STUDIES ON 2-SUBSTITUTED METHYLAZOLES: NOVEL SYNTHESIS OF 6-(N-PIPERIDINYL) AND 6-(N-MORPHOLINYL)-1,4-DIHYDROPYRIDINE DERIVATIVES INCORPORATING BENZIMIDAZOLE MOIETY WITH ANTICIPATED BIOLOGICAL ACTIVITY

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Abstract- The reaction of 2-(2-benzimidazolyl)acetonitrile with 3-(2-hydroxyaryl)propenones (2) in the presence of three equivalents of bases afforded the titled ring systems. When 2-(2-benzothiazolyl)acetonitrile was used instead of 2-(2-benzimidazolyl)acetonitrile the reaction afforded the 2-(benzopyran-3-yl)benzothiazole (9).

Benzimidazoles having the 2-pyridyl and/or piperidinyl moieties had been reported as analgesic and anti-inflammatory agents.[1,2] The reaction of 2-cyanomethylbenzimidazole with salicylaldehydes and salicylic esters is known to afford coumarin derivatives,[3,4] meantime coumarins are known to undergo aminolysis by nitrogen bases to give compounds having the corresponding amine moiety.[5] Accordingly, we investigated the reaction of 2-cyanomethylbenzimidazole (1) with the 3-(2-hydroxyaryl)propenones (2a,b) in the presence of piperidine or morpholine in order to synthesize new benzimidazoles having the nitrogen base moiety with anticipated biological activity. Thus, it has been found that 1a reacts with the propenone (2a) in the presence of three equivalents of piperidine in boiling ethanol to afford a colorless product of molecular formula $C_{29}H_{28}N_4O$ (*m/z* 448). Its ir spectrum showed the absence of the cyano and carbonyl absorptions and its ^{1}H nmr showed the N-substituted piperidine protons at δ 1.1, 3.2 ppm as two sets of multiplets. Similarly, the reaction of 1a with 2b under the same reaction conditions gave a colorless product, its ir spectrum revealed also the absence of the cyano and carbonyl absorptions and its ^{1}H nmr showed the characteristic[5] pattern of the piperidino moiety.

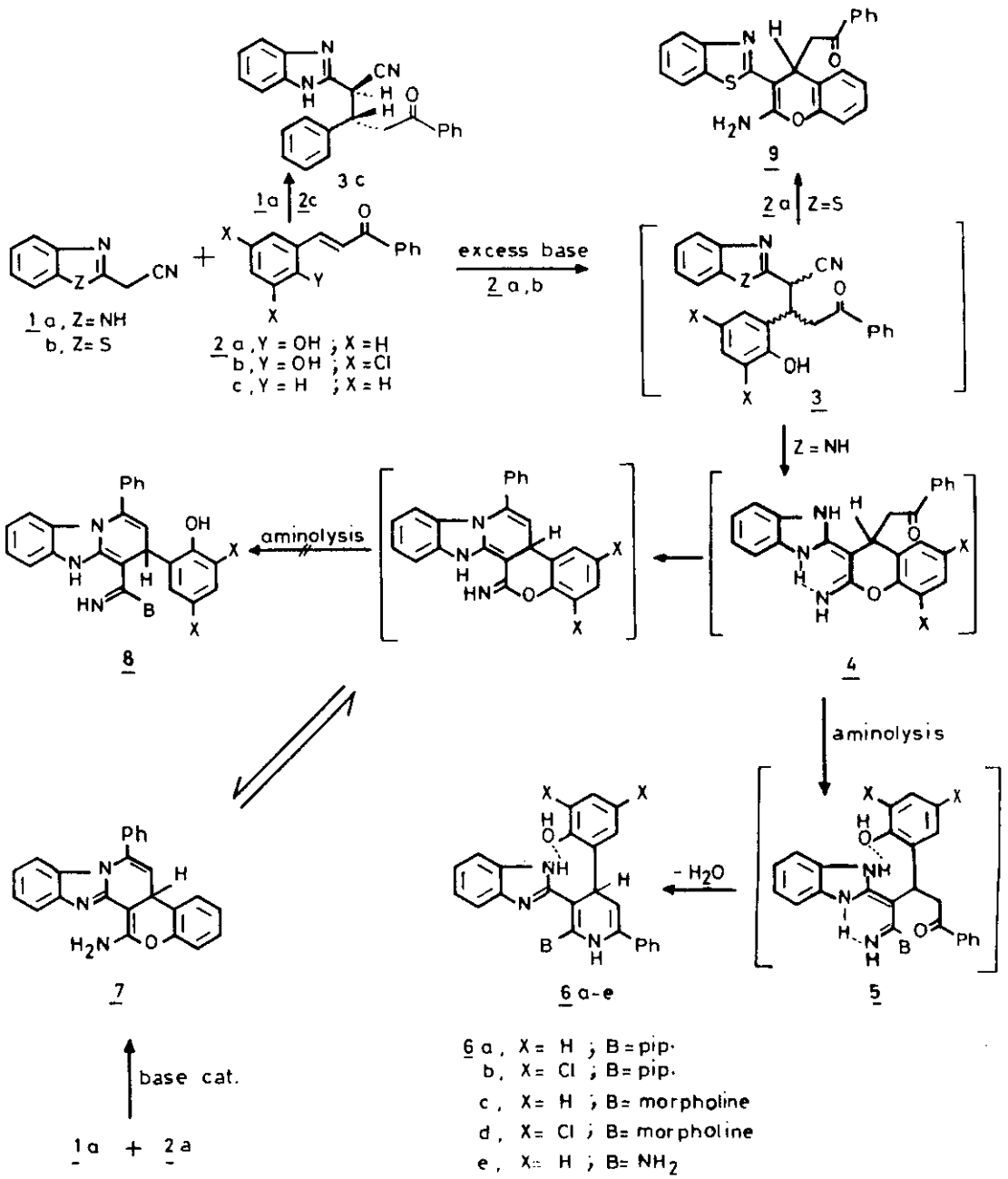
Two structures seemed possible for the obtained products (c.f. structures (6a) and (8a)) and a plausible mechanism to account for their formation could be suggested (c.f. Scheme 1). Although the differentiation between these structures by ir and ^{1}H nmr spectra is difficult (c.f. Table 2), structure (8a) could be ruled out based on the ms spectrum data which revealed the absence of a fragment ion at m/z = 111 corresponding to protonated N-cyanopiperidinium ion. This fragment together with a fragment ion at m/z = 338 (molecular ion minus N-cyanopiperidine) should constitute high abundance ratio in the fragmentation of structure (8a), which was not the case. Moreover, the presence of a fragment ion at m/z = 330 (44%) corresponding to the molecular ion minus benzimidazole molecule indicates that structure (6a) is the correct one;[6] since the splitting

of benzimidazole molecule in the fragmentation of structure (8a) is highly unlikely.[6]

The fact that the obtained product is colorless also supports the substituted 2-pyridyl structure rather than fused one, where it was previously noticed that the fused benzimidazole structures were colored.[6,7] In accordance with our postulated mechanism (c.f. Scheme 1), the ruled out structure (8) could not be obtained when the synthesized α-imino compound (7) was treated with excess piperidine. Thus when compound (1a) reacted with the propenone (2a) in boiling ethanol in presence of catalytic amount of piperidine, a bright yellow product of molecular formula $C_{24}H_{17}N_3O$ (m/z 363) was precipitated on hot. Structure (7) was given for this product based on its ir and ^1H nmr spectra. The former spectrum showed a (C=N) absorption at 1650 cm^{-1} along with a broad absorption at 3400-3200 cm^{-1} assigned for the benzimidazole NH and the amino or imino NH. Moreover, ^1H nmr showed the 4-H pyridine proton signal at δ 6.5 ppm and D_2O exchangeable proton at δ 11.6 ppm. As product (7) precipitated on hot, one would expect that it would also precipitate on hot if it was formed as an intermediate (c.f. Scheme 1), which was not observed. Furthermore, when compound (7) was boiled under reflux with three equivalents of piperidine in dimethylformamide, no reaction could be detected by tlc. It is postulated that compound (7) is predominantly present in dimethylformamide in its α-aminobenzopyran form than the o-imino one.

In order to investigate this reaction further, when the unsubstituted propenone (2c) was allowed to react with 1a in presence of three equivalents of piperidine, the obtained product, mp 184°C, showed the absence of the piperidine moiety in its spectral data. On the other hand its ir spectrum showed cyano and carbonyl absorptions at 2250 and 1680 cm^{-1} respectively. Moreover, its ^1H nmr spectrum showed the aliphatic signals at δ 3.6, 4.1 and 4.8 ppm assigned for the methylene and two methine protons (c.f. Table 2). These data could be interpreted for the Michael adduct structure (3c) which was existing in the threo configuration as the coupling constant for the two methine protons was found to be 7 Hz. The formation of 3c clarifying the role of the hydroxy group in the propenones (2a,b) in the formation of the iminocoumarin intermediate (4) which was subsequently aminolysed by piperidine affording intermediate (5) which then condensed to afford the final product (6). In absence of nitrogen nucleophile, intermediate (4) could undergo self condensation affording the isolable product (7).

The obtained results encouraged us to proceed with the reaction of 1a with 2a in presence of excess morpholine rather than piperidine. Thus, when 1a reacted with 2a and 2b, respectively, in presence of three equivalents of morpholine in boiling ethanol, colorless products were obtained with melting points 230 and 242°C, respectively. The ir spectra of these products also showed the absence of cyano and carbonyl absorptions, and the ^1H nmr showed the morpholine protons pattern at δ 3.4 and 3.5 ppm. These data are in accordance with the previously established structure (6) having the morpholino moiety instead of the piperidino one.


1a, Z=NH
b, Z=S
2a, Y=OH ; X=H
b, Y=OH ; X=Cl
c, Y=H ; X=H
excess base
2a,b
3c
1a 2c
2a Z=S
9
3
Z=NH
aminolysis
8
4
aminolysis
7
6a-e
-H2O
5
base cat.
1a + 2a
6a, X= H ; B=pip.
b, X= Cl ; B=pip.
c, X= H ; B= morpholine
d, X= Cl ; B= morpholine
e, X= H ; B= NH2

Scheme 1

When ammonia was utilized instead of piperidine or morpholine (8 equivalents of ammonium acetate were used) in the reaction of 1a with 2a colorless product, mp 274°C was obtained. Based on its spectral data (c.f. Table 2), structure (6e) was established. The ir spectra of this product showed an OH absorption at 3500 and an NH_2 and NH absorptions at 3350-3200 cm^{-1}. The ^1H nmr showed a 4-H pyridine signal at δ 5.8 ppm and three D_2O exchangeable signals at δ 11.2, 12.1 and 12.8 ppm.

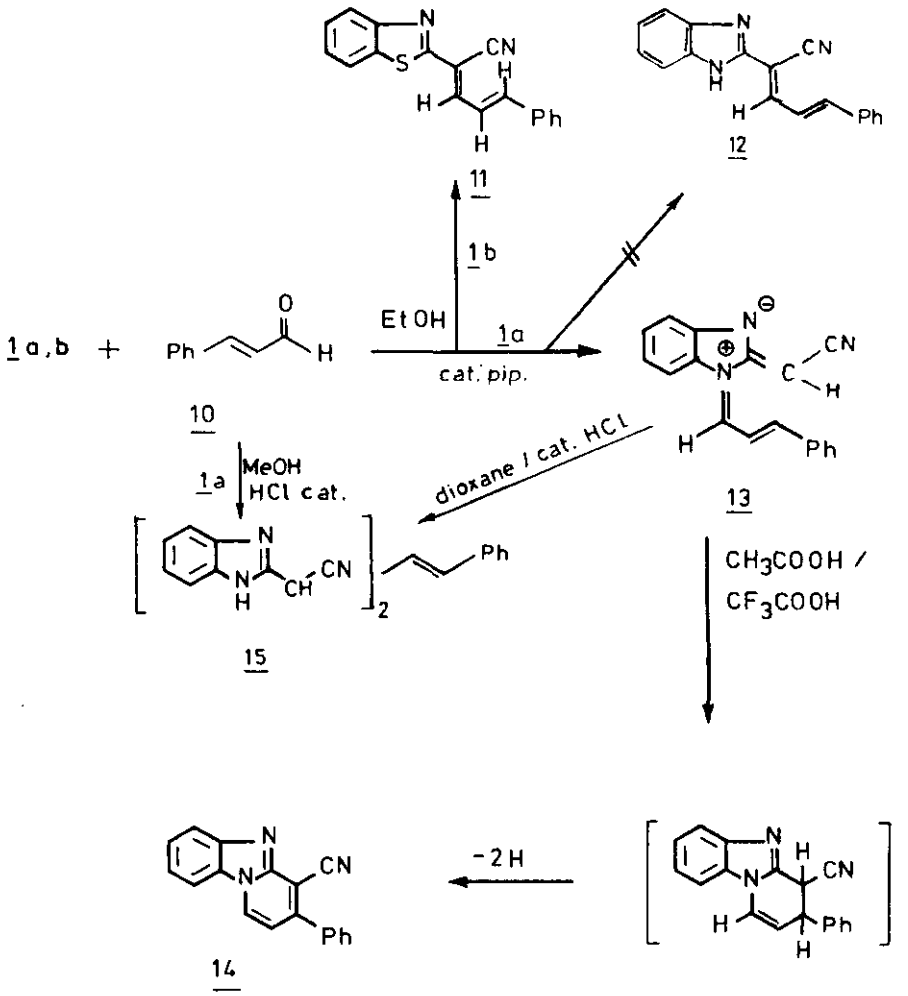
The predominance of the imino structure (4) rather than its amino isomer is due to the inter- and intramolecular H-bonding.[8] In accordance with this view when 2-cyanomethylbenzothiazole (1b) reacts with the propenone (2a) instead of 2-cyanomethylbenzimidazole, the reaction afforded the benzopyran derivative (9) regardless of the excess base used. Thus the ^1H nmr spectrum of 9 showed the 4H-pyran proton as a multiplet signal at δ 4.4-4.6 ppm and the amino group was detected as a D_2O exchangeable broad signal at δ 8.3-8.5 ppm. The other protons were detected in their expected location (c.f. Table 2). The ir spectrum of compound (9) showed an amino group absorption at 3400-3200 cm^{-1} and a carbonyl absorption at 1700 cm^{-1}.

The different behavior of 2-cyanomethylbenzothiazole (1b) and 2-cyanomethylbenzimidazole (1a) towards the propenones (2a,b) was also observed in their reactions with cinnamaldehyde (10). Thus while 2-cyanomethylbenzothiazole (1b) condensed readily with cinnamaldehyde (10) in ethanol in presence of catalytic amount of piperidine, affording the ylidene derivative (11) which has the trans (J=15 Hz) configuration about the styryl group (c.f. Table 2). 2-Cyanomethylbenzimidazole (1a) reacts with 10 under similar reaction conditions to afford a new product having the same microanalytical data as the expected ylidene derivative (12) but different ir and nmr spectra.

Thus, the ^1H nmr of this product revealed a characteristic downfield proton signal located at δ 8.5 ppm and the ir spectrum showed the absence of NH absorbance. Accordingly, the imminium ylide (13) was suggested for this new derivative and analogous result have been previously reported.[7] In addition the chemical behavior of the imminium ylide (13) towards thermal induced cyclisation and nucleophilic decomposition added further proof to its structure.

Thus, when compound (13) was boiled under reflux in acetic acid in presence of trifluoroacetic acid, as a catalyst, the pyrido[1,2-a]benzimidazole derivative (14) was obtained in good yield. Analytical and spectral data were in agreement with structure (14) (c.f. Tables 1, 2). Furthermore, the ^1H nmr revealed the absence of non-aromatic protons confirming that product (14) was oxidized under experimental conditions; similar oxidation has been previously reported for pyridobenzimidazole derivatives.[7] We postulated that compound (14) was obtained via electrocycloaddition which can take place in such dry condition. On the other hand, when ylidene (11) was boiled under the same reaction condition utilized with 13, no reaction could be detected by tlc and 11 was recovered unchanged. Also, when compound (13) was treated with hydrochloric acid in dioxane, a product of molecular formula $C_{27}H_{20}N_6$ (m/z 428) was obtained. Structure (15) was suggested

based on its spectral data. The ^1H nmr spectrum revealed a multiplet at 3.7-4.1 ppm integrated to three protons assigned to the methine (CH-CN) protons and to the allylic methine one. Moreover, the ir spectrum showed a broad band at 3200-2900 cm^{-1} for the benzimidazoles NH and a CN absorption at 2215 cm^{-1}. It is assumed that compound (13) had decomposed to its constituents 1a and cinnamaldehyde which recondensed in the presence of hydrochloric acid to give the arylidene bis-derivative (15). Similar arylidene bis-derivatives had been previously obtained from the condensation reactions of active methylene compounds with aldehydes.[9,10] Compound (15) could also be obtained from the reaction of 1a with cinnamaldehyde in the presence of a catalytic amount of hydrochloric acid in methanol.



Scheme 2

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra (KBr) were determined on a Pye-Unicam SP-1000 spectrophotometer. ^{1}H Nmr spectra were run on varian EM 390 (90 MHz) and GEMINI-200 spectrometers using tetramethylsilane as an internal reference. The mass spectra were recorded at 70 eV with a Varian MAT 311 A mass spectrometer. Elemental analyses were performed by the Central Service Laboratory in the National Research Center.

Preparation of 3-(α-cyanomethylbenzimidazol-2-yl)-1,3-diphenylpropan-1-one (3c); 5-(2-benzimidazolyl)-4-(3,5-disubstituted-2-hydroxyphenyl)-6-heteroaryl-2-phenyl-4H-pyridine (6a-d); 2-amino-3-(2-benzothiazolyl)-4-phenacyl-4H-benzopyran (9). General method - A mixture of each of the propenones (2a-c) (1 mmol) and the nitrile (1 a or b) in absolute ethanol (50 ml) containing piperidine or morpholine (3 mmol) was heated under reflux for 8 h. The reaction mixture was concentrated and left to cool. The separated solid was filtered off and crystallised from the proper solvent (see Table 1).

Preparation of 5-(benzimidazol-2-yl)-4-(2-hydroxyphenyl)-4,5-dihydro-2-phenyl-6-aminopyridine (6e). A mixture of the propenone (2a) (2.24 g, 1 mmol) and (1a) (1.57 g, 1 mmol) in absolute ethanol (50 ml) containing ammonium acetate (6.1 g, 8 mmol) was heated under reflux for 8 h then left to cool and poured into crushed ice. The separated solid was filtered off followed by crystallisation from the suitable solvent (see Table 1).

Preparation of 1-amino-8-phenylbenzimidazo[1',2':1,2]pyrido[3,4-c]-4H-benzopyran (7). Compound (1a) (1.57g, 1 mmol) was added to a solution of the propenone (2a) (2.24 g, 1 mmol) in absolute ethanol (50 ml) containing 2 drops of piperidine. The reaction mixture was boiled under reflux for 4 h, thereafter a solid product was precipitated on hot which was filtered off and crystallised from the proper solvent to give 7.

Preparation of 1-(benzothiazol-2-yl)-1-cyano-4-phenylbuta-1,3-diene (11) and 1-cinnamylidene-2-cyanomethinebenzimidazol-1-ium (13). General Procedure - A solution of (1 a or b) (1 mmol) in ethanol (30 ml) was treated each with cinnamaldehyde (1.32 g, 1 mmol) in presence of piperidine (2 drops). The reaction mixture was left at room temperature for 6 h till precipitation occurred. The resulting solid product was filtered off and crystallised from the proper solvent (see Table 1).

Preparation of 1-cyano-2-phenylpyrido[1,2-a]benzimidazole (14) - Compound (13) (2.7 g, 1 mmol) was refluxed in acetic acid (20 ml) in presence of trifluoroacetic acid (1 ml, 1.3 mmol) for 6 h. The reaction mixture was concentrated, cooled and water was added to the solution till precipitation occurred. The solid product formed was filtered off and crystallised (see Table 1).

Preparation of 1-phenyl-3,3-bis(2-benzimidazolyl-α-cyanomethyl)prop-1-ene (15)- Method I: Compound (13) (2.7 g, 1 mmol) was boiled under reflux in dioxane (40 ml) containing conc. hydrochloric

acid (0.5 ml, 1.6 mmol) for 6 h. The reaction mixture was then concentrated, cooled and water was added till precipitation commenced. The solid obtained was filtered off and crystallised. Method II: A solution of 1a (1.57 g, 1 mmol) in methanol (30 ml) was treated with cinnamaldehyde (1.32 g, 1 mmol) in presence of conc. hydrochloric acid (3 drops) for 4 h at room temperature. The solid product formed was filtered off and crystallised (see Table 1).

Table 1: List of compounds 3c, 6a-e, 7, 9, 11, 13, 14 and 15

Compd	Solvent of cryst.	mp (°C)	Yield (%)	Mol. formula	Analysis % Calc/ Found C	H	N	S	Cl	M^+ m/z
3c[i]	n-hexane	184-186	60	$C_{24}H_{19}N_3O$	78.9	5.2	11.5	-	-	365
					79.1	5.0	11.2	-	-	
6a[i]	EtOH	261-263	66	$C_{29}H_{28}N_4O$	77.7	6.3	12.5	-	-	448
					77.4	6.2	12.3	-	-	
6b[i]	MeOH	228-230	62	$C_{29}H_{26}N_4OCl_2$	67.4	5.0	10.9	-	13.6	516
					67.2	4.9	10.7	-	13.2	
6c[i]	dioxane	230	68	$C_{28}H_{26}N_4O_2$	74.7	5.8	12.4	-	-	450
					74.4	5.8	12.4	-	-	
6d[i]	MeOH	242	58	$C_{28}H_{24}N_4O_2Cl_2$	64.9	4.6	10.8	-	13.5	518
					64.6	4.5	10.4	-	13.2	
6e[i]	MeOH	274	68	$C_{24}H_{20}N_4O$	75.8	5.3	14.7	-	-	380
					75.7	5.1	14.4	-	-	
7[ii]	dioxane	300	40	$C_{24}H_{17}N_3O$	79.3	4.7	11.6	-	-	363
					79.0	4.7	11.3	-	-	
9[ii]	EtOH	193-195	65	$C_{24}H_{18}N_2O_2S$	72.4	4.5	7.0	8.0	-	398
					72.3	4.3	6.7	7.8	-	
11[ii]	pet. ether	153	90	$C_{18}H_{12}N_2S$	75.0	4.2	9.7	11.1	-	288
					74.8	4.1	9.4	10.8	-	
13[iii]	Acet./pet. ether	200	40	$C_{18}H_{13}N_3$	79.7	4.8	15.5	-	-	271
					79.5	4.7	15.3	-	-	
14[ii]	dioxane	251	63	$C_{18}H_{11}N_3$	80.3	4.1	15.6	-	-	269
					80.0	3.9	15.3	-	-	
15[ii]	EtOH	214	45*	$C_{27}H_{20}N_6$	75.7	4.7	19.6	-	-	428
			85**		75.9	4.4	19.2	-	-	

i = colorless, ii = yellow, iii = reddish

* = method I, ** = method II.

Table 2: Spectroscopic data for compounds listed in Table 1.

Compd	Ir (cm^{-1}) (selected bands)	^1H Nmr (ppm)
3c	3000-2800 (NH); 2250 (CN); 1680 (CO)	3.6 (m, 2H, CH_2); 4.1 (m, 1H, CH-CH_2); 4.8 (d, J=7 Hz, 1H, CH-CN); 7.0-7.7 (m, 14H, aromatics)

Compd	Ir (cm^{-1}) (selected bands)	^1H Nmr (ppm)
6a	3300-3280 (OH and NH)	1.1 (m, 6H, piperidine); 3.0-3.2 (m, 4H, piperidine); 5.8 (d, J=14 Hz, 1H, H-4 pyridine); 6.9-7.8 (m, 14H, aromatics); 11.2 (s, 1H, NH); 12.1 (br s, 1H, NH); 12.7 (br s, 1H, OH)
6b	3300-3280 (OH and NH)	1.1 (m, 6H, piperidine); 3.0-3.1 (m, 4H, piperidine); 5.9 (d, J=13 Hz, 1H, H-4 pyridine); 7.0-7.7 (m, 12H, aromatics); 11.2 (s, 1H, NH); 11.8 (s, 1H, NH benzimidazole); 12.5 (s, 1H, OH)
6c	3400-3260 (OH and NH)	3.4 (m, 4H, morpholine); 3.5 (m, 4H, morpholine); 5.8 (d, J=13Hz, 1H, H-4 pyridine); 6.8-7.7 (m, 14H, aromatics); 11.7 (s, 1H, NH); 12.1 (s, 1H, NH); 12.3 (s, 1H, OH)
6d	3430-3390 (OH and NH)	
6e	3500-2800 (OH,NH and NH_2)	5.8 (d, J=14 Hz, 1H, H-4 pyridine); 7.0-7.7 (m, 14H, aromatics); 11.2 (m, 3H, NH and NH_2); 12.1 (br s, NH); 12.8 (s, 1H, OH)
7	3400-3200 (NH_2,NH); 1650 (C=N)	6.5 (d, J=11 Hz, 1H, H-4 pyridine); 7.4-7.8 (m, 14H, aromatics); 8.0 (d, J=11 Hz, 1H, H-3 pyridine); 11.6 (br s, 2H, NH_2)
9	3400, 3200 (NH_2); 1700 (CO)	3.2-3.6 (m, 2H, Ph-CO-CH_2); 4.5 (m, 1H, H-4 pyran); 7.0-7.9 (m, 13H, aromatics); 8.4 (s, 2H, NH_2)
11	2250 (CN)	6.9 (d, J=15 Hz, 1H, olefinic); 7.2-7.8 (m, 10H, Ph, benzimidazole and 1H olefinic); 8.2 (m, 1H, olefinic)
13	2225 (CN); 1610 (C=N)	7.1-7.7 (m, 11H, Ph, benzimidazole and olefinic); 7.9 (s, 1H, ylidene H), 8.5 (m, 1H, azomethine H)
14	2225 (CN)	7.5-7.9 (m, 9H, Ph and benzimidazole); 8.5 (d, J=9 Hz, 1H, H-3 pyridine); 8.7 (d, J=9 Hz, 1H, H-2 pyridine)
15	3200-2900 (NH); 2215 (CN)	3.7-4.1 (m, 3H, 2CH-CN and H-allylic); 7.0-7.9 (m, 15H, Ph, benzimidazoles and olefinic); 10.0 (br s, 2H, 2NH)

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