Synthetic Utility of Catalytic Fe(III)/Fe(II) Redox Cycling Towards Fused Heterocycles: A Facile Access to Substituted Benzimidazole, Bis-benzimidazole and Imidazopyridine Derivatives

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Abstract: A catalytic Fe(III)/Fe(II) redox cycling approach has been examined and applied towards synthesis of a wide range of benzimidazole, bis-benzimidazole and imidazopyridine derivatives from oxidative coupling of aromatic ortho-diamines with aromatic as well as heterocyclic aldehydes bearing different types of substituents. This versatile and convenient method has further proven to be particularly useful in expeditiously affording a number of novel bis-benzimidazole class of Hoechst 33258 analogs towards potential development as fluorescent nucleic acid binding probes. Successful preparation and characterization of a diverse set of thirty different compounds is presented here.

Key words: benzimidazoles, bis-benzimidazoles, imidazopyridines, catalytic redox-cycling, fluorescent probes, heterocycles. Schiff bases

Fused heterocycles such as benzimidazoles, benzoxazoles, benzothiazoles, and closely related imidazopyridines, are very useful intermediates for the development of pharmaceutical compounds,[1–3] photochromic dyes,[4] and also as molecular probes,[5] due to their associated fluorescence characteristics. For example, the utility of bis-benzimidazole class of fluorescent dyes, such as Hoechst 33258 (*chemical name*: 2-(4-hydroxyphenyl)-5-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole), is well established in molecular genetics and cytofluorimetry studies,[6] owing to the fact that such compounds bind to selected DNA subsequences with high affinity and an accompanying large enhancement of the observed fluorescence quantum yields.[7,8] Synthetic interest in surrogate Hoechst 33258-like structures has been spurred by their potential gene-targeted biological activity.[2,3] As part of a leading initiative aimed at developing new benzimidazole-derived analogs of Hoechst 33258 and to seek a better understanding of the structure-fluorescence relationships for such compounds, we required a general procedure applicable to various types of substitution patterns in benzimidazole derivatives.[9] In this study we wish to report the use of a catalytic redox cycling approach to the synthesis of various benzimidazole derivatives, based on (Fe(III)/Fe(II))-redox-mediated oxidation of the Schiff's base intermediates derived from differently substituted aromatic ortho-diamines and a variety of aromatic and heterocyclic aldehydes.

From the synthesis standpoint, there are a number of different methods reported for the preparation of 2-arylbenzimidazole derivatives, such as cyclocondensation reactions of aromatic diamines with carboxylic acids,[10] or nitriles and equivalent imidate esters,[11] using strongly acidic conditions, and the applications of oxidative cyclodehydrogenation strategies towards initial condensation products from diamines and aryl aldehydes using either high-boiling oxidant/solvent like nitrobenzene[12] or very strong oxidants.[13] However, we determined during our early attempts that such reported procedures for the preparation of benzimidazole derivatives were not quite versatile nor compatible with differently substituted starting materials, and also posed practical difficulties in the form of laborious reaction workup protocols. For example, the use of very high temperatures appeared mandatory for the PPA-mediated condensation reaction for diamine-carboxylate combinations,[10b,c] and therefore not suitable for the compounds targeted in our program, whereas the nitrobenzene method required extensive removal (vacuum distillation followed by chromatography) of nitrobenzene and aniline (the reaction byproduct).[12] In addition, the targeted nitroaryl benzimidazole derivatives (*vide infra*) did not seem amenable to the use of nitrobenzene under high temperatures, due to anilino/amino byproduct formation. Much to our satisfaction, the presently developed Fe(III)-mediated oxidative cyclization approach, akin to one of our previous mechanistic studies of cyclocondensation reactions of amines with ortho-quinones,[14] has proven to be more versatile and straightforward towards expeditiously affording a variety of substituted benzimidazole and imidazopyridine derivatives with ease.

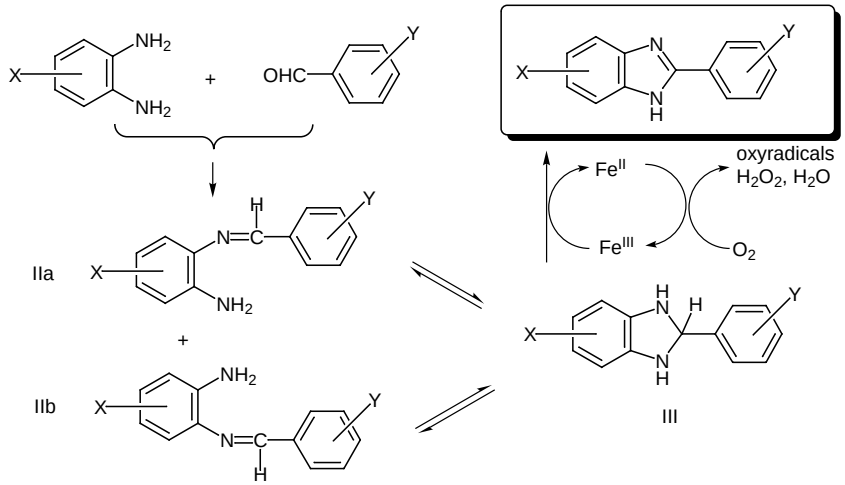
Our development of this method considered the putative mechanistic scheme (Scheme 1)[12,13] for the generation of benzimidazoles from initial Schiff's bases (IIa/b) generated from diamines and aldehydes, that exist in equilibrium with the cyclic reduced dihydrobenzimidazoles (III), and we reasoned that the final aromatization step to benzimidazoles could conceivably be mediated with the use of transition metal ions as the ultimate oxidants that could possibly be regenerated in situ with molecular O_2 or air exposure, thereby potentially capable of providing high catalytic turnover numbers. Judging from the literature survey, we found that the scarcely reported effectiveness of Cu(II),[15] and Fe(III)[16] in mediating oxidative aromatization of Schiff's base intermediates to benzimidazoles had not been fully capitalized upon for synthetic purposes, presumably due to the potential for loss in yields of the benzimidazole products through their strong coordination

with the transitional metal ions.[17] The conceptual aspects of the synthetic plan, as applied to the preparation of benzimidazole derivatives, are outlined in Scheme 1. Shown therein are the initial condensation products, the mono Schiff's bases present in equilibrium with the cyclic reduced form that is apparently readily aromatized to the benzimidazole product via two one-electron oxidation steps. These last steps are catalyzed by Fe(III) and the reduced Fe(II) form is then regenerated as part of the redox cycling schematic with O_2 that can be bubbled constantly through the reaction periods.

Our initial set of experiments with 4-(4-methylpiperazinyl)-1,2-phenylenediamine[12b–e] and either 2-imidazolecarboxaldehyde[18] or 2-pyridinecarboxaldehyde using less than stoichiometric amounts of Fe(III) (0.25 equiv ferric chloride hydrate), and the success in obtaining the corresponding benzimidazole derivatives (compounds **6a**/**7b** described further in Table 2) in >70% yields, free of iron contamination after silica gel flash chromatography, provided us with the impetus for developing this method further as a versatile and convenient one-pot procedure for the preparation of a variety of benzimidazole derivatives. That the actual oxidant is Fe(III) and not O_2 was confirmed in control experiments where mere bubbling of O_2 through the reaction mixture did not accelerate the reaction and was determined to be insufficient for complete product formation, until as long as >5 days, as monitored by TLC and NMR analysis of the reaction aliquots. In contrast, the addition of a catalytic amount of $FeCl_3$ typically resulted in completion of reactions in less than 6 h, rendering the procedure valuable for synthetic purposes. The optimum amounts of $FeCl_3$ required for the reactions were determined from several trial runs and applied towards developing a general protocol for reactions on a preparative scale. Briefly, this one-pot procedure entails initial mixing of the ortho-diamines with the aromatic aldehydes in stoichiometric amounts, followed by heating for a period of 1 hour, and treatment with a catalytic amount of $FeCl_3$ (0.01 molar equivalent dissolved in MeCN) under constant O_2 bubbling conditions. The benzimidazole products usually precipitate out of solution as they are formed, when the reactions are carried out in MeCN, and the reactions are typically complete within 5–8 h.

In order to test this procedure for preparative scale applications, a variety of benzaldehydes bearing electron-donating (Table 1, Entries 1–6) and electron-withdrawing substituents (Entries 7–12) were successfully employed to prepare the benzimidazole derivatives **4a**–**f** and **5a**–**f** in high yields. Dimethylformamide proved to be better than other polar solvents for the reactions with electron-deficient aldehydes. Note that the benzimidazole derivatives of type **5a**–**f** from such electron-deficient substrates are generally considered to be more difficult to obtain than those from electron-rich aldehydes,[12e] presumably due to the destabilization of the one-electron oxidized intermediates in the aromatization steps (Scheme 1).

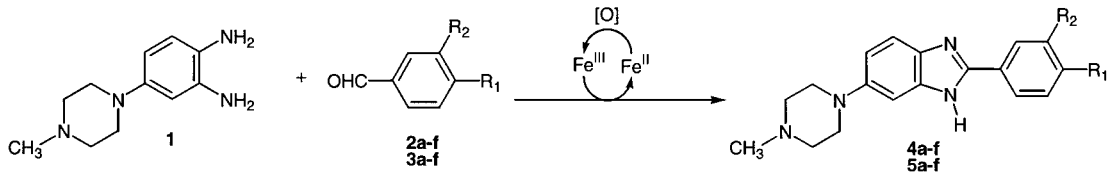
In the next steps towards examining the general scope and versatility of this method, differently substituted diamines were also successfully coupled with *N*-methyl-2-imidazolecarboxaldehyde to afford compounds **6a**–**e** (Table 2, Entries 13–17), with 0.03 equivalent $FeCl_3$ and DMF as the solvent (Method B), and eventually four additional hydroxymethylbenzimidazole derivatives **7a**–**d** were also obtained starting from 3,4-diaminobenzyl alcohol[19] and heterocyclic aldehydes as shown in Table 2 (Entries 18–21). The high yields of the benzimidazole products obtained in all the above cases clearly attest to the synthetic utility of this mild approach based upon redox cycling of the Fe(III)/Fe(II) couple and high catalytic turnover for benzimidazole formation.



Mechanistic scheme showing intermediate steps involved in the formation of Schiff's bases from aromatic diamines and aldehydes, and the role of Fe(III)/Fe(II) redox cycling in mediating oxidative cyclization to benzimidazole derivatives

Scheme 1

Table 1 Preparation of benzimidazole analogs **4a–f** (series I) and **5a–f** (series II)



Series I: from electron-rich aldehydes

entry	R_1	R_2	*Method*[a]	Product	Yields[b]
1	-OH	-H	*A*	**4a**	92
2	$-OCH_3$	-H	*A*	**4b**	94
3	$-OCH_3$	$-OCH_3$	*A*	**4c**	86
4	$-CH_3$	-H	*A*	**4d**	90
5	$-N(CH_3)_2$	-H	*A*	**4e**	94
6	$-NHCOCH_3$	-H	*A*	**4f**	92

Series II: from electron-deficient aldehydes

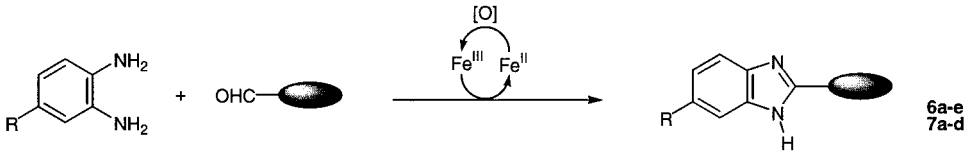
entry	R_1	R_2	*Method*[a]	Product	Yields[b]
7	$-NO_2$	-H	*B*	**5a**	82
8	-H	$-NO_2$	*B*	**5b**	84
9	-CN	-H	*B*	**5c**	85
10	-H	-CN	*B*	**5d**	82
11	-COOH	-H	*B*	**5e**	78
12	$-NHCOCH_3$	$-NO_2$	*B*	**5f**	84

[a] Method A: using 0.01 equiv $FeCl_3$ in MeCN at 90 °C with continuous O_2 bubbling; Method B: using 0.03 equiv $FeCl_3$ in DMF at 120 °C with continuous O_2 bubbling.

[b] Yields reported for isolated products, purified after silica gel flash chromatography and conversion to the HCl salts.

Towards our targeted objective of preparing Hoechst 33258 analogs, we further applied the $FeCl_3$-method to the preparation of bi-benzimidazole compounds **12**–**15** in high overall yields from the respective hydroxymethyl-benzimidazole derivatives by following a 2-step approach (Scheme 2), comprising of: (a) PCC-mediated preparation of the benzimidazole-5-carboxaldehydes **8**–**11**, and (b) their coupling with 4-(4-methylpiperazinyl)-1,2-phe-

Table 2 Preparation of benzimidazole analogs **6a–e** (series III) and **7a–d** (series IV).

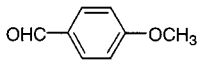
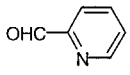
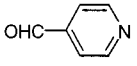
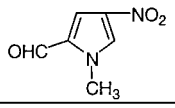


Series III: Benzimidazole products obtained from N-methyl-2-imidazole-carboxaldehyde and various diamines

entry	R	Product	*Method*[a]	Yields[b]
13	4-methylpiperazinyl	**6a**	*B*	86
14	$-CH_3$	**6b**	*A*	96
15	-COOH	**6c**	*B*	75
16	$-COOCH_3$	**6d**	*B*	83
17	$-CH_2OH$	**6e**	*A*	90

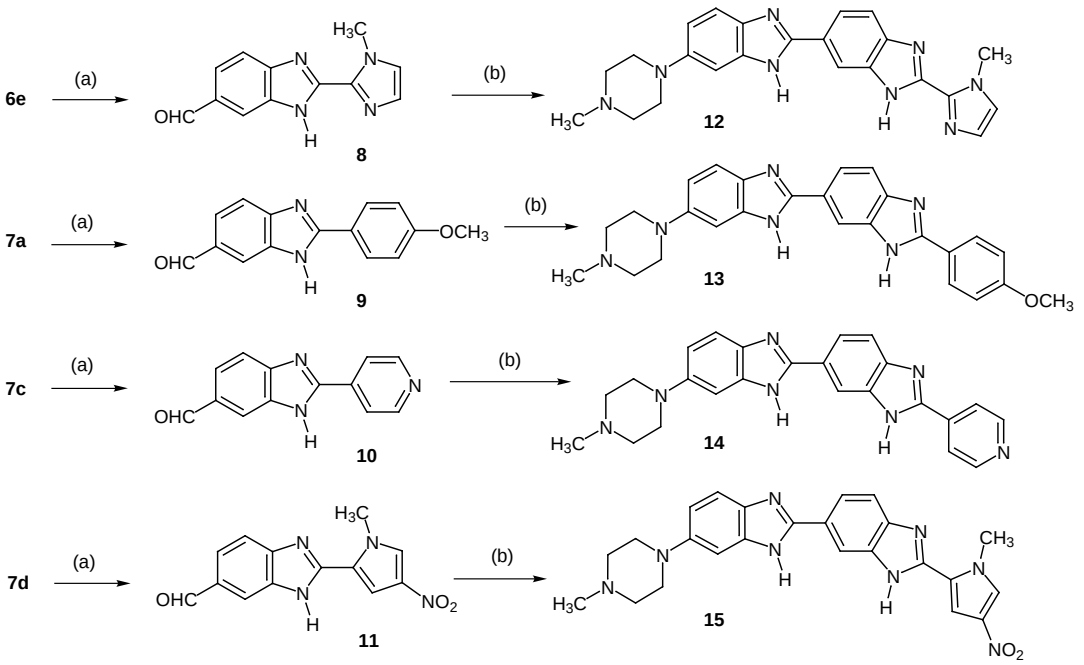
Series IV: Benzimidazoles derived from the same diamine (R = CH_2OH)

OHC— ≡ as shown below

entry		Product	*Method*[a]	Yields[b]
18		**7a**	*A*	91
19		**7b**	*A* *B*	68 82
20		**7c**	*A* *B*	70 92
21		**7d**	*A* *B*	76 94

[a] Method A: using 0.01 equiv $FeCl_3$ in MeCN at 90 °C with continuous O_2 bubbling; Method B: using 0.03 equiv $FeCl_3$ in DMF at 120 °C with continuous O_2 bubbling.

[b] Yields reported for isolated products, purified after silica gel flash chromatography and conversion to the HCl salts.



Reagents: a) PCC/CH_2Cl_2; b) 0.03 equiv. $FeCl_3/O_2$/DMF.
Preparation of 2,5'-bi(benzimidazole) analogs related to Hoechst 33258

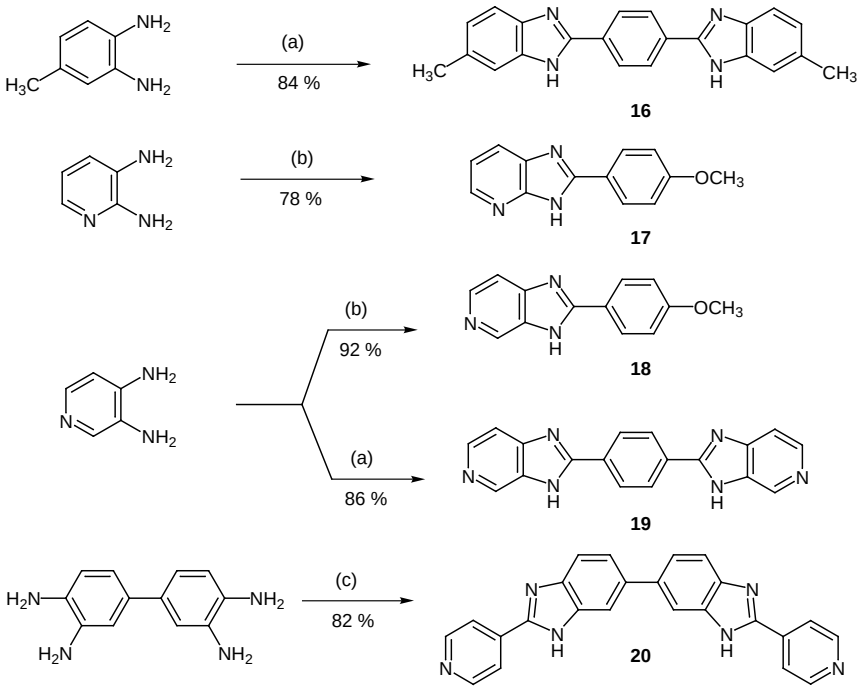
Scheme 2

nylenediamine in DMF, using the Fe(III)/Fe(II) redox cycling with O_2 exposure a second time. The procedure using $FeCl_3$ therefore compares better to the frequently employed PPA-mediated and nitrobenzene methods that often fail,[20] or afford lower yields,[12e] towards the preparation of such 2,5'-bi-benzimidazole assemblies. It is evident that the $FeCl_3$ method, owing to its simplicity and versatility, offers a more expeditious route to the development of Hoechst 33258 analogs derived from differently substituted benzimidazole and imidazopyridine subunits.

Finally, we have extended this synthetic method for the preparation of additional extended bis-benzimidazole and imidazopyridine derivatives **16**–**20**, using commercially available substrates, as depicted in Scheme 3. These compounds are also particularly interesting for the study of their photochemical properties, such as prototropic equilibria in the excited state and fluorescence emissions associated with the benzimidazole and imidazopyridine ring systems,[21] including their potential utility in the development of novel symmetrical Hoechst 33258 analogs as nucleic acid binding probes.[22]

In summary, the catalytic redox cycling approach based on Fe(III)/Fe(II) couple and molecular O_2 as co-oxidant serves well in providing a high-yielding and convenient access to 30 different benzimidazole and imidazopyridine derivatives, **4a**–**f**, **5a**–**f**, **6a**–**e**, **7a**–**d**, **12**–**20**, in a much more straightforward manner than from previously reported methods. Some particularly noteworthy features of the application of this procedure have emerged from the wide range of benzimidazole and imidazopyridine products prepared as part of this work: (1) compatibility of an oxidant with the diamine and aldehyde substrates with redox-sensitive substituents, such as hydroxymethyl, nitropyrrole, and the tertiary amine groups (*N*-methylpiperazine, dimethylanilino); (2) minimal loss in product yields due to metal ion complexation to benzimidazole products, despite the presence of suspected chelating units such as 2'-imidazole and 2'-pyridine (compare **5a**–**e**, **6b**, **12** and **17**); (3) relative ease of isolation of products in purified forms free of contamination due to transition metal ions (column chromatography); and (4) the environmental friendliness due to the use of catalytic amounts of Fe(III) and polar solvents. Considering the mechanistic similarities between the oxidative cyclization of Schiff's base intermediates from diamines and aldehydes to that for *o*-aminophenols,[23] the Fe(III)/Fe(II)-redox cycling method should be equally applicable to the preparation of benzoxazole and related classes of fused heterocycles. It would also be interesting to explore the amenability of this methodology towards solid-phase synthesis of diversified sets of analogous benzimidazole and imidazopyridine derivatives.[28] In terms of specific application of this mild redox cycling approach to benzimidazole derivatives, several analogs of Hoechst 33258 with a varying arrangement of the bis-benzimidazole units have been prepared. Data from our ongoing investigations of their fluorescence properties and DNA binding characteristics will be reported in due course.

Melting points, uncorrected, were recorded on a Electrothermal capillary melting point apparatus. All solvents and reagents were obtained from Aldrich Chemical Co. All the diamines and aldehyde compounds were obtained from Aldrich or Lancaster Inc. Literature



Reagents and conditions: (a) 1,4-Ph(CHO)$_2$/$FeCl_3$/O_2/DMF, 120 °C; (b) 4-MeOPhCHO/ $FeCl_3$/O_2/DMF, 120 °C; (c) 4-Pyridine-CHO/$FeCl_3$/O_2/DMF, 120 °C

Additional bis-benzimidazole and imidazopyridine analogs **16**–**20** prepared using Method B

Scheme 3

methods were followed for the preparation of 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (**1**),[12b–e] 3,4-diaminobenzyl alcohol,[19] 2-imidazolecarboxaldehyde,[18] 1-methyl-4-nitro-2-pyrrolecarboxaldehyde,[24] and 4-acetamido-3-nitrobenzaldehyde.[25] Anhydrous CH_3CN and DMF were distilled from BaO prior to use according to standard practices. The ^{1}H- and ^{13}C NMR spectra were obtained with a Bruker AMX-300 or AVANCE-500 spectrometers. All ^{1}H chemical shifts (in ppm) are reported relative to TMS as internal standard for solutions in DMSO-d_6, $CDCl_3$ and CD_3OD. In cases where D_2O was used, the residual HOD signal was taken as the reference. All ^{13}C chemical shifts are relative to the solvent signals when DMSO-d_6 or CD_3OD were used, and to the signal from trace amounts of MeOH added as a solute when using D_2O solutions. For assignment of the ^{1}H and ^{13}C signals, the use of abbreviations Ar, Bzi, Im, Py, and Pyr is made for relating to the aryl, benzimidazole, imidazole, pyrrole, and pyridine units, respectively. ^{13}C data includes the designations s (singlet), d (doublet), t (triplet), and q (quartet) determined from the standard APT (attached proton test) experiments. High resolution mass spectra (EI and FAB) were recorded using high voltage (70 eV) on a VG Analytical 70VSE mass spectrometer.

Oxidative Coupling of ortho-Diamines with Aromatic and Heteroaromatic Aldehydes; General Procedure

Method A: To a stirred solution of the diamine (3.2 mmol) in MeCN (25 mL) was added a solution of the aldehyde (3 mmol) in MeCN, and the solution was stirred for 1 h at 90 °C. The mixture was then evaporated to dryness and the resulting Schiff's base resuspended in MeCN (30 mL), and solid $FeCl_3$•$6H_2O$ (9 mg, 0.03 mmol, 0.01 molar equiv) was added. The mixture was stirred for 90 °C with continuous O_2 bubbling through the solution for 5–8 h, depending on the course of completion of the reaction as monitored by TLC and NMR analysis of the aliquots, drawn periodically and filtered through a short silica gel bed to remove iron salts to enable NMR analysis. Removal of the solvent and silica gel flash chromatography (gradient elution from EtOAc to a 1:1 EtOAc/MeOH solvent mixture) gave the benzimidazole analogs in the indicated yields with spectral data consistent with the assigned structures for the products. Hydrochloride salts were prepared by treatment with methanolic HCl, evaporation followed by crystallization from EtOH/Et_2O.

Method B: To a stirred solution of the diamine (3.2 mmol) in DMF (15 mL) was added a solution of the aldehyde (3 mmol) in DMF, and the solution was stirred for 1 h at 80 °C. Solid $FeCl_3$•$6H_2O$ (24 mg, 0.09 mmol, 0.03 molar equiv) was then added and the mixture stirred at 120 °C with continuous O_2 bubbling through the solution for 10 h. The progress of the reaction was monitored by TLC analysis of the aliquots. DMF was removed by evaporation and products isolated in pure form by silica gel flash chromatography (gradient elution from EtOAc to 1:1 EtOAc/MeOH solvent mixture). Hydrochloride salts were prepared by treatment with methanolic HCl, evaporation followed by crystallization EtOH/Et_2O.

In order to simplify the presentation of analytical and spectroscopic data, the benzimidazole and related analogs prepared in this study are grouped into series I-VI. Series I consists of the benzimidazole analogs **4a**–**f** obtained from the coupling of 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine[12c] **(1)** with electron-rich benzaldehyde derivatives. Series II comprises additional analogs **5a**–**f** derived from the same diamine and electron-deficient benzaldehyde substrates. Series III contains the benzimidazole products **6a**–**e** obtained from *N*-methyl-2-imidazolecarboxaldehyde and different diamines. Series IV comprises analogs **7a**–**d** prepared from heterocyclic aldehydes and 3,4-diaminobenzyl alcohol.[19] Series V and VI correspond to extended 2,5'-bi(benzimidazole) derivatives and imidazopyridine analogs as described below. The spectral data for the series I (**4a**–**f**) and series II (**5a**–**f**) products are collectively presented in Tables 3 and 4, respectively.

Series I (4a–f) (Table 3)

2-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4a)

Prepared from 4-hydroxybenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (92% yield); mp 228–230 °C (dec).

2-(4-Methoxyphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4b)

Prepared from 4-methoxybenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (94% yield); mp 193–195 °C.

2-(3,4-Dimethoxyphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4c)

Prepared from 3,4-dimethoxybenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (86% yield); mp 226–230 °C.

2-(4-Methylphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4d)

Prepared from 4-methylbenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (90% yield); mp 245–248 °C.

2-(4-Dimethylaminophenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4e)

Prepared from 4-(dimethylamino)benzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (94% yield); mp 289–293 °C.

2-(4-Acetamidophenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (4f)

Prepared from 4-acetamidobenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method A, and isolated as the hydrochloride salt after purification (92% yield); mp 180–182 °C.

Series II (5a–f) (Table 4)

5-(4-Methyl-1-piperazinyl)-2-(4-nitrophenyl)-1*H*-benzimidazole (5a)

Prepared from 4-nitrobenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification (82% yield); mp >300 °C.

5-(4-Methyl-1-piperazinyl)-2-(3-nitrophenyl)-1*H*-benzimidazole (5b)

Prepared from 3-nitrobenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification (84% yield); mp >300 °C.

2-(4-Cyanophenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (5c)

Prepared from 4-cyanobenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification (85% yield); mp 212–215 °C.

2-(3-Cyanophenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (5d)

Prepared from 3-cyanobenzaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification (82% yield); mp 296–299 °C.

Table 3 Spectral Data for Series I (**4a–f**) Analogs

Compound	EI-HRMS	^{1}H NMR (solvent, 300 MHz), δ, *J* (Hz)	^{13}C NMR (solvent, 75 MHz), δ
4a	calcd for $C_{18}H_{20}N_4O$ 308.1637 found 308.1638 (M^+, 100%), 238.0972 (M − C_4H_8N; 45%), 237.0903 (M − C_4H_9N; 43%)	(D_2O): 7.42 (d, 2 H, *J* = 9), 7.32 (d, 1 H, *J* = 8.7), 7.02 (d, 1 H, *J* = 8.7), 6.85 (s, 1 H), 6.69 (d, 2 H, *J* = 9), 3.59−3.70 (m, 4 H), 3.08 (m, 4 H), 2.94 (s, 3 H)	(D_2O, 318 K): 163.2 (s), 150.7 (s), 149.3 (s), 133.9 (s), 131.1 (d), 127.3 (s), 119.8 (d), 119.1 (d), 116.4 (d), 114.7 (s), 101.5 (d), 55.8 (t), 49.2 (t), 45.7 (q)
4b	calcd for $C_{19}H_{22}N_4O$ 322.1793 found 322.1799 (M^+, 100%), 252.1134 (M − C_4H_8N; 17%), 251.1058 (M − C_4H_9N; 19%)	(DMSO-d_6): 11.2 (s, 1 H, D_2O exch., NH), 8.40 (d, 2 H, *J* = 9), 7.68 (d, 1 H, *J* = 8.5), 7.33 (d, 1 H, *J* = 8.5), 7.29 (d, 2 H, *J* = 9), 7.19 (s, 1 H), 3.86 (s, 3 H), 3.50 (m, 4 H), 3.10 (m, 4 H), 2.80 (s, 3 H)	(D_2O): 164.8 (s), 150.6 (s), 148.2 (s), 133.5 (s), 130.2 (d), 126.9 (s), 119.7 (d), 117.1 (d), 116.1 (d), 114.7 (s), 101.2 (d), 58.0 (q), 55.6 (t), 49.1 (t), 45.4 (q)
4c	calcd for $C_{20}H_{24}N_4O_2$ 352.1899 found 352.1893 (M^+, 100%), 282.1236 (M − C_4H_8N; 38%), 281.1161 (M − C_4H_9N; 43%)	(D_2O): 6.99 (d, 1 H, *J* = 8.5), 6.85 (d, 1 H, *J* = 8.3), 6.75 (d, 1 H, *J* = 8.5), 6.57 (s, 1 H), 6.48 (s, 1 H), 6.40 (d, 1 H, *J* = 8.3), 3.59−3.73 (m, 4 H), 3.45 (s, 3 H), 3.39 (s, 3 H), 2.98−3.18 (m, 4 H), 2.94 (s, 3 H)	(D_2O): 154.3 (s), 150.8 (s), 150.5 (s), 148.2 (s), 133.6 (s), 126.9 (s), 122.6 (d), 119.8 (d), 116.0 (d), 114.7 (s), 113.8 (d), 109.5 (d), 100.8 (d), 58.3 (q), 58.1 (q), 55.6 (t), 49.1 (t), 45.4 (q)
4d	calcd for $C_{19}H_{22}N_4$ 306.1844 found 306.1843 (M^+, 100%), 236.1190 (M − C_4H_8N; 38%), 235.1116 (M − C_4H_9N; 41%)	(DMSO-d_6): 11.03 (s, 1 H, D_2O exch., NH), 8.26 (d, 2 H, *J* = 8.8), 7.71 (d, 1 H, *J* = 8.5), 7.53 (d, 2 H, *J* = 8.8), 7.35 (dd, 1 H, *J* = 8.5, 1.5), 7.20 (d, 1 H, *J* = 1.5), 3.60−3.71 (m, 4 H), 3.19 (m, 4 H), 2.81 (s, 3 H), 2.44 (s, 3 H)	(D_2O): 150.7 (s), 148.4 (s), 133.7 (s), 127.3 (s), 119.2 (d), 116.2 (s), 115.9 (d), 114.6 (s), 110.2 (d), 109.3 (d), 101.0 (d), 55.7 (t), 49.4 (t), 45.2 (q), 24.8 (q)
4e	calcd for $C_{20}H_{25}N_5$ 335.2109 found 335.2107 (M^+, 100%), 265.1465 (M − C_4H_8N; 36%), 264.1394 (M − C_4H_9N; 32%)	(D_2O): 7.13 (d, 1 H, *J* = 8.7), 6.93 (d, 1 H, *J* = 8.7), 6.91 (d, 2 H, *J* = 9), 6.80 (s, 1 H), 6.15 (d, 2 H, *J* = 9), 3.59−3.70 (m, 4 H), 2.98−3.17 (m, 4 H), 2.93 (s, 3 H), 2.25 (s, 6 H)	(D_2O): 153.9 (s), 150.2 (s), 150.0 (s), 133.9 (s), 130.1 (d), 127.7 (s), 119.0 (d), 115.7 (d), 113.9 (d), 109.4 (s), 101.7 (d), 55.8 (t), 49.6 (t), 45.4 (q), 41.8 (q)
4f	calcd for $C_{20}H_{23}N_5O$ 349.1902 found 349.1904 (M^+, 100%), 279.1240 (M − C_4H_8N; 28%), 278.1170 (M − C_4H_9N; 18%)	(D_2O): 7.20 (d, 1 H, *J* = 8.5), 7.12 (d, 2 H, *J* = 9), 7.00 (2 d, 3 H), 6.83 (s, 1 H), 3.60−3.74 (m, 4 H), 3.2 (m, 4 H), 3.01 (s, 3 H), 2.95 (s, 3 H)	(D_2O): 174.1 (s), 151.0 (s), 148.2 (s), 144.3 (s), 134.0 (s), 129.8 (d), 127.3 (s), 121.4 (d), 120.1 (d), 118.0 (s), 116.5 (d), 101.3 (d), 55.8 (t), 49.3 (t), 45.6 (q), 26.0 (q)

Table 4 Spectral Data for Series II (**5a–f**) Analogs

Compound	EI-HRMS data	^{1}H NMR (300 MHz), δ, *J* (Hz)	^{13}C NMR (solvent, 75 MHz), δ
5a	calcd for $C_{18}H_{19}N_5O_2$ 337.1538 found 337.1539 (M^+, 58%), 266.0802 (M − C_4H_9N; 16%)	(D_2O): 8.23 (d, 2 H, *J* = 9), 7.95 (d, 2 H, *J* = 9), 7.58 (d, 1 H, *J* = 8.7), 7.26 (d, 1 H, *J* = 8.7), 7.14 (s, 1 H), 3.66−3.90 (m, 4 H), 3.13−3.32 (m, 4 H), 2.97 (s, 3 H)	(D_2O): 151.8 (s), 151.4 (s), 148.3 (s), 135.8 (s), 130.6 (d), 129.2 (s), 128.2 (s), 127.3 (d), 121.4 (d), 117.5 (d), 102.3 (d), 55.6 (t), 49.5 (t), 45.8 (q)
5b	calcd for $C_{18}H_{19}N_5O_2$ 337.1538 found 337.1537 (M^+, 48%), 267.0879 (M − C_4H_8N; 12%), 266.0809 (M − C_4H_9N; 18%)	(D_2O): 8.61 (s, 1 H), 8.30 (d, 1 H, *J* = 8.5), 8.21 (d, 1 H, *J* = 8.5), 7.77 (t, 1 H, *J* = 8.5), 7.56 (d, 1 H, *J* = 8.7), 7.22 (d, 1 H, *J* = 8.7), 7.16 (s, 1 H), 3.58−3.88 (m, 4 H), 3.15−3.32 (m, 4 H), 2.97 (s, 3 H)	(D_2O, 318 K): 151.8 (s), 151.2 (s), 149.8 (s, C), 135.9 (d), 135.3 (s), 134.3 (d), 130.3 (d), 129.0 (s), 126.6 (s), 124.9 (d), 121.6 (d), 117.7 (d), 102.7 (d), 55.9 (t), 49.7 (t), 45.7 (q)
5c	calcd for $C_{17}H_{19}N_5$ 317.1640 found 317.1637 (M^+, 100%), 247.0974 (M − C_4H_8N; 23%), 246.0905 (M − C_4H_9N; 37%)	(D_2O): 7.69 (d, 4 H), 7.48 (d, 1 H, *J* = 8.7), 7.19 (d, 1 H, *J* = 8.7), 7.00 (s, 1 H), 3.72−3.81 (m, 4 H), 3.2 (m, 4 H), 2.98 (s, 3 H)	(D_2O): 151.5 (s), 147.4 (s), 136.0 (d), 134.7 (s), 129.5 (d), 128.2 (s), 128.0 (s), 121.4 (d), 120.4 (s), 117.4 (s), 117.2 (d), 101.7 (d), 55.5 (t), 49.1 (t), 45.7 (q)
5d	calcd for $C_{17}H_{19}N_5$ 317.1640 found 317.1642 (M^+, 100%), 247.0983 (M − C_4H_8N; 34%), 246.0918 (M − C_4H_9N; 61%)	(D_2O): 8.15 (m, 2 H), 7.95 (d, 1 H, *J* = 8.5), 7.77 (t, 1 H, *J* = 8.5), 7.60 (d, 1 H, *J* = 8.7), 7.27 (d, 1 H, *J* = 8.7), 7.22 (s, 1 H), 3.73 (m, 4 H), 3.25 (m, 4 H), 2.95 (s, 3 H)	(D_2O): 151.1 (s), 147.2 (s), 136.2 (s), 134.8 (s), 131.8 (d), 130.7 (d), 129.7 (s), 127.6 (d), 126.2 (s), 121.1 (d), 119.8 (s), 117.6 (d), 115.6 (d), 102.1 (d), 55.3 (t), 49.3 (t), 45.4 (q)
5e	calcd for $C_{19}H_{20}N_4O_2$ 336.1586 found 336.1577 (M^+, 100%)	(D_2O): 7.50 (s, 2 H), 7.36 (s, 2 H), 7.20 (d, 1 H, *J* = 8.7), 6.93 (d, 1 H, *J* = 8.7), 6.72 (s, 1 H), 3.75 (m, 4 H), 3.05 (m, 4 H), 2.88 (s, 3 H)	(D_2O, 318 K): 170.2 (s), 151.6 (s), 147.5 (s), 135.8 (s), 134.7 (s), 133.1 (d), 128.8 (d), 127.9 (s), 127.3 (s), 121.1 (d), 117.3 (d), 101.4 (d), 55.8 (t), 49.0 (t), 45.7 (q)
5f	calcd for $C_{20}H_{23}N_6O_3^+$ (MH^+) 395.1823 found 395.1828	(DMSO-d_6): 10.96 (s, 1 H), 10.71 (s, 1 H, exch), 8.78 (s, 1 H), 8.53 (d, 1 H, *J* = 8.7), 7.87 (d, 1 H, *J* = 8.7), 7.61 (d, 1 H, *J* = 8.7), 7.17 (d, 1 H, *J* = 8.7), 7.14 (s, 1 H), 3.62−3.76 (m, 4 H), 3.18 (m, 4 H), 2.89 (s, 3 H), 2.16 (s, 3 H)	(DMSO-d_6, 318 K): 173.7 (s), 150.9 (s), 150.7 (s), 147.8 (s), 143.8 (s), 133.7 (s), 130.1 (d), 129.2 (d), 126.4 (s), 123.1 (d), 122.3 (s), 119.6 (d), 115.7 (d), 102.6 (d), 55.6 (t), 49.1 (t), 45.7 (q), 26.2 (q)

2-(4-Carboxyphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (5e)

Prepared from 4-formylbenzoic acid and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification (78% yield); mp 278–280 °C.

2-(4-Acetamido-3-nitrophenyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (5f)

Prepared from 4-acetamido-3-nitrobenzaldehyde[25] and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B (84% yield); >300 °C.

Series III (6a–f). 2-(1-Methyl-2-imidazolyl)-substituted Benzimidazole Analogs

2-(1-Methyl-2-imidazolyl)-5-(4-methyl-1-piperazinyl)-1*H*-benzimidazole (6a)

Prepared from *N*-methyl-2-imidazolecarboxaldehyde and 4-(4-methyl-1-piperazinyl)-1,2-benzenediamine using Method B, and isolated as the hydrochloride salt after purification ; yield: 86%; mp 219–221 °C.

^{1}H NMR (300 MHz, D_2O): δ = 7.67 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.58 (s, 2 H, Im-CH), 7.28 (s, 1 H, Bzi-CH), 7.23 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 4.08 (s, 3 H, Im-NCH_3), 3.75 (m, 4 H, CH_2), 3.22 (m, 4 H, CH_2), 2.96 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, D_2O, 318 K): δ = 149.7 (s, C), 138.9 (s, C), 137.2 (s, C), 135.6 (s, C), 135.2 (s, C), 128.9 (d, CH), 124.1 (d, CH), 120.6 (d, CH), 118.5 (d, CH), 103.7 (d, CH), 55.4 (t, CH_2), 50.3 (t, CH_2), 45.4 (q, CH_3), 38.8 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{16}H_{20}N_6$ 296.1749, found 296.1749 (M^+, 100%), 226.1137 (M − C_4H_8N; 31%), 225.1059 (M − C_4H_9N; 26%).

5-Methyl-2-(1-methyl-2-imidazolyl)-1*H*-benzimidazole (6b)

Prepared from 1-methyl-2-imidazolecarboxaldehyde and 3,4-diaminotoluene using Method A; yield: 96%; mp 180–182 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.80 (s, D_2O exch., 1 H, NH), 7.54 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 7.26 (s, 1 H, Im-CH), 7.28 (s, 1 H, Bzi-CH), 7.11 (s, 1 H, Im-CH), 7.02 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 4.16 (s, 3 H, NCH_3), 2.41 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 144.5 (s, C), 143.0 (s, C), 138.7 (s, C), 136.2 (s, C), 132.3 (s, C), 129.8 (d, CH), 127.4 (d, CH), 122.2 (d, CH), 118.1 (d, CH), 110.1 (d, CH), 38.0 (q, CH_3), 24.8 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{12}H_{12}N_4$ 212.1063, found 212.1057 (M^+, 100%).

2-(1-Methyl-2-imidazolyl)-1*H*-benzimidazole-5-carboxylic Acid (6c)

Prepared from 1-methyl-2-imidazolecarboxaldehyde and 3,4-diaminobenzoic acid using Method B; yield: 75%; mp 265–268 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.82 (s, D_2O exch., 1 H, NH), 8.18 (s, 1 H, Bzi-CH), 7.84 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.65 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.49 (s, 1 H, Im-CH), 7.20 (s, 1 H, Im-CH), 4.19 (s, 3 H, NCH_3).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.20 (s, 1 H, Bzi-CH), 7.88 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.49 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.22 (s, 1 H, Im-CH), 7.06 (s, 1 H, Im-CH).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 170.2 (s, C), 148.2 (s, C), 143.2 (s, C), 138.9 (s, C), 131.3 (d, CH), 130.8 (s, C), 129.5 (d, CH), 128.1 (d, CH), 127.6 (s, C), 122.1 (d, CH), 199.6 (d, CH), 37.8 (q, CH_3).

FAB-HRMS: *m*/*z* calcd for $C_{12}H_{11}N_4O_2^+$ ($M + H^+$) 243.0885, found 243.0888.

Methyl 2-(1-Methyl-2-imidazolyl)-1*H*-benzimidazole-5-carboxylate (6d)

Prepared from 1-methyl-2-imidazolecarboxaldehyde and methyl 3,4-diaminobenzoate using Method B; yield: 83%; mp 195 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.78 (s, D_2O exch., 1 H, NH), 8.19 (s, 1 H, Bzi-CH), 7.85 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 7.69 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 7.46 (s, 1 H, Im-CH), 7.17 (s, 1 H, Im-CH), 4.19 (s, 3 H, NCH_3), 3.87 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 171.1 (s, C), 147.2 (s, C), 141.5 (s, C), 140.3 (s, C), 130.6 (d, CH), 129.5 (s, C), 129.1 (d, CH), 127.7 (d, CH), 127.3 (s, C), 120.8 (d, CH), 118.8 (d, CH), 52.6 (q, CH_3), 38.0 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{13}H_{12}N_4O_2$ 256.0961, found 256.0956 (M^+, 100%), 225.0777 (34%), 197.0816 (21%).

5-(Hydroxymethyl)-2-(1-methyl-2-imidazolyl)-1*H*-benzimidazole (6e)

Prepared from 1-methyl-2-imidazolecarboxaldehyde and 3,4-diaminobenzyl alcohol[19] using Method A; yield: 90%; mp 156 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.89 (s, D_2O exch., 1 H, NH), 7.59 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.46 (s, 1 H, Bzi-CH), 7.41 (s, 1 H, Im-CH), 7.20 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.12 (s, 1 H, Im-CH), 5.17 (t, exch, 1 H, *J* = 5 Hz, OH), 4.58 (d, 2 H, *J* = 5 Hz, CH_2), 4.18 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, CD_3OD, 310 K): δ = 147.1 (s, C), 145.9 (s, C), 140.5 (s, C), 139.0 (s, C), 136.1 (s, C), 131.0 (d, CH), 127.8 (d, CH), 124.3 (d, CH), 120.5 (d, CH), 112.9 (d, CH), 66.2 (t, CH_2), 37.9 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{12}H_{12}N_4O$ 228.1012, found 228.1013 (M^+, 100%), 211.0985 (38%).

Series IV (7a–d): 5-(Hydroxymethyl)-2-(aryl)benzimidazole Analogs

5-(Hydroxymethyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (7a)

Prepared from 4-methoxybenzaldehyde and 3,4-diaminobenzyl alcohol using Method A; yield: 91%; mp 224–226 °C (Lit.[26] mp 221–222 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.55 (s, D_2O exch., 1 H, NH), 7.92 (d, 2 H, *J* = 9 Hz, Ar-CH), 7.50 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.43 (s, 1 H, Bzi-CH), 7.11 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 6.94 (d, 2 H, *J* = 9 Hz, Ar-CH), 5.15 (t, exch, 1 H, OH), 4.57 (d, 2 H, *J* = 6 Hz, CH_2), 3.81 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 162.8 (s, C), 144.4 (s, C), 143.0 (s, C), 136.8 (s, C), 132.8 (s, C), 128.2 (d, CH), 121.2 (d, CH), 116.8 (d, CH), 115.1 (d, CH), 114.2 (s, C), 108.8 (d, CH), 63.6 (t, CH_2), 56.8 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{15}H_{14}N_2O_2$ 254.1056, found 254.1048 (M^+, 100%), 239.0808 ($M - CH_3$, 27%), 212.0861 ($M - C_2H_3O$, 42%).

5-(Hydroxymethyl)-2-(2-pyridinyl)-1*H*-benzimidazole (7b)

Prepared from 2-pyridinecarboxaldehyde and 3,4-diaminobenzyl alcohol using Method B; yield: 82%; mp 123–125 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.7 (s, D_2O exch., 1 H, NH), 8.91 (d, 1 H, *J* = 4.8 Hz, Pyr-CH), 8.18 (d, 1 H, *J* = 6.8 Hz, Pyr-CH), 7.95 (m, 1 H, Pyr-CH), 7.62 (d, 1 H, *J* = 8.5 Hz, Bzi-CH), 7.48 (d, 1 H, *J* = 8.5 Hz, Bzi-CH), 7.34 (s, 1 H, Bzi-CH), 7.21 (dd, 1 H, *J* = 7.0, 4.8 Hz, Pyr-CH), 5.18 (t, exch, 1 H, OH), 4.58 (d, 2 H, *J* = 5.6 Hz, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 153.8 (s, C), 152.3 (s, C), 148.9 (s, C), 144.4 (d, CH), 137.6 (s, C), 136.5 (s, C), 128.4 (d, CH), 125.2 (d, CH), 124.2 (d, CH), 122.8 (d, CH), 121.2 (d, CH), 112.7 (d, CH), 62.8 (t, CH_2).

FAB-HRMS: *m*/*z* calcd for $C_{13}H_{12}N_3O^+$ ($M + H^+$) 226.0980, found 226.0979.

5-(Hydroxymethyl)-2-(4-pyridinyl)-1*H*-benzimidazole (7c)

Prepared from 4-pyridinecarboxaldehyde and 3,4-diaminobenzyl alcohol using Method B; yield: 92%; mp 80–83 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.75 (s, D_2O exch., 1 H, NH), 8.72 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 8.07 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 7.71 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.52 (s, 1 H, Bzi-CH), 7.26 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 5.21 (t, exch, 1 H, OH), 4.60 (d, 2 H, *J* = 5.6 Hz, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 151.0 (s, C), 148.0 (s, C), 144.1 (d, CH), 141.3 (s, C), 137.2 (s, C), 136.8 (s, C), 125.6 (d, CH), 122.5 (d, CH), 121.4 (d, CH), 113.1 (d, CH), 62.6 (t, CH_2);

FAB-HRMS: *m*/*z* calcd for $C_{13}H_{12}N_3O^+$ ($M + H^+$) 226.0980, found 226.0984.

5-(Hydroxymethyl)-2-(1-methyl-4-nitro-2-pyrrolyl)-1*H*-benzimidazole (7d)

Prepared from 1-methyl-3-nitro-2-pyrrolecarboxaldehyde[24] and 3,4-diaminobenzyl alcohol using Method B; yield: 94%; mp 253 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.68 (s, D_2O exch., 1 H, NH), 8.24 (d, 1 H, *J* = 1.5 Hz, Py-CH), 7.59 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.51 (d, 1 H, *J* = 1.5 Hz, Py-CH), 7.45 (s, 1 H, Bzi-CH), 7.40 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 5.14 (t, exch, 1 H, OH), 4.59 (d, 2 H, *J* = 6 Hz, CH_2), 4.17 (s, 3 H, NCH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 318 K): δ = 144.2 (s, C), 143.1 (s, C), 137.3 (s, C), 135.0 (s, C), 133.4 (s, C), 127.7 (d, CH), 124.6 (s, C), 121.7 (d, CH), 117.7 (d, CH), 109.7 (d, CH), 106.0 (d, CH), 63.3 (t, CH_2), 38.0 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{13}H_{12}N_4O_3$ 272.0910, found 272.0911 (M^+, 100%), 226.0965 (21%), 225.0909 (37%), 196.0880 (12%).

Pyridinum Chlorochromate Oxidation of Alcohols 6e, 7a–d to Aldehydes 8–11

The following compounds **8**–**11** were prepared using pyridinum chlorochromate for oxidation of the corresponding hydroxymethylbenzimidazole derivatives from above, according to previously reported procedures.[12b–d]

2-(1-Methyl-2-imidazolyl)-1*H*-benzimidazole-5-carboxaldehyde (8)

This compound was obtained from **6e** in 78% yield after silica gel flash chromatography (2:1 MeOH/EtOAc eluent); mp 180–183 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05 (s, 1 H, CHO), 8.10 (s, 1 H, Bzi-CH), 7.82 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 7.62 (d, 1 H, *J* = 8.6 Hz, Bzi-CH), 7.29 (s, 1 H, Im-CH), 7.20 (s, 1 H, Im-CH), 4.38 (s, 3 H, NCH_3);

FAB-HRMS: *m*/*z* calcd for $C_{12}H_{11}N_4O^+$ ($M+H^+$) 227.0933, found 227.0940.

2-(4-Methoxyphenyl)-1*H*-benzimidazole-5-carboxaldehyde (9)

Prepared from **7a** in 82% yield after silica gel flash chromatography (EtOAc eluent); mp 174–176 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H, CHO), 8.20 (d, 2 H, *J* = 8.7 Hz, Ar-CH), 7.92 (s, 1 H, Bzi-CH), 7.76 (d, 1 H, *J* = 8.5 Hz, Bzi-CH), 7.48 (d, 1 H, *J* = 8.5 Hz, Bzi-CH), 7.17 (d, 2 H, *J* = 8.7 Hz, Ar-CH), 3.83 (s, 3 H, OCH_3).

EI-HRMS: *m*/*z* calcd for $C_{13}H_9N_3O$ 223.0788, found 223.0779 (M^+, 100%), 218.0538 (M – CH_3, 31%), 180.0605 (M – C_2H_3O, 22%).

2-(4-Pyridinyl)-1*H*-benzimidazole-5-carboxaldehyde (10)
This compound was obtained from **7c** in 69% yield after silica gel flash chromatography (MeOH eluent); mp 157–159 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 1 H, CHO), 8.87 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 8.37 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 7.90 (s, 1 H, Bzi-CH), 7.78 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.47 (d, 1 H, *J* = 8.4 Hz, Bzi-CH).

FAB-HRMS: *m*/*z* calcd for $C_{13}H_{10}N_3O^+$ (M + H^+) 224.0853, found 224.0848.

2-(1-Methyl-4-nitro-2-pyrrolyl)-1*H*-benzimidazole-5-carboxaldehyde (11)
Prepared from **7d** in 91% yield after silica gel flash chromatography (4:1 MeOH/EtOAc eluent); mp 303 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (s, 1 H, CHO), 7.74 (s, 1 H, Bzi-CH), 7.47 (d, 1 H, *J* = 1.2 Hz, Py-CH), 7.43 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.39 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.22 (d, 1 H, *J* = 1.2 Hz, Py-CH), 4.12 (s, 3 H, NCH_3).

EI-HRMS: *m*/*z* calcd for $C_{13}H_{10}N_4O_3$ 270.0758, found 270.0753 (M^+, 100%), 223.1137 (51%).

Series V (12–15): 2,5'-Bis-1*H*-benzimidazole Analogs of Hoechst 33258

2-(1-Methyl-2-imidazolyl)-5-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole (12)
Prepared from diamine **1** and compound **8** using Method B and isolated as the HCl salt; yield: 82%; mp 184–187 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.34 (d, 1 H, *J* = 1.5 Hz, Bzi-CH), 8.02 (dd, 1 H, *J* = 8.7, 1.5 Hz, Bzi-CH), 7.78 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.53 (d, 1 H, *J* = 8.5 Hz, Bzi'-CH), 7.35 (s, 1 H, Im-CH), 7.20 (s, 1 H, Im-CH), 7.16 (d, 1 H, *J* = 1.5 Hz, Bzi'-CH), 7.07 (dd, 1 H, *J* = 8.5, 1.5 Hz, Bzi'-CH), 4.23 (s, 3 H, Im-NCH_3), 3.25 (m, 4H, CH_2), 2.69 (m, 4H, CH_2), 2.39 (s, 3H, N-CH_3).

EI-HRMS: m/z calcd for $C_{23}H_{24}N_8$ 412.2124, found 412.2125 (M^+, 100%), 359.1889 (54%), 342.1516 (30%), 341.1388 (28%), 318 (44%), 274 (28%).

2-(4-Methoxyphenyl)-5-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole (13)
This compound was obtained from diamine **1** and compound **9** using Method B; yield: 76%; mp 248–250 °C.

^{1}H NMR (500 MHz, CD_3OD). δ = 8.23 (d, 1 H, *J* = 1.3 Hz, Bzi-CH), 7.96 (d, 2 H, *J* = 8.8 Hz, Ar-CH), 7.93 (dd, 1 H, *J* = 8.7, 1.3 Hz, Bzi-CH), 7.65 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.48 (d, 1 H, *J* = 8.5 Hz, Bzi'-CH), 7.11 (d, 1 H, *J* = 1.5 Hz, Bzi'-CH), 7.02 (dd, 1 H, *J* = 8.5, 1.5 Hz, Bzi'-CH), 6.98 (d, 2 H, *J* = 8.8 Hz, Ar-CH), 3.18 (m, 4 H, CH_2), 2.53 (m, 4 H, CH_2), 2.32 (s, 3 H, NCH_3).

EI-HRMS: *m*/*z* calcd for $C_{26}H_{26}N_6O$ 438.2168, found 438.2172 (M^+, 100%), 368.1562 (28%), 365.1440 (26%), 352 (48%).

5-[5-(4-Methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-2-(4-pyridinyl)-1*H*-benzimidazole (14)
Prepared from diamine **1** and the aldehyde derivative **10**, using Method B; yield: 78%; mp 276–280 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.76 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 8.30 (d, 1 H, *J* = 1.5 Hz, Bzi-CH), 8.16 (d, 2 H, *J* = 6.2 Hz, Pyr-CH), 8.01 (dd, 1 H, *J* = 8.7, 1.5 Hz, Bzi-CH), 7.72 (d, 1 H, *J* = 8.7 Hz, Bzi-CH), 7.49 (d, 1 H, *J* = 8.5 Hz, Bzi'-CH), 7.12 (d, 1 H, *J* = 1.5 Hz, Bzi'-CH), 6.96 (dd, 1 H, *J* = 8.5, 1.5 Hz, Bzi'-CH), 3.27 (m, 4 H, CH_2), 2.73 (m, 4 H, CH_2), 2.41 (s, 3 H, NCH_3).

EI-HRMS: *m*/*z* calcd for $C_{24}H_{23}N_7$ 409.2015, found 409.2013 (M^+, 100%), 339.1416 (38%), 338.1318 (30%), 325 (51%).

2-(1-Methyl-4-nitro-2-pyrrolyl)-5-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole (15)
This compound was obtained from the reaction of diamine **1** with **11** according to Method B; yield: 85%; mp 235–238 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.61 (s, exch, 1 H, NH), 8.33 (s, 1 H, Py-CH), 8.24 (s, 1 H, Bzi-CH), 8.03 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.68 (d, 1 H, *J* = 8.4 Hz, Bzi-CH), 7.58 (s, 1 H, Py-CH), 7.43 (d, 1 H, *J* = 8.7 Hz, Bzi'-CH), 6.99 (s, 1 H, Bzi'-CH), 6.92 (d, 1 H, *J* = 8.7 Hz, Bzi'-CH), 4.21 (s, 3 H, Py-NCH_3), 3.11 (m, 4 H, CH_2), 2.51 (m, 4 H, CH_2), 2.28 (s, 3 H, NCH_3).

FAB-HRMS: *m*/*z* calcd for $C_{24}H_{25}N_8O_2^+$ (M + H^+) 457.2101, found 457.2097.

Series VI (16–20): Extended Bis-benzimidazole and Imidazopyridine Derivatives

2,2'-(1,4-Phenylenebis)(5-methyl-1*H*-benzimidazole) (16)
Prepared from 1,4-benzenedicarboxaldehyde and 2 molar equiv of 3,4-diaminotoluene using Method B; yield: 84%; mp 176–178 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.86 (s, exch, 1 H, NH), 8.30 (s, 4 H, Ar-CH), 7.50 (d, 2 H, *J* = 8.4 Hz, Bzi-CH), 7.39 (s, 2 H, Bzi-CH), 7.06 (d, 2 H, *J* = 8.4 Hz, Bzi-CH), 2.43 (s, 6 H, CH_3).

^{13}C NMR (75 MHz, HCl salt in D_2O): δ = 145.6 (s, C), 143.9 (s, C), 136.8 (s, C), 132.2 (s, C), 123.1 (d, CH), 119.0 (d, CH), 117.3 (d, CH), 113.6 (s, C), 111.0 (d, CH), 24.6 (q, CH_3).

FAB-HRMS: *m*/*z* calcd for $C_{22}H_{19}N_4^+$ (M + H^+) 339.1611, found 339.1596.

2-(4-Methoxyphenyl)imidazo[4,5-*b*]pyridine (17)
Prepared from 4-methoxybenzaldehyde and 2,3-diaminopyridine using Method B; yield: 78%; mp 235–237 °C. (Lit.[27] mp 230–232 °C for free base).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.26 (s, D_2O exch., 1 H, NH), 8.29 (d, 1 H, *J* = 4.5 Hz, Pyr-CH), 8.17 (d, 2 H, *J* = 9 Hz, Ar-CH), 7.95 (d, 1 H, *J* = 7.2 Hz, Pyr-CH), 7.21 (dd, 1 H, *J* = 7.2, 4.5 Hz, Pyr-CH), 7.13 (d, 2 H, Ar-CH), 3.84 (s, 3 H, CH_3);

^{13}C NMR (75 MHz, HCl salt in D_2O): δ = 161.2 (d, CH), 155.2 (d, CH), 154.1 (s, C), 148.2 (s, C), 132.2 (s, C), 130.9 (s, C), 125.8 (d, CH), 119.2 (d, CH), 117.8 (d, CH), 117.1 (s, C), 55.3 (q, CH_3).

EI-HRMS: *m*/*z* calcd for $C_{13}H_{11}N_3O$ 225.0903, found 225.0907 (M^+, 100%), 210.0667 (M-CH_3, 36%), 182.0720 (M-C_2H_3O, 29%).

2-(4-Methoxyphenyl)imidazo[4,5-*c*]pyridine (18)
Prepared from 4-methoxybenzaldehyde and 3,4-diaminopyridine using Method B; yield: 92%; mp 265–268 °C. (Lit.[27] mp 271–273 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (s, 1 H, Pyr-CH), 8.21 (d, 1 H, *J* = 7.2 Hz, Pyr-CH), 8.03 (d, 2 H, *J* = 8.5 Hz, Ar-CH), 7.56 (d, 1 H, *J* = 7.2 Hz, Pyr-CH), 6.98 (d, 2 H, *J* = 8.5 Hz, Ar-CH), 3.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, HCl salt in D_2O): δ = 161.4 (s, C), 157.7 (s, C), 145.9 (s, C), 136.5 (s, C), 132.6 (d, CH), 129.5 (d, CH), 128.2 (d, CH), 116.9 (s, C), 113.6 (d, CH), 110.5 (d, CH), 55.2 (q, CH_3).

FAB-HRMS: *m*/*z* calcd for $C_{13}H_{12}N_3O^+$ (M + H^+) 226.0971, found 226.0973.

2,2'-(1,4-Phenylenebis)imidazo[4,5-*c*]pyridine (19)
Prepared from 1,4-benzenedicarboxaldehyde and 2 molar equiv of 3,4-diaminopyridine using Method B; yield: 86%; mp 228–230 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.48 (s, D_2O exch., 1 H, NH), 8.99 (s, 2 H, Pyr-CH), 8.34 (d, 2 H, *J* = 7.6 Hz, Pyr-CH), 8.26 (s, 4 H, Ar-CH), 7.66 (d, 2 H, *J* = 7.6 Hz, Pyr-CH).

^{13}C NMR (75 MHz, HCl salt in D_2O): δ = 157.4 (s, C), 145.6 (s, C), 136.2 (s, C), 132.9 (d, CH), 129.8 (d, CH), 117.1 (d, CH), 110.7 (d, CH), 112.9 (s, C).

FAB-HRMS: *m*/*z* calcd for $C_{18}H_{13}N_6^+$ (M + H^+) 312.1193, found 313.1186.

5,5'-Bis[2-(4-pyridinyl)-1*H*-benzimidazole] (20)
Prepared from 2 molar equiv of 4-pyridinecarboxaldehyde relative to 3,3'-diaminobenzidine using Method B; yield: 91%; mp >300 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.21 (s, D_2O exch., 1 H, NH), 8.78 (d, 4 H, *J* = 6 Hz, Pyr-CH), 8.14 (d, 4 H, *J* = 6 Hz, Pyr-CH), 7.75–7.88 (m, 4 H, Bzi-CH), 7.63 (s, 2 H, Bzi-CH).

^{13}C NMR (75 MHz, HCl salt in D_2O): δ = 148.6 (s, C), 147.5 (s, C), 142.9 (d. CH), 136.7 (s, C), 132.7 (s, C), 126.5 (s, C), 120.7 (d, CH), 119.1 (d, CH), 115.8 (d, CH), 112.6 (d, CH).

FAB-HRMS: *m*/*z* calcd for $C_{24}H_{17}N_6^+$ (M + H^+) 389.1518, found 389.1510.

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