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Synthesis of α-Aminonitriles with Benzimidazolic and Theophyllinic Backbones Using the Strecker Reaction

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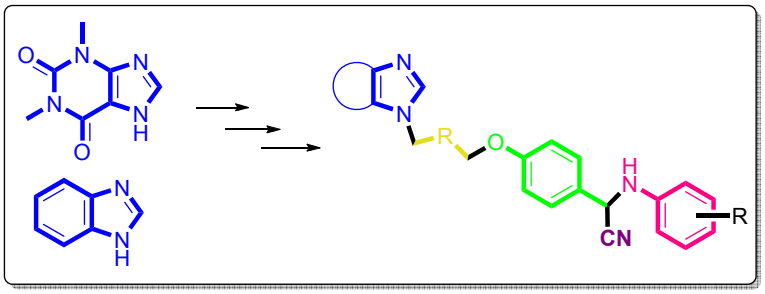
ABSTRACT.



An example of the Strecker reaction application in the synthesis of a new class of α-aminonitriles with benzimidazole and theophylline backbone has been developed. For the synthesis of these compounds, first, 4-hydroxybenzaldehyde was reacted with 1,3 and 1,5 dibromides/epibromohydrin to produce the corresponding bromo-substituted aldehydes. Then, benzimidazole/theophylline was reacted with the latter to generate the related benzimidazolic/theophyllinic aldehydes. Finally, the Strecker reactions of synthetic

benzimidazolic and theophyllinic aldehydes with different amines resulted in the production of target products.

INTRODUCTION

A large number of nitrile-containing compounds have been widely used as drugs for treatment of many diseases.[1] There is widespread interest on α-aminonitrile compounds due to their medical utilizations. Several α-aminonitriles have been developed as reversible inhibitors of dipeptidyl peptidase-4 (DPP-4) for treatment of diabetes.[2] The chemical structures of four important α-aminonitrile-based drugs are shown in Figure 1.

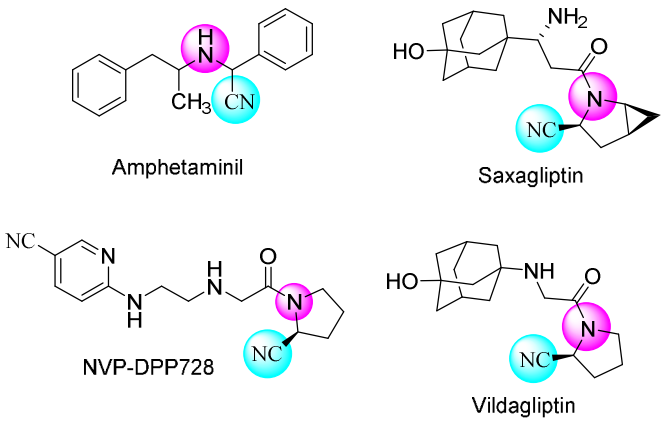


Figure 1. The chemical structure of some α-aminonitrile-based drugs

As a stimulant drug amphetaminil was used for the treatment of obesity and narcolepsy.[3] Saxagliptin, is a new anti-diabetic drug which classified as potent DPP-4 inhibitor drugs.[4] Also, NVP-DPP728 with a slow-binding inhibitory activity related to DPP-4 has been introduced as a new therapeutic approach for treatment of type 2 diabete.[5] Other most important DPP-4 inhibitor is vildagliptin which has been used as an efficient anti-diabetic drug in recent years.[6] Moreover, several α-aminonitrile products have been isolated from natural sources.[7]

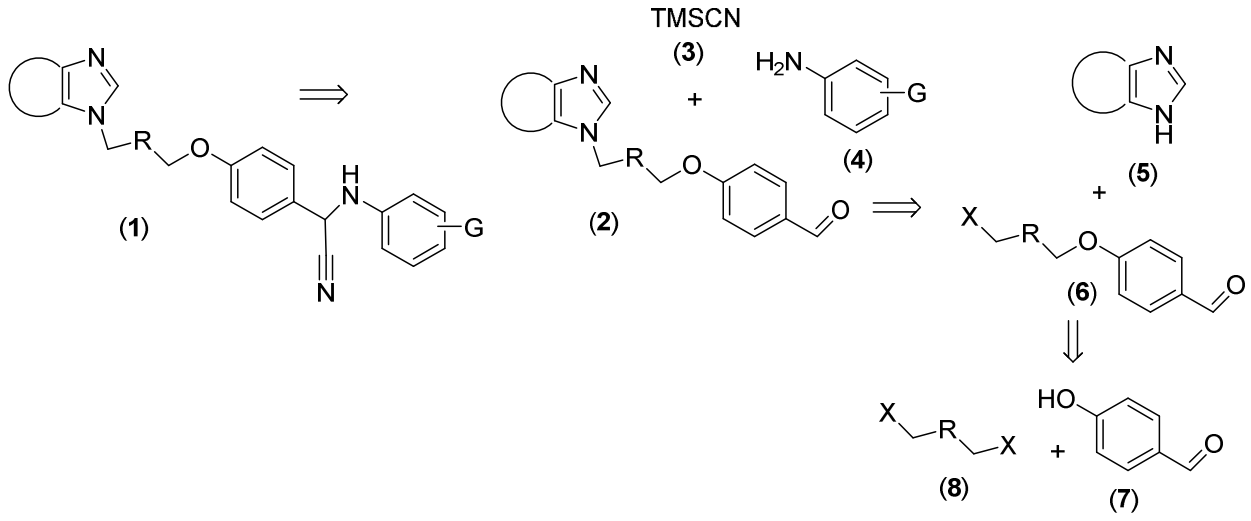
Accordingly, α-aminonitriles are important structural motifs in many biologically active molecules, pharmaceuticals and natural products. Thus, the development of efficient protocols to construct such moieties and synthesis of new α-aminonitriles are therefore of great importance to drug discovery.[8] One of the most important strategies for the synthesis of α-aminonitriles is the Strecker reaction, which was discovered in 1850. This reaction is the first multi-component reaction that involves the one-pot coupling reaction of an amine, an aldehyde, and hydrogen cyanide to afford α-aminonitriles.[9] Since, α-aminonitriles are precursors for the synthesis of α-amino acids and many of the materials, the Strecker reaction has clinical significance and for this reason several modifications of this reaction have been reported in the literature.[10] An efficient one-pot method has been developed for the synthesis of α-amino nitriles by combining aldehydes, amines, and trimethylsilyl cyanide (TMSCN).[11]

In the other hand, theophylline (naturally found in cocoa beans) has been used in therapeutic agents in treatment of diseases such as conic obstructive pulmonary and asthma. Several important drugs based on theophylline have been developed.[12] Also, benzimidazole is a recognized advantaged structure in medicinal chemistry, showing various biological activities.[13] There is a special interest towards synthesis of new benzimidazole derivatives due to their widespread biological and photophysical properties.

Along this line and in continuation of our previous studies on the synthesis of benzimidazole- and theophylline-based analogues,[13] herein, we report an efficient protocol for the synthesis of some novel α-aminonitriles with benzimidazole and theophylline backbones using the Strecker reaction as the key step.

RESULTS AND DISCUSSIONS

Our primary retrosynthetic approach for preparation of α-aminonitriles-based benzimidazole and theophylline compounds (**1**) is summarized in Scheme 1.

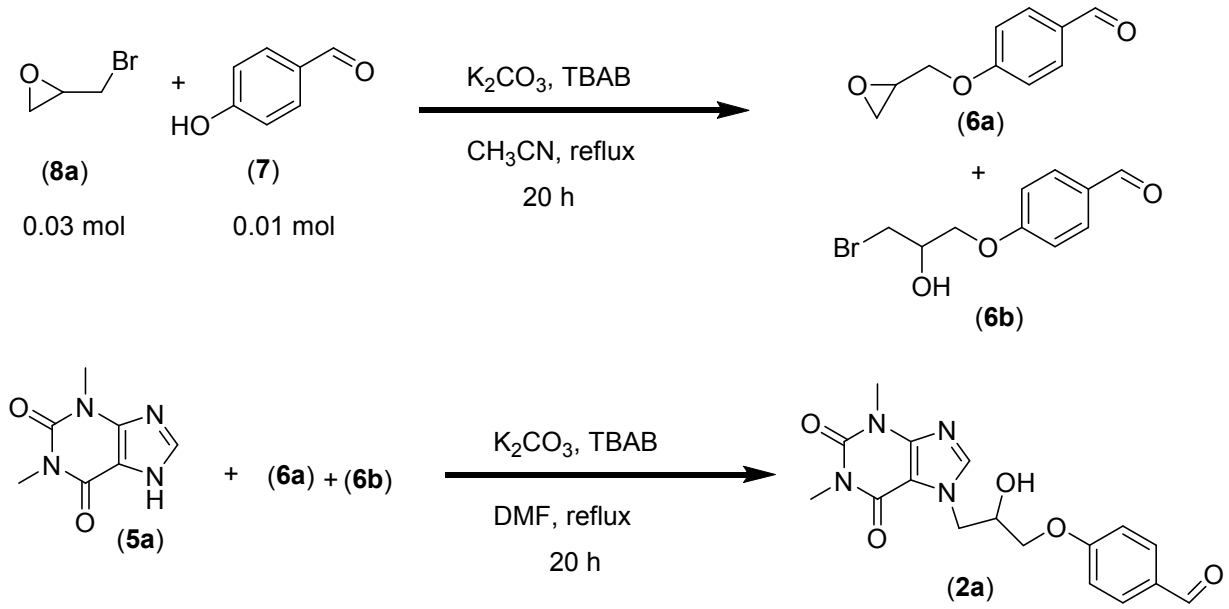


Scheme 1. Retrosynthetic analysis of the designed α-aminonitrile-based benzimidazole theophyllines

According to the retrosynthesis pathway which is shown in Scheme 1, the key intermediate is **2**. Thus, our study started with the production of compound **2**. This molecule (**2**), easily obtained from reaction of benzimidazole or theophylline (**5**) and aldehyde **6**. To prepare aldehyde **6**, 4-hydroxybenzaldehyde (**7**) was treated with epibromohydrin (**8a**)/1,3-dibromopropane (**8b**)/1,5-dibromopropane (**8c**), which gave the corresponding aldehydes (**6a-6d**) in high isolated yields.

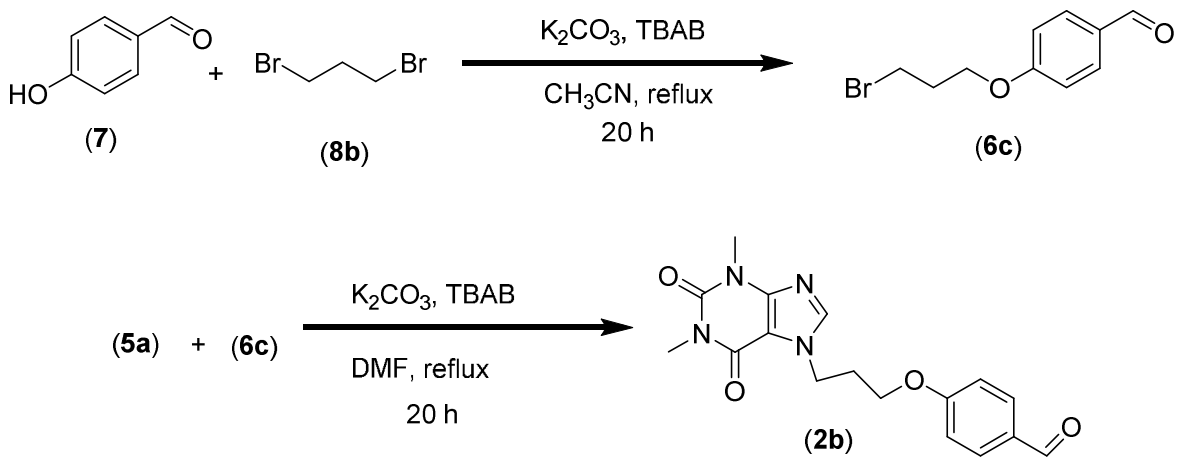
According to our synthetic approach, both products **6a** and **6b** are produced when theophylline was reacted with epibromohydrin. Thus, under the reaction conditions (K_2CO_3, TBAB, CH_3CN,

refux, 20 h), a mixture of **6a** and **6b** was generated. The resulting mixture, without purification was used for the next reaction with theophylline (**5a**) to synthesize aldehyde **2a** (Scheme 2).[14]



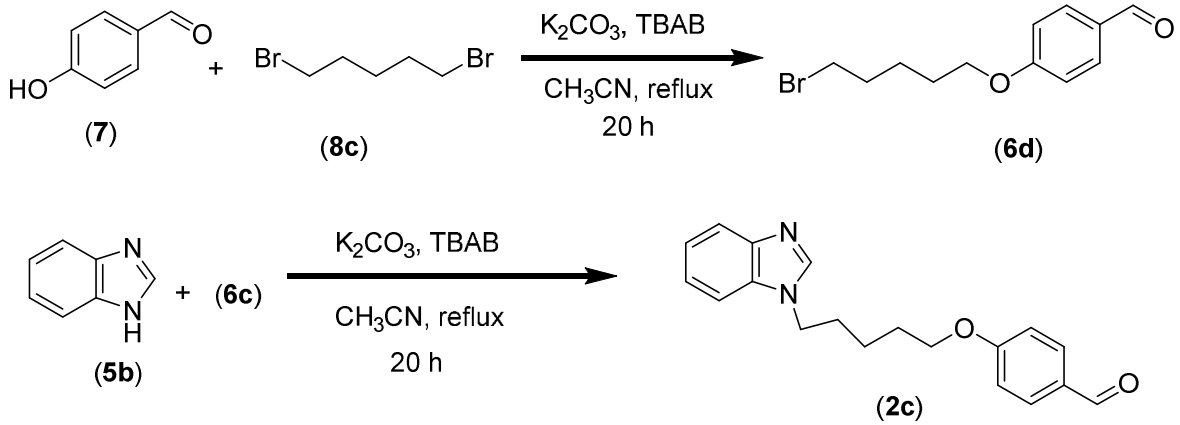
Scheme 2. Synthesis of the theophylline-based aldehyde **2a**

For synthesis of other theophylline-based aldehyde (**2b**), the following synthetic route was used. In the first step, 4-hydroxybenzaldehyde was reacted with 1,3-dibromopropane (**8b**) to produce 4-(3-bromopropoxy)benzaldehyde (**6c**). Then, addition of theophylline to **6c** resulted in the production of aldehyde **2b** in good yield (Scheme **3**).



Scheme 3. Synthesis route for the preparation of theophylline-based aldehyde **2b**

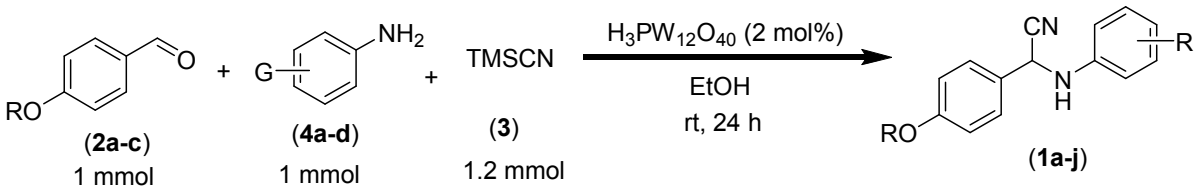
For synthesis of benzoxazole-based aldehyde (**2c**), first 4-hydroxybenzaldehyde was reacted with 1,5-dibromopropane (**8c**) to produce 4-((5-bromopentyl)oxy)benzaldehyde (**6d**) and then benzoxazole was treated with **6d** in order to produce aldehyde **2c** in good yield (Scheme 4).



Scheme 4. Synthesis route for the preparation of benzoxazole-based aldehyde **2c**

After preparation and characterization of the theophylline-based aldehyde **2a-c**, the Strecker reactions of these aldehydes with different amines were accomplished and a set of α-aminonitriles with benzoxazole/theophylline backbone were synthesized. Although the synthesis

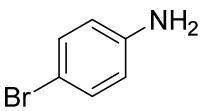
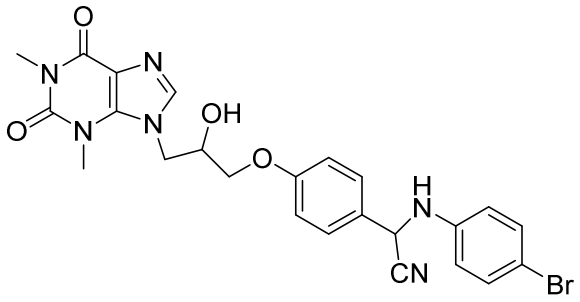
of α-aminonitriles has been widely developed previously we devised a modified procedure for the Strecker reaction of amines, aldehydes and TMSCN using tungstophosphoric acid ($H_3PW_{12}O_{40}$) as catalyst in EtOH solvent. To the best of our knowledge, up to now, there is no study on the preparation of α-aminonitriles using $H_3PW_{12}O_{40}$ as catalyst. Thus, we report an efficient method for the preparation of α-aminonitriles using the Strecker reaction in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ in EtOH at rt (Scheme 5). Our research group has widely used these optimized conditions in organic synthesis.[15] In this study, these conditions were found to be efficient for synthesis of α-aminonitriles using Strecker reaction under mild conditions.

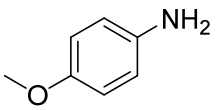
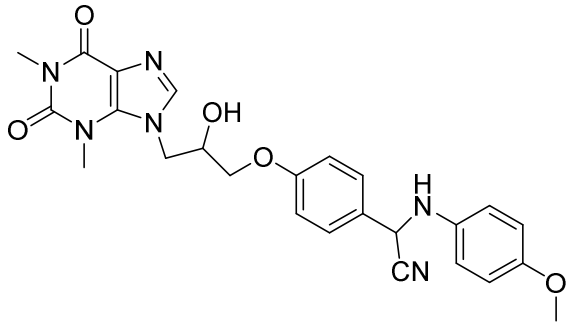
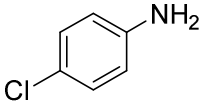
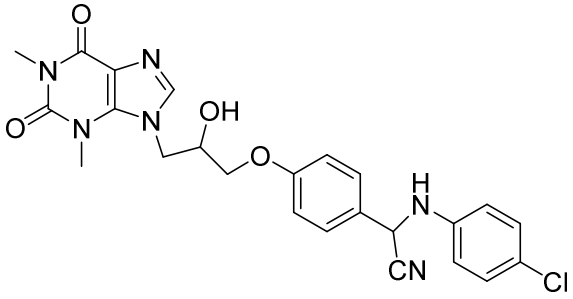
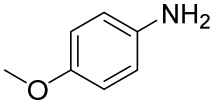
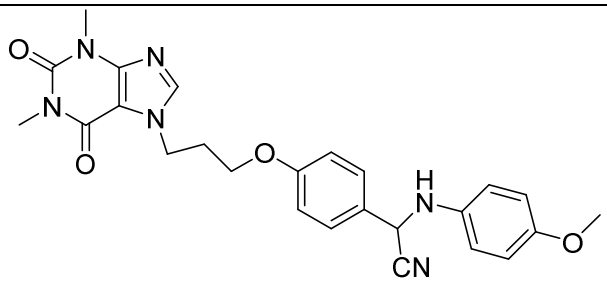
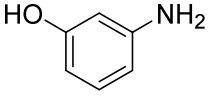
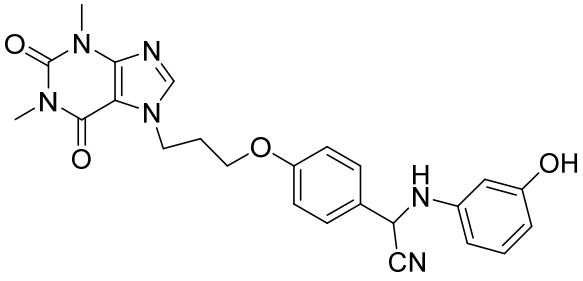
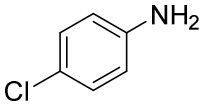
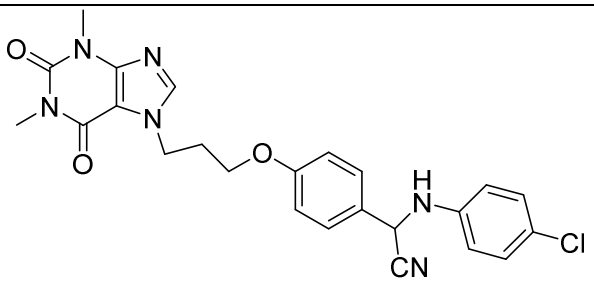


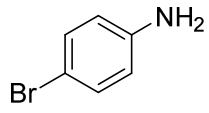
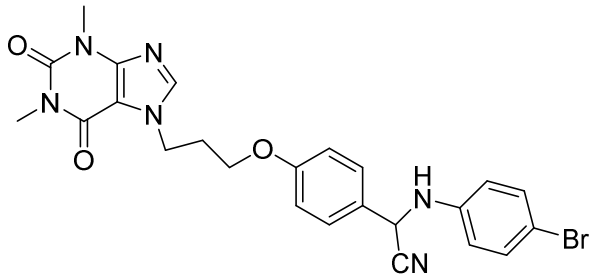
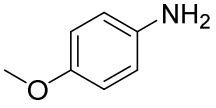
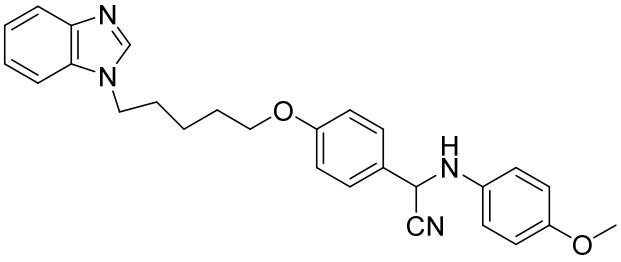
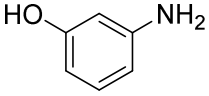
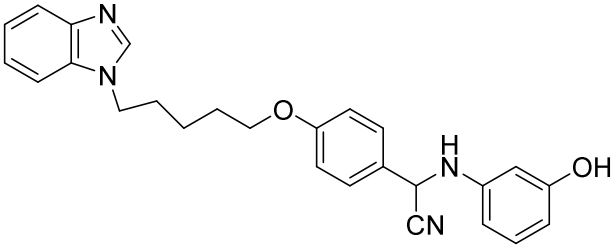
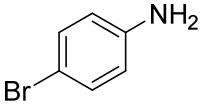
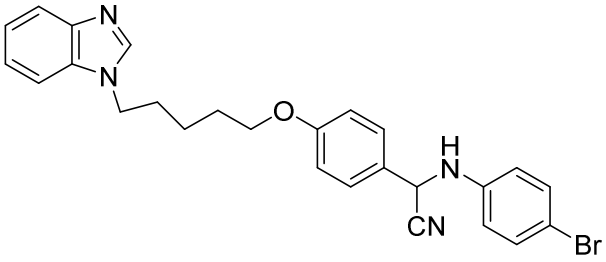
Scheme 5. Strecker synthesis of benzoxazole/theophylline-based α-aminonitriles **1a-j**

We synthesized α-aminonitriles **1a-j** using this procedure (Scheme 5) and results are summarized in Table 1.

Table 1. The Products of the Three-component Strecker Reactions of Aldehydes **2a-c**, TMSCN, and Amines[a]

Entry	Aldehyde & Amine	Product	Yield (%)[b]
1	**2a** & 	 **1a**	88

2	**2a** & 	 **1b**	90
3	**2a** & 	 **1c**	91
4	**2b** & 	 **1d**	94
5	**2b** & 	 **1e**	90
6	**2b** & 	 **1f**	90

7	**2b** & 	 **1g**	92
8	**2c** & 	 **1h**	92
9	**2c** & 	 **1i**	89
10	**2c** & 	 **1j**	92

[a] Reagents and conditions: aldehyde **2** (1 mmol), TMSCN (1.2 mmol), amine (1 mmol), $H_3PW_{12}O_{40}$ (0.04 g, 2 mol %), and EtOH (5 mL). [b] Isolated yields.

As shown in above, this is an efficient approach for the synthesis of divers benzimidazolic and theophyllinic α-aminonitriles based on three-component Strecker reactions of aldehydes, TMSCN, and amines. This facile protocol also can be applied to synthesize a wide range of α-aminonitriles by selecting the appropriate aldehydes and amines. As shown in Table 1, the

reaction was satisfactory accomplished for electron-withdrawing and electron-donating groups in amine component.

CONCLUSIONS

In summary, we have elaborated a three-step synthesis of new class of α-aminonitriles with benzimidazolic and theophyllinic backbones. In these syntheses, the formation of the bromo-substituted aldehydes (**6a**-**d**), and the subsequent reaction of **6a**-**d** with benzimidazole and theophylline yielded the related aldehydes **2a**-**c**. Finally, the acid-catalyzed Strecker reaction of different amines and pre-synthesized aldehydes **2a-c** with TMSCN led to the formation of the target molecules **1a**-**j** in good to excellent yields.

EXPERIMENTAL

General Experimental Details. All commercial reagents and solvents were used without further purification. Melting points were determined in open capillary tubes. FT-IR spectroscopy was employed for characterization of the synthesized compounds using film KBr pellet techniques. NMR spectra were acquired in DMSO-d_6 with tetramethylsilane (TMS) as the internal standard. The sample was analyzed by GC/MS for mass spectroscopy and micro-analyzer for elemental analyses. The reaction monitoring was accomplished by TLC on silica gel plates. Column chromatography was carried out on columns of silica gel 60 (70–230 mesh).

4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-2-hydroxypropoxy)benzaldehyde (2a)

Synthesis of **6a** and **6b**: In a double-necked round-bottomed flask (100 mL), equipped with a condenser, a mixture of the appropriate 4-hydroxylphenol (0.03 mol), K_2CO_3 (4.14 g, 0.03 mol),

epibromohydrin (4.92 g, 0.036 mol), and catalytic amounts of tetra butyl ammonium bromide (TBAB, 0.1 g) were dissolved in MeCN (40 mL). Then, the mixture was heated to reflux for 10 h (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in $CHCl_3$ (150 mL) and washed with H_2O (2 x 150 mL). The org. layer was dried (Na_2SO_4, 10 g) and concentrated to afford the crude product consisting of a mixture of 6a and 6b. The crude product was then used without any further purification for the synthesis of **2a** according to the procedure described below.

Synthesis of **2a**: In double-necked round bottom flask (100 mL) equipped with a condenser was added a mixture consisting of theophylline (0.01 mol, 1.8 g) K_2CO_3 (1.38 g, 0.01 mol), appropriate bromo alcohols (**6b**) & (**6a**) (0.015 mol), and catalytic amount of TBAB (0.1 g) in DMF (40 mL). The solution was refluxed until TLC monitoring indicated no further improvement in the reaction (8-10 hours). After cooling and solvent evaporation the resulted foam was dissolved in $CHCl_3$, (150 mL) and washed with water (2 x 200 mL). The organic layer was dried over anhydrous (Na_2SO_4) and evaporated. The crude was purified by column chromatography on silica gel eluting with proper solvent (mixture of *n*-hexane-EtOAc) (1:2) R_f = 0.5 the product was obtained in 70 % (2.5 g). IR (KBr): ν = 3207, 2851, 2365, 1682, 1640, 1737, 1590, 1354, 1157, cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm) 3.32(s, 3H), 3.51 (s, 3H), 4.00-4.06 (m, 2H), 4.38-4.44 (m, 2H),4.60-4.65(m, 1H), 693-7.79 (m, 5H), 8.06 (s, 1H), 9.80(s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm):28.12, 31,13, 80.1, 84.3, 107.1, 115.3, 122.0, 131.2, 142.3, 151.3, 154.2, 157.0, 160.2. Anal. Calcd. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63; Found: C, 57.07; H, 5.12; N, 15.71.

4-(3-bromopropoxy)benzaldehyde (6c)

In double-necked round bottom flask (100 mL) equipped with a condenser, a mixture, consisting of *p*-hydroxyl benzaldehyde (0.02 mol, 2.44 g), 1, 3-dibromopropane (0.06 mole), K_2CO_3 (2.76 g, 0.02 mole), and catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 10 hours. After cooling and solvent evaporation the resulted foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 x 150 mL). The organic layer was dried over anhydrous (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with proper solvent (mixture of *n*-hexane-EtOAc) (1:2) R_f = 0.6, this purification gave white solid in 80% (3.9 g). IR (KBr): ν = 3150, 2900, 2790, 1697, 1730, 1450, 1589, 1154, 1260,670, cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.13 (m, 2H), 3.50 (t, *J* = 5 Hz, 2H), 4.02 (t, *J* = 5 Hz, 2H), 7.20-7.80 (m, 4H), 9.87 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 29.9, 32.9, 67.0, 106.8, 114.4, 114.9, 122.0, 128.3, 132.0,190.2. Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Found: C, 49.48; H, 4.63.

4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propoxy)benzaldehyde (2b)

In double-necked round bottom flask (100 mL) equipped with a condenser, a mixture, consisting of 4-(3-bromopropoxy)benzaldehyde (0.01 mol, 2.43 g), theophylline (0.01 mol, 1.8 g), K_2CO_3 (1.38 g, 0.01 mol), and catalytic amount of TBAB (0.1 g) in DMF (50 mL) was refluxed for 10 hours. After cooling the solvent was evaporated under vacuum and then the resulted foam was dissolved in $CHCl_3$, (150 mL) and washed with water (3 x 150 mL). The organic layer was dried over anhydrous (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with proper solvent (mixture of *n*-

hexane-EtOAc) (1:2) R_f = 0.6 this purification gave white solid in 70% (2.4 g). IR (KBr): ν = 3217, 2854, 2360, 1672, 1640, 1735, 1590, 1350, 1150, cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.34-2.44 (m, 2H), 3.37 (s, 3H), 3.59 (s, 3H), 4.00 (t, *J* = 5 Hz, 2H), 4.48 (t, *J* = 5 Hz, 2H), 6.51-7.80 (m, 4H), 8.08 (s, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 29.0, 30.1, 30.7, 43.0, 64.1, 107.0, 114.9, 128.5, 131.9, 141.0, 148.4, 151.3, 154.8, 165.2, 191.0. Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; Found: C, 59.71; H, 5.35; N, 16.41.

4-((5-bromopentyl)oxy)benzaldehyde (6d)

In double-necked round bottom flask (100 mL) equipped with a condenser, a mixture, consisting of *p*-hydroxyl benzaldehyde (0.02 mol, 2.44 g), 1, 5-dibromopropane (0.06 mole), K_2CO_3 (2.76 g, 0.02 mole), and catalytic amount of tetra butyl ammonium bromide (TBAB, 0.1 g) in MeCN (50 mL) was refluxed for 10 hours. After cooling and solvent evaporation the resulted foam was dissolved in $CHCl_3$, (150 mL) and washed with water (3 x 150 mL). The organic layer was dried over anhydrous (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with proper solvent (mixture of *n*-hexane-EtOAc) (1:2) R_f = 0.7 this purification gave white solid in 75%. Yield: 75% (2.03g), white crystals,. IR (KBr): ν = 3155, 2920, 2795, 1690, 1735, 1450, 1581, 1250, 1150, 665, cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 1.55-1.61 (m, 2H), 1.81-1.97 (m, 4H), 3.62 (t, *J* = 5, 2H), 4.06 (t, *J* = 5, 2H),), 7.18-7.88(m, 4H), 9.86 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d6/TMS) δ (ppm): 24.0, 28.5, 32.9, 33.8, 68.7, , 114.2, 114.9, 130.2,190.6. Anal. Calcd. for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58; Found: C, 53.19; H, 5.62.

4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propoxy)benzaldehyde (2c)

In double-necked round bottom flask (100 mL) equipped with a condenser, a mixture, consisting of benzimidazole (0.01 mole, 1.18 g), performed compound **6d** (0.012 mol), K_2CO_3 (1.38 g, 0.01 mole), and catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 7 hours. After cooling and solvent evaporation the resulted foam was dissolved in $CHCl_3$, (150 mL) and washed with water (3 x 100 mL). The organic layer was dried over anhydrous (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with proper solvent (mixture of *n*-hexane-EtOAc) (1:1) $R_f = 0.7$ the white solid was obtained. Yield: 80% (2.15g), white crystals. IR (KBr): ν = 3125, 2910, 2815, 1690, 1737, 1450, 1581, 1256, 1115 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 1.58-1.64 (m, 2H), 1.83-1.97 (m, 4H), 3.99 (t, *J* = 5 Hz, 2H), 4.26 (t, *J* = 5 Hz, 2H),), 6.93-7.45(m, 4H), 8.27 (s, 1H) 9.87 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 23.3, 29.3, 29.6, 52.3, 66.7, 110.0, 114.9, 119.9, 123.0, 128.5, 131.9, 132.5, 143.8, 144.1, 165.2, 192.Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08; Found: C, 74.05; H, 6.58; N, 9.12.

General Producer for the synthesis of α-aminonitriles-based benzimidazole/theophylline compounds (1a-j)

A mixture of aldehyde (**2a-c**) (1mmol), aniline (1 mmol), TMSCN (1.2 mmol) and tungestophosphoric acid (0.04 g, 2 mol %) in EtOH (5mL) was stirred in room temperature for 24 hours. The completion of the reaction is confirmed by TLC (eluent/ EtOAc/ MeOH). Then, the precipitated product was filtered and washed with water (2 x 10 mL) and ethanol (10 mL) to afford the pure product.

2-((4-bromophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)acetonitrile (**1a**): Yield: 88% (0.47g), white crystals, mp: 186 ºC. IR

(KBR): ν = 3409, 2923, 2260, 1697, 1550, 1512, 1242, 946 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 3.32 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 4.00-4.06 (m, 4H, CH_2), 4.38-4.44 (m, 2H), 4.61 (s, 1H), 6.93-7.79 (m, 9H), 8.76 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4,114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: 538.12 (18, M^+). Anal. Calcd. for $C_{24}H_{23}BrN_6O_4$: C, 53.44; H, 4.30; N, 15.58; Found: C, 53.55; H, 4.27; N, 15.65.

2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**1b**): Yield: 90% (0.44g), white crystals, mp: 190 ºC. IR (KBr): ν = 3440, 3317, 2954, 2839, 1697, 1651, 1550, 1512, 1473, 1234, 1180, 825 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 3.32 (s, 3H), 3.51 (s, 3H), 3.82(s, 3H), 4.20-4.32 (m, 4H), 4.38-4.44 (m, 2H), 4.61(s, 1H), 7.20-7.65 (m, 10H), 8.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4,114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: 490.23 (15, M^+). Anal. Calcd. for $C_{25}H_{26}N_6O_5$: C, 61.22; H, 5.34; N, 17.13; Found: C, 61.30; H, 5.27; N, 17.20.

2-((4-chlorophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)-2-hydroxypropoxy)phenyl)acetonitrile (**1c**): Yield: 91% (0.45g), white crystals, mp: 190 ºC. IR (KBr): ν = 3442, 3317, 2950, 2837, 1692, 1651, 1550, 1514, 1473, 1234, 1180, 830 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 3.36 (s, 3H), 3.59 (s, 3H), 4.00-4.06 (m, 4H), 4.58-4.79 (m, 2H), 4.96(s, 1H), 6.93-7.79 (m, 10H), 8.58 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 27.9, 29.9, 30.0, 44.1, 55.4, 64.0, 70.5, 75.9, 106.8, 114.2, 114.4,114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.5. MS: 494.17 (19, M^+). Anal. Calcd. for $C_{24}H_{23}ClN_6O_4$: C, 58.24; H, 4.68; N, 16.98; Found: C, 58.35; H, 4.57; N, 17.01.

2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,4,5,6-hexahydro-9H-purin-9-yl)propoxy)phenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**1d**): Yield: 94% (0.44),white crystals, mp: 215 ºC. IR (KBr): ν = 3375, 2881, 2356, 1689, 1649, 1612, 1550, 1342, 1288, 1249, 1184, 1817, 769 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.34-2.44 (m, 2H), 3.34 (s, 3H), 3.53 (s, 3H), 3.74 (s, 3H), 3.97 (t, *J* = 5.0 Hz, 2H), 4.46 (t, *J* = 5.0 Hz, 2H), 4.85 (s, 1H), 6.85-7.84 (m, 9H), 8.39 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 27.9, 29.7, 29.9, 30.0, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: 474.21 (12, M^+). Anal. Calcd. for $C_{25}H_{26}N_6O_4$: C, 63.28; H, 5.52; N, 17.71; Found: C, 63.36; H, 5.57; N, 17.79.

2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propoxy)phenyl)-2-((3-hydroxyphenyl)amino)acetonitrile (**1e**): Yield: 90% (0.41g), white crystals, mp 175 ºC. IR (KBr): ν = 3379, 2885, 2360, 1697, 1651, 1612, 1550, 1342, 1288, 1249, 1180, 1817, 763 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.31-2.45 (m, 2H), 3.48 (s, 3H), 3.54 (s, 3H), 4.00 (t, *J* = 5 Hz, 2H), 4.48 (t, *J* = 5 Hz, 2H), 4.85 (s, 1H), 5.10 (s, 1H), 6.91-7.84 (m, 10H), 8.14 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 27.6, 29.5, 29.9, 30.9, 44.1, 53.6, 64.0, 68.2, 106.8, 114.2, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 174.8, 179.1. MS: 460.17 (15, M^+). Anal. Calcd. for $C_{24}H_{24}N_6O_4$: C, 62.60; H, 5.25; N, 18.25; Found: C, 62.68; H, 5.29; N, 18.31.

2-((4-chlorophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propoxy)phenyl)acetonitrile (**1f**): Yield: 90% (0.43g), white crystals, mp: 250 ºC. IR (KBr): ν = 3369, 2889, 2364, 1687, 1652, 1618, 1557, 1345, 1289, 1259, 1180, 1827, 768 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.34-2.44 (m, 2H), 3.24 (s, 3H), 3.46 (s, 3H), 3.94 (t, *J* = 7.5 Hz, 2H), 4.46 (t, *J* = 7.5, 2H), 4.81 (s, 1H), 6.60-7.83 (m, 10H), 8.05 (s, 1H). ^{13}C NMR (62.5

MHz, DMSO-d_6/TMS) δ (ppm): 27.4, 29.8, 29.9, 30.0, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 166.5, 174.8. MS: 478.18 (11, M^+). Anal. Calcd. for $C_{24}H_{23}ClN_6O_3$: C, 60.19; H, 4.84; N, 17.55; Found: C, 60.19; H, 4.84; N, 17.55.

2-((4-bromophenyl)amino)-2-(4-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propoxy)phenyl)acetonitrile (**1g**): Yield: 92% (0.48g),white crystals, mp: 175 ºC. IR (KBr): ν = 3317, 2954, 2360, 1697, 1651, 1589, 1542, 1512, 1404, 1242, 1180, 1072, 825 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 2.28-2.33 (m, 2H), 3.34 (s, 3H), 3.53 (s, 3H), 3.97 (t, *J* = 5, 2H), 4.46 (t, *J* = 5, 2H), 4.95 (s, 1H), 5.34 (s, 1H), 673-7.45 (m, 10H), 8.04 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d6/TMS) δ (ppm): 27.0, 29.5, 29.9, 30.9, 36.8, 44.2, 55.4, 64.0, 106.8, 114.2, 114.4, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6, 174.8, 179.1. MS: 522.12 (9, M^+). Anal. Calcd. for $C_{24}H_{23}BrN_6O_3$: C, 55.08; H, 4.43; N, 16.06; Found: C, 55.12; H, 4.48; N, 16.14.

2-(4-((5-(1H-benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**1h**): Yield: 92%(0.40g), white crystals, mp: 200 ºC. IR (KBr): ν = 3440, 3139, 2923, 2351, 1604, 1512, 1249, 108, 817 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 1.69-1.84 (m, 6H), 3.75 (s, 3H), 3.97 (t, *J* = 5.0 Hz, 2H), 4.46 (t, *J* = 5.0 Hz, 2H), 4.81 (s, 1H), 4.95 (s, 1H), 6.95-7.78 (m, 12H), 8.81 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 22.5, 28.0, 28.7, 44.8, 48.5, 67.41, 111.5, 114.3, 114.4, 114.5, 114.7, 115.3, 117.5, 119.9, 122.5, 123.3, 123.7, 128.5, 130.1, 132.5, 138.2, 139.7, 142.8, 152.2, 158.7, 161.0. MS: 440.20 (19, M^+). Anal. Calcd. for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72; Found: C, 73.68; H, 6.46; N, 12.79.

2-(4-((5-(1H-benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((3-hydroxyphenyl)amino)acetonitrile (**1i**): Yield: 94% (0.40g), white crystals, mp 230 ºC. IR (KBr): ν = 3446, 3134, 2927, 2361, 1608, 1522, 1249, 1108, 820 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 1.51-2.04 (m, 6H), 3.97 (t, *J* = 5.0 Hz, 2H), 4.46 (t, *J* = 5.0 2H), 4.90 (s, 1H), 5.15 (s, 1H), 6.73-7.67 (m, 12H); 8.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 22.5, 28.0, 28.7, 44.8, 48.5, 67.41, 111.5, 114.3, 114.4, 114.5, 114.7, 115.3, 117.5, 122.1, 123.3, 128.5, 130.1,131.7, 132.5, 138.2, 139.7, 142.8, 161.0. MS: 426.22 (17, M^+). Anal. Calcd. for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14; Found: C, 73.31; H, 6.21; N, 13.20.

2-(4-((5-(1H-benzo[d]imidazol-1-yl)pentyl)oxy)phenyl)-2-((4-bromophenyl)amino)acetonitrile (**1j**): Yield: 91% (0.44), white crystals, mp 156 ºC. IR (KBr): ν = 3438, 3136, 2925, 2349, 1614, 1518, 1259, 1108, 827 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS) δ (ppm): 1.69-1.84 (m, 6H), 3.98 (t, *J* = 5.0, 2H), 4.48 (t, *J* = 5.0 Hz, 2H), 4.89 (s, 1H), 5.84 (s, 1H), 6.73-7.67 (m, 12H), 8.33 (s, 1H). ^{13}CNMR (62.5 MHz, DMSO-d_6/TMS) δ (ppm): 27.9, 29.7, 29.9, 44.1, 55.4, 64.0, 106.8, 114.2, 114.4, 114.5, 122.0, 130.2, 132.0, 141.4, 144.9, 145.0, 149.0, 155.0, 157.5, 157.9, 160.6. MS: 488.14 (14, M^+). Anal. Calcd. for $C_{26}H_{25}BrN_4O$: C, 63.81; H, 5.15; N, 11.45; Found: C, 63.88; H, 5.19; N, 11.50.

ASSOCIATED CONTENT

Supporting Information. Copies of ^1H, ^{13}C NMR for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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