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Synthesis of a New Series of Imidazo-[1,5-*a*]pyrido[2,3-*e*]pyrazines as Potential Ligands for the *GABA* Receptor Complex

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Summary. Starting from 2-chloro-3-nitropyridine, 2-isopropyl-1,4-dihydropyrido[2,3-*b*]pyrazin-2(3*H*),3-dione was synthesized. This compound was reacted with potassium *tert*-butoxide and diethyl chlorophosphate to afford an intermediate dihydropyrido[2,3-*b*]pyrazin-2-ylphosphate derivative which in turn furnished the desired 1,2,4-oxadiazolylimidazo[1,5-*a*]pyrido[2,3-*e*]pyrazine derivatives with 5-alkyl-3-isocyanomethyl-1,2,4-oxadiazoles in the presence of additional *tert*-butoxide. The title compounds are potential ligands for the γ-aminobutyric acid A/benzodiazepine receptor complex.

Keywords. Annelation; *GABA* receptor complex; Heterocycles; Imidazo[1,5-*a*]pyrido[2,3-*e*]pyrazines.

Introduction

Associated with the $GABA_A$ ion channel are a variety of recognition sites for small molecules [1] which can directly influence the ability of this channel to transport chloride ions across neuronal membranes. When γ-aminobutyric acid (*GABA*), the major inhibitory neurotransmitter in the central nervous system, binds to the receptor, the flow of chloride ions through the channel is increased, and the excitability of the neuron is reduced. Of the many compounds influencing this *GABA*-induced chloride flux, the benzoediazepines have been the most widely studied. In general, all species which bind to this receptor complex may have a continuum of intrinsic activity, ranging from full agonists through antagonists to inverse agonists [2, 3]. Full agonists potentiate the *GABA*-induced chloride flux to further decrease the excitability of the neuron and have found wide-spread use as anxiolytic, hypnotic, and anticonvulsant agents. In contrast, inverse agonists which decrease the flow of chloride ion are proconvulsant and anxiogenic in nature. Antagonists which have minimal or no effect on the chloride flux have neutral efficacy.

In particular, the partial agonists may have reduced benzodiazepine-mediated side effects such as sedation, physical dependence, amnesia, muscle relaxation,

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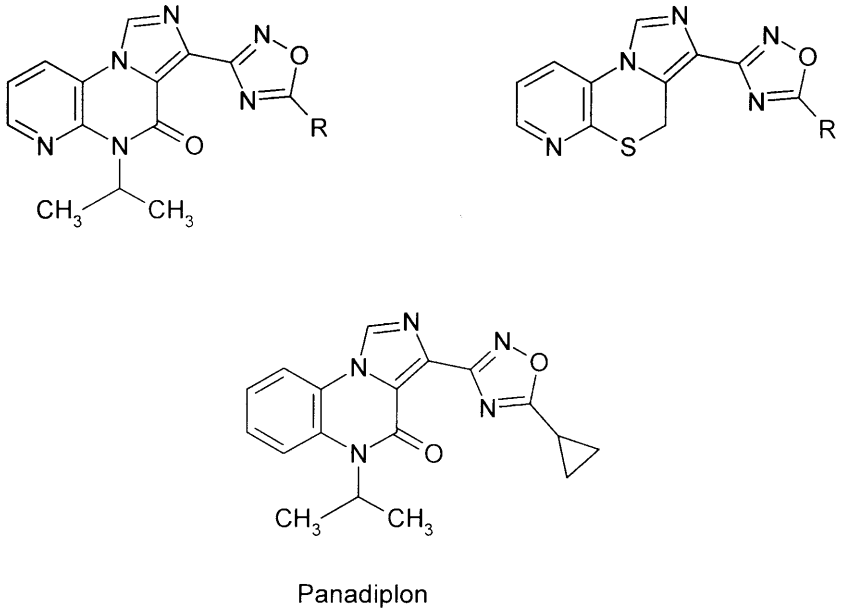


Panadiplon

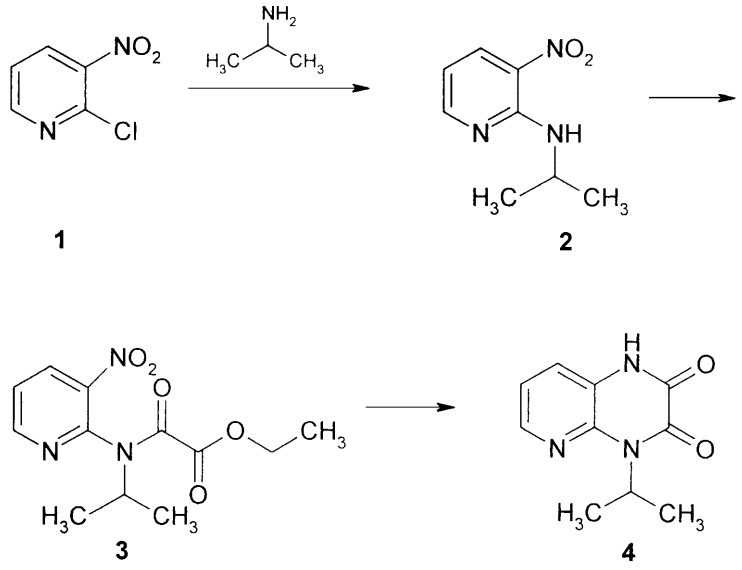
Scheme 1

and ethanol potentiation. The current interest in 1,2,4-oxadiazolylimidazo[1,5-*a*] pyrido[2,3-*e*]pyrazines originates from their potential usefulness as partial agonists for the treatment of anxiety and sleep disorders. One of the compounds that are reported to be partial agonist at the benzodiazepine receptor is panadiplon [4]. Unfortunately, this imidazo[1,5-*a*]quinoxaline derivative contains a 5-cyclopropyl-1,2,4-oxadiazole group at position 3, which is metabolized to release cyclopropanecarboxylic acid, leading to an increase in serum triglycerides [5, 6]. Therefore, we attempted to synthesize the pyrido analogues to achive an improved pharmacological profile; the target compounds are shown in Scheme 1. In an effort to find further replacement candidates for the partial agonist panadiplon, another analog with a 1,4-thiazin instead of a 1,4-diazin subunit was also a goal of this investigation.

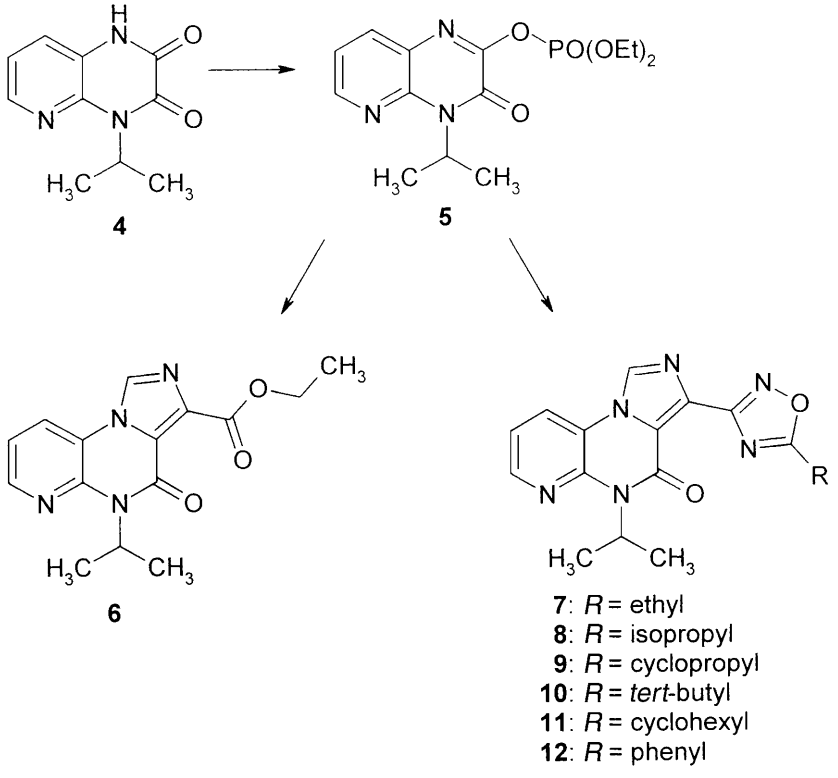
Results and Discussion

The synthesis of the starting pyrido[2,3-*b*]pyrazine-2,3-dione was carried out as shown in Scheme 2. Reaction of **1** with isopropylamine provided the substitution product **2** (92%), which was acylated with ethyl oxalyl chloride in the presence of triethylamine to yield amide **3** (78%). To accomplish the necessary lactam linkage, the nitro group of **3** was reduced by treatment with iron powder in glacial acetic acid at 70°C for 30 min to afford **4** (60%).

The desired 1,2,4-oxadiazolylimidazo[1,5-*a*]pyrido[2,3-*e*]pyrazines were synthesized according to Scheme 3. Reaction of **4** with potassium *tert*-butoxide and diethyl chlorophosphate provided the enol phosphate ester **5**. This intermediate, which was not isolated, was reacted with isocyanides in the presence of additional



Scheme 2



Scheme 3

potassium *tert*-butoxide to provide compounds **6**–**12** (74–93% with respect to **4**). The oxadiazole isocyanide reagents themselves were synthesized following the general procedure of *Watjen* [7].

Experimental

Melting ranges were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer (*TMS* as internal reference, δ values in ppm). Mass spectra were obtained by Shimadzu QP 5000 or Hewlett Packard 5970 spectrometers. Analytical TLC was performed on silica gel F254 plates, preparative layer chromatography on silica gel F254s plates. Column chromatography was done on Merck silica gel 60, 0.063–0.200 mm. Evaporation refers to evaporation under reduced pressure, drying of solutions refers to the use of anhydrous Na_2SO_4. The results of elemental analyses agreed with the calculated values within experimental error.

2-Isopropylamino-3-nitropyridine (**2**; $C_8H_{11}N_3O_2$)

A solution of **1** (10 mmol) and isopropylamine (30 mmol) in 20 cm^3 dry *DMF* was heated at 40°C for 6 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried, and the solvent was evaporated. The residue was purified *via* column chromatography on silica gel (eluent: toluene:ethyl acetate = 6:4) to give 1.66 g (92%) of **2** as an oil.

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.33 (d, $J = 6.6$ Hz, 6H, 2 CH_3), 4.51 (sept, $J = 6.6$ Hz, 1H, CH), 6.61 (dd, $J = 8.2$ Hz, $J = 4.6$ Hz, 1H, pyridine-H), 8.12 (s, br, 1H, NH), 8.35–8.45 (m, 2H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 22.6, 42.6, 111.1, 127.5, 135.1, 151.9, 155.7 ppm; MS: m/z (%) = 181 (M^+, 30), 166 (100), 133 (48), 119 (78), 93 (50).

Ethyl 2-(isopropyl-(3-nitro-2-pyridyl)-amino)-2-oxoacetate (**3**; $C_{12}H_{15}N_3O_5$)

To a solution of compound **2** (10 mmol) dissolved in 50 cm^3 of dry toluene under Ar, ethyl oxalyl chloride (12 mmol) and triethylamine (15 mmol) were added dropwise. The mixture was stirred under reflux for 24 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried, and the solvent was evaporated. The residue was purified *via* column chromatography on silica gel (eluent: toluene:ethyl acetate = 8:2) to give 2.11 g (54%) of **3** as an oil.

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.19–1.34 (m, 9H, 3 CH_3), 4.09 (q, $J = 7.1$ Hz, 2H, CH_2), 4.71 (sept, $J = 6.4$ Hz, 1H, CH), 7.58 (dd, $J = 7.8$ Hz, $J = 4.8$ Hz, 1H, pyridine-H), 8.39 (d, $J = 7.8$ Hz, 1H, pyridine-H), 8.79 (d, $J = 4.8$ Hz, 1H, pyridine-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 13.6, 19.9, 51.8, 62.4, 124.1, 134.2, 143.3, 146.0, 152.4, 158.2, 160.4 ppm; MS: m/z (%) = 282 (M^+, 0.2), 160 (100), 150 (38), 120 (27), 79 (28).

2-Isopropyl-1,4-dihydropyrido[2,3-b]pyrazin-2(3H),3-dione (**4**; $C_{10}H_{11}N_3O_2$)

A mixture of compound **3** (10 mmol), 80 cm^3 glacial acetic acid, and 5 cm^3 H_2O was heated to 70°C. Iron powder (0.1 mol) was added in small portions, and the mixture was stirred for 10 min. Then the iron powder was filtered off and washed with hot H_2O. The filtrate was cooled, neutralized with 5% $NaHCO_3$ solution, and extracted with ethyl acetate. The combined organic layers were dried, and the solvent was evaporated. The residue was recrystallized from toluene to give 1.23 g (60%) of **4** as white needles.

M.p.: 250°C; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 300 MHz): 1.58 (d, $J = 7.1$ Hz, 6H, 2 CH_3), 5.75 (sept, $J = 7.1$ Hz, 1H, CH), 7.15 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.55 (d, $J = 7.9$ Hz, 1H, pyridine-H), 8.17 (d, $J = 4.7$ Hz, 1H, pyridine-H), 12.18 (s, br, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$/*DMSO*-d_6, δ, 75 MHz): 17.2, 44.3, 117.4, 120.4, 121.5, 137.1, 139.7, 152.2, 154.1 ppm; MS: m/z (%) = 205 (M^+, 10), 163 (26), 135 (100), 107 (35), 91 (26).

General procedure for the synthesis of compounds **6–10**

A solution of the lactam **4** (2 mmol) in 30 cm^3 *THF* was cooled to −40°C, and potassium *tert*-butoxide (1.0 *M* in *THF*, 2.2 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature over 30 min and then cooled to −50°C. Diethyl chlorophosphate (2.6 mmol) was added dropwise over 5 min, and the mixture was allowed to warm from −50°C to −30°C over 1 h and then to room temperature over 30 min. The solution was cooled to −78°C, and the corresponding isocyanide (2.4 mmol) was added. Potassium *tert*-butoxide (1.0 *M* in *THF*, 2.4 mmol) was added dropwise over 10 min. The mixture was allowed to warm slowly to room temperature and stirred overnight. The mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried, and the solvent was evaporated.

Ethyl 5-isopropyl-4-oxo-4,5-dihydroimidazo[1,5-a]pyrido[2,3-e]pyrazine-3-carboxylate (**6**; $C_{15}H_{16}N_4O_3$)

The residue was recrystallized from petroleum ether to give 429 mg (72%) of **6** as light-brown crystals.

M.p.: 152 – 153°C; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 300 MHz): 1.45 (t, $J = 7.2$ Hz, 3H, CH_3), 1.66 (d, $J = 7.1$ Hz, 6H, 2 CH_3), 4.50 (q, $J = 7.2$ Hz, 2H, CH_2), 5.89 (sept, $J = 7.1$ Hz, 1H, CH), 7.27 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.22 (d, $J = 7.9$ Hz, 1H, pyridine-H), 8.50 (d, $J = 4.7$ Hz, 1H, pyridine-H), 8.53 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$/*DMSO*-d_6, δ, 75 MHz): 14.2, 19.5, 46.4, 61.6, 116.6, 118.2, 122.3, 123.2, 135.5, 142.2, 146.6, 153.4, 161.6 ppm; MS: m/z (%) = 300 (M^+, 37), 254 (42), 135 (100).

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**7**; $C_{16}H_{16}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 603 mg (93%) of **7** as white crystals.

M.p.: 203–205°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.45 (t, $J = 7.5$ Hz, 3H, CH_3), 1.67 (d, $J = 6.8$ Hz, 6H, 2 CH_3), 3.04 (q, $J = 7.5$ Hz, 2H, CH_2), 5.91 (sept, $J = 6.8$ Hz, 1H, CH), 7.26 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.17 (d, $J = 7.9$ Hz, 1H, pyridine-H), 8.50 (d, $J = 4.7$ Hz, 1H, pyridine-H), 8.58 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 10.8, 19.6, 20.3, 46.3, 117.0, 118.2, 120.8, 122.9, 131.8, 142.4, 146.4, 154.2, 163.6, 180.7 ppm; MS: m/z (%) = 324 (M^+, 8), 282 (21), 227 (28), 57 (100).

5-Isopropyl-3-(5-isopropyl-1,2,4-oxadiazol-3-yl)imidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**8**; $C_{17}H_{18}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 513 mg (76%) of **8** as white crystals.

M.p.: 195°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.49 (d, $J = 7.1$ Hz, 6H, 2 CH_3), 1.67 (d, $J = 6.9$ Hz, 6H, 2 CH_3), 3.36 (sept, $J = 7.1$ Hz, 1H, CH), 5.91 (sept, $J = 6.9$ Hz, 1H, CH), 7.26 (dd, $J = 8.0$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.21 (dd, $J = 8.0$ Hz, $J = 1.5$ Hz, 1H, pyridine-H), 8.50 (dd, $J = 4.7$ Hz, $J = 1.5$ Hz, 1H, pyridine-H), 8.62 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 19.5, 20.1, 27.4, 46.2, 116.9, 118.1, 120.7, 123.0, 131.8, 142.3, 146.4, 154.1, 163.3, 183.7 ppm; MS: m/z (%) = 338 (M^+, 7), 296 (13), 227 (19), 69 (100).

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**9**; $C_{17}H_{16}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 499 mg (74%) of **9** as white crystals.

M.p.: 203–205°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.20–1.43 (m, 4H, 2 CH_2), 1.66 (d, $J = 7.1$ Hz, 6H, 2 CH_3), 2.27–2.39 (m, 1H, CH), 5.90 (sept, $J = 7.1$ Hz, 1H, CH), 7.26 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.21 (d, $J = 7.9$ Hz, 1H, pyridine-H), 8.49 (d, $J = 4.7$ Hz, 1H, pyridine-H), 8.59 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 7.7, 10.1, 19.5, 46.2, 116.9, 118.2, 120.6, 123.0, 131.7, 142.3, 146.4, 154.1, 163.4, 181.4 ppm; MS: m/z (%) = 336 (M^+, 5), 294 (11), 227 (15), 69 (100).

3-(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**10**; $C_{18}H_{20}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 565 mg (80%) of **10** as white crystals.

M.p.: 227–228°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.53 (s, 9H, 3 CH_3), 1.67 (d, $J = 6.8$ Hz, 6H, 2 CH_3), 5.91 (sept, $J = 6.8$ Hz, 1H, CH), 7.26 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.17 (d, $J = 7.9$ Hz, 1H, pyridine-H), 8.50 (d, $J = 4.7$ Hz, 1H, pyridine-H), 8.58 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 19.5, 28.4, 33.6, 46.3, 116.9, 118.1, 120.7, 123.0, 131.9, 142.5, 146.4, 154.2, 163.2, 186.1 ppm; MS: m/z (%) = 352 (M^+, 4), 310 (10), 295 (9), 57 (100).

3-(5-Cyclohexyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**11**; $C_{20}H_{22}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 576 mg (76%) of **11** as yellow crystals.

M.p.: 220–222°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.24–1.51 (m, 3H, cyclohexyl-H), 1.66 (d, $J = 6.8$ Hz, 6H, 2 CH_3), 1.70–1.93 (m, 5H, cyclohexyl-H), 2.10–2.24 (m, 2H, cyclohexyl-H), 3.00–3.14 (m, 1H, cyclohexyl-H), 5.90 (sept, $J = 6.8$ Hz, 1H, CH), 7.26 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 8.20 (dd, $J = 8.1$ Hz, $J = 1.3$ Hz, 1H, pyridine-H), 8.49 (dd, $J = 4.7$ Hz, $J = 1.3$ Hz, 1H, pyridine-H), 8.61 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 19.5, 25.3, 25.4, 30.1, 36.3, 46.2, 116.9, 118.1, 120.6, 123.0, 131.9, 142.3, 146.4, 154.2, 163.3, 182.8 ppm; MS: m/z (%) = 378 (M^+, 7), 336 (10), 227 (21), 55 (100).

5-Isopropyl-3-(5-phenyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a]pyrido[2,3-e]pyrazine-4(5H)-one (**12**; $C_{20}H_{16}N_6O_2$)

The residue was recrystallized from petroleum ether/toluene to give 575 mg (77%) of **12** as brown crystals.

M.p.: 212–214°C; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ, 300 MHz): 1.65 (d, $J = 6.8$ Hz, 6H, 2 CH_3), 5.88 (sept, $J = 6.8$ Hz, 1H, CH), 7.44 (dd, $J = 8.1$ Hz, $J = 4.7$ Hz, 1H, pyridine-H), 7.65–7.81 (m, 3H, phenyl-H), 8.25 (d, $J = 6.8$ Hz, 2H, phenyl-H), 8.55 (dd, $J = 4.7$ Hz, $J = 1.5$ Hz, 1H, pyridine-H), 8.81 (dd, $J = 8.1$ Hz, $J = 1.5$ Hz, 1H, pyridine-H), 9.36 (s, 1H, imidazole-H) ppm; ^{13}C NMR ($CDCl_3$/*DMSO*-d_6, δ, 75 MHz): 19.2, 45.0, 117.1, 118.4, 120.6, 123.4, 124.5, 127.6, 129.2, 129.8, 132.8, 141.5, 146.8, 153.6, 164.1, 174.7 ppm; MS: m/z (%) = 372 (M^+, 9), 371 (16), 105 (100), 77 (76).

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