (10). Isoxazolyl substituted monoamides **1/5/8** (10 mmol) and 1,2-phenylene diamines (10 mmol) were dissolved in pyridine and refluxed for 24 hrs in the oil bath at 120°C. After completion of the reaction (monitored with TLC) the reaction mixture was allowed to cool and poured into ice cold water with stirring. The separated solid was collected by filtration and washed with water. Crude solid was purified by column chromatography by eluting with ethylacetate and hexane in 3:7 ratio and ethyl acetate and hexane in a 5:5 ratio respectively. 2-isoxazolyl substituted benzimidazoles (**3/6/9**) and undesired imides **4/7/10** are obtained in 2:3 ratio respectively from eluted solvent.

***N*-(3-Methyl-4-isoxazolyl-5-styryl)-phthalimide (4).** This compound was obtained as colourless crystals, yield 40%; m.p. 185-187°C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.22 (s, 3H, isoxazole-CH_3), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.04-7.94 (m, 10, Ar-H & CH=CH); MS (EI) *m/z* 330 (M^+) : IR (KBr): cm^{-1} 1725, 1785 (C=O). Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.24; N, 8.48%; found: C, 72.76; H, 4.20; N, 84.2%.

***N*-(3-Methyl-4-isoxazolyl-5-styryl)-maleimide (7).** This compound was obtained as pale yellow crystals, yield 55%; m.p. 150-152°C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.16 (s, 3H, isoxazole-CH_3), 6.62 (d, 2H, imide, CH=CH), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.04-7.78 (m, 6H, Ar-H & CH=CH); MS (EI) *m/z* 279 (M^+); IR (KBr): cm^{-1} 1660, 1730 (C=O). Anal. Calcd. For $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.28; N, 10.00; found: C, 68.50; H, 4.32; N, 10.05.

***N*-(3-Methyl-4-isoxazolyl-5-styryl)-succinimide (10).** This compound was obtained as colourless crystals, yield 52%; m.p. 95°C, ^{1}H NMR (300 MHz, $CDCl_3$): 2.25 (s, 3H, isoxazole-CH_3), 3.25 (t, 4H, -CH_2-CH_2-), 6.80 (d, J=12 Hz, 1H, CH=CH), 7.08-7.92 (m, 6H, Ar-H & CH=CH); MS (EI): *m/z* 282 (M^+). IR (KBr): cm^{-1} 1672, 1725 (C=O). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 4.96; N, 9.92%; found: C, 68.12; H, 4.92; N, 9.88%.

General procedure for synthesis of 2-isoxazolyl substituted benzimidazoles (3 / 6 / 9). To a well stirred solution of compound **1 / 5 / 8** (10 mmol) and 1,2-phenylene diamines (10 mmol) in dichloromethane (20 ml), BF_3·Et_2O (10 mmol) in dichloromethane (20 ml) was added dropwise with stirring and the reaction continued for 7-10 hr at room temperature (reaction monitored by TLC). After completion of the reaction, the solvent was evaporated under reduced pressure. The crude solid was purified by column chromatography over silicagel, elution with ethylacetate: *n*-hexane (1:9) afforded benzimidazoles (**3/6/9**) in 81-95% yields.

***N*$_1$-{3-Methyl-5[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-2-(1*H*-benzo[*d*]imidazol-2-yl)benzamide (3a).** This compound was obtained as colourless crystals; m.p. 181-183°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.65 (d, J=12 Hz, 1H, CH=CH), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.05-7.86 (m, 13H, Ar-H), 9.72 (bs, 1H, NHCO, D_2O exchangeable), 11.03 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 420 (M^+); IR (KBr): cm^{-1} 1708 (NHCO), 3380 (NHCO), 3460 (NH). *Anal*. Calcd. for $C_{26}H_{20}N_4O_2$: C, 74.28; H, 4.76; N, 13.33%; found: C, 75.34; H, 4.81; N, 13.39%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-2-(1*H*-benzo[*d*]imidazol-2-yl)benzamide (3b).** This compound was obtained as colourless crystals; m.p. 172-174°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, isoxazole-CH_3), 2.62 (s, 3H, CH_3), 6.70 (d, J=12 Hz, 1H, CH=CH), 6.93 (d, J=12 Hz, 1H, CH=CH), 7.20 - 7.85 (m, 12H, Ar-H), 10.02 (bs, 1H, NHCO, D_2O exchangeable), 11.24 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 434 (M^+); IR (KBr): cm^{-1} 1689 (NHCO), 3320 (NHCO), 3480 (NH). *Anal*. Calcd. for $C_{27}H_{22}N_4O_2$: C, 74.65; H, 5.06; N, 12.90%; found: C, 74.69; H, 5.11; N, 12.98%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methoxyphenyl)-1-ethenyl]-4-isoxazolyl}-2-(1*H*-benzo[*d*]imidazol-2-yl)benzamide (3c).** This compound was obtained as colourless crystals; m.p. 169-170°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.61 (d, J=12 Hz, 1H, CH=CH), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.10-7.90 (m, 12H, Ar-H), 10.55 (bs, 1H, NHCO, D_2O exchangeable), 11.52 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 450 (M^+); IR (KBr): cm^{-1} 1685 (NHCO), 3360 (NHCO), 3452 (NH). *Anal*. Calcd. for $C_{27}H_{22}N_4O_3$: C, 72.00; H, 4.88; N, 12.44%; found: C, 72.09; H, 4.81; N, 12.39%.

***N*$_1$-{3-Methyl-5[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-2-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)benzamide (3d).** This compound was obtained as colourless crystals; m.p. 191-193°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 6.62 (d, J=12 Hz, 1H, CH=CH), 6.85 (d, J=12 Hz, 1H, CH=CH), 7.02-8.05 (m, 11H, Ar-H), 9.91 (bs, 1H, NHCO, D_2O exchangeable), 10.95 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 488 (M^+); IR (KBr): cm^{-1} 1660 (NHCO), 3150 (NHCO), 3200 (NH). *Anal*. Calcd. for $C_{26}H_{18}Cl_2N_4O_2$: C, 63.81; H, 3.71; N, 11.45%; found: C, 63.97; H, 3.74; N, 11.40%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-2-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)benzamide (3e).** This compound was obtained as colourless crystals; m.p. 197-199°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H,

isoxazole-CH_3), 2.73 (s, 3H, CH_3), 6.75 (d, J=12 Hz, 1H, CH=CH), 6.93 (d, J=12 Hz, 1H, CH=CH), 7.12-8.05 (m, 10H, Ar-H), 9.23 (bs, 1H, NHCO, D_2O exchangeable), 10.8 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 502 (M^+); IR (KBr): cm^{-1} 1675 (NHCO), 3252 (NHCO), 3345 (NH). *Anal.* Calcd. for $C_{27}H_{20}Cl_2N_4O_2$: C, 64.54; H, 3.98; N, 11.15%; Found: C, 64.61; H, 3.91; N, 11.22%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methoxyphenyl]-1-ethenyl]-4-isoxazolyl}-2-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)benzamide (3f).** This compound was obtained as colourless crystals; m.p. 203-204°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 6.61 (d, J=12 Hz, 1H, CH=CH), 6.84 (d, J=12 Hz, 1H, CH=CH), 7.10-7.90 (m, 10H, Ar-H), 9.92 (bs, 1H, NHCO, D_2O exchangeable), 10.91 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 518 (M^+); IR (KBr): cm^{-1} 1682 (NHCO), 3288 (NHCO), 3375 (NH). *Anal.* Calcd. for $C_{27}H_{20}Cl_2N_4O_3$: C, 62.54; H, 3.86; N, 10.81%; Found: C, 62.61; H, 3.81; N, 10.89%.

***N*$_1$-{3-Methyl-5[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-(*E*)-3-(1*H*-benzo[*d*]imidazol-2-yl)-2-propenamide (6a).** This compound was obtained as colourless crystals; m.p. 178-179°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 6.65 (d, J=12 Hz, 1H, CH=CH), 6.80 (d, J=12 Hz, 1H, CH=CH), 7.02-8.05 (m, 11H, Ar-H & CH=CH), 9.92 (bs, 1H, NHCO, D_2O exchangeable), 10.98 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 370 (M^+); IR (KBr): cm^{-1} 1685 (NHCO), 3200 (NHCO), 3350 (NH). *Anal.* Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.35; H, 4.86; N, 15.13%; Found: C, 71.41; H, 4.80; N, 15.17%.

***N*$_1$-{3-Methyl-5[(*E*)-2(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-(*E*)-3-(1*H*-benzo[d]imidazol-2-yl)-2-propenamide (6b).** This compound was obtained as colourless crystals; m.p. 165-166°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, isoxazole-CH_3), 2.70 (s, 3H, CH_3), 6.73 (d, J=12 Hz, 1H, CH=CH), 6.92 (d, J=12 Hz, 1H, CH=CH), 7.20-8.12 (m, 10H, Ar-H & CH=CH), 9.12 (bs, 1H, NHCO, D_2O exchangeable), 10.25 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 384 (M^+); IR (KBr): cm^{-1} 1672 (NHCO), 3240 (NHCO), 3385 (NH). *Anal.* Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.87; H, 5.20; N, 14.58%; Found: C, 71.82; H, 5.27; N, 14.52%.

***N*$_1$-{5[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-(*E*)-3-(1*H*-benzo[*d*]-imidazol-2-yl)-2-propenamide (6c).** This compound was obtained as colourless crystals; m.p. 175-176°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.01 (d, J=12 Hz, 1H, CH=CH), 7.24-8.32 (m, 10H, Ar-H & CH=CH), 9.25 (bs, 1H, NHCO, D_2O exchangeable), 10.46 (bs, 1H, benzimidazole-1H, D_2O exchangeable); MS (EI) *m/z* 400 (M^+); IR (KBr): cm^{-1} 1691 (NHCO), 3255 (NHCO), 3395 (NH). *Anal.* Calcd. for $C_{23}H_{20}N_4O_3$: C, 69.00; H, 5.00; N, 14.00%; Found: C, 69.08; H, 5.05; N, 13.92%.

***N*$_1$-{3-methyl-5[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-(*E*)-3-(5,6-dichloro-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)-2-propenamide (6d).** This compound was obtained as colourless crystals; m.p. 188-190°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 6.70 (d, J=12 Hz, 1H, CH=CH), 6.92 (d, J=12 Hz, 1H, CH=CH), 7.12-7.92 (m, 9H, Ar-H & CH=CH), 9.45 (bs, 1H, NHCO, D_2O exchangeable), 9.82 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 438 (M^+); IR (KBr): cm^{-1} 1690 (NHCO), 3200 (NHCO), 3350 (NH). *Anal.* Calcd. for $C_{22}H_{16}Cl_2N_4O_2$: C, 60.27; H, 3.65; N, 12.78%; Found: C, 60.32; H, 3.69; N, 12.71%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-(*E*)-3-(5,6-dichloro-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)-2-propenamide (6e).** This compound was obtained as colourless crystals; m.p. 194-196°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, isoxazole-CH_3), 2.62 (s, 3H, CH_3), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.05 (d, J=12 Hz, 1H, CH=CH), 7.22-8.15 (m, 8H, Ar-H & CH=CH), 9.02 (bs, 1H, NHCO, D_2O exchangeable), 10.12 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 452 (M^+); IR (KBr): cm^{-1} 1685 (NHCO), 3225 (NHCO), 3382 (NH). *Anal.* Calcd. for $C_{23}H_{18}Cl_2N_4O_2$: C, 61.06; H, 3.98; N, 12.38%; Found: C, 61.14; H, 4.05; N, 12.32%.

***N*$_1$-{5[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-(*E*)-3-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)-2-propenamide (6f).** This compound was obtained as colourless crystals; m.p. 208-210°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 6.64 (d, J=12 Hz, 1H, CH=CH), 6.87 (d, J=12 Hz, 1H, CH=CH), 7.02-7.86 (m, 8H, Ar-H & CH=CH), 8.82 (bs, 1H, NHCO, D_2O exchangeable), 10.45 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 468 (M^+); IR (KBr): cm^{-1} 1673 (NHCO), 3245 (NHCO), 3372 (NH). *Anal.* Calcd. for $C_{23}H_{18}Cl_2N_4O_3$: C, 58.97; H, 4.05; N, 11.96%; Found: C, 58.90; H, 4.11; N, 11.92%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(2-phenyl)-1-ethenyl]-4-isoxazolyl}-3-(1*H*-benzo[*d*]imidazol-2-yl)-propanamide (9a).** This compound was obtained as colourless crystals; m.p. 155-158°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.02 (t, 2H, CH_2CH_2), 3.35 (t, 2H, CH_2CH_2), 6.62 (d, J=12 Hz, 1H, CH=CH), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.05-7.64 (m, 9H, Ar-H), 7.82 (bs, 1H, NHCO, D_2O exchangeable), 9.88 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 372 (M^+); IR (KBr): cm^{-1} 1675 (NHCO), 3265 (NHCO), 3290 (NH). *Anal.* Calcd. for $C_{22}H_{20}N_4O_2$: C, 70.96; H, 5.37; N, 15.05%; Found: C, 70.90; H, 5.41; N, 15.11%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-3-(1*H*-benzo[*d*]imidazol-2-yl)propanamide (9b).** This compound was obtained as colourless crystals; m.p. 142-144°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, isoxazole-CH_3), 2.82 (s, 3H, CH_3), 3.13 (t, 2H, CH_2CH_2), 3.45 (t, 2H, CH_2CH_2), 6.76 (d, J=12 Hz, 1H, CH=CH), 6.91 (d, J=12 Hz, 1H, CH=CH), 7.13-7.95 (m, 8H, Ar-H), 8.25 (bs, 1H, NHCO, D_2O exchangeable), 10.16 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 386 (M^+); IR (KBr): cm^{-1} 1698 (NHCO), 3289 (NHCO), 3310 (NH). *Anal.* Calcd. for $C_{23}H_{22}N_4O_2$: C, 71.50; H, 5.69; N, 14.50%; Found: C, 71.57; H, 5.61; N, 14.58%.

***N*$_1$-{5[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-3-(1*H*-benzo[*d*]imidazol-2-yl)propanamide (9c).** This compound was obtained as colourless crystals; m.p. 149-151°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H, CH_3), 3.22 (t, 2H, CH_2CH_2), 3.45 (t, 2H, CH_2CH_2), 3.76 (s, 3H, OCH_3), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.02 (d, J=12 Hz, 1H, CH=CH), 7.25-7.96 (m, 8H, Ar-H), 8.72 (bs, 1H, NHCO, D_2O exchangeable), 10.45 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 402 (M^+); IR (KBr): cm^1 1705 (NHCO), 3252 (NHCO), 3398 (NH). *Anal.* Calcd. for $C_{23}H_{22}N_4O_3$: C, 68.65; H, 5.47; N, 13.93%; Found: C, 68.59; H, 5.52; N, 13.87%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(2-phenyl)-1-ethenyl]-4-isoxazolyl}-3-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)propanamide (9d).** This compound was obtained as colourless crystals; m.p. 185-187°C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 2.92 (t, 2H, CH_2CH_2), 3.11 (t, 2H, CH_2CH_2), 6.65 (d, J=12 Hz, 1H,

CH=CH), 6.82 (d, J=12 Hz, 1H, CH=CH), 7.02-7.85 (m, 7H, Ar-H), 9.12 (bs, 1H, NHCO, D_2O exchangeable), 10.25 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 440 (M^+); IR (KBr): cm^{-1} 1685 (NHCO), 3295 (NHCO), 3400 (NH). *Anal*. Calcd. for $C_{22}H_{18}Cl_2N_4O_2$: C, 60.00; H, 4.09; N, 12.72%; Found: C, 60.09; H, 4.14; N, 12.80%.

***N*$_1$-{3-Methyl-5[(*E*)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-3-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)propanamide (9e).** This compound was obtained as colourless crystals; m.p. 200-202°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, isoxazolyl-CH_3), 2.75 (s, 3H, CH_3), 3.02 (t, 2H, CH_2CH_2), 3.25 (t, 2H, CH_2CH_2), 6.76 (d, J=12 Hz, 1H, CH=CH), 6.92 (d, J=12 Hz, 1H, CH=CH), 7.15-8.05 (m, 6H, Ar-H), 8.45 (bs, 1H, NHCO, D_2O exchangeable), 10.52 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 454 (M^+); IR (KBr): cm^{-1} 1710 (NHCO), 3305 (NHCO), 3350 (NH). *Anal*. Calcd. for $C_{23}H_{20}Cl_2N_4O_2$: C, 60.79; H, 4.40; N, 12.33%; Found: C, 60.84; H, 4.46; N, 12.39%.

***N*$_1$-{5[(*E*)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-3-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)propanamide (9f).** This compound was obtained as colourless crystals; m.p. 213-215°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.12 (t, 2H, CH_2CH_2), 3.34 (t, 2H, CH_2CH_2), 3.74 (s, 3H, OCH_3), 6.92 (d, J=12 Hz, 1H, CH=CH), 7.15 (d, J=12 Hz, 1H, CH=CH), 7.35-8.27 (m, 6H, Ar-H), 8.92 (bs, 1H, NHCO, D_2O exchangeable), 10.75 (bs, 1H, benzimidazole-H, D_2O exchangeable); MS (EI) *m/z* 470 (M^+); IR (KBr): cm^{-1} 1688 (NHCO), 3329 (NHCO), 3295 (NH). *Anal*. Calcd. for $C_{23}H_{20}Cl_2N_4O_3$: C, 58.72; H, 4.25; N, 11.91%; Found: C, 58.79; H, 4.31; N, 11.99%.

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