Electronic Supplementary Material (ESI) for MedChemComm.
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Experimental Section

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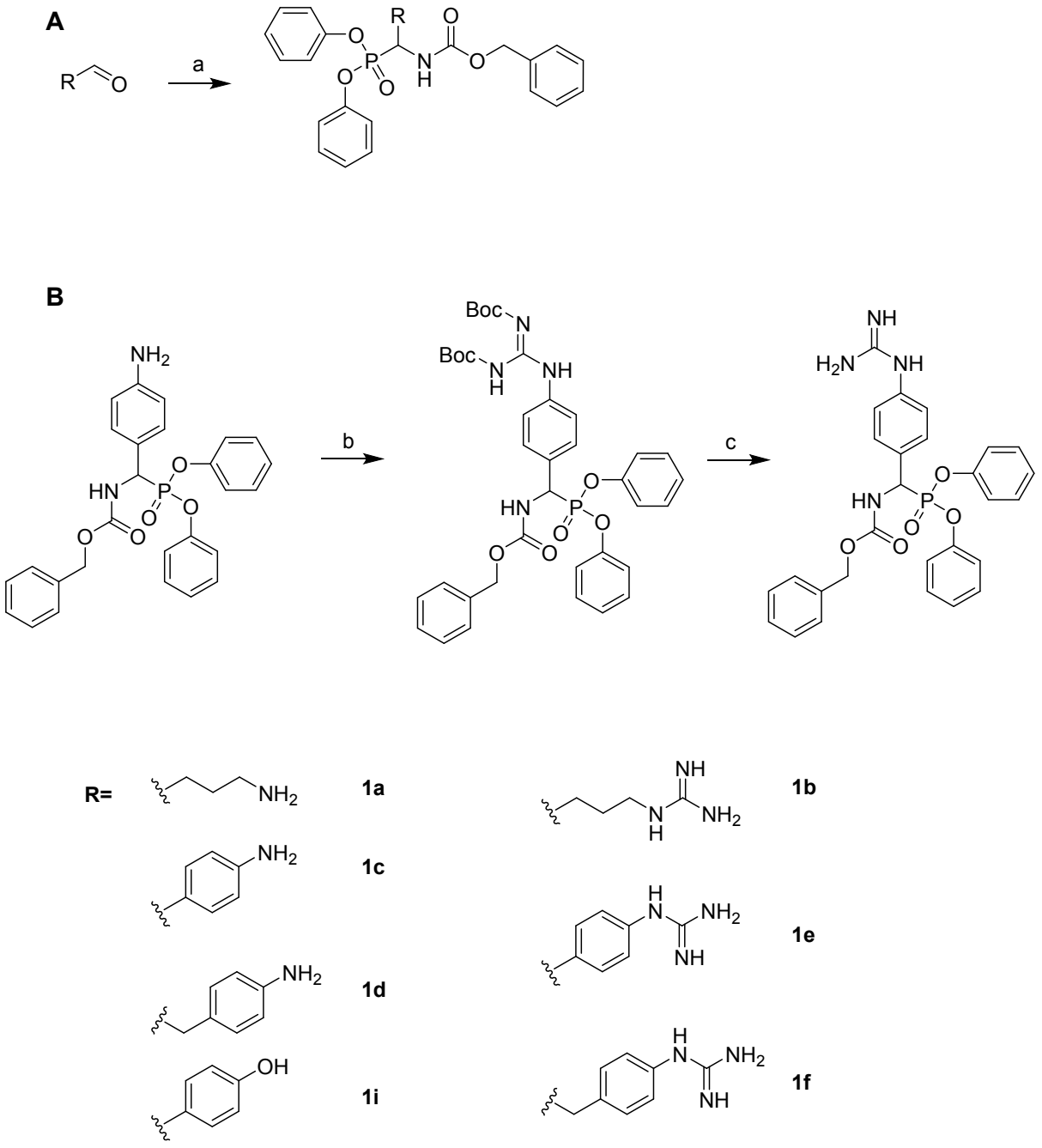
1. General

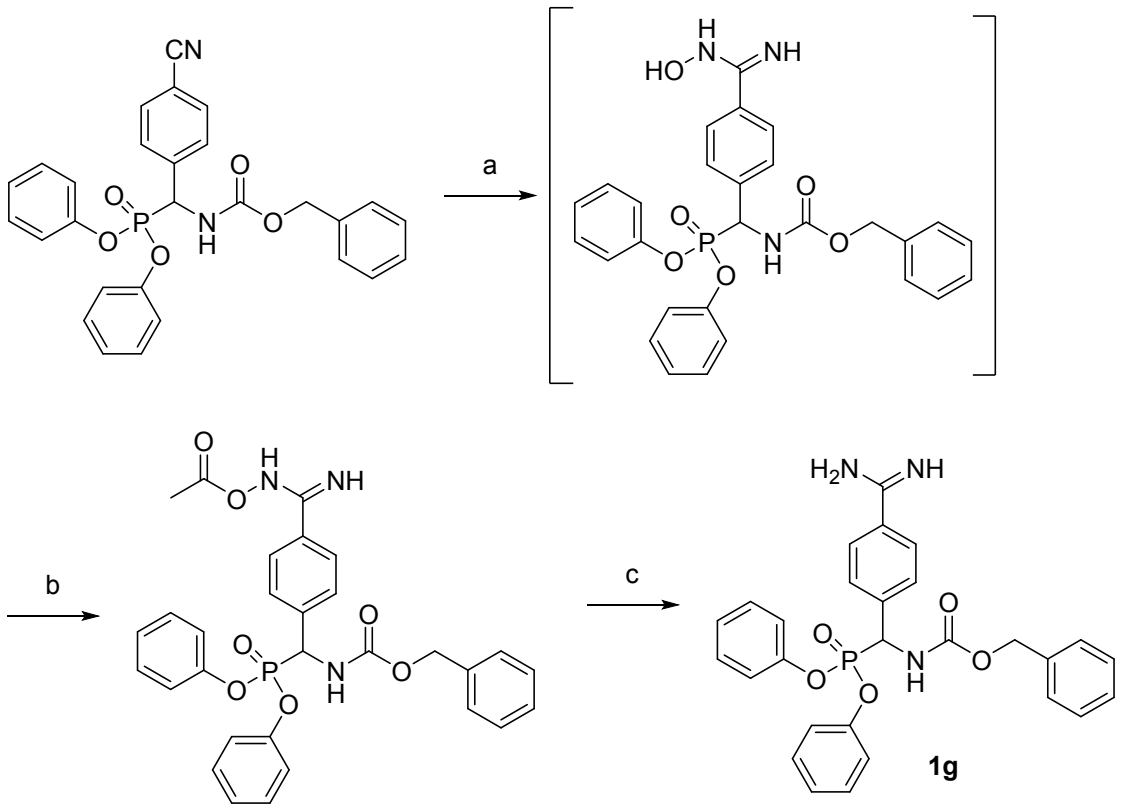
Reagents and solvents were obtained from Sigma-Aldrich, Acros, TCI or Fluorochem. Characterization of compounds was done with ^{1}H NMR and mass spectrometry. ^{1}H NMR spectra were recorded on a 400 MHz Bruker Avance III nanobay spectrometer. ES mass spectra were obtained from an Esquire 3000plus iontrap mass spectrometer from Bruker Daltonics. Purity was verified using one of the following methods: HPLC systems using a mass or UV-detector or UPLC. Water (A) and CH_3CN (B) were used as eluents. LC-MS spectra were recorded on an Agilent 1100 Series HPLC system using a Alltech Prevail C18 column (2.1 × 50 mm, 3 µm) coupled with an Esquire 3000plus MS detector and a 5–100% B, 20 min gradient was used with a flow rate from 0.2 mL/min. Formic acid 0.1% was added to solvents A and B. UPLC-MS-data were recorded on a Waters acquity UPLC system coupled to a Waters TQD ESI mass spectrometer and Waters TUV detector. A Waters acquity UPLC BEH C18 1.7 µM 2.1 x 50 mm column was used. A typical gradient was: 0.15 min 95% A, 5%B then in 1.85 min to 95% B and 5% A and finally 0.25 min 95% B and 5% A (flow rate 0.350 ml/min.), with solvent A: H_2O with 0.1% trifluoroacetic acid and solvent B: Acetonitrile Flash chromatography was performed on a Biotage ISOLERA One system with an internal variable dual-wavelength diode array detector (200-400 nm). SNAP cartridges (10-100g; flow rate 10 ml/min.-100 ml/min.) were used

2. Synthetic schemes



Scheme 1 **A Synthesis of the diaryl-phosphonates**
B Example of steps followed to obtain guanidylated compounds

Reagents and conditions: (a) (i) $Cu(OTf)_2$, $P(OPh)_3$, DCM (ii)for **1a,1c,1d** TFA,DCM (b) For **1b, 1e, 1f** TEA, DCM, *N*,*N*′-bis(*tert*-butoxycarbonyl)-1- guanylpyrazole (c) TFA, DCM



Scheme 2 Synthesis of the amidines
Reagents and conditions: (a) hydroxylammonium chloride, absolute ethanol (b) Acetic anhydride, ACN (c) Zinc, acetic acid

Birum-Oleksyzyn reaction for the synthesis of the diaryl phosphonates

To a mixture of aldehyde (1 eq.) and benzyl carbamate (1 eq.) in dichloromethane (25 ml) was added $Cu(Otf)_2$ (0.1 eq.) and triphenyl phosphite (1 eq.). the solution was allowed to stir overnight at room temperature. The solvent was evaporated and the crude mixture was dissolved in MeOH and stored at -20°C for 2-8 hours. The product precipitated and was obtained as a solid.

Boc-deprotection

The Boc protected product (1eq.) was dissolved in 20 ml dichloromethane and TFA (5eq.) was added. The mixture was allowed to stir for 1-3 hours at room temperature. Solvent was removed under educed pressure. The product was washed with diethyl ether to yield the Boc-deprotected product.

Guanylation

N,N'-bis-Boc-1-guanylpyrazole (1 eq) and triethylamine (3 eq) were added to a solution of the amino compound (1eq) in DCM . The solution was allowed to stir overnight at room temperature. Solvent was evaporated and the residue was dissolved in EtOAc and washed with 1N HCl, sat $NaHCO_3$ and Brine solution. Organic layer was dried on anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified with flash chromatography. (10% EtOAc in heptane to 100% EtOAc).

3. Characterisation

benzyl (4-amino-1-(diphenoxyphosphoryl)butyl)carbamate hydrochloride (1a)[1]

MS (ESI) *m/z* 455.1 $[M+H]^+$

UPLC: t_r 0.7 min (98.3%)

^{1}H NMR (CD_3OD, 400 MHz) δ 3.30 – 3.41 (m, 1H), 3.42 – 3.59 (m, 2H), 3.70 (dq, J = 12.3, 5.2, 4.4 Hz, 1H), 4.45 – 4.62 (m, 2H), 6.01 (ddd, J = 16.5, 10.9, 3.8 Hz, 1H), 6.61 – 6.79 (m, 2H), 8.62 – 8.97 (m, 16H), 10.10 (s, 1H).

Diphenyl *N*-(benzoylcarbonylamino)-(3-guandinopropyl)methanephosphonate 2,2,2-trifluoroacetate (1b) [1]

MS (ESI) *m/z* 497 $[M+Na]^+$

LCMS: t_r 13.2 min (100%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 1.6 (m, 1H), 1.7-1.9 (m, 2H), 2.1 (m, 1H), 3.2 (m, 2H), 4.5 (m, 1H), 5.1 (q, 1H), 7.1-7.3 (m, 15H)

benzyl (4-aminophenyl)(diphenoxyphosphoryl)methylcarbamate 2,2,2-trifluoroacetate (1c) [2]

MS (ESI) *m/z* 489.5 $[M+H]^+$

UPLC: t_r 1.93 min (100%)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.01-5.09 (m, 2H), 5.5 (dd, 1H), 6.15 (br s, 2H), 6.79-7.32 (m, 19H)

benzyl 2-(4-aminophenyl)-1-(diphenoxyphosphoryl)ethylcarbamate 2,2,2-trifluoroacetate (1d) [1]

MS (ESI) *m/z* 503.0 $[M+Na]^+$

LCMS: t_r 14.8 min (99.0%)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.1 (m, 1H), 3.4 (m, 1H), 4.65 (m, 1H), 4.92 (d, J=12.4 Hz, 1H), 5.0 (d, J=12.5 Hz, 1H), 7.0-7.5 (m, 19H)

benzyl (diphenoxyphosphoryl)(4-guanidinophenyl)methylcarbamate 2,2,2-trifluoroacetate (1e) [2]

MS (ESI) *m/z* 531.1 $[M+H]^+$

LCMS: t_r 14.2 min (98.3%)

^{1}H NMR (400 MHz, CD_3OD) δ 5.05 – 5.27 (m, 2H), 5.63 – 5.76 (m, 1H), 6.95 – 7.16 (m, 4H), 7.15 – 7.46 (m, 13H), 7.62 – 7.77 (m, 2H), 8.75 (d, *J* = 9.9 Hz, 1H).

Diphenyl 1-(benzyloxycarbonylamino)-2-(4-guanidinophenyl)-ethanephosphonate 2,2,2-trifluoroacetate (1f) [1]

MS (ESI) *m/z* 545 $[M+H]^+$

LCMS: t_r 13.9 min (100%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 3.0 (m, 1H), 3.4 (m, 1H), 4.7 (m,1H), 5.1 (m,2H), 4.5 (m, 1H), 5.1 (q, 1H), 7.1-7.3 (m,15H)

benzyl ((4-carbamimidoylphenyl)(diphenoxyphosphoryl)methyl)carbamate 2,2,2-trifluoroacetate (1g)[1]

MS (ESI) *m/z* 516.1 $[M+H]^+$

UPLC: t_r 0.78 min (100%)

^{1}H NMR (400 MHz, CD_3OD) δ 5.17 (m, 2H), 5.63 – 5.76 (m, 1H), 6.95 – 7.16 (m, 4H), 7.15 – 7.39 (m, 9H), 7.86 (s, 4H).

Diphenyl 1-(*N*-benzyloxycarbonylamino)-1-(4-amidinophenyl)propanephosphonate (1h) [1]

MS (ESI) *m/z* 544 $[M+H]^+$

LCMS: t_r 14.7 min (97%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 2.2 (m, 1H), 2.35 (m, 1H), 2.8 (m, 1H), 3.05 (m, 1H), 4.3 (m, 1H), 5.1 (q, 2H), 7.1-7.4 (m, 17H), 7.7 (d,2H)

benzyl (diphenoxyphosphoryl)(4-hydroxyphenyl)methylcarbamate (1i)[3]

MS (ESI) *m/z* 512.1 $[M+Na]^+$

LCMS: t_r 17.5 min (100%)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.1 (q, 2H), 5.46 (dd, 1H), 5.76 (s, 2H), 6.67 (d, 2H), 6.85 (d, 2H), 6.62-7.31 (m, 15H)

^{13}C-NMR (DMSO-*d*^{6}), 101 MHz) δ 157.89, 156.46, 150.30, 137.18, 130.38, 130.31, 130.28, 130.25, 128.83, 128.40, 125.71, 125.63, 124.78, 120.86, 120.82, 120.80, 120.76, 115.66, 115.64, 66.57, 53.58

4. Biochemical Evaluation

Materials and methods

For KLK4 Enzymatic activity was measured at 37 °C in a Biotek Synergy Mx Monochromator-Based Multi-Mode Microplate Reader using the fluorogenic substrate Bachem I-1120 (Boc-Val-Pro-Arg-AMC), with a K_m of 20 µM.

The substrate was obtained from Bachem and the enzyme was provided by Prof. Viktor Magdolen (TUM). The recombinant human KLKs were expressed in E. coli, purified, refolded and activated in a similar manner as reported by Debela et al. 2006.[4]

The reaction was monitored with an excitation wavelength of 355 nm and emission wavelength of 460 nm. The initial rate was measured in a fluorescence range corresponding to less than 10% of converted substrate. The reaction mixture contained 25 µM substrate and approximately 1 mU of enzyme in a final volume of 200 µL. A 50 mM Tris buffer, pH 8.3, was used. From each inhibitor stock solution (in DMSO), 5 µL was added, obtaining a final concentration from 0 to 250 µM in a total volume of 0.2 mL. The final amount of DMSO was 2.5 %. Activity measurements were routinely performed in duplicate. The IC_{50} value is defined as the concentration of inhibitor required to reduce the enzyme activity to 50% after a 15 min pre-incubation with the enzyme at 37 °C before addition of the substrate. IC_{50} values were obtained by fitting the data with the four-parameter logistics equation using Grafit 7.

$$v = \frac{v\,range}{1 + e^{s\ln\left|{I_0}/{IC_{50}}\right|}} + background$$

where *s* = slope factor, *v* = rate, I_0 = inhibitor concentration, and range = the fitted uninhibited value minus the background. The equation assumes that *y* falls with increasing *x*.

Inhibitor stock solutions were prepared in DMSO and stored at -20 °C. Because the compounds described in this paper completely inactivate uPA following pseudo first-order kinetics, the IC_{50} value for uPA is inversely correlated with the second-order rate constant of inactivation. For a simple pseudo first-order inactivation process, the activity after incubation with inhibitor (v_i) varies with the inhibitor concentration (*i*), as described in the following equation: $v_i = v_0 \times e^{-kit}$,

where v_o is the activity in absence of inhibitor, *k* is the second-order rate constant of inactivation, I is the total inhibitor concentration and *t* is the time. The inactivation rate constant was determined from the time course of inhibition.

The inhibitor was mixed with the substrate (250 µM final concentration), and the buffer solution with the enzyme was added at the time zero. The inhibitor concentrations were chosen to obtain total inhibition of the enzyme within 20 min. Depending on the type of substrate used, the progress curves show the absorbance (A) or fluorescence produced as a function of time. Initially, no inhibitor is bound to the enzyme, and the tangent to the progress curve (d*A*/d*t*) is proportional to the concentration of the free enzyme. The concentration of free enzyme decreases over time due to the kinetics of inhibitor binding,

as described above. Progress curves were recorded in pseudo first-order conditions ($[I]_0$ >> $[E]_0$) and with less than 10% conversion of the substrate during the entire time course. In these conditions, dA/dt decreases exponentially with time. The progress curves were fitted with the integrated rate equation to yield a value for k_{obs}, a pseudo first-order rate constant

$$A_t = v_0\left[1 - e^{-k_{obs}t}\right]/k_{obs} + A_0$$

where A_t = absorbance at time t, A_0 = absorbance at time zero, and v_0 = uninhibited initial rate.

The apparent second-order rate constant (k_{app}) was calculated from the slope of the linear part of the plot of k_{obs} versus the inhibitor concentration ($[I]_0$). In case of competition between the inhibitor and the substrate, k_{app} is smaller than the "real" second order rate constant k discussed above because a certain fraction of the enzyme is present as an enzyme–substrate complex. k_{app} depends on the substrate concentration used in the experiment, as described by Lambeir et al. 1996.[5]

A second experiment is conducted to verify the irreversibility of the interaction. The enzyme is incubated at a 100 fold higher concentration than normally used to obtain the initial rate together with an inhibitor with a concentration of 100 times the IC_{50} for 15 min at 37°C. The final volume is 10 µl. After incubation the solution is diluted with assay buffer to yield a final Inhibitor concentration of 1/10th of the IC_{50}. Substrate is added and the reaction is then monitored for 1 hour by absorbance or fluorescence, depending on the type of substrate used. With an irreversible binding mode there will be no recovery of enzymatic activity after the dilution. With a reversible binding mode there will be recovery of enzymatic activity.

The IC_{50} values For KLK1, KLK2 and KLK8 were obtained in a similar way. For plasmin, tPA, thrombin, Fxa, HNE, chromogenic substrates were used (absorption: 405 nm) as described.[2]

(KLK2, KLK4, KLK8 were supplied by Viktor Magdolen,TUMunich (TUM)).

For Acetylcholinesterase an adapted procedure was used. Stock solutions were made in 0,1M PBS buffer, pH 7,8 with 1% DMSO. The final amount of DMSO was 0,25%. Acetylthiocholine Iodide was used as a substrate. Substrate conversion was measured using the indicator 5-5'-dithiobis(2-nitrobenzoic acid). Absorbance was measured at 412 nm.

Plasmin (from human plasma)

Supplier: Sigma-Aldrich

Substrate: Biophen CS-21(66) (pyroGlu- Pro-Arg-pNA·HCl) K_m: 400 µM

Buffer Tris buffer pH 7.4

uPA (recombinant)

Supplier: Nodia

Substrate: Biophen CS-61(44) (PyroGlu—Gly-Arg-pNa.HCl) K_m: 80 µM

Buffer: Tris buffer pH 8.8

tPA (recombinant)

Supplier: Nodia

Substrate: Biophen CS-05(88) (H-D- Ile-Pro-Arg-pNa·2HCl) K_m: 1 mM

Buffer: Tris buffer pH 8.3

Thrombin (from human plasma)

Supplier: Sigma-Aldrich

Substrate: Biophen CS-21(66) (pyroGlu- Pro-Arg-pNA·HCl) K_m: 150 µM

Buffer: Tris buffer pH 8.3

FXa

Supplier: Nodia

Substrate: Biophen CS-11(32) (Suc-Ile-Glu(γPip)Gly-Arg-pNa, HCl) K_m: 1.5 mM

Buffer: Tris buffer pH 8.3

KLK1 (human)

Supplier: Prospec

Substrate: Bachem I-1295 H-Pro-Phe-Arg-AMC K_m: 20 µM

Buffer: Tris buffer pH 7.8

KLK2 (human)

Delivered by Prof. Viktor Magdolen

Substrate: Bachem I-1295 H-Pro-Phe-Arg-AMC K_m: 20 µM

Buffer: Tris buffer pH 8.3

KLK8 (human)

Delivered by Prof. Viktor Magdolen

Substrate: Bachem I-1120 Boc-Val-Pro-Arg-AMC K_m: 20 µM

Buffer: Tris buffer pH 8

Acetylcholinesterase (from *Electrophorus electricus*)

Supplier: Sigma Aldrich

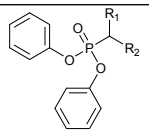
Substrate: Sigma-Aldrich Acetylthiocholine iodide k_m: 0,42 mM

Indicator: Sigma-Aldrich 5-5'-Dithiobis(2-nitrobenzoic acid)

Buffer: PBS buffer pH 7.8

4.1 Additional k_{app} values

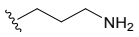
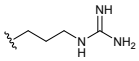
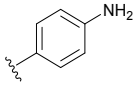
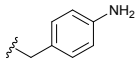
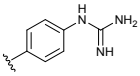
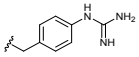
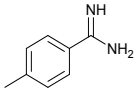
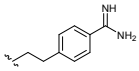
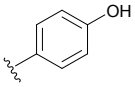
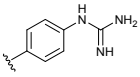
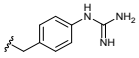
Table 1 k_{app} values on enzymes other then KLK4



ND: Not determined

N/A: $IC_{50} > 1\mu M$

Rev: Reversible Inhibitor

Cpd	R_1	R2	k_{app} ($M^{-1}s^{-1}$)								
			KLK2	KLK1	KLK8	uPA	tPA	Thrombin	Plasmin	FXa	AcHe
1a		NH-Cbz	N/D	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1b		NH-Cbz	**Rev**	ND	ND	**100 ±60**	N/A	**Rev**	N/A	N/A	ND
1c		NH-Cbz	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1d		NH-Cbz	N/A	N/A	N/A	N/A	N/A	N/A	ND	N/A	ND
1e		NH-Cbz	**Rev**	**Rev**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1f		NH-Cbz	**Rev**	N/A	**Rev**	**$42x10^3$± $3x10^3$**	N/A	**Rev**	N/A	N/A	N/A
1g		NH-Cbz	**Rev**	N/A	**$1.6x10^3$±$0.1x10^3$**	N/A	N/A	**Rev**	N/A	N/A	N/A
1h		NH-Cbz	**Rev**	N/A	N/A	**140±10**	N/A	N/A	N/A	N/A	N/A
1i		NH-Cbz	N/A	**$4.1x10^3$ ±$0.2x10^3$**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2a		H	**40±4**	N/A	**Rev**	**Rev**	N/A	N/A	N/A	N/A	N/A
2b		H	**23±1**	N/A	**Rev**	**$3.20x10^3$±$0.09x\ 10^3$**	N/A	N/A	N/A	N/A	N/A

4.2 Progress curves and dilution experiments

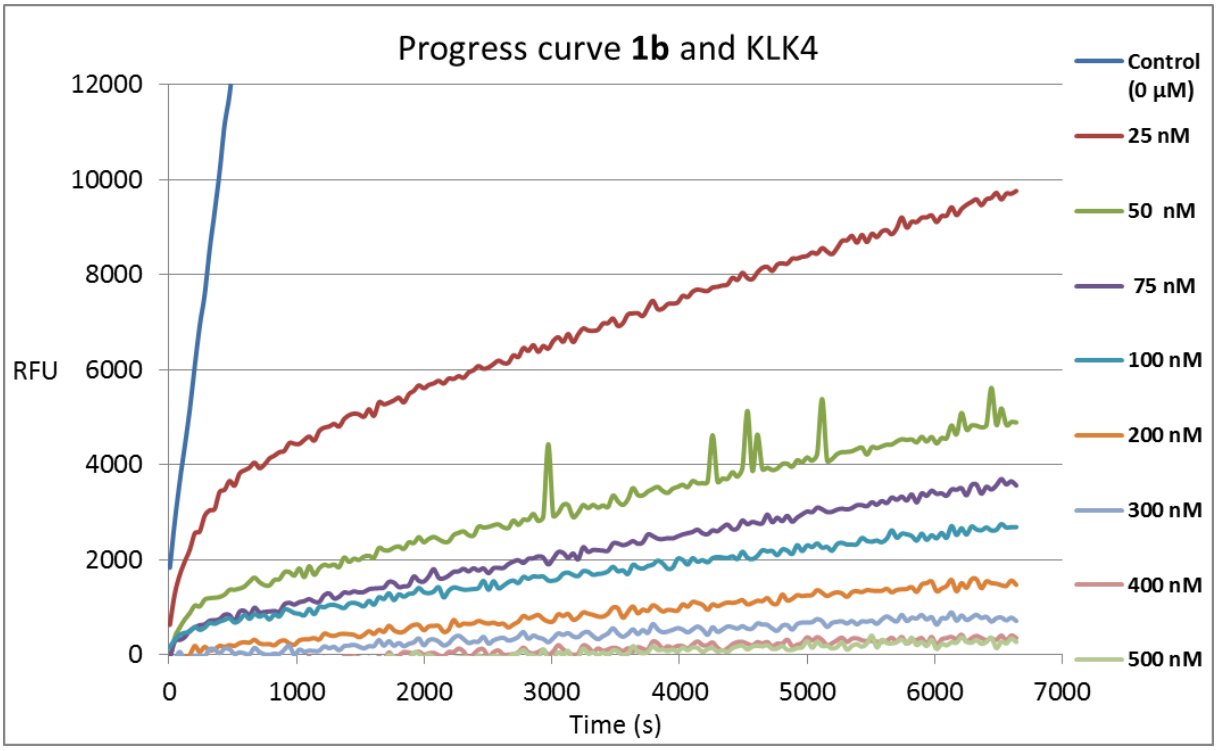
Progress curve: Time course of product formation during binding of the compound to the active enzyme. Each curve represents a different concentration of the compound **Dilution experiment**: This graph represents the results of a dilution experiment. The compound is incubated at an enzyme concentration 100 times higher than within the IC50 assay. After 15 minutes the mixture is diluted 100 timeswith buffer. If the compound is an irreversible inhibitor the enzyme activity will be completely inhibited also after dilution (no increase of RFU). However, due to the 100 fold dilution the enzyme activity is restored for a reversible inhibitor.

For KLK2 no dilution experiments were performed due to the instability of the enzyme in the specific conditions used for the dilution experiment.

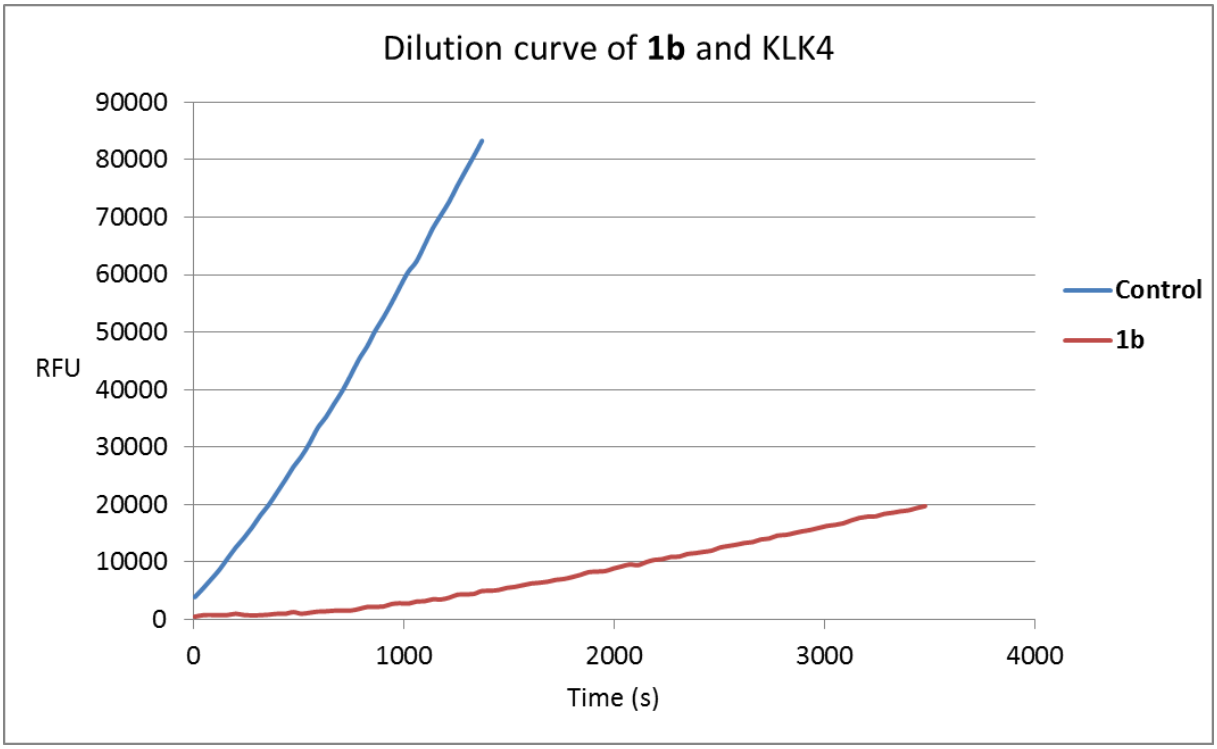
4.2.1 KLK 4

1b (reversible)

Progress curve

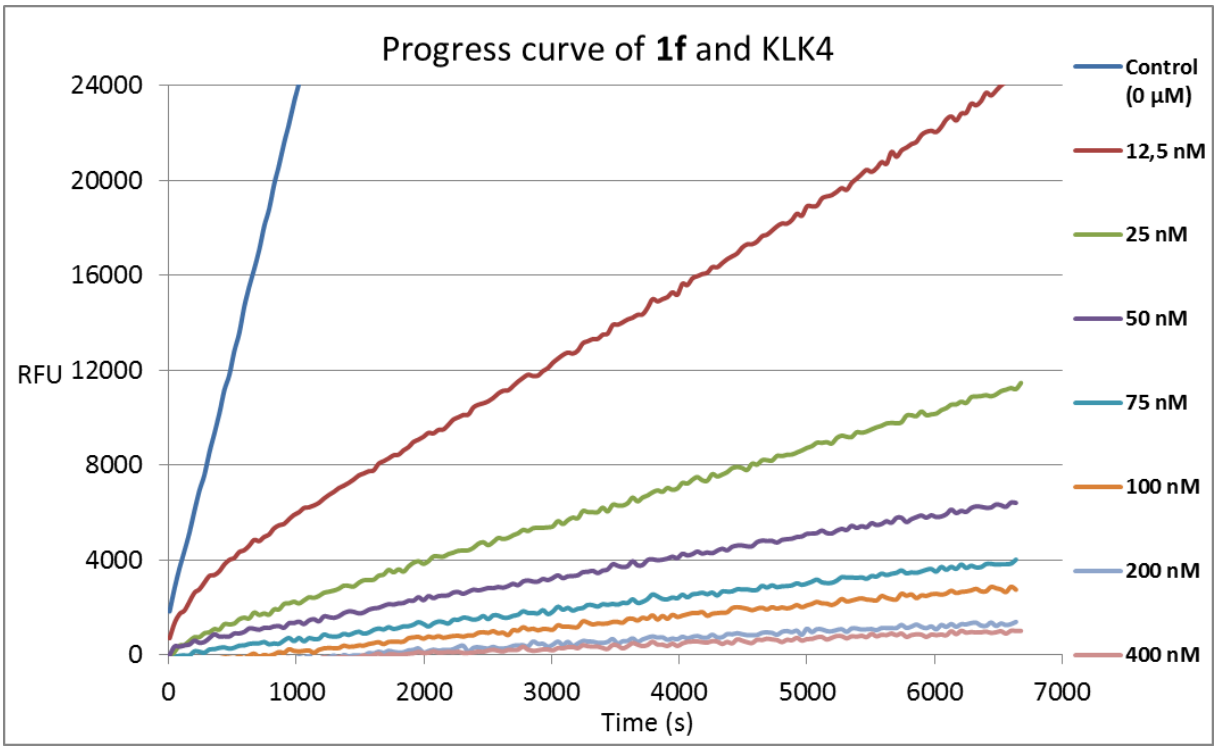


Dilution experiment

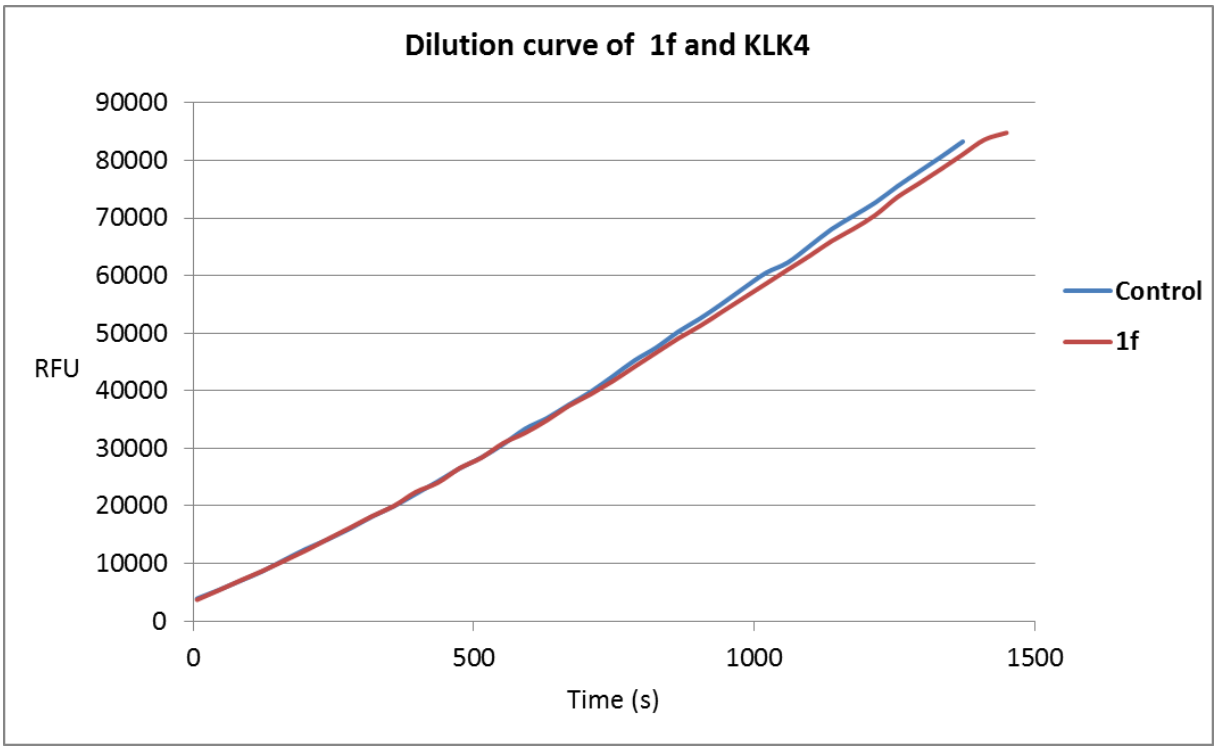


1f (reversible)

Progress curve

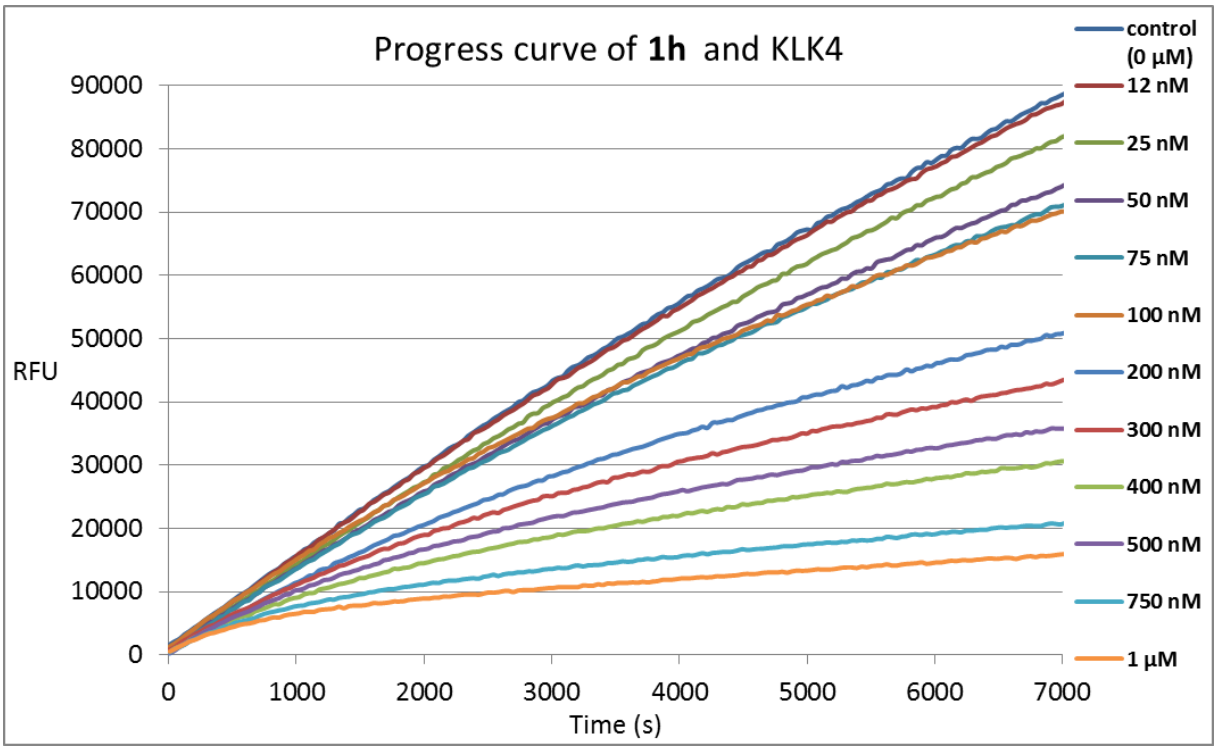


Dilution experiment

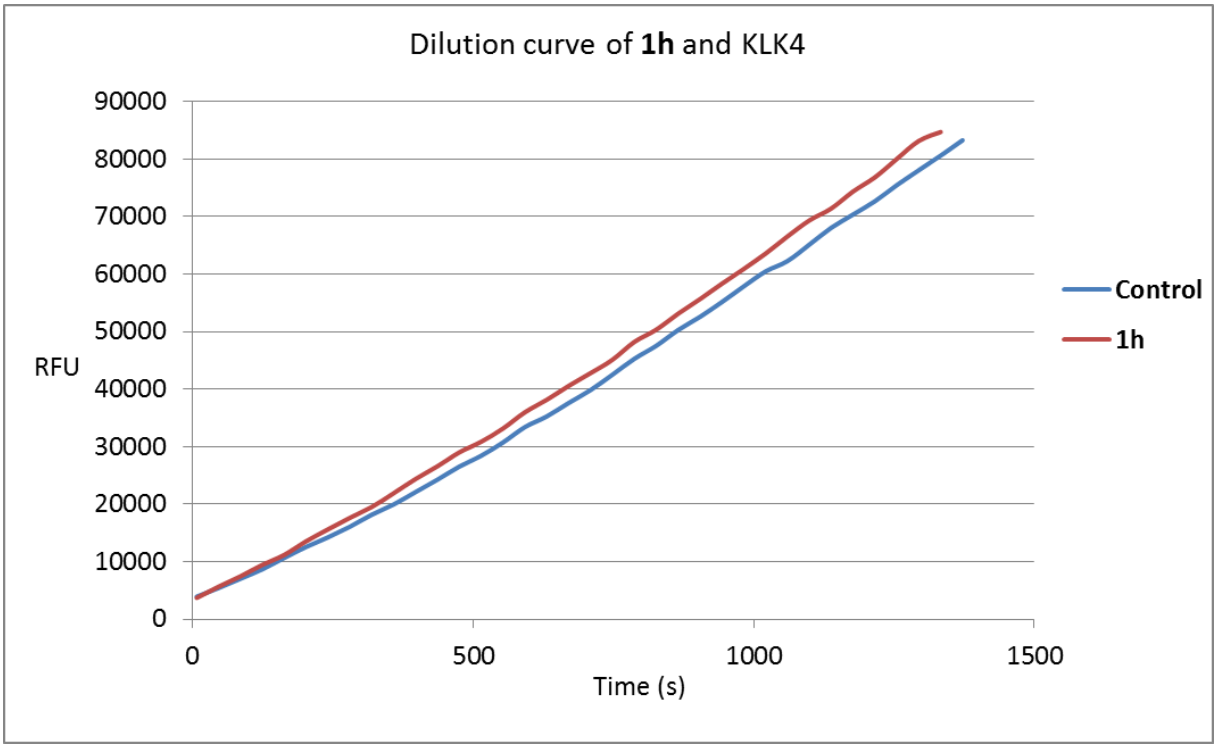


1h (reversible)

Progress curve

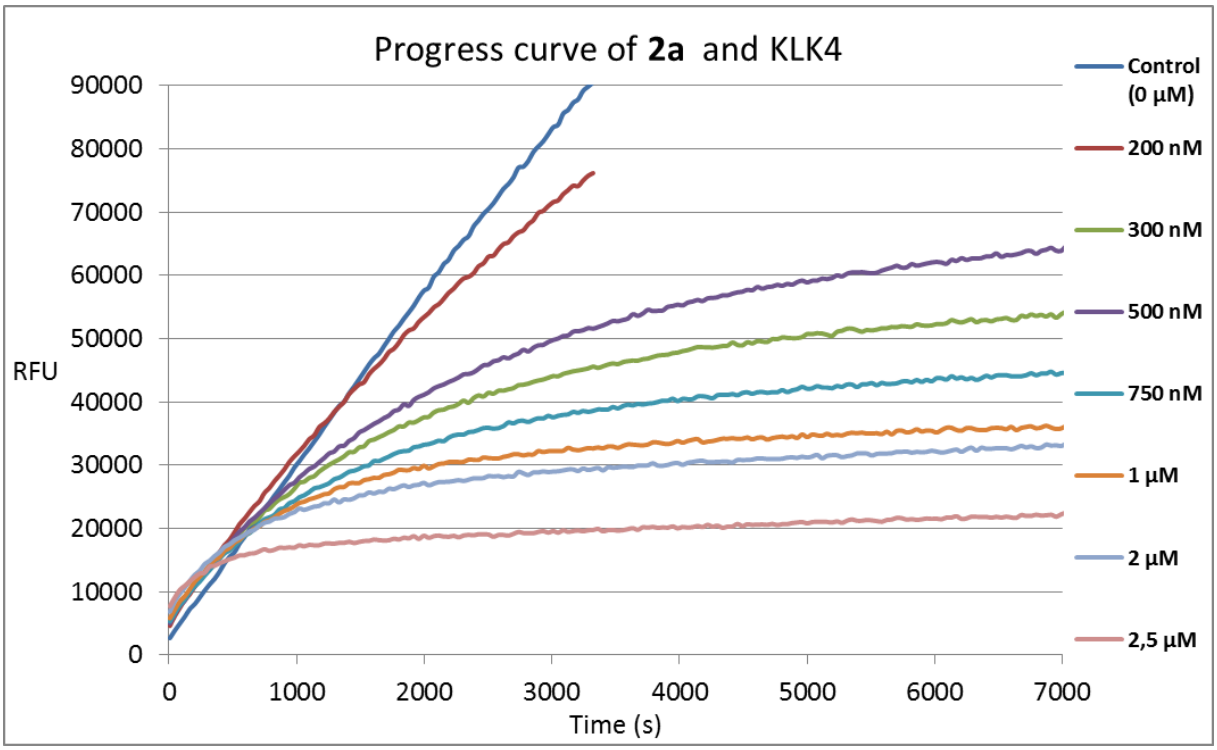


Dilution experiment

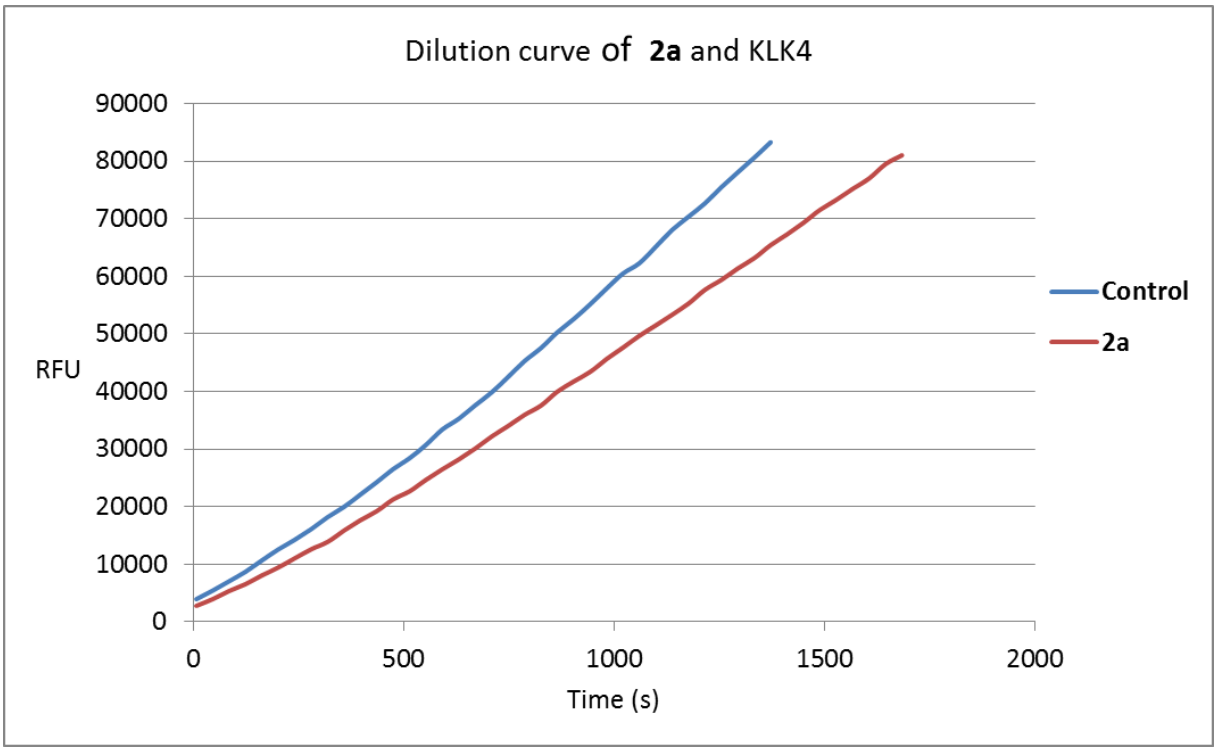


2a (reversible)

Progress curve

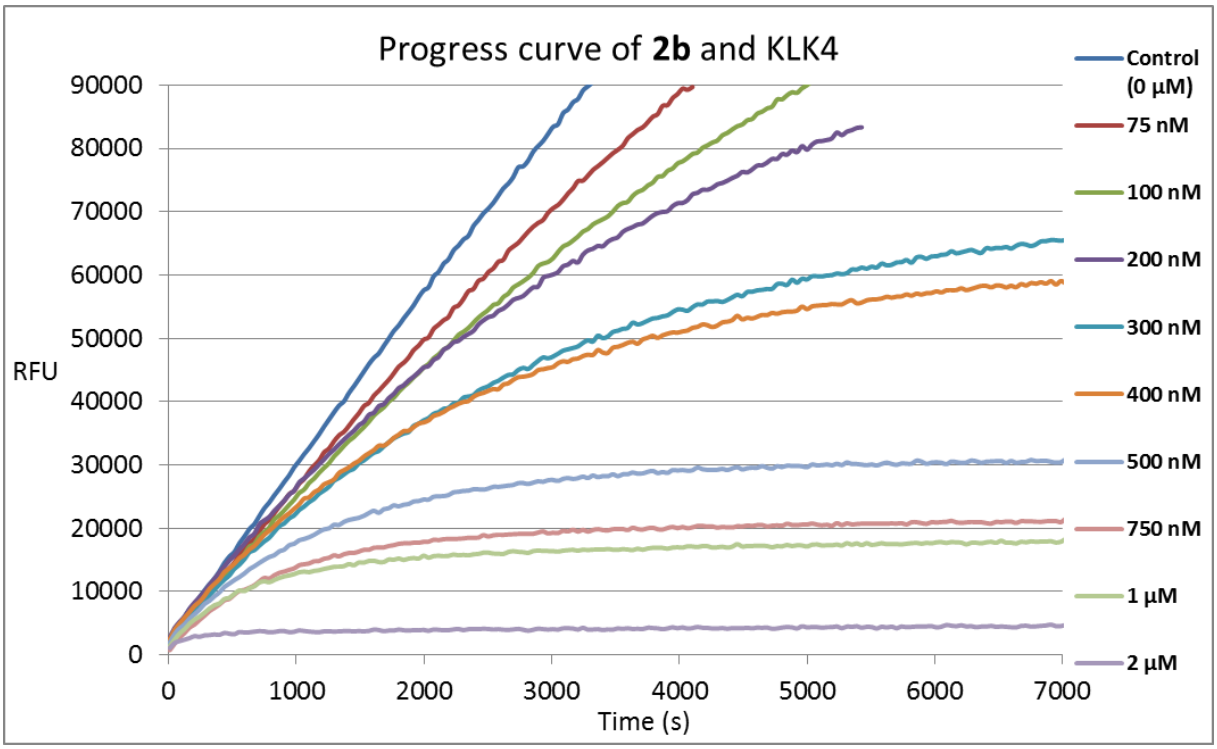


Dilution experiment

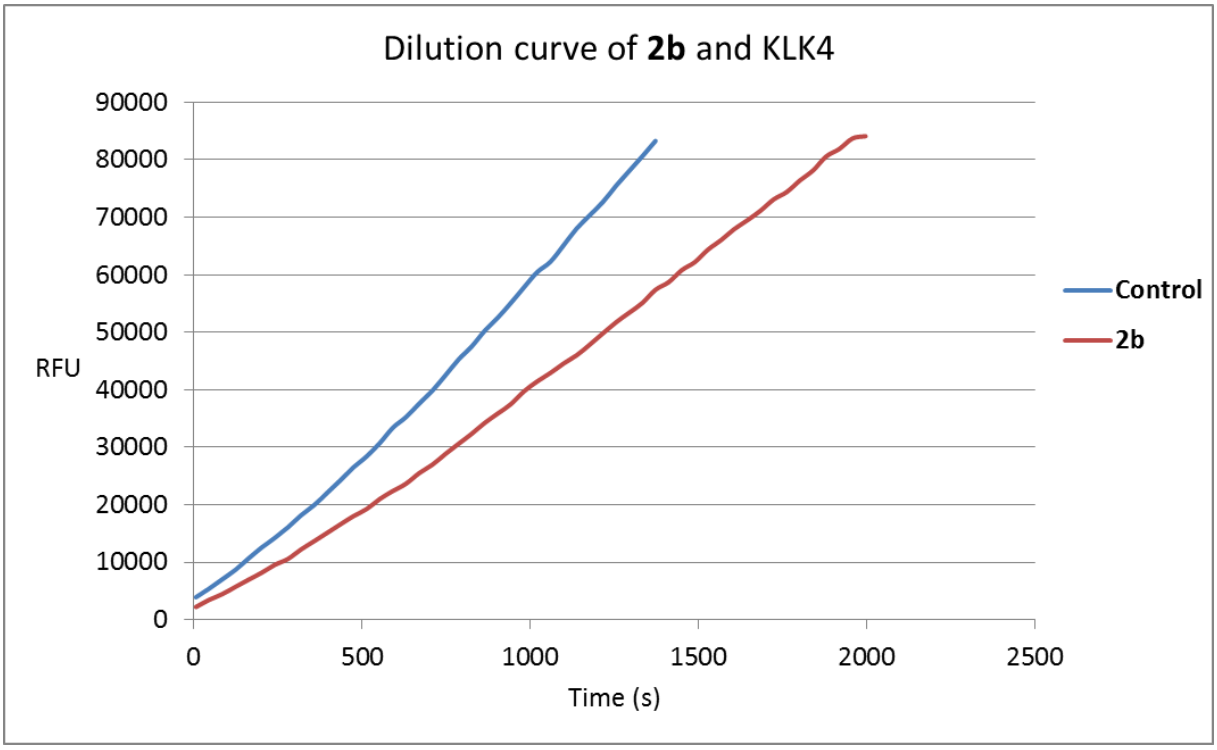


2b (reversible)

Progress curve



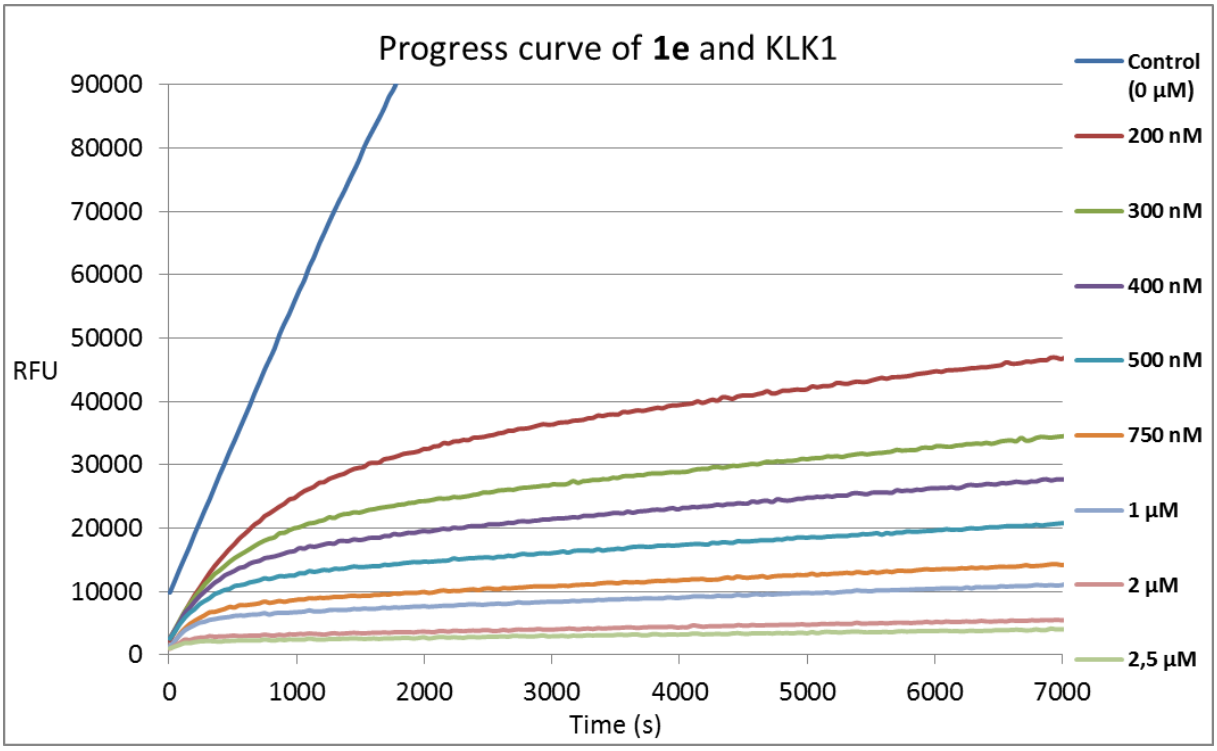
Dilution experiment



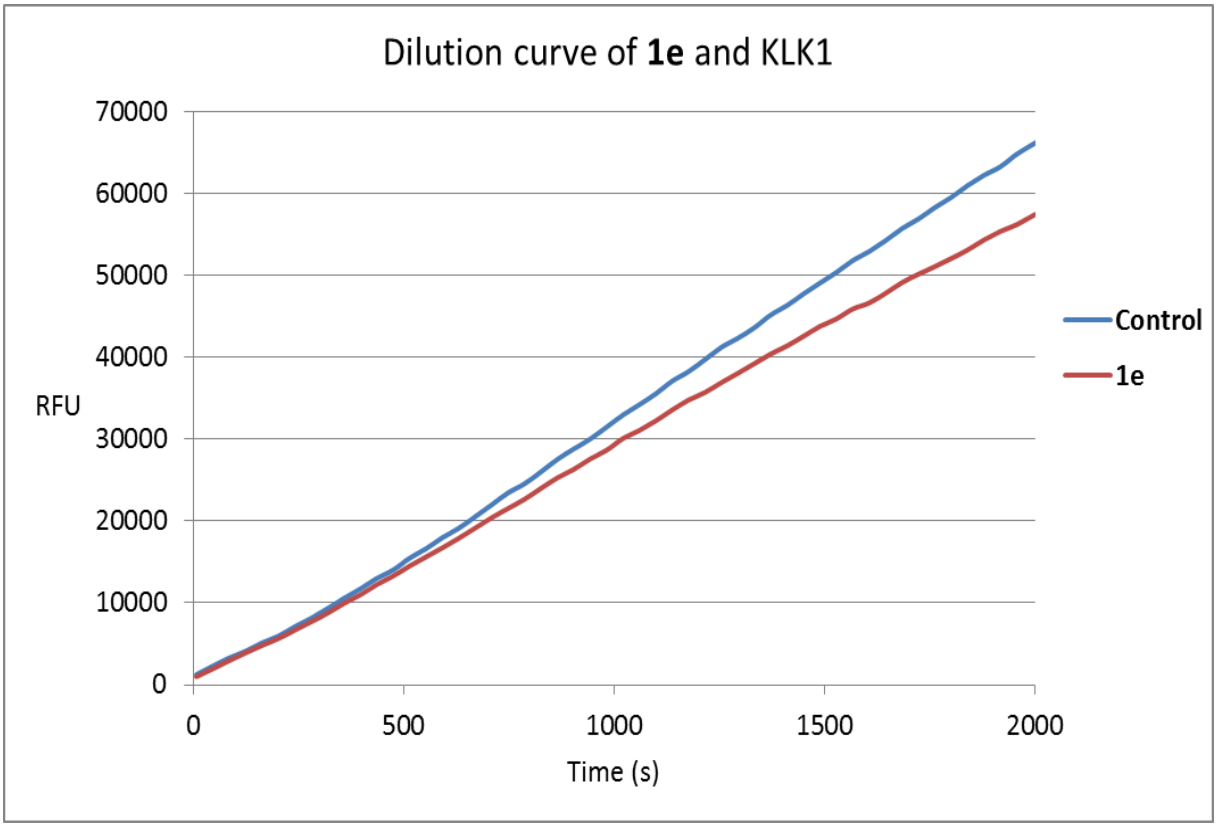
4.2.2 KLK 1

1e (reversible)

Progress curve

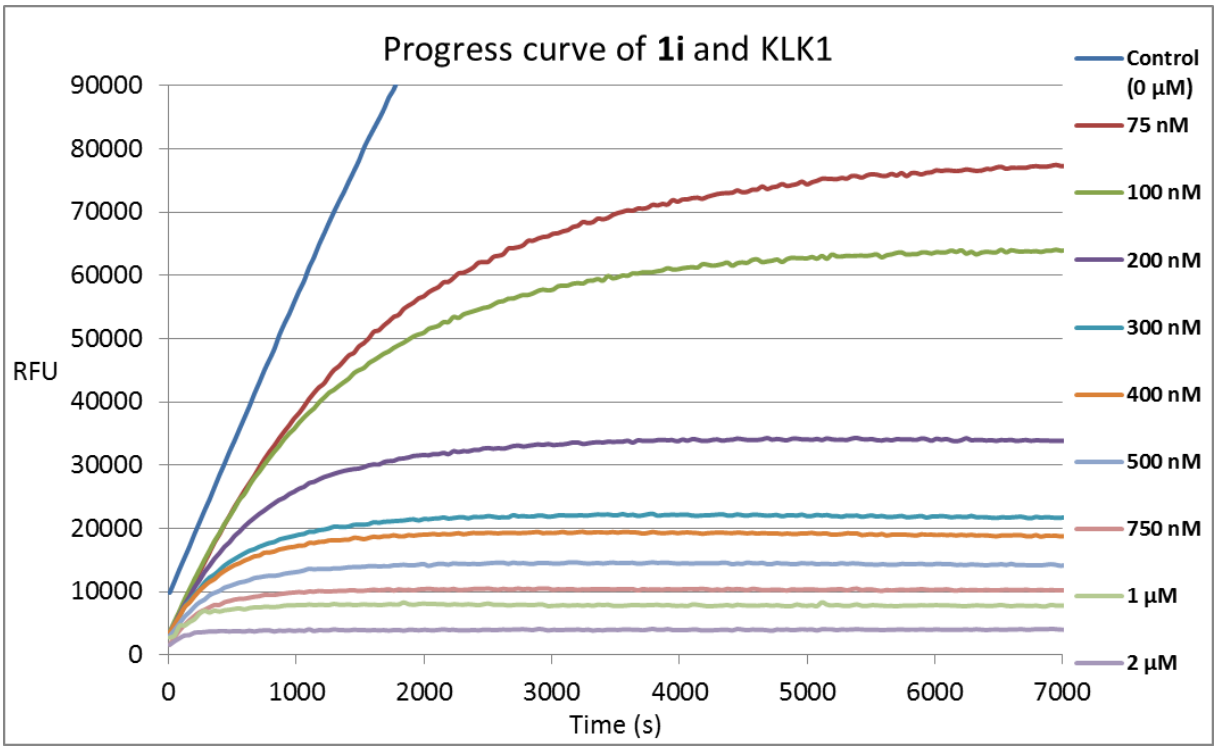


dilution experiment

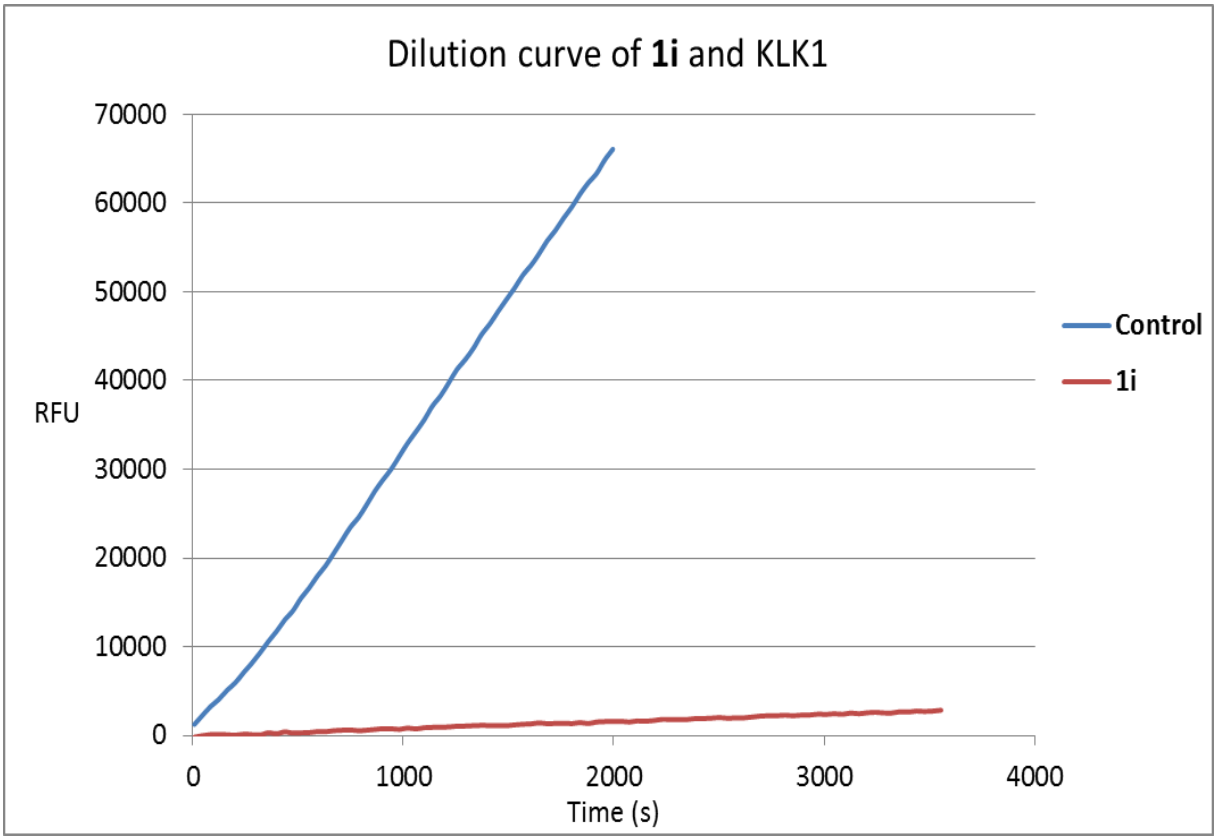


1i (irreversible)

Progress curve



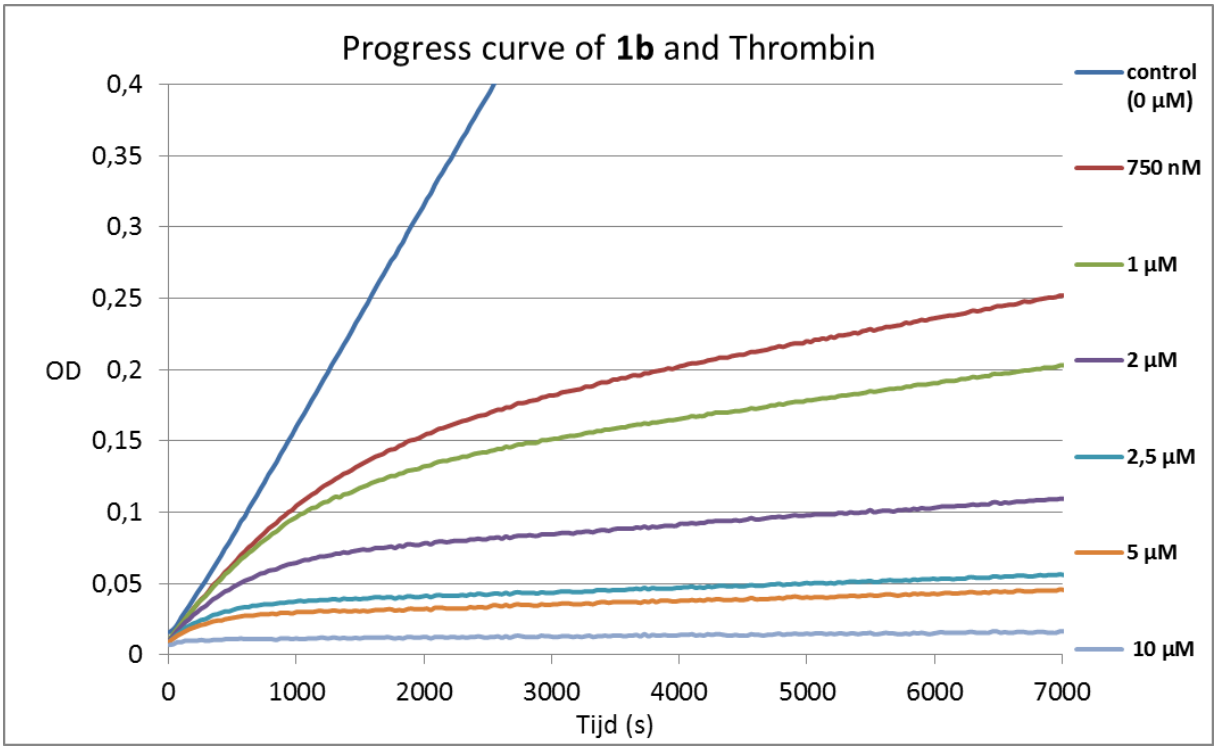
Dilution experiment



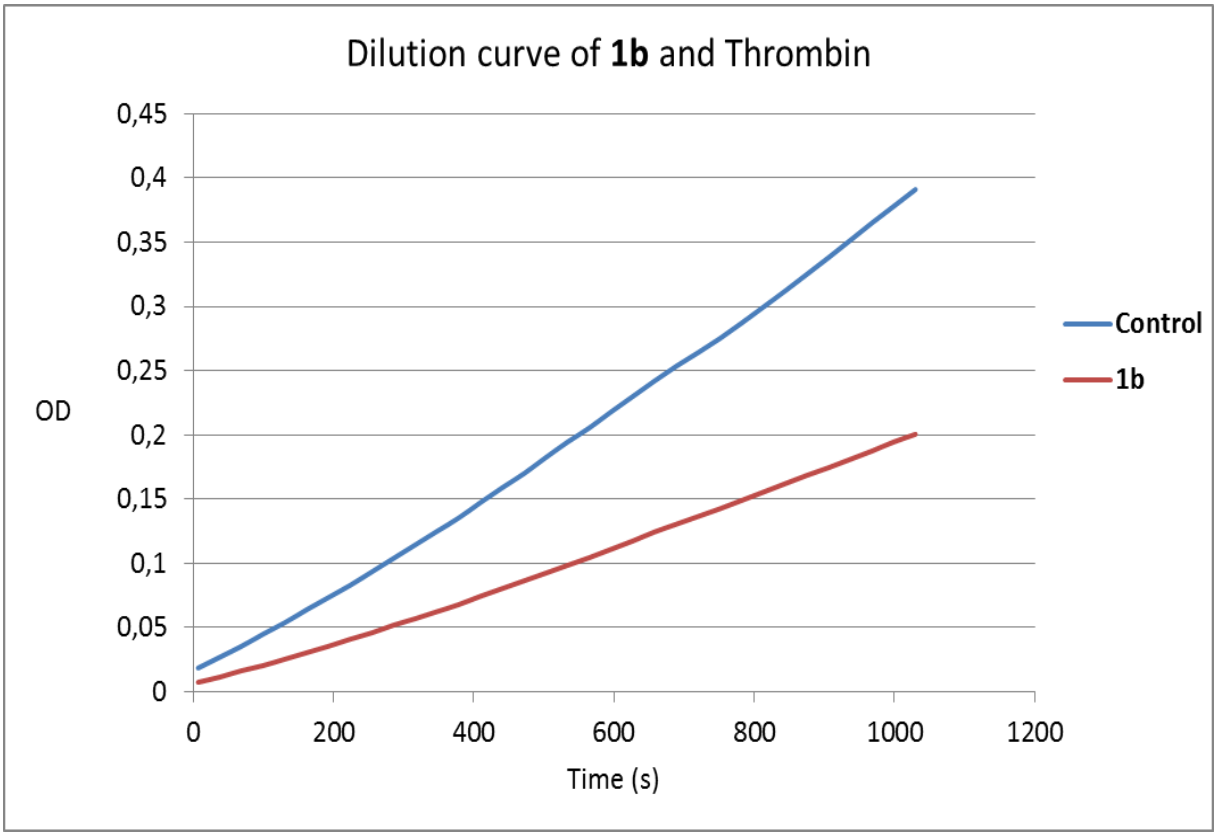
4.2.3 Thrombin

1b (reversible)

Progress curve

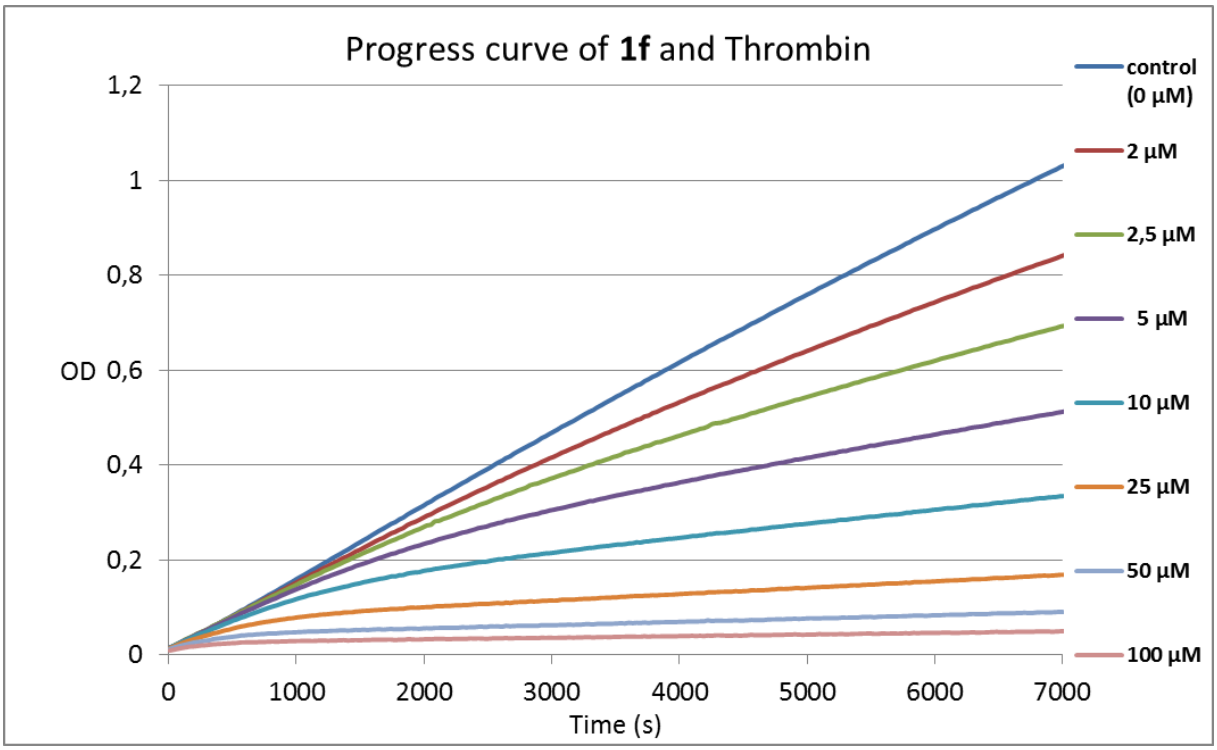


Dilution experiment

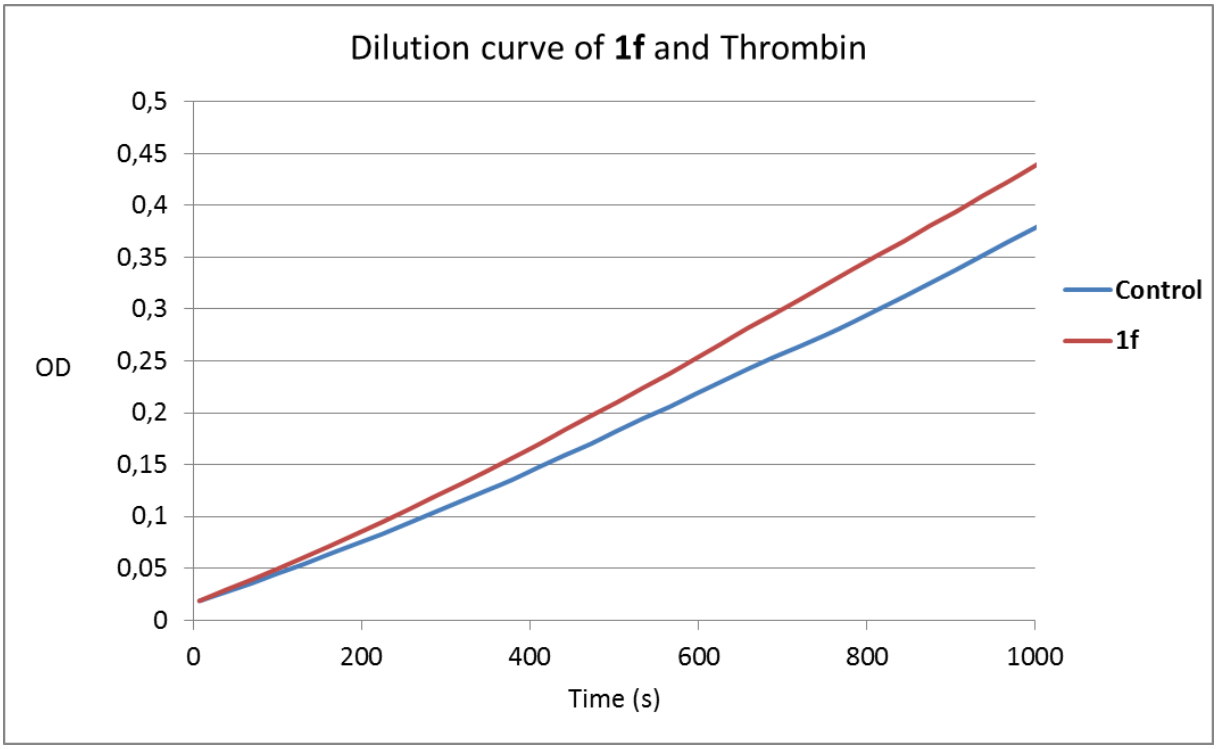


1f (reversible)

Progress curve

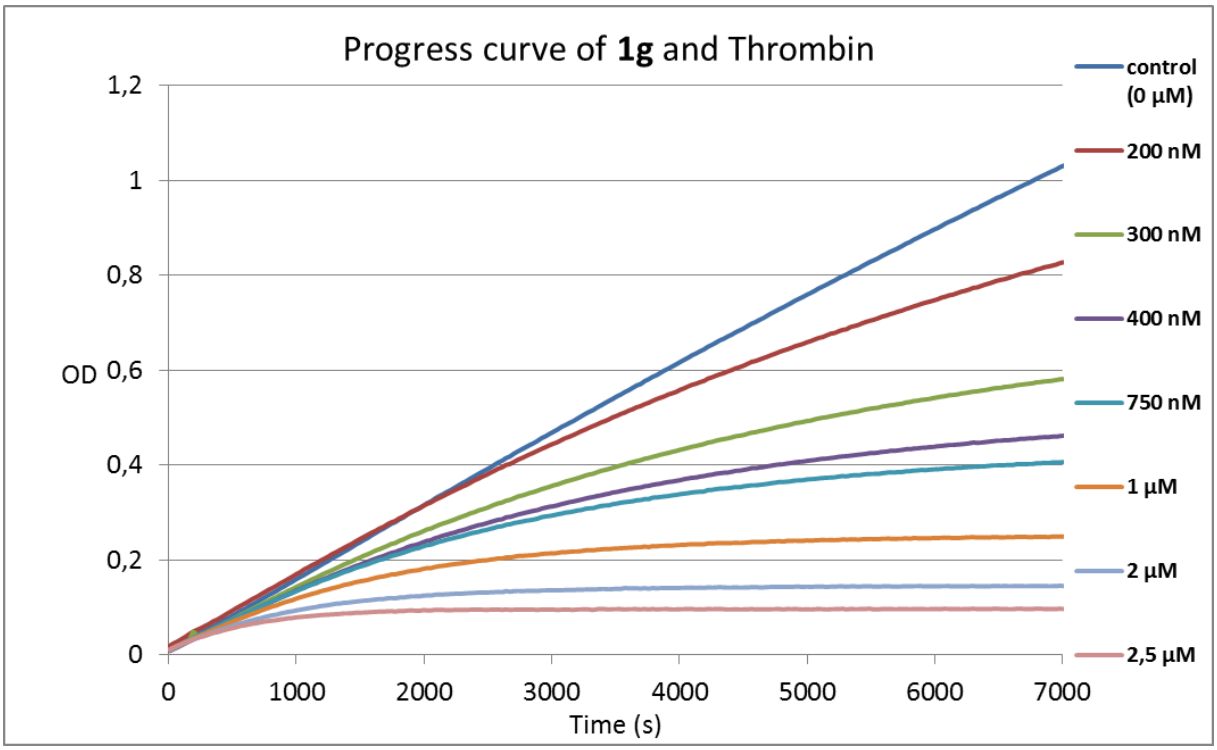


Dilution experiment

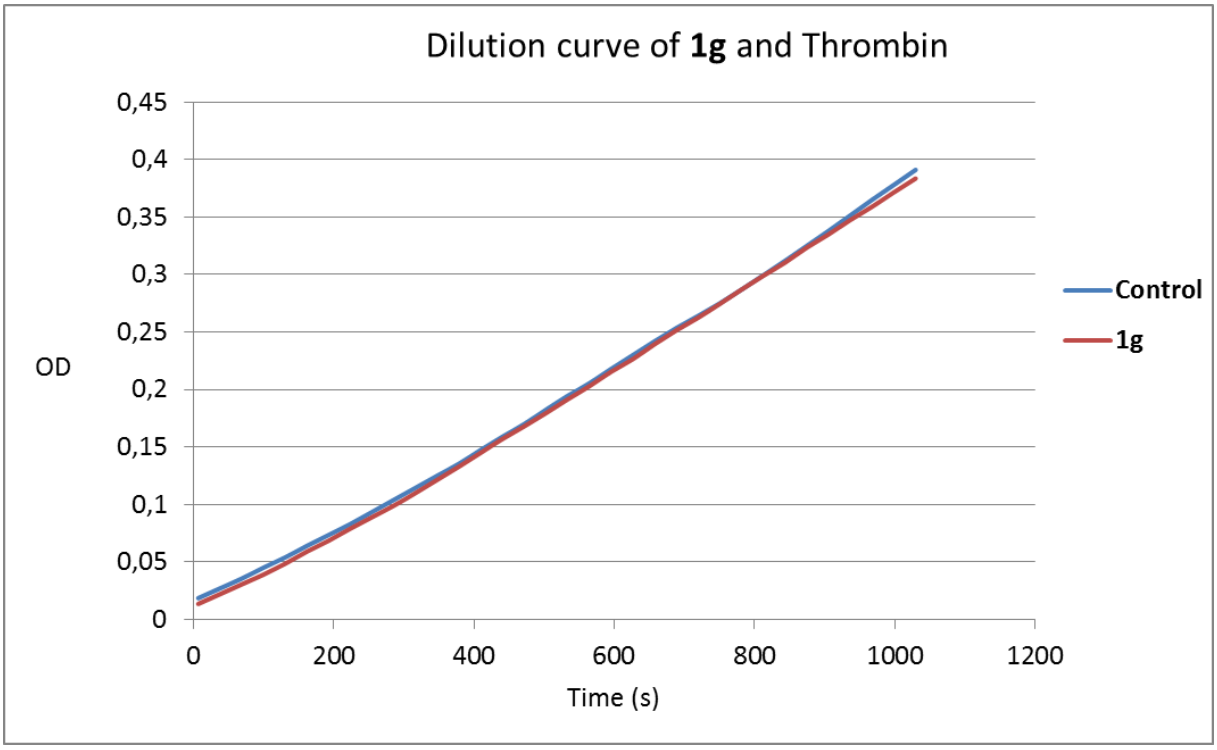


1g (reversible)

Progress curve



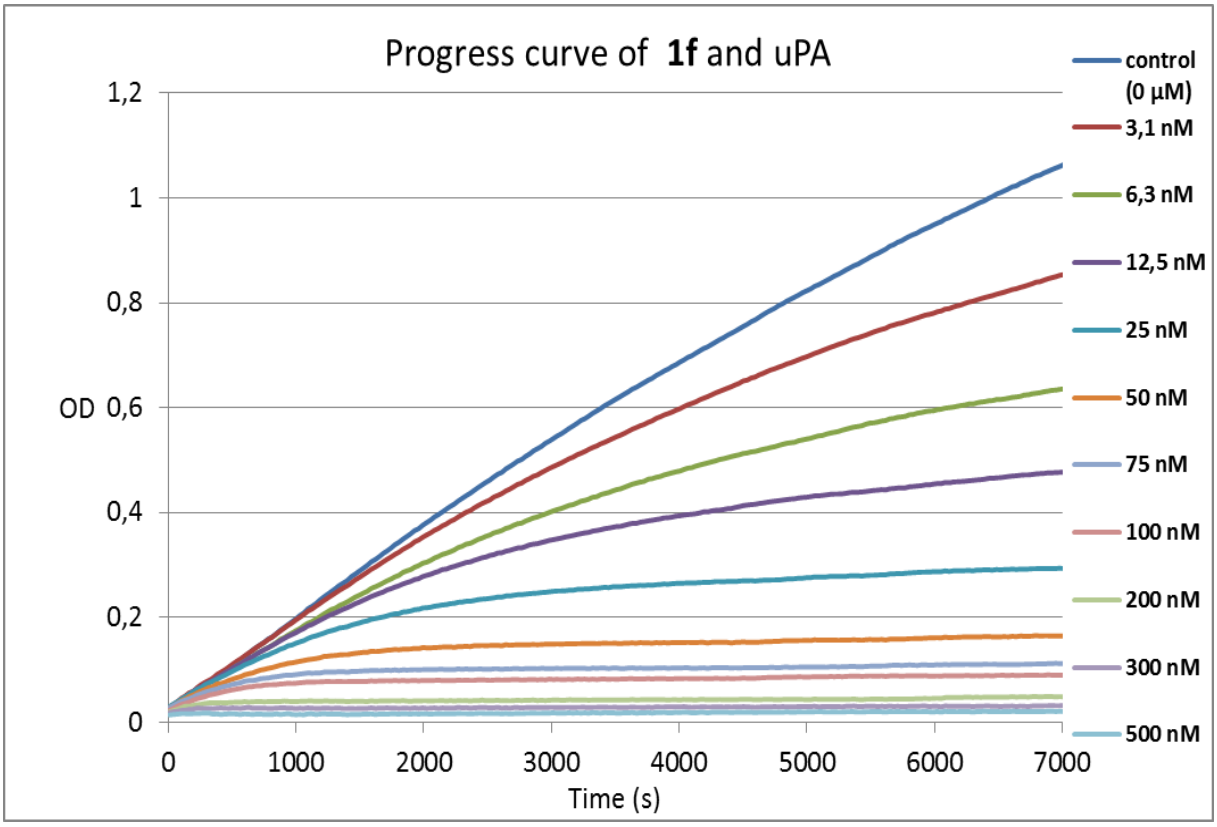
Dilution experiment



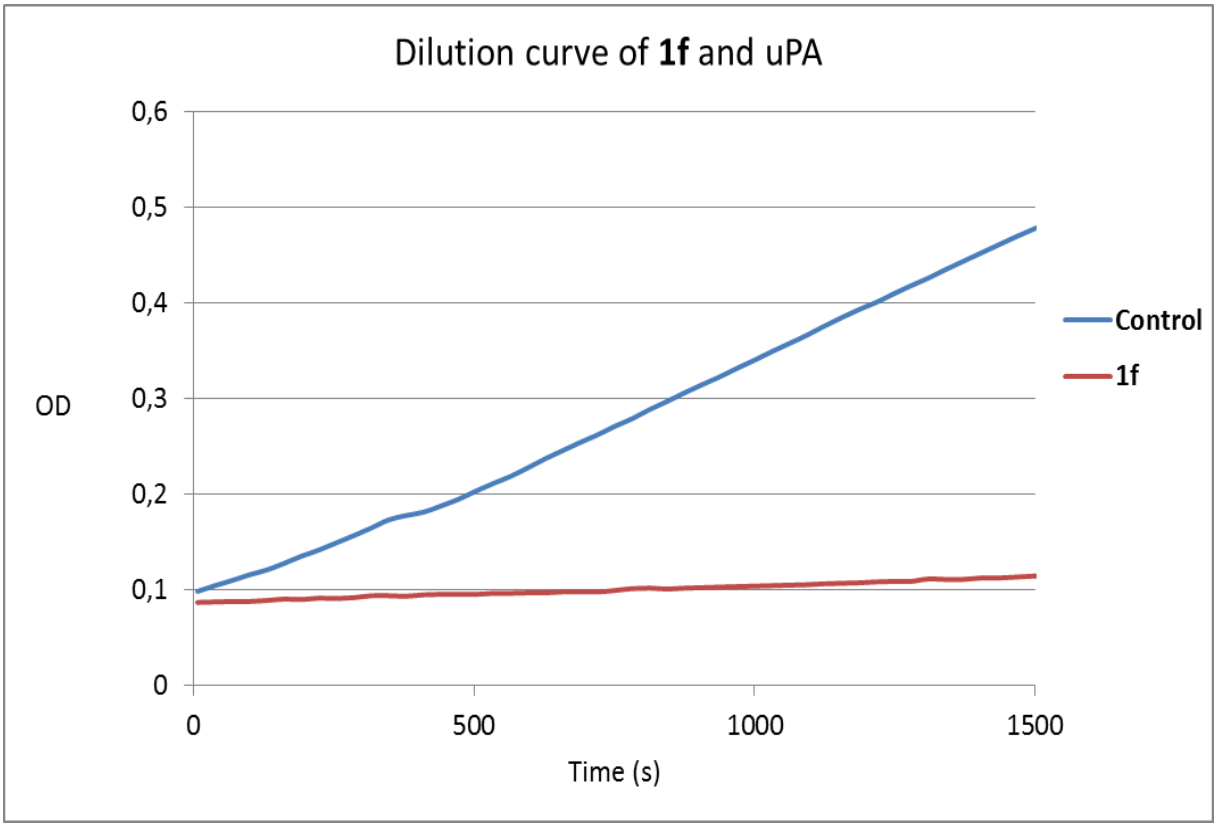
4.2.4 uPA

1f (irreversible)

Progress curve

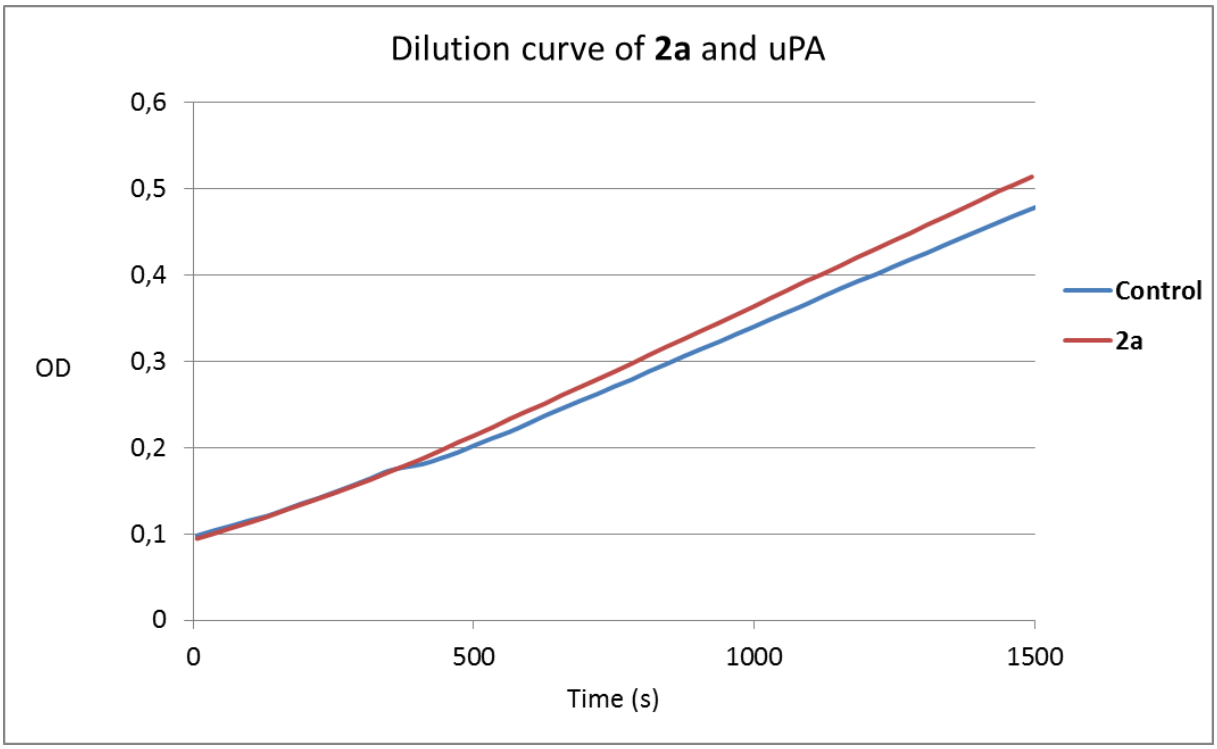


Dilution experiment



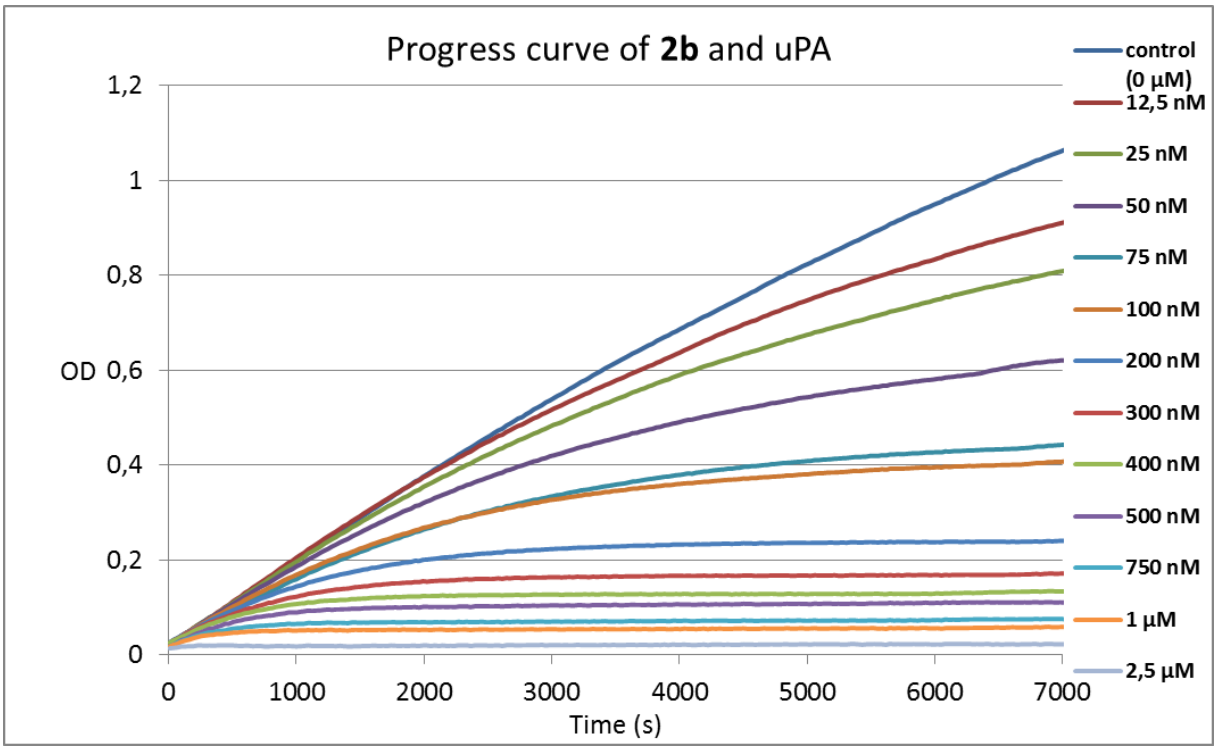
2a (reversible)

Dilution experiment

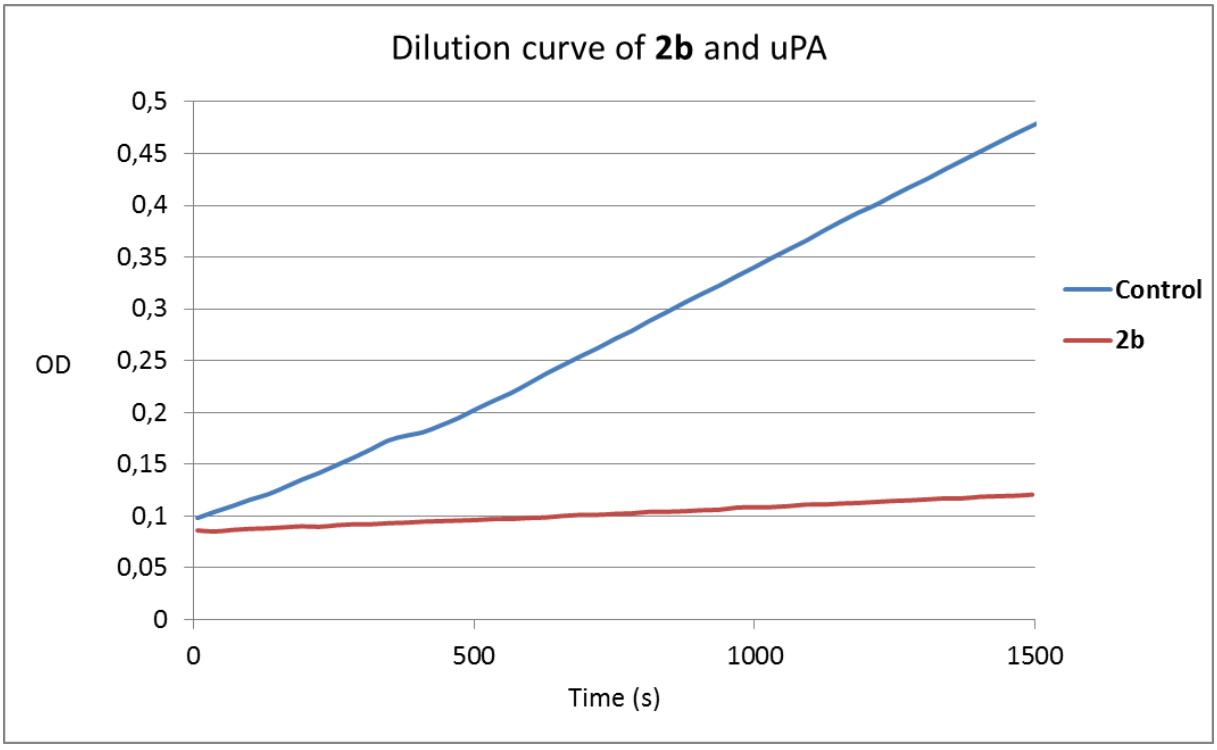


2b (irreversible)

Progress curve



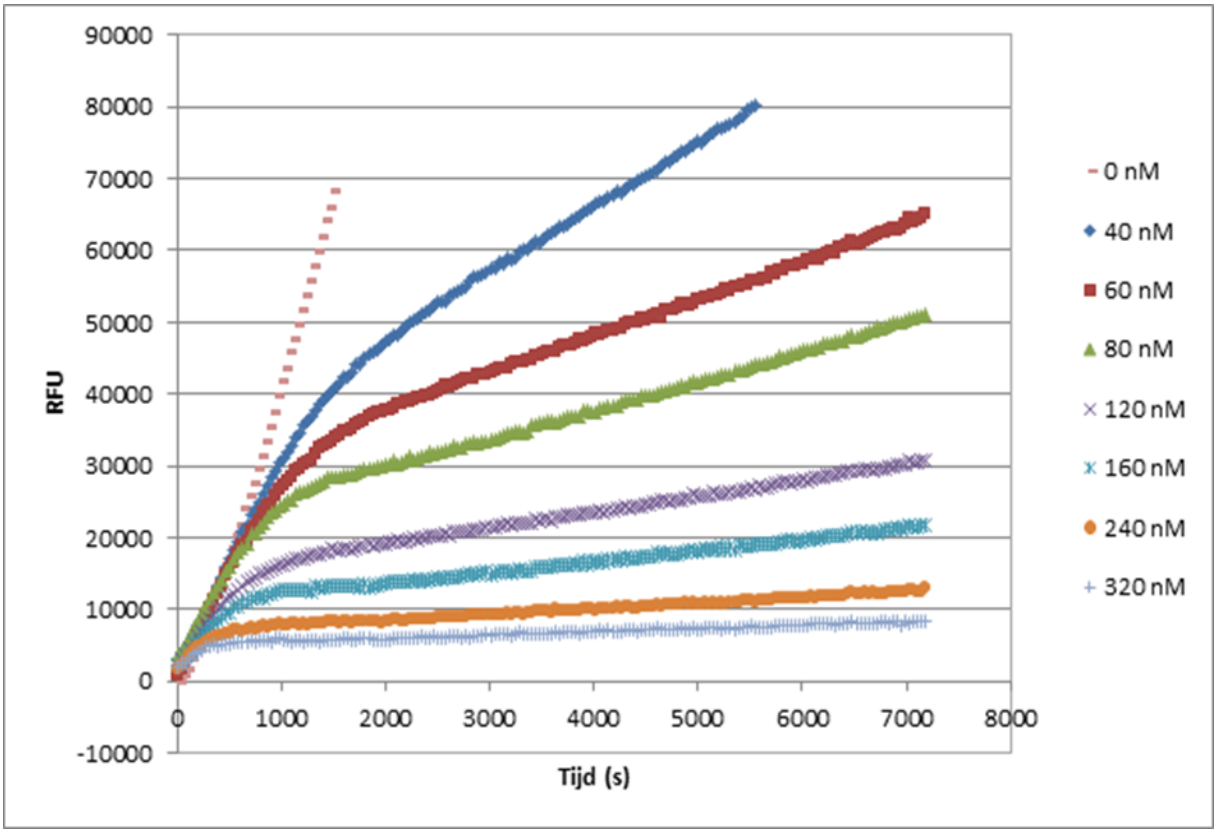
Dilution experiment



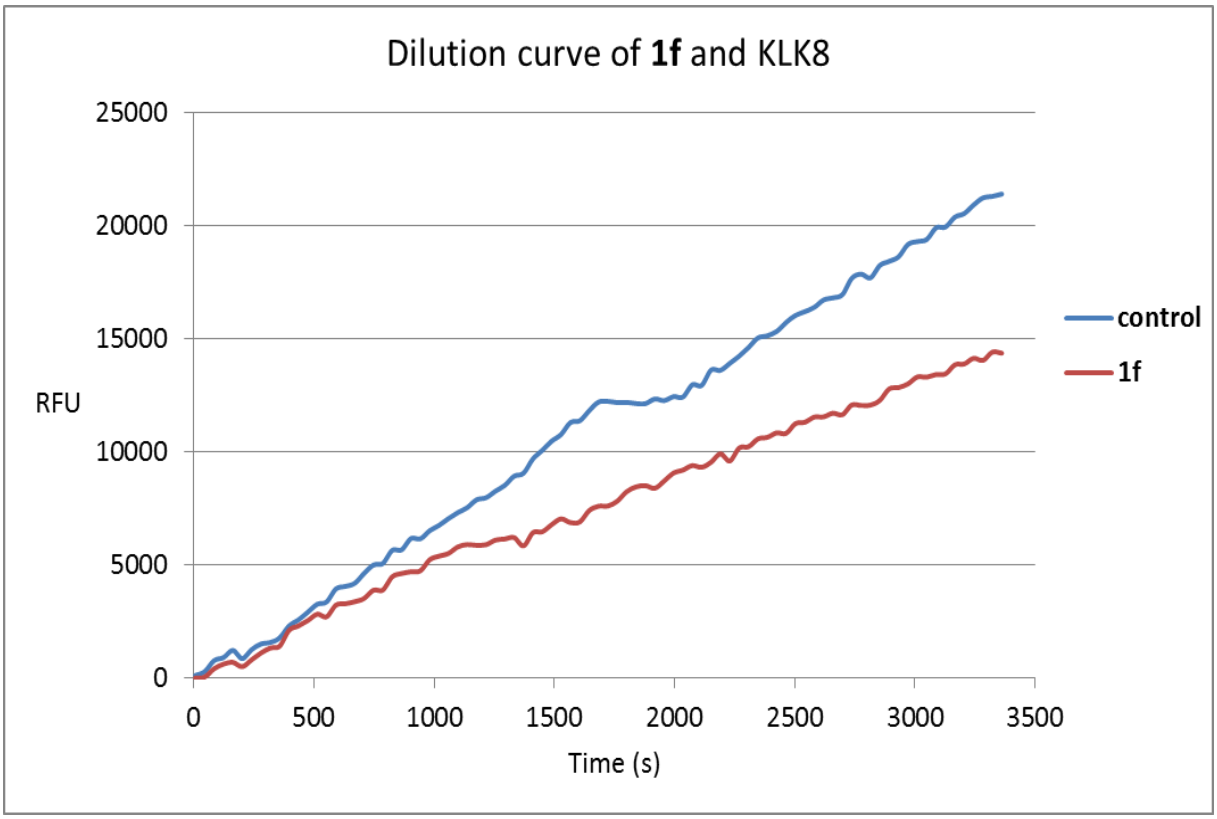
4.2.5 KLK8

1f (reversible)

Progress curve

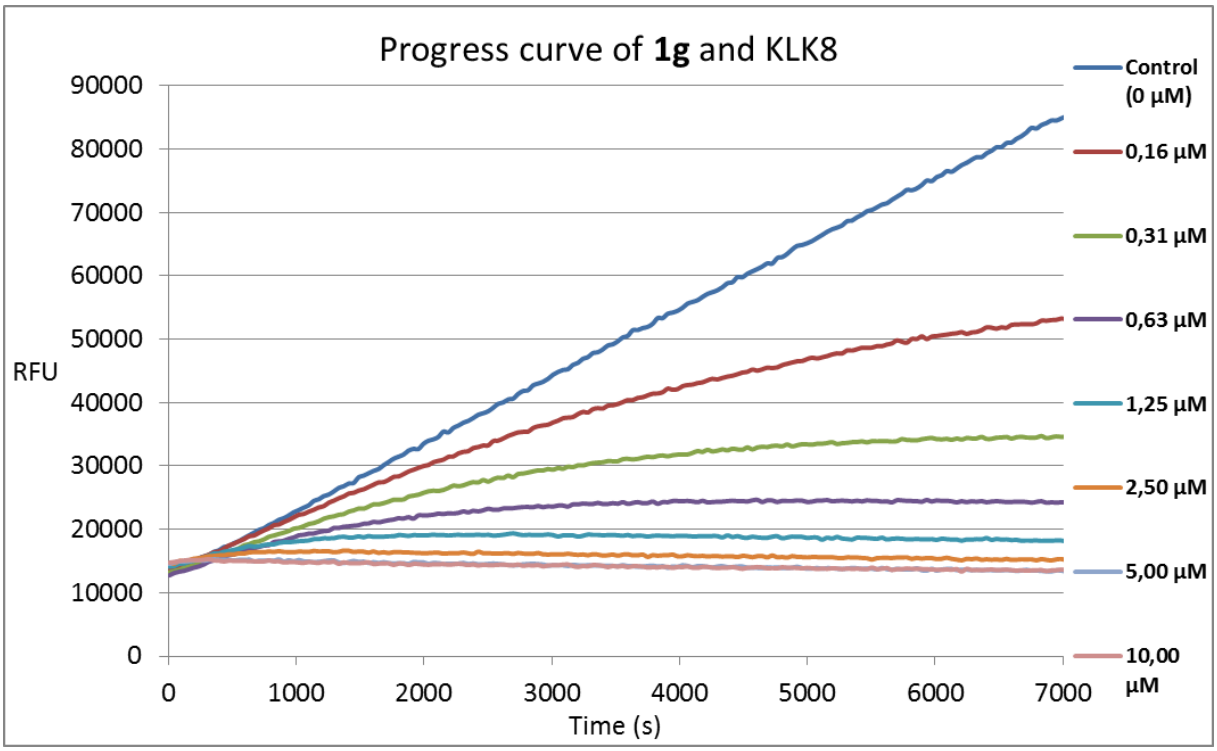


Dilution experiment



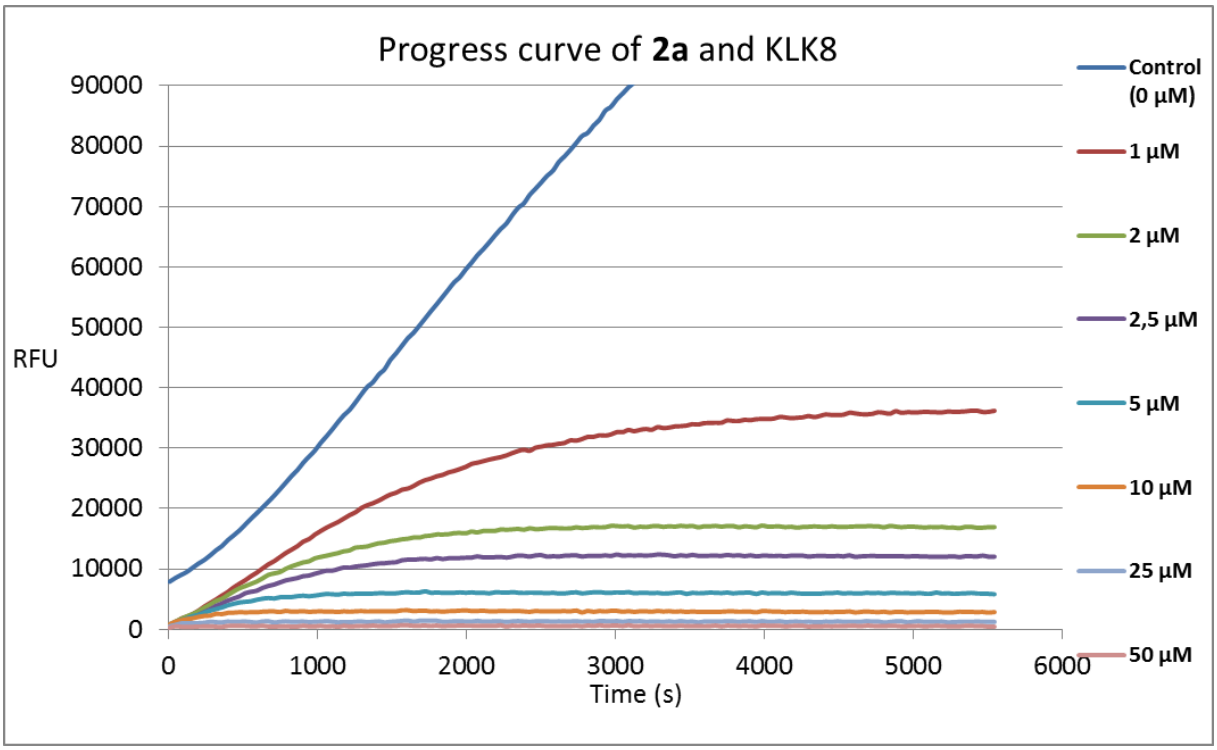
1g (irreversible)

Progress curve

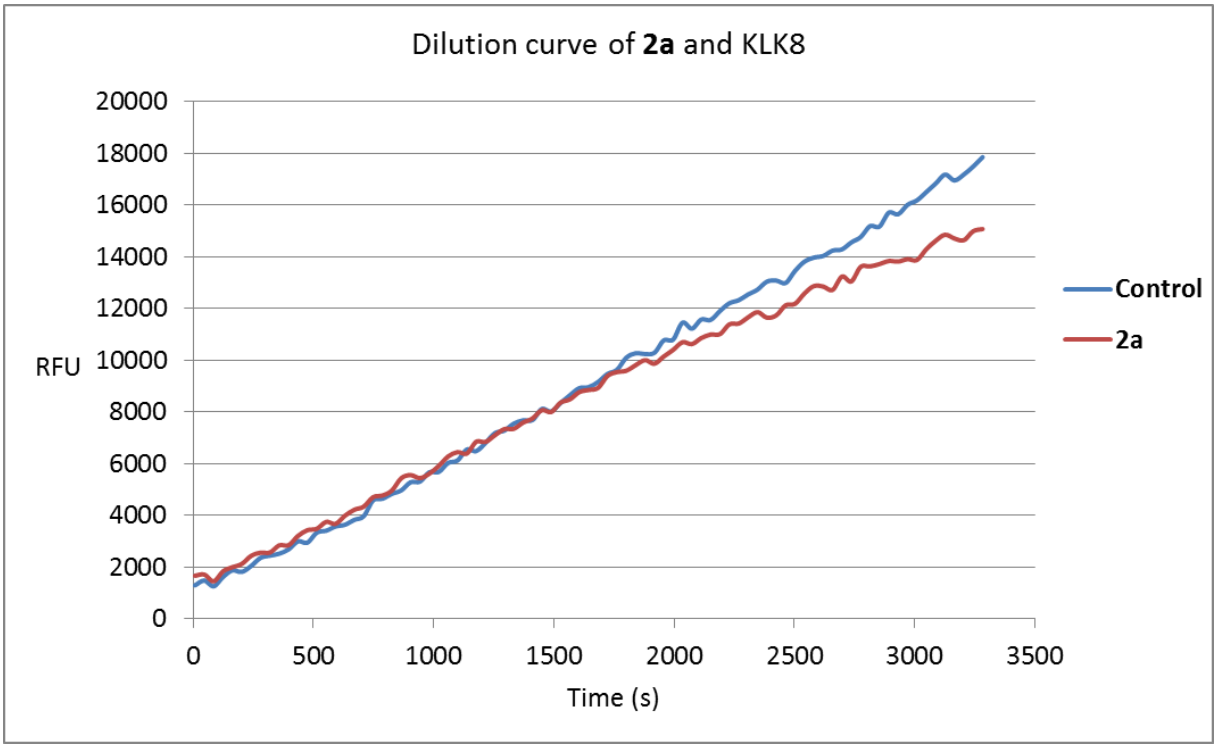


2a (reversible)

Progress curve

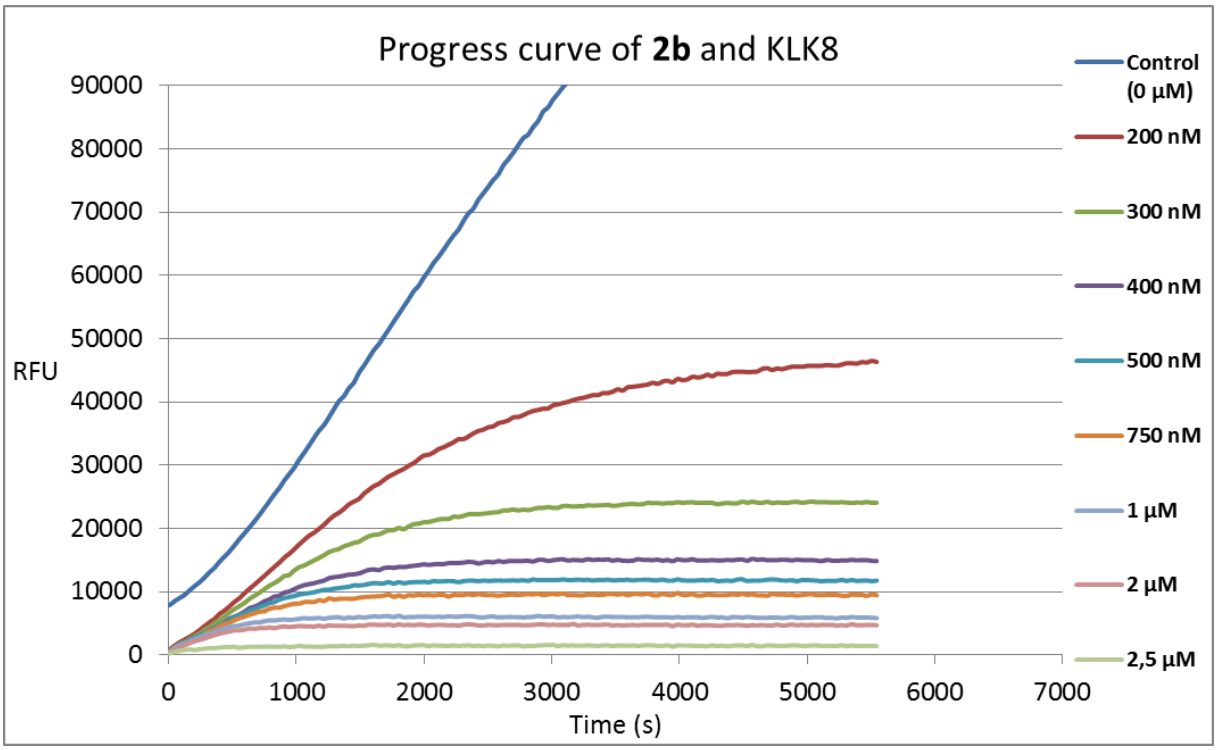


Dilution experiment

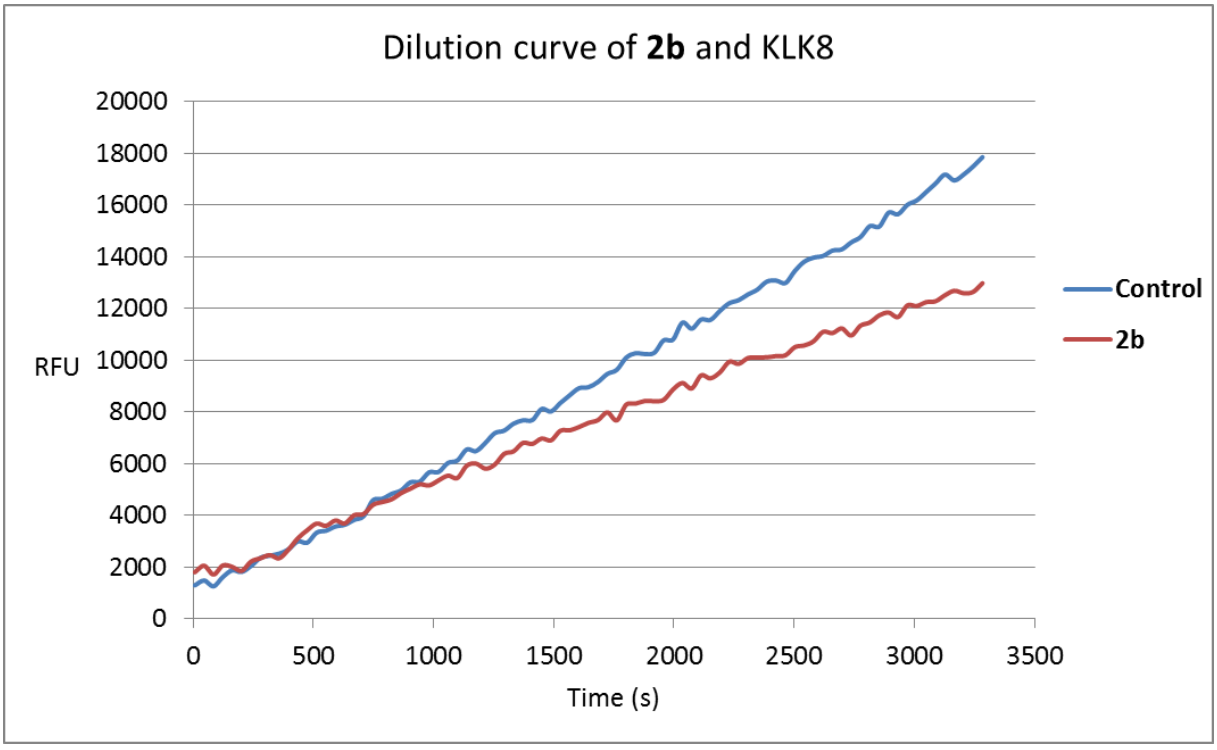


2b (reversible)

Progress curve



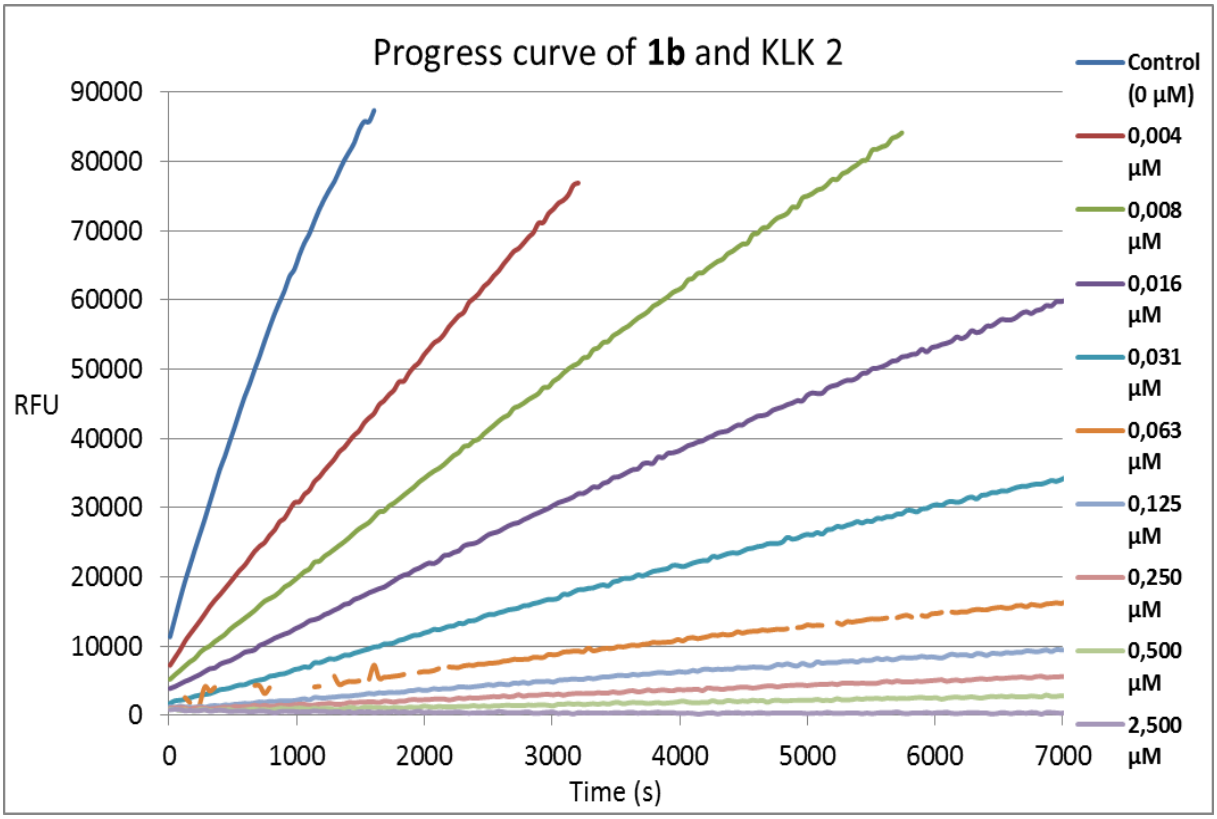
Dilution experiment



4.2.6 KLK2

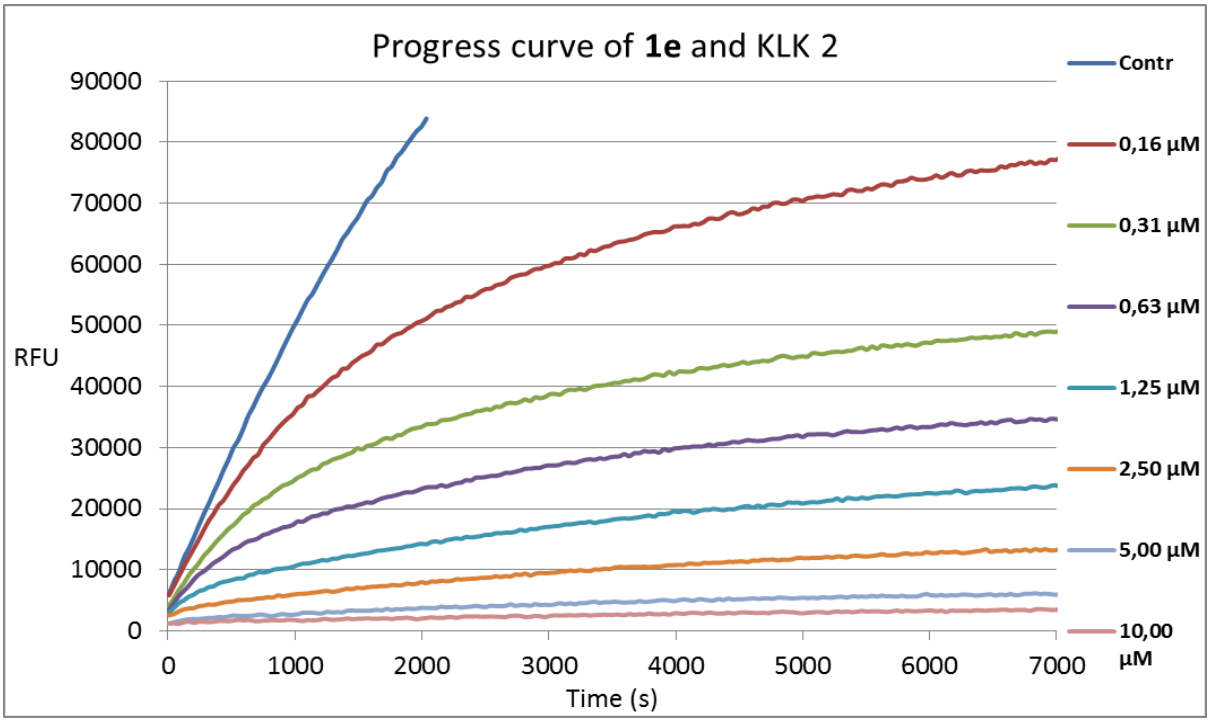
1b (reversible)

Progress curve



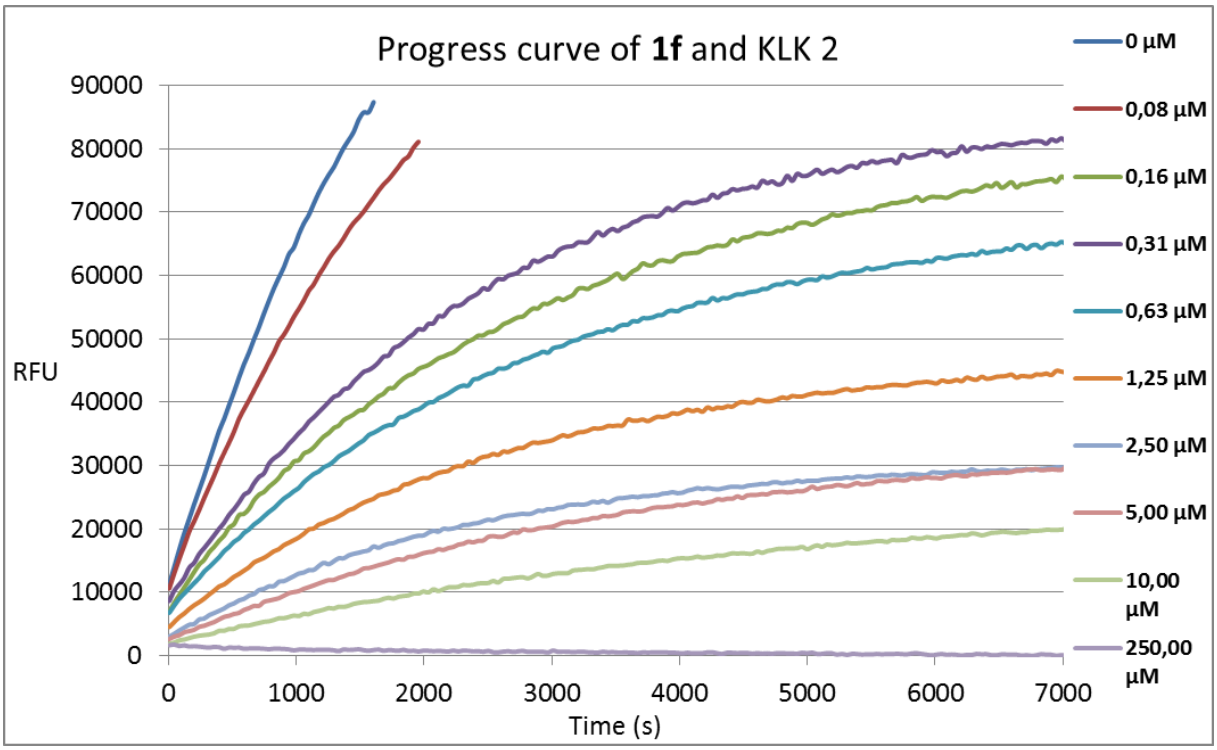
1e (reversible)

Progress curve



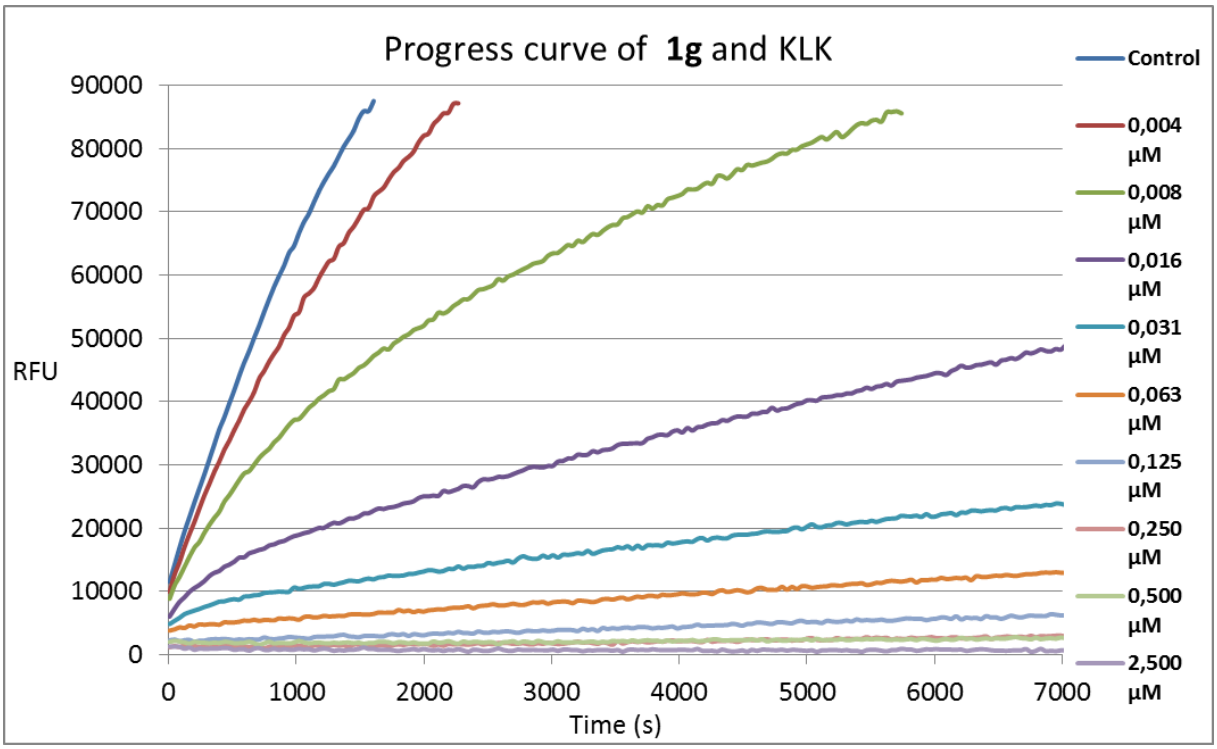
1f (reversible)

Progress curve



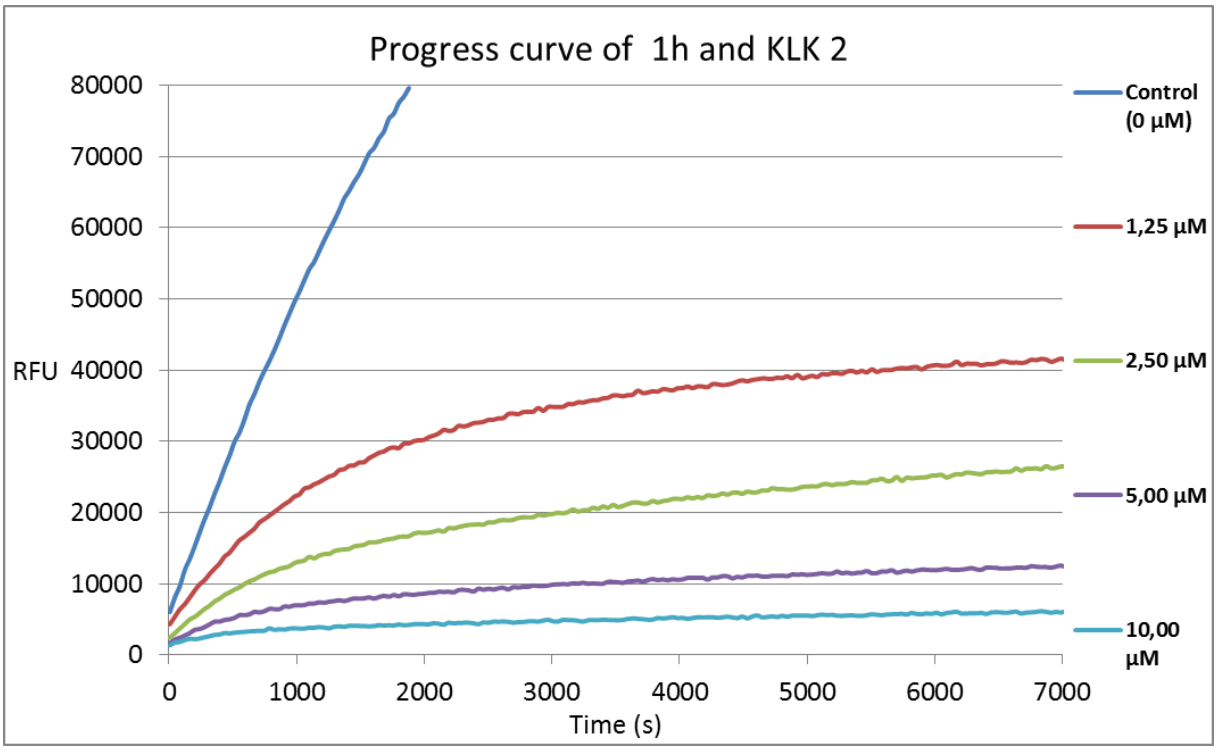
1g (reversible)

Progress curve



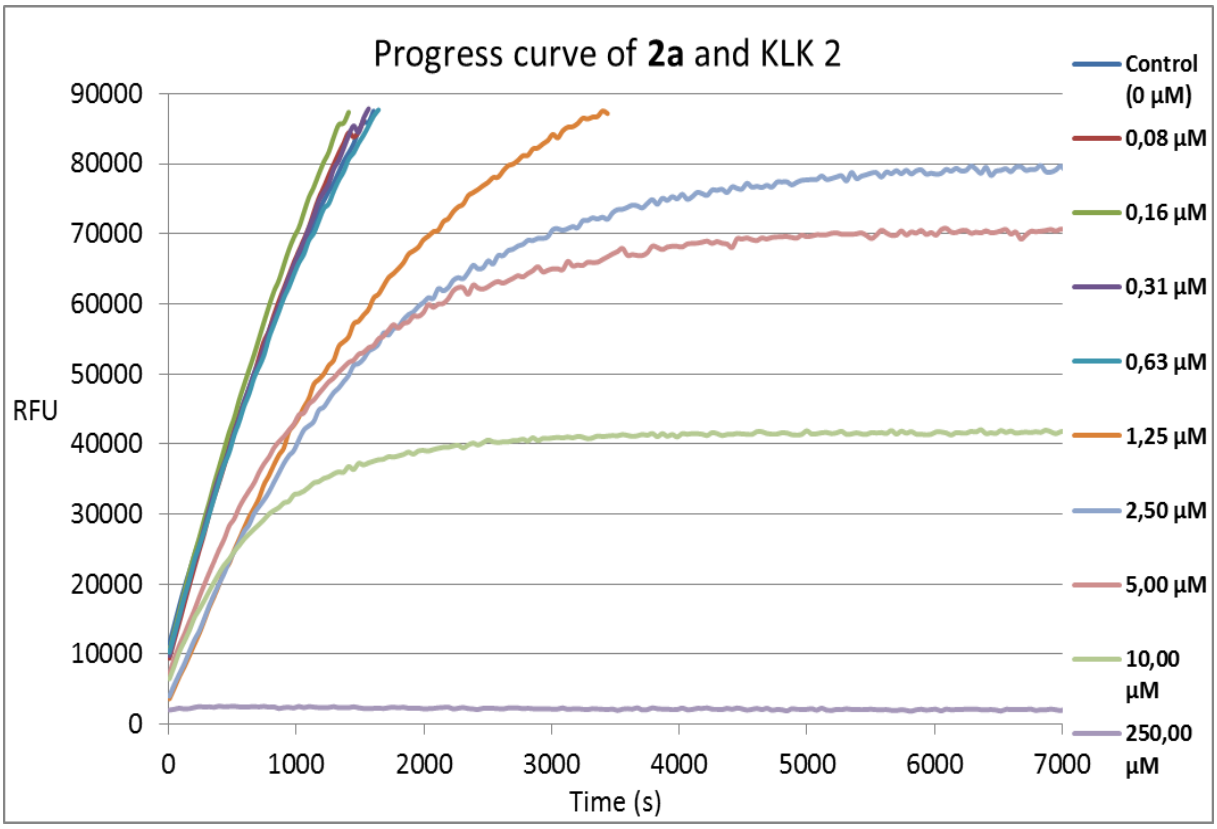
1h (reversible)

Progress curve



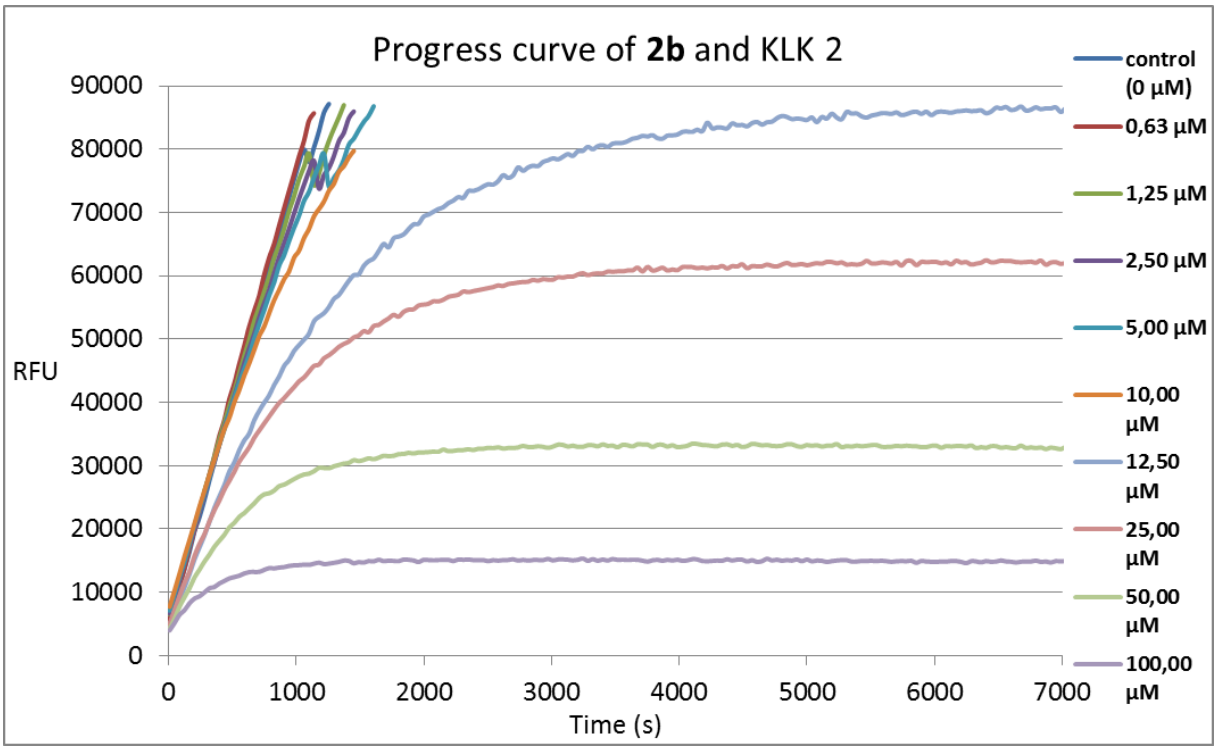
2a (irreversible)

Progress curve

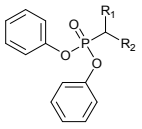


2b (irreversible)

Progress curve



4.3 Standard error on the fit for the IC50 values



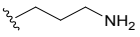
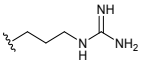
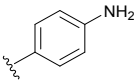
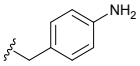
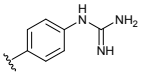
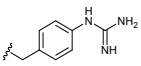
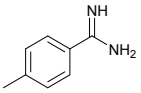
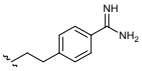
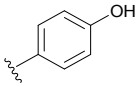
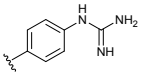
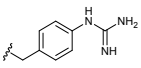
Cpd	R_1	R2	IC_{50} (μM)									
			KLK4	KLK2	KLK1	KLK8	uPA	tPA	Thrombin	Plasmin	FXa	AcHe
1a		NH-Cbz	>2.5	>2.5	>10	>10	>250	>2.5	>2.5	>250	>250	>10
1b		NH-Cbz	0.04	7.28 ± 0.27	0.817 ± 0.35	ND	0.84 ± 0.20	44 ± 20	0.80 ± 0.04	30 ± 2	>10	ND
1c		NH-Cbz	>10	>2.5	>10	>10	>10	>10	>10	>10	>10	>10
1d		NH-Cbz	>10	>10	>10	>10	>2.5	>2.5	>10	ND	>10	ND
1e		NH-Cbz	0.0034 ± 0.0003	0.22 ± 0.02	0.24 ± 0.02	1.16 ± 0.46	2.70 ±0.19	±250	±250	4.90 ± 0.13	3.60 ±0.45	>10
1f		NH-Cbz	0.012	0.53 ± 0.04	>10	0.17	0.007 ± 0.002	12 ± 1	2.40 ± 0.4	3 ±1	>10	>20
1g		NH-Cbz	0.041 ±0.005	>2.5	>2.5	0.79 ± 0.07	>2.5	>2.5	0.196	>2.5	>2.5	ND
1h		NH-Cbz	0.015	0.72 ± 0.08	1.37	>5	0.90 ± 0.08	68 ± 9	17 ±2	6.20 ±0.4	13.7 ± 1.3	>20
1i		NH-Cbz	>10	>2.5	0.086 ± 0.01	>10	>10	>10	>10	>10	>10	>10
2a		H	0.25 ± 0.03	2.44 ± 0.26	>2.5	1.44 ± 0.19	1.40 ± 0.06	>10	>10	>10	>10	>10
2b		H	0.08 ± 0.02	3.02 ± 0.86	>2.5	0.17 ± 0.01	0.0079 ± 0.0003	>10	>10	>10	>10	>10

Table 2 Standard error on the fit for the IC50 values

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3. C. Bergin, R. Hamilton, B. Walker, and B. J. Walker, Chem. Commun. (Camb)., 1996, 10, 1155–1156.
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5. A. M. Lambeir, M. Borloo, I. DeMeester, A. Belyaev, K. Augustyns, D. Hendriks, S. Scharpe and A. Haemers, *Biochimica Et Biophysica Acta-General Subjects,* 1996, **1290**, 76-82