Synthesis and Antimicrobial Activity of Novel Analogs of Trifenagrel

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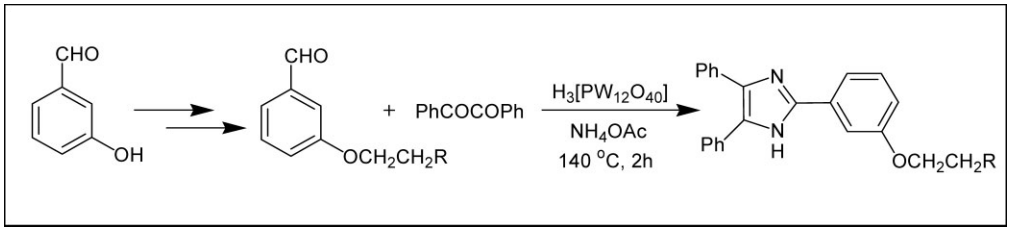

Novel analogs of trifenagrel were synthesized by using inexpensive and reusable phosphotungstic acid, $H_3[PW_{12}O_{40}]$ (3 mol %) catalyst under classical heating. Two of the newly synthesized triaryl imidazoles exhibited moderate antibacterial activity.

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INTRODUCTION

In 1858, Debus [1] reported the reaction between glyoxal and ammonia and this reaction pioneered a novel synthetic route to imidazole. Subsequently imidazoles have received significant attention because of their synthesis, reactions, and biochemical properties [2]. The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles. Even today, research in imidazole chemistry continues unabated because compounds containing an imidazole moiety have biological and pharmaceutical importance.

Synthesizing analogs of biologically active molecules is part of the drug discovery process and is a basic application of synthetic organic chemistry. One such pharmacologically potent 2,4,5-triaryl imidazole is trifenagrel (**1**) (Fig. 1) that inhibits both arachidonate and collagen induced aggregation of platelets with equal or greater potency (5–12 fold) than indomethacin and aspirin, without exhibiting the gastric damage associated with these typical cyclogenase inhibitors [3]. The potential of trifenagrel (as an antithrombic compound) rekindled an interest in us to synthesize its analogs for detailed structural activity relationship studies, efficient lead structure identification, and optimization in a drug discovery program.

Trifenagrel was first synthesized by Phillips *et al*. [4], by reaction of 2-(2-dimethylaminoethoxy) benzaldehyde, benzil, and ammonium acetate using glacial acetic acid as solvent under reflux condition. Later Wolkenberg *et al*. [5] reported the same reaction under microwave irradiation. The synthetic methods proposed for trifenagrel have limitations of harsh reaction conditions and use of polar solvent (acetic acid) leading to complex isolation and recovery procedures. Therefore, there is merit in using a nonsophisticated, recoverable, and reusable catalyst for the synthesis of analogs of trifenagrel.

In recent years, heteropoly acids (HPAs) have proved to be good catalysts in one-pot multicomponent construction of heterocyclic compounds. HPAs have a very strong Bronsted acidity and are efficient oxidants, exhibiting fast reversible multielectron redox transformations under mild conditions. HPAs are useful as catalysts because of the following unique characteristics: (a) catalytic performance, (b) chemical and physical properties, (c) molecular and bulk composition, and (d) method of synthesis of the catalyst [6]. One such mild HPA is phosphotungstic acid (PTA), $H_3[PW_{12}O_{40}]$ which has emerged as a powerful catalyst in recent years due to economic and environmental considerations. Recently, Heravi *et al*. [7] reported synthesis of tetrasubstituted imidazoles using HPAs as green and reusable catalysts. Therefore, we decided to investigate its catalytic activity for synthesis of novel triaryl imidazoles. In continuation of our work [8,9] in exploring applications of HPAs in fine organic chemistry, we have developed a method for solvent free synthesis of novel analogs of trifenagrel by using inexpensive and reusable PTA, $H_3[PW_{12}O_{40}]$ (3.0 mol %) catalyst under classical heating in a highly efficient manner.

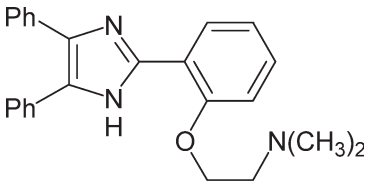

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Figure 1. Trifenagrel.

RESULTS AND DISCUSSION

As a starting point of our study, we have selected 3-hydroxybenzaldehyde (**2**) and allowed it to react with 1,2-dibromoethane in the presence of 6*N* NaOH to give 3-(2-bromoethoxy) benzaldehyde (**3**) with 62% yield (Scheme 1). The formation of compound (**3**) was evident from the ^{1}H NMR by the appearance of aliphatic protons at δ 3.58 and δ 4.24 as triplets. Compound (**3**) was then treated with dimethylamine in the presence of methanol to afford compound (**4a**) in 90% yield. In the ^{1}H NMR spectrum of compound (**4a**) characteristic methyl protons appeared as a singlet at δ 2.90.

Similarly two more amine derivatives (**4b, 4c**) were prepared from compound (**3**). 3-(2-Piperidinoethoxy) benzaldehyde (**4a**) was obtained in 66% yield by the reaction of piperidine with compound (**3**). In the ^{1}H NMR spectrum of compound (**4b**), the aliphatic protons of piperidine appeared at δ 1.45 as multiplet and at δ 3.48 as triplet, respectively. In an identical manner, compound (**4c**) was prepared in 73% yield and ^{1}H NMR spectrum of this compound showed two triplets at δ 2.45 and δ 3.68.

The three-component condensation of benzil (**5**), aldehydes (**4a–c**), and ammonium acetate in the presence of 3 mol % of PTA gave trisubstituted imidazoles (**6a–c**) (Scheme 1). The compound (**6a**) was characterized from mass spectrum (ESI) by the appearance of $[M + H]^+$ peak at *m*/*z* 384 and from ^{1}H NMR by the appearance of increased aromatic protons at δ 7.22–7.60 and the absence of CHO proton at δ 10.01. Similarly the compounds (**6b, 6c**) were synthesized and their spectroscopic features fully supported the assigned structures.

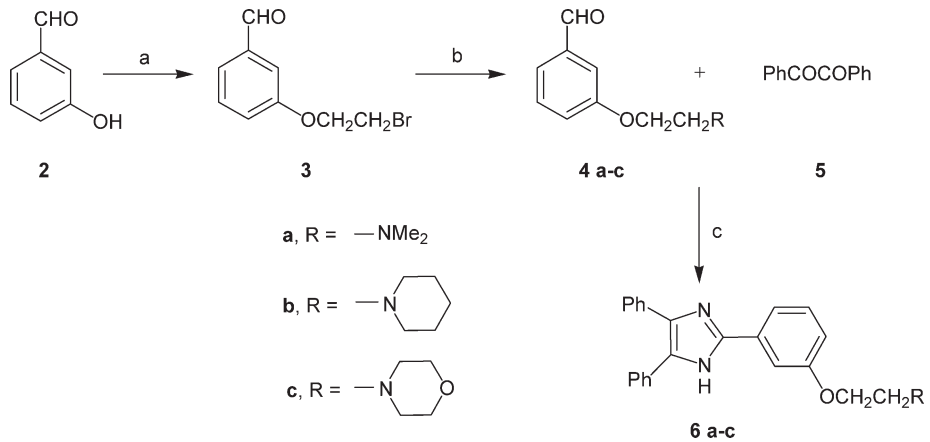
The scope of the reaction was further extended for the preparation of 4-hydroxybenzaldehyde (**7**) and vanillin (**8**) derived analogs of trifenagrel. Thus, compounds (**7** and **8**) on reaction with 1,2-dibromoethane in the presence of 6*N* NaOH provided the compounds (**9** and **10**), respectively. The formation of compounds (**9** and **10**) was evident from the appearance of $[M + H]^+$ peak at *m*/*z* 230 and 250 in mass spectrum (ESI) respectively, —C=O stretching of aldehyde at 1684 and 1680 cm^{-1} respectively in IR and the appearance of methylene protons as triplets at δ 3.66 and δ 4.36 respectively in ^{1}H NMR of both the compounds (**9** and **10**).

Compounds (**9** and **10**) were then treated with dimethylamine in the presence of methanol to afford compounds (**11a** and **11b**) as liquids in excellent yield (Scheme 2). The formation of the compound (**11a** and **11b**) was evident by the appearance of $[M + H]^+$ peak at *m*/*z* 193 and 224 respectively in the mass spectrum (ESI), —C=O stretching of aldehyde at 1690 and 1682 cm^{-1} in IR and by the appearance of a singlet at δ 2.33 and δ 2.32 respectively in ^{1}H NMR spectra corresponding to methyl protons of amine.

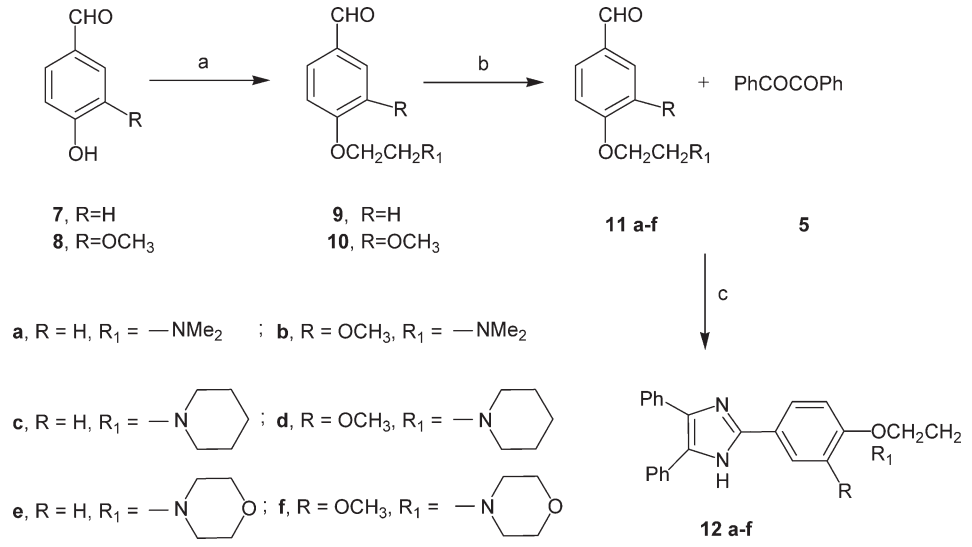
In a similar way two more derivatives for each (**11c, 11d, 11e,** and **11f**) were synthesized and their spectroscopic features fully supported its assigned structure.

The three-component condensation of benzil (**5**), aldehydes (**11a–f**), and ammonium acetate in the presence of 3 mol % of PTA gave trisubstituted imidazoles (**12a–f**) (Scheme 2). The compound (**12a**) was characterized

Scheme 1. Reagents and conditions: (a) $BrCH_2CH_2Br$, 6N NaOH (b) amine, MeOH (c) PTA (3.0 mol %), NH_4OAc, 2h.



Scheme 2. Reagents and conditions: (a) $BrCH_2CH_2Br$, 6N NaOH (b) amine, MeOH (c) PTA (3 mol %), NH_4OAc, 2h.



from mass spectrum (ESI) by the appearance of $[M + H]^+$ peak at *m/z* 384, IR by the appearance of —NH band at 3058 cm^{-1} and from ^1H NMR by the appearance of increased aromatic protons at δ 7.30–7.90 and the absence of CHO proton at δ 9.93. Similarly the compounds **(11b-f)** were synthesized and their spectroscopic data are in agreement with the assigned structures.

All the newly synthesized compounds **6a–c** and **12a–f** were screened for antibacterial and antifungal activities [10]. All the compounds were active against Gram-negative and Gram-positive bacteria. Among the screened compounds, **12a** showed good activity against Gram-negative and Gram-positive bacteria. Compounds **12a** and **12b** exhibited moderate activity against *Bacillus subtilis* (Table 1).

All the compounds were screened for antifungal activity against *Sacchromyces cerevisiae*, *Aspergillus niger*, *Rhizopus oryzae*, and *Candida albicans* by agar cup diffusion method [11] using Amphotericin-B as standard. All the compounds showed mild antifungal activity.

In summary, novel analogs of trifenagrel were synthesized by using inexpensive and reusable PTA, $H_3[PW_{12}O_{40}]$ catalyst under classical heating and screened for antibacterial and antifungal activities. Compounds **12a** and **12b** showed moderate antibacterial activity.

EXPERIMENTAL

Melting points were measured with Fiescher-Johns melting point apparatus. ^1H NMR spectra were recorded with an AVANCE 300 Bruker (at 300 MHz) and Gemini 200 MHz

Table 1

Antibacterial activies as MIC (μg/mL) for **6a–c** and **12a–f**.

	Gram-positive organisms			Gram-negative organisms		
Compound no.	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeroginosa*	*K. pneumoniae*
6a	150	150	150	150	150	150
6b	75	150	150	75	150	150
6c	150	150	150	150	150	150
12a	18.75	37.5	37.5	150	37.5	37.5
12b	75	75	150	150	150	150
12c	150	150	150	150	150	150
12d	37.5	37.5	75	150	75	75
12e	150	150	150	150	150	150
12f	150	150	150	150	150	150
Streptomycin	6.25	1.562	1.562	2.35	3.125	3.125
Pencillin	1.526	6.25	3.125	7.81	12.5	6.25

spectrometers in $CDCl_3$. Chemical shifts relative to TMS as internal standard are given as δ values in ppm. ^{13}C NMR was recorded in $CDCl_3$ on a Varian (75 Hz) spectrometer. IR spectra were taken with a Perkin-Elmer 1725A FT-IR spectrophotometer. EI-MS mass spectra were measured at 70 eV (EI).

3-(2-Bromoethoxy)-benzaldehyde (3). A mixture of 3-hydroxybenzaldehyde (6.20 g, 50.8 mmol), 1,2-dibromoethane (38.14 g, 203 mmol), and methanol (50 mL) were heated to reflux. Then, 6*N* NaOH (10 mL) was added in 1.0 mL portions with 30 min intervals. After 18 h of stirring at reflux, the methanol was removed on rotary evaporator. Water (25 mL) was added to the residue and the mixture was extracted into ether (2 × 25 mL). The ethereal extracts were combined and washed with 6*N* NaOH (2 × 10 mL). Again ether layer was separated, dried over Na_2SO_4, concentrated to obtain crude product as brown syrup which was chromatographed over silica gel (60–120 mesh) using hexane:ethyl acetate (8:2) as eluent to obtain titled compound (7.21 g, 62%) (**3**) as brown liquid. IR (Neat): ν 3448, 1695, 1258 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, 2H, —CH_2), 4.24 (t, 2H, —CH_2), 7.03–7.15 (m, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.32–7.43 (m, 2H, Ar-H), 9.89 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.77, 67.78, 112.81, 121.65, 123.73, 129.97, 137.54, 158.39, 191.61. EI-MS: *m*/*z* 229 $[M]^+$. Anal.Cacld. for: $C_9H_9O_2Br$: C, 47.19; H, 3.95. Found: C, 47.02; H, 3.98.

3-(2-Dimethylaminoethoxy)benzaldehyde (4a). A mixture of 3-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.36 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) was stirred at room temperature for 60 h. After completion of the reaction, methanol was removed on rotary evaporator to obtain the titled compound (**4a**) (0.75 g, 90%) as pale yellow solid. mp: 175–177°C, IR (KBr): ν 3423, 2958, 1679 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.90 (s, 6H, 2 × CH_3), 3.58 (t, 2H, —CH_2), 4.44 (t, 2H, —CH_2), 7.30–7.40 (m, 1H, Ar-H), 7.48–7.53 (m, 1H, Ar-H), 7.60–7.63 (m, 2H, Ar-H), 10.01 (s, 1H, —CHO), ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.68, 55.17, 62.31, 113.61, 121.44, 123.30, 130.39, 137.49, 157.91, 192.76. EI-MS: *m*/*z* 193 $[M]^+$. Anal. Cacld. for: $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.33; H, 7.89.

2-(3-[2-Dimethylaminoethoxy) phenyl]-4,5-diphenylimidazole (6a). A mixture of benzil (0.42 g, 2.0 mmol), 3-(2-dimethylaminoethoxy) benzaldehyde (0.42 g, 2.0 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) was heated at 140°C for 2 h. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with acetone (20 mL). Reaction mixture was filtered to remove catalyst and the filtrate was concentrated on rotary evaporator to syrup. Basification (of the syrup) with ammonium hydroxide (4 mL) resulted in separation of solid, which was collected by filtration *in vacuo* to obtain the titled compound (0.66 g, 86%) (**6a**) as white solid. mp: 182–183°C, IR (KBr): ν 3423, 2928, 1594, 1461 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.38 (s, 6H, 2 × CH_3), 2.80 (t, 2H, —CH_2), 4.17 (t, 2H, —CH_2), 6.72–6.81 (m, 1H, Ar-H), 7.22–7.40 (m, 7H, Ar-H), 7.55–7.60 (m, 4H, Ar-H), 7.65–7.72 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.26, 57.45, 65.57, 110.95, 114.57, 117.71, 125.21, 127.10, 127.65, 128.37, 129.76, 131.61, 135.11, 145.33, 158.69. ESI-MS: *m*/*z* 384 $[M + H]^+$. Anal. Cacld. for: $C_{25}H_{25}N_30$: C, 78.30; H, 6.57. Found: C, 78.36; H, 6.51.

3-(2-Piperidinoethoxy)benzaldehyde (4b). A mixture of 3-(2-bromoethoxy)-benzaldehyde (1.50 g, 6.55 mmol), piperidine (1.55 g, 18.2 mmol), and methanol (15 mL) was refluxed for 3 h. After completion of the reaction, methanol was removed on rotary evaporator and to the resulting residue 4*N* NaOH (10 mL) was added and stirred for 10 min. Then reaction mixture was extracted into ether (3 × 25 mL) and the combined ethereal phases were extracted into 4*N* HCl (2 × 10 mL) and water (2 × 10 mL). The combined HCl and water extracts were basified with 8*N* NaOH (20 mL) and extracted into ether (2 × 25 mL). The ethereal extracts were washed with water (2 × 50 mL). Organic phase was separated, dried over Na_2SO_4, concentrated to obtain the titled compound (**4b**) (1.0 g, 66%) as brown syrup. IR (Neat): ν 3422, 2932, 1697, 1262 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.63 (m, 6H, 3 × —CH_2), 2.48 (t, 4H, 2 × —CH_2), 2.74 (t, 2H, —CH_2), 4.14 (t, 2H, —CH_2), 6.95–6.98 (m, 1H, Ar-H), 7.77–7.81 (m, 3H, Ar-H), 9.85 (s, 1H, —CHO). ESI-MS: *m*/*z* 234 $[M + H]^+$. Anal. Cacld. for: $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 72.02; H, 8.01.

2-(3-[2-(Piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (6b). Prepared following the procedure described for (**6a**) using benzil (0.42 g, 2.0 mmol), 3-(2-piperidinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) to obtain the titled compound (**6b**) (0.70 g, 83%) as brown solid. mp: 142–145°C, IR (Neat): ν 3421, 2923, 1026 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.47–1.53 (m, 2H, —CH_2), 1.66–1.71 (m, 4H, 2 × —CH_2), 2.63–2.72 (m, 2H, —CH_2), 2.90 (t, 2H, —CH_2), 4.27 (t, 2H, —CH_2), 6.78 (d, 2H, Ar-H), 7.18–7.30 (m, 5H, Ar-H), 7.53–7.56 (d, J = 6.98 Hz, 4H, Ar-H), 7.64–7.67 (m, 2H, Ar-H), 7.84 (m, 1H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 125.73, 125.95, 126.58, 127.40, 127.68, 127.79, 128.10, 128.25, 128.37, 130.01,135.93, 144.91, 145.43, 159.26. ESI-MS: *m*/*z* 424 $[M + H]^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O$: C, 79.40; H, 6.89. Found: C, 79.48; H, 6.94.

3-(2-Morpholinoethoxy)-benzaldehyde (4c). Prepared following the procedure described for (**4b**) using 3-(2-bromoethoxy)-benzaldehyde (2.50 g, 10.9 mmol), morpholine (2.62 g, 30.1 mmol), and methanol (25 mL) to obtain the titled compound (**4c**) (1.88 g, 73%) as brown syrup. IR (Neat): ν 3446, 1696,1263 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (t, 4H, 2 × —CH_2), 2.78 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.14 (t, 2H, —CH_2), 7.12–7.17 (m, 1H, Ar-H), 7.26 (m, 1H, Ar-H), 7.40–7.43 (m, 2H, Ar-H), 9.94 (s, 1H, —CHO). ESI-MS: *m*/*z* 236 $[M + H]^+$. Anal. Cacld. for: $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.30.

2-(3-[2-(Morpholino)ethoxy)phenyl]-4,5-diphenylimidazole (6c). Prepared following the procedure described for (**6a**) using benzil (0.42 g, 2.0 mmol), 3-(2-morpholinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), and PTA (0.1 g, 3 mol %) to obtain the titled compound (**6c**) (0.68 g, 81%) as pale brown solid. mp: 218–219°C, IR (Neat): ν 3422, 1654, 1026 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.58 (t, 4H, 2 × —CH_2), 2.79 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.18 (t, 2H, —CH_2), 6.81–6.86 (m, 1H, Ar-H), 7.15–7.70 (m, 13H, Ar-H), 12.26 (brs, 1H, —NH), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 52.62, 56.16, 65.29, 76.99, 109.80, 113.45, 116.65, 126.94, 128.25, 136.49, 144.56, 157.58. ESI-MS: *m*/*z* 426 $[M + H]^+$.

Anal. Cacld. for: $C_{27}H_{27}N_3O_2$: C, 76.28; H, 6.31. Found: C, 76.28; H, 6.31.

4-(2-Bromoethoxy) benzaldehyde (9). Prepared following the procedure described for (**3**) using 4-hydroxybenzaldehyde (6.20 g, 50.8 mmol), 1,2-dibromoethane (38.14 g, 203 mmol), and methanol (50 mL) to obtain the titled compound (7.55 g, 65%) (**9**) as white solid. mp: 55–58°C, IR (KBr): ν 3349, 2927, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (t, 2H, —CH_2), 4.36 (t, 2H, —CH_2), 7.00 (d, J = 9.06 Hz, 2H, Ar-H), 7.81 (d, J = 8.30 Hz, 2H, Ar-H), 9.82 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.59, 29.66, 67.98, 76.72, 77.14, 77.57, 114.90, 130.47, 131.98, 163.00, 190.63. EI-MS: m/z 229 $[M]^+$. Anal. Cacld. for: $C_9H_9O_2Br$: C, 47.19; H, 3.95. Found: C, 47.10; H, 4.01.

4-(2-Dimethylaminoethoxy)benzaldehyde (11a). Prepared following the procedure described for (**4a**) using 4-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.36 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) to obtain the title compound (0.77 g, 92%) (**11a**) as brown liquid. IR (Neat): υ 3437, 1690, 1600 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H, 2 × CH_3), 2.78 (t, 2H, —CH_2), 4.16 (t, 2H, —CH_2), 6.99–6.94 (m, 2H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 9.80 (s, 1H, —CHO). EI-MS: m/z 193 $[M]^+$. Anal. Cacld. for: $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.41; H, 7.80.

2-(4-[2-Dimethylaminoethoxy)phenyl]-4,5-diphenylimidazole (12a). Prepared following the procedure described for (**6a**) using benzil (0.14 g, 0.67 mmol), 4-(2-dimethylaminoethoxy) benzaldehyde (0.15 g, 0.77 mmol), ammonium acetate (0.18 g, 2.30 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (0.22 g, 89%) (**12a**) as brown solid. mp: 120–125°C, IR (Neat): ν 3058, 2928, 1494, 1245 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.32 (s, 6H, 2 × CH_3), 2.72 (t, 2H, —CH_2), 4.08 (t, 2H, —CH_2), 6.90 (d, J = 6.86 Hz, 3H, Ar-H), 7.24–7.28 (m, 5H, Ar-H), 7.54 (d, J = 7.55 Hz, 4H, Ar-H), 7.98 (d, J = 10.98 Hz, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 21.81, 44.77, 64.77, 122.85, 125.64, 113.93, 126.46, 127.61, 127.37, 127.92, 128.04,129.77, 132.71, 145.73, 158.11. ESI-MS: m/z 384 $[M + H]^+$. Anal. Cacld. for: $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57. Found: C, 78.36; H, 6.51.

4-(2-Piperidinoethoxy) benzaldehyde (11c). Prepared following the procedure described for (**4b**) using 4-(2-bromoethoxy)-benzaldehyde (0.85 g, 3.71 mmol), piperidine (0.80 g, 9.41 mmol), and methanol (15 mL) to obtain the titled compound (**11c**) (0.83 g, 95%) as brown syrup. IR (Neat): υ 2934, 1692, 1601 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.42–1.64 (m, 6H, 3 × CH_2), 2.47 (t, 4H, 2 × —CH_2), 2.74 (t, 2H, —CH_2), 4.11 (t, 2H, —CH_2), 7.09–7.15 (m, 2H, Ar-H), 7.34–7.45 (m, 2H, Ar-H), 9.93 (s, 1H, —CHO). ESI-MS: m/z 234 $[M + H]^+$. Anal. Cacld. for: $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 72.02; H, 8.01.

2-(4-[2-(Piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (12c). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-piperidinoethoxy)-benzaldehyde (0.51 g, 2.1 mmol), ammonium acetate (0.54 g, 7.0 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (0.74 g, 88%) (**12c**) as pale brown solid. mp: 188–190°C, IR (Neat): ν 3419, 1651, 1025 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.38 (m, 6H, 3 × CH_2), 2.50 (t, 4H, 2 × —CH_2), 2.74 (t, 2H, —CH_2), 4.11 (t, 2H, —CH_2), 6.90–6.94 (d, J = 8.86 Hz, 2H, Ar-H), 7.21–7.33 (m, 6H, Ar-H), 7.53–7.56 (d, J = 7.55 Hz, 4H, Ar-H), 7.97–8.02 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 19.71, 21.69, 66.60, 108.53, 112.11, 113.14, 120.12, 121.91, 125.49, 126.42, 126.79, 127.61, 128.86, 129.68, 132.04, 133.50, 136.23, 150.13, 157.10, 190.60. ESI-MS: m/z 424 $[M + H]^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O$: C, 79.40; H, 6.89. Found: C, 79.48; H, 6.94.

4-(2-Morpholino)ethoxy)benzaldehyde (11e). Prepared following the procedure described for **(5b)** using 4-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.3 mmol), morpholine (1.06 g, 12.18 mmol), and methanol (12.5 mL) to obtain the titled compound (**11e**) (0.97 g, 97%) as brown syrup. IR (Neat): ν 2953, 1689, 1600 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.54 (t, 4H, 2 × —CH_2), 2.79 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.15 (t, 2H, —CH_2), 6.95–7.00 (d, J = 9.06 Hz, 2H, Ar-H), 7.79 (d, J = 8.30 Hz, 2H, Ar-H), 9.85 (s, 1H, —CHO). ESI-MS: m/z 236 $[M + H]^+$. Anal. Cacld. for: $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.30.

2-(4-[2-(Morpholino)ethoxy)phenyl]-4,5-diphenylimidazol (12e). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-morpholinoethoxy) benzaldehyde (0.51 g, 2.1 mmol), ammoniumacetate (0.54 g, 7.0 mmol), catalyst phosphotungsticacid (0.1 g, 3 mol %) to obtain the titled compound (**11e**) (0.65 g, 70%) as brown semisolid. IR (Neat): ν 3059, 1603, 1247 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.55 (t, 4H, 2 × —CH_2), 2.78 (t, 2H, —CH_2), 3.68 (t, 4H, 2 × —CH_2), 4.13 (t, 2H, —CH_2), 6.90 (d, J = 8.86 Hz, 2H, Ar-H), 7.20–7.57 (m, 10H, Ar-H), 8.00 (m, 2H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 23.57, 53.42, 56.85, 65.22, 66.07, 100.85, 113.96, 122.97, 125.67, 125.88, 126.40, 127.33, 127.67, 128.31, 129.59,132.01, 129.95, 145.58, 158.23, 163.30. ESI-MS: m/z 426 $[M + H]^+$. Anal. Cacld. for: $C_{27}H_{27}N_3O_2$: C, 76.28; H, 6.31. Found: C, 76.28; H, 6.31.

4-(2-Bromoethoxy)-3-methoxybenzaldehyde (10). Prepared following the procedure described for (**3**) using 4-(3-methoxy) hydroxybenzaldehyde (8.00 g, 52.2 mmol), 1,2-dibromoethane (39.19 g, 208.6 mmol), and methanol (50 mL) to obtain the titled compound (**10**) (9.30 g, 68%) as white crystalline solid. mp: 62–65°C, IR (KBr): ν 3342, 1680, 1270 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.37 (t, 2H, —CH_2), 6.94 (d, J = 8.30 Hz, 2H, Ar-H), 7.36–7.40 (m, 2H, Ar-H), 9.82 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.09, 56.03, 68.67, 109.77, 112.34, 126.30, 130.75, 149.92, 152.80, 190.75. ESI-MS: m/z 261 $[M + H]^+$. Anal. Cacld. for: $C_{10}H_{11}O_3Br$: C, 46.35; H, 4.27. Found: C, 46.30; H, 4.30.

4-(2-Dimethylaminoethoxy)-3-methoxybenzaldehyde (11b). Prepared following the procedure described for (**5a**) using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol), and methanol (20 mL) to obtain the title compound (**11b**) (0.77 g, 89%) as yellow syrup. IR (Neat): ν 2941,1682, 1270 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H, 2 × CH_3), 2.77 (t, 2H, —CH_2), 3.91 (s, 3H, —OCH_3), 4.15 (t, 2H, —CH_2), 6.93 (d, 1H, Ar-H), 7.36 (d, 2H, Ar-H), 9.81 (s, 1H, —CHO), ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.60, 55.76, 57.58, 66.66, 109.06, 111.28, 126.58, 129.96, 149.59, 153.60, 190.74. EI-MS: m/z 224 $[M]^+$. Anal. Cacld. for: $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67. Found: C, 64.49; H, 7.73.

2-(4-[2-Dimethylaminoethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole (12b). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-

dimethylaminoethoxy)-3-methoxybenzaldehyde (0.49 g, 2.23 mmol), ammonium acetate (0.54 g, 7.0 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (**12b**) (0.70 g, 85%) as gray solid. mp: 188–190°C, IR (KBr): ν 3386, 1506, 1264 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.29 (s, 6H, 2 × CH_3), 2.69 (t, 2H, —CH_2), 3.91 (s, 3H, —OCH_3), 4.09 (t, 2H, —CH_2), 6.98 (d, J = 6.86 Hz, 1H, Ar-H), 7.21–7.39 (m, 5H, Ar-H), 7.52–7.71 (m, 7H, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.97, 55.60, 57.19, 65.79, 108.95, 113.38, 117.87, 123.57, 128.35, 145.59, 147.90, 148.99. ESI-MS: m/z 414 $[M + H]^+$. Anal. Cacld. for: $C_{26}H_{27}N_3O_2$: C, 75.48; H, 6.51. Found: C, 75.40; H, 6.59.

4-(2-Piperidino)ethoxy)-3-methoxybenzaldehyde (11d). Prepared following the procedure described for (**5b**) using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), piperidine (0.81 g, 9.41 mmol), and methanol (15 mL) to obtain the titled compound (**11d**) (0.84 g, 83%) as brown syrup. IR (Neat): ν 2934, 1683, 1269 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 1.41–1.48 (m, 2H, —CH_2), 1.59–1.64 (m, 4H, 2 × —CH_2), 2.49 (t, 4H, 2 × —CH_2), 2.80 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.18 (t, 2H, —CH_2), 6.93 (d, J = 7.55 Hz, 1H, Ar-H), 7.36–7.39 (m, 2H, Ar-H), 9.81 (s, 1H, —CHO), ESI-MS: m/z 264 $[M + H]^+$. Anal. cacld. for: $C_{15}H_{21}NO_3$: C, 68.39; H, 8.04. Found: C, 68.43; H, 8.01.

2-(4-[2-(Piperidino)ethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole (12d). Prepared following the procedure described for (**7a**) using benzil (0.42 g, 2.0 mmol), 4-(2-piperidinoethoxy)-3-methoxybenzaldehyde (0.58 g, 2.2 mmol), ammonium acetate (0.64 g, 8.3 mmol), catalyst PTA (0.10 g, 3 mol %) to obtain the titled compound (**12d**) (0.72 g, 80%) as yellow solid. mp: 100–102°C, IR (Neat): ν 3422, 1647, 1025 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 1.45–1.61 (m, 6H, 3 × CH_2), 2.52 (t, 4H, 2 × —CH_2), 2.79 (t, 2H, —CH_2), 3.92 (s, 3H, —OCH_3), 4.14 (t, 2H, —CH_2), 5.05 (brs, 1H, —NH), 6.88 (d, J = 8.86 Hz, 1H, Ar-H), 7.20–7.33 (m, 6H, Ar-H), 7.53–7.67 (m, 6H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ 21.39, 22.05, 23.27, 24.66, 53.97, 55.55, 56.77, 65.23, 109.04, 112.53, 117.96, 123.54, 126.58, 127.63, 127.88, 132.92, 145.91, 147.76, 148.76, 172.88, 173.86. ESI-MS: m/z 454 $[M + H]^+$. Anal. Cacld. for: $C_{29}H_{31}N_3O_2$: C, 76.79; H, 6.88. Found: C, 76.87; H, 6.80.

4-(2-Morpholino)ethoxy)-3-methoxybenzaldehyde (11f). Prepared following the procedure described for (**5b**) using, 4-(2-bromoethoxy)-3-methoxybenzaldehyde (1.00 g, 3.84 mmol), morpholine (0.93 g, 10.7 mmol), and methanol (15 mL) to obtain the titled compound (**11f**) (0.99 g, 97%) as brown syrup. IR (Neat): υ 2924, 1681, 1269 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.57 (t, 4H, 2 × —CH_2), 2.84 (t, 2H, —CH_2), 3.67 (t, 4H, 2 × —CH_2), 3.91 (s, 3H, —OCH_3), 4.18 (t, 2H, —CH_2), 6.92 (d, J = 9.06 Hz, 1H, Ar-H), 7.37 (d, J = 8.30 Hz, 2H, Ar-H), 9.81 (s, 1H, —CHO). ESI-MS: m/z 266 $[M + H]^+$. Anal. Cacld. for: $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21. Found: C, 63.32; H, 7.28.

2-(4-[2-(Morpholino)ethoxy)-3-methoxyphenyl]-4,5-di-phenylimidazole (12f). Prepared following the procedure described for (**7a**) using, benzil (0.42 g, 2.0 mmol), 4-(2-morpholinoethoxy)-3-methoxybenzaldehyde (0.58 g, 2.1 mmol), ammonium acetate (0.64 g, 8.3 mmol), catalyst PTA (0.1 g, 3 mol %) to obtain the titled compound (**12f**) (0.78 g, 86%) as pale brown solid. mp: 198–200°C, IR (Neat): ν 3061, 2939, 1500 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 2.51–2.56 (m, 4H, 2 × —CH_2), 2.76 (t, 2H, —CH_2), 3.61 (t, 4H, 2 × —CH_2), 3.89 (s, 3H, —OCH_3), 4.12 (t, 2H, —CH_2), 6.95–7.65 (m, 13H, Ar-H), 12.34 (brs, 1H, —NH), ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.13, 55.67, 56.48, 65.20, 65.36, 113.71, 117.94, 127.06, 127.69, 128.38, 145.53, 147.87, 149.07. ESI-MS: m/z 456 $[M + H]^+$. Anal. Cacld. for: $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.41. Found: C, 73.74; H, 6.49.

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