

Asymmetric Synthesis of Arylpropionic Acids and Aryloxy Acids by Using Lactamides as Chiral Auxiliaries

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Two different dynamic kinetic resolution methods have been applied for the asymmetric synthesis of pharmaceutical arylpropionic acids and aryloxy acids by using amides of (*S*)-lactic acid as chiral auxiliaries. For arylpropionic acids the esterification mediated by dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) proceeds with good

asymmetric induction, while for aryloxyacetic acids the key-step is a diastereoselective substitution reaction in the presence of triethylamine and *n*-hexylammonium iodide as additives.

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Introduction

High levels of diastereoselection have been recently achieved in the chiral auxiliary-mediated dynamic kinetic resolution (DKR).^[1] In this synthetic strategy is essential to start from a configurationally labile substrate, that forms a mixture of two diastereomers with a chiral auxiliary; the stereochemical control of subsequent step is governed by different reactivity of the two diastereomers, under the influence of chiral auxiliary.^[2]

Amides or esters derived from lactic acid have been found to be very efficient in a variety of asymmetric syntheses;^[3] thus, we have recently developed lactamide chiral auxiliaries and we applied them in DKR of two pharmaceutical agents: the antiinflammatory ibuprofen^[4] and the 2-(*p*-chlorophenoxy)butanoic acid,^[5] an analog of antilipidemic drug clofibrate. In our previous investigations we have used dimethyl-, dibenzyl- and pyrrolidine-derived lactamide as chiral auxiliaries; the most successful results in diastereoselectivity by using the (*S*)-pyrrolidine-derived lactamide prompted us to investigate the extension to new chiral amides, in which the *N*-substituents were incorporated in an aliphatic cycle. Herein, we report the results of our studies on dynamic kinetic resolution mediated by piperidine-, 4-methylpiperazine-, morpholine- and pyrrolidine-derived lactamide auxiliaries in two different synthetic strategies: (1) the asymmetric esterification of ibuprofen, flurbiprofen and fenoprofen and (2) the nucleophilic substitution of α -bromobutanoic esters with an aryloxy.

Results and Discussion

Our investigations started with the preparation of the chiral auxiliaries (*S*)-**1a–d** (Figure 1) by simple aminolysis of ethyl (*S*)-lactate with a slight excess of amine, according to the literature procedures.^[6] A summary of experimental conditions is given in Table 1. The first application of DKR strategy was the asymmetric esterification of racemic ibuprofen, flurbiprofen and fenoprofen^[7] (Figure 2) with all lactamides, performed in the presence of 1.0 equiv. each of DCC and DMAP, in toluene or CH₂Cl₂; the reactions of fenoprofen were performed only in CH₂Cl₂, because its weak solubility in toluene; for explanation of the mechanism of reaction, we have assumed the initial formation of an intermediate acyl 4-(dimethylamino)pyridinium salt from racemic arylacetic acid, that increases the reactivity of carbonyl toward the nucleophilic attack of lactic amides, as proposed by Calmes for a similar esterification (Scheme 1).^[8] As shown in Table 2, the diastereomeric mixtures of lactamic esters of ibuprofen, flurbiprofen and fenoprofen (*R,S*)-**2a–d** to (*R,S*)-**4a–d** and (*S,S*)-**2a–d** to (*S,S*)-**4a–d** were obtained with good yields and with diastereoselectivity varying upon the solvent and the auxiliary used. As a general trend, reactions performed in toluene were faster and with higher diastereomeric ratios respect to those in CH₂Cl₂. Reactions of ibuprofen, flurbiprofen and fenoprofen with piperidine-containing lactamide (*S*)-**1a** afforded the corresponding esters (*S,S*)-**2a–4a** and (*R,S*)-**2a–4a** with excellent diastereomeric ratios, ranging from 90:10 to 95:5, both in toluene and CH₂Cl₂ (Entries 1–5). Lower ratios (*S,S*)-**2b–4b**/*(R,S)*-**2b–4b** (the greatest being 70:30) were observed with the auxiliary 4-methylpiperazine-derived lactamide (*S*)-**1b** (Entries 6–10). Good diastereoselectivity was observed with morpholine-derived lactamide (*S*)-**1c**, going

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from ibuprofen esters (*dr* 68:32 and 61:39, Entries 11–12) to flurbiprofen and fenopropfen esters (*dr* 97:3, 91:9 and 96:4, Entries 13–15). Regarding the esterifications with pyrrolidine-derived lactamide auxiliary (*S*)-**1d**, good results for mixtures **2d–4d** were obtained in toluene (*dr* 85:15, 90:10 and 81:19, Entries 16, 18 and 20) respect to those in CH₂Cl₂ (Entries 17 and 19). Noteworthy, the adducts of each diastereomeric mixture have different chromatographic mobilities under the conditions used for purification; in this way, it was possible to obtain the main compounds in diastereomerically pure form. These good stereochemical results could be attributed to the sufficiently fast equilibration with respect to the esterification rate of the above pyridinium intermediate, showing that the pathway of asymmetric induction is a dynamic kinetic resolution process. In a previous work we reported a close examination of the reasons of stereoselectivity for reaction of ibuprofen and pyrrolidine-derived lactamide, by using molecular mechanic calculations, confirming a DKR process.^[4]

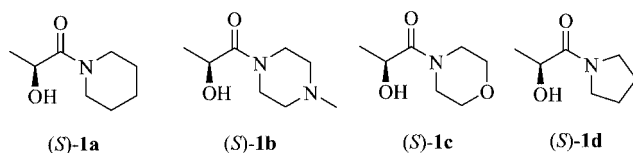


Figure 1. Lactamides.

Table 1. Synthesis of chiral auxiliaries (*S*)-**1a–d**.

Entry	Amide	Amine	Amine [equiv.]	Temp. [°C]	Time [h]	Yield [%] ^[a]
1	(<i>S</i>)- 1a	piperidine	1.0	20	24	33
2	(<i>S</i>)- 1b	piperazine	1.0	20	72	31
3	(<i>S</i>)- 1c	morpholine	1.2	90	72	35
4	(<i>S</i>)- 1d	pyrrolidine	1.2	20	72	66

[a] Isolated yield after purification.

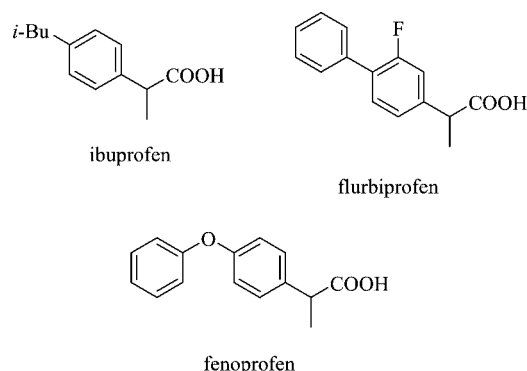
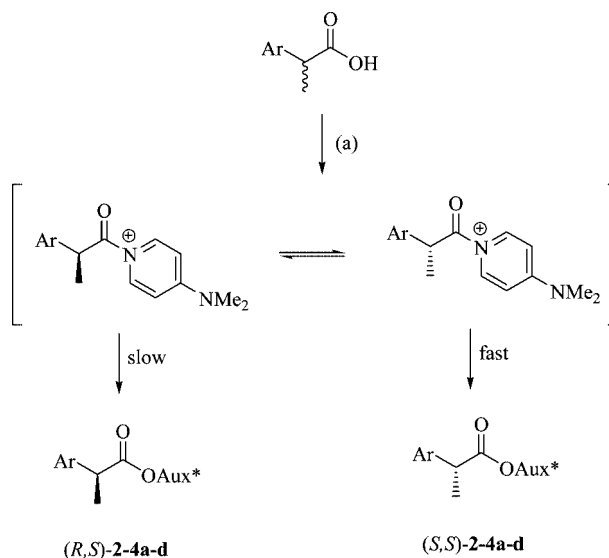


Figure 2. Arylpropionic acids.

In the second instance, we have examined the lactamide-mediated DKR for asymmetric synthesis of 2-(4-chlorophenoxy)butanoic acid, an analog of antilipidemic drug clofibrate. In an effort to improve the stereoselectivity previously obtained with other lactamidic auxiliaries,^[5] we

Aux–OH: lactamides **1a–d****a:** (*S*)-**1a**, **b:** (*S*)-**1b**, **c:** (*S*)-**1c**, **d:** (*S*)-**1d**Scheme 1. Reagents and conditions: (a) (*S*)-**1a–d**, DCC, DMAP, toluene (0 °C) or CH₂Cl₂ (–20 °C).

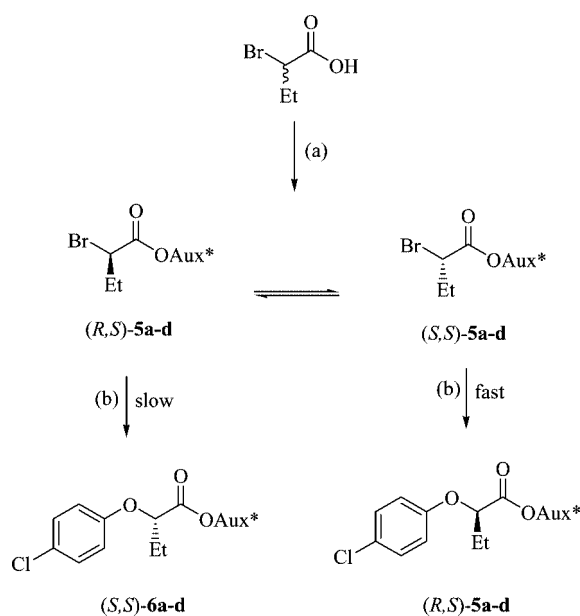
have investigated the nucleophilic substitution reaction of 2-bromobutanoyl esters **5a–d**, derived by coupling of racemic 2-bromobutanoyl chloride and lactamides (*S*)-**1a–d** in equimolar ratios. Much like in a typical DKR,^[9] treatment of **5a–d** with sodium 4-chlorophenoxide was performed in THF at 0 °C or 60 °C, in the presence of NEt₃ and *n*-hexylammonium iodide as additives, gaining the diastereomeric mixtures of aryloxy esters (*R,S*)-**6a–d** and (*S,S*)-**6a–d** with good yields (Scheme 2). Thus, we have investigated the effects of chiral auxiliary and temperature on stereochemical outcome of substitution reaction, gaining diastereomeric ratios from 88:12 to 99:1 (Table 3); the diastereoselectivities are excellent and almost identical at 0 °C (Entries 1,3,5,7), while a mild decrease was observed at 60 °C (Entries 2,4,6,8); no substantial differences were found varying the lactamide. These data are in agreement with the reported results^[10] and suggest that the chiral information of (*S*) auxiliaries has been transferred to the 2-bromocarbon center via dynamic kinetic resolution; the effect of bulky chiral auxiliary is clear and reflect the intrinsic differences in activation energies of substitution reaction between each epimer of interconverting 2-bromo esters.

The diastereomeric ratios were determined through ¹H NMR spectra of the crude mixtures **2–4** and **6**, based on the signals related to the protons at stereogenic centers of lactic amides and the 2-carbon of arylpropionic and aryloxyacetic acids. Finally, the configuration of the chiral center in the main isomer of all diastereomeric mixtures was proven to be (*S*) for arylpropionic acids and (*R*) for aryloxyacetic acids after conversion into the corresponding enantiomeric acids in 6 M HCl at reflux. The lactamides were recovered after purification without racemization.

Table 2. Asymmetric esterification of arylpropionic acids with (*S*)-**1a–d**.

Entry	Auxiliary	Arylpropionic acid	Solvent	Time [h]	Yield [%] ^[a]	Product	<i>dr</i> (<i>S,S</i>)- 2–4 / <i>(R,S)</i> - 2–4 ^[b]
1	<i>(S)</i> - 1a	ibuprofen	toluene	5	78	2a	95:5
2		ibuprofen	CH ₂ Cl ₂	24	82	2a	84:16
3		flurbiprofen	toluene	24	72	3a	96:4
4		flurbiprofen	CH ₂ Cl ₂	36	80	3a	90:10
5		fenopropfen	CH ₂ Cl ₂	48	55	4a	92:8
6	<i>(S)</i> - 1b	ibuprofen	toluene	5	20	2b	67:33
7		ibuprofen	CH ₂ Cl ₂	48	38	2b	61:39
8		flurbiprofen	toluene	1	28	3b	70:30
9		flurbiprofen	CH ₂ Cl ₂	20	64	3b	60:40
10		fenopropfen	CH ₂ Cl ₂	20	63	4b	63:37
11	<i>(S)</i> - 1c	ibuprofen	toluene	0.5	62	2c	68:32
12		ibuprofen	CH ₂ Cl ₂	48	22	2c	61:39
13		flurbiprofen	toluene	1	77	3c	97:3
14		flurbiprofen	CH ₂ Cl ₂	20	65	3c	91:9
15		fenopropfen	CH ₂ Cl ₂	20	74	4c	96:4
16	<i>(S)</i> - 1d	ibuprofen	toluene	1	71	2d	85:15
17		ibuprofen	CH ₂ Cl ₂	21	74	2d	70:30
18		flurbiprofen	toluene	1.5	87	3d	90:10
19		flurbiprofen	CH ₂ Cl ₂	48	82	3d	75:25
20		fenopropfen	CH ₂ Cl ₂	24	62	4d	81:19

[a] Isolated yield after flash chromatography. [b] Diastereomeric ratios determined by ¹H NMR analysis of crude mixtures **2–4a–d**.



Scheme 2. Reagents and conditions: (a) (*S*)-**1a–d** (Aux*H), NEt₃, CH₂Cl₂, (–20 °C); (b) NEt₃, *n*-Hex₄N⁺I[–], THF (0 °C or 60 °C).

Table 3. Diastereoselective substitution of α-bromo esters **5a–d**.

Entry	Amide	Temp. [°C]	Time [h]	Yield [%] ^[a]	<i>dr</i> ^[b] (<i>R,S</i>)- 6 / <i>(S,S)</i> - 6
1	<i>(S)</i> - 1a	0	3	90	97:3
2	<i>(S)</i> - 1a	60	1	99	89:11
3	<i>(S)</i> - 1b	0	24	87	99:1
4	<i>(S)</i> - 1b	60	1	95	98:2
5	<i>(S)</i> - 1c	0	2	99	96:4
6	<i>(S)</i> - 1c	60	72	60	88:12
7	<i>(S)</i> - 1d	0	1.5	99	98:2
8	<i>(S)</i> - 1d	60	0.5	99	88:12

[a] Isolated yield after flash chromatography. [b] Diastereomeric ratios determined by ¹H NMR of crude mixtures **6a–d**.

Conclusions

In conclusion, we have described our progress in the study of chiral auxiliary-mediated DKR. The good to excellent selectivities are in agreement with our previous studies; in particular, we have shown that the incorporation in a cycle of the amidic nitrogen of lactamide auxiliary improves significantly the diastereomeric ratios.

Experimental Section

General: The infrared spectra were recorded with a FT-IR 1600 Perkin–Elmer spectrometer. The NMR spectra were run at 300 MHz with a Varian spectrometer; chemical shifts (δ) are reported in ppm. Elemental analyses were carried out with an Euro-vector Euro EA 3000 model analyzer. Gas chromatographic analyses were run with an autosystem GC Perkin–Elmer apparatus using a fused silica capillary column (30 m, 0.53 mm ID), SPB-5 Supelco. Specific rotations were measured with a Perkin–Elmer 241 polarimeter. Commercial reagents were used as received from Aldrich. THF was distilled from sodium/benzophenone.

General Procedure for Diastereoselective Esterification of Racemic Arylpropionic Acids: The chiral auxiliary (*S*)-**1** (1.22 mmol) in CH₂Cl₂ or toluene (2 mL) was added dropwise to a solution of racemic ibuprofen, fenopropfen or flurbiprofen (1.2 mmol), DCC (1.22 mmol) and DMAP (1.2 mmol) in CH₂Cl₂ (15 mL) or toluene (15 mL). At the end of reaction, the mixture was filtered off and washed with 0.5 M HCl (20 mL) and saturated solutions of NaHCO₃ (20 mL) and NaCl (20 mL). The organic phase was dried with Na₂SO₄, and the solvent was evaporated at reduced pressure. The crude diastereomeric mixture containing the esters **2–4** was purified by column chromatography on silica gel. The times, yields and diastereomeric ratios are indicated in Table 2.

Data for Esters (*S,S*)-2–4** (isolated and purified from mixtures with the best diastereomeric ratios):** (1*S*)-1-methyl-2-oxo-2-(piperidin-1-yl)ethyl (2*S*)-2-(4-isobutylphenyl)propanoate [(*S,S*)-**2a**] (from a diastereomeric mixture, *dr* = 95:5, Entry 1, Table 2), colorless oil, puri-

fied on silica gel, eluent cyclohexane/ethyl acetate, 7:3. $[\alpha]_D^{25} = +5.4$ ($c = 6.2$, CHCl_3). IR (KBr): $\tilde{\nu} = 1732$, 1656 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 0.88$ [d, $J = 6.6 \text{ Hz}$, 6 H, $(\text{CH}_3)_2\text{CH}$], 1.31–1.41 [m, 6 H, $\text{NCH}_2(\text{CH}_2)_3$], 1.41 (d, $J = 6.6 \text{ Hz}$, 3 H, OCHCH_3), 1.52 (d, $J = 6.9 \text{ Hz}$, 3 H, ArCHCH_3), 1.80–1.89 [m, 1 H, $(\text{CH}_3)_2\text{CH}$], 2.43 (d, $J = 6.9 \text{ Hz}$, 2 H, CH_2Ar), 3.07–3.11 and 3.45–3.50 (both m, 4 H, CH_2NCH_2), 3.74 (q, $J = 6.9 \text{ Hz}$, 1 H, ArCHCH_3), 5.42 (q, $J = 6.6 \text{ Hz}$, 1 H, OCHCH_3), 7.08 and 7.22 (both d, $J = 8.1 \text{ Hz}$, 4 H, aromatic) ppm. ^{13}C NMR (CDCl_3): $\delta = 17.0$ (ArCHCH_3), 18.6 (OCHCH_3), 22.5 [$(\text{CH}_3)_2\text{CH}$], 24.6 and 26.4 [$\text{NCH}_2(\text{CH}_2)_3$], 30.3 [$(\text{CH}_3)_2\text{CH}$], 43.4 (CH_2NCH_2), 45.2 (CH_2Ar), 46.3 (ArCHCH_3), 67.6 (OCHCH_3), 127.5 and 129.4 (CH aromatic), 137.5 and 140.8 (C aromatic), 168.0 (CON), 174.2 (COO) ppm. $\text{C}_{21}\text{H}_{31}\text{NO}_3$ (345.476): calcd. C 73.01, H 9.04, N 4.05; found C 73.04, H 9.02, N 4.04.

(1S)-1-Methyl-2-(morpholin-4-yl)-2-oxoethyl (2S)-2-(2-Fluoro-1,1'-biphenyl-4-yl)propanoate [(S,S)-3c]: Isolated from a diastereomeric mixture with $dr = 97:3$, see Entry 13 in Table 2), white solid, purified on silica gel, eluent cyclohexane/ethyl acetate, 7:3. $[\alpha]_D^{25} = +8.5$ ($c = 1.0$, CHCl_3). IR (KBr): $\tilde{\nu} = 1735$, 1653 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 1.45$ (d, 3 H, $J = 6.9 \text{ Hz}$, OCHCH_3), 1.57 (d, $J = 7.2 \text{ Hz}$, 3 H, ArCHCH_3), 3.31–3.64 [m, 8 H, $\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$], 3.82 (q, $J = 7.2 \text{ Hz}$, 1 H, ArCHCH_3), 5.39 (q, $J = 6.9 \text{ Hz}$, 1 H, OCHCH_3), 7.12–7.55 (m, 8 H, aromatic) ppm. ^{13}C NMR (CDCl_3): $\delta = 16.9$ (ArCHCH_3), 18.5 (OCHCH_3), 44.7 (CH_2NCH_2), 46.1 (ArCHCH_3), 66.6 (CH_2OCH_2), 67.4 (OCHCH_3), 115.7, 123.9, 127.9, 128.6, 129.1 and 131.0 (CH aromatic), 135.6, 141.7, 158.2 and 161.5 (C aromatic), 168.9 (CON), 173.8 (COO) ppm. $\text{C}_{22}\text{H}_{24}\text{NO}_4$ (385.429): calcd. C 68.56, H 6.28, N 3.63; found C 68.82, H 6.29, N 3.62.

(1S)-1-Methyl-2-(morpholin-4-yl)-2-oxoethyl (2S)-2-(4-Phenoxyphenyl)propanoate [(S,S)-4c]: Isolated from a diastereomeric mixture with $dr = 96:4$, see Entry 15 in Table 2), colorless oil, purified on silica gel, eluent cyclohexane/ethyl acetate, 7:3. $[\alpha]_D^{25} = +3.6$ ($c = 1.8$, CHCl_3). IR (KBr): $\tilde{\nu} = 1730$, 1653 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 1.41$ (d, $J = 6.9 \text{ Hz}$, 3 H, OCHCH_3), 1.52 (d, $J = 7.2 \text{ Hz}$, 3 H, ArCHCH_3), 3.21–3.67 [m, 8 H, $\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$], 3.73 (q, $J = 7.2 \text{ Hz}$, 1 H, ArCHCH_3), 5.38 (q, $J = 6.9 \text{ Hz}$, 1 H, OCHCH_3), 6.86–7.36 (m, 9 H, aromatic) ppm. ^{13}C NMR (CDCl_3): $\delta = 16.9$ (ArCHCH_3), 18.5 (OCHCH_3), 45.4 (ArCHCH_3), 46.0 (CH_2NCH_2), 66.6 (CH_2OCH_2), 67.5 (OCHCH_3), 117.7, 118.4, 119.1, 122.6, 123.6, 130.0 and 130.1 (CH aromatic), 142.2, 157.2 and 157.7 (C aromatic), 168.9 (CON), 173.9 (COO) ppm. $\text{C}_{22}\text{H}_{23}\text{NO}_5$ (383.438): calcd. C 68.91, H 6.57, N 3.65; found C 69.01, H 6.56, N 3.66.

General Procedure for Diastereoselective S_N2 Reaction of 2-Bromo Esters 5a–d with 4-Chlorophenoxide: Sodium 4-chlorophenoxide was preformed by adding a solution of 4-chlorophenol (1.1 mmol) to a stirred suspension of sodium (1.0 mmol) in dry THF (10 mL), at room temperature under nitrogen. The resulting solution, occasionally preheated, was then added dropwise to a solution of bromo esters **5** (1.0 mmol in 6 mL of dry THF) and stirred until completion of reaction. After quenching with saturated NaCl (10 mL), the mixture was extracted with CH_2Cl_2 ($3 \times 15 \text{ mL}$). The organic phase was washed with H_2O ($3 \times 15 \text{ mL}$), dried with Na_2SO_4 and concentrated at reduced pressure. The residue was purified by column chromatography of silica gel (cyclohexane/ethyl acetate, 7:3) to give the diastereomeric mixture of 4-chlorophenoxy esters **6**. The times,

temperatures, yields and diastereomeric ratios are indicated in Table 3.

(1S)-1-Methyl-2-oxo-2-pyrrolidin-1-ylethyl (2R,S)-2-(4-Chlorophenoxy)butanoate [(R,S)-6d] and (S,S)-6d]: (diastereomeric mixture dr 98:2, Entry 7, Table 3) oil. IR (KBr): $\tilde{\nu} = 1746$, 1652 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 1.08$ (dt, $J = 7.2 \text{ Hz}$, 3 H, CH_3CH_2), 1.45 (dd, $J = 7.2 \text{ Hz}$, 3 H, CH_3CHCON), 1.78–2.10 [m, 6 H, CH_3CH_2 and $\text{NCH}_2(\text{CH}_2)_2$], 3.26–3.60 (m, 4 H, CH_2NCH_2), 4.44–4.62 (m, 1 H, ArOCH), 5.23 (dq, $J = 7.2 \text{ Hz}$, 1 H, CH_3CHCON), 6.79 and 7.21 (both d, $J = 9.0 \text{ Hz}$, 4 H, aromatic) ppm. ^{13}C NMR (CDCl_3): $\delta = 9.8$ (CH_3CH_2), 16.6 (CH_3CHCON), 22.6 [$\text{NCH}_2(\text{CH}_2)_2$], 26.2 (CH_3CH_2), 46.4 (CH_2NCH_2), 69.1 (CH_3CHCON), 78.1 (ArOCH), 117.2 and 129.5 (CH aromatic), 156.2 (C aromatic), 168.6 (CON), 171.2 (C aromatic), 173.4 (COO) ppm. $\text{C}_{17}\text{H}_{22}\text{ClNO}_4$ (339.814): calcd. C 60.09, H 6.53, N 4.12; found C 60.18, H 6.51, N 4.13.

Acknowledgments

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