

## L-proline/cholesterol and diosgenin based thiourea cooperative system for the direct asymmetric aldol reaction in the presence of water

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Received: 16.03.2020 • Accepted/Published Online: 01.07.2020 • Final Version: 26.10.2020

**Abstract:** A series of cholesterol and based hydrophobic urea and thiourea compounds were synthesized and successfully used as a cocatalyst for L-proline catalyzed aldol reactions in the presence of water. The anticonfigured products were obtained with good yields (up to 94%), high diastereoselectivities (up to 95:5), and high enantiomeric excesses (up to 93% *ee*). The successful results for catalytic efficiency of L-proline in the presence of water reveal the importance of the hydrophobic nature of cholesterol and diosgenin parts of thiourea on the reactivity and selectivity in the presence of water.

**Key words:** Aldol, organocatalyst, proline, asymmetric synthesis

### 1. Introduction

Direct asymmetric aldol reaction is one of the most effective strategies inspired by nature for stereoselective carbon-carbon bond-forming reactions in synthetic organic chemistry [1–3]. Following the pioneering studies on L-proline catalyzed direct asymmetric aldol reactions by List et al. in the early 2000s [4], much effort has been made to develop the effective metal-free small organic molecules as organocatalytic systems for direct aldol reactions, which generally involves structural modifications of catalysts and optimization of the reaction conditions. However, classical organocatalyst synthesis requires a painstaking strategy and can involve challenging synthesis steps. Since only one catalyst is used in these organocatalyst samples, reactivities and selectivity are also expected to be limited [5,6]. Most recently, there has been considerable interest in employing self-assembled organocatalysts in catalytic asymmetric reactions [5,6]. The use of such self-assembled organocatalytic systems has advantages over the conventional organocatalysts; such as (i) the structure of self-assembled organocatalysts is easy for modification and optimization, (ii) it is very easy to create a large catalyst library by changing selected suitable additives. We have successfully investigated and determined that the self-assembled proline-thioureasupramolecular complex was an efficient organocatalyst for a direct enantioselective aldol reaction in nonpolar solvents such as hexane [7]. Also, researchers have shown that the use of suitable additives, such as water [8–10], chiral alcohols [11,12], thioureas [13–17], thiuronium salts [18], imidazolium salts [19], and guanidinium salts [20] has been documented as a powerful method to accelerate the rate of reaction and improve the stereoselectivity of aldol reactions.

Due to environmental concerns, reactions using water as a solvent have recently received significant attention from a wide range of synthetic chemists [21,22]. L-proline is known as an efficient catalyst for direct aldol reactions in generally polar organic solvents [23,24]. Nevertheless, the high polarity of these organic solvents has continued to be a major problem from a viewpoint of green chemistry. While L-proline was known to be an inefficient catalyst in water, Barbas and Hayashi's groups revealed that hydrophobic proline derivatives could effectively catalyze asymmetric aldol reactions in the presence of water [25–28]. This concept opens a new avenue for the development of new hydrophobic water-compatible organocatalysts [29–31]. Inspired by the introduction of a suitable hydrophobic moiety into organocatalytic systems, we recently showed that the use of calixarene-linked thiourea as a hydrophobic cocatalyst that has good H-bonding ability in supramolecular interactions increased the yield and selectivity of the catalytic asymmetric aldol reactions in the presence of water [15].

Cholesterol and diosgenin are known to be essential components of mammalian cellular membranes; they provide the membranes with improved lipophilic characteristics over linear alkyl chains [32]. When one considers the natural

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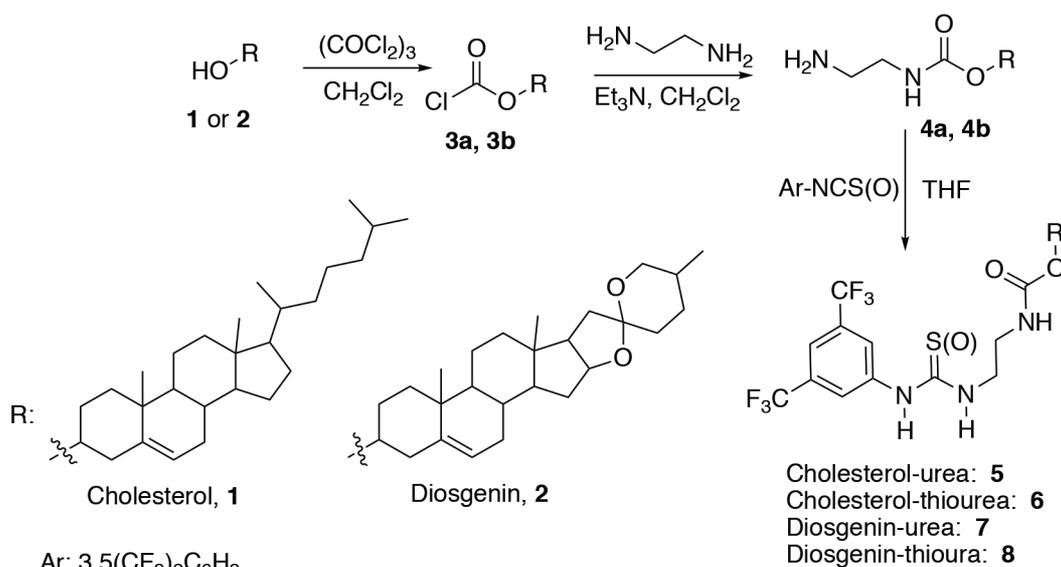
amphiphilic structures of cholesterol and diosgenin molecules, it is surprising that their use as a hydrophobic part of water-compatible organocatalysts has only received limited attention [33].

We are still keenly interested in improving the efficiency of L-proline catalyzed aldol reactions in water. Previously, we have successfully established that calixarene-linked thiourea was an effective cocatalyst for the highly stereoselective intermolecular aldol reaction in the presence of water [15]. The results clearly confirmed that the hydrophobic calix[4]arene part of thiourea has a positive effect on both reactivity and stereoselectivity. Since the development of suitable cocatalysts that form assemblies with proline, direct aldol reactions in the presence of water are still desirable; herein we turned our attention to the synthesis of new thiourea and urea derivatives bearing cholesterol and diosgenin moieties as hydrophobic motifs. The aim of this study was to develop a small cocatalyst library of cholesterol and diosgenin based (thio)ureas which can self-assemble with L-proline to catalyze the asymmetric aldol reaction of cyclohexanone and aromatic aldehydes in the presence of water.

## 2. Results and discussion

The synthetic route to a series of thiourea catalysts is illustrated in Scheme 1. Carbamate derivatives 4a and 4b were synthesized according to a published procedure [33,34]. First, the reaction of cholesterol (1) and diosgenin (2) with triphosgene gave chloroformate derivatives 3a and 3b, respectively. Then, the compounds 3a and 3b were reacted with ethylenediamine, and the corresponding carbamate derivatives 4a and 4b were obtained. Finally, these carbamate derivatives were converted into their thiourea derivatives 6 and 8 by treatment with phenyl isothiocyanate. A similar synthetic route was used to prepare the urea derivatives 5 and 7. The structures of compounds 3–8 were fully identified by using  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectroscopy.

With the desired cholesterol and diosgenin (thio)urea derivatives in hand, we next studied the possibility of using these thiourea derivatives 5–8 as new cocatalysts in the L-proline catalyzed aldol reaction in the presence of water. As a test reaction, the aldol reaction of cyclohexanone and p-nitrobenzaldehyde was conducted in the presence of water. As shown in Table 1, all the examined cocatalysts 5–8 showed similar levels of catalytic efficiencies, with high conversions, diastereo- and enantioselectivities. The best result in terms of selectivity was obtained by using L-proline (10 mol %) / cholesterol-based thiourea 6 (10 mol %), and the reaction furnished the expected product in nearly full conversion with 93% *ee* (entry 2, Table 1). Next, we screened the amount of water and found that our system showed high catalytic efficiency in 0.250 mL of water. We observed that an increase in the amount of water (0.5 mL) decreases the enantioselectivity of the aldol product (entry 5, Table 1). Reducing the amount of water to 0.125 mL also reduced enantioselectivity (entry 6, Table 1). Next, we examined the effect of additives on the enantioselectivity of the reaction. However, no enhancement in selectivity was observed with different acidic additives (entries 7–9; Table 1). L-proline was found to not help the reaction (entry 12; Table 1). It was also found that cholesterol-thiourea (6) was not effective when L-proline was not used (entry 11, Table 1).

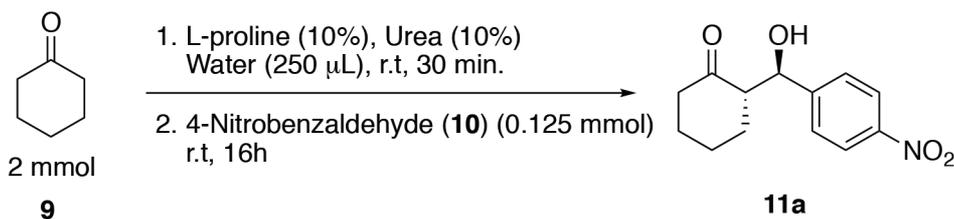


**Scheme 1.** Synthesis of urea derivatives 5–8.

With these optimal reaction conditions in hand, we next studied the substrate scope of the aldol reaction of different aldehydes with cyclohexanone, and the results are presented in Table 2. The results indicated that L-proline-cholesterol based thiourea 6 host-guest complex can catalyze the aldol reaction very well in the presence of water. As seen, various substituted aromatic aldehydes with electron-withdrawing groups can be tolerated. The reaction can provide aldol products 11a to 11l in good yields with moderate to good enantioselectivity and diastereoselectivity.

Among the substituted benzaldehydes, the best enantioselectivities were obtained with the p-nitrobenzaldehyde and p-chlorobenzaldehyde, giving high enantioselectivities with 93% and 91% *ee*, respectively (entries 1 and 4, Table 2). Also, the reaction is tolerant of other p-substituted benzaldehydes, which affords the aldol product with moderate to good enantioselectivities ranging from 83% to 90%. Besides, the reaction allowed electron-withdrawing substituents at the o- and m- positions of the phenyl ring (entries 2, 3, 5, and 6, Table 2). Anisaldehyde, an electron-rich aromatic aldehyde, reacted with cyclohexanone, and the corresponding anti-aldol product **11k** was obtained in only low yields and low enantioselectivity (36% *ee*) (entry 11, Table 2). We also found that cyclopentanone underwent a smooth reaction with p-nitrobenzaldehyde to give mainly the syn-product in high yield with low enantioselectivities (entry 12, Table 2).

In conclusion, we have synthesized a series of novel cholesterol-(thio)urea and diosgenin-(thio)urea conjugates as a cocatalyst that can self-assemble with L-proline to catalyze the direct aldol reactions of cyclohexanone with benzaldehyde derivatives in the presence of water. Under the optimum reaction conditions, the reaction of electron-deficient aromatic aldehydes with cyclohexanone gave anti-configured aldol products in moderate to high *ee* values (up to 93% *ee*) in the presence of water. The successful results for catalytic efficiency of L-proline indicate the importance of the hydrophobic



**Table 1.** Effect of cholesterol and diosgenin based urea and thiourea compounds 5-8 on proline catalyzed direct aldol reaction.

Entry	Co-catalyst	Additive	Conv. (%) <sup>a</sup>	<i>anti:syn</i> <sup>a</sup>	<i>ee</i> <sup>b</sup> (%)
1	5	-	> 99	81:19	93
2	6	-	> 99	95:5	93
3	7	-	79	89:11	90
4	8	-	94	91:9	93
5 <sup>c</sup>	6	-	85	90:10	89
6 <sup>d</sup>	6	-	78	89:11	90
7	6	ClCH <sub>2</sub> COOH	91	88:12	90
8	6	CH <sub>3</sub> COOH	93	89:11	71
9	6	PhCOOH	94	90:10	89
10 <sup>e</sup>	6	-	72	89:11	71
11 <sup>f</sup>	6	-	< 5	N.D. <sup>g</sup>	N.D.
12	-	-	< 5	N.D.	N.D.

a: Determined by <sup>1</sup>H NMR analysis of crude reaction mixture.

b: Determined by chiral HPLC analysis.

c: 0.5 mL water was used.

d: 0.125 mL water was used.

e: 4.0 equiv. of ketone was used.

f: L-proline was not used.

g: N.D. = not determined.

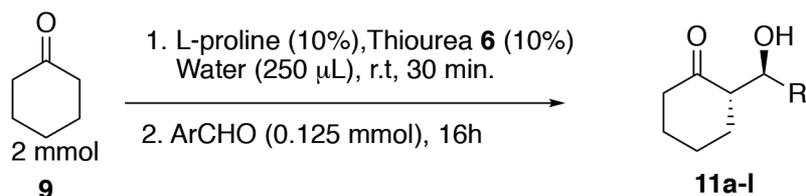


Table 2. Scope of aromatic aldehydes.

Entry	Aldehyde (R)	Yield (%) <sup>a</sup>	<i>anti:syn</i>	<i>ee</i> (%)
1	4-NO <sub>2</sub> Ph	94	95:5	93
2	3-NO <sub>2</sub> Ph	93	84:16	90
3	2-NO <sub>2</sub> Ph	65	90:10	90
4	4-ClPh	73	84:16	91
5	3-ClPh	87	90:10	88
6	2-ClPh	62	87:13	85
7	4-BrPh	75	90:10	90
8	4-FPh	90	85:15	87
9	4-CNPh	83	88:12	84
10	4-CF <sub>3</sub> Ph	86	85:15	83
11	4-MeOPh	44	85:15	36
12 <sup>b</sup>	4-NO <sub>2</sub> Ph	88	42:58	68

a. Yields of isolated aldol product.

b. Cyclopentanone was used.

nature of cholesterol and diosgenin parts of thiourea on both the reactivity and selectivity in the presence of water at room temperature.

### 3. Materials

#### 3.1. General

All reagents were used as received without purification. <sup>1</sup>H NMR(400 MHz) and <sup>13</sup>C NMR(100 MHz) spectra were taken on a Bruker Avance 400 spectrometer. TMS was used as internal standard. Precoated Merck 60 F254TLC plates were used for thin layer chromatography (TLC). Flash column chromatography was performed using silica gel (60-mesh; Merck). The <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS spectra for compounds 5–8 and HPLC chromatograms of compounds 11a–11l can be found under the ‘supplementary information’ given at the end of the article.

#### 3.2. Synthesis and characterization

##### 3.2.1. Synthesis of catalysts 5–8

Compound 4a (or compound 4b) (1.5 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(30 mL) in a round-bottom flask and cooled to ice salt temperature. Then, 3,5-bis(trifluoromethyl)phenyl isocyanate (or 3,5-bis(trifluoromethyl)phenyl isothiocyanate) (1.65 mmol) was added through a syringe and the mixture was stirred at ambient temperature for 24 h to provide a precipitate. This precipitate was washed with n-hexane and then filtered and dried in a vacuum. The crude product was crystallized with petroleum ether-methanol.

**3.2.1.1.** Compound 5; 74% yield; white solid, mp: 213–218 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.62 (s, 3H), 0.75–1.60 (m, 33H), 1.70–2.00 (m, 5H), 2.10–2.30 (m, 2H), 2.98–3.35 (m, 4H), 4.30 (m, 1H), 5.25 (broad, 1H), 6.40 (broad, 1H), 7.02 (s, 1H), 7.46 (s, 1H), 8.07 (s, 2H), 9.39 (broad, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 11.7, 18.6, 19.0, 20.9, 22.4, 22.6, 23.7, 24.2, 27.9, 28.0, 28.1, 31.8, 36.7, 35.7, 36.1, 36.4, 36.9, 38.4, 39.4, 39.7, 39.8, 40.7, 42.2, 50.0, 56.1, 56.6, 74.8, 114.8, 117.8, 121.9, 122.5, 124.7, 131.4, 131.8, 132.1, 132.4, 139.6, 141.4, 156.1, 157.6; LCMS (ESI<sup>+</sup>): C<sub>39</sub>H<sub>55</sub>F<sub>6</sub>N<sub>3</sub>O<sub>3</sub>, calculated value 727.4100 ([M+H]<sup>+</sup>); experimental 728.4210 ([M+H]<sup>+</sup>).

**3.2.1.2.** Compound 6; 70% yield, white solid, mp: 68–70 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.69 (s, 3H), 0.80–2.10 (m, 38H), 2.20–2.40 (m, 2H) 3.15–3.55 (m, 2H), 3.60–4.00 (m, 2H), 4.20–4.60 (m, 1H), 5.11 (s, 1H), 5.25–5.40 (m, 1H), 7.43–8.17 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 11.8, 18.7, 19.2, 21.0, 22.6, 22.8, 23.9, 24.3, 28.0, 28.2, 31.8, 35.8, 36.2, 36.5, 36.8, 38.4, 39.5, 39.7, 42.3, 49.9, 56.2, 56.6, 75.7, 118.9, 120.4, 120.5, 121.1, 121.6, 122.8, 123.8, 124.0, 124.4, 125.8, 127.1, 133.2, 133.6, 134.0, 139.3, 158.1, 181.3; LCMS (ESI<sup>+</sup>): C<sub>39</sub>H<sub>55</sub>F<sub>6</sub>N<sub>3</sub>O<sub>2</sub>S, calculated value 744.3900 ([M+H]<sup>+</sup>); experimental 744.4027 ([M+H]<sup>+</sup>).

**3.2.1.3.** Compound 7; 75% yield, white solid; mp: 165–169 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.76–0.83 (m, 6H), 0.85–2.10 (m, 30H), 2.23–2.50 (m, 2H), 3.30–3.55 (m, 4H), 4.38–4.58 (m, 2H), 5.15–5.35 (m, 2H), 5.92 (s, 1H), 7.54 (s, 1H), 7.90 (s, 2H), 8.17 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.1, 14.5, 16.2, 17.1, 19.2, 19.3, 20.8, 22.6, 28.0, 28.8, 30.3, 31.3, 31.4, 31.6, 31.8, 31.9, 36.6, 36.8, 39.7, 40.2, 41.6, 49.9, 56.4, 62.1, 66.9, 75.5, 80.8, 109.4, 118.3, 118.5, 121.8, 122.5, 124.5, 132.0, 132.3, 139.4, 140.8, 155.8, 158.0; LCMS (ESI<sup>+</sup>): C<sub>39</sub>H<sub>51</sub>F<sub>6</sub>N<sub>3</sub>O<sub>5</sub> calculated value 756.3733 ([M+H]<sup>+</sup>); experimental 756.3761 ([M+H]<sup>+</sup>).

**3.2.1.4.** Compound 8; 71% yield, white solid; mp: 75–78 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.77–0.83 (m, 6H), 0.90–2.05 (m, 29H), 2.20–2.45 (m, 2H), 3.25–3.55 (m, 4H), 3.77 (broad, 1H), 4.20–4.55 (m, 2H), 5.05–5.40 (m, 2H), 7.40–8.10 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.6, 16.4, 17.3, 19.4, 20.9, 28.1, 28.9, 30.4, 31.5, 32.0, 36.8, 36.9, 38.5, 39.8, 40.4, 41.7, 50.0, 56.5, 62.1, 67.0, 80.9, 109.2, 118.5, 119.0, 120.6, 121.1, 121.3, 121.6, 121.8, 122.6, 124.0, 124.2, 124.5, 125.9, 126.7, 133.0, 133.4, 133.7, 134.0, 134.2, 139.5, 141.0, 158.2, 181.4; LCMS (ESI<sup>+</sup>): C<sub>39</sub>H<sub>51</sub>F<sub>6</sub>N<sub>3</sub>O<sub>4</sub>S calculated value 772.3504 ([M+H]<sup>+</sup>); experimental 772.3377 ([M+H]<sup>+</sup>).

### 3.2.2. General procedure for the synthesis of aldol products (11a–11i)

A mixture of L-proline (0.025 mmol), cholesterol based thiourea 6 (0.0125 mmol), cyclohexanone (0.75 mmol), and 0.25 mL water was stirred for 30 min at ambient temperature. Then, aldehyde (0.25 mmol) was added and the reaction mixture was left stirring until no further conversion is seen by TLC. The reaction mixture was treated with saturated aqueous NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. The product was purified with column chromatography over silica gel using ethyl acetate-hexane as an eluent.

**3.2.2.1.** (S)-2-[(R)-hydroxy(*p*-nitrophenyl)methyl]-cyclohexanone (11a) [35,36]. Yield: 94%, anti/syn: 95:5, ee: 93%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 20:80,0.5 mL/min, *l* = 254 nm, *t<sub>r</sub>* (min): 29.7 (minor), 38.6 (major).

**3.2.2.2.** (S)-2-[(R)-hydroxy(*m*-nitrophenyl)methyl]-cyclohexanone(11b) [36]. Yield: 93%, anti/syn: 84:16, ee: 90%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 20:80,0.5 mL/min,*l* = 254 nm, *t<sub>r</sub>* (min): 22.7 (major), 27.6 (minor).

**3.2.2.3.** (S)-2-[(R)-hydroxy(*o*-nitrophenyl)methyl]-cyclohexanone (11c) [36]. Yield: 65%, anti/syn: 90:10, ee: 90%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 20:80,0.5 mL/min, *l* = 254 nm, *t<sub>r</sub>* (min): 24.9 (major), 26.8 (minor).

**3.2.2.4.** (S)-2-[(R)-hydroxy(*p*-chlorophenyl)methyl]-cyclohexanone (11d) [37]. Yield: 73%, anti/syn: 84:16, ee: 91%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 5:95,1.0 mL/min, *l* = 220 nm, *t<sub>r</sub>* (min): 22.0 (minor), 26.0(major).

**3.2.2.5.** (S)-2-[(R)-hydroxy(*m*-chlorophenyl)methyl]-cyclohexanone (11e) [38]. Yield: 87%, anti/syn: 90:10, ee: 88%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 4:96,1.0 mL/min, *l* = 220 nm, *t<sub>r</sub>* (min): 23.7 (major), 26.4 (minor).

**3.2.2.6.** (S)-2-[(R)-hydroxy(*o*-chlorophenyl)methyl]-cyclohexanone (11f) [38]. Yield: 62%, anti/syn: 87:13, ee: 85%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 5:95,1.0 mL/min, *l* = 220 nm, *t<sub>r</sub>* (min): 17.5(minor), 19.9 (major).

**3.2.2.7.** (S)-2-[(R)-hydroxy(*p*-bromophenyl)methyl]-cyclohexanone (11g) [35,36]. Yield: 75%, anti/syn: 90:10, ee: 90%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 10:90,0.5 mL/min, *l* = 220 nm, *t<sub>r</sub>* (min): 31.4 (minor) ,36.5 (major).

**3.2.2.8.** (S)-2-[(R)-hydroxy(*p*-fluorophenyl)methyl]-cyclohexanone (11h) [37]. Yield: 90%, anti/syn: 85:15, ee: 87%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 5:95,0.5 mL/min, *l* = 254 nm, *t<sub>r</sub>* (min): 43.5 (minor), 49.4 (major).

**3.2.2.9.** (S)-2-[(R)-hydroxy(*p*-cyanophenyl)methyl]-cyclohexanone(11i) [38]. Yield: 83%, anti/syn:88:12, ee: 84%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 5:95,1.0 mL/min, *l* = 220 nm, *t<sub>r</sub>* (min): 27.8 (minor), 35.6 (major).

**3.2.2.10.** (S)-2-[(R)-hydroxy(*p*-trifluoromethylphenyl)methyl]cyclohexanone (11j) [38]. Yield: 86%, anti/syn: 85:15, ee: 83%. HPLC: Chiralpak OD-H, *i*PrOH/hexane 5:95,1.0 mL/min, *l* = 254 nm, *t<sub>r</sub>* (min): 17.2(minor), 22.3 (major).

**3.2.2.11.** (S)-2-[(R)-hydroxy(*p*-methoxyphenyl)methyl]-cyclohexanone (11k) [35,36]. Yield: 44%, anti/syn: 85:15, ee: 36%. HPLC: Chiralpak AD-H, *i*PrOH/hexane 10:90,0.5 mL/min, *l* = 254 nm, *t<sub>r</sub>* (min): 27.9 (major), 39.9 (minor).

**3.2.2.12.** (R)-2-[(R)-hydroxy(*p*-nitrophenyl)methyl]-cyclopentanone (11l) [39]. Yield: 88%, anti/syn: 42:58, ee: 68%. HPLC: Chiralpak AD-H, *i*PrOH/hexane 5:95,0.5 mL/min, *l* = 210 nm, *t<sub>r</sub>* (min): 106.8(minor), 113.3(major).

### Acknowledgment

We thank the Scientific and Technological Research Council of Turkey (TÜBİTAK) for financial support (project no. 114Z050).

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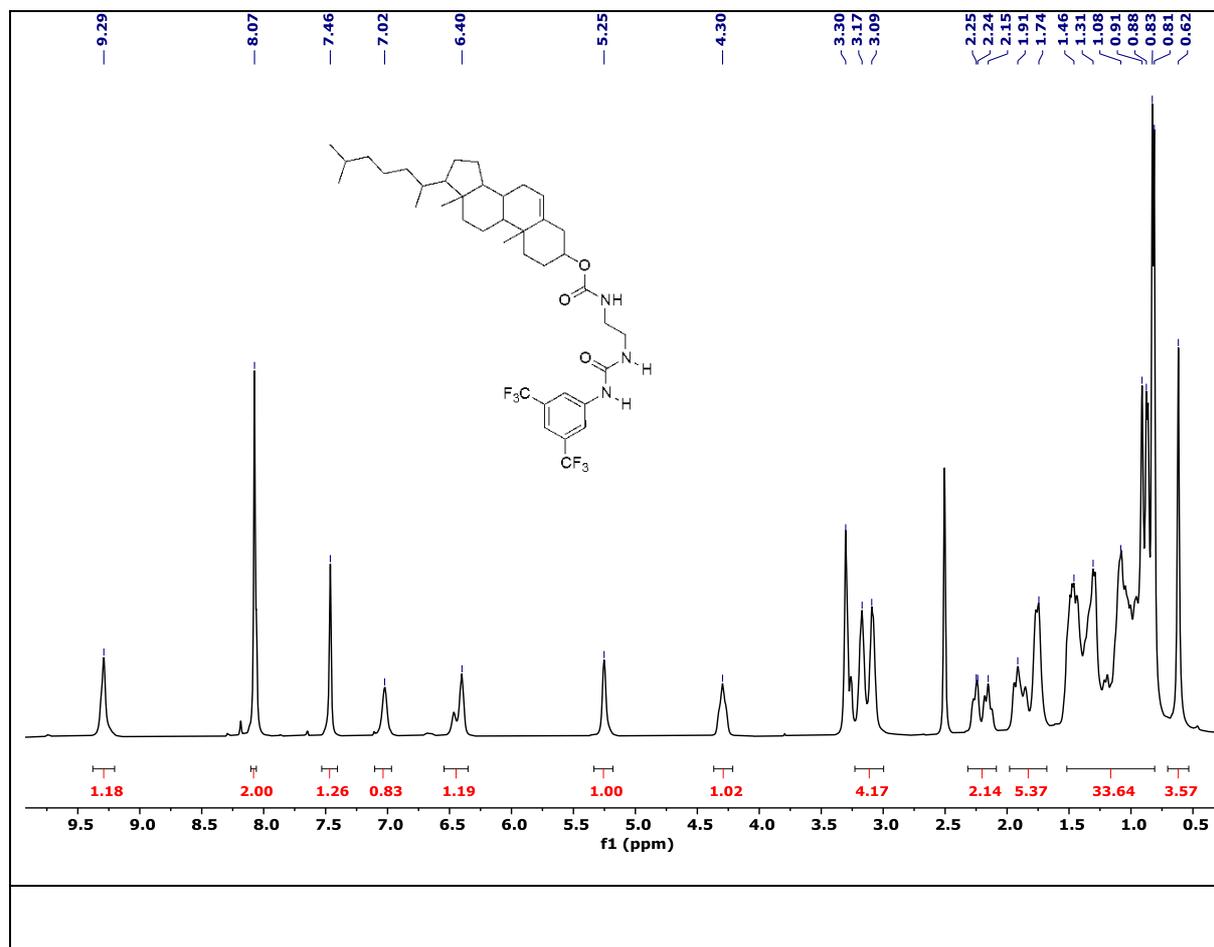
## SUPPORTING INFORMATION

### **L-proline/cholesterol and diosgenin based thiourea cooperative system for the direct asymmetric aldol reaction in the presence of water**

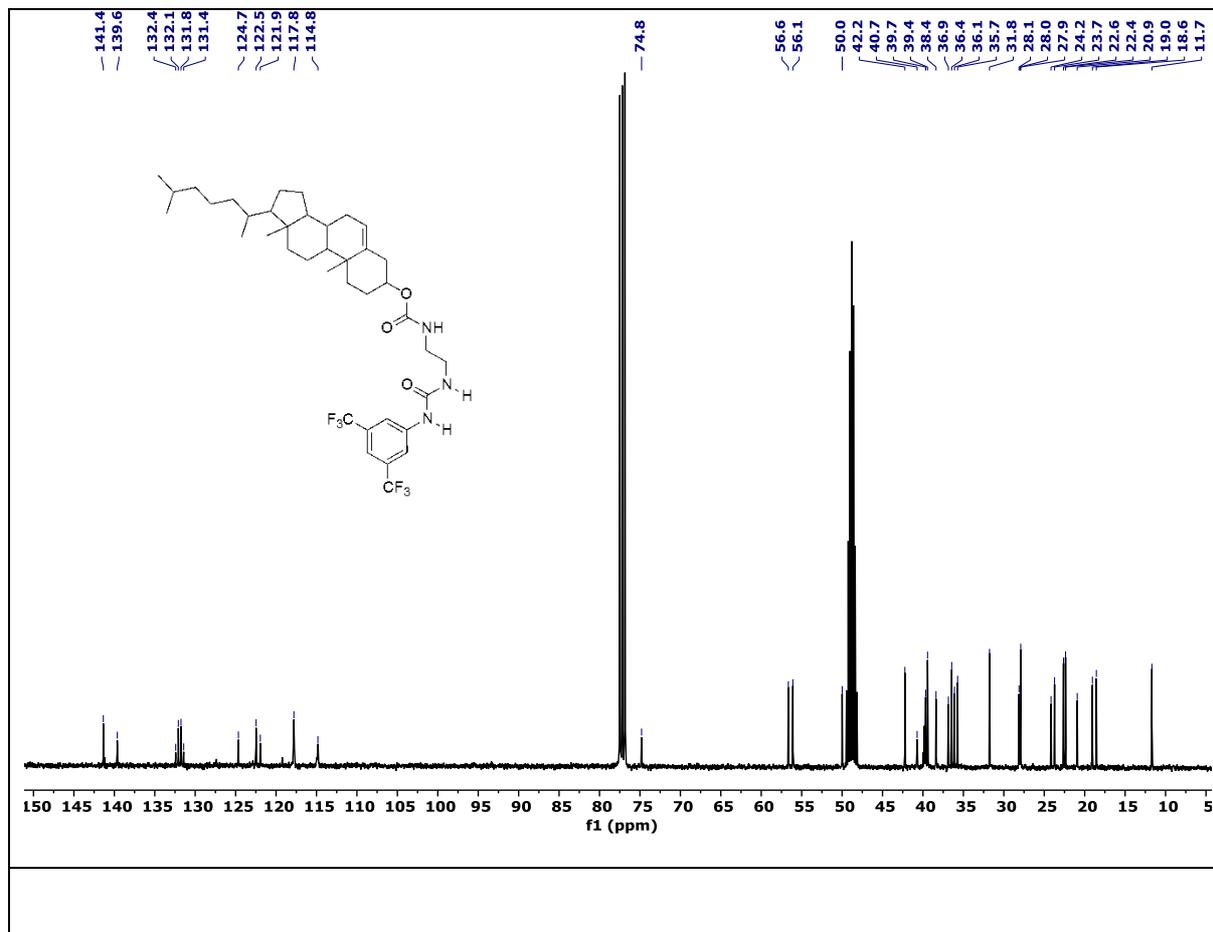
#### **General**

All reagents were used as received without purification.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were taken on a Bruker Avance 400 spectrometer. TMS was used as internal standard. For thin layer chromatography (TLC) pre-coated Merck 60 F254 TLC plates were used. Flash column chromatography was performed using silica gel (60-mesh; Merck).

<sup>1</sup>H NMR spectrum of compound 5



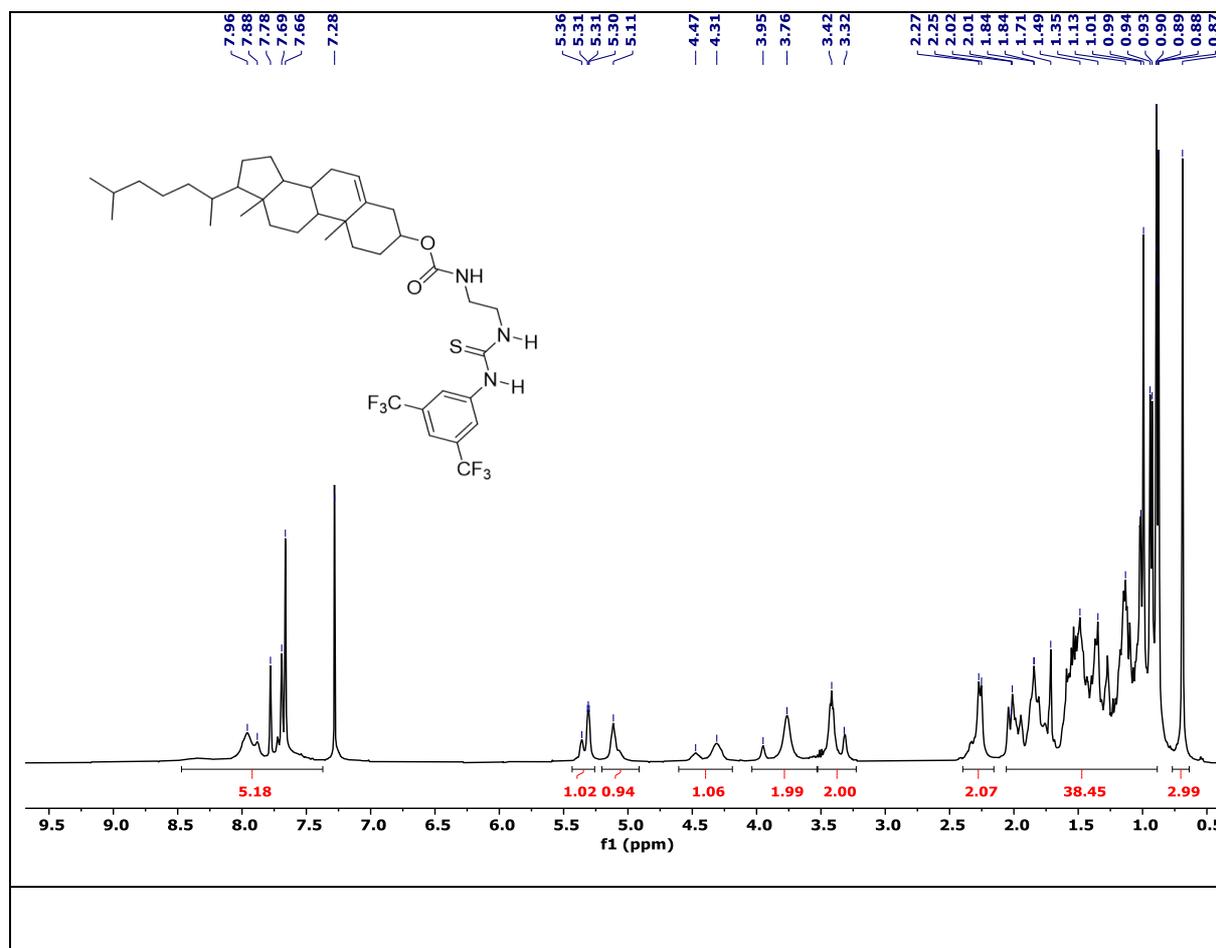
### $^{13}\text{C}$ NMR spectrum of compound 5



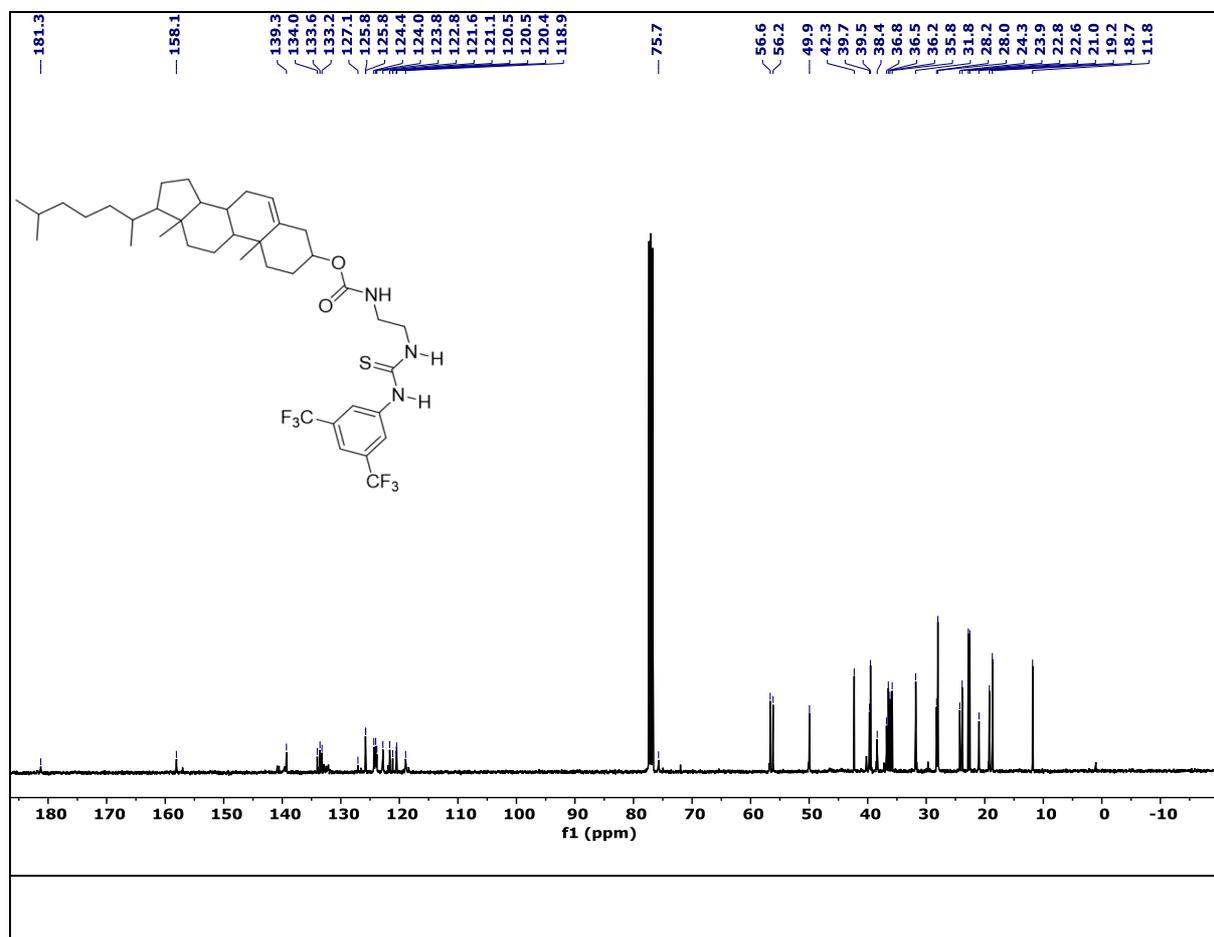
### High Resolution Mass Spectra (HRMS) of compound 5



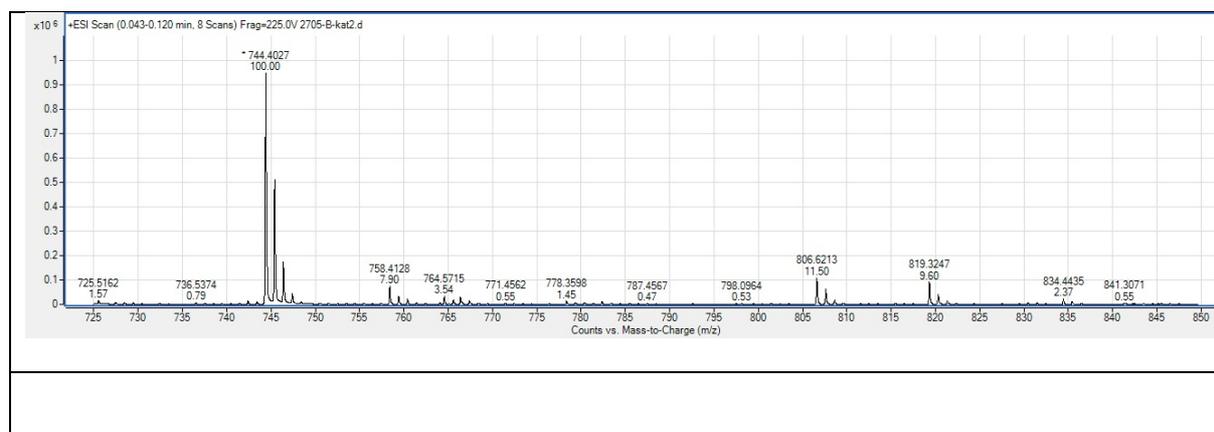
<sup>1</sup>H NMR spectrum of compound 6



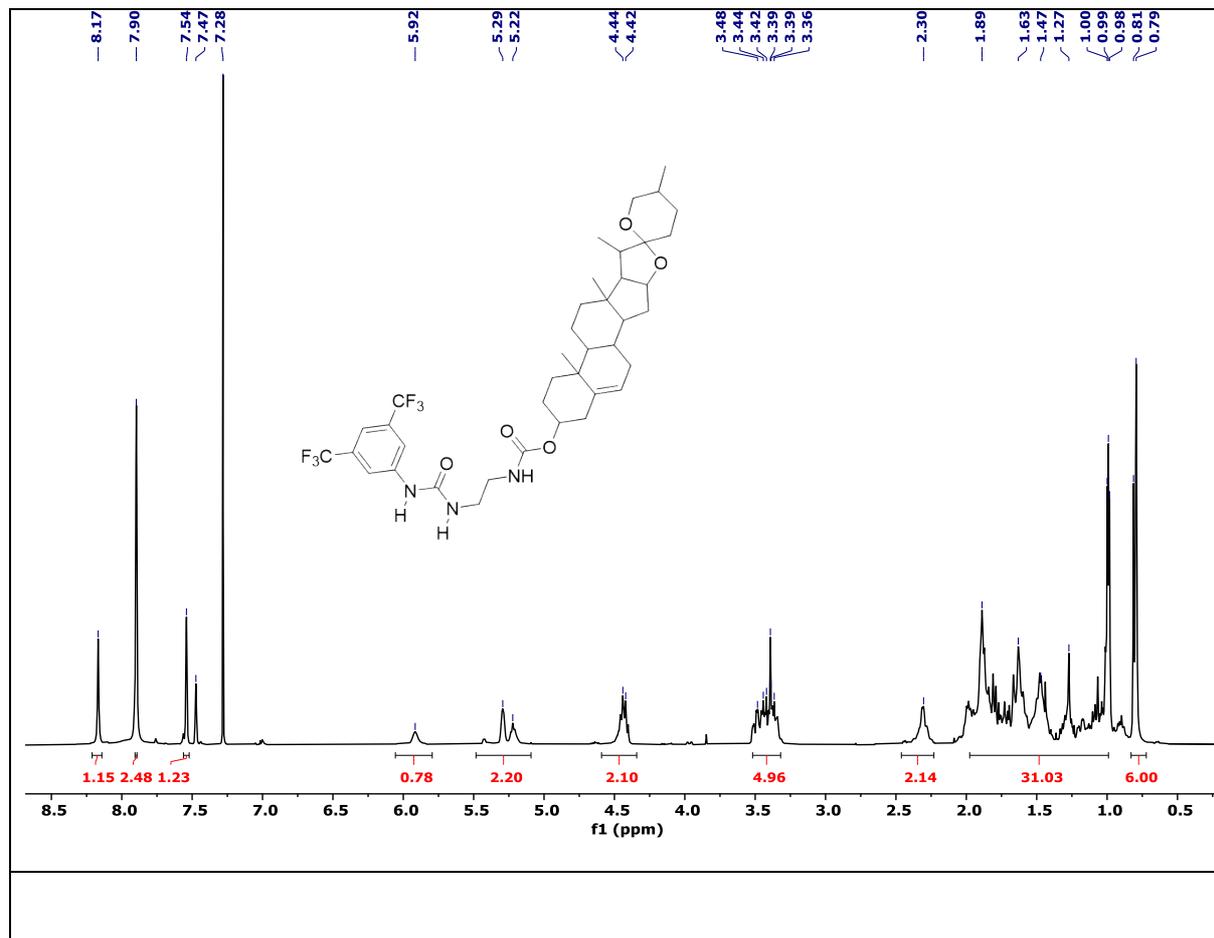
### $^{13}\text{C}$ NMR spectrum of compound 6



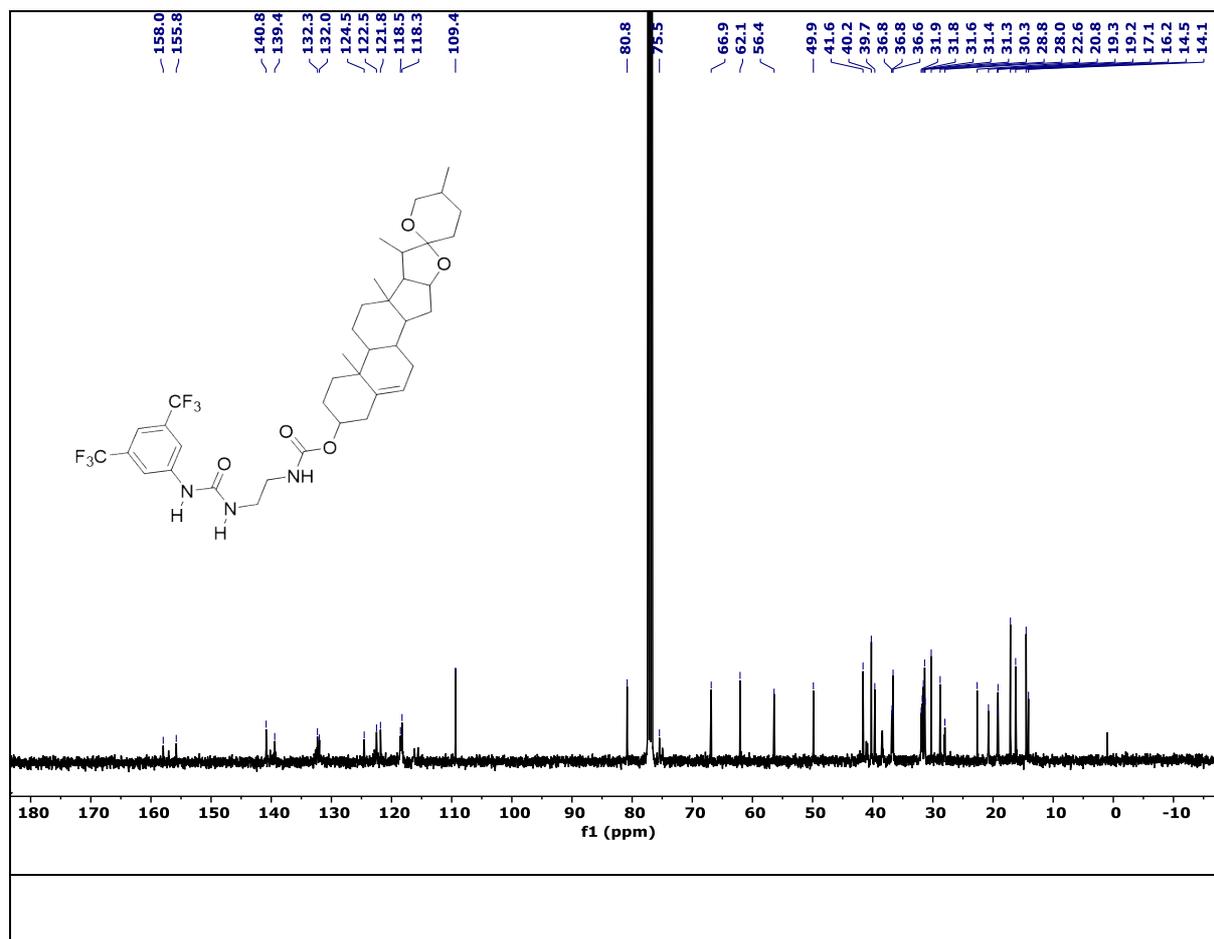
### High Resolution Mass Spectra (HRMS) of compound 6



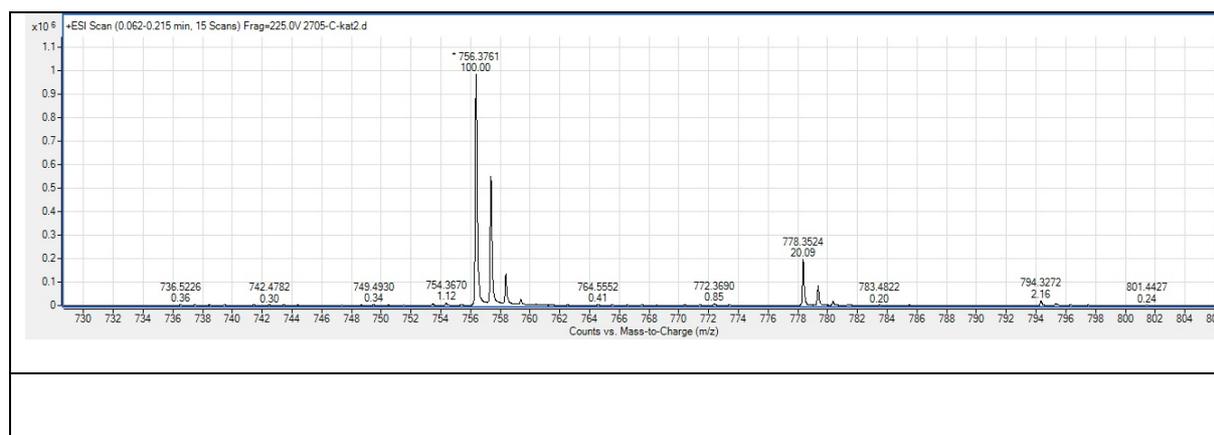
<sup>1</sup>H NMR spectrum of compound 7



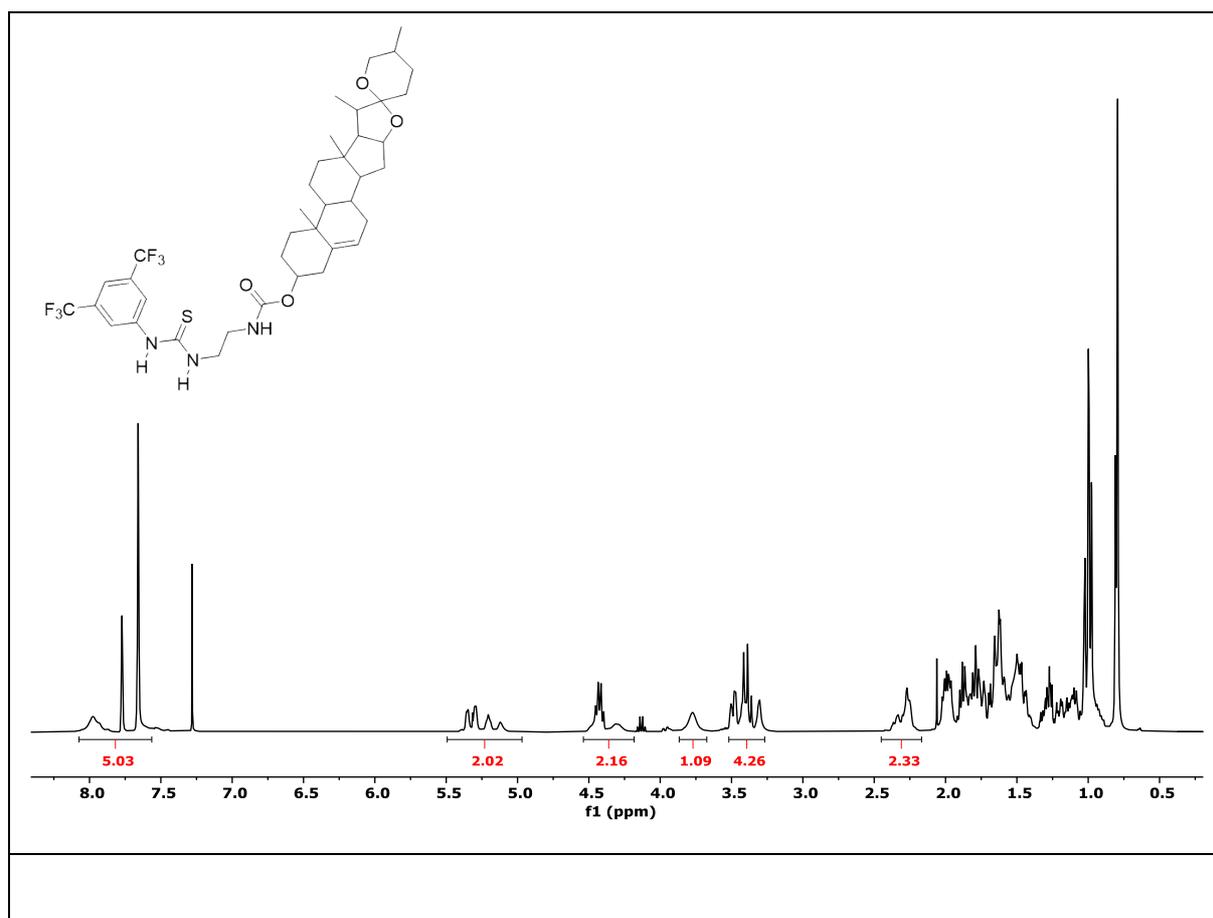
### <sup>13</sup>C NMR spectrum of compound 7



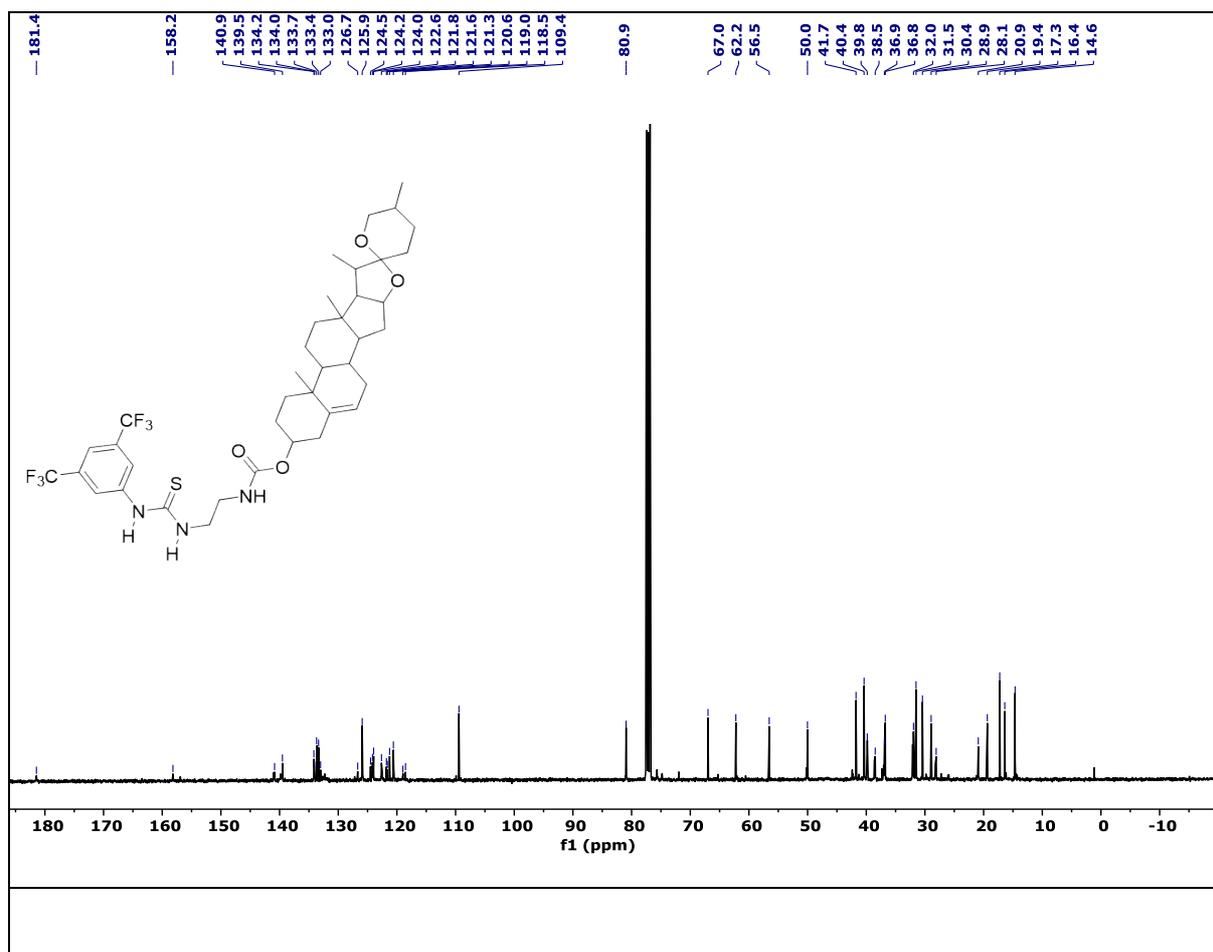
### High Resolution Mass Spectra (HRMS) of compound 7



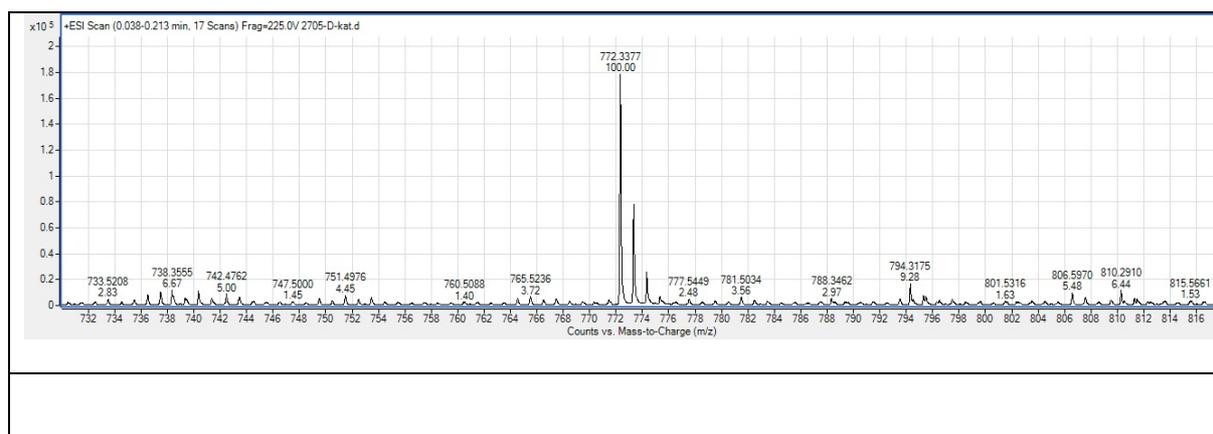
<sup>1</sup>H NMR spectrum of compound **8**



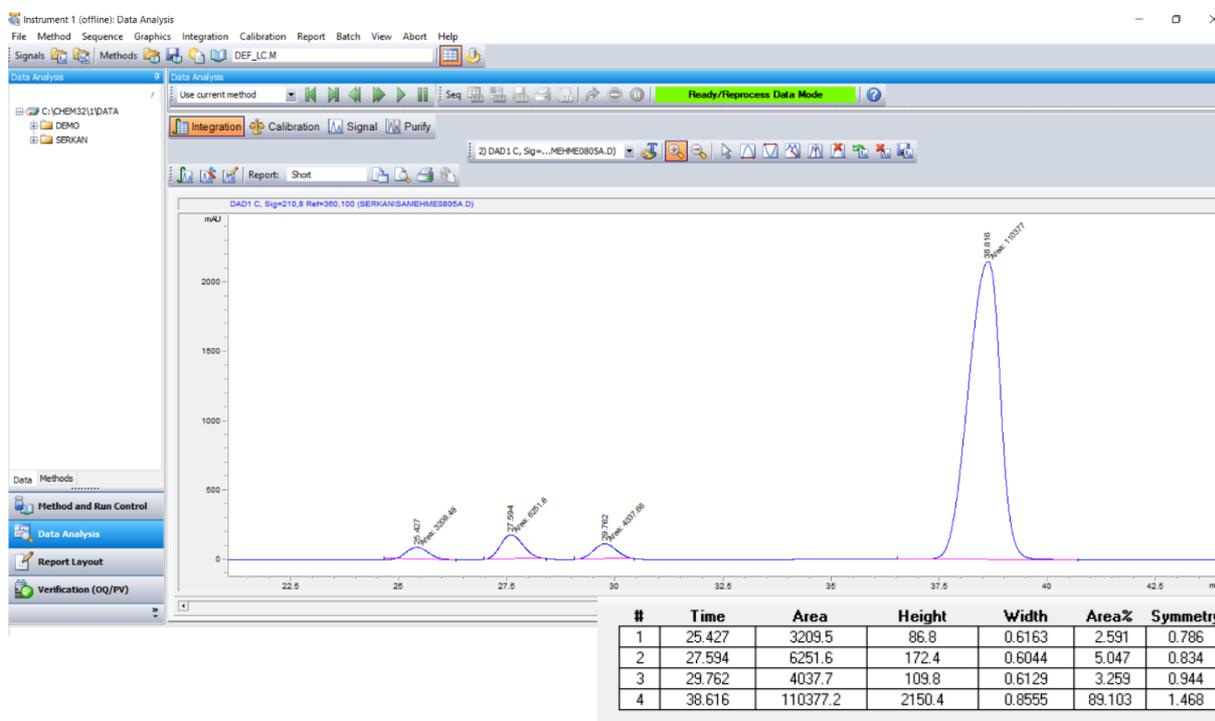
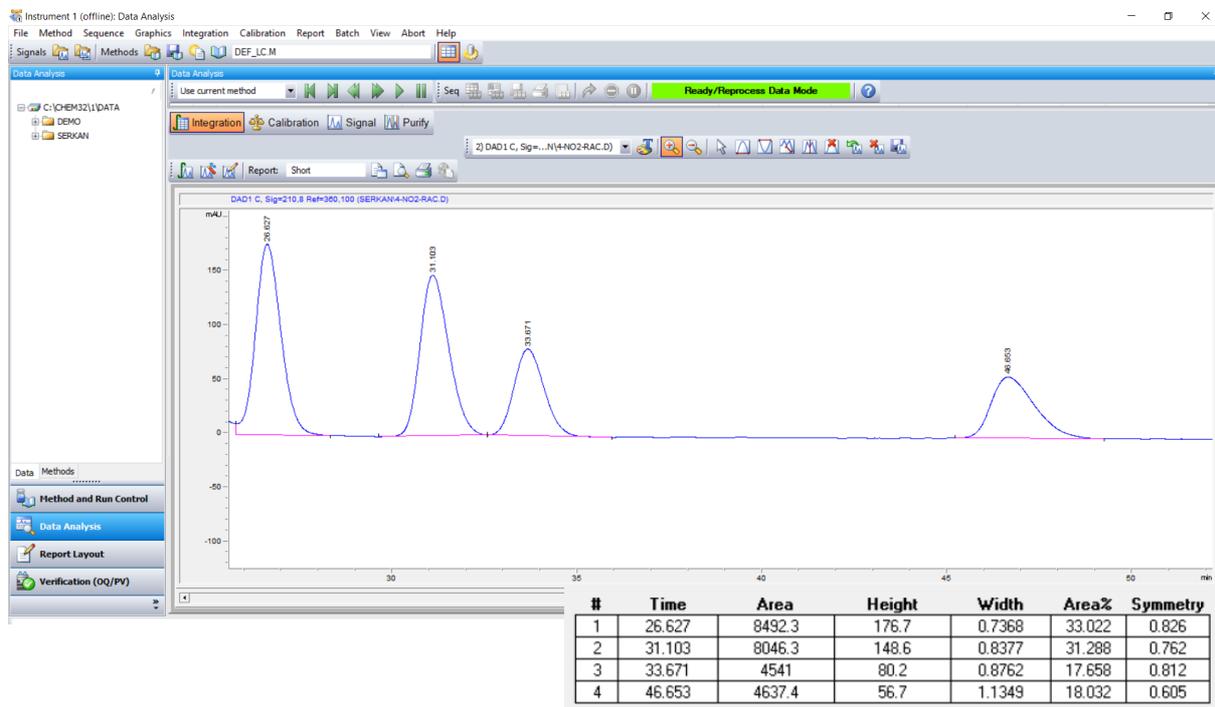
### $^{13}\text{C}$ NMR spectrum of compound **8**



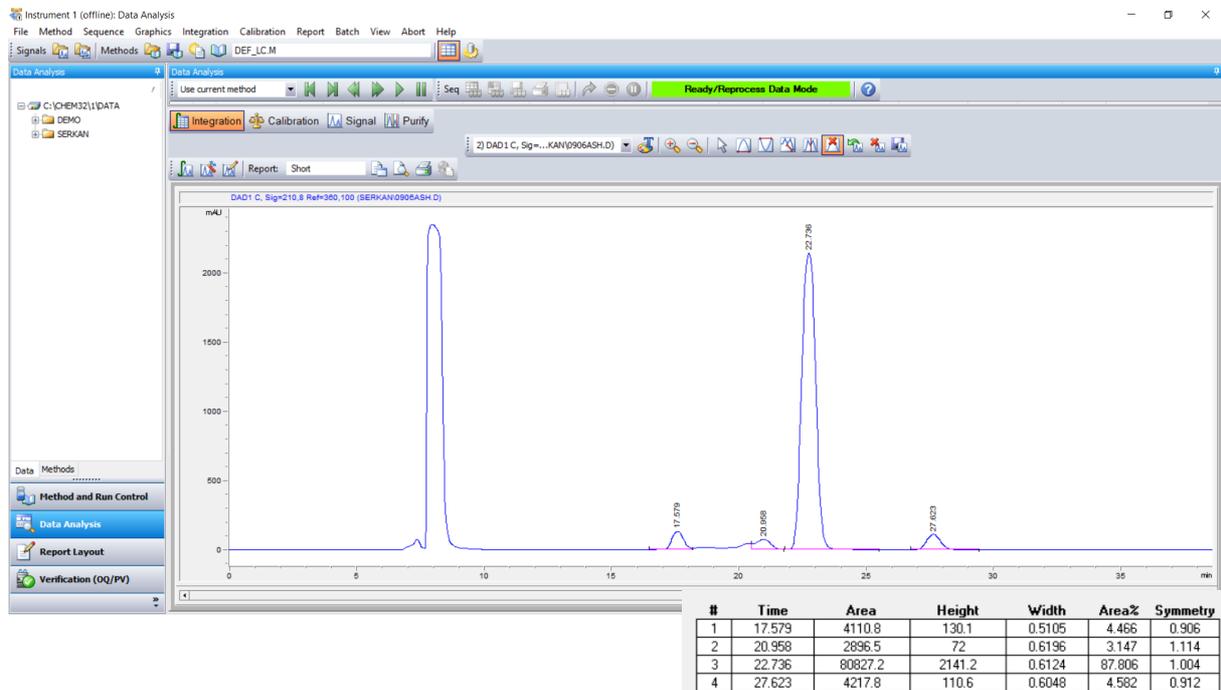
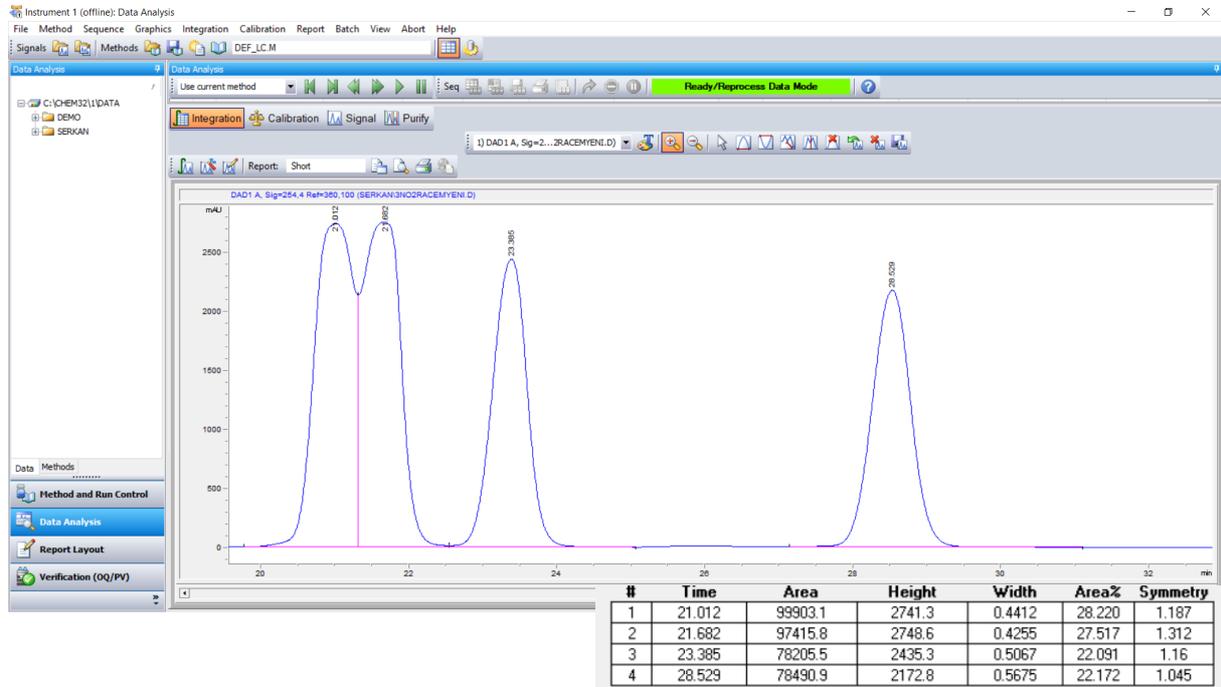
### High Resolution Mass Spectra (HRMS) of compound **8**



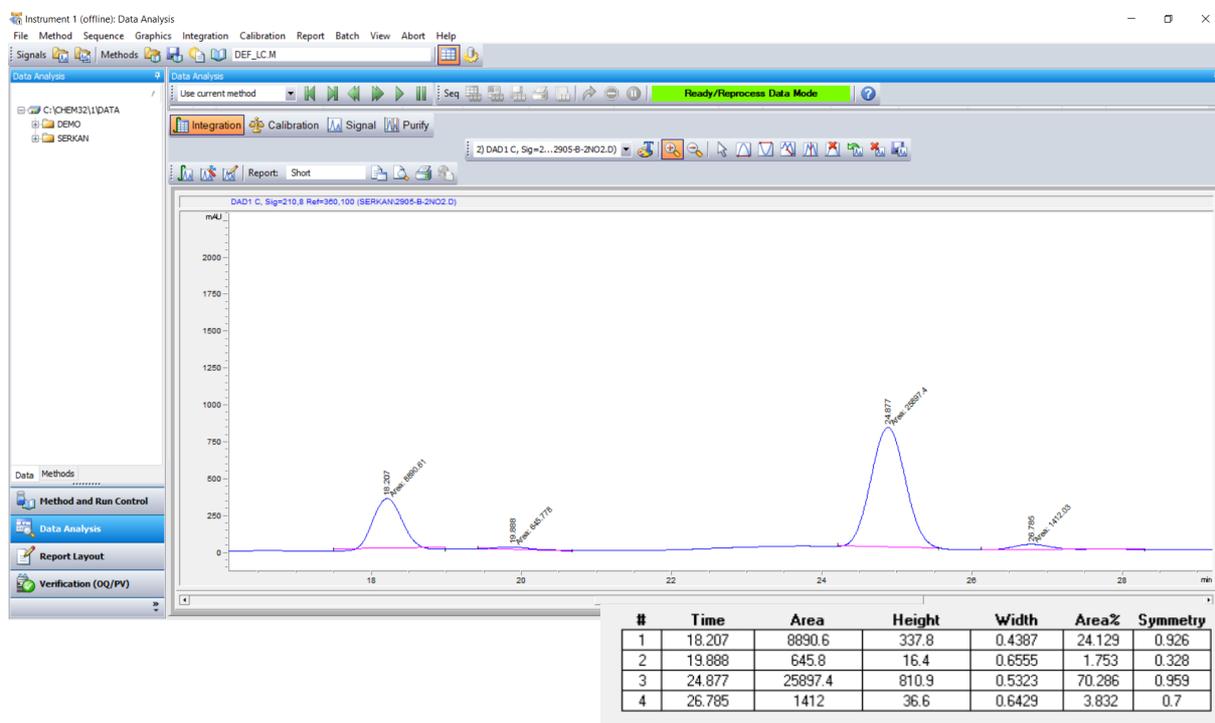
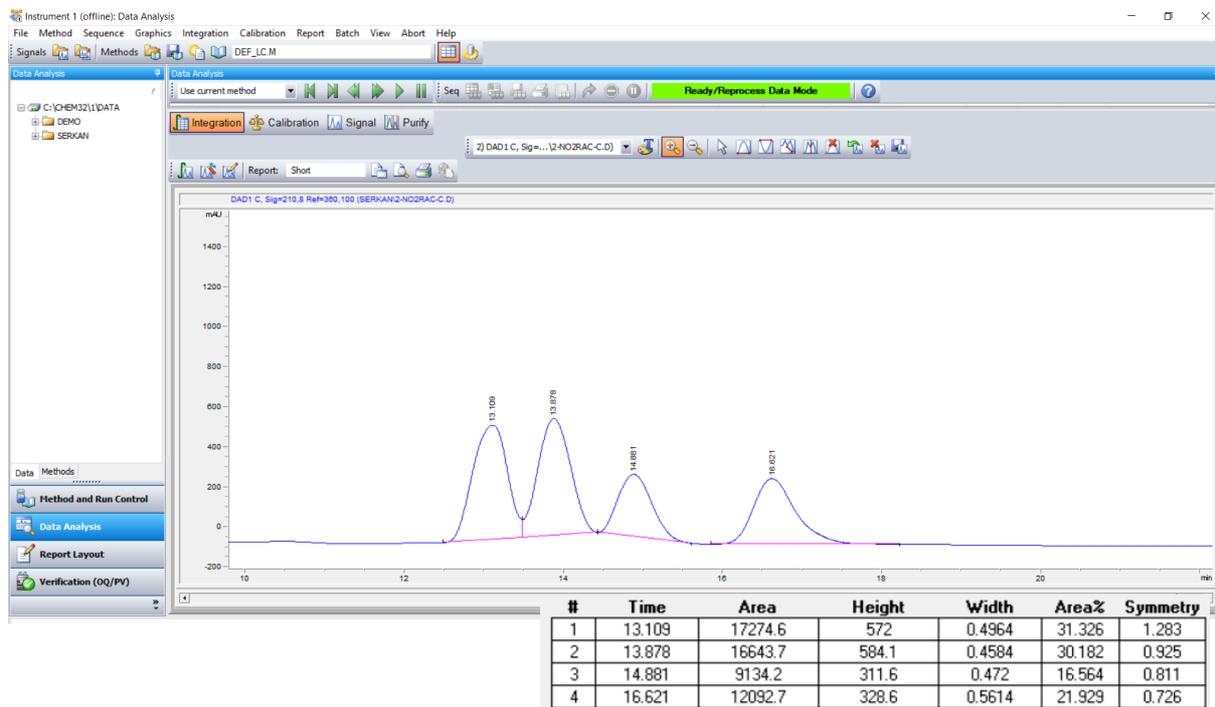
# HPLC chromatograms of compound 11a



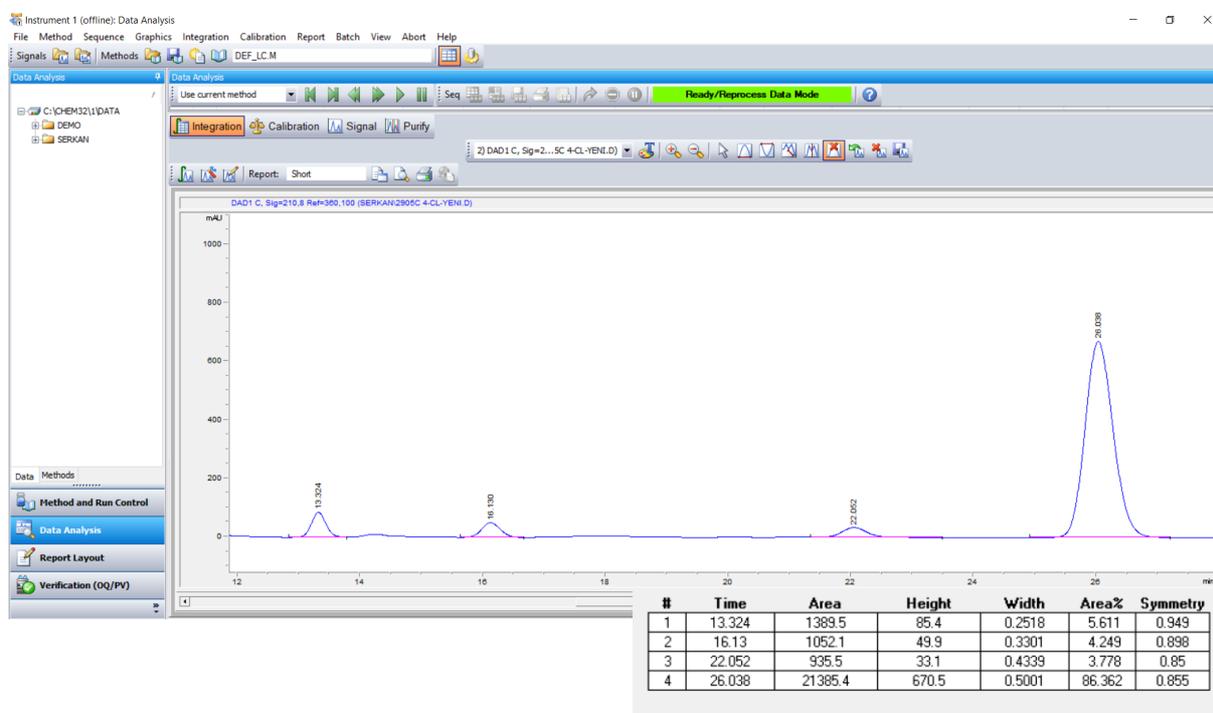
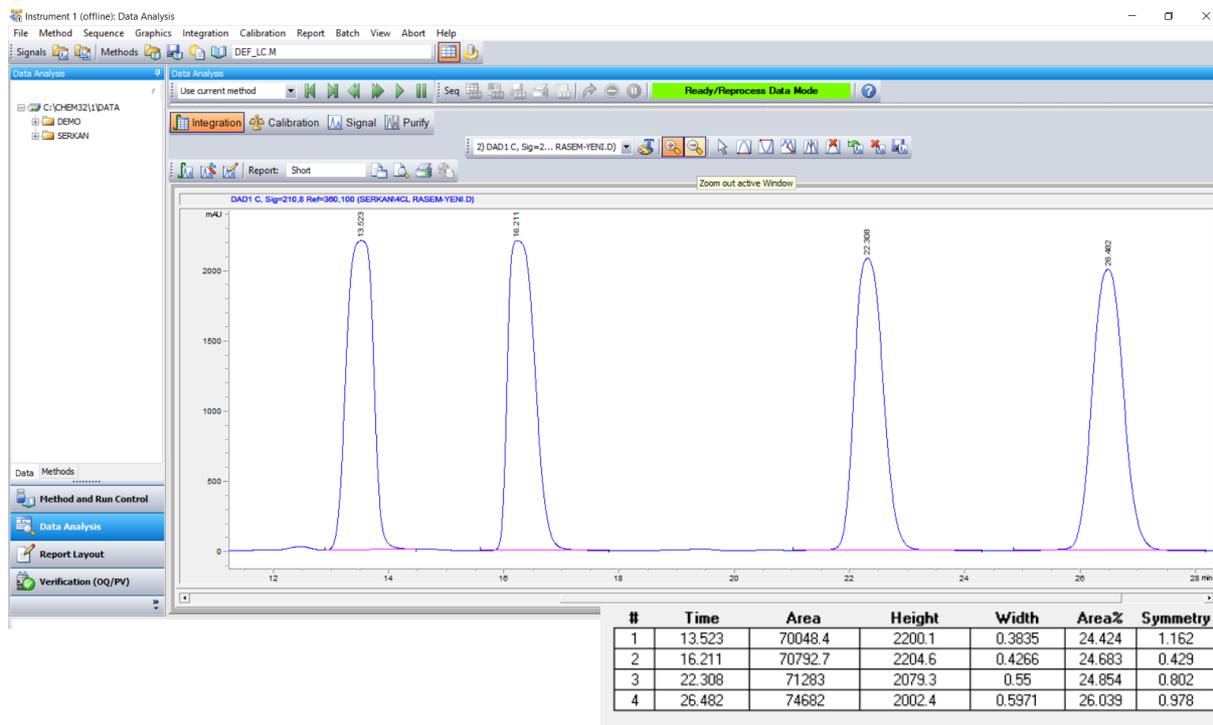
## HPLC chromatograms of compound 11b



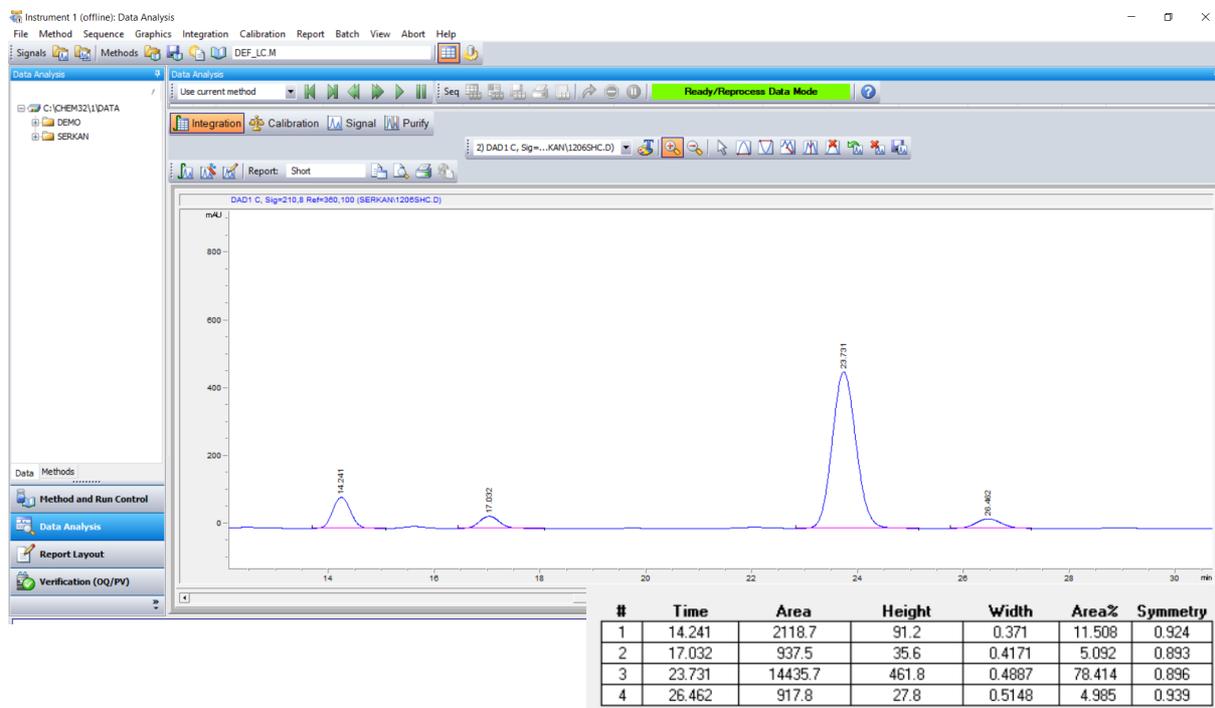
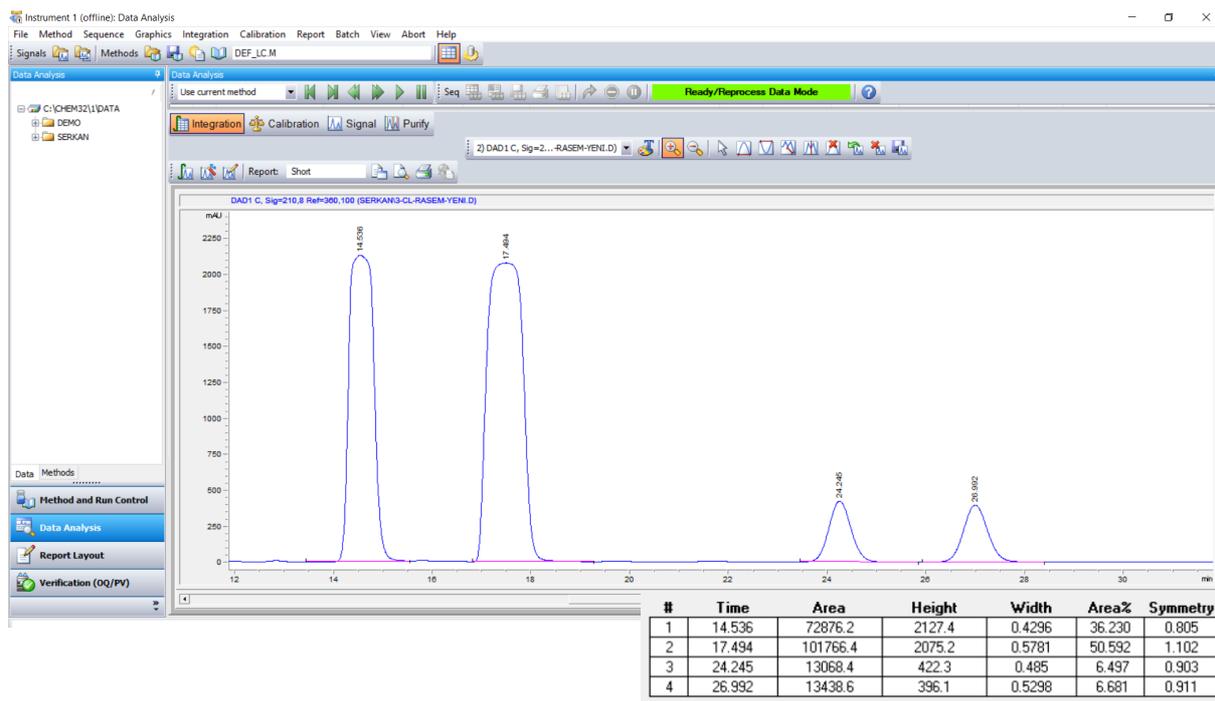
# HPLC chromatograms of compound 11c



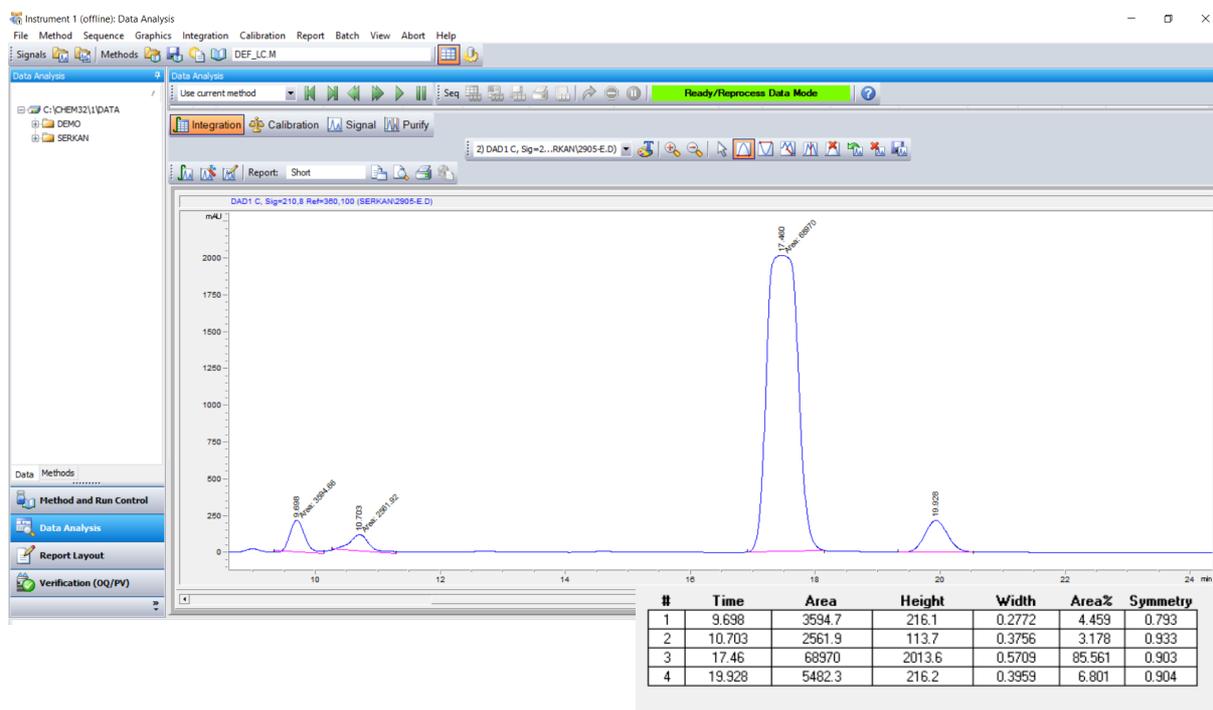
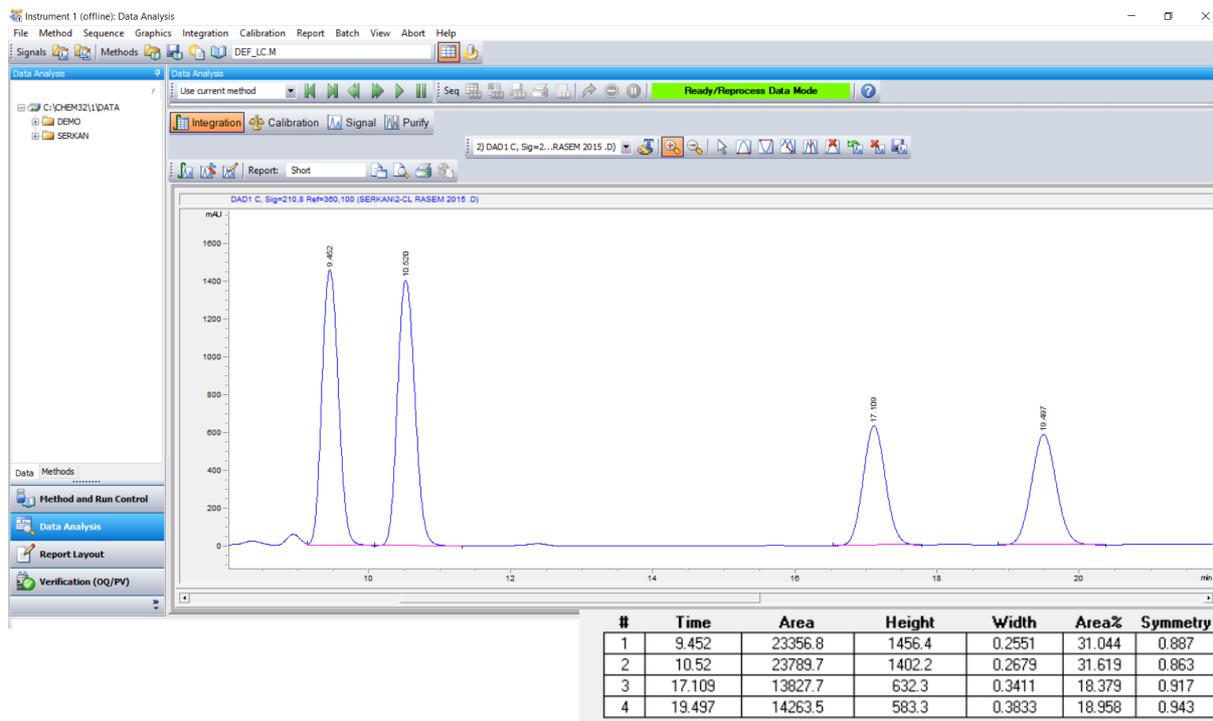
# HPLC chromatograms of compound 11d



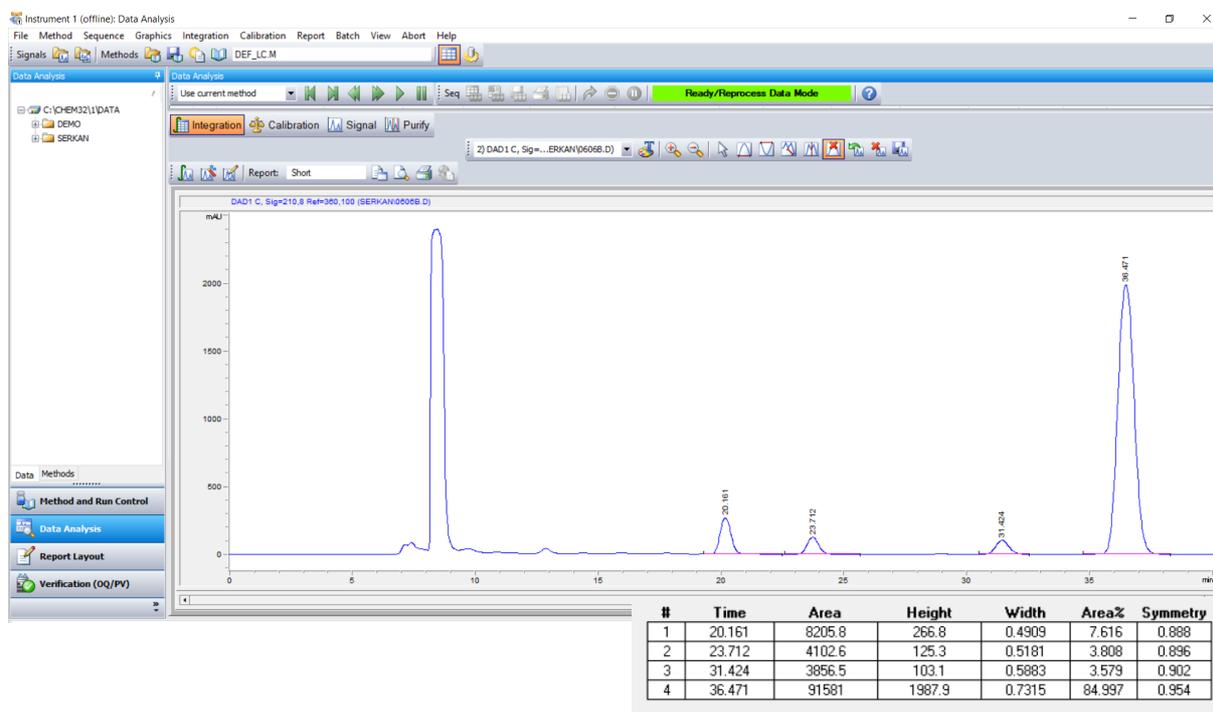
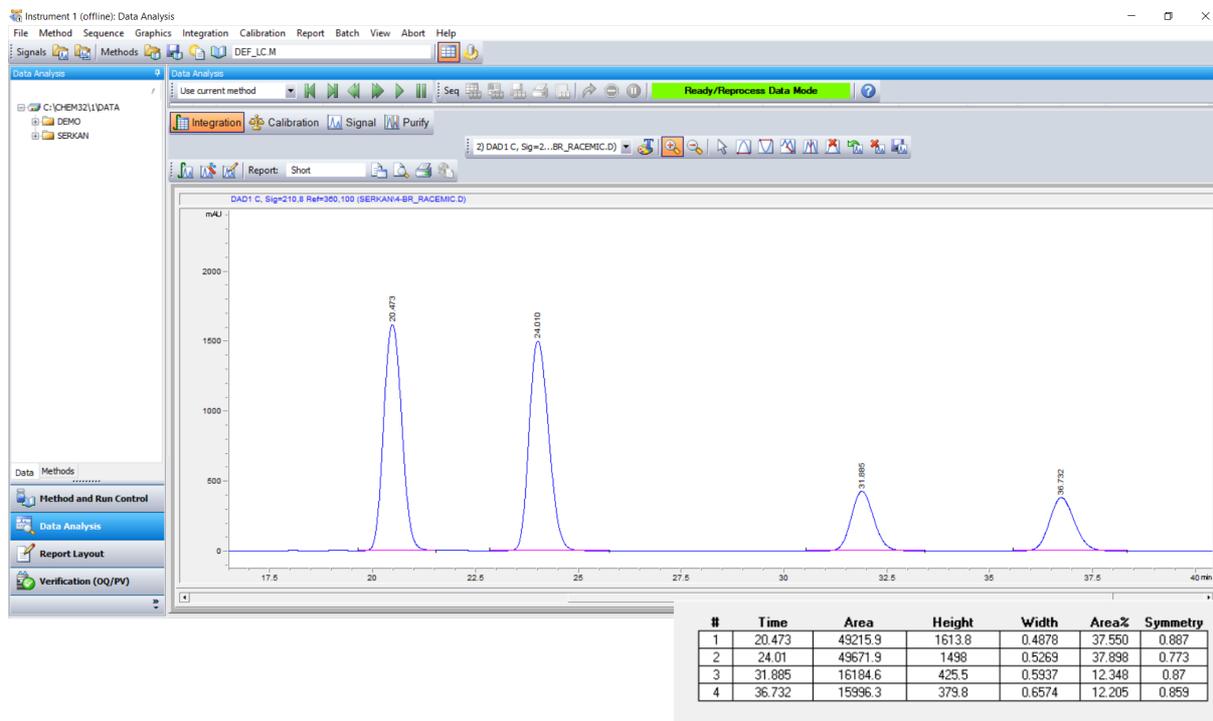
# HPLC chromatograms of compound 11e



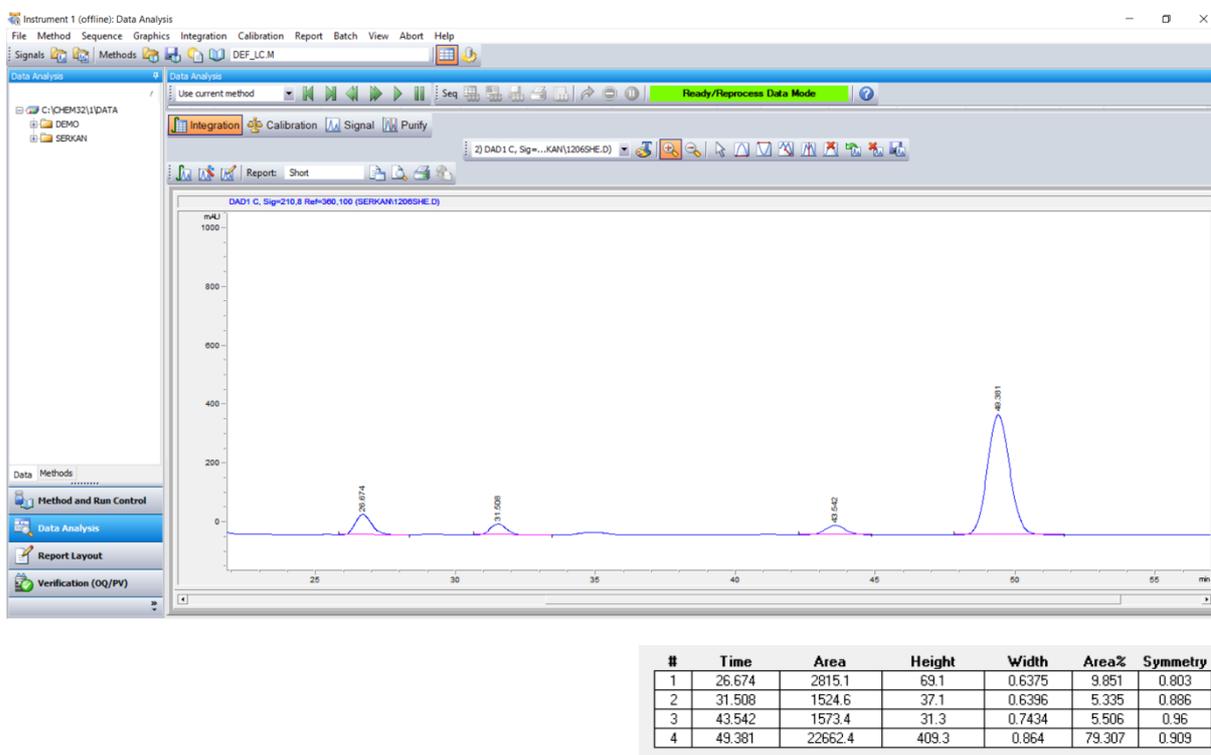
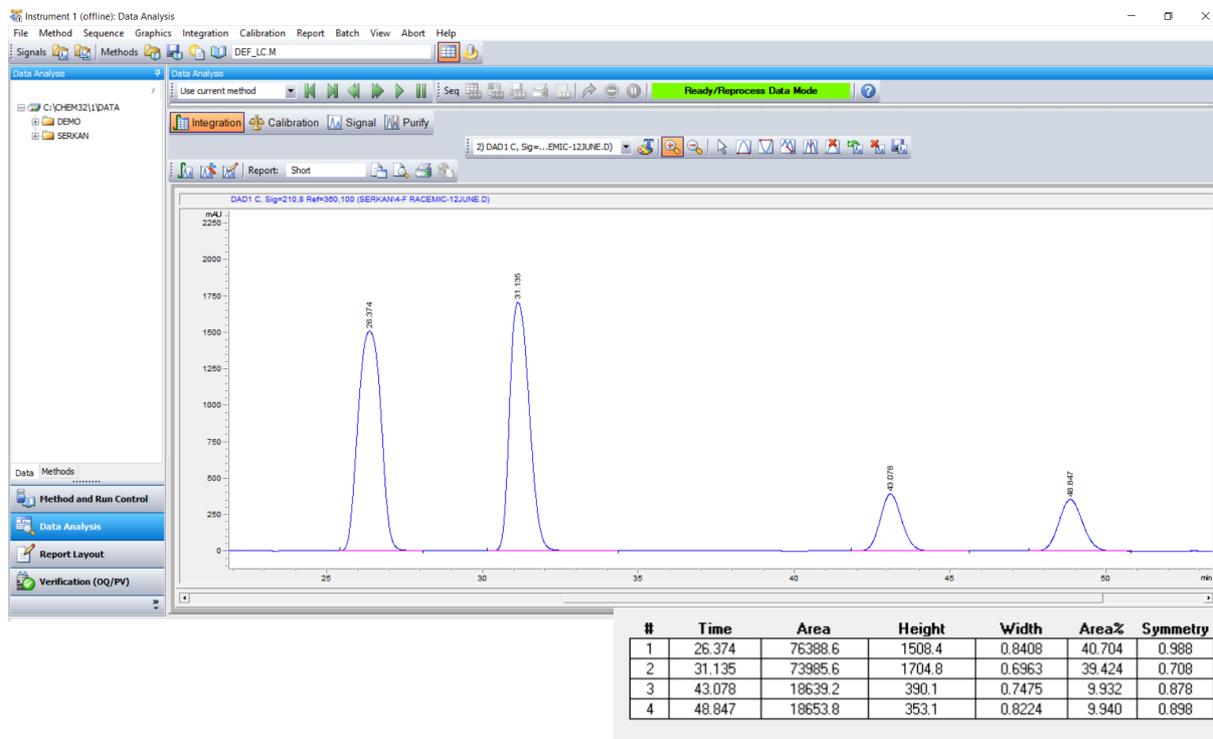
# HPLC chromatograms of compound 11f



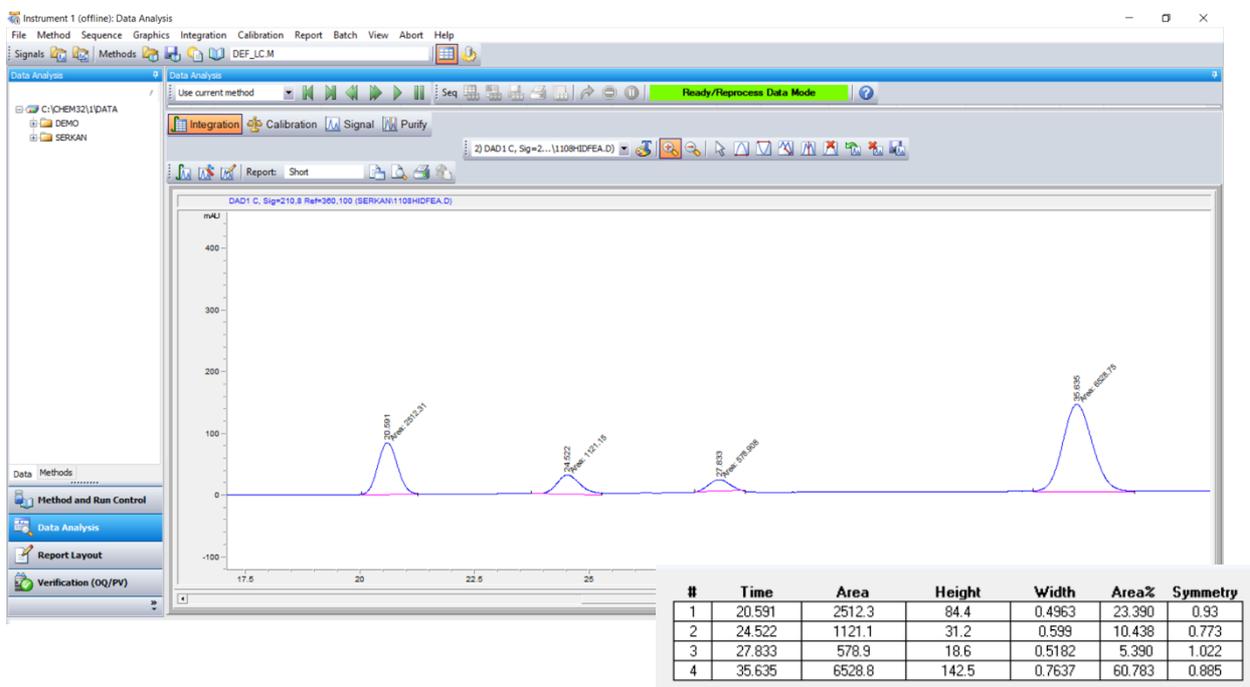
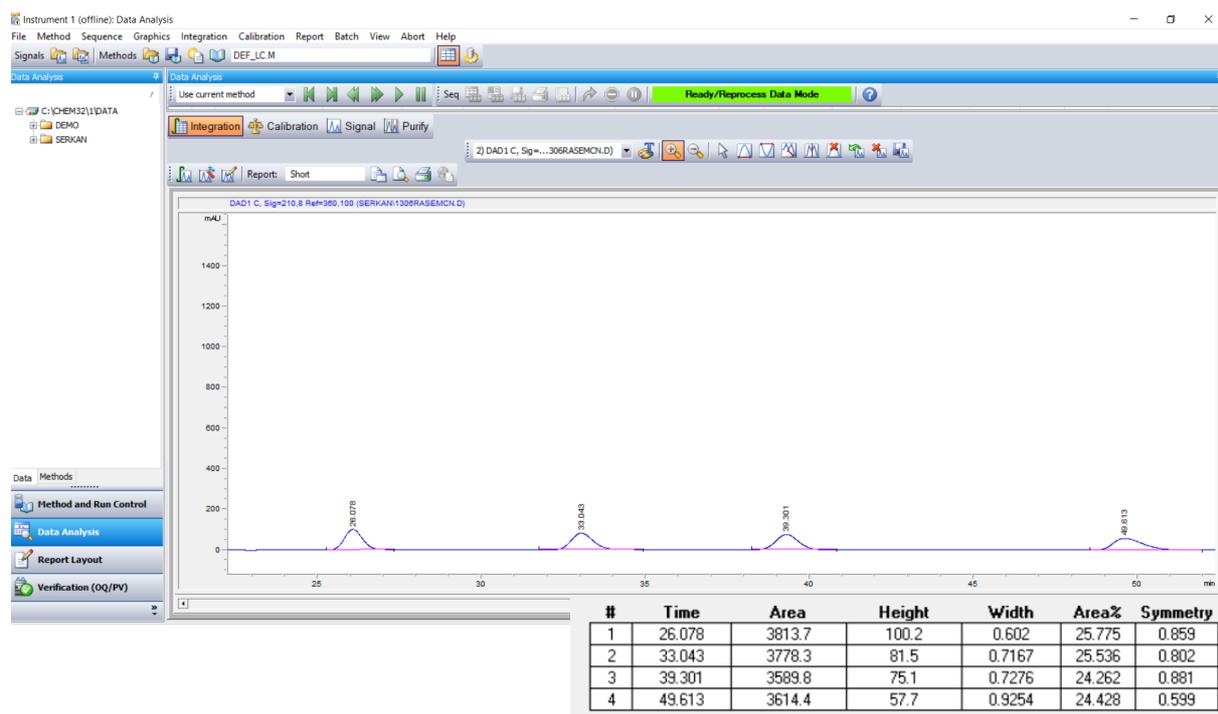
# HPLC chromatograms of compound 11g



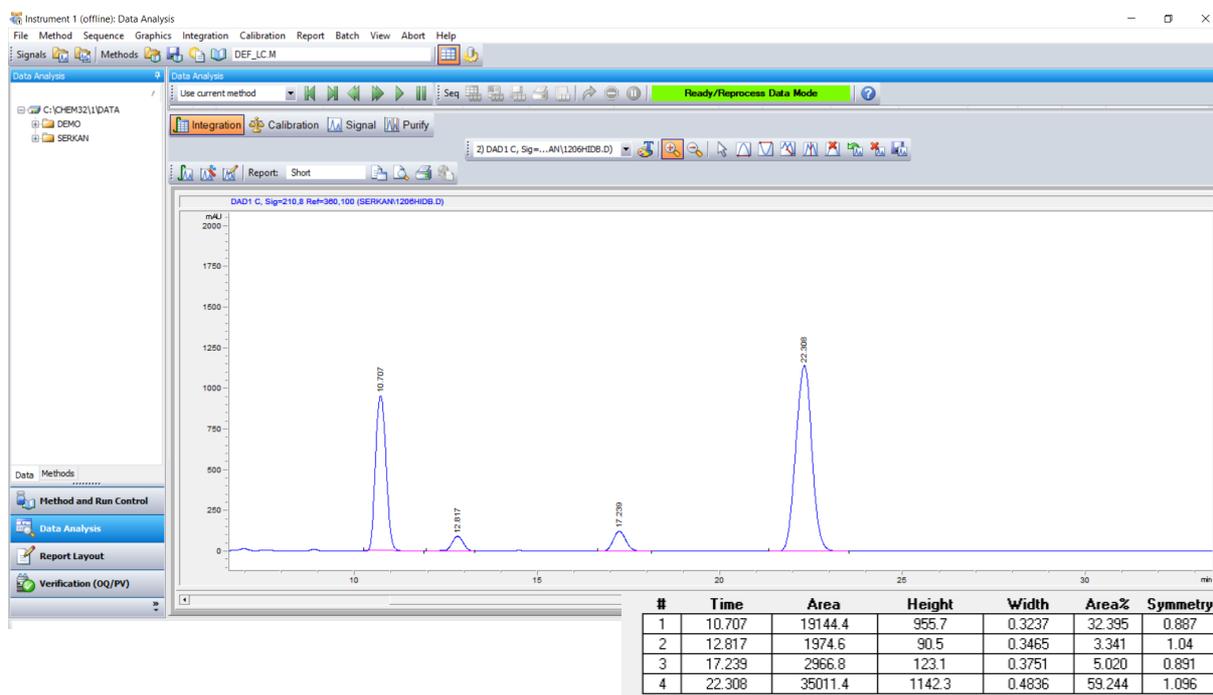
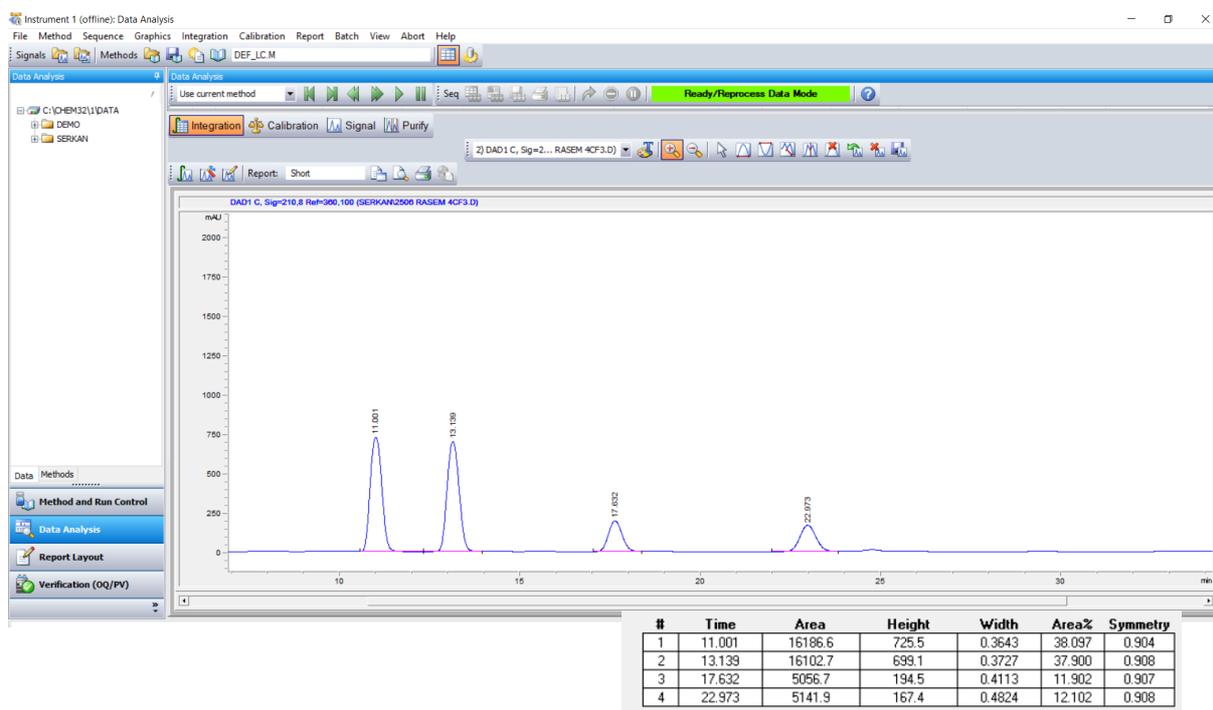
# HPLC chromatograms of compound 11h



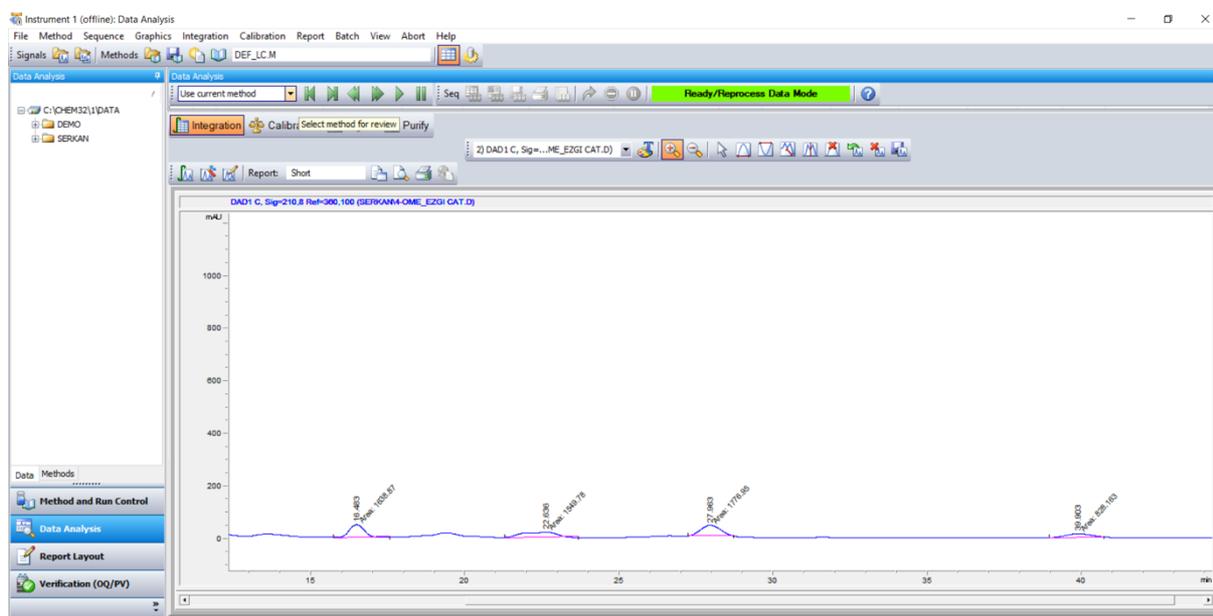
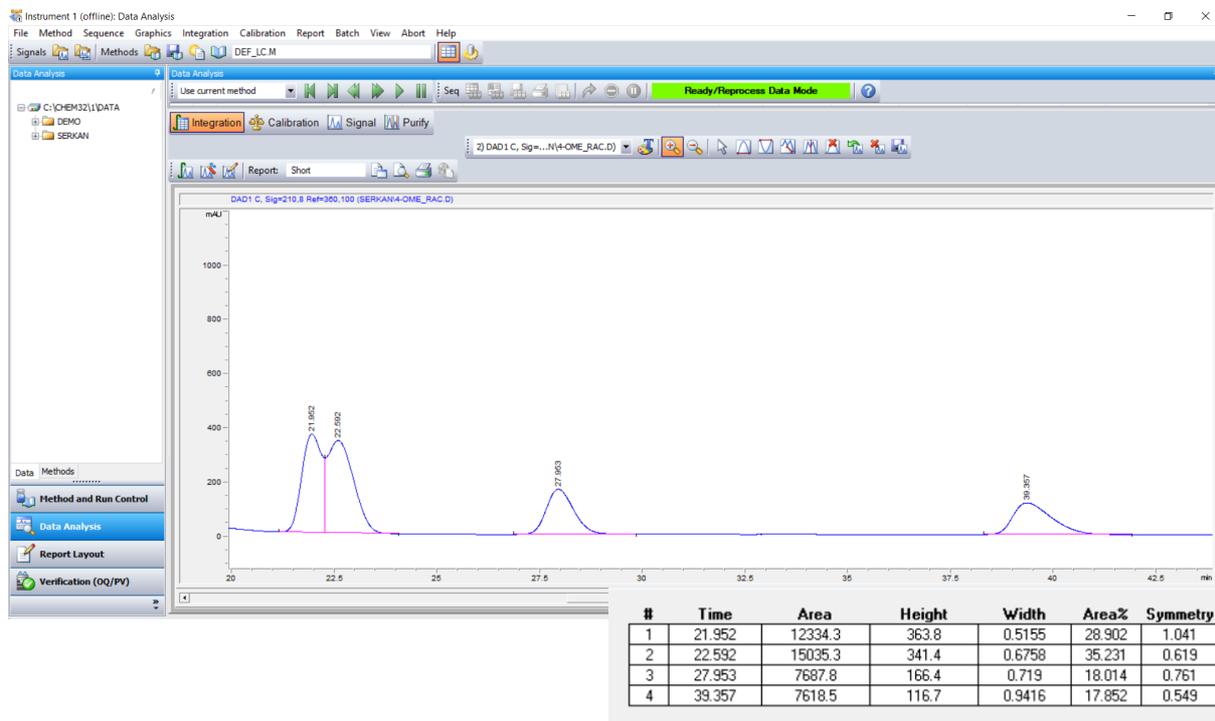
# HPLC chromatograms of compound 11i



# HPLC chromatograms of compound 11j



# HPLC chromatograms of compound 11k



#	Time	Area	Height	Width	Area%	Symmetry
1	16.483	1638.9	48.5	0.5637	28.287	1.072
2	22.636	1549.8	19.2	1.3433	26.749	2.72
3	27.963	1776.9	40.1	0.7383	30.670	0.878
4	39.903	828.2	14.1	0.9758	14.294	1.004

# HPLC chromatogram of compound 111

