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Synthesis of *N*-alkylanthranilamides with a chiral substituent at the nitrogen atom

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ABSTRACT

Novel anthranilamides containing a chiral substituent at the nitrogen atom and different substituents on the benzene ring were prepared from the corresponding isatins in good yields and high enantioselectivities (up to 98%).

1. Introduction

Anthranilic acids and its derivatives are usually used as non-steroidal anti-inflammatory drugs[1] and antibacterial agents.[2] In recent years, among a wide variety of anticancer drugs, a great interest has been focused on the synthesis of different derivatives of anthranilic acids. It is true not only for anthranilic acids and its esters, but also for its amides, which may reveal high anticancer activity.[3] The anthranilamides inhibit angiogenesis[4] and are regarded as new selective antagonists of cholecystokinin-2 receptors, which are used for the treatment of adenocarcinoma such as Barrett's metaplasia and pancreatic cancer.[5]

Many pharmaceuticals are chiral and consist of two or more enantiomers/stereoisomers, which may differ in biological activity, toxicity, and effects on non-target organisms. In the last few years, several racemic compounds have been substituted by enantiomer-enriched or single-isomer compounds ('chiral switch').[6,7] At the present time, approximately 15% of all pharmaceuticals synthesized correspond to pure enantiomers, such as levomicetin, levofloxacin, esomeprazole, levosalbutamol, and (*S*)-ketamine. In this context, the stereoselective synthesis of new heterocycles is an important task. Thus, the use of single enantiomer with an optimal ratio of therapeutic efficiency and safety versus racemic mixtures has become an area of significant interest.

2. Results and discussion

Herein, we report the development of a methodology, which encompasses a broad range of new derivatives of anthranilamides, achieves substrate-controlled enantioselectivity, and allows access to enantio-enriched products. During our investigation, we found a new synthetic approach to novel derivatives of anthranilamides with high enantiomeric purity. To the best of our knowledge, these compounds have not been previously described.

We also report the synthesis of the derivatives of anthranilic acids with a chiral substituent at the nitrogen atom. Surprisingly, there has been little synthetic work directed toward such compounds which could exhibit interesting properties not only as new building-blocks, but also as new biologically active compounds.

Two major approaches for the synthesis of *N*-alkanthranilic acids could be applied: (1) the direct alkylation of anthranilic acids and (2) the formation of anthranilic acids with a chiral substituent at the nitrogen atom from optically active isatins. The first method was not suitable for the preparation of optically active anthranilic acids, because the racemization of the reaction products takes place in basic media.[8] Therefore, we focused our research on the second method where the synthesis of enantiomerically pure anthranilic acids from the corresponding isatins can be used. Recently we reported the synthesis of the enantiomerically pure substituted isatins, which were prepared from the substituted (*R*)-arylalanines by Sandmeyer's method in high yield and good enantioselectivity (up to 99%).[9] The enantiomerically pure derivatives of anthranilic acids may be obtained from isatins with a chiral substituent at the nitrogen atom (vide supra Scheme 1).

Our major goal was to develop a synthetic route for the racemic derivatives of anthranilic acids and thereafter apply it to the optically active substrates.

In the first set of experiments, we turned our attention to the synthesis of N-alkylated isatins. Racemic N-alkylated isatins **1a–c** were prepared in high yields (>70%) from the corresponding commercially available isatins by a standard procedure.[10] The alkylation was carried out in DMF at room temperature over 12–14 h. We used 10% molar excess of ethyl 2-bromopropionate as an alkylating agent and K_2CO_3 as a base (Scheme 2).

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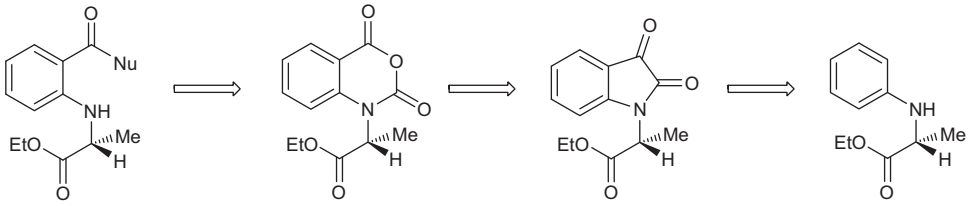
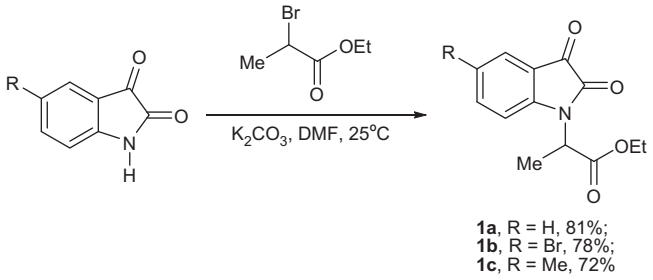


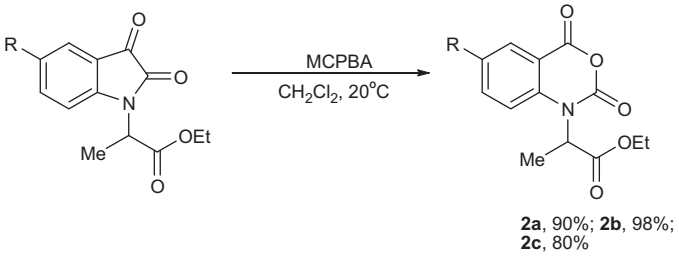
Scheme 1. Retrosynthetic strategy for the synthesis of the derivatives of anthranilic acids with a chiral substituent at the nitrogen atom.



Scheme 2. The synthesis of racemic N-alkylated isatins **1a**–**c**.

In order to obtain N-alkylated isatoic anhydrides from the corresponding isatins several approaches were attempted. The oxidation of isatins can be carried out under a mild condition by using hydrogen peroxide,[11] chromium trioxide,[12] or various peracids[11,13] as oxidants. Preliminary results indicated that these isatins could not be easily oxidized using chromium trioxide in a solvent mixture of AcOH/Ac_2O (1:1) and the reaction led to the formation of a complex mixture. The experiments carried out with freshly prepared Et_2O solution of monoperphthalic acid[14] for 40 h at room temperature resulted in the formation of isatoic anhydride **2a**–**c** in 10–30% yield.

None of these approaches allowed the synthesis of isatoic anhydrides in high yields. It is known from the literature data that *m*-chloroperoxybenzoic acid (MCPBA) is often used as the oxidative reagent for the synthesis of isatoic anhydrides. The standard reaction conditions were defined as follows: small excess of MCPBA (5 mol %), room temperature, and about 48 h.[11] However, we did not obtain the desired isatoic anhydrides under these conditions. We found that the use of a large excess of MCPBA (80 mol %) gave better results. Under these conditions, the reactions generally proceeded to completion in less than 6–8 h at room temperature and the products were obtained in excellent yields (80–98%) (Scheme 3).



Scheme 3. Oxidation of isatins to isatoic anhydride **2a**–**c**.

It is well-known that the amides of *N*-alkylanthranilic acids may be obtained from the corresponding isatoic anhydrides and nucleophiles under various conditions, for example, at reflux in CH_3CN[15] (method *a*), stirring in a solvent mixture of DMF/THF in the presence of 4-dimethylaminopyridine (DMAP) as a catalyst[5] (method *b*), or in DMF at different temperatures[4,5,15] (method *c*). It was found that method *b* was more effective and gave higher yields of the target anthranilamides in comparison with the other methods.

This is due to the fact that the addition of DMAP to the reaction of isatoic anhydride and nucleophiles ensures the intermediacy of an active *ortho*-aminobenzoylating agent **A**,[16] generated in situ in the presence of the nucleophile. Intermediate **A** is the orders of magnitude more potent as a reagent for the introduction of the anthraniloyl moiety when compared to either isatoic anhydride or the range of active esters of anthranilic acid previously described (Fig. 1).[17,18]

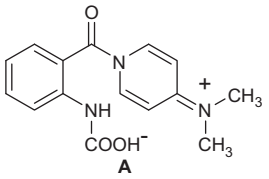


Figure 1. Intermediate **A**.

We carried out a comparative analysis of the methods listed above. In order to obtain the amides of *N*-alkylanthranilic acids, we used secondary cyclic amines and α-methylbenzylamine as nucleophiles (Table 1).

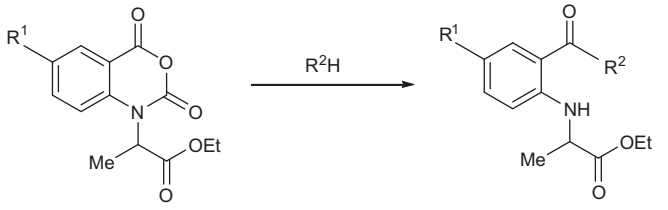
The method *b* was more effective in most cases (see Table 1) and provided better yields in mild conditions. Thus, a convenient approach to the synthesis of racemic *N*-alkylanthranilamides was developed and applied on the optically active substrates. In the following part of the study, we endeavored to use these conditions for the synthesis of *N*-alkylanthranilamides with a chiral substituent at the nitrogen atom.

We synthesized isatoic anhydride (*R*)-**2a** from an optically active isatin (*R*)-**1a** by using MCPBA as an oxidizing reagent, as described above. Isatoic anhydride (*R*)-**2a** was purified by column chromatography on silica gel to yield (*R*)-**2a** (78%). The analysis of the isatoic anhydride (*R*)-**2a** enantiomeric purity by HPLC method indicated that there was no racemization under our reaction conditions and its enantiomeric purity was 98% ee.

In order to obtain the optically active amides of *N*-alkylanthranilic acids, we carried out the reaction between isatoic anhydride (*R*)-**2a** and azepane via a methodology well established in the synthesis of racemic compounds. Amide **8a** (85%) was purified by column chromatography and its enantiomeric purity was 98% ee, which was determined by HPLC with a chiral stationary phase. Interestingly enough, isatoic anhydride (*R*)-**2a** reacted with enantiomerically pure (*S*)-α-methylbenzylamine to give only one diastereoisomer **9a**′. The reaction between enantiopure isatoic anhydride (*R*)-**2a** and racemic α-methylbenzylamine ((*S*)/(*R*) = 3/1) provided the mixture of diastereoisomers **9a** with a ratio that correlates with the ratio of (*S*)- and (*R*)-isomers of the initial α-methylbenzylamine (Fig. 2).

The aforementioned observations proved our assumption that the racemization did not occur under our reaction conditions at the stage of isatoic anhydride opening. The enantiomeric purity

Table 1
The comparison of the methods *a*, *b* and *c* on a number of racemic anthranilamides **3–7a–c**



2a-c **3-7 a-c**

Product	R^1	R^2	Method	Yields%
3a	H		Method *a*[a] Method *b*[b]	61 54
3b	Br		Method *b*	51
3c	Me		Method *b*	43
4a	H		Method *b*	56
4b	Br		Method *b*	59
4c	Me		Method *b*	42
5a	H		Method *b*	83
5b	Br		Method *b*	70
5c	Me		Method *b*	45
6a	H		Method *a* Method *b*	57 69
6b	Br		Method *a* Method *b*	49 72
6c	Me		Method *b*	42
7a	H		Method *a* Method *b* Method *c*[c]	48 85 57
7b	Br		Method *a* Method *b*	50 53
7c	Me		Method *b*	43

[a] Method *a*: CH_3CN, 85 °C, 10–15 min.
[b] Method *b*: DMAP (cat. amounts), THF/DMF (0.2 M), 25°C, 16 h;
[c] Method *c*: DMF, 80°C, 3 h.

of the resulting amides of *N*-alkylanthranilic acids was determined by the enantiomeric purity of the initial enantiomerically pure isatins (Table 2).

3. Conclusion

In conclusion, we have developed a synthetic route for new anthranilamides containing a chiral substituent at the nitrogen atom and different substituents on the benzene ring. The results of our research work indicate that the sequential conversion of an optically active isatin into the isatoic anhydride (*R*)-**2a** under oxidative conditions (MCPBA) and combination of the isatoic anhydride (*R*)-**2a** and 4-dimethylaminopyridine (DMAP) is an effective method for the synthesis of new enantiomerically pure *N*-alkylanthranilamides with high enantioselectivities (up to 98%). We have also found that under these conditions racemization did not occur when using active substrates.

4. Experimental

4.1. General

The NMR spectra were recorded on a 'Bruker Avance-400' spectrometer (400.1 and 100.6 MHz for ^1H and ^{13}C, respectively) at room temperature; the chemical shifts δ were measured in ppm with respect to the solvent (^1H: $CDCl_3$, $\delta = 7.27$ ppm; ^{13}C: $CDCl_3$, $\delta = 77.13$ ppm), coupling constants *J* are given in Hertz. IR spectra were recorded on Thermo Nicolet IR200 FT-IR spectrometer. Mass spectral detector ITD-700 (Finnigan MAT), EU, energy of ionizing electrons 70 eV, range of mass *m*/*z* 45–400. Optical rotations were measured using a Jasco DIP-360 (589 nm) polarimeter. Melting points were measured in an open capillary tube. Analytical thin layer chromatography (TLC) was carried out with 'Silufol' silica gel plates (supported on aluminum); the revelation was done by UV lamp (254 and 365 nm), and chemical staining (iodine vapor and potassium permanganate solution in water). Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Enantiomeric purities were tested using HPLC with a chiral stationary phase: Chiralpak AD-RH 4.6 × 150 mm 5 mkm, eluent: $H_2O + CF_3COOH/CH_3CN$ 50/50 flow: 1.0 mL/min, rt, 250 nm. All the reagents, except for the commercial products of satisfactory quality, were purified according to the literature procedures before use. Compounds obtained as mixtures of diastereomers were not separated into the single isomers.

4.2. General procedure for the preparation of isatins 1a–c

4.2.1. Ethyl 2-(isatin-1-yl)propanoate (1a)

At first, K_2CO_3 (2.11 g, 0.015 mol) was added to a solution of isatin (1.5 g, 0.01 mol) in DMF (30 mL), the reaction mixture was stirred until isatin was completely dissolved. After 30 min, the solution became bright red, after which ethyl 2-bromopropanoate (1.46 mL, 0.011 mol) was added dropwise to a reaction mixture, and then stirred at rt for 12–14 h. The resulting mixture was diluted with water, extracted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 10/1) to afford **1a** (2.01 g, 81%) as an orange solid, mp 58 °C (petroleum ether/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 1.22$ (t, $J = 7.2$, 3H, CH_2CH_3), 1.69 (d, $J = 7.5$, 3H, $CHCH_3$), 4.18–4.27 (m, 2H, CH_2CH_3), 5.16 (q, $J = 7.5$, 1H, $CHCH_3$), 6.85 (br d, $J = 7.7$, 1H, CH_{Ar}), 7.15 (ddd, $J = 7.7$, 7.7, 0.7, 1H, CH_{Ar}), 7.57 (ddd, $J = 7.7$, 7.7, 1.4, 1H, CH_{Ar}), 7.65 (ddd, $J = 7.7$, 1.4, 0.7, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 14.08$ (CH_3), 14.27 (CH_3), 49.18 (CH), 62.16 (CH_2), 111.46 (CH), 117.89 (C), 123.89 (CH), 125.64 (CH), 138.19 (CH), 149.45 (C), 157.69 (CO), 169.43 (CO), 182.70 (CO) ppm. IR (KBr) *v*: 3467, 2993, 1739 (CO), 1608, 1468, 1367, 1309, 1246, 1113, 750, 476 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 247 [M^+], 174 [$M^+ - CO_2Et$], 146 [$M^+ - CH_3CHCO_2Et$], 128 (0.8), 117 (6), 91 (12), 77 (26), 51 (9). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.20; H, 5.43; N, 5.81.

4.2.2. Ethyl 2-(5-bromisatin-1-yl)propanoate (1b)

Compound **1b** was obtained as an orange solid, 78%, mp 125°C (petroleum ether/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 1.25$ (t, $J = 7.1$, 3H, CH_2CH_3), 1.69 (d, $J = 7.5$, 3H, $CHCH_3$), 4.24

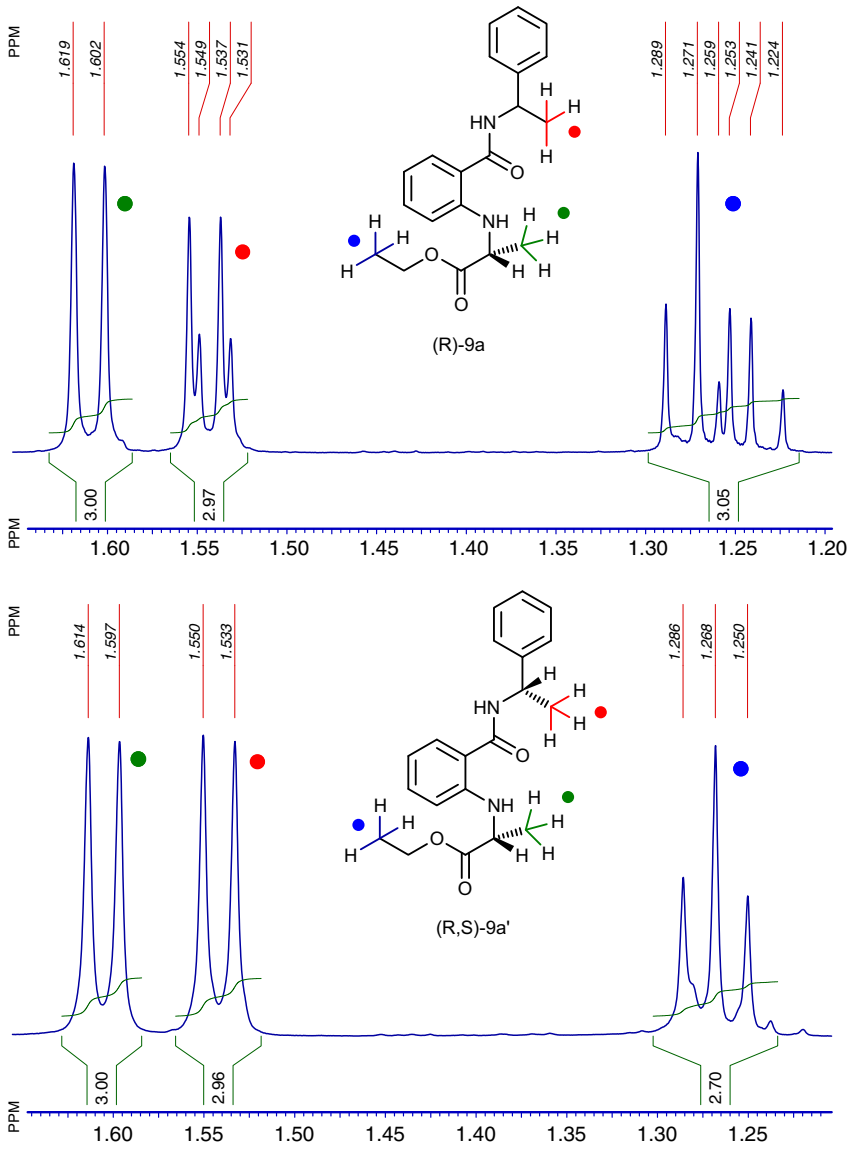


Figure 2. Fragments of the spectrum (range of aliphatic protons) of the mixture of diastereomers (*R*)-**9a** and (*R*,*S*)-diastereomer **9a′** in $CDCl_3$.

(q, *J* = 7.1, 2H, CH_2CH_3), 5.18 (q, *J* = 7.5, 1H, $CHCH_3$), 6.77 (d, *J* = 8.4, 1H, CH_{Ar}), 7.69 (dd, *J* = 8.4, 2.0, 1H, CH_{Ar}), 7.77 (br d, *J* = 2.0, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.10 (CH_3), 14.26 (CH_3), 49.30 (CH), 62.33 (CH_2), 113.23 (CH), 116.81 (C), 119.13 (C), 128.41 (CH), 140.34 (CH), 148.18 (C), 156.98 (CO), 169.18 (CO), 181.53 (CO) ppm. IR (KBr) *v*: 3086, 2989, 1736 (CO), 1604, 1469, 1439, 1242, 841, 719, 474 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 327 (13) [M^+], 325 (13) [M^+], 254 (14) [M^+-CO_2Et], 252 (14) [M^+-CO_2Et], 226 (95) [$M^+-CH_3CHCO_2Et$], 224 (98) [$M^+-CH_3CHCO_2Et$], 197 (8), 170 (24), 168 (24), 155 (32), 145 (70) [$M^+-CH_3CHCO_2Et$, −Br], 117 (100), 90 (86), 75 (95), 63 (49), 45 (37). Anal. Calcd for $C_{13}H_{12}BrNO_4$: C, 47.88; H, 3.71; N, 4.29. Found: C, 47.69; H, 3.69; N, 4.40.

4.2.3. Ethyl 2-(5-methylisatin-1-yl)propanoate (1c)

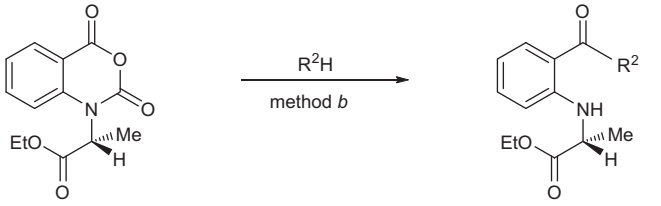
Compound **1c** was obtained as a red solid, 72%, mp 64°C (petroleum ether/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, *J* = 7.1, 3H, CH_2CH_3), 1.68 (d, *J* = 7.4, 3H, $CHCH_3$), 2.35 (s, 3H, CH_{3Ar}), 4.23 (q, *J* = 7.1, 2H, CH_2CH_3), 5.16 (q, *J* = 7.4, 1H, $CHCH_3$), 6.74 (d, *J* = 8.0, 1H, CH_{Ar}), 7.37 (br d, *J* = 8.0, 1H, CH_{Ar}), 7.48 (br s, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.08 (CH_3), 14.27 (CH_3), 20.59 (CH_3), 49.13 (CH), 62.09 (CH_2), 111.28 (CH), 117.94 (C), 125.92 (CH), 133.74 (C), 138.60 (CH), 147.26 (C), 157.83 (CO), 169.54 (CO), 182.95 (CO) ppm. IR (KBr) *v*: 3456, 2989, 1739 (CO), 1622, 1597, 1491, 1309, 1227, 1107, 837, 478 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 261 (23) [M^+], 188 (12) [M^+-CO_2Et], 160 (100) [$M^+-CH_3CHCO_2Et$], 130 (11), 117 (33), 91 (40), 65 (44), 51 (20). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.32; H, 5.92; N, 5.23.

4.3. General procedure for the preparation of isatoic anhydride 2a–c

4.3.1. Ethyl 2-(2,4-dioxo-2*H*-3,1-benzoxazin-1(4*H*)-yl)propanoate (2a)

Isatin **1a** (2 g, 0.008 mol) was added to a solution of *meta*-chloroperoxybenzoic acid (2.51 g, 0.0145 mol) in CH_2Cl_2. The reaction mixture was stirred at rt for 6–8 h. The resulting mixture was washed with an aqueous solution of sodium carbonate (2.5 g Na_2CO_3 in 250 mL H_2O), saturated with a solution of $NaHSO_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Purification of the residue was carried out by

Table 2
The synthesis of *N*-alkylanthranilamides **8a**, **9a**, **9a′** from optically active isatoic anhydride (*R*)-**2a**



(*R*)-**2a**

Product	R^2	Yield%	Isomeric composition
8a		85	(*R*)-Enantiomer 98% ee, $[\alpha]_D^{20} = +9$ (*c* 1.00 CH_2Cl_2)
9a		80[a]	The mixture of diastereomers
9a′		83	(*R*,*S*)-Diastereomer, $[\alpha]_D^{20} = -114$ (*c* 1.00 CH_2Cl_2)

[a] Compound **9a** obtained as mixture of diastereomers was not separated into the single isomers.

recrystallization from ethanol to afford **2a** as a white solid (1.89 g, 90%, mp 104–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, *J* = 7.1, 3H, CH_2CH_3), 1.76 (d, *J* = 7.1, 3H, $CHCH_3$), 4.18–4.31 (m, 2H, CH_2CH_3), 5.34–5.43 (m, 1H, $CHCH_3$), 7.06 (d, *J* = 7.9, 1H, CH_{Ar}), 7.34 (ap.t, *J* = 7.9, 1H, CH_{Ar}), 7.72–7.79 (m, 1H, CH_{Ar}), 8.22 (dd, *J* = 7.9, 1.1, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.92 (CH_3), 14.02 (CH_3), 53.64 (CH), 62.30 (CH_2), 112.05 (C), 113.76 (CH), 124.26 (CH), 131.37 (CH), 137.06 (CH), 140.47 (CO), 146.63 (C), 158.04 (CO), 169.07 (CO) ppm. IR (KBr) *ν*: 2993, 1772, 1726, 1606, 1475, 1335, 1209, 1038, 756 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 263 (8) [M^+], 218 (2), 191 (1) [M^+-CO_2Et], 160 (100) [$M^+-CH_3CH(NH)CO_2Et$], 130 (11), 117 (33), 91 (40), 65 (44), 51 (20). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.55; H, 5.07; N, 5.15.

4.3.2. Ethyl 2-(6-bromo-2,4-dioxo-2*H*-3,1-benzoxazin-1(4*H*)-yl)propanoate (2b)

Compound **2b** was obtained as a pale brown solid, 98%, mp 118–120 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, *J* = 7.0, 3H, CH_2CH_3), 1.74 (d, *J* = 6.8, 3H, $CHCH_3$), 4.16–4.32 (m, 2H, CH_2CH_3), 5.28–5.45 (m, 1H, $CHCH_3$), 6.95 (br d, *J* = 8.7, 1H, CH_{Ar}), 7.82 (br d, *J* = 8.7, 1H, CH_{Ar}), 8.32 (br s, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.92 (CH_3), 14.05 (CH_3), 53.86 (CH), 62.49 (CH_2), 115.65 (CH), 117.07 (C), 126.48 (C), 133.58 (CH), 139.79 (CH), 143.59 (CO), 156.83 (C), 163.84 (CO), 179.41 (CO) ppm. IR (KBr) *ν*: 2985, 1782, 1741, 1603, 1487, 1439, 1315, 1061, 816, 748 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 343 (11) [M^+], 341 (11) [M^+], 298 (2), 271 (2) [M^+-CO_2Et], 269 (2) [M^+-CO_2Et], 226 (100) [$M^+-CH_3CH(NH)CO_2Et$], 224 (100) [$M^+-CH_3CH(NH)CO_2Et$], 197 (4), 160 (8), 155 (15), 145 (30) [$M^+-CH_3CH(NH)CO_2Et$, −Br], 117 (57), 90 (29), 75 (35), 63 (13). Anal. Calcd for $C_{13}H_{12}BrNO_5$: C, 45.64; H, 3.54; N, 4.09. Found: C, 45.82; H, 3.52; N, 4.28.

4.3.3. Ethyl 2-(6-methyl-2,4-dioxo-2*H*-3,1-benzoxazin-1(4*H*)-yl)propanoate (2c)

Compound **2c** was obtained as a white solid, 80%, mp 112–114 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, *J* = 7.2, 3H, CH_2CH_3), 1.73 (d, *J* = 7.1, 3H, $CHCH_3$), 2.43 (s, 3H, CH_{3Ar}), 4.18–4.28 (m, 2H, CH_2CH_3), 5.31–5.40 (m, 1H, $CHCH_3$), 6.96 (d, *J* = 8.6, 1H, CH_{Ar}), 7.55 (dd, *J* = 8.6, 1.5, 1H, CH_{Ar}), 8.00 (br s, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.93 (CH_3), 14.03 (CH_3), 20.37 (CH_3), 53.57 (CH), 62.25 (CH_2), 113.72 (CH), 126.30 (C), 130.99 (CH), 134.38 (C), 138.06 (CH), 138.27 (CO), 147.39 (C), 158.26 (CO), 169.20 (CO) ppm. IR (KBr) *ν*: 2985, 1774, 1720, 1512, 1304, 1225, 1063, 750, 540 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 277 (10) [M^+], 249 (2), 204 (1) [M^+-CO_2Et], 176 (34), 160 (100) [$M^+-CH_3CH(NH)CO_2Et$], 117 (23), 91 (13), 65 (11), 39 (5). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.60; H, 5.50; N, 5.10.

4.3.4. (*R*)-Ethyl 2-(2,4-dioxo-2*H*-3,1-benzoxazin-1(4*H*)-yl)propanoate ((*R*)-2a)

Compound (*R*)-**2a** was obtained as a white solid, 78%, mp 105 °C (petroleum ether/ethyl acetate) after purification by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1/10), $[\alpha]_D^{20} = +15$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, *J* = 7.1, 3H, CH_2CH_3), 1.75 (d, *J* = 7.1, 3H, $CHCH_3$), 4.20–4.29 (m, 2H, CH_2CH_3), 5.32–5.44 (m, 1H, $CHCH_3$), 7.07 (d, *J* = 8.5, 1H, CH_{Ar}), 7.32–7.37 (m, 1H, CH_{Ar}), 7.76 (ddd, *J* = 8.5, 7.6, 1.6, 1H, CH_{Ar}), 8.22 (dd, *J* = 7.6, 1.6, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.93 (CH_3), 14.03 (CH_3), 53.64 (CH), 62.31 (CH_2), 111.50 (C), 113.75 (CH), 124.25 (CH), 131.39 (CH), 137.02 (CH), 140.38 (CO), 146.03 (C), 158.03 (CO), 169.09 (CO) ppm.

4.4. General procedure for the preparation of anthranilamides 3–9a–c

Method a: A mixture of morpholine (0.1 g, 1.045 mmol) and isatoic anhydride **2a** (0.25 g, 0.95 mmol) in the acetonitrile (8 mL) was stirred at reflux for 10–15 min. The reaction mixture was cooled to rt, after which the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1/10) to afford **6a** (57%) as a yellowish oil.

Method b: 4-Dimethylaminopyridine (DMAP, 9.3 mg, 0.076 mmol) and pyrrolidine (0.063 mL, 0.76 mmol) were added to a solution of isatoic anhydride **2a** (0.2 g, 0.76 mmol) in a mixture of THF/DMF = 5/1 (0.2 M). The reaction mixture was stirred at rt for 16 h. Then ethyl acetate was added to a reaction mixture, after which the organic layer was washed with water twice and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1/10) to afford **3a** (54%) as a yellowish oil.

Method c: A mixture of α-methylbenzylamine (2.25 g, 0.021 mol) in DMF (4 mL) and isatoic anhydride **2a** (3.26 g, 0.020 mol) in DMF (10 mL) was stirred at 45–50 °C for 3 h. The reaction mixture was cooled to rt, diluted with cold water (100 mL), and then basified with 50% KOH to a medium basic pH of 9. The resulting mixture was extracted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1/10) to afford **7a** (57%) as a yellowish oil.

All of these anthranilamides **3**–**9a**–**c** were obtained by using method *b*.

4.4.1. Ethyl *N*-[2-(pyrrolidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (3a)

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, *J* = 7.1, 3H, CH_2CH_3), 1.46 (d, *J* = 7.1, 3H, $CHCH_3$), 1.76–1.99 (m, 4H, 2 × CH_2CH_2N), 3.33–3.70 (m, 4H, 2 × CH_2CH_2N), 4.08 (q, *J* = 7.1, 1H, $CHCH_3$), 4.15 (q, *J* = 7.1, 2H, CH_2CH_3), 5.99 (br d, 1H, NH), 6.52 (d, *J* = 7.6, 1H, CH_{Ar}), 6.61–6.66 (m, 1H, CH_{Ar}), 7.14–7.21 (m, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.19 (CH_3),

18.71 (CH_3), 24.44 (CH_2), 26.32 (CH_2), 46.03 (CH_2), 49.68 (CH_2), 51.97 (CH), 61.03 (CH_2), 111.67 (CH), 116.27 (CH), 120.72 (C), 128.27 (CH), 130.94 (CH), 145.69 (C), 169.49 (CO), 174.35 (CO) ppm. IR (KBr) *v*: 3340, 2976, 2877, 1739 (CO), 1622, 1585, 1516, 1410, 1174, 1051, 752, 658, 513 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 290 (17) [M^+], 217 (73) [M^+-CO_2Et], 146 (100) [$M^+-C_4H_8N$], 118 (15), 91 (14), 77 (23), 70 (28), 42 (22). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.28; H, 7.59; N, 9.50.

4.4.2. Ethyl *N*-[4-bromo-2-(pyrrolidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (3b)

Compound **3b** was obtained as a yellowish oil, 51%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, *J* = 7.1, 3H, CH_2CH_3), 1.47 (d, *J* = 6.8, 3H, $CHCH_3$), 1.79–2.04 (m, 4H, 2 × CH_2CH_2N), 3.35–3.71 (m, 4H, 2 × CH_2CH_2N), 3.98–4.07 (m, 1H, $CHCH_3$), 4.17 (q, *J* = 7.1, 2H, CH_2CH_3), 5.97 (br d, 1H, NH), 6.43 (d, *J* = 8.7, 1H, CH_{Ar}), 7.27 (dd, *J* = 8.7, 2.4, 1H, CH_{Ar}), 7.31 (d, *J* = 2.4, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.18 (CH_3), 18.56 (CH_3), 24.40 (CH_2), 26.32 (CH_2), 46.13 (CH_2), 49.65 (CH_2), 51.89 (CH), 61.18 (CH_2), 107.88 (C), 113.38 (CH), 122.40 (C), 130.69 (CH), 133.45 (CH), 144.65 (C), 167.88 (CO), 173.87 (CO) ppm. IR (KBr) *v*: 3298, 2978, 2873, 1724 (CO), 1620, 1448, 1319, 1288, 1178, 1053, 806, 679 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 370 (1) [M^+], 368 (1) [M^+], 297 (10) [M^+-CO_2Et], 295 (11) [M^+-CO_2Et], 226 (25) [$M^+-C_4H_8N$], 146 (28) [$M^+-C_4H_8N$, Br], 117 (68), 90 (37), 73 (100), 42 (48). Anal. Calcd for $C_{16}H_{21}BrN_2O_3$: C, 52.04; H, 5.73; N, 7.59. Found: C, 52.10; H, 5.81; N, 7.40.

4.4.3. Ethyl *N*-[4-methyl-2-(pyrrolidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (3c)

Compound **3c** was obtained as a yellowish oil, 43%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, *J* = 7.1, 3H, CH_2CH_3), 1.47 (d, *J* = 6.9, 3H, $CHCH_3$), 1.78–2.02 (m, 4H, 2 × CH_2CH_2N), 2.21 (s, 3H, CH_{3Ar}), 3.34–3.73 (m, 4H, 2 × CH_2CH_2N), 4.05 (q, *J* = 6.9, 1H, $CHCH_3$), 4.17 (q, *J* = 7.1, 2H, CH_2CH_3), 5.65 (br s, 1H, NH), 6.48 (d, *J* = 8.2, 1H, CH_{Ar}), 6.98–7.05 (m, 2H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.17 (CH_3), 18.76 (CH_3), 20.24 (CH_3), 24.47 (CH_2), 26.25 (CH_2), 45.94 (CH_2), 49.52 (CH_2), 52.24 (CH), 60.95 (CH_2), 112.01 (CH), 121.43 (C), 125.67 (C), 128.49 (CH), 131.33 (CH), 143.10 (C), 169.54 (CO), 174.53 (CO) ppm. IR (KBr) *v*: 3342, 2976, 2875, 1739 (CO), 1628, 1520, 1423, 1279, 1174, 1053, 810, 671, 526 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 304 (4) [M^+], 231 (37) [M^+-CO_2Et], 176 (2), 160 (100) [$M^+-C_4H_8N$], 117 (23), 91 (38), 70 (50), 43 (44). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.29; H, 8.07; N, 9.35.

4.4.4. Ethyl *N*-[2-(piperidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (4a)

Compound **4a** was obtained as a yellowish oil, 56%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, *J* = 7.1, 3H, CH_2CH_3), 1.46 (d, *J* = 6.9, 3H, $CHCH_3$), 1.50–1.71 (m, 6H, $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 3.32–3.70 (m, 4H, 2 × CH_2CH_2N), 4.05–4.12 (m, 1H, $CHCH_3$), 4.15 (q, *J* = 7.1, 2H, CH_2CH_3), 5.14–5.27 (br s, 1H, NH), 6.55 (d, *J* = 8.3, 1H, CH_{Ar}), 6.67 (ap.t, *J* = 7.5, 1H, CH_{Ar}), 7.08 (dd, *J* = 7.5, 1.4, 1H, CH_{Ar}), 7.14–7.21 (m, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 14.14 (CH_3), 18.69 (CH_3), 24.59 (3C, 3 × CH_2), 26.19 (2C, 2 × CH_2), 51.73 (CH), 60.98 (CH_2), 111.57 (CH), 116.80 (CH), 120.98 (C), 127.83 (CH), 130.45 (CH), 144.63 (C), 169.60 (CO), 174.09 (CO) ppm. IR (KBr) *v*: 3365, 2981, 2935, 2856, 1739 (CO), 1626, 1512, 1423, 1271, 1173, 1001, 854, 750, 632 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 304 (20) [M^+], 231 (81) [M^+-CO_2Et], 188 (3), 146 (100) [$M^+-C_5H_{10}N$], 118 (16), 91 (14), 84 (46), 77 (20), 42 (13). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.21; H, 8.15; N, 9.25.

4.4.5. Ethyl *N*-[4-bromo-2-(piperidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (4b)

Compound **4b** was obtained as a yellowish oil, 59%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, *J* = 7.1, 3H, CH_2CH_3), 1.45 (d, *J* = 7.0, 3H, $CHCH_3$), 1.52–1.71 (m, 6H, $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 3.34–3.70 (m, 4H, 2 × CH_2CH_2N), 4.01–4.10 (m, 1H, $CHCH_3$), 4.15 (q, *J* = 7.1, 2H, CH_2CH_3), 5.07–5.25 (br s, 1H, NH), 6.44 (d, *J* = 8.8, 1H, CH_{Ar}), 7.18 (d, *J* = 2.3, 1H, CH_{Ar}), 7.27 (dd, *J* = 8.8, 2.3, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.18 (CH_3), 18.58 (CH_3), 24.52 (3C, 3 × CH_2), 26.16 (2C, 2 × CH_2), 51.71 (CH), 61.21 (CH_2), 108.57 (C), 113.22 (CH), 122.81 (C), 130.28 (CH), 133.04 (CH), 143.56 (C), 167.95 (CO), 173.74 (CO) ppm. IR (KBr) *v*: 3390, 2981, 2937, 2856, 1736 (CO), 1630, 1506, 1433, 1311, 1163, 1003, 808, 638 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 384 (9) [M^+], 382 (9) [M^+], 311 (45) [M^+-CO_2Et], 309 (49) [M^+-CO_2Et], 226 (99) [$M^+-C_5H_{10}N$], 224 (88) [$M^+-C_5H_{10}N$], 198 (5), 146 (63) [$M^+-C_5H_{10}N$, −Br], 117 (54), 84 (100), 42 (40). Anal. Calcd for $C_{17}H_{23}BrN_2O_3$: C, 53.27; H, 6.05; N, 7.31. Found: C, 53.32; H, 6.12; N, 7.31.

4.4.6. Ethyl *N*-[4-methyl-2-(piperidin-1-ylcarbonyl)phenyl]-2-aminopropionic acid (4c)

Compound **4c** was obtained as a yellowish oil, 42%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, *J* = 7.1, 3H, CH_2CH_3), 1.46 (d, *J* = 6.9, 3H, $CHCH_3$), 1.54–1.73 (m, 6H, $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 2.23 (s, 3H, CH_{3Ar}), 3.27–3.78 (m, 4H, 2 × CH_2CH_2N), 4.09 (q, *J* = 6.9, 1H, $CHCH_3$), 4.16 (q, *J* = 7.1, 2H, CH_2CH_3), 4.79–5.05 (br s, 1H, NH), 6.49 (d, *J* = 8.3, 1H, CH_{Ar}), 6.92 (br d, *J* = 1.8, 1H, CH_{Ar}), 7.01 (dd, *J* = 8.3, 1.8, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.18 (CH_3), 18.79 (CH_3), 20.26 (CH_3), 24.63 (3C, 3 × CH_2), 26.22 (2C, 2 × CH_2), 52.04 (CH), 60.98 (CH_2), 111.85 (CH), 121.57 (C), 126.28 (C), 128.20 (CH), 130.92 (CH), 142.06 (C), 169.66 (CO), 174.38 (CO) ppm IR (KBr) *v*: 3363, 2981, 2935, 2856, 1739 (CO), 1630, 1518, 1442, 1174, 1025, 810, 644 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 318 (5) [M^+], 245 (31) [M^+-CO_2Et], 160 (100) [$M^+-C_5H_{10}N$], 132 (6), 117 (10), 84 (56), 41 (40). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.95; H, 8.19; N, 8.71.

4.4.7. Ethyl *N*-[2-(azepan-1-ylcarbonyl)phenyl]-2-aminopropionic acid (5a)

Compound **5a** was obtained as a yellowish oil, 83%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19 (t, *J* = 7.1, 3H, CH_2CH_3), 1.43 (d, *J* = 6.9, 3H, $CHCH_3$), 1.48–1.90 (m, 8H, 2 × $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 3.24–3.78 (m, 4H, 2 × CH_2CH_2N), 4.03–4.10 (m, 1H, $CHCH_3$), 4.13 (q, *J* = 7.1, 2H, CH_2CH_3), 5.02 (br d, 1H, NH), 6.53 (d, *J* = 8.2, 1H, CH_{Ar}), 6.65 (ap.t, *J* = 7.4, 1H, CH_{Ar}), 7.05 (dd, *J* = 7.4, 1.2, 1H, CH_{Ar}), 7.11–7.18 (m, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.14 (CH_3), 18.73 (CH_3), 26.36 (CH_2), 27.43 (CH_2), 27.79 (CH_2), 29.20 (CH_2), 45.96 (CH_2), 49.69 (CH_2), 51.70 (CH), 61.00 (CH_2), 111.49 (CH), 116.85 (CH), 122.24 (C), 127.26 (CH), 130.11 (CH), 144.05 (C), 170.67 (CO), 174.07 (CO) ppm. IR (KBr) *v*: 3373, 2979, 2931, 2856, 1739 (CO), 1626, 1514, 1419, 1303, 1173, 750, 737, 633 cm^{-1}. Mass-spectr., *m*/*z* (*I*,%): 318 (9) [M^+], 245 (30) [M^+-CO_2Et], 146 (100) [$M^+-C_6H_{12}N$], 98 (37), 77 (27), 42 (22). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.07; H, 8.36; N, 9.01.

4.4.8. Ethyl *N*-[4-bromo-2-(azepan-1-ylcarbonyl)phenyl]-2-aminopropionic acid (5b)

Compound **5b** was obtained as a yellowish oil, 70%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, *J* = 7.1, 3H, CH_2CH_3), 1.44 (d, *J* = 7.0, 3H, $CHCH_3$), 1.51–1.93 (m, 8H, 2 × $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 3.29–3.79 (m, 4H, 2 × CH_2CH_2N), 4.00–4.09 (m, 1H, $CHCH_3$), 4.16 (q, *J* = 7.1, 2H, CH_2CH_3), 5.02 (br d, 1H, NH), 6.44 (d, *J* = 8.7, 1H, CH_{Ar}), 7.17 (br d, *J* = 2.3, 1H, CH_{Ar}), 7.26 (dd, *J* = 8.7, 2.3, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.16 (CH_3),

18.60 (CH_3), 26.37 (CH_2), 27.39 (CH_2), 27.75 (CH_2), 29.17 (CH_2), 46.08 (CH_2), 49.76 (CH_2), 51.71 (CH), 61.18 (CH_2), 108.61 (CH), 113.19 (CH), 123.98 (C), 129.77 (CH), 132.72 (CH), 143.11 (C), 169.04 (CO), 173.66 (CO) ppm. IR (KBr) ν: 3386, 2979, 2929, 2856, 1739 (CO), 1626, 1506, 1425, 1306, 1213, 1167, 808, 638 cm^{-1}. Mass-spectr., m/z (I,%): 398 (11) [M^+], 396 (12) [M^+], 325 (53) [M^+-CO_2Et], 323 (58) [M^+-CO_2Et], 226 (77) [$M^+-C_6H_{12}N$], 224 (69) [$M^+-C_6H_{12}N$], 198 (3), 146 (65) [$M^+-C_6H_{12}N$, −Br], 117 (53), 98 (100), 42 (89). Anal. Calcd for $C_{18}H_{25}BrN_2O_3$: C, 54.42; H, 6.34; N, 7.05. Found: C, 54.25; H, 6.40; N, 7.18.

4.4.9. Ethyl *N*-[4-methyl-2-(azepan-1-ylcarbonyl)phenyl]-2-aminopropionic acid (5c)

Compound **5c** was obtained as a yellowish oil, 45%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, J = 7.1, 3H, CH_2CH_3), 1.45 (d, J = 6.9, 3H, $CHCH_3$), 1.52–1.95 (m, 8H, 2 × $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 2.22 (s, 3H, CH_{3Ar}), 3.23–3.85 (m, 4H, 2 × CH_2CH_2N), 4.02–4.23 (m, 3H, $CHCH_3$, CH_2CH_3), 4.77 (br d, 1H, NH), 6.49 (d, J = 8.3, 1H, CH_{Ar}), 6.90 (br d, J = 1.7, 1H, CH_{Ar}), 7.00 (dd, J = 8.3, 1.7, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.19 (CH_3), 18.83 (CH_3), 20.29 (CH_3), 26.44 (CH_2), 27.46 (CH_2), 27.84 (CH_2), 29.23 (CH_2), 45.93 (CH_2), 49.67 (CH_2), 52.02 (CH), 61.00 (CH_2), 111.79 (CH), 122.77 (C), 126.29 (C), 127.68 (CH), 130.55 (CH), 141.56 (C), 170.78 (CO), 174.38 (CO) ppm. IR (KBr) ν: 3373, 2979, 2927, 2858, 1739 (CO), 1630, 1518, 1425, 1308, 1173, 1053, 808, 642 cm^{-1}. Mass-spectr., m/z (I,%): 332 (14) [M^+], 259 (56) [M^+-CO_2Et], 160 (100) [$M^+-C_6H_{12}N$], 132 (13), 117 (22), 98 (58), 91 (32), 41 (15). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.53; H, 8.47; N, 8.21.

4.4.10. Ethyl (*R*)-*N*-[2-(azepan-1-ylcarbonyl)phenyl]-2-aminopropionic acid ((*R*)-8a)

Compound (*R*)-**8a** was obtained as a yellowish oil, 85%, $[\alpha]_D^{20} = +9$ (c 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, J = 7.1, 3H, CH_2CH_3), 1.48 (d, J = 6.9, 3H, $CHCH_3$), 1.53–1.99 (m, 8H, 2 × $CH_2CH_2CH_2N$, 2 × CH_2CH_2N), 3.31–3.84 (m, 4H, 2 × CH_2CH_2N), 4.06–4.16 (m, 1H, $CHCH_3$), 4.18 (q, J = 7.1, 2H, CH_2CH_3), 5.05 (br d, 1H, NH), 6.58 (d, J = 8.2, 1H, CH_{Ar}), 6.66–6.75 (m, 1H, CH_{Ar}), 7.09 (dd, J = 7.5, 1.4, 1H, CH_{Ar}), 7.16–7.24 (m, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.17 (CH_3), 18.77 (CH_3), 26.41 (CH_2), 27.48 (CH_2), 27.81 (CH_2), 29.26 (CH_2), 46.02 (CH_2), 49.73 (CH_2), 51.77 (CH), 61.05 (CH_2), 111.53 (CH), 116.88 (CH), 122.28 (C), 127.31 (CH), 130.14 (CH), 144.10 (C), 170.71 (CO), 174.14 (CO) ppm.

4.4.11. Ethyl *N*-[2-(morpholin-4-ylcarbonyl)phenyl]-2-aminopropionic acid (6a)

Compound **6a** was obtained as a yellowish oil, 69%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, J = 7.2, 3H, CH_2CH_3), 1.46 (d, J = 6.9, 3H, $CHCH_3$), 3.49–3.76 (m, 8H, 2 × NCH_2CH_2O), 4.06–4.13 (m, 1H, $CHCH_3$), 4.15 (q, J = 7.2, 2H, CH_2CH_3), 5.30 (br d, 1H, NH), 6.56 (d, J = 8.2, 1H, CH_{Ar}), 6.68 (ap.t, J = 7.5, 1H, CH_{Ar}), 7.07 (dd, J = 7.5, 1.3, 1H, CH_{Ar}), 7.18–7.22 (m, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.17 (CH_3), 18.71 (CH_3), 42.87–47.74 (2C, 2 × CH_2), 51.68 (CH), 61.12 (CH_2), 67.00 (2C, 2 × CH_2), 111.86 (CH), 116.93 (CH), 119.68 (C), 128.19 (CH), 131.01 (CH), 144.92 (C), 169.92 (CO), 174.06 (CO) ppm. IR (KBr) ν: 3330, 2979, 2927, 2866, 1743 (CO), 1626, 1466, 1325, 1186, 1115, 1014, 758, cm^{-1}. Mass-spectr., m/z (I,%): 306 (11) [M^+], 233 (39) [M^+-CO_2Et], 146 (100) [$M^+-C_4H_8NO$], 118 (10), 77 (16), 42 (6). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.77; H, 7.44; N, 9.13.

4.4.12. Ethyl *N*-[4-bromo-2-(morpholin-4-ylcarbonyl)phenyl]-2-aminopropionic acid (6b)

Compound **6b** was obtained as a yellowish oil, 72%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, J = 7.1, 3H, CH_2CH_3), 1.46 (d, J = 7.0, 3H, $CHCH_3$), 3.50–3.77 (m, 8H, 2 × NCH_2CH_2O), 4.01–4.11 (m, 1H, $CHCH_3$), 4.17 (q, J = 7.1, 2H, CH_2CH_3), 5.25 (br d, 1H, NH), 6.45 (d, J = 8.7, 1H, CH_{Ar}), 7.19 (br d, J = 2.2, 1H, CH_{Ar}), 7.29 (dd, J = 8.7, 2.2, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.18 (CH_3), 18.58 (CH_3), 43.23–47.92 (2C, 2 × CH_2), 51.68 (CH), 61.29 (CH_2), 66.93 (2C, 2 × CH_2), 108.64 (C), 113.54 (CH), 121.58 (C), 130.56 (CH), 133.58 (CH), 143.84 (C), 168.25 (CO), 173.61 (CO) ppm. IR (KBr) ν: 3381, 2979, 2856, 1738 (CO), 1631, 1506, 1427, 1238, 1174, 1115, 1020, 810, 737, 609 cm^{-1}. Mass-spectr., m/z (I,%): 386 (15) [M^+], 384 (16) [M^+], 313 (56) [M^+-CO_2Et], 311 (63) [M^+-CO_2Et], 226 (100) [$M^+-C_4H_8NO$], 224 (99) [$M^+-C_4H_8NO$], 197 (4), 146 (69) [$M^+-C_4H_8NO$, −Br], 117 (58), 90 (25), 56 (42), 42 (43). Anal. Calcd for $C_{16}H_{21}BrN_2O_4$: C, 49.88; H, 5.49; N, 7.27. Found: C, 49.80; H, 5.54; N, 7.20.

4.4.13. Ethyl *N*-[4-methyl-2-(morpholin-4-ylcarbonyl)phenyl]-2-aminopropionic acid (6c)

Compound **6c** was obtained as a yellowish oil, 42%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, J = 7.1, 3H, CH_2CH_3), 1.45 (d, J = 6.9, 3H, $CHCH_3$), 2.21 (s, 3H, CH_{3Ar}), 3.48–3.77 (m, 8H, 2 × NCH_2CH_2O), 4.08 (q, J = 6.9, 1H, $CHCH_3$), 4.16 (q, J = 7.1, 2H, CH_2CH_3), 4.83–5.18 (br s, 1H, NH), 6.50 (d, J = 8.4, 1H, CH_{Ar}), 6.91 (br d, J = 2.1, 1H, CH_{Ar}), 7.02 (ddd, J = 8.4, 2.1, 0.6, 1H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.18 (CH_3), 18.78 (CH_3), 20.22 (CH_3), 43.78–47.69 (2C, 2 × CH_2), 51.98 (CH), 61.04 (CH_2), 67.02 (2C, 2 × CH_2), 112.17 (CH), 120.35 (C), 126.46 (C), 128.43 (CH), 131.46 (CH), 142.31 (C), 169.93 (CO), 174.24 (CO) ppm. IR (KBr) ν: 3354, 2970, 2864, 1743 (CO), 1626, 1527, 1439, 1178, 1111, 1028, 804, cm^{-1}. Mass-spectr., m/z (I,%): 320 (4) [M^+], 247 (22) [M^+-CO_2Et], 160 (100) [$M^+-C_4H_8NO$], 132 (6), 117 (10), 91 (13), 56 (14), 42 (10). Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.45; H, 7.75; N, 8.81.

4.4.14. Ethyl *N*-[2-{[(1-phenylethyl)amino]carbonyl}phenyl]-2-aminopropionic acid (7a)

Compound **7a** was obtained as a yellowish oil, 85%, mixture of diastereomers A:B = 1:2.4. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (mixture of two diastereomers A:B = 1:2.4): δ = 1.24, 1.27 (both t, J_A = 7.1, J_B = 7.1, sum 3H, CH_2CH_3), 1.54 (d, J = 7.0, 3H, PhCHCH_3), 1.59, 1.60 (both d, J_A = 6.9, J_B = 7.0, sum 3H, $CHCH_3$), 4.10–4.24 (m, 3H, PhCHCH$_3$, CH_2CH_3), 5.27–5.36 (m, 1H, $CHCH_3$), 6.54–6.65 (m, 3H, 2×CH_{Ar}, NH), 7.25–7.31 (m, 2H, 2 × CH_{Ar}), 7.34–7.45 (m, 5H, 5 × CH_{Ar}), 7.90–7.95 (m, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer A): δ = 14.20 (CH_3), 18.68 (CH_3), 21.94 (CH_3), 48.92 (CH), 51.78 (CH), 61.07 (CH_2), 112.05 (CH), 115.81 (CH), 116.10 (C), 126.25 (2C, 2 × CH), 127.35 (CH), 127.68 (CH), 128.71 (2C, 2 × CH), 132.73 (CH), 143.40 (C), 148.31 (C), 168.69 (CO), 174.24 (CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer B): δ = 14.24 (CH_3), 18.63 (CH_3), 22.01 (CH_3), 48.92 (CH), 51.72 (CH), 61.07 (CH_2), 111.97 (CH), 115.76 (CH), 115.99 (C), 126.18 (2C, 2 × CH), 127.30 (CH), 127.68 (CH), 128.71 (2C, 2 × CH), 132.73 (CH), 143.53 (C), 148.31 (C), 168.74 (CO), 174.30 (CO) ppm. IR (KBr) ν: 3330, 2979, 2877, 1736 (CO), 1633, 1583, 1520, 1452, 1174, 1051, 748, 700, 569 cm^{-1}. Mass-spectr., m/z (I,%): 340 (13) [M^+], 267 (30) [M^+-CO_2Et], 163 (45), 146 (100) [$M^+-C_8H_9N$], 105 (69), 77 (29), 42 (7). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.35; H, 7.20; N, 8.17.

4.4.15. Ethyl *N*-[4-bromo-2-{[(1-phenylethyl)amino]carbonyl}phenyl]-2-aminopropionic acid (7b)

Compound **7b** was obtained as a yellowish oil, 53%, mixture of diastereomers A:B =1:2.7. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (mixture of two diastereomers A:B = 1:2.7): δ = 1.25, 1.31 (both t, J_A = 7.15, J_B = 7.15, sum 3H, CH_2CH_3), 1.52 (d, J = 7.0, 3H, PhCHCH_3), 1.56–1.64 (m, 3H, $CHCH_3$), 4.04–4.12 (m, 1H, PhCHCH$_3$), 4.20, 4.26

(both q, J_A = 7.15, J_B = 7.15, sum 2H, CH_2CH_3), 5.22–5.31 (m, 1H, $CHCH_3$), 6.39, 6.43 (both d, J_A = 8.9, J_B = 8.8, sum 1H, CH_{Ar}), 6.67, 6.93 (br d and br t, sum 1H, NH), 7.23–7.52 (m, 8H, 8 × CH_{Ar}), 7.84, 7.88 (both br d, sum 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer A): δ = 14.20 (CH_3), 18.51 (CH_3), 21.88 (CH_3), 49.20 (CH), 51.70 (CH), 61.28 (CH_2), 107.22 (C), 113.64 (CH), 117.66 (C), 126.31 (2C, 2 × CH), 127.42 (CH), 128.77 (2C, 2 × CH), 130.19 (CH), 135.17 (CH), 143.12 (C), 147.13 (C), 167.46 (CO), 173.97 (CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer B): δ = 14.24 (CH_3), 18.51 (CH_3), 22.08 (CH_3), 49.27 (CH), 51.46 (CH), 61.42 (CH_2), 107.27 (C), 113.25 (CH), 117.47 (C), 126.16 (2C, 2 × CH), 127.25 (CH), 128.67 (2C, 2 × CH), 130.14 (CH), 135.17 (CH), 143.61 (C), 146.94 (C), 167.53 (CO), 174.40 (CO) ppm. IR (KBr) ν: 3350, 2979, 2935, 1739 (CO), 1631, 1506, 1321, 1240, 1178, 1020, 893, 806, 700, 542 cm^{-1}. Mass-spectr., m/z (I,%): 420 (4) [M^+], 418 (4) [M^+], 347 (9) [M^+-CO_2Et], 345 (10) [M^+-CO_2Et], 268 (1) [M^+-CO_2Et, -Ph], 241 (25), 226 (19) [$M^+-C_8H_9N$], 224 (20) [$M^+-C_8H_9N$], 163 (5), 146 (13) [$M^+-C_8H_9N$, −Br], 120 (14), 105 (100), 77 (25), 42 (10). Anal. Calcd for $C_{20}H_{23}BrN_2O_3$: C, 57.29; H, 5.53; N, 6.68. Found: C, 57.21; H, 5.66; N, 6.27.

4.4.16. Ethyl *N*-[4-methyl-2-{[(1-phenylethyl)amino]carbonyl} phenyl]-2-aminopropionic acid (7c)

Compound **7c** was obtained as a yellowish oil, 43%, mixture of diastereomers A:B =1:2.2. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (mixture of two diastereomers A:B = 1:2.2): δ = 1.23, 1.27 (both t, J_A = 7.1, J_B = 7.1, sum 3H, CH_2CH_3), 1.48–1.55 (m, 3H, PhCHCH_3), 1.60 (d, J = 6.9, 3H, CHCH_3), 2.23, 2.24 (both s, sum 3H, CH_{3Ar}), 4.06–4.24 (m, 3H, PhCHCH$_3$, CH_2CH$_3$), 5.26–5.37 (m, 1H, CHCH$_3$), 6.47–6.58 (m, 2H, 2 × CH_{Ar}), 7.05–7.13 (m, 1H, CH_{Ar}), 7.17–7.24 (m, 1H, NH), 7.25–7.32 (m, 1H, CH_{Ar}), 7.34–7.45 (m, 4H, 4 × CH_{Ar}), 7.52–7.66 (m, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer A): δ = 14.23 (CH_3), 18.67 (CH_3), 20.29 (CH_3), 21.90 (CH_3), 48.88 (CH), 52.08 (CH), 61.00 (CH_2), 112.52 (CH), 116.42 (C), 125.11 (C), 126.29 (2C, 2 × CH), 127.34 (CH), 127.87 (CH), 128.69 (2C, 2 × CH), 133.43 (CH), 143.40 (C), 146.04 (C), 168.61 (CO), 174.46 (CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer B): δ = 14.23 (CH_3), 18.67 (CH_3), 20.29 (CH_3), 22.00 (CH_3), 48.88 (CH), 52.00 (CH), 61.00 (CH_2), 112.36 (CH), 116.25 (C), 125.00 (C), 126.21 (2C, 2 × CH), 127.28 (CH), 127.87 (CH), 128.69 (2C, 2 × CH), 133.43 (CH), 143.54 (C), 146.04 (C), 168.67 (CO), 174.52 (CO) ppm. IR (KBr) ν: 3336, 2979, 2933, 1738 (CO), 1643, 1520, 1450, 1279, 1174, 1051, 810, 700, 542 cm^{-1}. Mass-spectr., m/z (I,%): 354 (4) [M^+], 281 (10) [M^+-CO_2Et], 204 (0.7) [M^+-CO_2Et, -Ph], 177 (25), 160 (83) [$M^+-C_8H_9N$], 105 (100), 91 (19), 77 (19), 42 (8). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.14; H, 7.50; N, 7.94.

4.4.17. Ethyl (*R*)-*N*-[2-{[(1-phenylethyl)amino]carbonyl} phenyl]-2-aminopropionic acid ((*R*)-9a)

Compound (*R*)-**9a** was obtained as a yellowish oil, 80%, mixture of diastereomers A:B = 1:2.8. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (mixture of two diastereomers A:B = 1:2.8): δ = 1.24, 1.27 (both t, J_A = 7.1, J_B = 7.1, sum 3H, CH_2CH_3), 1.54, 1.55 (both d, J_A = 7.0, J_B = 7.0, sum 3H, PhCHCH_3), 1.61 (d, J = 6.9, 3H, CHCH_3), 4.09–4.26 (m, 3H, PhCHCH$_3$, CH_2CH$_3$), 5.27–5.36 (m, 1H, CHCH$_3$), 6.30–6.41 (m, 1H, NH), 6.56–6.68 (m, 2H, 2 × CH_{Ar}), 7.25–7.33 (m, 2H, 2 × CH_{Ar}), 7.34–7.44 (m, 5H, 5 × CH_{Ar}), 7.83–7.92 (m, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer A): δ = 14.22 (CH_3), 18.66 (CH_3), 21.91 (CH_3), 48.90 (CH), 51.76 (CH), 61.05 (CH_2), 112.12 (CH), 115.78 (CH), 116.02 (C), 126.23 (2C, 2 × CH), 127.41 (CH), 127.47 (CH), 128.75 (2C, 2 × CH), 132.76 (CH), 143.35 (C), 148.33 (C), 168.61 (CO), 174.20 (CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) (isomer B): δ = 14.22 (CH_3), 18.62 (CH_3), 21.98 (CH_3), 48.90 (CH), 51.72 (CH), 61.05 (CH_2), 112.06 (CH), 115.74 (CH), 115.92 (C), 126.16 (2C, 2 × CH), 127.37 (CH), 127.47 (CH), 128.75 (2C, 2 × CH), 132.76 (CH), 143.35 (C), 148.33 (C), 168.64 (CO), 174.24 (CO) ppm.

4.4.18. Ethyl (*R*)-*N*-[2-{[(*S*)-1-phenylethyl)amino]carbonyl} phenyl]-2-aminopropionic acid ((*R,S*)-9a′)

Compound (*R,S*)-**9a′** was obtained as a yellowish oil, 83%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, J = 7.1, 3H, CH_2CH_3), 1.54 (d, J = 7.0, 3H, PhCHCH_3), 1.60 (d, J = 6.9, 3H, CHCH_3), 4.09–4.26 (m, 3H, PhCHCH$_3$, CH_2CH$_3$), 5.26–5.36 (m, 1H, CHCH$_3$), 6.37 (br d, 1H, NH), 6.55–6.67 (m, 2H, 2 × CH_{Ar}), 7.25–7.33 (m, 2H, 2 × CH_{Ar}), 7.34–7.44 (m, 5H, 5 × CH_{Ar}), 7.89 (br d, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.22 (CH_3), 18.62 (CH_3), 21.98 (CH_3), 48.91 (CH), 51.72 (CH), 61.06 (CH_2), 112.02 (CH), 115.74 (CH), 115.92 (C), 126.16 (2C, 2 × CH), 127.35 (CH), 127.50 (CH), 128.73 (2C, 2 × CH), 132.75 (CH), 143.39 (C), 148.32 (C), 168.67 (CO), 174.25 (CO) ppm.

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