

SUPPORTING INFORMATION

Encoded library technology as a source of hits for the discovery and lead optimization of a potent and selective class of direct inhibitors of *Mycobacterium tuberculosis* InhA

Lourdes Encinas,[§] Heather O'Keefe,[†] Margarete Neu,[¶] Modesto J. Remuiñán,[§] Amish A. Patel,[†] Ana Guardia,[§] Christopher P. Davie,[†] Natalia Pérez-Macías,^{||} Hongfang Yang,[†] Maire A Convery,[¶] Jeff A. Messer,[†] Esther Pérez-Herrán,[§] Paolo A. Centrella,^{††} Daniel Álvarez-Gómez,[§] Matthew A. Clark,^{††} Sophie Huss,[§] Gary K. O'Donovan,[†] Fátima Ortega-Muro,[§] William McDowell,[⊥] Pablo Castañeda,[§] Christopher C. Arico-Muendel,[†] Stane Pajk,[#] Joaquín Rullás,[§] Iñigo Angulo-Barturen,[§] Emilio Álvarez-Ruiz,[‡] Alfonso Mendoza-Losana,[§] Lluís Ballell Pages,[§] Julia Castro-Pichel*[§] and Ghotas Evindar*[†]

This section provides information on additional tables, schemes and figures mentioned in the main text. It also includes a detailed description of the preparative details and spectroscopic data for the rest of compounds and protocols and experimental procedures of some assays.

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Supplementary Tables, Schemes and Figures

Characterization of the major metabolites of compound 7 in mouse and human hepatocytes.

All samples were examined by ACD (Advanced Chemistry Development, Toronto, Ontario) IntelliXtract software for potential metabolites. Major metabolites were *N*-deacylation (*N*-deethylation most abundant metabolite M-A), mono-oxidation, and dehydrogenation. All typical and atypical possible metabolites were looked for but not detected.

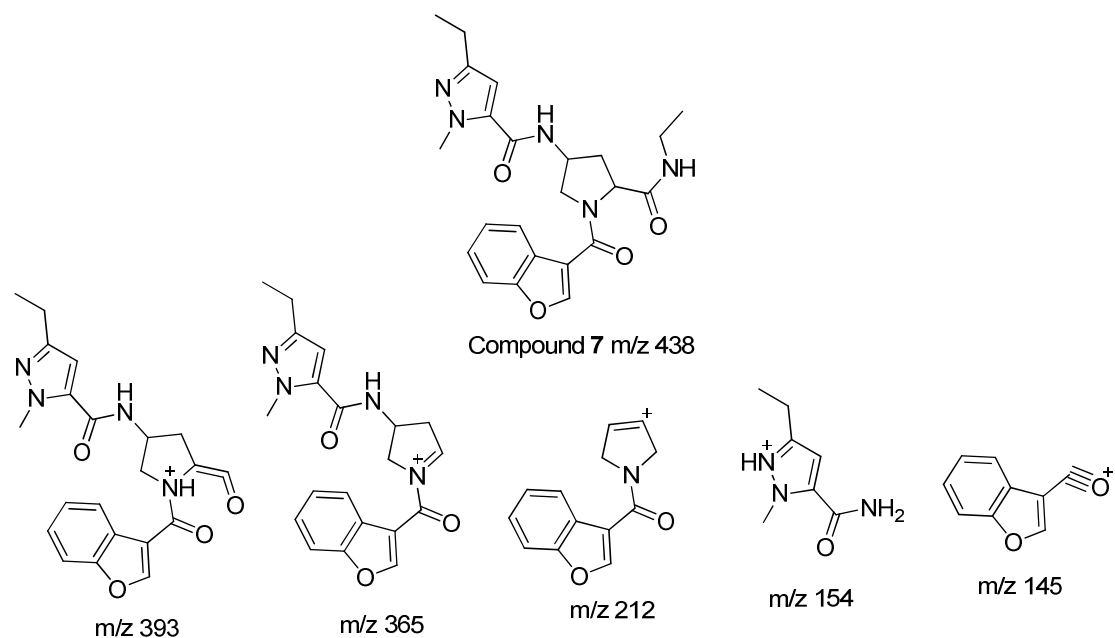
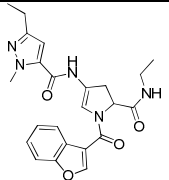
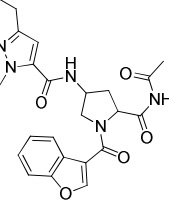
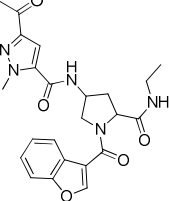
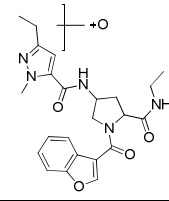
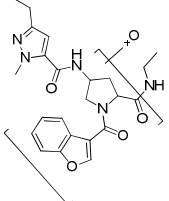
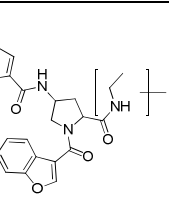
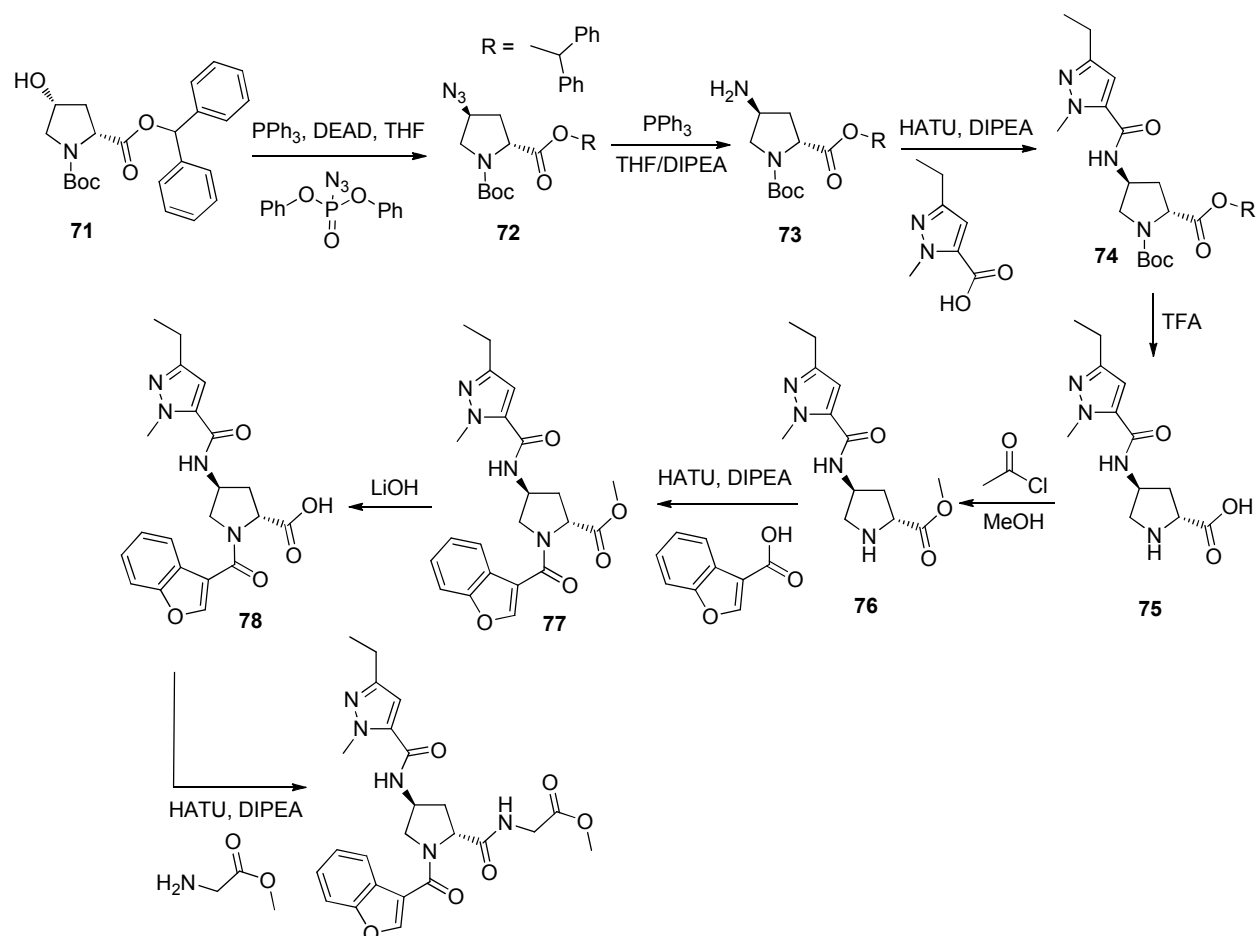


Figure S1. Proposed fragmentation of compound 7 in positive ion mode

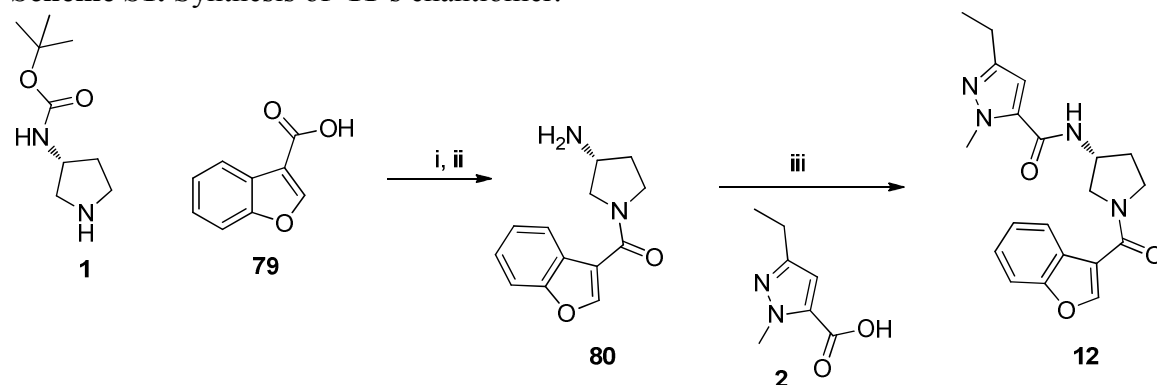
Table S1. Metabolites of 7 in mouse and human hepatocytes

Structure	t _r (min)	m/z	Compds species	Common Fragments
	5.3	438	Compound 7	393, 365, 212, 154, 145
	4.9	410	M-A, mouse and human	393, 365, 212, 154, 145
	4.8	424	M-B, mouse and human	379, 351, 212, 140
	4.1	436	M-C, mouse and human	395

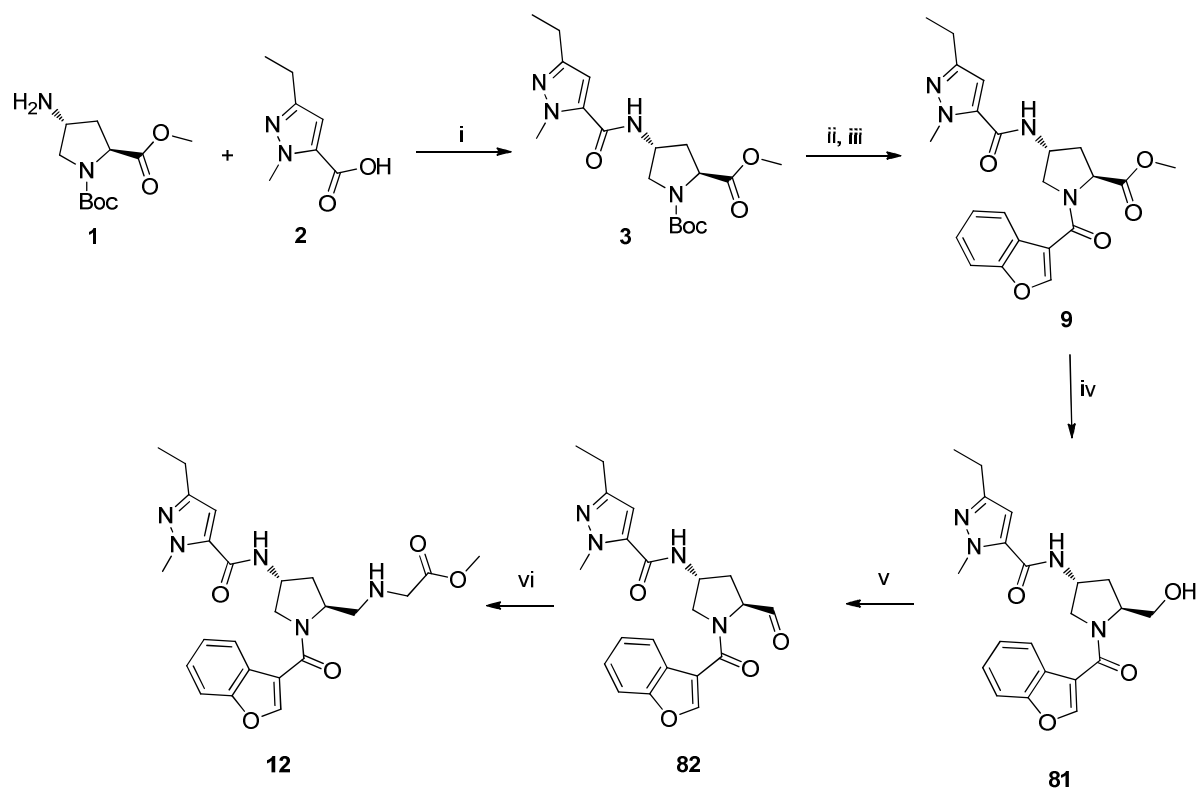
	4.4	436	M-D, mouse and human	391, 210
	4.1	452	M-E, mouse and human	393
	5.1	452	M-F, human	407, 379, 212, 168
	4.3	454	M-G, mouse and human	409, 381, 170, 152
	4.5	454	M-H, human	409, 381, 154
	4.8	454	M-I, mouse	393



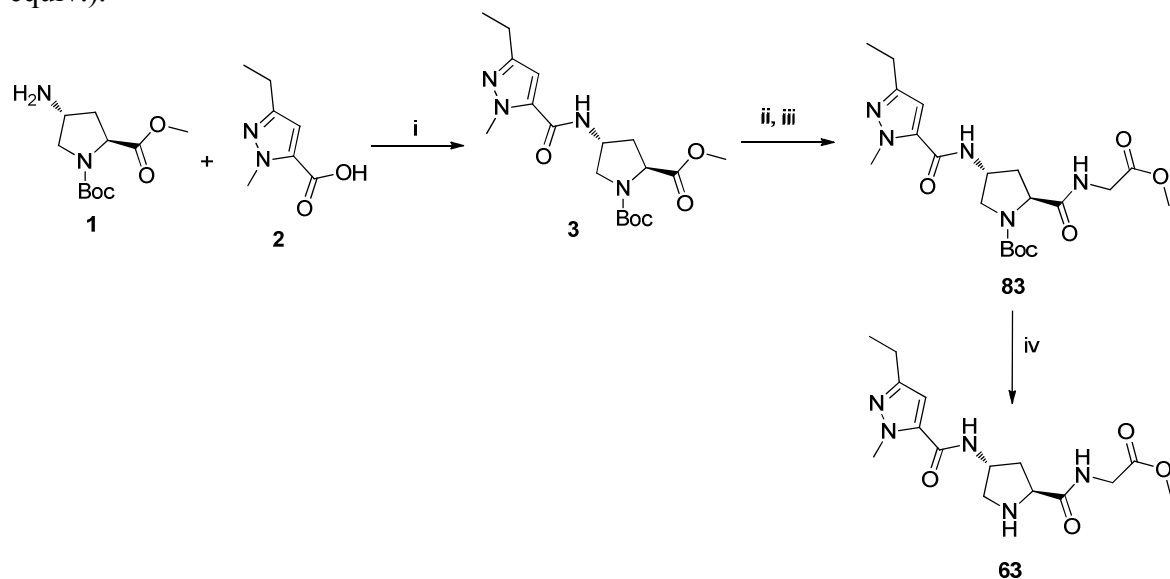
Scheme S1. Synthesis of **11**'s enantiomer.



Scheme S2. Synthesis of **12**.^a Reagents and conditions: (i) 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.2 equiv.), *N,N*-diisopropylethylamine (DIPEA, 3.0 equiv.), *N,N*-dimethylformamide; (ii) 20% trifluoroacetic acid in dichloromethane; (iii) carboxylic acid (RCOOH, 1.2 equiv.), HATU (1.2 equiv.), DIPEA (3.0 equiv.), *N,N*-dimethylformamide (DMF).

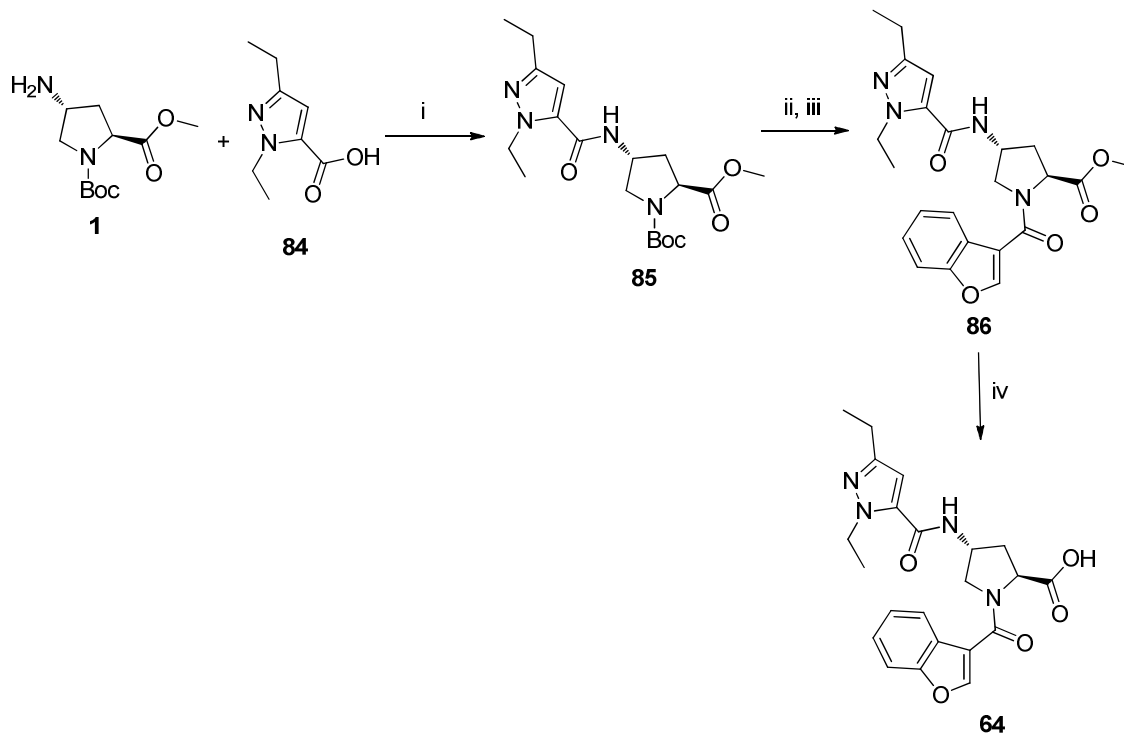


Scheme S3. Synthesis of **12**^a Reagents and conditions: (i) 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.2 equiv.), *N,N*-diisopropylethylamine (DIPEA, 3.0 equiv.), *N,N*-dimethylformamide; (ii) 20% trifluoroacetic acid in dichloromethane; (iii) carboxylic acid (benzofuran-3-carboxylic acid, 1.2 equiv.), HATU (1.2 equiv.), DIPEA (3.0 equiv.), *N,N*-dimethylformamide; (iv) LiAlH₄ (1.7 equiv.), Et₂O; (v) Dess-Martin periodinane (1 equiv.), NaHCO₃ (3.6 equiv.), CH₂Cl₂; (vi) sodium triacetoxyborohydride (2.0 equiv.), glycine methyl ester hydrochloride (1.0 equiv.), Et₃N (1.0 equiv.).



Scheme S4. Synthesis of **64**^a Reagents and conditions: (i) 2-(1*H*-7-azabenzotriazol-1-yl)-

1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.2 equiv.), *N,N*-diisopropylethylamine (DIPEA, 3.0 equiv.), *N,N*-dimethylformamide; (ii) lithium hydroxide (LiOH, 3.0 equiv); (iii) 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.2 equiv.), *N,N*-diisopropylethylamine (DIPEA, 3.0 equiv.); ethylamine hydrochloride (2.0 equiv.); (iv) 20% trifluoroacetic acid in dichloromethane.



Scheme S5. Synthesis of **64**^a Reagents and conditions: (i) 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU, 1.2 equiv.), *N,N*-diisopropylethylamine (DIPEA, 3.0 equiv.), *N,N*-dimethylformamide; (iii) 20% trifluoroacetic acid in dichloromethane; (iii) carboxylic acid (benzofuran-3-carboxylic acid, 1.2 equiv.), HATU (1.2 equiv.), DIPEA (3.0 equiv.), *N,N*-dimethylformamide (DMF), (iv) lithium hydroxide (LiOH, 3.0 equiv).

Table S2. SAR of the pyrazole Derivatives

Comp.	R ₂	InhA IC ₅₀ [μM]	<i>MtbH37Rv</i> MIC ₉₀ [μM]

87		0.90	>31
88		0.25	>31
89		0.33	>31
90		0.42	>31
91		0.46	>31
92		>1	>31
93		>1	>31
94		0.078	31.25

Table S3. SAR around the benzofuran position

Comp.	R ₃	InhA IC ₅₀ [μM]	<i>MtbH37Rv</i> MIC ₉₀ [μM]
7		0.034	8
95		0.007	4
96		0.195	31.25

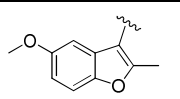
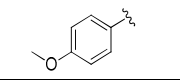
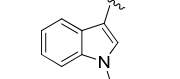
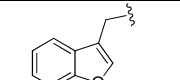
97		0.445	>31
98		0.855	>31
99		>1	>31
100		>1	>31

Table S4. SAR around the benzofuran position

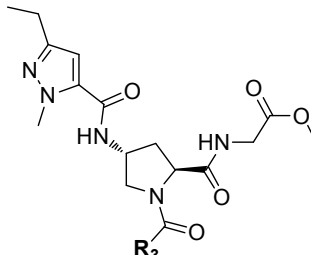
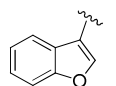
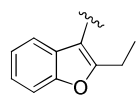
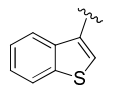
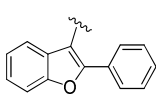
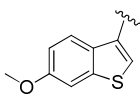
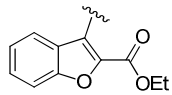
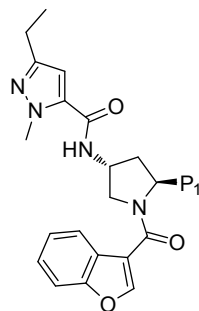
				
Comp.	R ₃	chromlogD	InhA IC ₅₀ [μM]	<i>MtbH37Rv</i> MIC ₉₀ [μM]
11		2.96	0.005	0.5
101		3.71	0.005	0.7
102		3.17	0.029	1
103		4.52	0.003	1.5
104		3.40	0.823	>31
105		4.24	>1	>31

Table S5. SAR around the P1 position



Comp.	P ₁	IC ₅₀ [μM]	MIC [μM]	Mouse Blood stability					
				0	15	30	60	120	t _{1/2} (min)
11		0.005	0.5	100.0	26.9	8.5	0.6	0.3	<15
106		0.014	31.1	-	-	-	-	-	-
107		0.026	0.24	100.0	0.5	0.0	0.0	0.0	<15
108		0.018	2	100.0	13.1	1.9	0.0	0.0	<15
109		0.009	0.50	100.0	-	0.2	0.0	0.0	<30
110		0.002	2	100.0	0.0	0.0	0.0	0.0	<30
111		0.007	2	-	-	-	-	-	-
112		0.011	1	100.0	0.0	0.0	0.0	0.0	<30
113		0.007	1	-	-	-	-	-	-
114		0.018	4	-	-	-	-	-	-
115		0.022	8	-	-	-	-	-	-
116		0.008	2	-	-	-	-	-	-
45		0.005	1	100.0	97.6	98.6	93.1	94.1	>120

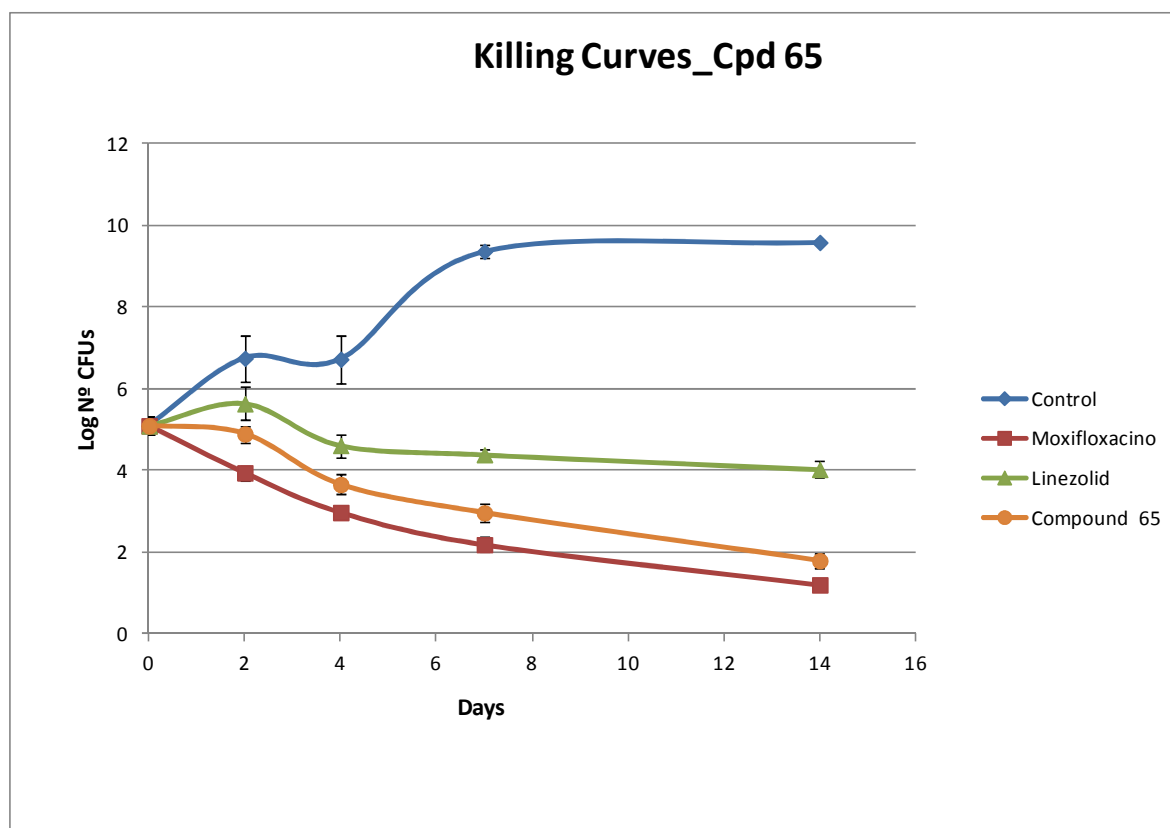
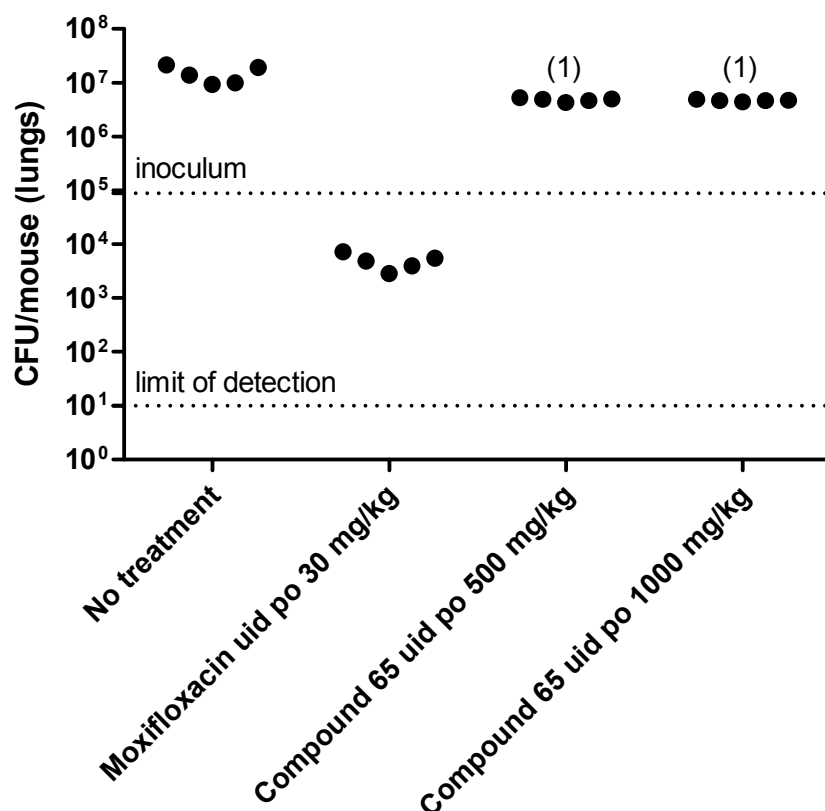


Figure S2. *M. tuberculosis* killing kinetics of **65** at 20xMIC. The number of cfus were quantified after incubation with the different compounds at different times in 10 mL of 7H9 10% ADC 0,05% Tween 80 medium containing 5 μ M of **1**, 7.5 μ M of **2**, 9.4 μ g/mL of Linezolid, 1.2 μ g/mL of Moxifloxacin and also for internal growth control. The mean and the standard deviations of at triplicate cultures of each point are shown.

Figure S3. Antitubercular efficacy of **65** in a murine acute model of *M. tuberculosis* infection. Mice were infected with 100.000 cfu and lung homogenates were obtained 9 days after infection (n=5 mice/group for all groups). Every dot represents a mouse. Moxifloxacin was used as a positive control in the assay.



(1) Minimum values

Chemistry: complete experimental part

***N*-((3*R*,5*S*)-1-(Benzofuran-5-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (6).** Compound (6) was synthesized from Boc-deprotection of (2*S*,4*R*)-*tert*-butyl 4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)-2-(ethylcarbamoyl)pyrrolidine-1-carboxylate (4) using the protocol described in the general **method C** follow up by coupling with benzofuran-5-carboxylic acid using the procedure described in the general **method A**. The reaction mixture was concentrated in *vacuo* and the residue was purified by preparative HPLC to afford the title compound (78 mg, 53% yield). MS (ESI) m/z $[M+H]^+$ = 438.0.

***N*-((3*R*,5*S*)-1-(Benzo[*b*]thiophene-5-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (8).** The title compound was prepared as described in 7 synthesis. After preparative HPLC purification the reaction afforded the title compound (67 mg, 47% yield). MS (ESI) m/z $[M+H]^+$ = 453.9.

(2*S*,4*R*)-Methyl 1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxylate (9). Compound (9) was synthesized from (2*S*,4*R*)-1-*tert*-butyl 2-methyl 4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-1,2-dicarboxylate (3) using the protocol described in the general **method C** follow up by coupling with benzofuran-5-carboxylic acid using the procedure described in the general **method A**. The reaction mixture was concentrated in *vacuo* and the residue was purified by preparative HPLC to afford the title compound (390 mg, 99% yield). MS (ESI) m/z $[M+H]^+$ = 425.1; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.59 (s, 1H), 8.56 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* =

8.2 Hz, 1H), 7.37 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.31 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.63 (s, 1H), 4.73 (t, $J = 6.8$ Hz, 1H), 4.58 (m, 1H), 4.12 (dd, $J = 10.4, 6.0$ Hz, 1H), 3.89 (s, 3H), 3.72 (m, 1H), 3.67 (s, 3H), 3.47 (m, 2H), 2.36 (m, 1H), 2.19 (m, 1H), 1.11 (t, $J = 7.2$, 3H).

(2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylic acid (10). Compound **(10)** was synthesized from saponification of (2S,4R)-methyl 1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylate (**9**) using the protocol described in the general **method B**. The reaction mixture was concentrated in *vacuo* and the residue was purified by preparative HPLC to afford the title compound (280 mg, 95% yield). MS (ESI) m/z $[M+H]^+ = 411.1$; ^1H NMR (400 MHz, DMSO- d_6): about 84:16 mixture of rotamers, major rotamer description; δ 12.71 (s, 1H), 8.56 (s, 1H), 8.54 (d, $J = 7.6$ Hz, 1H), 7.96 (m, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.42-7.29 (m, 2H), 6.64 (s, 1H), 4.69-4.54 (m, 2H), 4.15 (m, 1H), 3.91 (s, 3H), 3.73-3.70 (m, 1H), 2.54-2.46 (m, 2H), 2.43-2.31 (m, 1H), 2.27-2.14 (m, 1H), 1.15-1.11 (m, 3H).

(R)-N-(1-(benzofuran-3-carbonyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (11). The title compound was synthesized from **80** using the protocol described in the general **method A** (see **Scheme S2**.) After preparative HPLC purification (XBridge-30, BASIC_10-100, 35 ml/min, 10 mM NH_4HCO_3 -ACN, 20 min) the reaction afforded the title compound (50 mg, 32% yield). MS (ESI) m/z $[M+H]^+ = 367$; ^1H NMR (400 MHz, DMSO- d_6): δ 8.54-8.50 (m, 2H), 8.01 (m, 1H), 7.66 (d, $J = 7.9$ Hz, 1H), 7.41-7.29 (m, 2H), 6.72-6.68 (m, 1H), 4.49 (m, 1H), 4.04-3.55 (m, 7H), 3.36-3.23 (m, 2H), 2.23-1.94 (m, 2H), 1.20-1.10 (m, 3H).

methyl 2-((((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidin-2-yl)methyl)amino)acetate 2,2,2-trifluoroacetate (12). The title compound was prepared using the protocol described in **Scheme S3**. After preparative HPLC purification (SunFire-19, 17 ml/min, 20 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (32 mg, 30% yield). MS (ESI) m/z $[M+H]^+ = 468$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.30 (br s, 1H), 9.05 (br s, 1H), 8.56 (s, 1H), 8.57 (d, $J = 4.5$ Hz, 1H), 8.00 (d, $J = 7.18$ Hz, 1H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.39 (m, 2H), 6.59 (s, 1H), 4.79-4.70 (m, 1H), 4.59-4.52 (m, 1H), 4.16-4.03 (m, 3H), 3.90 (s, 3H), 3.77 (s, 3H), 3.42-3.17 (m, 3H), 2.54-2.45 (m, 2H), 2.28-2.07 (m, 2H), 1.13 (t, $J = 7.6$ Hz, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-carbamoylpyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (13). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 20 min) the reaction afforded the title compound (40 mg, 71% yield). MS (ESI) m/z $[M+H]^+ = 410$, ^1H NMR (400 MHz, DMSO- d_6): about 81:19 mixture of rotamers, major rotamer description; δ 8.57-8.49 (m, 2H), 7.99 (d, $J = 7.6$ Hz, 1H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.55-7.47 (br s, 1H), 7.40-7.29 (m, 2H), 7.05 (br s, 1H), 6.63 (s, 1H), 4.76-4.47 (m, 2H), 4.16-4.09 (m, 1H), 3.71-3.66 (m, 1H), 3.91 (s, 3H), 2.54-2.46 (m, 2H), 2.36-2.22 (m, 1H), 2.17-2.06 (m, 1H), 1.16-1.10 (m, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-(diethylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (14). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100 % water in acetonitrile 0.1% TFA, 15 ml/min, 20 min) the reaction afforded the title compound (41 mg, 58% yield). MS (ESI) m/z $[M+H]^+ = 466$, ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$): δ 8.46-8.33 (m, 2H), 7.92 (br s, 1H), 7.63-7.60 (m, 1H), 7.40-7.28 (m, 2H), 6.61 (s, 1H),

5.16 (m, 1H), 4.65 (m, 1H), 4.05 (m, 1H), 3.92 (s, 3H), 3.75-3.70 (m, 1H), 3.46 (m, 2H), 3.21-3.09 (m, 2H), 2.57-2.51 (m, 2H), 2.45-2.33 (m, 1H), 2.14-2.06 (m, 1H), 1.37-0.97 (m, 9H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2,2,2-trifluoroethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (15).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-19, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH₄HCO₃, 20 min) the reaction afforded the title compound (25 mg, 40% yield). MS (ESI) *m/z* [M+H]⁺ = 492; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.74-8.68 (m, 1H), 8.56 (s, 1H), 8.54 (d, *J* = 6.8 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.41-7.35 (m, 1H), 7.35 -7.28 (m, 1H), 6.63 (s, 1H), 4.71 (m, 1H), 4.57 (m, 1H), 4.15 (m, 1H), 3.96 (m, 2H), 3.92 (s, 3H), 3.72 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.13 (t, *J* = 7.6 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(propylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (16).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100 % water in acetonitrile 0.1% TFA, 15 ml/min, 20 min) the reaction afforded the title compound (22 mg, 40% yield). MS (ESI) *m/z* [M+H]⁺ = 452; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.39-8.28 (m, 2H), 7.96-7.93 (m, 1H), 7.81-7.75 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.41-7.29 (m, 2H), 6.62 (s, 1H), 4.73-4.69 (m, 1H), 4.63-4.56 (m, 1H), 4.13-4.04 (m, 1H), 3.94 (s, 3H), 3.72-3.66 (m, 1H), 3.11-2.96 (m, 2H), 2.58-2.49 (m, 2H), 2.34-2.15 (m, 2H), 1.54-1.30 (m, 2H), 1.17 (t, *J* = 7.6 Hz, 3H), 0.90-0.75 (m, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2-methoxyethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (17).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1 % TFA, 20 min) the reaction afforded the title compound (62 mg, 85% yield). MS (ESI) *m/z* [M+H]⁺ = 468; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.33-8.31 (m, 2H), 7.95-7.87 (m, 2H), 7.64-7.61 (m, 1H), 7.41-7.29 (m, 2H), 6.62 (s, 1H), 4.73 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.64-4.53 (m, 1H), 4.12-4.01 (m, 1H), 3.94 (s, 3H), 3.72-3.67 (m, 1H), 3.52-3.20 (m, 4H), 3.24 (s, 3H), 2.58-2.49 (m, 2H), 2.36-2.15 (m, 2H), 1.17 (t, *J* = 7.5 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2-(dimethylamino)ethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide 2,2,2-trifluoroacetate (18).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 20 min) the reaction afforded the title compound (48 mg, 66% yield). MS (ESI) *m/z* [M+H]⁺ = 481; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 9.20 (br s, 1H), 8.42-8.35 (m, 2H), 8.21-8.16 (m, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.42-7.30 (m, 2H), 6.61 (s, 1H), 4.72-4.58 (m, 2H), 4.16-4.07 (m, 1H), 3.93 (s, 3H), 3.76-3.71 (m, 1H), 3.51-3.41 (m, 2H), 3.23-3.07 (m, 2H), 2.83 (s, 6H), 2.57-2.47 (m, 2H), 2.44-2.17 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (11). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 20 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (249 mg, 56% yield). MS (ESI) *m/z* [M+H]⁺ = 482; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.40-8.28 (m, 3H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.42-7.29 (m, 2H), 6.62 (s, 1H), 4.83-4.79 (m, 1H), 4.66-4.55 (m, 1H), 4.13-4.02

(m, 1H), 3.94 (s, 3H), 3.90-3.87 (m, 2H), 3.75-3.69 (m, 1H), 3.66 (s, 3H), 2.58-2.49 (m, 2H), 2.39-2.22 (m, 2H), 1.17 (t, $J = 7.6$ Hz, 3H).

ethyl 3-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)propanoate (20). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 21 min) the reaction afforded the title compound (44 mg, 59% yield). MS (ESI) m/z $[M+H]^+ = 495$; 1H NMR (400 MHz, DMSO- d_6): δ 8.32-8.30 (m, 2H), 7.94-7.87 (m, 2H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.40-7.28 (m, 2H), 6.61 (s, 1H), 4.69 (dd, $J = 8.2, 4.8$ Hz, 1H), 4.60-4.52 (m, 1H), 4.09-4.02 (m, 3H), 3.93 (s, 3H), 3.71-3.66 (m, 1H), 3.31 (m, 2H), 2.56-2.50 (m, 2H), 2.45-2.13 (m, 4H), 1.20-1.11 (m, 6H).

***N*-((3*R*,5*S*)-5-((2-acetamidoethyl)carbamoyl)-1-(benzofuran-3-carbonyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (21).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (62 mg, 79% yield). MS (ESI) m/z $[M+H]^+ = 510$; 1H NMR (400 MHz, DMSO- d_6): about 81:19 mixture of rotamers, major rotamer description; δ 8.56-8.53 (m, 2H), 8.09 (br s, 1H), 8.02-7.99 (m, 1H), 7.85-7.78 (m, 1H), 7.69-7.65 (m, 1H), 7.41-7.29 (m, 2H), 6.64 (s, 1H), 4.65-4.54 (m, 2H), 4.18-4.11 (m, 1H), 3.92 (s, 3H), 3.76-3.70 (m, 1H), 3.20-2.85 (m, 4H), 2.58-2.49 (m, 2H), 2.29-2.09 (m, 2H), 1.77 (s, 3H), 1.17-1.12 (m, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2-oxotetrahydrofuran-3-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (22).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 21 min) the reaction afforded the title compound (44 mg, 60% yield). MS (ESI) m/z $[M+H]^+ = 494$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.47-8.31 (m, 3H), 7.97-7.93 (m, 1H), 7.64-7.61 (m, 1H), 7.42-7.29 (m, 2H), 6.62 (s, 1H), 4.81-4.72 (m, 1H), 4.63-4.47 (m, 2H), 4.38-4.16 (m, 2H), 4.15-4.02 (m, 1H), 3.94 (s, 3H), 3.77-3.68 (m, 2H), 2.58-2.49 (m, 2H), 2.43-2.05 (m, 3H), 1.17 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(((tetrahydrofuran-2-yl)methyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (23).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 21 min) the reaction afforded the title compound (48 mg, 80% yield). MS (ESI) m/z $[M+H]^+ = 494$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.43-8.29 (m, 2H), 7.98-7.90 (m, 1H), 7.87-7.81 (m, 1H), 7.63-7.61 (m, 1H), 7.41-7.29 (m, 2H), 6.62 (s, 1H), 4.79-4.74 (m, 1H), 4.63-4.55 (m, 1H), 4.14-4.04 (m, 1H), 3.94 (s, 3H), 3.87-3.56 (m, 4H), 3.18-3.10 (m, 2H), 2.58-2.49 (m, 2H), 2.35-2.16 (m, 2H), 1.87-1.70 (m, 3H), 1.55-1.45 (m, 1H), 1.17 (t, $J = 7.5$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(cyclopentylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (24).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (45.6 mg, 74.5% yield). MS (ESI) m/z $[M+H]^+ = 478$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.28-8.23 (m, 2H), 7.91 (m, 1H), 7.64-7.60 (m, 2H), 7.40-7.30 (m, 2H), 6.62 (s, 1H), 4.71-4.68 (m, 1H), 4.62-4.57 (m, 1H), 4.08-4.05 (m, 1H), 4.01-3.92 (m,

1H), 3.94 (s, 3H), 3.70-3.66 (m, 1H), 2.57-2.52 (m, 2H), 2.34-2.27 (m, 1H), 2.21-2.15 (m, 1H), 1.87-1.85 (m, 8H), 1.19 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(benzylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (25).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 21 min) the reaction afforded the title compound (34 mg, 45% yield). MS (ESI) m/z $[M+H]^+ = 500$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.34 (br s, 3H), 7.97 (m, 1H), 7.63 (d, $J = 8.2$ Hz 1H), 7.41-7.20 (m, 7H), 6.62 (s, 1H), 4.80 (dd, $J = 8.1, 5.0$ Hz, 1H), 4.60 (m, 1H), 4.30 (m, 2H), 4.12 (m, 1H), 3.93 (s, 3H), 3.74-3.68 (m, 1H), 2.57-2.50 (m, 2H), 2.40-2.19 (m, 1H), 1.16 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((4-(trifluoromethoxy)benzyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (26).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (39 mg, 52% yield). MS (ESI) m/z $[M+H]^+ = 478$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.39-8.26 (m, 3H), 7.94 (d, $J = 7.83$ Hz, 1H), 7.61 (d, $J = 8.07$ Hz, 1H), 7.40-7.29 (m, 4H), 7.24-7.20 (m, 2H), 6.61 (s, 1H), 4.81-4.78 (m, 1H), 4.67-4.59 (m, 1H), 4.39-4.27 (m, 2H), 4.15-4.07 (m, 1H), 3.93 (s, 3H), 3.74-3.70 (m, 1H), 2.56-2.49 (m, 2H), 2.41-2.30 (m, 1H), 2.27-2.21 (m, 1H), 1.17 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((4-(trifluoromethyl)benzyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (27).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 40 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (27 mg, 37.4% yield). MS (ESI) m/z $[M+H]^+ = 568$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.45-8.32 (m, 3H), 8.24 (s, 1H), 7.96 (d, $J = 7.34$ Hz, 1H), 7.64-7.57 (m, 3H), 7.48 (br s, 1H), 7.40 (t, $J = 7.82$ Hz, 1H), 7.33 (t, $J = 7.58$ Hz, 1H), 6.63 (s, 1H), 4.84-4.80 (m, 1H), 4.68-4.59 (m, 1H), 4.46-4.34 (m, 2H), 4.18-4.08 (m, 1H), 3.95 (s, 3H), 3.76-3.72 (m, 1H), 2.58-2.50 (m, 2H), 2.42-2.31 (m, 1H), 2.31-2.21 (m, 1H), 1.18 (t, $J = 7.6$ Hz, 3H).

(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-*N*-[(3,4-difluorophenyl)methyl]-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinamide (28). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 40-100 Water/ACN (0.1% TFA)) purification the reaction afforded the title compound (15 mg, 22% yield). MS (ESI) m/z $[M+H]^+ = 536$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.40-8.30 (m, 3H), 7.98 (d, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.43-7.23 (m, 4H), 7.03 (br s, 1H), 6.63 (s, 1H), 4.82-4.76 (m, 1H), 4.68-4.58 (m, 1H), 4.30 (br s, 2H), 4.17-4.09 (m, 1H), 3.95 (s, 3H), 3.78-3.70 (m, 1H), 2.55 (q, $J = 7.58$ Hz, 2H), 2.41-2.30 (m, 1H), 2.27-2.20 (m, 1H), 1.18 (t, $J = 7.58$ Hz, 3H).

(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*N*-[(5-methyl-2-pyrazinyl)methyl]-*L*-prolinamide (29). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 40-100% Water/ACN) purification the reaction afforded the title compound (32 mg, 30% yield). MS (ESI) m/z $[M+H]^+ = 516$; 1H NMR (400 MHz, DMSO- d_6): about 85:15 mixture of rotamers, major rotamer description; δ 8.80-8.71 (m, 1H), 8.58-8.51 (m,

2H), 8.30 (s, 1H), 8.00 (d, $J = 7.58$ Hz, 1H), 7.66 (d, 1H), 7.50-7.28 (m, 2H), 6.64 (s, 1H), 4.82-4.76 (m, 1H), 4.68-4.58 (m, 1H), 4.40 (br s, 2H), 4.20-4.14 (m, 1H), 3.92 (s, 3H), 3.74-3.72 (m, 1H), 3.20 (s, 2H), 2.45 (s, 3H), 2.41-2.30 (m, 1H), 2.20-2.14 (m, 1H), 1.13 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(pyridin-2-ylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (30).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 30 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (19 mg, 31% yield). MS (ESI) m/z $[M+H]^+ = 487$; 1H NMR (400 MHz, DMSO- d_6): about 90:10 mixture of rotamers, major rotamer description; δ 10.69 (br s, 1H), 8.61 (br s, 1H), 8.60 (d, 1H), 8.33 (d, $J = 3.8$ Hz, 1H), 8.10 (d, $J = 8.3$ Hz, 1H), 8.00 (d, $J = 7.3$ Hz, 1H), 7.81-7.71 (m, 1H), 7.68 (d, $J = 8.3$ Hz, 1H), 7.38-7.42 (m, 1H), 7.35-7.31 (m, 1H), 8.00 (dd, $J = 6.4, 4.9$ Hz, 1H), 6.65 (s, 1H), 4.95-4.92 (m, 1H), 4.70-4.62 (m, 1H), 4.24-4.19 (m, 1H), 3.94 (s, 3H), 3.79-3.75 (m, 1H), 2.55-2.49 (m, 2H), 2.45-2.38 (m, 1H), 2.26-2.20 (m, 1H), 1.19 (t, $J = 7.6$ Hz, 3H).

***(4R)*-1-(1-benzofuran-3-ylcarbonyl)-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonylamino]-*N*-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-6-yl)-*L*-prolinamide (31).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (XTerra-30, 30-100% Water/ACN) purification the reaction afforded the title compound as a white solid (16 mg, 15% yield). MS (ESI) m/z $[M+H]^+ = 542$; 1H NMR (400 MHz, DMSO- d_6) δ 10.17 (s, 1H), 9.19 (s, 1H), 8.30 (s, 1H), 8.60 (s, 2H), 8.04-8.00 (m, 1H), 7.69-7.63 (m, 2H), 7.41-7.29 (m, 3H), 6.65 (s, 1H), 4.94 (s, 1H), 4.84-4.77 (m, 1H), 4.72-4.63 (m, 1H), 4.25-4.16 (m, 1H), 3.93 (s, 3H), 3.81-3.73 (m, 1H), 2.45-2.36 (m, 1H), 2.28-2.19 (m, 1H), 1.14 (t, $J = 7.58$ Hz, 3H).

***N*-(1-(benzofuran-3-carbonyl)-5-(((1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-6-yl)methyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (32).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 35 ml/min, 20 to 100% acetonitrile in water 0.1% TFA, 20 min) purification the reaction afforded the title compound as a yellow solid (20 mg, 28% yield). MS (ESI) m/z $[M+H]^+ = 556$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.33-8.31 (m, 3H), 7.97-7.95 (m, 1H), 7.65-7.61 (m, 2H), 7.41-7.30 (m, 4H), 6.62 (s, 1H), 4.96 (s, 2H), 4.82-4.79 (m, 1H), 4.66-4.61 (m, 1H), 4.39-4.31 (m, 2H), 4.15-4.09 (m, 1H), 3.95 (s, 3H), 3.75-3.71 (m, 1H), 2.58-2.52 (m, 2H), 2.40-2.33 (m, 1H), 2.29-2.22 (m, 1H), 1.18 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((4-fluorophenethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (33).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (XBridge-30, 35 ml/min, 25 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) purification the reaction afforded the title compound (35.6 mg, 49.5% yield). MS (ESI) m/z $[M+H]^+ = 532$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.40 (br s, 1H), 8.28 (d, $J = 7.34$ Hz, 1H), 7.98-7.95 (m, 1H); 7.83-7.81 (m, 1H), 7.63 (d, $J = 8.07$ Hz, 1H), 7.39 (t, $J = 7.58$ Hz, 1H), 7.33 (t, $J = 7.09$ Hz, 1H), 7.28-7.17 (m, 2H), 7.03 (t, $J = 8.8$ Hz, 2H), 6.62 (s, 1H), 4.75-4.67 (m, 1H), 4.63-4.53 (m, 1H), 4.13-4.03 (m, 1H), 3.95 (s, 3H), 3.71-3.67 (m, 1H), 3.40-3.24 (m, 2H), 2.71 (m, 2H); 2.58-2.52 (m, 2H), 2.35-2.23 (m, 1H), 2.18-2.10 (m, 1H), 1.18 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (34).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After

preparative HPLC (XBridge-30, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH₄HCO₃, 20 min) purification the reaction afforded the title compound (35.6 mg, 49.5% yield). MS (ESI) m/z [M+H]⁺ = 544; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.25-8.23 (m, 2H), 7.93 (d, J = 7.58 Hz, 1H), 7.60 (d, J = 8.07 Hz, 1H), 7.57 (d, J = 8.31 Hz, 1H), 7.39-7.30 (m, 2H), 7.24-7.11 (m, 5H), 6.60 (s, 1H), 4.73-4.70 (m, 1H), 4.58-4.51 (m, 1H), 4.45 (t, J = 5.38 Hz, 1H), 4.06-3.98 (m, 1H), 3.94 (s, 3H), 3.70-3.66 (m, 1H), 3.38-3.35 (m, 2H), 2.85 -2.75 (m, 1H), 2.67-2.65 (m, 1H), 2.56-2.51 (m, 2H), 2.28-2.21 (m, 1H), 2.21-2.17 (m, 1H), 1.16 (t, J = 7.58 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2-(pyridin-2-yl)ethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (35).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (XBridge-30, 35 ml/min, 20 to 100% acetonitrile in water 10nM of NH₄HCO₃, 20 min) purification the reaction afforded the title compound (34 mg, 51.7% yield). MS (ESI) m/z [M+H]⁺ = 515; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.46 (d, J = 4.40 Hz, 1H), 8.33 (br s, 1H), 8.28 (d, J = 6.11 Hz, 1H), 7.94 (d, J = 7.83 Hz, 1H), 7.89-7.82 (m, 1H), 7.63 (d, J = 8.31 Hz, 1H), 7.66-7.64 (m, 1H), 7.39 (t, J = 7.09 Hz, 1H), 7.32 (t, J = 7.58 Hz, 1H), 7.26-7.206 (m, 1H), 7.19-7.14 (m, 1H), 6.62 (s, 1H), 4.74-4.69 (m, 1H), 4.62-4.54 (m, 1H), 4.11-4.04 (m, 1H), 3.95 (s, 3H), 3.72-3.68 (m, 1H), 3.52-3.41 (m, 2H), 2.92-2.83 (m, 2H), 2.58-2.52 (m, 2H), 2.33-2.25 (m, 1H), 2.21-2.15 (m, 1H), 1.18 (t, J = 7.58 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((5-methylisoxazol-3-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (36).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 35 ml/min, 40 to 100% acetonitrile in water 0.1% TFA, 20 min) purification the reaction afforded the title compound (19 mg, 27.2% yield). MS (ESI) m/z [M+H]⁺ = 491; ¹H NMR (400 MHz, CDCl₃): δ 9.90 (br s, 1H), 7.94-7.91 (m, 1H), 7.89-7.82 (m, 1H), 7.49 (d, J = 8.34 Hz, 1H), 7.35-7.32 (m, 1H), 7.26-7.22 (m, 1H), 6.62 (br s, 1H), 6.49 (br s, 1H), 6.29 (s, 1H), 5.24- 5.18 (m, 1H), 4.81-4.77 (m, 1H), 4.24-4.20 (m, 1H), 4.03 (s, 3H), 3.89-3.86 (m, 1H), 2.81-2.72 (m, 1H), 2.55 (q, J = 7.66 Hz, 2H), 2.36 (s, 3H), 2.34-2.17 (m, 4H), 1.18 (t, J = 7.58 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((4-methyloxazol-2-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (37).** The title compound was synthesized from **10** using the protocol described in the general **method A**. The crude was added to a silica gel column and was eluted with CH₂Cl₂/MeOH. The reaction afforded the title compound (12 mg, 10% yield). MS (ESI) m/z [M+H]⁺ = 491; ¹H NMR (400 MHz, CDCl₃): δ 7.95-7.93 (m, 2H), 7.52-7.49 (m, 1H), 7.39-7.31 (m, 1H), 7.28-7.26 (m, 2H), 7.08 (br s, 1H), 6.43-6.38 (m, 1H), 6.30 (s, 1H), 4.81-4.73 (m, 1H), 4.22 (dd, J = 10.6, 6.1 Hz, 1H), 4.03 (s, 3H), 3.86 (dd, J = 10.6, 3.8 Hz, 1H), 2.79-2.88 (m, 1H), 2.53 (q, J = 7.5 Hz, 2H), 2.35-2.26 (m, 2H), 2.13 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (38).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min), the reaction afforded the title compound (225 mg, 57% yield). MS (ESI) m/z [M+H]⁺ = 490; ¹H NMR (400 MHz, DMSO-*d*₆): about 88:12 mixture of rotamers, major rotamer description; δ 10.57 (s, 1H), 8.58 (br s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 2.0

Hz, 1H), 7.41-7.31 (m, 2H), 6.64 (s, 1H), 6.45 (d, $J = 2.3$ Hz, 1H), 4.82 (dd, $J = 7.7, 5.9$ Hz, 1H), 4.68-4.60 (m, 1H), 4.20 (dd, $J = 10.2, 6.7$ Hz, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 3.78-3.69 (m, 1H), 2.56-2.48 (m, 2H), 2.40-2.30 (m, 1H), 2.21-2.13 (m, 1H), 1.15 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((2-ethyl-2*H*-1,2,3-triazol-4-yl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (39).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 35 ml/min, 10 to 100 % acetonitrile in water 0.1% TFA, 20 min) purification the reaction afforded the title compound (36 mg, 55.6% yield). MS (ESI) m/z $[M+H]^+ = 505$; 1H NMR (400 MHz, DMSO- d_6): about 91:9 mixture of rotamers, major rotamer description; δ 11.07 (s, 1H), 8.62-8.60 (m, 2H), 8.00 (d, $J = 7.58$ Hz, 1H), 7.85 (s, 1H), 7.67 (d, $J = 8.07$ Hz, 1H), 7.41-7.31 (m, 2H), 6.65 (s, 1H), 4.83 (t, $J = 6.97$ Hz, 1H), 4.69-4.61 (m, 1H), 4.35 (q, $J = 7.09$ Hz, 2H), 4.22 (dd, $J = 10.03, J = 6.60$ Hz, 1H), 3.94 (s, 3H), 3.76 (dd, $J = 10.04, J = 4.30$ Hz, 1H), 2.55-2.49 (m, 2H), 2.42-2.33 (m, 1H), 2.23-2.17 (m, 1H), 1.42 (t, $J = 7.21$ Hz, 3H), 1.15 (t, $J = 7.58$ Hz, 3H).

(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-*N*-[1-(cyclohexylmethyl)-1*H*-pyrazol-3-yl]-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinamide (40). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (Sunfire-30, 50-100% Water/ACN) purification the reaction afforded the title compound as a pale yellow solid (26 mg, 30% yield). MS (ESI) m/z $[M+H]^+ = 572$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.32 (br s, 2H), 7.63 (br s, 1H), 7.61 (br s, 1H), 7.50 (s, 1H), 7.42-7.30 (m, 2H), 6.62 (s, 1H), 4.96-4.90 (m, 1H), 4.74-4.60 (m, 1H), 4.25-4.20 (m, 1H), 3.95 (s, 3H), 3.85 (br s, 2H), 3.77-3.70 (m, 1H), 2.58-2.53 (m, 2H), 2.45-2.35 (m, 1H), 2.25-2.20 (m, 1H), 1.80-1.55 (m, 6H), 1.22-1.15 (m, 6H), 0.90-0.80 (m, 2H).

(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*N*-{1-[(4-fluorophenyl)methyl]-1*H*-pyrazol-3-yl}-*L*-prolinamide (41). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 50-100 Water/ACN) purification the reaction afforded the title compound as a yellow solid (48 mg, 54% yield). MS (ESI) m/z $[M+H]^+ = 584$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 10.66 (s, 1H), 8.57 (s, 2H), 7.99 (br s, 1H), 7.76 (s, 1H), 7.68 (br s, 1H), 7.40-7.30 (m, 4H), 7.22-7.15 (m, 2H), 6.64 (s, 1H), 6.52 (s, 1H), 5.22 (s, 2H), 4.80-4.76 (m, 1H), 4.70-4.62 (m, 1H), 4.20-4.15 (m, 1H), 3.93 (s, 3H), 3.71 (s br, 1H), 2.40-2.30 (m, 1H), 2.20-2.15 (m, 1H), 1.14 (t, $J = 7.58$ Hz, 3H).

(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-*N*-{1-[(2,6-difluorophenyl)methyl]-1*H*-pyrazol-3-yl}-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinamide (42). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 10-100% Water 0.1% TFA/ACN) purification the reaction afforded the title compound as a pale yellow solid (65 mg, 70% yield). MS (ESI) m/z $[M+H]^+ = 602$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 10.68 (s, 1H), 8.57 (s, 2H), 7.98 (br s, 1H), 7.78-7.66 (m, 2H), 7.45-7.30 (m, 3H), 7.20-7.15 (m, 2H), 6.63 (s, 1H), 6.49 (s, 1H), 5.30 (s, 2H), 4.80-4.76 (m, 1H), 4.72-4.60 (m, 1H), 4.22-4.13 (m, 1H), 3.93 (s, 3H), 3.71 (br s, 1H), 2.40-2.30 (m, 1H), 2.20-2.15 (m, 1H), 1.13 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(((1-ethyl-1*H*-pyrazol-3-yl)methyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (43).** The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1% TFA,

20 min) purification the reaction afforded the title compound (26 mg, 39.5% yield). MS (ESI) m/z $[M+H]^+ = 517$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.35-8.30 (m, 2H), 8.22-8.22 (m, 1H), 7.60 (d, $J = 8.05$ Hz, 1H), 7.54 (br s, 1H), 7.40-7.28 (m, 2H), 6.61 (s, 1H), 6.20 (br s, 1H), 4.80-4.75 (m, 1H), 4.63-4.58 (m, 1H), 4.24 (br s, 2H), 4.11-4.02 (m, 3H), 3.93 (s, 3H), 3.75-3.35 (m, 4H), 2.20-2.35 (m, 1H), 1.34 (t, $J = 7.32$ Hz, 3H), 1.13 (t, $J = 7.62$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((thiazol-2-ylmethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (44)** The title compound was synthesized from **10** using the protocol described in the general **method A**. The crude was added to a silica gel column and was eluted with $CH_2Cl_2/MeOH$. The reaction afforded the title compound (13 mg, 20% yield). MS (ESI) m/z $[M+H]^+ = 507$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.74-8.67 (m, 1H), 8.41-8.32 (m, 1H), 8.32 (d, $J = 6.6$ Hz, 1H), 7.96 (d, $J = 7.82$, 1H), 7.69 (d, $J = 3.18$ Hz, 1H), 7.63 (d, $J = 8.07$, 1H), 7.55 (d, $J = 2.93$, 1H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 1H), 6.62 (s, 1H), 4.85-4.82 (m, 1H), 4.65-4.56 (m, 3H), 4.08-3.88 (m, 1H), 3.94 (s, 3H), 3.76-3.72 (m, 1H), 2.56-2.52 (m, 2H), 2.37-2.25 (m, 2H), 1.18 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-((oxazol-2-ylmethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (45)**. The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 40 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (25.2 mg, 40% yield). MS (ESI) m/z $[M+H]^+ = 491$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.48 (br s, 1H), 8.35 (br s, 1H), 8.30 (d, $J = 6.6$ Hz, 1H), 7.96-7.93 (m, 2H), 7.63 (d, $J = 8.30$ Hz, 1H), 7.41-7.38 (m, 1H), 7.35-7.31 (m, 1H), 7.12 (s, 1H), 6.62 (s, 1H), 4.84-4.81 (m, 1H), 4.66-4.57 (m, 1H), 4.49-4.37 (m, 2H), 4.14-4.06 (m, 1H), 3.95 (s, 3H), 3.75-3.71 (m, 1H), 2.39-2.23 (m, 2H), 2.40-2.31 (m, 1H), 2.31-2.24 (m, 1H), 1.18 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (46)**. The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 25 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (24.2 mg, 37.3% yield). MS (ESI) m/z $[M+H]^+ = 506$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.63 (br s, 1H), 8.36 (br s, 1H), 8.30 (d, $J = 6.6$ Hz, 1H), 7.95 (d, $J = 8.07$ Hz, 1H), 7.63 (d, $J = 8.30$ Hz, 1H), 7.41-7.36 (m, 1H), 7.35-7.31 (m, 1H), 6.62 (s, 1H), 4.85-4.82 (m, 1H), 4.66-4.50 (m, 3H), 4.06-4.13 (m, 1H), 3.94 (s, 3H), 3.72-3.76 (m, 1H), 2.57-2.52 (m, 2H), 2.38-2.24 (m, 2H), 2.32 (s, 3H), 1.18 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-5-((benzo[d]oxazol-2-ylmethyl)carbamoyl)-1-(benzofuran-3-carbonyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (47)**. The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 40 to 100% acetonitrile in water 10nM of NH_4HCO_3 , 20 min) the reaction afforded the title compound (36.4 mg, 52.5% yield). MS (ESI) m/z $[M+H]^+ = 541$; 1H NMR (400 MHz, DMSO- d_6); about 77:23 mixture of rotamers, major rotamer description; δ 8.86-8.84 (m, 1H), 8.56-8.54 (m, 2H), 7.98 (d, $J = 7.58$ Hz, 1H), 7.72-7.68 (m, 3H), 7.40-7.29 (m, 4H), 6.64 (s, 1H), 4.79-4.75 (m, 1H), 4.68-4.52 (m, 3H), 4.19-4.15 (m, 1H), 3.92 (s, 3H), 3.74-3.70 (m, 1H), 2.53-2.47 (m, 2H), 2.30-2.38 (m, 1H), 2.17-2.25 (m, 1H), 1.13 (t, $J = 7.58$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(((5-methylfuran-2-yl)methyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (48).**

The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-19, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH₄HCO₃, 20 min) the reaction afforded the title compound (26.4 mg, 40.9% yield). MS (ESI) *m/z* [M+H]⁺ = 504; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.32 (br s, 1H), 8.30 (d, *J* = 6.36 Hz, 1H), 8.22 (br s, 1H), 7.95 (d, *J* = 7.34 Hz, 1H), 7.62 (d, *J* = 8.07 Hz, 1H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 1H), 6.62 (s, 1H), 6.07 (br s, 1H), 5.95 (br s, 1H), 4.79-4.76 (m, 1H), 4.64-4.56 (m, 1H), 4.28-4.19 (m, 2H), 4.13-4.07 (m, 1H), 3.94 (s, 3H), 3.74-3.69 (m, 1H), 2.57-2.51 (m, 2H), 2.35-2.29 (m, 1H), 2.25-2.205 (m, 1H), 2.23 (s, 3H), 1.18 (t, *J* = 7.58 Hz, 3H).

(2*S*,4*R*)-tert-butyl 4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-(ethylcarbamoyl)pyrrolidine-1-carboxylate (50). (4*R*)-1-{(1,1-dimethylethyl)oxy}carbonyl}-4-({(9*H*-fluoren-9-ylmethyl)oxy}carbonyl}amino)-*L*-proline (1.5 g, 3.22 mmol) was dissolved in *N,N*-Dimethylformamide (10.72 ml) and Ethylamine (70% wt in water) (0.3 ml, 3.73 mmol) was added in one portion. To this mixture, HATU (1.467 g, 3.86 mmol) and DIPEA (0.9 ml, 5.15 mmol) were added and the reaction was stirred for 2 h. The reaction mixture was diluted in EtOAc (200 mL), washed with sat aq. NH₄Cl (200 mLx2), sat NaHCO₃ (200 mL), sat NaCl (200 mL), dried over Na₂SO₄ and concentrated to dryness to obtain the title compound as a pale yellow solid (1.8 g, the yield was >100% because the product contained DMF, purity >90%). MS (ESI) *m/z* [M+H]⁺ = 480; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 7.88 (d, *J* = 7.47 Hz, 2H), 7.68 (d, *J* = 7.47 Hz, 2H), 7.65-7.59 (m, 1H), 7.45-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.32-7.26 (m, 1H), 4.37-4.34 (m, 2H), 4.25-4.21 (m, 1H), 4.17-4.05 (m, 2H), 3.59 (dd, *J* = 10.62, 6.66 Hz, 1H), 3.21-3.15 (m, 3H), 2.12-1.92 (m, 2H), 1.39 (s, 9H), 1.05 (t, *J* = 7.25 Hz, 3H).

Methyl(4*R*)-1-{(1,1-dimethylethyl)oxy}carbonyl}-4-({(9*H*-fluoren-9-ylmethyl)oxy}carbonyl}amino)-*L*-prolylglycinate (51). Glycine methyl ester hydrochloride (1.083 g, 12.15 mmol) was dissolved in dimethylformamide (5 ml) and DIPEA (1.5 eq) was added. After 30 minutes at room temperature, 25 ml of dimethylformamide and (4*R*)-1-{(1,1-dimethylethyl)oxy}carbonyl}-4-({(9*H*-fluoren-9-ylmethyl)oxy}carbonyl}amino)-*L*-proline (5 g, 11.05 mmol) were added followed by HATU (8.84 g, 14.36 mmol) and 1.5 eq of DIPEA. The reaction was left under stirring overnight. Next morning, TLC EtOAc/Hexane (70%) showed completion. Dimethylformamide was removed under high vacuum. Corresponding crude was dissolved in EtOAc and was washed with NH₄Cl sat and NaCl. Organic layers were dried over Na₂SO₄ and volatiles were removed under vacuum. Corresponding crude was purified using ISCO sistem, SI II 150 g, Hexane-EtOAc (0-100%) to afford the title compound as a yellow solid (4.69 g, 81% yield). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.38-8.29 (m, 1H), 7.89 (d, *J* = 7.58 Hz, 2H), 7.68 (d, *J* = 7.33 Hz, 2H), 7.60-7.54 (m, 1H), 7.43-7.40 (m, 2H), 7.35-7.31 (m, 2H), 4.37-4.29 (m, 2H), 4.25-4.19 (m, 2H), 4.11-4.05 (m, 1H), 3.86-3.81 (m, 2H), 3.62 (s, 3H), 3.57-3.53 (m, 1H), 3.17-3.16 (m, 1H), 2.13-1.94 (m, 2H), 1.38 (s, 3H), 1.34 (s, 6H).

(9*H*-fluoren-9-yl)methyl ((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)carbamate (52). Compound **50** (2.143 g, 4.47 mmol) was suspended in Dichloromethane (30 ml) and trifluoroacetic acid (6.89 ml, 89 mmol) was then added in one portion. The reaction was stirred for 5 h at room temperature. There was a little white solid very insoluble so it was filtered first and then the liquid phase was concentrated to dryness (co-evap. with CH₂Cl₂x3) to give the free amine (2.32g) Slightly impure (4*R*)-*N*-ethyl-4-({(9*H*-fluoren-9-

ylmethyl)oxy]carbonyl}amino)-*L*-prolinamide (2.2 g, 4.24 mmol) and 1-benzofuran-3-carboxylic acid (0.755 g, 4.66 mmol) were dissolved in *N,N*-Dimethylformamide (14 ml). HATU (2.093 g, 5.51 mmol) and DIPEA (2.219 ml, 12.71 mmol) were then added to the mixture. The resulting solution was stirred for 2 h at room temperature. The reaction mixture was diluted in EtOAc (150 mL), washed with sat aq. NH_4Cl (150 mLx2), sat NaHCO_3 (150 mL), sat NaCl (150 mL), dried over Na_2SO_4 and concentrated to dryness. The crude was added to a silica gel column (Analogix cartridge, 70g) and was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 6.7% to afford the title compound (1.34 g, 54.4% yield; 90% purity). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 524$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 °C): δ 8.33 (br s, 1H), 7.98-7.62 (m, 7H), 7.42-7.27 (m, 7H), 4.65-4.60 (m, 1H), 4.37-4.35 (m, 2H), 4.24-4.19 (m, 2H), 3.96-3.94 (m, 1H), 3.59-3.54 (m, 1H), 3.13-3.04 (m, 2H), 2.24-2.04 (m, 2H), 1.07-0.90 (m, 3H).

Methyl(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-((9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-*L*-prolylglycinate (53). Compound 51 (4.69 g, 8.96 mmol) was suspended in Dichloromethane (30 ml) and trifluoroacetic acid (3.45 ml, 44.8 mmol) was then added in one portion. The reaction was stirred overnight. Volatiles were removed under vacuum and NaHCO_3 10% was added to basify the mixture and it was extracted with EtOAc several times. Organic layers were dried over Na_2SO_4 and volatiles were removed under vacuum to afford the free amine as a yellow solid (2.49 g, 68% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.88 (d, $J = 7.58$ Hz, 2H), 7.68 (d, $J = 7.07$ Hz, 2H), 7.40 (t, $J = 7.33$ Hz, 2H), 7.32 (t, $J = 7.33$ Hz, 2H), 4.39-4.36 (m, 2H), 4.24-4.17 (m, 1H), 3.91-3.83 (m, 1H), 3.84 (d, $J = 6.06$ Hz, 2H), 3.72-3.65 (m, 1H), 3.61 (s, 3H), 2.90-2.70 (m, 2H), 1.95-1.80 (m, 2H). Methyl (4*R*)-4-((9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-*L*-prolylglycinate (2.5 g, 5.90 mmol) and 1-benzofuran-3-carboxylic acid (1.053 g, 6.49 mmol) were dissolved in dichloromethane (35 ml). EDC (1.358 g, 7.08 mmol) and HOBt (1.085 g, 7.08 mmol) were then added to the mixture. The resulting solution was stirred overnight. Reaction was washed with NaHCO_3 sat and NaCl sat, dried over Na_2SO_4 and volatiles were removed under vacuum. Corresponding crude was purified by Flash Master Si II 70g using Hexane/EtOAc (0-100%). After collecting the appropriate fractions it was obtained the titled compound as a yellow solid (1.5 g, 45% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 568$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.52 (br s, 1H), 8.37-8.44 (m, 1H), 7.98 (d, $J = 7.58$ Hz, 1H), 7.90-7.84 (m, 2H), 7.68-7.64 (m, 3H), 7.41-7.24 (m, 7H), 4.69-4.66 (m, 1H), 4.34-4.32 (m, 2H), 4.25-4.19 (m, 2H), 3.88-3.85 (m, 1H), 3.82-3.77 (m, 1H), 3.63 (s, 3H), 3.63-3.53 (m, 2H), 2.25-2.15 (m, 1H), 2.12-2.04 (m, 1H).

(2*S*,4*R*)-4-amino-1-(benzofuran-3-carbonyl)-*N*-ethylpyrrolidine-2-carboxamide (54). Compound 52 (1.34 g, 2.56 mmol) was dissolved in *N,N*-Dimethylformamide (4 mL) and piperidine (0.507 mL, 5.12 mmol) was then added to the mixture. The resulting solution was stirred at room temperature for 1 h. The remaining piperidine and *N,N*-Dimethylformamide were removed by rotary evaporator heating at 80 °C. This crude was dissolved in MeOH and a white precipitated appeared. The undissolved solid was filtered off. The crude was added to a silica gel column and was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 8% to afford the title compound (0.48 g, 58.7% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 302$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 °C) δ 8.33 (br s, 1H), 7.98-7.94 (m, 1H), 7.70 (bs, 1H), 7.62 (d, $J = 8.20$ Hz, 1H), 7.42-7.30 (m, 2H), 4.63-4.58 (m, 1H), 3.92-3.83 (m, 1H), 3.66-3.57 (m, 1H), 3.39 (dd, $J = 10.30, 4.76$ Hz, 1H), 3.06-2.97 (m, 2H), 2.05-1.91 (m, 2H), 1.62 (br s, 2H), 1.06-0.91 (m, 3H).

Methyl(4*R*)-4-amino-1-(1-benzofuran-3-ylcarbonyl)-*L*-prolylglycinate (55). Compound 53 (1 g, 1.762 mmol) was dissolved in 1 ml of *N,N*-Dimethylformamide and piperidine was added at

room temperature. After 1 h the reaction was completed. Volatiles were removed under high vacuum and resultant crude was purified by flash master 70 g Si II, CH₂Cl₂/MeOH (0-20%) to afford the title compound as a white solid (0.45 g, 70% yield). MS (ESI) *m/z* [M+H]⁺ = 346; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 8.33 (s, 1H), 8.15 (s, 1H), 7.95 (d, *J* = 7.58 Hz, 1H), 7.63 (d, *J* = 8.08 Hz, 1H), 7.41-7.30 (m, 2H), 4.74-4.67 (m, 1H), 3.92-3.82 (m, 3H), 3.64 (t, 3H), 3.42-3.38 (m, 1H), 3.05 (br s, 2H), 2.07-2.12 (m, 1H), 2.02-1.95 (m, 1H), 1.60 (br s, 1H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(1-methyl-3-propyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (56). The title compound was synthesized from **55** using the protocol described in the general **method A**. After silica chromatography purification (BP cartridge, 5g, eluted with mixtures of CH₂Cl₂/MeOH), the reaction afforded the

title compound (46 mg, 61% yield). MS (ESI) *m/z* [M+H]⁺ = 496; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.39-8.22 (m, 3H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.41-7.30 (m, 2H), 6.61 (s, 1H), 4.83-4.80 (m, 1H), 4.63-4.58 (m, 1H), 4.11-4.03 (m, 1H), 3.94 (s, 3H), 3.89-3.87 (m, 2H), 3.75-3.72 (m, 1H), 3.66 (s, 3H), 2.52-2.48 (m, 2H), 2.36-2.27 (m, 2H), 1.65-1.56 (m, 2H), 0.94-0.90 (m, 3H).

Methyl (4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-({[1-methyl-3-(2-methylpropyl)-1*H*-pyrazol-5-yl]carbonyl}amino)-*L*-prolylglycinate (57). The title compound was synthesized from **55** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 10-100% Water 0.1% TFA/ACN) purification the reaction afforded the title compound as a white solid (45 mg, 58% yield). MS (ESI) *m/z* [M+H]⁺ = 510; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.45 (br s, 1H), 8.26 (br s, 2H), 7.93 (br s, 1H), 7.62- 7.59 (m, 1H), 7.40-7.34 (m, 1H), 7.33-7.28, (m, 1H), 6.59 (s, 1H), 4.80-4.76 (m, 1H), 4.65-4.55 (m, 1H), 4.12-4.00 (m, 1H), 3.93 (s, 3H), 3.90-3.84 (m, 2H), 3.75-3.67 (m, 1H), 3.65 (s, 3H), 2.43-2.25 (m, 4H), 1.80-1.90 (m, 1H), 0.93-0.87 (m, 6H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(3-cyclopropyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (58). The title compound was synthesized from **55** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 30 to 100% acetonitrile in water 10nM of NH₄HCO₃, 20 min) the reaction afforded the title compound (47 mg, 38% yield). MS (ESI) *m/z* [M+H]⁺ = 494; ¹H NMR (400 MHz, DMSO-*d*₆); about 73:27 mixture of rotamers, major rotamer description: δ 8.54 (s, 1H); 8.44-8.50 (m, 2H); 7.98 (d, *J* = 7.58 Hz, 1H); 7.65 (d, *J* = 8.08 Hz, 1H); 7.36-7.40 (m, 1H); 7.30-7.36 (m, 1H); 6.49 (s, 1H); 4.71-4.78 (m, 1H); 4.55-4.62 (m, 3H); 4.12-4.17 (m, 1H); 3.83-3.93 (m, 5H); 3.64-3.69 (m, 1H); 3.61-3.63 (m, 4H); 3.29 (s, 3H); 2.23-2.34 (m, 2H); 2.12-2.19 (m, 1H); 1.79-1.87 (m, 1H); 0.81-0.87 (m, 2H); 0.56-0.91 (m, 2H).

Methyl(4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-{{(1,3-diethyl-1*H*-pyrazol-5-yl)carbonyl}amino}-*L*-prolylglycinate (59). The title compound was synthesized from **55** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 40-100% Water/ACN) purification the reaction afforded the title compound as a white solid (25 mg, 44% yield). MS (ESI) *m/z* [M+H]⁺ = 496; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (br s, 1H), 7.87 (br s, 1H), 7.51-7.48 (m, 2H), 7.36-7.30 (m, 1H), 7.28-7.23 (m, 1H), 6.53-6.49 (m, 1H), 6.29 (s, 1H), 5.19-5.15 (m, 1H), 4.77-4.74 (m, 1H), 4.47-4.41 (m, 2H), 4.20-4.00 (m, 3H), 3.88-3.85 (m, 1H), 3.73 (s, 3H), 2.80-2.75 (m, 1H), 2.54-2.50 (m, 2H), 2.32-2.28 (m, 1H), 2.90-2.80 (m, 2H), 1.33 (t, *J* = 7.07 Hz, 3H), 1.13 (t, *J* = 7.58 Hz, 3H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-propyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (60). The title compound was synthesized

from **55** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-19, 17 ml/min, 30 to 100% acetonitrile in water, 10nM NH₄HCO₃, BASIC, 20 min) the reaction afforded the title compound (13 mg, 36% yield). MS (ESI) *m/z* [M+H]⁺ = 510; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.35 (br s, 1H), 8.29 (d, 1H), 8.24 (br s, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.41-7.37 (m, 1H), 7.34-7.30 (m, 1H), 6.59 (s, 1H), 4.82 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.63-4.55 (m, 1H), 4.31 (t, *J* = 7.1 Hz, 2H), 4.10-4.00 (m, 1H), 3.94-3.83 (m, 2H), 3.76-3.72 (m, 1H), 3.67 (s, 3H), 2.58-2.50 (m, 2H), 2.38-2.25 (m, 2H), 1.74-1.65 (m, 2H), 1.18 (t, *J* = 7.6 Hz, 3H), 0.78 (t, *J* = 7.6 Hz, 3H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-(2-hydroxyethyl)-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (61). The title compound was synthesized from **55** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 25 to 100% acetonitrile in water, 10nM NH₄HCO₃, BASIC, 20 min) the reaction afforded the title compound (11 mg, 63% yield). MS (ESI) *m/z* [M+H]⁺ = 512; ¹H NMR (400 MHz, DMSO-*d*₆): about 80:20 mixture of rotamers, major rotamer description; δ 8.56 (br s, 1H), 8.49-8.47 (m, 1H), 8.25 (d, *J* = 7.1 Hz, 1H), 8.01 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.41-7.31 (m, 2H), 6.41 (s, 1H), 4.90-4.87 (m, 1H), 4.80-4.60 (m, 2H), 4.15-4.04 (m, 3H), 3.95-3.80 (m, 2H), 3.74-3.68 (m, 3H), 3.65 (s, 3H), 2.68-2.60 (m, 2H), 2.40-2.32 (m, 1H), 2.20-2.11 (m, 1H), 1.18 (t, *J* = 7.6 Hz, 3H).

methyl 2-((2*S*,4*R*)-1-(benzofuran-3-carbonyl)-4-(1-benzyl-3-ethyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (62). The title compound was synthesized from **55** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 30 to 100% acetonitrile in water, 10nM NH₄HCO₃, BASIC, 20 min) the reaction afforded the title compound (71 mg, 72% yield). MS (ESI) *m/z* [M+H]⁺ = 558; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.36-8.33 (m, 2H), 8.24 (br s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.41-7.31 (m, 2H), 7.25-7.13 (m, 5H), 6.67 (s, 1H), 5.59 (br s, 2H), 4.81 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.61-4.56 (m, 1H), 4.10-4.02 (m, 1H), 3.94-3.82 (m, 2H), 3.69 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.66 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.35-2.25 (m, 2H), 1.18 (t, *J* = 7.6 Hz, 3H).

methyl 2-(4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate 2,2,2-trifluoroacetate (63). Compound (**63**) was synthesized from methyl (4*R*)-1-[(1,1-dimethylethyl)oxy]carbonyl-4-[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolylglycinate (**83**) using the protocol described in the general **method C**. The crude material after evaporation was further purified by silica chromatography (Analogix cartridge, 24g) and was eluted with CH₂Cl₂/MeOH 7.6% to afford the title compound (0.34 g, 66.5% yield). The crude product was carried on to next step as it is.

1-(benzofuran-3-carbonyl)-4-(1,3-diethyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxylic acid (64). Compound (**64**) was synthesized from saponification of methyl (4*R*)-1-(1-benzofuran-3-ylcarbonyl)-4-[(1,3-diethyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinate (**86**) (0.959 g, 2.187 mmol) using the protocol described in the general **method B**. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc (100 mL) and washed with 10% aq. KHSO₄ (75 mL), sat aq. NaCl (75 mL), dried over Na₂SO₄, filtered and concentrated to dryness to afford the title compound as a beige solid (0.97 g, 2.171 mmol, 99% yield). MS (ESI) *m/z* [M+H]⁺ = 425; ¹H NMR (400 MHz, DMSO-*d*₆): about 86:14

mixture of rotamers, major rotamer description; δ 12.72 (br s, 1H), 8.58 (s, 1H), 8.56 (d, $J = 6.57$ Hz, 1H), 7.97 (d, $J = 7.33$ Hz, 1H), 7.66 (d, $J = 8.08$ Hz, 1H), 7.40-7.30 (m, 2H), 6.63 (s, 1H), 4.69-4.65 (m, 1H), 4.60-4.56 (m, 1H), 4.36-4.30 (m, 2H), 4.12-4.08 (m, 1H), 3.75-3.71 (m, 1H), 2.55-2.49 (m, 2H), 2.40-2.31 (m, 1H), 2.23-2.16 (m, 1H), 1.21-1.11 (m, 6H).

(4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[(1,3-diethyl-1H-pyrazol-5-yl)carbonylamino]-N-[(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-6-yl)methyl]-L-prolinamide (66). The title compound was synthesized from **64** using the protocol described in the general **method A**. After preparative HPLC (SunFire-30, 30-100% Water-Formic acid 1% / ACN) purification the reaction afforded the title compound as a pale yellow solid (30 mg, 50% yield). MS (ESI) m/z $[M+H]^+ = 570$; ^1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.30 (br s, 2H), 7.94 (br s, 1H), 7.67-7.58 (m, 2H), 7.44-7.25 (m, 4H), 6.60 (s, 1H), 4.96 (s, 2H), 4.84-4.76 (m, 1H), 4.70-4.56 (m, 1H), 4.42-4.28 (m, 4H), 4.17-4.05 (m, 1H), 3.78-3.70 (m, 1H), 2.61-2.52 (m, 2H), 2.40-2.30 (m, 1H), 2.29-2.22 (m, 1H), 1.27 (t, $J = 7.09$ Hz, 3H), 1.19 (t, $J = 7.58$ Hz, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)carbamoyl)pyrrolidin-3-yl)-1,3-diethyl-1H-pyrazole-5-carboxamide (67). The title compound was synthesized from **64** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 10 to 100% acetonitrile in water, 10nM NH_4HCO_3 , BASIC, 20 min) the reaction afforded the title compound (423 mg, 76.6% yield).

MS (ESI) m/z $[M+H]^+ = 520$; ^1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.62 (br s, 1H), 8.36 (br s, 1H), 8.30 (d, $J = 6.4$ Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.41-7.31 (m, 2H), 6.60 (s, 1H), 4.84 (dd, $J = 8.3, 4.4$ Hz, 1H), 4.64-4.50 (m, 3H), 4.40-4.35 (m, 2H), 4.11-4.07 (m, 1H), 3.77-3.73 (m, 1H), 2.59-2.53 (m, 2H), 2.41-2.25 (m, 2H), 2.33 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.19 (t, $J = 7.6$ Hz, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-((2-(pyridin-2-yl)ethyl)carbamoyl)pyrrolidin-3-yl)-1,3-diethyl-1H-pyrazole-5-carboxamide (68). The title compound was synthesized from **64** using the protocol described in the general **method A**. After preparative HPLC (XBridge-30, 30-100% Water 10 nM NH_4HCO_3 /ACN) purification the reaction afforded the title compound as a pale yellow solid (75 mg, 38% yield). MS (ESI) m/z $[M+H]^+ = 529$; ^1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.46 (d, $J = 4.65$ Hz, 1H), 8.35 (br s, 1H), 8.27 (d, $J = 6.60$ Hz, 1H), 7.94 (d, $J = 7.34$ Hz, 2H), 7.86-7.82 (m, 1H), 7.67-7.61 (m, 2H), 7.39 (t, $J = 7.34$ Hz, 1H), 7.32 (t, $J = 7.34$ Hz, 1H), 7.22 (d, $J = 7.34$ Hz, 1H), 7.19-7.15 (m, 1H), 6.60 (s, 1H), 4.74-4.70 (m, 1H), 4.41-4.35 (m, 2H), 4.07-4.03 (m, 1H), 3.73-3.79 (m, 1H), 3.50-3.40 (m, 2H), 2.93-2.83 (m, 1H), 2.59-2.53 (m, 2H), 2.34-2.24 (m, 1H), 2.23-2.15 (m, 1H), 1.27 (t, $J = 7.09$ Hz, 3H), 1.19 (t, $J = 7.58$ Hz, 3H).

(4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[(1,3-diethyl-1H-pyrazol-5-yl)carbonylamino]-N-(2-hydroxyethyl)-L-prolinamide (69). The title compound was synthesized from **64** using the protocol described in the general **method A**. After preparative HPLC (XBridge-30, 20-100% Water 10 nM NH_4HCO_3 /ACN) purification the reaction afforded the title compound as a pale yellow solid (30 mg, 50% yield). MS (ESI) m/z $[M+H]^+ = 468$; ^1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.30 (br s, 1H), 8.27 (d, $J = 6.60$ Hz, 1H), 7.94 (d, $J = 7.58$ Hz, 2H), 7.70-7.75 (m, 1H), 7.61 (d, $J = 8.07$ Hz, 1H), 7.39 (t, $J = 7.09$ Hz, 1H), 7.32 (t, $J = 7.09$ Hz, 1H), 6.60 (s, 1H), 4.78-4.72 (m, 1H), 4.65-4.56 (m, 1H), 4.41-4.31 (m, 3H), 4.10-4.03 (m, 1H), 3.75-3.68 (m, 1H), 3.50-3.40 (m, 2H), 3.25-3.15 (m, 2H), 3.01 (s, 2H), 2.56 (q, $J = 7.58$ Hz, $J = 15.16$ Hz, 2H), 2.34-2.20 (m, 2H), 1.27 (t, $J = 7.09$ Hz, 3H), 1.19 (t, $J = 7.58$ Hz, 3H).

(4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[(1,3-diethyl-1H-pyrazol-5-yl)carbonyl]amino}-N-(2-pyridinylmethyl)-L-prolinamide (70). The title compound was synthesized from **64** using the protocol described in the general **method A**. After preparative HPLC (SunFire-19, 17 ml/min, 30 to 100% acetonitrile in water 0.1% TFA, 20 min) purification the reaction afforded the title compound as a white solid (39 mg, 67% yield). MS (ESI) m/z $[M+H]^+$ = 515; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.47 (d, J = 4.40 Hz, 1H), 8.42-8.36 (m, 2H), 8.31 (d, J = 6.60 Hz, 1H), 7.97 (d, J = 7.34 Hz, 1H), 7.75-7.64 (m, 1H), 7.63 (d, J = 8.07 Hz, 1H), 7.38-7.41 (m, 1H), 7.35-7.31 (m, 1H), 7.25-7.22 (m, 1H), 6.61 (s, 1H), 4.88-4.84 (m, 1H), 4.67-4.61 (m, 1H), 4.45-4.25 (m, 4H), 4.15-4.08 (m, 1H), 3.77-3.73 (m, 1H), 2.60-2.54 (m, 2H), 2.42-2.28 (m, 2H), 1.27 (t, J = 7.09 Hz, 3H), 1.19 (t, J = 7.58 Hz, 3H).

1-(1,1-dimethylethyl) 2-(diphenylmethyl) (2R,4S)-4-azido-1,2-pyrrolidinedicarboxylate (72). To a solution of 1-(1,1-dimethylethyl) 2-(diphenylmethyl) (2R,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate (2 g, 5.03 mmol) and triphenylphosphine (1.346 g, 5.13 mmol) in Tetrahydrofuran (30 ml) was added DEAD (0.87 ml, 5.33 mmol) at 0 °C. diphenylphosphoryl azide (1.140 ml, 5.13 mmol) was then added and the temperature was allowed to rise to room temperature. The reaction mixture was stirred overnight and then it was concentrated almost completely. The crude product was carried on to next step as it is.

(2R,4S)-2-benzhydryl 1-tert-butyl 4-aminopyrrolidine-1,2-dicarboxylate (73). To a solution of 1-(1,1-dimethylethyl) 2-(diphenylmethyl) (2R,4S)-4-azido-1,2-pyrrolidinedicarboxylate (2.126 g, 5.03 mmol) in Tetrahydrofuran (25 mL) was added triphenylphosphine (2.64 g, 10.06 mmol) and then Water (5mL), 5ml more of water were added after 8h. The mixture was heated at 60 °C for 24h. TLC (CH₂Cl₂/MeOH 9:1) showed the product (R_f =0.75) revealed using ninhydrin solution. The sample was evaporated and dissolved in methanol to loaded onto a preconditioned SCX cartridge (50 g), eluting with MeOH first and then the product was eluted with ammonia in MeOH 7N. The crude material after evaporation was further purified by silica chromatography (Analogix cartridge, 80 g) and was eluted with CH₂Cl₂/MeOH 4.4%. The reaction produced a white solid in 41% yield after 2 steps (0.87 g) with a purity of 95%. MS (ESI) m/z $[M+H]^+$ = 397; 1H NMR (400 MHz, DMSO- d_6): δ 7.40-7.24 (m, 9H), 6.84-6.77 (m, 1H), 4.39-4.36 (m, 1H), 4.11-4.07 (m, 1H), 3.50-3.40 (m, 2H), 3.04-2.99 (m, 1H), 2.05-1.85 (m, 2H), 1.66 (br s, 2H), 1.36 (s, 3H), 1.14 (s, 6H).

(2R,4S)-2-benzhydryl 1-tert-butyl 4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-1,2-dicarboxylate (74). 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.078 g, 0.504 mmol) and HATU (0.230 g, 0.605 mmol) were dissolved in *N,N*-Dimethylformamide (1.5 ml) and DIPEA (0.220 ml, 1.261 mmol) was then added to the mixture. To the resulting solution, 1-(1,1-dimethylethyl) 2-(diphenylmethyl) (2R,4S)-4-amino-1,2-pyrrolidinedicarboxylate (0.200 g, 0.504 mmol) was added and the reaction was stirred at room temperature for 1.5 h. The reaction mixture was diluted in EtOAc (20 mL), washed with sat aq. NH₄Cl (20 mLx2), sat NaHCO₃ (20 mL), sat NaCl (20 mL), dried over Na₂SO₄ and concentrated to dryness to obtain an orange oil (287 mg). MS (ESI) m/z $[M+H]^+$ = 533. This compound is only an intermediate and it is going to be used in the reaction, without further purification.

(2R,4S)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylic acid (75). 1-(1,1-dimethylethyl) 2-(diphenylmethyl) (2R,4S)-4-[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino}-1,2-pyrrolidinedicarboxylate (0.269 g, 0.505 mmol) was suspended in Dichloromethane (1.4 ml) and trifluoroacetic acid (0.6 ml, 7.79 mmol) was then added in one portion. The reaction was stirred for 3 h at room temperature and then concentrated to dryness

(co-evap. with CH₂Cl₂x3). To remove the trifluoroacetic acid salts and the TFA, the crude was passed through a SCX cartridge (5g), washed with MeOH first, eluted with NH₃ in MeOH 7N and the next day it was concentrated. The residue was used in the next step without further purification.

(2R,4S)-methyl 4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylate (76). Acetyl chloride (0.117mL, 1.65 mmol) was added to methanol (2 mL, 50 mmol) at 0 °C. The resulting solution was stirred for 5 min and was added to a suspension of (4S)-4-{[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino}-D-proline (0.147 g, 0.552 mmol) in Methanol (2 mL). The mixture was allowed to warm to room temperature and was stirred at room temperature for 16h. Starting material remained, so more acetyl chloride (0.117mL, 1.65 mmol) in methanol (2 mL, 50 mmol) was added. Then, the mixture was heated at 50 °C for 2h, at room temperature overnight and finally the crude was evaporated. The crude product was carried on to next step as it is.

(2R,4S)-methyl 1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylate (77). methyl (4S)-4-{[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino}-D-prolinate (0.175 g, 0.552 mmol) and 1-benzofuran-3-carboxylic acid (0.090 g, 0.552 mmol) were dissolved in *N,N*-Dimethylformamide (2 ml). HATU (0.252 g, 0.663 mmol) and DIPEA (0.289 ml, 1.657 mmol) were then added to the mixture. The reaction was stirred at room temperature for 4h. The reaction mixture was diluted with EtOAc (20 mL), washed with sat aq. NH₄Cl (20 mLx2), sat NaHCO₃ (20 mL), sat NaCl (20 mL), dried over Na₂SO₄ and concentrated to dryness. The crude was added to a silica gel column (Analogix, 40 g) and was eluted with CH₂Cl₂/MeOH 5%. The reaction produced a pale brown solid in 47% yield (0.116 g) with a purity of 95%. MS (ESI) *m/z* [M+H]⁺ = 425; ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C): δ 8.62-8.57 (m, 2H), 7.98 (d, *J* = 7.32 Hz, 1H), 7.69-7.66 (m, 1H), 7.42-7.30 (m, 2H), 6.66 (s, 1H), 4.79-4.71 (m, 1H), 4.65-4.54 (m, 1H), 4.18-4.10 (m, 1H), 3.92 (s, 3H), 3.80-3.73 (m, 1H), 3.70 (s, 3H), 2.60-2.45 (m, 2H), 2.45-2.35 (m, 1H), 2.29-2.16 (m, 1H), 1.14 (t, *J* = 7.62 Hz, 3H).

(2R,4S)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxylic acid (78). To a solution of methyl (4S)-1-(1-benzofuran-3-ylcarbonyl)-4-{[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino}-D-prolinate (0.100 g, 0.236 mmol) in Tetrahydrofuran (2 ml) and Methanol (0.200 ml), stirred at room temperature, was added a suspension of lithium hydroxide (0.030 g, 0.707 mmol) in Water (0.300 ml). In that moment, a white precipitate appeared in suspension. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (20 mL) and washed with 10% aq. KHSO₄ (15 mLx2), sat aq. NaCl (15 mL), dried over Na₂SO₄ and concentrated to dryness. The crude product (96 mg) was carried on to next step as it is.

methyl 2-((2R,4S)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (7'ENANTIOMER). The title compound was prepared using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1 % TFA, 20 min) the reaction afforded the title compound (10 mg, 13% yield). MS (ESI) *m/z* [M+H]⁺ = 482; ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.42-8.26 (m, 3H), 7.97-7.94 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.42-7.30 (m, 2H), 6.62 (s, 1H), 4.84-4.79 (m, 1H), 4.64-4.55 (m, 1H), 4.13-4.04 (m, 1H), 3.94 (s, 3H), 3.90-3.87 (m, 2H), 3.75-3.69 (m, 1H), 3.66 (s, 3H), 2.58-2.49 (m, 2H), 2.38-2.23 (m, 2H), 1.17 (t, *J* = 7.6 Hz, 3H).

(3R)-1-(1-benzofuran-3-ylcarbonyl)-3-pyrrolidinamine (80). 1,1-dimethylethyl (3R)-3-pyrrolidinylcarbamate (0.075 g, 0.403 mmol) and 1-benzofuran-3-carboxylic acid (0.065 g, 0.403 mmol) were dissolved in *N,N*-Dimethylformamide (8 ml). HATU (0.184 g, 0.483 mmol) and DIPEA (0.2 ml, 1.145 mmol) were then added to the mixture. The reaction was stirred for 4 h. The reaction mixture was diluted in EtOAc (10 mL), washed with sat aq. NH_4Cl (10 mLx2), sat NaHCO_3 (10 mL), sat NaCl (10 mL), dried over Na_2SO_4 and concentrated to dryness. The crude after the work was used in the deprotection reaction without further purification. 1,1-dimethylethyl [(3R)-1-(1-benzofuran-3-ylcarbonyl)-3-pyrrolidinyl]carbamate (0.133 g, 0.403 mmol) was suspended in Dichloromethane (2 ml) and trifluoroacetic acid (0.7 ml, 9.09 mmol) was then added in one portion. The reaction was stirred for 3 h at room temperature and then concentrated to dryness (co-evap. with CH_2Cl_2 x3) to give the product (297 mg, brown oil) that was carried on to next step as it is.

***N*-((3R,5S)-1-(benzofuran-3-carbonyl)-5-(hydroxymethyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (81).** To a solution of methyl (4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[[[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino]-*L*-prolinate (0.270 g, 0.541 mmol) in anhydrous Diethyl ether (14 mL), at 0 °C under argon atmosphere, was added lithium aluminium hydride (0.034 g, 0.896 mmol) in two portions. The mixture was refluxed for 2 h. After the mixture was cooled, Ethyl acetate (3.00 ml) was added and the crude was stirred 10 min. Then, water (1 ml) and aq. 2N NaOH (1 mL) were added dropwise (vigorous exotherm, white precipitate). The mixture was filtered, rinsed with plenty of EtOAc and dried. The crude was re-dissolved in CH_2Cl_2 and the salts were separated by filtration. The filtered was concentrated under vacuum. Then, it was added to a silica gel column (Merck cartridge, 5 g) and it was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 2-10%. The product was obtained so the purification (Merck cartridge, 5 g, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5%) was repeated but no separation was obtained. The compound was used without further purification in the next step.

***N*-((3R,5S)-1-(benzofuran-3-carbonyl)-5-formylpyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (82).** To an ice cold solution of *N*-[(3R,5S)-1-(1-benzofuran-3-ylcarbonyl)-5-(hydroxymethyl)-3-pyrrolidinyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (0.0764 g, 0.193 mmol) in Dichloromethane (2 ml) was added sodium bicarbonate (0.058 g, 0.694 mmol) and Dess-Martin periodinane (0.082 g, 0.193 mmol). The ice bath was removed and the mixture was stirred at room temperature. After 4h the reaction was judged complete by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1, $R_f = 0.52$). 2 mL each of 1N Na_2CO_3 and 4 mL of saturated $\text{Na}_2\text{S}_2\text{O}_3$ were added along with 4 mL of EtOAc and 4 mL of CH_2Cl_2 . Stirred for 2 h. Layers were separated and the organic layer was washed with saturated NaHCO_3 and brine, dried with Na_2SO_4 , filtered and concentrated to get the product as an orange solid. (The HNMR analysis showed the proton peak at 9.75 ppm indicates the presence of the aldehyde). The compound was used in the next step without further purification.

tert-butyl 4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (83). To a solution of compound (3) 1-(1,1-dimethylethyl) 2-methyl (2S,4R)-4-[[[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino]-1,2-pyrrolidinedicarboxylate (3 g, 7.89 mmol) in Tetrahydrofuran (50 mL) and Methanol (5.00 mL), stirred at room temp, was added dropwise a solution of lithium hydroxide (0.993 g, 23.66 mmol) in Water (5.00 mL). In that moment, a white precipitate appeared in suspension. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc (200

mL) and washed with 10% aq. KHSO₄ (200 mL), sat aq. NaCl (100 mL), dried over Na₂SO₄ and concentrated to dryness. The solid was recrystallized from EtOAc to give the title compound (1.93g, 63 :5%,) as a white solid. (4*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-{[(3-ethyl-1-methyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-proline (0.4195 g, 1.145 mmol) and glycine methyl ester hydrochloride (0.147 g, 1.168 mmol) were dissolved in *N,N*-Dimethylformamide (16.3 ml). HATU (0.566 g, 1.488 mmol) and DIPEA (0.640 ml, 3.66 mmol) were then added to the mixture. The reaction was stirred at room temperature for 1.5h. The reaction mixture was diluted with EtOAc (70 mL), washed with sat aq. NH₄Cl (70 mL x 2), sat NaHCO₃ (70 mL), sat NaCl (70 mL), dried over Na₂SO₄ and concentrated to dryness to obtain the title product (0.8 g). This compound was used without further purification.

1-tert-butyl 2-methyl 4-(1,3-diethyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-1,2-dicarboxylate (85). 1,3-diethyl-1*H*-pyrazole-5-carboxylic acid (780 mg, 4.64 mmol) and HATU (2116 mg, 5.57 mmol) were dissolved in *N,N*-Dimethylformamide (10 ml) and DIPEA (2.430 ml, 13.91 mmol) was then added to the mixture. To the resulting solution, 1-(1,1-dimethylethyl) 2-methyl (2*S*,4*R*)-4-amino-1,2-pyrrolidinedicarboxylate (1302 mg, 4.64 mmol) was added and all together was stirred at room temperature overnight. Dimethylformamide was removed under high vacuum. The crude was added to a silica gel column and was eluted with CH₂Cl₂/MeOH 0-20% to afford the title compound as a brown oil (1.7 g, 93% yield). The compound was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C): δ 8.25 (d, *J* = 6.36 Hz, 1H), 6.62 (s, 1H), 4.50-4.44 (m, 1H), 4.42-4.37 (m, 2H), 3.69 (s, 3H), 3.67-3.64 (m, 1H), 3.36-3.32 (m, 1H), 3.03-3.01 (m, 1H), 2.59-2.52 (m, 2H), 2.34-2.27 (m, 1H), 1.39 (s, 9H), 1.29 (t, *J* = 7.09 Hz, 3H), 1.19 (t, *J* = 7.58 Hz, 3H).

methyl 1-(benzofuran-3-carbonyl)-4-(1,3-diethyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxylate (86). Compound (86) was synthesized from Boc-deprotection of compound 85 (1.7 g, 4.31 mmol) using the protocol described in the general **method C**. Solvent was evaporated under reduced pressure. The crude was dissolved with MeOH (30 ml) and then SCX resin (20 g) ("Silicycle" Si-Propulsulfonic acid, loading:0.7mmol/gr, 40-63 micron) was added to the solution. The suspension was stirred at room temperature for 30min and it was filtered and washed with MeOH (250 ml) to remove impurities. Then, the resin was stirred for 15 min with 40 ml of a solution of Ammonia Anhydrous in MeOH 7N and it was filtered and washed with Ammonia Anhydrous in MeOH 7N. The methanolic ammonia layer was evaporated under reduced pressure to afford 990 mg of methyl (4*R*)-4-{[(1,3-diethyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinate (0.99 g, 3.36 mmol, 78 % yield) as a brown oil that was used in the next step without further purification.

Methyl (4*R*)-4-{[(1,3-diethyl-1*H*-pyrazol-5-yl)carbonyl]amino}-*L*-prolinate (960 mg, 3.26 mmol) and 1-benzofuran-3-carboxylic acid (529 mg, 3.26 mmol) were dissolved in *N,N*-Dimethylformamide (10 mL). HATU (1488 mg, 3.91 mmol) and DIPEA (1.709 mL, 9.78 mmol) were then added to the mixture. The reaction was stirred at room temperature for 5 h. TLC (CH₂Cl₂/MeOH 10%) showed completion. The resulting crude was washed with NH₄Cl sat and NaHCO₃. Dried over Na₂SO₄ and filtered. Volatiles were removed under vacuum. The crude was added to a silica gel column and was eluted with CH₂Cl₂/MeOH 0-20% to afford the title compound as a yellow solid (0.96 g, 67% yield). The compound was used in the next step without further purification.

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-2-ethyl-4-methyloxazole-5-carboxamide (87).** The title compound was synthesized from 54 using the

protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 30 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (19 mg, 43% yield). MS (ESI) m/z $[M+H]^+$ = 439; 1H NMR (400 MHz, DMSO- d_6): about 80:20 mixture of rotamers, major rotamer description; δ 8.55 (s, 1H), 8.47 (d, J = 6.9 Hz, 1H), 8.03-7.99 (m, 2H), 7.66-7.60 (m, 1H), 7.40-7.30 (m, 2H), 4.65-4.50 (m, 2H), 4.14-4.10 (m, 1H), 3.72-3.68 (m, 1H), 3.12-3.07 (m, 2H), 2.78-2.66 (m, 2H), 2.34-2.26 (m, 1H), 2.29 (s, 3H), 2.15-2.00 (m, 1H), 1.25-1.21 (m, 1H), 1.03 (t, J = 7.2 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (88)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (31 mg, 68% yield). MS (ESI) m/z $[M+H]^+$ = 438; 1H NMR (400 MHz, DMSO- d_6): about 81:19 mixture of rotamers, major rotamer description; δ 8.55 (s, 1H), 8.15-7.94 (m, 4H), 7.67-7.60 (m, 1H), 7.41-7.31 (m, 2H), 4.71-4.42 (m, 2H), 4.15-4.00 (m, 3H), 3.66-3.62 (m, 1H), 3.14-2.88 (m, 1H), 2.31-2.20 (m, 1H), 2.26 (s, 3H), 2.12-2.05 (m, 1H), 1.34-1.30 (t, 3H), 1.03 (t, J = 7.1 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (89)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (45 mg, 99% yield). MS (ESI) m/z $[M+H]^+$ = 424; 1H NMR (400 MHz, DMSO- d_6): about 81:19 mixture of rotamers, major rotamer description; δ 8.55-8.51 (m, 2H), 8.01-7.98 (m, 2H), 7.68-7.65 (m, 1H), 7.41-7.30 (m, 2H), 6.59 (s, 1H), 4.65-4.49 (m, 2H), 4.18-4.10 (m, 1H), 3.91 (s, 3H), 3.71-3.64 (m, 1H), 3.15-2.84 (m, 2H), 2.33-2.06 (m, 2H), 2.13 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (90)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 10-100% water in acetonitrile 0.1% TFA, 35 ml/min, 20 min) the reaction afforded the title compound (50 mg, 99% yield). MS (ESI) m/z $[M+H]^+$ = 478; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.64-8.62 (m, 1H), 8.42-8.25 (m, 1H), 7.93-7.91 (m, 1H), 7.82-7.75 (m, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.40-7.28 (m, 2H), 6.59 (s, 1H), 4.71-4.56 (m, 2H), 4.14-4.10 (m, 1H), 4.09 (s, 3H), 3.73-3.68 (m, 1H), 3.16-3.02 (m, 2H), 2.37-2.15 (m, 2H), 1.06-0.92 (m, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-(tert-butyl)-1-methyl-1*H*-pyrazole-5-carboxamide (91)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 20 to 100% acetonitrile in water 0.1 % TFA, 20 min) the reaction afforded the title compound (42 mg, 86% yield). MS (ESI) m/z $[M+H]^+$ = 466; 1H NMR (400 MHz, DMSO- d_6): about 79:21 mixture of rotamers, major rotamer description; δ 8.56 (s, 1H), 8.52 (d, J = 7.0 Hz, 1H), 8.03-7.98 (m, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.42-7.30 (m, 2H), 6.69 (s, 1H), 4.67-4.57 (m, 2H), 4.19-4.10 (m, 1H), 3.93 (s, 3H), 3.72-3.66 (m, 1H), 3.16-2.83 (m, 2H), 2.32-2.22 (m, 1H), 2.16-2.07 (m, 1H), 1.22 (s, 9H), 1.04 (t, J = 7.3 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1-methyl-3-phenyl-1*H*-pyrazole-5-carboxamide (92)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-

30, 10-100% water in acetonitrile 0.1% TFA, 35 ml/min, 20 min) the reaction afforded the title compound (45 mg, 89% yield). MS (ESI) m/z $[M+H]^+$ = 486; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.52-8.37 (m, 2H), 7.95 (d, J = 6.9 Hz, 1H), 7.84-7.79 (m, 1H), 7.76-7.74 (m, 2H), 7.63 (d, J = 8.1 Hz, 1H), 7.44-7.29 (m, 5H), 7.21 (s, 1H), 4.74-4.60 (m, 2H), 4.18-4.10 (m, 1H), 4.07 (s, 3H), 3.76-3.71 (m, 1H), 3.16-3.02 (m, 2H), 2.39-2.16 (m, 2H), 1.00 (m, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-(furan-2-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (93)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 17 ml/min, 20 min) the reaction afforded the title compound (45 mg, 90% yield). MS (ESI) m/z $[M+H]^+$ = 476; 1H NMR (400 MHz, DMSO- d_6): about 79:21 mixture of rotamers, major rotamer description; δ 8.73 (d, J = 6.3 Hz, 1H), 8.56 (s, 1H), 8.04-7.99 (m, 2H), 7.72-7.60 (m, 2H), 7.41-7.30 (m, 2H), 7.10 (s, 1H), 6.69 (d, J = 3.2 Hz, 1H), 6.57-6.55 (m, 1H), 4.72-4.52 (m, 2H), 4.21-4.12 (m, 1H), 4.03 (s, 3H), 3.79-3.71 (m, 1H), 3.17-2.79 (m, 2H), 2.37-2.22 (m, 1H), 2.21-2.08 (m, 1H), 1.04 (t, J = 7.1 Hz, 3H).

***N*-((3*R*,5*S*)-1-(benzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1-ethyl-3-methyl-1*H*-pyrazole-5-carboxamide (94)**. The title compound was synthesized from **54** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (46 mg, 99% yield). MS (ESI) m/z $[M+H]^+$ = 438; 1H NMR (400 MHz, DMSO- d_6): about 78:22 mixture of rotamers, major rotamer description; δ 8.55-8.51 (m, 2H), 8.06-7.96 (m, 2H), 7.67-7.60 (m, 1H), 7.41-7.30 (m, 2H), 6.57 (s, 1H), 4.66-4.52 (m, 2H), 4.41-4.30 (m, 2H), 4.16-4.10 (m, 1H), 3.72-3.67 (m, 1H), 3.15-2.80 (m, 2H), 2.33-2.27 (m, 1H), 2.18-2.05 (m, 1H), 2.14 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H).

3-ethyl-*N*-((3*R*,5*S*)-1-(2-ethylbenzofuran-3-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (95). The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10 to 100% acetonitrile in water 0.1 % TFA, 17 ml/min, 20 min) the reaction afforded the title compound (34 mg, 43% yield). MS (ESI) m/z $[M+H]^+$ = 466; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.33-8.23 (m, 1H), 7.79-7.59 (m, 1H), 7.54-7.49 (m, 2H), 7.31-7.19 (m, 2H), 6.62 (s, 1H), 4.85-4.43 (m, 2H), 3.89 (s, 3H), 3.90-3.68 (m, 1H), 3.30-3.00 (m, 2H), 2.86-2.79 (m, 2H), 2.58-2.45 (m, 3H), 2.40-2.27 (m, 1H), 2.24-2.12 (m, 1H), 1.25 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.12-0.92 (m, 3H).

***N*-((3*R*,5*S*)-1-(2,3-dihydrobenzofuran-5-carbonyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide (96)**. The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10 to 100% acetonitrile in water, 17 ml/min, 20 min) the reaction afforded the title compound (35 mg, 37% yield). MS (ESI) m/z $[M+H]^+$ = 440; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.27 (br s, 1H), 7.65 (br s, 1H), 7.38 (br s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.61 (s, 1H), 4.56 (t, J = 8.6 Hz, 2H), 4.40-4.50 (m, 1H), 3.86-3.90 (m, 1H), 3.61 (br s, 1H), 3.49-3.53 (m, 1H), 3.15-3.22 (m, 1H), 3.08 (m, 1H), 2.50-2.57 (m, 2H), 2.09-2.29 (m, 2H), 1.17 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 6.9 Hz, 3H).

3-ethyl-*N*-((3*R*,5*S*)-5-(ethylcarbamoyl)-1-(5-methoxy-2-methylbenzofuran-3-carbonyl)pyrrolidin-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (97). The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 17 ml/min, 20 min)

the reaction afforded the title compound (26 mg, 54% yield). MS (ESI) m/z $[M+H]^+ = 482$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.35-8.26 (m, 1H), 7.61 (br s, 1H), 7.39 (d, $J = 8.9$ Hz, 1H), 6.99 (d, $J = 2.6$ Hz, 1H), 6.85 (dd, $J = 8.9$ Hz, $J = 2.5$ Hz, 1H), 6.68-6.58 (m, 1H), 4.75-4.42 (m, 2H), 3.89 (s, 3H), 3.90-3.75 (m, 2H), 3.74 (s, 3H), 3.18-2.80 (m, 2H), 2.57-2.49 (m, 2H), 2.41 (s, 3H), 2.38-2.26 (m, 1H), 2.20-2.10 (m, 1H), 1.17 (t, $J = 7.5$ Hz, 3H), 1.10-0.92 (m, 3H).

3-ethyl-*N*-((3*R*,5*S*)-5-(ethylcarbamoyl)-1-(4-methoxybenzoyl)pyrrolidin-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (98). The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-10, 10-100% water in acetonitrile, 4 ml/min, 20 min) the reaction afforded the title compound (21 mg, 48% yield). MS (ESI) m/z $[M+H]^+ = 428$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.27 (d, $J = 5.6$ Hz, 1H), 7.66 (d, $J = 5.2$ Hz, 1H), 7.50-7.45 (m, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.61 (s, 1H), 4.62-4.44 (m, 2H), 3.95-3.86 (m, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.54-3.47 (m, 1H), 2.58-2.49 (m, 2H), 2.46-2.44 (m, 1H), 2.28-1.99 (m, 3H), 1.22-1.13 (m, 3H), 1.05-0.97 (m, 3H).

3-ethyl-*N*-(5-(ethylcarbamoyl)-1-(1-methyl-1*H*-indole-3-carbonyl)pyrrolidin-3-yl)-1-methyl-1*H*-pyrazole-5-carboxamide (99). The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile, 15 ml/min, 21 min) the reaction afforded the title compound (32 mg, 33% yield). MS (ESI) m/z $[M+H]^+ = 451$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.33 (br s, 1H), 7.71 (br s, 1H), 7.58 (d, $J = 8.2$ Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.4$ Hz, 1H), 6.75 (br s, 1H), 6.63 (s, 1H), 4.66 (dd, $J = 8.2$ and 5 Hz m, 1H), 4.50 (m, 1H), 3.93 (s, 3H), 3.78 (s, 3H), 3.66-3.72 (m, 1H), 2.50-2.58 (m, 2H), 2.27-2.37 (m, 1H), 2.12-2.20 (m, 1H), 1.17 (t, $J = 7.6$ Hz, 3H).

***N*-((3*R*,5*S*)-1-(2-(benzofuran-3-yl)acetyl)-5-(ethylcarbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamide 2,2,2-trifluoroacetate (100)**. The title compound was synthesized from **5** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile, 15 ml/min, 21 min) the reaction afforded the title compound (40 mg, 70% yield). MS (ESI) m/z $[M+H]^+ = 450$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.5-8.45 (m, 1H), 8.28 (br s, 1H), 7.88 (br s, 1H), 7.58 (d, $J = 7.62$ Hz, 1H), 7.52 (d, $J = 7.77$ Hz, 2H), 7.31-7.24 (m, 2H), 6.63 (br s, 1H), 4.50-4.65 (m, 1H), 4.40-4.34 (m, 1H), 4.03-3.92 (m, 4H), 3.85-7.65 (m, 3H), 3.52-3.48 (m, 2H), 3.20-2.98 (m, 2H), 2.25-2.00 (m, 2H), 1.15 (t, $J = 7.62$ Hz, 3H), 0.99 (t, $J = 7.32$ Hz, 3H).

methyl 2-((2*S*,4*R*)-4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)-1-(2-ethylbenzofuran-3-carbonyl)pyrrolidine-2-carboxamido)acetate (101). The title compound was synthesized from **63** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 10-100% water in acetonitrile 0.1% TFA, 35 ml/min, 21 min) the reaction afforded the title compound (32 mg, 55% yield). MS (ESI) m/z $[M+H]^+ = 510$; 1H NMR (400 MHz, DMSO- d_6): δ 8.23 (br s, 1H), 7.95 (br s, 1H), 7.52 (d, $J = 7.83$ Hz, 2H), 7.31-7.19 (m, 2H), 6.62 (s, 1H), 4.84 (br s, 1H), 4.51-4.43 (m, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 3.84-3.33 (m, 4H), 2.83 (q, $J = 7.58$ Hz, 2H), 2.55 (q, $J = 7.58$ Hz, 2H), 2.42-2.27 (m, 2H), 1.24 (t, $J = 7.58$ Hz, 3H), 1.19 (t, $J = 7.58$ Hz, 3H).

methyl 2-((2*S*,4*R*)-1-(benzo[*b*]thiophene-3-carbonyl)-4-(3-ethyl-1-methyl-1*H*-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (102). The title compound was synthesized from **63** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 20 to 100% acetonitrile in water 0.1% TFA, 20 min) the

reaction afforded the title compound (47 mg, 81% yield). MS (ESI) m/z $[M+H]^+ = 498$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.33-8.26 (m, 2H), 8.03-7.95 (m, 3H), 7.44-7.36 (m, 2H), 6.61 (s, 1H), 4.85-4.71 (m, 1H), 4.54-4.47 (m, 1H), 3.92-3.86 (m, 3H), 3.90 (s, 3H), 3.67 (s, 3H), 3.39-3.46 (m, 1H), 2.58-3.50 (m, 2H), 2.36-2.21 (m, 2H), 1.18 (t, $J = 7.5$ Hz, 3H).

methyl 2-((2S,4R)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)-1-(2-phenylbenzofuran-3-carbonyl)pyrrolidine-2-carboxamido)acetate (103). The title compound was synthesized from **63** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 10-100% water in acetonitrile 0.1% TFA, 35 ml/min, 21 min) the reaction afforded the title compound (28 mg, 44% yield). MS (ESI) m/z $[M+H]^+ = 558$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.25-8.11 (m, 2H), 7.91-7.81 (m, 2H), 7.63 (d, $J = 8.08$ Hz, 2H), 7.46-7.36 (m, 4H), 7.28-7.23 (m, 1H), 6.53 (s, 1H), 4.99-4.96 (m, 1H), 4.45-4.38 (m, 1H), 4.11-3.83 (m, 2H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62-3.55 (m, 1H), 3.30-3.25 (m, 1H), 2.54-2.49 (m, 2H), 2.41-2.27 (m, 2H), 1.16 (t, $J = 7.45$ Hz, 3H),

methyl 2-((2S,4R)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)-1-(6-methoxybenzo[b]thiophene-3-carbonyl)pyrrolidine-2-carboxamido)acetate (104). The title compound was synthesized from **63** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 17 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (31 mg, 57% yield). MS (ESI) m/z $[M+H]^+ = 528$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.31-8.25 (m, 2H), 7.85-7.80 (m, 2H), 7.57 (d, $J = 2.3$ Hz, 1H), 7.00 (dd, $J = 8.8$ Hz, 2.3 Hz, 1H), 6.61 (s, 1H), 4.87-4.68 (m, 1H), 4.56-4.45 (m, 1H), 3.95-3.83 (m, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 3.39-3.46 (m, 1H), 2.58-3.50 (m, 2H), 2.38-2.20 (m, 2H), 1.18 (t, $J = 7.6$ Hz, 3H).

ethyl 3-((2S,4R)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carbonyl)benzofuran-2-carboxylate (105). The title compound was synthesized from **63** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 10-100% water in acetonitrile 0.1% TFA, 35 ml/min, 21 min) the reaction afforded the title compound (26 mg, 41% yield). MS (ESI) m/z $[M+H]^+ = 554$; 1H NMR (400 MHz, CDCl₃): δ 8.02-7.93 (m, 2H), 7.79-7.70 (m, 1H), 7.45-7.33 (m, 2H), 7.22-7.19 (m, 1H), 6.50 (s, 1H), 5.29-5.25 (m, 1H), 4.45-4.31 (m, 2H), 4.25-4.17 (m, 2H), 4.05-3.98 (m, 2H), 3.95 (s, 3H), 3.76 (s, 3H), 3.71-3.66 (m, 1H), 2.72-2.66 (m, 2H), 2.47-2.31 (m, 2H), 1.44 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.5$ Hz, 3H).

2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetic acid (106). The title compound was synthesized from **11** using the protocol described in the general **method B**. The reaction afforded the title compound (910 mg, 90% yield). MS (ESI) m/z $[M+H]^+ = 467$; 1H NMR (400 MHz, DMSO- d_6): about 74:26 mixture of rotamers, major rotamer description; δ 12.58 (br s, 1H), 8.56-8.52 (m, 2H), 8.37-8.32 (m, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 8.1$ Hz, 1H), 7.41-7.31 (m, 2H), 6.64 (s, 1H), 4.77-4.74 (m, 1H), 4.62-4.48 (m, 1H), 4.18-4.14 (m, 1H), 3.92 (s, 3H), 3.84-3.69 (m, 3H), 2.56-2.50 (m, 2H), 2.33-2.26 (m, 1H), 2.21-2.15 (m, 1H), 1.16-1.12 (m, 3H).

Methyl (4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino-L-prolyl-L-alaninate (107). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC (XBridge-30, 20-100%, Water 10 nM NH₄HCO₃/ACN) purification the reaction afforded the title compound as a white solid (13 mg, 17% yield). MS (ESI) m/z $[M+H]^+ = 496$; 1H NMR (400 MHz, DMSO- d_6):

δ 8.30 (br s, 1H), 8.28 (d, $J = 6.60$ Hz, 1H), 8.20 (d, $J = 7.34$ Hz, 1H), 7.94 (d, $J = 7.34$ Hz, 1H), 7.62 (d, $J = 8.07$ Hz, 1H), 7.39 (t, $J = 7.34$ Hz, 1H), 7.33 (t, $J = 7.83$ Hz, 1H), 6.63 (s, 1H), 4.81-4.78 (m, 1H), 4.72-4.63 (m, 1H), 4.38-4.27 (m, 1H), 4.11-4.02 (m, 1H), 3.95 (s, 3H), 3.73-3.68 (m, 1H), 3.65 (s, 3H), 2.58-2.53 (m, 2H), 2.40-2.32 (m, 1H), 2.28-2.22 (m, 1H), 1.19 (t, $J = 7.58$ Hz, 3H).

(S)-methyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)-3-hydroxypropanoate (108)- The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (XBridge-30, 35 ml/min, 10 to 100% acetonitrile in water, 10nM NH_4HCO_3 , BASIC, 20 min) the reaction afforded the title compound (42 mg, 70% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 511$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$): δ 8.35 (br s, 1H), 8.28 (d, $J = 6.4$ Hz, 1H), 8.09-8.08 (m, 1H), 7.94 (d, $J = 7.3$ Hz, 1H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.40-7.38 (m, 2H), 6.62 (s, 1H), 4.89-4.86 (m, 1H), 4.79-4.77 (m, 1H), 4.61-4.56 (m, 1H), 4.40-4.35 (m, 1H), 4.08-4.03 (m, 1H), 3.95 (s, 3H), 3.73-3.70 (m, 2H), 3.66 (s, 3H), 2.57-2.51 (m, 2H), 2.39-2.26 (m, 2H), 1.18 (t, $J = 7.6$ Hz, 3H).

ethyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (109). The title compound was synthesized from **10** using the protocol described in the general **method A**. The crude was added to a silica gel column and was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 15:1 to afford the title compound as a beige solid (26 mg, 58.3% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 496$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$): about 75:25 mixture of rotamers, major rotamer description; δ 8.55 (s, 1H), 8.53 (d, $J = 7.07$ Hz, 1H), 8.47-8.45 (m, 1H), 7.99 (d, $J = 7.58$ Hz, 1H), 7.65 (d, $J = 8.08$ Hz, 1H), 7.40-7.30 (m, 2H), 6.63 (s, 1H), 4.76-4.72 (m, 1H), 4.63-4.57 (m, 1H), 4.18-4.14 (m, 1H), 4.09 (q, $J = 7.24$ Hz, 2H), 3.91 (s, 3H), 3.87-3.83 (m, 2H), 3.71-3.67 (m, 1H), 2.53-2.47 (m, 2H), 2.35-2.28 (m, 1H), 2.20-2.15 (m, 1H), 1.20-1.11 (m, 6H).

isopropyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (110). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 35 ml/min, 40 to 100% acetonitrile in water, 20 min) the reaction afforded the title compound (31.6 mg, 79% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 510$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$): δ 8.36 (br s, 1H), 8.29 (d, $J = 6.36$ Hz, 1H), 8.23 (br s, 1H), 7.96 (d, $J = 7.34$ Hz, 1H), 7.63 (d, $J = 8.30$ Hz, 1H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 1H), 6.62 (s, 1H), 4.95 (sept, $J = 6.17$ Hz, 1H), 4.83-4.80 (m, 1H), 4.64-4.59 (m, 1H), 4.09 (br s, 1H), 3.94 (s, 3H), 3.89-3.77 (m, 2H), 3.75-3.71 (m, 1H), 2.55 (m, 2H), 2.39-2.26 (m, 2H), 1.23-1.21 (m, 6H), 1.18 (t, $J = 7.58$ Hz, 3H).

tert-butyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (111). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 20 to 100% acetonitrile in water 0.1 % TFA, 20 min) the reaction afforded the title compound (40 mg, 60% yield). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 524$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, 80 $^\circ\text{C}$): δ 8.38 (br s, 1H), 8.33 (d, $J = 6.7$ Hz, 1H), 8.20 (br s, 1H), 7.95 (d, $J = 7.2$ Hz, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.41-7.29 (m, 2H), 6.62 (s, 1H), 4.82-4.78 (m, 1H), 4.66-4.55 (m, 1H), 4.15-4.03 (m, 1H), 3.93 (s, 3H), 3.83-3.67 (m, 3H), 2.57-2.51 (m, 2H), 2.39-2.23 (m, 2H), 1.43 (s, 9H), 1.17 (t, $J = 7.6$ Hz, 3H).

cyclopentyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (112). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 35 ml/min, 40 to 100% acetonitrile in water, 20 min) the reaction afforded the title compound (23 mg, 54.3% yield). MS (ESI) m/z $[M+H]^+ = 536$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.36 (br s, 1H), 8.29 (d, $J = 6.60$ Hz, 1H), 8.22 (br s, 1H), 7.96 (d, $J = 7.34$ Hz, 1H), 7.63 (d, $J = 8.30$ Hz, 1H), 7.41-7.27 (m, 1H), 7.34-7.31 (m, 1H), 6.62 (s, 1H), 5.15-5.10 (m, 1H), 4.83-4.80 (m, 1H), 4.63-4.58 (m, 1H), 4.13-4.06 (m, 1H), 3.94 (s, 3H), 3.89-3.76 (m, 2H), 3.74-3.70 (m, 1H), 2.59-2.52 (m, 2H), 2.39-2.28 (m, 2H), 1.88-1.81 (m, 2H), 1.70-1.60 (m, 4H), 1.59-1.51 (m, 2H), 1.18 (t, $J = 7.58$ Hz, 3H).

benzyl 2-((2S,4R)-1-(benzofuran-3-carbonyl)-4-(3-ethyl-1-methyl-1H-pyrazole-5-carboxamido)pyrrolidine-2-carboxamido)acetate (113). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 10 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (45 mg, 53% yield). MS (ESI) m/z $[M+H]^+ = 558$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.44-8.28 (m, 3H), 7.95 (d, $J = 8.3$ Hz, 1H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.41-7.29 (m, 7H), 6.62 (s, 1H), 5.15 (s, 2H), 4.83-4.79 (m, 1H), 4.62-4.56 (m, 1H), 4.14-4.02 (m, 1H), 3.96-3.91 (m, 2H), 3.94 (s, 3H), 3.74-3.69 (m, 1H), 2.58-2.48 (m, 2H), 2.37-2.20 (m, 2H), 1.17 (t, $J = 7.5$ Hz, 3H).

N-((3R,5S)-5-((2-amino-2-oxoethyl)carbamoyl)-1-(benzofuran-3-carbonyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (114). To methyl (4R)-1-(1-benzofuran-3-ylcarbonyl)-4-[(3-ethyl-1-methyl-1H-pyrazol-5-yl)carbonyl]amino-L-prolylglycinate **11** (0.020 g, 0.042 mmol) was added a solution of ammonia (1.5 mL). The resulting mixture was stirred at room temperature overnight. The reaction was concentrated to dryness to the title compound as a light brown solid (17 mg, 83% yield). MS (ESI) m/z $[M+H]^+ = 467$; 1H NMR (400 MHz, DMSO- d_6 , 80 °C): δ 8.57 (s, 1H), 8.57-8.55 (m, 1H), 8.51-8.48 (m, 1H), 7.97 (d, $J = 7.58$ Hz, 1H), 7.66 (d, $J = 8.31$ Hz, 1H), 7.41-7.30 (m, 2H), 7.20 (d, $J = 6.36$ Hz, 2H), 6.64 (s, 1H), 4.67-4.60 (m, 2H), 4.19-4.15 (m, 1H), 3.92 (s, 3H), 3.75-3.71 (m, 1H), 3.65-3.62 (m, 2H), 2.53-2.47 (m, 2H), 2.33-2.28 (m, 1H), 2.20-2.13 (m, 1H), 1.13 (t, $J = 7.58$ Hz, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-((2-(methylamino)-2-oxoethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (115). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-19, 10-100% water in acetonitrile 0.1% TFA, 15 ml/min, 21 min) the reaction afforded the title compound (25 mg, 43% yield). MS (ESI) m/z $[M+H]^+ = 481$; 1H NMR (400 MHz, DMSO- d_6): δ 8.61-8.49 (m, 3H), 8.04-8.01 (m, 1H), 7.75-7.67 (m, 2H), 7.43-7.31 (m, 2H), 6.65 (s, 1H), 4.69-4.59 (m, 2H), 4.23-4.15 (m, 1H), 3.94 (s, 3H), 3.71-3.59 (m, 3H), 2.63 (d, $J = 4.4$ Hz, 3H), 2.55-2.44 (m, 2H), 2.37-2.12 (m, 2H), 1.14 (t, $J = 7.6$ Hz, 3H).

N-((3R,5S)-1-(benzofuran-3-carbonyl)-5-((2-(dimethylamino)-2-oxoethyl)carbamoyl)pyrrolidin-3-yl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (116). The title compound was synthesized from **10** using the protocol described in the general **method A**. After preparative HPLC purification (SunFire-30, 35 ml/min, 30 to 100% acetonitrile in water 0.1% TFA, 20 min) the reaction afforded the title compound (42 mg, 76% yield). MS (ESI) m/z $[M+H]^+ = 495$; 1H NMR (400 MHz, DMSO- d_6): about 70:30 mixture of rotamers, major rotamer description; δ 8.59-8.50 (m, 2H), 8.08-8.06 (m, 1H), 7.98 (d, $J = 7.58$ Hz, 1H), 7.66-7.63 (m,

1H), 7.40-7.30 (m, 2H), 6.63 (s, 1H), 4.81-4.77 (m, 1H), 4.63-4.53 (m, 1H), 4.16-4.12 (m, 1H), 4.03-3.82 (m, 2H), 3.91 (s, 3H), 3.69-3.65 (m, 1H), 2.95 (s, 3H), 2.83 (s, 3H), 2.53-2.47 (m, 2H), 2.33-2.20 (m, 2H), 1.15-1.11 (m, 3H).

X-ray Statistics, Crystallisation and crystallography material and methods

X-ray statistics; Omit maps; detailed experimental

Accession Codes

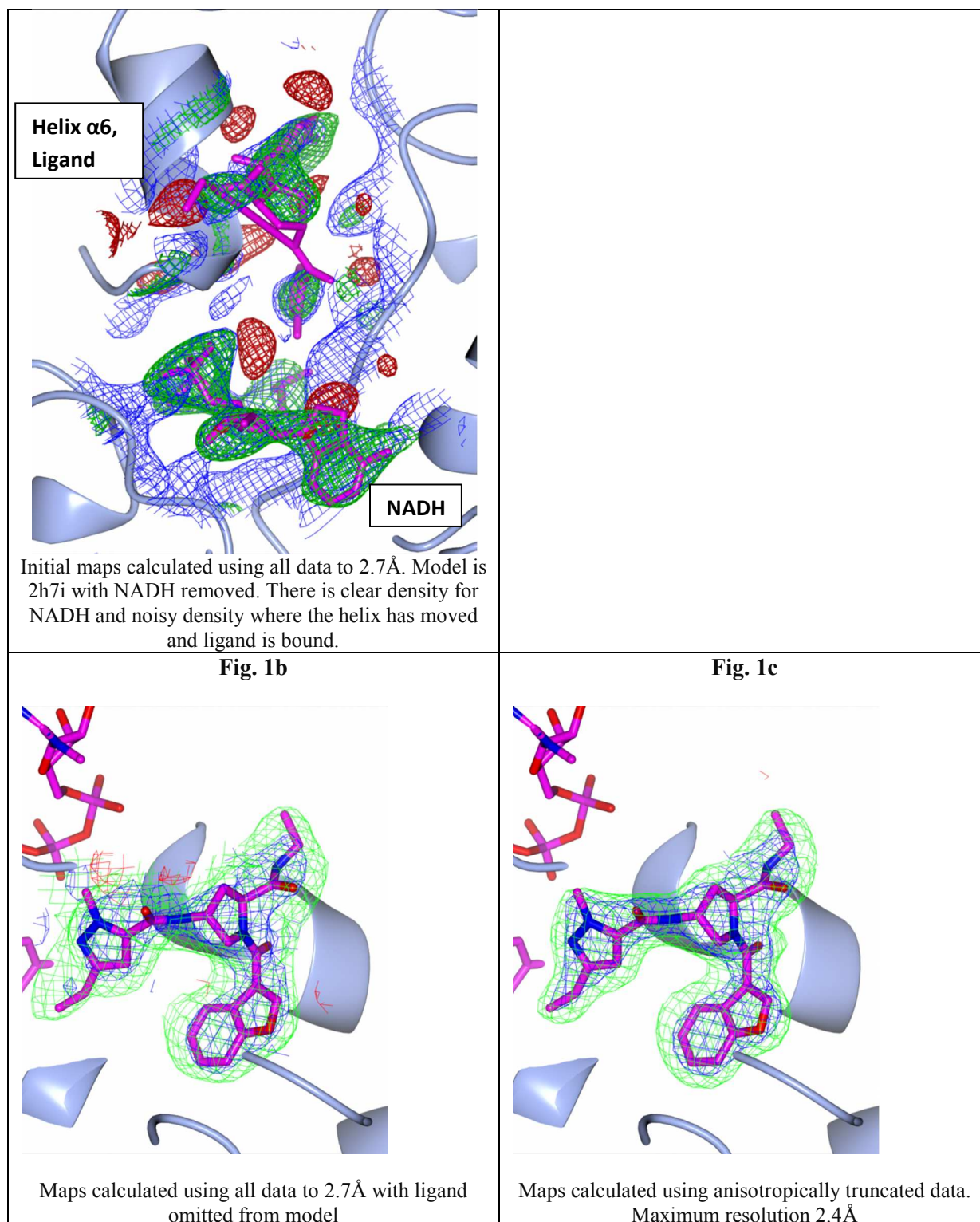
Coordinates have been deposited with the Protein Data Bank XXXX and will be released immediately on publication.

Table of X-ray Statistics

InhA	Compound 7 All data to 2.4 Å	Compound 7 All data to 2.7 Å	Compound 7 Anisotropic corrected data
	(xxxx.pdb)		
Data collection			
Space Group	P212121	P212121	P212121
Cell Dimensions			
a,b,c (Å)	100.18, 102.35, 179.36	100.18, 102.35, 179.36	100.18, 102.35, 179.36
α, β, γ (°)	90.00,90.00, 90.00	90.00,90.00, 90.00	90.00,90.00, 90.00
Resolution (Å)	2.4 (2.53)	2.7 (2.85)	
R _{merge} ^b	0.158 (1.977)	0.122 (0.751)	
Average I/ σ	10.3 (1.0)	13.3 (2.6)	
Completeness (%)	100 (100)	100 (100)	
Redundancy	7.2 (7.0)	7.2 (7.4)	
No. Reflections	525679 (73628)	371090 (54702)	
No. Unique Reflections	72859 (10480)	1451 (7392)	
Refinement			
Resolution (Å)			35.14-2.40
R _{work} /R _{free}			0.1703(0.2064)
No. Reflections			51787
Completeness in range			71.2%
No. atoms			9056
Protein			7984
Ligand/ion			688
Water			384
B-factors			
Protein			63.46
NAD/Ligand			61.04/57.50
Water			52.55
R.m.s deviations			
Bond lengths (Å)			0.010
Bond angles (°)			1.22

Supporting Figure 1. Electron Density maps for compound 7.

Fig. 1a	<p>In all figures: Dark blue = 2Fo – Fc 1.0 sigma Red = Fo–Fc -3.0 sigma, Green = Fo-Fc 3.0 sigma Magenta = NADH and Ligand Light blue = InhA</p>
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Crystallisation and crystallography material and methods

Untagged InhA was expressed in *E. Coli* and purified in two steps by IEC (Resource 15Q column) and Size Exclusion (HiLoad Superdex 75 Prep-grade column) chromatography. The protein (4.15 mg/ml in 20 mM Tris pH 8.0, 0.1 M NaCl, 2mM DTT) was incubated with NADH

(300 μ M) and compound (150 μ M) prior to crystallisation. The complex crystallised in 10% PEG 8000 & 0.1 M Tris pH 8.5 (Mb Class II suite from Qiagen) by vapour diffusion in 100 nl + 100 nl sitting drops at 20 °C. Cryoprotection prior to data collection was carried out by briefly transferring a crystal to a drop containing 25% ethylene glycol and well solution. Data was collected at European Synchrotron Radiation Facility, Grenoble, on beamline ID23 eh1 using an ADSC detector.

The diffraction was very anisotropic, spots were observed to 2.4Å in some directions, but only 3.4Å in other directions. For initial structure solution the data was processed using MOSFLM¹ and SCALA² from the CCP4 suite³ to 2.7Å. The structure was solved using PHASER⁴ and a high resolution structure for InhA, pdb code 2h7i⁵. There are four molecules in the asymmetric unit. Initial maps showed clear density for the NADH which was not included in the model and a large movement in the helix close to the putative compound binding site, see Figure 1a for the initial map with final model superposed at the ligand 1 binding site.

The maps were very noisy and model building was difficult. Different ways of dealing with the data were explored and using the "Diffraction Anisotropy Server"⁶ with the data to 2.4Å produced the best maps. The server performed an ellipsoidal truncation of the data, truncating data in the a* direction to 3.4Å but leaving the data to 2.4Å in the other directions and subsequently anisotropic scaling was applied. Model building was carried out in COOT⁷ and the final refinement in BUSTER⁸ with anisotropic B-factor refinement. Figure 1b and 1c show Fo-Fc omit maps in a region of ligand 1 using all data to 2.7Å and the anisotropic truncated data to 2.4Å respectively.

The final model is deposited in the protein data bank under accession code 4cod.

General antimicrobial activity assay

Whole-cell antimicrobial activity was determined by broth microdilution using the Clinical and Laboratory Standards Institute (CLSI) recommended procedure, Document M7-A7, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". Some compounds have been evaluated against a panel of Gram-positive and Gram-negative organisms, including *Enterococcus faecium*, *Enterococcus faecalis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Escherichia coli* and *Streptococcus pyogenes*. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound producing a >80 % reduction in fluorescence observed.

Plasma protein binding (PPB)

Typically 200ul plasma were spiked with test compound at final concentration 1uM (max org solvent 1%) and dialyzed against 350ul PBS (pH 7.4) for 4-6 hours at 37 °C. After incubation, the contents of each plasma and buffer compartment were transferred to a 96-well plate with equal volumes of control buffer or plasma as appropriate to maintain matrix equivalence for analysis. Plasma proteins were then precipitated by the addition of acetonitrile/methanol (80:20) containing internal standard. The plates were centrifuged for 15 min at 3700 rpm (4 °C), and the supernatant was removed for analysis by mass spectrometry (LC-MS/MS) to determine the percentage of test compound in the buffer and plasma chambers from Analyte peak areas relative to the internal standard peak areas. The percentage bound and unbound was calculated as follows:

$$\% \text{unbound} = ([\text{Buffer chamber}] / [\text{Plasma chamber}] \times 100$$

$$\% \text{PPB} = 100 - \% \text{Unbound}$$

Blood stability assay

The stability of each compound was assessed in either CD1 or C57/BL6 mouse whole blood collected on the day of the experiment in EDTA tubes. Typically 1 mL of blood was spiked with 1 μ L of a 10 mM of each test compound solution to produce a 10 μ M incubation. Three separate 300 μ L aliquots were then taken from each tube and incubated at 37 $^{\circ}$ C. At each time point (0, 15, 30, 60 and 120 min), 50 μ L of blood were collected from each sample over 50 μ L of MilliQ water. Samples were extracted by protein precipitation with 250 μ L of 0.1% AcOH acetonitrile methanol 3-1 v:v containing 1 μ M internal standard and centrifuged for 10min at 7000 rpm. Supernatants were collected prior the injection onto an LC-MS/MS system Analyte/Internal standard peak area ratios were referenced to the zero time-point samples as 100% in order to determine the percentage of compound remaining for each time-point. Ln plots of the % remaining for each compound were used to determine the half-life for the blood incubations.

Kinetic solubility assay

5 ml of 10 mM DMSO stock solution diluted to 100 ml with pH 7.4 phosphate buffered saline, equilibrated for 1 h at RT, filtered through Millipore Multiscreen HTS-PCF filter plates (MSSL BPC). The eluent is quantified by suitably calibrated flow injection CLND.

Hydrophobicity assay

10 ml of 10 mM DMSO stock solution diluted to 750 ml with octanol saturated pH 7.4 phosphate buffer and 160 ml buffer saturated octanol in a 96 well deep well block. Block sealed and inverted for 3 sets of 50 inversions, then centrifuged at 300 g for 20 min. Both phases are then quantified using generic gradient UV-HPLC.IC50

Microsomal fraction stability experimental procedure

Pooled mouse and human liver microsomes are purchased from Xenotech. Microsomes (final protein concentration 0.5 mg/mL, $MgCl_2$ (final concentration = 5 mM) and test compound (final substrate concentration = 0.5 μ M; final DMSO concentration = 0.5%) in 0.1 M phosphate buffer pH 7.4 are pre-incubated at 37 $^{\circ}$ C prior to the addition of NADPH (final concentration = 1 mM) to initiate the reaction. The final incubation volume is 600 μ L. A control incubation is included for each compound tested where 0.1 M phosphate buffer pH 7.4 is added instead of NADPH (minus NADPH). One control compound is included with each species. All incubations are performed singularly for each test compound. Each compound is incubated for 30 minutes and samples (90 μ L) of incubate are taken at 0, 5, 15, 20 and 30 min. The control (minus NADPH) is sampled at 30 min only. The reactions are stopped by the addition of sample to 200 μ L Acetonitrile: Methanol 3:1 containing internal standard. The terminated samples are centrifuged at 2,500 rpm for 20 min at 4 $^{\circ}$ C to precipitate the protein. Quantitative analysis: following protein precipitation, the samples were analyzed using specific LC-MS/MS conditions. Data analysis: from a plot of ln peak area ratio (compound peak area/internal standard peak area) against time, the gradient of the line was determined. Subsequently, half-life and intrinsic clearance were calculated using the equations below:

Elimination rate constant (k) = (- gradient)

$$\text{Half life } (t_{1/2}) \text{ (min)} = \frac{0.693}{k}$$

$$\text{Intrinsic Clearance } (CL_{int}) \text{ (ml/min/g protein)} = \frac{V \times 0.693}{t_{1/2}} \text{ where } V = \text{Incubation volume ml/g microsomal protein.}$$

Hepatocyte assays for MetID

Mouse and human cryopreserved hepatocytes were thawed and re-suspended in 5 mL DEMEM according to XenoTech's standard Protocol. Cells were diluted to the desired concentration of 1.0×10^6 cells/mL with supplemented DMEM at 37 °C and approximately 0.5 mL suspension was pre-incubated for each compound. After a 10 min pre-incubation, test compounds and control were added and incubations were performed in a humidified incubator at 37 °C on a rotary shaker at a final test or control compounds concentration of 10 µM (1µM for Cli determination) and a cell density of 0.5×10^6 viable cells/mL. After 4 hours incubation (2h for Cli determination), samples were removed from the incubation mixture and added to 80:20 acetonitrile/methanol (1 mL) to stop the reaction. After centrifugation, aliquots of the supernatants were analyzed using high resolution LCMS/MS. Incubations without cells were performed in order to determine the stability of the compound and propranolol was used a control for both species.

All samples were examined by ACD (Advanced Chemistry Development, Toronto, Ontario) IntelliXtract software for potential metabolites. All typical and atypical possible metabolites were looked for. $Cl_{int} = (0.693/t_{1/2}) \times (\text{mL per incubation} / \# \text{ cells per incubation}) \times (\# \text{ cells/gram wet weight tissue}) \times (\text{gram wet weight tissue/kg body weight})$

Cytochrome P450 (CYP450)

The P450 inhibition profile of the InhA inhibitors was determined as previously described in reference 9.

hERG dofetilide

The hERG inhibition profile of the InhA inhibitors was determined as previously described in reference 10.

HepG2 cytotoxicity assay

Cell line HepG2 (HB-8065) were cultured with fresh medium (Essential Minimum Eagle Medium, EMEM, supplemented with 5% fetal calf serum and 2mM L-glutamine) the day before subculturing the plates. On the day of the assay, cells (10,000 cells/well) were seeded in a black 96-well collagen coated microplate with clear bottom, (Becton Dickinson®) except in column 11, that was dispensed only 100µL of culture medium.

Stock solution from each test substances was prepared in 100% DMSO. Ten serial 1:2 dilutions were prepared of each test compound and, finally, a 1:200 dilution was made, in medium, to achieve a final concentration of 0.5% of DMSO. Resazurin tablets (Merck®) were dissolved in phosphate buffer saline at a concentration of 0.0042%.

After 24h of incubation of the cells (37 °C, 5% CO₂, 95% relative humidity), a volume of 150 µL of culture medium containing the appropriate test concentrations of the compounds dilutions were added to cells in two replicates. In column 12, only 150µL of 0.5% DMSO was added (blank control). Then, cells were exposed to test compounds for 48 h. After that, medium was removed and Resazurin solution was added to each well and incubated for further 1.5h. Fluorescence was measured at an excitation wavelength of 515 nm and an emission wavelength of 590nm in a Microplate reader 1420 Multilabel HTS counter, Victor 2, (Wallac®) The fluorescence value of each well is corrected by subtracting the background value (average of column 11) from the absolute value. The percentages of inhibition are calculated relatively to the DMSO control wells (average of column 12). For each compound, the average value of the duplicate samples is calculated. Data were processed using an Excel spreadsheet and GraphPad Software analysis. Tox50 values were calculated from the Sigmoidal dose-response (variable slope) curves by nonlinear regression analysis.

Intracellular Growth assay

Human THP-1 monocytes have been shown as a good model to study the intracellular stages of *Mycobacterium tuberculosis*. A luminescent strain was used to infect the monocytes. This provides a much more rapid assessment of the bacterial viability (5 days) as compared to colony forming unit (CFU) assay which takes more than 3 weeks to form countable colonies. The objective of this assay is to identify intracellular inhibitors of the *M. tuberculosis* growth as part of a global effort focused on the search of new antitubercular drugs. The assay determines the effect of the compounds on mycobacteria growing inside phagocytes by determining luciferase activity per well, which is related to the number of living bacteria.

Mycobacterial preparation

Prior to day of infection subculture mycobacteria cultures at density needed to have an OD 600 nm that will be between 0.6-1 at time of infection 0. Pellet 160 ml (5 x 50 mL sterile tubes) of mycobacterial cultures at 3500 rpm for 10 min. Aseptically disperse the bacterial pellet of each tube by shaking with 10 glass beads during 60 seconds. Add 6 mL of RPMI fresh media and incubate for 5 min. Pipette 5 mL of the supernatant carefully and discard the rest. Collect all the supernatants into the same sterile tube and centrifuge at 1500 rpm for 8 min. Collect the supernatant and discard the pellet. Measure OD 600 nm of dispersed bacterial suspension using a 1:3 or 1:4 dilution into RPMI-0.05% Tween 80. Calculate MOI of 1 for H37Rv, using the following conversion: An OD of 0.1 = 10^7 CFU/mL.

THP1 cell preparation

THP1 cells are maintained in suspension with RPMI-1640 media containing 10% FBS, 1 mM of Pyruvate, 2 mM of L-Glutamine, and incubated at 37 °C with 5% CO₂. Monocytes are grown to sub-confluence (5×10^5 cell/ml) and infected ON in a cell roller bottle with a MOI of 10 for BCG or infected during 4 h. with a MOI of 1 for H37Rv. Excess bacteria are removed by washing five times in RPMI media (1500 rpm 5min.). 100 ul/well (50.000 cells/well) of infected cells are dispensed in 96 well white plates. 1:3 serial dilutions of antitubercular agents are added to the cell plates. As DMSO damages cells, the percentage must be reduced under 0.5% by diluting 1:400 in culture medium. Luminescence is measured after 5 days using the Steady-Glo Promega kit into a Victor 1420 system. Results are processed by using an Excel spreadsheet and Graft software. MIC90 values are calculated from the dose-response curves by non-linear regression analysis.

Killing kinetics assay

From a exponential culture of *M. tuberculosis* H37Rv 5×10^5 cfus/ml were been inoculated in 10 ml Middlebrook 7H9 10% ADC and 0.05% Tween 80 with 20xMIC of the compound to be tested (in triplicated).. At specified time points, aliquots of cultures were withdrawn, serially diluted in 7H9 broth Tween and plated on solid culture medium. Plates were then incubated at 37 °C and CFU were counted after 3 to 4 weeks.

Tolerability studies

For Tolerability studies C57BL/6 female mice of 18-20 g weight were used (n=6 mice). Drugs were administered as 1% methyl cellulose suspensions. The Up-and-Down method of experimentation is an adaptive procedure for conducting dose-response experiments having yes/no end-point. Animals are dosed one at a time at the best estimate MNLD. The dose for each successive animal is adjusted up or down, depending on the outcome of the previous animal. After reaching the reversal of the initial direction (the point where a decreasing dose pattern requires an increase due a tested animal's survival or an increasing dose pattern results in a decrease due to lethality), four additional animals are dosed using the same up and down dose

pattern. The maximal no lethal dose is calculated using the maximum likelihood algorithm. If any animal died or acute clinical signs were noted, the Up-&-Down procedure was carried out based on toxicological signs (functional observational battery). According to the Up-&-Down statistical procedure based on if, two dose levels were determined; a dose that caused adverse clinical signs to 5% of animals (SD05) and a higher one that causes signs of toxicity at 95% of animals (SD95). Functional observational battery (FOB) and bodyweight gain were recorded and the animals were killed 24 hours and 48 hours after treatment and blood was sampled by intra-cardiac puncture for clinical chemistry and hematology analysis in He-Li tubes. Necropsy was carried out and the major organs were weighed and preserved in formalin.

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