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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF N-(2-(1-BENZO [*d*] IMIDAZOL-2-YL)PHENYL)-SUBSTITUTED BENZAMINES

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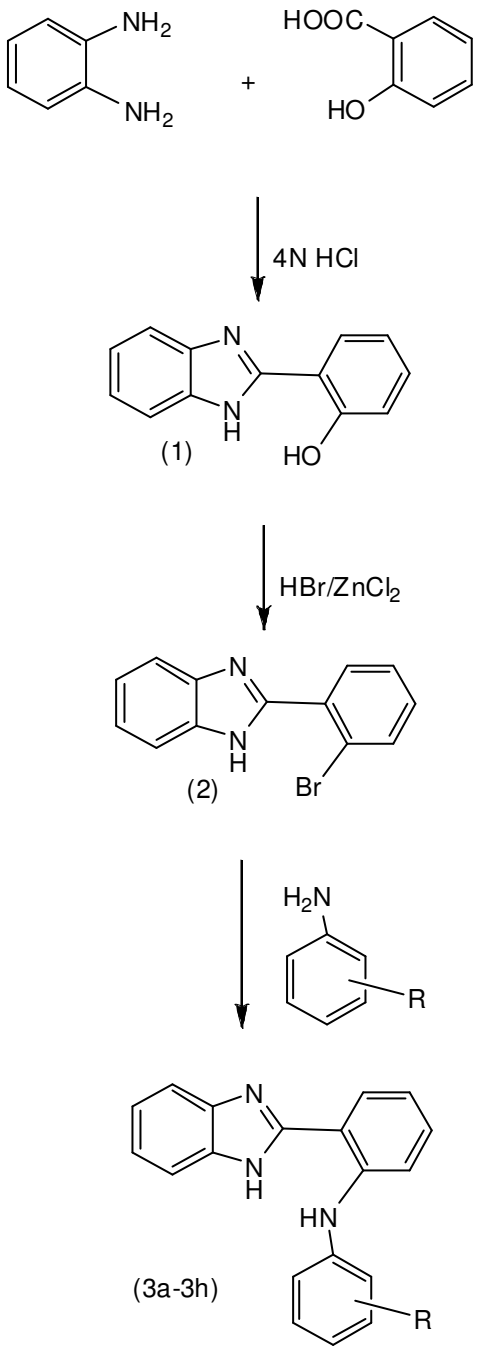
A series of N-(2-(1-benzo [*d*] imidazol-2-yl) phenyl)-substituted benzamines (**3**a-**3**h) was synthesized by using *o*-phenylenediamine and salicylic acid resulting in the formation of 2-(1*H*-benzo [*d*] imidazol-2-yl) phenol (**1**). Compound (**1**) on bromination yielded 2-(2-bromophenyl)-1*H*-benzo [*d*] imidazol-2-yl (**2**) which on further reaction with aniline derivatives gave the final compounds. The structures of the synthesized compounds have been established by FTIR, ^{1}H NMR, Mass spectral and elemental analysis. Each analogue was tested *in vitro* for their antimicrobial and anthelmintic activity. Anthelmintic activity was performed against *Phaeritima posthuma* species of earthworms by the identification of paralyzing and death time by using mebendazole as standard. Antimicrobial activity was performed through disc diffusion method against *Staphylococcus aureus, Bacillus subtilis* (Gram positive) and *Escherichia coli, Pseudomonas aeruginosa* (Gram negative) bacterial strains and *Aspergillus niger* and *Candida albicans* fungal strains by using ciprofloxacin and fluconazole as standard for antibacterial and antifungal activity. Compounds **3**c, **3**d and **3**e were found to be potent for antimicrobial as well as for anthelmintic activity.

Benzimidazole derivatives are an important class of nitrogen containing heterocycles and is the most promising heteroaryl moiety which has yielded many successful drugs[1-2]. Benzimidazole and its derivatives have been found to possess biological activities such as antibacterial[3-9], anticancer[10,11], antidiabetic[12], anthelmintic[13], analgesic[14], antiinflammatory[15] and antioxidant[16] with substitution at various positions. Substituted benzimidazoles have attracted the interest of various research groups. It has been reported that the influence of the substitution at the 1st, 2nd and 5th positions of the benzimidazole ring is very important for possessing pharmacological activities[17-23]. A number of heterocyclic compounds of medicinal interest have already been reported from our research laboratory[24-28]. Moreover benzimidazoles are important intermediates in organic reactions. A number of methods have been reported for the synthesis of benzimidazoles and its derivatives[29,30].

In the same direction a series of benzimidazole derivatives (**3**a-**3**h) was prepared (as shown in Scheme-1) and characterized by physical parameters (as shown in Table-1), chromatographic methods and spectroscopic methods. The resultant products have consistent values of C,H and N contents with predicted structure. The structures of newly synthesized benzimidazole derivatives were accomplished through FTIR, ^{1}H NMR and mass spectral data. In FTIR spectra significant bands appeared at 1192 (aromatic C-C), 1329 (aromatic C-N), 1668 (aromatic C=N), 3312 (aromatic N-H), 3080 (aromatic C-H) and 3485 cm^{-1} (phenolic O-H). In ^{1}H NMR spectra of these compounds a broad multiplet of aromatic proton appeared between δ 6.30-8.50 ppm and a characteristic peak was appeared at 4.53 ppm for N-H. All derivatives showed M+1 peak in their mass spectra. All the synthesized derivatives were evaluated for antibacterial activity against *Staphylococcus*


NH2
NH2
+
HOOC
HO
4N HCl
N
N
H
HO
(1)
HBr/ZnCl2
N
N
H
Br
(2)
H2N
R
N
N
H
HN
R
(3a-3h)

SCHEME-1

Table-1
Physical data of the synthesized compounds (**3**a-**3**h)

Compd	R	M.P. (^{0}C)	*R_f value	Yield (%)
3a	3-fluoro	184-185	0.64	88
3b	3-nitro	204-205	0.68	72
3c	4-methoxy	129-130	0.71	85
3d	4-chloro	127-128	0.61	79
3e	2-nitro	164-165	0.70	75
3f	2-fluoro	187-188	0.65	68
3g	3-methoy	131-132	0.76	65
3h	2-chloro	125-126	0.65	72

*Solvent system : Diethyl ether : n-Hexane : Acetic acid (7:2.6:0.4)

aureus, Bacillus subtilis (Gram positive) and *Escherichia coli, Pseudomonas aeruginosa* (Gram negative) strains, for antifungal activity *Aspergillus niger* and *Candida albicans* fungal strains were used. Compounds were also evaluated for anthelmintic activity against *Phaeritima posthuma* species of earthworms. The results revealed that the compounds **3**c, **3**d and **3**e were found to be most active against Gram +ve, Gram-ve bacteria, fungal strains and also show vermifuge and vermicidal effect for anthelmintic activity.

Pharmacology

Antibacterial activity

In vitro antimicrobial study was carried on Muller Hinton agar (Hi-media) plates (37^0 24 hr) by agar diffusion cup plate method. All the benzimidazole derivatives synthesized were screened for their latent biological activities, for instance, antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* (Gram positive) and *Escherichia coli, Pseudomonas aeruginosa* (Gram negative) bacterial strains by disc diffusion method. Ciprofloxacin was used as standard drug. Prelude screening for all the synthesized derivatives was performed at conc of 50 μg/ml. DMSO was used as a solvent control for antibacterial activity. The antibacterial screening exposed that all the tested compounds possess moderate to good inhibition towards all the bacterial strains (both Gram positive and Gram-negative). Beyond them the significant antibacterial activity was found in derivatives with *p*-chloro, *o*-nitro and *p*-methoxy substituent. Results are given in Table-2.

Antifungal activity

All the derivatives were also evaluated for antifungal activity against *Aspergillus niger* and *Candida albicans* fungal strains. Fluconazole was used as standard drug for comparative study. The fungal strains were grown on agar medium. Prologue screening for all the synthesized derivatives was performed at conc of 50 μg/ml. The Petri plates were incubated at 26^0 for 72 hr and zones of inhibition formed were measured. The antifungal screening exposed that all the tested compounds possess moderate to good inhibition

Table-2
Antimicrobial activity shown by the compounds (Zone of inhibition)

Compd	Zone of inhibition (mm)					
	Gram + ve bacteria		Gram-ve bacteria		Fungal strains	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
3a	12.2 ± 0.57	13.2 ± 0.45	11.5 ± 0.65	13.8 ± 0.36	13.6 ± 0.56	14.5 ± 0.56
3b	12.6 ± 0.63	11.9 ± 0.65	14.5 ± 0.98	13.2 ± 0.12	11.5 ± 0.12	13.6 ± 0.23
3c	18.2 ± 0.36	17.2 ± 0.65	16.2 ± 0.12	16.2 ± 0.45	15.2 ± 0.45	16.3 ± 0.12
3d	17.5 ± 0.36	15.2 ± 0.32	15.6 ± 0.36	16.8 ± 0.36	17.2 ± 0.69	16.5 ± 0.45
3e	18.8 ± 0.56	18.6 ± 0.65	17.5 ± 0.45	17.2 ± 0.89	18.3 ± 0.56	18.2 ± 0.78
3f	15.2 ± 0.58	11.5 ± 0.65	10.6 ± 0.65	14.6 ± 0.45	18.5 ± 0.25	16.5 ± 0.79
3g	13.6 ± 0.25	13.8 ± 0.69	14.5 ± 0.25	12.5 ± 0.36	12.3 ± 0.36	11.6 ± 0.96
3h	13.6 ± 0.36	10.5 ± 0.56	11.5 ± 0.23	13.4 ± 0.12	11.4 ± 0.12	13.5 ± 0.36
Standard	20.5 ± 0.12	21.6 ± 0.65	21.3 ± 0.45	25.6 ± 0.13	23.5 ± 0.89	24.3 ± 0.34

Standard : Ciprofloxacin for antibacterial; Fluconazole for antifungal activity

The results of antimicrobial activity are reported as zone of inhibition in mm.

Data are given as mean ± S.D. (*n*=3), S.D. = Standard deviation

towards the fungal strains. Away from all the derivatives the compounds with *p*-methoxy, *o*-nitro, *p*-chloro and *p*-bromo show potent antifungal activity as shown in Table-2.

Anthelmintic activity

The synthesized derivatives were tested *in vitro* for anthelmintic activity against *Phaeritima posthuma* species of earthworms due their anatomical and physiological resemblance with the intestinal round worm parasites of human beings. The anthelmintic activity of the compounds was carried out by Garg and Atal method at 2mg/ml concentration and compared with standard drug Mebendazole (2mg/ml). Tween 80 was used as solvent control. Among all the newer benzimidazole derivatives the compounds with *o*-chloro, *o*-nitro and 2,4-dichloro groups were found to be most active. Data for anthelmintic activity are shown in Table-3.

Experimental

The purity of all the newly synthesized compounds was monitored by TLC on silica gel G plates. Melting points were taken in open capillary tube and are uncorrected. The UV spectra were recorded on a SHIMADZU spec-1700 spectrophotometer, IR spectra on a SHIMADZU 8400S spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DRX 300 MHz spectrometer in DMSO using TMS (tetramethylsilane) as an internal standard and Mass spectra on a MS-ESI (SHIMADZU-2010 AT, software class VP), Elemental analysis was carried out on Elemental Vario EL III Carlo Erba 1108.

Table-3
Anthelmintic activity data for compounds (**3**a-**3**h)

Compd	Time (in minutes) Mean paralyzing time ± S.D. 2 mg/ml	Mean Death time time ± S.D. 2 mg/ ml
3a	34.16 ± 0.57	39.16 ± 0.87
3b	28.39 ± 0.52	37.08 ± 0.07
3c	25.00 ± 0.70	39.75 ± 0.66
3d	26.75 ± 0.35	34.66 ± 0.43
3e	18.78 ± 0.35	22.41 ± 0.51
3f	28.29 ± 1.70	37.87 ± 0.53
3g	32.04 ± 0.50	38.41 ± 0.52
3h	33.91 ± 0.38	38.30 ± 0.50
Mebendazole	22.44 ± 0.62	26.75 ± 0.66

Data are given as means ± S.D. (n=3), S.D. = Standard Deviation

Synthesis of 2-(1*H*-benzo [*d*] imidazole-2-yl) phenol (1)

Equimolar quantity of *o*-phenylenediamine (0.04 mol) and salicylic acid (0.04 mol) was refluxed for 20 hr in 90 ml of 4N hydrochloric acid. On cooling, needle shaped crystals were obtained, washed with ice-cold water, recrystallized from hot water to get pure white crystalline compound (**1**) (m.p. 148-149^0, Yield : 74%).

Synthesis of 2-(2-bromophenyl)-1*H*-benzo [*d*] imidazole (2)

A mixture of zinc chloride (0.02 mol) and 2-(1*H*-benzo [*d*] imidazole-2-yl) phenol (**1**) (0.02 mol) and 30 ml of hydrobromic acid was refluxed for 15 hr. The completion of reaction was monitored by TLC. Then reaction mixture was kept overnight in refrigerator, crude product thus obtained was filtered, recrystallized from water to obtain the pale brown coloured compound (**2**) (m.p. 167-168^0, Yield : 68%).

N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-substituted benzimidazoles (3a-3h) : General procedure

Equimolar quantity of 2-(2-bromophenyl)-1*H*-benzo [*d*] imidazole (**2**) and aniline derivatives in 45 ml of 1,4-dioxan was refluxed for 14 hr with continuous stirring at 80^0. The completion of reaction was checked by TLC. The reaction mixture was kept overnight in a refrigerator. The solvent was evaporated and a gummy solid mass was obtained. The gummy solid was then washed with cold water and recrystallized from ethanol and water (4:6) to obtain the compounds (**3**a-**3**h).

Spectral analysis

3a : N-2-(1-benzo [*d*] imidazole-2-yl) phenyl-4-fluoro benzimidazole

FTIR (KBr) υ(cm^{-1}): 3227 (aromatic N-H str. (2^0 amine)), 3089 (aromatic C-H str), 1664 (aromatic C=N str), 1608 (aromatic C-C str.), 1345 (aromatic C-N str , 1039 (C-F str), 837 (C-H *p*-disubstituted benzene (def.); ^{1}H NMR (300 MHz, DMSO, δ ppm): 4.36 (s, 1H, Ar N-H, D_2O exchangeable), 5.19 (s, 1H, Ar N-H), 6.42-6.44 (d, 1H, ArH), 6.44-6.49 (d, 1H, ArH), 6.52-6.54 (d, 1H, ArH), 6.67-6.68 (t, 1H, ArH), 6.721-6.729 (d, 1H, ArH), 6.97-6.98 (d, 1H, ArH), 7.26-7.27 (t, 1H, ArH), 7.283-7.288 (d, 1H, ArH), 7.35-7.36 (t, 1H, ArH), 7.54-7.56 (t, 1H, ArH), 7.77-7.78 (d, 1H, ArH), 7.861-7.869 (d, 1H, ArH). MS (ESI) m/z [% rel. abundance]: 303 (100) $[M]^+$, 304 (26) $[M+1]^+$, Fragments : 284 (53), 193 (78), 117 (61), 91 (45). [Found : C, 75.21, H, 4.63, N, 13.83 $C_{19}H_{14}FN_3$ requires C, 75.23, H, 4.65, N, 13.85%].

3b: N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-3-nitro benzimidazole

FTIR (KBr): 3304 (aromatic N-H str. (2^0 amine), 3059 (aromatic C-H str.), 1675 (aromatic C=N str.), 1605 (aromatic C-C str.), 1475 (asymmetric N=O str.), 1361 (symmetric N=O str.), 1445 (aromatic C-N str.),

695 (C-H m-disubstituted benzene (def.)); ^{1}H NMR (300 MHz, DMSO): 4.26 (s, 1H, Ar, N-H, D_2O exchangeable), 5.19 (s, 1H, Ar, N-H, D_2O exchangeable), 6.52-6.54 (d, 1H, ArH), 6.66-6.69 (t, 1H, ArH), 6.73-6.74 (d, 1H, ArH), 6.85-6.93 (t, 1H, ArH), 6.97-7.12 (d, 1H, ArH), 7.22-7.23 (t, 1H, ArH), 7.26-7.27 (t, 1H, ArH), 7.37-7.38 (t, 1H, ArH), 7.39-7.41 (s, 1H, ArH), 7.54-7.55 (d, 1H, ArH), 7.70-7.71 (d, 1H, ArH), 7.88-7.89 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 330 (100) $[M]^+$, 331 (25) $[M + 1]^+$, Fragments : 284 (44), 208 (88), 117 (71), 91 (46). [Found : C, 60.05, H, 4.24, N, 16.93 $C_{19}H_{14}N_4O_2$ requires C, 60.8, H, 4.27, N, 16.96%].

3c: N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-4-methoxy benzimidazole

FTIR (KBr): 3327 (aromatic N-H str (2^0 amine)), 3079 (aromatic C-H str.), 1606 (aromatic C=N str.), 1621 (aromatic C-C str.), 1341 (aromatic C-N str.), 1079 (aliphatic C-O-C str.), 817 (C-H *p*-disubstituted benzene (def.); ^{1}H NMR (300 MHz, DMSO)), 3.34 (s, 3H, OCH_3), 4.53 (s, 1H, Ar, N-H, D_2O exchangeable), 5.23 (s, 1H, Ar, N-H, D_2O exchangeable), 6.41-6.42 (d, 1H, ArH), 6.551-6.551 (d, 1H, ArH), 6.562-6.566 (d, 1H, ArH), 6.65-6.67 (t, 1H, ArH), 6.711-6.719 (d, 1H, ArH), 7.12-7.13 (d, 1H, ArH), 7.27-7.28 (t, 1H, ArH), 7.31-7.32 (d, 1H, ArH), 7.441-7.446 (t, 1H, ArH), 7.44-7.52 (t, 1H, ArH), 7.54-7.60 (d, 1H, ArH), 7.77-7.78 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 315 (100) $[M]^+$, 316 (30) $[M+1]^+$, Fragments: 284 (43), 193 (58), 117 (69), 91 (48). [Found : C, 76.15, H, 5.41, N, 13.30 $C_{20}H_{17}N_3O$ requires C, 76.17, H, 5.43, N, 13.32%].

3d: N-2-(1-Benzo [*d*] imidazole-2-yl)-phenyl-4-chloro benzimidazole

FTIR (KBr): 3217 (aromatic C-H str. (2^0 amine)), 3088 (aromatic C-H str.), 1571 (aromatic C=N str.), 1610 (aromatic C-C str.), 1375 (aromatic C-N str.), 1048 (C-Cl str.), 814 (C-H (*p*-disubstituted benzene) (def.)); ^{1}H NMR (300 MHz, DMSO): 4.18 (s, 1H, Ar, N-H, D_2O exchangeable), 5.25 (s, 1H, Ar, N-H, D_2O exchangeable), 6.40-6.44 (d, 1H, Ar-H), 6.45-6.47 (d, 1H, ArH), 6.52-6.54 (d, 1H, ArH), 6.68-6.79 (t, 1H, ArH), 6.973-6.979 (d, 1H, ArH), 7.02-7.03 (d, 1H, ArH), 7.06-7.08 (t, 1H, ArH), 7.23-7.24 (d, 1H, ArH), 7.28-7.29 (t, 1H, ArH), 7.48-7.56 (t, 1H, ArH), 7.70-7.71 (d, 1H, ArH), 7.74-7.81 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 319 (100) $[M]^+$, 320 (23) $[M+1]^+$, 321 (53) $[M+2]^+$, Fragments : 284 (64), 193 (82), 117 (31), 91 (26). [Found : C, 71.34, H, 4.38, N, 13.12 $C_{19}H_{14}N_4O_2$ requires C, 71.36, H, 4.41, N, 13.14%].

3e : N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-2-nitro benzimidazole

FTIR (KBr): 3247 (aromatic C-H stretching (2^0 amine)), 3083 (aromatic C-H stretching), 1651 (aromatic C=N stretching), 1577 (aromatic C-C stretching), 1464 (asymmetric N=O stretching), 1340 (symmetric N=O stretching), 1425 (aromatic C-N stretching), 749 (C-H (*o*-disubstituted benzene) (def.)); ^{1}H NMR (300 MHz, DMSO): 4.24 (s, 1H, Ar, N-H, D_2O exchangeable), 5.39 (s, 1H, Ar, N-H, D_2O exchangeable), 6.52-6.53 (d, 1H, ArH), 6.681-6.687 (d, 1H, ArH), 6.85-6.86 (d, 1H, ArH), 6.981-6.997 (t, 1H, ArH), 7.22-7.23 (d, 1H, ArH), 7.35-7.36 (d, 1H, ArH), 7.39-7.42 (t, 1H, ArH), 7.54-7.55 (d, 1H, ArH), 7.70-7.72 (t, 1H, ArH), 7.75-7.76 (t, 1H, ArH), 7.76-7.77 (d, 1H, ArH), 7.84-7.89 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 330 (100) $[M]^+$, 331 (25) $[M+1]^+$, Fragments : 284 (24), 193 (34), 117 (21), 91 (86). [Found : C, 69.06, H, 4.25, N, 16.67 $C_{19}H_{14}N_4O_2$ requires C, 69.08, H, 4.27, N, 16.69%].

3f: N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-2-fluoro benzimidazole

FTIR (KBr) : 3189 (aromatic N-H str. (2^0 amine)), 3018 (aromatic C-H str.), 1663 (aromatic C=N str.), 1610 (aromatic C-C str.), 1340 (aromatic C-N str), 1039 (C-F str.), 835 (C-H *p*-disubstituted benzene (def)); ^{1}H NMR (300 MHz, DMSO): 4.22 (s, 1H, Ar, N-H, D_2O exchangeable), 5.12 (s, 1H, Ar, N-H), 6.42-4.44 (d, 1H, ArH), 6.44-6.48 (d, 1H, ArH), 6.32-6.44 (d, 1H, ArH), 6.67-6.68 (t, 1H, ArH), 6.721-6.729 (d, 1H, ArH),

6.97-6.98 (d, 1H, ArH), 7.26-7.27 (t, 1H, ArH), 7.283-7.288 (d, 1H, ArH) 7.35-7.36 (t, 1H, ArH), 7.54-7.56 (t, 1H, ArH), 7.88-7.92 (d, 1H, ArH), 7.861-7.869 (d, 1H, ArH). MS (ESI): m/z [% rel. abundance]: 303 (100) $[M^+]$, 304 (25) $[M+1]^+$, Fragments: 284 (45), 193(78), 117 (61), 91 (45). [Found : C, 75.21, H, 4.63, N, 13.83 $C_{19}H_{14}FN_3$ requires C, 75.23, H, 4.65, N, 13.85%].

3g: N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-3-methoxy benzimidazole

Greenish-Black colored crystal, FTIR (KBr): 3325 (aromatic N-H str. (2^0 amine)); 3110 (aromatic C-H str.), 1589 (aromatic C=N str.), 1616 (aromatic C-C str.), 1341 (aromatic C-N str.), 1079 (aliphatic C-O-C str.), 817 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR (300 MHz, DMSO): 3.22 (s, 3H, OCH_3), 4.54 (s, 1H, Ar N-H, D_2O exchangeable), 5.32 (s, 1H, Ar N-H, D_2O exchangeable), 6.44-6.56 (d, 1H, ArH), 6.552-6.559 (d, 1H, ArH), 6.562-6.566 (d, 1H, ArH), 6.65-6.67 (t, 1H, ArH), 6.711-6.719 (d, 1H, ArH), 7.12-7.13 (d, 1H, ArH), 7.27-7.28 (t, 1H, ArH), 7.31-7.32 (d, 1H, ArH), 7.441-7.446 (t, 1H, ArH), 7.44-7.52 (t, 1H, ArH), 7.54-7.60 (d, 1H, ArH), 7.77-7.78 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 315 (100) [M+1], 316 (21) $[M+1]^+$, Fragments : 284 (43), 193 (58), 117 (69), 91 (48). [Found : C, 76.15, H, 5.41, N, 13.30 $C_{20}H_{17}N_3O$ requires C, 76.17, H, 5.43, N, 13.32%].

3h : N-2-(1-Benzo [*d*] imidazole-2-yl) phenyl-2-chloro benzimidazole

FTIR (KBr): 3210 (aromatic N-H str. (2^0 amine)); 3080 (aromatic C-H str.), 1585 (aromatic C=N str.), 1609 (aromatic C-C str.), 1311 (aromatic C-N str.), 1005 (C-Cl str.), 814 (C-H (*p*-disubstituted benzene) (def.)); ^{1}H NMR (300 MHz, DMSO): 4.25 (s, 1H, N-H, D_2O exchangeable), 5.29 (s, Ar, N-H, D_2O exchangeable), 6.40-6.44 (d, 1H, ArH), 6.45-6.47 (d, 1H, ArH), 6.52-6.54 (d, 1H, ArH), 6.68-6.79 (t, 1H, ArH), 6.973-6.979 (d, 1H, ArH), 7.02-7.03 (d, 1H, ArH), 7.06-7.08 (t, 1H, ArH), 7.23-7.24 (d, 1H, ArH), 7.28-7.29 (t, 1H, ArH), 7.48-7.56 (t, 1H, ArH), 7.70-7.71 (d, 1H, ArH), 7.74-7.81 (d, 1H, ArH); MS (ESI) m/z [% rel. abundance]: 319 (100) $[M]^+$, 320 (23) $[M+1]^+$, 321 (15) $[M+2]^+$, Fragments : 284 (82), 117 (31), 91(26). [Found : C, 71.34, H, 4.38, N, 13.12 $C_{19}H_{14}N_4O_2$ requires C, 71.36, H, 4.41, N, 13.14%].

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