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Design and Synthesis of 3-(2-Ethyl-4-{2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]ethoxy}phenyl)propanoic Acid: A Novel Triple-acting PPARα, -γ, and -δ Agonist

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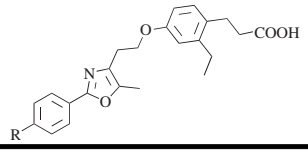
The design and synthesis of triple-acting PPARα, -γ, and -δ agonist 3-(2-ethyl-4-{2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]-ethoxy}phenyl)propanoic acid (**1a**) is described. The compound possesses a potent triple-acting PPARα, -γ, and -δ agonist profile with an EC_{50} of 0.029, 0.013, and 0.029 μM, respectively. The synthetic route, involving the synthesis of oxazole rings as the key step, starts from commercially available 3-oxopentanoic acid methyl ester and 3-hydroxyacetophenone to afford the target compound **1** with an overall yield of 32%.

Insulin resistance is a basic etiological factor for type 2 diabetes and is also linked to a wide spectrum of other pathophysiologic conditions including hypertension, hyperlipidemia, atherosclerosis, and obesity which are collectively called syndrome X or insulin resistance associated disorders (IRAD).[1] Peroxisome proliferator-activated receptors (PPARs), attractive diabetes target proteins, are members of the nuclear hormone receptor superfamily and function as transcription factors in the regulation of genes involved in glucose and lipid fatty acid metabolism and vessel wall function.[2,3] To date, three distinct PPAR subtypes (PPARα, PPARγ, and PPARδ or PPARβ) have been identified in most mammalian species.[4]

Currently the two drugs rosiglitazone and pioglitazone on the market are potent ligands of PPARγ and show efficient insulin sensitization in type 2 diabetes patients.[5] But to effectively target insulin resistance/hyperglycemia and associated conditions including dyslipidemia and hypertension (i.e., the metabolic syndrome), the concept of simultaneously activating PPARα, -γ, and -δ through a single compound has received considerable attention over the past few years.[6] A number of PPAR pan agonists have been described in the literature.[7–13] However, to the best of our knowledge there are no triple-acting PPARs drugs on the market currently. Thus the development of novel and efficacious triple-acting PPARα, -γ, and -δ agonists has extensively clinical significance. We herein present the design and synthesis of a new class of triple-acting PPARα, -γ, and -δ agonists below.

Because selective PPARδ agonist GW501516 has weak potency on PPARα,[14,15] we sought to improve selectivity for PPARα and subsequently optimize potency and selectivity. The modifications of the GW501516 included the replacement of thiazolyl by oxazolidinyl and the head group by the biaryl unit. Further exploring the effects of modifying the terminal trifluoromethyl substituent by a range of groups showed that substitution in this position was largely well tolerated and the potency correlated well with the lipophilicity of the substituent (Table 1). Thus we have accomplished a new class of triple-acting PPARα, -γ, and -δ agonists, one of which, **1a**, is currently in clinical trials for the treatment of dyslipidemia (Figure 1).

Table 1. Effects of modifying the terminal trifluoromethyl substituent



Compound	R	EC_{50}/μM[a]		
		PPARα	PPARγ	PPARδ
Rosiglitazone		Ia[b]	0.001	5.248
1a	F	0.029	0.013	0.029
1b	CH_3	1.175	0.004	0.007
1c	NO_2	2.884	0.025	0.003
1d	*t*-Bu	5.495	0.089	0.851
1e	CHN_4	2.630	6.761	6.761

[a]EC_{50} value is the molar concentration of the test compound that causes 50% of the maximal reporter activity. [b]Ia: inactivated.

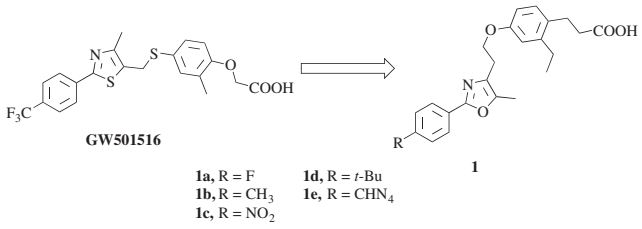
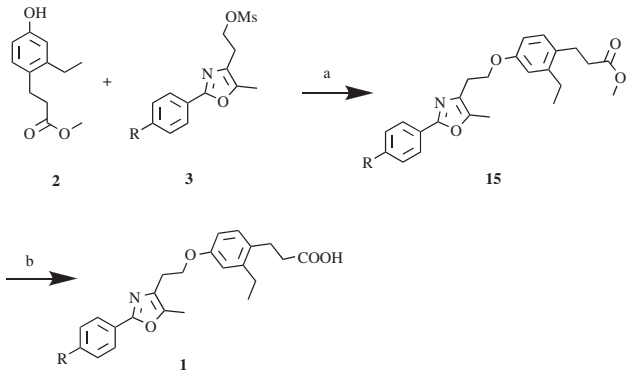
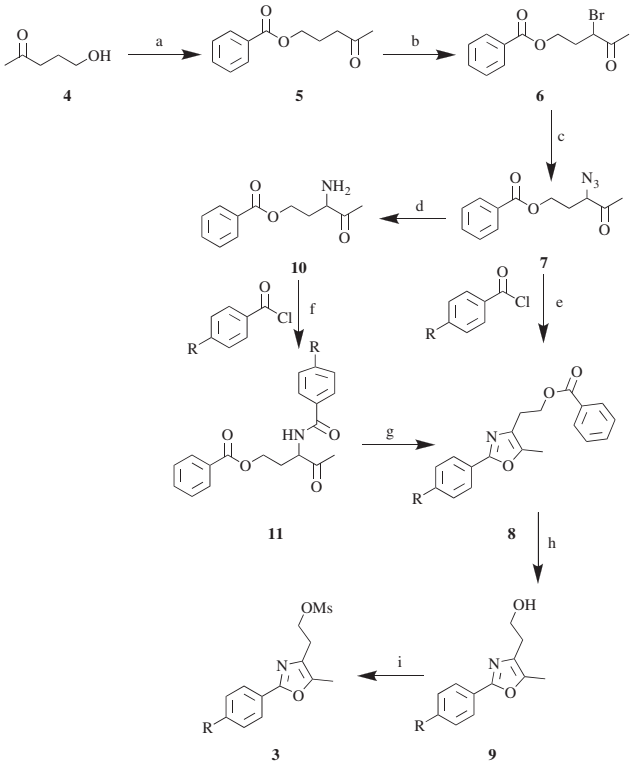


Figure 1. A new class of triple-acting PPARα, -γ, and -δ agonists.



Scheme 1. Reagents and conditions: (a) K_2CO_3, MeCN, reflux, 1 d, 70–90%; (b) NaOH, EtOH, r.t., overnight, 85–95%.

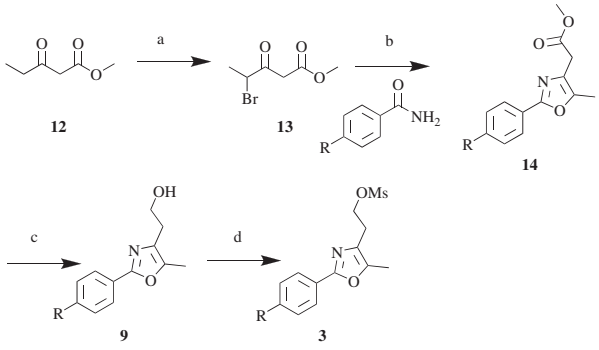
We envisaged the compound **1** to be efficiently formed via intermolecular coupling of the key intermediate **2** and **3** (Scheme 1). The phenol derivative **2** was obtained following the procedures reported by WO054176.[16] For compound **3**, we



Scheme 2. Reagents and conditions: (a) benzoyl chloride, pyridine, CH_2Cl_2, 1 d, 90%; (b) Br_2, ether, 5 °C, 95%; (c) NaN_3, H_2O, acetone, r.t., 92%; (d) Pd–C, HCl, H_2O, EtOAc, H_2, r.t., 12 h, 80–97%; (e) PPh_3, 1,4-dioxane, 75 °C, 3 h, 15–29%; (f) K_2CO_3, H_2O, EtOAc, 0 °C, overnight; (g) $POCl_3$, toluene, reflux, 3 h, 32–41% in two steps; (h) NaOH, EtOH, r.t., 2 h, 87–97%; (i) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h, 92–98%.

tried several synthetic routes. The key step was the formation of oxazole rings as depicted in Schemes 2 and 3. We first attempted to prepare intermediate **8** by reacting azide **7** with triphenylphosphine and acyl chloride.[17,18] Azide **7** was produced from 5-hydroxy-2-pentanone through protection, bromination, and reaction with NaN_3.[19] However, the yield of this process was disappointingly low (less than 20%). Efforts to enhance the efficiency of this reaction by varying the solvents were unsuccessful. Next, we tried another route employing the reduction of azide **7** to amide **10** through catalytic hydrogenation over the Pd/C catalyst. Then the reaction of compound **10** with acyl chloride gave intermediate **11**. Subsequent dehydration of compound **11** with $POCl_3$, produced intermediate **8** with an overall yield of 32%.[18] However, the above procedures failed to generate large quantity of intermediate **8** and, as a result, they are not applicable to large-scale synthesis. So we turned to the third route which was much simpler, safer, and more efficient.

In this route, as shown in Scheme 3, the commercially available 3-oxopentanoic acid methyl ester (**12**) was brominated to give bromo ketone **13**.[19] Compound **13** was cyclized with acid amides in the absence of solvent under elevated temperatures to yield the oxazole intermediate **14**.[20,21] Subsequently, the oxazole ester was reduced with $NaBH_4$ in methanol to provide the oxazole alcohol **9**.[22] Then, elaboration of the hydroxy moiety with MsCl under alkaline conditions was adopted to afford the key intermediate **3** with a yield of 56%.[21] In this approach, the reaction of cyclizing compound **13** with acid amides to prepare



Scheme 3. Reagents and conditions: (a) Br_2, CH_2Cl_2, 5 °C, overnight, 98%; (b) 90 °C, 18 h, 65–75%; (c) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C, 80–95%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95–98%.

intermediate **14** as the key step can easily form an oxazole-olefin under low pH conditions. Meanwhile, the HBr produced by cyclization must be timely removed.

The synthesis route for compound **1** is outlined in Scheme 1. The condensation of phenol **2** with intermediate **3** in acetonitrile under alkaline conditions was conducted under reflux for 24 h to generate the ester **15**.[23] Then saponification of ester **15** with 3 M NaOH, as a final step, afforded the target compound **1** with an overall yield of 32%.[24–29]

In conclusion, compound **1a** was designed and synthesized as a novel triple-acting PPARα, -γ, and -δ agonist in high purity and yield. Moreover, the development of these methods to synthesize oxazole rings is a very useful protocol for the preparation of other pharmaceutical drugs including oxazole compounds.

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21 **Methyl 2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]acetate (14a)**. Crude compound **13** (10 g, 48 mmol) was stirred with 4-fluorobenzamide (10 g, 72 mmol) at 90 °C for 18 h under a vacuum of 400 mbar. After cooling to room temperature, the mixture was treated under argon with 60 mL of toluene and 30 mL of aqueous sodium bicarbonate solution. Then the resulting suspension was stirred in ice-water bath for 1 h and the precipitate benzamide was filtered off with suction. The combined aqueous phases were extracted in a separatory funnel with 150 mL of toluene. Thereafter the combined organic phase was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to give crude **14a** following by recrystallization to afford pure product **14a** (8.6 g, 70%) as a white solid. Mp: 97–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3), 7.10 (t, $J = 8.8$ Hz, 2H, ArH), 7.96 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.2, 31.9, 52.1, 115.6, 115.8, 123.2, 128.7, 129.3, 145.7, 158.7, 162.5, 164.9, 170.7. IR (KBr) ν_{max} (cm^{-1}): 2958, 1735, 1602, 1496, 1222, 1199, 1172, 1159. HR-MS m/z: calcd for $C_{13}H_{13}FNO_3$ [M + H]: 250.0874; found: 250.0877.
22 **2-[2-(4-Fluorophenyl)-5-methyloxazol-4-yl]ethanol (9a)**. To a solution of compound **14a** (0.2 g, 0.8 mmol) in 3 mL of methanol and 2 mL of dichloromethane was added $NaBH_4$ (30.5 mg, 0.8 mmol) three times and the mixture solution was stirred in an ice bath for 1 h. When **14a** was no longer detected by TLC, solvent was removed followed by recrystallization with ethyl acetate to afford pure product **9a** (0.168 g, 94%) as a white solid. Mp: 114–115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.32 (s, 3H, CH_3), 2.71 (t, $J = 5.6$ Hz, 2H, CH_2), 3.35 (br, 1H, OH), 3.92 (m, 2H, OCH_2), 7.11 (t, $J = 8.8$ Hz, 2H, ArH), 7.95 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1, 28.2, 61.8, 115.7, 115.9, 123.9, 128.0, 133.9, 144.2, 158.7, 162.5, 165.0. IR (KBr) ν_{max} (cm^{-1}): 3279, 2928, 1647, 1500. HR-MS m/z: calcd for $C_{12}H_{12}FNO_2Na$ [M + Na]: 244.0744; found: 244.0748.
23 **2-[2-(4-Fluorophenyl)-5-methyloxazol-4-yl]ethyl methanesulfonate (3a)**. To a solution of **9a** (2.7 g, 12 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (3.4 mL, 24 mmol) at 0 °C under argon. The mixture was kept at 0 °C for 30 min and then MsCl (1.42 mL, 18 mmol) was added dropwise. After stirring for 1 h at 0 °C and **9a** was no longer detected by TLC, ammonium chloride solution was added. Thereafter, the mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to afford product **3a** (3.58 g, 98%) as a white solid. Mp: 90–92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.32 (s, 3H, CH_3), 2.95 (m, 5H, CH_2 and SO_2CH_3), 4.51 (t, $J = 6.4$ Hz, 2H, OCH_2), 7.11 (m, 2H, ArH), 7.93 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1, 26.2, 37.2, 68.6, 115.8, 116.0, 123.9, 128.0, 131.1, 145.5, 158.9, 162.5, 165.0. IR (KBr) ν_{max} (cm^{-1}): 2955, 1635, 1498, 1338. HR-MS m/z: calcd for $C_{13}H_{15}FNO_4S$ [M + H]: 300.0661; found: 300.0698.
24 **Methyl 3-(2-ethyl-4-{2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]ethoxy}phenyl)propanoate (15a)**. To a solution of compound **2** (1.5 g, 4.13 mmol) in 15 mL of acetonitrile was added K_2CO_3 (0.86 g, 6.2 mmol) and compound **3a** (2.3 g, 8.26 mmol). The mixture was heated under reflux for overnight. Then the acetonitrile was evaporated to dryness and the residues were dissolved in water, extracted in a separatory funnel with ethyl acetate, dried over anhydrous sodium sulfate, and evaporated to dryness to give a crude of product **15a** (1.7 g, 85%) as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (t, $J = 7.6$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.56 (m, 4H, $2CH_2$), 2.93 (m, 4H, $2CH_2$), 3.66 (s, 3H, OCH_3), 4.21 (t, $J = 6.6$ Hz, 2H, OCH_2), 6.73 (m, 2H, ArH), 7.06 (m, 3H, ArH), 7.94 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.2, 15.2, 25.7, 26.4, 27.0, 35.5, 51.6, 66.6, 111.7, 114.9, 115.7, 115.9, 124.2, 127.9, 129.7, 130.1, 132.8, 143.3, 145.0, 157.5, 158.6, 162.4, 164.9, 173.5; IR (KBr) ν_{max} (cm^{-1}): 2964, 1735, 1608, 1498, 1259, 1232, 1195, 1155. HR-MS m/z: calcd for $C_{24}H_{26}FNO_4Na$ [M + Na]: 434.1738; found: 434.1746.
25 **3-(2-Ethyl-4-{2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]ethoxy}phenyl)propanoic acid (1a)**. To a solution of crude compound **15a** (1.2 g, 2.86 mmol) in 15 mL of ethanol was added dropwise 10% solution of sodium hydroxide (2.3 mL, 5.72 mmol) at room temperature. After stirring for overnight, dilute hydrochloric acid was added until the pH was adjusted to 3 to precipitate solid which was filtered to give crude **1a**. Then the rude was recrystallized with ethyl acetate to afford pure product **1a** (1.2 g, 92%) as a white solid. Mp: 148–149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (t, $J = 7.6$ Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.62 (m, 4H, $2CH_2$), 2.92 (m, 2H, CH_2), 2.97 (t, $J = 6.4$ Hz, 2H, CH_2), 4.22 (t, $J = 6.4$ Hz, 2H, OCH_2), 6.73 (m, 2H, ArH), 7.10 (m, 1H, ArH), 7.68 (m, 2H, ArH), 7.97 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.2, 15.1, 25.7, 26.3, 26.7, 35.4, 66.6, 111.7, 114.9, 115.0, 115.7, 115.9, 124.0, 128.1, 130.0, 132.7, 143.3, 145.1, 157.5, 158.8, 162.5, 165.0, 179.1; IR (KBr) ν_{max} (cm^{-1}): 2962, 1716, 1614, 1315, 1288, 1155, 1105. HR-MS m/z: calcd for $C_{23}H_{25}FNO_4$ [M + H]: 398.1723; found: 398.1775.
26 **3-{2-Ethyl-4-[2-(5-methyl-2-*p*-tolyloxazol-4-yl)ethoxy]phenyl}propanoic acid (1b)**. White solid. Mp: 103–104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (t, $J = 7.6$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.59 (m, 4H, $2CH_2$), 2.88 (t, $J = 7.6$ Hz, 2H, CH_2), 2.96 (t, $J = 6.4$ Hz, 2H, CH_2), 4.18 (t, $J = 6.4$ Hz, 2H, CH_2), 6.68 (m, 2H, ArH), 7.03 (d, $J = 8.0$ Hz, 1H, ArH), 7.23 (d, $J = 8.0$ Hz, 2H, ArH), 7.85 (d, $J = 7.6$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.3, 15.2, 21.5, 25.7, 26.2, 26.9, 35.7, 66.6, 111.6, 114.9, 124.7, 126.0 (2C), 129.4 (2C), 129.7, 130.1, 132.3, 140.2, 143.3, 144.8, 157.4, 159.8, 178.3; IR (KBr) ν_{max} (cm^{-1}): 2922, 1709, 1603, 1286, 1259, 1087, 1022. HR-MS m/z: calcd for $C_{24}H_{28}NO_4$ [M + H]: 394.1974; found: 394.2040. Elemental Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56%. Found: C, 73.21; H, 6.90; N, 3.62%.
27 **3-(2-Ethyl-4-{2-[5-methyl-2-(4-nitrophenyl)oxazol-4-yl]ethoxy}phenyl)-propanoic acid (1c)**. Yellow solid. Mp: 180–182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.20 (t, $J = 7.6$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.57–2.61 (m, 4H, $2CH_2$), 2.89 (t, $J = 7.6$ Hz, 2H, CH_2), 2.99 (t, $J = 6.4$ Hz, 2H, CH_2), 4.21 (t, $J = 6.4$ Hz, 2H, OCH_2), 6.67–6.73 (m, 2H, ArH), 7.05 (d, $J = 8.0$ Hz, 1H, ArH), 8.13 (d, $J = 8.0$ Hz, 2H, ArH), 8.29 (d, $J = 7.6$ Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 9.8, 15.0, 25.0, 25.5, 26.2, 35.0, 65.7, 111.4, 114.3, 124.1, 126.2, 129.4, 130.2, 132.2, 134.0, 142.7, 146.9, 147.5, 156.4, 156.6, 173.9; IR (KBr) ν_{max} (cm^{-1}): 2974, 1711, 1603, 1556, 1386, 1338, 1303, 1145, 1105. HR-MS m/z: calcd for $C_{23}H_{25}N_2O_6$ [M + H]: 425.1668; found: 425.1708.
28 **3-[4-(2-{2-[4-(*tert*-Butyl)phenyl]-5-methyloxazol-4-yl}ethoxy)-2-ethylphenyl]propanoic acid (1d)**. White solid. Mp: 123–124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, $J = 7.6$ Hz, 3H, CH_3), 1.27 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, CH_3), 2.57 (m, 4H, $2CH_2$), 2.86 (m, 2H, CH_2), 2.96 (t, $J = 6.4$ Hz, 2H, CH_2), 4.17 (t, $J = 6.4$ Hz, 2H, OCH_2), 6.67 (m, 2H, ArH), 7.02 (d, $J = 4.0$ Hz, 1H, ArH), 7.43 (d, $J = 4.4$ Hz, 2H, ArH), 7.89 (d, $J = 4.4$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.2, 15.1, 25.6, 26.2, 26.8, 31.1 (3C), 34.8, 35.6, 66.5, 111.5, 114.8, 124.6, 125.6 (2C), 125.7 (2C), 129.6, 130.0, 132.3, 143.2, 144.7, 153.1, 157.3, 159.6, 178.5; IR (KBr) ν_{max} (cm^{-1}): 2962, 1711, 1606, 1506, 1292, 1197. HR-MS m/z: calcd for $C_{27}H_{34}NO_4$ [M + H]: 436.2443; found: 436.2523. Elemental Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22%. Found: C, 74.41; H, 7.63; N, 3.25%.
29 **3-[2-Ethyl-4-(2-{5-methyl-2-[4-(1*H*-tetrazol-5-yl)phenyl]oxazol-4-yl}-ethoxy)phenyl]propanoic acid (1e)**. White solid. Mp: 145–146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (t, $J = 7.6$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.43–2.63 (m, 4H, $2CH_2$), 2.74 (t, $J = 6.4$ Hz, 2H, CH_2), 2.90 (t, $J = 6.4$ Hz, 2H, CH_2), 4.17 (t, $J = 6.4$ Hz, 2H, OCH_2), 6.61–6.68 (m, 2H, ArH), 6.70 (d, $J = 2.4$ Hz, 1H, ArH), 7.67 (d, $J = 8.4$ Hz, 2H, ArH), 8.08 (d, $J = 8.4$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.8, 15.1, 25.0, 25.6, 26.2, 35.0, 65.9, 111.5, 114.4, 126.1, 127.3, 128.7, 129.5, 130.2, 133.2, 142.8, 145.6, 155.6, 156.7, 157.5, 173.8; IR (KBr) ν_{max} (cm^{-1}): 3451, 2960, 1712, 1616, 1577, 1499, 1438, 1238. HR-MS m/z: calcd for $C_{24}H_{26}N_5O_4$ [M + H]: 448.1940; found: 448.1968.

