Supporting Information

Pyrrolyl Pyrazoles as Non-Diketo Acid Inhibitors of the HIV-1 Ribonuclease H Function of Reverse Transcriptase.

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Chemistry Experimental section

General Instrumentation. Melting points were determined on a Bobby Stuart Scientific SMP1 melting point apparatus and are uncorrected. Compound purity was always >95% as determined by NMR. Analytical results of combustion analysis agreed to within ±0.40% of the theoretical values. IR spectra were recorded on a PerkinElmer Spectrum-One spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker AC 400 Ultrashield 10 spectrophotometer (400 MHz). Dimethyl sulfoxide-d_6 99.9% (CAS 2206-27-1), deuterochloroform 98.8% (CAS 865-49-6) and acetone-d_6 99.9% (CAS 666-52-4) of isotopic purity (Aldrich) were used. Column chromatographies were performed on silica gel (Merck; 70−230 mesh). All compounds were routinely checked on TLC by using aluminum-baked silica gel plates (Fluka DC-Alufolien Kieselgel 60 F_{254}). Developed plates were visualized by UV light. Solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of rotary evaporator (Büchi) operating at a reduced pressure (ca. 20 Torr). Organic solutions were dried over anhydrous sodium sulfate (Merck). All solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. Analytical results agreed to within ±0.40% of the theoretical values.

General Chemistry.

Scheme 1: The *N*-alkylpyrrole derivatives **13f-h** were obtained by reaction of 1-(4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one[1] or derivative **12** (previously synthesized via a Van Leusen reaction of (*E*)-4-(naphthalen-2-yl)but-3-en-2-one[2] with toluene-4-sulfonylmethylisocyanide (TosMIC**)** with the appropriate aryl-alkyl halide in alkaline medium. Subsequently, pyrroles **13f-h**, 1-(4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one,[1] 1-(1-methyl-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one,[3] 1-(1-(4-fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one,[1] 1-(1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)ethan-1-one[1] or 1-(1*H*-pyrrol-3-yl)ethan-1-one[1] underwent a Claisen-Schmidt condensation with diethyl oxalate using sodium ethoxide as the base, to give diketobutanoic ethyl esters **14b,d-h**. Similar conditions have

also been applied to obtain ethyl (*Z*)-4-(1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate and ethyl (*Z*)-4-(1-(4-fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate, as previously reported by us.[1] Follows, then, a Knorr pyrazole synthesis with hydrazine dihydrochloride in acidic medium, obtaining pyrazole derivatives **6a-h** that were in turn hydrolyzed with NaOH to give the corresponding acids **7a-h**.

Scheme 2: Ethyl (*Z*)-4-([1,1'-biphenyl]-2-yl)-2-hydroxy-4-oxobut-2-enoate[4] underwent ring closure as described above to give pyrazole derivative **8c** that furnished the corresponding acid **9c** after an alkaline hydrolysis.

Scheme 3: α,β-Unsatured ketones **15b,d,f,g,h** furnished the corresponding pyrroles **16b,d,f,g,i** by reacting with TosMIC, in a similar fashion to that described in Scheme 1. Noteworthy, derivatives **15b,d,f,g,h** were obtained by condensation with acetone in alkaline medium of the corresponding *O*-alkylaldehydes, commercially available (as for the synthesis of compounds **15d,f**) or properly synthesized (**15b**[5], **15g**[6], **15i**[7]). Similarly, pyrrole derivative **16a** was synthesized from (*E*)-4-(4-(benzyloxy)phenyl)but-3-en-2-one[8] by applying the same reaction conditions. Follows an alkylation reaction with the proper aryalkyl halide, commercially available, using K_2CO_3 as base, resulting *N*-alkylated pyrrolyl compounds **17a-i** that were subsequently converted into the corresponding diketo esters **18a-i** via a Claisen-Schmidt condensation in the same conditions described above. Finally, the intermediates **18a-i** thus obtained were reacted with hydrazine dihydrochloride under acid conditions to give the corresponding pyrazole carboxylic ester derivatives **10a-i** that were converted to acids **11a-i** by alkaline hydrolysis.

General Experimental Procedures.

General procedure A (GP-A) to obtain Pyrrolyl Derivatives (12, 16a,b,d,f,g,i). A solution of α,β-unsaturated ketone (5.42 mmol) and toluene-4-sulfonylmethyl isocyanide (5.96 mmol) dissolved in a mixture of anhydrous dimethyl sulfoxide/diethyl ether (30:15 mL) was added dropwise into a well-stirred suspension of sodium hydride (60% in paraffine oil; 11.93 mmol) in

diethyl ether anhydrous (30 mL) under argon atmosphere. After the addition, the mixture was stirred at room temperature for 1 h. The reaction was treated with water (100 mL) and extracted with ethyl acetate (3 x 150 mL). The organic layer was washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum to give the subtitled compounds. For each compound amount of α,β-unsaturated ketone; chromatography eluent; recrystallization solvent; R_f; yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

General procedure B (GP-B) to obtain *N*-Alkyl pyrrolyl Derivatives (13f-h, 17a-i). A mixture of the appropriate pyrrole (1.1 mmol), alkylating agent (3.3 mmol) and K_2CO_3 (1.5 mmol) in DMF (10 mL) was stirred at 80 °C for the proper time. Upon reaction completed, the mixture was cooled, treated with water (40 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by chromatography (SiO_2) to afford the pure product. For each compound amount of pyrrole; alkylating agent; chromatography eluent; time of reaction; recrystallization solvent; R_f; yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

General procedure C (GP-C) to obtain Diketo Esters (14b,d-h, 18a-i). Freshly prepared sodium ethoxide, obtained by the dissolution of Na (0.155 mol) in 170 mL of absolute ethanol, was added to a solution of the proper acetyl derivative (0.77 mol) and diethyl oxalate (0.85 mol) in anhydrous THF (70 mL) under argon atmosphere. The mixture was stirred at room temperature for 2 h and then was poured into *n*-hexane (200 mL); the resulting solid was filtered, washed with water (50 mL) and dried under IR lamp to afford the pure diketo esters. For each compound amount of acetyl pyrrole; recrystallization solvent; R_f; yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

General procedure D (GP-D) to obtain Pyrazole Carboxylic Ester Derivatives (6a-h, 8c, 10a-i). To a mixture of the starting compound (5 mmol), hydrazine dihydrochloride (25 mmol), Et_3N (25

mmol) in MeOH (100 ml) were added 5 drops of glacial acetic acid. The reaction was stirring at room temperature for 2 h. Upon reaction completed, the organic phase was reduced under vacuum and the crude was treated with water water (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the organic fractions were combined, washed with saturated sodium chloride solution (200 mL), dried over sodium sulfate, and evaporated under vacuum, affording pure pyrazole esters. For each compound amount of diketo ester derivative; recrystallization solvent; R_f; yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

General procedure E (GP-E) to obtain Pyrazole Carboxylic Acid Derivatives (7a-h, 9c, 11a-i). A solution of NaOH 20% (15 mmol) in distilled water was added to a suspension of the appropriate ester (3 mmol) in THF (36 mL) and the reaction was stirred vigorously at 90 °C for 12 h (at 100°C for 6 h for derivatives **6c,e-h** and **7c,e-h**). The organic phase was removed under vacuum and the resulting suspension was acidified with 1N HCl (pH 4-5). The solid that formed was filtered, then washed with water and dried under IR lamp (or extracted with ethyl acetate, dried over sodium sulfate, filtered and evaporated under reduced pressure for derivatives **7g**, **11a-c**) to afford pure acids. For each compound amount of ester; recrystallization solvent; R_f, yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

General procedure F (GP-F) to obtain α,β-unsatured Ketone Derivatives (15b,d,f,g,i). A mixture of the proper aldehyde (0.016 mol) in 400 mL of acetone and 1N NaOH (40 mL) was stirred at 80°C for 5 h. Afterwards, the mixture was neutralized with 1N HCl and ethyl acetate (250 mL) was added. The organic fractions were combined, washed with water (2 × 100 mL), with saturated sodium chloride solution (200 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain pure products. For each compound amount of aldehyde; chromatography eluent; recrystallization solvent; R_f; yield (%); melting point (°C); IR; ^{1}H NMR and elemental analysis are reported.

Specific Procedures and Characterization.

Ethyl 3-(1-(4-fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (6a). Compound **6a** was prepared from ethyl (*Z*)-4-(1-(4-fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate[9] by means of GP-D. Ethyl (*Z*)-4-(1-(4-fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate (0.50 g, 1.30 mmol); benzene/cyclohexane; R_f (chloroform/methanol 6:1): 0.74; 100% as a yellow solid; 205 °C; IR ν 2854 (NH), 1716 (C=O) cm^{-1}; ^1H NMR (acetone d_6) δ 1.27 (t, 3H, J = 8 Hz, CH_3CH_2), 4.26 (q, 2H, J = 4 Hz, CH_3CH_2), 5.20 (s, 2H, CH_2Bn), 6.47 (s, 1H, CH pyrazole), 7.02 (d, 1H, J = 2.3 Hz, C5-H pyrrole), 7.20 (d, 1H, J = 2.4 Hz, C2-H pyrrole), 7.11-7.15 (m, 3H, CH Ar), 7.25-7.29 (m, 4H, CH Ar), 7.40-7.44 (m, 2H, CH Ar), 12.42 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{23}H_{20}FN_3O_2$: C, 70.94; H, 5.18; F, 4.88; N, 10.79%. Found: C, 71.01; H, 5.20; F, 4.90; N, 10.81%.

Ethyl 3-(1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (6b). Compound **6b** was prepared from **14b** by means of GP-D. **14b** (2.00 g, 9.60 mmol); toluene; R_f (chloroform/ethyl acetate 5:2): 0.48; 65% as a light yellow solid; 141 °C; IR ν 3304 (NH pyrrole), 2941 (NH pyrazole), 1714 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.30 (t, 3H, J = 8 Hz, CH_3CH_2), 4.25 (q, 2H, J = 4 Hz, CH_3CH_2), 6.22 (br d, 1H, C4-H pyrrole), 6.85-6.89 (m, 2H, C2-H pyrrole and C5-H pyrrole), 7.09 (s, 1H, CH pyrazole), 9.54 (bs, 1H, NH pyrrole), 13.79 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48%. Found: C, 58.58; H, 5.42; N, 20.51%.

Ethyl 3-(1-(4-fluorobenzyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (6c). Compound **6c** was prepared from ethyl (*Z*)-4-(1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate[9] by means of GP-D. Ethyl (*Z*)-4-(1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate (2.00 g, 6.70 mmol); toluene; R_f (*n*-hexane/ethyl acetate 7:3): 0.41; 60% as a light yellow solid; 142 °C; IR ν 2934 (NH), 1711 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.20 (t, 3H, J = 8 Hz, CH_3CH_2), 4.17 (q, 2H, J = 4 Hz, CH_3CH_2), 5.20 (s, 2H, CH_2Bn), 6.37 (d, 1H, J_o = 8 Hz, C4-H pyrrole), 6.66 (s, 1H, CH pyrazole), 6.83 (d, 1H, J_o = 8 Hz, C5-H pyrrole), 7.10 (d, 2H, J_o = 8 Hz, CH Ar), 7.16 (d, 1H, J_o = 8 Hz, C2-H pyrrole), 7.20 (d, 2H, J_o = 8 Hz, CH Ar), 13.32 (bs, 1H, NH pyrazole). Anal. Calcd

for $C_{17}H_{16}FN_3O_2$: C, 65.17; H, 5.15; F, 6.06; N, 13.41%. Found: C, 65.21; H, 5.17; F, 6.08; N, 13.46%.

Ethyl 3-(4-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (6d). Compound **6d** was prepared from **14d** by means of GP-D. **14d** (0.05 g, 0.18 mmol); toluene; R_f (*n*-hexane/ethyl acetate 1:1): 0.39; 60% as a yellow solid; 135 °C; IR ν 3319 (NH pyrrole), 2944 (NH pyrazole), 1715 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.28 (t, 3H, J = 8 Hz, CH_3CH_2), 4.42 (q, 2H, J = 4 Hz, CH_3CH_2), 7.00-7.16 (m, 3H, C2-H pyrrole, C5-H pyrrole and CH pyrazole), 7.41 (t, 1H, J_o = 8 Hz, CH Ar), 7.46 (t, 2H, J_o = 8 Hz, CH Ar), 7.51 (d, 2H, J_o = 8 Hz, CH Ar), 9.61 (bs, 1H, NH pyrrole), 13.76 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94%. Found: C, 68.40; H, 5.39; N, 14.96%.

Ethyl 3-(1-methyl-4-phenyl-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (6e). Compound **6e** was prepared from **14e** by means of GP-D. **14e** (1.00 g, 3.30 mmol); toluene; R_f (ethyl acetate/methanol 98:2): 0.73; 100% as a brown solid; 62 °C; IR *ν* 2926 (NH), 1721 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.17 (t, 3H, J = 8 Hz, CH_3CH_2), 3.59 (s, 3H, CH_3), 4.15 (q, 2H, J = 4 Hz, CH_2CH_3), 6.23 (m, 1H, C5-H pyrrole), 6.88 (s, 1H, CH pyrazole), 7.01 (m, 1H, C2-H pyrrole), 7.10-7.15 (m, 3H, CH Ar), 7.22 (t, 2H, J_o = 8 Hz, CH Ar), 13.26 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23%. Found: C, 69.19; H, 5.82; N, 14.25%.

Ethyl 3-(1-(naphthalen-1-ylmethyl)-4-phenyl-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (6f). Compound **6f** was prepared from **14f** by means of GP-D. **14f** (2.00 g, 4.70 mmol); toluene; R_f (*n*-hexane/ethyl acetate 3:2): 0.51; 65% as a light yellow solid; 132 °C; IR *ν* 2983 (NH), 1704 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.16 (t, 3H, J = 8 Hz, CH_3CH_2), 4.13 (q, 2H, J = 4 Hz, CH_2CH_3), 5.59 (s, 2H, CH_2Bn), 6.22 (m, 1H, C5-H pyrrole), 7.10-7.21 (m, 6H, CH naphthalene and CH pyrazole), 7.30 (d, 2H, J_o = 8 Hz, CH naphthalene), 7.29-7.56 (m, 3H, CH Ar and C2-H pyrrole), 7.87 (d, 2H, J_o = 8 Hz, CH Ar), 8.15 (d, 1H, J_o = 8.4 Hz, CH Ar), 13.23 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97%. Found: C, 77.18; H, 5.52; N, 10.00%.

Ethyl 3-(4-phenyl-1-(4-phenylbutyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (6g). Compound **6g** was prepared from **14g** by means of GP-D. **14g** (1.50 g, 3.60 mmol); toluene; R_f (*n*-hexane/ethyl acetate 3:2): 0.48; 86% as a white solid; 142 °C; IR *ν* 2934 (NH), 1698 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.17 (t, 3H, J = 8 Hz, CH_3CH_2), 1.49-1.54 (m, 2H, γ CH_2 alkyl), 1.67-1.71 (m, 2H, β CH_2 alkyl), 2.54 (t, 2H, J = 8 Hz, δ CH_2 alkyl), 3.86 (t, 2H, J = 8 Hz, α CH_2 alkyl), 4.14 (q, 2H, J = 4 Hz, CH_2CH_3), 6.24 (s, 1H, CH pyrazole), 6.93 (m, 1H, C5-H pyrrole), 7.06-7.23 (m, 11H, CH Ar), 13.21 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16%. Found: C, 75.60; H, 6.61; N, 10.19%.

Ethyl 3-(1-(4-fluorobenzyl)-4-(naphthalen-2-yl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (6h). Compound **6h** was prepared from **14h** by means of GP-D. **14h** (1.30 g, 2.90 mmol); toluene; R_f (*n*-hexane/ethyl acetate 3:2): 0.32; 45% as a yellow solid; 119 °C; IR *ν* 2990 (NH), 1717 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.26 (t, 3H, J = 8 Hz, CH_3CH_2), 4.12 (q, 2H, J = 4 Hz, CH_2CH_3), 5.09 (s, 2H, CH_2Bn), 6.25 (m, 1H, C5-H pyrrole), 7.10-7.16 (m, 4H, CH naphthalene and CH pyrazole), 7.30-7.38 (m, 6H, CH naphthalene and CH Ar), 7.67-7.79 (m, 3H, CH Ar and C2-H pyrrole), 13.28 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{27}H_{22}FN_3O_2$: C, 73.79; H, 5.05; F, 4.32; N, 9.56%. Found: C, 73.86; H, 5.09; F, 4.34; N, 9.58%.

3-(1-(4-Fluorobenzyl)-4-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylic acid (7a).[10] Compound **7a** was prepared **6a** by means of GP-E. **6a** (0.68 g, 1.70 mmol); benzene/cyclohexane; R_f (ethyl acetate): 0.09; 65% as a brown solid; 118 °C; IR ν 3224 (OH), 2839 (NH), 1714 (C=O) cm^{-1}; ^1H NMR (acetone d_6) δ 5.21 (s, 2H, CH_2Bn), 6.48 (s, 1H, CH pyrazole), 7.03 (d, 1H, J = 1.7 Hz, C5-H pyrrole), 7.13 (d, 2H, J_o = 8 Hz, CH Ar), 7.21 (d, 1H, J = 1.7 Hz, C2-H pyrrole), 7.27-7.29 (m, 5H, CH Ar), 7.41 (t, 2H, J_o = 8 Hz, CH Ar). Anal. Calcd for $C_{21}H_{16}FN_3O_2$: C, 69.80; H, 4.46; F, 5.26; N, 11.63%. Found: C, 69.90; H, 4.47; F, 5.28; N, 11.66%.

3-(1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylic acid (7b). Compound **7b** was prepared from **6b** by means of GP-E. **6b** (0.50 g, 2.60 mmol); isopropanol; R_f (chloroform/ethyl acetate 5:2): 0.08; 87% as a brown solid; 270 °C dec.; IR ν 3323 (OH), 3308 (NH pyrrole), 2934 (NH pyrazole), 1707

(C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 6.20 (br d, 1H, C4-H pyrrole), 6.48 (s, 1H, CH pyrazole), 6.86-6.88 (m, 2H, C2-H pyrrole and C5-H pyrrole), 9.57 (bs, 1H, NH pyrrole), 12.23 (bs, 1H, OH), 13.83 (bs, 1H, NH pyrazole). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72%. Found: C, 54.27; H, 3.99; N, 23.74%.

3-(1-(4-Fluorobenzyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (7c). Compound **7c** was prepared from **6c** by means of GP-E. **6c** (0.50 g, 1.70 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 7:3): 0.08; 85% as a light yellow solid; 151 °C dec.; IR *ν* 3109 (OH), 2868 (NH), 1686 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 5.02 (s, 2H, CH_2Bn), 6.35 (d, 1H, J_o=8 Hz, C4-H pyrrole), 6.64 (s, 1H, CH pyrazole), 6.81 (d, 1H, J_o=8 Hz, C5-H pyrrole), 7.07-7.19 (m, 5H, CH Ar and C2-H pyrrole). Anal. Calcd for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; F, 6.66; N, 14.73%. Found: C, 63.22; H, 4.25; F, 6.69; N, 14.75%.

3-(4-Phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylic acid (7d). Compound **7d** was prepared from **6d** by means of GP-E. **6d** (0.05 g, 0.17 mmol); isopropanol; R_f (ethyl acetate/methanol 98:2): 0.07; 90% as a brown solid; 210 °C dec.; IR ν 3323 (NH pyrrole), 3244 (OH), 2912 (NH pyrazole), 1707 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 6.20 (s, 1H, CH pyrazole), 6.89 (br d, 1H, C5-H pyrrole), 7.06 (br d, 1H, C2-H pyrrole), 7.14 (t, 1H, J_o = 8 Hz, CH Ar), 7.17-7.24 (m, 4H, CH Ar), 11.16 (bs, 1H, NH pyrrole), 12.70 (bs, 1H, OH), 12.93 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59%. Found: C, 66.48; H, 4.40; N, 16.62%.

3-(1-Methyl-4-phenyl-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (7e). Compound **7e** was prepared from **6e** by means of GP-E. **6e** (0.80 g, 2.70 mmol); isopropanol; R_f (ethyl acetate/methanol 98:2): 0.11; 70% as a yellow solid; 160 °C dec.; IR *ν* 3277 (OH), 2919 (NH), 1681 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 3.59 (s, 3H, CH_3), 6.23 (m, 1H, C5-H pyrrole), 6.86 (s, 1H, CH pyrazole), 6.99 (m, 1H, C2-H pyrrole), 7.11-7.16 (m, 3H, CH Ar), 7.23 (t, 2H, J_o=8 Hz, CH Ar), 12.88 (bs, 2H, NH pyrazole and OH). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%. Found: C, 67.43; H, 4.91; N, 15.74%.

3-(1-(Naphthalen-1-ylmethyl)-4-phenyl-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (7f). Compound **7f** was prepared from **6f** by means of GP-E. **6f** (0.50 g, 1.20 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.12; 98% as a brown solid; 146 °C dec.; IR *v* 3278 (OH), 2916 (NH), 1699 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.59 (s, 2H, CH_2Bn), 6.19 (m, 1H, C5-H pyrrole), 7.06 (s, 1H, CH pyrazole), 7.11-7.23 (m, 5H, CH naphthalene), 7.30 (d, 2H, J_o=8 Hz, CH naphthalene), 7.42-7.54 (m, 3H, CH Ar and C2-H pyrrole), 7.88 (d, 2H, J_o=8 Hz, CH Ar), 8.15 (d, 1H, J_o=8.4 Hz, CH Ar), 13.23 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68%. Found: C, 76.39; H, 4.89; N, 10.70%.

3-(4-Phenyl-1-(4-phenylbutyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (7g). Compound **7g** was prepared from **6g** by means of GP-E. **6g** (0.40 g, 1.30 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.12; 98% as a brown solid; 151 °C; IR *v* 3256 (OH), 2900 (NH), 1698 (C=O acid) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.49-1.53 (m, 2H, γ CH_2 alkyl), 1.68-1.71 (m, 2H, β CH_2 alkyl), 2.54 (t, 2H, J = 8, δ CH_2 alkyl), 3.87 (t, 2H, J = 8, α CH_2 alkyl), 6.20 (s, 1H, CH pyrazole), 6.92 (m, 1H, C5-H pyrrole), 7.04-7.23 (m, 11H, CH Ar), 13.81 (bs, 2H, NH pyrazole and OH). Anal. Calcd for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90%. Found: C, 74.81; H, 6.02; N, 10.91%.

3-(1-(4-Fluorobenzyl)-4-(naphthalen-2-yl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (7h). Compound **7h** was prepared from **6h** by means of GP-E. **6h** (0.30 g, 1.10 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.11; 92% as a yellow solid; 162 °C; IR *v* 3250 (OH), 2923 (NH), 1692 (C=O acid) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.10 (s, 2H, CH_2Bn), 6.24 (m, 1H, C5-H pyrrole), 7.12-7.19 (m, 4H, CH naphthalene and CH pyrazole), 7.31-7.38 (m, 6H, CH naphthalene and CH Ar), 7.68-7.79 (m, 3H, CH Ar and C2-H pyrrole), 12.91 (bs, 2H, NH pyrazole and OH). Anal. Calcd for $C_{25}H_{18}FN_3O_2$: C, 72.98; H, 4.41; F, 4.62; N, 10.21%. Found: C, 73.02; H, 4.43; F, 4.63; N, 10.23%.

Ethyl 3-methyl-1H-pyrazole-5-carboxylate (8a). Synthesis, analytical and spectroscopic data are reported in literature.[11]

Ethyl 3-phenyl-1H-pyrazole-5-carboxylate (8b). Synthesis, analytical and spectroscopic data are reported in literature.[12]

Ethyl 3-([1,1'-biphenyl]-2-yl)-1*H*-pyrazole-5-carboxylate (8c). Compound **8c** was prepared from ethyl (*Z*)-4-([1,1'-biphenyl]-2-yl)-2-hydroxy-4-oxobut-2-enoate[13] by means of GP-D. Ethyl (*Z*)-4-([1,1'-biphenyl]-2-yl)-2-hydroxy-4-oxobut-2-enoate (2.50 g, 8.40 mmol); cyclohexane; R_f (chloroform): 0.31; 100% as a yellow solid; 40 °C; IR ν 2940 (NH pyrazole), 1723 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.09 (t, 3H, J = 8 Hz, CH_3CH_2), 4.13 (q, 2H, J = 4 Hz, CH_3CH_2), 6.04 (s, 1H, CH pyrazole), 7.09 (d, 2H, J_o = 8 Hz, CH Ar), 7.25-7.39 (m, 6H, CH Ar), 7.55 (d, 1H, J_o = 8 Hz, CH Ar), 13.43 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%. Found: C, 74.01; H, 5.54; N, 9.60%.

3-Methyl-1H-pyrazole-5-carboxylic acid (9a). Synthesis, analytical and spectroscopic data are reported in literature.[11]

3-Phenyl-1H-pyrazole-5-carboxylic acid (9b). Synthesis, analytical and spectroscopic data are reported in literature.[12]

3-([1,1'-Biphenyl]-2-yl)-1*H*-pyrazole-5-carboxylic acid (9c). Compound **9c** was prepared from **8c** by means of GP-E. **8c** (2.00 g, 6.90 mmol); toluene; R_f (ethyl acetate/methanol 98:2): 0.16; 78% as a yellow solid; 217 °C; IR ν 3290 (OH), 2901 (NH pyrazole), 1687 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.93 (s, 1H, CH pyrazole), 7.10 (d, 2H, J_o = 8 Hz, CH Ar), 7.24-7.38 (m, 6H, CH Ar), 7.59 (d, 1H, J_o = 8 Hz, CH Ar), 13.21 (bs, 2H, OH and NH pyrazole). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60%. Found: C, 72.76; H, 4.60; N, 10.63%.

Ethyl 3-(1-(4-fluorobenzyl)-4-(4-(benzyloxy)phenyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10a). Compound **10a** was prepared from **18a** by means of GP-D. **18a** (2.50 g, 4.90 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 4:1): 0.25; 50% as a yellow solid; 65-68 °C; IR *ν* 2930 (NH), 1704 (C=O), 1223 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.15 (t, 3H, CH_3CH_2, J=6.8), 4.14 (q, 2H, CH_2CH_3, J=6.8Hz), 5.05 (s, 2H, CH_2), 5.16 (s, 2H, CH_2), 6.19 (s, 1H, CH pyrrole), 6.22 (s, 1H, CH pyrrole), 6.9 (d, 1H, CH Ar), 7.13-7.2 (m, 4H, Ar), 7.37 (d, 1H, CH Ar), 8.03 (s,

1H, CH pyrazole), 13.16 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{30}H_{26}FN_3O_3$: C, 72.71; H, 5.29; F, 3.83; N, 8.48%. Found: C, 72.80; H, 5.30; F, 3.84; N, 8.50%.

Ethyl 3-(4-(4-(3-phenylbutoxy)phenyl)-1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10b). Compound **10b** was prepared from **18b** by means of GP-D. **18b** (0.40 g, 0.74 mmol); R_f (*n*-hexane/ethyl acetate 1:1): 0.57; 23% as a brown oil; IR *v* 2938 (NH), 1706 (C=O), 1218 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.16 (t, 3H, CH_3CH_2, J=6,8Hz); 1.60-1.65 (m, 4H, β and γ CH_2 alkyl); 2.55 (t, 2H, δ CH_2 alkyl); 3.88 (t, 2H, α CH_2 alkyl); 4.15 (q, 2H, CH_2CH_3, J=6,8Hz); 5.04 (s, 2H, CH_2); 6.20 (s, 1H, CH pyrrole); 6.77 (d, 1H, Ar); 6.95 (s, 1H, CH); 7.02-7.10 (m, 4H, Ar); 7.19 (t, 1H, Ar, J=7,2Hz); 7.31 (t, 1H, Ar, J=6,4Hz); 13.20 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{33}H_{32}FN_3O_3$: C, 73.72; H, 6.00; F, 3.53; N, 7.82%. Found: C, 73.79; H, 6.02; F, 3.54; N, 7.84%.

Ethyl 3-(1-(naphthalen-1-ylmethyl)-4-(3-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (10c). Compound **10c** was prepared from **18c** by means of GP-D. **18c** (0.28 g, 0.49 mmol); R_f (*n*-hexane/ethyl acetate 7:3): 0.23; 41% as a yellow oil; IR *v* 2925 (NH), 1719 (C=O), 1240 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.15 (t, 3H, CH_3CH_2, J=6,8Hz), 1.63-1.66 (m, 4H, β and γ CH_2 alkyl); 2.55 (t, 2H, δ CH_2 alkyl); 3.88 (t, 2H, α CH_2 alkyl); 4.14 (q, 2H, CH_2CH_3, J=6,8Hz); 5.57 (s, 2H, CH_2); 5.67 (s, 1H, CH pyrrole); 6.20 (s, 1H, CH pyrrole); 6.77 (d, 1H, Ar); 7.02 (t, 2H, Ar, J=8Hz); 7.10 (t, 1H, CH, J=3,2Hz); 7.19 (t, 1H, CH Ar); 7.43-7.47 (m, 4H, Ar); 7.80 (d, 1H, CH Ar); 8.13 (s, 1H, CH); 13.18 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{37}H_{35}N_3O_3$: C, 78.01; H, 6.19; N, 7.38%. Found: C, 78.11; H, 6.20; N, 7.40%.

Ethyl 3-(1-(4-fluorobenzyl)-4-(4-(naphthalen-1-ylmethoxy)phenyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10d). Compound **10d** was prepared from **18d** by means of GP-D. **18d** (1.10 g, 2.00 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 7:3): 0.10; 20% as a yellow solid; 61-63 °C; IR *v* 3253 (NH), 1711 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.15 (t, 3H, CH_3CH_2, J=6,8), 4.14 (q, 2H, CH_2CH_3, J=6,8Hz), 5.05 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 6.20 (s, 1H, CH pyrrole), 6.24 (s, 1H, CH pyrrole), 6.95 (d, 1H, CH Ar), 7.3 (t, 1H, CH Ar); 7.41-7.48 (m, 4H,

Ar); 7.51 (d, 1H, CH Ar); 7.80 (d, 1H, CH Ar); 8.03 (s, 1H, CH pyrazole); 13.30 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{34}H_{28}FN_3O_3$: C, 74.85; H, 5.17; F, 3.48; N, 7.70%. Found: C, 74.90; H, 5.19; F, 3.49; N, 7.72%.

Ethyl 3-(4-(4-(naphthalen-8-ylmethoxy)phenyl)-1-(naphthalene-1-ylmethyl)1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylate (10e). Compound **10e** was prepared from **18e** by means of GP-D. **18e** (2.00 g, 4.00 mmol); ethanol; R_f (*n*-hexane/ethyl acetate 7:3): 0.11; 65% as a yellow solid; 95-98 °C; IR *v* 2934 (NH), 1716 (C=O), 1236 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.15 (t, 3H, CH_3CH_2, J=6.8), 4.14 (q, 2H, CH_2CH_3, J=6.8Hz), 5.44 (s, 2H, CH_2), 5.78 (s, 2H, CH_2), 6.20 (s, 1H, CH pyrrole), 6.80 (s, 1H, CH pyrrole), 7.02 (m, 4H, Ar), 7.30 (d, 1H, CH Ar), 7.45 (m, 4H, CH Ar), 7.51 (d, 1H, CH Ar), 7.80 (d, 1H, CH Ar), 8.13 (s, 1H, CH pyrazole), 12.79 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{38}H_{31}N_3O_3$: C, 79.01; H, 5.41; N, 7.27%. Found: C, 79.11; H, 5.43; N, 7.29%.

4-(2-(4-(4-(5-(Ethoxycarbonyl)-1*H*-pyrazol-3-yl)-1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)phenoxy)acetamido)benzoic acid (10f). Compound **10f** was prepared from **18f** by means of GP-D. **18f** (0.20 g, 0.33 mmol); R_f (ethyl acetate/methanol 3:7): 0.71; 20% as a white oil; IR *v* 2983 (NH), 1728 (C=O ester), 1701 (C=O amide), 1690 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.22 (t, 3H, CH_3CH_2, J=6.8), 4.22 (q, 2H, CH_2CH_3, J=6.8Hz), 4.66 (s, 2H, CH_2), 5.04 (s, 2H, CH_2Bz), 6.19 (s, 1H, CH pyrazole), 6.86 (d, 2H, J=8.8, Ar), 6.93 (s, 1H, pyrrole), 7.11 (d, 2H, J=8.8, Ar), 7.29 (d, 2H, J=8,8, Ar), 7.33 (s, 1H, pyrrole), 7.71 (d, 2H, J=8.8, Ar), 7.84 (d, 2H, J=8.8, Ar), 10.35 (s, 1H, NH amide), 13.20 (bd, 2H, OH and NH pyrazole). Anal. Calcd for $C_{32}H_{27}FN_4O_6$: C, 65.97; H, 4.67; F, 3.26; N, 9.62%. Found: C, 66.00; H, 4.69; F, 3.27; N, 9.64%.

Ethyl 3-(1-(4-fluorobenzyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy)phenyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10g). Compound **10g** was prepared from **18g** by means of GP-D. **18g** (0.50 g, 0.92 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 7:3): 0.79; 43% as a slightly yellow solid; 160-161 °C; IR *v* 3110 (NH), 1723 (C=O ester), 1711 (C=O amide), 1683 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.15 (t, 3H, CH_3CH_2, J=8), 4.13 (q, 2H, CH_2CH_3, J=6.8Hz), 4.60 (s, 1H, CH_2), 5.09 (s, 2H, CH_2Bz), 6.88 (s, 1H, pyrazole), 6.94 (d, 2H, J=16, Ar), 6.99 (d, 2H,

J=8.4, Ar), 7.12 (t, 2H, J=8.8, Ar), 7.22 (d, 2H, J=8, Ar), 7.25 (t, 2H, J=8.8, Ar), 7.32 (d, 2H, J=8, Ar), 7.33 (s, 1H, pyrrole), 7.56 (d, 2H, J=8.8, Ar), 10.02 (s, 1H, NH amide), 13.22 (s, 1H, NH) pyrazole). Anal. Calcd for $C_{31}H_{27}FN_4O_4$: C, 69.13; H, 5.05; F, 3.53; N, 10.40%. Found: C, 69.21; H, 5.07; F, 3.54; N, 10.42%.

Ethyl 3-(1-(naphthalen-1-yl-methyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy)phenyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10h). Compound **10h** was prepared from **18h** by means of GP-D. **18h** (0.20 g, 0.35 mmol); diethyl ether; R_f (methanol): 0.88; 22% as a yellow solid; 185-187 °C; IR *v* 3210 (NH), 1733 (C=O ester), 1714 (C=O amide), 1684 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.10 (t, 3H, CH_3CH_2, J=8), 4.06 (q, 2H, CH_2CH_3, J=6.8Hz), 4.60 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 5.62 (s, 2H, CH_2Bz), 6.75 (s, 1H, CH pyrazole), 6.86 (d, 2H, J=8.8, Ar), 6.95 (s, 1H, pyrrole), 6.99 (t, 1H, Ar), 7.22 (d, 4H, Ar), 7.42-7.56 (m, 4H, naphtalene), 7.85 (d, 2H, J=8, Ar), 7.89 (d, 2H, J=8, Ar), 8.05 (s, 1H, pyrrole), 8.14 (d, 1H, J=8, Ar), 10.01 (s, 1H, NH amide), 13.21 (s, 1H, NH). Anal. Calcd for $C_{35}H_{30}N_4O_4$: C, 73.67; H, 5.30; N, 9.82%. Found: C, 73.71; H, 5.31; N, 9.84%.

Ethyl 3-(1-(4-fluorobenzyl)-4-(4-((5-phenylpentyl)oxy)phenyl)-1*H*-pyrrol-3-yl)-1*H*-pyrazole-5-carboxylate (10i). Compound **10i** was prepared from **18i** by means of GP-D. **18i** (0.80 g, 1.40 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.69; 41% as a brown solid; 95 °C; IR *v* 2856 (NH), 1718 (C=O), 1228 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.22 (t, 3H, CH_3CH_2, J=6.8Hz), 1.28-1.31 (m, 2H, γ CH_2 alkyl), 1.53-1.66 (m, 4H, β,δ CH_2 alkyl), 2.45 (t, 2H, J = 8, ε CH_2 alkyl), 3.37 (t, 2H, J = 8, α CH_2 alkyl), 3.84 (q, 2H, CH_2CH_3, J=6.8Hz), 5.20 (s, 2H, CH_2), 6.80 (s, 1H, CH pyrrole), 6.76 (s, 1H, CH pyrrole), 6.91 (d, 1H, CH Ar), 7.13 (m, 4H, Ar), 7.15 (t, 1H, CH Ar), 7.37 (d, 1H, CH Ar), 8.19 (s, 1H, CH pyrazole), 13.09 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{34}H_{34}FN_3O_3$: C, 74.03; H, 6.21; F, 3.44; N, 7.62%. Found: C, 74.12; H, 6.23; F, 3.45; N, 7.64%.

3-(1-(4-Fluorobenzyl)-4-(4-(benzyloxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11a). Compound **11a** was prepared from **10a** by means of GP-E. **10a** (0.40 g, 0.91 mmol); propanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.09; 100% as a yellow solid; 57-60 °C; IR *v* 3034 (NH

and OH), 1698 (C=O), 1221 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.00 (s, 2H, CH_2), 5.05 (s, 2H, CH_2), 6.20 (s, 1H, CH pyrrole), 6.22 (s, 1H, pyrrole), 6.87 (d, 2H, J=8 Hz, Ar), 6.93 (s, 1H, CH pyrazole), 7.11 (m, 4H, Ar), 7.24 (d, 1H, J=8, Ar), 7.33 (d, 1H, CH Ar), 7.38 (d, 1H, CH Ar), 12.00 (bs, 1H, OH), 12.90 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{28}H_{22}FN_3O_3$: C, 71.94; H, 4.74; F, 4.06; N, 8.99%. Found: C, 72.05; H, 4.76; F, 4.07; N, 9.01%.

3-(1-(4-Fluorobenzyl)-4-(4-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11b). Compound **11b** was prepared from **10b** by means of GP-E. **10b** (0.30 g, 0.40 mmol); ethanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.11; 62% as a yellow solid; 40-43 °C; IR *v* 3109 (OH), 2926 (NH), 1697 (C=O), 1221 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.60-1.62 (m, 4H, β and γ CH_2 alkyl); 2.55 (t, 2H, δ CH_2 alkyl); 3.88 (t, 2H, α CH_2 alkyl); 5.04 (s, 2H, CH_2), 6.20 (s, 1H, CH pyrrole), 6.77 (d, 1H, J=8 Hz, Ar), 6.95 (s, 1H, pyrrole), 6.93 (s, 1H, CH pyrazole), 7.06 (m, 4H, Ar), 7.19 (t, 1H, J=7,2, Ar), 7.31 (t, 1H, J=6,4, CH Ar), 12.94 (bs, 1H, OH), 13.20 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{31}H_{28}FN_3O_3$: C, 73.07; H, 5.54; F, 3.73; N, 8.25%. Found: C, 73.12; H, 5.56; F, 3.74; N, 8.27%.

3-(1-(Naphthalen-1-ylmethyl)-4-(3-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11c). Compound **11c** was prepared from **10c** by means of GP-E. **10c** (0.12 g, 0.18 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 3:2): 0.16; 100% as a brown solid; 100 °C, carbonises; IR *v* 3012 (OH), 2925 (NH), 1679 (C=O), 1240 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.43-1.63 (m, 4H, β and γ CH_2 alkyl); 2.55 (t, 2H, δ CH_2 alkyl); 3.88 (t, 2H, α CH_2 alkyl); 5.57 (s, 2H, CH_2); 5.67 (s, 1H, CH pyrrole); 6.20 (s, 1H, CH pyrrole); 6.77 (d, 1H, Ar); 7.02 (t, 2H, Ar, J=8Hz); 7.10 (t, 1H, CH, J=3.2Hz); 7.19 (t, 1H, CH Ar); 7.43 (m, 4H, Ar); 7.80 (d, 1H, CH Ar); 8.13 (s, 1H, CH); 12.54 (bs, 1H, OH), 13.18 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{35}H_{31}N_3O_3$: C, 77.61; H, 5.77; N, 7.76%. Found: C, 77.69; H, 5.78; N, 7.78%.

3-(1-(4-Fluorobenzyl)-4-(4-(naphthalen-1-ylmethoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11d). Compound **11d** was prepared from **10d** by means of GP-E. **10d** (0.30 g, 0.40 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 3:2): 0.18; 100% as a yellow oil; IR *v* 2956

(NH and OH), 1684 (C=O), 1222 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.04 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 6.22 (s, 1H, CH pyrrole), 6.24 (s, 1H, pyrrole), 6.94 (d, 1H, J=8 Hz, Ar), 7.11 (s, 1H, CH Ar), 7.31 (d, 1H, CH Ar), 7.44 (m, 4H, Ar), 7.51 (d, 1H, CH Ar), 7.80 (d, 1H, CH Ar), 8.09 (s, 1H, CH pyrazole), 12.03 (bs, 1H, OH), 12.91 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{32}H_{24}FN_3O_3$: C, 74.26; H, 4.67; F, 3.67; N, 8.12%. Found: C, 74.30; H, 4.68; F, 3.68; N, 8.14%.

3-(4-(4-(Naphthalen-8-ylmethoxy)phenyl)-1-(naphthalene-1ylmethyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11e). Compound **11e** was prepared from **10e** by means of GP-E. **10e** (0.65 g, 1.00 mmol); ethanol; R_f (*n*-hexane/ethyl acetate 3:2): 0.10; 100% as a yellow solid; 105-107 °C; IR *v* 3004 (OH), 2934 (NH), 1712 (C=O), 1234 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 5.44 (s, 2H, CH_2), 5.53 (s, 2H, CH_2), 6.02 (s, 1H, CH pyrrole), 6.91 (m, 4H, Ar), 7.01 (s, 1H, CH pyrrole), 7.31 (d, 1H, J=7.2, Ar), 7.44 (m, 4H, Ar), 7.51 (d, 1H, CH Ar), 7.80 (d, 1H, CH Ar), 8.13 (s, 1H,CH pyrazole), 11.00 (bs, 1H, OH), 12.80 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{36}H_{27}N_3O_3$: C, 78.67; H, 4.95; N, 7.65%. Found: C, 78.75; H, 4.97; N, 7.66%.

3-(4-(4-(2-((4-Carboxyphenyl)amino)-2-oxoethoxy)phenyl)-1-(4-fluorobenzyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11f). Compound **11f** was prepared from **10f** by means of GP-E. **10f** (0.03 g, 0.10 mmol); diethyl ether; R_f (ethyl acetate/methanol 3:7): 0.12; 100% as a brown solid; 130-131 °C; IR *v* 3186 (OH), 2983 (NH), 1710 (C=O amide), 1704 (C=O acid), 1690 (C=O acid), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 4.56 (s, 2H, CH_2), 5.03 (s, 2H, CH_2Bz), 6.19 (s, 1H, CH pyrazole), 6.76 (d, 2H, J=8.8 Hz, Ar), 6.94 (s, 1H, pyrrole), 7.09 (s, 1H, pyrrole), 7.13 (d, 2H, J=8,8 Hz, Ar), 7.29 (d, 2H, J=8.8 Hz, Ar), 7.68 (d, 2H, J=8.8, Ar), 7.82 (d, 2H, J=8.8, Ar), 10.05 (s, 1H, NH amide), 12.90 (bs, 3H, OH and NH pyrazole). Anal. Calcd for $C_{30}H_{23}FN_4O_6$: C, 64.98; H, 4.18; F, 3.43; N, 10.10%. Found: C, 65.03; H, 4.19; F, 3.44; N, 10.11%.

3-(1-(4-Fluorobenzyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11g). Compound **11g** was prepared from **10g** by means of GP-E. **10g** (0.12 g, 0.22 mmol); diethyl ether; R_f (methanol): 0.77; 100% as a brown oil; IR *v* 3010 (OH), 2987 (NH), 1701 (C=O amide), 1690 (C=O acid), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 4.60 (s,

1H, CH_2), 5.09 (s, 2H, CH_2Bz), 6.88 (s, 1H, pyrazole), 6.94 (d, 2H, J=16, Ar), 6.99 (d, 2H, J=8,4, Ar), 7.12 (t, 2H, J=8.8, Ar), 7.22 (d, 2H, J=8, Ar), 7.25 (t, 2H, J=8.8, Ar), 7.32 (d, 2H, J=8, Ar), 7.33 (s, 1H, pyrrole), 7.56 (d, 2H, J=8.8, Ar), 10.21 (s, 1H, NH amide), 13.12 (bs, 2H, OH and NH pyrazole). Anal. Calcd for $C_{29}H_{23}FN_4O_4$: C, 68.23; H, 4.54; F, 3.72; N, 10.97%. Found: C, 68.27; H, 4.55; F, 3.73; N, 10.98%.

3-(1-(Naphthalen-1-ylmethyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11h). Compound **11h** was prepared from **10h** by means of GP-E. **10h** (0.20 g, 0.37 mmol); diethyl ether; R_f (methanol): 0.80; 100% as a yellow solid; 115-116 °C; IR *v* 3196 (OH), 2967 (NH), 1699 (C=O amide), 1685 (C=O acid), 1217 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 4.60 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 5.62 (s, 2H, CH_2Bz), 6.75 (s, 1H, CH pyrazole), 6.86 (d, 2H, J=8,8, Ar), 6.95 (s, 1H, pyrrole), 6.99 (t, 1H, Ar), 7, 22 (d, 4H, Ar), 7.42-7.56 (m, 4H, naphtyl), 7.85 (d, 2H, J=8, Ar), 7.89 (d, 2H, J=8, Ar), 8.05 (s, 1H, pyrrole), 8.14 (d, 1H, J=8, Ar), 10.01 (s, 1H, NH amide), 13.26 (bs, 2H, OH and NH). Anal. Calcd for $C_{33}H_{26}N_4O_4$: C, 73.05; H, 4.83; N, 10.33%. Found: C, 73.07; H, 4.84; N, 10.34%.

3-(1-(4-Fluorobenzyl)-4-(4-((5-phenylpentiloxy)phenyl)-1H-pyrrol-3-yl)-1H-pyrazole-5-carboxylic acid (11i). Compound **11i** was prepared from **10i** by means of GP-E. **10i** (0.04 g, 0.06 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.09; 100% as a brown solid; 88 °C; IR *v* 3026 (OH and NH), 1703 (C=O), 1242 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.36-1.39 (m, 2H, γ CH_2 alkyl); 1.54-1.65 (m, 4H, β,δ CH_2 alkyl), 2.52 (t, 2H, J = 8, ε CH_2 alkyl), 3.96 (t, 2H, J = 8, α CH_2 alkyl), 5.22 (s, 2H, CH_2Bn), 6.18 (s, 1H, CH pyrrole), 6.76 (d, 1H, J=8 Hz, Ar), 7.05 (t, 2H, J=8, Ar), 7.17 (t, 1H, J=7,2, Ar), 12.24 (bs, 1H, OH), 13.15 (bs, 1H, NH pyrazole). Anal. Calcd for $C_{32}H_{30}FN_3O_3$: C, 73.40; H, 5.78; F, 3.63; N, 8.03%. Found: C, 73.46; H, 5.79; F, 3.64; N, 8.04%.

1-(4-(Naphthalen-2-yl)-1H-pyrrol-3-yl)ethan-1-one (12). Compound **12** was prepared from (*E*)-4-(naphthalen-2-yl)but-3-en-2-one[14] by means of GP-A. **(***E*)-4-(naphthalen-2-yl)but-3-en-2-one (1.35 g, 6.90 mmol); cyclohexane; R_f (*n*-hexane/ethyl acetate 4:1): 0.24; 100% as a yellow solid; 93 °C; IR *v* 3191 (NH), 1650 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.29 (s, 3H, CH_3), 6.98 (m, 1H, C5-

H pyrrole), 7.38-7.78 (m, 7H, CH naphthalene), 7.83 (m, 1H, C2-H pyrrole), 11.56 (bs, 1H, NH). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95%. Found: C, 82.01; H, 5.58; N, 5.96%.

1-(1-(Naphthalen-1-ylmethyl)-4-phenyl-1H-pyrrol-3-yl)ethanone (13f). Compound **13f** was prepared from 1-(4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one[9] by means of GP-B. 1-(4-Phenyl-1*H*-pyrrol-3-yl)ethan-1-one (3.00 g, 16.00 mmol); 1-chloromethylnaphthalene; *n*-hexane/ethyl acetate 3:2; overnight; R_f (dichloromethane/ethyl acetate 6:1): 0.89; 55% as a dark yellow oil; IR ν 1655 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.20 (s, 3H, CH_3), 5.61 (s, 2H, CH_2Bn), 6.95 (s, 1H, C5-H pyrrole), 7.11 (d, 1H, J_o=8 Hz, CH naphthalene), 7.18 (t, 2H, J_o=8 Hz, CH naphthalene), 7.24-7.28 (m, 2H, CH Ar), 7.40-7.56 (m, 3H, CH naphthalene), 7.78 (s, 1H, C2-H pyrrole), 7.81-7.90 (m, 2H, CH Ar), 8.14 (d, 1H, J_o=8 Hz, CH naphthalene). Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30%. Found: C, 85.00; H, 5.90; N, 4.31%.

1-(4-Phenyl-1-(4-phenylbutyl)-1H-pyrrol-3-yl)ethanone (13g). Compound **13g** was prepared from 1-(4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one[9] by means of GP-B. 1-(4-Phenyl-1*H*-pyrrol-3-yl)ethan-1-one (2.00 g, 10.00 mmol); 4-bromobutylbenzene; *n*-hexane/ethyl acetate 3:2; overnight; R_f (dichloromethane/ethyl acetate 8:1): 0.87; 70% as a yellow oil; IR ν 1655 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.41-1.50 (m, 2H, γ CH_2 alkyl), 1.60-1.74 (m, 2H, β CH_2 alkyl), 2.20 (s, 3H, CH_3), 2.52 (t, 2H, J = 8, δ CH_2 alkyl), 3.87 (t, 2H, J = 8, α CH_2 alkyl), 6.87 (s, 1H, C5-H pyrrole), 7.09-7.13 (m, 4H, CH Ar), 7.17-7.21 (m, 4H, CH Ar), 7.30 (d, 2H, J_o=8 Hz, CH Ar), 7.63 (s, 1H, C2-H pyrrole). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41%. Found: C, 83.40; H, 7.32; N, 4.42%.

1-(1-(4-Fluorobenzyl)-4-(naphthalen-2-yl)-1H-pyrrol-3-yl)ethan-1-one (13h). Compound **13h** was prepared from **12** by means of GP-B. **12** (1.90 g, 8.00 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 3:2; overnight; R_f (*n*-hexane/ethyl acetate 3:2): 0.49; 65% as a slightly yellow oil; IR ν 1652 (C=O) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.34 (s, 3H, CH_3), 5.19 (s, 2H, CH_2Bn), 7.17-7.26 (m, 3H, C5-H pyrrole and CH Ar), 7.44-7.54 (m, 5H, CH naphthalene and CH Ar), 7.79-7.92

(m, 5H, CH naphthalene and CH Ar and C2-H pyrrole). Anal. Calcd for $C_{23}H_{18}FNO$: C, 80.45; H, 5.28; F, 5.53; N, 4.08%. Found: C, 80.51; H, 5.29; F, 5.54; N, 4.09%.

Ethyl (*Z*)-2-hydroxy-4-oxo-4-(1*H*-pyrrol-3-yl)but-2-enoate (14b). Compound **14b** was prepared from 1-(1*H*-pyrrol-3-yl)ethan-1-one[9] by means of GP-C. 1-(1*H*-pyrrol-3-yl)ethan-1-one (0.10 g, 0.92 mmol); benzene/cyclohexane; R_f (chloroform/ethyl acetate 5:2): 0.68; 100% as a slightly yellow solid; 93 °C; IR *v* 3500-2500 (OH enol), 1725 (C=O ester), 1625 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.20 (t, 3H, J = 8 Hz, CH_3CH_2), 4.20 (q, 2H, J = 4 Hz, CH_2CH_3), 6.62 (m, 1H, pyrrole C4-H), 6.75 (s, 1H, butenoate C3-H), 6.87 (m, 1H, pyrrole C5-H), 7.53 (s, 1H, pyrrole C2-H), 9.54 (bs, 1H, NH), 15.01 (bs, 1H, OH enol). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70%. Found: C, 57.44; H, 5.31; N, 6.71%.

Ethyl (*Z*)-2-hydroxy-4-oxo-4-(4-phenyl-1*H*-pyrrol-3-yl)but-2-enoate (14d). Compound **14d** was prepared from 1-(4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one[9] by means of GP-C. 1-(4-Phenyl-1*H*-pyrrol-3-yl)ethan-1-one (3.00 g, 16.20 mmol); benzene/cyclohexane; R_f (*n*-hexane/ethyl acetate 9:1): 0.66; 100% as a slightly yellow solid; 154 °C dec.; IR *v* 3249 (OH enol), 1721 (C=O ester), 1621 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.16 (t, 3H, J = 8 Hz, CH_3CH_2), 4.14 (q, 2H, J = 4 Hz, CH_2CH_3), 6.61 (s, 1H, butenoate C3-H), 6.91 (br d, 1H, pyrrole C5-H), 7.18 (t, 1H, J_o = 8 Hz, CH Ar), 7.25 (t, 2H, J_o = 8 Hz, CH Ar), 7.31 (d, 2H, J_o = 8 Hz, CH Ar), 7.89 (br d, 1H, pyrrole C2-H), 11.87 (bs, 1H, NH), 14.90 (bs, 1H, OH enol). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%. Found: C, 67.39; H, 5.31; N, 4.92%.

Ethyl 4-(1-methyl-4-phenyl-1H-pyrrol-3-yl)-2,4-dioxobutanoate (14e). Compound **14e** was prepared from 1-(1-methyl-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one[15] by means of GP-C. 1-(1-methyl-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one (1.50 g, 7.50 mmol); benzene; R_f (ethyl acetate/methanol 98:2): 0.81; 100% as a dark yellow solid; 101 °C; IR *v* 2982 (OH enol), 1731 (C=O ester), 1611 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.16 (t, 3H, CH_3CH_2), 3.63 (t, 3H, CH_3), 4.14 (q, 2H, CH_2CH_3), 6.55 (s, 1H, C5-H pyrrole), 6.88 (s, 1H, butanoate), 7.19 (t, 1H, J_o=8 Hz, CH Ar), 7.24 (t, 2H, J_o=8 Hz, CH Ar), 7.31 (d, 2H, J_o=8 Hz, CH Ar), 7.87 (s, 1H, C2-H pyrrole), 15.23 (bs, 1H,

enol). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68%. Found: C, 68.26; H, 5.73; N, 4.69%.

Ethyl-4-(1-(naphthalen-1-ylmethyl)-4-phenyl-1H-pyrrol-3-yl)-2,4-dioxobutanoate (14f). Compound **14f** was prepared from **13f** by means of GP-C. **13f** (2.00 g, 6.10 mmol); toluene; R_f (*n*-hexane/ethyl acetate 3:2): 0.88; 98% as a light yellow solid; 167 °C; IR *v* 2983 (OH enol), 1732 (C=O ester), 1617 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.14 (t, 3H, CH_3CH_2), 4.12 (q, 2H, CH_2CH_3), 5.65 (s, 2H, CH_2Bn), 6.49 (s, 1H, butanoate), 7.01 (s, 1H, C5-H pyrrole), 7.16-7.30 (m, 6H, CH naphthalene and CH Ar), 7,43-7,56 (m, 3H, CH naphthalene and CH Ar), 7.88 (d, 2H, J_o=8 Hz, CH Ar), 8.05 (s, 1H, C2-H pyrrole), 8.15 (d, 1H, J_o=8 Hz, CH Ar), 15.00 (bs, 1H, enol). Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29%. Found: C, 76.33; H, 5.46; N, 3.30%.

Ethyl 2,4-dioxo-4-(4-phenyl-1-(4-phenylbutyl)-1H-pyrrol-3-yl)butanoate (14g). Compound **14g** was prepared from **13g** by means of GP-C. **13g** (1.50 g, 4.70 mmol); R_f (*n*-hexane/ethyl acetate 3:2): 0.89; 97% as a brown oil; IR *v* 2939 (OH enol), 1737 (C=O ester), 1615 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.17 (t, 3H, CH_3CH_2), 1.45-1.49 (m, 2H, γ CH_2 alkyl), 1.70-1.74 (m, 2H, β CH_2 alkyl), 2.53 (t, 2H, J = 8, δ CH_2 alkyl), 3.92 (t, 2H, J = 8, α CH_2 alkyl), 4.17 (q, 2H, CH_2CH_3), 6.57 (s, 1H, butanoate), 6.96 (s, 1H, C5-H pyrrole), 7.08-7.32 (m, 10H, CH Ar), 7.95 (s, 1H, C2-H pyrrole), 15.20 (bs, 1H, enol). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35%. Found: C, 74.89; H, 6.53; N, 3.36%.

Ethyl (Z)-4-(1-(4-fluorobenzyl)-4-(naphthalen-2-yl)-1H-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate (14h). Compound **14h** was prepared from **13h** by means of GP-C. **13h** (1.50 g, 4.40 mmol); toluene; R_f (*n*-hexane/ethyl acetate 3:2): 0.86; 100% as a yellow solid; 145 °C; IR *v* 2998 (OH enol), 1736 (C=O ester), 1621 (C=O ketone) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.24 (t, 3H, CH_3CH_2), 4.16 (q, 2H, CH_2CH_3), 5.58 (s, 2H, CH_2Bn), 6.51 (s, 1H, butanoate), 7.11 (s, 1H, C5-H pyrrole), 7.19-7.33 (m, 6H, CH naphthalene and CH Ar), 7.47-7.59 (m, 3H, CH naphthalene and CH Ar), 7.91 (d, 1H, J_o=8 Hz, CH Ar), 8.25 (s, 1H, C2-H pyrrole), 8.41 (d, 1H, J_o=8 Hz, CH Ar), 15.22 (bs,

1H, enol). Anal. Calcd for $C_{27}H_{22}FNO_4$: C, 73.13; H, 5.00; F, 4.28; N, 3.16%. Found: C, 73.39; H, 5.01; F, 4.29; N, 3.17%.

4-(4-(4-Phenylbutoxy)phenyl)but-3-en-2-one (15b). Compound **15b** was prepared from 4-(4-phenylbutoxy)benzaldehyde[16] by means of GP-F. 4-(4-Phenylbutoxy)benzaldehyde (1.80 g, 7.10 mmol); R_f (*n*-hexane/ethyl acetate 9:1): 0.44; 53% as a brown oil; IR *v* 1679 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 4H, β, γ CH_2 alkyl), 2.28 (s, 3H, CH_3), 2.63 (t, 2H, J = 8, δ CH_2 alkyl), 3.92 (t, 2H, J = 8, α CH_2 alkyl), 6.53 (d, 1H, J_t=16 Hz, CH ethylene), 6.82 (d, 2H, J_o=8 Hz, CH Ar), 7.12 (d, 2H, J_o=8 Hz, CH Ar), 7.21-7.40 (m, 6H, CH Ar and CH ethylene). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53%. Found: C, 81.90; H, 7.55%.

4-(4-(Naphthalen-1-ylmethoxy)phenyl)but-3-en-2-one (15d). Compound **15d** was prepared from 4-(naphthalen-1-ylmethoxy)benzaldehyde by means of GP-F. 4-(naphthalen-1-ylmethoxy)benzaldehyde (10.00 g, 38.00 mmol); THF; R_f (*n*-hexane/ethyl acetate 7:3): 0.57; 59% as a yellow solid; 125-127 °C; IR *v* 1680 (C=O), 1218 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.23 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 6.78 (d, 1H, J_t=16 Hz, CH ethylene), 7.14 (d, 2H, J_o=8 Hz, CH Ar), 7.32-7.35 (m, 3H, CH Ar), 7.40-8.01 (m, 5H, and CH Ar and CH ethylene). Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00%. Found: C, 83.51; H, 6.01%.

Methyl 4-(2-(4-(3-oxobut-1-en-1-yl)phenoxy)acetamido)benzoate (15f). Compound **15f** was prepared methyl 4-(2-(4-formylphenoxy)acetamido)benzoate by means of GP-F. Methyl 4-(2-(4-formylphenoxy)acetamido)benzoate (1.59 g, 6.22 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.31; 41% as a brown solid; 137-139 °C; IR *v* 3250 (NH), 1730 (C=O ester), 1690 (C=O amide), 1680 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 6.58 (d, 1H, J_t=16 Hz, CH ethylene), 6.97 (d, 2H, J_o=8,CH Ar), 7.41 (d, 1H, J_t=16 Hz, CH ethylene), 7.51 (d, 2H, J_o=8, CH Ar), 7.62 (d, 2H, J_o=8, CH Ar), 7.98 (d, 2H, J_o=8, CH Ar), 8.28 (s, 1H, NH). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96%. Found: C, 68.01; H, 5.43; N, 3.97%.

2-(4-(3-Oxobut-1-en-1-yl)phenoxy)-*N*-phenylacetamide (15g). Compound **15g** was prepared from 4-(naphthalen-1-ylmethoxy)benzaldehyde[17] by means of GP-F. 4-(Naphthalen-1-ylmethoxy)benzaldehyde (10.00 g, 38.00 mmol); diethyl ether; R_f (*n*-hexane/ethyl acetate 7:3): 0.58; 55% as a brown solid; 138-140 °C; IR *v* 3300 (NH), 1688 (C=O amide), 1683 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 4.57 (s, 2H, CH_2), 6.55 (d, 1H, J_t=16 Hz, CH ethylene), 7.10 (t, 1H, J=8.8, CH Ar), 7.29 (t, 2H, J=8, CH Ar), 7.41 (d, 1H, J_t=16 Hz, CH ethylene), 7.50 (t, 2H, J=8, CH Ar), 7.54 (d, 2H, J_o=8, CH Ar), 7.58 (d, 2H, J_o=8, CH Ar), 8.13 (s, 1H, NH). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%. Found: C, 73.31; H, 5.81; N, 4.75%.

4-(4-(5-Phenylpentyloxy)phenyl)but-3-en-2-one (15i). Compound **15i** was prepared from 4-((5-phenylpentyl)oxy)benzaldehyde[18] by means of GP-F. 4-((5-Phenylpentyl)oxy)benzaldehyde (1.00 g, 3.15 mmol); benzene/cyclohexane; R_f (*n*-hexane/ethyl acetate 4:1): 0.51; 63% as a yellow solid; 65 °C dec.; IR *v* 1657 (C=O), 1230 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.32-1.35 (m, 2H, γ CH_2 alkyl), 1.51-1.65 (m, 4H, β,δ CH_2 alkyl), 2.20 (s, 3H, CH_3), 2.49 (t, 2H, J = 8, ε CH_2 alkyl), 3.90 (t, 2H, J = 8, α CH_2 alkyl), 6.55 (d, 1H, J_t=16 Hz, CH ethylene), 6.87 (d, 2H, J_o=8 Hz, CH Ar), 7.07-7.18 (m, 5H, CH Ar), 7.47 (d, 1H, J_t=16 Hz, CH ethylene), 7.54 (d, 2H, J_o=8 Hz, CH Ar). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84%. Found: C, 82.03; H, 7.86%.

1-(4-(4-(Benzyloxy)phenyl)-1*H*-pyrrol-3-yl)ethan-1-one (16a). Compound **16a** was prepared from (*E*)-4-(4-(benzyloxy)phenyl)but-3-en-2-one[19] by means of GP-A. (*E*)-4-(4-(benzyloxy)phenyl)but-3-en-2-one (1.31 g, 5.20 mmol); *n*-hexane/diethyl ether; R_f (*n*-hexane/ethyl acetate 4:1): 0.35; 100% as a yellow solid; 81-83 °C; IR *v* 3188 (NH), 1700 (C=O), 1218 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.22 (s, 3H, CH_3), 5.01 (s, 2H, CH_2), 6.76-6.84 (m, 3H, CH pyrrole and CH Ar), 7.23-7.36 (m, 7H, CH Ar), 7.57 (bs, 1H, CH pyrrole), 11.46 (bs, 1H, NH). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.40; H, 5.89; N, 4.82%.

1-(4-(3-(4-Phenylbutoxy)phenyl)-1H-pyrrol-3-yl)ethanone (16b). Compound **16b** was prepared from **15b** by means of GP-A. **15b** (0.80 g, 2.70 mmol); R_f (ethyl acetate): 0.85; 100% as a

brown oil; IR *v* 3197 (NH), 1687 (C=O), 1240 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.75 (m, 4H, β and γ CH_2 alkyl), 2.21 (s, 3H, CH_3), 2.62 (t, 2H, J = 8, δ CH_2 alkyl), 3.95 (t, 2H, J = 8, α CH_2 alkyl), 6.72 (d, 2H, J_o=8 Hz, CH Ar), 6.85 (m, 1H, CH pyrrole), 7.22 (s, 1H, NH), 7.39-7.53 (m, 5H, CH Ar), 7.72 (m, 1H, CH pyrrole), 7.83-7.91 (m, 3H, CH Ar), 8.12 (d, 2H, J_o=8 Hz, CH Ar). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20%. Found: C, 79.31; H, 6.96; N, 4.21%.

1-(4-(4-(Naphthalen-1-ylmethoxy)phenyl)-1H-pyrrol-3-yl)ethanone (16d). Compound **16d** was prepared from **15d** by means of GP-A. **15d** (8.00 g, 25.49 mmol); R_f (ethyl acetate): 0.83; 100% as a brown oil; IR *v* 3214 (NH), 1710 (C=O), 1214 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.23 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 6.78-6.93 (m, 3H, CH pyrrole and CH Ar), 7.14 (d, 1H, J=4 Hz, CH Ar), 7.18 (s, 1H, CH pyrrole), 7.32-8.01 (m, 8H, CH Ar), 11.42 (bs, 1H, NH). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10%. Found: C, 81.15; H, 5.62; N, 4.11%.

Methyl 4-(2-(4-(4-acetyl-1H-pyrrol-3-yl)phenoxy)acetamido)benzoate (16f). Compound **16f** was prepared from **15f** by means of GP-A. **15f** (0.80 g, 2.30 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.48; 87% as a yellow solid; 197-198°C; IR *v* 3214 (NH), 1730 (C=O ester), 1690 (C=O amide), 1687 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H, CH_3), 3,82 (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 5.84 (m, 1H, CH pyrrole), 6.68 (m, 1H, CH pyrrole), 6.90 (d, 2H, J_o=8, CH Ar), 7.36 (d, 2H, J_o=8, CH Ar), 7.63 (d, 2H, J_o=8, CH Ar), 7.97 (d, 2H, J_o=8, CH Ar), 8.43 (s, 1H, NH amide), 8.65 (bd, 1H, pyrrole). Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14%. Found: C, 67.38; H, 5.15; N, 7.16%.

2-(4-(4-Acetyl-1H-pyrrol-3-yl)phenoxy)-N-phenylacetamide (16g). Compound **16g** was prepared from **15g** by means of GP-A. **15g** (1.70 g, 6.80 mmol); ethanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.21; 91% as a white solid; 191-193 °C; IR *v* 3214 (NH), 1690 (C=O amide), 1678 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2,22 (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 6.77 (m, 1H, CH pyrrole), 6.80 (d, 2H, J_o=8, CH Ar), 6.99 (t, 1H, J_o=8, CH Ar), 7.22 (m, 1H, CH pyrrole), 7.25-7.57 (m, 6H, CH Ar), 10.01 (s, 1H, NH amide), 11.42 (bd, 1H, pyrrole). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38%. Found: C, 71.89; H, 5.44; N, 8.39%.

1-(4-(3-((5-Phenylpentyl)oxy)phenyl)-1H-pyrrol-3-yl)ethan-1-one (16i). Compound **16i** was prepared from **15i** by means of GP-A. **15i** (10.00 g, 31.01 mmol); benzene/cyclohexane; R_f (*n*-hexane/ethyl acetate 1:4): 0.34; 100% as a yellow solid; 131°C; IR *v* 3277 (NH), 1636 (C=O), 1242 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.30-1.37 (m, 2H, γ CH_2 alkyl), 1.55-1.65 (m, 4H, β,δ CH_2 alkyl), 2.22 (s, 3H, CH_3), 2.53 (t, 2H, J = 8, ε CH_2 alkyl), 3.87 (t, 2H, J = 8, α CH_2 alkyl), 6.75 (d, 2H, J_o=8 Hz, CH Ar), 7.11-7.57 (m, 9H, CH Ar), 11,39 (s, 1H, pyrrole). Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03%. Found: C, 79.65; H, 7.26; N, 4.04%.

1-(1-(4-Fluorobenzyl)-4-(4-(benzyloxy)phenyl)-1H-pyrrol-3-yl)ethanone (17a). Compound **17a** was prepared from **16a** by means of GP-B. **16a** (2.50 g, 8.50 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 3:2; overnight; R_f (*n*-hexane/ethyl acetate 1:4): 0.51; 40% as a yellow oil; IR *v* 1637 (C=O), 1220 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 2.29 (s, 3H, CH_3), 5.09 (s, 2H, CH_2Bn), 5.43 (s, 2H, CH_2Bn), 6.91 (s, 1H, pyrrole C5-H), 7.28−7.75 (m, 14H, pyrrole C2-H, benzene H and benzyl H). Anal. Calcd for $C_{22}H_{26}FNO_2$: C, 78.18; H, 5.55; F, 4.76; N, 3.51%. Found: C, 78.29; H, 5.56; F, 4.77; N, 3.52%.

1-(1-(4-Fluorobenzyl)-4-(4-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yL)ethanone (17b). Compound **17b** was prepared from **16b** by means of GP-B. **16b** (2.00 g, 6.00 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 7:3; overnight; R_f (*n*-hexane/ethyl acetate 7:3): 0.41; 23% as a brown oil; IR *v* 1649 (C=O), 1216 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (m, 4H, β and γ CH_2 alkyl), 2.19 (s, 3H, CH_3), 2.63 (m, 2H, δ CH_2 alkyl), 3.90 (m, 2H, α CH_2 alkyl), 4.60 (s, 2H, CH_2Bn), 4.78 (m, 1H, pyrrole C5-H), 6.52 (m, 1H, pyrrole C2-H), 6.78−7.29 (m, 13H, CH Ar). Anal. Calcd for $C_{29}H_{28}FNO_2$: C, 78.89; H, 6.39; F, 4.30; N, 3.17%. Found: C, 78.99; H, 6.40; F, 4.31; N, 3.18%.

1-(1-(Naphthalen-1-ylmethyl)-4-(3-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yl)ethanone (17c). Compound **17c** was prepared from **16b** by means of GP-B. **16b** (2.00 g, 6.00 mmol); 1-chloromethylnaphthalene; *n*-hexane/ethyl acetate 7:3; overnight; R_f (*n*-hexane/ethyl acetate 7:3): 0.43; 17% as a yellow oil; IR *v* 1657 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.75 (m,

4H, β and γ CH_2 alkyl), 2.21 (s, 3H, CH_3), 2.62 (m, 2H, δ CH_2 alkyl), 3.95 (m, 2H, α CH_2 alkyl), 5.57 (s, 2H, CH_2), 6.72(d, 2H, J_o=8 Hz, CH Ar), 6.85 (m, 1H, pyrrole C5-H), 7.08-7.18 (m, 7H, CH naphthalene), 7.39-7.53 (m, 5H, CH Ar), 7.72 (m, 1H, pyrrole C2-H), 7.83-7.91 (m, 3H, CH Ar), 8.12 (d, 1H, J_o=8 Hz, CH Ar). Anal. Calcd for $C_{33}H_{31}NO_2$: C, 83.69; H, 6.60; N, 2.96%. Found: C, 84.00; H, 6.61; N, 2.96%.

1-(1-(4-Fluorobenzyl)-4-(4-(naphthalen-1-ylmethoxy)phenyl)-1H-pyrrol-3-yl)ethanone (17d). Compound **17d** was prepared from **16d** by means of GP-B. **16d** (4.00 g, 11.73 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 7:3; hexane/diethyl ether; overnight; R_f (*n*-hexane/ethyl acetate 7:3): 0.47; 43% as a yellow solid; 85-88 °C; IR *v* 1651 (C=O), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.23 (s, 3H, CH_3), 4.97 (s, 2H, CH_2Bn), 5.44 (s, 2H, CH_2Ar), 6.55 (m, 1H, pyrrole C5-H), 6.96−7.15 (m, 6H, CH Ar and naphthalene), 7.19 (m, 1H, pyrrole C2-H), 7.25−8.01 (m, 9H, CH Ar and naphthalene). Anal. Calcd for $C_{30}H_{24}FNO_2$: C, 80.16; H, 5.38; F, 4.23; N, 3.12%. Found: C, 80.22; H, 5.39; F, 4.24; N, 3.12%.

1-(4-(4-(Naphthalen-1-ylmethoxy)phenyl)-1-(naphthalen-1-ylmethyl)-1H-pyrrol-3-yl)ethanone (17e). Compound **17e** was prepared from **16d** by means of GP-B. **16d** (5.00 g, 14.66 mmol); 1-chloromethylnaphthalene; *n*-hexane/ethyl acetate 7:3; cyclohexane; overnight; R_f (*n*-hexane/ethyl acetate 7:3): 0.49; 59% as a yellow solid; 98 °C; IR *v* 1635 (C=O), 1223 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.21 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 6,61 (m, 1H, pyrrole), 6.96 (d, 2H, J_o=8 Hz, CH Ar), 7.19-7.86 (m, 15H, CH Ar and CH pyrrole), 8.00 (d, 2H, J_o=8 Hz, CH Ar). Anal. Calcd for $C_{34}H_{27}NO_2$: C, 84.80; H, 5.65; N, 2.91%. Found: C, 84.88; H, 5.66; N, 2.91%.

Methyl 4-(2-(4-(4-acetyl-1-(4-fluorobenzyl)-1H-pyrrol-3-yl)phenoxy)acetamido) benzoate (17f). Compound **17f** was prepared from **16f** by means of GP-B. **16f** (5.00 g, 14.66 mmol); *p*-fluorobenzyl bromide; dichloromethane/ethyl acetate 4:1; 2 h; R_f (*n*-hexane/ethyl acetate 1:1): 0.51; 20% as a brown oil; IR *v* 1730 (C=O ester), 1690 (C=O amide), 1657 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 2.21 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 5.03 (s, 2H,

CH_2), 6.82 (d, 2H, J_o=8, CH Ar), 6.88 (m, 1H, CH pyrrole), 7.11 (m, 1H, CH pyrrole), 7.13 (d, 2H, J_o=8, CH Ar), 7.21 (d, 2H, J_o=8, CH Ar), 7.32 (d, 2H, J_o=8, CH Ar), 7.72 (d, 2H, J_o=8, CH Ar), 7.85 (d, 2H, J_o=8, CH Ar), 10.29 (s, 1H, NH amide). Anal. Calcd for $C_{29}H_{25}FN_2O_5$: C, 69.59; H, 5.03; F, 3.80; N, 5.60%. Found: C, 69.61; H, 5.04; F, 3.80; N, 5.61%.

2-(4-(4-Acetyl-1-(4-fluorobenzyl)-1H-pyrrol-3-yl)phenoxy)-N-phenylacetamide (17g). Compound **17g** was prepared from **16g** by means of GP-B. **16g** (2.00 g, 7.80 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 1:1; 5 h; R_f (*n*-hexane/ethyl acetate 1:1): 0.32; 15% as a yellow oil; IR *v* 1683 (C=O amide), 1650 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 6.54 (m, 1H, CH pyrrole), 6.85 (d, 2H, J_o=8, CH Ar), 7.03 (t, 2H, J_o=8, CH Ar), 7.09 (t, 1H, J_o=8, CH Ar), 7.12 (d, 2H, J_o=8, CH Ar), 7.25 (d, 2H, J_o=8, CH Ar), 7.28 (m, 1H, CH pyrrole), 7.33 (d, 2H, J_o=8, CH Ar), 8.32 (s, 1H, NH amide). Anal. Calcd for $C_{27}H_{23}FN_2O_3$: C, 73.29; H, 5.24; F, 4.29; N, 6.33%. Found: C, 73.34; H, 5.25; F, 4.30; N, 6.34%.

2-(4-(4-Acetyl-1-(naphthalen-1-ylmethyl)-1H-pyrrol-3-yl)phenoxy)-*N*-phenylacetamide (17h). Compound **17h** was prepared from **16g** by means of GP-B. **16g** (1.00 g, 3.00 mmol); 1-chloromethylnaphthalene; *n*-hexane/ethyl acetate 1:1; diethyl ether; 5 h; R_f (*n*-hexane/ethyl acetate 1:1): 0.44; 46% as a yellow solid; 85-86 °C; IR *v* 1683 (C=O amide), 1650 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.18 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.82 (d, 2H, J_o=8, CH Ar), 6.90 (m, 1H, CH pyrrole), 6.99 (t, 1H, J=4, CH Ar), 7.22 (d, 2H, J=6, CH Ar), 7.42-7.57 (m, 5H, naphthalene), 7.76 (m, 1H, CH pyrrole), 7.84 (d, 2H, J_o=8, CH Ar), 7.90 (d, 2H, J_o=8, CH Ar), 8.13 (d, 1H, J_o=8, CH Ar), 9.99 (s, 1H, NH amide). Anal. Calcd for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90%. Found: C, 78.51; H, 5.53; N, 5.91%.

1-(1-(4-Fluorobenzyl)-4-(3-((5-phenylpentyl)oxy)phenyl)-1H-pyrrol-3-yl)ethan-1-one (17i). Compound **17i** was prepared from **16i** by means of GP-B. **16i** (1.00 g, 2.88 mmol); *p*-fluorobenzyl bromide; *n*-hexane/ethyl acetate 7:3; cyclohexane; overnight; R_f (*n*-hexane/ethyl acetate 7:3): 0.47; 47% as a brown solid; 110 °C; IR *v* 1640 (C=O), 1243 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.29-

1.33 (m, 2H, γ CH_2 alkyl), 1.55-1.65 (m, 4H, β,δ CH_2 alkyl), 1.97 (s, 3H, CH_3), 2.51 (t, 2H, J = 8, ε CH_2 alkyl), 3.84 (t, 2H, J = 8, α CH_2 alkyl), 5.05 (s, 2H, CH_2), 6.73 (d, 2H, J_o=8 Hz, CH Ar), 6.86 (m, 1H, pyrrole), 7.03-7.36 (m, 7H, CH Ar), 7.71 (m, 1H, pyrrole). Anal. Calcd for $C_{30}H_{30}FNO_2$: C, 79.09; H, 6.64; F, 4.17; N, 3.07%. Found: C, 79.20; H, 6.65; F, 4.18; N, 3.07%.

Ethyl 4-(4-(4-(benzyloxy)phenyl)-1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)-2,4-dioxobutanoate (18a). Compound **18a** was prepared from **17a** by means of GP-C. **17a** (0.90 g, 2.20 mmol); benzene; R_f (*n*-hexane/ethyl acetate 4:1): 0.53; 100% as a yellow solid; 86-89 °C; IR *v* 3200 (OH enol), 1720 (C=O ester), 1620 (C=O ketone), 1227 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.43 (t, 3H, *CH*$_3$$CH_2$), 4.40 (q, 2H, *CH*$_2$$CH_3$), 5.20 (s, 2H, CH_2Bn), 5.31 (s, 2H, CH_2Bn), 6.73 (s, 1H, butanoate), 7.01 (s, 1H, pyrrole C5-H), 7.08−7.54 (m, 14H, pyrrole C2-H, benzene H and benzyl H), 15 (bs, 1H, enol). Anal. Calcd for $C_{30}H_{26}FNO_5$: C, 72.13; H, 5.25; F, 3.80; N, 2.80%. Found: C, 72.20; H, 5.26; F, 3.81; N, 2.80%.

Ethyl 4-(4-(4-(3-phenylbutoxy)phenyl)-1-(4-fluorobenzyl)-1H-pyrrol-3-yl)-2,4-dioxobutanoate (18b). Compound **18b** was prepared from **17a** by means of GP-C. **17a** (0.23 g, 0.52 mmol); R_f (*n*-hexane/ethyl acetate 3:2): 0.51; 100% as a brown oil; IR *v* 3226 (OH enol), 1738 (C=O ester), 1630 (C=O ketone), 1229 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.19 (t, 3H, *CH*$_3$$CH_2$), 1.81 (m, 4H, β and γ CH_2 alkyl), 2.76 (m, 2H, δ CH_2 alkyl), 3.99 (m, 2H, α CH_2 alkyl), 4.11 (q, 2H, *CH*$_2$$CH_3$), 5.21 (s, 2H, CH_2Bn), 6.59 (s, 1H, butanoate), 6.70 (m, 1H, pyrrole C5-H), 7.09−8.01 (m, 14H, pyrrole C2-H and CH Ar), 15.03 (bs, 1H, enol). Anal. Calcd for $C_{33}H_{32}FNO_5$: C, 73.18; H, 5.96; F, 3.51; N, 2.59%. Found: C, 73.21; H, 5.97; F, 3.51; N, 2.59%.

Ethyl 2-hydroxy-4-(1-(naphthalen-1-ylmethyl)-4-(3-(4-phenylbutoxy)phenyl)-1H-pyrrol-3-yl)-4-oxobut-2-enoate (18c). Compound **18c** was prepared from **17c** by means of GP-C. **17c** (0.30 g, 0.60 mmol); R_f (*n*-hexane/ethyl acetate 7:3): 0.48; 98% as a brown oil; IR *v* 3245 (OH enol), 1727 (C=O ester), 1656 (C=O ketone), 1240 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) *δ* 1.15 (t, 3H, *CH*$_3$$CH_2$), 1.63 (m, 4H, β and γ CH_2 alkyl), 2.55 (m, 2H, δ CH_2 alkyl), 3.88 (m, 2H, α CH_2 alkyl),

4.14 (q, 2H, *CH*$_2$CH$_3$), 5.57 (s, 2H, CH$_2$), 5.67 (m, 1H, pyrrole C5-H), 6.22 (d, 1H, J$_o$=8 Hz, CH Ar), 6.77 (d, 1H, J$_o$=8 Hz, CH Ar), 7.02 (t, 2H, J$_o$=8 Hz, CH Ar), 7.10-7.19 (m, 3H, CH naphthalene and pyrrole C2-H), 7.43-7.80 (m, 7H, CH naphthalene and CH Ar), 8.01-8.13 (m, 3H, CH naphthalene). Anal. Calcd for $C_{37}H_{35}NO_5$: C, 77.46; H, 6.15; N, 2.44%. Found: C, 77.50; H, 6.16; N, 2.44%.

Ethyl 4-(1-(4-fluorobenzyl)-4-(4-(naphthalen-1-ylmethoxy)phenyl)-1H-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate (18d). Compound **18d** was prepared from **17d** by means of GP-C. **17d** (1.00 g, 2.20 mmol); benzene;R$_f$ (*n*-hexane/ethyl acetate 7:3): 0.54; 99% as a yellow solid; 65-68 °C; IR *v* 3208 (OH enol), 1732 (C=O ester), 1638 (C=O ketone), 1221 (C-O-C) cm^{-1}; ^{1}H NMR (DMSO d$_6$) *δ* 1.16 (t, 3H, *CH*$_3$CH$_2$), 4.15 (q, 2H, *CH*$_2$CH$_3$), 5.09 (s, 2H, CH$_2$Bn), 5.47 (s, 2H, CH$_2$Ar), 6.55 (s, 1H, butanoate), 6.99 (d, 2H, J$_o$=8Hz, CH Ar), 7.11−8.04 (m, 15H, pyrrole C2-H and C5-H, CH Ar and naphthalene), 15.26 (bs, 1H, enol). Anal. Calcd for $C_{34}H_{28}FNO_5$: C, 74.30; H, 5.14; F, 3.46; N, 2.55%. Found: C, 74.37; H, 5.15; F, 3.46; N, 2.55%.

Ethyl 4-(4-(4-(naphthalen-1-ylmethoxy)phenyl)-1-(naphthalen-1-ylmethyl)-1H-pyrrol-3-yl)-2,4-dioxobutanoate (18e). Compound **18e** was prepared from **17e** by means of GP-C. **17e** (1.50 g, 3.00 mmol); R$_f$ (*n*-hexane/ethyl acetate 3:2): 0.39; 60% as a yellow oil; IR *v* 3239 (OH enol), 1729 (C=O ester), 1631 (C=O ketone), 1227 (C-O-C) cm^{-1}; ^{1}H NMR (DMSO d$_6$) *δ* 1.09 (t, 3H, *CH*$_3$CH$_2$), 4.07 (q, 2H, *CH*$_2$CH$_3$), 5.45 (s, 2H, CH$_2$ naphthalene), 5.62 (s, 2H, CH$_2$ O-naphthalene), 6.93-6.97 (m, 3H, butanoate and pyrrole C5-H), 7.23-7.29 (m, 3H, pyrrole C5-H and CH naphthalene), 7.42−7.60 (m, 6H, pyrrole C2-H and CH naphthalene), 7.84−7.91 (m, 5H, CH naphthalene), 8.01 (d, 2H, J$_o$=8 Hz, CH Ar), 8.14 (d, 2H, J$_o$=8 Hz, CH Ar), 15.21 (bs, 1H, enol). Anal. Calcd for $C_{38}H_{31}NO_5$: C, 78.47; H, 5.37; N, 2.41%. Found: C, 78.51; H, 5.38; N, 2.41%.

Methyl (*Z*)-4-(2-(4-(4-(4-ethoxy-3-hydroxy-4-oxobut-2-enoyl)-1-(4-fluorobenzyl)-1*H*-pyrrol-3-yl)phenoxy)acetamido)benzoate (18f). Compound **18f** was prepared from **17f** by means of GP-C. **17f** (0.14 g, 0.30 mmol); isopropanol; R$_f$ (chloroform/ethyl acetate 3:2): 0.58; 99% as a yellow solid; 113-115 °C; IR *v* 3211 (OH enol), 2937 (NH), 1723 (C=O ester), 1648 (C=O ketone), 1219

(C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.22 (t, 3H, CH_3CH_2), 4.20 (q, 2H, CH_2CH_3), 4.66 (s, 2H, CH_2), 5.07 (s, 2H, CH_2Bn), 6.57 (s, 1H, butanoate), 6.87 (d, 2H, J_o=8 Hz, CH Ar), 7.09 (m, 1H, pyrrole C5-H), 7.13 (d, 2H, J_o=8 Hz, CH Ar), 7.24 (d, 2H, J_o=8 Hz, CH Ar), 7.35 (m, 1H, pyrrole C2-H), 7.36 (d, 2H, J_o=8 Hz, CH Ar), 7.72 (d, 2H, J_o=8 Hz, CH Ar), 7.85 (d, 2H, J_o=8 Hz, CH Ar), 8.04 (s, 1H, NH), 10,34 (bd, 1H, OH). Anal. Calcd for $C_{33}H_{29}FN_2O_8$: C, 65.99; H, 4.87; F, 3.16; N, 4.66%. Found: C, 66.09; H, 4.88; F, 3.16; N, 4.67%.

Ethyl 4-(1-(4-fluorobenzyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy)phenyl)-1H-pyrrol-3-yl)-2-hydroxy-4-oxobut-2-enoate (18g). Compound **18g** was prepared from **17g** by means of GP-C. **17g** (0.61 g, 1.40 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 7:3): 0.77; 100% as a brown solid; 150-151 °C; IR *v* 3206 (OH enol), 2943 (NH), 1732 (C=O ester), 1638 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.16 (t, 3H, CH_3CH_2), 4.15 (q, 2H, CH_2CH_3), 4.60 (s, 2H, CH_2), 5.09 (s, 2H, CH_2Bn), 6.56 (s, 1H, butanoate), 6.86 (d, 2H, J_o=8 Hz, CH Ar), 6.99 (m, 1H, pyrrole C5-H), 7.12 (t, 2H, J_o=8 Hz, CH Ar), 7.14 (d, 2H, J_o=8 Hz, CH Ar), 7.20 (t, 1H, J_o=8 Hz, CH Ar), 7.22 (m, 1H, pyrrole C2-H), 7.33 (d, 2H, J_o=8 Hz, CH Ar), 7.55 (d, 2H, J_o=8 Hz, CH Ar), 7.75 (d, 2H, J_o=8 Hz, CH Ar), 8.04 (s, 1H, NH), 10.32 (bd, 1H, OH). Anal. Calcd for $C_{31}H_{27}FN_2O_6$: C, 68.63; H, 5.02; F, 3.50; N, 5.16%. Found: C, 68.70; H, 5.03; F, 3.50; N, 5.17%.

Ethyl 2-hydroxy-4-(1-(naphthalen-1-ylmethyl)-4-(4-(2-oxo-2-(phenylamino)ethoxy) phenyl)-1H-pyrrol-3-yl)-4-oxobut-2-enoate (18h). Compound **18h** was prepared from **17h** by means of GP-C. **17h** (0.40 g, 0.84 mmol); isopropanol; R_f (*n*-hexane/ethyl acetate 1:1): 0.38; 100% as a yellow solid; 103-105 °C; IR *v* 3200 (OH enol), 2933 (NH), 1732 (C=O ester), 1638 (C=O ketone), 1219 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.18 (t, 3H, CH_3CH_2), 4.21 (q, 2H, CH_2CH_3), 4.60 (s, 2H, CH_2 Bn), 5.61 (s, 2H, CH_2), 6.19 (s, 1H, butanoate), 6.86 (d, 2H, J_o=8 Hz, CH Ar), 6.95 (m, 1H, pyrrole C5-H), 6.99 (t, 1H, J_o=8 Hz, CH Ar), 7.22 (d, 4H, J_o=8 Hz, CH Ar), 7.42-7.56 (m, 5H, CH naphthalene), 7.85 (d, 2H, J_o=8 Hz, CH Ar), 7.89 (d, 2H, J_o=8 Hz, CH Ar), 8.05 (m, 1H, pyrrole C5-H), 8.14 (s, 1H, NH), 10.01 (bd, 1H, OH). Anal. Calcd for $C_{35}H_{30}N_2O_6$: C, 73.16; H, 5.26; N, 4.88%. Found: C, 73.19; H, 5.27; N, 4.89%.

Ethyl 4-(1-(4-fluorobenzyl)-4-(4-((5-phenylpentyl)oxy)phenyl)-1H-pyrrol-3-yl)-2,4-dioxobutanoate (18i). Compound **18i** was prepared from **17i** by means of GP-C. **17i** (0.50 g, 1.09 mmol); cyclohexane; R_f (*n*-hexane/ethyl acetate 3:2): 0.81; 55% as a brown solid; 80 °C; IR *v* 3242 (OH enol), 1721 (C=O ester), 1630 (C=O ketone), 1240 (C-O-C) cm^{-1}; ^1H NMR (DMSO d_6) δ 1.19 (t, 3H, CH_3CH_2), 1.29-1.33 (m, 2H, γ CH_2 alkyl), 1.53-1.67 (m, 4H, β,δ CH_2 alkyl), 2.59 (t, 2H, J = 8, ε CH_2 alkyl), 3.84 (t, 2H, J = 8, α CH_2 alkyl), 4.13 (q, 2H, CH_2CH_3), 5.18 (s, 2H, CH_2Bn), 6.52 (s, 1H, butanoate), 6.74 (d, 2H, J_o=8 Hz, CH Ar), 6.78-7.43 (m, 9H, pyrrole C2-H and C5-H and CH Ar). Anal. Calcd for $C_{34}H_{34}FNO_5$: C, 73.50; H, 6.17; F, 3.42; N, 2.52%. Found: C, 73.60; H, 6.18; F, 3.42; N, 2.52%.

Molecular Modeling Experimental Section.

The latest version of the docking software AutoDock Vina (version 1.1.2)[20] in conjunction with the graphical user interface AutoDockTools (**ADT**)[21] was used to perform the ensemble docking calculations. AutoDock Vina docking performances and accuracy are assured by a Lamarckian algorithm and an empirical binding free energy force field. The HIV-1 reverse transcriptase X-ray structure used for the experiment had the PDB code 3QIP.[22] The 3D structure was prepared using the Protein Preparation Wizard of the Maestro suite,[23] which assigns bond orders, adds hydrogen atoms, deletes water molecules and generates the appropriate protonation states. The 2D Sketcher tool of Maestro was used to build compounds **6a**, **6h**, **10a**, and **10b**. The ligands possible protonation and tautomeric states, as well as their geometry, were optimized through LigPrep, part of the Maestro suite. Afterwards, both the ligands and the receptor had to be converted to the pdbqt format. The latter is very similar to a standard pdb but it includes ′Q′ (partial charges) and ′T′ atom types. Each atom has one line, and special keywords are used if some are required to be flexible in the docking calculations. Preparing the structures involves ensuring that its atoms are assigned the correct atom types, adding Gasteiger charges if necessary, merging non-polar hydrogens, detecting aromatic carbons, and setting up the ′torsion tree' in the case of ligands. Therefore, the python scripts prepare_receptor4.py and prepare_ligand4.py, part of ADT, were employed applying default settings. However, ADT has no parameters for the charge of the two Mg^{2+} ions present in the binding site. Therefore, a partial charge of 1.4 was manually assigned to both of them in pdbqt file of the protein. After the preparation, the docking was performed using the default settings of Vina, setting the midpoint of the binding site as the center of the box. The length of the box was fixed at 22 Å for the X, Y and Z coordinates. The figures were generated using UCSF Chimera.[24]

Biology Experimental Section.

Expression and purification of recombinant HIV-1 RTs. His-tagged p66/p51 HIV-1 RT group M subtype B coded in a p6HRT-prot plasmid was expressed in *E. coli* strain M15.[25] Heterodimeric RT were expressed essentially and purified as described.[26] Briefly, *E. coli* containing the expression vector were grown to an optical density at 600 nm of 0.7 and induced with 1.7 mM isopropyl β-D-1-thiogalactopyranoside for 4 h. Protein purification was carried out with a BioLogic LP system (BioRad), using a combination of immobilized metal affinity and ion exchange chromatography. Cell pellets were re-suspended 1:2 volumes in lysis buffer (50 mM sodium phosphate buffer pH 7.8, containing 0.5 mg/ml lysozyme), incubated on ice for 20 min, and after adding NaCl to a final concentration of 0.3 M, were sonicated for four cycles of 60 seconds, one second on and one second off, and centrifuged at 30,000×g for 1 hour. The supernatant was loaded onto a Ni^{2+}-NTA-Sepharose GE (Healthcare Lifescience) column pre-equilibrated with loading buffer (50 mM sodium phosphate buffer pH 7.8, containing 0.3M NaCl, 10% glycerol, and 10 mM imidazole) and washed with buffer containing 50 mM sodium phosphate buffer pH 6.0, containing 0.3 M NaCl, 10% glycerol, and 80 mM imidazole. RT was eluted with an imidazole gradient (0.08 – 0.5 M) in wash buffer. Enzyme-containing fractions were pooled and diluted 1:1 with 50 mM sodium phosphate buffer pH 7.0, containing 10% glycerol and then loaded into a Hi-trap heparin HP GE (Healthcare Lifescience) pre-equilibrated with 10 column volumes of loading buffer (50 mM sodium phosphate buffer pH 7.0, containing 10% glycerol and 150 mM NaCl). The column was washed with loading buffer and the RT was eluted with Elute Buffer 2 (50 mM Sodium Phosphate pH 7.0, 10% glycerol, 1M NaCl). Fractions were collected, and purified protein was dialyzed and stored in buffer containing 50 mM Tris-HCl pH 7.0, 25 mM NaCl, 1mM EDTA, and 50% glycerol. Catalytic activities and protein concentrations were determined. Enzyme-containing fractions were pooled and aliquots were stored at −80 °C.

Site directed mutagenesis. Amino acid substitutions were introduced into the p66 HIV-1 RT subunit of a HIV-1 RT using a QuikChange mutagenesis kit, following the manufacturer's instructions (Agilent Technologies Inc., Santa Clara, CA).

RNase H polymerase-independent cleavage assay. The HIV- RT was purified as described[27] and the HIV-1 RT-associated RNase H activity was measured as described.[28] Briefly in 100 µL reaction volume containing 50 mM Tris-HCl buffer pH 7.8, 6 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 80 mM KCl, 0.25 µM hybrid RNA/DNA 5'-GAUCUGAGCCUGGGAGCU-Fluorescin-3', 5'-Dabcyl-AGCTCCCAGGCTCAGATC-3' and 20 ng of wt RT according to a linear range of dose-response curve. The reaction mixture was incubated for 1 hour at 37 °C in a multilabel counter plate reader Victor 3 (Perkin Elmer model 1420-051) and product were quantified with at 490/528 nm (excitation/emission wavelength). Data were analyzed as described.[29] Mean ± standard deviation of IC_{50} values were determined and p values were calculated between IC_{50} value against the wt and IC_{50} value against the mutants by paired, two-tailed t tests using GraphPad Prism 6.01 software (GraphPad Software, Inc.; San Diego, CA, USA). Figures were made with GraphPad Prism 6 version 6.01.

Expression and purification of recombinant INs and LEDGFs. Recombinant 6xHis tagged WT IN and LEDGF proteins were expressed in *E. coli* BL21(DE3) form an expression vector pKB-IN-6H encoding an IN from HIV-1 subtype B NL4-3 and pFT-1-LEDGF encoding 6His-LEDGF.[30] Briefly, His-IN was purified by loading the ammonium sulfate precipitate of cell lysate onto a Ni^{2+}-NTA-Sepharose column and eluted with an imidazole gradient (0–500 mM) in a HEPES buffer (50 mM, pH 7.5) containing 1M NaCl, 7.5 mM CHAPS and 2 mM β-mercaptoethanol. Fractions containing protein were pooled and stored in glycerol (10%) at -80 °C. His-LEDGF was purified by loading the ammonium sulfate precipitate of cell-lysate onto a heparin column and eluting with NaCl gradient (0.2- 1 M) in purification buffer Peak fractions were pooled, loaded onto a Superdex 200GL column, and eluted with purification buffer. Fractions containing LEDGF were pooled and stored in glycerol (10%) at -80 °C.

HTRF LEDGF-dependent IN assays. This assay quantifies the inhibition of 3'-processing and strand-transfer IN reactions in the presence of recombinant LEDGF/p75 protein. 50 nM IN was pre-incubated with increasing concentration of compounds for 1 hour at room temperature in reaction buffer containing 20 mM HEPES pH 7.5, 1 mM DTT, 1% glycerol, 20 mM $MgCl_2$, 0.05% Brij-35 and 0.1 mg/ml BSA. DNA donor substrate, DNA acceptor substrate and 50 nM LEDGF/p75 protein were added and incubated at 37 °C for 90 minutes. After the incubation, 4 nM of Europium-Streptavidine was added to the reaction mixture and the HTRF signal was recorded using a Perkin Elmer Victor 3 plate reader using an excitation wavelength a 314 nm and 668 and 620 nm wavelength filters of acceptor and donor substrates emission, respectively.[31]

Cellular assays. HeLa-CD4-LTR-β-gal cells were maintained in DMEM supplemented with 10% foetal calf serum (Eurobio scientific) and 1 mg/mL Geneticin™ (G418 sulfate from ThermoFisher Scientific). Antiviral activity of compounds was determined according to the procedure described previously[32] using native HIV particles produced from H9-Laï cells. Briefly, 96-well pates were prepared 24 hours before infection with 10,000 cells per well. Serial dilution of drugs or an equivalent amount of solvent (DMSO) was added to the cell culture at the time of infection. After 24 hours, cells were lysed by addition of the β-galactosidase activity buffer [50 mM Tris-HCl pH 8, 100 mM β-mercaptoethanol, 0.05% Triton X-100, 5 mM 4-Methyl-Umbelliferyl-βD-Galactopyranoside (4-MUG, Sigma)]. HIV replication was assessed by measuring fluorescence using a CytoFluor™ II plate reader (PerSeptive Biosystems, $\lambda_{ex/em}$=360/460nm). In parallel, cytotoxicity was determined in the same cell line (HeLa-CD4-LTR-β-gal) using the CellTiter 96® AQueous One Solution Cell Proliferation Assay (MTS, Promega). Cells were incubated for 24 hours with serial dilution of the drugs or an equivalent amount of DMSO before the addition of 10µl of the CellTiter reagent. The plate was further incubated for 2 hours before reading the optical density at 490nm using an Apollo 1 LB-911 plate reader (Berthod Technologies). The EC_{50}, CC_{50} and standard deviation were calculated from the mean of at least 3 independent determinations using Prism 6.07 (GraphPad).

General procedure for human serum stability assay. The reaction solutions were prepared by mixing 10 µL water solution (50% DMSO) of the tested compounds (5 mM) and 90 µL human serum (at concentration 0.5 mM, 90% serum, 5% DMSO) and incubated at 37 °C. 20 µL aliquots were collected at different times (0, 15, 30 min, 60 min, 120 min and 180 min), subjected to precipitation by addition of 40 µL ACN/ 0.1% TFA solution, and then centrifuged (12 000 rpm, 15 min, 4 °C). The supernatant was recovered and analyzed by ESI-RP-HPLC (Shimadzu LC-MS 2020) equipped with a Phenomenex Kinetex column (C18, 150 mm × 4.6 mm, 2.6 µm, 100 Å) with a flow rate of 0.5 mL/min, using a linear elution gradient from 10% to 90% ACN (0.1% TFA) in water (0.1% TFA) in 20 min.

Table S1. Cytotoxicity, antiviral, and anti-IN activities of compounds **3**,**4**, **6a,h, 7a,h, 10a,b** and **11a,b**.

Cpd	Cellular activities			Activity in enzyme assay, IN (ST)[d]	
	EC_{50}[a]	CC_{50}[b]	SI[c]	IC_{50}[e]	Selectivity[f]
6a	4.01 ± 0.3	6.08± 0.65	1.5	75 ± 4	5.2
7a	>100	>100	-	-	
6h	17.9 ± 2.1	>200	>11.2	>100	>10.6
7h	>100	>100	-		
10a	41 ± 11	67± 11	1.6	>100	>18.5
11a	>100	58± 11			
10b	18.6 ± 2.0	>200	>10.8	>100	>5.6
11b	>100	>100			
3[g]	2.9 ± 0.5	68 ± 10	23.4	>100	>13.7
4	0.024 ± 0.005	>100	>4166	0.054 ± 0.003	

[a]Effective concentration 50% (μM). [b]Cytotoxic concentration 50% (μM). [c]SI = CC_{50}/EC_{50}. [d]Experiments performed against HIV-1 IN ST activity. [e]Inhibitory concentration 50% (μM) determined from dose response curves. [f]Selectivity for RT associated RNase H inhibition over IN inhibition (IC_{50} for ST/IC_{50} for RNase H). [g]See ref. 33.

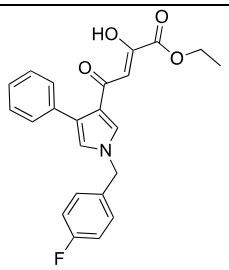
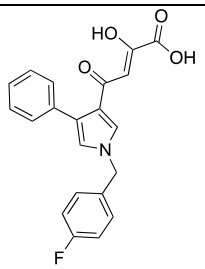
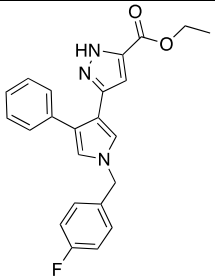
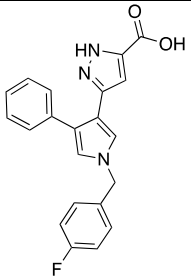
Table S2. Effect of selected non-DKA pyrrolyl derivatives on RT-associated RNase H activity of mutated HIV-1 RTs

Cpd		wt	R448A	K451A	N474A	Q475A	Y501A	W535A	K540A
3	IC_{50}[a]	20.1 ± 0.9	28.6 ± 3.0	19.7 ± 3.5	>100	100	>100	>100	23.2 ± 1.3
	P value		0.0605	0.8915	0.0078	0.0078	0.0030	0.0078	0.1043
			ns	ns	**	**	**	**	ns
	Fold[b]		1.4	1.0	>5.0	5.0	>5.0	>5.0	1.2
6a	IC_{50}[a]	14.3 ± 2.3	67.2 ± 3.0	16.7 ± 2.4	>100	>100	>100	>100	30.4 ± 2.7
	P value		0.0026	0.4235	>0.0001	>0.0001	>0.0001	>0.0001	0.0237
			**	ns	***	***	***	***	*
	Fold[b]		4.7	1.2	7.0	7.0	7.0	7.0	2.1
6h	IC_{50}[a]	9.4 ± 0.7	72.4 ± 7.0	55.6 ± 4.9	>100	>100	>100	>100	60.0 ± 0.7
	P value		0.01	0.004	>0.0001	>0.0001	>0.0001	>0.0001	0.0002
			**	**	****	****	****	****	***
	Fold[b]		7.65	5.89	10.60	10.60	10.60	10.60	6.36
10a	IC_{50}[a]	5.4 ± 1.2	29.3 ± 1.3	13.6 ± 1.3	>100	>100	>100	>100	17.2 ± 1.3
	P value		0.0029	0.0228	>0.0001	>0.0001	>0.0001	>0.0001	0.0109
			**	*	****	****	****	****	*
	Fold[b]		5.4	2.5	>8.8	>8.8	>8.8	>8.8	3.2
10b	IC_{50}[a]	17.8 ± 1.2	89.8 ± 1.6	69.3 ± 1.7	>100	>100	>100	>100	73.4 ± 2.1

P value	0.0004	0.0008	>0.0001	>0.0001	>0.0001	>0.0001	0.0017
	***	***	****	****	****	****	**
Fold[b]	5.0	3.9	5.6	5.6	5.6	5.6	4.1

The table reports the mean and standard deviation of three independent experiments. [a]Concentration required to inhibit HIV-1 RT-associated RNase H activity by 50% obtained by three independent experiments (reported as mean ± standard deviation). p value < 0.05 (*); p value < 0.01 (**); p value < 0.001 (***); p value < 0.0001(****). [b]Fold increase in IC_{50} compared to WT RT.

Table S3. ESI-MS characterizations of **1**, **1-COOH**, **6a** and **7a** at different time intervals of incubation.

Cmpd	Structure	M + H^+ (Calc.)	m/z[a]					
			0 min	15 min	30 min	60 min	120 min	180 min
1		394.4	394.1	394.1 294.1[b]	394.1 294.1	394.1 294.1	394.1 294.1	394.10 294.10
1-COOH		366.4	366.1 294.1	366.1 294.1	366.1 294.1	366.1 294.1	294.1	294.1
6a		390.4	390.4	390.4	390.4	390.4	390.4	390.4
7a		362.4	362.4	362.4	362.4	362.4	362.4	362.4

[a]Found ESI-MS, M + H^+

[b]Retro-Claisen Adduct

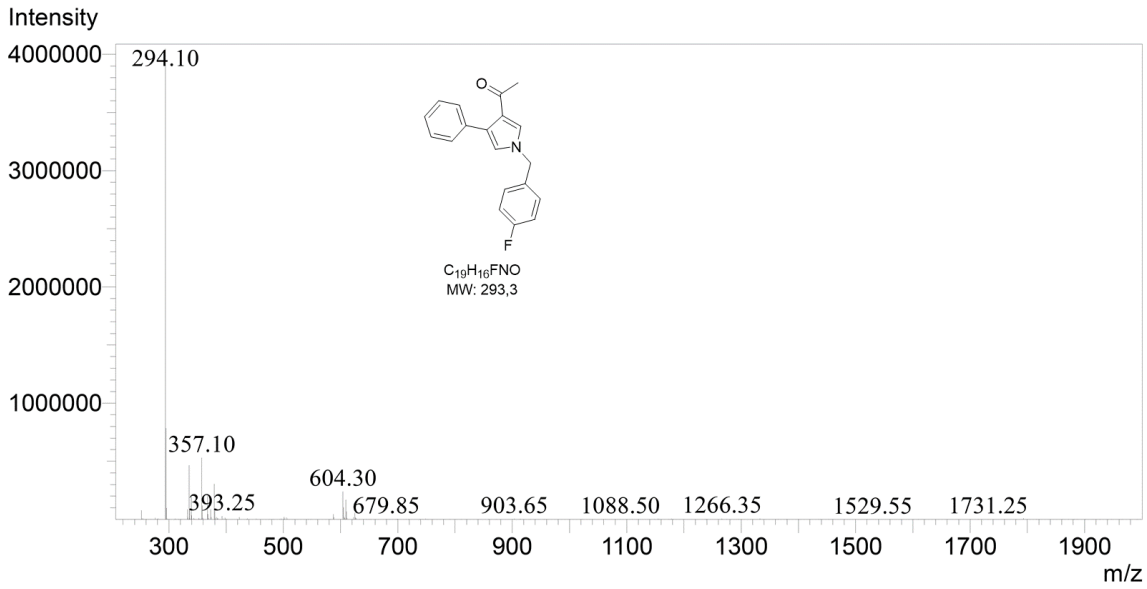


Figure S1. Mass spectrum and hypothesized structure of the main metabolite identified during the human serum stability assessment **1-COOH**.

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