Synthesis and Insecticidal Activities of *cis*-Configuration Nitenpyram Analogues with Benzoyl Hydrazines

Xiao Xu[a], Chuan-wen Sun[a]*, Ding-rong Yang[a], Hong-fei Bu[a], Jing Wang[b] and Yong-hua Xu[b]

[a]College of Life and Environment Sciences, Shanghai Normal University, Shanghai 200234, China
[b]Bioassay Department, Branch of National Pesticide R&D, Hangzhou 310023, China
*E-mail: willin112@163.com

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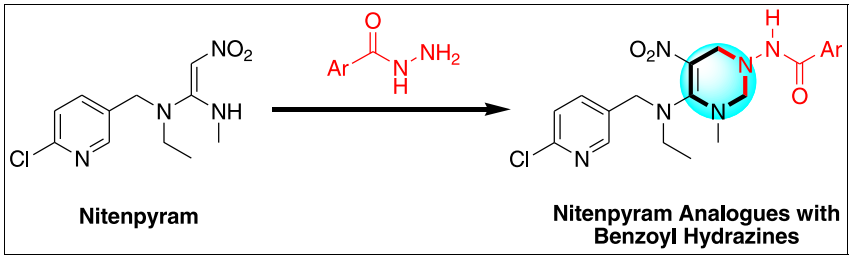

To research on the structure–activity relationships of our designed neonicotinoid compounds, a series of novel *cis*-configuration nitenpyram analogues with benzoyl hydrazines were designed and synthesized. The structures of all compounds were confirmed by IR, ^{1}H NMR, MS, and elemental analysis. Preliminary bioassays indicated that all the analogues exhibited good insecticidal activities against *Nilaparvata legen* and *Aphis medicagini* at 500 mg L^{-1}.

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INTRODUCTION

Neonicotinoid insecticides (NNSs) act selectively on the insect central nervous system as agonists of the postsynaptic nicotinic acetylcholine receptors [1–3]. Because of their unique properties such as high insecticidal potency, low mammalian toxicity, broad insecticidal spectra, and no cross-resistance to conventional insecticide classes [4–6], NNSs have gained dramatic development and are fruitful in modern agricultural pest management and environmental protection [7]. However, during the past decades, frequent field applications have inevitably led to insects' resistance to the major class of neonicotinoid insecticides [8–10].

As we have known, structure modification of the existing commercial NNSs is one of the most effective resistance management tactics [11–13]. It is worth pointing out that because of the existence of the C═C or C═N double bond, neonicotinoids can exist as an isomer in which the nitro or cyano group is located away from the aromatic heterocycle (*trans*) or as an isomer in which the nitro or cyano group is pointed in the same direction as the aromatic heterocycle (*cis*), which suggested that the double bond is indispensable to this kind of compound and plays a crucial role in its modes of action [14]. The nitro groups in all commercialized neonicotinoids have a *trans*-configuration [15], the nitenpyram does. It was found that many neonicotinoid analogues with *cis*-configuration also exhibited good insecticidal activities and shown a different mechanism from the *trans*-configuration neonicotinoids [11]. So, compounds with the *cis*-configuration offer an opportunity for further optimization. In other words, fixing the nitro group in the *cis*-configuration provided a new approach for neonicotinoid molecular design.

Lightened by the earlier views, in our group, we had focused our attention on introductions of the heterocycle or a bulky group into the nitenpyram to fix the nitro group in the *cis* position (Scheme 1). In this manuscript, by using nitenpyram as the leading compound, a series of novel nitenpyram analogues were designed by introducing the substituent benzoyl hydrazines into nitenpyram and forming a tetrahydropyrimidine ring fixed as *cis* configuration.

The new designed nitenpyram analogues **(3a–3j)** were synthesized and characterized by ^{1}H NMR, IR, and elemental analysis. The preliminary insecticidal activity tests indicated that the investigated compounds gave ≥90% mortality against *Nilaparvata legen* and *Aphis medicagini* at 500 mg L^{-1}.

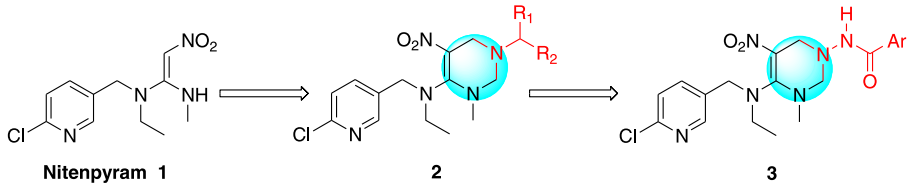
RESULTS AND DISCUSSION

Synthesis of compounds. The target products (**3a–3l**) were obtained using compounds **4**, formaldehyde, and the substituent benzoyl hydrazines by Mannich reaction (Scheme 2). The reaction of **1** with the substituent benzoyl hydrazine could proceed readily under microwave irradiation, which was a highly efficient way with a good yield, as compared with those obtained under conventional conditions by refluxing of the starting materials in ethanol for 6 h.

Insecticidal activity. The insecticidal activities of these novel nitenpyram analogues were evaluated against *N. legen* and *A. medicagini* according to the standard test [16]

with a slight modification. As depicted in Table 1, most compounds exhibited good *in vitro* insecticidal activities against *N. legen* and *A. medicagini* had >90% mortality at 500 mg L^{-1}. In genenal, the insecticidal activities against *A. medicagini* were better than *N. legen*. Among these compounds, **3e** and **3i** showed 100% mortality against *A. medicagini* at 100 mg L^{-1}, and 3c, 3d, and 3j also showed good insecticidal activites.

Scheme 1. Development of novel nitenpyram analogues in our group.



Scheme 2. General synthetic route for the target compounds **3a–3j**.

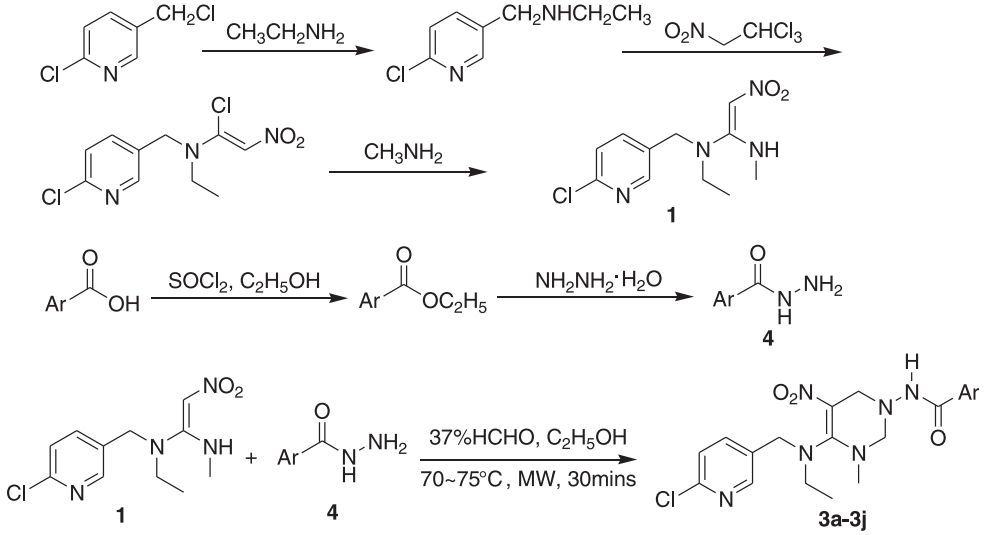


Table 1

Insecticidal activities of compounds **3a–j** against *Nilaparvata lugen* and *Aphis medicagini*.

		N. legen		*A. medicagini*	
		Mortality (%) at different concentrations (mg L^{-1})			
Compound	Ar	500	100	500	100
3a	Ph	95	31[a]	100	56
3b	2-F-Ph	100	31	100	73
3c	2-Cl-Ph	100	36[a]	100	96
3d	2-Br-Ph	91	30	100	92
3e	3,5-Cl_2-Ph	100	35[a]	100	100
3f	4-Me-Ph	93	38[a]	98	67
3g	4-$(CH_3)_3$C-Ph	90	32	95	58
3h	3-$(CH_3)_2$N-Ph	93	36	90	62
3i	C_4H_3O	100	41	100	100
3j	C_4H_3S	96	38	100	98
Nitenpyram		100	100	100	100

[a]The date from Reference [20].

When different substituents Ar were introduced to the nitenpyram analogues, their insecticidal activities decreased in the order C_4H_3O, 3,5-Cl_2-Ph > 2-Cl-Ph, C_4H_3S, 2-Cl-Ph > 2-F-Ph > 3-$(CH_3)_2$N-Ph, 4-$(CH_3)_3$C-Ph, Ph, which indicated that Ar was strongly related to their insecticidal potency. When Ar group was contained in the electron-withdrawing group, the corresponding nitenpyram analogues showed good insecticidal activities. On the other hand, the nitenpyram analogues with the electron-donating group showed the much less activity. These observations may be related to their relatively strong affinities with their target.

EXPERIMENTAL

Melting points were measured using an uncorrected RK-1 microscopic melting-point apparatus. ^{1}H NMR spectra were recorded on a Bruker AVANCE (400 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. The IR spectra were obtained from KBr disks in the range 4000–400 cm^{-1} on a Nicolet 5DXFT-IR spectrophotometer. Combustion analyses for elemental composition were made with a Perkin-Elmer 2400 instrument. All microwave experiments were performed using YL8023B1 microwave reactor possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz.

General synthetic procedure for synthesis of 1 and **4**. Starting from 2-chloro-5-chloro-methylpridine, a set of (*E*)-*N*-(6-chloro-3-pyridylmethyl)-*N*-ethyl-1-chloro-2-nitroethylene-1-amine and **1** was prepared on the basis of the procedures in the literatures [17,18]. The substituent benzoyl hydrazine was also prepared according to the procedures given in the literatures [19].

General synthetic procedure for synthesis of 3a–3j. Ethanol (20 mL) was added to a mixture of nitenpyram **1** (2.65 g, 9.8 mmol), substituent benzoyl hydrazine (11.95 mmol), and formaldehyde (1.96 mL, 37%) in a microwave reactor. The resulting mixture was heated to 70–75°C for 5 min with temperature maintained for 25 min. After completion of the reaction, the mixture was cooled to room temperature and filtered to give the solid products **3a–3j**, which were washed with ethanol and dried in air. Tetrahydropyrimidine derivatives **3a–3j** were obtained in high purity (>98% by ^{1}H NMR) and did not require further purification. The analytical data for the compounds **3a–3j** were summarized as follows.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]benzamide (3a)**. Yield, 72.5%; mp 235–237°C; ^{1}H NMR (DMSO-d_6), δ 9.97(s, 1H, NNHCO), 8.36 (d, J = 2.4 Hz, 1H, Py-H), 7.78 (dd, J_1 = 3.2 Hz, J_2 = 8.0 Hz, 1H, Py-H), 7.47–7.57 (m, 5H, Ph-H), 7.36 (d, J = 8.0 Hz, 1H, Py-H), 4.54(d, J = 16.0, 1H, Py-CH_2), 4.21 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.79–3.83 (m, 4H), 3.10–3.17 (m, 1H), 2.95 (s, 3H, NCH_3), 2.84–2.92 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3252, 3077, 1682, 1541, 1311, 752; MS (EI + 70 eV) *m/z* (%): 430.5 (M^+, 7.5), 126.2(64.5), 104.1 (100),78.5 (67.4); *Anal*. Calcd for $C_{20}H_{23}ClN_6O_3$: C, 55.75;H, 5.38; N, 19.50. Found: C, 55.67; H, 5.31; N, 19.58.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-fluorobenzamide (3b)**. Yield, 70.5%; mp 213–215°C; ^{1}H NMR (DMSO-d_6), δ 9.92(s, 1H, NNHCO), 8.35 (d, J = 2.0 Hz, 1H, Py-H), 7.78 (dd, J_1 = 3.2 Hz, J_2 = 8.4 Hz, 1H, Py-H), 7.60–7.76 (m,3H, Ph-H), 7.33 (d, J = 8.0 Hz, 1H, Py-H), 4.53(d, J = 16.4, 1H, Py-CH_2), 4.23 (d, J = 16.4 Hz, 1H, Py-CH_2), 3.85–3.89 (m, 4H), 3.12–3.18 (m, 1H), 2.92 (s, 3H, NCH_3), 2.83–2.94 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3256, 3079, 1683, 1542, 1310, 758; MS (EI + 70 eV) *m/z* (%): 448.8 (M^+, 5.3), 126.2(67.4), 122.5 (100), 96.0 (54.2); *Anal*. Calcd for $C_{20}H_{21}Cl_2FN_6O_3$: C, 49.72; H, 4.37; N, 17.41. Found: C, 49.70; H, 4.38; N, 17.39.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-chlorobenzamide (3c)**. Yield, 68.9%; mp 208–210°C; ^{1}H NMR (DMSO-d_6), δ 9.94(s, 1H, NNHCO), 8.32 (d, J = 2.4 Hz, 1H, Py-H), 7.75 (dd, J_1 = 3.0 Hz, J_2 = 8.0 Hz, 1H, Py-H), 7.50–7.80 (m, 4H, Ph-H), 7.32 (d, J = 8.2 Hz, 1H, Py-H), 4.51(d, J = 16.0, 1H, Py-CH_2), 4.21 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.82–3.87 (m, 4H), 3.10–3.16 (m, 1H), 2.95 (s, 3H, NCH_3), 2.80–2.92 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3253, 3080, 1679, 1541, 1309, 749; MS (EI + 70 eV) *m/z* (%): 465.7 (M^+, 5.6), 138.0 (100), 126.2(64.7), 112.4 (50.4); *Anal*. Calcd for $C_{20}H_{22}Cl_2N_6O_3$: C, 51.62; H, 4.77; N, 18.06. Found: C, 51.69; H, 4.71; N, 18.11.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-bromobenzamide (3d)**. Yield, 73.4%; mp 213–215°C; ^{1}H NMR (DMSO-d_6), δ 9.92(s, 1H, NNHCO), 8.30 (d, J = 2.4 Hz, 1H, Py-H), 7.73(dd, J_1 = 3.2 Hz, J_2 = 8.0 Hz, 1H, Py-H), 7.53–7.76 (m, 4H, Ph-H), 7.30 (d, J = 8.0 Hz, 1H, Py-H), 4.50(d, J = 16.0, 1H, Py-CH_2), 4.23 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.80–3.86 (m, 4H), 3.12–3.17 (m, 1H), 2.94 (s, 3H, NCH_3), 2.82–2.90 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H, NCH_2CH_3). IR (KBr, cm^{-1}) 3258, 3088, 1671, 1546, 1314, 739; MS (EI + 70 eV) *m/z* (%): 509.6 (M^+, 7.8), 183.7 (100), 156.8 (42.3), 126.2 (65.3); *Anal*. Calcd for $C_{20}H_{22}BrClN_6O_3$: C, 47.12; H, 4.35; N, 16.49. Found: C, 47.18; H, 4.39; N, 16.41.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3,5-dichlorobenzamide (3e)**. Yield, 71.3%; mp 209–211°C; ^{1}H NMR (DMSO-d_6), δ 9.93 (s, 1H, NNHCO), 8.33 (d, J = 2.0 Hz, 1H, Py-H), 7.76 (dd, J_1 = 3.0 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.58–7.73 (m, 3H, Ph-H), 7.34 (d, J = 8.0 Hz, 1H, Py-H), 4.52 (d, J = 16.2, 1H, Py-CH_2), 4.22 (d, J = 16.2 Hz, 1H, Py-CH_2), 3.81–3.87 (m, 4H), 3.11–3.17 (m, 1H), 2.94 (s, 3H, NCH_3), 2.81–2.92 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}): 3257, 3083, 1684, 2544, 1308, 823, 703; MS (EI + 70 eV) *m/z* (%): 499.5 (M^+, 3.5), 174.1 (100), 147.2 (69.4), 126.3 (67.5); *Anal*. Calcd for $C_{20}H_{21}Cl_3N_6O_3$: C, 48.06; H, 4.24; N, 16.82. Found: C, 48.12; H, 4.32; N, 16.88.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-4-methylbenzamide (3f)**. Yield, 72.8%; mp 219–220°C; ^{1}H NMR (DMSO-d_6), δ 9.93 (s, 1H, NNHCO), 8.31 (d, J = 2.0 Hz, 1H, Py-H), 7.76 (dd, J_1 = 3.2 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.42–7.64 (m, J = 8.2 Hz, J = 8.2 Hz, 4H, Ph-H), 7.34 (d, J = 8.0 Hz, 1H, Py-H), 4.53(d, J = 16.2, 1H, Py-CH_2), 4.23 (d, J = 16.2 Hz, 1H, Py-CH_2), 3.82–3.85 (m, 4H), 3.13–3.17 (m, 1H), 2.97 (s, 3H, NCH_3), 2.81–2.94 (m, 1H), 2.36 (s, 3H, Ph-CH_3), 1.15 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}): 3251, 3080, 1682, 1541, 1308, 805; MS (EI + 70 eV) *m/z* (%): 445.1 (M^+, 5.3), 126.3(61.5), 119.0 (100), 92.3 (72.5); *Anal*. Calcd for $C_{21}H_{25}ClN_6O_3$: C, 56.69; H, 5.66; N, 18.89. Found: C, 56.75; H, 5.73; N, 18.95.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-4-(2,2-dimethyl)ethylbenzamide (3g)**. Yield, 82.2%; mp 218–221°C; ^{1}H NMR (DMSO-d_6), δ 9.90(s, 1H, NNHCO), 8.31 (d, J = 2.0 Hz, 1H, Py-H), 7.73(dd, J_1 = 3.0 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.46–7.78 (m, 4H, Ph-H), 7.30 (d, J = 8.0 Hz, 1H, Py-H), 4.50(d, J = 16.4, 1H, Py-CH_2), 4.20 (d, J = 16.4 Hz, 1H, Py-CH_2), 3.80–3.85 (m, 4H), 3.12–3.17 (m, 1H), 2.93 (s, 3H, NCH_3), 2.82–2.90 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3245, 3074, 1672, 1540, 1303, 701; MS (EI + 70 eV) *m/z* (%): 487.1 (M^+, 5.1), 161.3 (100), 134.4 (62.4), 126.2 (69.4); *Anal*. Calcd for $C_{24}H_{31}ClN_6O_3$: C, 59.19; H, 6.42; N, 17.26. Found: C, 59.12; H, 6.48; N, 17.31.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-3-(*N*,*N*′-dimethyl)amino benzamide (3h)**. Yield, 70.5%; mp 210–213°C; ^{1}H NMR (DMSO-d_6), δ 9.94(s, 1H, NNHCO), 8.33 (d, J = 2.0 Hz, 1H, Py-H), 7.76(dd, J_1 = 3.2 Hz, J_2 = 8.0 Hz, 1H, Py-H), 7.67–7.75 (m, 3H, Ph-H), 7.32 (d, J = 8.4 Hz, 1H, Py-H), 4.52(d, J = 16.0, 1H, Py-CH_2), 4.21 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.81–3.87 (m, 4H), 3.13–3.17 (m, 1H), 2.91 (s, 3H, NCH_3), 2.81–2.94 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3259, 3083, 1679, 1541, 1316, 758; MS (EI + 70 eV) *m/z* (%): 474.2 (M^+, 4.3), 148.3 (100), 126.2 (61.4), 121.3 (65.3); *Anal*. Calcd for $C_{22}H_{28}Cl_1N_7O_3$: C, 55.75; H, 5.95; N, 20.69. Found: C, 55.70; H, 6.03; N, 20.63.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-furylamide (3i)**. Yield, 82.4%; mp 225–227°C; ^{1}H NMR (DMSO-d_6), δ 9.90 (s, 1H, NNHCO), 8.35 (d, J = 2.4 Hz, 1H, Py-H), 7.75 (dd, J_1 = 3.2 Hz, J_2 = 8.2 Hz, 1H, Py-H), 7.54 (d, J = 8.0 Hz, 1H, Fr-H), 7.32 (d, J = 8.4 Hz, 1H, Py-H), 7.14 (d, J = 3.2 Hz, 1H, Fr-H), 6.65 (dd, J_1 = 2.0 Hz, J_2 = 2.0 Hz, 1H, Fr-H), 4.53 (d, J = 16.0, 1H, Py-CH_2), 4.25 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.80–3.85 (m, 4H), 3.13–3.18 (m, 1H), 2.95 (s, 3H, NCH_3), 2.83–2.96 (m, 1H), 1.12 (t, J = 7.6 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{-1}) 3253, 3079, 1691, 1541, 1310, 1244; MS (EI + 70 eV) *m/z* (%): 420.4 (M^+, 1.02), 354.5 (1.25), 67.3 (69.32), 326.4 (2.34), 95.3 (100), 236.3 (43.55), 126.2 (68.31); *Anal*. Calcd for $C_{18}H_{21}ClN_6O_4$: C, 51.35; H, 5.04; N, 19.98. Found: C, 51.37; H, 5.03; N, 19.97.

***N*-[(4Z)-4-[[(6-Chloro-3-pyridinyl)methyl]ethylamino]-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-1-yl]-2-thienylamide (3j)**. Yield, 78.1%; mp 218–219°C; ^{1}H NMR (DMSO-d_6), δ 9.93 (s, 1H, NNHCO), 8.33 (d, J = 2.0 Hz, 1H, Py-H), 7.72 (dd, J_1 = 3.6 Hz, J_2 = 8.0 Hz, 1H, Py-H), 7.62 (d, J = 4.0 Hz, 1H, Tp-H), 7.58 (d, J = 3.6 Hz, 1H, Tp-H), 7.31 (d, J = 8.4 Hz, 1H, Py-H), 7.09 (dd, J_1 = 3.2 Hz, J_2 = 3.2 Hz, 1H, Tp-H), 4.51 (d, J = 16.0, 1H, Py-CH_2), 4.26 (d, J = 16.0 Hz, 1H, Py-CH_2), 3.78–3.82 (m, 4H), 3.10–3.21 (m, 1H), 2.93 (s, 3H, NCH_3), 2.80–2.92 (m, 1H), 1.10 (t, J = 7.6 Hz, 3H, NCH_2CH_3). IR (KBr, cm^{-1}) 3254, 3082, 1683, 1542, 1308, 1248; MS (EI + 70 eV) *m/z* (%): 436.5 (M^+, 2.1), 126.3 (62.4), 111.2 (100), 84.3 (64.3); *Anal*. Calcd for $C_{18}H_{21}ClN_6O_3S$: C, 49.48; H, 4.84; N, 19.23. Found: C, 49.46; H, 4.85; N, 19.25.

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