Mono- and Bis-Pyrimido[1,2-a]benzimidazoles: Alum Catalyzed Regioselective Three- or Pseudo Five-Component Reaction of 2-Aminobenzimidazole with Aldehyde and Malononitrile

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Abstract: A series of mono- and bis-pyrimido-[1,2-a]benzimidazole derivatives is synthesized by the regioselective multicomponent condensation reaction of aldehyde and malononitrile with 2-aminobenzimidazole in the presence of alum as a recyclable and efficient catalyst for this condensation.

Keywords: 2-Aminobenzimidazole, alum, multicomponent reaction, pyrimido[1,2-a]benzimidazole, regioselectivity,.

INTRODUCTION

Multicomponent reaction (MCR) has emerged as a powerful strategy in modern synthetic organic chemistry, which allows molecular complexity and diversity needed in the combinatorial chemistry for the preparation of bioactive compounds [1].

Benzimidazole is an important heterocyclic system, having become increasingly important in medicinal chemistry and organic synthesis. The benzo-fused imidazoles are used as antineoplastic and anti cancer agents [2]. These heterocycles also constitute a structural unit of many drugs such as mebendazole [3], albendazole [4], astemizole [5] and omeprazole [6]. Pyrimido[1,2-a]benzimidazole derivatives exhibit anti-inflammatory [7], macrofilaricidal [8], antibiotic [9], antiarrythemic [10], anthelmintic [11], antibacterial [12], antifungal [13], antihistaminic [14] and anticancer [15] properties and they have attracted strong interest as angiotension receptor antagonist [16], potent and selective 5-HT_4 receptor antagonist, antitumor, antiviral [17], and antiproliferative [18].

Although there are many reported methods for the synthesis of pyrans by three-component condensation of aldehyde, malononitrile or β–dicarbonyl compounds, only a few reports are available for the synthesis of pyrimido[1,2-a]benzimidazoles. A number of efforts have been made to develop methods for preparation of pyrimido[1,2-a]benzimidazoles. They are prepared *via* two-component condensation of 2-aminobenzimidazole with alkenenitriles [19] or alkynenitriles [20] and also by three-component condensation of 2-aminobenzimidazole with aldehyde and malononitrile in water [21a-c] under classical heating or microwave irradiation or in ethanol using amine as a catalyst [21d]. They are obtained by the reaction of 2-aminobenzimidazole, aldehyde and β–dicarbonyl compounds such as dimedone, acetylacetone, 1,3-indandione and ethyl acetoacetate in the presence of sulfamic acid [22], $H_6P_2W_{18}O_{62}$ [23], or tetramethylguanidinium trifluoroacetate (TMGT) [24]. The known methods suffered from the drawbacks of low yield, prolonged reaction time and the use of toxic solvents and catalysts. Consequently, there is a need for milder conditions, increased variation of the substituents in the components and better yields.

Alum is an inexpensive, water-soluble, non-toxic and commercially available compound that can be used in the laboratory without special precautions [25a]. $KAl(SO_4)_2.12H_2O$ (alum) with mild acidity, involatility, and incorrosivity, is insoluble in common organic solvents and was used recently as an easily available acidic catalyst in different reactions [25b].

As a continuation of our research in the selective synthesis of heterocyclic compounds [26] and with the aim of using alum as a catalyst [27], herein we report a simple one-pot, multi-component synthesis of potentially biologically important scaffold pyrimido[1,2-a]benzimidazoles **4a-j** (Schemes **1** and **2**). In this work we developed a rapid and efficient protocol for the solution phase synthesis of mono and bis-pyrimido[1,2-a]benzimidazole derivatives.

RESULTS AND DISCUSSION

The synthesis of mono-pyrimido[1,2-a]benzimidazoles **4a-h** was achieved by the three-component condensation of aldehydes **1a-h**, malononitrile **3** and 2-aminobenzimidazole **1** in the presence of 10 mol% alum as a catalyst. The reaction was carried out in ethanol at 70 °C or room temperature to give products **4a–h** in good to high yields (Scheme **1**).

Bis-pyrimido[1,2-a]benzimidazole derivatives **4i-j** were obtained by pseudo five-component reaction of isophthalaldehyde **2i** or terephthalaldehyde **2j** (1 mmol), malononitrile **3** (excess) and 2-aminobenzimidazole **1** (2 mmol) in the presence of 10 mol% alum in ethanol. First the reaction was stirred at room temperature for 2h. The reaction mixture is then refluxed for 3 hours (Scheme **2**). In order to optimize the best possible conditions, a different set of reactions was carried out with respect to different molar ratios of alum, temperature, and solvent. The condensation of 3-chloroben-

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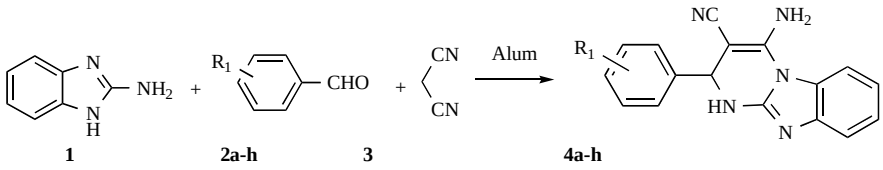
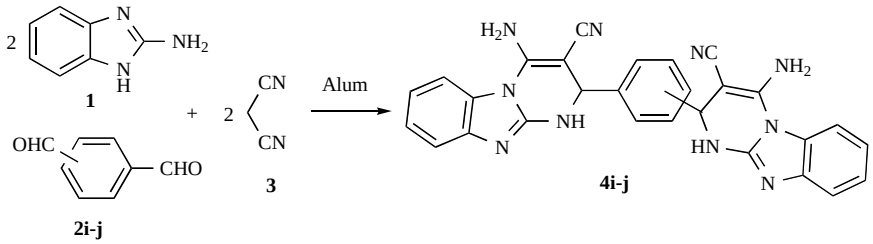


1 **2a-h** **3** **4a-h**

Scheme 1. Three-component synthesis of mono-pyrimido[1,2-a]benzimidazoles **4a-h**.



Scheme 2. Pseudo five-component synthesis of bis-pyrimido[1,2-a]benzimidazoles **4i-j**.

zaldehyde **2a** with malononitrile **3** and 2-aminobenzaldehyde **1** was chosen as a model.

Initially the effect of catalyst quantity on the yield of reaction was evaluated by varying the amounts of catalyst from 0 to 15 mol% at 70 °C (Table **1**, entries 1-4). However, the results indicated that in the absence of alum the product **4a** was obtained in low yield. In addition, the yield decreased by using 15 mol% of alum. Thus the best result was achieved with 10 mol% of alum. Optimization of amounts of catalyst was repeated for mentioned reaction at room temperature (Table **1**, entries 5-7). After 12 h with 5, 10, and 15 mol% of alum, yields of 40, 80, and 70% were obtained.

The investigation of solvent effect (Table **1**, entries 8-18) on the reaction at 70 °C and room temperature with optimum amount of catalyst (10 mol%) indicated that the yield gradually decreased as we moved from polar (except H_2O and EtOH) to less polar solvents. In H_2O medium no reaction occurred. The reaction hardly performed in EtOH/H_2O (3:2). Side products were obtained when EtOH/H_2O (3:2), CH_3CN, THF, and CH_2Cl_2 were used as solvent. Moreover, the yields were higher when the reactions were carried out at 70 °C rather than room temperature. Hence, the best reaction condition was obtained by using 10 mol% of alum in ethanol medium at 70 °C.

Table 1. Optimization of Reaction for the Synthesis of 4a

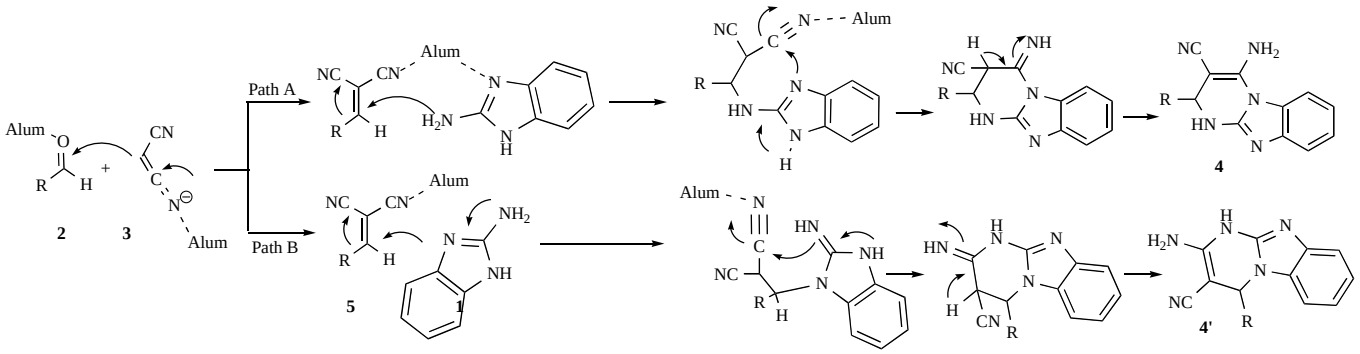
Entries	Catalyst	solvent	Temp.	Yield
1[a]	Alum (5 mol%)	EtOH	70 °C	60
2[a]	Alum (10 mol%)	EtOH	70 °C	90
3[a]	Alum (15 mol%)	EtOH	70 °C	85
4[a]	-	EtOH	70 °C	trace
5[b]	Alum (5 mol%)	EtOH	r.t	40
6[b]	Alum (10 mol%)	EtOH	r.t	80
7[b]	Alum (15 mol%)	EtOH	r.t	70
8[b]	Alum (10 mol%)	H_2O	r.t.	N.R.
9[b]	Alum (10mol%)	EtOH-H_2O[f]	r.t.	15
10[b]	Alum (10 mol%)	CH_3CN	r.t	60
11[b]	Alum (10 mol%)	THF	r.t	52
12[b]	Alum (10 mol%)	CH_2Cl_2	r.t	45
13[c]	Alum (10 mol%)	EtOH	r.t	70
14[d]	Alum (10 mol%)	EtOH	r.t	65
15[e]	Alum (10 mol%)	EtOH	r.t.	22
16[a]	Alum (10 mol%)	CH_3CN	70 °C	70
17[a]	Alum (10 mol%)	THF	70 °C	60
18[a]	Alum (10 mol%)	EtOH-H_2O[f]	70 °C	22

[a]reaction time =2h,[b] reaction time =12h,[c] reaction time = 7h,[d] reaction time = 5h,[e] reaction time = 3h, [f]EtOH-H_2O (3:2).

Table 2. Alum Catalyzed Synthesis of Mono- and Bis-Pyrimido[1,2-a]benzimidazoles

Entry	Aldehyde	product	Yield[b]	Yield[c]	M.p. (°C)	Lit. M.p. (°C)[d]
1	3-chlorobenzaldehyde	**4a**	90% (2h)	78%	222 dec	-
2	4-chlorobenzaldehyde	**4b**	86% (3.5h)	73%	230 dec	238 dec [20]
3	3-bromobenzaldehyde	**4c**	87% (2h)	70%	217 dec	240 dec [20]
4	3-methoxybenzaldehyde	**4d**	86% (2h)	71%	216 dec	-
5	4-methoxybenzaldehyde	**4e**	70% (6h)	-	224 dec	-
6	2-chloro-6-fluorobenzaldehyde	**4f**	90% (1.5 h)	79%	227 dec	-
7	benzaldehyde	**4g**	88% (2.5h)	72%	219 dec	235-236 [20]
8[a]	4-pyridinecarbaldehyde	**4h**	83% (5h)	-	236 dec	-
9[a]	isoterephthalaldehyde	**4i**	73% (5h)	-	235 dec	-
10[a]	terphthaldehyde	**4j**	70% (5h)	-	237 dec	-

[a]2 h at room temperature and then 3h at 70 °C. [b]yields refer to isolated products at 70 °C. [c]yields refer to isolated products at room temperature for 12h. [d]Lit. M.p. for **4'** isomer.



Scheme 3. Plausible mechanism of the Alum-catalyzed synthesis of **4**.

We next examined a wide variety of aldehydes to establish the scope of this catalytic transformation. It is noteworthy that for mono aldehydes **2a-g** the reaction mixture was refluxed at 70 °C in ethanol for appropriate time (Table **2**) but for 4-pyridine carbaldehyde **2h** and dialdehydes **2i-j** the reaction mixture was stirred at room temperature for 2h and then it was refluxed for 3h. Furthermore, for mono aldehydes all of the reactants are used in stoichiometric amounts although for dialdehydes excess malononitrile is necessary to achieve complete reaction (Table **2**).

The reaction presumably proceeds in two steps: initial condensation of aldehyde **2** and malononitrile **3** by standard Knoevenagel reaction takes place to form an intermediate called arylidene malononitrile **5**. Then the reaction of 2-aminobenzimidazole **1** with arylidene malononitrile **5** may proceed by two possible mechanistic pathways depending on whether the initial attack of the alkenenitrile is by the nitrogen of the side chain (path A) or by the ring nitrogen (path B) to give the isomeric pyrimido[1,2-a]benzimidazoles **4** or **4'** (Scheme **3**).

In order to distinguish between the isomeric pyrimido[1,2-a]benzimidazoles **4c** and **4c'**, ^{1}H nuclear overhauser effect (NOE) experiment was used. No enhancement of the H-b signal was observed when the methine proton (H-a) was irradiated in compound **4c**. These results confirm that the pyrimido[1,2-a]benzimidazoles obtained in this work are of structure **4c** (Fig. **1**).

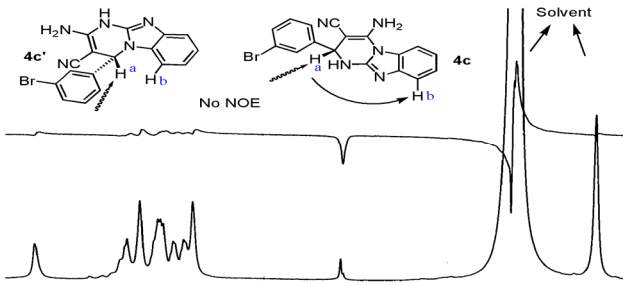
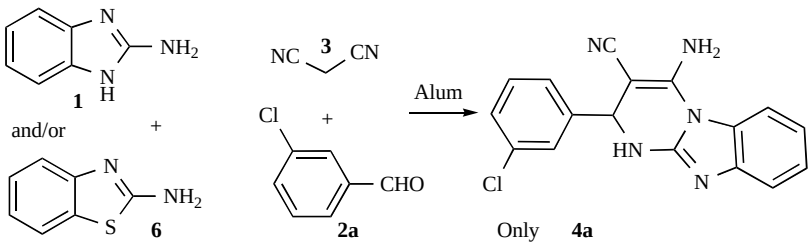


Fig. (1). NOE spectra of **4c**. Solvent: DMSO-d_6.

Although three component condensation of 2-aminobenzimidazole and malononitrile and aldehyde has been reported by Shaabani et. al. in H_2O medium without catalyst, but the reaction led to the formation of **4'** isomer. The mentioned reaction was heated at 90 °C for 7-12 h. [21a]. Nonetheless S. A. Komykhov [19a] and M. B. Deshmukh [21d] and co-workers reported the reaction of N,N-unsaturated nitrile with 2-aminobenzimidazole in ethanol with amine catalyst to get 1,2-dihydro-benzo[4,5] imidazo[1,2-a]-pyrimidine-3-carbonitrile derivatives, but it suffers from the drawbacks of low yield and the use of toxic catalyst while alum which is used in our article is a co-friendly catalyst [27].



Scheme 4. 2-aminobenzothioazole has not participated in this reaction.

Under the same conditions this reaction almost could not be observed when 2-aminobenzothiazole **6** was used as a starting material (Scheme **4**). It is noticeable that when 2-aminobenzimidazole **1**, 2-aminobenzothioazole **6**, 3-chlorobenzaldehyde **2a** and malononitrile **3** in the presence of alum were heated for 2 h, the reaction led to the formation of only **4a**. It means that the 2-aminobenzothioazole **6** has not participated in this reaction. Therefore, the alum is a selective catalyst for the synthesis of pyrimido[1,2-a]benzimidazoles by reaction of 2-aminobenzimidazole, aldehyde and malononitrile in the presence of 2-aminobenzothiazole (Scheme **4**).

In this study, the products were characterized by melting point, IR, ^{1}H NMR and ^{13}C NMR spectral data, as well as by elemental analyses.

CONCLUSION

In conclusion, we have described an efficient, one-pot, and three- or pseudo five-component method for the synthesis of Mono- and Bis-pyrimido[1,2-a]benzimidazoles catalyzed by alum as a co-friendly catalyst. Short reaction times, regioselectivity, high yields and easy workup are the advantages of this protocol. The reaction is also performed at room temperature with desirable yield.

EXPERIMENTAL

IR spectra were obtained on a Unicom Galaxy Series FTIR 5000 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker Avance 300 MHz spectrometer. Elemental analyses were performed using a Vario EL III elemental analyzer.

General Procedure for the Preparation of Products 4a-h

A mixture of aldehyde **2a-h** (1mmol), malononitrile **3** (1 mmol), 2-aminobenzimidazole **1** (1 mmol), and alum (10 mol%) in EtOH was stirred at r.t or 70 ^{o}C for several hours (Table **2**). Upon completion of the reaction as monitored by TLC, the reaction was filtered off and washed with hot ethanol and hot water to give the desired products.

General Procedure for the Preparation of Products 4i-j

A mixture of aldehyde **2i-j** (1mmol), malononitrile **3** (3 mmol), 2-aminobenzimidazole **1** (2 mmol), and alum (10 mol% with respect to aldehyde) in EtOH was stirred at r.t for 2h and then refluxed at 70 ^{o}C for 3h (Table **2**). Upon completion of the reaction as monitored by TLC, the reaction was filtered off and washed with hot ethanol and hot water to give the desired products.

Spectral Data

(4a): IR (KBr) (ν_{max}, cm^{-1}): 3448, 3319, 3213, 3059, 2914, 2197, 1682, 1639, 1602, 1471. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.29 (1H, s, CH), 6.93 (2H, s, NH_2), 7.00 (1H, t, *J*=7.66 Hz, H_{arom}), 7.12 (1H, t, *J*=7.42 Hz, H_{arom}), 7.24 (2H, d, *J*=7.57 Hz, H_{arom}), 7.35-7.45 (3H, m, H_{arom}), 7.64 (1H, d, *J*=7.82 Hz, H_{arom}), 8.67 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 52.97, 61.52, 112.97, 116.63, 119.55, 120.47, 123.7, 125.11, 126.48, 128.29, 129.68, 131.24, 133.66, 143.97, 145.83, 149.83, 152.

(4b): IR (KBr) (ν_{max}, cm^{-1}): 3447, 3310, 3211, 3059, 2916, 2197, 1682, 1637, 1602, 1471. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.26 (1H, s, CH), 6.89 (2H, s, NH_2), 7.00 (1H, t, *J*=7.64 Hz, H_{arom}), 7.12 (1H, t, *J*=7.28 Hz, H_{arom}), 7.23 (1H, d, *J*=7.72 Hz, H_{arom}), 7.31 (2H, d, *J*=8.16 Hz, H_{arom}), 7.43 (2H, d, *J*=8.06 Hz, H_{arom}), 7.64 (1H, t, *J*=7.85 Hz, H_{arom}), 8.16 (1H, s, NH). Anal. Calcd for $C_{17}H_{12}ClN_5$: C, 63.46; H, 3.76; N, 21.77. Found: C, 64.01; H, 3.91; N, 22.03.

(4c): IR (KBr) (ν_{max}, cm^{-1}): 3448, 3319, 3213, 3059 , 2914, 2197, 1682, 1639, 1602, 1471. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.28 (1H, s, CH), 6.91 (2H, s, NH_2), 7.01 (1H, m, H_{arom}), 7.12 (1H, m, H_{arom}), 7.22-7.38 (3H, m, H_{arom}), 7.49-7.63 (3H, m, H_{arom}), 8.64 (1H, s, NH). Anal. Calcd for $C_{17}H_{12}BrN_5$: C, 55.75; H, 3.30; N, 19.12. Found: C, 55.84; H, 3.21; N, 19.51.

(4d): IR (KBr) (ν_{max}, cm^{-1}): 3429, 3317, 3217, 3065, 2937, 2193, 1680, 1637, 1601, 1469. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 3.71 (3H, s, CH_3), 5.17 (1H, s, CH), 6.83-6.87 (5H, m, NH_2 and H_{arom}), 7.02 (1H, t, *J*=7.62 Hz, H_{arom}), 7.12 (1H, t, *J*=7.41 Hz, H_{arom}), 7.21-7.29 (2H, m, H_{arom}), 7.62 (1H, d, *J*=7.91 Hz, H_{arom}), 8.58 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 53.46, 55.48, 62.24, 112.57, 112.87, 113.1, 116.55 118.38, 119.69, 120.36, 123.81, 129.72, 130.39, 144.02, 144.97, 149.65, 152.26, 159.82.

(4e): IR (KBr) (ν_{max}, cm^{-1}): 3448, 3323, 3217, 2916, 2187, 1680, 1601, 1465. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 3.71 (3H, s, CH_3), 5.14 (1H, s, CH), 6.81 (2H, s, NH_2), 6.91 (2H, d, *J*=8.43 Hz, H_{arom}), 6.99 (1H, t, *J*=7.65 Hz, H_{arom}), 7.11 (1H, t, *J*=7.57 Hz, H_{arom}), 7.18-7.23 (3H, m, H_{arom}), 7.62 (1H, d, *J*=7.93 Hz, H_{arom}), 8.51 (1H, s, NH). Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 67.87; H, 4.60; N, 22.21.

(4f): IR (KBr) (ν_{max}, cm^{-1}):3450, 3315, 3082, 2183, 1672, 1631, 1601, 1446. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.96 (1H, s, CH), 6.85 (2H, s, NH_2), 6.99 (1H, t, *J*=7.62 Hz, H_{a-}

$_{rom}$), 7.1 (1H, t, *J*=7.53 Hz, H_{arom}), 7.19-7.25 (2H, m, H_{arom}), 7.35-7.45 (2H, m, H_{arom}), 7.53 (2H, d, *J*=7.94 Hz, H_{arom},), 8.5 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ_C: 48.73, 59.09, 112.6, 115.91, 116.30, 118.91, 120.21, 123.69, 126.51, 127.69, 127.87, 129.76, 131.06, 131.19, 132.96, 133.04, 144.01, 149.96, 151.72, 160.73, 164.04.

(4g): IR (KBr) (ν_{max}, cm^{-1}): 3448, 3313, 3211, 2191, 1683, 1639, 1602, 1469. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.20 (1H, s, CH), 6.82 (1H, s, NH_2), 7.0 (1H, t *J*=7.89 Hz, H_{arom}), 7.12 (2H, t, *J*=7.49 Hz, H_{arom}), 7.37-7.21(6H, m, H_{a-rom}), 7.62 (1H, d, *J*=8.03 Hz, H_{arom}), 8.58 (1H, s, NH). Anal. Calcd for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.37. Found: C, 71.33; H, 4.41; N, 24.44.

(4h): IR (KBr) (ν_{max}, cm^{-1}): 3367, 2931, 2204, 1628, 1606, 1485. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.29 (1H, s, CH), 6.97 (2H, s, NH_2), 7.01 (1H, t, *J*=7.76 Hz, H_{arom}), 7.13 (1H, t, *J*=7.58 Hz, H_{arom}), 7.25-7.3 (3H, m, H_{arom}), 7.62 (1H, d, *J*=7.93 Hz, H_{arom}), 8.45 (2H, d, *J*=5.98 Hz, H_{arom}), 8.73 (1H, s, NH). Anal. Calcd for $C_{16}H_{12}N_6$: C, 66.66; H, 4.20; N, 29.15. Found: C, 67.05; H, 4.24; N, 29.50.

(4i): IR (KBr) (ν_{max}, cm^{-1}): 3485, 3373, 3169, 2191, 1678, 1633, 1602, 1475. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.35 (2H, s, CH), 6.91 (4H, s, NH_2), 7.0 (2H, t, *J*=7.62 Hz, H_{arom}), 7.12 (2H, t, *J*=7.53 Hz, H_{arom}), 7.23 (2H, d, *J*=7.63 Hz, H_{arom}), 7.64 (4H, d, *J*=5.29 Hz, H_{arom}), 7.87 (2H, bs, H_{arom}), 8.58 (2H, s, NH). Anal. Calcd for $C_{28}H_{22}N_{10}$: C, 67.46; H, 4.45; N, 28.10. Found: C, 67.88; H, 4.61; N, 27.81.

(4j): IR (KBr) (ν_{max}, cm^{-1}): 3412, 3288, 3086, 2185, 1682, 1631, 1589, 1473. ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H: 5.36 (2H, s, CH), 6.93 (4H, s, NH_2), 7.0 (2H, t, *J*=7.5 Hz, H_{arom}), 7.13 (2H, t, *J*=7.53 Hz, H_{arom}), 7.25 (2H, d, *J*=8.09 Hz, H_{arom}), 7.51 (2H, d, *J*=8.28 Hz, H_{arom}), 7.62 (2H, d, *J*=7.96 Hz, H_{arom}), 7.93 (2H, d, *J*=8.29 Hz, H_{arom}), 8.51 (2H, s, NH). Anal. Calcd for $C_{28}H_{22}N_{10}$: C, 67.46; H, 4.45; N, 28.10. Found: C, 67.79; H, 4.32; N, 28.30.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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