Supplementary Information

Diaryl urea LDV peptidomimetics as $\alpha_4\beta_1$ integrin antagonists: synthesis, adhesion inhibition and toxicity evaluation on CCRF-CEM cell line

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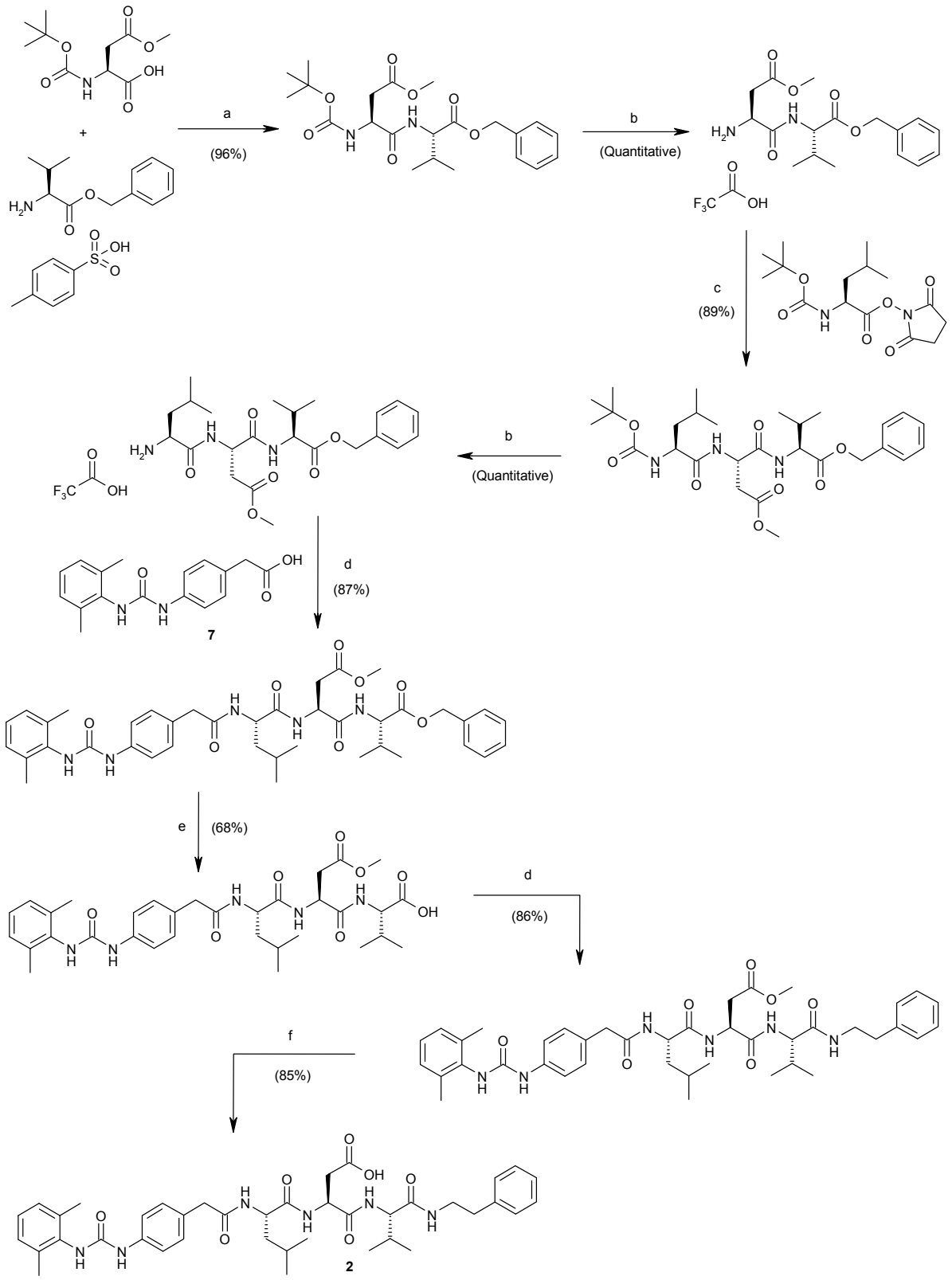
‡ Abbreviations: COMU, 1-[(1-(cyano-2-ethoxy-2-oxo-ethylideneaminooxy)-dimethylamino-morpholinomethylene)]methanaminium hexafluorophosphate; DCM, dichloromethane; DEAD, diethylazodicarboxylate; DIPEA, *N*,*N*-diisopropylethylamine, DMF, *N*,*N*-dimethylformamide; EDC.HCl, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBt, *N*-hydroxybenzotriazole, PyBOP, benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate; THF, tetrahydrofuran; TFA, trifluoroacetic acid.

Content:

1. Synthesis of "LDV" modified peptides (2) and (3).

1.1. *Synthesis of peptide* **(2)**.

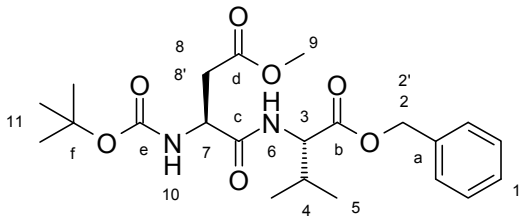


Scheme S1 Synthesis of compound **2**. *Reagents and conditions*: (a) COMU, DIPEA, DMF; (b) TFA, DCM; (c) Et_3N, DCM; (d) PyBOP, Et_3N, DMF; (e) H_2, Pd/C (10%), EtOH, DMF; (f) 1N LiOH/H_2O, DMF, MeOH and then HCl.

Methyl (3*S*)-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-3-[(*tert*-butoxy carbonyl)amino]-4-oxobutanoate.

To a solution of *N*-(*tert*-butoxycarbonyl)-L-aspartic acid β-methyl ester (0.196 g, 0.79 mmol, 1.0 equiv), L-valine-benzyl-ester *p*-toluenesulfonate salt (0.300 g, 0.79 mmol, 1.0 equiv) and DIPEA (0.28 mL, 1.58 mmol, 2.0 equiv) in DMF (20 mL) cooled at 0°C, was added COMU (0.336 g, 0.79 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 0°C, and then overnight at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 0.05 N aqueous hydrochloric acid (2x), saturated aqueous $NaHCO_3$ (2x) and brine (2x), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (elution with EtOAc/Hexane: 3/7) to give the title compound as a colorless oil (0.331 g, 96%).

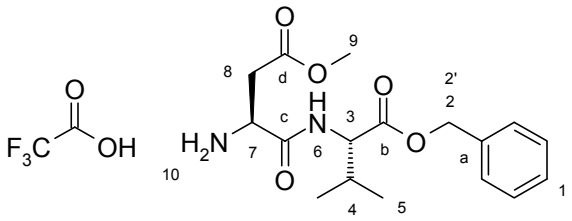
$\boldsymbol{R_f}$ = 0.27 (EtOAc/Hexane: 3/7, $KMnO_4$); **IR** (thin film, cm^{-1}) ν: 3327, 2966, 1740, 1684, 1522, 1456, 1393, 1367, 1250, 1165, 754, 698; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.84-0.92 (m, 6H, H_5), 1.45 (s, 9H, H_{11}), 2.13-2.24 (m, 1H, H_4), 2.66 (dd, $J_{8'\text{-}8}$ = 17.1 Hz, $J_{8'\text{-}7}$ = 6.4 Hz, 1H, $H_{8'}$), 2.97 (dd, $J_{8\text{-}8'}$ = 17.1 Hz, $J_{8\text{-}7}$ = 4.3 Hz, 1H, H_8), 3.68 (s, 3H, H_9), 4.50-4.55 (m, 2H, H_3, H_7), 5.11 (d, $J_{2'\text{-}2}$ = 12.2 Hz, 1H, $H_{2'}$), 5.18 (d, $J_{2\text{-}2'}$ = 12.2 Hz, 1H, H_2), 5.75-5.78 (m, 1H, NH_{10}), 7.06-7.09 (m, 1H, NH_6), 7.32-7.34 (m, 5H, H_1); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.5, 19.1 (C_5), 28.4 (C_{11}), 31.2 (C_4), 35.8 ($C_{8,8'}$), 50.6 (C_7), 52.2 (C_9), 57.4 (C_3), 67.1 ($C_{2,2'}$), 80.6 (C_f), 128.4, 128.7 (C_1), 135.4 (C_a), 155.7 (C_e), 170.8 (C_c), 171.4 (C_b), 172.7 (C_d); **MS** (ESI^+) *m/z* (rel intensity): 894.7 ($[2M+Na]^+$, 10), 475.0 ($[M+K]^+$, 7), 459.1 ($[M+Na]^+$, 100), 436.8 ($[M+H]^+$, 16), 380.9 ($[M+H\text{-}C_4H_9]^+$, 59), 337.1 ($[M+H\text{-}CO_2C_4H_8]^+$, 54); **HRMS** ($ESI^+$) *m/z* for $C_{22}H_{32}N_2O_7Na$ $[M+Na]^+$: calcd 459.2107; found 459.2096.



Methyl (3*S*)-3-amino-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-4-oxobutanoate trifluoroacetate.

A solution of methyl-(3*S*)-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-3-[(*tert*-butoxycarbonyl)amino]-4-oxobutanoate (0.330 g, 0.76 mmol) in a mixture of DCM (7 mL) and trifluoroacetic acid (7 mL) was stirred for 2 h. After concentration under vacuum, the residue was dissolved in DCM and the solvent was evaporated under reduced pressure (3x) to give the title compound as a TFA salt and a colorless oil (0.341 g, quantitative).

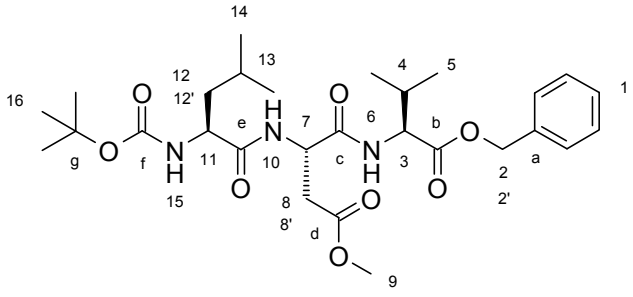
$\boldsymbol{R_f}$ = 0.27 (EtOAc/DCM: 4/1, $KMnO_4$); **IR** (thin film, cm^{-1}) ν: 2964, 1734, 1684, 1558, 1541, 1508, 1456, 1317, 1204, 1138, 837, 800, 721, 698; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.83-0.89 (m, 6H, H_5), 2.14-2.25 (m, 1H, H_4), 2.87-3.03 (m, 2H, H_8), 3.66 (s, 3H, H_9), 4.41-4.45 (m, 1H, H_3), 4.59-4.62 (m, 1H, H_7), 5.06 (d, $J_{2'\text{-}2}$ = 12.1 Hz, 1H, $H_{2'}$), 5.18 (d, $J_{2\text{-}2'}$ = 12.1 Hz, 1H, H_2), 7.31-7.34 (m, 5H, H_1), 7.64 (d, $J_{6\text{-}3}$ = 8.2 Hz, 1H, NH_6); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.4, 18.8 (C_5), 30.4 (C_4), 34.9 (C_8), 49.7 (C_7), 52.9 (C_9), 58.5 (C_3), 67.4 ($C_{2,2'}$), 128.6, 128.8 (C_1), 135.2 (C_a), 168.3 (C_c), 170.9 (C_b), 171.6 (C_d); **MS** ($APCI^+$) *m/z* (rel intensity): 337.0 ($[M+H]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{17}H_{24}N_2O_5Na$ $[M+Na]^+$: calcd 359.1583; found 359.1572.



Benzyl (6*S*,9*S*,12*S*)-9-(2-methoxy-2-oxoethyl)-2,2-dimethyl-6-(2-methylpropyl)-4,7,10-trioxo-12-(propan-2-yl)-3-oxa-5,8,11-triazatridecan-13-oate.

To a stirred solution of methyl (3*S*)-3-amino-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-4-oxobutanoate trifluoroacetate (0.338 g, 0.75 mmol, 1.0 equiv) in DCM (20 mL), was added dropwise triethylamine (0.5 mL, 3.60 mmol, 4.8 equiv) and *N*-(*tert*-butoxycarbonyl)-L-leucine *N*-hydroxysuccinimide ester (0.246 g, 0.75 mmol, 1.0 equiv). The reaction mixture was stirred overnight, and then concentrated under vacuum. The residue was dissolved in DCM. The organic layer was washed with 0.05 N aqueous hydrochloric acid (2x), saturated aqueous $NaHCO_3$ (2x) and brine (2x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (elution with EtOAc/Hexane: 1/1) to give the title compound as a colorless oil (0.367 g, 89%).

R_f = 0.40 (EtOAc/Hexane: 1/1, $KMnO_4$); **IR** (thin film, cm^{-1}) ν: 3298, 2961, 1742, 1651, 1541, 1522, 1508, 1456, 1366, 1173; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.83-0.93 (m, 12H, H_5, H_{14}), 1.42 (s, 9H, H_{16}), 1.42-1.53 (m, 1H, $H_{12'}$), 1.59-1.75 (m, 2H, H_{12}, H_{13}), 2.12-2.25 (m, 1H, H_4), 2.63 (dd, $J_{8'-8}$ = 17.1 Hz, $J_{8'-7}$ = 6.8 Hz, 1H, $H_{8'}$), 2.95 (dd, $J_{8-8'}$ = 17.1 Hz, J_{8-7} = 3.3 Hz, 1H, H_8), 3.67 (s, 3H, H_9), 4.06-4.16 (m, 1H, H_{11}), 4.39-4.50 (m, 1H, H_3), 4.77-4.86 (m, 1H, H_7), 4.94 (d, J_{15-11} = 6.6 Hz, 1H, NH_{15}), 5.09 (d, $J_{2'-2}$ = 12.2 Hz, 1H, $H_{2'}$), 5.17 (d, $J_{2-2'}$ = 12.2 Hz, 1H, H_2), 7.12 (d, J_{6-3} = 8.6 Hz, 1H, NH_6), 7.28-7.46 (m, 6H, H_1, NH_{10}); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.6, 19.1 (C_5), 21.9, 23.0 (C_{14}), 24.9 (C_{13}), 28.4 (C_{16}), 31.0 (C_4), 35.5 ($C_{8,8'}$), 41.4 ($C_{12,12'}$), 49.3 (C_7), 52.2 (C_9), 53.4 (C_{11}), 57.7 (C_3), 67.0 (C_2), 80.3 (C_g), 128.4, 128.5, 128.7 (C_1), 135.5 (C_a), 155.7 (C_f), 170.3 (C_c), 171.2 (C_b), 172.6 (C_d), 172.9 (C_e); **MS** (ESI^+) *m/z* (rel intensity): 572.1 ($[M+Na]^+$, 100), 516.1 ($[M+Na-C_4H_8]^+$, 18), 493.9 ($[M+H-C_4H_8]^+$, 8), 450.1 ($[M+H-CO_2C_4H_8]^+$, 11); **HRMS** (ESI^+) *m/z* for $C_{28}H_{43}N_3O_8Na$ $[M+Na]^+$: calcd 572.2948; found 572.2932.

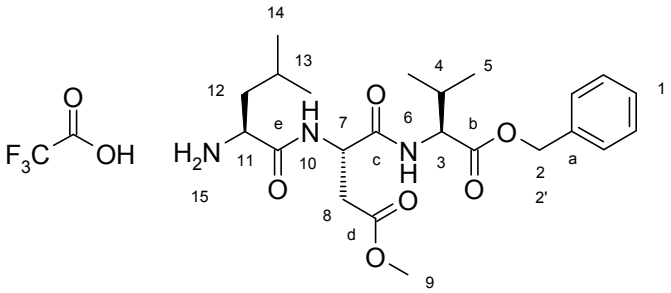


Methyl (3*S*)-3-{[(2*S*)-2-amino-4-methylpentanoyl]amino}-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-4-oxobutanoate trifluoroacetate.

A solution of benzyl-(6*S*,9*S*,12*S*)-9-(2-methoxy-2-oxoethyl)-2,2-dimethyl-6-(2-methylpropyl)-4,7,10-trioxo-12-(propan-2-yl)-3-oxa-5,8,11-triazatridecan-13-oate (0.305 g, 0.55 mmol) in a mixture of DCM (10 mL) and trifluoroacetic acid (7 mL) was stirred for 2 h. After concentration under vacuum, the residue was dissolved in DCM and the solvent was

evaporated under reduced pressure (4x) to give the title compound as a TFA salt and a colorless oil (0.313 g, quantitative).

R_f = 0.56 (EtOAc/MeOH: 4/1, $KMnO_4$); **IR** (thin film, cm^{-1}) ν: 3310, 2961, 1734, 1663, 1558, 1541, 1436, 1373, 1202, 1140, 721, 698; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.81-0.93 (m, 12H, H_5, H_{14}), 1.62-1.74 (m, 3H, H_{12}, H_{13}), 2.12-2.28 (m, 1H, H_4), 2.78 (d, $J_{8\text{-}7}$ = 6.2 Hz, 2H, H_8), 3.61 (s, 3H, H_9), 4.17-4.25 (m, 1H, H_{11}), 4.53-4.58 (m, 1H, H_3), 5.06-5.11 (m, 2H, $H_{2'}$, H_7), 5.21(d, $J_{2\text{-}2'}$ = 12.1 Hz, 1H, H_2), 7.31-7.35 (m, 5H, H_1), 7.79 (d, $J_{6\text{-}3}$ = 8.7 Hz, 1H, NH_6), 8.06 (d, $J_{10\text{-}7}$ = 7.8 Hz, 1H, NH_{10}); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.4, 18.9 (C_5), 21.9, 22.0 (C_{14}), 24.5 (C_{13}), 31.1 (C_4), 35.7 (C_8), 40.6 (C_{12}), 50.0 (C_7), 52.4 (C_9), 52.7 (C_{11}), 57.8 (C_3), 67.6 ($C_{2,2'}$), 128.6, 128.8 (C_1), 135.1 (C_a), 169.8 (C_e), 170.9 (C_c), 171.7 (C_b), 171.8 (C_d); **MS** (ESI^+) *m/z* (rel intensity): 472.2 ($[M+Na]^+$, 11), 450.1 ($[M+H]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{23}H_{36}N_3O_6$ $[M+H]^+$: calcd 450.2604; found 450.2584.

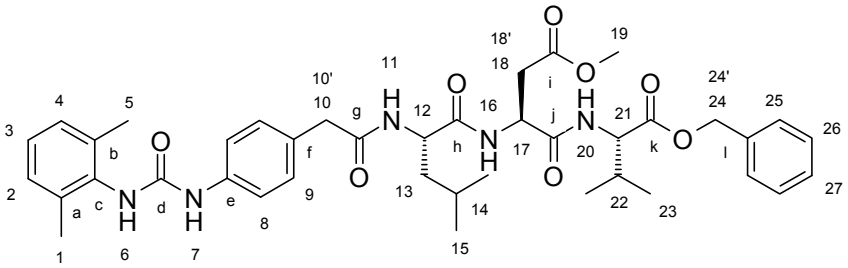


Methyl (3*S*)-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-3-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-4-methylpentanoyl] amino}-4-oxobutanoate.

To a solution of [4-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]acetic acid **7** (0.164 g, 0.55 mmol, 1.0 equiv) in anhydrous DMF (20 mL) under argon atmosphere, were added PyBOP (0.286 g, 0.55 mmol, 1.0 equiv) and triethylamine (0.15 mL, 1.10 mmol, 2.0 equiv). The reaction mixture was stirred for 20 min. A solution of methyl-(3*S*)-3-{[(2*S*)-2-amino-4-methylpentanoyl]amino}-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-4-oxobutanoate trifluoroacetate (0.310 g, 0.55 mmol, 1.0 equiv) in DMF (4 mL) was introduced dropwise, and the reaction mixture was stirred overnight. The mixture was diluted with ethyl acetate. The organic layer was washed with 0.05 N aqueous hydrochloric acid (1x) and water (4x), and then concentrated under vaccum. The resulting residue was triturated with ethyl acetate. The precipitate formed was collected by filtration, washed with ethyl acetate and hexane, dried *in vacuo* to give the title compound as a yellow solid (0.350 g, 87%).

R_f = 0.29 (DCM/MeOH: 95/5, $KMnO_4$); **mp**: 230-232°C; **IR** (thin film, cm^{-1}) ν: 3279, 3063, 2957, 1732, 1634, 1539, 1369, 1213, 1190, 1142, 764, 696; **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 0.78-0.86 (m, 12H, H_{15}, H_{23}), 1.42 (t, J = 7.3 Hz, 2H, H_{13}), 1.52-1.60 (m, 1H, H_{14}), 1.98-2.08 (m, 1H, H_{22}), 2.19 (s, 6H, H_1, H_5), 2.56 (dd, $J_{18'\text{-}18}$ = 16.2 Hz, $J_{18'\text{-}17}$ = 8.4 Hz, 1H, $H_{18'}$), 2.69-2.74 (m, 1H, H_{18}), 3.31-3.35 (m, 1H, $H_{10'}$), 3.41 (d, $J_{10\text{-}10'}$ = 14.0 Hz, 1H, H_{10}), 3.55 (s, 3H, H_{19}), 4.16-4.19 (m, 1H, H_{21}), 4.24-4.29 (m, 1H, H_{12}), 4.61-4.66 (m, 1H, H_{17}), 5.09 (d, $J_{24'\text{-}24}$ = 12.5 Hz, 1H, $H_{24'}$), 5.15 (d, $J_{24\text{-}24'}$ = 12.5 Hz, 1H, H_{24}), 7.02-7.08 (m, 3H, H_2, H_3, H_4), 7.11 (d, $J_{9\text{-}8}$ = 8.5 Hz, 2H, H_9), 7.31-7.39 (m, 7H, H_8, H_{25}, H_{26}, H_{27}), 7.67 (s, 1H, NH_6), 7.92 (d, $J_{20\text{-}21}$ = 8.2 Hz, 1H, NH_{20}), 8.17 (d, $J_{11\text{-}12}$ = 8.0 Hz, 1H, NH_{11}), 8.34 (d, $J_{16\text{-}17}$ = 7.7 Hz, 1H, NH_{16}), 8.65 (br s, 1H, NH_7); **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 17.95, 18.27, 18.80 (C_1, C_5, C_{23}), 21.64, 22.95 (C_{15}), 24.13 (C_{14}), 29.87 (C_{22}), 35.57 ($C_{18,18'}$), 41.06 (C_{13}), 41.37 ($C_{10,10'}$), 49.25 (C_{17}), 50.97 (C_{12}), 51.49 (C_{19}), 57.49 (C_{21}), 65.96 ($C_{24,24'}$), 117.73 (C_8), 125.89 (C_3), 127.71 (C_2, C_4), 128.05 (C_{25}), 128.11 (C_{27}), 128.42 (C_{26}), 129.21 (C_9, C_f), 135.37 (C_c), 135.51 (C_a,

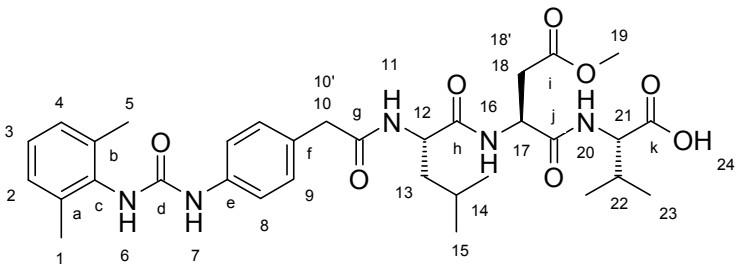
C_b), 135.83 (C_l), 138.61 (C_e), 153.13 (C_d), 170.41, 170.44, 170.49 (C_g, C_i, C_j), 170.98 (C_k), 172.33 (C_h); **MS** (ESI^+) *m/z* (rel intensity): 1480.8 ($[2M+Na]^+$, 8), 752.3 ($[M+Na]^+$, 100), 730.0 ($[M+H]^+$, 58); **HRMS** (ESI^+) *m/z* for $C_{40}H_{51}N_5O_8Na$ $[M+Na]^+$: calcd 752.3635; found 752.3626.



(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl] amino}-4-methylpentanoyl]amino}-4-methoxy-4-oxobutanoyl]amino}-3-methylbutanoic acid.

To a solution of methyl (3*S*)-4-{[(2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl]amino}-3-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-4-methyl pentanoyl]amino}-4-oxobutanoate (0.300 g, 0.41 mmol) in ethanol (30 mL) and DMF (9 mL), was added Pd/C (10 %) as catalyst. The reaction mixture was stirred overnight under hydrogen atmosphere (1 atm). Then, the mixture was filtered through a Celite pad and eluted with a mixture of ethyl acetate and methanol. The filtrate was concentrated under vacuum. The crude residue was dissolved in ethyl acetate. The organic layer was washed with 0.05 N aqueous hydrochloric acid (4x), and then concentrated under reduced pressure. The resulting residue was triturated with acetonitrile. The precipitate formed was collected by filtration, washed with acetonitrile and hexane, dried *in vacuo* to give the title compound as a colorless solid (0.180 g, 68%).

$\boldsymbol{R_f}$ = 0.20 (DCM/MeOH: 4/1, $KMnO_4$); **mp**: 214-215°C; **IR** (thin film, cm^{-1}) *ν*: 3277, 3063, 2957, 1728, 1636, 1543, 1215, 768; **^{1}H NMR** (500 MHz, DMSO-d_6) *δ*: 0.79-0.86 (m, 12H, H_{15}, H_{23}), 1.43 (t, J = 7.3 Hz, 2H, H_{13}), 1.54-1.60 (m, 1H, H_{14}), 1.98-2.07 (m, 1H, H_{22}), 2.20 (s, 6H, H_1, H_5), 2.58 (dd, $J_{18'\text{-}18}$ = 16.2 Hz, $J_{18'\text{-}17}$ = 8.1 Hz, 1H, $H_{18'}$), 2.77 (dd, $J_{18\text{-}18'}$ = 16.2 Hz, $J_{18\text{-}17}$ = 6.0 Hz, 1H, H_{18}), 3.33 (d, $J_{10'\text{-}10}$ = 14.0 Hz, 1H, $H_{10'}$), 3.41 (d, $J_{10\text{-}10'}$ = 14.0 Hz, 1H, H_{10}), 3.56 (s, 3H, H_{19}), 4.09-4.12 (m, 1H, H_{21}), 4.26-4.31 (m, 1H, H_{12}), 4.61-4.66 (m, 1H, H_{17}), 7.03-7.08 (m, 3H, H_2, H_3, H_4), 7.11 (d, $J_{9\text{-}8}$ = 8.5 Hz, 2H, H_9), 7.34 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8), 7.62 (d, $J_{20\text{-}21}$ = 8.6 Hz, 1H, NH_{20}), 7.70 (s, 1H, NH_6), 8.18 (d, $J_{11\text{-}12}$ = 8.0 Hz, 1H, NH_{11}), 8.39 (d, $J_{16\text{-}17}$ = 7.8 Hz, 1H, NH_{16}), 8.68 (br s, 1H, NH_7); **^{13}C NMR** (125 MHz, DMSO-d_6) *δ*: 17.7, 18.3, 18.9 (C_1, C_5, C_{23}), 21.6, 22.9 (C_{15}), 24.1(C_{14}), 29.9 (C_{22}), 35.5 ($C_{18,18'}$), 41.2 (C_{13}), 41.4 ($C_{10,10'}$), 49.3 (C_{17}), 50.9 (C_{12}), 51.5 (C_{19}), 57.1 (C_{21}), 117.7 (C_8), 125.9 (C_3), 127.7 (C_2, C_4), 129.2 (C_9, C_f), 135.4 (C_c), 135.5 (C_a, C_b), 138.6 (C_e), 153.1 (C_d), 170.2, 170.3, 170.6 (C_g, C_i, C_j), 172.4 (C_h), 172.6 (C_k); **MS** (ESI^+) *m/z* (rel intensity): 662.3 ($[M+Na]^+$, 100), 640.1 ($[M+H]^+$, 7); **HRMS** (ESI^+) *m/z* for $C_{33}H_{45}N_5O_8Na$ $[M+Na]^+$: calcd 662.3166; found 662.3152.



Methyl (3*S*)-3-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl] amino}-4-methylpentanoyl]amino}-4-({(2*S*)-3-methyl-1-oxo-1-[(2-phenylethyl)amino] butan-2-yl}amino)-4-oxobutanoate.

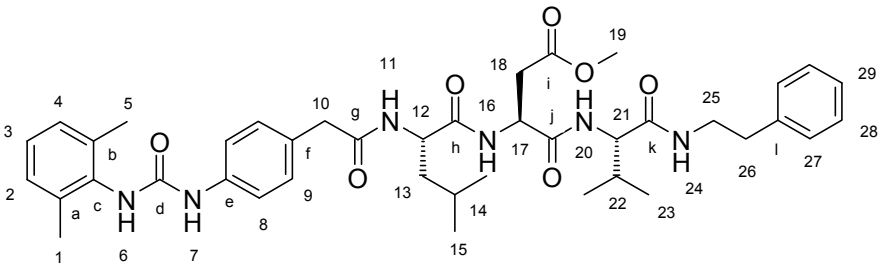
To a solution of (2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino} phenyl)acetyl]amino}-4-methylpentanoyl]amino}-4-methoxy-4-oxobutanoyl]amino}-3-methylbutanoic acid (0.050 g, 0.078 mmol, 1.0 equiv) in anhydrous DMF (6 mL) under argon atmosphere, were added PyBOP (0.041 g, 0.078 mmol, 1.0 equiv) and triethylamine (0.011 mL, 0.078 mmol, 1.0 equiv). The reaction mixture was stirred for 20 min. A solution of phenethylamine (0.010 g, 0.078 mmol, 1.0 equiv) in DMF (0.5 mL) was introduced dropwise, and the reaction mixture was stirred overnight. The mixture was diluted with ethyl acetate. The organic layer was washed with 0.05 N aqueous hydrochloric acid (2x) and water (2x), and then concentrated under vaccum. The resulting residue was triturated with ethyl acetate. The precipitate formed was collected by filtration, washed with ethyl acetate and hexane, dried *in vacuo* to give the title compound as a colorless solid (0.050 g, 86%).

R_f = 0.17 (DCM/MeOH: 95/5, UV); **mp**: 262-264°C; **IR** (thin film, cm^{-1}) ν: 3261, 2921, 1732, 1630, 1539, 1506, 1456, 1161, 761, 696;

2 rotamers observed in NMR analysis: a coalescence of some peaks was observed by performing the NMR analysis at 40°C. A heating at a higher temperature led to a loss of resolution.

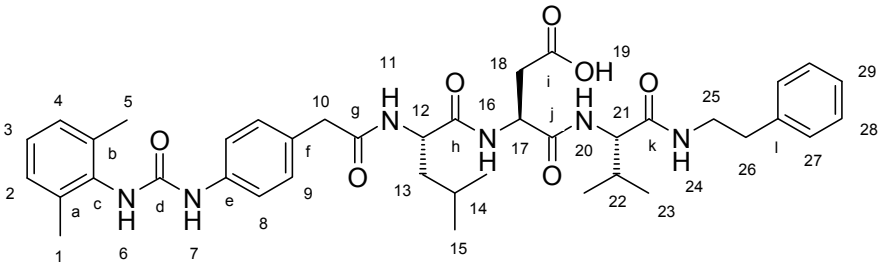
Rotamer 1 (63 %): **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 0.72-0.86 (m, 12H, H_{15}, H_{23}), 1.40-1.46 (m, 2H, H_{13}), 1.54-1.60 (m, 1H, H_{14}), 1.83-1.93 (m, 1H, H_{22}), 2.20 (s, 6H, H_1, H_5), 2.55-2.82 (m, 4H, H_{18}, H_{26}), 3.21-3.56 (m, 4H, H_{10}, H_{25}), 3.56 (s, 3H, H_{19}), 4.03-4.08 (m, 1H, H_{21}), 4.26-4.31 (m, 1H, H_{12}), 4.58-4.61 (m, 1H, H_{17}), 7.01-7.08 (m, 3H, H_2, H_3, H_4), 7.11 (d, $J_{9\text{-}8}$ = 8.4 Hz, 2H, H_9), 7.17-7.29 (m, 5H, H_{27}, H_{28}, H_{29}), 7.34 (d, $J_{8\text{-}9}$ = 8.4 Hz, 2H, H_8), 7.44 (d, $J_{20\text{-}21}$ = 8.9 Hz, 1H, NH_{20}), 7.68 (s, 1H, NH_6), 7.96-8.01 (m, 1H, NH_{24}), 8.18-8.21 (m, 1H, NH_{11}), 8.43 (d, $J_{16\text{-}17}$ = 7.7 Hz, 1H, NH_{16}), 8.65 (br s, 1H, NH_7); **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 17.68, 18.27, 19.12 (C_1, C_5, C_{23}), 21.62, 22.94 (C_{15}), 24.15 (C_{14}), 30.70 (C_{22}), 35.02, 35.05, 35.25, 35.86 (C_{18}, C_{26}), 40.91, 41.16, 41.36 (C_{10}, C_{13}), 49.41 (C_{17}), 50.88 (C_{12}), 51.48 (C_{19}), 57.64 (C_{21}), 117.74 (C_8), 125.89 (C_3), 126.07 (C_{29}), 127.71 (C_2, C_4), 128.29 (C_{27}), 128.61 (C_{28}), 129.21 (C_9, C_f), 135.37 (C_c), 135.51 (C_a, C_b), 138.61 (C_e), 139.31 (C_l), 153.13 (C_d), 169.78, 169.97, 170.29, 170.35, 170.46, 170.72 (C_g, C_i, C_j, C_k), 172.47 (C_h). C_{25} not visible (in DMSO peak).

Rotamer 2 (37 %): **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 0.72-0.86 (m, 12H, H_{15}, H_{23}), 1.40-1.46 (m, 2H, H_{13}), 1.54-1.60 (m, 1H, H_{14}), 1.83-1.93 (m, 1H, H_{22}), 2.20 (s, 6H, H_1, H_5), 2.55-2.82 (m, 4H, H_{18}, H_{26}), 3.21-3.56 (m, 4H, H_{10}, H_{25}), 3.56 (s, 3H, H_{19}), 4.03-4.08 (m, 1H, H_{21}), 4.26-4.31 (m, 1H, H_{12}), 4.58-4.61 (m, 1H, H_{17}), 7.01-7.08 (m, 3H, H_2, H_3, H_4), 7.11 (d, $J_{9\text{-}8}$ = 8.4 Hz, 2H, H_9), 7.17-7.29 (m, 5H, H_{27}, H_{28}, H_{29}), 7.34 (d, $J_{8\text{-}9}$ = 8.4 Hz, 2H, H_8), 7.64 (d, $J_{20\text{-}21}$ = 8.9 Hz, 1H, NH_{20}), 7.68 (s, 1H, NH_6), 7.96-8.01 (m, 1H, NH_{24}), 8.18-8.21 (m, 1H, NH_{11}), 8.35 (d, $J_{16\text{-}17}$ = 7.5 Hz, 1H, NH_{16}), 8.65 (br s, 1H, NH_7); **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 17.68, 18.27, 19.15 (C_1, C_5, C_{23}), 21.62, 22.94 (C_{15}), 24.15 (C_{14}), 30.43 (C_{22}), 35.02, 35.05, 35.25, 35.86 (C_{18}, C_{26}), 40.91, 41.16, 41.36 (C_{10}, C_{13}), 49.58 (C_{17}), 50.99 (C_{12}), 51.48 (C_{19}), 57.64 (C_{21}), 117.74 (C_8), 125.89 (C_3), 126.07 (C_{29}), 127.71 (C_2, C_4), 128.29 (C_{27}), 128.61 (C_{28}), 129.21 (C_9, C_f), 135.37 (C_c), 135.51 (C_a, C_b), 138.61 (C_e), 139.31 (C_l), 153.13 (C_d), 169.78, 169.97, 170.29, 170.35, 170.46, 170.72 (C_g, C_i, C_j, C_k), 172.47 (C_h). C_{25} not visible (in DMSO peak); **MS** (ESI^+) *m/z* (rel intensity): 765.4 ($[M+Na]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{41}H_{54}N_6O_7Na$ $[M+Na]^+$: calcd 765.3952; found 765.3924.



***N*-[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]-L-leucyl-L-α-aspartyl-*N*-(2-phenylethyl)-L-valinamide (2).**

To a solution of methyl (3*S*)-3-{[(2*S*)-2-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-4-methylpentanoyl]amino}-4-({(2*S*)-3-methyl-1-oxo-1-[(2-phenylethyl)amino]butan-2-yl}amino)-4-oxobutanoate (0.039 g, 0.052 mmol, 1.0 equiv) in methanol (1.5 mL) and DMF (3 mL), was added an aqueous solution of 1 N lithium hydroxyde (0.16 mL, 3.0 equiv). The reaction mixture was stirred overnight. A solution of 1 N hydrochloric acid was introduced until pH=1. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with 0.1 N aqueous hydrochloric acid (3x) and water, and then concentrated under vacuum. The resulting residue was triturated with a mixture of acetone and hexane. The precipitate formed was collected by filtration, washed with hexane, dried *in vacuo* to give **2** as a colorless solid (0.032 g, 85%).

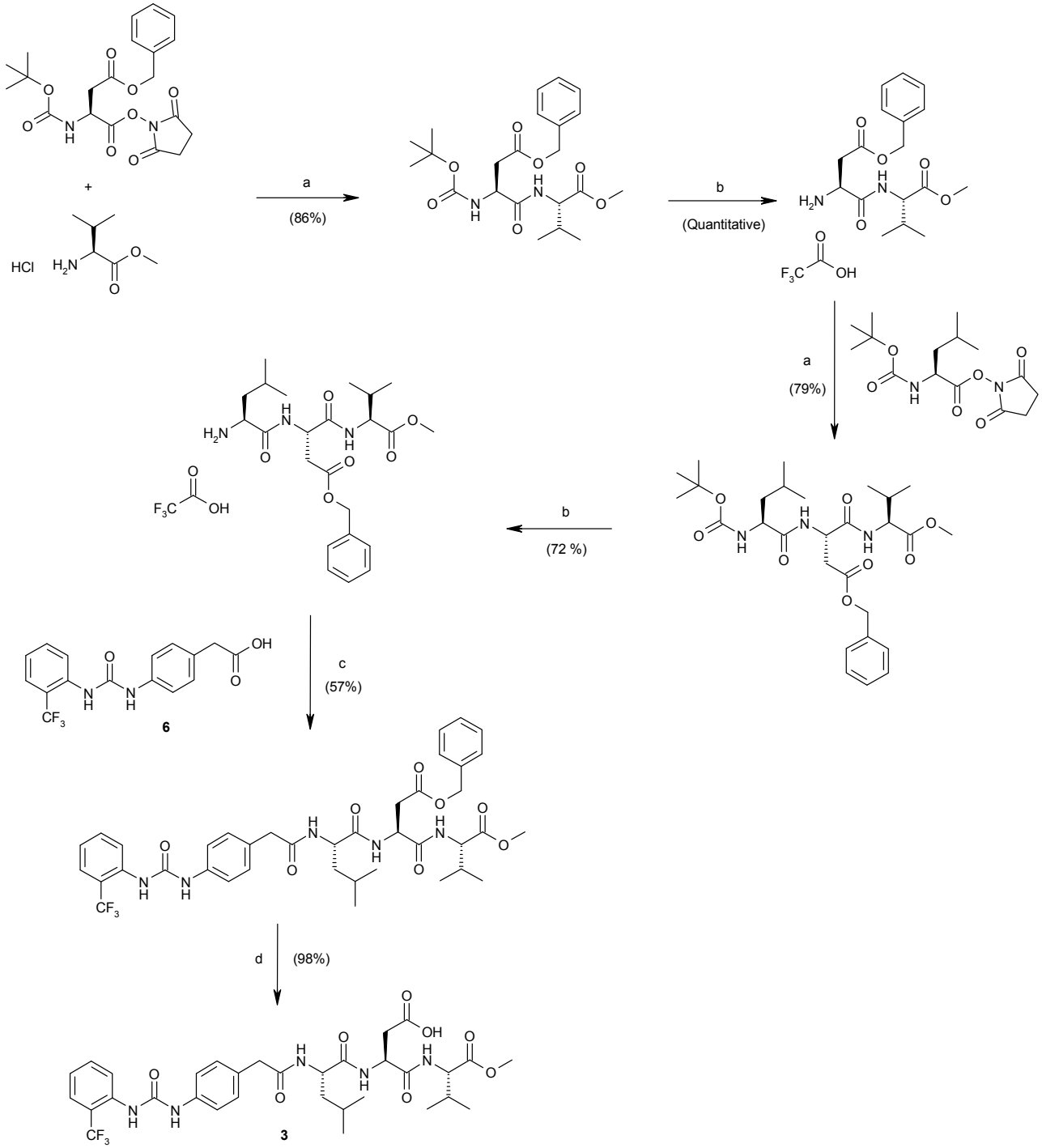


***R*$_f$** = 0.35 (DCM/MeOH: 7/3, $KMnO_4$); **mp**: 212-214°C; **IR** (thin film, cm^{-1}) *ν*: 3263, 3057, 2924, 1699, 1636, 1539, 1506, 1456, 1213, 1157, 790, 696;

Several rotamers observed in NMR analysis: **^{1}H NMR** (500 MHz, DMSO-d_6) *δ*: 0.71-0.87 (m, 12H, H_{15}, H_{23}), 1.36-1.60 (m, 3H, H_{13}, H_{14}), 1.84-1.92 (m, 1H, H_{22}), 2.20 (s, 6H, H_1, H_5), 2.53-2.68 (m, 2H, H_{18}), 2.69 (d, $J_{26\text{-}25}$ = 7.3 Hz, 2H, H_{26}), 3.20-3.44 (m, 4H, H_{10}, H_{25}), 4.06-4.11 (m, 1H, H_{21}), 4.30-4.37 (m, 1H, H_{12}), 4.48-4.58 (m, 1H, H_{17}), 7.04-7.08 (m, 3H, H_2, H_3, H_4), 7.11 (d, $J_{9\text{-}8}$ = 8.5 Hz, 2H, H_9), 7.17-7.29 (m, 5H, H_{27}, H_{28}, H_{29}), 7.34 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8), 7.68 (s, 1H, NH_6), 7.87-8.24 (m, 4H, NH_{11}, NH_{16}, NH_{20}, NH_{24}), 8.66 (br s, 1H, NH_7), 12.57 (br s, 1H, OH_{19}); **^{13}C NMR** (125 MHz, DMSO-d_6) *δ*: 18.02, 18.28, 19.20, 19.27 (C_1, C_5, C_{23}), 21.46, 21.56, 21.67, 22.97, 23.06 (C_{15}), 24.09, 24.16 (C_{14}), 30.39, 30.45 (C_{22}), 35.06 (C_{26}), 36.78, 36.91 (C_{18}), 41.24, 41.30, 41.40 (C_{10}, C_{13}), 49.01, 49.06 (C_{17}), 50.61, 50.67 (C_{12}), 57.75, 57.81, 57.89 (C_{21}), 117.75 (C_8), 125.89 (C_3), 126.05 (C_{29}), 127.70 (C_2, C_4), 128.27 (C_{27}), 128.61 (C_{28}), 129.23 (C_9), 129.31 (C_f), 135.37 (C_c), 135.51 (C_a, C_b), 138.57 (C_e), 139.35 (C_l), 153.14 (C_d), 169.03, 169.09, 169.16 (C_k), 170.05, 170.13, 170.32 (C_j), 170.66, 170.71, 170.75 (C_g), 171.80, 171.86, 171.93 (C_i), 172.48, 172.61, 172.67, 172.83 (C_h), C_{25} not visible (in DMSO peak); **MS** (APCI$^+$) *m/z* (rel intensity): 767.2 ([M+K]$^+$, 7), 751.3 ([M+Na]$^+$, 100), 729.1 ([M+H]$^+$, 6); **HRMS** (ESI$^+$) *m/z* for $C_{40}H_{52}N_6O_7Na$ [M+Na]$^+$: calcd 751.3795; found 751.3799.

1.2. *Synthesis of peptide* **(3)**.

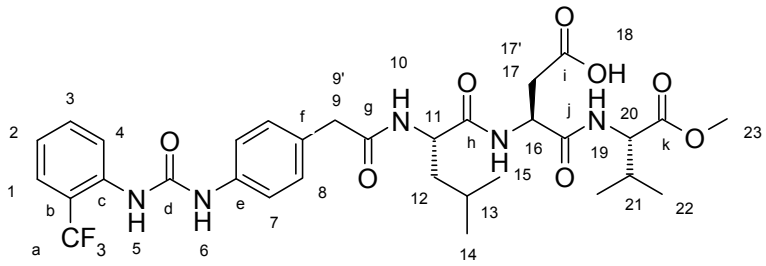
The synthesis of peptide **3** was similar to the synthesis of peptide **2** and adapted from Lin K-C. *et al*., *J. Med. Chem.*, 1999, **42**, 920.



Scheme S2 Synthesis of compound **3**. *Reagents and conditions*: (a) Et_3N, DCM, 4 h; (b) TFA, DCM, 4 h; (c) EDC.HCl, HOBt, Et_3N, DMF, 40°C, overnight; (d) H_2, Pd/C (10%), DMF, overnight.

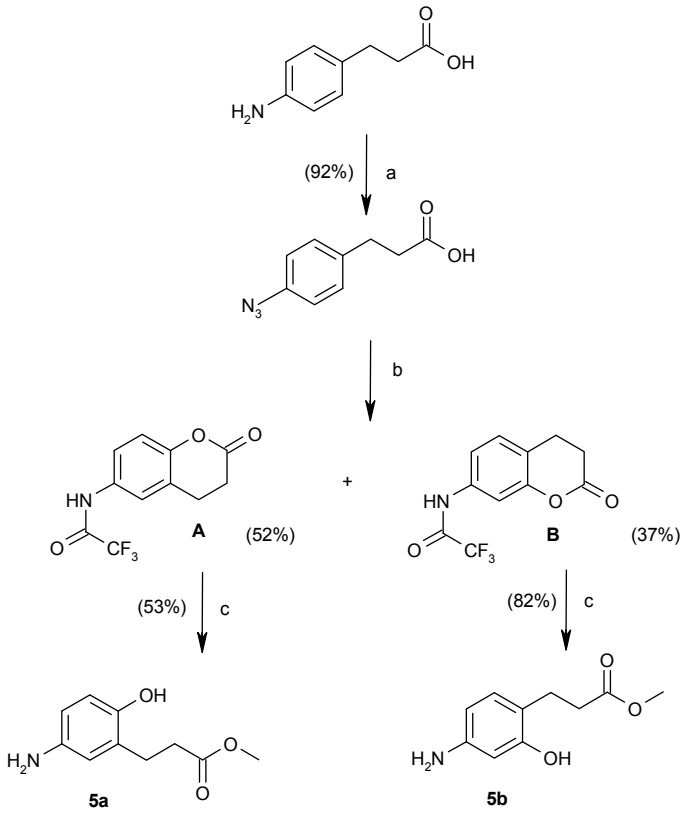
Methyl *N*-{[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}-L-leucyl-L-α-aspartyl-L-valinate (3).

Colorless solid; R_f = 0.48 (DCM/MeOH: 4/1, UV); **mp**: 237-240°C; **IR** (thin film, cm^{-1}) ν: 3292, 2959, 1628, 1458, 1319, 1275, 1175, 1119, 766; **^{1}H NMR** (500 MHz, CD_3OD) δ: 0.86-0.96 (m, 12H, H_{14}, H_{22}), 1.59-1.68 (m, 3H, H_{12}, H_{13}), 2.08-2.15 (m, 1H, H_{21}), 2.60 (dd, $J_{17'\text{-}17}$ = 16.2 Hz, $J_{17'\text{-}16}$ = 6.5 Hz, 1H, $H_{17'}$), 2.67 (dd, $J_{17\text{-}17'}$ = 16.2 Hz, $J_{17\text{-}16}$ = 6.3 Hz, 1H, H_{17}), 3.52 (d, $J_{9\text{-}9'}$ = 14.5 Hz, 1H, H_9), 3.56 (d, $J_{9'\text{-}9}$ = 14.5 Hz, 1H, $H_{9'}$), 3.70 (s, 3H, H_{23}), 4.31 (d, $J_{20\text{-}21}$ = 5.7 Hz, 1H, H_{20}), 4.38 (t, $J_{11\text{-}12}$ = 7.5 Hz, 1H, H_{11}), 4.71 (t, $J_{16\text{-}17}$ = 6.4 Hz, 1H, H_{16}), 7.22-7.29 (m, 3H, H_2, H_8), 7.39 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.59 (t, J = 7.9 Hz, 1H, H_3), 7.65 (d, $J_{1\text{-}2}$ = 7.9 Hz, 1H, H_1), 7.92 (d, $J_{4\text{-}3}$ = 8.3 Hz, 1H, H_4); **^{13}C NMR** (125 MHz, CD_3OD) δ: 18.55, 19.45 (C_{22}), 21.83, 23.45 (C_{14}), 25.96 (C_{13}), 31.91 (C_{21}), 39.46 ($C_{17,17'}$), 41.66 (C_{12}), 42.92 ($C_{9,9'}$), 51.97 (C_{16}), 52.50 (C_{23}), 53.60 (C_{11}), 59.29 (C_{20}), 120.49 (C_7), 122.93 (q, $^2J_{C\text{-}F}$ = 29.8 Hz, C_b), 125.30 (C_2), 125.60 (q, $^1J_{C\text{-}F}$ = 268.1 Hz, C_a), 127.04 (q, $^3J_{C\text{-}F}$ = 5.3 Hz, C_1), 127.43 (C_4), 130.70 (C_8), 131.27 (C_f), 133.76 (C_3), 137.45 (C_c), 139.27 (C_e), 155.25 (C_d), 173.34, 173.90, 174.55, 174.58 (C_g, C_h, C_j, C_k), 178.76 (C_i); **^{19}F NMR** (282 MHz, CD_3OD, $CFCl_3$) δ: -60.82 (s, 3F, CF_3); **MS** (ESI^+) *m/z* (rel intensity): 718.1 ($[M+K]^+$, 53), 702.2 ($[M+Na]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{32}H_{40}F_3N_5O_8Na$ $[M+Na]^+$: calcd 702.2727; found 702.2710.



2. Synthesis of the building blocks (5a) and (5b).

The synthesis of compounds **5a** and **5b** was previously described in Momtaz M. *et al*., *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1084 and Kawada K. *et al*., *J. Med. Chem*., 1989, **32**, 256.



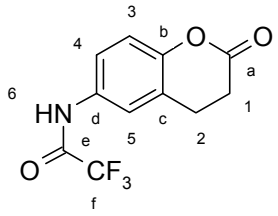
Scheme S3 Synthesis of compounds **5a** and **5b**. *Reagents and conditions*: (a) $NaNO_2$, NaN_3, HCl, H_2O, 0°C, 2 h; (b) TFA, 0°C, 2 h and then TFAA, overnight; (c) 6 M HCl, MeOH, reflux, overnight and then H_3PO_4 (cat.), MeOH, reflux, overnight.

2,2,2-trifluoro-*N*-(2-oxochroman-6-yl)acetamide (A) and 2,2,2-trifluoro-*N*-(2-oxochroman-7-yl)acetamide (B).

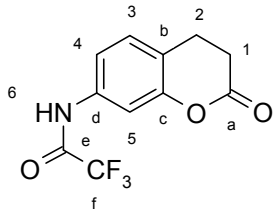
3-(4-Azidophenyl)propanoic acid (0.20 g, 1.05 mmol) was added in small portions, at 0°C over a period of 5 h, to a solution of trifluoroacetic acid (10 mL). The reaction mixture was stirred for 2 h at 0°C. Trifluoroacetic anhydride (3 mL) was added. The reaction mixture was stirred overnight at room temperature. After evaporation under reduced pressure, the residue was dissolved in ethyl acetate. The organic layer was washed with water (4x), saturated aqueous Na_2CO_3 solution (1x), and brine (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (gradient elution with EtOAc/Hexane: 2/3 to EtOAc/MeOH: 4/1) to give **A** as a colorless solid (0.14 g, 52%) and **B** as a beige solid (0.10 g, 37%).

(A) R_f = 0.52 (EtOAc/Hexane: 2/3, UV); **mp**: 205 °C; **IR** (thin film, cm^{-1}) ν: 3317, 2908, 1755, 1717, 1624, 1566, 1497, 1423, 1211, 1149, 822, 702; **^{1}H NMR** (300 MHz, CD_3OD) δ: 2.77-2.82 (m, 2H, H_1), 2.98-3.05 (m, 2H, H_2), 7.04 (d, $J_{3\text{-}4}$ = 8.8 Hz, 1H, H_3), 7.50 (dd, $J_{4\text{-}3}$ = 8.8 Hz, $J_{4\text{-}5}$ = 2.5, 1H, H_4), 7.60 (d, $J_{5\text{-}4}$ = 2.5, 1H, H_5); **^{13}C NMR** (75 MHz, CD_3OD) δ: 24.6

(C_2), 29.7 (C_1), 118.1 (C_3), 122.1 (C_4, C_5), 125.4 (C_c), 134.0 (C_d), 150.9 (C_b), 170.3 (C_a), C_e and C_f not visible; **^{19}F NMR** (282 MHz, CD_3OD, $CFCl_3$) δ: -75.38 (s, 3F, C$\underline{F}_3$); **MS** (APCI$^+$) *m/z* (rel intensity): 260.1 ([M+H]$^+$, 100); **HRMS** (ESI$^+$) *m/z* for $C_{11}H_9F_3NO_3$ [M+H]$^+$: calcd 260.0529; found 260.0533.



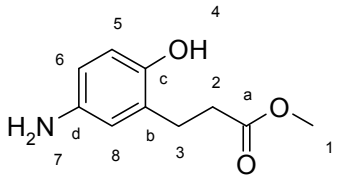
(B) R_f = 0.24 (EtOAc, UV); **mp**: 185 °C; **IR** (thin film, cm^{-1}) ν: 3321, 2928, 1712, 1690, 1624, 1570, 1435, 1292, 1223, 1200, 1161, 872; **^{1}H NMR** (300 MHz, acetone-d_6) δ: 2.62 (t, $J_{1\text{-}2}$ = 7.6 Hz, 2H, H_1), 2.89 (t, $J_{2\text{-}1}$ = 7.6 Hz, 2H, H_2), 7.08 (dd, $J_{4\text{-}3}$ = 8.2 Hz, $J_{4\text{-}5}$ = 2.0, 1H, H_4), 7.17 (d, $J_{3\text{-}4}$ = 8.2 Hz, 1H, H_3), 7.39 (d, $J_{5\text{-}4}$ = 2.0 Hz, 1H, H_5), 10.13 (br s, 1H, NH_6); **^{13}C NMR** (75 MHz, acetone-d_6) δ: 26.8 (C_2), 35.0 (C_1), 109.3 (C_5), 113.5 (C_4), 126.7 (C_b), 132.0 (C_3), 137.3 (C_d), 156.9 (C_c), 175.4 (C_a), C_e and C_f not visible; **^{19}F NMR** (282 MHz, acetone-d_6, $CFCl_3$) δ: -75.09 (s, 3F, C$\underline{F}_3$); **MS** (APCI$^+$) *m/z* (rel intensity): 260.2 ([M+H]$^+$, 100), 149.2 ([M+H-CF_3CON]$^+$, 32); **HRMS** (ESI$^+$) *m/z* for $C_{11}H_9F_3NO_3$ [M+H]$^+$: calcd 260.0529; found 260.0539.



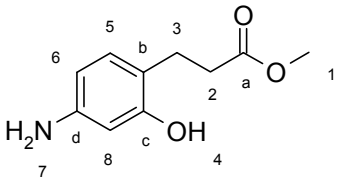
General procedure for the synthesis of compounds (5a) and (5b).
A solution of dihydrocoumarin (2.31 g, 8.91 mmol, 1.0 equiv) in 60 mL aqueous hydrochloric acid (6 N) and 90 mL methanol was refluxed for 21 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in methanol (60 mL). 5 drops of concentrated phosphoric acid were added. The reaction mixture was refluxed overnight. After concentration, the residue was dissolved in ethyl acetate. The organic layer was washed with a solution of 1 N aqueous hydrochloric acid (2x, pH=1). The pH of the aqueous layer was adjusted to 8 with saturated aqueous Na_2CO_3 solution and extracted with ethyl acetate (3x). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure.

Methyl 3-(5-amino-2-hydroxyphenyl)propanoate (5a).
The title compound was obtained from 2,2,2-trifluoro-*N*-(2-oxochroman-6-yl)acetamide **A** (2.31 g, 8.91 mmol, 1.0 equiv) according to the general procedure. The crude residue was dissolved in ethyl acetate and dichloromethane was added until a precipitate was formed. This precipitate was collected by filtration and dried under vacuum to give **5a**. Additional product was isolated by column chromatography on silica gel (elution with EtOAc/DCM: 4/1) of the residue after concentration of the filtrate. 0.92g (53%) in all of **5a** was obtained as a beige solid.

R_f = 0.42 (EtOAc/Hexane: 4/1, UV); **mp**: 124-125°C; **IR** (thin film, cm^{-1}) *v*: 3356, 3286, 3016, 2955, 2928, 1724, 1604, 1516, 1454, 1396, 1323, 1219, 1192, 1169, 937, 872, 825; **^{1}H NMR** (300 MHz, $CDCl_3$) *δ*: 2.67-2.72 (m, 2H, H_2), 2.79-2.84 (m, 2H, H_3), 3.68 (s, 3H, H_1), 6.46 (d, $J_{8\text{-}6}$ = 2.7 Hz, 1H, H_8), 6.49 (dd, $J_{6\text{-}5}$ = 8.3 Hz, $J_{6\text{-}8}$ = 2.7 Hz, 1H, H_6), 6.72 (d, $J_{5\text{-}6}$ = 8.3 Hz, 1H, H_5); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ*: 24.6 (C_3), 35.1 (C_2), 52.2 (C_1), 115.2 (C_6), 117.3 (C_8), 118.3 (C_5), 128.3 (C_b), 139.9 (C_d), 147.0 (C_c), 175.9 (C_a); **MS** (ESI^+) *m/z* (rel intensity): 196.1 ($[M+H]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{10}H_{13}NO_3Na$ $[M+Na]^+$: calcd 218.0793; found 218.0789.



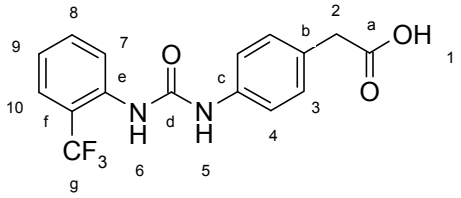
Methyl 3-(4-amino-2-hydroxyphenyl)propanoate (5b).
The title compound was obtined from 2,2,2-trifluoro-*N*-(2-oxochroman-7-yl)acetamide **B** (0.91 g, 3.51 mmol, 1.0 equiv). The crude residue was purified by column chromatography on silica gel (elution with EtOAc/Hexane: 4/1) and dried in the air to give **5b** as a maroon solid (0.56 g, 82%).
R_f = 0.50 (EtOAc/Hexane: 4/1, UV); **mp**: 77°C; **IR** (thin film, cm^{-1}) *v*: 3371, 2951, 1717, 1620, 1508, 1439, 1366, 1238, 1204, 1169, 841; **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 2.63-2.69 (m, 2H, H_2), 2.76-2.81 (m, 2H, H_3), 3.68 (s, 3H, H_1), 6.20-6.25 (m, 2H, H_6, H_8), 6.85 (d, $J_{5\text{-}6}$ = 7.8 Hz, 1H, H_5); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ*: 23.8 (C_3), 35.4 (C_2), 52.2 (C_1), 104.0 (C_8), 108.1 (C_6), 117.4 (C_b), 131.2 (C_5), 146.4 (C_d), 155.1 (C_c), 176.4 (C_a); **MS** ($APCI^+$) *m/z* (rel intensity): 196.1 ($[M+H]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{10}H_{13}NO_3Na$ $[M+Na]^+$: calcd 218.0793; found 218.0786.



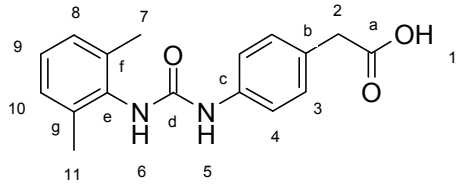
3. Synthesis of the building blocks (6) and (7).

{4-[({[2-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}acetic acid (6).
To a refluxing solution of *p*-aminophenylacetic acid (4.00 g, 26.46 mmol, 1.0 equiv) in anhydrous THF (55 mL), was added dropwise a solution of α,α,α-trifluoro-*o*-tolyl-isocyanate (4.06 mL, 26.46 mmol, 1.0 equiv) in THF (40 mL) followed by a solution of triethylamine (0.37 mL, 2.65 mmol, 0.1 equiv) in THF (5 mL). The reaction mixture was stirred overnight at reflux. After evaporation under reduced pressure, the residue was dissolved in DCM, and 1 N aqueous hydrochloric acid was added. The precipitate formed was collected by filtration, washed with DCM, and dried under vacuum to give **6**. The filtrate was extracted with DCM (2x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. After trituration of the residue with DCM, the precipitate formed was filtered and dried *in vacuo*. 8.84 g (98%) in all of **6** was obtained as a colorless solid.

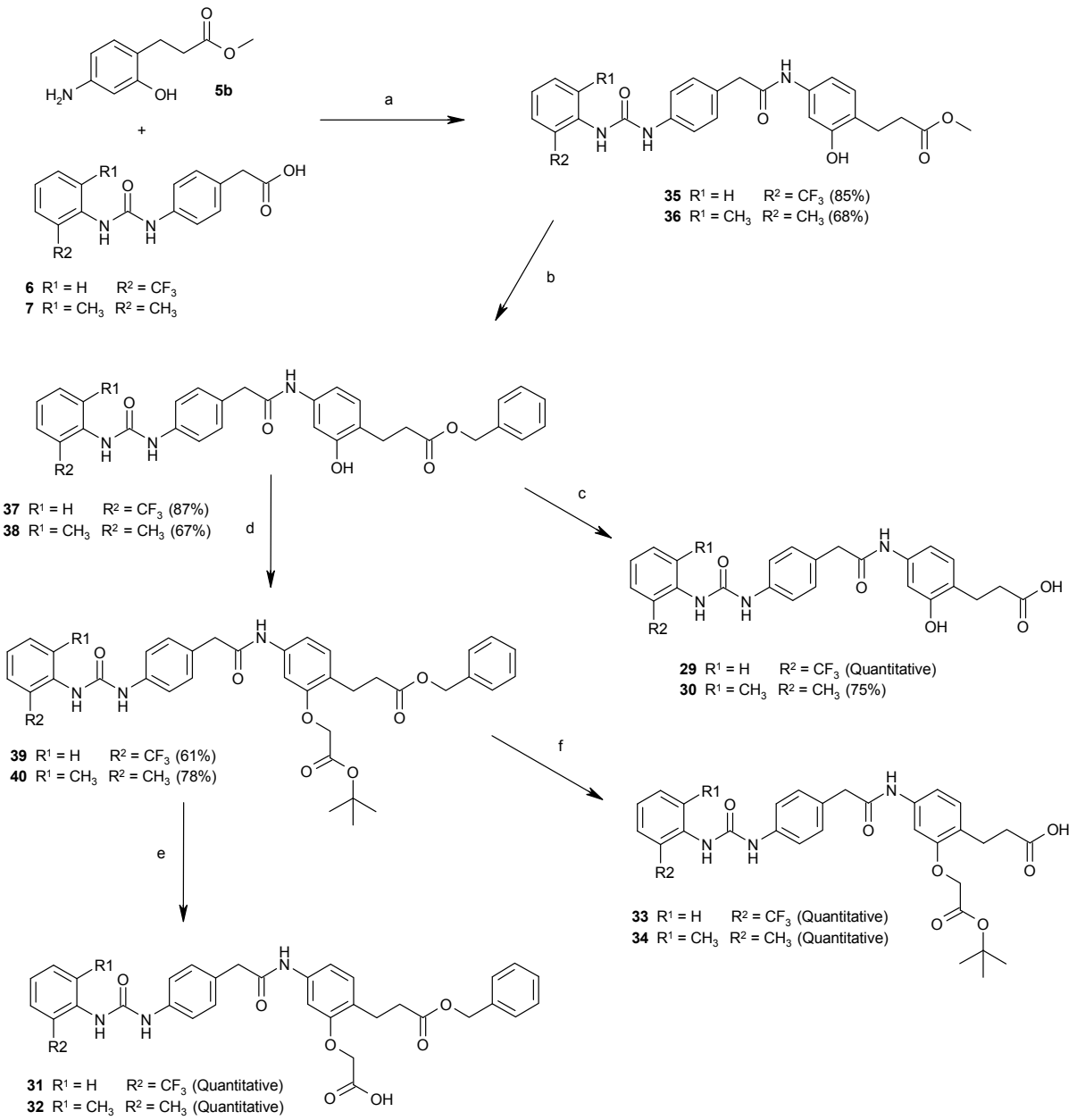
R_f = 0.25 (DCM/MeOH: 95/5, UV); **mp**: 193°C; **IR** (thin film, cm^{-1}) *ν*: 3294, 1701, 1643, 1609, 1589, 1555, 1516, 1458, 1416, 1319, 1173, 1115, 768; **^{1}H NMR** (500 MHz, CD_3OD) *δ*: 3.55 (s, 2H, H_2), 7.21 (d, J_{3-4} = 8.5 Hz, 2H, H_3), 7.27 (t, J = 7.7 Hz, 1H, H_9), 7.40 (d, J_{4-3} = 8.5 Hz, 2H, H_4), 7.59 (t, J = 7.8 Hz, 1H, H_8), 7.65 (d, J_{10-9} = 7.8 Hz, 1H, H_{10}), 7.91 (d, J_{7-8} = 8.2 Hz, 1H, H_7); **^{13}C NMR** (125 MHz, CD_3OD) *δ*: 41.3 (C_2), 120.3 (C_4), 122.8 (q, $^2J_{C-F}$ = 29.3 Hz, C_f), 125.3 (C_9), 125.5 (q, $^1J_{C-F}$ = 270.4 Hz, C_g), 127.0 (q, $^3J_{C-F}$ = 5.3 Hz, C_{10}), 127.4 (C_7), 130.6 (C_b), 130.9 (C_3), 133.8 (C_8), 137.4 (C_e), 139.2 (C_c), 155.3 (C_d), 175.8 (C_a); **^{19}F NMR** (282 MHz, CD_3OD, $CFCl_3$) *δ*: -60.84 (s, 3F, CF_3); **MS** (ESI^+) *m/z* (rel intensity): 361.0 ($[M+Na]^+$, 39), 339.1 ($[M+H]^+$, 73); **HRMS** (ESI^+) *m/z* for $C_{16}H_{13}F_3N_2O_3Na$ $[M+Na]^+$: calcd 361.0776; found 361.0777.



[4-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]acetic acid (7).
To a refluxing solution of *p*-aminophenylacetic acid (0.20 g, 1.32 mmol, 1.0 equiv) in anhydrous THF (8 mL), was added a solution of 2,6-dimethylphenyl-isocyanate (0.19 g, 1.32 mmol, 1.0 equiv) in THF (1 mL) dropwise. The reaction mixture was stirred for 5 h at reflux, and then concentrated under reduced pressure. The residue was triturated with DCM. The precipitate formed was collected by filtration, washed with DCM, and dried *in vacuo* to give **7** as a beige solid (0.38 g, 96%).
R_f = 0.25 (DCM/MeOH: 9/1, UV); **mp**: 248-249°C; **IR** (thin film, cm^{-1}) *ν*: 3288, 1701, 1643, 1597, 1558, 1411, 1250, 773; **^{1}H NMR** (300 MHz, DMSO-d_6) *δ*: 2.20 (s, 6H, H_7, H_{11}), 3.47 (s, 2H, H_2), 7.05-7.06 (m, 3H, H_8, H_9, H_{10}), 7.13 (d, J_{3-4} = 8.5 Hz, 2H, H_3), 7.37 (d, J_{4-3} = 8.5 Hz, 2H, H_4), 7.69 (br s, 1H, NH_6), 8.69 (br s, 1H, NH_5), 12.18 (br s, 1H, OH_1); **^{13}C NMR** (75 MHz, DMSO-d_6) *δ*: 18.3 (C_7, C_{11}), 117.8 (C_4), 125.9 (C_9), 127.7 (C_8, C_{10}), 127.9 (C_b), 129.6 (C_3), 135.4 (C_e), 135.5 (C_f, C_g), 138.9 (C_c), 153.1 (C_d), 173.0 (C_a), C_2 not visible (in DMSO peak); **MS** (ESI^+) *m/z* (rel intensity): 337.1 ($[M+K]^+$, 8), 321.2 ($[M+Na]^+$, 69), 299.2 ($[M+H]^+$, 100); **HRMS** (ESI^+) *m/z* for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: calcd 299.1396; found 299.1400.



4. Synthesis of the peptidomimetics of family B.



Scheme S4 Peptidomimetics family B synthesis. *Reagents and condtions:* (a) PyBOP, Et_3N, DMF, rt; (b) benzyl alcohol, H_2SO_4 (cat.), CH_3CN, 60°C; (c) H_2, Pd/C (10%), EtOH, EtOAc, rt; (d) Cs_2CO_3, *tert*-butyl 2-bromoacetate, DMF, rt; (e) TFA, DCM, rt; (f) H_2, Pd/C (10%), EtOH, DMF, rt.

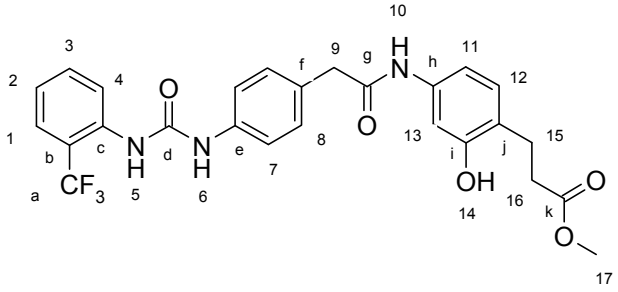
General procedure for the coupling of acid (6) or (7) with amine (5b).
To a solution of acid compound **6** or **7** (3.58 mmol, 1.0 equiv) in anhydrous DMF (20 mL) under argon atmosphere were added PyBOP (1.87 g, 3.58 mmol, 1.0 equiv) and triethylamine (0.50 mL, 3.58 mmol, 1.0 equiv). The reaction mixture was stirred for 15 min. A solution of methyl 3-(4-amino-2-hydroxyphenyl)propanoate **5b** (0.70 g, 3.38 mmol, 1.0 equiv) in DMF (7 mL) was introduced dropwise. The reaction mixture was stirred overnight and then diluted with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid solution (1x),

saturated aqueous NH_4Cl solution (1x) and brine (3x). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure.

Methyl 3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl] carbamoyl}amino)phenyl] acetyl}amino)phenyl]propanoate (35).

The title compound was obtained from {4-[({[2-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenyl}acetic acid **6** (1.21 g, 3.58 mmol, 1.0 equiv) and methyl 3-(4-amino-2-hydroxyphenyl)propanoate **5b** (0.70 g, 3.38 mmol, 1.0 equiv). The crude residue was purified by column chromatography on silica gel (elution with EtOAc/hexane: 3/2) to give **35** as a beige solid (1.58 g, 85%).

$\boldsymbol{R_f}$ = 0.38 (EtOAc/Hexane: 3/2, UV); **mp**: 194°C; **IR** (thin film, cm^{-1}) ν: 3279, 1728, 1693, 1659, 1632, 1547, 1420, 1369, 1285, 1234, 1173, 1114, 876, 798, 768; **^{1}H NMR** (300 MHz, acetone-d_6) δ: 2.57 (t, $J_{16\text{-}15}$ = 7.7 Hz, 2H, H_{16}), 2.83 (t, $J_{15\text{-}16}$ = 7.7 Hz, 2H, H_{15}), 3.60 (s, 5H, H_9, H_{17}), 6.89 (dd, $J_{11\text{-}12}$ = 8.2 Hz, $J_{11\text{-}13}$ = 1.7 Hz, 1H, H_{11}), 7.00 (d, $J_{12\text{-}11}$ = 8.2 Hz, 1H, H_{12}), 7.23-7.30 (m, 3H, H_2, H_8), 7.42 (d, $J_{13\text{-}11}$ = 1.7 Hz, 1H, H_{13}), 7.49 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.60-7.68 (m, 3H, H_1, H_3, NH_5), 8.17 (d, $J_{4\text{-}3}$ = 8.3 Hz, 1H, H_4), 8.38 (s, 1H, OH_{14}), 8.79 (br s, 1H, NH_6), 9.13 (br s, 1H, NH_{10}); **^{13}C NMR** (75 MHz, acetone-d_6) δ: 26.21 (C_{16}), 34.60 (C_{15}), 44.15 (C_9), 51.53 (C_{17}), 107.33 (C_{13}), 111.27 (C_{11}), 119.72 (C_7), 122.96 (C_j), 124.17 (C_2), 125.92 (C_4), 126.70 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, C_1), 130.42 (C_8), 130.76 (C_{12}), 130.98 (C_f), 133.61 (C_3), 137.86 (C_c), 139.24 (C_e), 139.72 (C_h), 153.21 (C_d), 155.99 (C_i), 169.95 (C_g), 173.93 (C_k), C_a and C_b not visible; **MS** (ESI^+) *m/z* (rel intensity): 1052.7 ($[2M+Na]^+$, 100), 538.2 ($[M+Na]^+$, 75), 516.1 ($[M+H]^+$, 29); **HRMS** (ESI^+) *m/z* for $C_{26}H_{24}F_3N_3O_5Na$ $[M+Na]^+$: calcd 538.1566; found 538.1548.

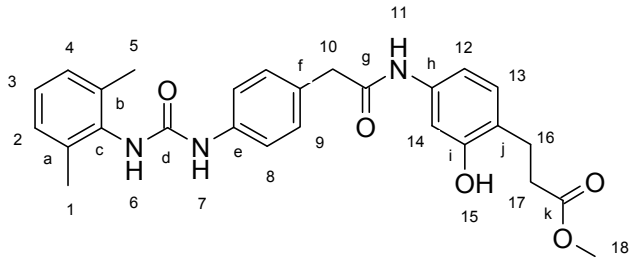


Methyl 3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-2-hydroxyphenyl)propanoate (36).

The title compound was obtained from [4-({[(2,6-dimethylphenyl)amino]carbonyl} amino)phenyl]acetic acid **7** (0.23 g, 0.77 mmol, 1.0 equiv) and methyl 3-(4-amino-2-hydroxyphenyl)propanoate **5b** (0.15 g, 0.77 mmol, 1.0 equiv). The crude residue was purified by column chromatography on silica gel (elution with EtOAc/Hexane: 4/1) to give **36** as a beige solid (0.25 g, 68%).

$\boldsymbol{R_f}$ = 0.59 (EtOAc/Hexane: 4/1, UV); **mp**: 197-200°C; **IR** (thin film, cm^{-1}) ν: 3286, 2924, 1717, 1641, 1610, 1549, 1423, 1362, 1296, 1231, 847, 768; **^{1}H NMR** (300 MHz, DMSO-d_6) δ: 2.20 (s, 6H, H_1, H_5), 2.70 (t, $J_{16\text{-}17}$ = 7.4 Hz, 2H, H_{16}), 3.50 (s, 2H, H_{10}), 3.56 (s, 3H, H_{18}), 6.84 (dd, $J_{12\text{-}13}$ = 8.2 Hz, $J_{12\text{-}14}$ = 1.8 Hz, 1H, H_{12}), 6.93 (d, $J_{13\text{-}12}$ = 8.2 Hz, 1H, H_{13}), 7.04-7.06 (m, 3H, H_2, H_3, H_4), 7.19 (d, $J_{9\text{-}8}$ = 8.5 Hz, 2H, H_9), 7.23 (d, $J_{14\text{-}12}$ = 1.8 Hz, 1H, H_{14}), 7.38 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8), 7.68 (br s, 1H, NH_6), 8.68 (br s, 1H, NH_7), 9.41 (s, 1H, OH_{15}), 9.90 (br s, 1H, NH_{11}), H_{17} not visible (in DMSO peak); **^{13}C NMR** (75 MHz, DMSO-d_6) δ: 18.3 (C_1, C_5), 25.2 (C_{16}), 33.5 (C_{17}), 42.7 (C_{10}), 51.2 (C_{18}), 106.2 (C_{14}), 109.9 (C_{12}), 117.9 (C_8), 121.4 (C_j), 125.9 (C_3), 127.7 (C_2, C_4), 129.0 (C_f), 129.3 (C_9), 129.5 (C_{13}), 135.4 (C_c), 135.5 (C_a, C_b),

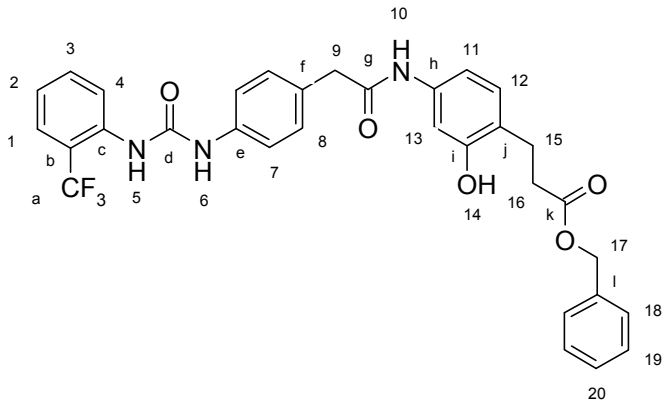
138.4 (C_h), 138.8 (C_e), 153.2 (C_d), 155.1 (C_i), 169.2 (C_g), 173.0 (C_k); **MS** (ESI^+) *m/z* (rel intensity): 498.3 ($[M+Na]^+$, 35), 476.1 ($[M+H]^+$, 55); **HRMS** (ESI^+) *m/z* for $C_{27}H_{29}N_3O_5Na$ $[M+Na]^+$: calcd 498.2005; found 498.2015.



Benzyl 3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl] acetyl}amino)phenyl]propanoate (37).

To a solution of methyl 3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl} amino)phenyl] acetyl}amino)phenyl]propanoate **35** (1.09 g, 2.12 mmol, 1.0 equiv) in anhydrous acetonitrile (35 mL), were added benzyl alcohol (8 mL) and 3 drops of concentrated sulfuric acid. The reaction mixture was heated at 60°C for 3 days under argon atmosphere. After concentration under reduced pressure, the residue was dissolved in ethyl acetate. The organic layer was washed with a saturated aqueous Na_2CO_3 solution (2x) and brine (2x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (gradient elution with EtOAc/Hexane: 2/3 to pure EtOAc) to give **37** as a colorless solid (1.09 g, 87%).

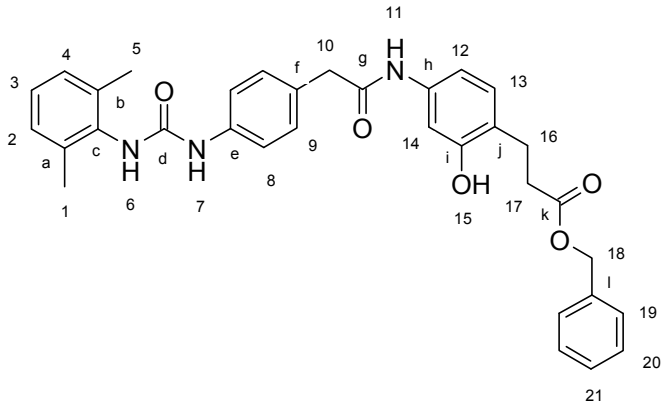
R_f = 0.37 (EtOAc/Hexane: 1/1, UV); **mp**: 177-182°C; **IR** (thin film, cm^{-1}) *ν*: 3337, 2955, 1697, 1659, 1612, 1543, 1516, 1454, 1419, 1389, 1319, 1285, 1234, 1169, 1111, 752, 698; **^{1}H NMR** (300 MHz, acetone-d_6) *δ*: 2.64 (t, $J_{16\text{-}15}$ = 7.4 Hz, 2H, H_{16}), 2.87 (t, $J_{15\text{-}16}$ = 7.4 Hz, 2H, H_{15}), 3.60 (s, 2H, H_9), 5.09 (s, 2H, H_{17}), 6.88 (dd, $J_{11\text{-}12}$ = 8.2 Hz, $J_{11\text{-}13}$ = 1.9 Hz, 1H, H_{11}), 6.99 (d, $J_{12\text{-}11}$ = 8.2 Hz, 1H, H_{12}), 7.23-7.37 (m, 8H, H_2, H_8, H_{18}, H_{19}, H_{20}), 7.41 (d, $J_{13\text{-}11}$ = 1.9 Hz, 1H, H_{13}), 7.49 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.60-7.68 (m, 3H, H_1, H_3, NH_5), 8.17 (d, $J_{4\text{-}3}$ = 8.4 Hz, 1H, H_4), 8.33 (br s, 1H, OH_{14}), 8.76 (br s, 1H, NH_6), 9.10 (br s, 1H, NH_{10}); **^{13}C NMR** (75 MHz, acetone-d_6) *δ*: 26.3 (C_{15}), 34.8 (C_{16}), 44.2 (C_9), 66.3 (C_{17}), 107.4 (C_{13}), 111.4 (C_{11}), 119.6 (C_7), 122.9 (C_j), 124.3 (C_2), 126.0 (C_4), 126.7 (q, $^3J_{C\text{-}F}$ = 6.6 Hz, C_1), 128.7 (C_{18}), 128.8 (C_{20}), 129.2 (C_{19}), 130.4 (C_8), 130.8 (C_{12}), 131.0 (C_f), 133.6 (C_3), 137.5 (C_l), 137.8 (C_c), 139.2 (C_e), 139.7 (C_h), 153.1 (C_d), 156.0 (C_i), 170.0 (C_g), 173.4 (C_k), C_a, C_b not visible; **MS** (ESI^+) *m/z* (rel intensity): 614.1 ($[M+Na]^+$, 100), 592.0 ($[M+H]^+$, 31); **HRMS** (ESI^+) *m/z* for $C_{32}H_{28}F_3N_3O_5Na$ $[M+Na]^+$: calcd 614.1879; found 614.1866.



Benzyl 3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-2-hydroxyphenyl)propanoate (38).

To a solution of methyl 3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-2-hydroxyphenyl)propanoate **36** (0.20 g, 0.42 mmol, 1.0 equiv) in anhydrous acetonitrile (20 mL), were added benzyl alcohol (1.6 mL) and 3 drops of concentrated sulfuric acid. The reaction mixture was heated at 60°C for 5 days under argon atmosphere. After concentration under reduced pressure, the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), and concentrated *in vacuo*. The residue was triturated in a mixture (1/1) of ethyl acetate and hexane. The precipitate formed was collected by filtration, washed with hexane, and dried under vacuum to give **38** as a colorless solid (0.16 g, 67%).

R_f = 0.28 (EtOAc/Hexane: 3/2, UV); **mp**: 182-189°C; **IR** (thin film, cm^{-1}) ν: 3277, 1653, 1603, 1541, 1508, 1418, 1242, 1178, 768; **^{1}H NMR** (500 MHz, acetone-d_6) δ: 2.26 (s, 6H, H_1, H_5), 2.64 (t, $J_{17\text{-}16}$ = 7.6 Hz, 2H, H_{17}), 3.56 (s, 2H, H_{10}), 5.09 (s, 2H, H_{18}), 6.87 (dd, $J_{12\text{-}13}$ = 8.2 Hz, $J_{12\text{-}14}$ = 1.9 Hz, 1H, H_{12}), 6.97 (d, $J_{13\text{-}12}$ = 8.2 Hz, 1H, H_{13}), 7.02-7.06 (m, 3H, H_2, H_3, H_4), 7.22-7.24 (m, 3H, H_9, NH_6), 7.27-7.35 (m, 5H, H_{19}, H_{20}, H_{21}), 7.40 (d, $J_{14\text{-}12}$ = 1.9 Hz, 1H, H_{14}), 7.47 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8), 8.14 (br s, 1H, NH_7), 8.40 (br s, 1H, OH_{15}), 9.10 (br s, 1H, NH_{11}), H_{16} not visible (in H_2O peak); **^{13}C NMR** (125 MHz, acetone-d_6) δ: 18.62 (C_1, C_5), 26.29 (C_{16}), 34.81 (C_{17}), 44.21 (C_{10}), 66.39 (C_{18}), 107.31 (C_{14}), 111.25 (C_{12}), 119.33 (C_8), 122.81 (C_j), 127.19 (C_3), 128.73, 128.83 (C_2, C_4, C_{19}, C_{21}), 129.24 (C_{20}), 130.16 (C_f), 130.21 (C_9), 130.79 (C_{13}), 136.26 (C_c), 137.02 (C_a, C_b), 137.57 (C_l), 139.76 (C_h), 140.11 (C_e), 154.15 (C_d), 155.99 (C_i), 169.94 (C_g), 173.35 (C_k); **MS** (ESI^+) *m/z* (rel intensity): 1124.8 ($[2M+Na]^+$, 43), 1103.0 ($[2M+H]^+$, 24), 574.3 ($[M+Na]^+$, 51), 552.0 ($[M+H]^+$, 29); **HRMS** (ESI^+) *m/z* for $C_{33}H_{34}N_3O_5$ $[M+H]^+$: calcd 552.2498; found 552.2479.

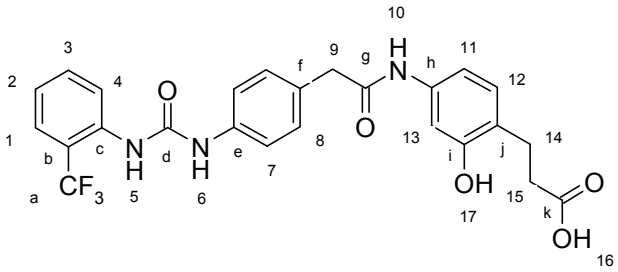


3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoic acid (29).

To a solution of benzyl 3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoate **37** (0.030 g, 0.051 mmol, 1.0 equiv) in ethanol (2.5 mL) and ethyl acetate (1.5 mL) was added Pd/C (10 %) as catalyst. The reaction mixture was stirred for 7 h under hydrogen atmosphere (1 atm). Then the mixture was filtered through a Celite pad and concentrated under vacuum to give **29** as a beige solid (0.025 g, quantitative).

R_f = 0.45 (EtOAc/*i*PrOH: 95/5, UV); **mp**: 199-200°C; **IR** (thin film, cm^{-1}) ν: 3275, 1637, 1609, 1543, 1508, 1456, 1414, 1319, 1286, 1167, 1111, 766; **^{1}H NMR** (500 MHz, CD_3OD) δ: 2.54 (t, $J_{15\text{-}14}$ = 7.6 Hz, 2H, H_{15}), 2.82 (t, $J_{14\text{-}15}$ = 7.6 Hz, 2H, H_{14}), 3.60 (s, 2H, H_9), 6.83 (dd, $J_{11\text{-}12}$ = 8.1 Hz, $J_{11\text{-}13}$ = 2.0 Hz, 1H, H_{11}), 7.00 (d, $J_{12\text{-}11}$ = 8.1 Hz, 1H, H_{12}), 7.18 (d, $J_{13\text{-}11}$ = 2.0 Hz, 1H, H_{13}), 7.25-7.29 (m, 3H, H_2, H_8), 7.41 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.59 (t, J = 7.7 Hz, 1H, H_3), 7.65 (d, $J_{1\text{-}2}$ = 7.8 Hz, 1H, H_1), 7.92 (d, $J_{4\text{-}3}$ = 8.2 Hz, 1H, H_4); **^{13}C NMR** (125 MHz,

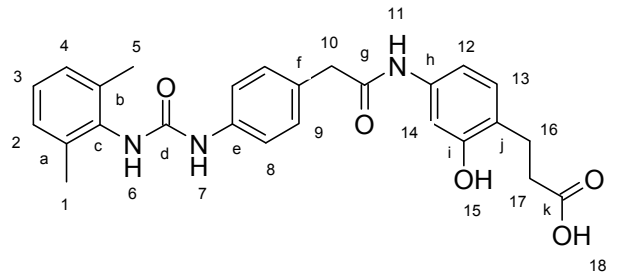
CD_3OD) δ: 26.9 (C_{14}), 35.8 (C_{15}), 44.0 (C_9), 108.6 (C_{13}), 112.4 (C_{11}), 120.5 (C_7), 122.8 (q, $^2J_{C\text{-}F}$ = 29.4 Hz, C_b), 124.9 (C_j), 125.3 (C_2), 125.5 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, C_a), 127.0 (q, $^3J_{C\text{-}F}$ = 5.2 Hz, C_1), 127.4 (C_4), 130.6 (C_8), 131.0 (C_{12}), 131.5 (C_f), 133.8 (C_3), 137.4 (C_c), 139.0 (C_e), 139.2 (C_h), 155.2 (C_d), 156.6 (C_i), 172.3 (C_g), 178.2 (C_k); **^{19}F NMR** (282 MHz, CD_3OD, $CFCl_3$) δ: -60.84 (s, 3F, $C\underline{F}_3$); **MS** (ESI^+) *m/z* (rel intensity): 1024.6 ($[2M+Na]^+$, 19), 524.1 ($[M+Na]^+$, 67); **HRMS** (ESI^+) *m/z* for $C_{25}H_{22}F_3N_3O_5Na$ $[M+Na]^+$: calcd 524.1409; found 524.1397.



3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-2-hydroxy phenyl)propanoic acid (30).

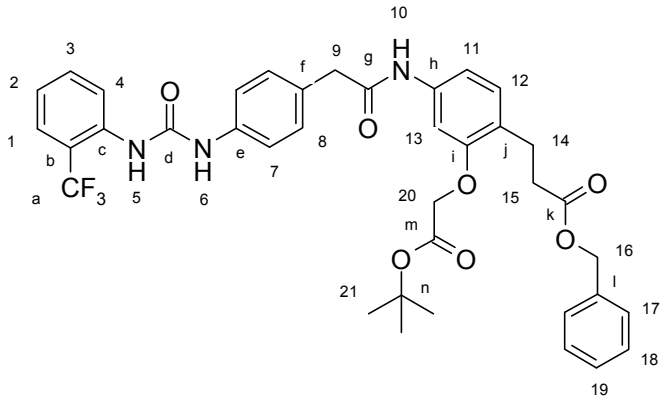
To a solution of benzyl 3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino} phenyl)acetyl]amino}-2-hydroxyphenyl)propanoate **38** (0.024 g, 0.043 mmol, 1.0 equiv) in ethanol (4 mL) and ethyl acetate (2 mL) was added Pd/C (10 %) as catalyst. The reaction mixture was stirred overnight under hydrogen atmosphere (1 atm). Then the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was washed with hexane and dried *in vacuo* to give **30** as a colorless solid (0.015 g, 75%).

***R*$_f$** = 0.34 (EtOAc/MeOH: 9/1, UV); **mp**: 189-193°C; **IR** (thin film, cm^{-1}) ν: 3286, 2924, 2854, 1707, 1639, 1603, 1545, 1416, 1377, 1232, 766; **^{1}H NMR** (500 MHz, CD_3OD) δ: 2.27 (s, 6H, H_1, H_5), 2.55 (t, $J_{17\text{-}16}$ = 7.7 Hz, 2H, H_{17}), 2.82 (t, $J_{16\text{-}17}$ = 7.7 Hz, 2H, H_{16}), 3.58 (s, 2H, H_{10}), 6.81 (dd, $J_{12\text{-}13}$ = 8.2 Hz, $J_{12\text{-}14}$ = 2.0 Hz, 1H, H_{12}), 6.99 (d, $J_{13\text{-}12}$ = 8.2 Hz, 1H, H_{13}), 7.08 (s, 3H, H_2, H_3, H_4), 7.19 (d, $J_{14\text{-}12}$ = 2.0 Hz, 1H, H_{14}), 7.25 (d, $J_{9\text{-}8}$ = 8.5 Hz, 2H, H_9), 7.36 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8); **^{13}C NMR** (125 MHz, CD_3OD) δ: 18.5 (C_1, C_5), 26.7 (C_{16}), 35.2 (C_{17}), 44.0 (C_{10}), 108.5 (C_{14}), 112.4 (C_{12}), 120.7 (C_8), 124.6 (C_j), 128.0 (C_3), 129.1 (C_2, C_4), 130.5 (C_9), 131.0 (C_{13}), 131.1 (C_f), 135.7 (C_c), 137.7 (C_a, C_b), 139.0 (C_h), 139.6 (C_e), 156.6 (C_i), 172.3 (C_g), 177.5 (C_k), C_d not visible; **MS** (ESI^+) *m/z* (rel intensity): 484.2 ($[M+Na]^+$, 100), 462.1 ($[M+H]^+$, 35); **HRMS** (ESI^+) *m/z* for $C_{26}H_{28}N_3O_5$ $[M+H]^+$: calcd 462.2029; found 462.2032.



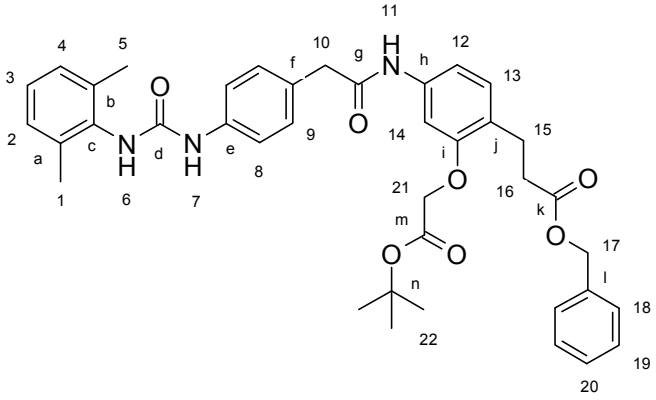
General procedure for the phenol *O*-alkylation.
To a solution of phenol compound (0.33 mmol, 1.0 equiv) in anhydrous acetonitrile (11 mL) and DMF (3 mL) cooled at 0°C, was added cesium carbonate (0.107 g, 0.40 mmol, 1.2 equiv). The reaction mixture was stirred for 20 min at 0°C under argon atmosphere. A solution of *tert*-butyl 2-bromoacetate (0.064 g, 0.40 mmol, 1.2 equiv) in DMF (1 mL) was introduced dropwise. The reaction mixture was stirred overnight at room temperature. After concentration under reduced pressure, the residue was diluted with ethyl acetate. The organic layer was washed with water (5x), dried over $MgSO_4$, filtered and concentrated under vacuum.

Benzyl 3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoate (39).
The title compound was obtained from benzyl 3-[2-hydroxy-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoate **37** and was purified by column chromatography on silica gel (elution with EtOAc/Hexane: 1/1) to give **39** as a colorless solid (0.022 g, 61%).
$\boldsymbol{R_f}$ = 0.48 (EtOAc/Hexane: 1/1, UV); **mp**: 114-117°C; **IR** (thin film, cm^{-1}) ν: 3313, 3067, 2980, 1734, 1649, 1607, 1541, 1512, 1456, 1418, 1369, 1321, 1286, 1261, 1236, 1157, 1121;
^{1}H NMR (300 MHz, acetone-d_6) δ: 1.44 (s, 9H, H_{21}), 2.68 (t, $J_{15\text{-}14}$ = 7.6 Hz, 2H, H_{15}), 2.91 (t, $J_{14\text{-}15}$ = 7.6 Hz, 2H, H_{14}), 3.62 (s, 2H, H_9), 4.57 (s, 2H, H_{20}), 5.10 (s, 2H, H_{16}), 7.00 (dd, $J_{11\text{-}12}$ = 8.2 Hz, $J_{11\text{-}13}$ = 1.4 Hz, 1H, H_{11}), 7.06 (d, $J_{12\text{-}11}$ = 8.2 Hz, 1H, H_{12}), 7.23-7.37 (m, 8H, H_2, H_8, H_{17}, H_{18}, H_{19}), 7.44 (d, $J_{13\text{-}11}$ = 1.4 Hz, 1H, H_{13}), 7.49 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.61-7.68 (m, 3H, H_1, H_3, NH_5), 8.17 (d, $J_{4\text{-}3}$ = 8.3 Hz, 1H, H_4), 8.77 (br s, 1H, NH_6), 9.21 (br s, 1H, NH_{10});
^{13}C NMR (75 MHz, acetone-d_6) δ: 26.4 (C_{14}), 28.2 (C_{21}), 34.7 (C_{15}), 44.2 (C_9), 66.1 (C_{20}), 66.2 (C_{16}), 82.1 (C_n), 103.8 (C_{13}), 112.2 (C_{11}), 119.5 (C_7), 124.1 (C_2), 124.7 (C_j), 125.9 (C_4), 126.6 (q, $^3J_{C\text{-}F}$ = 5.9 Hz, C_1), 128.7 (C_{17}), 128.8 (C_{19}), 129.2 (C_{18}), 130.4 (C_8), 130.8 (C_{12}), 130.9 (C_f), 133.6 (C_3), 139.2 (C_e), 140.0 (C_h), 153.1 (C_d), 156.8 (C_i), 168.4 (C_m), 169.8 (C_g), 173.1 (C_k), C_a, C_b, C_c, C_l not visible; **MS** (ESI^+) *m/z* (rel intensity): 744.0 ($[M+K]^+$, 16), 728.0 ($[M+Na]^+$, 100), 672.1 ($[M+Na\text{-}C_4H_8]^+$, 67), 650.0 ($[M+H\text{-}C_4H_8]^+$, 20); **HRMS** (ESI^+) *m/z* for $C_{38}H_{38}F_3N_3O_7Na$ $[M+Na^+]$: calcd 728.2560; found 728.2551.



Benzyl 3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}phenyl]propanoate (40).
The title compound was obtained from benzyl 3-(4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}-2-hydroxyphenyl)propanoate **38** (0.182 g, 0.33 mmol, 1.0 equiv). The crude residue was dissolved in acetone and hexane was

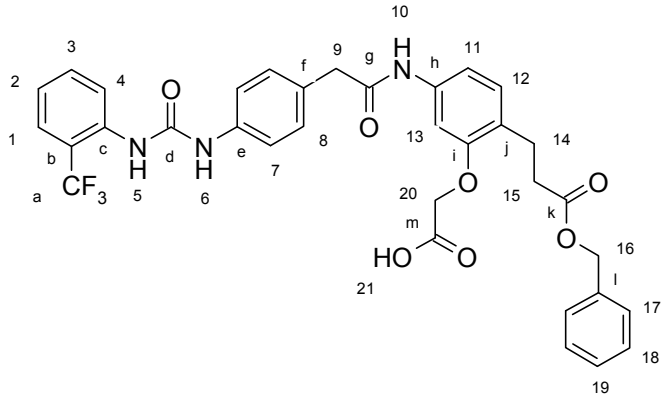
added until a precipitate was formed. This precipitate was collected by filtration, washed with hexane and dried *in vacuo* to give **40** as a colorless solid (0.172 g, 78%).
R_f = 0.36 (EtOAc/Hexane: 3/2, UV); **mp**: 166-169°C; **IR** (thin film, cm^{-1}) *v*: 3290, 3063, 2976, 1732, 1647, 1605, 1539, 1508, 1416, 1313, 1228, 1153, 842, 770, 698; **^{1}H NMR** (500 MHz, acetone-d_6) δ: 1.43 (s, 9H, H_{22}), 2.26 (s, 6H, H_1, H_5), 2.68 (t, $J_{16\text{-}15}$ = 7.6 Hz, 2H, H_{16}), 2.91 (t, $J_{15\text{-}16}$ = 7.6 Hz, 2H, H_{15}), 3.58 (s, 2H, H_{10}), 4.56 (s, 2H, H_{21}), 5.09 (s, 2H, H_{17}), 6.99 (dd, $J_{12\text{-}13}$ = 8.1 Hz, $J_{12\text{-}14}$ = 1.8 Hz, 1H, H_{12}), 7.02-7.07 (m, 4H, H_2, H_3, H_4, H_{13}), 7.21-7.24 (m, 3H, H_9, NH_6), 7.27-7.35 (m, 5H, H_{18}, H_{19}, H_{20}), 7.43 (d, $J_{14\text{-}12}$ = 1.8 Hz, 1H, H_{14}), 7.47 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8), 8.13 (br s, 1H, NH_7), 9.18 (br s, 1H, NH_{11}); **^{13}C NMR** (125 MHz, acetone-d_6) δ: 18.6 (C_1, C_5), 26.5 (C_{15}), 28.2 (C_{22}), 34.8 (C_{16}), 44.3 (C_{10}), 66.1 (C_{21}), 66.3 (C_{17}), 82.2 (C_n), 103.8 (C_{14}), 111.2 (C_{12}), 119.3 (C_8), 124.7 (C_j), 127.2 (C_3), 128.7, 128.8 (C_2, C_4, C_{18}, C_{20}), 129.2 (C_{19}), 130.0 (C_f), 130.2 (C_9), 130.8 (C_{13}), 136.3 (C_c), 137.0 (C_a, C_b), 137.6 (C_l), 140.1 (C_h), 140.2 (C_e), 154.1 (C_d), 155.8 (C_i), 168.4 (C_m), 170.0 (C_g), 173.2 (C_k); **MS** (APCI$^-$) *m/z* (rel intensity): 664.0 ([M-H]$^-$, 100), 608.2 ([M-H-C_4H_8]$^-$, 7); **HRMS** (ESI$^-$) *m/z* for $C_{39}H_{42}N_3O_7$ [M-H]$^-$: calcd 664.3023; found 664.3015.



General procedure for the deprotection of *tert*-butyl ester.
A solution of *tert*-butyl ester compound in a mixture (1/1) of DCM and trifluoroacetic acid (28 mL/mmol of ester compound) was stirred for 3 h. After concentration of the reaction mixture under vacuum, the residue was dissolved in DCM and the volatiles were removed under reduced pressure (3x).

{2-[3-(benzyloxy)-3-oxopropyl]-5-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino) phenyl]acetyl}amino)phenoxy}acetic acid (31).
The title compound was obtained from benzyl 3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoate **39** (0.023 g, 0.033 mmol, 1.0 equiv) to give **31** as a colorless solid (0.021 g, quantitative).
R_f = 0.20 (EtOAc/MeOH: 4/1, UV); **mp**: 129-132°C; **IR** (thin film, cm^{-1}) *v*: 3325, 3067, 2930, 1701, 1655, 1607, 1541, 1508, 1456, 1418, 1321, 1286, 1263, 1236, 1171, 1122, 764; **^{1}H NMR** (500 MHz, CD_3OD) δ: 2.69 (t, $J_{15\text{-}14}$ = 7.5 Hz, 2H, H_{15}), 2.94 (t, $J_{14\text{-}15}$ = 7.5 Hz, 2H, H_{14}), 3.61 (s, 2H, H_9), 4.65 (s, 2H, H_{20}), 5.06 (s, 2H, H_{16}), 7.00 (dd, $J_{11\text{-}12}$ = 8.2 Hz, $J_{11\text{-}13}$ = 1.8 Hz, 1H, H_{11}), 7.03 (d, $J_{12\text{-}11}$ = 8.2 Hz, 1H, H_{12}), 7.22-7.31 (m, 9H, H_2, H_8, H_{13}, H_{17}, H_{18}, H_{19}), 7.43 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.59 (t, J = 8.0 Hz, 1H, H_3), 7.65 (d, $J_{1\text{-}2}$ = 7.9 Hz, 1H, H_1), 7.92 (d, $J_{4\text{-}3}$ = 8.2 Hz, 1H, H_4); **^{13}C NMR** (125 MHz, CD_3OD) δ: 26.83 (C_{14}), 35.20 (C_{15}), 44.14 (C_9), 65.86 (C_{20}), 67.11 (C_{16}), 104.99 (C_{13}), 113.71 (C_{11}), 120.51 (C_7), 125.27 (C_2), 126.11 (C_j), 127.02 (q, $^3J_{C\text{-}F}$= 5.4 Hz, C_1), 127.37 (C_4), 129.05, 129.09 (C_{17}, C_{19}), 129.46 (C_{18}), 130.64 (C_8), 131.32 (C_{12}), 131.39 (C_f), 133.76 (C_3), 137.44 (C_c), 137.64 (C_l), 139.28

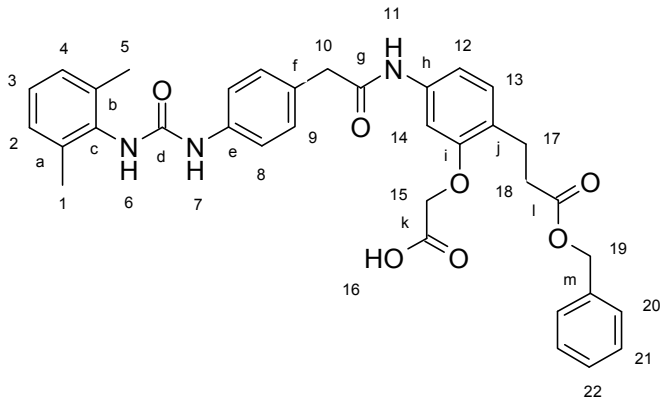
(C_e), 139.53 (C_h), 155.25 (C_d), 157.37 (C_i), 172.32 (C_g), 172.38 (C_m), 174.87 (C_k), C_a, C_b not visible; **^{19}F NMR** (282 MHz, CD_3OD, $CFCl_3$) δ: -60.84 (s, 3F, CF_3); **MS** (ESI^+) *m/z* (rel intensity): 672.1 ($[M+Na]^+$, 100), 649.9 ($[M+H]^+$, 10); **HRMS** (ESI^-) *m/z* for $C_{34}H_{29}F_3N_3O_7$ $[M-H]^-$: calcd 648.1958; found 648.1955.



(2-[3-(benzyloxy)-3-oxopropyl]-5-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl) acetyl]amino}phenoxy)acetic acid (32).

The title compound was obtained from benzyl 3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl)acetyl]amino}phenyl]propanoate **40** (0.018 g, 0.027 mmol, 1.0 equiv) to give **32** as a colorless solid (0.016 g, quantitative).

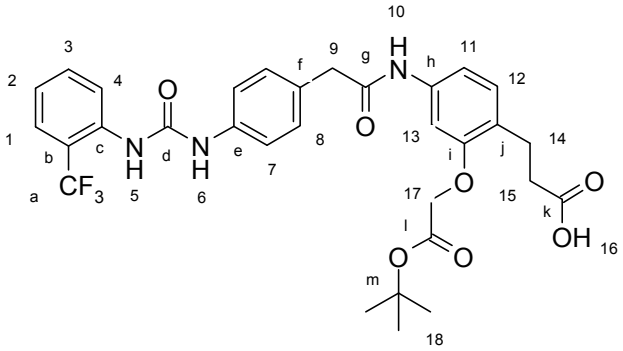
R_f = 0.21 (EtOAc/MeOH: 9/1, UV); **mp**: 177-181°C; **IR** (thin film, cm^{-1}) ν: 3240, 2924, 1732, 1716, 1651, 1603, 1541, 1508, 1416, 1225, 1119, 839, 771, 700; **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 2.20 (s, 6H, H_1, H_5), 2.64 (t, $J_{18\text{-}17}$ = 7.6 Hz, 2H, H_{18}), 2.81 (t, $J_{17\text{-}18}$ = 7.6 Hz, 2H, H_{17}), 3.52 (s, 2H, H_{10}), 4.62 (s, 2H, H_{15}), 5.07 (s, 2H, H_{19}), 7.04-7.08 (m, 4H, H_2, H_3, H_4, H_{13}), 7.09 (dd, $J_{12\text{-}13}$ = 8.2 Hz, $J_{12\text{-}14}$ = 1.8 Hz, 1H, H_{12}), 7.18-7.20 (m, 3H, H_9, H_{14}), 7.28-7.36 (m, 5H, H_{20}, H_{21}, H_{22}), 7.39 (d, $J_{8\text{-}9}$ = 8.6 Hz, 2H, H_8), 7.68 (s, 1H, NH_6), 8.69 (br s, 1H, NH_7), 10.06 (s, 1H, NH_{11}); **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 18.27 (C_1, C_5), 25.08 (C_{17}), 33.53 (C_{18}), 42.74 (C_{10}), 64.45 (C_{15}), 65.33 (C_{19}), 102.60 (C_{14}), 111.25 (C_{12}), 117.91 (C_8), 123.02 (C_j), 125.90 (C_3), 127.71 (C_2, C_4), 127.89 (C_{20}), 127.93 (C_{22}), 128.39 (C_{21}), 128.82 (C_f), 129.33 (C_9), 129.76 (C_{13}), 135.36 (C_c), 135.52 (C_a, C_b), 136.22 (C_m), 138.85 (C_e, C_h), 153.14 (C_d), 155.53 (C_i), 169.29 (C_g), 170.01(C_k), 172.33 (C_l); **MS** ($APCI^-$) *m/z* (rel intensity): 608.1 ($[M-H]^-$, 47), 461.2 ($[M-H-C_8H_8NHCO]^-$, 100); **HRMS** (ESI^-) *m/z* for $C_{35}H_{34}N_3O_7$ $[M-H]^-$: calcd 608.2397; found 608.2384.



3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-({[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino) phenyl]acetyl}amino)phenyl]propanoic acid (33).

To a solution of benzyl 3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-({[4-({[2-(trifluoromethyl) phenyl]carbamoyl}amino)phenyl]acetyl}amino)phenyl]propanoate **39** (0.100 g, 0.14 mmol) in ethanol (7 mL), was added Pd/C (10 %) as catalyst. The reaction mixture was stirred overnight under hydrogen atmosphere (1 atm). Then, the reaction mixture was filtered through a Celite pad, and concentrated *in vacuo* to give **33** as a colorless solid (0.087 g, quantitative).

R_f = 0.42 (EtOAc, UV); **mp**: 109-113°C; **IR** (thin film, cm^{-1}) ν: 3333, 3074, 2978, 2930, 1699, 1652, 1607, 1541, 1512, 1456, 1418, 1369, 1321, 1286, 1236, 1159, 1122, 766; **^{1}H NMR** (300 MHz, acetone-d_6) δ: 1.44 (s, 9H, H_{18}), 2.60 (t, $J_{15\text{-}14}$ = 7.7 Hz, 2H, H_{15}), 2.88 (t, $J_{14\text{-}15}$ = 7.7 Hz, 2H, H_{14}), 3.61 (s, 2H, H_9), 4.57 (s, 2H, H_{17}), 7.02 (dd, $J_{11\text{-}12}$ = 8.1 Hz, $J_{11\text{-}13}$ = 1.5 Hz, 1H, H_{11}), 7.09 (d, $J_{12\text{-}11}$ = 8.1 Hz, 1H, H_{12}), 7.22-7.29 (m, 3H, H_2, H_8), 7.44 (d, $J_{13\text{-}11}$ = 1.5 Hz, 1H, H_{13}), 7.48 (d, $J_{7\text{-}8}$ = 8.5 Hz, 2H, H_7), 7.58-7.69 (m, 3H, H_1, H_3, NH_5), 8.15 (d, $J_{4\text{-}3}$ = 8.3 Hz, 1H, H_4), 8.86 (br s, 1H, NH_6), 9.24 (br s, 1H, NH_{10}); **^{13}C NMR** (75 MHz, acetone-d_6) δ: 26.44 (C_{14}), 28.25 (C_{18}), 34.56 (C_{15}), 44.17 (C_9), 66.13 (C_{17}), 82.17 (C_m), 103.83 (C_{13}), 112.31 (C_{11}), 119.56 (C_7), 124.17 (C_2), 125.17 (C_j), 126.02 (C_4), 126.67 (q, $^3J_{C\text{-}F}$ = 5.4 Hz, C_1), 130.37 (C_8), 130.75 (C_{12}), 130.81 (C_f), 133.56 (C_3), 137.81 (C_c), 139.28 (C_e), 139.85 (C_h), 153.17 (C_d), 156.83 (C_i), 168.47 (C_l), 170.02 (C_g), 174.77 (C_k), C_a, C_b not visible; **^{19}F NMR** (282 MHz, acetone-d_6, $CFCl_3$) δ: -60.26 (s, 3F, CF_3); **MS** (ESI^+) *m/z* (rel intensity): 653.9 ($[M+K]^+$, 14), 638.0 ($[M+Na]^+$, 50), 582.1 ($[M+Na\text{-}C_4H_8]^+$, 100), 560.1 ($[M+H\text{-}C_4H_8]^+$, 17); **HRMS** (ESI^+) *m/z* for $C_{31}H_{32}F_3N_3O_7Na$ $[M+Na]^+$: calcd 638.2090; found 638.2070.

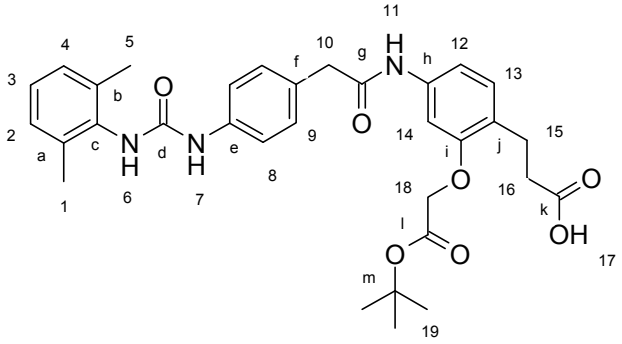


3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(4-{[(2,6-dimethylphenyl)carbamoyl]amino}phenyl) acetyl]amino}phenyl]propanoic acid (34).

To a solution of benzyl-3-[2-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(4-{[(2,6-dimethylphenyl) carbamoyl]amino}phenyl)acetyl]amino}phenyl]propanoate **40** (0.025 g, 0.038 mmol) in ethanol (2 mL) and ethyl acetate (2 mL), was added Pd/C (10 %) as catalyst. The reaction mixture was stirred overnight under hydrogen atmosphere (1 atm). Then, the mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo* to give **34** as a colorless solid (0.022 g, quantitative).

R_f = 0.47 (EtOAc/MeOH: 95/5, UV); **mp**: 168-171°C; **IR** (thin film, cm^{-1}) ν: 3288, 2926, 1732, 1645, 1605, 1543, 1508, 1418, 1313, 1242, 1153, 1124, 842, 768; **^{1}H NMR** (300 MHz, CD_3OD) δ: 1.45 (s, 9H, H_{19}), 2.28 (s, 6H, H_1, H_5), 2.58 (t, $J_{16\text{-}15}$ = 7.7 Hz, 2H, H_{16}), 2.89 (t, $J_{15\text{-}16}$ = 7.7 Hz, 2H, H_{15}), 3.59 (s, 2H, H_{10}), 4.58 (s, 2H, H_{18}), 6.95 (dd, $J_{12\text{-}13}$ = 8.1 Hz, $J_{12\text{-}14}$ = 1.8 Hz, 1H, H_{12}), 7.07-7.12 (m, 4H, H_2, H_3, H_4, H_{13}), 7.24-7.27 (m, 3H, H_9, H_{14}), 7.38 (d, $J_{8\text{-}9}$ = 8.5 Hz, 2H, H_8); **^{13}C NMR** (125 MHz, CD_3OD) δ: 18.5 (C_1, C_5), 26.9 (C_{15}), 28.3 (C_{19}), 35.3

(C_{16}), 44.1 (C_{10}), 66.6 (C_{18}), 83.4 (C_m), 104.9 (C_{14}), 113.6 (C_{12}), 120.7 (C_8), 126.4 (C_j), 128.0 (C_3), 129.1 (C_2, C_4), 130.5 (C_9, C_f), 131.2 (C_{13}), 135.7 (C_c), 137.7 (C_a, C_b), 139.4 (C_h), 139.7 (C_e), 157.2 (C_i), 169.9 (C_l), 172.4 (C_g), 177.4 (C_k), C_d not visible; **MS** (ESI$^-$) *m/z* (rel intensity): 574.1 ([M-H]$^-$, 100), 427.3 ([M-H-C_8H_8NHCO]$^-$, 64); **HRMS** (ESI$^-$) *m/z* for $C_{32}H_{36}N_3O_7$ [M-H]$^-$: calcd 574.2553; found 574.2562.



5. Biological assays

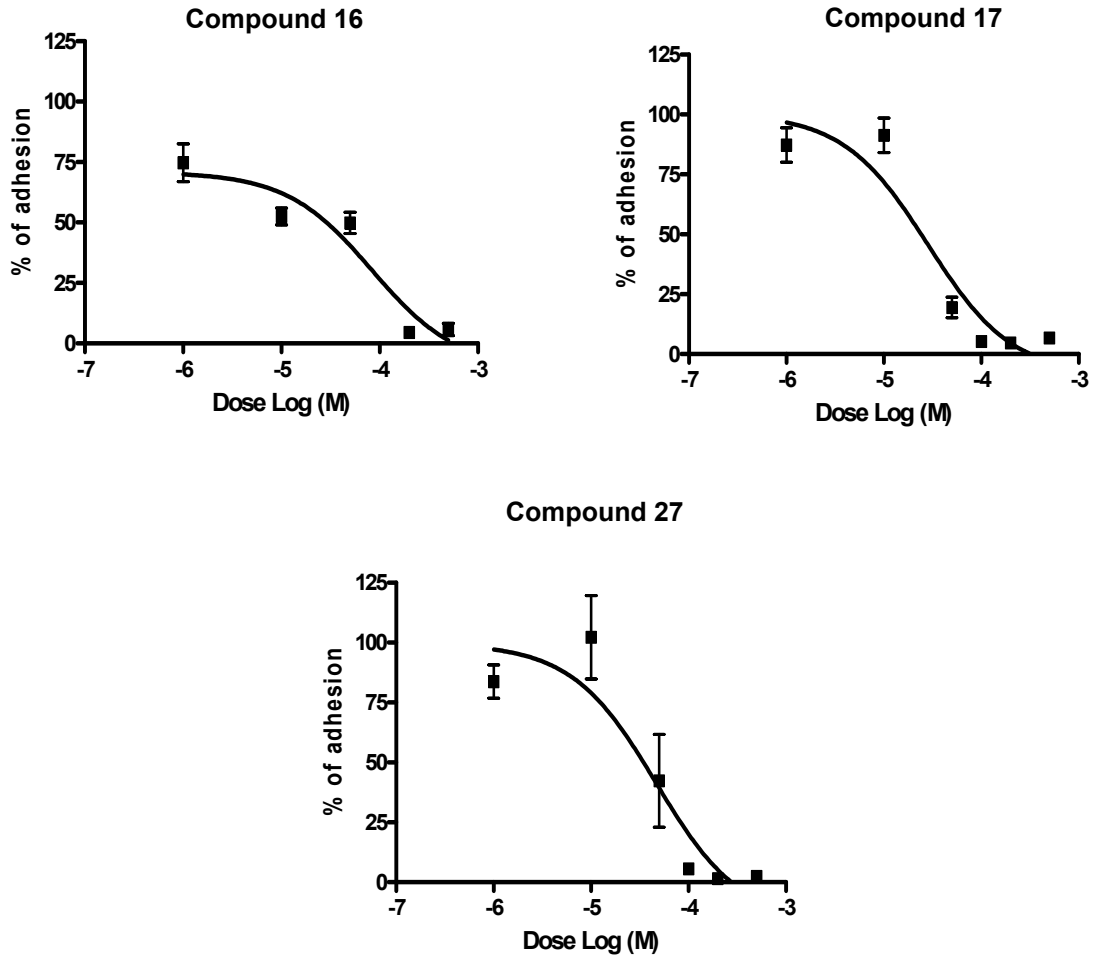


Fig.S1 Inhibition curves of peptidomimetics **16**, **17** and **27** on CCRF-CEM adhesion to fibronectin (10 µg/mL) during 1 h at 37°C (mean of three independent experiments).

6. ^{13}C NMR scans

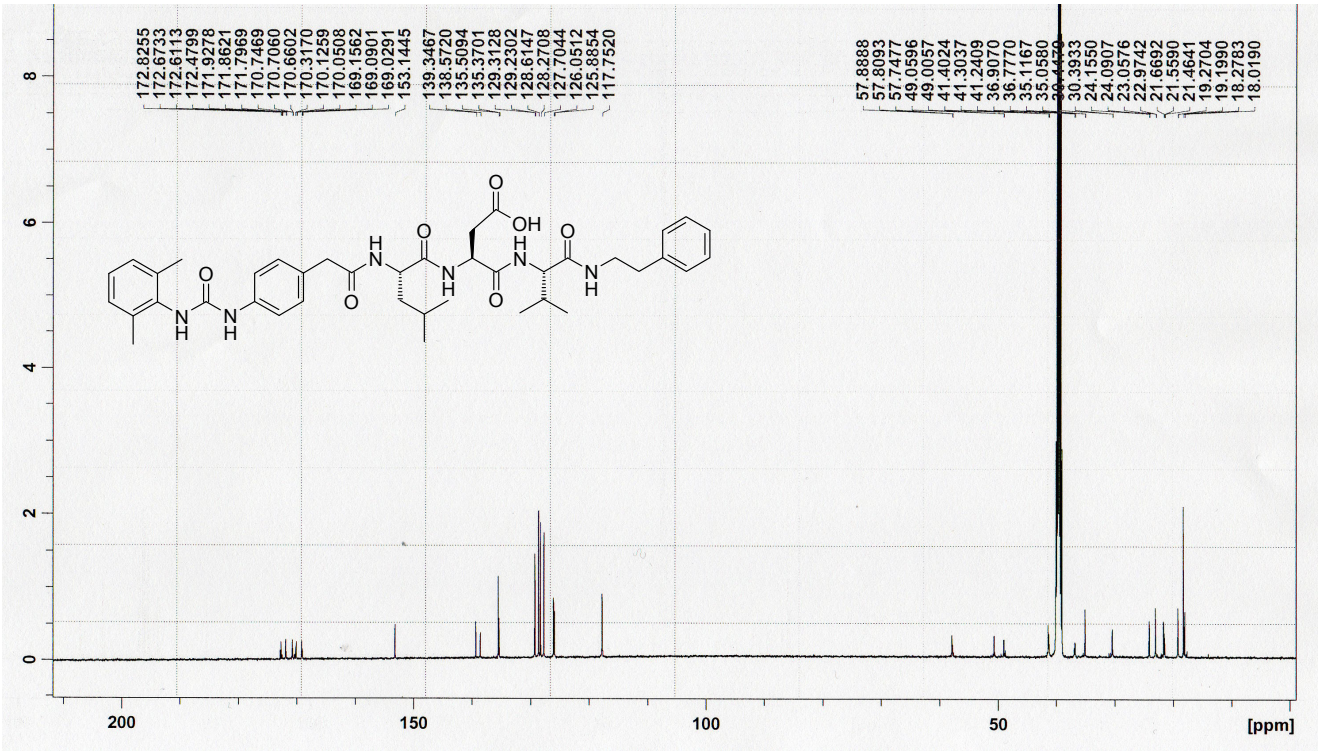


Fig.S2 ^{13}C NMR spectrum of compound **2**

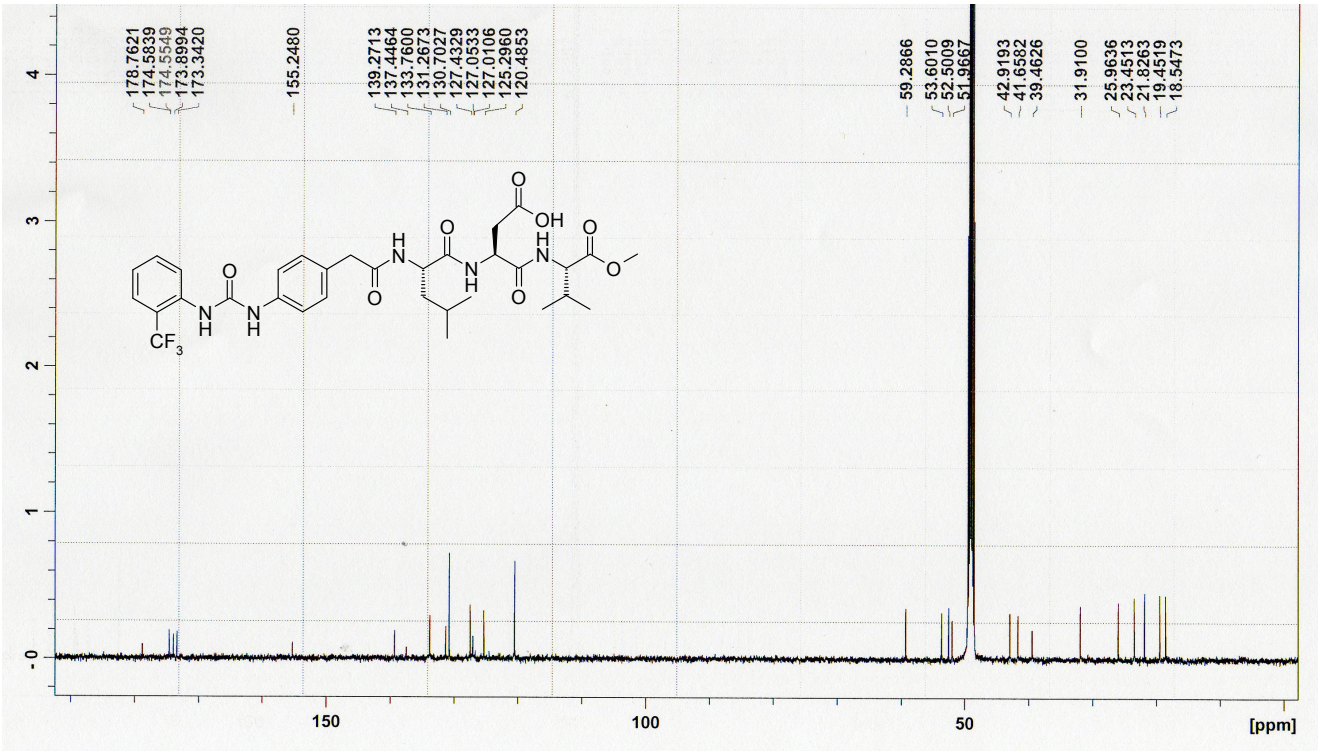


Fig.S3 ^{13}C NMR spectrum of compound **3**

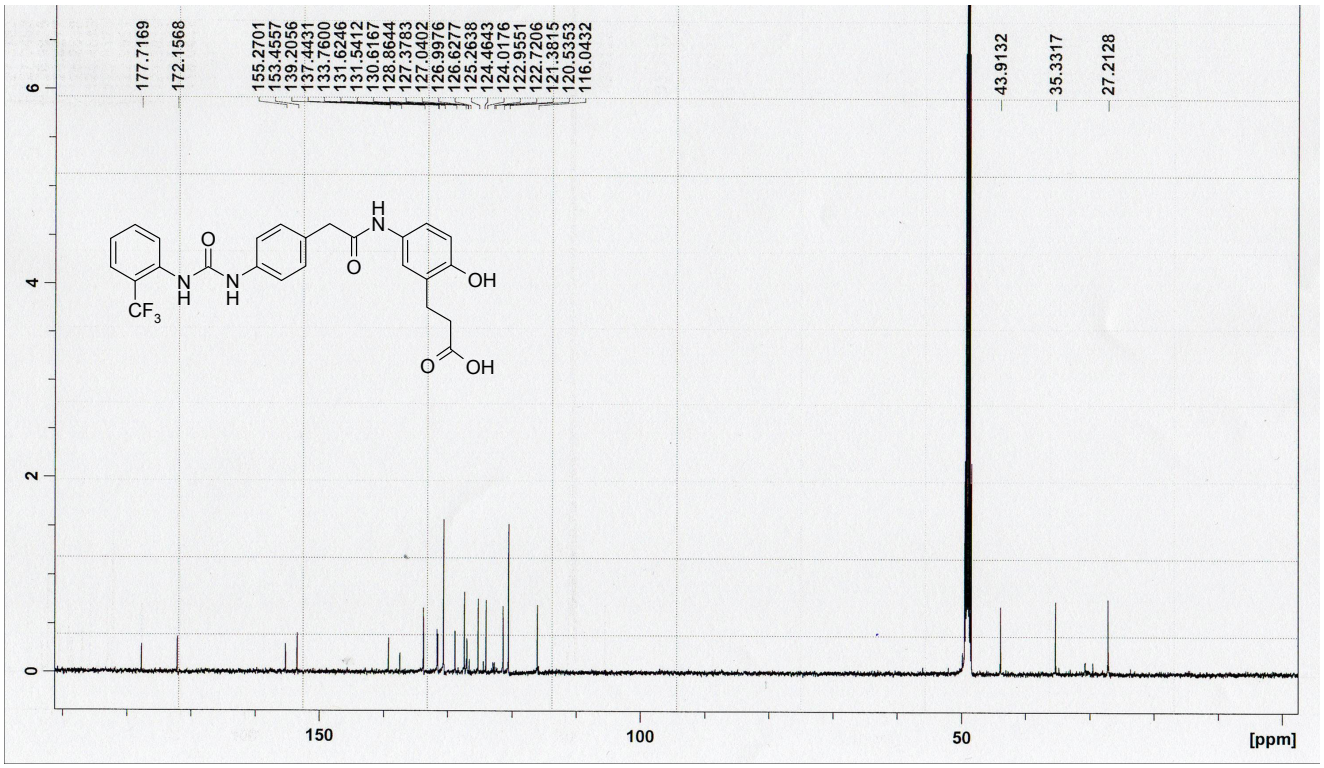


Fig.S4 ^{13}C NMR spectrum of compound **12**

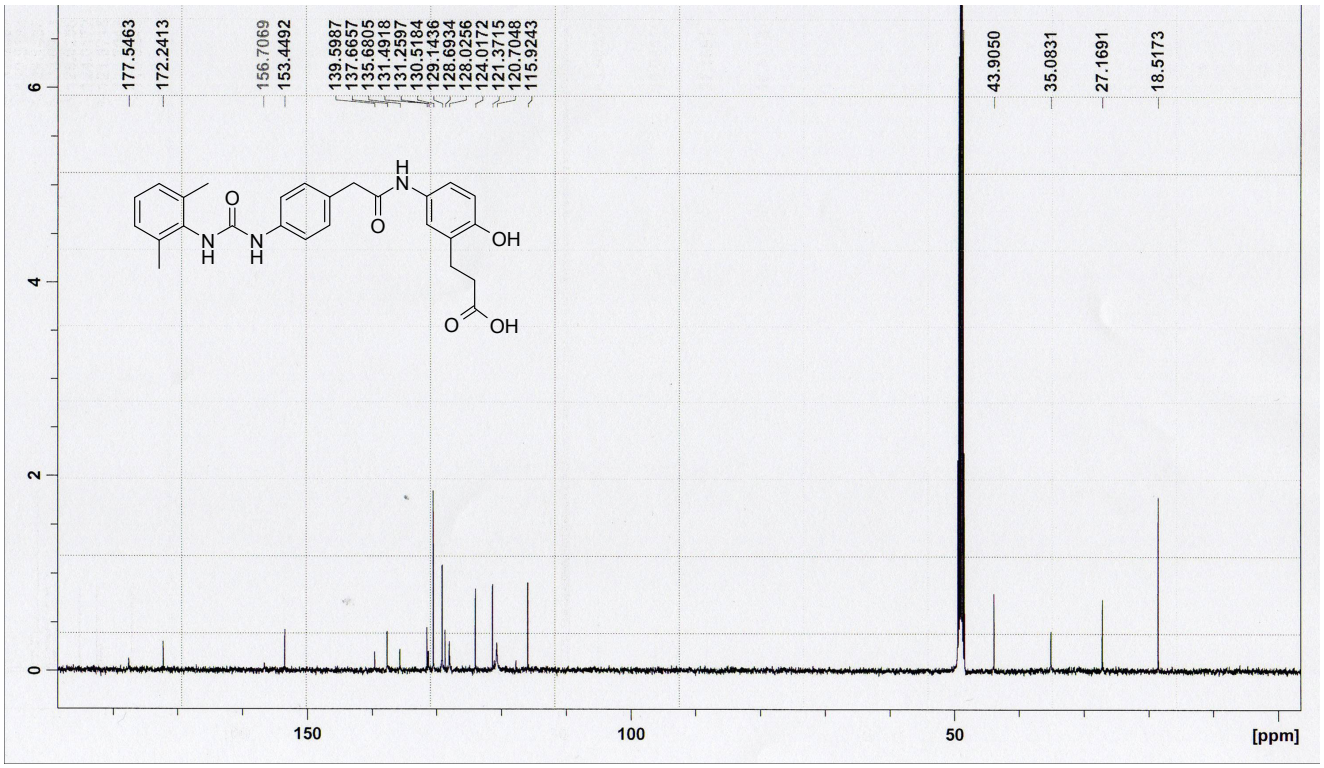


Fig.S5 ^{13}C NMR spectrum of compound **13**

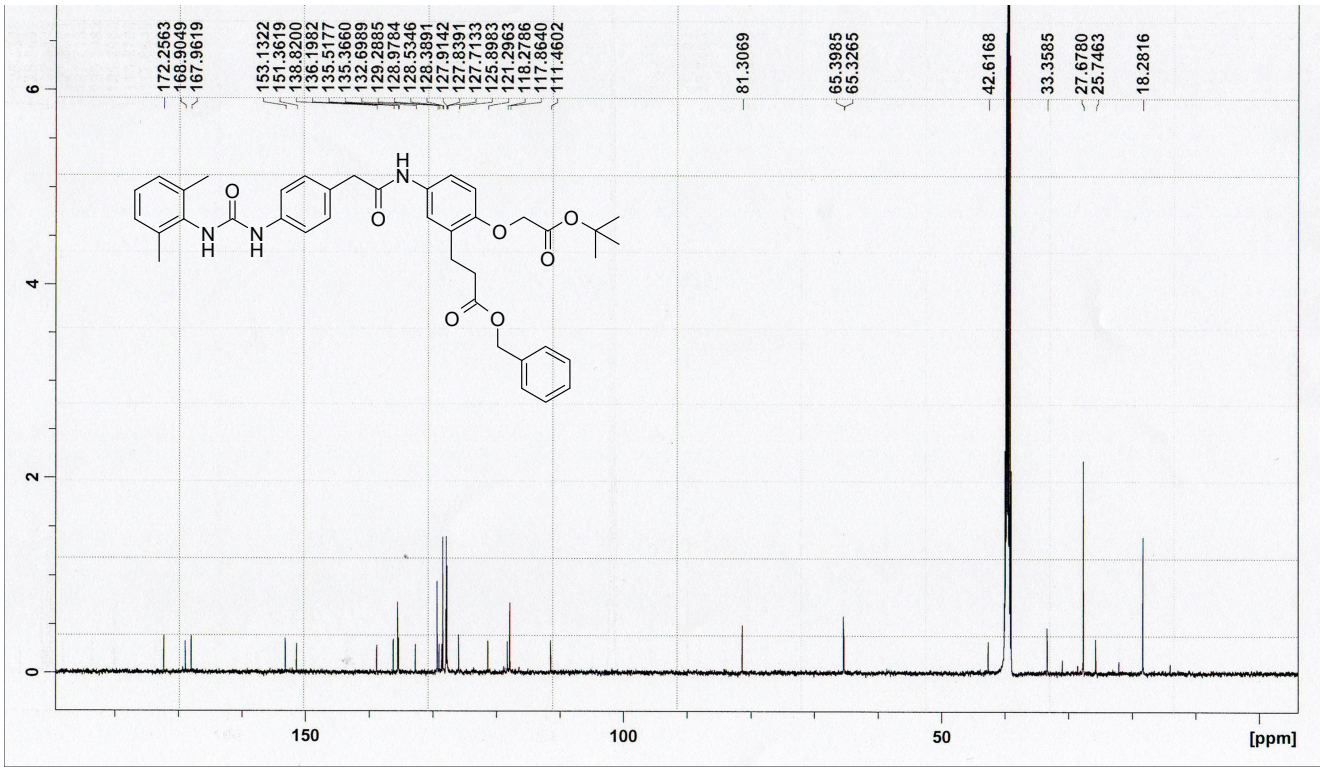


Fig.S6 ^{13}C NMR spectrum of compound **15**

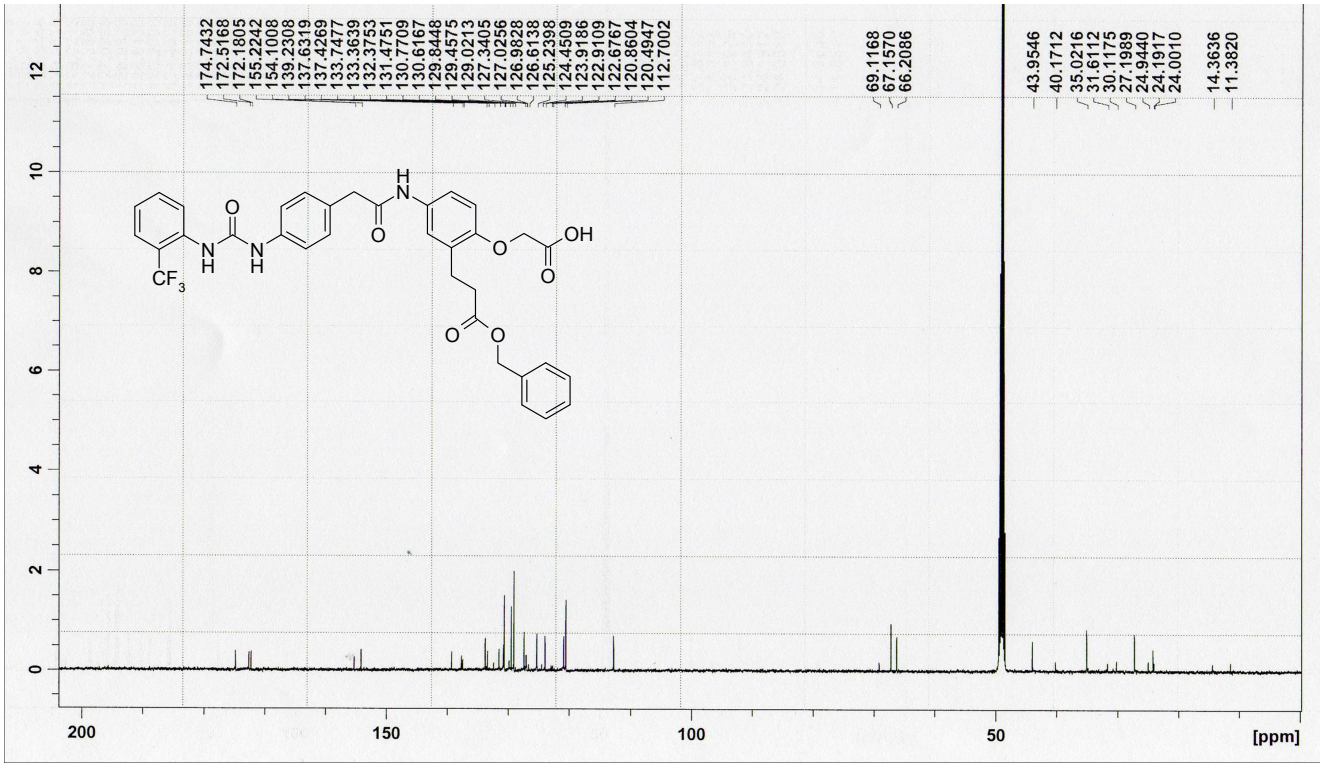


Fig.S7 ^{13}C NMR spectrum of compound **16**

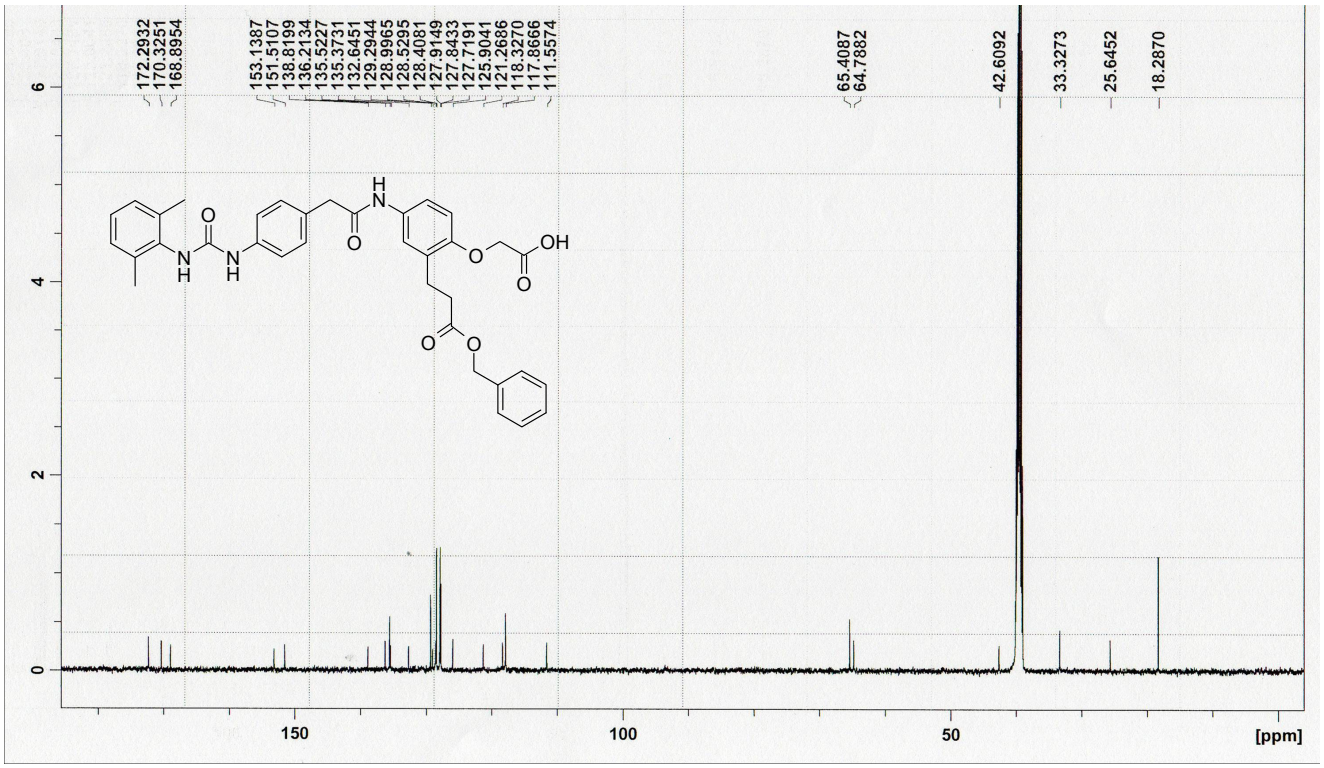


Fig.S8 ^{13}C NMR spectrum of compound **17**

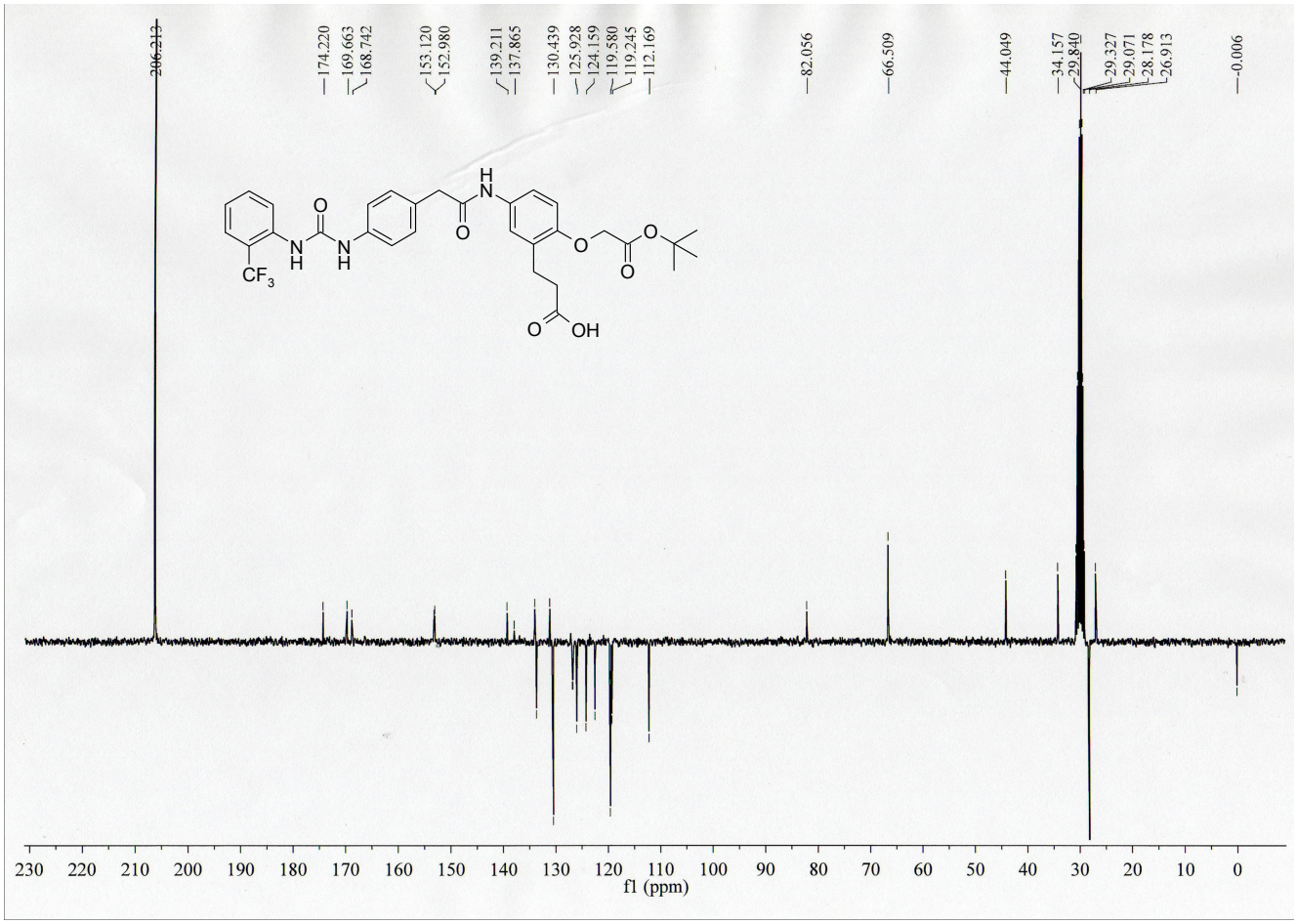


Fig.S9 APT NMR spectrum of compound **18**

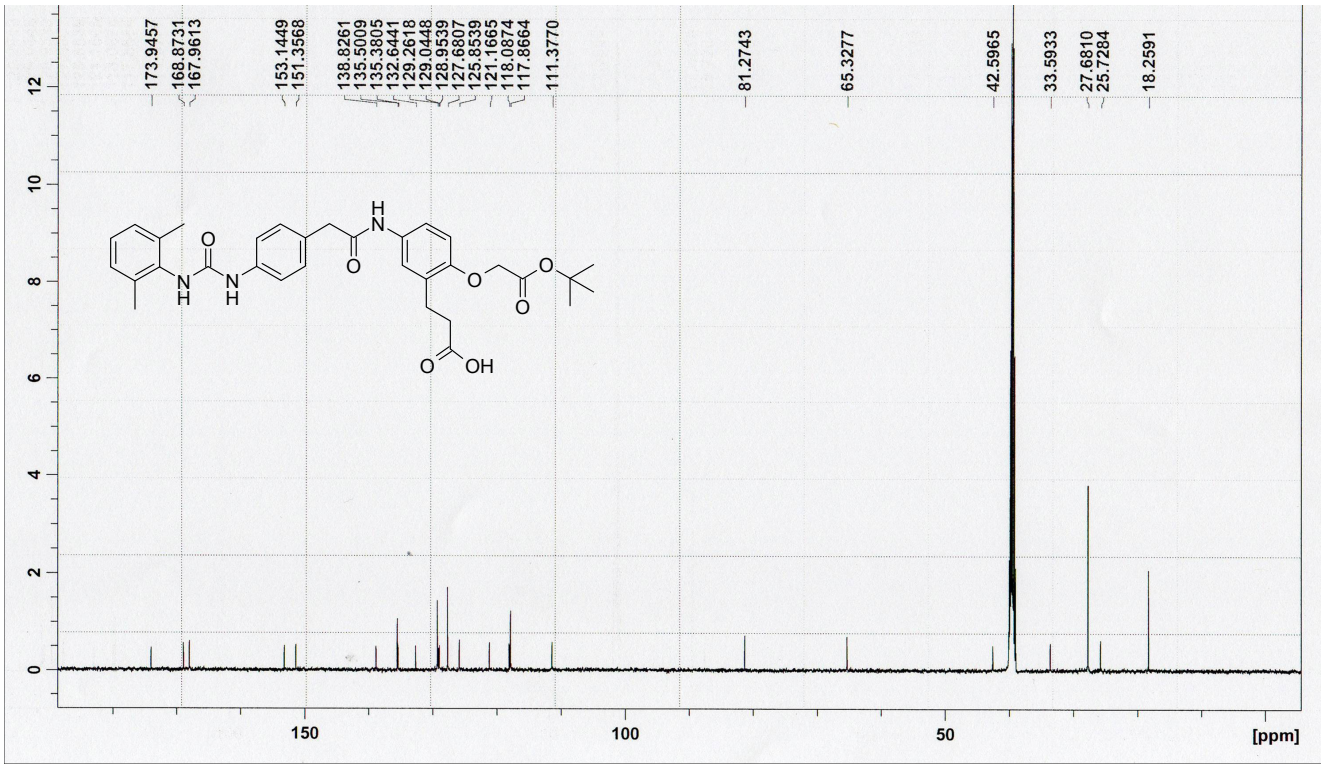


Fig.S10 ^{13}C NMR spectrum of compound **19**

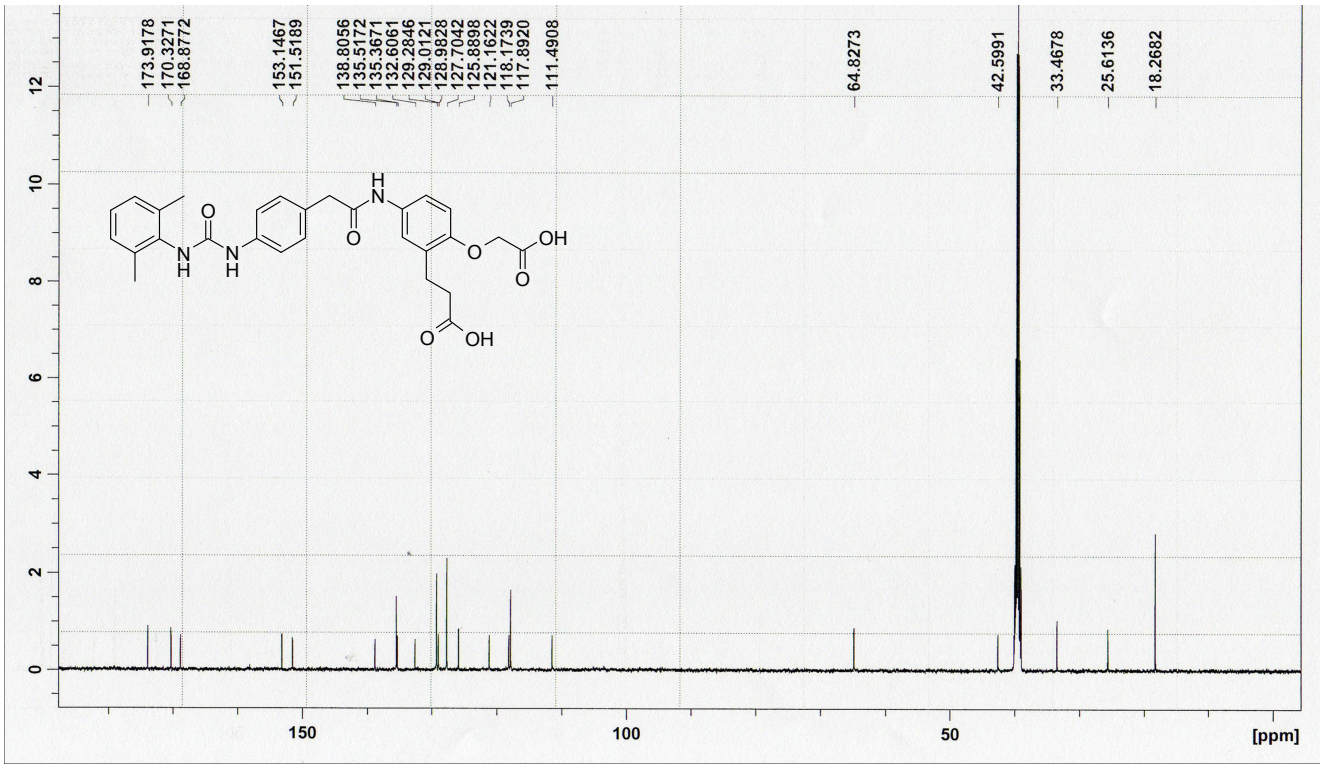


Fig.S11 ^{13}C NMR spectrum of compound **20**

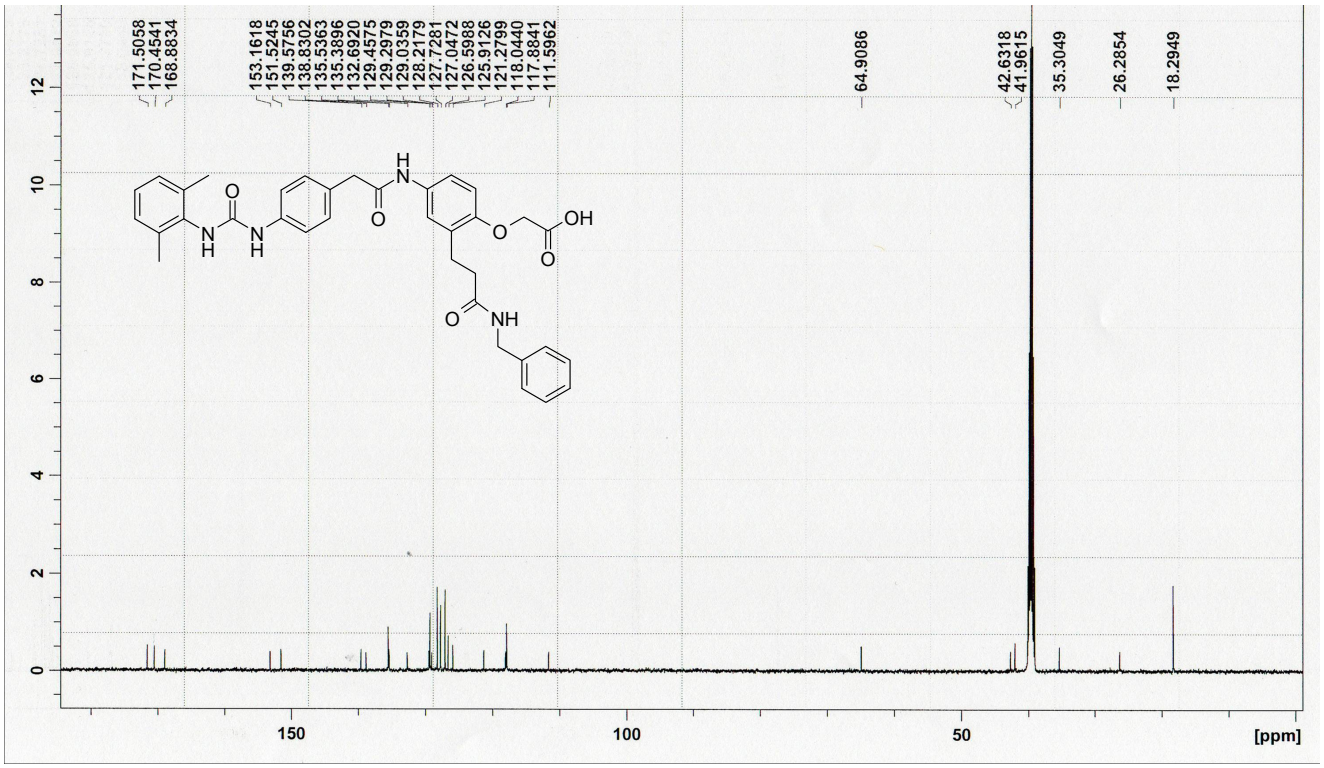


Fig.S12 ^{13}C NMR spectrum of compound **25**

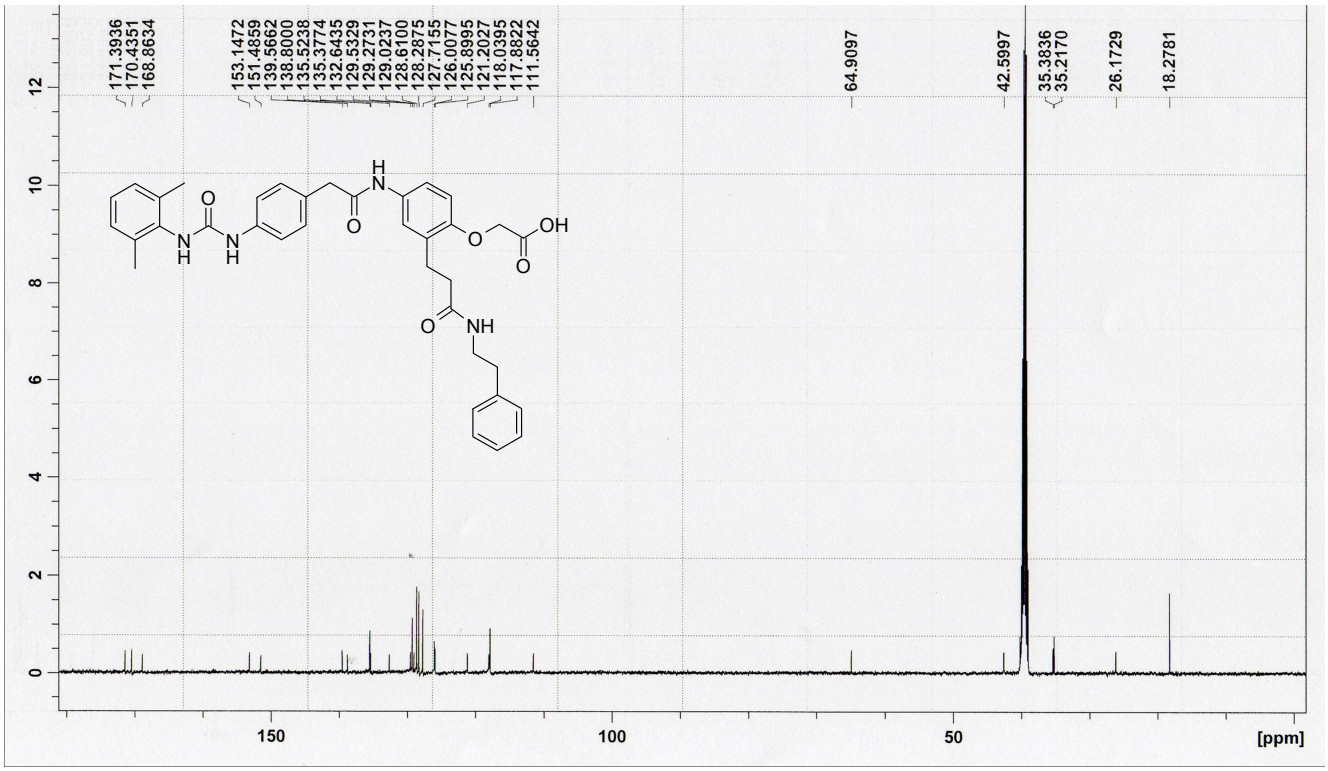


Fig.S13 ^{13}C NMR spectrum of compound **26**

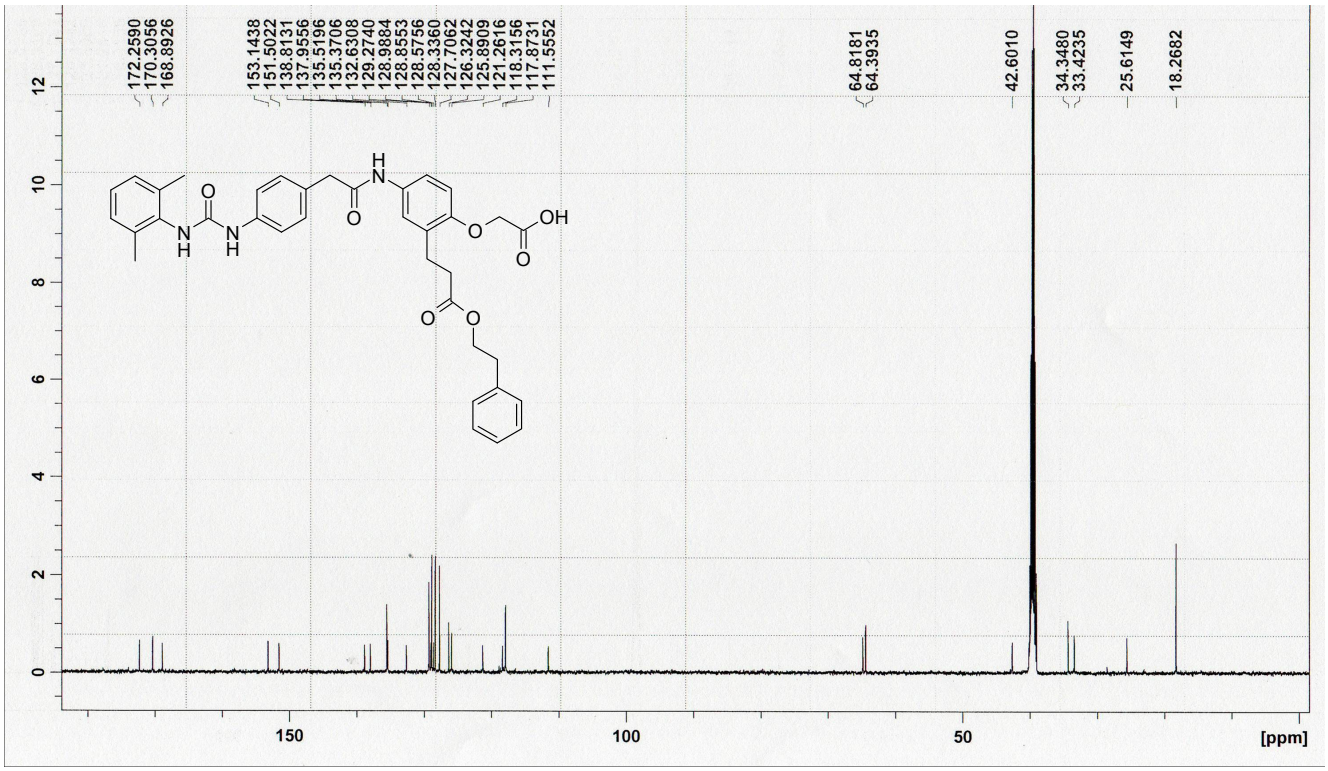


Fig.S14 ^{13}C NMR spectrum of compound **27**

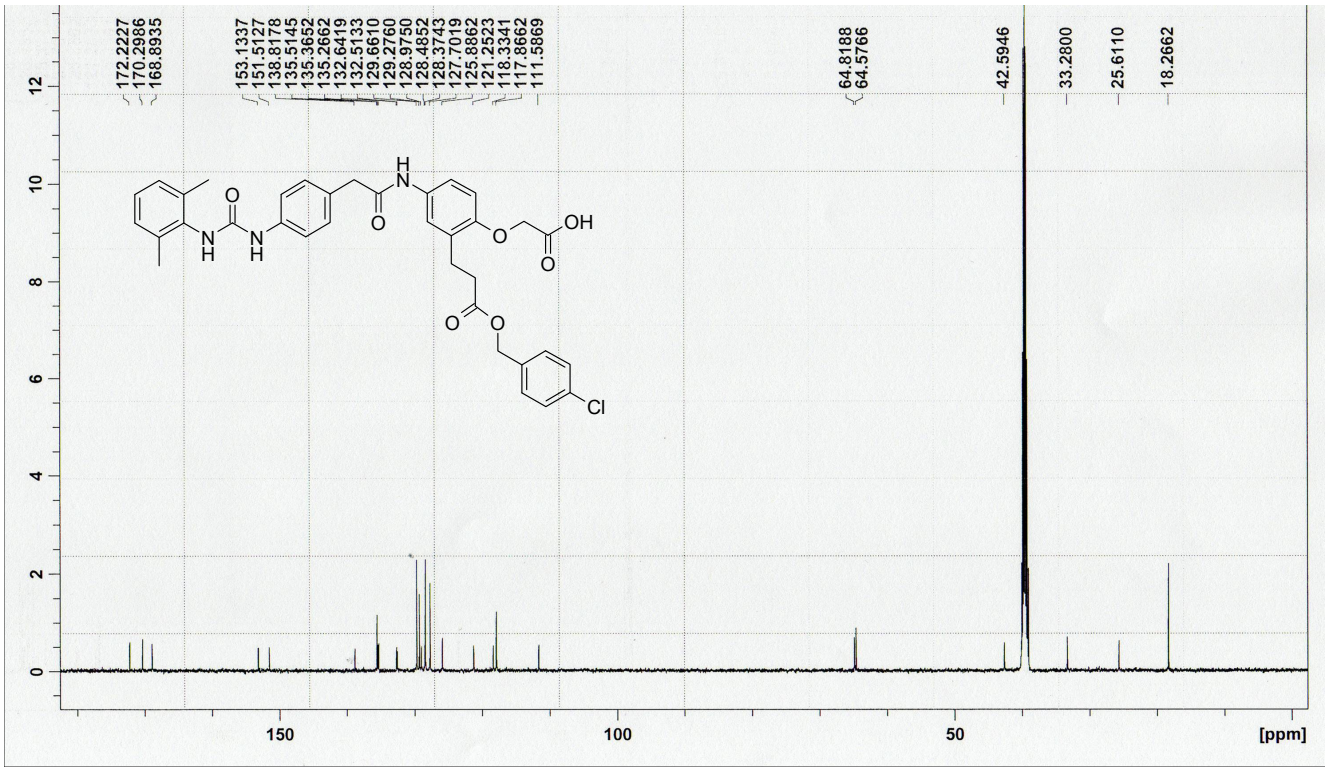


Fig.S15 ^{13}C NMR spectrum of compound **28**

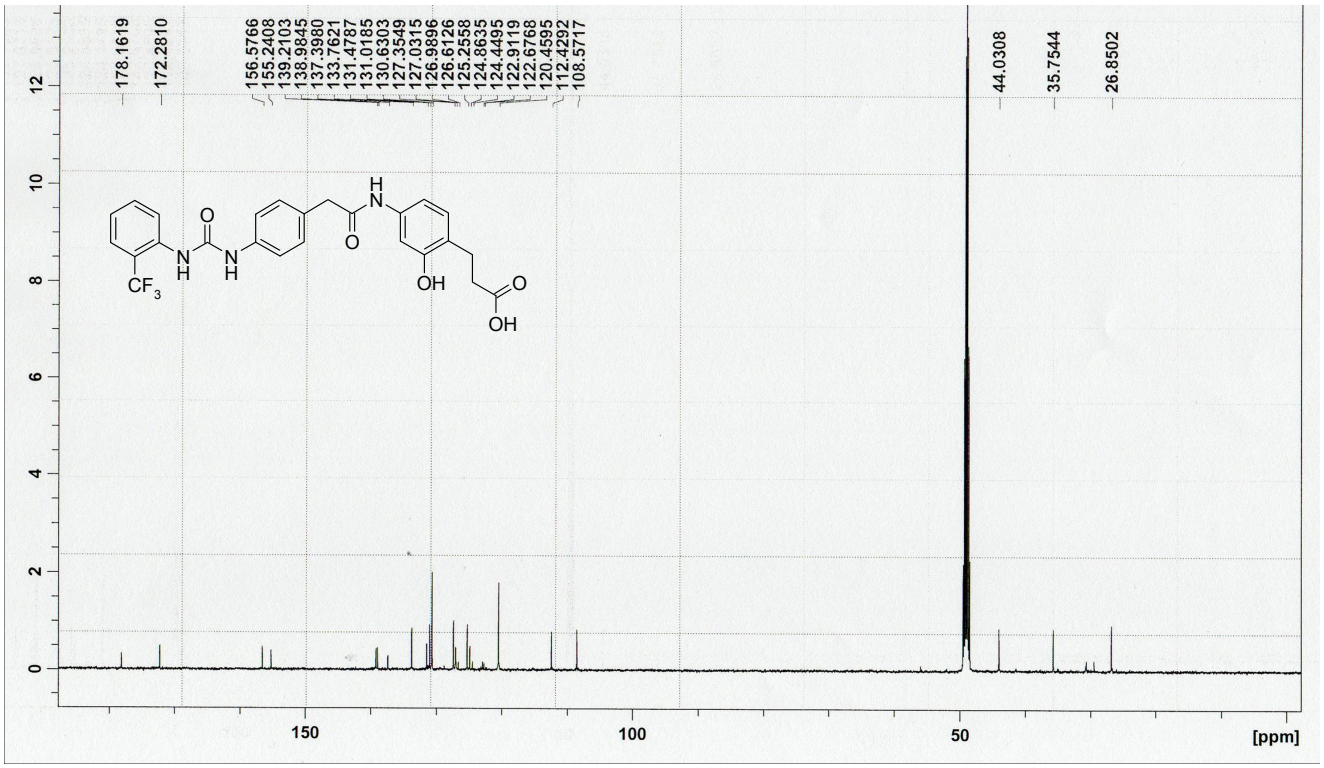


Fig.S16 ^{13}C NMR spectrum of compound **29**

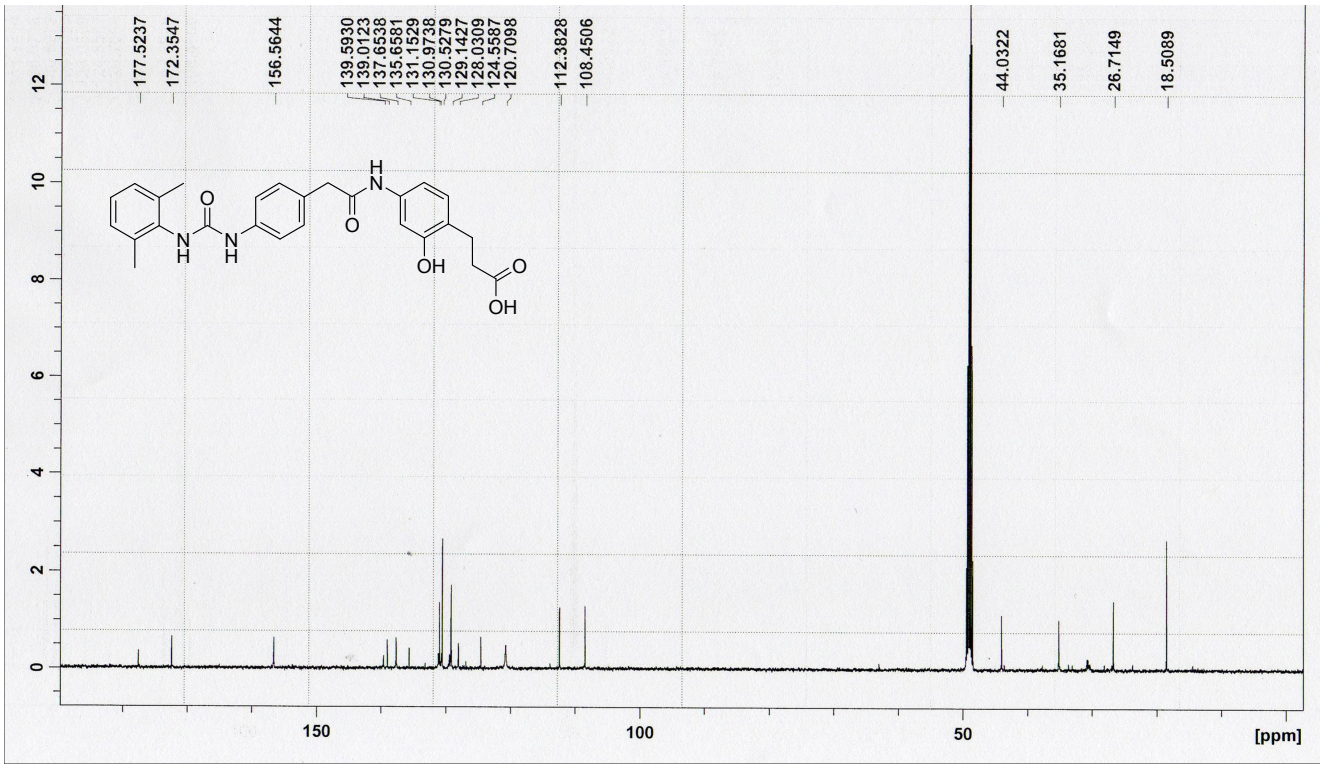


Fig.S17 ^{13}C NMR spectrum of compound **30**

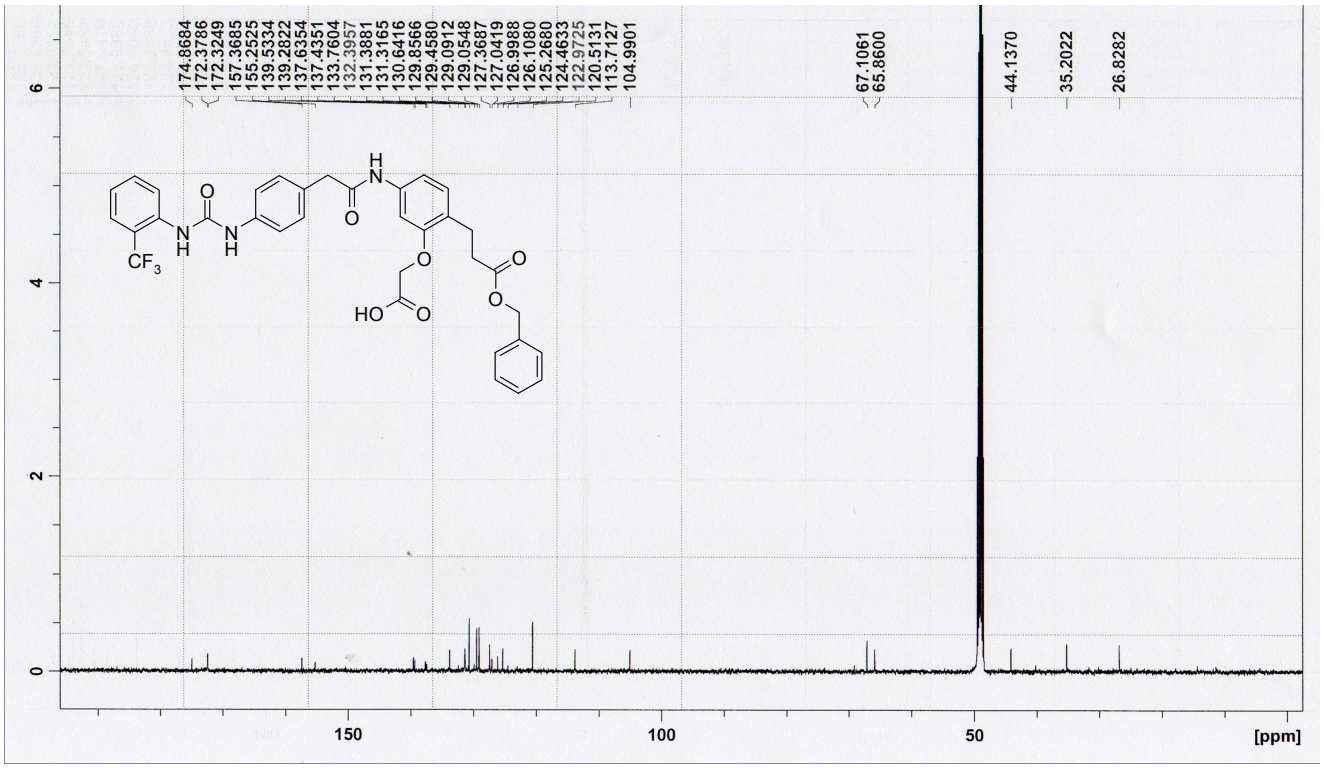


Fig.S18 ^{13}C NMR spectrum of compound **31**

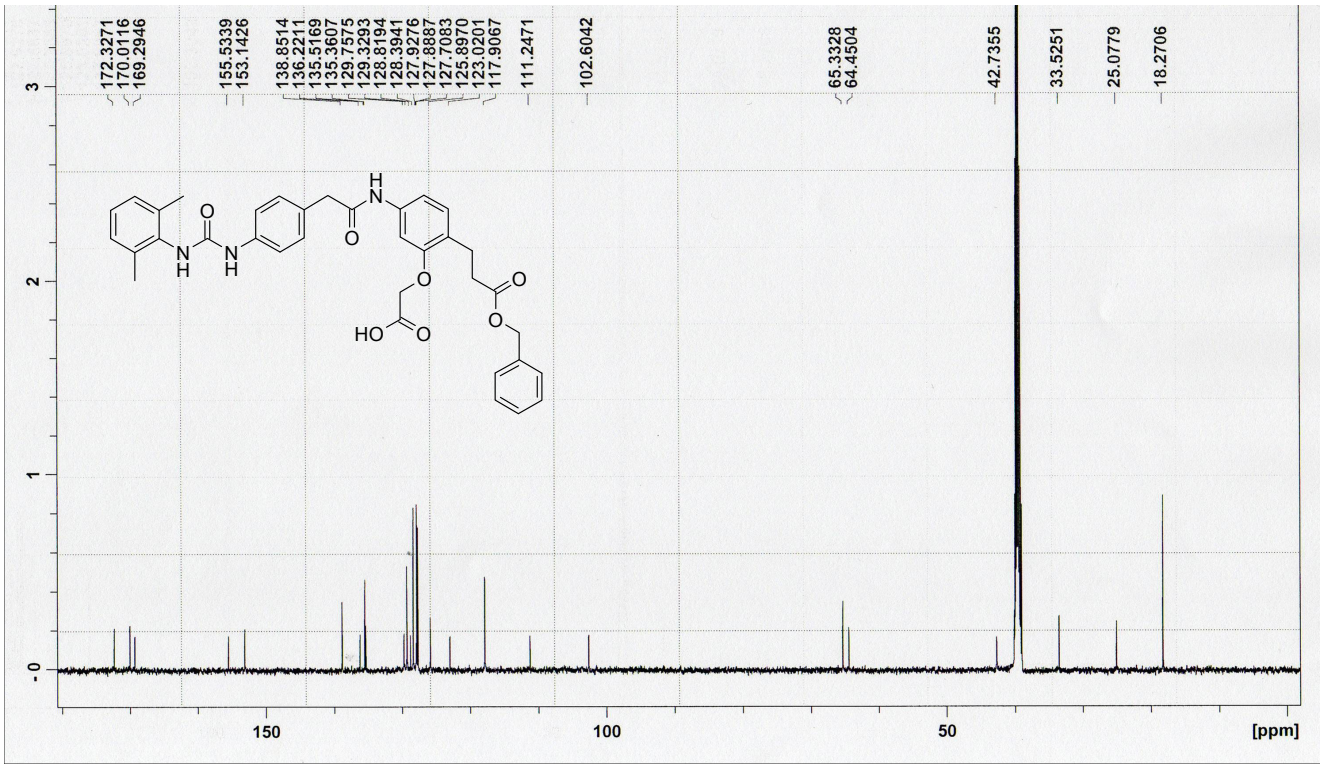


Fig.S19 ^{13}C NMR spectrum of compound **32**

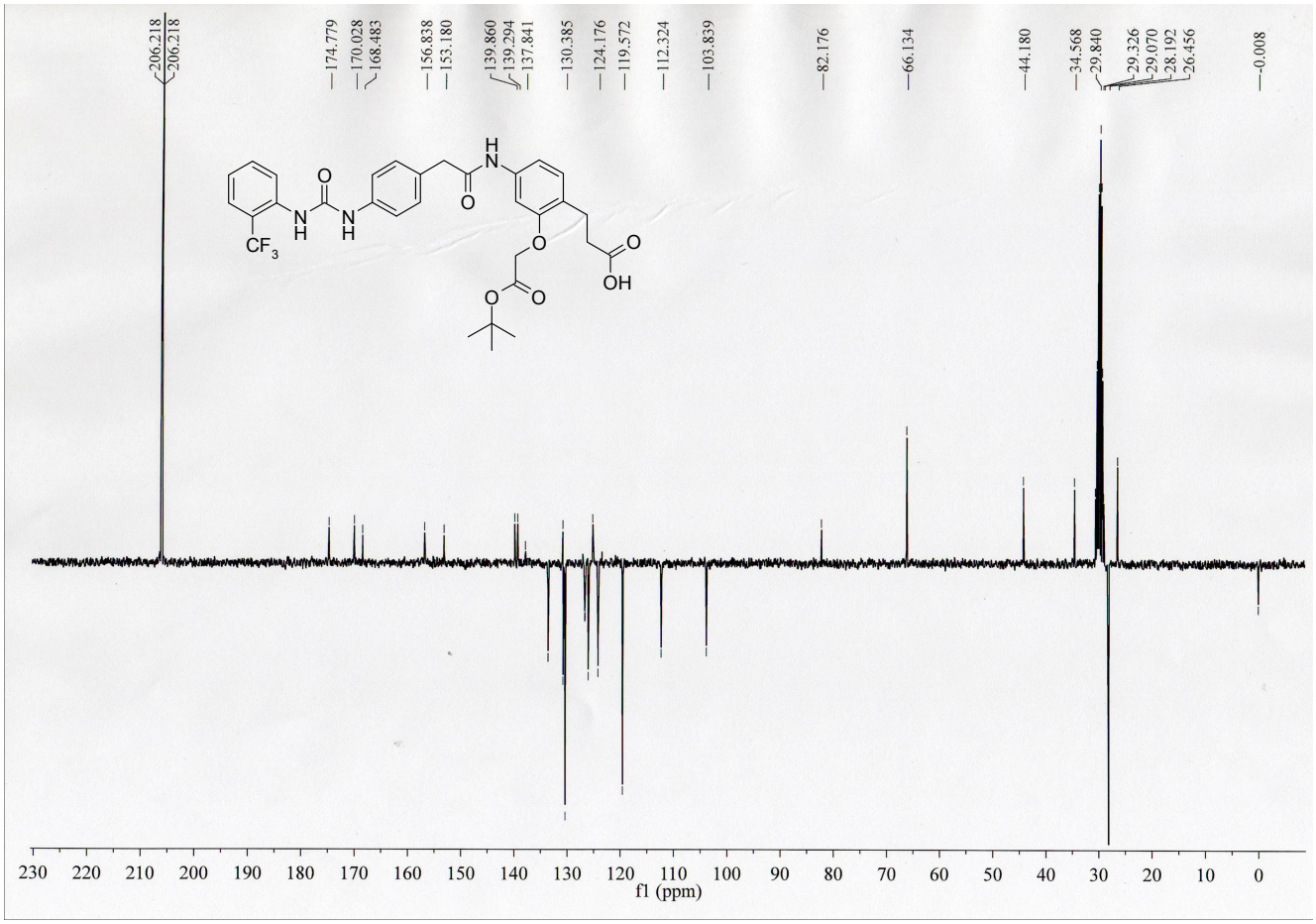


Fig.S20 APT NMR spectrum of compound **33**

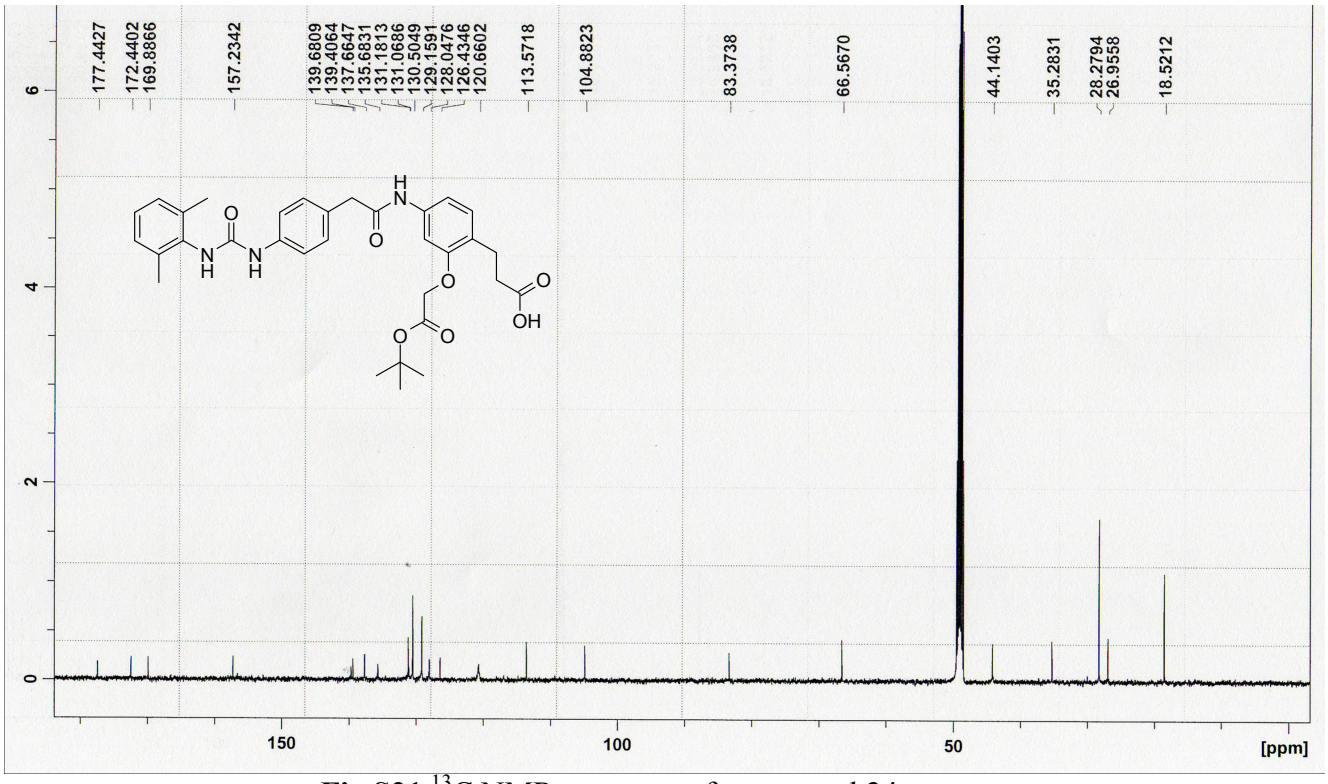


Fig.S21 ^{13}C NMR spectrum of compound **34**