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Synthesis and antiamoebic activity of new oxime ether derivatives containing 2-acetylpyridine/2-acetylfuran

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Abstract—Various oxime ether derivatives of 2-acetylpyridine and 2-acetylfuran series have been synthesised. O-Alkylation of the oximes by various alkylaminoethyl halides gave the corresponding oxime ether derivatives. The structures of these compounds were elucidated by UV, IR, ^{1}H NMR, ^{13}C NMR spectroscopic methods and elemental analyses. All the compounds were screened in vitro against the *HM1:IMSS* strain of *Entamoeba histolytica*. Based on the 50% inhibitory concentration (IC_{50}) data of the 12 compounds evaluated, two of the 2-acetylpyridine series and two in the 2-acetylfuran series showed better IC_{50} values in vitro when compared with the standard amoebicidal drug, metronidazole. Moreover, one compound showed the most promising antiamoebic activity (IC_{50} = 0.5 μM vs IC_{50} = 1.9 μM of metronidazole).

1. Introduction

Few pathogens are more aptly named than *Entamoeba histolytica*, the tissue-lysing amoeba that causes amoebic colitis and amoebic liver abscess. Amoebiasis is the second leading cause of death from parasitic disease worldwide. More than 50 million people worldwide are infected and up to 110,000 die every year due to amoebiasis.[1] Metronidazole is the most widely used amoebicidal. Toxicity and resistance to the drug have increased.[2–6] Therefore, there is an urgent need to screen new compounds for the development of new amoebicidal.

The study of oxime ether derivatives has become of much interest in recent years on account of their antiprotozoan, antibacterial activity, antienteroviral, antifungal, antineoplastic, anticonvulsant, and antimicrobial activities.[7–12] Different oxime ether derivatives have also been reported to possess anticholinergic, insecticidal and acaricidal activities[13–15] and furthermore, the significant antiprotozoan activity of 5-nitrothiophene-oxime ether derivatives[16] led us to study the antiamoebic activity of new oxime ether derivatives derived from 2-acetylpyridine and 2-acetylfuran. We have synthesised oxime ethers with different cyclic and aliphatic amines in order to establish the contributions of the type and the size of the alkyl chain and cyclic ring to the antiamoebic activity. As part of our continuous efforts towards the identification of more potent antiamoebic agents,[17–19] a series of new oxime ether derivatives (**1**–**12**) containing 2-acetylpyridine/2-acetylfuran were synthesised and assayed for antiamoebic activity against *HM1:IMSS* strain of *E. histolytica*.

2. Chemistry

In this study, we aimed to synthesise oxime and oxime ether derivatives of 2-acetylpyridine/2-acetylfuran as potential antiameobic agents according to the previous studies in the literature.[20] All the oxime ether derivatives were prepared by the literature procedure.[16] Oximes (**a** and **b**) were obtained by oximation of 2-acetylpyridine/2-acetylfuran (0.12 mol) using hydroxylamine hydrochloride (0.13 mol) in ethanol and pyridine (2:1) under reflux for 22 h. After cooling, the reaction mixture was concentrated and poured into 600 ml of ice water. The precipitated solid was collected, washed with water and recrystallised from methanol. The compounds proved to have mainly E-configuration with traces of the Z-isomer being present according to NMR analyses before recrystallisation. O-Alkylation of oximes **a** and **b** (12 mmol) with hydrochlorides of 2-chloroethylamine,

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2-(dimethyl amino) ethyl chloride, 2-(diisopropyl amino) ethyl chloride, 1-(2-chloroethyl) pyrrolidine, 1-(2-chloroethyl) piperidine and 4-(2-chloroethyl) morpholine (13.8 mmol) in anhydrous methanol (10 mL) under reflux for 24 h gave the corresponding oxime ether derivatives (Figs. 1 and 2). Sodium methoxide (27.6 mmol) was used as a base to obtain oximates before alkylation. After the solution cooled, it was evaporated under vacuo and the residue was dissolved in water and extracted with chloroform. The organic solution was dried over magnesium sulfate, and an oily residue was obtained. Finally, oxime ethers were treated with hydrogen chloride gas in anhydrous ethanol at room temperature to get the salts of the compounds. The oxime ether derivatives as E-isomer were identified by ^{1}H NMR analysis and their purity established by thin-layer chromatography (TLC) and elemental analyses.

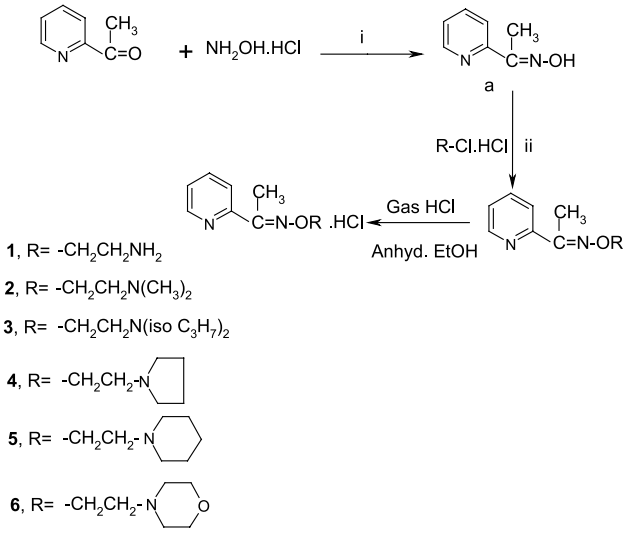

Figure 1. Reagents and conditions: (i) ethanol/pyridine (2:1), reflux, 22 h; (ii) methanol, CH_3ONa, reflux, 24 h.

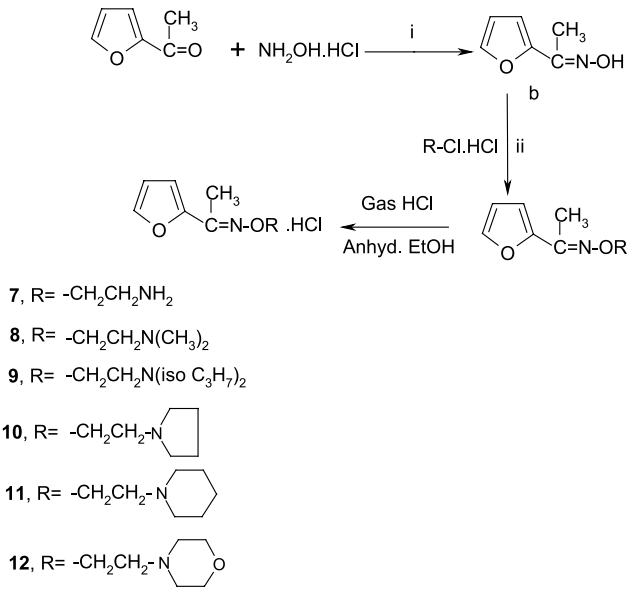

Figure 2. Reagents and conditions: (i) ethanol/pyridine (2:1), reflux, 22 h; (ii) methanol, CH_3ONa, reflux, 24 h.

We have synthesised oxime ethers with different alkyl and cyclic groups attached via ethereal oxygen or oximino group, in order to establish the contribution of the type and size of the substituted groups on antiamoebic activity. For this purpose, saturated alkyl groups of different chain lengths (dimethyl and diisopropyl), cyclic groups (piperidine, pyrrolidine and morpholine) were used to obtain the oxime ethers (Figs. 1 and 2). The oxime ether derivatives **1**–**12** were obtained in satisfactory yields. The structures of the compounds (Figs. 1 and 2) were confirmed by electronic, IR, ^{1}H NMR and ^{13}C NMR spectroscopic data and elemental analysis. Analytical and spectral data (IR, electronic, ^{1}H NMR and ^{13}C NMR) are in good agreement with the composition of the compounds.[21] Other analytical and physiochemical data of the compounds are presented inTable 1. The electronic spectral data of the oxime ether derivatives of 2-acetylpyridine (**1**–**6**) studied in the UV region, exhibit three spectral bands at 374–288.2, 277–242.2 and 238.3–204.7 nm assignable to $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions of azomethine nitrogen (C=N), pyridine ring and ethereal oxygen, respectively. The UV spectral data of 2-acetylfuran oxime ether derivatives (**7**–**12**) were also studied and showed the same type of transitions as observed in 2-acetylpyridine oxime ether derivatives. It showed three spectral bands at 374–267.5, 260–238 and 232–202.2 nm assigned to $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions of azomethine nitrogen (C=N), furan ring and ethereal oxygen, respectively. IR spectra of the compounds (**1**–**6**) showed a band in the range 1583–1650 cm^{-1} due to C=N stretch, while compounds (**7**–**12**), showed this band at 1634–1661 cm^{-1}. Two bands in the range 1211–1295 and 1133–1180 cm^{-1} were assigned due to the C–O and C–N stretching vibrations of the compounds (**1**–**6**), respectively. The compounds of 2-acetylfuran series showed these bands at 1209–1267 and 1118–1187 cm^{-1}. An absorption band at 3208–3434 cm^{-1} was also observed due to $\mathbf{N^+}$–H stretch in all the compounds (**1**–**12**). The ^{1}H NMR spectra showed two triplets in the region 4.47–4.67 ppm (J = 5.8–6.1 Hz) and 3.19–3.78 ppm (J = 5.8–6.8 Hz) due to OCH_2 and CH_2N protons, respectively, in compounds (**1**–**6**). The compounds (**7**–**12**) also showed two triplets at 3.37–4.53 ppm (J = 6.3–6.6 Hz) and 2.50–3.7 ppm (J = 6.2–6.7 Hz) due to the same protons. The strong deshielding of the OCH_2 protons compared to CH_2N protons was assumed due to more electronegativity of oxygen than nitrogen. All the compounds showed a singlet at 10.8–11.21 ppm due to N^+–*H* proton. The CH_3 protons of the acetyl group appeared as singlets at 2.05–2.29 ppm. *N*-Methylenes of pyrrolidino, piperidino and morpholino functionality appeared in the ^{1}H NMR spectra as multiplets at 1.78–3.70, 1.38–3.69 and 3.1–4.22 ppm for the compounds **4**–**6** and **10**–**12**. The protons of 2-acetylpyridine ring and 2-acetylfuran ring were observed at 7.54–8.77 and 6.52–7.76 ppm. Protons of other aliphatic groups were observed with the expected chemical shift and integral values. The compounds (**1**–**6**) in ^{13}C NMR spectra showed a signal at 153.4–157.6 ppm due to the azomethine carbon (C=N), while in compounds (**7**–**12**), this signal was observed at 152.1–157.2 ppm. The signals from 121.5 to 149.6 and from 119.7 to 148.5 ppm were assigned to the pyridine

Table 1. Analytical and physicochemical data of oxime ether derivatives (1–12)

S. No.	Compound/stoichiometry	Colour	Yield (%)	mp (°C)	Found (Calcd)		
					C	H	N
1.	AEE-2-ACP-OX $C_9H_{14}N_3OCl$	Light pink	67	140	50.07 (50.12)	6.52 (6.50)	19.44 (19.50)
2.	*N*,*N*-DMAEE-2-ACP-OX $C_{11}H_{18}N_3OCl$	Light yellow	59	210	54.29 (54.21)	7.27 (7.40)	17.34 (17.25)
3.	*N*,*N*-DIPAEE-2-ACP-OX $C_{15}H_{26}N_3OCl$	Light brown	61	200	60.04 (60.10)	8.79 (8.70)	14.15 (14.02)
4.	PYR-AEE-2-ACP-OX $C_{13}H_{20}N_3OCl$	Golden yellow	56	205	57.92 (57.90)	7.39 (7.42)	15.51 (15.60)
5.	PIP-AEE-2-ACP-OX $C_{14}H_{22}N_3OCl$	Colourless	49	196	59.21 (59.26)	7.81 (7.76)	14.79 (14.81)
6.	MOR-AEE-2-ACP-OX $C_{13}H_{20}N_3O_2Cl$	Brown	44	192	54.71 (54.64)	6.97 (7.01)	14.65 (14.71)
7.	AEE-2-ACF-OX $C_8H_{13}N_2O_2Cl$	Dark brown	73	122	46.50 (46.94)	6.33 (6.36)	13.99 (13.70)
8.	*N*,*N*-DMAEE-2-ACF-OX $C_{10}H_{17}N_2O_2Cl$	Brown	65	163	51.67 (51.61)	7.29 (7.31)	12.15 (12.04)
9.	*N*,*N*-DIPAEE-2-ACF-OX $C_{14}H_{25}N_2O_2Cl$	Brown	57	194	58.31 (58.23)	8.59 (8.66)	9.65 (9.71)
10.	PYR-AEE-2-ACF-OX $C_{12}H_{19}N_2O_2Cl$	Brown	59	181	55.36 (55.71)	7.32 (7.35)	10.56 (10.83)
11.	PIP-AEE-2-ACF-OX $C_{13}H_{21}N_2O_2Cl$	Colourless	44	168	57.32 (57.25)	7.29 (7.71)	10.45 (10.28)
12.	MOR-AEE-2-ACF-OX $C_{12}H_{19}N_2O_3Cl$	Colourless	39	185	52.55 (52.46)	6.29 (6.92)	10.45 (10.20)

and furan ring carbons, respectively. The *O*CH_2 and CH_2*N* carbons were resonated at 66.2–69.7 and 52.2–56.2 ppm, respectively, in all the compounds (**1**–**12**). The signal for methyl carbon of acetyl group appeared at 11.1–13.6 ppm in both the series. The carbons at other aliphatic groups resonate at their usual positions.

3. In vitro antiamoebic activity

All the oxime ether derivatives (**1**–**12**) were screened in vitro for antiamoebic activity against *HM1:IMSS* strain of *E. histolytica* by microdilution method.[22] *E. histolytica* trophozoites were cultured in TYIS-33 growth medium, as described previously, in a 96-well microtiter plate.[23] All the compounds were dissolved in DMSO (40 μL) at which level no inhibition of amoeba occurs[24,25] and the stock solutions of the compounds were prepared freshly before use at a concentration of 1 mg/mL. The IC_{50} values in μM are shown in Table 2. Metronidazole was used as the reference drug with IC_{50} = 1.9 μM. The results were estimated as the percentage of growth inhibition compared with the untreated controls and plotted as probit values as a function of the drug concentration. The IC_{50} and 95% confidence limits were interpolated in the corresponding dose–response curve. Here we have three types of O-substituents, namely the unsubstituted amino group (**1** and **7**), N,N-disubstituted amino group (**2**, **3**, **8** and **9**) and N contained in a medium sized ring (**4**–**6** and **10**–**12**). In terms of structure–activity relationship, the results of in vitro antiamoebic activity showed that the activity was found in those oxime ether derivatives, which have piperidine and morpholine as the substituents. The better antiamoebic activity was found in those derivatives substituted with bulkier groups. The biological data suggest that the compounds with aliphatic amines as the N-substituents do not show any activity. Compared to the activity of the commonly used drug metronidazole, the activities of compounds **5**, **6**, **11** and **12** are noteworthy since they showed lower IC_{50} values than metronidazole. Compound **4** showed an IC_{50} value comparable to the reference drug (IC_{50} = 2.2 μM vs. IC_{50} = 1.9 μM metronidazole). Compounds **6** and **12** (IC_{50} = 0.5 μM of **6**, IC_{50} = 0.6 μM of **12**) are the most active of the tested compounds of all the oxime ether derivatives. Detailed studies of the toxicity, in vivo and mechanism of action of these compounds are in progress.

Table 2. In vitro antiamoebic activity of oxime ether derivatives of 2-acetylpyridine and 2-acetylfuran against *HM1:IMSS* strain of *E. histolytica*

Compound	IC_{50} (μM)	SD[a]
1	14.7	0.23
2	10.3	0.36
3	7.4	0.17
4	2.2	0.30
5	1.4	0.21
6	0.5	0.38
7	17.2	0.12
8	13.4	0.10
9	8.1	0.15
10	2.5	0.10
11	1.7	0.12
12	0.6	0.50
Metronidazole	1.9	0.08

[a] Standard deviation.

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21. All the new compounds (**a**, **b** and **1**–**12**) gave satisfactory spectral data consistent with their proposed structures. Selected spectral data for compounds **1**–**12**. Compound **a**: yield 68%; light pink solid (methanol), mp 123 °C. Anal. Calcd for $C_7H_8N_2O$: C, 61.70; H, 5.88; N, 20.57. Found: C, 61.65; H, 5.79; N, 20.41; λ_{max} (nm): 377.4, 246.5, 212; ν_{max} (cm^{-1}): 3257 (OH), 3063 (C–H), 1591 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 11.48 (1H, s, O-*H*), 8.76 (d, 1H, Py-*H*, *J* = 5.6 Hz), 8.16 (d, 1H, Py-*H*, *J* = 6.5 Hz), 7.81 (t, 1H, Py-*H*, *J* = 5.12 Hz), 7.72 (t, 1H, Py-*H*, *J* = 7.01 Hz), 2.21 (s, 3H, –C*H*$_3$). Compound **b**: yield 73%; brown solid (methanol), mp 104 °C. Anal. Calcd for $C_6H_7NO_2$: C, 57.54; H, 5.60; N, 11.19. Found: C, 56.98; H, 5.3; N, 11.12; λ_{max} (nm): 321.5, 250.3, 243, 208.5; ν_{max} (cm^{-1}): 3346 (OH), 3000 (C–H), 1613 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 11.06 (1H, s, O-*H*), 7.08 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 6.64 (t, 1H, Fu-*H*, *J* = 6.4 Hz), 6.44 (d, 1H, Fu-*H*, *J* = 6.4 Hz), 2.37 (3H, s, –C*H*$_3$); Compound **1**: λ_{max} (nm): 373, 301.4, 288.2, 243.3, 205.4; ν_{max} (cm^{-1}): 3325 (N^+–H) 3046 (CH), 1618 (C=N), 1221 (C–O), 1175 (C–N); ^1H NMR ($(CD_3)_2SO$) δ (ppm): 11.02 (s, 3H, N^+-*H*) 8.65 (d, 1H, Py-*H*, *J* = 6.41 Hz), 8.05 (d, 1H, Py-*H*, *J* = 5.17 Hz), 7.96 (t, 1H, Py-*H*, *J* = 8.28 Hz), 7.59 (t, 1H, Py-*H*, *J* = 8.69 Hz), 2.23 (3H, s, –C*H*$_3$), 4.47 (t, 2H, O-C*H*$_2$, *J* = 6.02 Hz), 3.29 (t, 2H, C*H*$_2$-N, *J* = 5.96 Hz); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 155.6 (C=N), 123.3, 126.7, 139.8, 144.5, 147.9 (Py–C), 69.7 (O–CH_2), 56.2 (CH_2–N), 12.6 (CH_3); Compound **2**: λ_{max} (nm): 369, 277, 248, 207; ν_{max} (cm^{-1}): 3412 (N^+–H), 2915 (CH), 1585 (C=N), 1263 (C–O), 1171 (C–N); ^1H NMR ($(CD_3)_2SO$) δ (ppm): 10.98 (s, 1H, N^+-*H*), 8.26 (d, 1H, Py-*H*, *J* = 5.0 Hz), 8.08 (d, 1H, Py-*H*, *J* = 7.16 Hz),7.91 (t, 1H, Py-*H*, *J* = 9.0 Hz), 7.81 (t, 1H, Py-*H*, *J* = 8.0 Hz), 2.26 (s, 3H, C*H*$_3$), 4.63 (t, 2H, O–C*H*$_2$, *J* = 5.8 Hz), 3.41 (t, 2H, C*H*$_2$-N, *J* = 6.1 Hz), 2.35 (s, 6H, C*H*$_3$); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 153.7 (C=N), 122.8, 125.8, 141.6, 145.8, 149.4 (Py–C), 68.7 (O–CH_2), 54.3 (CH_2–N), 12.0 (CH_3), 47.7 ($2CH_3$). Compound **3**: λ_{max} (nm): 371.9, 292.3, 249.5, 204.7; ν_{max} (cm^{-1}): 3421 (N^+-H), 2910 (CH), 1622 (C=N), 1295 (C–O), 1172 (C–N); ^1H NMR ($(CD_3)_2SO$) δ ppm: 11.19 (s, 1H, N^+-H), 8.56 (d, 1H, Py-*H*, *J* = 6.66 Hz), 8.17 (d, 1H, Py-*H*, *J* = 7.01 Hz), 7.94 (t, 1H, Py-*H*, *J* = 7.33 Hz), 7.81 (t, 1H, Py-*H*, *J* = 8.0 Hz), 2.29 (s, 3H, –C*H*$_3$), 4.65 (t, 2H, O-C*H*$_2$, *J* = 6.1 Hz), 3.38 (t, 2H, C*H*$_2$-N, *J* = 6.8 Hz), 3.58–3.72 (m, 2H, –C*H*), 1.25 (d, 12H, C*H*$_3$); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 155.4 (C=N), 121.6, 124.9, 140.8, 145.8, 148.7 (Py–C), 67.2 (O–CH_2), 53.4 (CH_2–N), 13.6 (CH_3), 11.8 ($4CH_3$), 58.2 (2CH). Compound **4**: λ_{max} (nm): 374, 301.8, 238.3, 242.8; ν_{max} (cm^{-1}): 3325 (N^+–H), 2915 (CH), 1650 (C=N), 1243 (C–N), 1133 (N–O), ^1H NMR ($(CD_3)_2SO$) δ (ppm): 10.87 (s, 1H, N^+-*H*), 8.76 (d, 1H, Py-*H*, *J* = 5.33 Hz), 8.08 (d, 1H, Py-*H*, *J* = 6.66 Hz), 7.91 (t, 1H, Py-*H*, *J* = 4.0 Hz), 7.77 (t, 1H, Py-*H*, *J* = 8.0 Hz), 2.27 (s, 3H, –C*H*$_3$), 4.60 (t, 2H, O-C*H*$_2$, *J* = 5.9 Hz), 3.46 (t, 2H, C*H*$_2$-N, *J* = 6.7 Hz), 3.62–3.70 (m, 4H, N-C*H*$_2$ (pyrrolidine)), 1.79–1.97 (m, 4H, –C*H*$_2$ (pyrrolidine)), ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 156.7 (C=N), 122.2, 125.3, 139.8, 144.7, 149.2 (Py–C), 66.2 (O–CH_2), 54.3 (CH_2–N), 12.5 (CH_3), 51.8 ($2CH_2$), 24.5 ($2CH_2$). Compound **5**: λ_{max} (nm): 363.3, 274.8, 245, 236.6, 206.6; ν_{max} (cm^{-1}): 3381(N^+–H), 2950 (CH), 1585 (C=N), 1287 (C–O), 1180 (N–O); ^1H NMR($(CD_3)_2SO$) δ (ppm): 11.12 (s, 1H, N^+-*H*), 8.77 (d, 1H, Py-*H*, *J* = 7.4 Hz), 8.19 (d, 1H, Py-*H*, *J* = 5.5 Hz), 7.89 (t, 1H, Py-*H*, *J* = 9.26 Hz), 7.72 (t, 1H, Py-*H*, *J* = 7.4 Hz), 2.06 (s, 3H, –C*H*$_3$), 4.67 (t, 2H, O-C*H*$_2$, *J* = 5.8 Hz), 3.19 (t, 2H, C*H*$_2$-N, *J* = 6.1 Hz), 3.35–3.69 (m, 4H, C*H*$_2$-N (piperidine)), 1.38–2.38 (m, 6H, –C*H*$_2$ (piperidine)); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 157.6 (C=N), 121.5, 126.2, 141.8, 143.7, 149.6 (Py–C), 67.5 (O–CH_2), 53.3 (CH_2–N), 11.9 (CH_3), 47.9 ($2CH_2$), 25.5 ($2CH_2$), 21.2 (CH_2). Compound **6**: λ_{max} (nm): 365, 271.4, 242.2; ν_{max} (cm^{-1}): 3381 (N^+–H), 2900 (CH), 1583 (C=N), 1211 (C–O), 1139 (C–N); ^1H NMR ($(CD_3)_2SO$) δ (ppm): 11.18 (s, 1H, N^+-*H*), 8.66 (d, 1H, Py-*H*, *J* = 5.23 Hz), 7.95 (d, 1H, Py-*H*, *J* = 6.16 Hz), 7.83 (t, 1H, Py-*H*, *J* = 4.2 Hz), 7.54 (t, 1H, Py-*H*, *J* = 3.5 Hz), 2.11 (s, 3H, –C*H*$_3$), 4.62 (t, 2H, O-C*H*$_2$, *J* = 5.8 Hz), 3.78 (t, 2H, C*H*$_2$-N, *J* = 5.8 Hz), 3.12–3.47 (m, 4H, –C*H*$_2$-N (morpholine)), 3.98–4.22 (m, 4H, –C*H*$_2$-O (morpholine)); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 153.4 (C=N), 122.6, 125.1, 141.2, 145.2, 149.1 (Py–C), 68.3 (O–CH_2), 54.1 (CH_2-N), 11.1 (CH_3), 63.7 ($2CH_2$), 49.9 ($2CH_2$). Compound **7**: λ_{max} (nm): 372, 294, 267.5, 240, 206.5; ν_{max} (cm^{-1}): 3208 (N^+–H), 2925 (C–H),

1661 (C═N), 1209 (C–O), 1187 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 11.17 (s, 3H, N^+-*H*), 6.52 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 6.72 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 7.70 (d, 1H, Fu-*H*, *J* = 1.6 Hz), 2.05 (s, 3H, –C*H*$_3$), 3.37 (t, 2H, O-C*H*$_2$, *J* = 6.4 Hz), 2.50 (t, 2H, C*H*$_2$-N, *J* = 6.6 Hz); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 152.1 (C═N), 120.2, 124.6, 141.6, 144.7 (Furan-C), 68.1 (O–CH_2), 52.2 (CH_2–N), 12.1 (CH_3). Compound **8**: λ_{max} (nm): 365, 294, 260, 232, 204.3; ν_{max} (cm^{-1}): 3434 (N^+–H), 2945 (C–H), 1660 (C═N), 1211 (C–O), 1130 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 11.01 (s, 1H, N^+-H), 6.69 (d, 1H, Fu-*H*, *J* = 6.4 Hz), 6.91 (d, 1H, Fu-*H*, *J* = 6.4 Hz), 7.76 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 2.13 (s, 3H, –C*H*$_3$), 4.47 (t, 2H, O-C*H*$_2$, *J* = 6.4 Hz), 3.56 (t, 2H, C*H*$_2$-N, *J* = 6.6 Hz), 2.81 (s, 6H, C*H*$_3$)); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 153.7 (C═N), 122.3, 124.5, 143.1, 148.1 (Furan-C), 68.7 (O–CH_2), 54.3 (CH_2–N), 12.4 (CH_3), 47.7 ($2CH_3$). Compound **9**: λ_{max} (nm): 374, 296, 262, 240, 208.5; ν_{max} (cm^{-1}): 3404 (N^+–H), 2986 (C–H), 1638 (C═N), 1223 (C–O), 1161 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 11.02 (s, 1H, N^+-*H*), 6.69 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 6.92 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 7.74 (d, 1H, Fu-*H*, *J* = 1.6 Hz), 2.15 (s, 3H, –C*H*$_3$), 4.45 (t, 2H, O-C*H*$_2$, *J* = 6.6 Hz), 3.55 (t, 2H, C*H*$_2$-N, *J* = 6.7 Hz), 3.32–3.36 (m, 1H, –C*H*), 1.3 (d, 12H, –C*H*$_3$); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 156.4 (C═N), 122.3, 120.7, 142.6, 145.1 (Furan-C), 66.2 (O–CH_2), 53.7 (CH_2–N), 13.2 (CH_3), 11.8 ($4CH_3$), 58.2 (2CH). Compound **10**: λ_{max} (nm): 364, 288, 262, 236, 204.2; ν_{max} (nm): 3399 (N^+-H), 2937 (C–H), 1652 (C═N), 1267 (C–O), 1118 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 11.02 (s, 1H, N^+-*H*), 6.69 (d, 1H, Fu-*H*, *J* = 6.4 Hz), 6.92 (d, 1H, Fu-*H*, *J* = 6.3 Hz), 7.74 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 2.13 (s, 3H, –C*H*$_3$), 4.45 (t, 2H, O-C*H*$_2$, *J* = 6.3 Hz), 3.64 (t, 2H, CH_2-N, *J* = 6.4 Hz), 3.29–3.44 (m, 4H, N-CH_2 (pyrrolidine)), 1.78–2.05 (m, 4H, –CH_2 (pyrrolidine)), ^{13}C NMR($(CD_3)_2SO$) δ (ppm): 155.5 (C═N), 124.6, 121.6, 14.1, 148.2 (Furan-C), 67.4 (O-CH_2), 52.8 (CH_2–N), 11.4 (CH_3), 51.8 ($2CH_2$), 24.5 ($2CH_2$). Compound **11**: λ_{max} (nm): 373, 292, 260, 238, 205.1; ν_{max} (cm^{-1}): 3418 (N^+-H), 2950 (C–H), 1634 (C═N), 1254 (C–O), 1118 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 10.80 (s, 1H, N^+-*H*), 6.69 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 6.91 (d, 1H, Fu-*H*, *J* = 3.6 Hz), 7.75 (d, 1H, Fu-*H*, *J* = 1.6 Hz), 2.12 (s, 3H, –C*H*$_3$), 4.53 (t, 2H, O-C*H*$_2$, *J* = 6.53 Hz), 3.70 (t, 2H, C*H*$_2$-N, *J* = 6.61 Hz), 3.36–3.43 (m, 4H, –C*H*$_2$-N (piperidine)), 2.93–2.94 (m, 4H, –C*H*$_2$ (piperidine)), 1.64–1.76 (m, 2H, –C*H*$_2$ (piperidine)); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 157.2 (C═N), 119.7, 121.2, 144.6, 148.5 (Furan-C), 67.5 (O–CH_2), 52.3 (CH_2–N), 11.7 (CH_3), 47.9 ($2CH_2$), 25.5 ($2CH_2$), 21.2 (CH_2). Compound **12**: λ_{max} (nm): 373, 290, 262, 232, 202.2; ν_{max} (cm^{-1}): 3423 (N^+-H), 2967 (C–H), 1637 (C═N), 1226 (C–O), 1119 (C–N); ^{1}H NMR ($(CD_3)_2SO$) δ (ppm): 11.21 (s, 1H, N^+-*H*), 6.68 (d, 1H, Fu-*H*, *J* = 3.5 Hz), 6.90 (d, 1H, Fu-*H*, *J* = 3.5 Hz), 7.75 (d, 1H, Fu-*H*, *J* = 1.6 Hz), 2.13 (s, 3H, –C*H*$_3$), 4.43 (t, 2H, O-C*H*$_2$, *J* = 6.4 Hz), 3.47 (t, 2H, C*H*$_2$-N, *J* = 6.2 Hz), 3.73–4.02 (m, 4H, O-C*H*$_2$ (morpholine)), 3.1–3.45 (m, 4H, N-CH_2 (morpholine)); ^{13}C NMR ($(CD_3)_2SO$) δ (ppm): 153.4 (C═N), 124.3, 125.2, 144.0, 145.1 (Furan-C), 66.3 (O–CH_2), 54.1 (CH_2–N), 12.1 (CH_3), 63.7 ($2CH_2$), 49.9 ($2CH_2$).

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