Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted 2-(4-styrylphenyl)-1*H*-benzimidazole and N- substituted-3[4-(1*H*-benzimidazole-2-yl)-phenyl]-acrylic acid *tert*-butyl ester

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Abstract
Synthesis of a series of novel substituted benzimidazole derivatives by the condensation of *o*-phenylenediamine **(**OPDA, **1)** with 4-bromobenzoic acid **(2)** and subsequent reactions of the benzimidazole with different electrophilic reagents is reported. The latter compounds were reacted with styrene and *tert*-butyl acrylate following Heck Coupling. All the compounds synthesized were screened for their potential anti-bacterial, anti-asthmatic and anti-diabetic properties, which exibibited some promising results towards testing organism in vivo.

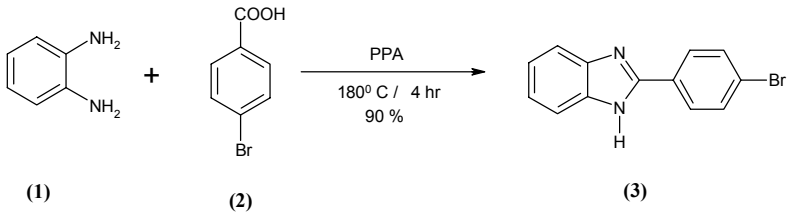
Keywords: Antibacterial activity, benzimidazole, alkylation and Heck coupling

Introduction

Benzimidazoles are among the important heterocyclic compounds found in several natural and non-natural products such as Vitamin B12[1], marine alkaloid kealiiquinone[2], benzimidazole nucleosides[3] etc. Some of their derivatives are marketed as anti-fungal agents such as Carbendazim[4], anti-helmintic agents such as Mebendazole and thiabendazole[5] and anti-psychotic drug such as Pimozide [6] and other derivatives have been found to possess some interesting bioactivities such as anti-tubercular[7], anti-cancer[8] etc. Recently, we have also published some series of biologically active benzimidazoles[9]. Owing to the immense biological importance of benzimidazole derivatives, we synthesized some substituted alkenylbenzimidazoles and screened them for biological activity.

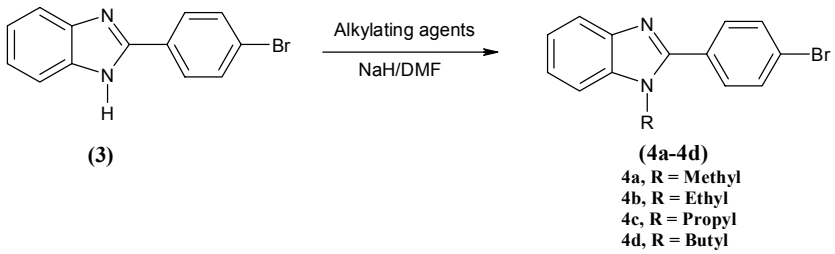
Results and Discussion

The condensation of *o*-phenylenediamine (OPDA) (**1**) with 4-bromobenzoic acid **(2**) was carried out in presence of polyphosphoric acid at 180 ^{o}C for 4 h to obtain the known 2-(4-bromo-phenyl)-1*H*-benzimidazole (**3**)[10] (Scheme-1).



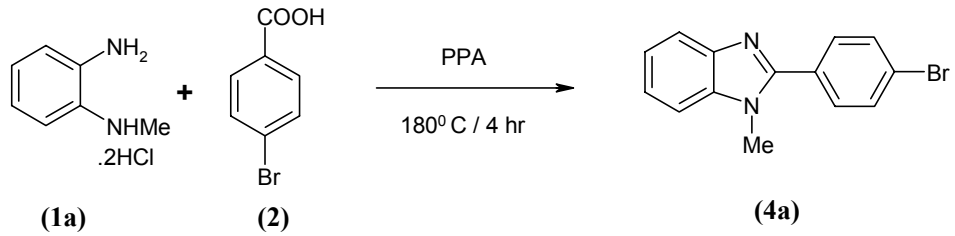
Scheme 1

Initially, we thought of alkylating the benzimidazole –NH with suitable electrophilic reagents to generate N-alkylatedbenzimidazoles. In this regard, compound **3** was alkylated with different alkylating agents in N, N'-dimethylformamide and in presence of sodium hydride as base to obtain the corresponding alkylated derivatives **4a**[10c]**, 4b, 4c**[10a] and **4d**[10a] (Scheme 2).



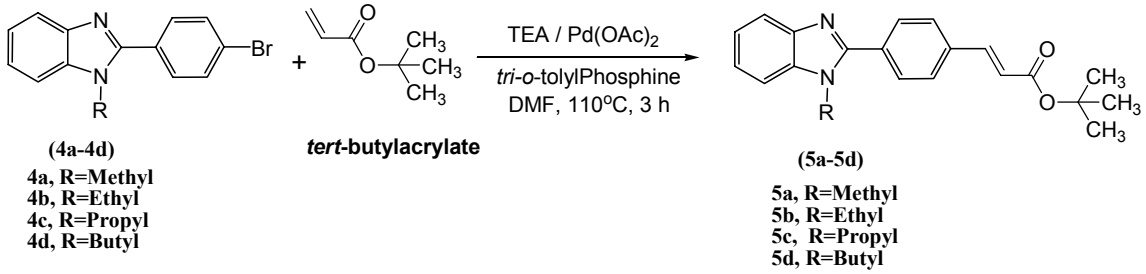
Scheme 2

It is noteworthy to mention here that, in an alternative approach, compound **4a** has also been prepared by condensing *N*-methyl-OPDA dihydrochloride[11] (**1a)** with 4-bromobenzoic acid (**2**) in the presence of polyphosphoric acid at 180 ^{o}C (Scheme 3). The structure of compound **4a** obtained *via* **1a** was confirmed by its physical and spectral characteristics and also by comparison with the compound obtained by direct methylation of compound **3**.



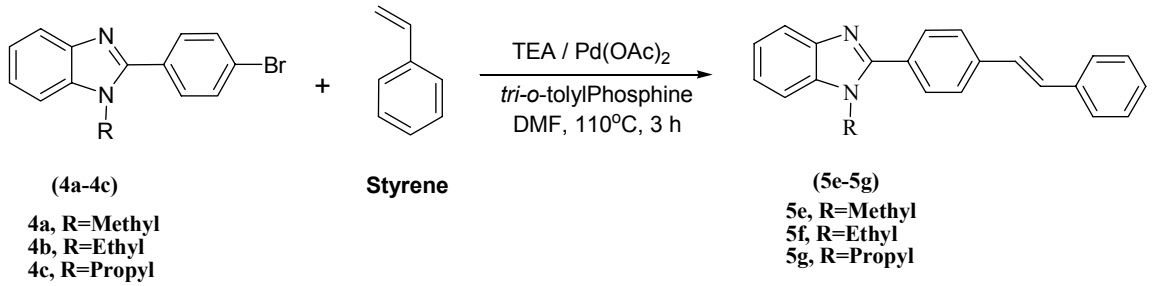
Scheme 3

Compounds **4a - 4d** were then reacted with *tert*-butylacrylate in presence of tri-*o*-tolylphosphine, triethylamine and palladium acetate as catalyst under Heck coupling conditions[12] to get **5a-5d** (Scheme 4).



Scheme 4

We then reacted compounds **4a-4c** with styrene to get the corresponding alkenylbenzimidazoles **5e-5g**[13] respectively (Scheme5).



Scheme 5

Biological activity

All the compounds prepared herein were screened for their potential biological activities such as, anti-bacterial activity[14] against Staphylococcus *aureus* (gram positive) and Salmonella *typhimurium* (gram negative) bacterial strains[15] at concentration 500, 200, 100, 10 and 0.1µg/ml. Cephalexin was used as a reference standard. The results of the anti-bacterial activity screening of the tested compound are summarized in Table 1 & Table 2. Most of the compounds tested were found to have good anti-bacterial activity against Salmonella *typhimurium*, however, they were found to have poor activity against Staphylococcus *aureus*. Also they were tested against PDE – IV for potential anti-asthmatic effect, and against DPP-IV and PTP1B for potential anti-diabetic effects. No activity was found. The anti-asthmatic activity was carried out using *Phosphodiesterase* IV enzyme (PDE-IV)[16] (Table 3) and the primary screening of the compounds was done at 1uM concentration using human PDIV enzyme, where Rolipram & Ariflo were used as standard compounds.

The anti-diabetic activity was carried out with dipeptidyl peptidase (DPP-IV)[17] enzyme (Table 3) and the primary screening of the compounds was carried at 300 nM concentration using recombination human DPP-IV enzyme by the use of 1-(2-amino -3,3-dimethylbutanoyl pyrrolidine -2-carbonitrile as the standard compound at 100 nM. Similarly, the PTP1B[18] (In-house compound, also for anti-diabetic) activity (Table 3) was done using the test compounds at 30 μM with the standard compound N-[5-[N-Acetyl-4-[N-(2-carboxyphenyl)-N-(2-hydroxyoxalyl)amino]-3-ethyl-DL-phenylalanyl-amino]-pentanoyl]-L-methionine at a concentration of 0.3 μM.

Protocol for PDE-IV-inhibition assay

Phosphodiesterase IV enzyme converts [^{3}H] cAMP to the corresponding [^{3}H] 5'-AMP in proportion to the amount of *Phosphodiesterase* IV present. The [^{3}H] 5'-AMP then was quantitatively converted to free [^{3}H] adenosine and phosphate by the action of snake venom 5'-nucleotidase hence the amount of [^{3}H] adenosine liberated is proportional to *Phosphodiesterase* IV activity.

The assay was performed at 34 ^{o}C in a 200 mL total reaction mixture. The reaction mixture contained 25 mM of tris-buffer, 10 mM $MgCl_2$, 1 μM cAMP (cold) and [^{3}H] cAMP(0.1μCi) stock solutions of the compounds to be investigated were prepared in dimethyl sulfoxide in concentrations such that the dimethyl sulfoxide content in the test samples did not exceed 0.05% by volume to avoid affecting the *Phosphodiesterase* IV activity. Compounds were then added in the reaction mixture (25μL/tube). The assay was initiated by addition of enzyme mix (75μL) and the mixture was incubated for 20 minutes at 34 ^{o}C. The reaction was stopped by boiling the tubes for 2 min at 100 ^{o}C in a water bath. After cooling on ice for 5 minutes and addition of 50 μg 5'-nucleotidase snake venom from *Crotalus atrox* incubation was carried out again for 20 min at 34 ^{o}C. The un-reacted substrate was separated from (^{3}H) adenosine by addition of Dowex AG 1X-8 (400 μL), which was pre equilibrated in (1:1) water:ethanol. Reaction mixture was then thoroughly mixed, placed on ice for 15 minutes, vortexed and centrifuged at 14,000 rpm. for 2 min. After centrifugation, a sample of the supernatent (150 μL) was taken and added in 24 well optiplates containing scinillant (1 mL) and mixed well. The samples in the plates were then determined for radioactivity in a Top Counter and the *Phosphodiesterase* IV activity was calculated. *Phosphodiesterase* IV enzyme was present in quantities that yield < 30% total hydrolysis of substrate (linear assay conditions). Rolipram and Cilomilast were used as a standard in all assays.

Protocol for the DPP-IV assay

DPPIV inhibition measurement in vitro:

DPPIV activity was determined by the cleavage rate of 7-amino-4-methyl coumarin (AMC) from synthetic substrate Glycyl-Prolyl-AMC. In brief, the assay was conducted by adding 10 ng of human recombinant Dipeptidyl peptidase IV enzyme (DPPIV, available commercially from R & D Systems) in 50 μl of the assay buffer (25 mM Tris, p^H 7.4, 140 mM NaCl, 10 mM KCl, 1%

BSA) to 96 well black flat bottom micro-titer plates. The reaction was initiated by adding 50 µl of 100 µM substrate Gly-Pro-AMC. The incubation was carried out in the kinetic mode at 30 ^{o}C for 30 min. Fluorescence was measured using Fluorostar at excitation filter of 380 nm and emission filter of 460 nm) Test compounds and solvent controls were added as 1 µl additions. Test compounds were dissolved in DMSO and tested at 300 nM concentration. Percent inhibition was calculated with respect to the solvent control sample (no test compound added). Dipeptidyl peptidase (i.e., anti-diabetic).

Protocol for PTB1B assay

In house generated human recombinant enzyme: ~35 ng in assay
Paranitrophenyle phosphate (SRL144916): 25 mM
Buffer: Hepes 25 mM, 3 mM DTT, 0.15M NaOH, 1 mM EDTA, p^{H} 7.4
Dilution buffer (for enzyme): 2 X reaction buffer (3 mM DTT) DMSO (Calbiochem)
Test compound in DMSO
DMSO concentration not to exceed 1% in the assay
Protocol

	Blank	Control	Test
DMSO	1 µl	1 µl	-
Compound	-	-	1 µl
Buffer	89 µl	88 µl	88 µl
Enzyme	-	1 µl	1 µl
PNPP	10 µl	10 µl	10 µl

Incubate and continuously monitor at 30 ^{o}C for 30 minutes at 405 nm.

NaOH	100 µl	100 µl	100 µl

Read at 405 nm.
Evaluation of the study observation:
Calculations: Activity = % of control; % Inhibition = 100- activity.

Table 1. Antibacterial activity of compounds against Staphylococcus *aureus*

Compd. No.	Concentration						
	0.1µg/ml	1µg/ml	10µg/ml	100µg/ml	200µg/ml	500µg/ml	APP.MIC
3	++	++	++	+	--	--	200 µg/ml
4a	++	++	+	P	--	--	200 µg/ml
4b	++	++	++	+	--	--	200 µg/ml
4c	++	++	++	+	P	--	500 µg/ml
4d	++	++	++	+	P	--	500 µg/ml
5a	++	++	+	P	P	--	500 µg/ml
5b	++	++	++	+	P	--	500 µg/ml
5c	++	++	++	+	P	--	500 µg/ml
5d	++	++	+	P	P	--	500 µg/ml
5e	+	+	+	P	--	--	200 µg/ml
5f	+	+	P	P	--	--	200 µg/ml
5g	+	+	+	P	--	--	200 µg/ml
Cephalexin	++	++	--	--	--	--	10 µg/ml

Table 2. Antibacterial activity of compounds against Salmonella *typhimurium*

Compd. No.	Concentration						
	0.1µg/ml	1µg/ml	10µg/ml	100µg/ml	200µg/ml	500µg/ml	APP.MIC
3	++	++	++	+	--	--	200µg/ml
4a	++	++	+	P	--	--	200µg/ml
4b	++	++	++	+	--	--	200µg/ml
4c	++	++	++	+	P	--	500µg/ml
4d	++	++	++	+	P	--	500µg/ml
5a	++	++	++	P	--	--	200µg/ml
5b	++	++	++	+	--	--	200 µg/ml
5c	++	++	++	++	P	--	500 µg/ml
5d	++	++	++	+	--	--	200 µg/ml
5e	++	++	+	P	--	--	200 µg/ml
5f	+	+	P	P	--	--	200 µg/ml
5g	++	++	+	P	--	--	200 µg/ml
Cephalexin	++	++	+	P	--	--	200µg/ml

Table 3. Anti-diabetic & anti- asthmatic activity of compounds

Compound No	**PTP1B** (30μM) % Inhibition	**PDE-IV** (1μM) % Inhibition	**DPP-IV** (0.3μM) % Inhibition
3	3.87	33.25	13
4a	5.01	22.05	2
4b	7.21	10.86	3
4c	12.45	15.86	2
4d	8.95	12.11	5
5a	0.42	4.48	0
5b	3.79	35.54	0
5c	3.43	13.53	0
5d	11.66	0	0
5e	14.35	38.78	0
5f	12.78	0	0
5g	0	29.30	0

Symbols: -- Total Inhibition, no growth of organism; P - Poor growth compared to controls; + - Medium growth compared to controls; ++ - Confluent growth, no inhibition.

Standard compound assay

1. **PTP-1B:** N-[5-[Acetyl]-4-[N-(2-carboxypheyl)-N-(2-hydroxalyl)amino]-3-ethyl-DL-phenyl-alanylamino]pentanoyl]-L-methionine is used as a standard in all assays and shows percentage inhibition of 49.09 % at a concentration of 0.3 μM.
2. **PDE IV:** Rolipram and Cilomilast were used as a standard in all assays. Rolipram shows percentage inhibition 67.41% at a concentration of 2μM. Cilomilast shows percentage inhibition 45.28% at a concentration of 0.075 μM.
3. **DPP IV:** 1-(2-amino-3, 3-dimethylbutyryl) pyrrolidine-2-carbonitrile is used as a standard in all assays and shows percentage inhibition of 96 % at a concentration of 0.1 μM.

Conclusions

In conclusion, we synthesized a series of novel substituted benzimidazole derivatives by the condensation of OPDA with 4-bromobenzoic acid and subsequent reactions of the benzimidazole with different electrophilic reagents. All the compounds thus obtained were reacted with styrene and *tert*-butyl acrylate following Heck Coupling to obtain the substituted alkenylbenzimidazole derivatives. Some of the compounds were found to have good anti-bacterial activity against Salmonella *typhimurium,* however they were found to have less activity against S. *aureus*. These compounds were also tested against PDE–IV for potential anti-asthmatic effect, and against DPP-IV and PTP1B for potential anti-diabetic effects. Unfortunately, the results were disappointing.

Experimental Section

General Procedures. Melting points are uncorrected and were recorded on a MRVIS Series, Lab India Instrument. TLC analysis was done using pre-coated silica gel plates and visualization was done using Iodine / UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H & ^{13}C-NMR spectra were recorded on a Varian Mercury Vx SWBB 300MHz spectrometer with $CDCl_3$ as solvent unless otherwise mentioned. Elemental analysis was carried out on a Perkin–Elmer Series–II CHNS/O Analyzer 2400**.** *o*-phenylenediamine, alkylating and acylating agents were obtained from commercial suppliers. Styrene and *tert.*-Butyl acrylate were obtained from Aldrich. All the solvents used were of commercial grade only.

Table 4. Physical and analytical data of compounds **3**, **4a-4d**, **5a-5g**

Compound	R	Time in Hours	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd. (Found)		
						C	**H**	**N**
3	H	4	295-296	90	$C_{13}H_9BrN_2$	57.17	3.32	10.26
						(57.01)	(3.40)	(10.32)
4a	Methyl	1	115-116	91	$C_{14}H_{11}BrN_2$	58.56	3.86	9.30
						(58.50)	(3.91)	(9.33)
4b	Ethyl	1	137-138	87	$C_{15}H_{13}BrN_2$	59.82	4.35	9.30
						(59.90)	(4.48)	(9.28)
4c	Propyl	1	94-95	89	$C_{16}H_{15}BrN_2$	60.97	4.80	8.89
						(61.01)	(4.91)	(8.85)
4d	Butyl	1	79-80	90	$C_{17}H_{17}BrN_2$	62.02	5.20	8.51
						(62.05)	(5.32)	(8.60)
5a	Methyl	1-3	172-173	90	$C_{21}H_{22}N_2O_2$	75.42	6.63	8.38
						(75.40)	(6.75)	(8.42)
5b	Ethyl	1-3	192-194	90	$C_{22}H_{24}N_2O_2$	75.83	6.94	8.04
						(75.70)	(7.00)	(7.94)
5c	Propyl	1-3	129-131	89	$C_{23}H_{26}N_2O_2$	76.21	7.23	7.73
						(76.15)	(7.32)	(7.68)
5d	Butyl	1-3	89-90	91	$C_{24}H_{28}N_2O_2$	76.56	7.50	7.44
						(76.48)	(7.65)	(7.38)
5e	Methyl	1-3	162-164	82	$C_{22}H_{18}N_2$	85.13	5.85	9.02
						(85.14)	(5.98)	(9.13)
5f	Ethyl	1-3	112-113	86	$C_{23}H_{20}N_2$	85.15	6.21	8.63
						(85.04)	(6.38)	(8.59)
5g	Propyl	1-3	150-152	90	$C_{24}H_{22}N_2$	85.17	6.55	8.28
						(85.18)	(6.60)	(8.27)

Synthesis of 2-(4-bromophenyl)-1*H*-benzimidazole (3)

A mixture of *o*-phenylenediamine OPDA (**1**) (5.40g, 50 mmole), 4-bromobenzoic acid (**2**) (12.06g, 60 mmole) and polyphosphoric acid (50 ml) was heated slowly to 180 ^{o}C for 4h. The reaction mixture was then cooled and neutralized with ice-cold concentrated potassium hydroxide solution (200 ml). The solid separated out was filtered, washed with water (3 x 100 ml) and dried under vacuum to afford an off-white solid (2.45g, 90 %). The crude product was recrystallized from hot aq. ethanol to obtain the pure compound **3**. m. p. 295-296°C (Lit.[10] 296 – 298°C). (See Table 4).

Synthesis of compound 3 *via* Microwave Irradiation

A mixture of *o*-phenylenediamine OPDA **(1)** (1.08g, 10 mmole), 4-bromobenzoic acid (**2**) (2.01g, 10 mmole) and polyphosphoric acid (10 ml) were irradiated in a microwave oven at 100W for 3 min at 170 ^{o}C. The reaction mixture was then cooled to room temperature and neutralized with ice-cold concentrated potassium hydroxide solution (50 ml). The solid separated out was filtered, washed with water (3 x 50 ml) and dried under vacuum to afford an off-white solid (2.48g, 91%). The crude product was recrystallized from hot aq. ethanol to obtain the pure **3**. m. p. 294-296°C (Lit.[10] 296 – 298 °C). (See Table 4).

General procedure for the synthesis of compounds 4a-4d

To a solution of 2-(4-bromo-phenyl)-1*H*-benzimidazole (**3,** 2 mmole) in dimethyl formamide (10 ml) was added sodium hydride (60 %, 2.4 mmole) lot wise at 0 ^{o}C. After completion of addition the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 1 h. The reaction mixture was again cooled to 0 ^{o}C and the respective alkyl halide (2.4 mmole) was added at 0 ^{o}C. The temperature of the reaction mixture was then allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, water (50 ml) was slowly added to reaction mixture and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with water (2 x 25 ml), brine and dried over anhydrous magnesium sulfate and concentrated under vacuum to yield the corresponding N-substituted derivatives **4a-4d.** The crude compounds were recrystallized from hot aq. ethanol to obtain pure products. (See Table 4).

Alternative synthesis of the compound 4a

A mixture of N-methy1-*o*-phenylenediamine dihydrochloride (**1a**) (1.95g, 10 mmole), 4-bromobenzoic acid (**2**) (2.41g, 12 mmole) and polyphosphoric acid (25 ml) were heated slowly to 180 ^{o}C for 4h. The reaction mixture was then cooled to room temperature and neutralized with ice-cold concentrated potassium hydroxide solution (50 ml). The reaction mass was then extracted with ethyl acetate (2 x 50 ml) and washed with water (2 x 10 ml), brine and dried over anhydrous magnesium sulfate. The crude compound was purified by recrystallisation from hot aq. ethanol to obtain pure **4a** (2.70g, 86 %). (See Table 4).

General procedure for the synthesis of compounds 5a-5g under Heck coupling conditions
To a solution of compounds **4a-4d** (2.5 mmole) in DMF (50 ml) was added styrene or *tert*-butyl acrylate (3 mmole), triethylamine (3 mmole), tri-(*o*-tolyl) phosphine (0.125 mmole) and palladium acetate (0.125 mmole). The reaction mixture was then heated to 100-110 ^{o}C for 3 h. The reaction mixture was then allowed to cool to room temperature and filtered through hyflo. Evaporation of the solvent yielded crude products, which were subjected to column chromatography to isolate the pure products. (See Table 4).

2-(4-Bromo-phenyl)-1*H*-benzimidazole(3). IR (KBr): 2970(-NH) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$): δ 7.23-7.28 (m, 2H, Ar- H), 7.63-7.64 (m, 2H, Ar-H), 7.78 (d, *J* = 8.4Hz, 2H, Ar-H), 8.17 (d, *J* = 8.4Hz, 2H, Ar-H), 13.05 (bs, 1H, -NH). ^{13}C-NMR (DMSO-d$_6$) (75 MHz): 121.53, 123.47, 128.56, 129.60, 132.18, 150.44 (aromatic carbons).EI-MS: 274 (M^{+}+1).
1-Methyl-2-(4-bromophenyl)-1*H*-benzimidazole (4a). IR (KBr):1460,1399 cm^{-1}. ^{1}H-NMR: δ 3.87 (s, 3H), 7.30-7.42 (m, 3H), 7.63-7.70 (m, 4H), 7.81-7.84 (m, 1H). ^{13}C-NMR (75 MHz): 31.63, 109.62, 119.79, 122.56, 122.96, 124.23, 129.02, 130.81, 131.87, 136.49, 142.77, 152.48. EI-MS: 288 (M^{+}+1).
1-Ethyl-2-(4-bromophenyl)-1*H*-benzimidazole(4b). IR (KBr):1447,1408 cm^{-1}. ^{1}H-NMR : δ 1.46 (t, *J* = 7.2Hz, 3H), 4.26 (q, *J* = 7.2Hz, 2H), 7.30-7.44 (m, 3H), 7.58-7.68 (m, 4H), 7.81-7.84 (m, 1H). ^{13}C-NMR (75 MHz): 15.21, 39.55, 109.90, 119.94, 122.45, 122.86, 124.18, 129.39, 130.63, 131.90, 135.31, 143.03, 152.14. EI-MS: 301.8 (M^{+}+1).
1-Propyl-2-(4-bromophenyl)-1*H*-benzimidazole(4c). IR (KBr):1611,1446 cm^{-1}. ^{1}H-NMR : δ 0.86 (t, *J*=7.3Hz, 3H), 1.80-1.88 (m, 2H), 4.17 (t, *J* = 7.5Hz, 2H), 7.28-7.34 (m, 2H), 7.40-7.43 (m, 1H), 7.57-7.68 (m, 4H), 7.80-7.83 (m, 1H). ^{13}C-NMR (75 MHz): 11.10, 23.04, 46.21, 110.07, 119.84, 122.37, 122.77, 124.07, 129.51, 130.67, 131.83, 135.52, 142.89, 152.39. EI-MS: 315.8 (M^{+}+1).
1-Butyl-2-(4-bromophenyl)-1*H*-benzimidazole(4d). IR (KBr):1595,1445 cm^{-1}. ^{1}H-NMR : δ 0.87 (t, *J* = 7.2Hz, 3H), 1.24-1.31(m, 2H), 1.74-1.84 (m, 2H), 4.21 (t, *J* = 7.5Hz, 2H), 7.28-7.43 (m, 3H), 7.59 (d, *J* = 8.4Hz, 2H), 7.67 (d, *J* = 8.7Hz, 2H), 7.80-7.83 (m, 1H). ^{13}C-NMR (75 MHz): 13.44, 19.81, 31.72, 44.43, 110.06, 119.88, 122.36, 122.76, 124.07, 129.53, 130.68, 131.84, 135.52, 142.94,152.35. EI-MS: 329.8 (M^{+}+1).
3[4-(1-Methyl-1*H*-benzimidazol-2-yl)phenyl]-acrylic acid *tert*-butyl ester (5a). IR (KBr):1712 (C=O) cm^{-1}. ^{1}H-NMR : δ 1.55 (s, 9H), 3.86 (s, 3H), 6.46 (d, *J* = 16.2Hz, 1H), 7.30-7.40 (m, 3H), 7.61-7.66 (m, 3H), 7.77-7.84 (m, 3H). ^{13}C-NMR (75 MHz): 28.10, 31.73, 80.69, 109.61, 119.83, 121.49, 122.53, 122.96, 128.06, 129.71, 131.37, 135.80, 136.59, 142.32, 142.87, 152.80, 165.94. EI-MS: 335.1 (M^{+}+1).
3[4-(1-Ethyl-1*H*-benzimidazol-2-yl)phenyl]-acrylic acid *tert*-butylester (5b). IR (KBr):1706 (C=O), 1639 cm^{-1}. ^{1}H-NMR : 1.48 (t, *J* = 7.2Hz, 3H), 1.55 (s, 9H), 4.29 (q, *J* = 7.2Hz, 2H), 6.46 (d, *J* = 16.2Hz, 1H), 7.30-7.35 (m, 2H), 7.41-7.44 (m, 1H), 7.61-7.67 (m, 3H), 7.75 (d, *J* = 8.4Hz, 2H), 7.82-7.85 (m, 1H). ^{13}C-NMR (75 MHz): 15.23, 28.10, 39.63, 80.69, 109.90, 119.97,

121.47, 122.44, 122.86, 128.11, 129.54, 131.73, 135.41, 135.82, 142.33, 143.13, 152.47, 165.95. EI-MS: 349.4 (M^++1).

3[4-(1-Propyl-1*H*-benzimidazol-2-yl)-phenyl]-acrylic acid *tert*-butyl ester (5c). IR (KBr):1704(C=O) cm^{-1}. ^{1}H-NMR : 0.87 (t, *J* = 7.2Hz, 3H), 1.55 (s, 9H), 1.81-1.89 (m, 2H), 4.20 (t, *J* = 7.8Hz, 2H), 6.47 (d, *J* = 16.2Hz, 1H), 7.27-7.33 (m, 2H), 7.40-7.43 (m, 1H), 7.61-7.66 (m, 3H), 7.74 (d, *J* = 7.8Hz, 2H), 7.81-7.84 (m, 1H). ^{13}C-NMR (75 MHz): 11.17, 23.13, 28.10, 46.35, 80.67, 110.10, 119.94, 121.46, 122.40, 122.81, 128.10, 129.62, 131.93, 135.68, 135.75, 142.34, 143.05, 152.78, 165.94. EI-MS: 363.3 (M^++1).

3[4-(1-Butyl-1*H*-benzimidazol-2-yl)-phenyl]-acrylic acid *tert*-butyl ester (5d). IR (KBr):1703(C=O) cm^{-1}. ^{1}H-NMR : δ 0.86 (t, *J* = 7.2Hz, 3H), 1.21-134 (m, 2H), 1.55 (s, 9H), 1.75-1.85 (m, 2H), 4.23 (t, *J* = 7.8Hz, 2H), 6.47 (d, *J* = 15.9Hz, 1H), 7.27-7.32 (m, 2H), 7.40-7.43 (m, 1H), 7.62-7.66 (m, 3H), 7.74 (d, *J* = 8.1Hz, 2H), 7.80-7.84 (m, 1H). ^{13}C-NMR (75 MHz): δ 13.46, 19.85, 28.10, 31.77, 44.52, 80.65, 110.09, 119.95, 121.46, 122.38, 122.79, 128.09, 129.62, 131.92, 135.65, 135.75, 142.34, 143.08, 152.74, 165.93. EI-MS: 377.2 (M^++1).

1-Methyl-2-(4-styryl-phenyl)1*H*-benzimidazole(5e). IR (KBr):1611,1463 cm^{-1}. ^{1}H-NMR : δ 3.85 (s, 3H), 7.17 (d, *J* = 6.3Hz, 2H), 7.24-7.39 (m, 6H), 7.53 (d, *J* = 7.8Hz, 2H), 7.64 (d, *J* = 8.4Hz, 2H), 7.76 (d, *J* = 8.4Hz, 2H), 7.82-7.85 (m, 1H). ^{13}C-NMR (75 MHz): δ 31.73, 109.55, 119.72, 122.41, 122.72, 126.61, 127.63, 127.96, 128.70, 129.01, 129.65, 130.10, 136.61, 136.85, 138.60, 142.93, 153.38. EI-MS: 311.5 (M^++1).

1-Ethyl-2-(4-styryl-phenyl)1*H*-benzimidazole(5f). IR (KBr):1610,1467 cm^{-1}. ^{1}H-NMR : δ 1.49 (t, *J* = 7.2Hz, 3H), 4.31 (q, *J* = 7.2Hz, 2H), 7.19 (d, *J* = 6Hz, 2H), 7.25-7.40 (m, 6H), 7.55 (d, *J* = 8.4Hz, 2H), 7.66 (d, *J* = 8.4Hz, 2H), 7.74 (d, *J* = 8.4Hz, 2H), 7.81-7.85 (m, 1H). ^{13}C-NMR (75 MHz): δ 15.29, 39.65, 109.87, 119.92, 122.36, 122.68, 126.65, 126.70, 127.68, 127.99, 128.73, 129.40, 129.51, 130.12, 135.47, 136.90, 138.66, 143.21, 153.12. EI-MS: 325.6 (M^++1).

1-Propyl-2-(4-styryl-phenyl)1*H*-benzimidazole(5g). IR (KBr):1611,1481 cm^{-1}. ^{1}H-NMR : δ 0.87 (t, *J* = 7.2Hz, 3H), 1.81-189 (m, 2H), 4.19 (t, *J* = 7.5Hz, 2H), 7.18 (d, *J* = 6.6Hz, 2H), 7.24-7.41 (m, 6H), 7.53 (d, *J* = 7.5Hz, 2H), 7.64 (d, *J* = 7.8Hz, 2H), 7.71 (d, *J* = 6.9Hz, 2H), 7.82-7.85 (m, 1H). ^{13}C-NMR (75 MHz): δ 11.19, 23.12, 46.33, 110.03, 119.83, 122.26, 122.57, 126.59, 126.63, 127.64, 127.93, 128.68, 129.52, 130.03, 135.70, 136.86, 138.51, 143.10, 153.36. EI-MS: 339.5 (M^++1).

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