

Synthesis and Anti-Inflammatory Evaluation of a Library of Chiral Derivatives of Xanthones Conjugated with Proteinogenic Amino Acids

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1. ENANTIOMERIC PURITY

The normal-phase mode LC evaluation was carried out in a commercially available CSP Lux® 3 µm Cellulose-2 (150 x 4.6 mm), at room temperature. The mobile phase consisted in a mixture of 0.01% trifluoroacetic acid in n-hexane:ethanol (50:50 *v/v*) at a flow rate of 1 mL/min in isocratic mode. The sample injections (10 µL) were carried out in duplicate, and the diode array detection was at 264 nm. The dead time (*t*₀) was considered to be the front solvent peak and was taken from each run. The stock solutions of all the CDXs were prepared in ethanol at the concentration of 1 mg/mL.

The retention factor (*k*) was calculated using equation S1, where *t_R* is the retention time.

$$k = \frac{[t_R - t_0]}{t_0} \text{ (S1)}$$

The separation factor (*α*) was calculated using equation S2.

$$\alpha = \frac{K_2}{K_1} \text{ (S2)}$$

The resolution factor (*R_s*) was calculated using equation S3, where *t_{R1}* and *t_{R2}* are the retention times of the first and second eluted enantiomers, respectively, and 1/2*W*₁ and 1/2*W*₂ are the corresponding peak width measured on half height.

$$R_s = 1.18 * \frac{[t_{R2} - t_{R1}]}{[\frac{1}{2}W_1 + \frac{1}{2}W_2]} \text{ (S3)}$$

The formula used for the calculation of the percentage of % e.r. was the following; where *E*₁ and *E*₂ are the first and the second and eluted enantiomer, respectively.

$$\% e.r. = \frac{[E_1]}{[E_1] + [E_2]} * 100 \text{ (S4)}$$

Before the enantiomeric purity evaluation of the synthesised CDXs, it was necessary to determine the chromatographic parameters of each enantiomeric mixture. For that, a stock solutions of enantiomeric mixtures of CDX in ethanol were prepared with equal aliquots of each enantiomer and analyzed at room temperature. The obtained chromatographic parameters of CDX of amino esters and peak purity are displayed in **Table S1**.

Table S1: cLC data of the enantioseparation of the of amino esters of CDXs in enantiomeric mixtures.

| Enantiomeric Mixtures | RT (min) D | RT (min) L | Peak Purity D | Peak Purity L | <i>k</i> ₁ D | <i>k</i> ₂ L | <i>R_s</i> | <i>α</i> |
|-----------------------|------------|------------|---------------|---------------|-------------------------|-------------------------|----------------------|----------|
| X1AE_Ala | 9.34 | 6.40 | 1.0000 | 1.0000 | 3.94 | 2.39 | 6.34 | 1.65 |
| X1AE_Leu | 9.22 | 7.14 | 1.0000 | 1.0000 | 4.15 | 2.99 | 4.24 | 1.39 |
| X1AE_Prol | 27.09 | 17.76 | 0.9995 | 1.0000 | 13.34 | 8.40 | 4.59 | 1.59 |
| X1AE_Val | 12.10 | 5.32 | 1.0000 | 1.0000 | 5.40 | 1.96 | 12.45 | 2.76 |

| | | | | | | | | |
|-------------|-------|-------|--------|--------|-------|-------|------|------|
| X1AE_PG | 16.00 | 12.99 | 1.0000 | 1.0000 | 7.47 | 5.87 | 3.62 | 1.27 |
| X1AE_PA | 23.84 | 13.16 | 1.0000 | 1.0000 | 12.32 | 6.35 | 9.86 | 1.94 |
| X1AE_Tryp | 17.12 | 12.57 | 0.9997 | 1.0000 | 8.56 | 6.03 | 4.65 | 1.42 |
| X1AE_T | 12.27 | 8.44 | 0.9999 | 1.0000 | 5.49 | 3.47 | 5.48 | 1.59 |
| X1AE_Ser | 19.71 | 17.68 | 1.0000 | 1.0000 | 10.01 | 8.88 | 1.87 | 1.13 |
| X1AE_AspA. | 30.34 | 24.31 | 0.9999 | 0.9999 | 15.95 | 12.58 | 3.87 | 1.27 |
| X1AE_GlutA. | 21.54 | 19.22 | 0.9998 | 0.9998 | 11.03 | 9.74 | 1.96 | 1.13 |
| X1AE_Threo | 12.34 | 8.18 | 1.0000 | 1.0000 | 5.89 | 3.57 | 6.25 | 1.65 |
| X1AE_Cys | 15.28 | 12.64 | 1.0000 | 0.9998 | 7.08 | 5.69 | 3.36 | 1.25 |
| X1AE_Met | 15.92 | 12.69 | 1.0000 | 1.0000 | 7.89 | 6.09 | 3.91 | 1.30 |

RT: Retention Time; k: Retention Factor; Alfa (α): Enantioselectivity; Rs: Resolution.

The same evaluation was performed with amino acids of the CDXs of , that are presented in **Table S2**.

Table S2: cLC data of the enantioseparation of the amino acids of CDXs in enantiomeric mixtures.

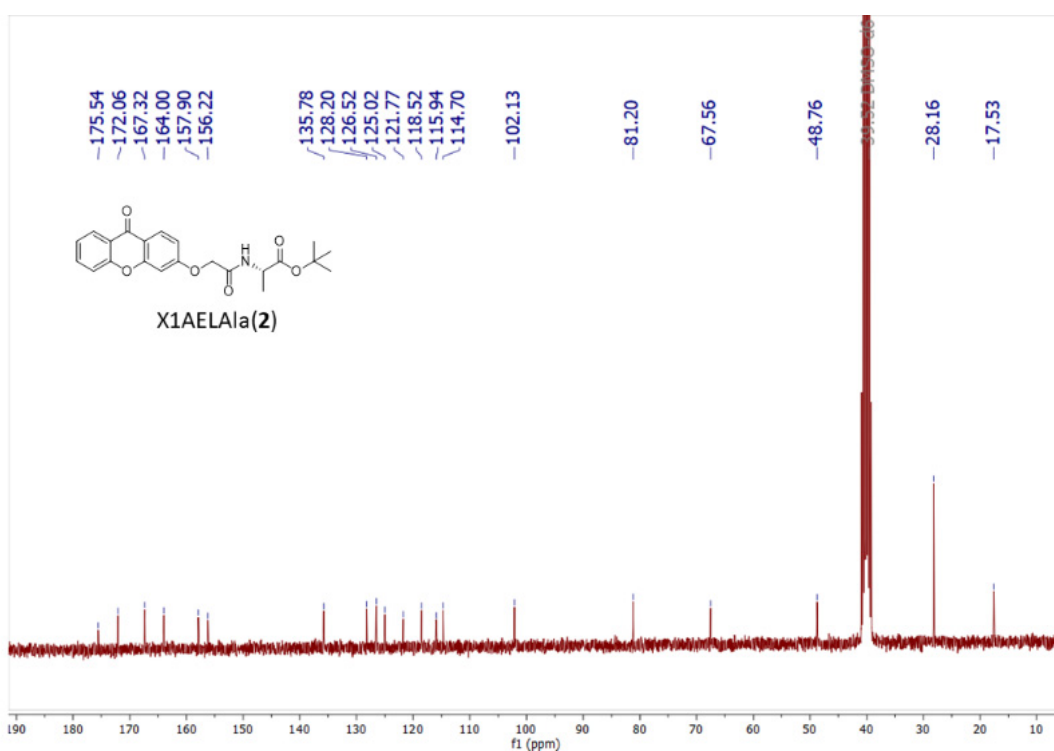
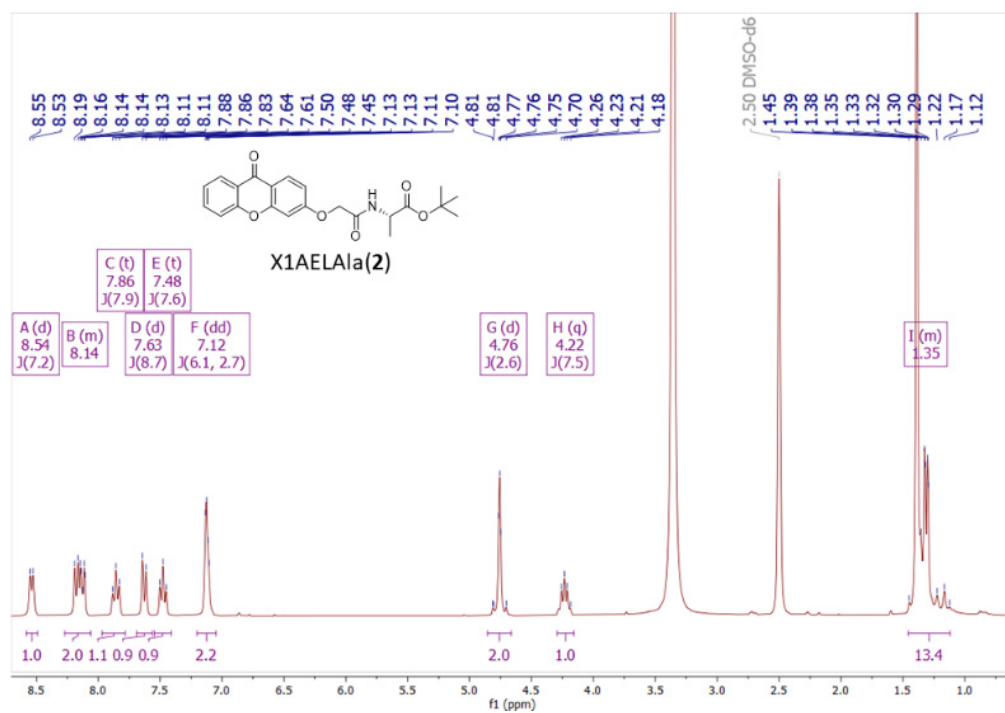
| Enantiomeric Mixtures | RT (min) D | RT (min) L | Peak Purity D | Peak Purity L | K D | K L | Rs | α |
|-----------------------|---------------|---------------|------------------|------------------|--------|--------|------|----------|
| X1AA_Ala | 6.68 | 5.46 | 1.0000 | 1.0000 | 2.73 | 2.05 | 2.88 | 1.34 |
| X1AA_Leu | 7.63 | 5.57 | 1.0000 | 1.0000 | 3.26 | 2.11 | 4.19 | 1.54 |
| X1AA_Prol | 11.27 | 9.00 | 1.0000 | 1.0000 | 5.30 | 4.03 | 1.72 | 1.31 |
| X1AA_Val | 5.73 | 4.77 | 1.0000 | 1.0000 | 2.20 | 1.67 | 2.40 | 1.32 |
| X1AA_PG | 8.83 | 7.68 | 1.0000 | 1.0000 | 3.67 | 3.06 | 1.93 | 1.20 |
| X1AA_PA | 8.83 | 7.16 | 1.0000 | 0.9999 | 3.93 | 3.00 | 3.00 | 1.31 |
| X1AA_Tryp | 11.80 | 8.98 | 1.0000 | 1.0000 | 5.59 | 4.02 | 3.57 | 1.39 |
| X1AA_Tyr | 8.40 | 6.77 | 1.0000 | 1.0000 | 3.69 | 2.78 | 2.60 | 1.33 |
| X1AA_Ser | 10.48 | 7.76 | 0.9999 | 0.9999 | 4.85 | 3.34 | 3.75 | 1.46 |

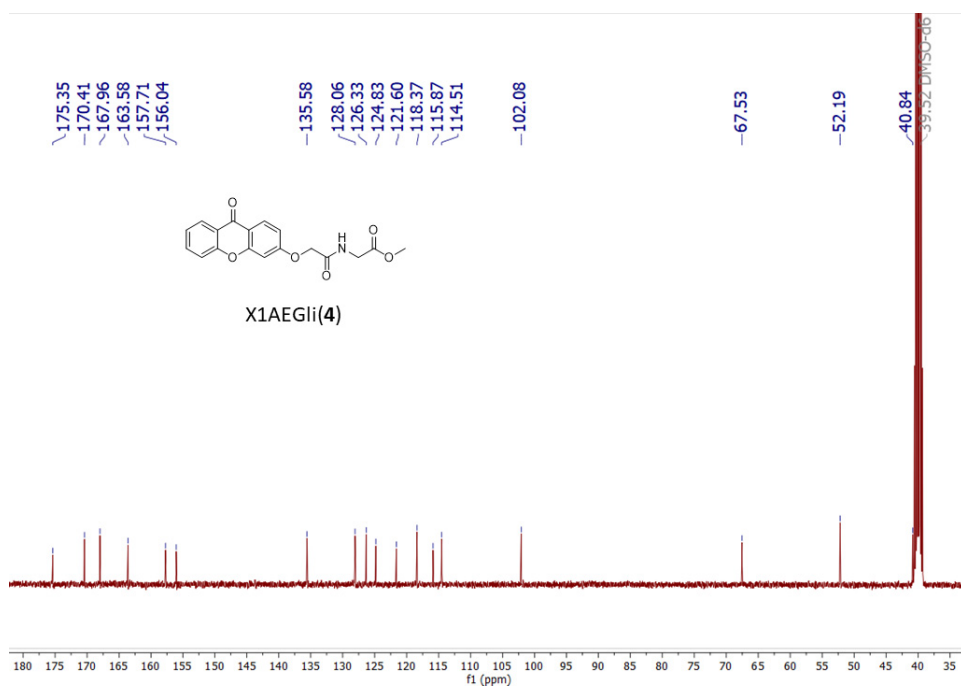
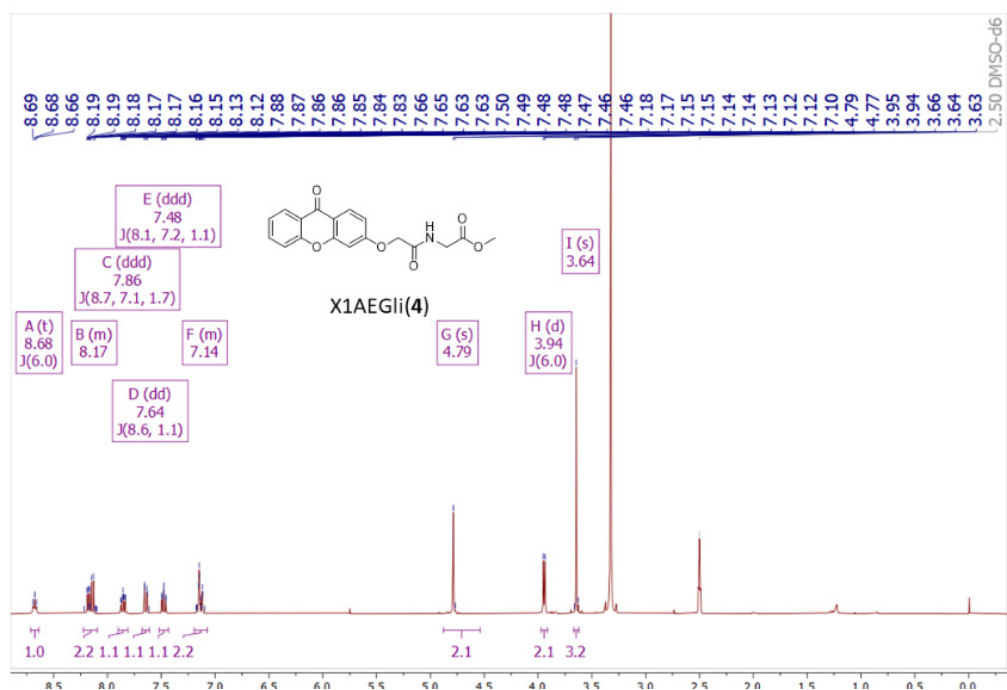
| | | | | | | | | |
|------------|-------|------|--------|--------|------|------|------|------|
| X1AA_AspA | 7.20 | 6.56 | 0.9998 | 1.0000 | 3.02 | 2.66 | 1.10 | 1.13 |
| X1AA_GlutA | 6.78 | 5.44 | 1.0000 | 1.0000 | 2.59 | 1.88 | 2.43 | 1.38 |
| X1AA_Threo | 10.63 | 5.59 | 1.0000 | 1.0000 | 4.94 | 2.12 | 6.42 | 2.33 |
| X1AA_Met | 8.20 | 6.75 | 1.0000 | 1.0000 | 3.58 | 2.77 | 2.78 | 1.30 |

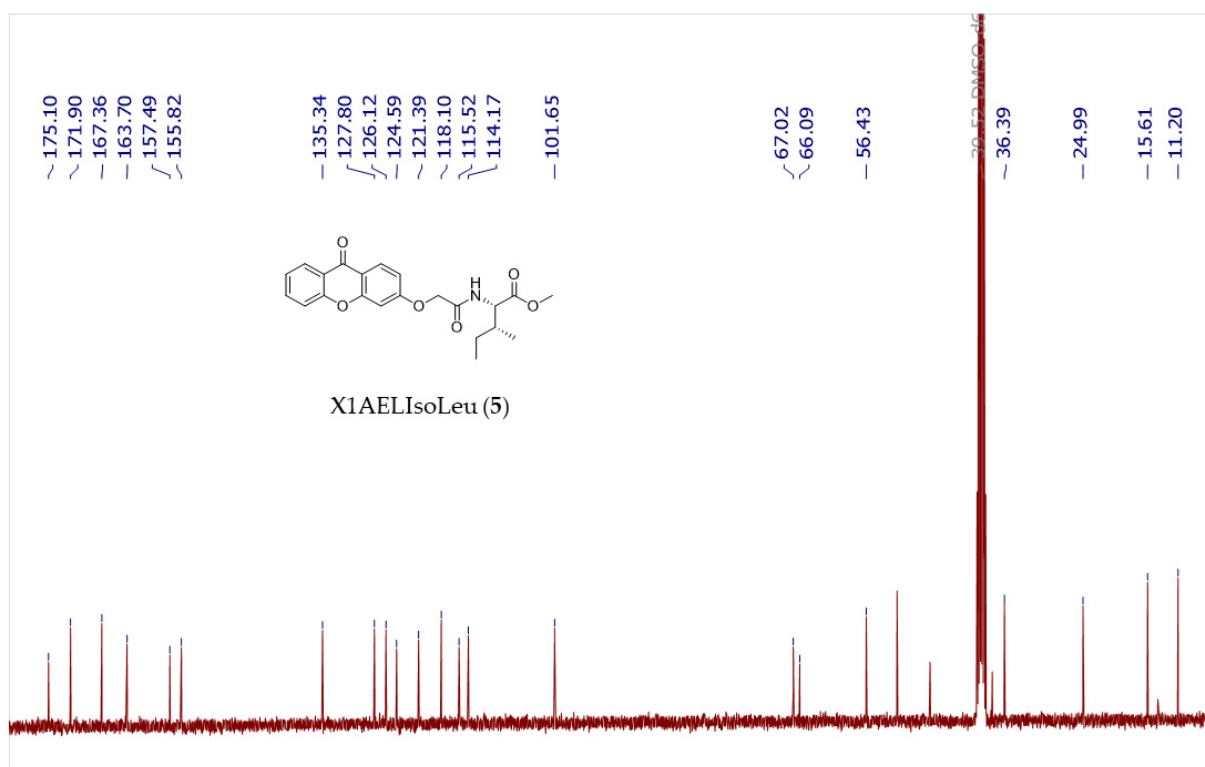
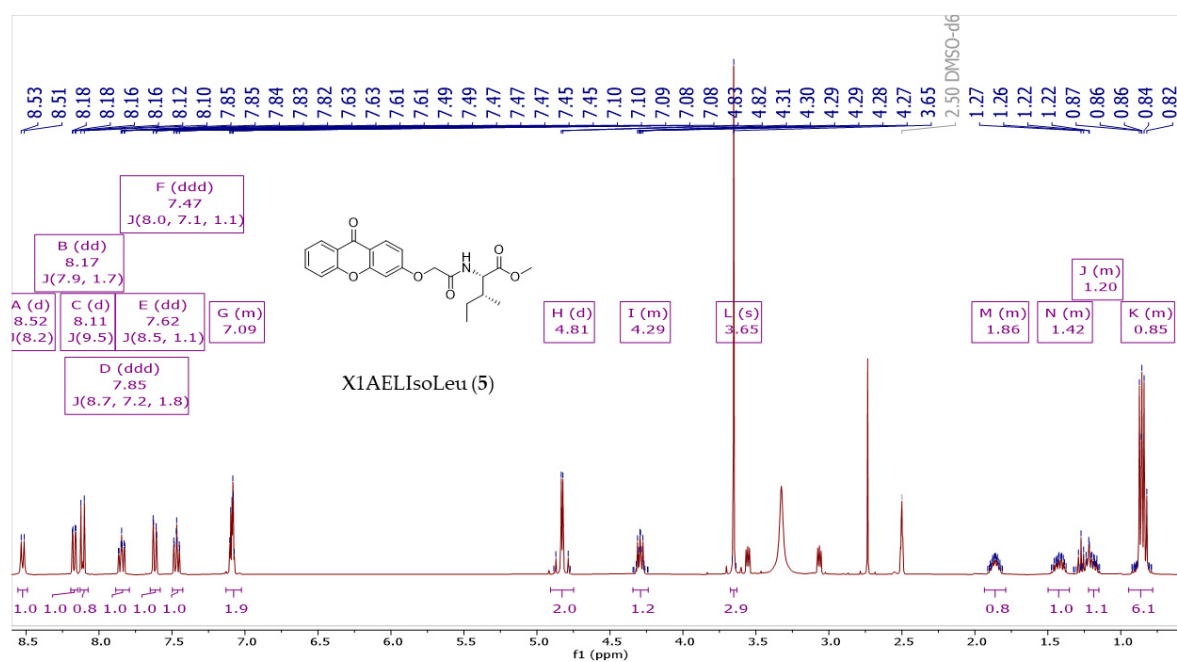
RT: Retention Time; K: Retention Factor; Alfa (α): Enantioselectivity; Rs: Resolution.

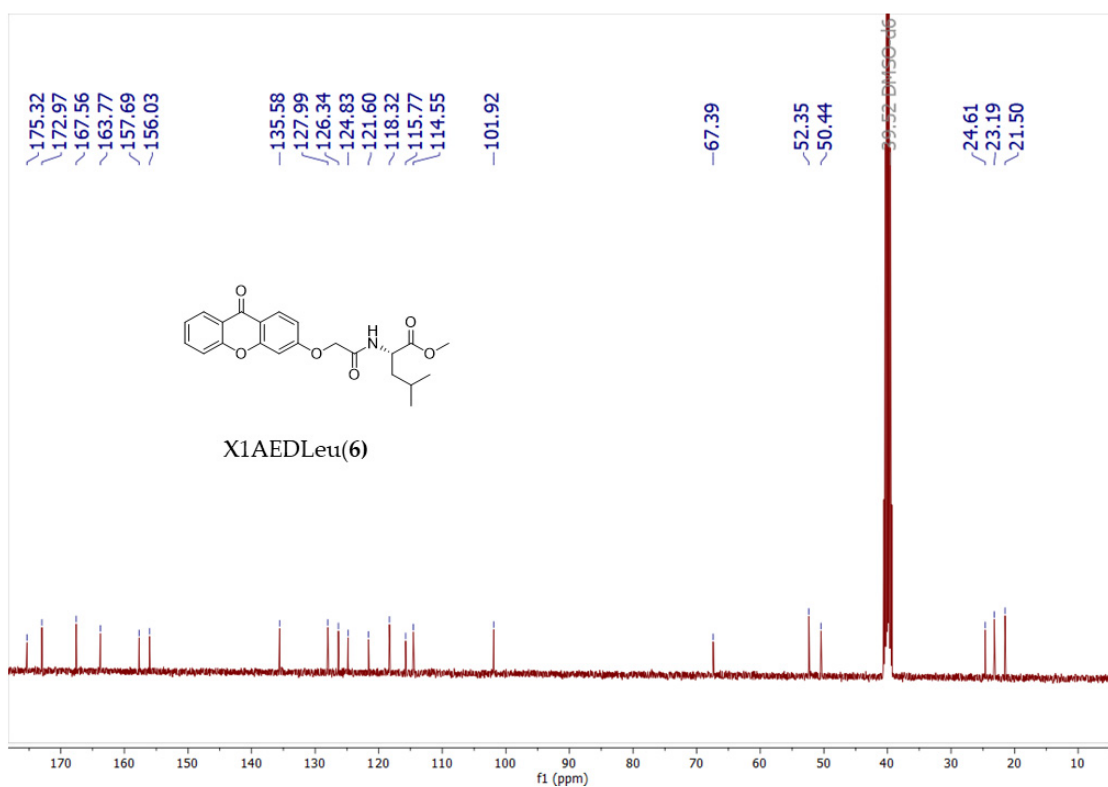
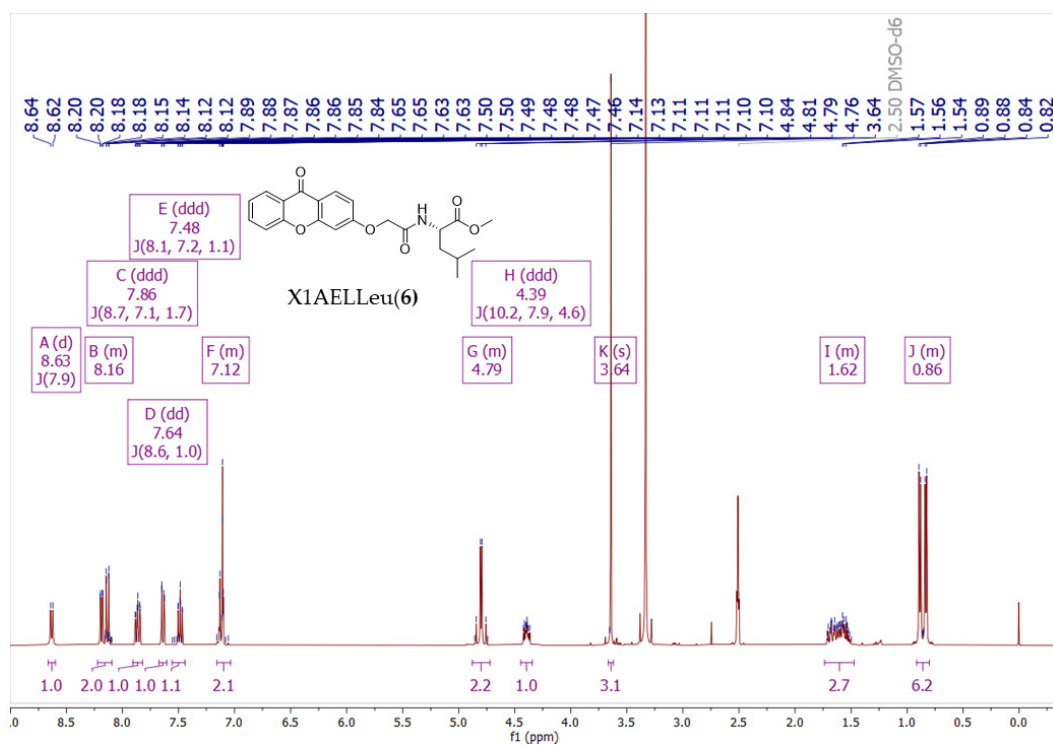
¹H and ¹³C NMR spectra of CDXs

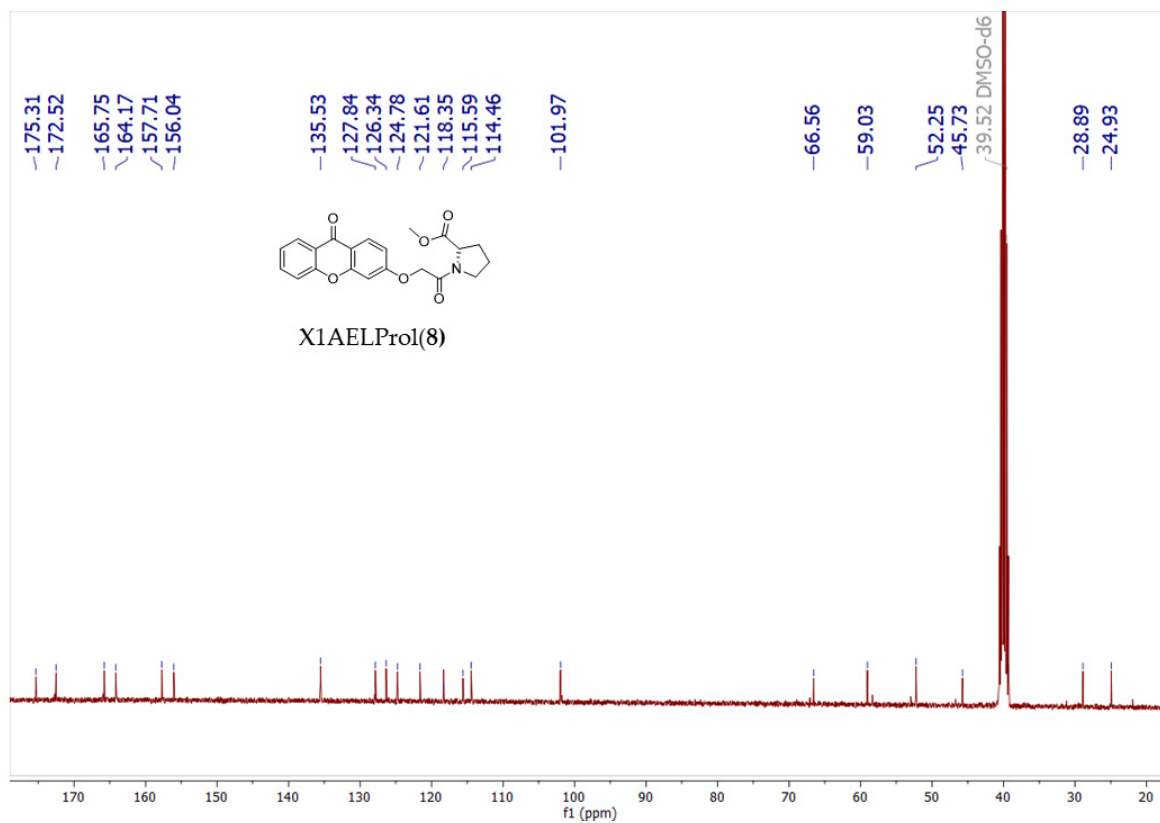
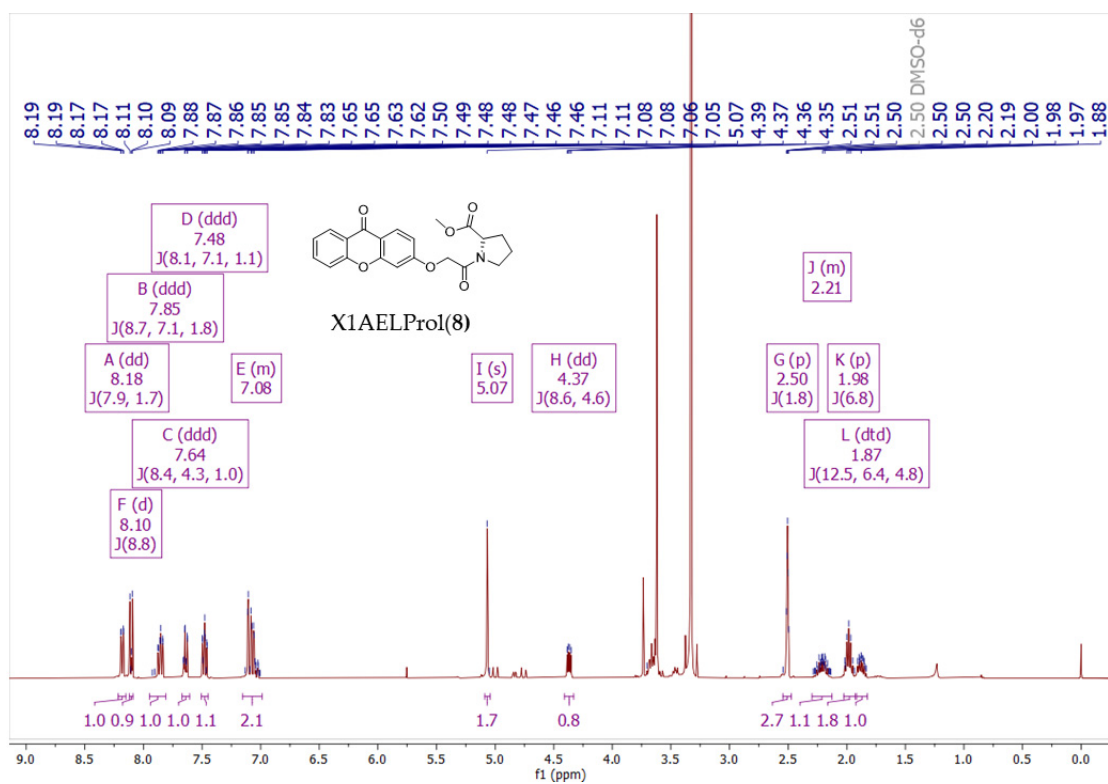
As the spectra of the enantiomers are identical, the spectra of only one of each enantiomeric pair was selected (Figure S1):

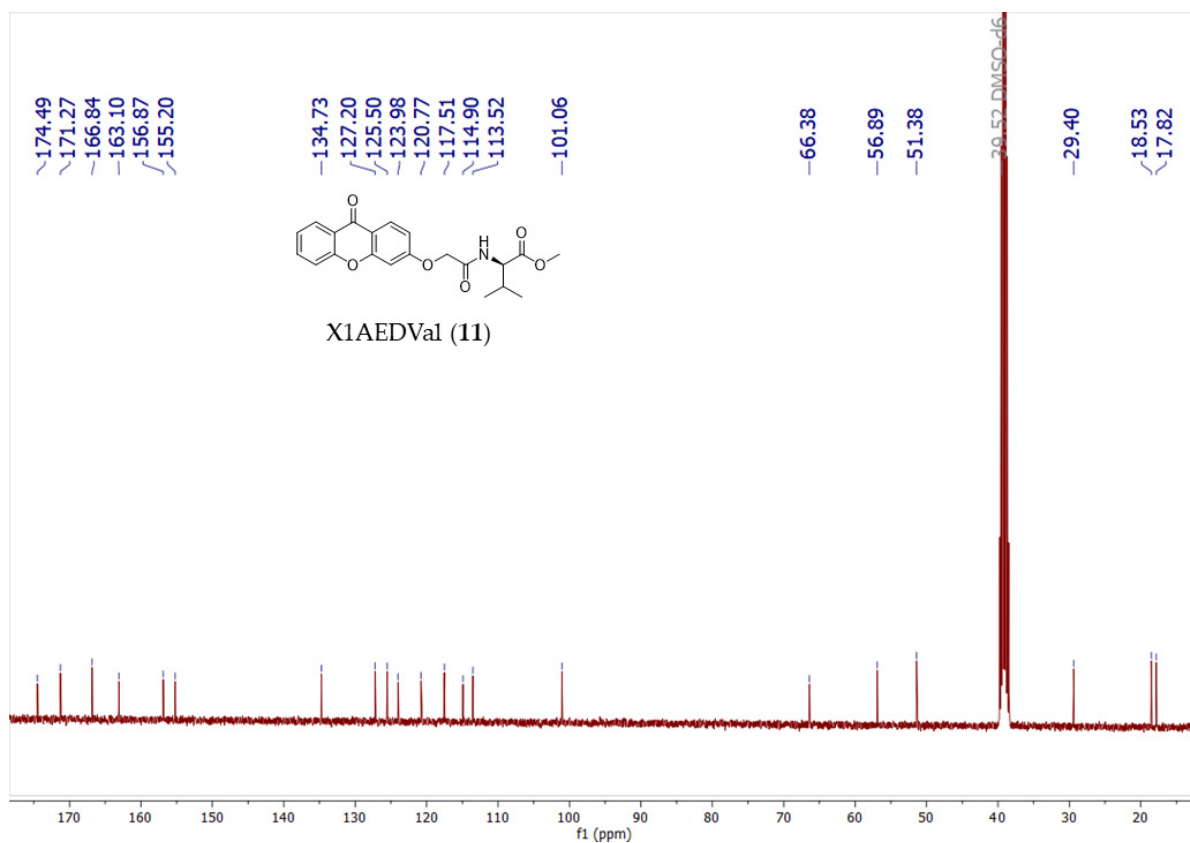
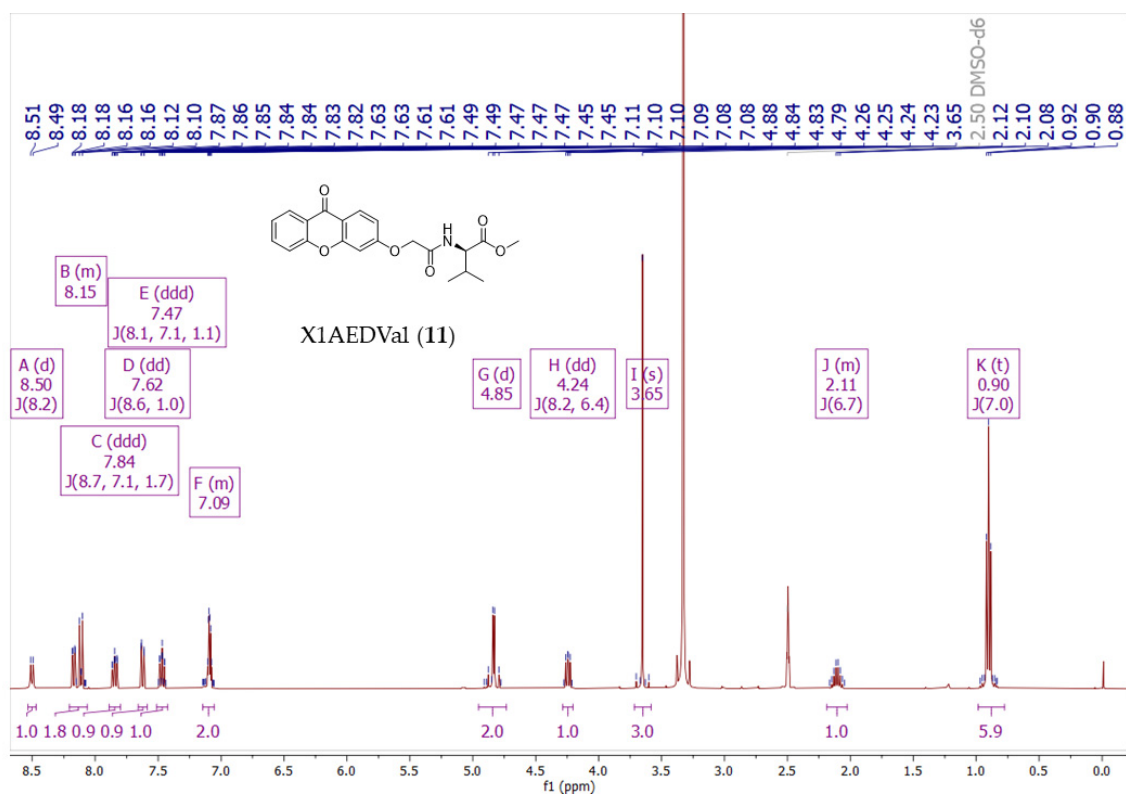


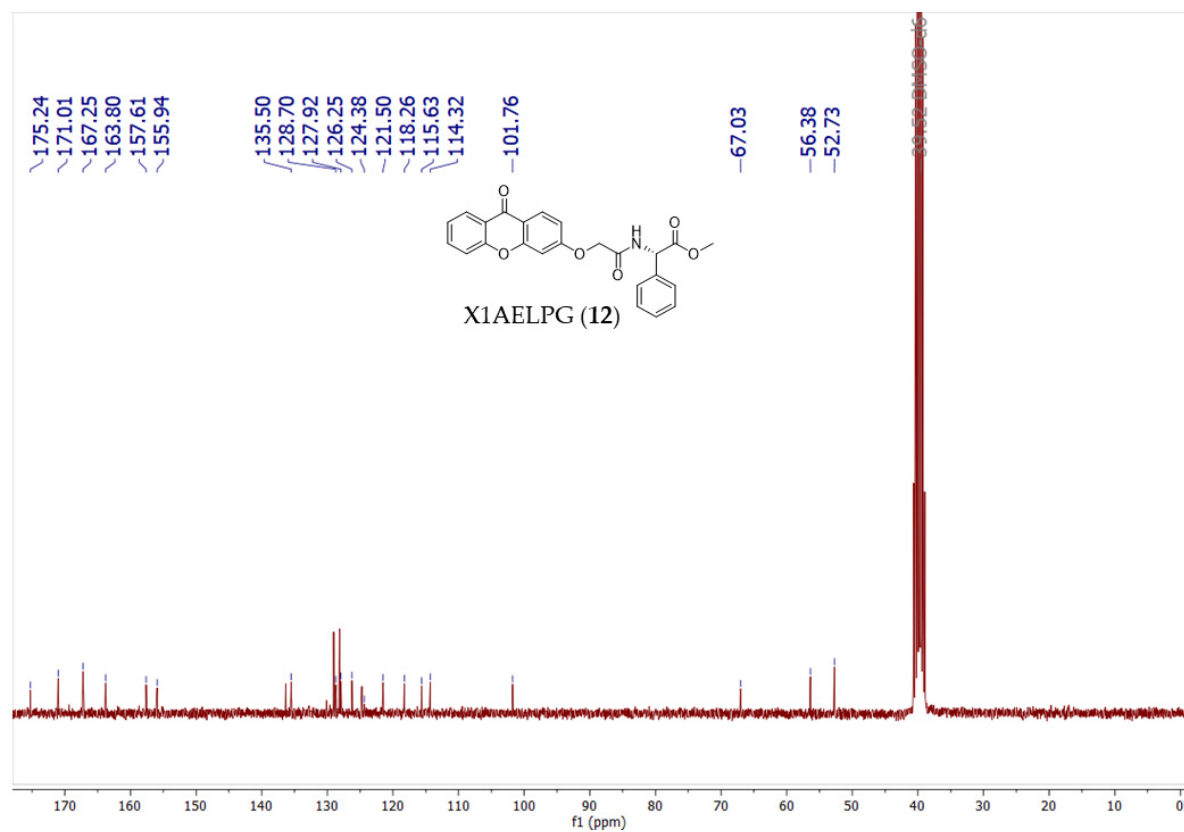
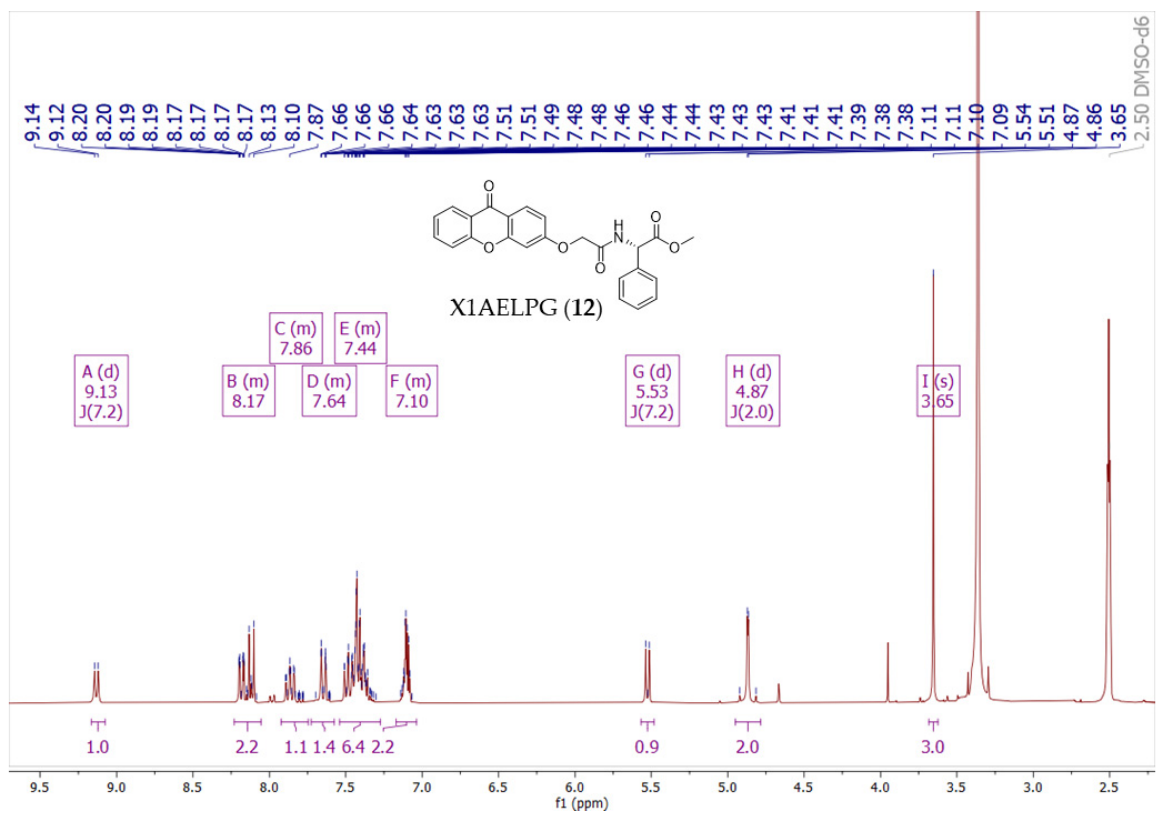


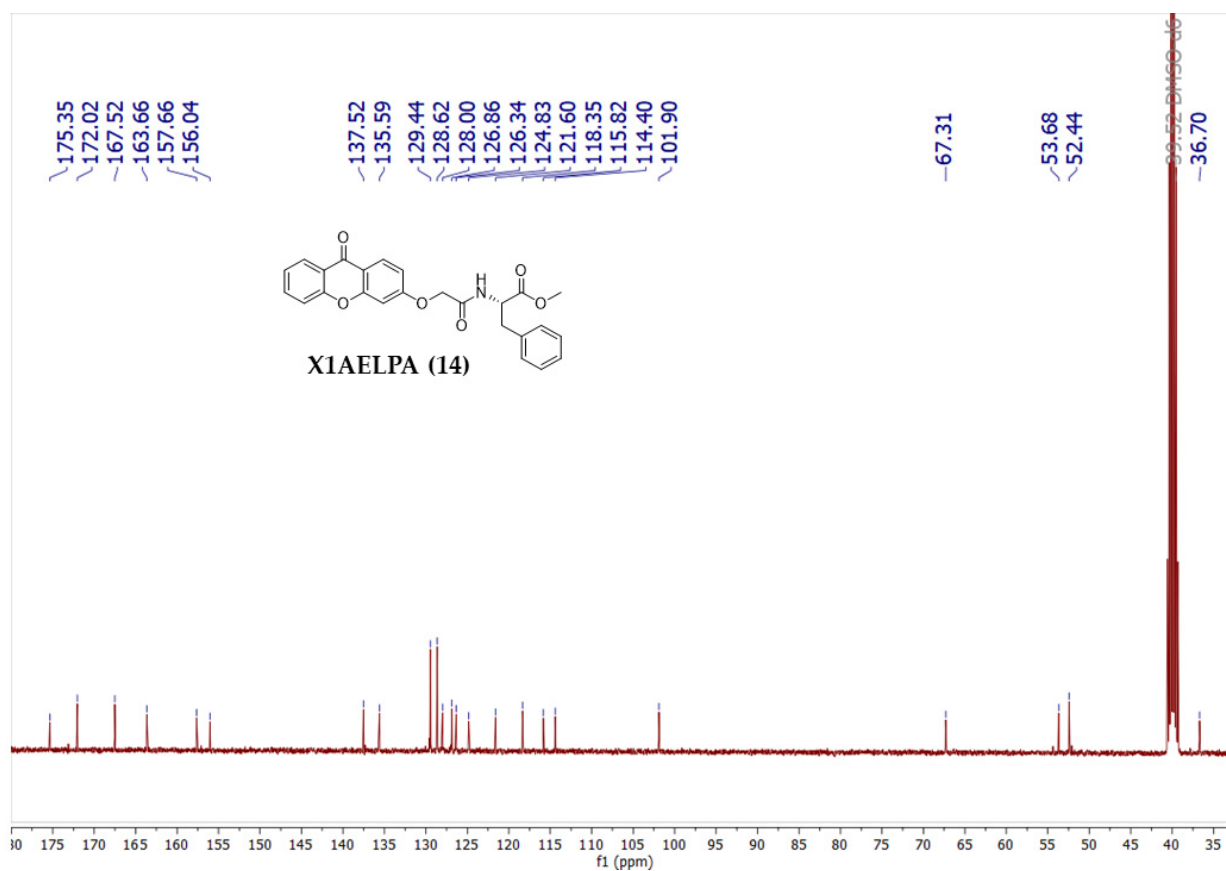
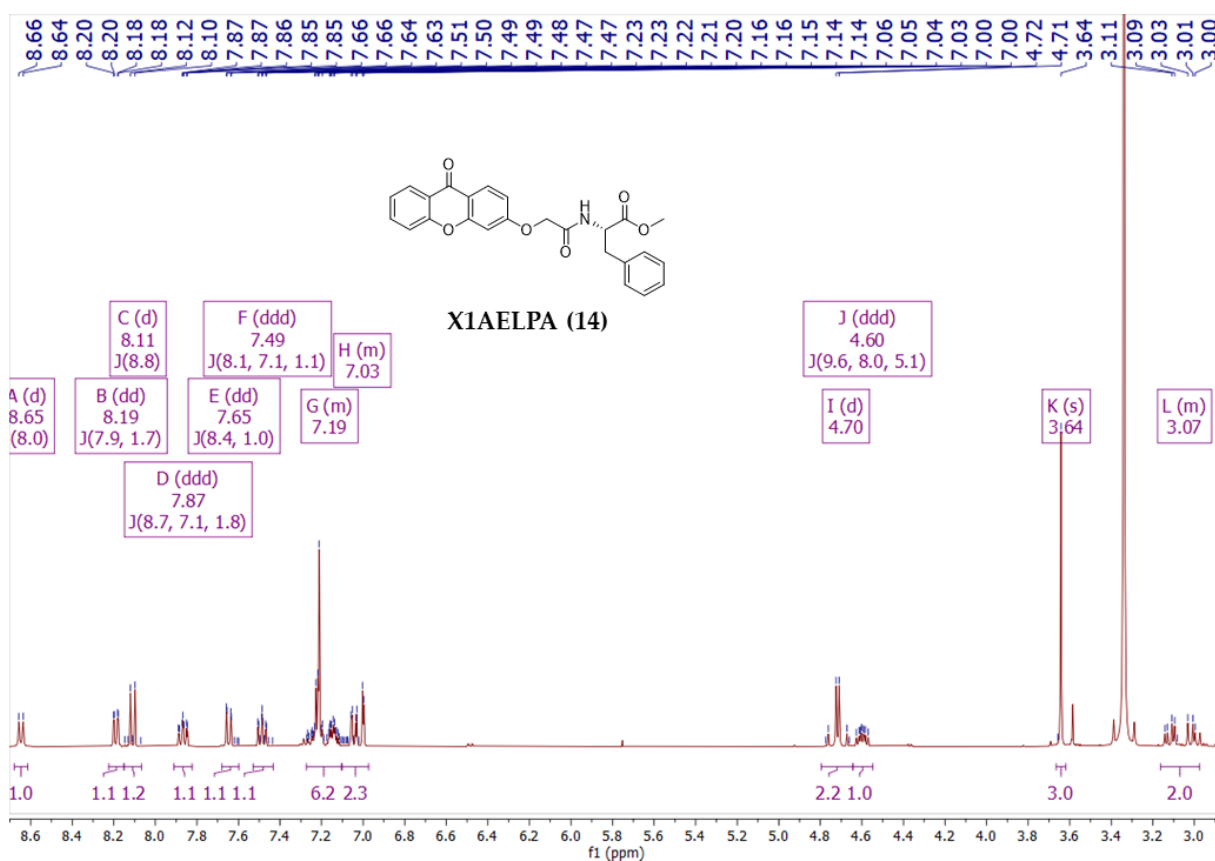


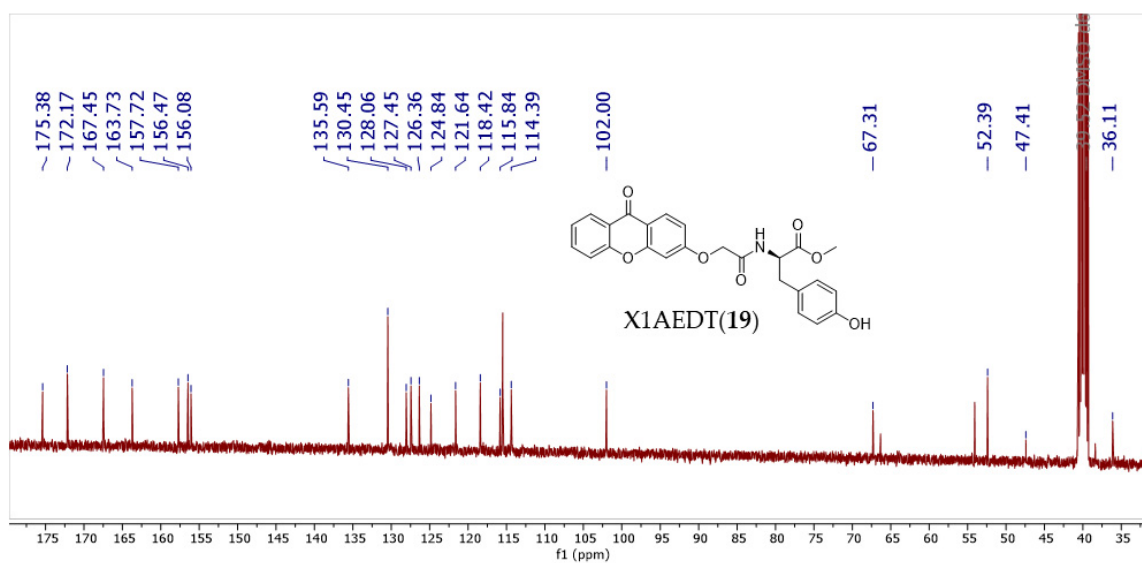
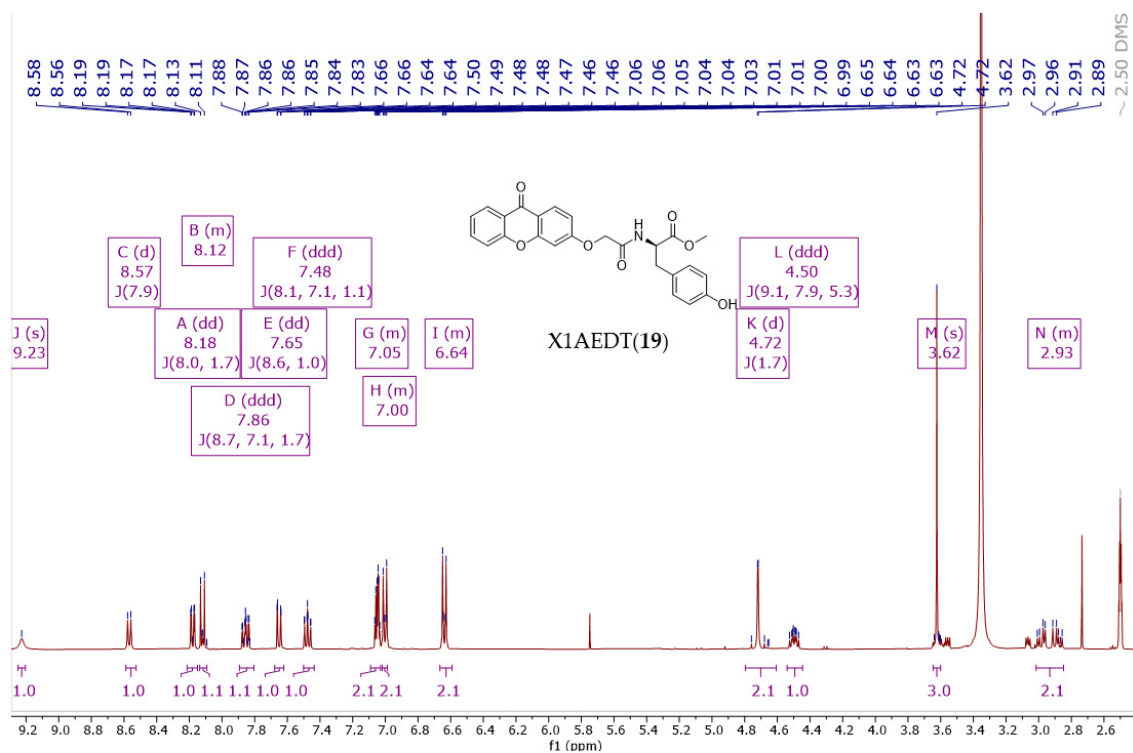


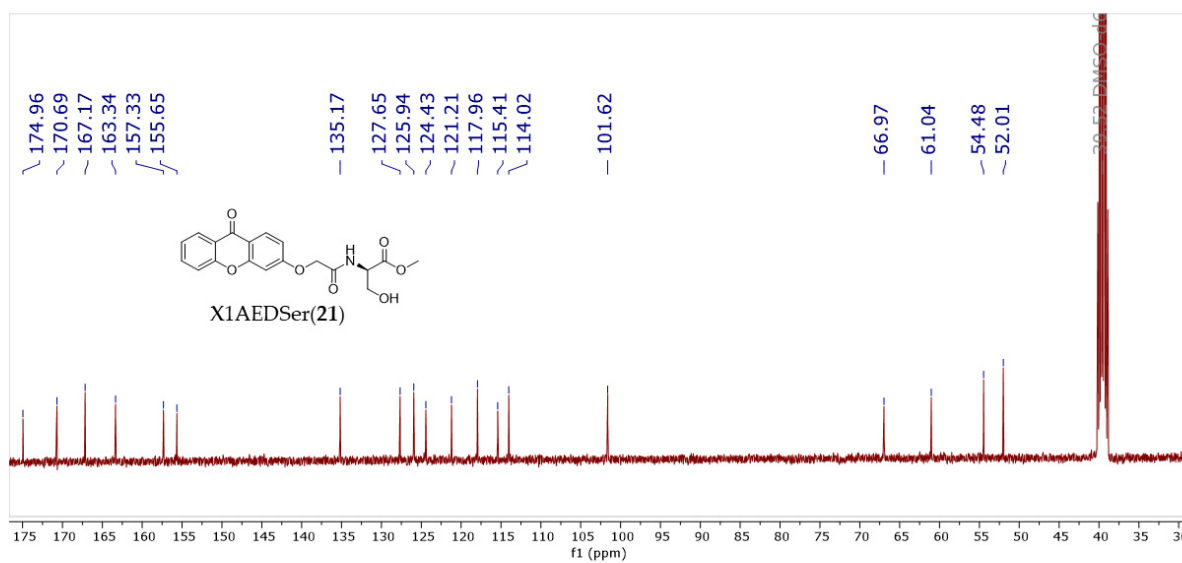
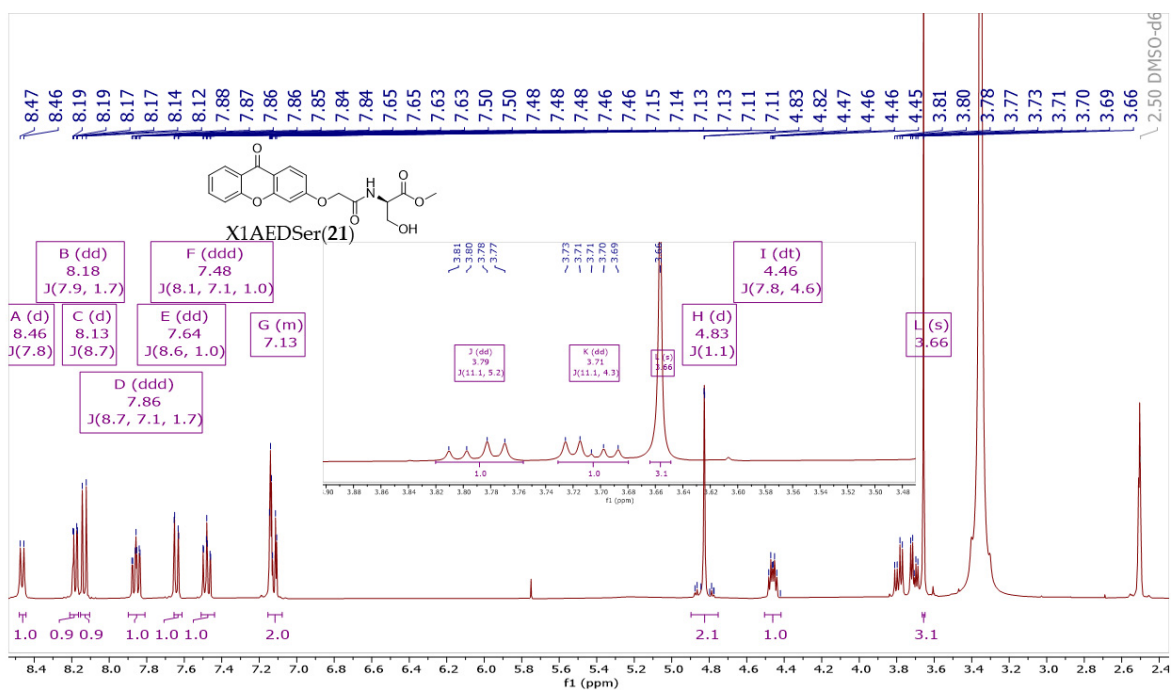


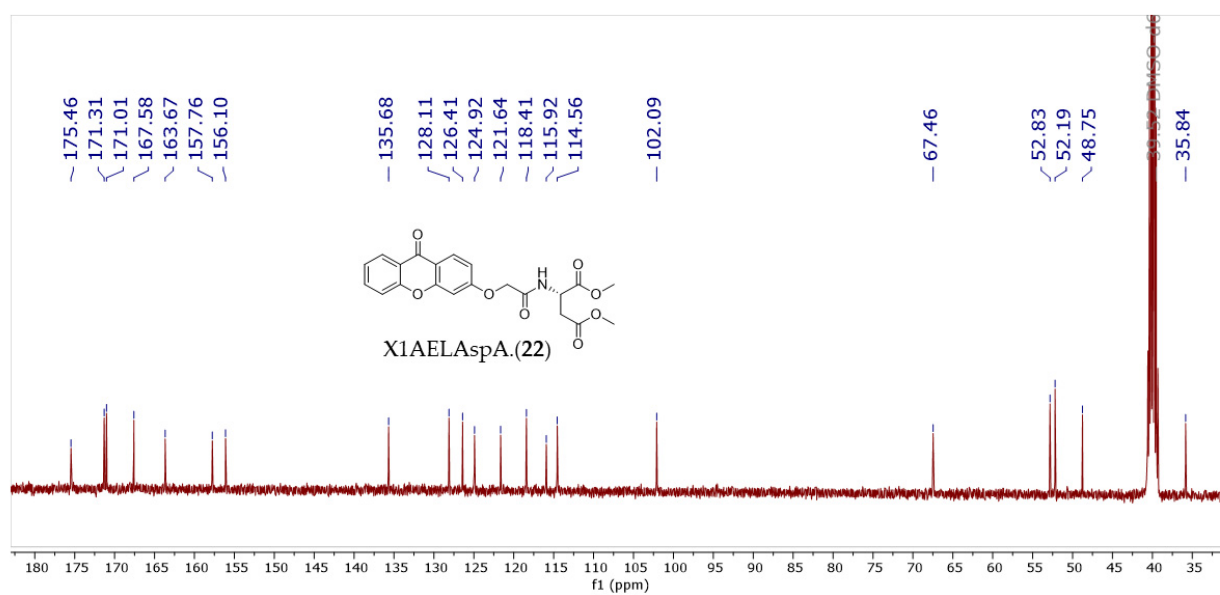
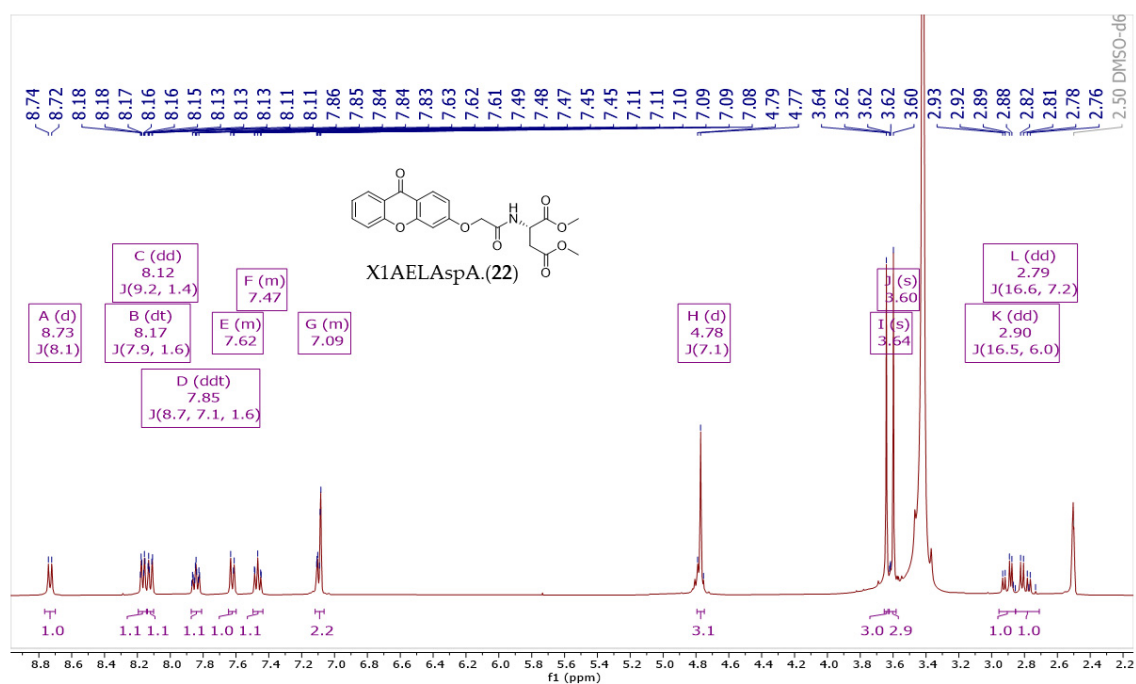


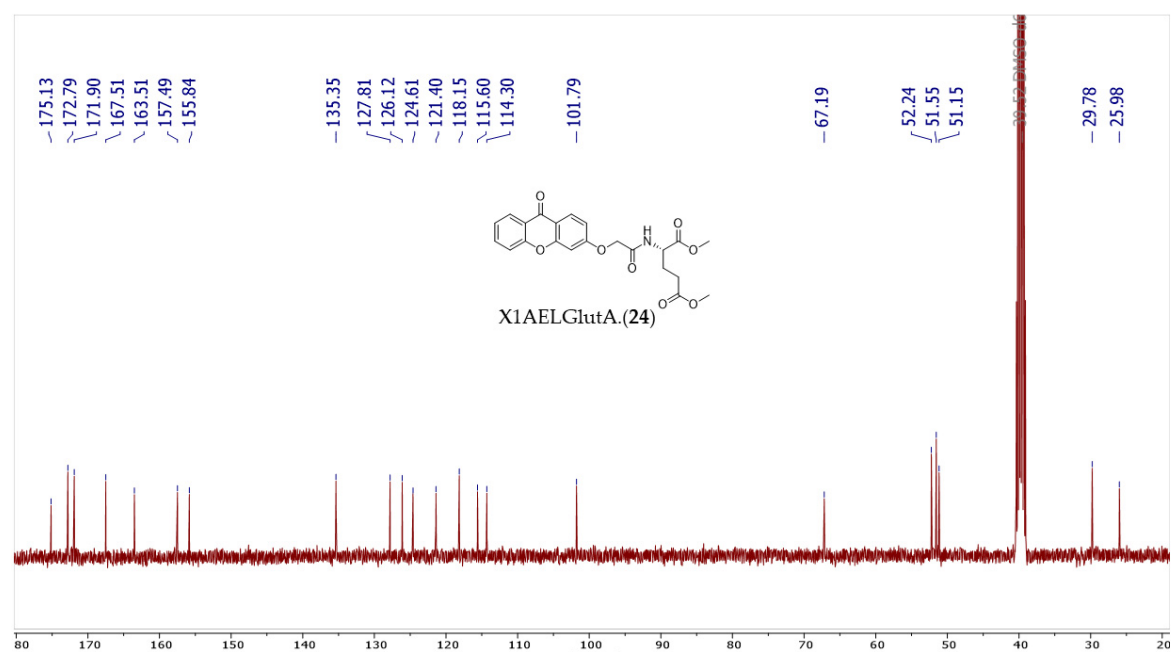
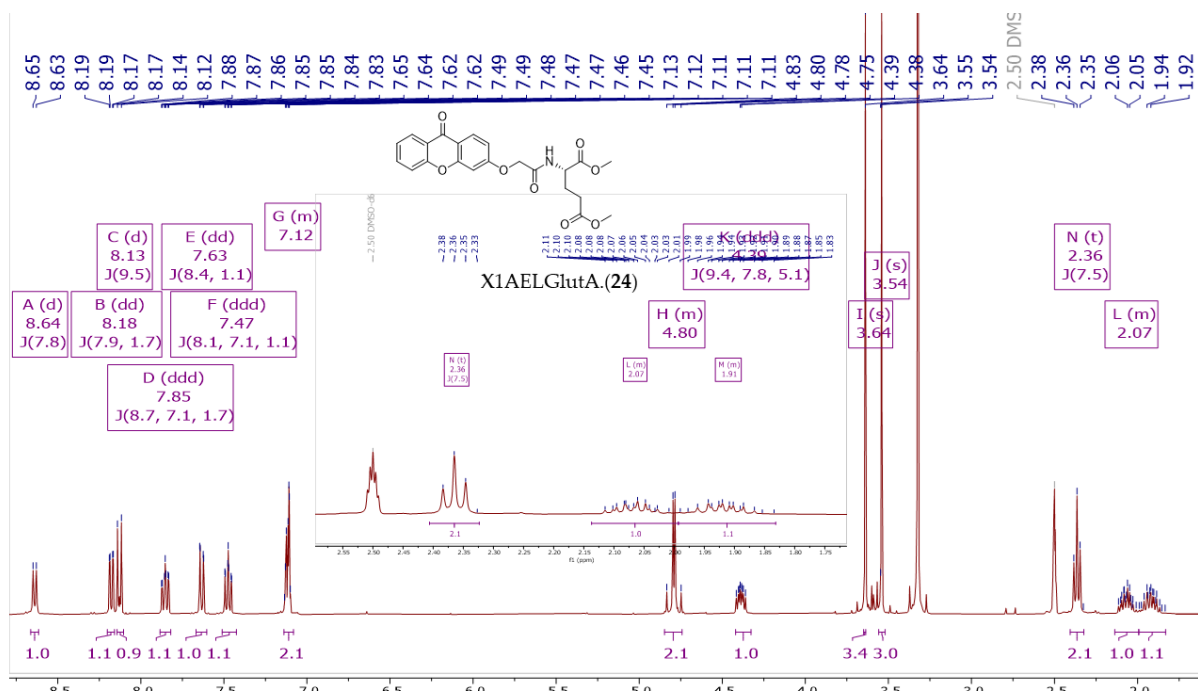


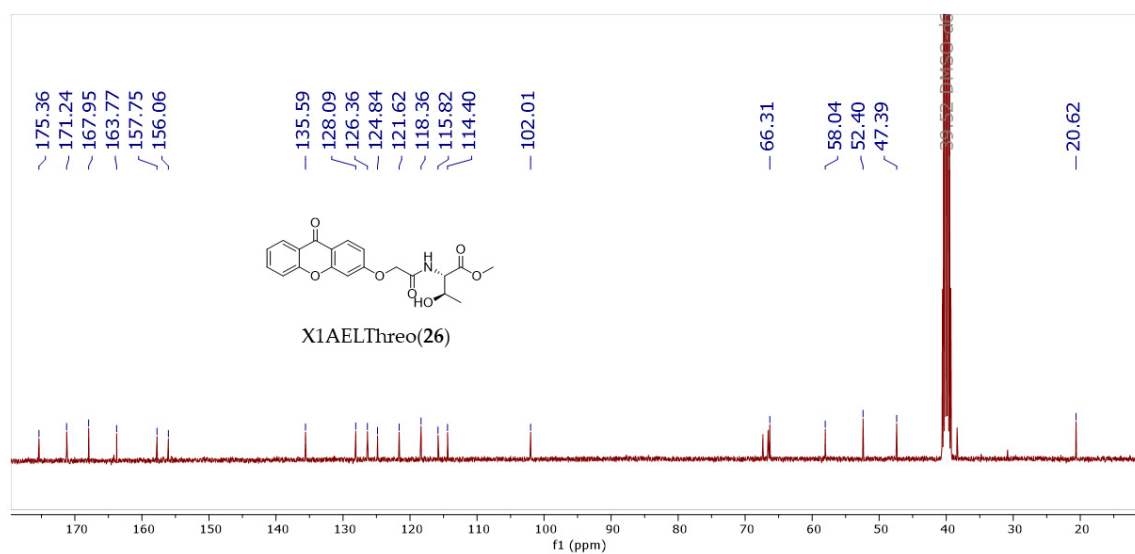
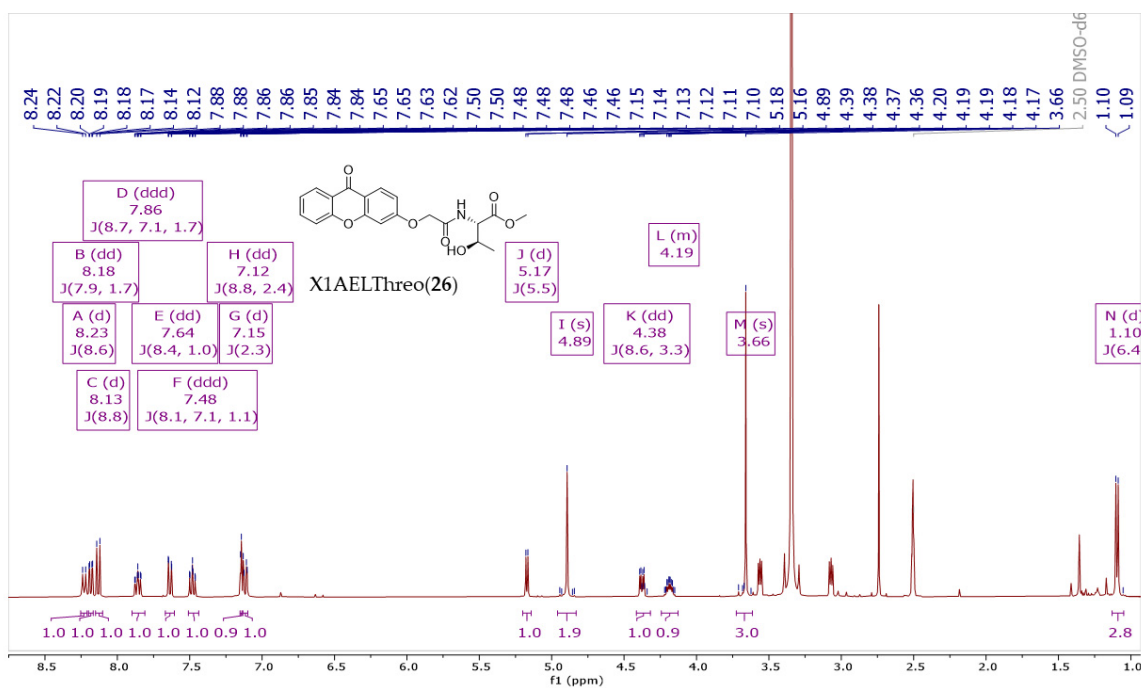


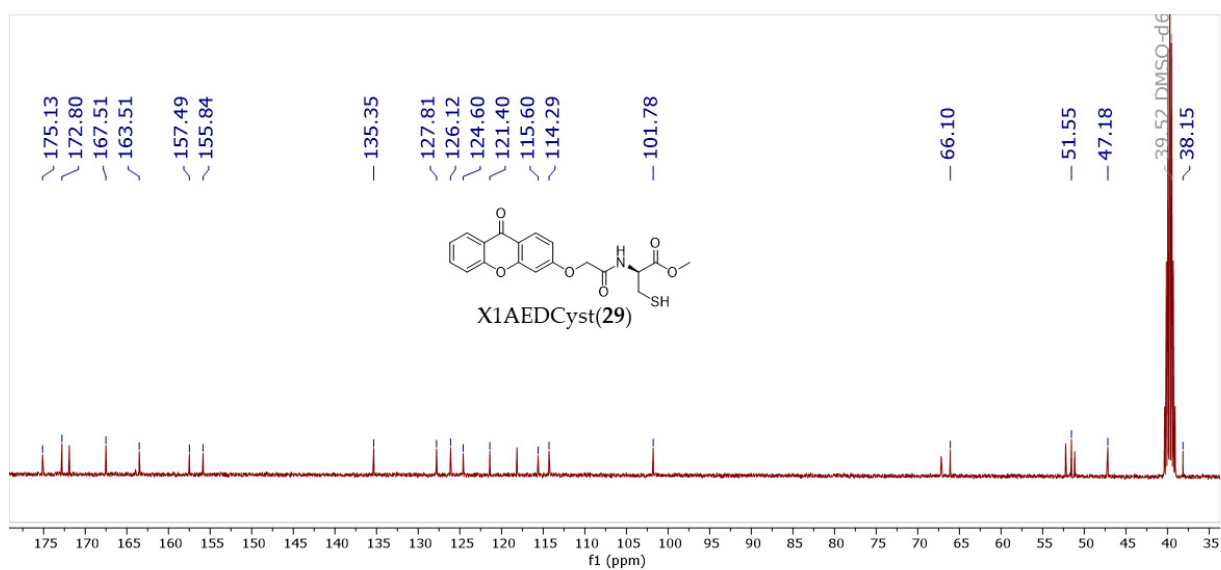
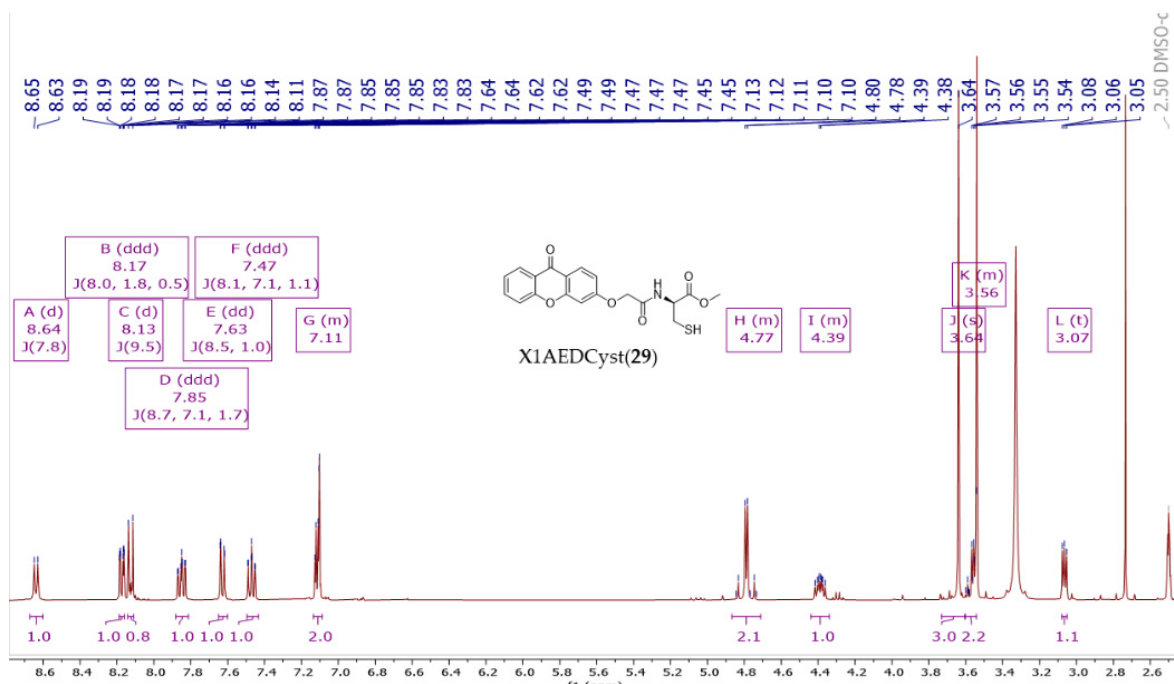


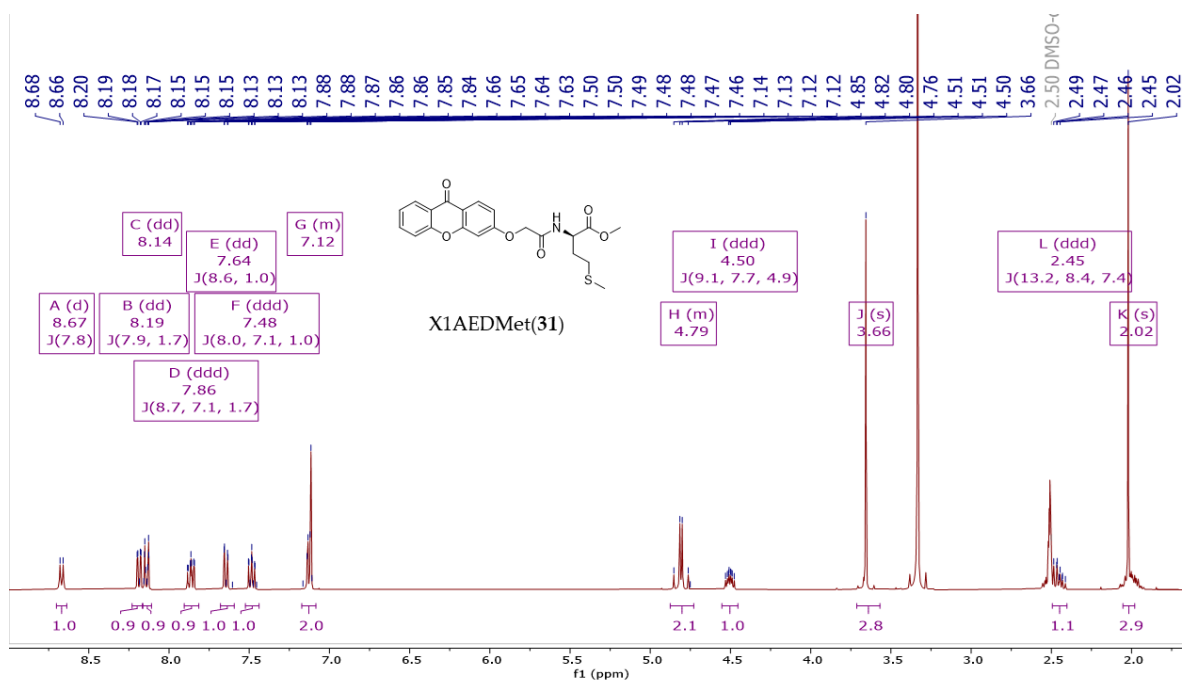
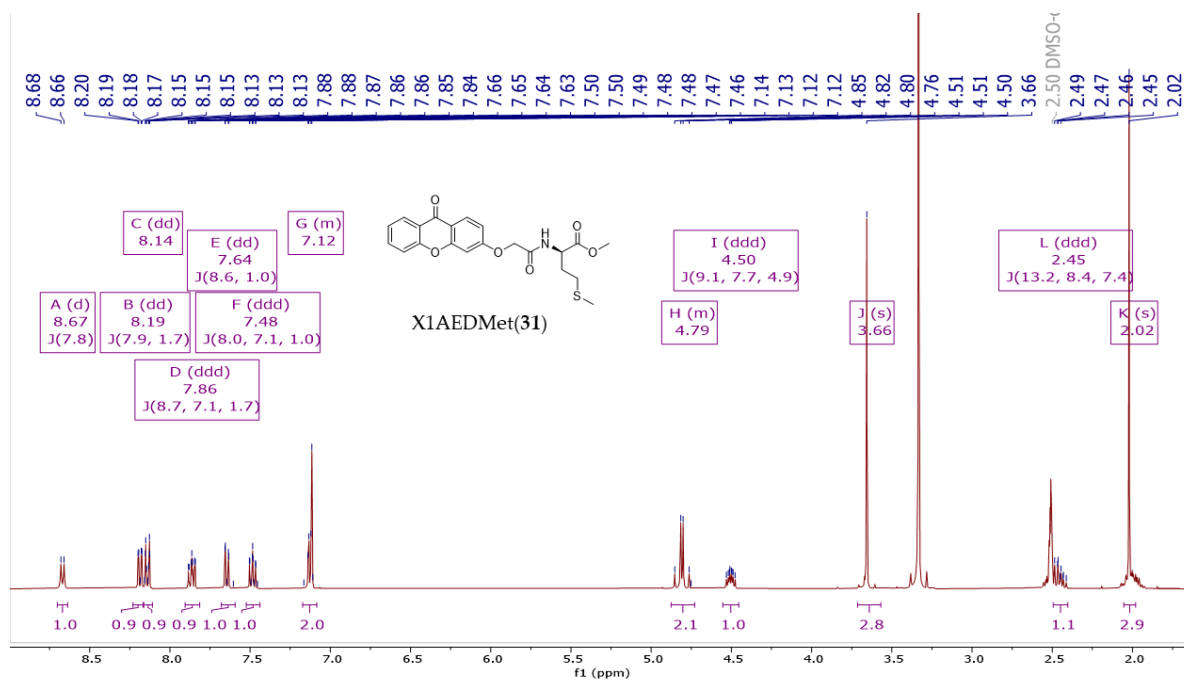


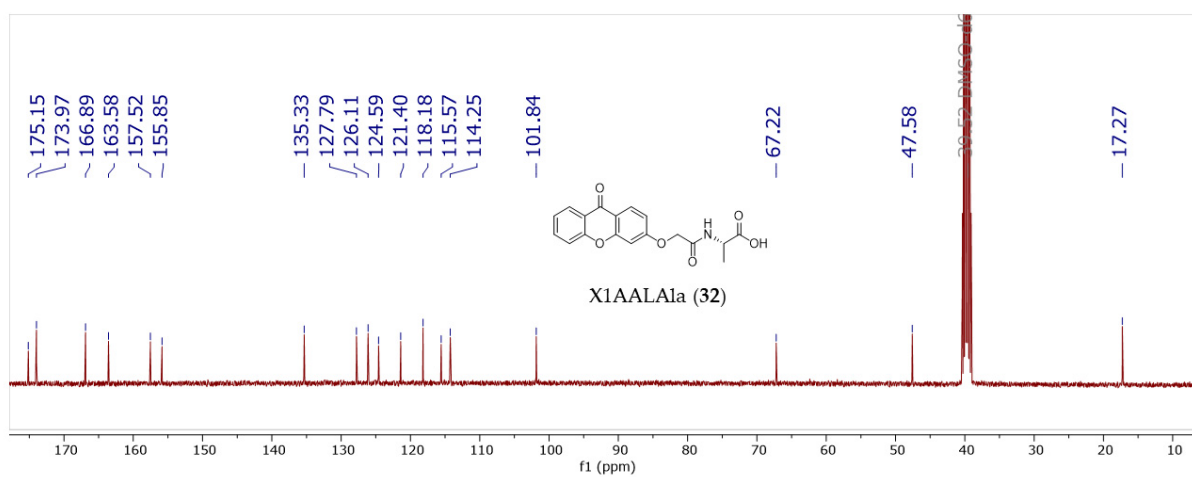
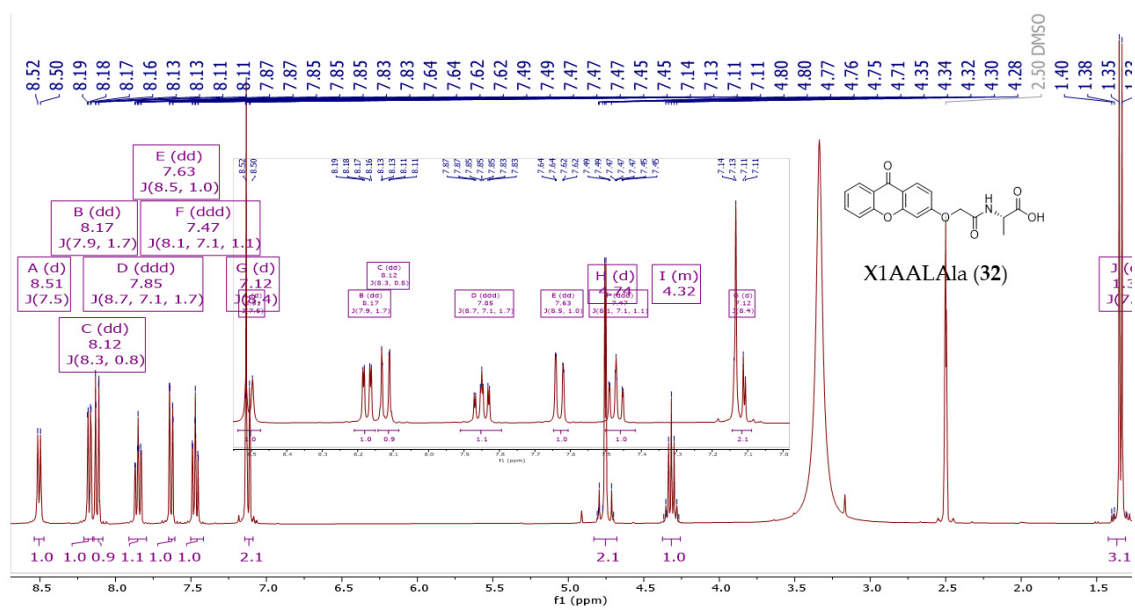


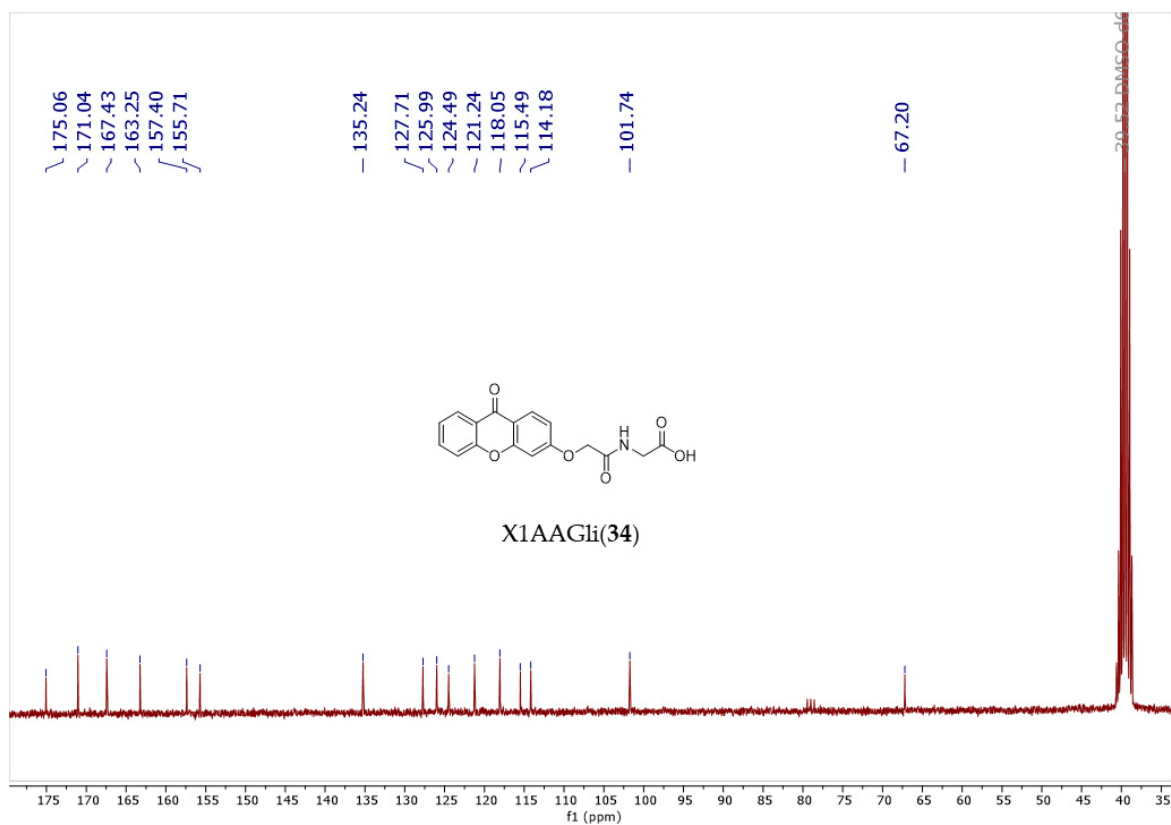
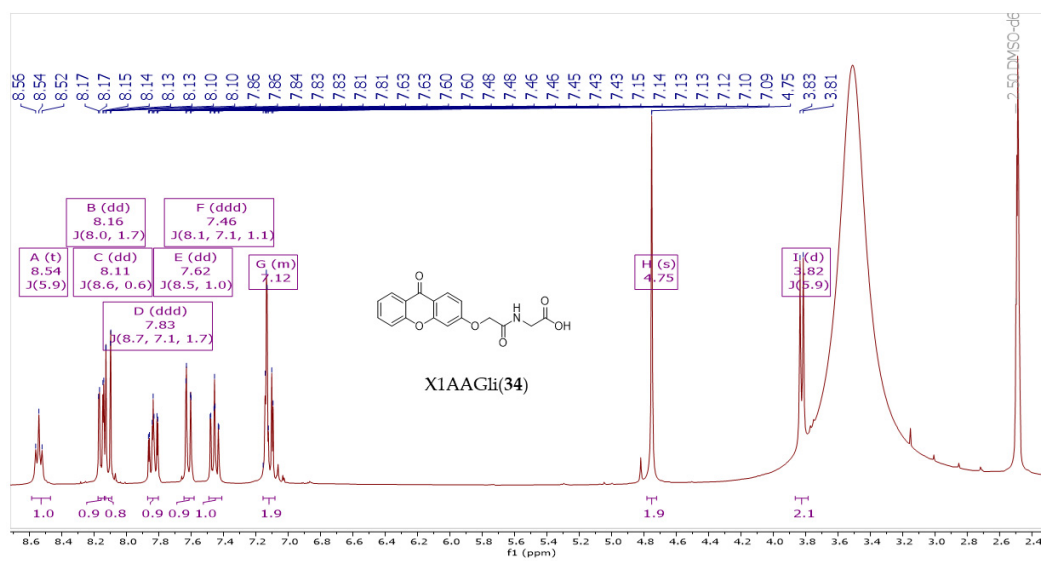


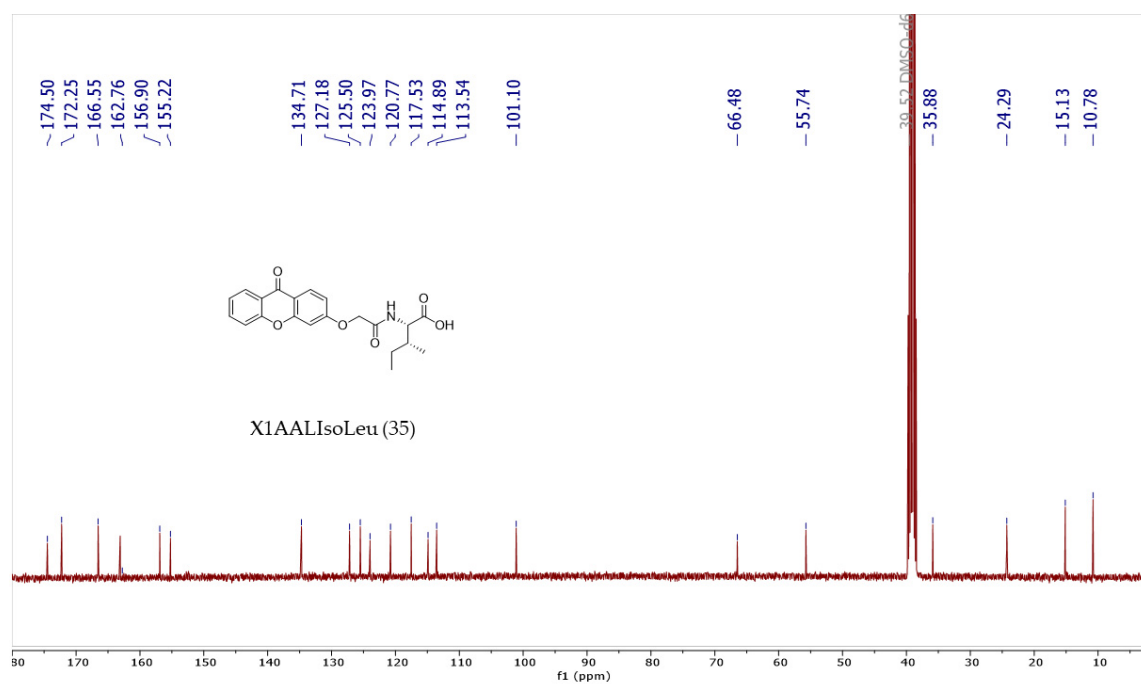
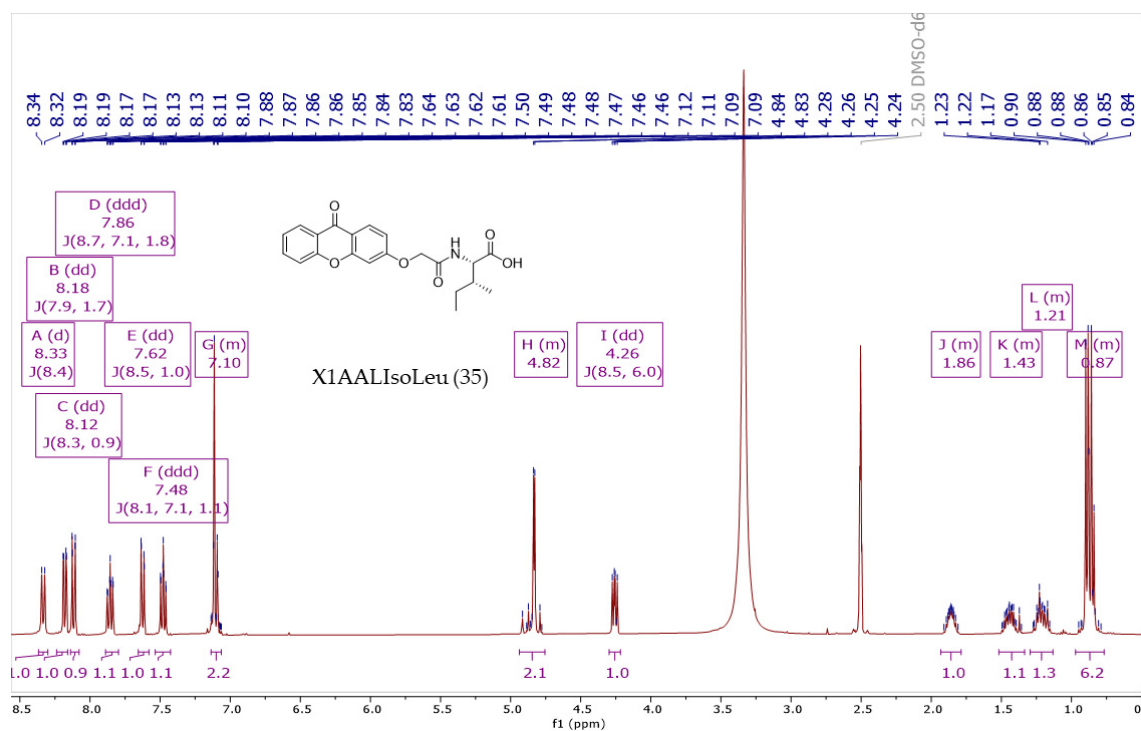


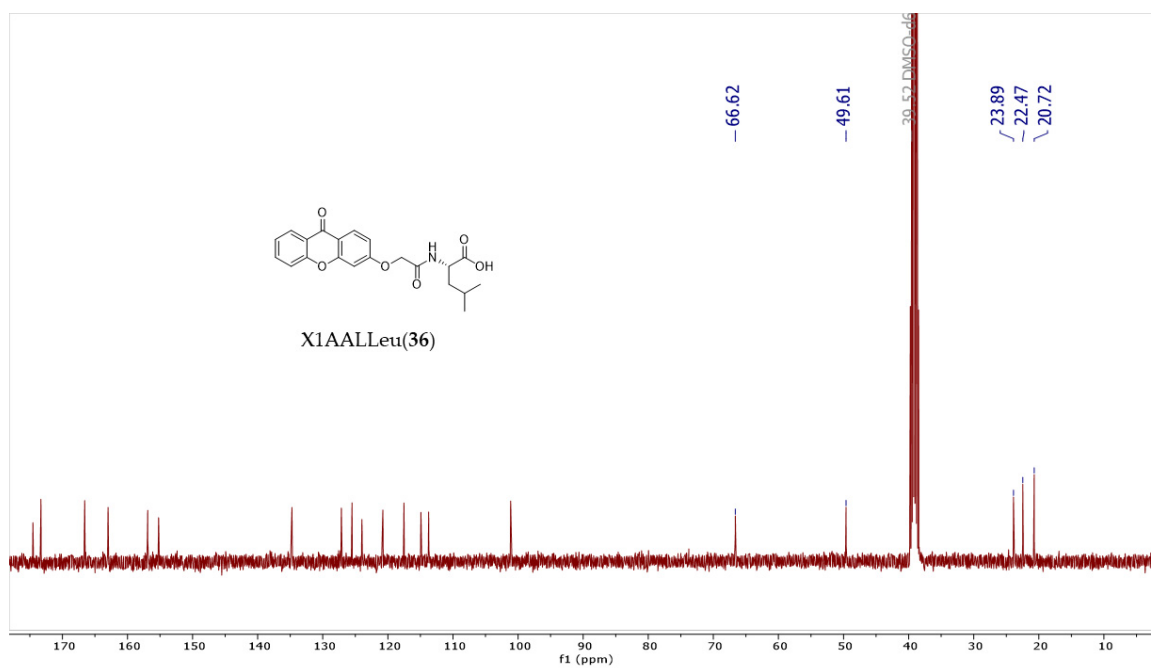
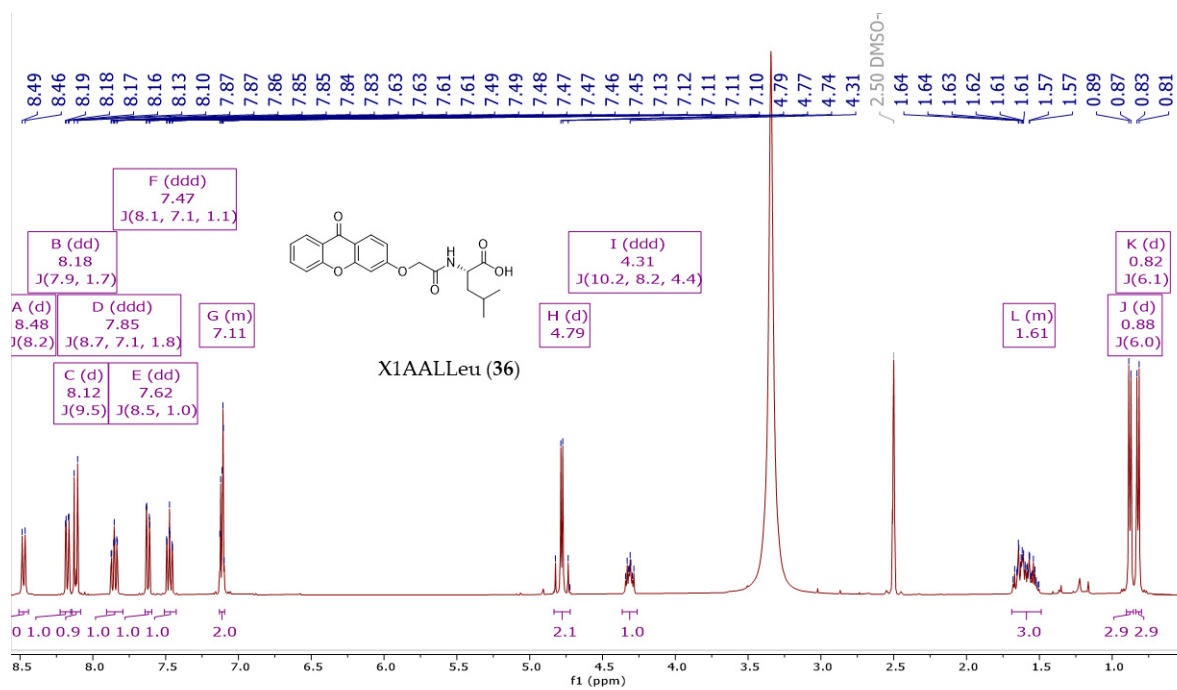


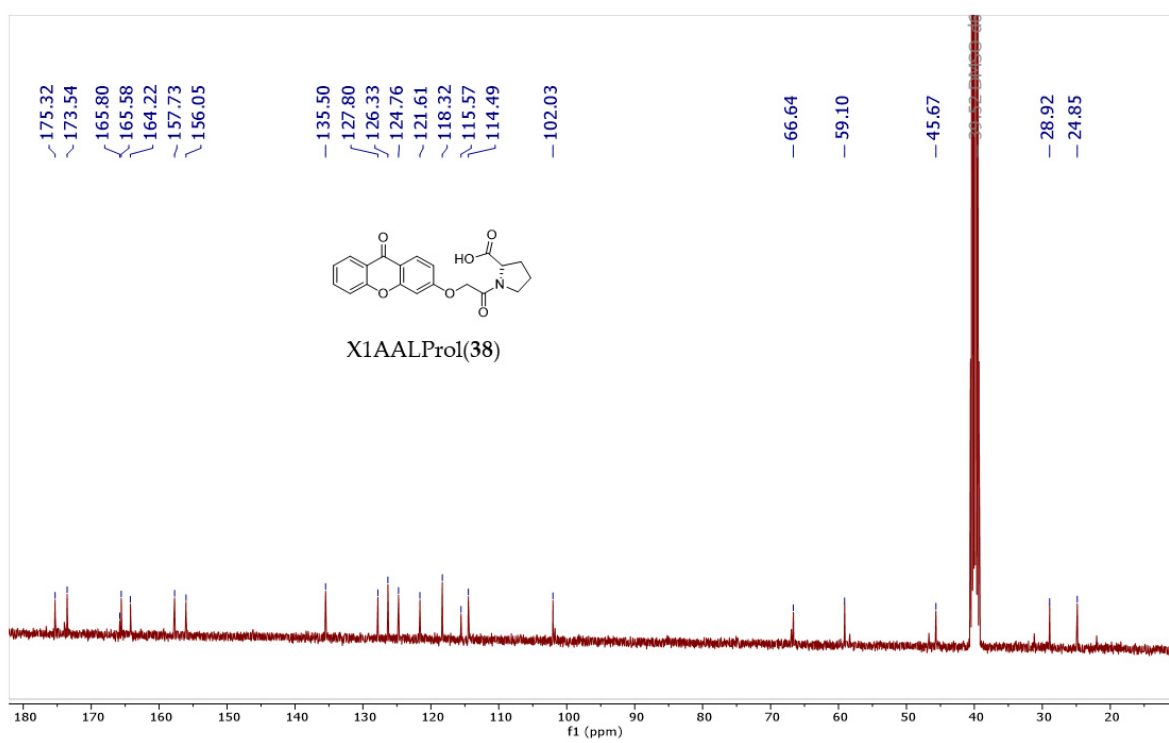
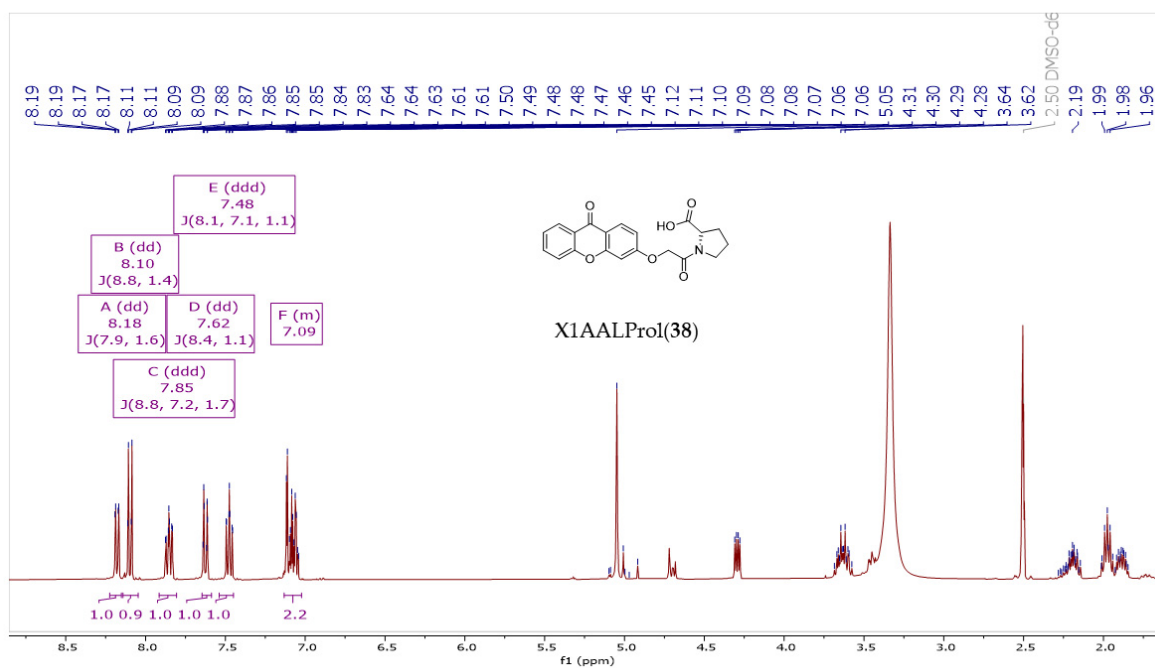


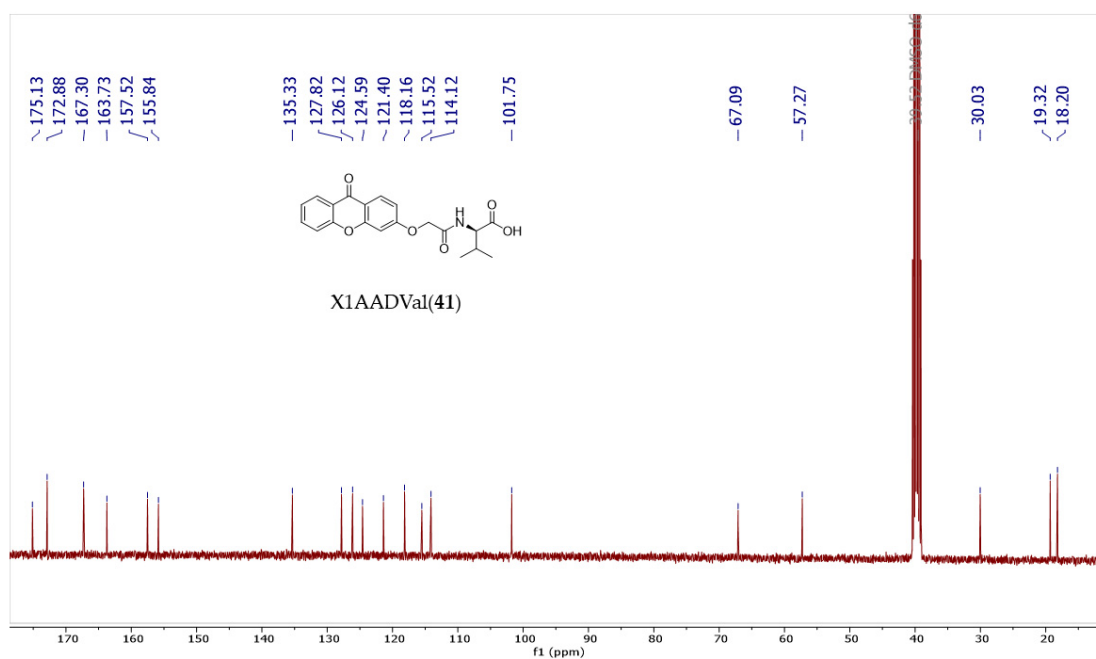
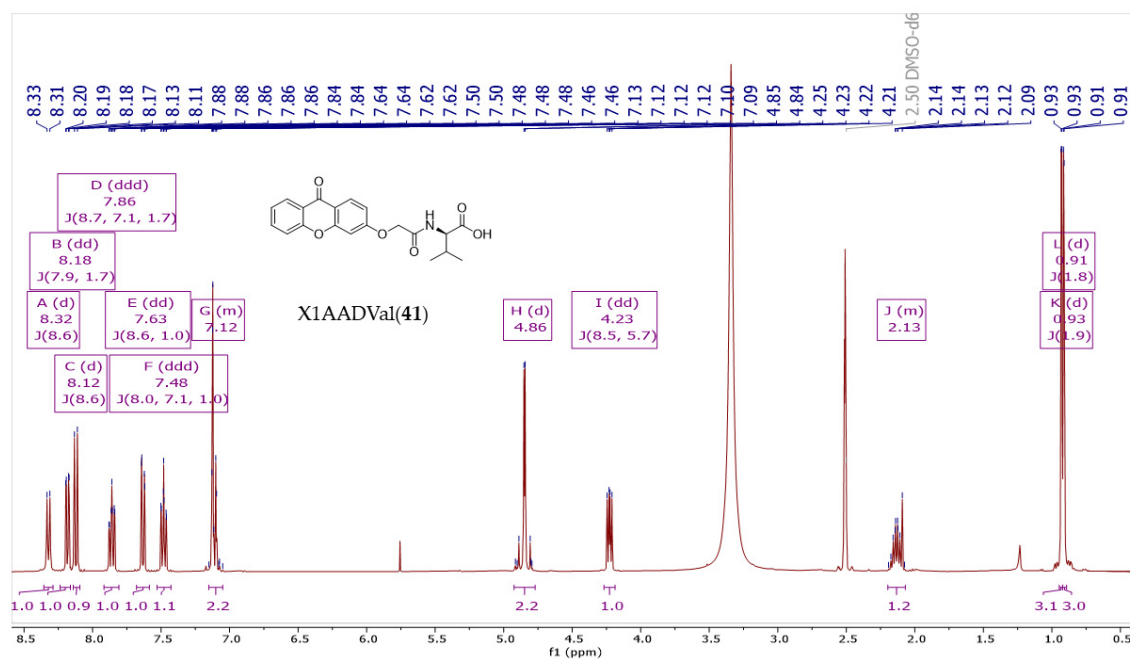


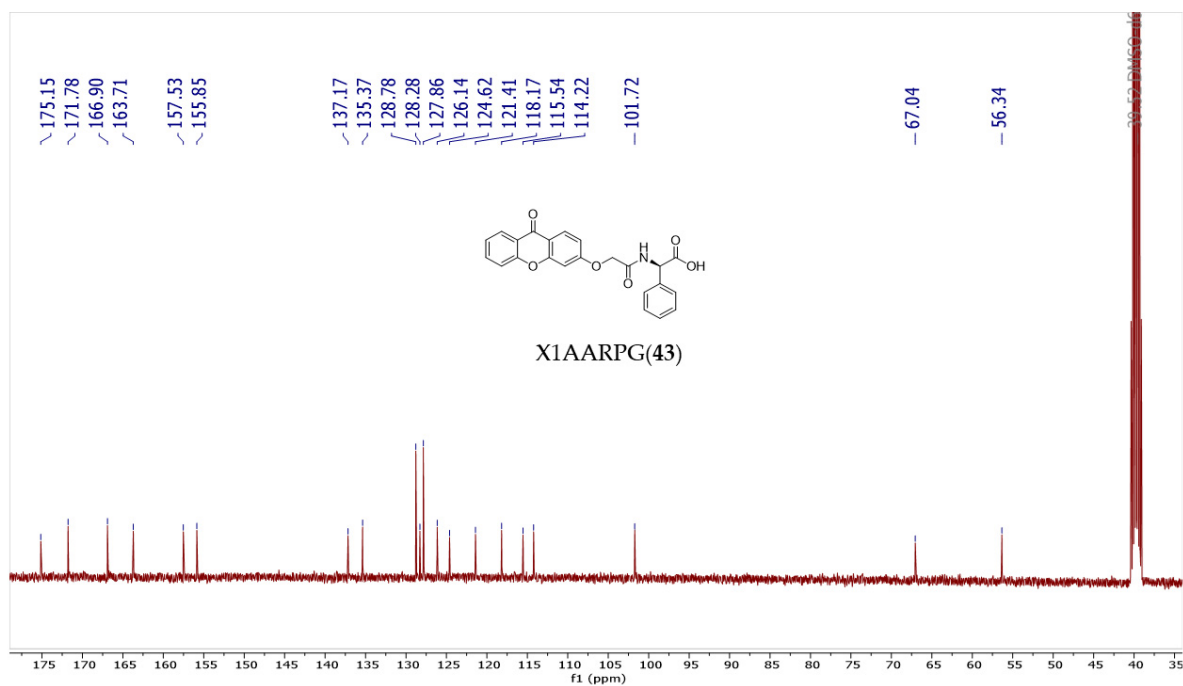
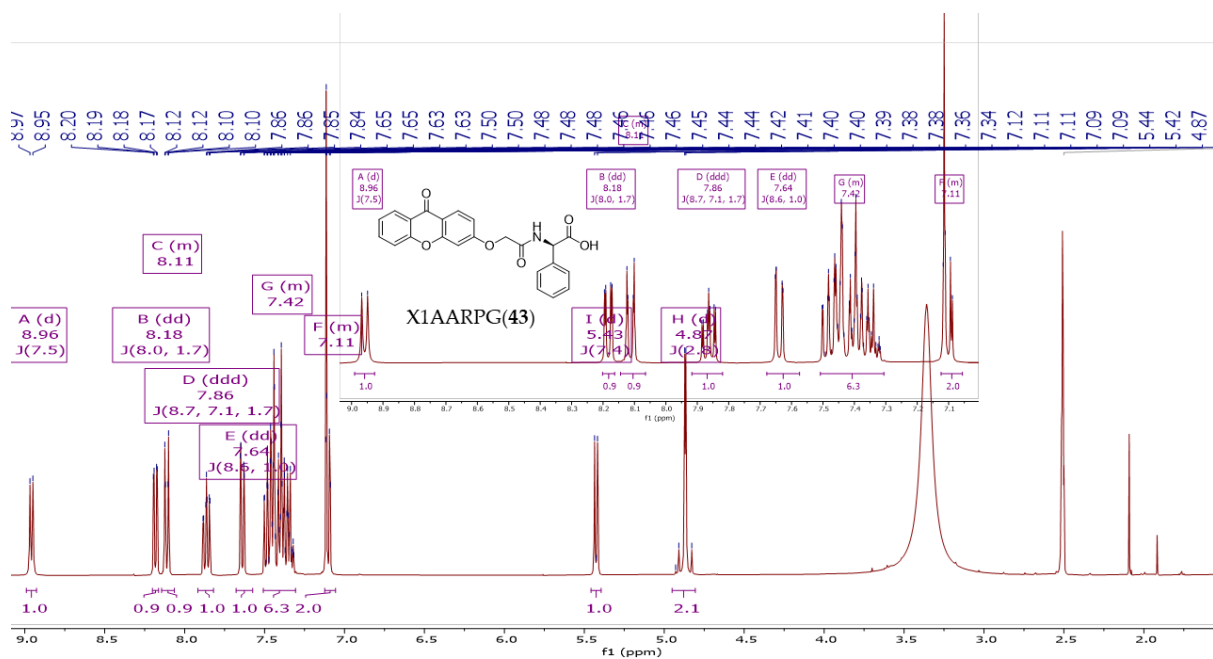


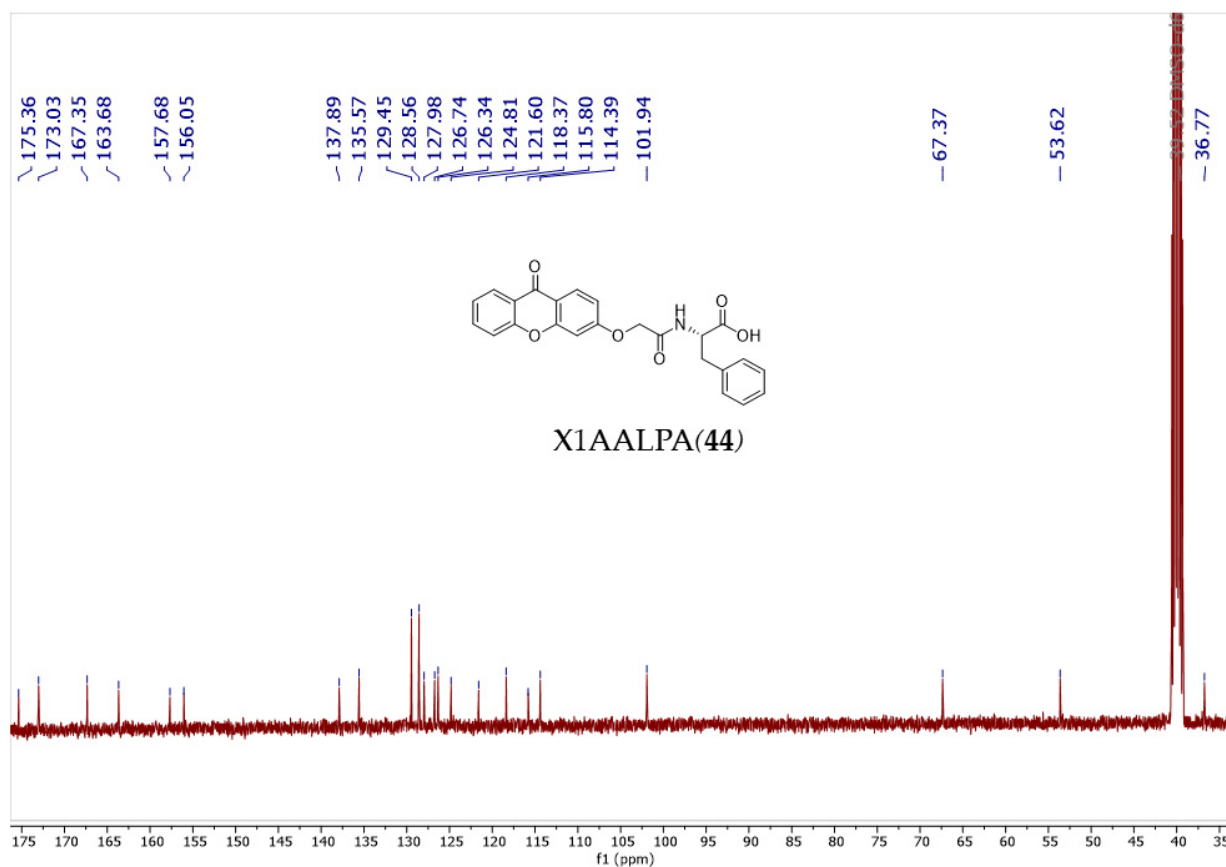
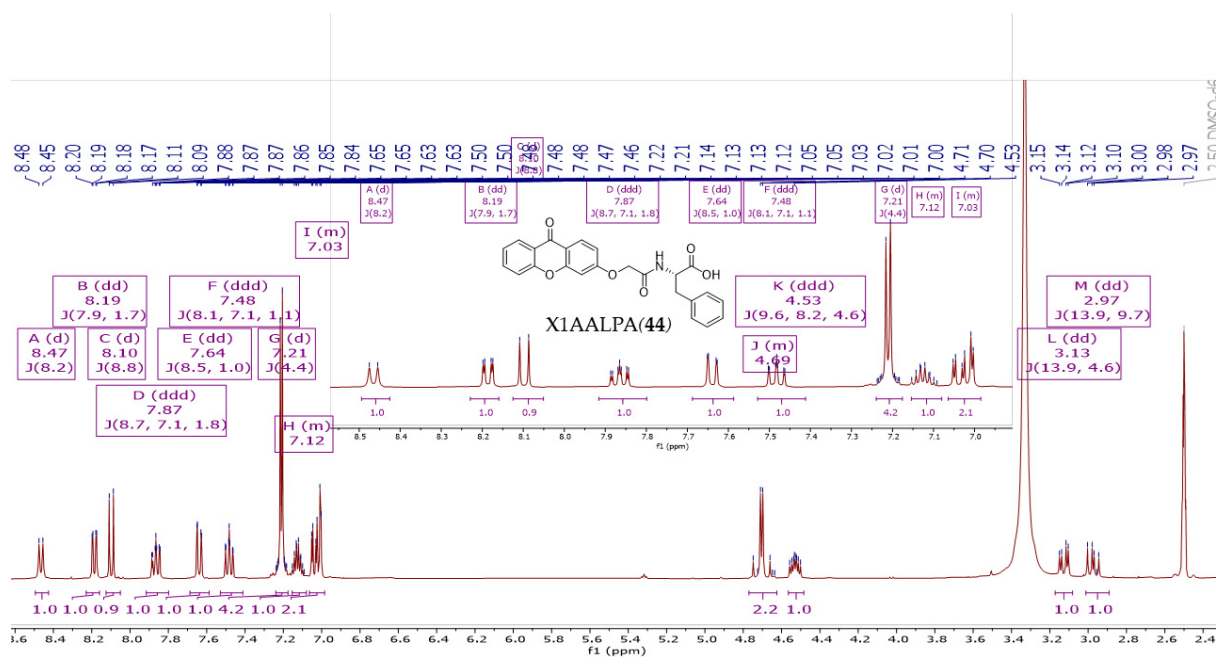


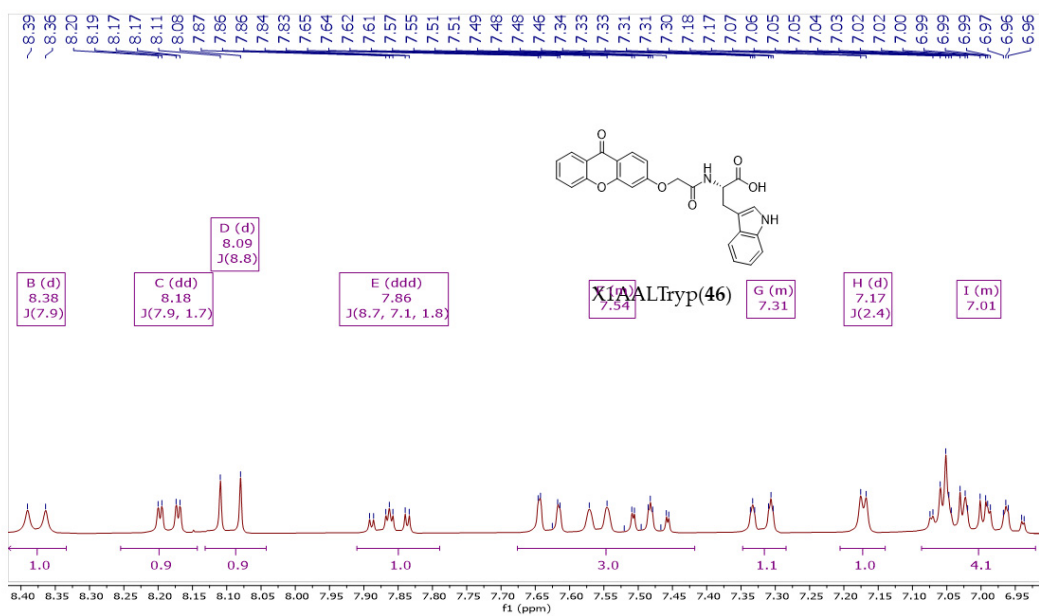
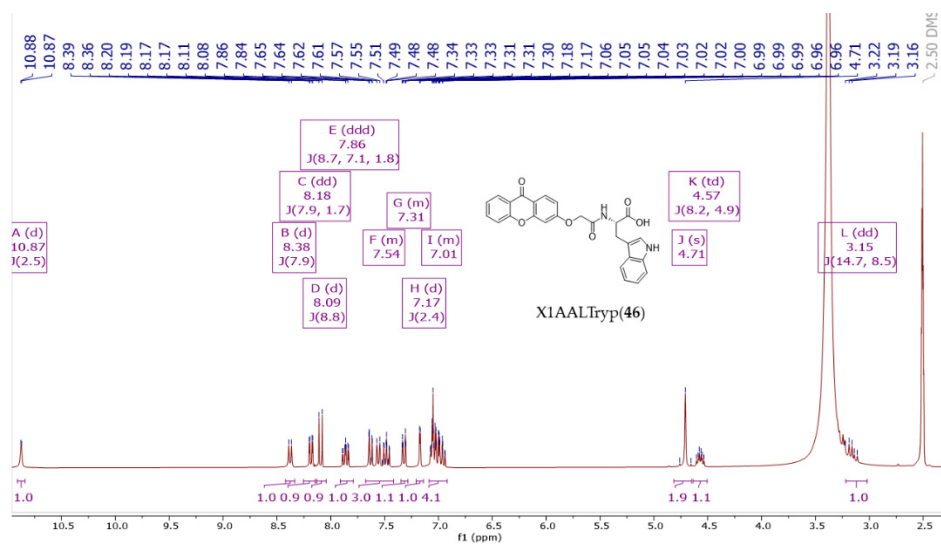


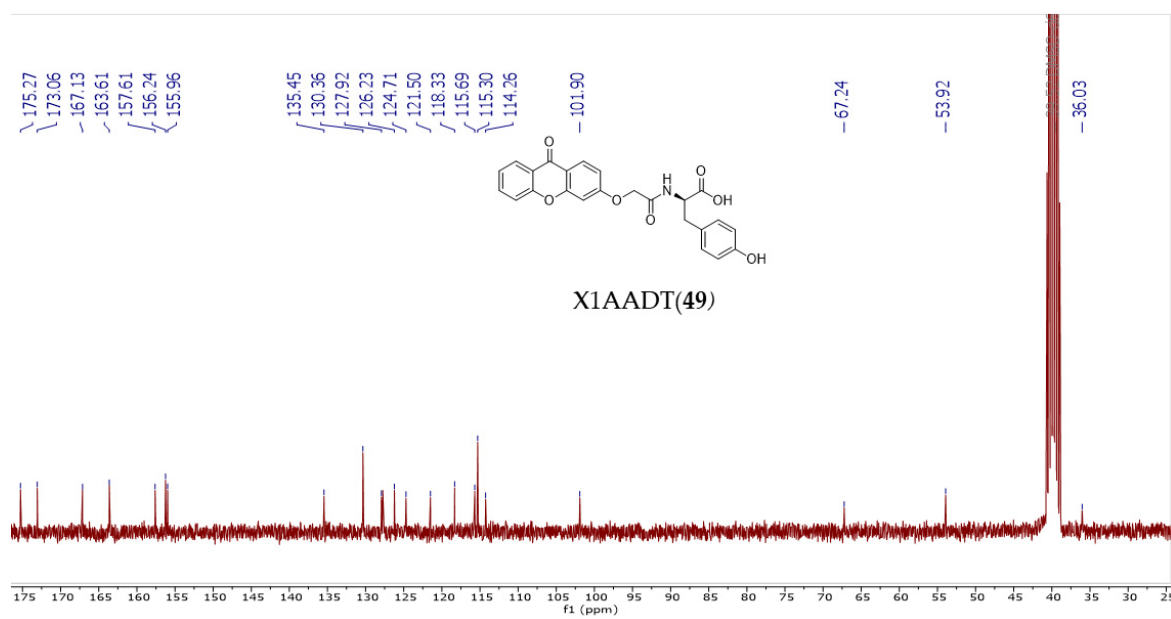


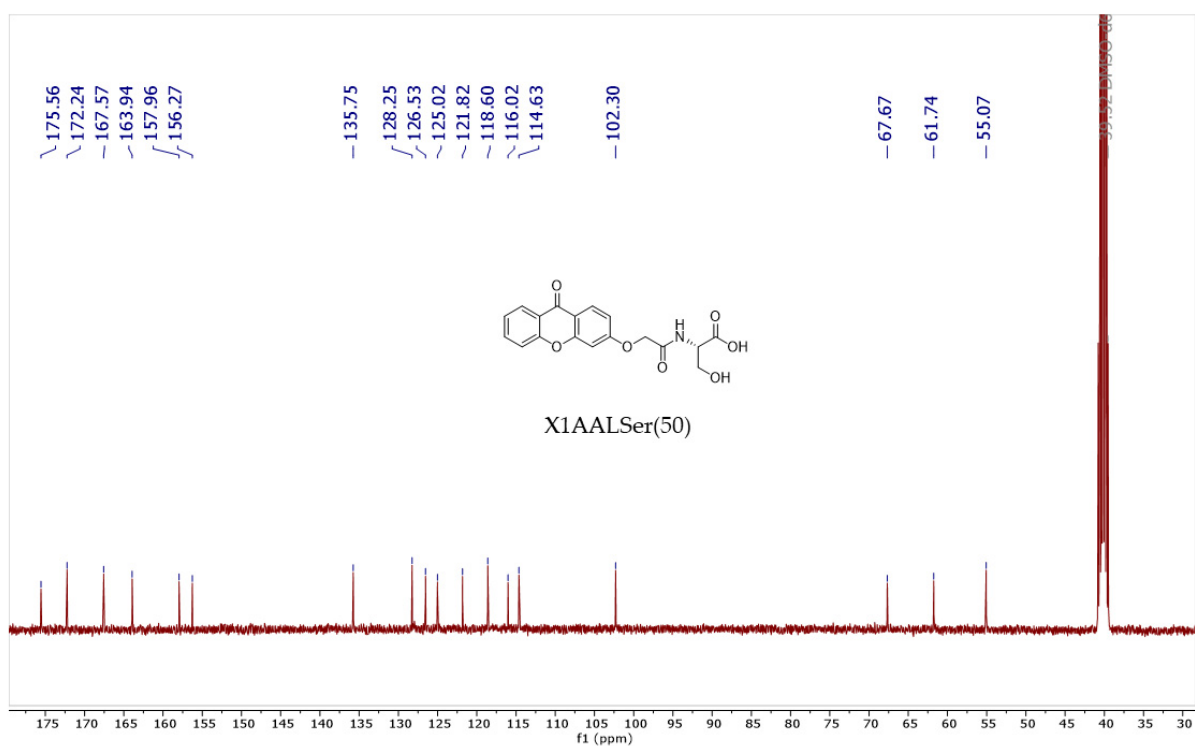
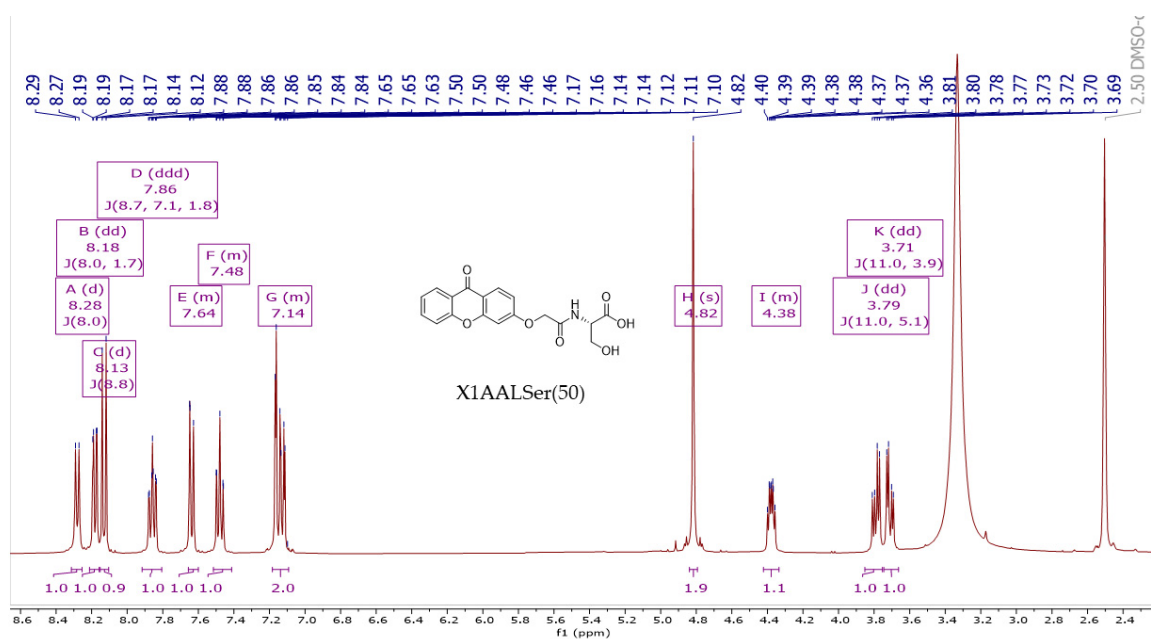


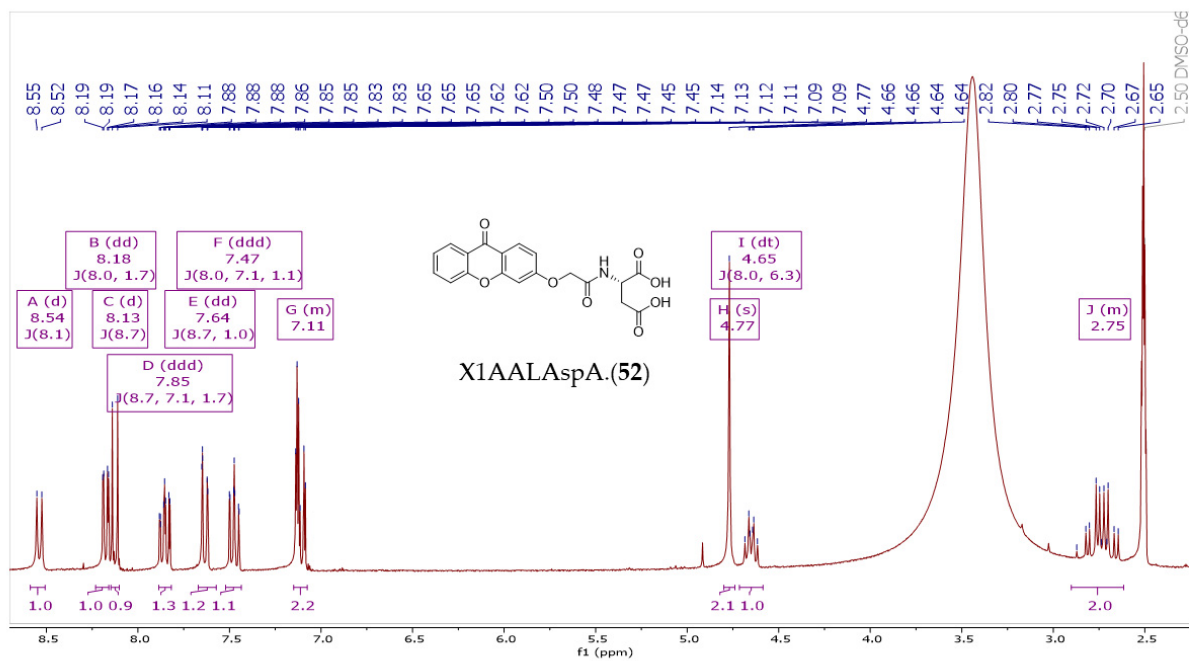


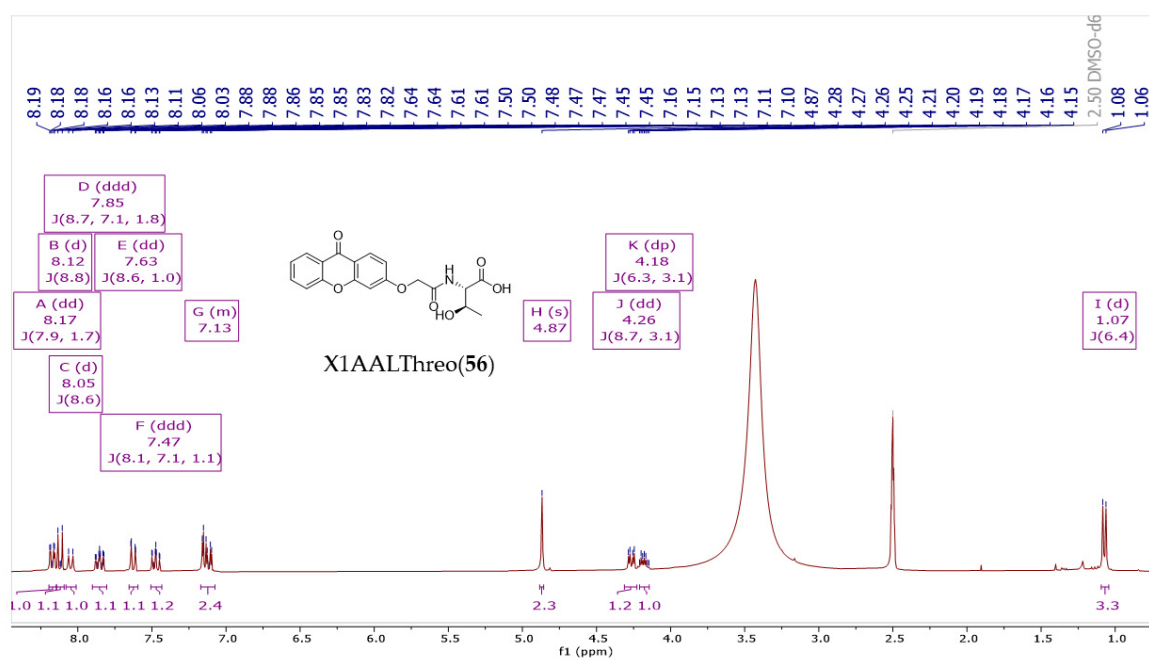
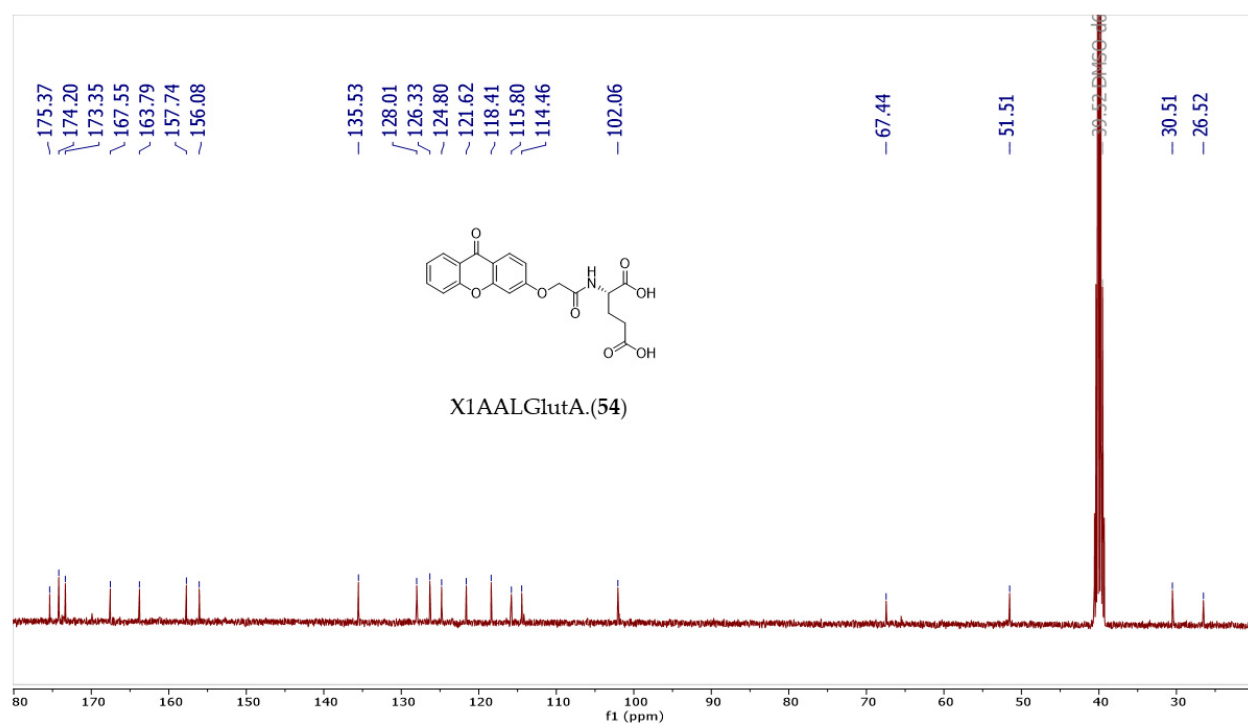


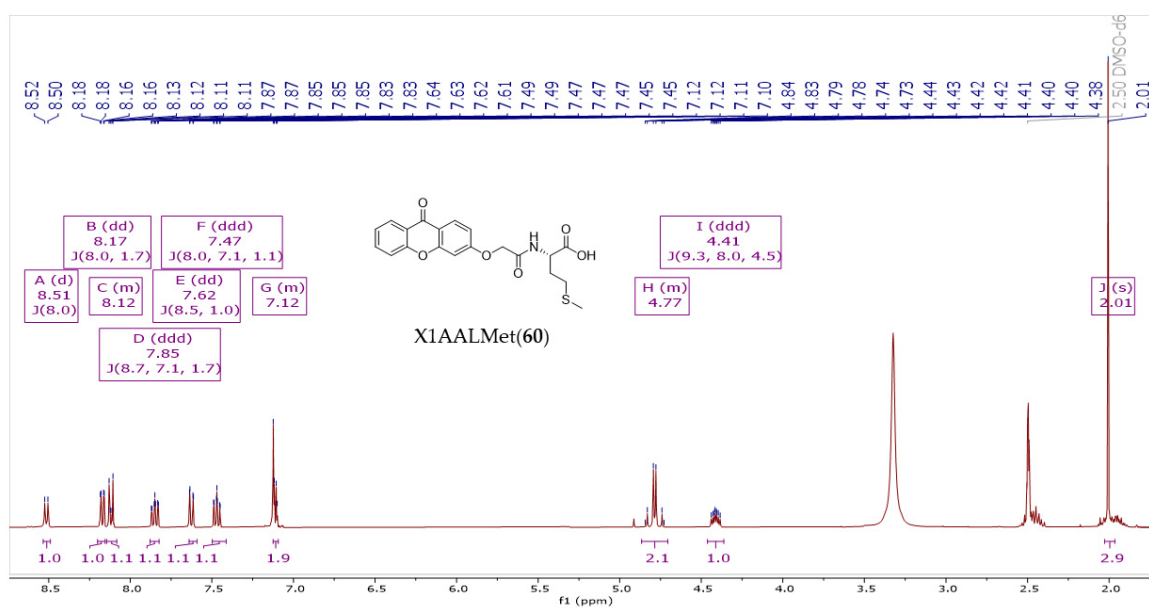
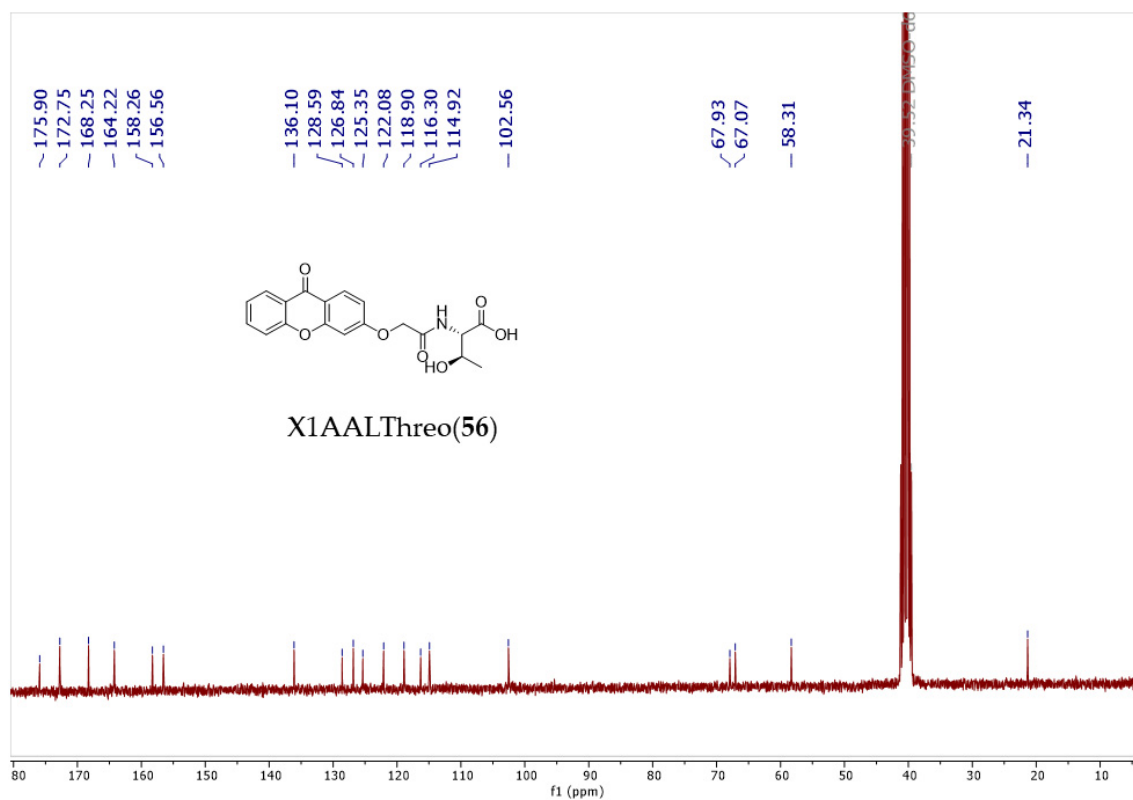












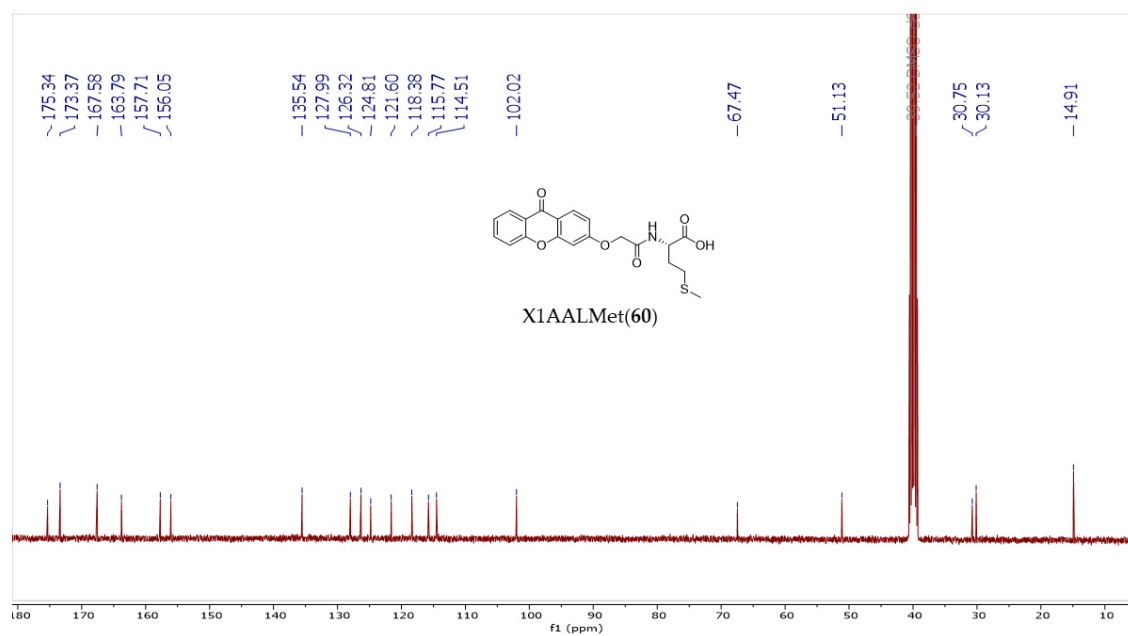


Figure S1. ^1H and ^{13}C NMR spectra of CDXs.

Table S3. Physicochemical descriptors and predicted ADME parameters, pharmacokinetic properties, and drug-like nature for CDXs of amino ester and amino acids.

| CDXs | Molecular weight (g/mol) | TPSA (Å ²) | Log <i>P</i> _{o/w} (iLOGP) | GI absorption | BBB permeant | P-gp substrate | CYP3A4 inhibitor | Lipinski | Veber | Bioavailability Score |
|-------------------|-----------------------------|---------------------------|--|------------------|-----------------|-------------------|---------------------|---------------------|-------|--------------------------|
| X1AELAla 2 | 397.42 | 94.84 | 3.48 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AEGli 4 | 341.31 | 94.84 | 2.67 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELIsoLeu 5 | 397.42 | 94.84 | 3.30 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELLeu 6 | 397.42 | 94.84 | 3.50 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELProl 8 | 381.38 | 86.05 | 3.24 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELVal 10 | 383.39 | 86.05 | 3.33 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AESPG 12 | 417.41 | 86.05 | 3.40 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELPA 14 | 431.44 | 86.05 | 3.31 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELTryp 16 | 470.47 | 110.63 | 3.38 | High | No | Yes | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELT 18 | 447.44 | 115.07 | 2.84 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELSer 20 | 371.34 | 115.07 | 2.96 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELAspA. 22 | 413.38 | 121.14 | 3.32 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELGlutA. 24 | 427.40 | 121.14 | 3.15 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |

| | | | | | | | | | | |
|-------------------|--------|--------|------|------|----|----|-----|---------------------|-----|------|
| X1AELThreo 26 | 385.37 | 115.07 | 2.75 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELCyst 28 | 387.41 | 133.64 | 2.79 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AELMet 30 | 415.46 | 120.14 | 3.13 | High | No | No | Yes | Yes; 0 violation | Yes | 0.55 |
| X1AALAla 32 | 341.31 | 105.84 | 1.97 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AAGli 34 | 327.29 | 105.84 | 1.82 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALIsoLeu 35 | 383.39 | 105.84 | 2.82 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALLeu 36 | 383.39 | 105.84 | 2.64 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALProl 38 | 367.35 | 97.05 | 2.30 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALVal 40 | 369.37 | 105.84 | 2.52 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALPG 42 | 403.38 | 105.84 | 2.64 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALPA 44 | 417.41 | 105.84 | 2.56 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALTryp 46 | 456.45 | 121.63 | 2.53 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |
| X1AALTyr 48 | 433.41 | 126.07 | 2.08 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALSer 50 | 357.31 | 126.07 | 1.74 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALAspA. 52 | 385.32 | 143.14 | 1.67 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALGlutA. 54 | 399.35 | 143.14 | 1.41 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |
| X1AALThreo 56 | 371.34 | 126.07 | 2.08 | High | No | No | No | Yes; 0 violation | Yes | 0.56 |

| | | | | | | | | | | |
|-----------------|--------|--------|------|------|----|----|-----|---------------------|-------------------|------|
| X1AALCyst 58 | 373.38 | 144.64 | 2.00 | Low | No | No | No | Yes; 0 violation | No; 1 TPSA>140 | 0.56 |
| X1AALMet 60 | 401.43 | 131.14 | 2.19 | High | No | No | Yes | Yes; 0 violation | Yes | 0.56 |

Table S4: Results of HRMS-ESI in positive and negative ions mode

| CDXs | Calculate d | Polarit y | ESI/MS ⁿ | |
|-------------------|--|--------------|---------------------|--------------------|
| | | | [M-H] ⁻ | [M+H] ⁺ |
| X1AEDA1a | C ₂₂ H ₂₃ NO ₆ | - | 396.1455 | |
| (3) | 397,1525 | + | | 398.1612 |
| X1AELLeu | C ₂₂ H ₂₃ NO ₆ | - | 396.1469 | |
| (6) | 397,1525 | + | | 398.1622 |
| X1AEDLeu | C ₂₂ H ₂₃ NO ₆ | - | 396.1466 | |
| (7) | 397,1525 | + | | 398.1616 |
| X1AEDVal | C ₂₁ H ₂₁ NO ₆ | - | 382.1310 | |
| (11) | 383.1369 | + | | 384.1453 |
| X1AELPG | C ₂₄ H ₁₉ NO | - | 416.1149 | |
| (12) | 6 | + | | 418.1297 |
| X1AELTryp | C ₂₇ H ₂₂ N ₂ | - | 469.1408 | |
| (16) | O ₆ | + | | 471.1566 |
| X1AELSer | C ₂₁ H ₁₉ NO ₈ | - | 370.0936 | |
| (20) | 371,1005 | + | | 372.1084 |
| X1AEDAspA | C ₂₁ H ₁₉ NO ₈ | - | 412.1052 | |
| . | 413.1111 | + | | 414.1207 |
| X1AAGli | C ₁₇ H ₁₃ NO ₆ | - | 326.0686 | |
| (34) | 327.0743 | + | | 328.0838 |
| X1AALIsoLe | C ₂₁ H ₂₁ NO ₆ | - | 382.1325 | |
| u | 383.1369 | + | | 384.1464 |
| X1AALLeu | C ₂₁ H ₂₁ NO ₆ | - | 382.1319 | |
| (36) | 383.1369 | + | | 384.1443 |
| X1AADVal | C ₂₀ H ₁₉ NO ₆ | - | 368.1166 | |
| (41) | 369.1212 | + | | 370.1296 |
| X1AADPG | C ₂₃ H ₁₇ NO ₆ | - | 402.1010 | |
| (43) | 403.3900 | + | | 404.1137 |
| X1AALPA | C ₂₄ H ₁₉ NO ₆ | - | 416.1165 | |
| (44) | 417.1212 | + | | 418.1292 |
| X1AALTryp | C ₂₆ H ₂₀ N ₂ O | - | 455.1279 | |
| (46) | 6 | + | | 457.1409 |
| | | - | 356.0799 | |

| | | | | |
|------------------|--------------------|---|----------|----------|
| X1AALSer | $C_{18}H_{15}NO_7$ | + | | 358.0955 |
| X1AALAspA | $C_{19}H_{15}NO_8$ | - | 384.0737 | |
| . | 385.0798 | + | | 386.0879 |
| X1AALGluA | $C_{20}H_{17}NO_8$ | - | 398.0908 | |
| . | 399.0954 | + | | 400.1048 |
| X1AADThre | $C_{19}H_{17}NO_7$ | - | 370.0957 | |
| o | 371.1005 | + | | 372.1086 |

2. CYTOTOXICITY AND ANTI-INFLAMMATORY ACTIVITY

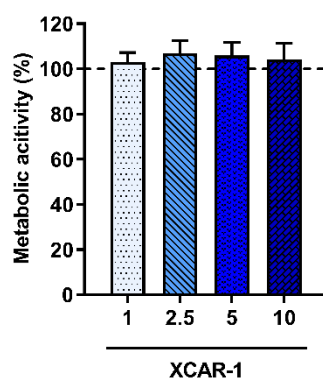


Figure S2. Metabolic activity of LPS-activated macrophages cultured in the presence of XCAR-1 at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

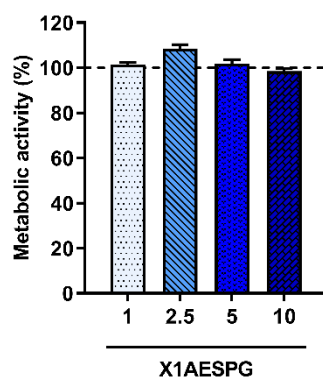


Figure S3. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AESPG at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

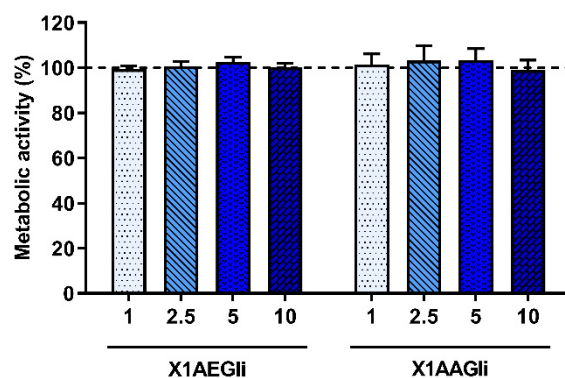


Figure S4. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AEGli and X1AAGli at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

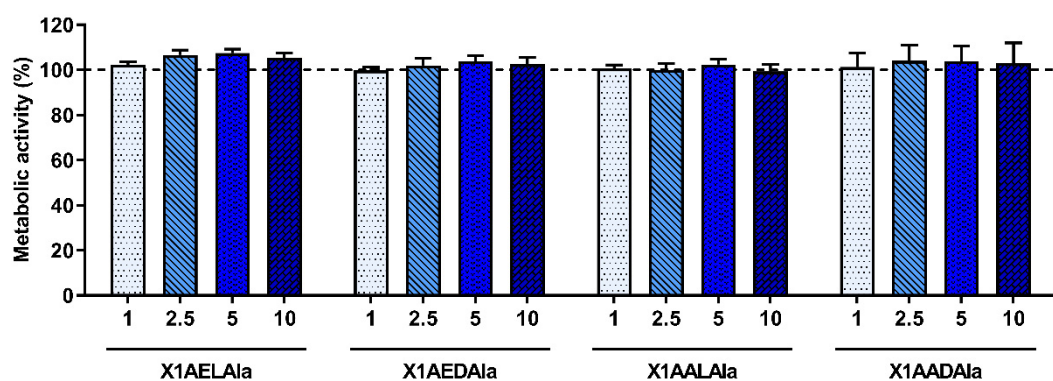


Figure S5. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELAla, X1AEDAla, X1AALAla, and X1AADAla at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

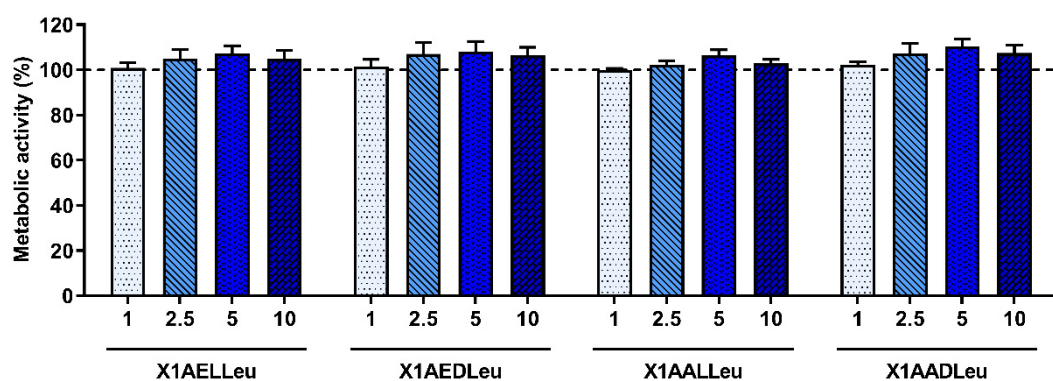


Figure S6. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELLEu, X1AEDLeu, X1AALLeu, and X1AADLeu at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

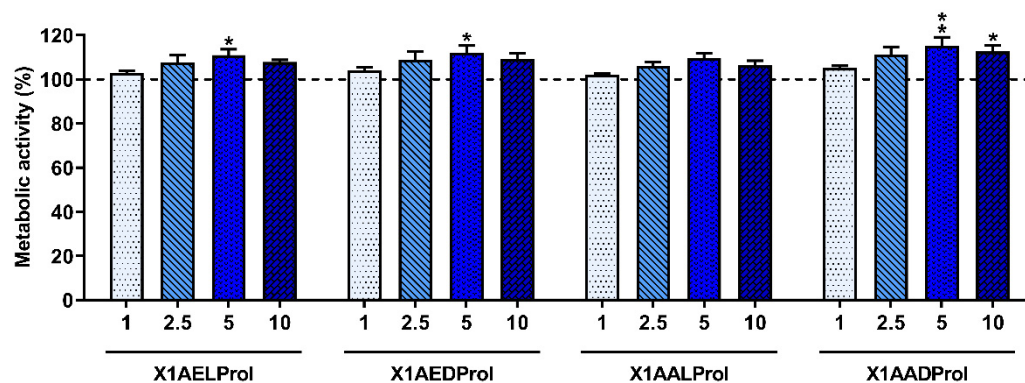


Figure S7. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELProl, X1AEDProl, X1AALProl, and X1AADProl at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0435$) and ** ($p < 0.084$) in comparison with non-treated LPS-stimulated macrophages.

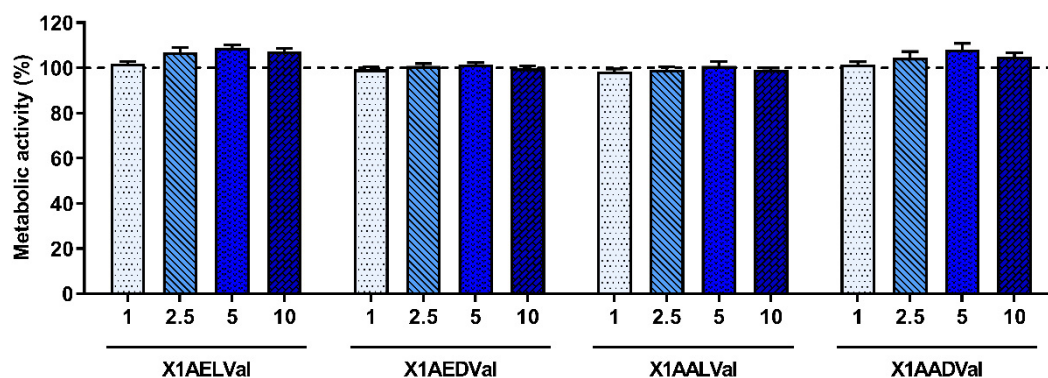


Figure S8. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELVal, X1AEDVal, X1AALVal, and X1AADVal at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

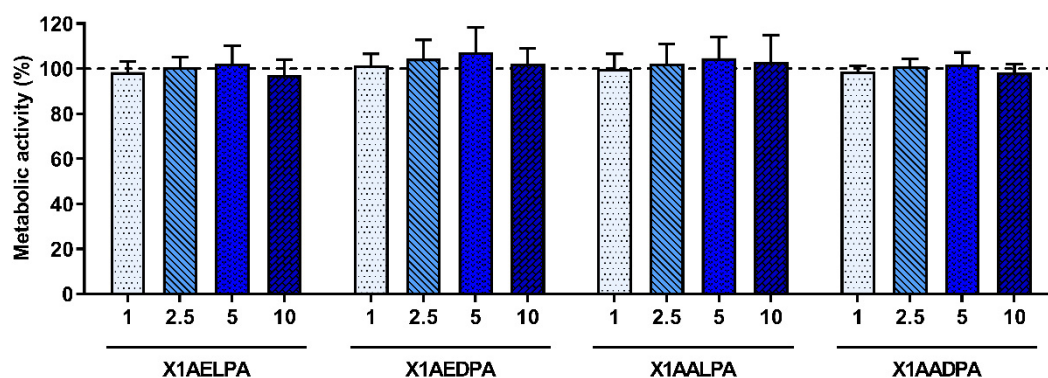


Figure S9. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELPA, X1AEDPA, X1AALPA, and X1AADPA at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

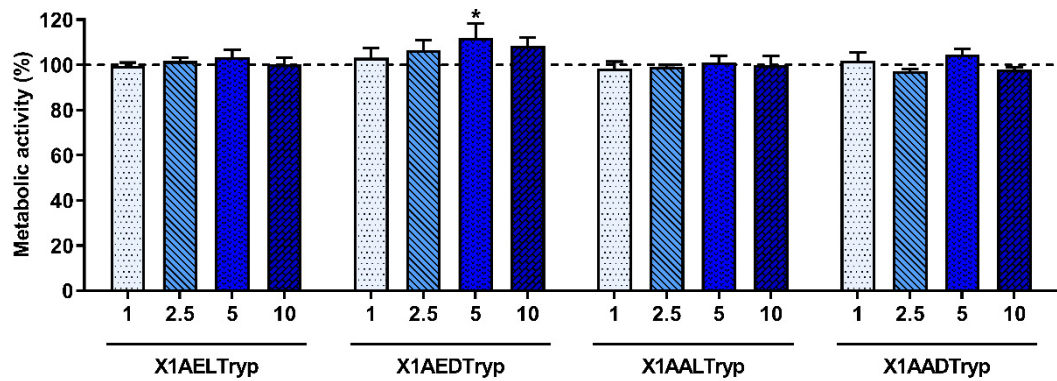


Figure S10. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELTryp, X1AEDTryp, X1AALTryp, and X1AADTryp at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0238$) in comparison with non-treated LPS-stimulated macrophages.

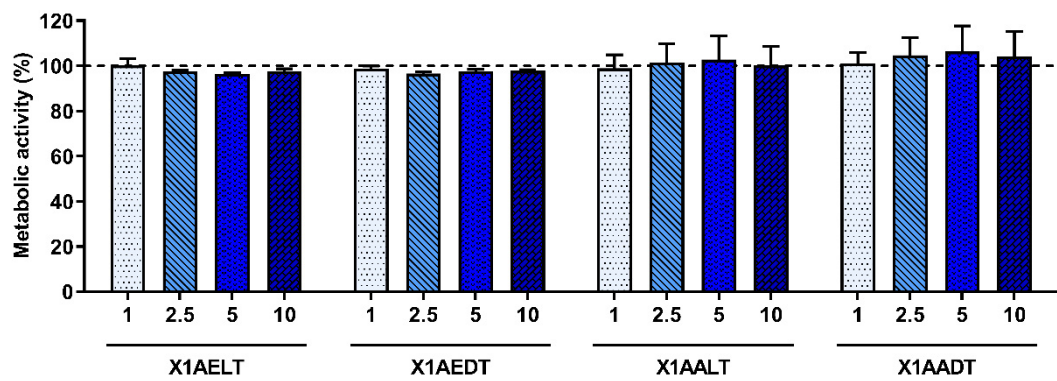


Figure S11. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELT, X1AEDT, X1AALT, and X1AADT at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

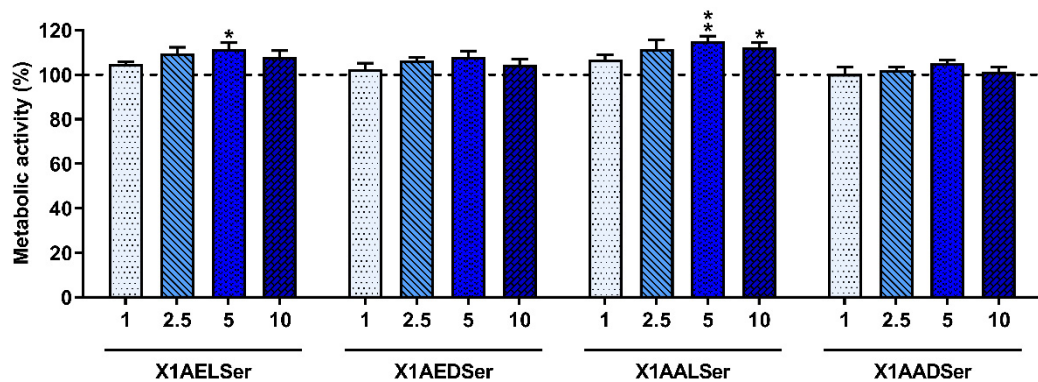


Figure S12. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELSer, X1AEDSer, X1AALSer, and X1AADSer at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0435$) and ** ($p < 0.084$) in comparison with non-treated LPS-stimulated macrophages.

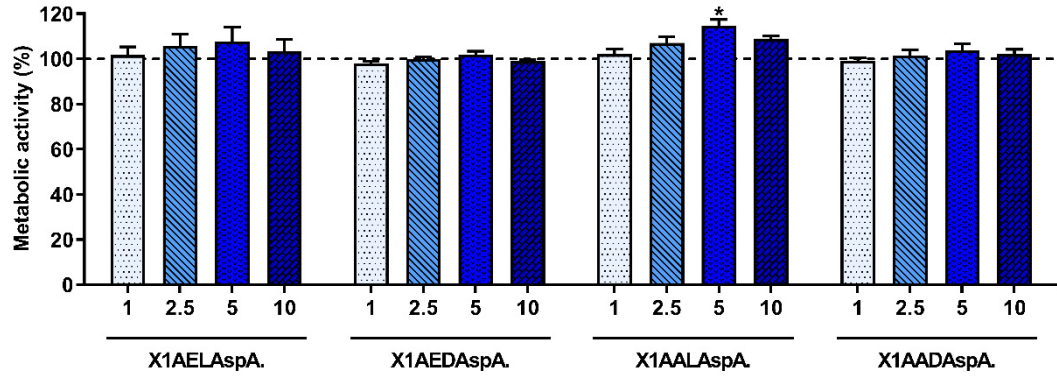


Figure S13. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELAspA, X1AEDAspA, X1AALAspA, and X1AADAspA at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0435$) in comparison with non-treated LPS-stimulated macrophages.

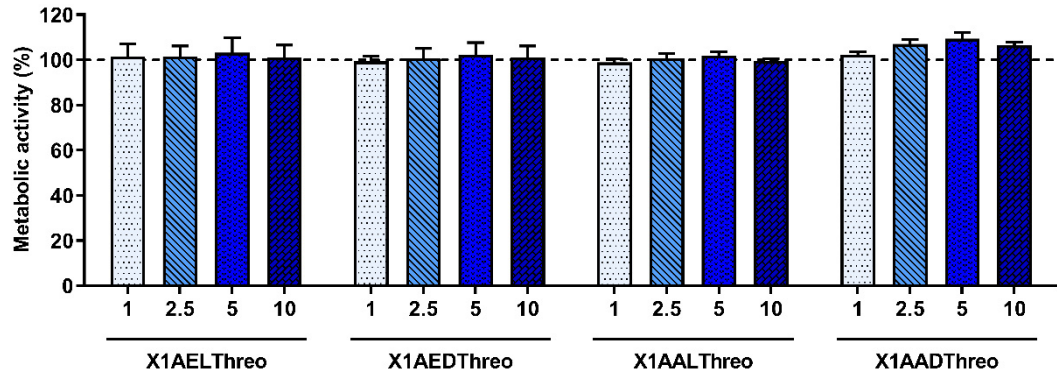


Figure S14. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELThreo, X1AEDThreo, X1AALThreo, and X1AADThreo at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

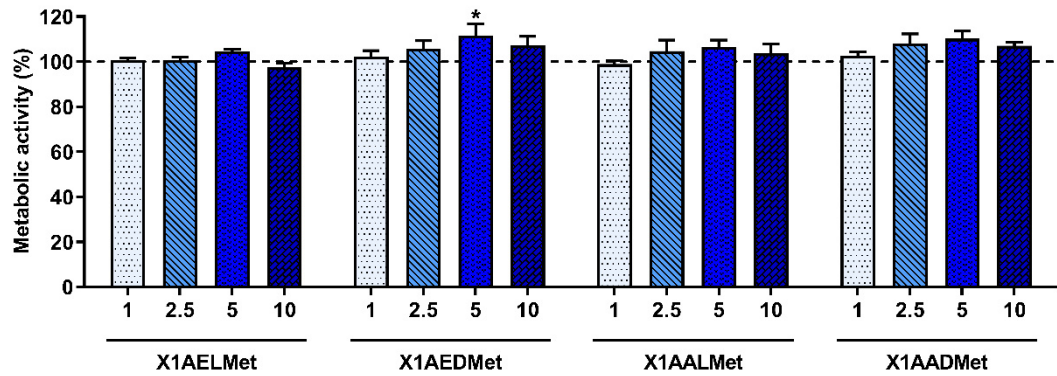


Figure S15. Metabolic activity of LPS-activated macrophages cultured in the presence of X1AELMet, X1AEDMet, X1AALMet, and X1AADMet at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0238$) in comparison with non-treated LPS-stimulated macrophages.

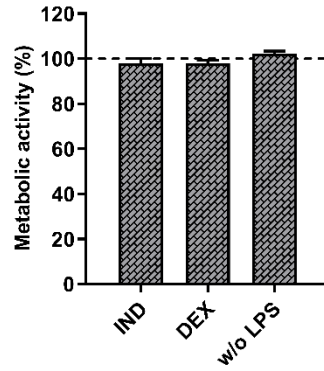


Figure S16. Metabolic activity of LPS-activated macrophages cultured in the presence of clinically used anti-inflammatory drugs (indomethacin – IND – and dexamethasone – DEX –, at 10 μ M), and non-stimulated macrophages (w/o LPS), for 22 h of culture. No statistically significant differences were observed.

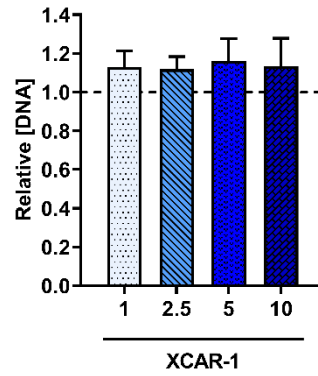


Figure S17. DNA relative concentration of LPS-activated macrophages cultured in the presence of XCAR-1 at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

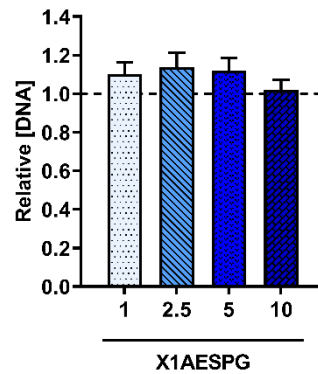


Figure S18. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AESP at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

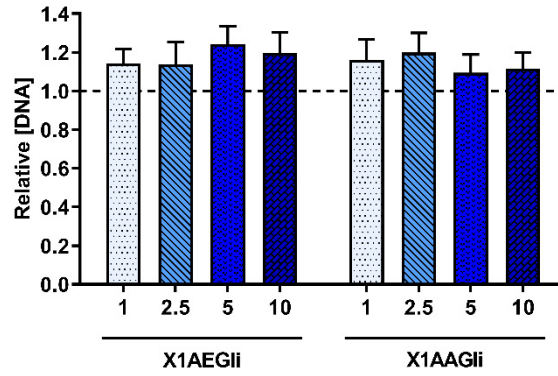


Figure S19. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AEGli and X1AAGli at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

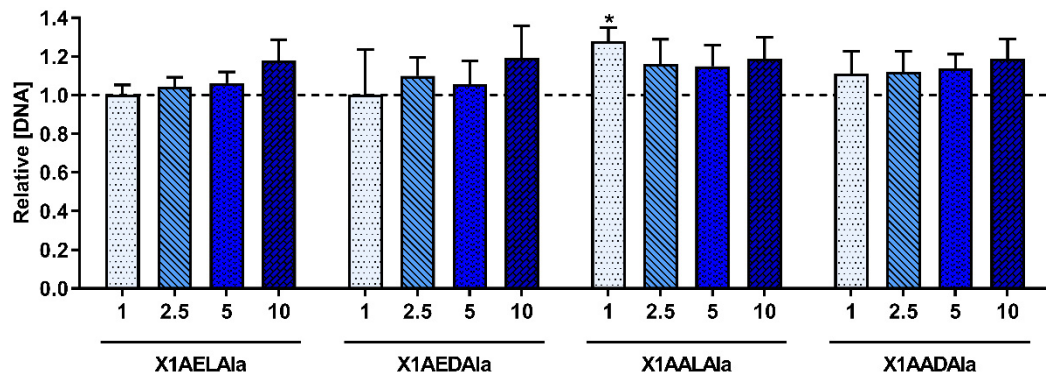


Figure S20. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELAla, X1AEDAla, X1AALAla, and X1AADAla at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0140$) in comparison with non-treated LPS-stimulated macrophages.

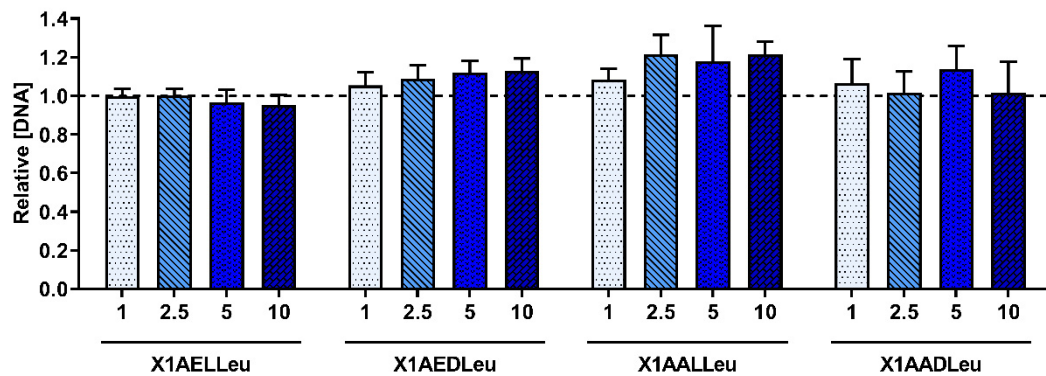


Figure S21. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELLEu, X1AEDLeu, X1AALLeu, and X1AADLeu at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

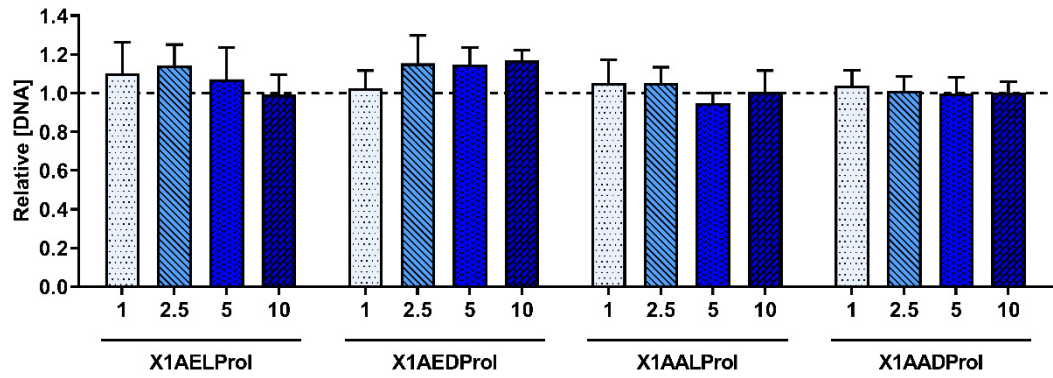


Figure S22. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELProl, X1AEDProl, X1AALProl, and X1AADProl and at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

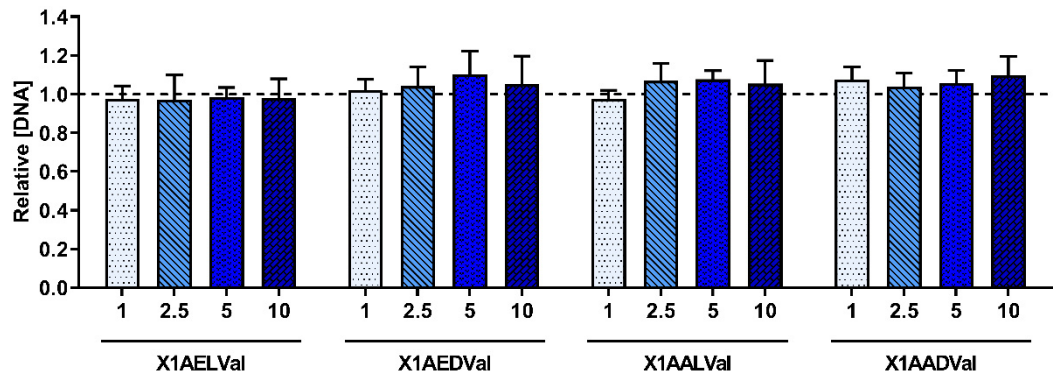


Figure S23. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELVal, X1AEDVal, X1AALVal, and X1AADVal at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

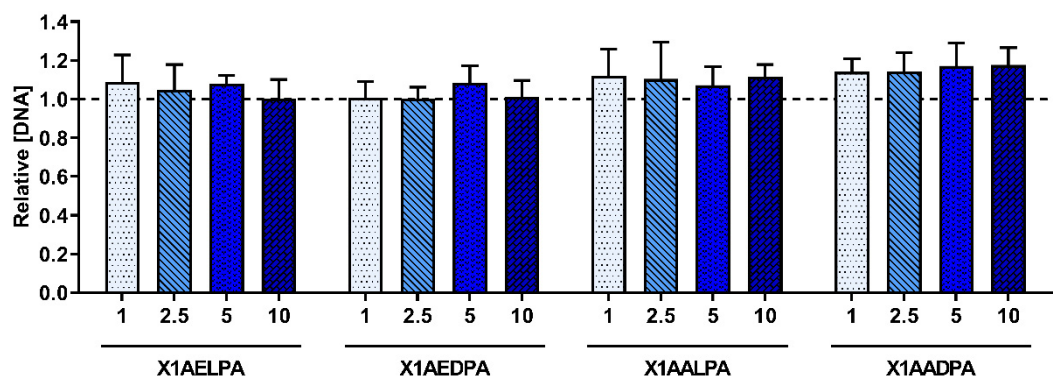


Figure S24. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELPA, X1AEDPA, X1AALPA, and X1AADPA at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

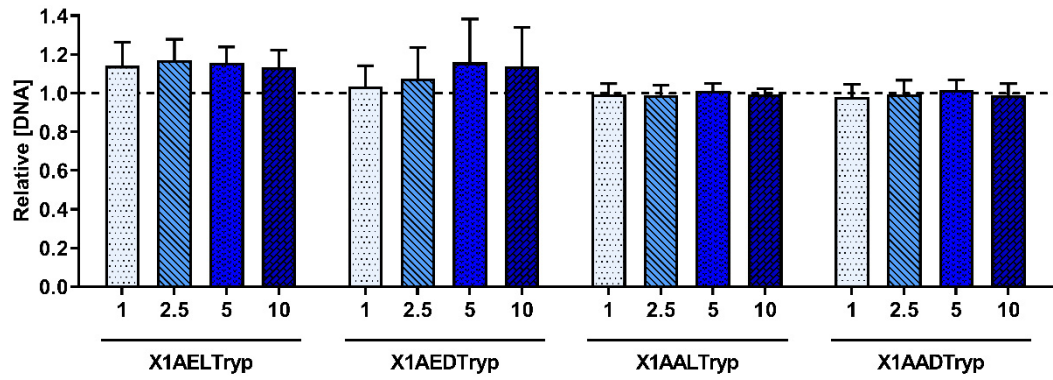


Figure S25. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELTryp, X1AEDTryp, X1AALTryp, and X1AADTryp at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

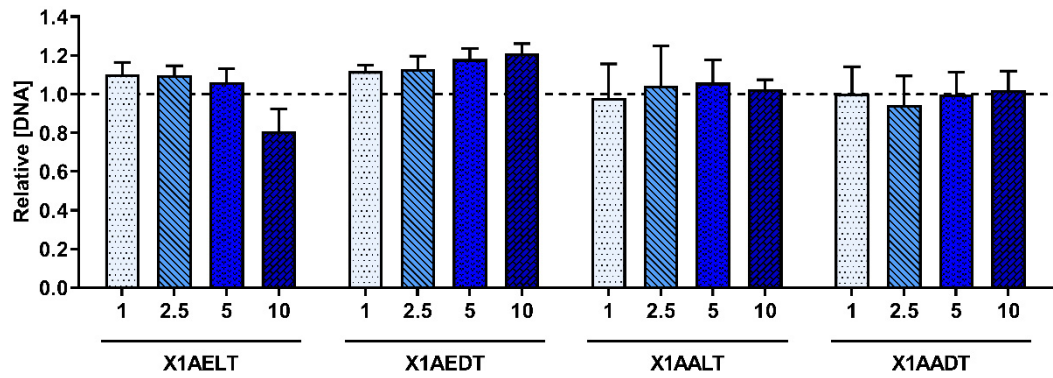


Figure S26. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELT, X1AEDT, X1AALT, and X1AADT at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

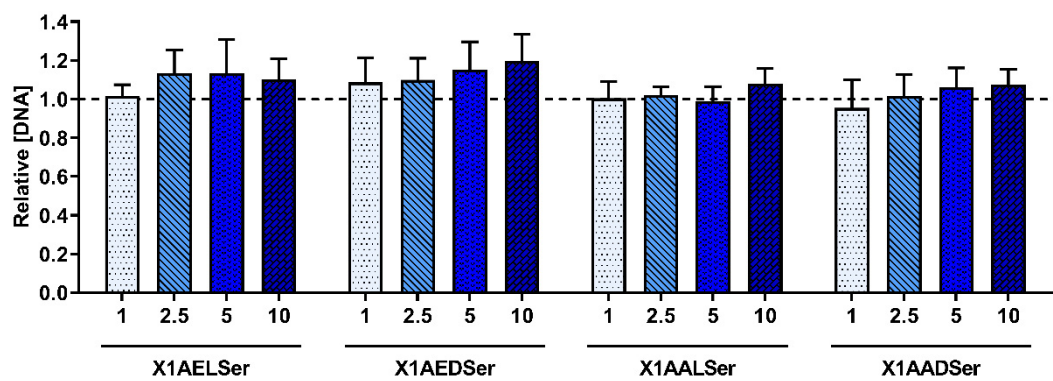


Figure S27. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELSer, X1AEDSer, X1AALSer, and X1AADSer at different concentrations (μ M) for 22 h of culture. No statistically significant differences were observed.

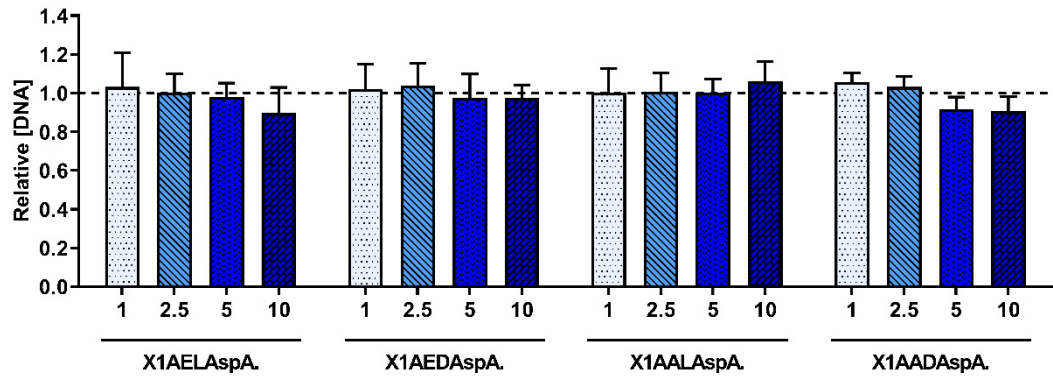
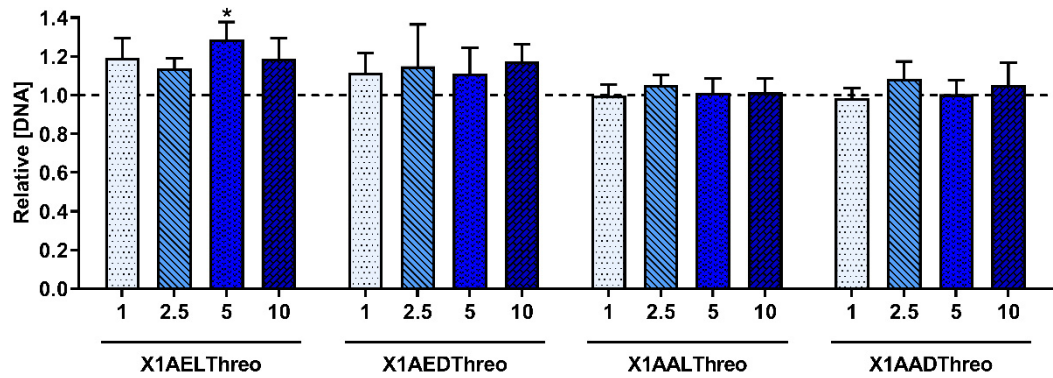


Figure S28. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELAspA, X1AEDAspA, X1AALAspA, and X1AADAspA. at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.



*Figure S29. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELThreo, X1AEDThreo, X1AALThreo, and X1AADThreo at different concentrations (μM) for 22 h of culture. Statistically significant differences are * ($p < 0.0322$) in comparison with non-treated LPS-stimulated macrophages.*

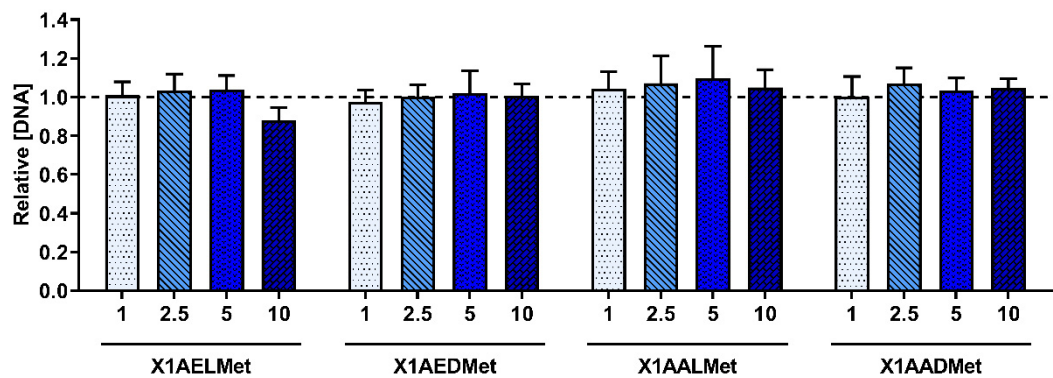


Figure S30. DNA relative concentration of LPS-activated macrophages cultured in the presence of X1AELMet, X1AEDMet, X1AALMet, and X1AADMet at different concentrations (μM) for 22 h of culture. No statistically significant differences were observed.

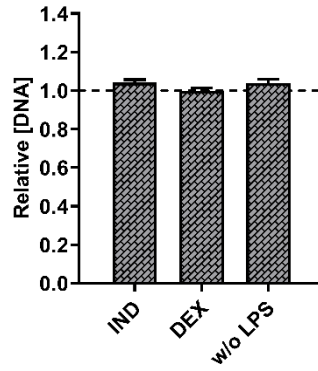


Figure S31. DNA relative concentration of LPS-activated macrophages cultured in the presence of clinically used anti-inflammatory drugs (indomethacin – INDO – and dexamethasone – DEX –, at 10 μ M), and non-stimulated macrophages (w/o LPS), for 22 h of culture. No statistically significant differences were observed.

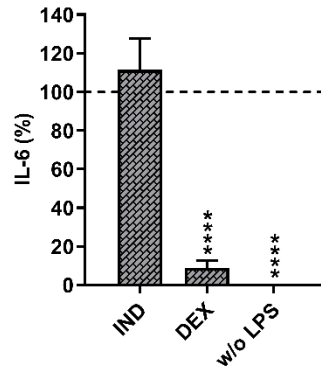


Figure S32. IL-6 percentage of LPS-activated macrophages cultured in the presence of clinically used anti-inflammatory drugs (indomethacin – INDO – and dexamethasone – DEX, at 10 μ M), and non-stimulated macrophages (w/o LPS), for 22 h of culture. Statistically significant differences are **** ($p < 0.0001$) in comparison with non-treated LPS-stimulated macrophages.