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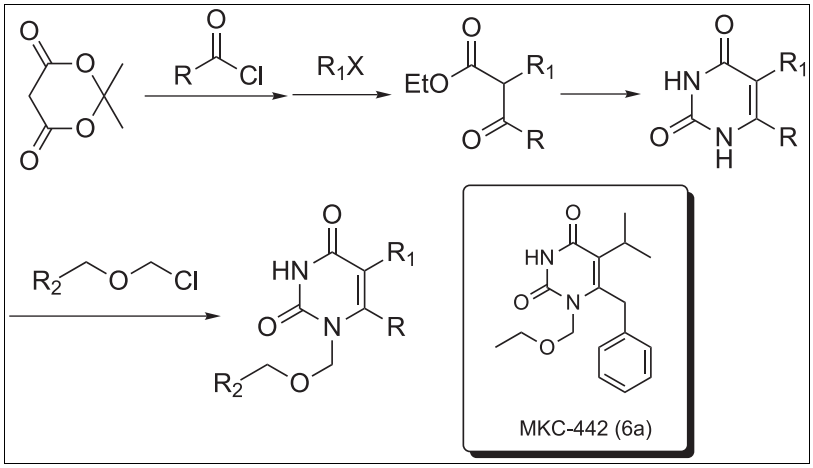

A revised synthetic route to Emivirine (MKC-442) via properly substituted β-keto ester converted from Meldrum's Acid was developed. This method could be applied to the synthesis of a variety of MKC-442 analogues and open the way for their systematic biological evaluation.

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INTRODUCTION

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a class of structurally diverse aromatic compounds that targets the retrovirus HIV-1 by binding to an allosteric pocket (near the catalytic site) of the HIV-1 reverse transcriptase (RT). Among all the representatives, 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil [1] (emivirine, or MKC-442) and the corresponding 1-benzyloxymethyl analogue [2] (TNK-651) showed high activity against HIV-1, and MKC-442 was chosen as a candidate for clinical trials with AIDS patients. However, the rapid development of drug resistance mediate by mutations seriously restricts their practical application. For this reason, there has been a growing interest these years in the design and synthesis of MKC-442 analogs with improved activity against drug-resistant HIV mutant [3].

Although the structure-activity relationship on the anti-HIV of MKC-442 analogues has been well studied, the C-5 substituents of the pyrimidine skeleton are always limited in ethyl group or isopropyl group. Because such groups could act as a triger to improve interaction between reside Tyr181 in the protein and the 6-benzyl group of the inhibitors which stabilizes the structure of the complex [2]. However, in the previous work of our group, we found that the aromatic ring linked to C-5 by 2–3 carbon (nitrogen) units possesses conformational similarity of C-6 benzyl group of MKC-442 or TNK-651, and MKC-442 analogues with C-5 bulky substituents and C-6 small alkyl substituents also have potent anti-HIV RT activities. This encourages us to continue our QSAR studies on different C-5 and C-6 substituents of MKC-442 analogues.

A quick access to the MKC-442 analogs bearing different substitutions of uracil skeleton relies on an efficient and versatile synthetic route to MKC-442. After literature research, we find that the synthesis of this kind of structures are starting from uracil derivatives or properly substituted β-keto esters. In practice, the modifications of uracil derivatives need lithiation reagents [4], Grignard reagents and expensive catalysts [5], and the uracil derivatives themselves sometimes are not readily available either. Another, the β-keto ester is prepared (taking ethyl 2-ethyl-3-oxo-4-phenylbutyrate for example [6]) by Reformatsky reaction of benzyl cyanide with 2-bromobutyrate, or by condensation of phenylacetyl chloride with potassium ethyl 2-ethylmalonade. We investigated these two methods; there are, however, limitations in preparing the β-keto esters

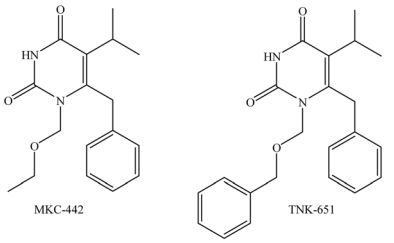

Figure 1. Structures of MKC-442 and TNK-651.

corresponding to MKC-442 or other C-5 bulky substituted analogues, because the materials are not readily available in the first method, and the steric influences of isopropyl or other bulky groups prohibit the reaction in the second method.

RESULTS AND DISCUSSION

At the same time, as part of our research program in this area, we have developed a new route to MKC-442 and its analogs as potential HIV-1 RT inhibitors (Scheme 1). Since the reactivities of compound **2** and **3** are apparent, these new molecules can also be used to introduce other functional groups at 5 and 6-positions of pyrimidine ring.

To obtain intermediate **3**, Meldrums acid was first selectively acylated with phenylacetyl chloride to give the C-acylated derivative. When heated with alcohol, the acyl derivative is rapidly converted into the appropriate β-keto ester **2** in quantitative yield [7]. Compound **2** was then alkylated through treatment with i-PrBr to afford the corresponding substituted β-keto ester **3**.

The key step whether this new route could perform as expected is the alkylation of the compound **2**. Although the protons alpha to carbonyl groups are easily deprotonated, the deprotonated β-keto esters are ambident nucleophiles, which also leads to the possibility of O-alkylation of enolic-OH. To our knowledge, the alkylation of ethyl 3-oxo-4-phenylbutyrate **2** has not been reported. First, we investigated the reaction of the compound **2** with 2-bromopropane under the condition of sodium ethoxide in anhydrous ethanol, by which the solvent effect on oxygen anion is believed to be in favor of C-alkylation. Surprisingly, none of the desired product was obtained and starting material was recovered quantitatively. We assumed that the anion generated by deprotonation of the compound **2** may have less nucleophilicity in protonic solvent.

Therefore, the condition with a stronger base in aprotic solvent (sodium hydride and tetrahydrofuran), was explored but no desired product was observed, probably due to the facts that 2-bromopropane tends to eliminate in strong bases and the substrate is not stable in such condition. A moderate base may be an alternative.

Our attention then turned to moderate inorganic bases. The approach of replacing NaH with K_2CO_3 was attempted. We supposed that alkali metal carbonates in presence of phase transfer catalyst would be efficient, which applies to quite weak carbon acids like phenylacetonitrile [8]. As we expected, the reaction of ethyl 3-oxo-4-phenylbutyrate **2** with 2-bromopropane in the presence of potassium carbonate and tetra-*n*-butylammonium bromide in *N,N*-dimethylacetamide at room temperature gave ethyl 2-isopropyl-3-oxo-4-phenylbutyrate **3a** as clear oil with 71% yield. To optimize of the conditions, the alkylation reaction was carried out in different amounts of potassium carbonate (5, 3, 1 equiv.), solvents (DMF, DMAc, THF) and temperatures (20–90°C), unfortunately the yield did not increase, and the O-alkylation byproduct appeared when temperature raised higher than 60°C. (Table 1)

Herein, a convenient method to access the key intermediate **3** was obtained. From the starting material 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's Acid), which is either commercial available or easily prepared from malonic acid and acetone, substituted β-keto esters corresponding to different 5,6-substituted analogues could be prepared only by the change of acyl halide at the first step, or alkyl halide at the second step. Methyl iodide and ethyl bromide were tried as examples here, from which methyl or ethyl substituted β-keto esters could be acquired considerably with high yield. And it is quite certain that the target 5-methyl or 5-ethyl uracil derivatives could be obtained by three subsequent steps, and the 5-methyl target products were unreported. These results

Scheme 1.

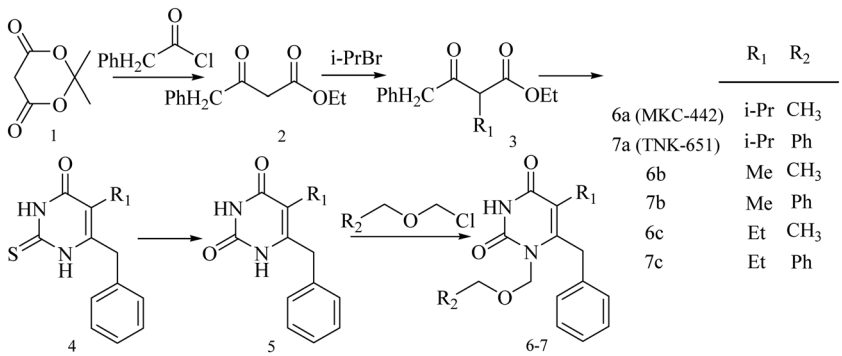

Table 1

Reaction conditions and the yields of ethy1 2-isopropyl-3-oxo-4-phenylbutyrate (**3a**).

Entry	Amount of base	Solvent	Temperature (°C)	Yield (%)
1	1:1	DMF	20	52.70
2	1:3	DMF	20	71.30
3	1:5	DMF	20	68.50
4	1:1	THF	20	27.10
5	1:3	THF	20	39.50
6	1:5	THF	20	38.30
7	1:1	DMAc	20	57.50
8	1:3	DMAc	20	68.70
9	1:5	DMAc	20	66.30
10	1:3	DMF	40	65.80
11	1:3	DMF	60	62.70
12	1:3	DMF	90	48.80

encouraged and facilitated our thought of the study on QSAR of different substituents at 5- and 6-position of uracil and anti-HIV-activities. The follow-up work is in progress in our group.

With the necessary β-keto esters in hand, we were able to complete the synthetic route with established reactions. Cyclization of ethyl 2-isopropyl-3-oxo-4-phenylbutyrate **3** with thiourea in sodium ethoxide/ethanol, followed by desulfurizing in 10% chloroacetic acid afforded 6-benzyl-5-isopropyluracil with 64% yield. Treatment of 6-benzyl-5-isopropyluracil with chloromethyl ethyl ether and chloromethyl benzyl ether after silylating with *N,O*-bis-(trimethylsilyl)acetamid (BSA) gave MKC-442[10] and TNK-651[11], with yield of 97% and 89%, respectively (Scheme 1). The reactions from methyl and ethyl substituted β-keto esters to their corresponding target products were also smoothly and successfully.

CONCLUSIONS

In summary, an effective and flexible route to MKC-442 and its derivatives has been developed, with three significant practical advantages including, (a) easily available starting materials and mild reaction condition, which favors to large-scale preparation; (b) the high overall yields, which are 43.7% (five steps) and 40.1% for MKC-442 and TNK-651, respectively; (c) special, effective synthesis of a variety of MKC-442 analogues for its systematic biological evaluation.

EXPERIMENTAL

Melting points were determined on an X4-type melting-point apparatus and are uncorrected. NMR spectra were recorded on a Jeol-AL-300 Fourier Transform (FT) spectrometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR with TMS as the internal standard. The ESI-MS spectra were obtained with a Liner Scientific LDI-1700 mass spectrometer. ESI-HRMS spectra were obtained with a Bruker APEX IV mass spectrometer. Silica gel (0.040–0.064 mm) was used for column chromatography.

Ethyl 3-oxo-4-phenylbutyrate (2) [9]. To the solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's Acid) (23.75 g, 0.165 mol) and anhydrous pyridine (32.5 mL, 0.4 mol) in CH_2Cl_2 (100 mL), phenylacetyl chloride (25.50 g, 0.165 mol) was added dropwise under 0°C. The mixture was stirred at 0°C for 1 hour and raised to room temperature for another 1 hour. One hundred milliliter 2N aq HCl was added to stop the reaction. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2. The organic layer was collected, evaporated the solvent to give light yellow solid. After washing by little amount of EtOH, white crystal was obtained and directly refluxed with anhydrous EtOH (250 mL) for 2.5 hours. After concentration under reduced pressure, light yellow oil was obtained which can be used in the next step without purification. Purification by column chromatography with EtOAc-petroleum ether (1:80) yields compound **2** as colorless oil (33.05 g, 98.8%). ESI-MS: *m/z* = 207.1[M+H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.20 (m, 5H, Ar*H*), 4.20–4.13 (q, 2H, OCH_2Me), 3.83 (s, 2H, CH_2-Ph), 3.51 (s, 2H, CH_2), 1.29–1.24 (t, 3H, OCH_2CH_3).

Ethyl 2-isopropyl-3-oxo-4-phenylbutyrate (3a). The mixture of ethyl 3-oxo-4-phenylbutyrate (16.50 g, 0.080 mol), 2-bromopropane (11.8 g, 0.096 mol), anhydrous K_2CO_3 (26.20 g, 0.24 mol) and TBAB (cat. 10% mol, 2.56 g, 0.008 mol) in anhydrous DMF (25 mL) was stirred at room temperature for 12 hours. The mixture was diluted by 50 mL EtOAc, washed by brine. The organic layer was dried with anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography with EtOAc-petroleum ether (1:80) to yield the compound **3** as colorless oil (14.2 g, 71.3%). ESI-MS: *m/z* = 249.1[M+H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.22 (5H, m, Ar*H*), 5.07 (1H, s, COC*H*CO), 4.42–4.36 (1H, m, C*H*Me$_2$), 4.21–4.16 (2H, q, OCH_2CH$_3$), 4.11 (2H, s, CH_2Ph), 1.32–1.29 (3H, t, OCH_2CH_3) 1.26–1.24 (6H, d, CH*Me*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.01 (C-3), 167.84 (C-1), 138.14, 129.18, 128.14, 126.20 (C-aryl), 91.69 (COCHCO), 70.23 (CH_2Ph), 59.37 (OCH_2CH_3), 37.81 (CHMe$_2$), 21.35 (CHMe$_2$), 14.43 (OCH_2CH_3).

Ethyl 2-methyl-3-oxo-4-phenylbutyrate (3b). This compound was prepared as clear oil following the procedure described for the preparation of **3**. Yield: 92.6%; ESI-MS: *m/z* = 221.1 [M+H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.20 (m, 5H, Ar*H*), 4.19–4.13 (q, 2H, OC*H*CH$_3$), 3.83 (s, 2H, CH_2-Ph), 3.41–3.32 (m, 1H, CH_2), 1.35–1.33 (d, 3H, CHCH_3) 1.29–1.23 (t, 3H, OCH_2CH_3).

Ethyl 2-ethyl-3-oxo-4-phenylbutyrate (3c). This compound was prepared as clear oil following the procedure described for the preparation of **3**. Yield: 86.5%; ESI-MS: *m/z* = 235.1 [M+H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.13 (5H, m, Ar*H*), 4.23–4.18 (2H, q, OCH_2Me), 3.95 (2H, s, CH_2-Ph), 3.80–3.71 (1H, m, COC*H*CO), 1.97–1.66 (2H, m, CH_2Me), 1.27–1.21 (3H, t, OCH_2CH_3), 0.96–0.90 (3H, t, CH_2CH_3).

6-benzyl-5-isopropyluracil (5a) [10]. Sodium (2.2 g, 96 mmol) was dissolved in anhydrous EtOH (200 mL), and thiourea (4.96 g, 64 mmol) and ethyl 2-isopropyl-3-oxo-4-phenylbutyrate (**3**) (6.56 g, 32 mmol) were added to the clear solution. The reaction mixture was refluxed for 6 hours, evaporated under reduced pressure, and the residue redissolved in H_2O (50 mL). The 6-benzyl-5-isopropyl-2-thiouracil **4** was precipitated by acidification to pH 4 with 2 N aq HCl. The precipitated

compound **4** was desulfurized by suspension in 10% aq chloroacetic acid (200 mL) and subsequent reflux for 24 h. After cooling to room temperature the precipitate was filtered off, washed with cold EtOH and Et_2O and finally dried to give compound **5** as white solid (5.48 g, 66.1%). mp 224–226°C. ESI-MS: *m/z* = 244.2 $[M+H]^+$.

6-Benzyl-5-methyluracil (5b). This compound was prepared as white solid following the procedure described for the preparation of **5**. Yield: 63.6%; mp 257–258°C. ESI-MS: *m/z* = 217.2 $[M+H]^+$.

6-Benzyl-5-ethyluracil (5c) [6]. This compound was prepared as white solid following the procedure described for the preparation of **5**. Yield: 68.2%; mp 236–237°C. ESI-MS: *m/z* = 231.2 $[M+H]^+$.

6-Benzyl-1-ethoxymethyl-5-isopropyluracil (MKC-442). To a suspension of the compound **5** (1.2 g, 5.0 mmol) in anhydrous CH_2Cl_2 (30 mL) was added *N,O*-bis-(trimethylsilyl)-acetamid (BSA) (3.2 mL, 11.0 mmol) and stirring was continued until all the starting material had dissolved. Then chloromethyl phenyl ether (0.57 g, 6.0 mmol) and LiI (0.07 g, 0.5 mmol) was added and stirred at r.t for 3 h. Saturated aq $NaHCO_3$ (10 mL) was added to quench the reaction. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phase was dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the product was purified by column chromatography with EtOAc-PE (1:5) to obtain the pure product as white solid (1.38 g, 91.5%). mp.105–108°C. (Lit [1]. mp. 109–110°C); ^{1}H NMR (300 MHz, $CDCl_3$)δ: 8.97 (1H,br s,N*H*), 7.36–7.11 (5H,m,Ar*H*), 5.13 (2H,s,NCH_2O), 4.18 (2H,s,CH_2Ph), 3.65–3.60 (2H,q,OCH_2Me), 2.90–2.82 (1H,m, C*H*Me$_2$), 1.29–1.27 (6H,d, CH*Me*$_2$), 1.20–1.17 (3H,t, OCH$_2$*Me*); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 162.23 (C-4), 151.82 (C-2), 148.46 (C-6), 135.44, 129.19, 127.26, 127.22 (C-aryl), 119.71 (C-5), 72.91 (NCH$_2$O), 65.00 (OCH$_2$CH$_3$), 33.50 (CH$_2$Ph), 28.34 (CHMe$_2$), 20.39 (CHMe$_2$), 15.03 (OCH$_2$CH$_3$); HRESI-MS *m/z*: calcd for $C_{17}H_{22}N_2O_3$, 303.17090$[M+H]^+$; found 303.17032.

6-Benzyl-1-benzyloxymethyl-5-isopropyluracil (TNK-651). To a suspension of the compound **5** (1.2 g, 5.0 mmol) in anhydrous CH_2Cl_2 (30 mL) was added N,O-bis-(trimethylsilyl)-acetamid (BSA) (3.2 mL, 11.0 mmol) and stirring was continued until all the starting material had dissolved. Then chloromethyl phenyl ether (0.94 g, 6.0 mmol) and LiI (0.07 g, 0.5mmol) was added and stirred at r.t for 3h. Saturated aq $NaHCO_3$ (10mL) was added to quench the reaction. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phase was dried with Na_2SO_4. After evaporation of the solvent under reduce pressure, the product was purified by column chromatography with EtOAc-PE (1:5) to obtain the pure product as white solid (1.57 g, 86.5%). mp.112–115°C. (Lit [2]. mp. 112–113°C); ^{1}H NMR (300 MHz, $CDCl_3$)δ: 8.87 (1H, s, N*H*), 7.33–7.25 (8H, m, Ar*H*), 7.06–7.04 (2H, d, Ar*H*), 5.21(2H, s, NCH_2O), 4.65 (2H, s, OCH_2Ph), 4.16 (2H, s, CH_2Ph), 2.88–2.81 (1H, m, C*H*Me$_2$), 1.27–1.25 (6H, d, CH*Me*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 162.09 (C-4), 151.79 (C-2), 148.37 (C-6), 137.33, 135.29, 129.21, 128.48, 128.00, 127.78, 127.27 (C-aryl), 119.79 (C-5), 72.96 (NCH$_2$O), 71.81 (OCH$_2$Ph), 33.48 (CH$_2$Ph), 28.32 (CHMe$_2$), 20.40 (CHMe$_2$); HRESI-MS *m/z*: calcd for $C_{22}H_{24}N_2O_3$, 365.18536$[M+H]^+$; found 365.18597.

6-Benzyl-1-ethoxymethyl-5-methyluracil (7b). This compound was prepared as white solid following the procedure described for the preparation of **MKC-442**. Yield: 83.9%; mp 129–130°C. ESI-MS: *m/z* = 275.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 9.48 (1H, s, N*H*), 7.37–7.14 (5H, m, Ar*H*), 5.17 (2H, s, NCH_2O), 4.19 (2H, s, CH_2Ph), 3.70–3.61 (2H, q, OCH_2CH$_3$), 2.06 (3H, s, CH_3-C5), 1.22–1.18 (3H, t, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 163.75 (C-4), 151.84 (C-2), 149.72 (C-6), 134.76, 129.29, 128.82, 127.35 (C-aryl), 111.01 (C-5), 72.82 (NCH$_2$O), 64.99(OCH$_2$Me), 34.01 (CH$_2$Ph-C6), 15.05 (OCH$_2$CH$_3$) 10.97 (CH$_3$-C5).

6-Benzyl-1-ethoxymethyl-5-ethyluracil (7c). This compound was prepared as white solid following the procedure described for the preparation of **MKC-442**. Yield: 90.6%; mp 103–104° C. ESI-MS: *m/z* = 289.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 9.46 (1H, s, N*H*), 7.36–7.01 (5H, m, Ar*H*), 5.15 (2H, s, NCH_2O), 4.12 (2H, s, CH_2Ph), 3.68–3.58 (2H, q, OCH_2Me), 2.52–2.43 (2H, q, CH_2Me), 1.21–1.13 (3H, t, OCH$_2$CH_3), 1.09–1.02 (3H, t, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$)δ: 163.74 (C-4), 152.90 (C-2), 148.53 (C-6), 135.23, 129.29, 127.89, 127.36 (C-aryl), 116.01 (C-5), 72.59 (NCH$_2$O), 64.67 (OCH$_2$Me), 33.02 (CH$_2$Ph-C6), 18.92 (CH$_2$CH$_3$), 14.86 (OCH$_2$CH$_3$), 13.97 (CH$_2$CH$_3$).

6-Benzyl-1-benzyloxymethyl-5-methyluracil (8b). This compound was prepared as white solid following the procedure described for the preparation of **TNK-651**. Yield: 73.6%; mp 94–95°C. ESI-MS: *m/z* = 337.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 9.44 (1H, s, N*H*), 7.39–7.07 (10H, m, Ar*H*), 5.25 (2H, s, NCH_2O), 4.67 (2H, s, OCH_2Ph), 4.17 (2H, s, CH_2Ph), 2.03 (CH$_3$-C5); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 163.74 (C-4), 151.90 (C-2), 149.53 (C-6), 137.23, 134.66, 129.29, 128.48, 128.03, 127.89, 127.36 (C-aryl), 111.01 (C-5), 72.19 (NCH$_2$O), 71.67 (OCH$_2$Ph), 34.02 (CH$_2$Ph-C6), 10.97 (CH$_3$-C5).

6-Benzyl-1-benzyloxymethyl-5-ethyluracil (8c). This compound was prepared as white solid following the procedure described for the preparation of **TNK-651**. Yield: 78.5%. mp 92–93°C. ESI-MS: *m/z* = 351.2 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 9.96 (1H, s, N*H*), 7.43–7.07 (10H, m, Ar*H*), 5.39 (2H, s, NCH_2O), 4.67 (2H, s, OCH_2Ph), 4.15 (2H, s, CH_2Ph), 2.48–2.41 (2H, q, CH_2CH$_3$), 1.12–1.06 (3H, t, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 162.24 (C-4), 151.90 (C-2), 148.53 (C-6), 137.33, 135.36, 129.19, 128.58, 128.03, 127.89, 127.26 (C-aryl), 119.01 (C-5), 73.09 (NCH$_2$O), 71.87 (OCH$_2$Ph), 33.52 (CH$_2$Ph-C6), 28.24 (CH$_2$CH$_3$), 20.97 (CH$_2$CH$_3$).

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