Supporting Information

Facile and efficient N-arylation of amino acid esters with (-)-methyl-3-dehydroshikimiate(3-MDHS): a bio-based and metal-free strategy leading to N-aryl amino acid derivatives†

Yong Zou,*[a] Ensheng Zhang,[a,b] Tianlong Xu,[a,b] Wei Wu,[a,b] Yu Chen,[a] Mu Yuan,[c] Wen Wei[a] and Xuejing Zhang[d]

[a]*Guangzhou Institute of Chemistry, Chinese Academy of Sciences, Guangzhou 510650, P. R. of China. Fax: +86(20)85231119; Tel: +86(20)85231309; E-mail: zou_jinan@163.com;*
[b]*University of Chinese Academy of Sciences, Beijing, 100039, P. R. of China*
[c]*Guangzhou Medical University, Guangzhou, 510182, P. R. of China. E-mail: mryuanmu@yahoo.com.cn*
[d]*Sun Yat-sen University, Guangzhou, 510006, P. R. of China. E-mail: zhangxj33@mail.sysu.edu.cn*

Contents

I- Instrumentation and Chemicals

(-)-Shikimic acid was kindly provided by Guangxi WanShan Spice Co. Ltd. with chromatography grade as a natural product. Amino acid methyl ester hydrochloride was prepared according to the reference (Bioorganic & Medicinal Chemistry 18 (2010) 2165–2172). Other reagents and chromatography grade solvents were purchased from commercial sources and used after dehydrated (3Å molecule sieve). Petroleum ether (PE) used in the experiments refers to the boiling fraction 60-90°C. The purity determination of the products and reactions monitoring were accomplished by thin layer chromatography (TLC) on silica gel Polygram SILG/UV 254 plates.

(-)-Methyl-3-dehydroshikimate (3-MDHS) was readily prepared by using IBX as oxidant in THF, starting from the renewable and biomass-based compound (-)-shikimic acid through an elegant and high yielding strategy according to the effort of our laboratory.

Melting points of compounds were uncorrected and measured on Thiele apparatus. ^{1}H-NMR and ^{13}CNMR spectra were performed on Brucker DRX-400 spectrometer for DMSO-d_6 solution, and chemical shifts were reported as δ values using tetramethylsilane (TMS) as an internal standard. Mass spectrometry was measured on a Shimadzu GC-MSQP5050A and VG ZAB-HS mass spectrometer in

electron ionization mode. Specific rotation was measured on U.S. Rudolph's Autopol IV type polarimeter. IR spectra were recorded on a RFX-65A spectrometer.

II-1 Typical procedure for the preparation of (-)-methyl shikimate

A solution of (-)-shikimic acid (17.4 g, 0.10 mol) in MeOH (150 ml) was added $SOCl_2$ (15 ml, 0.20 mol) drop wise at 10-20°C over 1 h. The resulting mixture was heated to 40°C for 3h until completion of the reaction. The mixture was filtered and evaporated under reduced pressure to afford a pale yellow oil, which was purified by recrystallization from EtOAc to give compound (-)-methyl shikimate as white powder solid.

II-2 Typical procedure for the preparation of 3-MDHS

To a mixture of (-)-methyl shikimate (9.4g, 0.05mol) and IBX (16.8g, 0.06mol) was added THF (220 ml). The resulting mixture was stirred at 10-20°C for the completion of the reaction. The IBA byproduct was filtered off and the filtrate was concentrated under reduced pressure to afford crude 3-MDHS as white solid. The crude product was recrystallized from EtOAc to give chromatography grade 3-MDHS as white crystals.

II-3 General procedure for the preparation of compounds (table 2 entry 1-14, table 3 entry 1-4)

To a stirred solution of amino acid methyl ester hydrochloride (5.0mmol) in ethanol (20ml) was added CH_3ONa (0.27g, 5.0mmol), after stirring for 0.5 h, 3-MDHS (0.93g, 5.0mmol), *p*-toluenesulfonic acid (0.05g, 0.25mmol) and 3Å molecule sieves (10g) was added into the reaction mixture, then heated at 75°C for the indicated hours and monitored by TLC. Upon cooling, the mixture was filtered off and the resulting filtrate was evaporated under reduced pressure to provide the crude product which could further be purified by recrystallization or by column chromatography on silica gel (200-300) using EtOAc-PE system as eluent.

II-4 General procedure for the preparation of compounds (table 3 entry 5-6)

To a stirred solution of carbamate (5.0mmol) in ethanol (20ml) was added 3-MDHS (0.93g, 5.0mmol), *p*-toluenesulfonic acid (0.05g, 0.25mmol) and 3Å molecule sieves (10g). The mixture was heated at 75°C for the indicated hours and monitored by TLC. After completion of the reaction, the mixture was filtered and the resulting filtrate was evaporated under reduced pressure to provide the crude product, which was subsequently crystallized from EtOAc-PE to give the pure product.

II-5 Procedure for the preparation of compound 5f (table 3 entry 7)

To a solution of acetamide (0.29g, 5.0mmol) in ethanol (20ml) was added 3-MDHS (0.93g, 5.0mmol), *p*-toluenesulfonic acid (0.05g, 0.25mmol) and 3Å molecule sieve (10g). The reaction mixture was stirred at 75°C for 24 hours. Then the reaction mixture was washed with brine, extracted with ethyl acetate and dried over $MgSO_4$ filtered and concentrated under vacuum to furnish the crude product, which was subsequently crystallized from EtOAc-PE to give the pure product.

II-6 General procedure for the preparation of compounds (table 3 entry 8-10)

A mixture of the aromatic amino acid (5.0mmol), 3-MDHS (0.93g, 5.0mmol) and 3Å molecule sieve (10g) in ethanol (20ml) was heated at 75°C for the indicated time (monitored by TLC). After cooling to r.t., ethanol was removed under reduced pressure and the residue was purified by recrystallization to give the desired product.

II-7 Procedure of microwave assisted for the preparation of compound (3m)

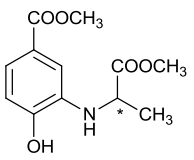
To a stirred solution of L-Serine methyl ester hydrochloride (0.78g, 5.0mmol) in methanol (20ml) was added CH_3ONa (0.27g, 5.0mmol) and stirring for 0.5 h, then filtered and the filtrate was evaporated under reduced pressure to afford a oily liquid. The oily liquid was dissolved in DMF (5ml), and 3-MDHS (0.93g, 5.0mmol), *p*-toluenesulfonic acid (0.05g, 0.25mmol) and 3Å molecule sieves (10g) was added into that mixture. The reaction mixture was heated at 130°C in microwave reactor for the indicated times and monitored by TLC. Upon cooling, the mixture was filtered and the resulting filtrate was washed with brine, extracted with ethyl acetate and dried over $MgSO_4$. Then filtered and concentrated under vacuum to furnish the crude product, which was subsequently purified by column chromatography on silica gel (200-300) using EtOAc-PE system as eluent.

II-8 General procedure for the preparation of compound (6)

To a stirred solution of 3-MDHS (0.93g, 5.0mmol) in THF (20 ml) was added 2-amino-4-chlorobenzoic acid (0.86g, 5.0mmol). The mixture was refluxed for the completion of the N-arylation reaction (monitored by TLC). Upon cooling, DCC (2.06g, 10mmol), DMAP (0.03g, 0.25mmol) was added into the mixture and stirred for 12h. The solid byproduct was filtered off and the filtrate was removed under reduced pressure. DCM (10ml) was added into the flask to dissolve the residue, and the resulting organic layer was sequentially washed with 1N HCl solution (3×10 ml), 10% aqueous $NaHCO_3$ (3×10 ml) and brine (3×10 ml), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was further crystallized from EtOAc-PE to give the pure product of 6.

III-Characterization Data for Products

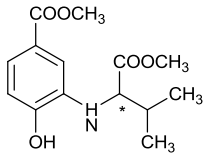
III-1 Characterization Data for Products Table 2 Entry 1-14



N-(2-hydroxy-5-methoxycarbonylphenyl)alanine methyl ester (**3a**):

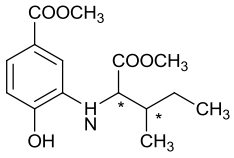
Pale yellow oil, $([\alpha]_D^{25}$ =-63.79, c=0.59 in ethanol), ^{1}HNMR (400 MHz, DMSO-d_6)

ppm: 10.40 (s, 1H), 7.19 (dd, J_1 = 8.15 Hz, J_2 = 1.74Hz, 1H), 6.95 (d, J = 1.74 Hz, 1H), 6.75 (d, J = 8.15 Hz, 1H), 4.99 (d, J = 0.94 Hz, 1H), 4.16 (q, J = 6.96 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 1.41 (d, J = 6.96 Hz, 3H); MS (EI): m/z=253$[M]^+$, 222$[M\text{-}OCH_3]^+$, 194$[M\text{-}COOCH_3]^+$, 194, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)valine methyl ester (**3b**):

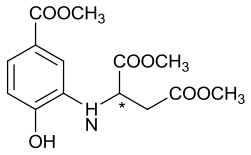
Yellow solid, m.p.79～81°C, ($[\alpha]^{25}_D$ =-116.19, c=0.20 in ethanol), ^{1}HNMR (400 MHz, DMSO-d_6) ppm: 10.47 (s, 1H), 7.19 (dd, J_1 = 8.17 Hz, J_2 = 1.91 Hz, 1H), 7.04 (d, J = 1.91 Hz, 1H), 6.76 (d, J = 8.16 Hz, 1H), 4.81 (d, J = 9.33 Hz, 1H), 3.89 (t, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 2.12 (m, 1H), 0.98 (d, J = 6.80 Hz, 3H), 0.93 (d, J = 6.80 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.5(C=O), 166.5(C=O), 149.1, 136.0, 120.8, 119.8, 113.2, 110.5, 61.4, 51.6, 51.5, 30.7, 18.7, 18.8; MS (EI): m/z=281$[M]^+$, 250$[M\text{-}OCH_3]^+$, 222$[M\text{-}COOCH_3]^+$, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)isoleucine methyl ester (**3c**):

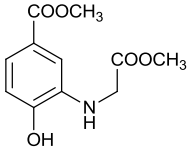
Yellow solid, m.p.109～111°C, ($[\alpha]^{25}_D$ =-83.80, c=0.28 in ethanol), ^{1}HNMR (400 MHz, DMSO-d_6) ppm: 10.47 (s, 1H), 7.19 (dd, J_1 = 8.18 Hz, J_2 = 1.86 Hz, 1H), 7.03 (d, J = 1.86 Hz, 1H), 6.76 (d, J = 8.18 Hz, 1H), 4.83 (d, J = 8.00 Hz, 1H), 3.95 (m, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 1.89 (m, 1H), 1.57 (m, 1H), 1.24 (m, 1H), 0.90 (m, 6H). ^{1}HNMR (400 MHz, DMSO-d_6 and D_2O) ppm: 7.18 (dd, J_1 = 8.40 Hz, J_2 = 1.60 Hz, 1H), 6.97 (d, J = 1.60 Hz, 1H), 6.73 (d, J = 8.40 Hz, 1H), 3.85 (d, J = 6.4 Hz, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 1.81 (m, 1H), 1.46 (m, 1H), 1.18 (m, 1H), 0.82 (m, 6H); ^{13}C NMR (100 MHz,DMSO-d_6) ppm: 173.4 (C=O), 166.4 (C=O), 149.0, 135.8, 120.8, 119.7, 113.1, 110.4, 60.0, 51.6, 51.5, 36.9, 25.1, 15.3, 11.1; MS (EI):

m/z=295[M]$^+$, 264[M-OCH_3]$^+$, 236[M-$COOCH_3$]$^+$, 178, 77[C_6H_5]$^+$.



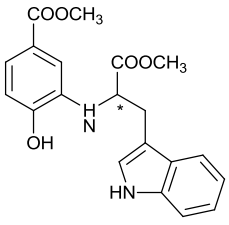
N-(2-hydroxy-5-methoxycarbonylphenyl)aspartate dimethyl ester (**3d**):

Yellow oil, ([α]$_D^{25}$ =-8.35, c=0.27 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.43 (s, 1H), 7.20 (dd, J_1 = 8.15 Hz, J_2 =1.79 Hz, 1H), 7.10 (s, 1H), 6.76 (d, J = 8.15 Hz, 1H), 5.29 (d, J = 8.00 Hz,1H), 4.51 (d, J = 7.99 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.60 (s, 3H), 2.91 (d, J_1 = 6.40 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 172.3 (C=O), 170.9 (C=O), 166.5(C=O), 149.3, 135.2, 120.6, 120.1, 113.4, 110.9, 52.2, 51.7, 51.6, 51.6, 36.4; MS (EI): m/z=311[M]$^+$, 280[M-OCH3]$^+$, 252[M-$COOCH_3$]$^+$, 178, 77[C_6H_5]$^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)glycine methyl ester (**3e**):

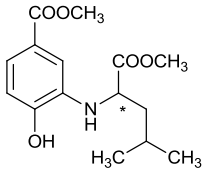
Yellow solid, m.p.110～112°C, ^{1}HNMR (400 MHz, DMSO-d_6) ppm:10.36 (s, 1H), 7.18 (dd, J_1 = 8.00, J_2 =1.74 Hz, 1H), 6.89 (d, J = 1.74 Hz, 1H), 6.75 (d, J = 8.00Hz, 1H), 5.30 (s, 1H), 3.96 (s, 2H), 3.74 (s, 3H), 3.65 (s, 3H); MS (EI): m/z=239[M]$^+$, 208[M-OCH_3]$^+$, 180[M-$COOCH_3$]$^+$, 77[C_6H_5]$^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)tryptophan methyl ester (**3f**):

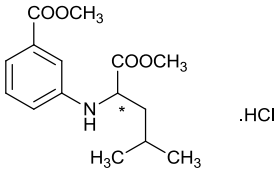
Brown solid, m.p. 159～161°C, ([α]$_D^{25}$ =-21.67, c=0.10 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.93 (s, 1H), 10.39 (s, 1H), 7.47 (d, J = 7.60 Hz, 1H), 7.33 (d,

J = 8.00 Hz, 1H), 7.14-7.20 (m, 2H), 7.06 (t, *J* = 7.51 Hz, 1H), 6.94-7.00 (m, 2H), 6.73 (d, *J* = 8.00 Hz, 1H), 4.95 (d, *J* = 8.40 Hz, 1H), 4.38 (d, *J* = 6.80 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 3.26 (d, *J* = 6.00 Hz, 2H); ^{13}C NMR (100 MHz,DMSO-d_6) ppm: 173.5 (C=O), 166.5 (C=O), 148.9, 136.1, 135.6, 127.2, 123.9, 121.0, 120.8, 119.6, 118.5, 118.0, 113.0, 111.5, 110.2, 108.9, 56.2, 51.8, 51.5, 27.8; MS (EI): m/z=368$[M]^+$, 337$[M\text{-}OCH_3]^+$, 309$[M\text{-}COOCH_3]^+$, 178, 130, 77$[C_6H_5]^+$.



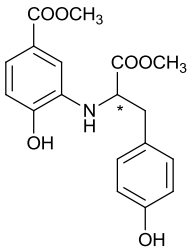
N-(2-hydroxy-5-methoxycarbonylphenyl)leucine methyl ester (**3g**):

Brown oil, ($[\alpha]_D^{25}$ =-47.84, c=0.38 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.41 (s, 1H), 7.20 (dd, J_1 = 8.00 Hz, J_2 = 1.60 Hz, 1H), 6.99 (d, *J* = 1.60 Hz, 1H), 6.76 (d, *J* = 8.00 Hz, 1H), 4.92 (d, *J* = 9.11 Hz, 1H), 4.06 (m, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 1.74 (m, 2H), 1.60 (m, 1H), 0.92 (d, *J* = 6.00 Hz, 3H), 0.87 (d, *J*=6.00 Hz, 3H); MS (EI): m/z=295$[M]^+$, 264$[M\text{-}OCH_3]^+$, 236$[M\text{-}COOCH_3]^+$, 178, 77$[C_6H_5]^+$.



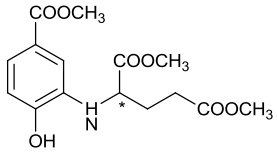
N-(3-methoxycarbonylphenyl)leucine methyl ester (**3g´**):

White solid, m.p. 147～149°C ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 7.13-7.19 (m, 3H), 6.79 (m, 1H), 5.96 (disproportion), 3.99 (m, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 1.55-1.74 (m, 3H), 0.92 (d, *J* = 6.80Hz, 3H), 0.85 (d, *J* = 6.80Hz, 3H); MS (EI): m/z=279$[M]^+$, 248$[M\text{-}OCH_3]^+$, 220$[M\text{-}COOCH_3]^+$, 178, 164, 77$[C_6H_5]^+$, 36.



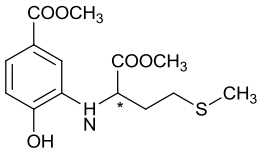
N-(2-hydroxy-5-methoxycarbonylphenyl)tyrosine methyl ester (**3h**):

Pale yellow oil, ($[\alpha]_D^{25}$ =+7.49, c =0.67 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.40 (s, 1H), 9.26 (s, 1H), 7.19 (m, 1H), 6.99 (m, 3H), 6.74 (d, J_1 = 33.96 Hz, J_2 = 8.30 Hz, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 4.90 (s, 1H), 4.29 (d, J = 4.00 Hz, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 2.99 (d, J = 6.4 Hz, 2H); MS (EI): m/z=345$[M]^+$, 313$[M\text{-}HOCH_3]^+$, 286$[M\text{-}COOCH_3]^+$, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)glutamic dimethyl ester (**3i**):

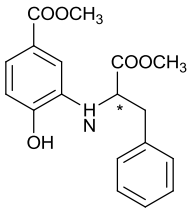
Pale yellow oil, ($[\alpha]_D^{25}$ =+7.49, c=0.67 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.43 (s, 1H), 7.21 (dd, J_1 = 8.15 Hz, J_2 = 1.79 Hz, 1H), 7.00 (s, 1H), 6.77 (d, J = 8.15 Hz, 1H), 5.06 (d, J = 8.00 Hz, 1H), 4.18 (dd, J_1 = 14.32 Hz, J_2 = 8.25 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H), 2.47 (t, 2H), 2.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.4 (C=O), 172.8 (C=O), 166.5 (C=O), 149.6, 135.2, 120.7, 120.3, 113.4, 111.1, 55.0, 52.0, 51.6, 51.4, 29.8, 26.9; MS (EI): m/z=325$[M]^+$, 294$[M\text{-}OCH_3]^+$, 266$[M\text{-}COOCH_3]^+$, 234, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)methionine methyl ester (**3j**):

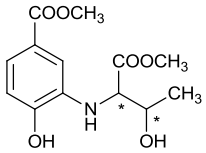
Brown oil, ($[\alpha]_D^{25}$ =-23.26, c=0.38 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.43 (s, 1H), 7.21 (dd, J_1 = 8.00 Hz, J_2 = 1.60Hz, 1H), 7.02 (d, J = 1.60 Hz, 1H), 6.77 (d, J = 8.00 Hz, 1H), 5.13 (d, J = 8.00 Hz, 1H), 4.27 (m, 1H), 3.76 (s, 3H), 3.65

(s, 3H), 2.58 (m, 2H), 2.05-2.10 (m, 5H); MS (EI):m/z=315$[M+2]^+$, 313$[M]^+$, 282$[M\text{-}OCH_3]^+$, 254$[M\text{-}COOCH_3]^+$, 206, 178, 77$[C_6H_5]^+$.



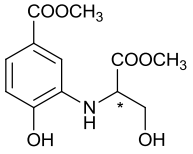
N-(2-hydroxy-5-methoxycarbonylphenyl)phenylalanine methyl ester (**3k**):

Orange-yellow oil, $([\alpha]_D^{25}$ =-17.00, c=0.46 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.39 (s, 1H), 7.25 (m, 5H), 7.18 (dd, J_1 = 8.00 Hz, J_2 = 1.60 Hz, 1H), 7.00 (d, J = 1.60 Hz, 1H), 6.73 (d, J = 8.00 Hz, 1H), 4.98 (d, J = 8.35 Hz, 1H), 4.38 (d, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 3.11 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.06 (C=O), 166.50 (C=O), 149.5, 149.4, 136.9, 135.0, 129.2, 129.2, 128.3, 126.7, 120.7, 120.2, 113.3, 111.0, 57.1, 51.8, 51.6, 37.5; MS (EI): m/z=329$[M]^+$, 298$[M\text{-}OCH_3]^+$, 270$[M\text{-}COOCH_3]^+$, 238, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)threonine methyl ester (**3l**):

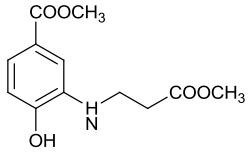
White solid, m.p.150～152°C, $([\alpha]_D^{25}$ =-65.30, c =0.25 in ethanol) , ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.46 (s, 1H), 7.18 (dd, J_1 = 8.40, J_2 = 1.60Hz, 1H), 6.93 (d, J = 1.60 Hz, 1H), 6.76 (d, J = 8.40 Hz, 1H), 5.21 (d, J = 5.20 Hz, 1H), 5.00 (d, J = 9.60 Hz, 1H), 4.17 (d, J = 2.40 Hz, 1H), 4.03 (m, 1H), 3.73 (s, 3H), 3.61 (s, 3H), 1.18 (m, 3H); MS (EI):m/z=283$[M]^+$, 252$[M\text{-}OCH_3]^+$, 224$[M\text{-}COOCH_3]^+$, 178, 77$[C_6H_5]^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)serine methyl ester (**3m**):

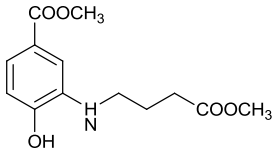
White solid, m.p.150～152°C, ($[\alpha]_D^{25}$ =-65.30, c =0.25 in ethanol), ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.46 (s, 1H), 7.19 (dd, J_1 = 8.00, J_2 = 1.60 Hz, 1H), 6.95 (d, J = 1.60Hz, 1H), 6.76 (d, J = 8.00Hz, 1H), 5.22 (s, 1H), 5.11 (d, J = 9.20 Hz, 1H), 4.18 (m, 1H), 3.76-3.86 (m, 2H), 3.74 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 172.3 (C=O), 166.5 (C=O), 149.0, 135.8, 120.7, 119.6, 113.0, 110.3, 61.8, 57.4, 51.8, 51.5; MS (EI):m/z=269$[M]^+$, 238$[M\text{-}OCH_3]^+$, 210$[M\text{-}COOCH_3]^+$, 192, 178, 77$[C_6H_5]^+$.

III-2 Characterization Data for Products Table 3 Entry 2-8



N-(2-hydroxy-5-methoxycarbonylphenyl)-β-alanine methyl ester (**5a**):

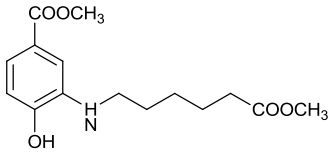
Colorless crystal, m.p.118～120°C, ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.27 (s, 1H), 7.16 (dd, J_1 = 8.04, J_2 = 2.00 Hz, 1H), 7.04 (d, J = 2.00 Hz, 1H), 6.73 (d, J = 8.04Hz, 1H), 4.95 (s, 1H), 3.75 (s, 3H), 3.60(s, 3H), 3.32 (t, 2H), 2.62 (t, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 172.2 (C=O), 166.7 (C=O), 149.1, 136.5, 120.9, 119.2, 112.9, 109.9, 51.5, 51.4, 38.8, 33.2; MS (EI): m/z=253$[M]^+$, 222$[M\text{-}OCH_3]^+$, 194$[M\text{-}COOCH_3]^+$, 178, 77$[C_6H_5]^+$.



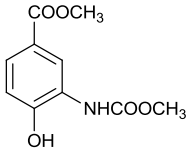
N-(2-hydroxy-5-methoxycarbonylphenyl)-γ-aminobutyric acid methyl ester (**5b**):

Colorless crystal, m.p.114～116°C, ^{1}H NMR (400 MHz, DMSO-d_6) ppm: 10.30 (s, 1H), 7.13 (dd, J_1 = 8.00, J_2 = 2.00 Hz, 1H), 7.00 (d, J = 2.00 Hz, 1H), 6.71 (d, J = 8.00 Hz, 1H), 4.85 (s, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 3.07 (t, J = 6.81 Hz, 2H), 2.39 (t, J = 7.30 Hz, 2H), 1.81 (m, 2H); ^{13}C NMR (100 MHz,DMSO-d_6) ppm: 173.3 (C=O), 166.7（C=O, 148.8, 137.1, 120.9, 118.5, 112.7, 109.4, 51.5, 51.3, 42.0, 31.0,

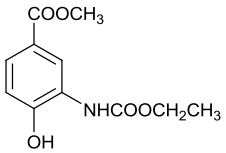
23.9; MS (EI):m/z=267[M]$^+$, 236[M-OCH_3]$^+$, 204, 178, 77[C_6H_5]$^+$.



N-(2-hydroxy-5-methoxycarbonylphenyl)-6-aminohexanoic acid methyl ester (**5c**): Whirte solid, m.p.76～78°C, ^{1}HNMR (400 MHz, DMSO-d_6) ppm: 10.24 (s, 1H), 7.14 (dd, J_1 = 8.40, J_2 = 1.60 Hz, 1H), 7.02 (d, J = 1.60 Hz, 1H), 6.72 (d, J = 8.40Hz, 1H), 4.87 (s, 1H), 3.75 (s, 3H), 3.57 (s, 3H), 3.04 (t, 2H), 2.30 (t, 2H), 1.55 (m, 4H), 1.32 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.3.0 (C=O), 166.7 (C=O), 148.8, 137.1, 120.9, 118.5, 112.7, 109.5, 51.4, 51.1, 42.7, 33.2, 28.1, 26.1, 24.3; MS (EI): m/z=295[M]$^+$, 264 [M-OCH_3]$^+$, 236[M-$COOCH_3$]$^+$, 180, 77[C_6H_5]$^+$.

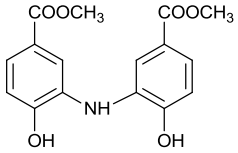


N-(2-hydroxy-5-methoxycarbonylphenyl)methyl carbamate (**5d**): White solid, m.p.167～169°C, ^{1}HNMR (400 MHz, DMSO-d_6) ppm: 10.72 (s, 1H), 8.49 (s, 1H), 8.22 (s, 1H), 7.56 (d, J=8.00, 1H), 6.90 (d, J=8.00 Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz,DMSO-d_6) ppm: 166.0 (C=O), 154.3 (C=O), 152.7, 126.1, 126.0, 122.9, 120.3, 114.9, 51.9, 51.7; MS (EI): m/z=225[M]$^+$, 194[M-OCH_3]$^+$, 166[M-$COOCH_3$]$^+$, 97, 77[C_6H_5]$^+$.

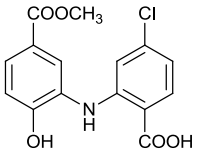


N-(2-hydroxy-5-methoxycarbonylphenyl)ethyl carbamate (**5e**): White solid, ^{1}H NMR ($CDCl_3$, 400 MHz), ppm: 8.80 (s, 1H, 4-OH), 7.86 (d, J = 2.0 Hz, 1H), 7.72 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H, NH), 4.26 (q, 2H), 3.86 (s, 3H, CH_3), 1.32 (t, 3H, CH_3); IR(KBr, ν/cm^{-1}): 3431, 3185, 3004, 2954, 1718, 1689, 1604, 1548, 1452, 1278, 1230, 1058, 767, 690; MS

(EI): m/z=239[M]$^+$, 208 [M-OCH_3] $^+$, 167, 136.



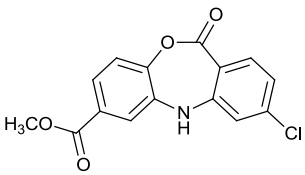
Methyl 3-(5-methoxycarbonyl-2-hydroxyphenylamino)-4-hydroxybenzoate (**5f**): Yellow solid, ^{1}H NMR (DMSO-d_6, 400 MHz), ppm: 10.72 (s, 2H, OH), 7.68 (d, J = 2.0 Hz, 2H), 7.42 (dd, J_1 = 8.4 Hz, J_2 =2.0 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.76 (s, 1H, NH), 3.76 (s, 6H, CH_3); IR (KBr, ν/cm^{-1}): 3359, 3016, 2950, 1689, 1604, 1537, 1517, 1427, 1375, 1278, 1112, 875, 763, 640; MS (EI): m/z=317[M]$^+$, 285, 257, 198 , 127.



Methyl 3-(5-chloro-2-acetylphenylamino)-4-hydroxybenzoate (**5g**)

Yellow solid, m.p.＞200°C, ^{1}H NMR (DMSO-d_6, 400 MHz) ppm: 11.25 (s, 1H, COOH), 10.80 (s, 1H), 9.62 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 2.0 Hz 1H), 7.63 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.79 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 3.79 (s, 3H); MS (EI): m/z=323, 321[M]$^+$, 271, 244.

III-3 Characterization Data for compound (**6**)

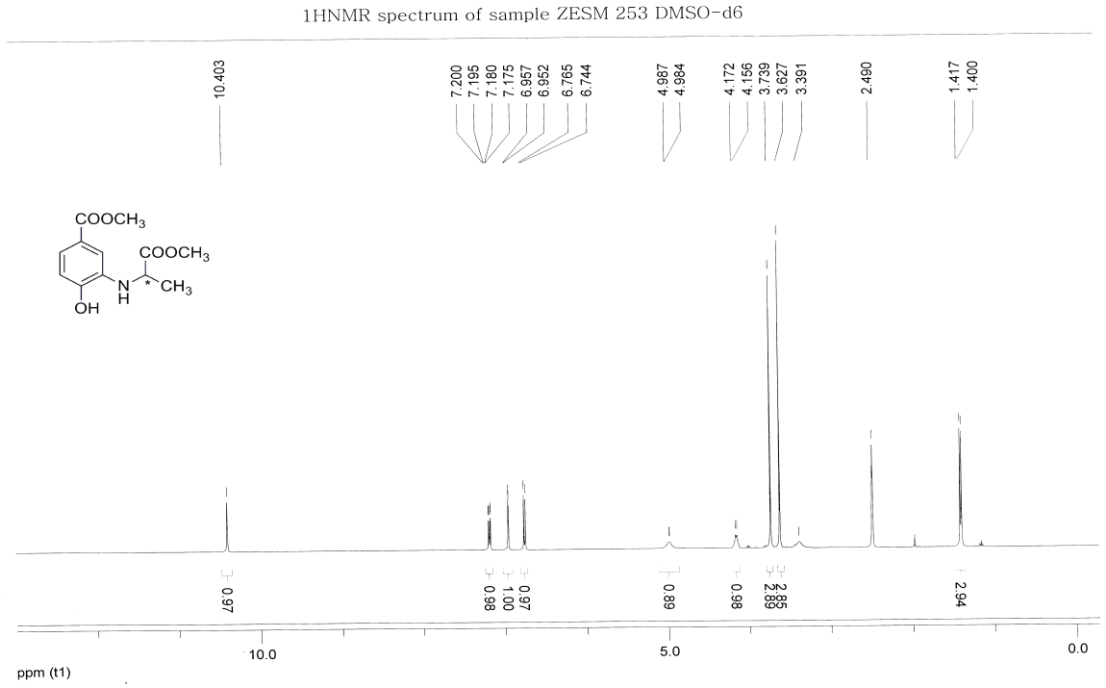


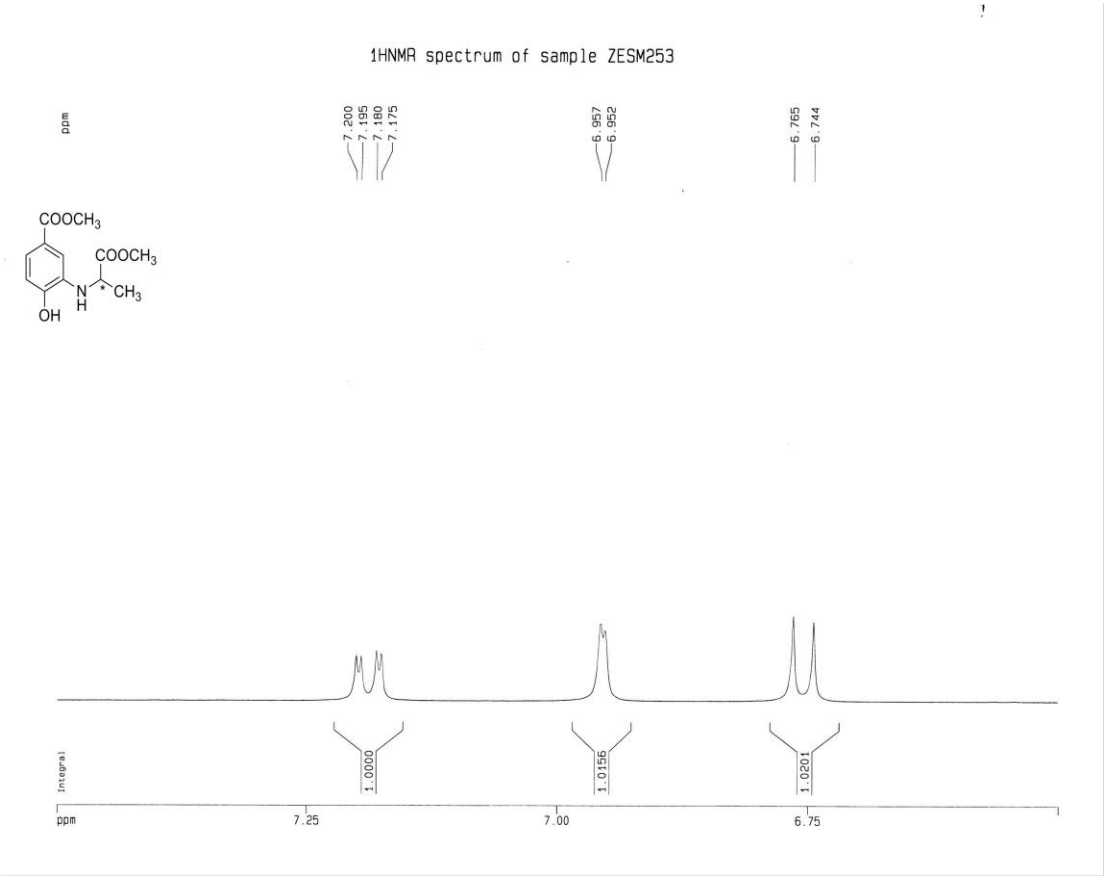
3-chloro-7-methoxycarbonyl-dibenz[b,e][1,4]oxazepin-11(5H)-one(6)

Yellow solid, m.p.＞200°C, ^{1}HNMR (400 MHz, DMSO-d_6) ppm: 9.33 (s, 1H), 7.87 (d, J = 8.80, 1H), 7.83 (d, J = 2.40 Hz, 1H), 7.64 (dd, J_1 = 8.80Hz, J_2 =2.40Hz, 1H), 7.30 (d, J =8.40, 1H), 7.24 (d, J = 2.00 Hz ,1H), 6.99 (dd, J_1 = 8.40Hz, J_2 = 2.00Hz, 1H), 3.84 (s, 3H); MS (EI): m/z=303[M]$^+$, 272[M-OCH_3]$^+$, 244[M-$COOCH_3$]$^+$, 188, 77[C_6H_5]$^+$, 44.

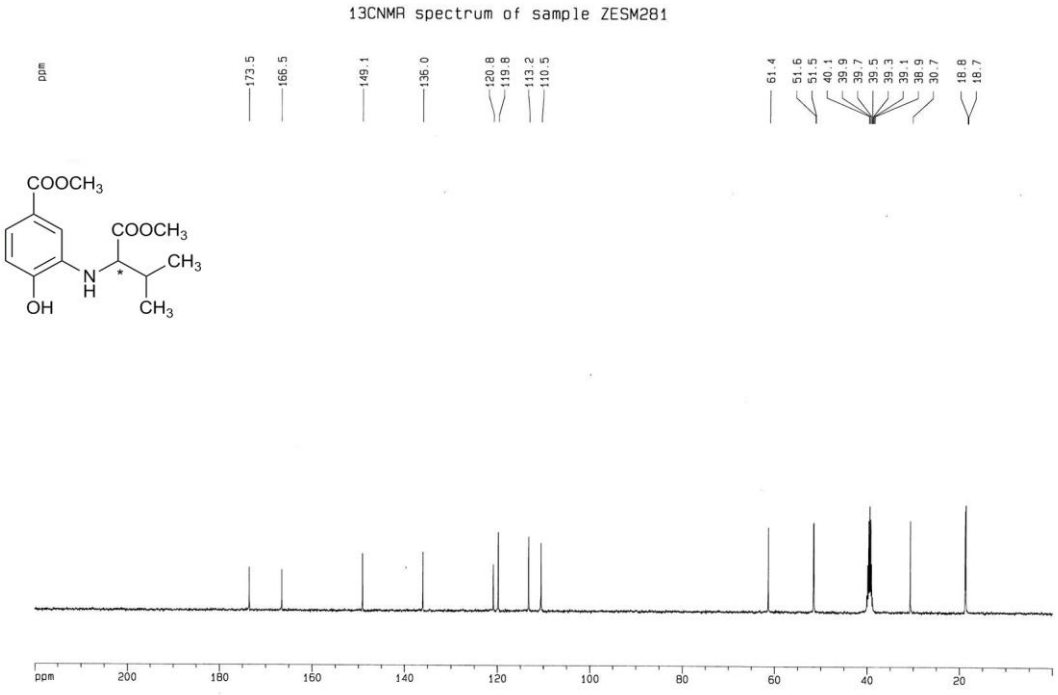
III-4 ^{13}C NMR, ^{1}H NMR spectra for all products

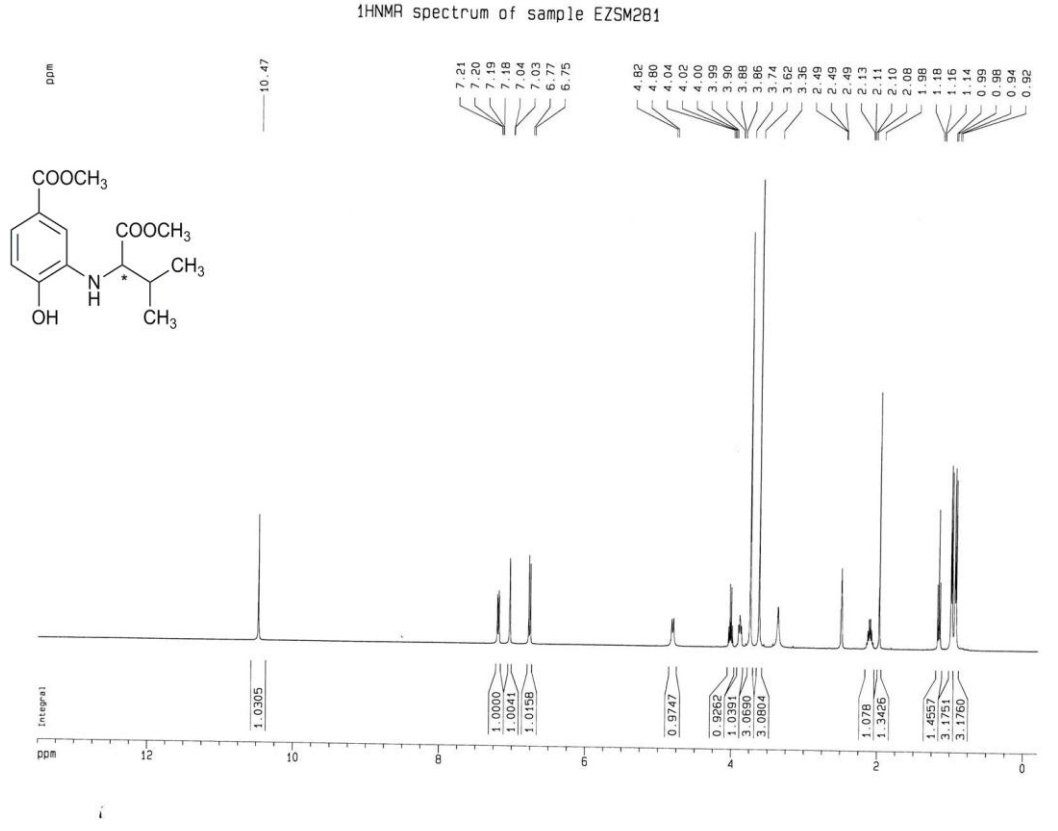
(Table 2 Entry 1, 3a)

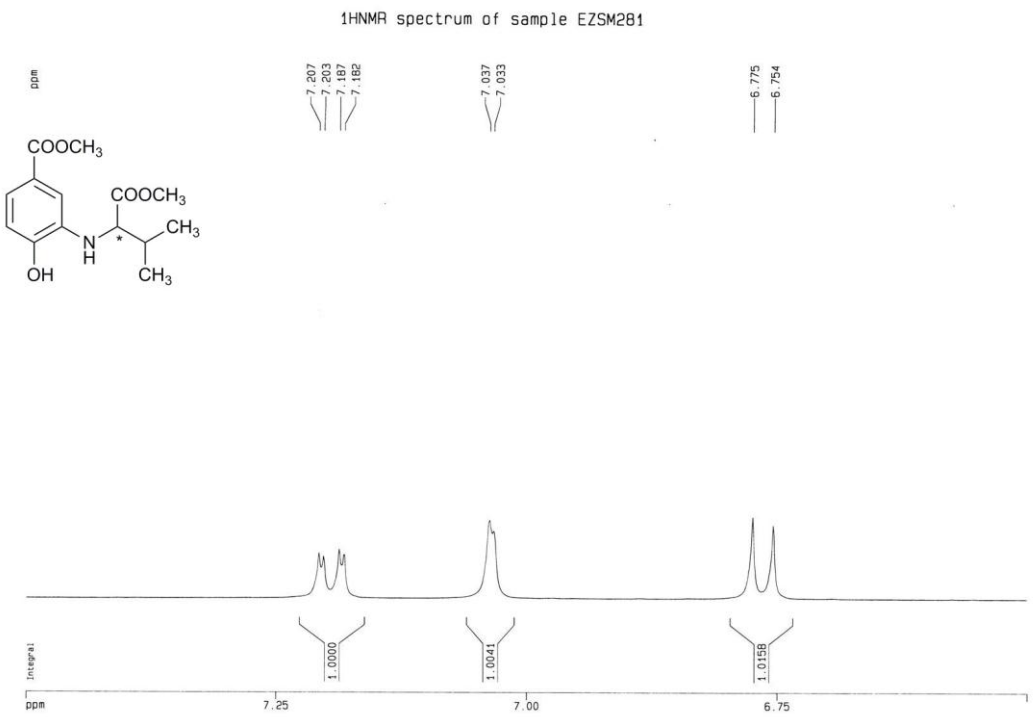




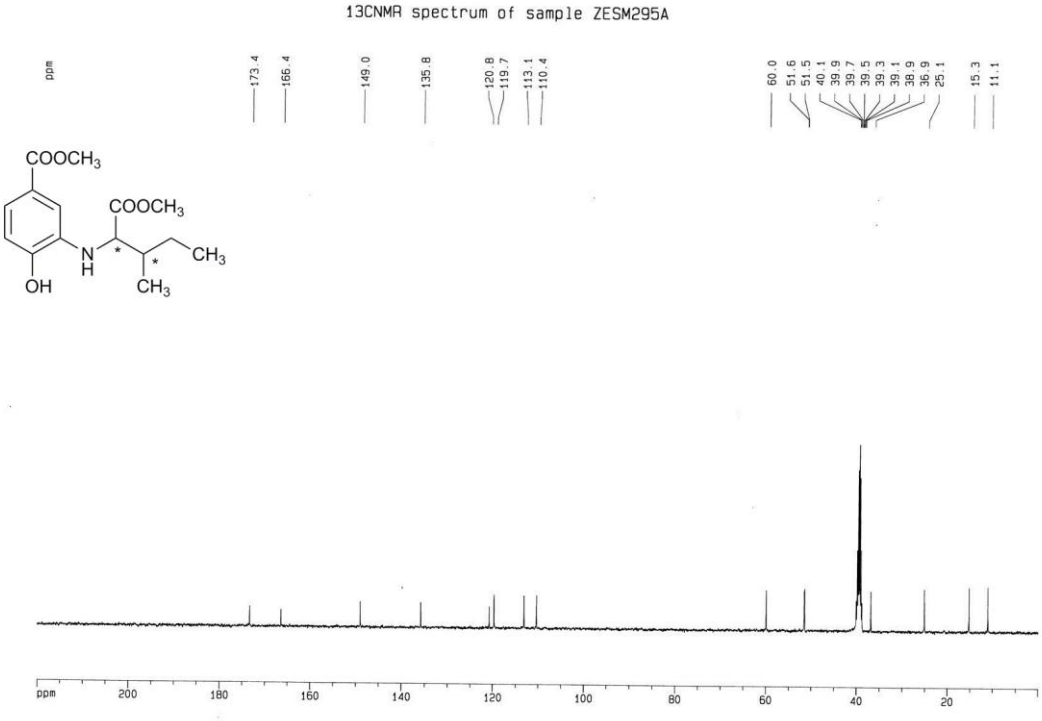
(Table 2 Entry 2, 3b)



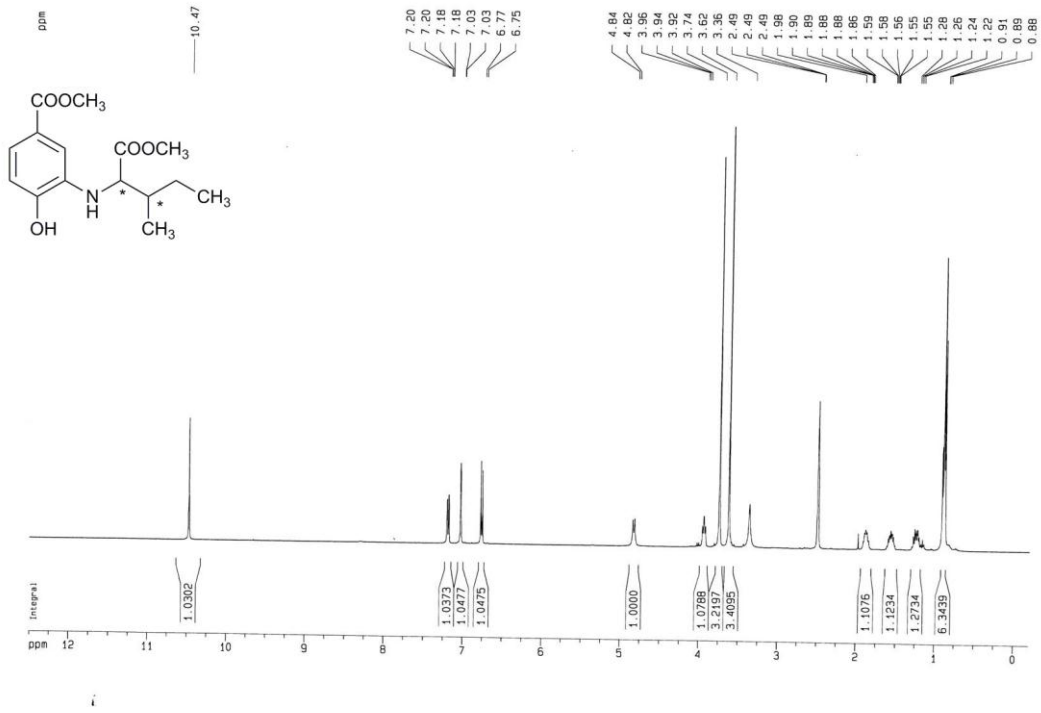




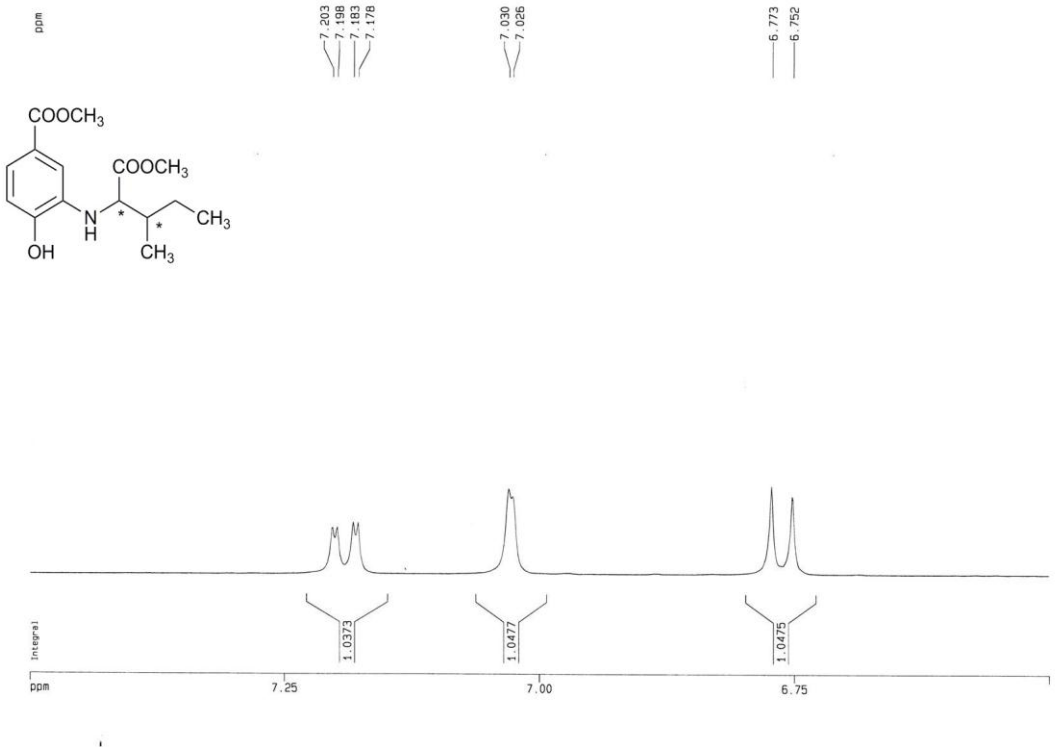
(Table 2 Entry 3, 3c)

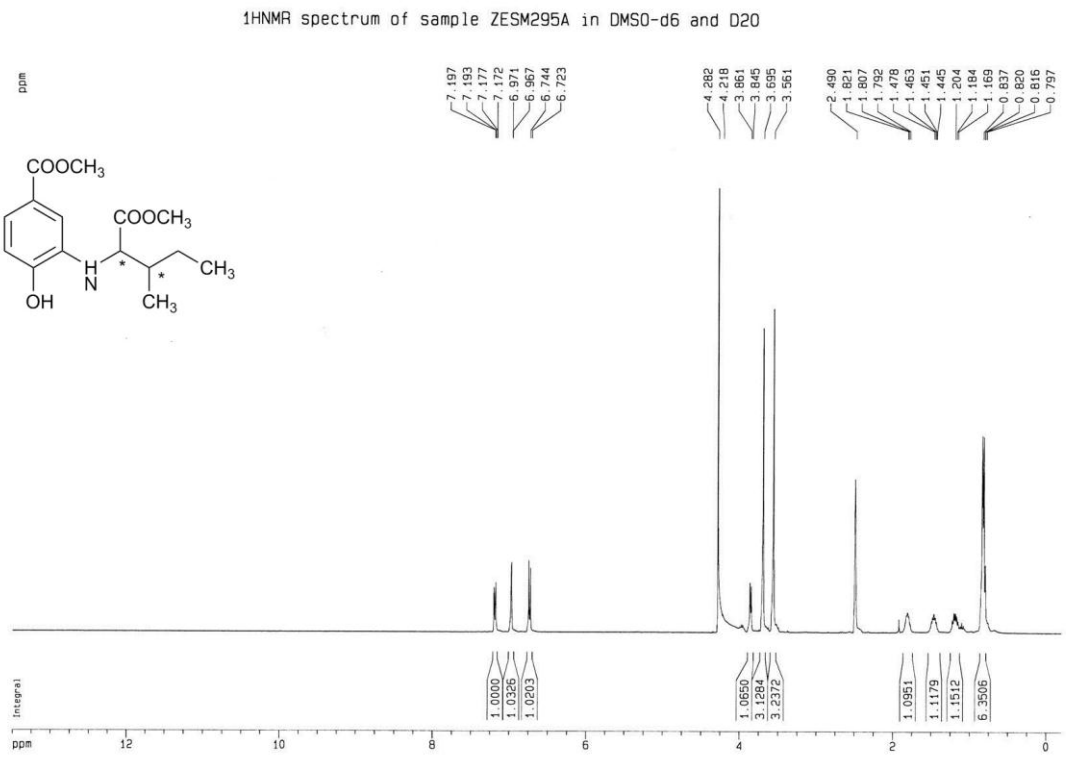


1HNMR spectrum of sample ZESM295A



1HNMR spectrum of sample ZESM295A




1HNMR spectrum of sample ZESM295A in DMSO-d6 and D2O
ppm
7.197
7.193
7.177
7.172
6.971
6.967
6.744
6.723
4.282
4.218
3.861
3.845
3.695
3.561
2.490
1.821
1.807
1.792
1.478
1.463
1.451
1.445
1.204
1.184
1.169
0.837
0.820
0.816
0.797
COOCH3
COOCH3
H
N
CH3
CH3
OH
Integral
1.0000
1.0326
1.0203
1.0650
3.1284
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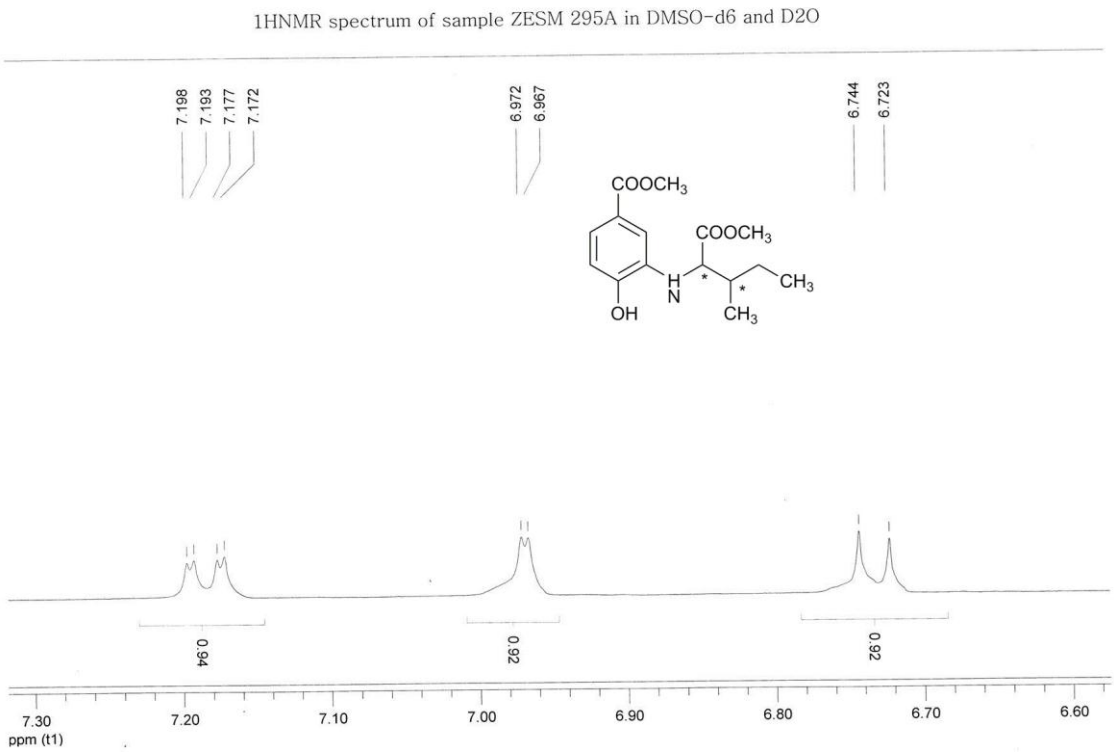
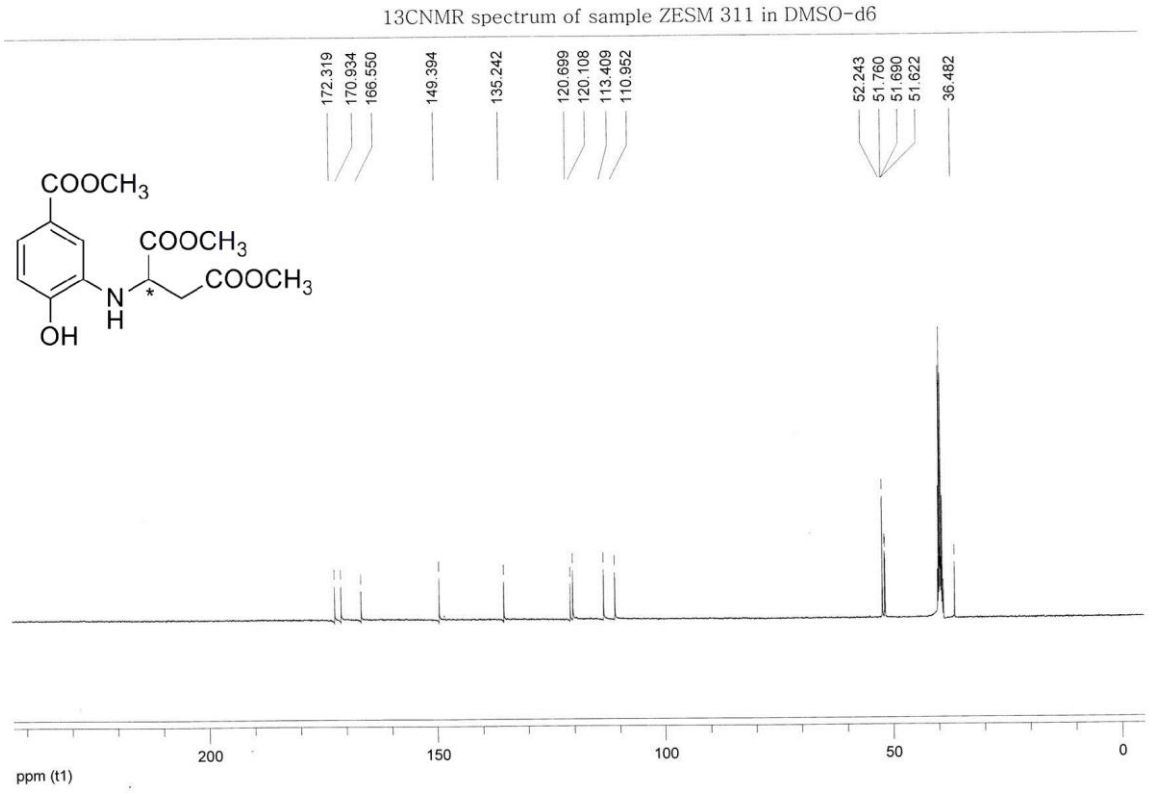
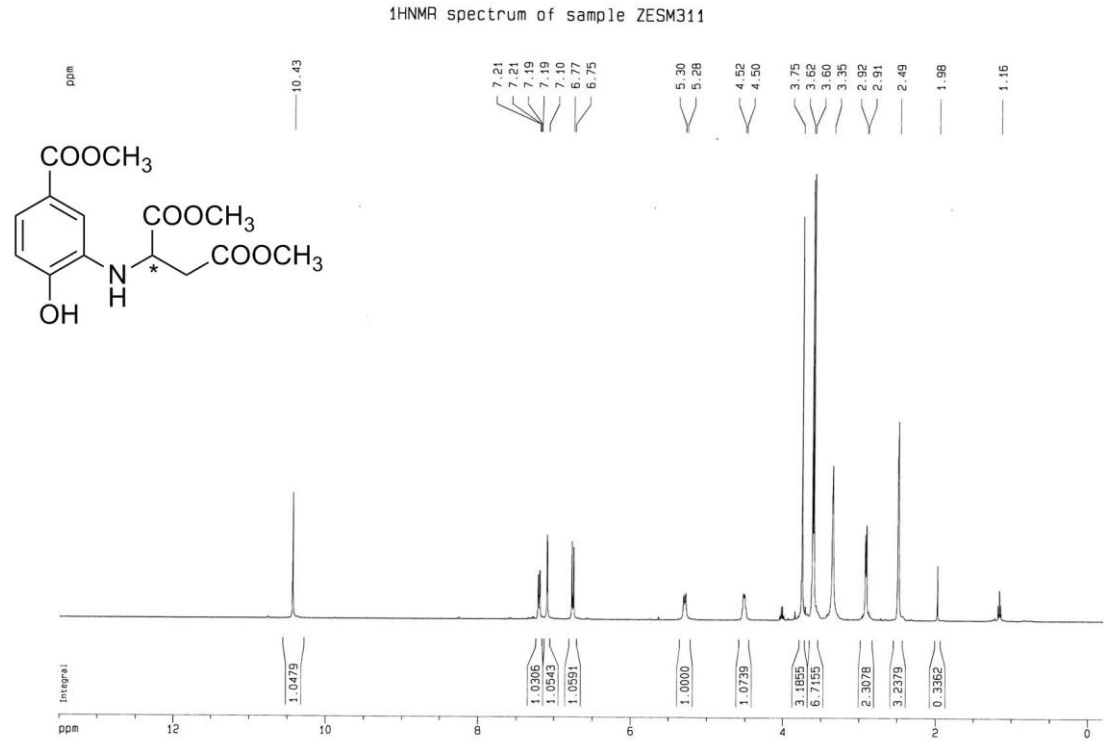
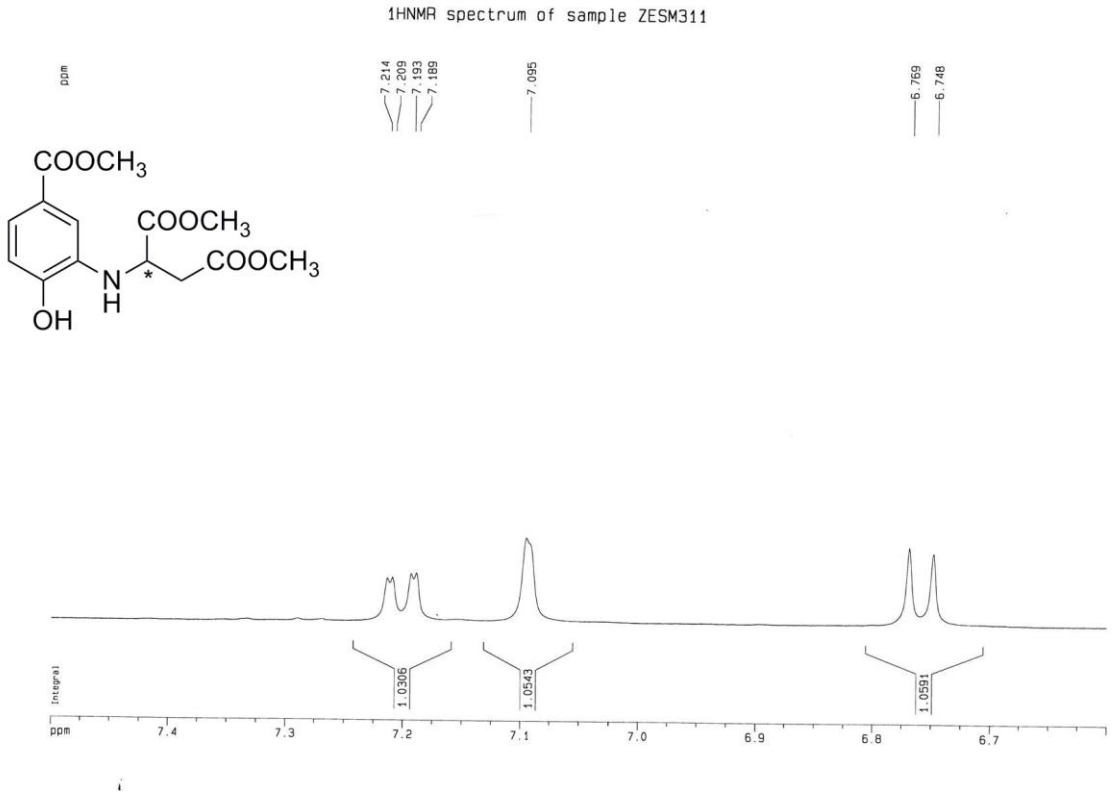
6.3506
ppm
12
10
8
6
4
2
0


1HNMR spectrum of sample ZESM 295A in DMSO-d6 and D2O
7.198
7.193
7.177
7.172
6.972
6.967
6.744
6.723
COOCH3
COOCH3
H
N
CH3
CH3
OH
0.94
0.92
0.92
7.30
ppm (t1)
7.20
7.10
7.00
6.90
6.80
6.70
6.60

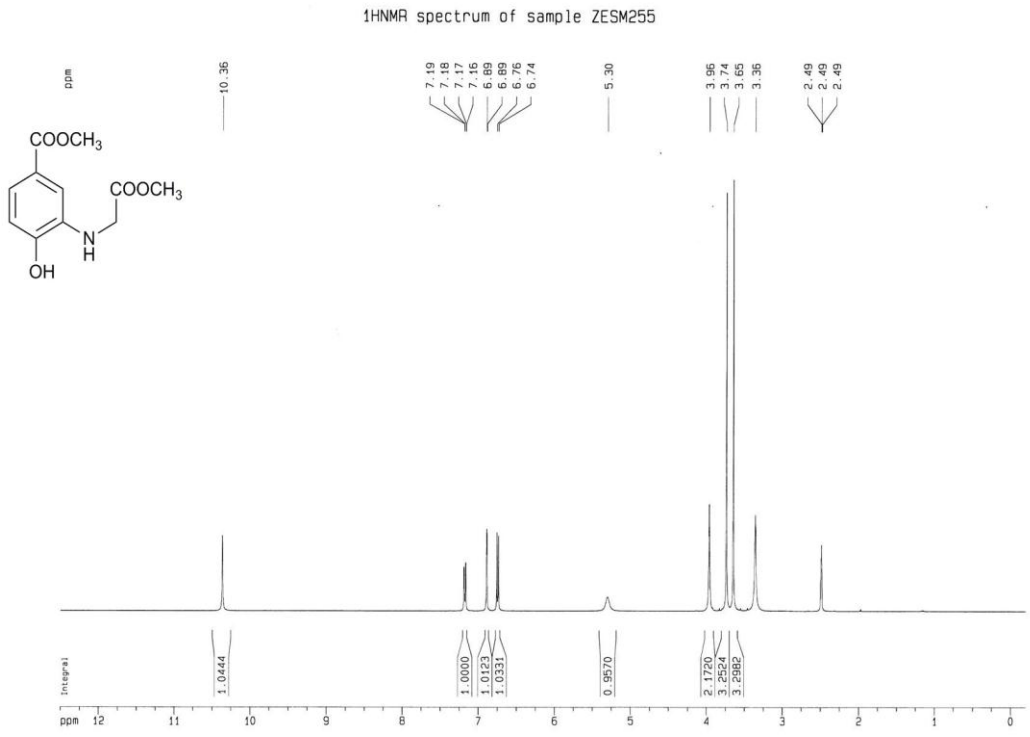
(Table 2 Entry 4, 3d)

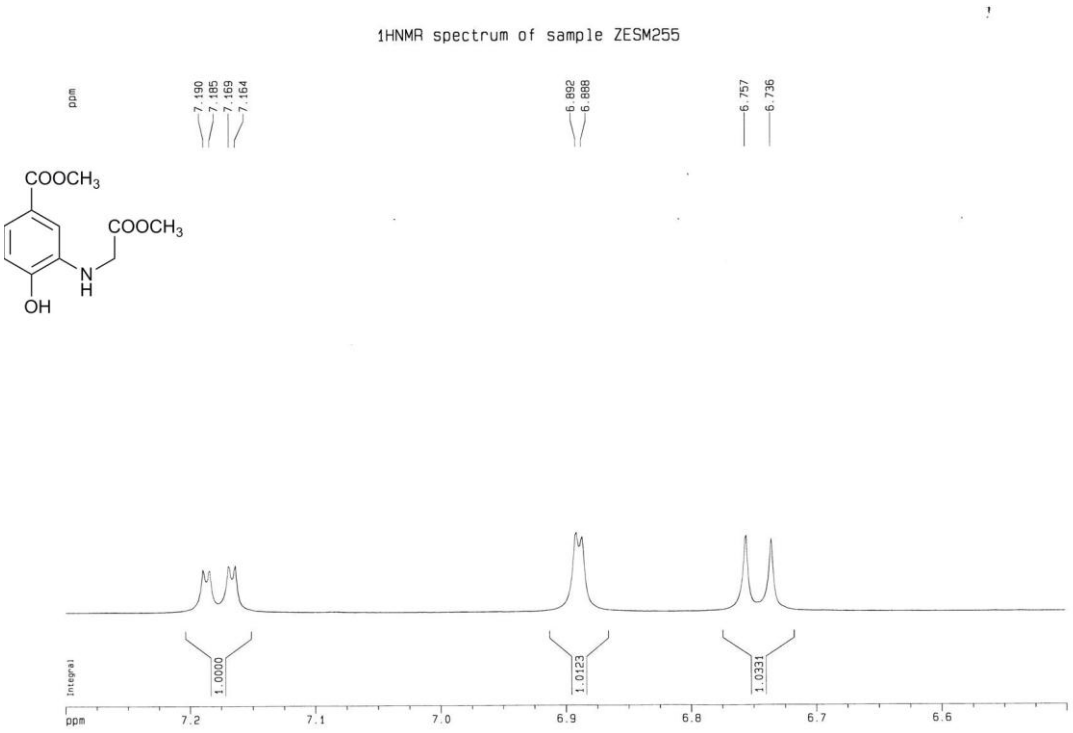




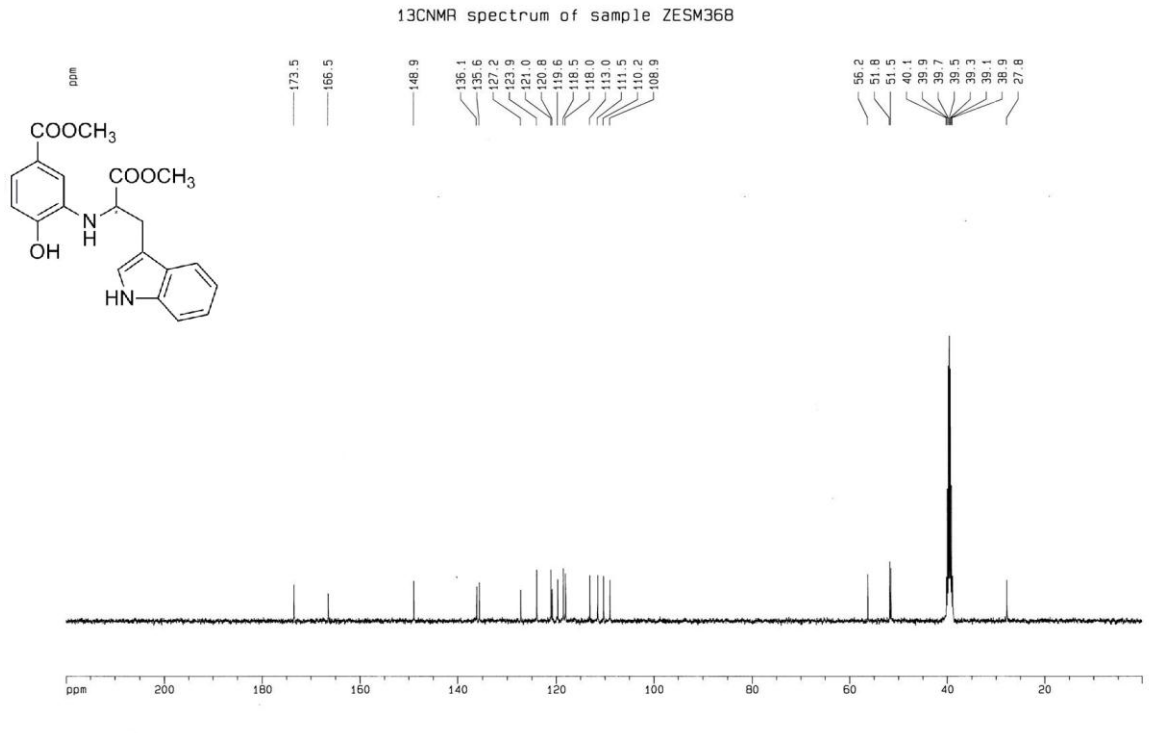


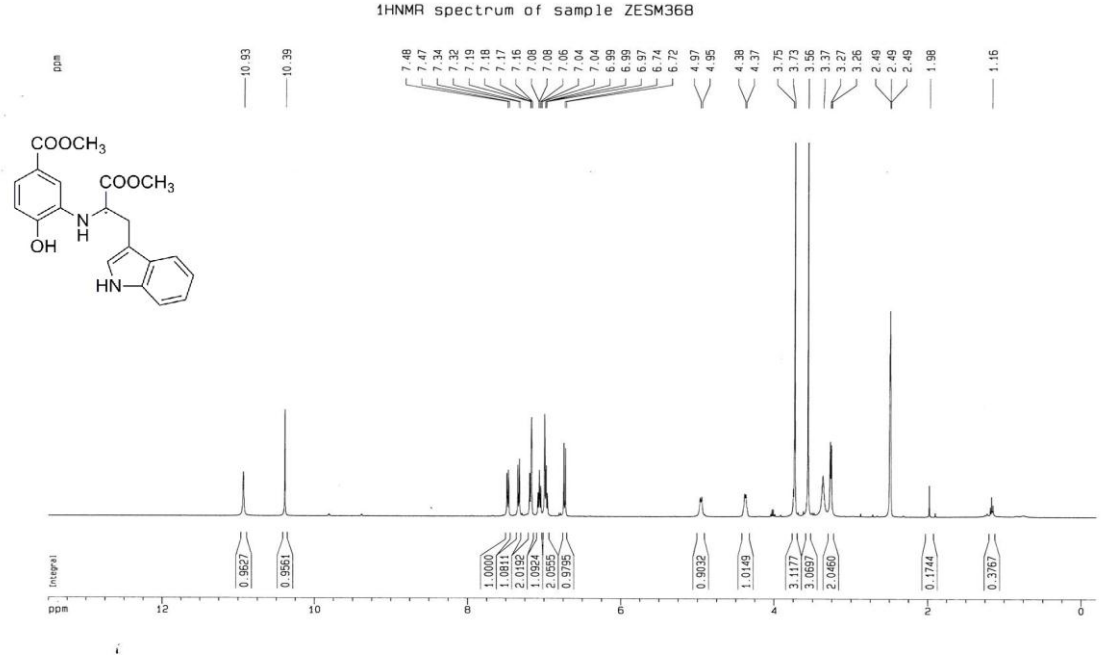
(Table 2 Entry 5, 3e)

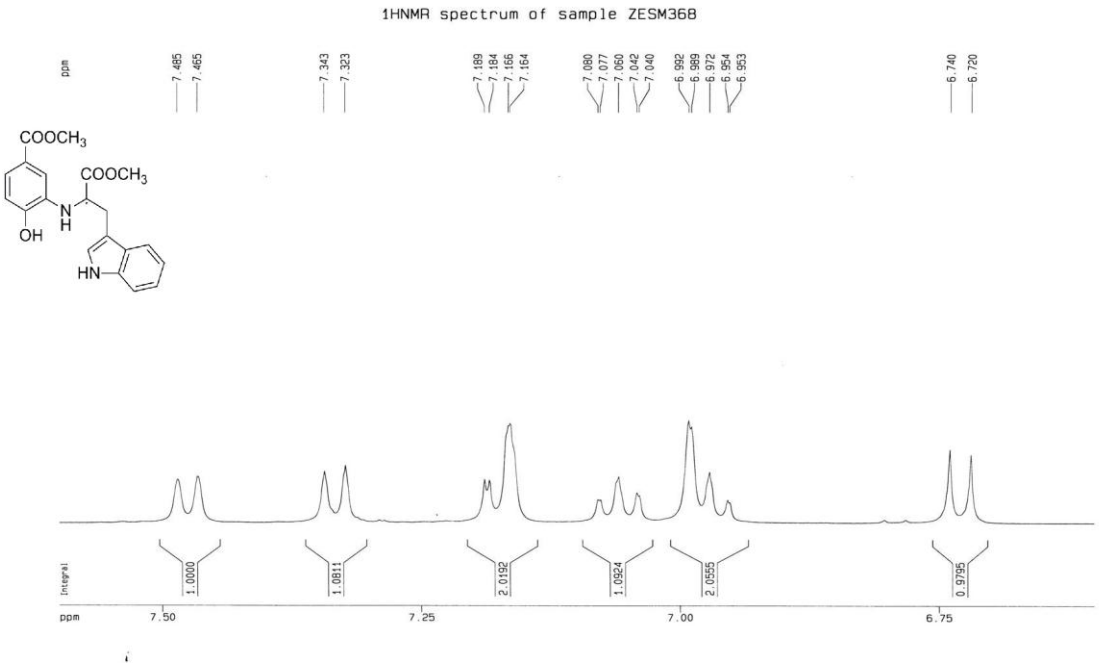




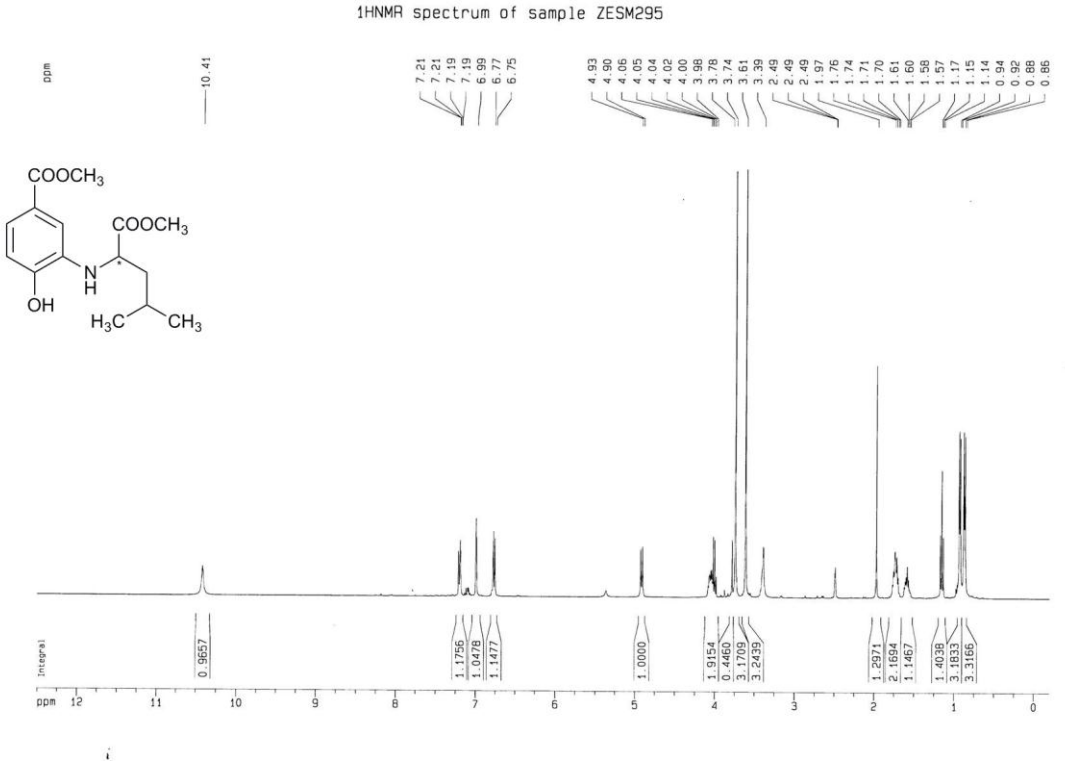
(Table 2 Entry 6, 3f)

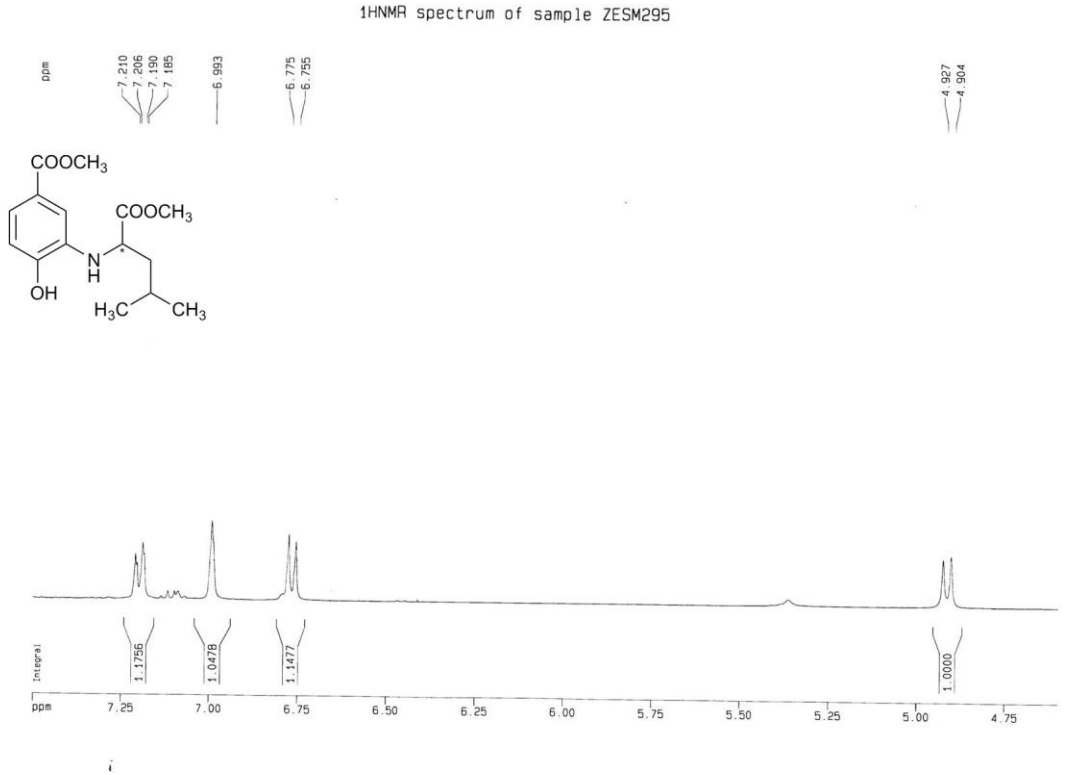



1HNMR spectrum of sample ZESM368
COOCH3
COOCH3
N
H
OH
HN
integral
ppm

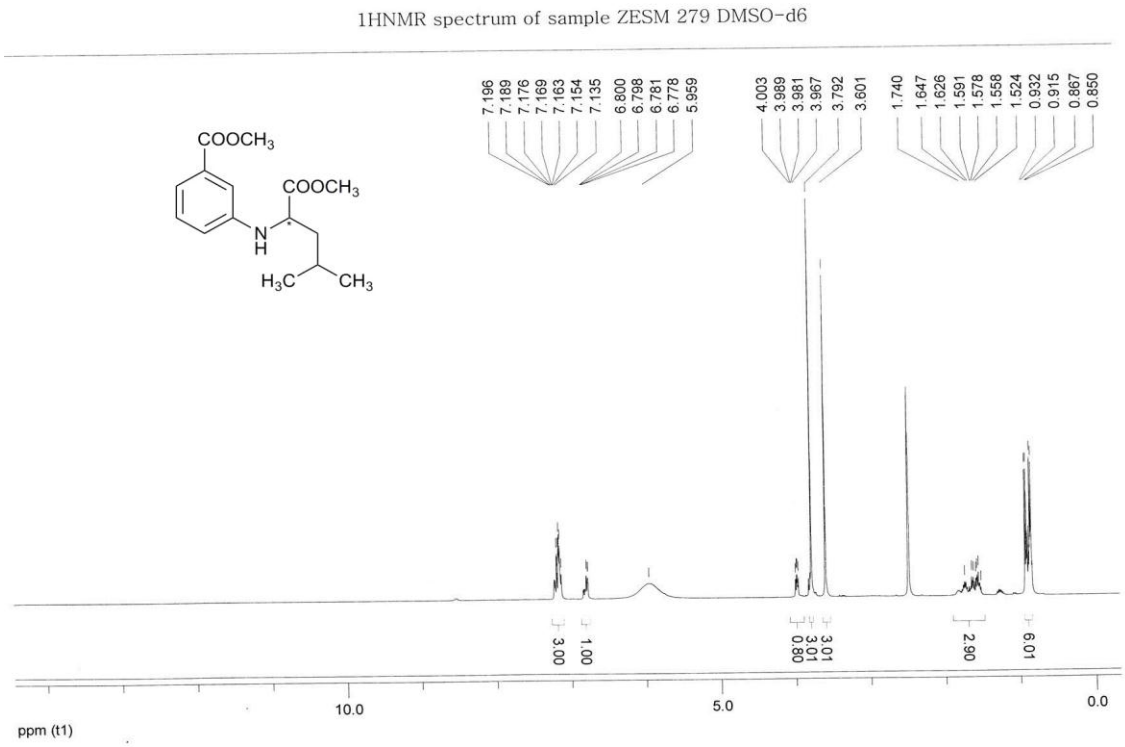

1HNMR spectrum of sample ZESM368
COOCH3
COOCH3
N
H
OH
HN
integral
ppm

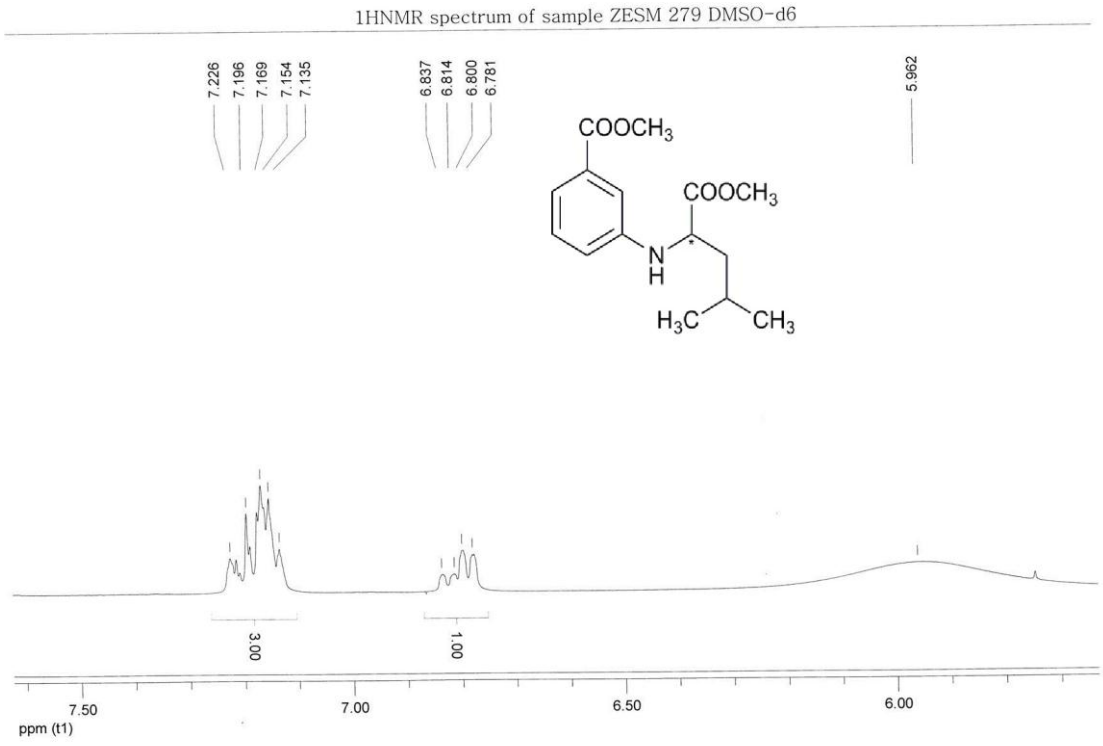
(Table 2 Entry 7, 3g)



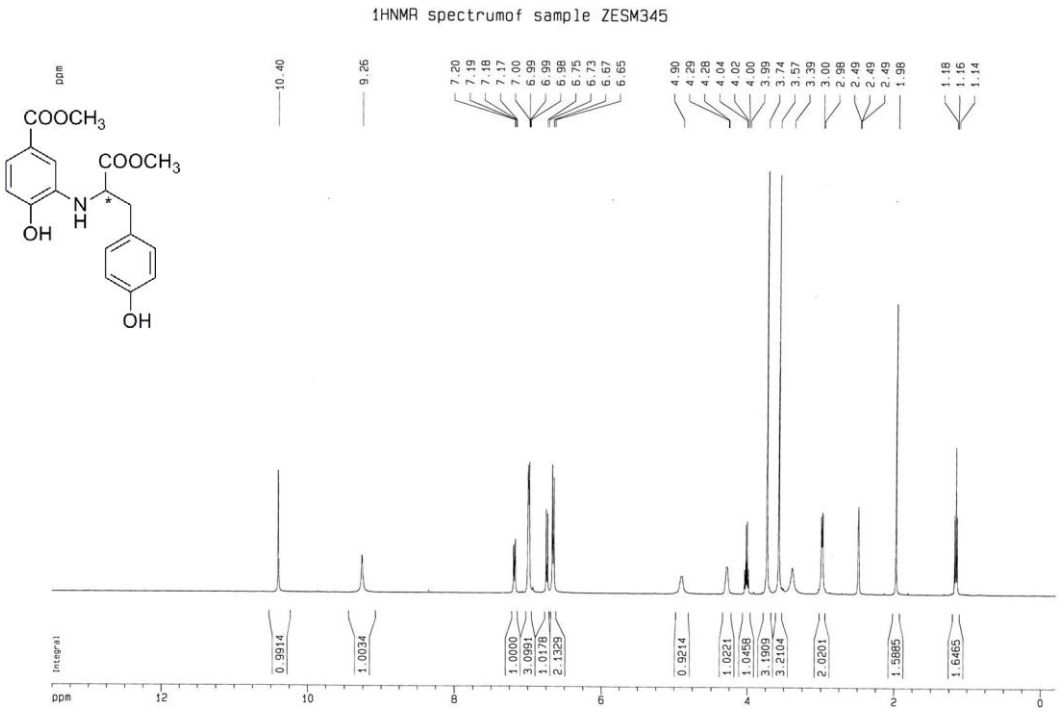


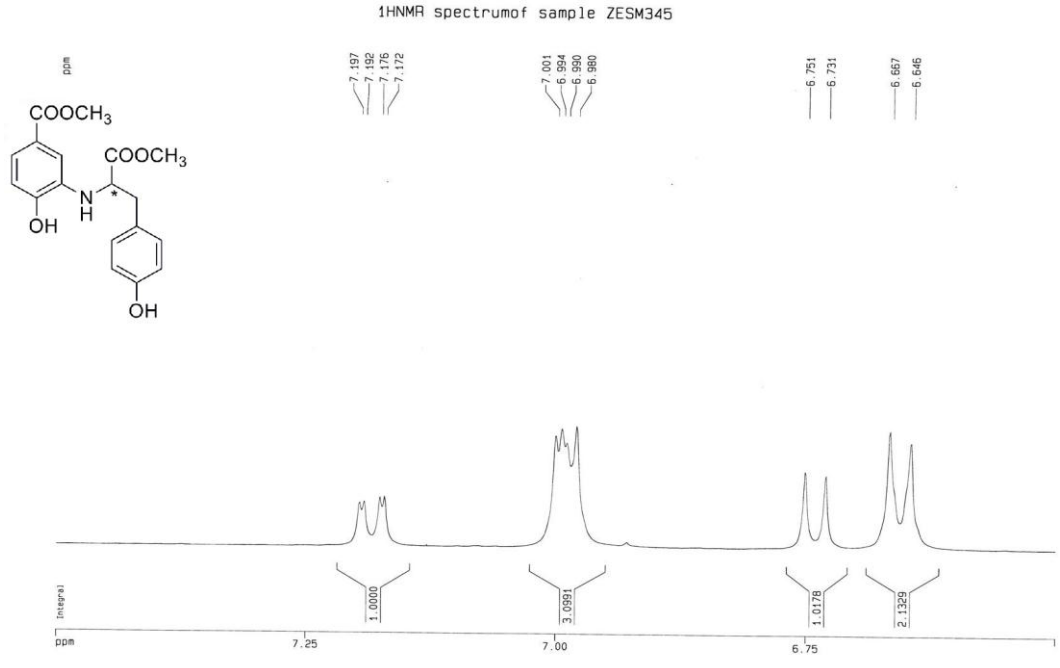
(Table 2 Entry 7, 3g´)



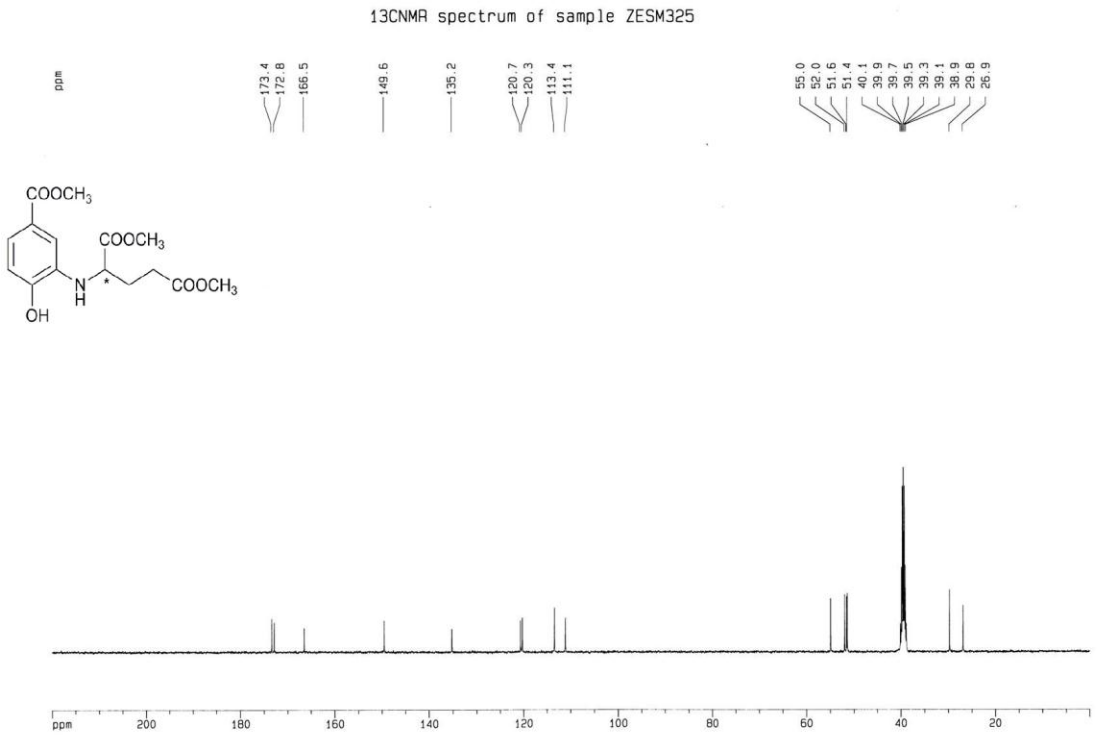


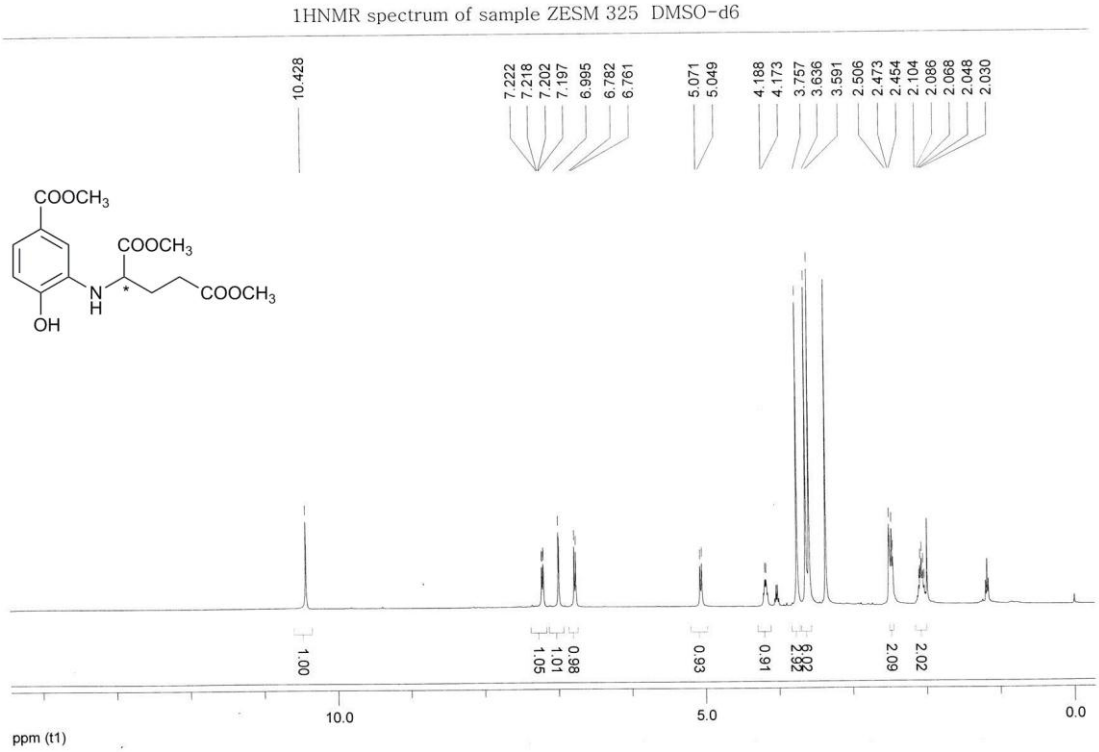
(Table 2 Entry 8, 3h)

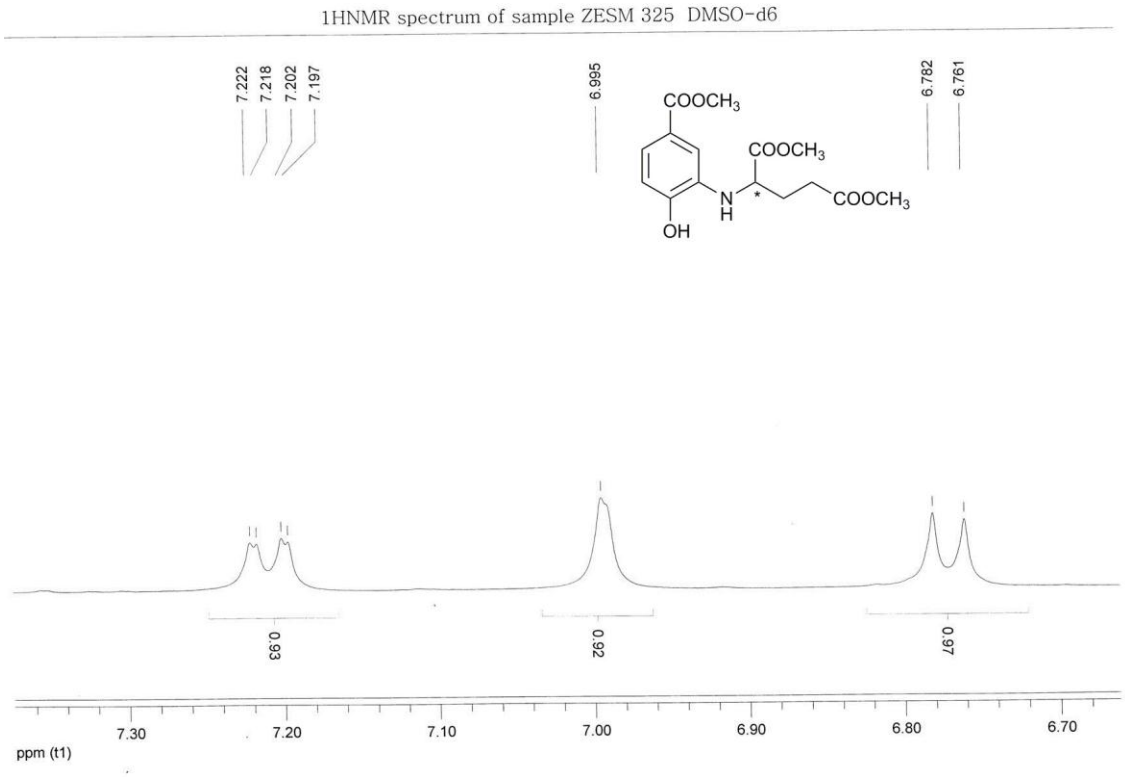




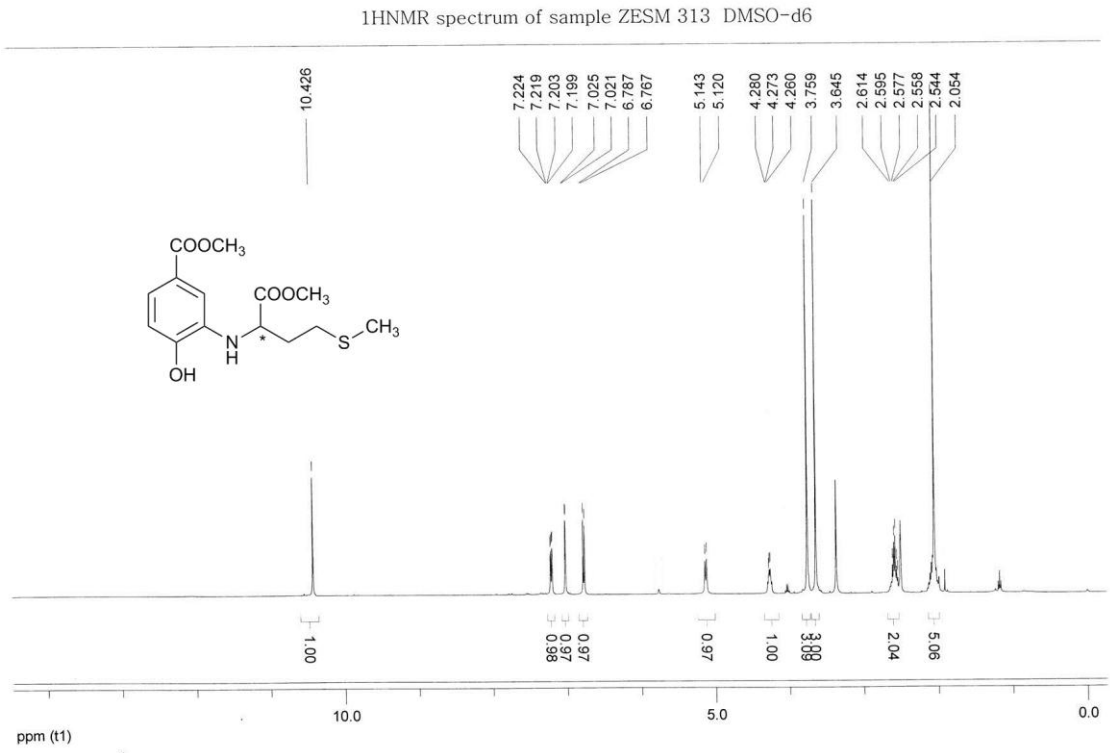
(Table 2 Entry 9, 3i)

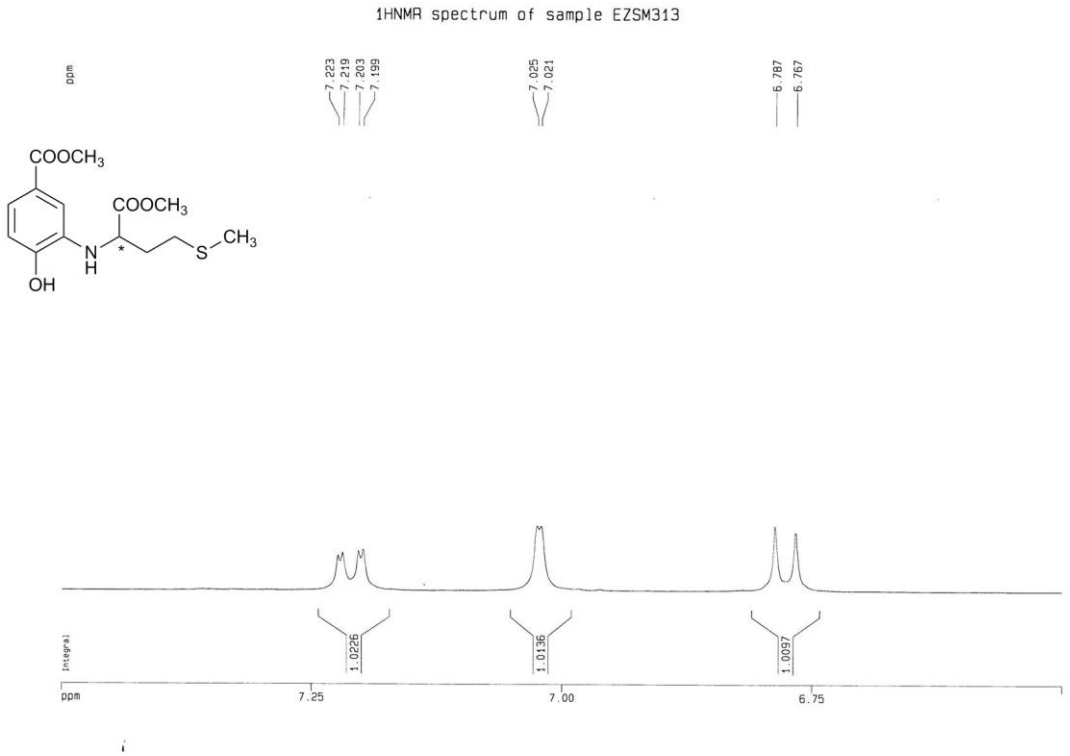




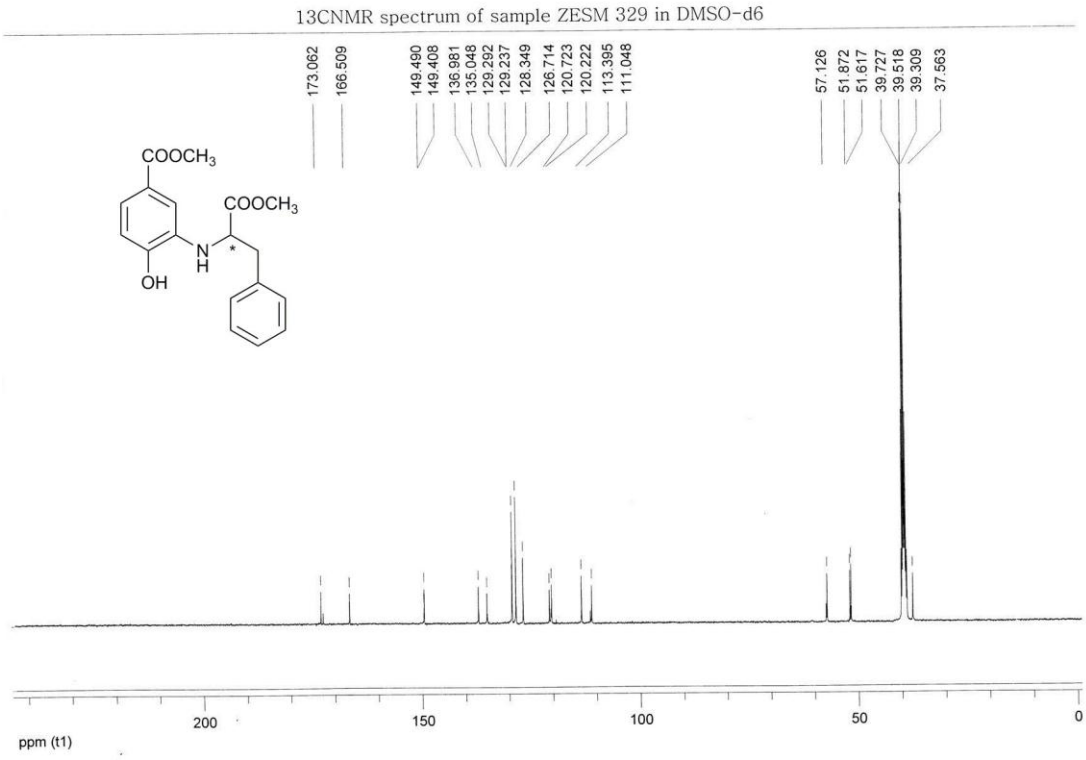


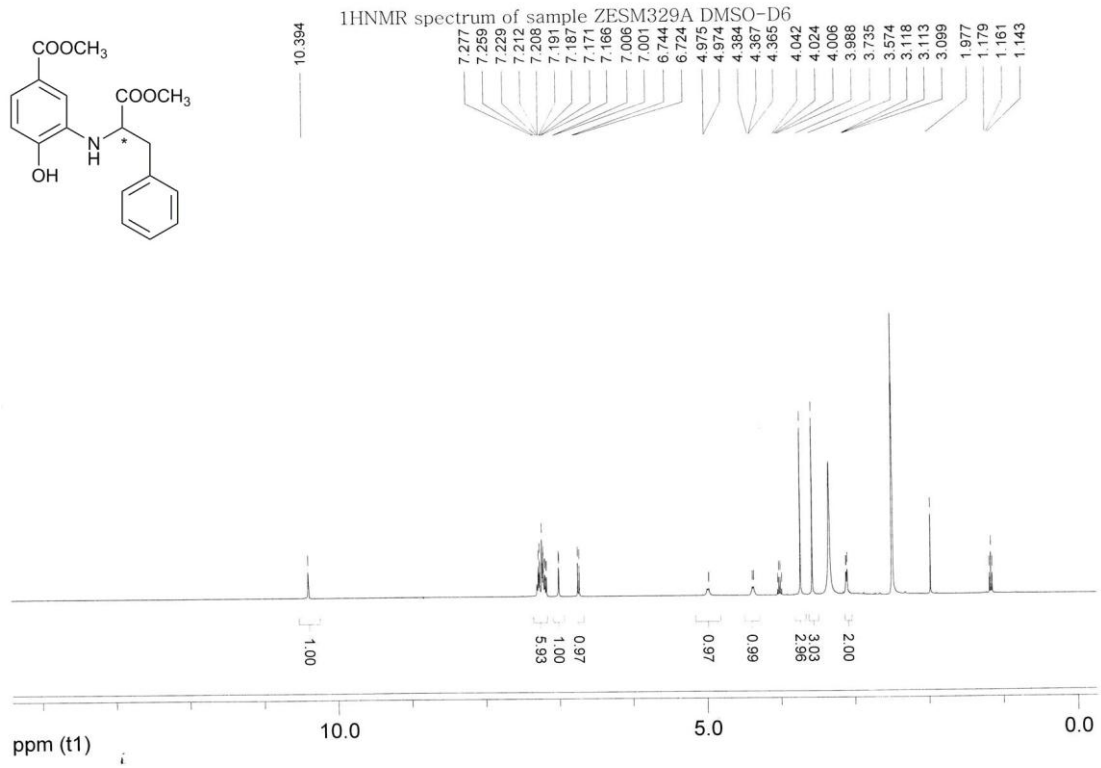
(Table 2 Entry 10, 3j)

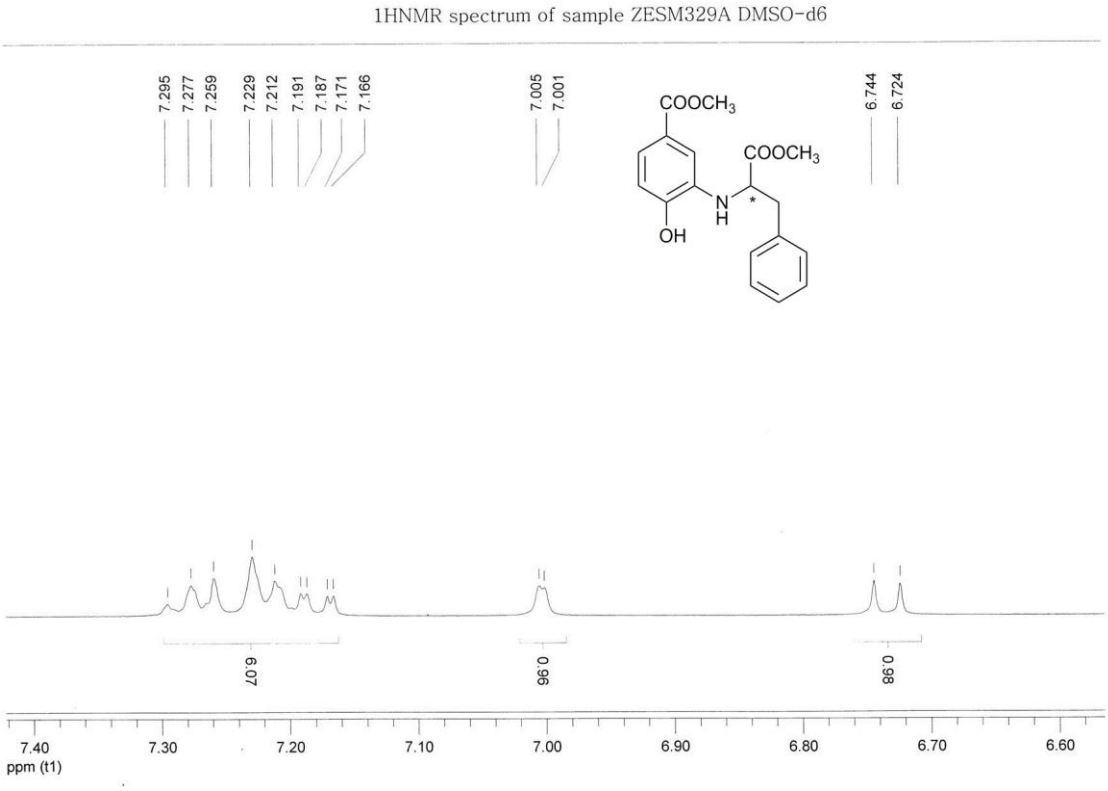




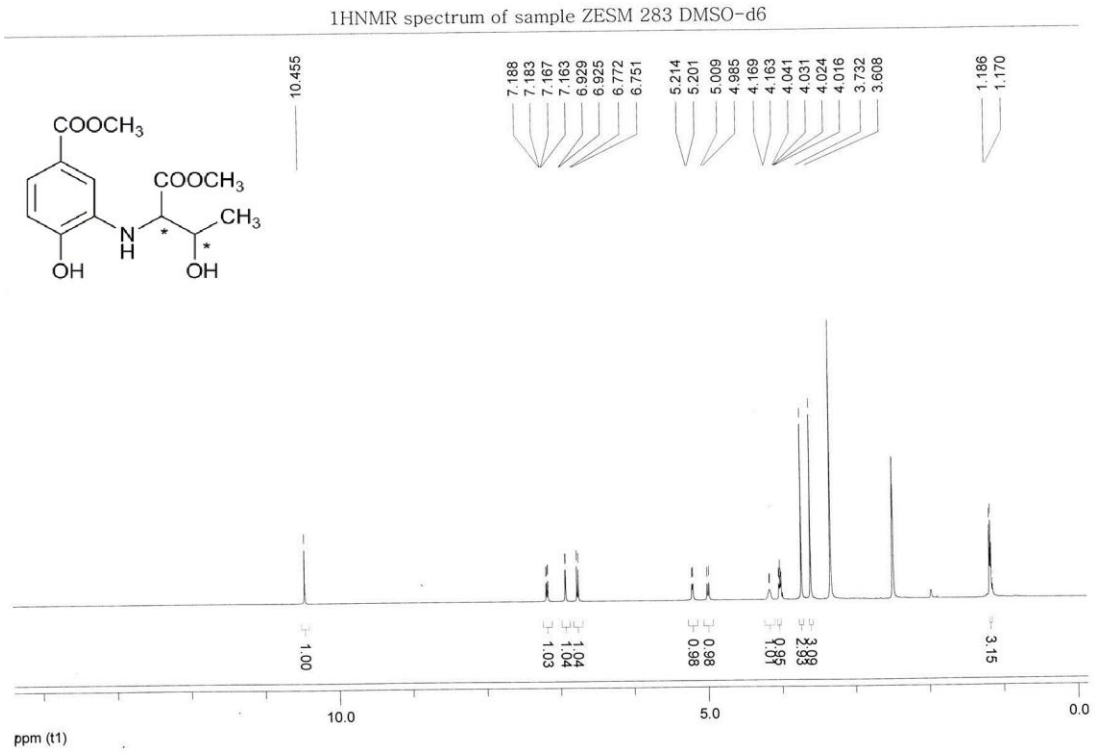
(Table 2 Entry 11, 3k)

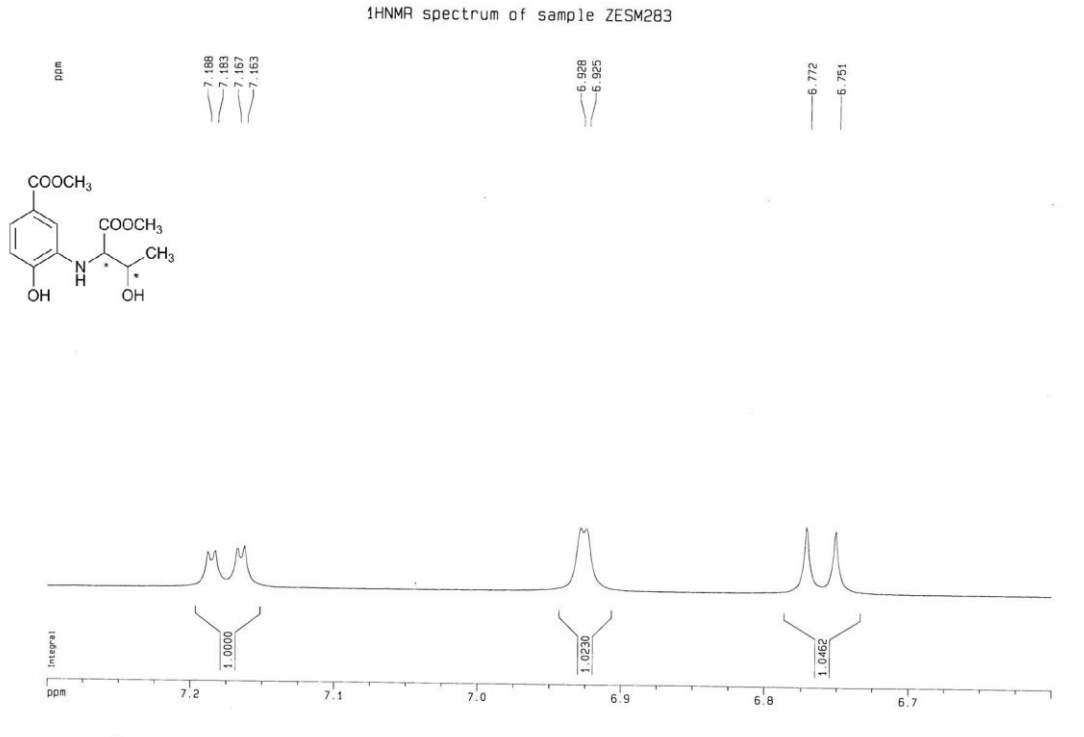



1HNMR spectrum of sample ZESM329A DMSO-D6
COOCH3
COOCH3
N
H
OH
10.394
7.277
7.259
7.229
7.212
7.208
7.191
7.187
7.171
7.166
7.006
7.001
6.744
6.724
4.975
4.974
4.384
4.367
4.365
4.042
4.024
4.006
3.988
3.735
3.574
3.118
3.113
3.099
1.977
1.179
1.161
1.143
1.00
5.93
1.00
0.97
0.97
0.99
2.96
3.03
2.00
ppm (t1)
10.0
5.0
0.0

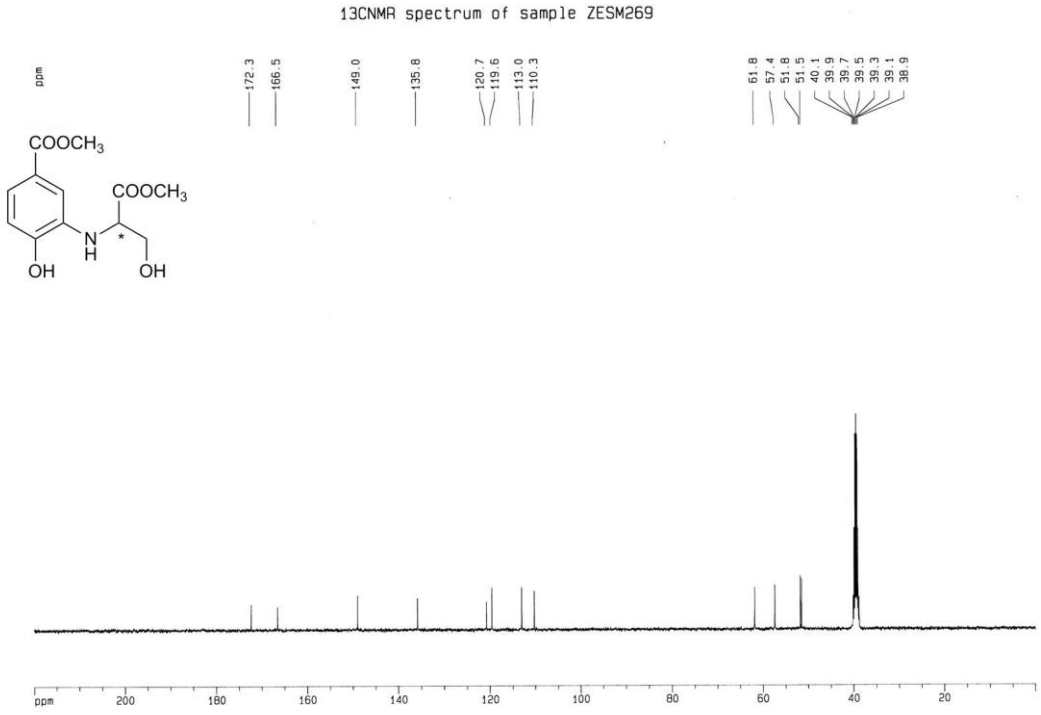

1HNMR spectrum of sample ZESM329A DMSO-d6
7.295
7.277
7.259
7.229
7.212
7.191
7.187
7.171
7.166
7.005
7.001
6.744
6.724
COOCH3
COOCH3
N
H
OH
6.07
0.96
0.98
7.40
ppm (t1)
7.30
7.20
7.10
7.00
6.90
6.80
6.70
6.60

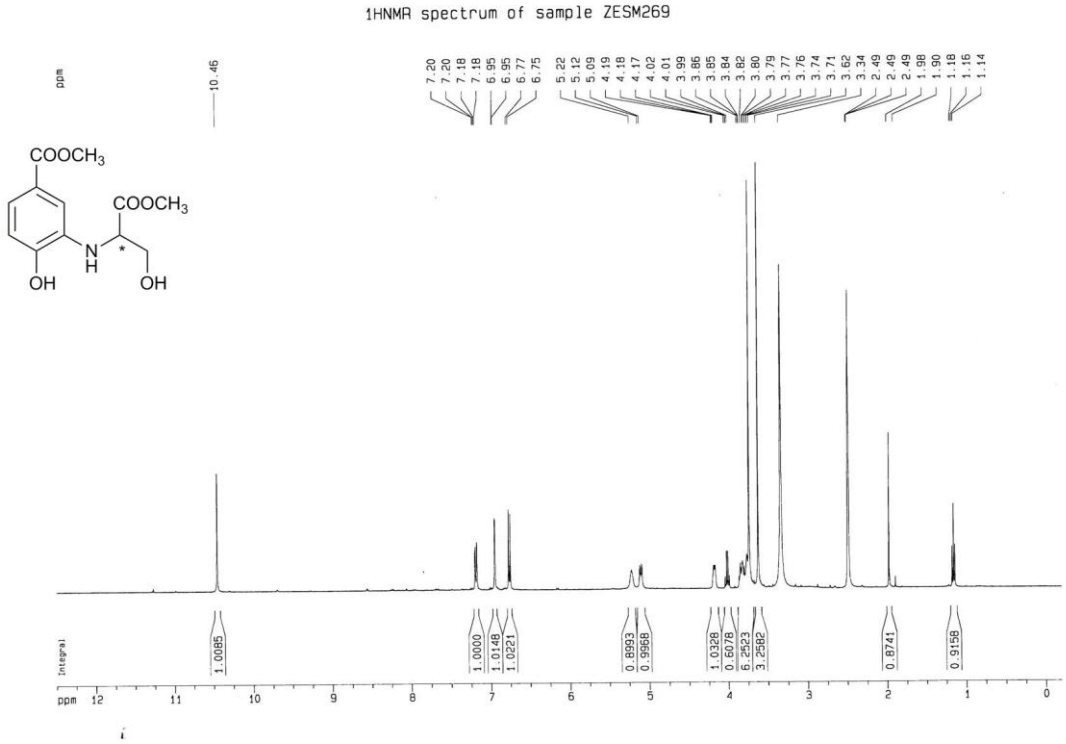
(Table 2 Entry 12, 3l)

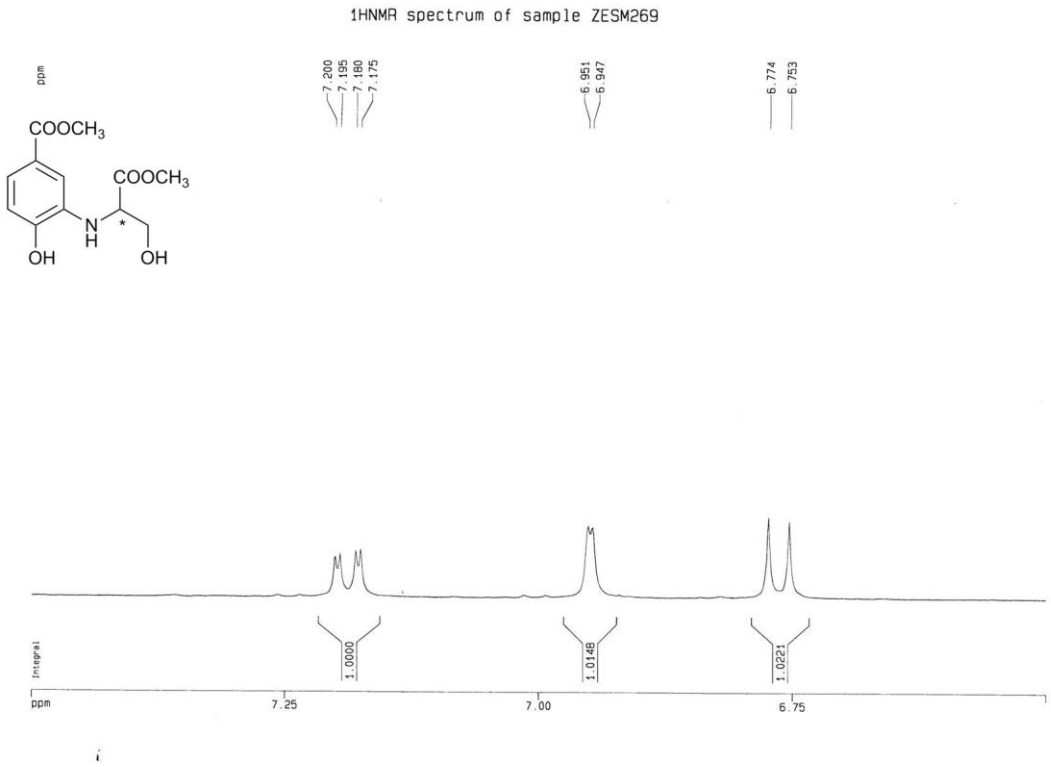




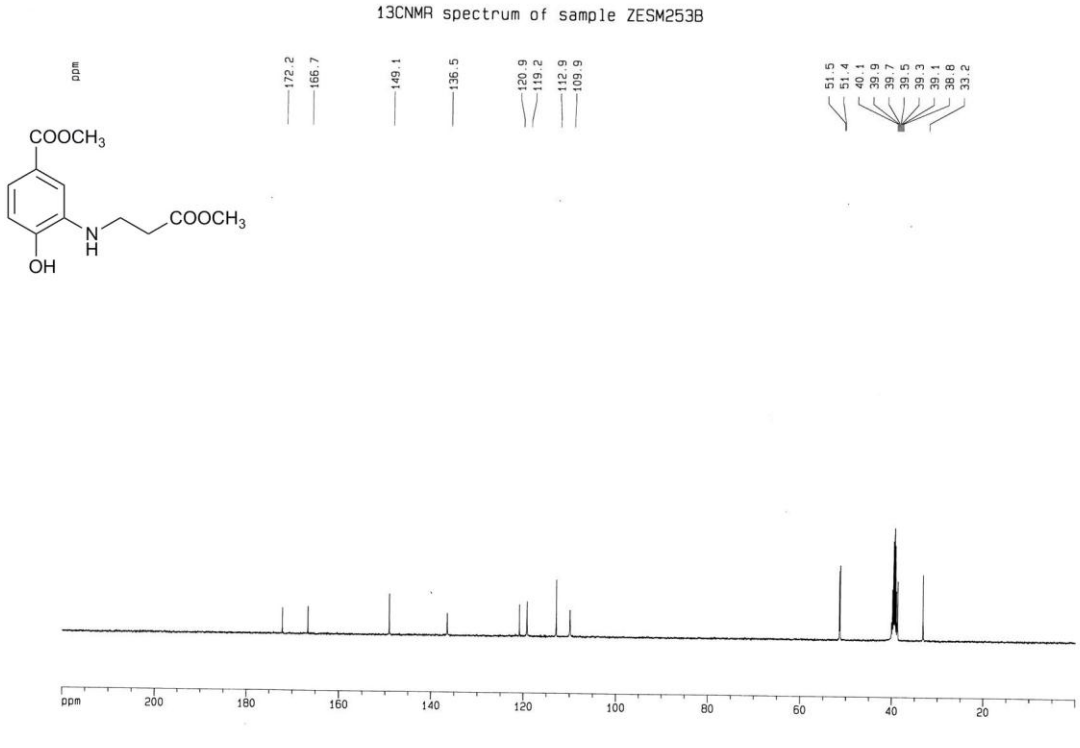
(Table 2 Entry 13, 3m)



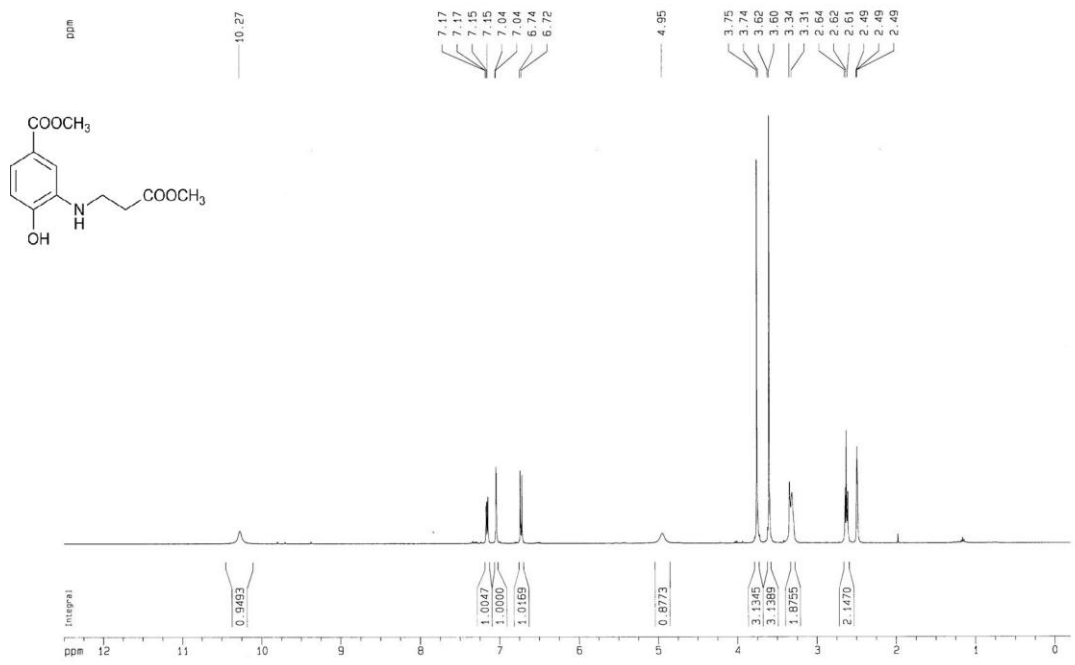




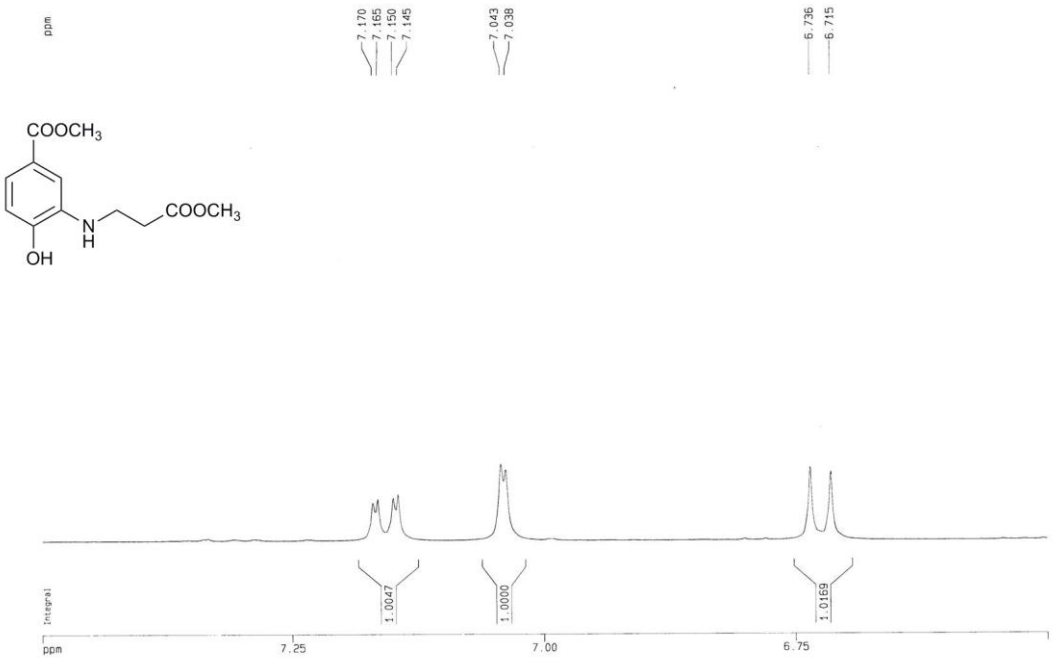
(**Table 3 Entry 2, 5a**)



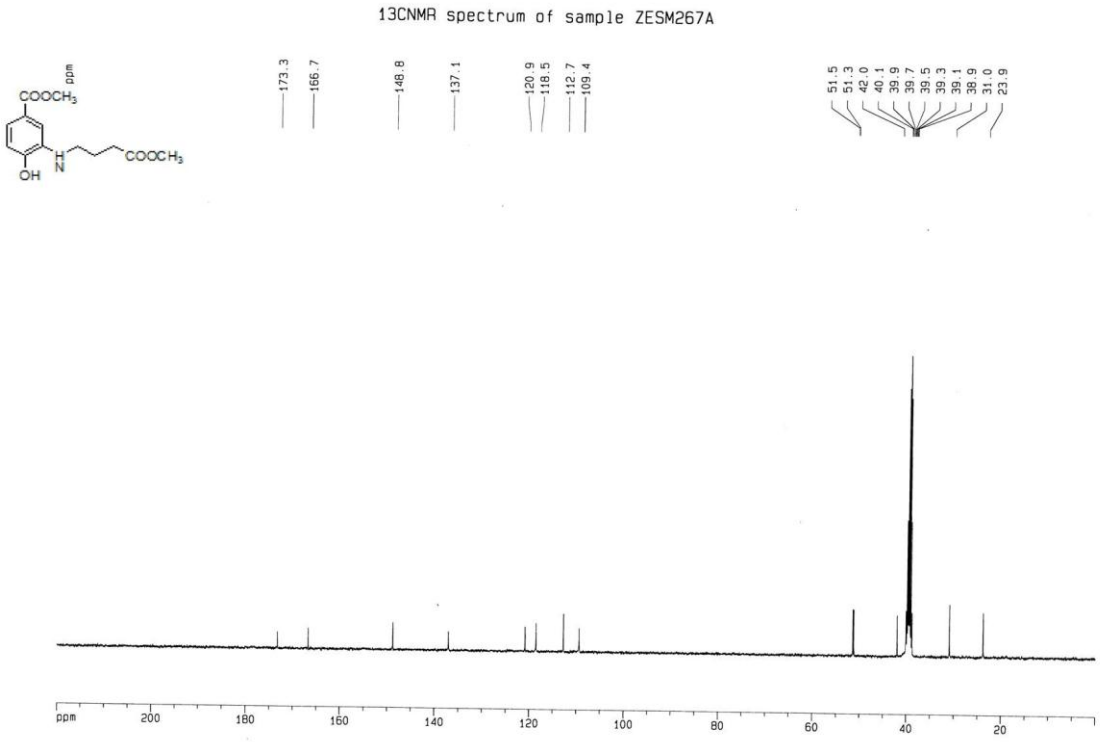
1HNMR spectrum of sample B-EZSM253

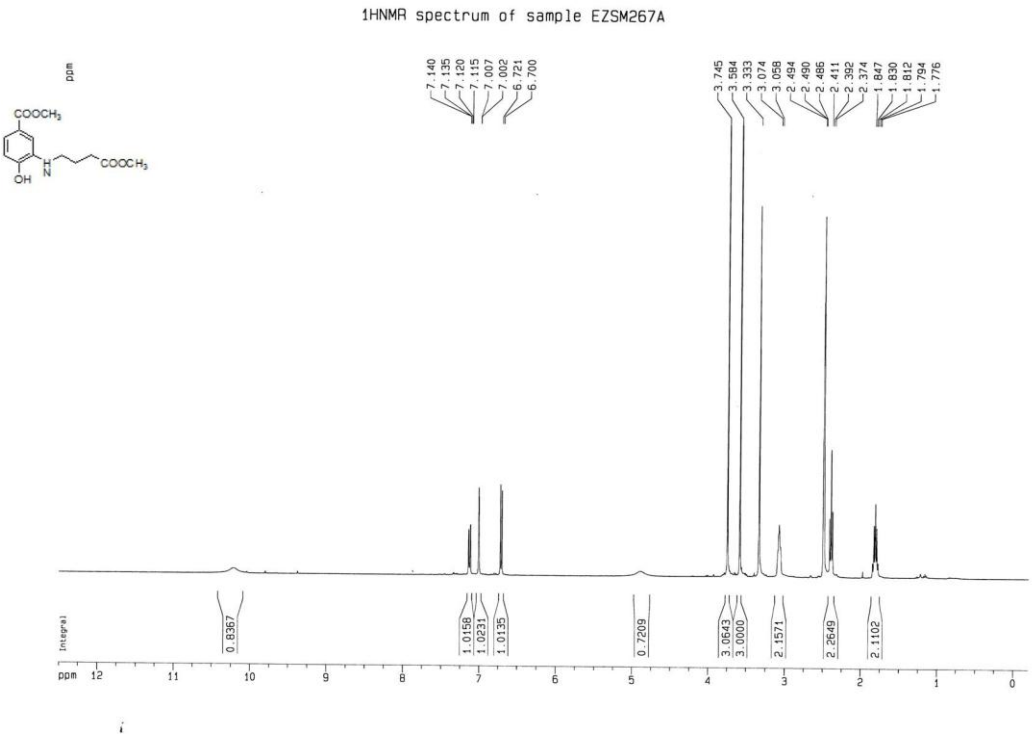


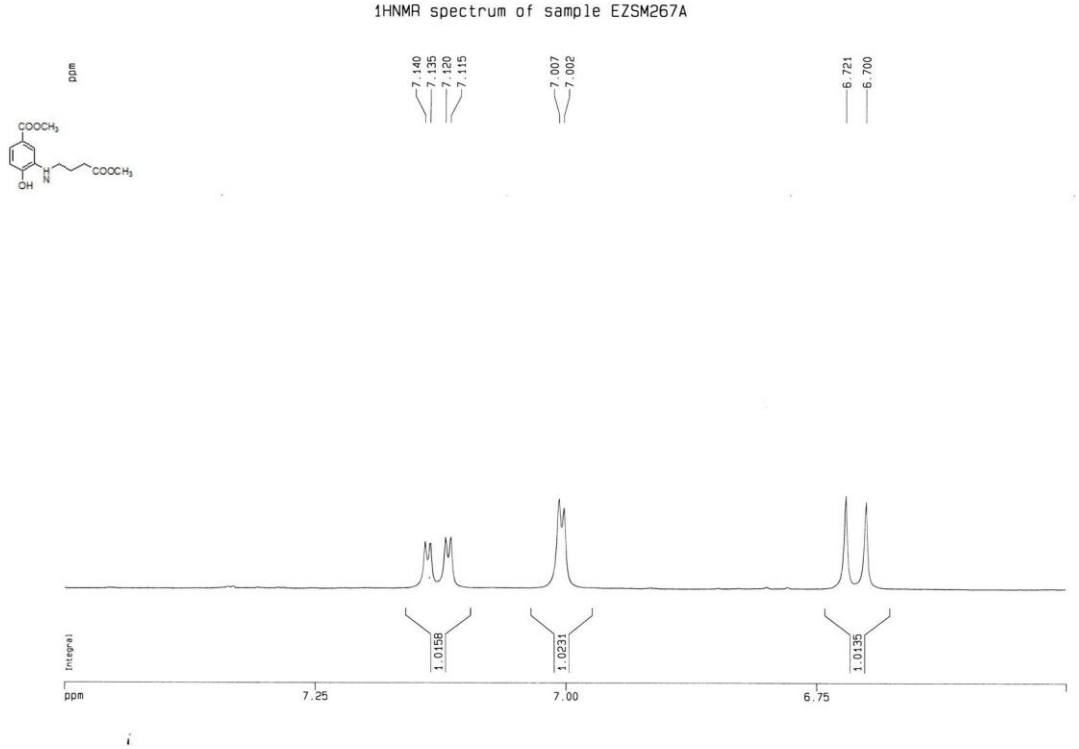
1HNMR spectrum of sample B-EZSM253



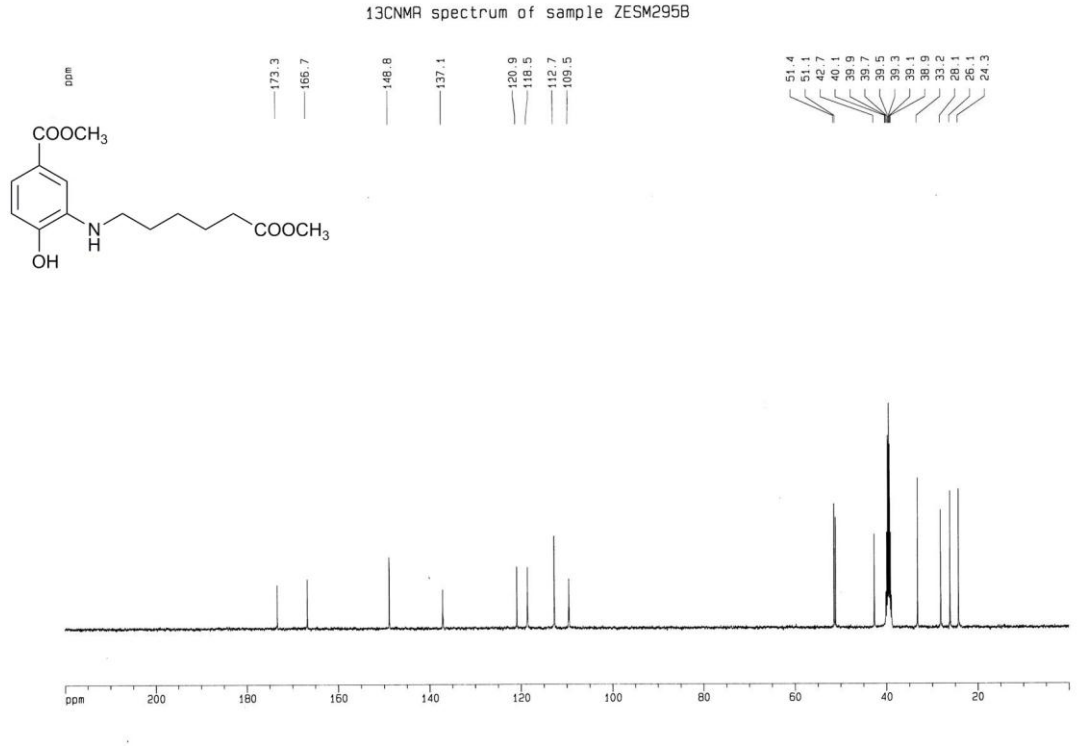
(Table 3 Entry 3, 5b)

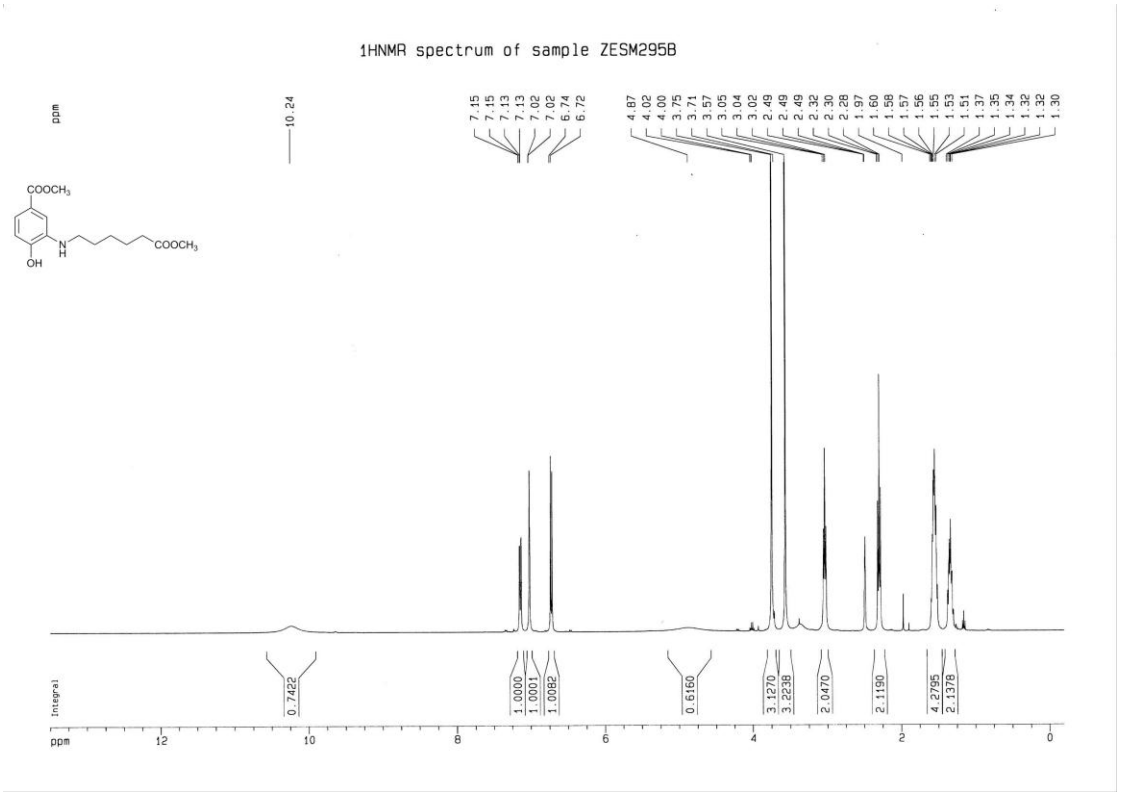


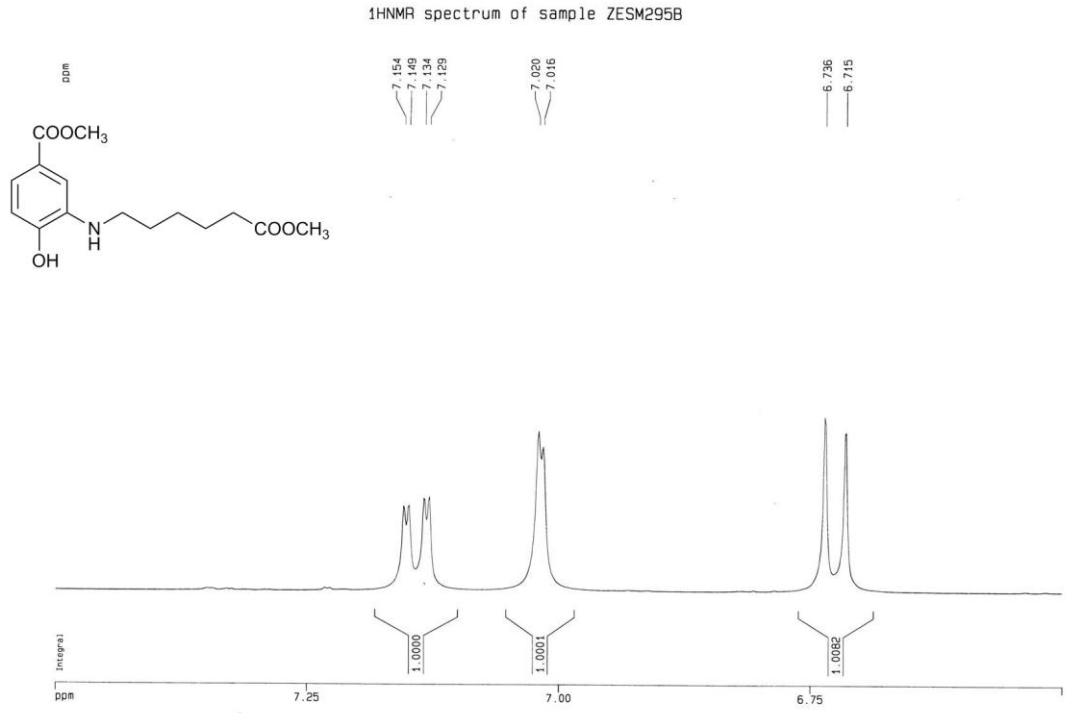




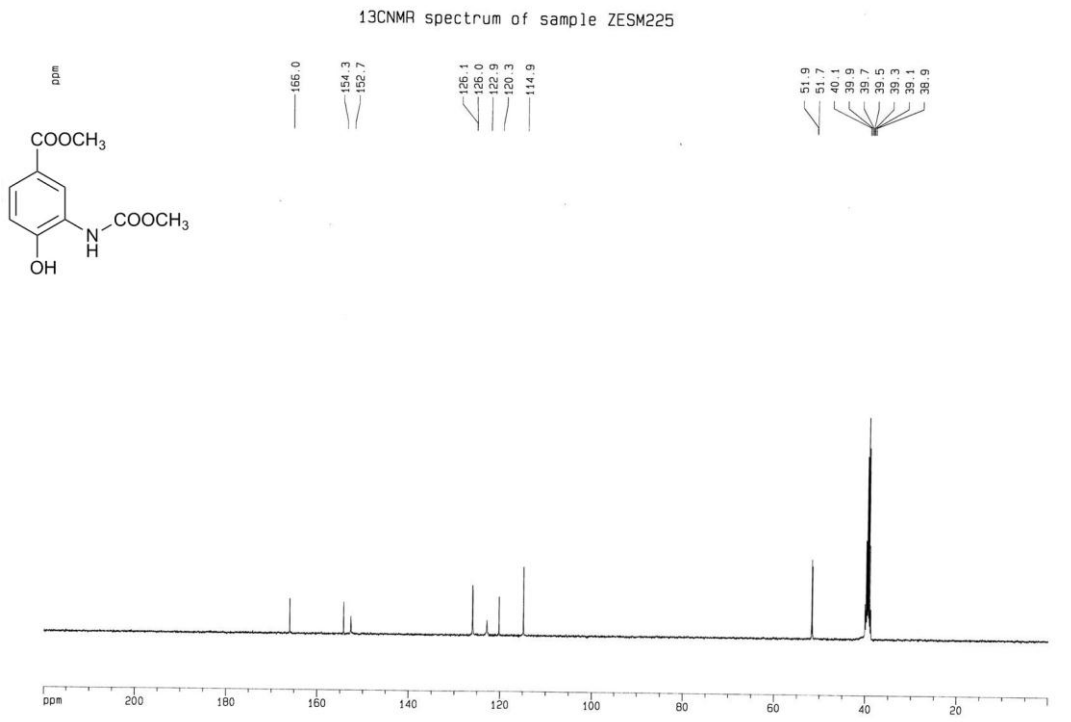
(Table 3 Entry 4, 5c)

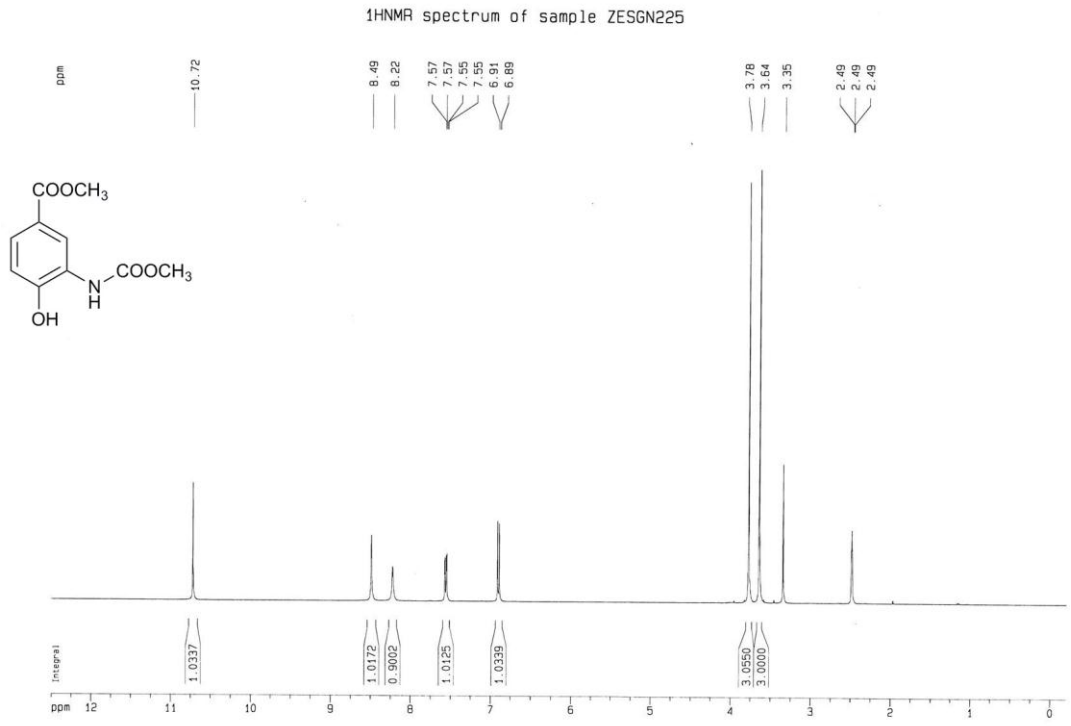


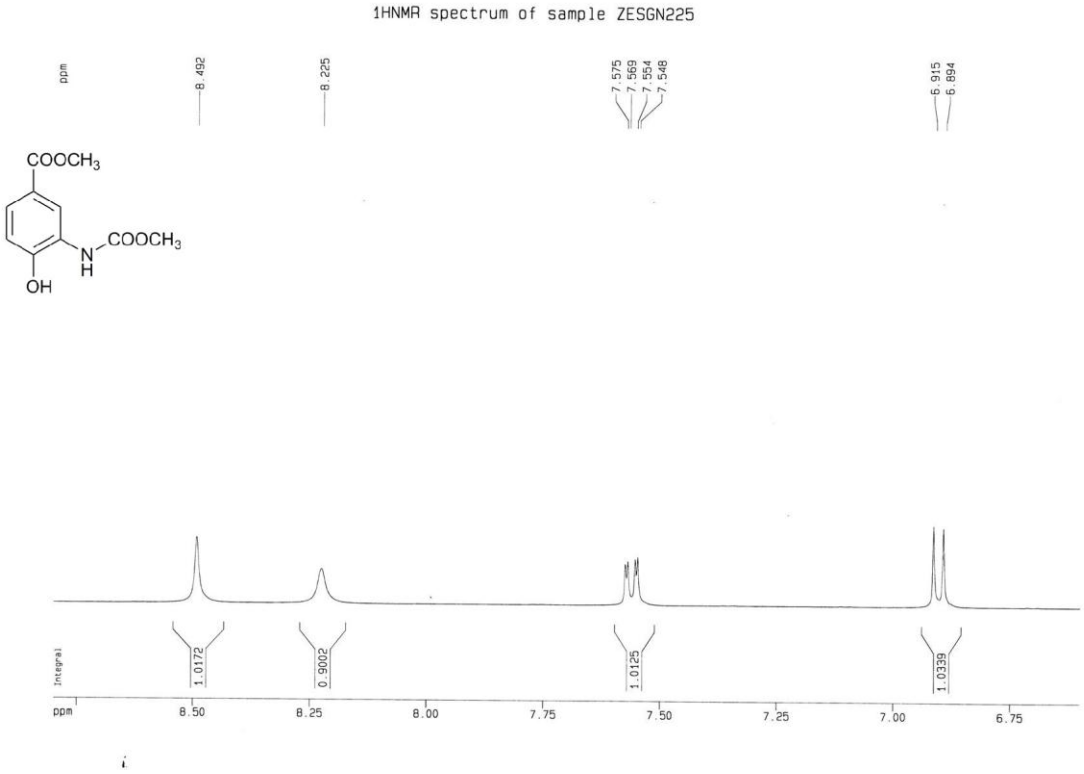

1HNMR spectrum of sample ZESM295B
ppm
10.24
7.15
7.15
7.13
7.13
7.02
7.02
6.74
6.72
4.87
4.02
4.00
3.75
3.71
3.57
3.05
3.04
3.02
2.49
2.49
2.49
2.32
2.30
2.28
1.97
1.60
1.58
1.57
1.56
1.55
1.53
1.51
1.37
1.35
1.34
1.32
1.32
1.30
COOCH3
N
H
COOCH3
OH
Integral
0.7422
1.0000
1.0001
1.0082
0.6160
3.1270
3.2238
2.0470
2.1190
4.2795
2.1378
ppm
12
10
8
6
4
2
0


1HNMR spectrum of sample ZESM295B
ppm
7.154
7.149
7.134
7.129
7.020
7.016
6.736
6.715
COOCH3
N
H
COOCH3
OH
Integral
1.0000
1.0001
1.0082
ppm
7.25
7.00
6.75

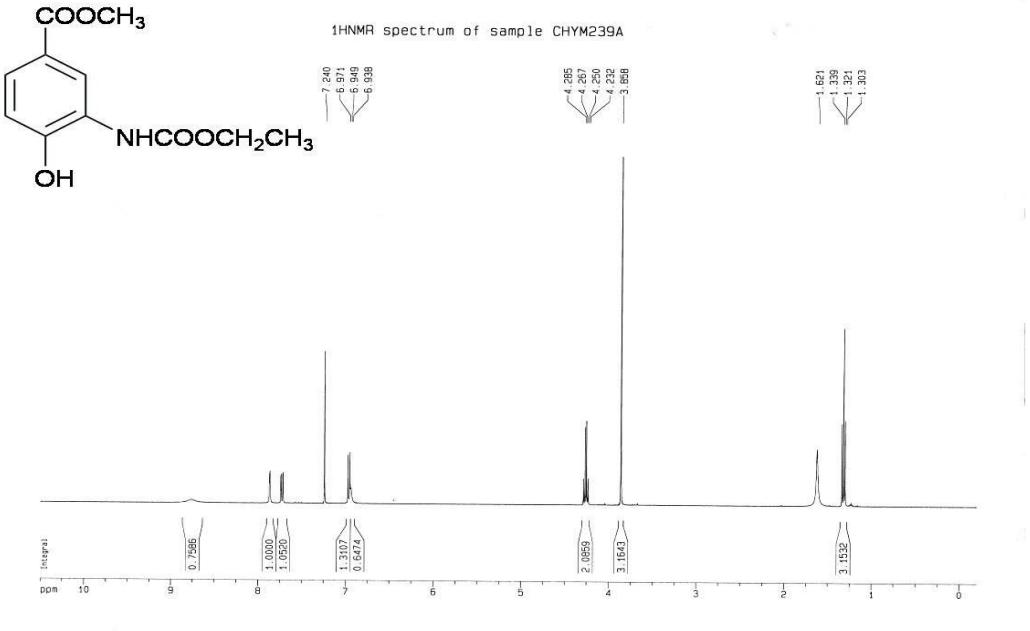
(Table 3 Entry 5, 5d)





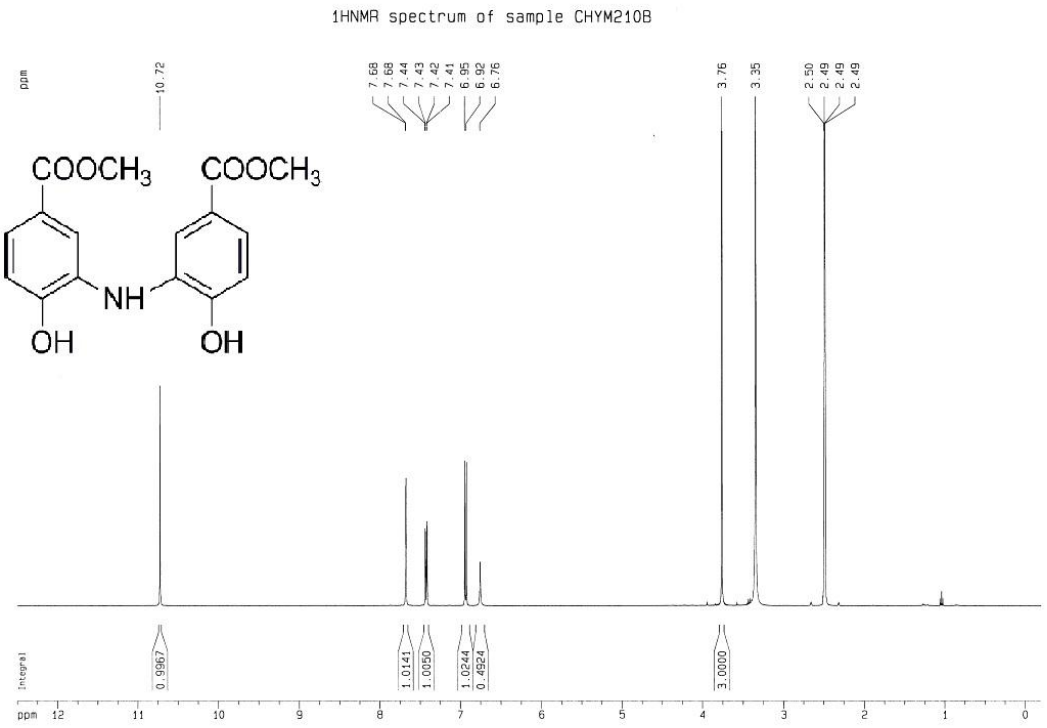


(**Table 3 Entry 6, 5e**)



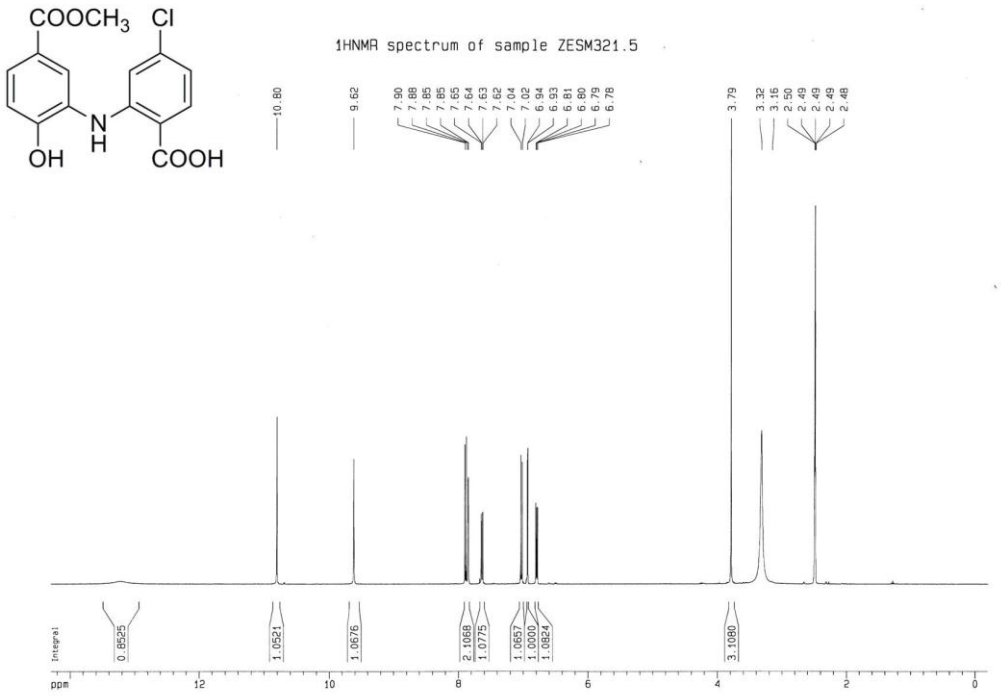
^{1}H NMR (400 MHz, CD_3COCD_3)

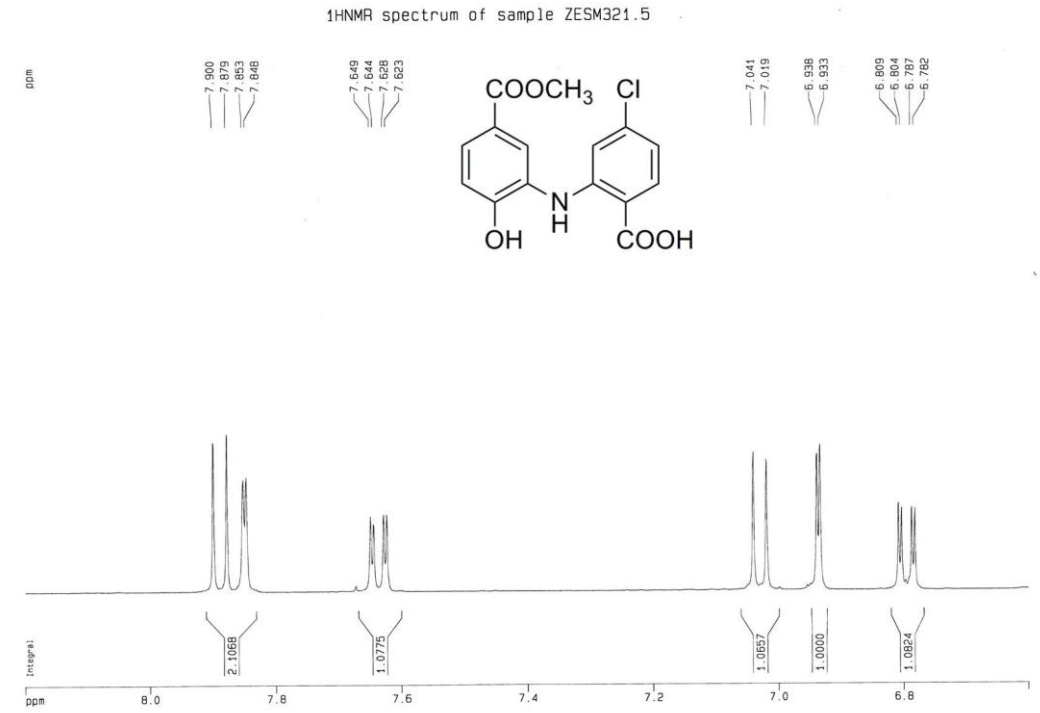
(Table 3 Entry 7, 5f)



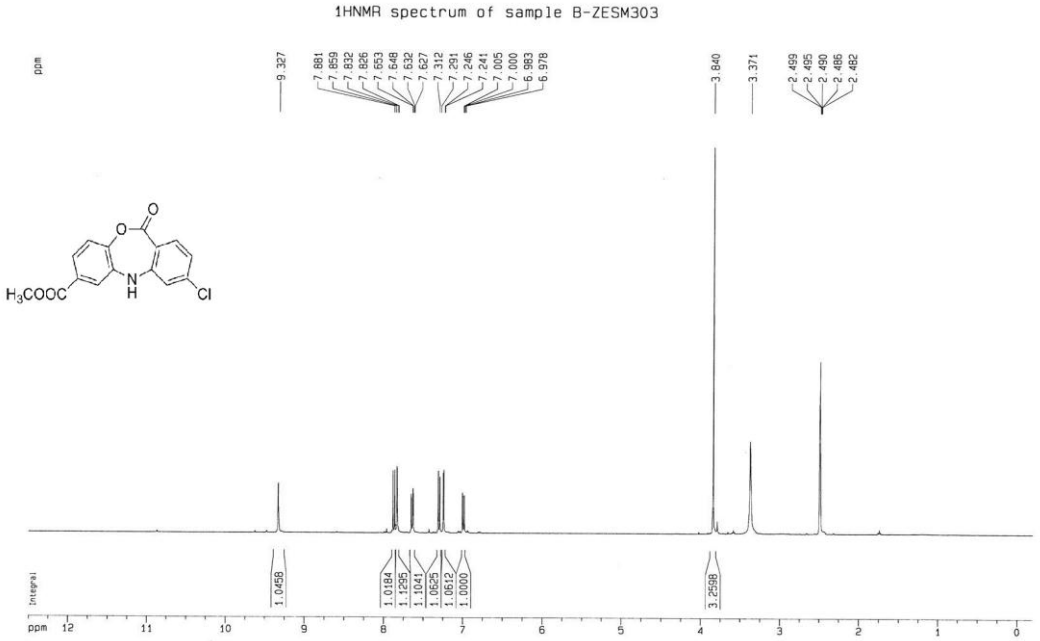
^{1}H NMR (400 MHz, DMSO-d_6）

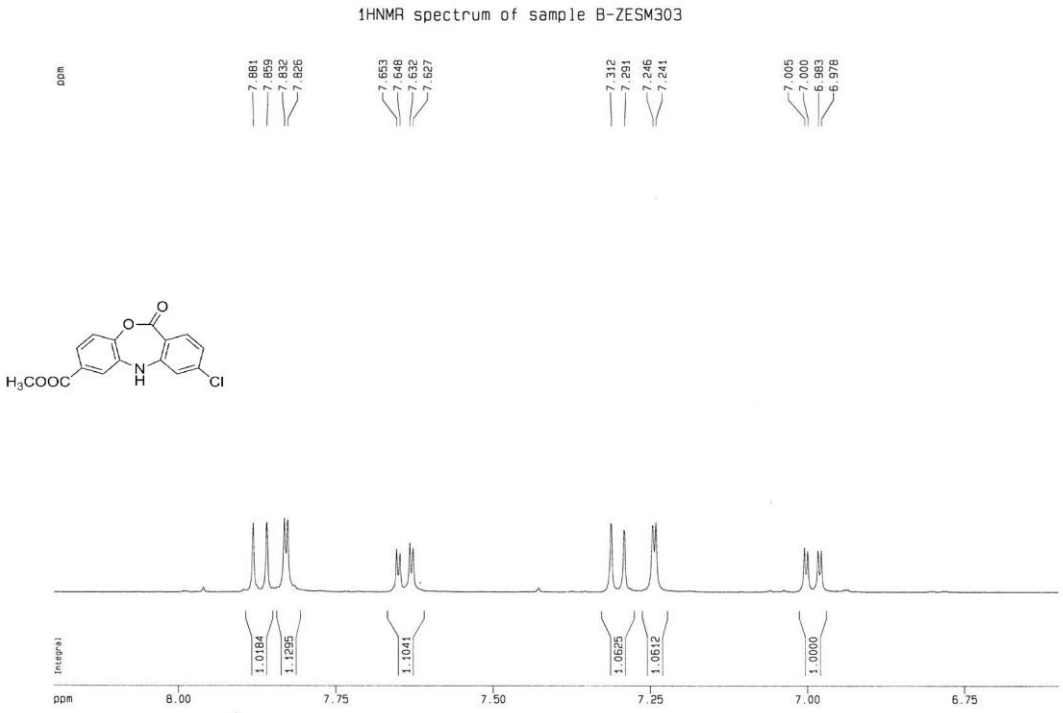
(Table 3 Entry 8, 5g)





Spectra for compound (**6**)




1HNMR spectrum of sample B-ZESM303
ppm
7.881
7.859
7.832
7.826
7.653
7.648
7.632
7.627
7.312
7.291
7.246
7.241
7.005
7.000
6.983
6.978
O
O
N
H
H3COOC
Cl
Integral
1.0184
1.1295
1.1041
1.0625
1.0612
1.0000
ppm
8.00
7.75
7.50
7.25
7.00
6.75

The chiral HPLC analysis for the product of L-serine methyl ester hydrochloride.

2012-7-5 17:43:33 1 / 1

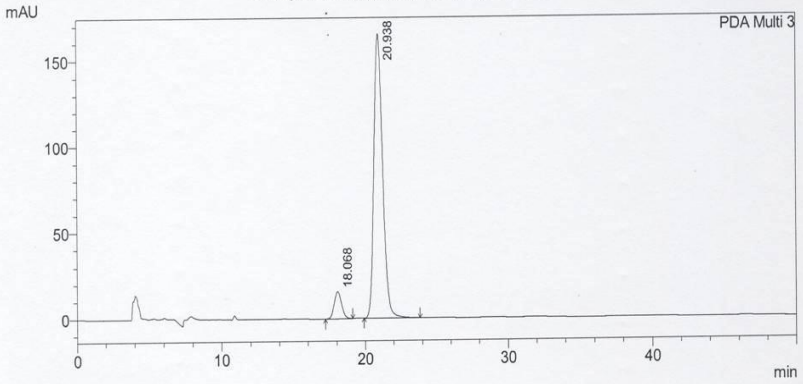
==== solution Analysis Report ====

D:\wwj\20120705\新建文件夹\ZESM269L1.lcd

Acquired by	: Admin
Sample Name	: zesm269
Sample ID	: AS-H 0.8mL/min, 85/15
Tray#	: 1
Vail #	: 19
Injection Volume	: 10 uL
Data File Name	: ZESM269L1.lcd
Method File Name	: wwj-20120514.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 2012-7-5 14:56:39
Data Processed	: 2012-7-5 15:46:42

<Chromatogram>

D:\wwj\20120705\新建文件夹\ZESM269L1.lcd



1 PDA Multi 3/220nm 4nm

PeakTable

PDA Ch3 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.068	570222	15986	7.495	8.811
2	20.938	7037326	165454	92.505	91.189
Total		7607548	181440	100.000	100.000

D:\wwj\20120705\新建文件夹\ZESM269L1.lcd

The chiral HPLC analysis for the product of DL-serine methyl ester hydrochloride.

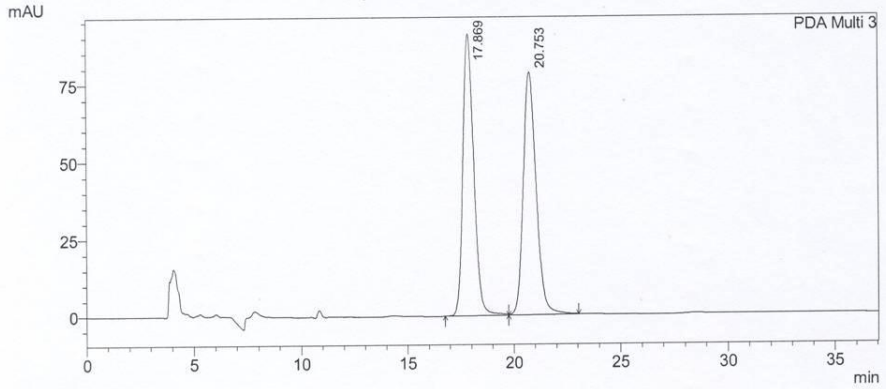
solution Analysis Report ====

D:\wwj\20120705\ZESM269DL.lcd

Acquired by	: Admin
Sample Name	: zesm269-DL
Sample ID	: AS-H 0.8mL/min, 85/15
Tray#	: 1
Vail #	: 19
Injection Volume	: 10 uL
Data File Name	: ZESM269DL.lcd
Method File Name	: wwj-20120514.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 2012-7-5 15:48:35
Data Processed	: 2012-7-5 16:25:41

<Chromatogram>

D:\wwj\20120705\ZESM269DL.lcd



1 PDA Multi 3/220nm 4nm

PeakTable

PDA Ch3 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.869	3273823	91249	49.723	53.755
2	20.753	3310352	78500	50.277	46.245
Total		6584176	169749	100.000	100.000

D:\wwj\20120705\ZESM269DL.lcd