Supplemental Information

DISCOVERY AND STRUCTURE ACTIVITY RELATIONSHIP OF SMALL MOLECULE INHIBITORS OF TOXIC β-AMYLOID-42 FIBRIL FORMATION

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*Running title: *Small molecule inhibitors of toxic beta-amyloid*

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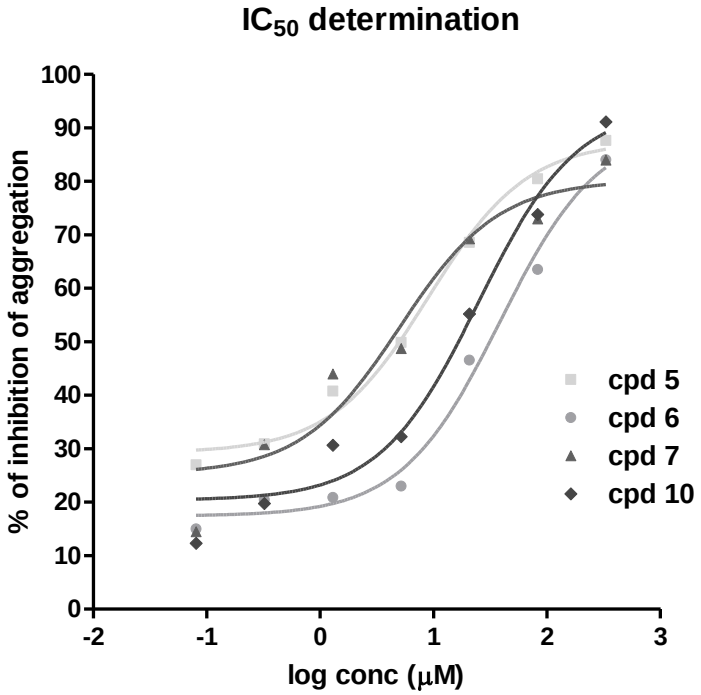
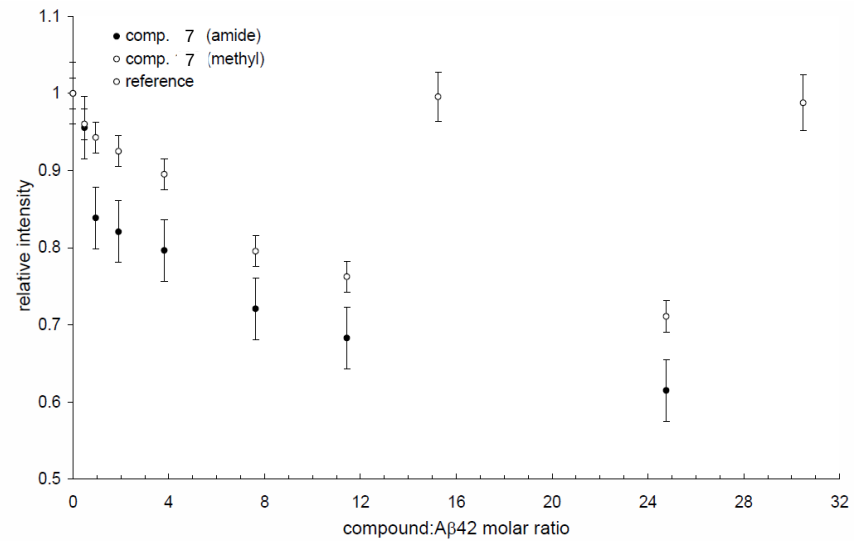
Sup. Fig. 1



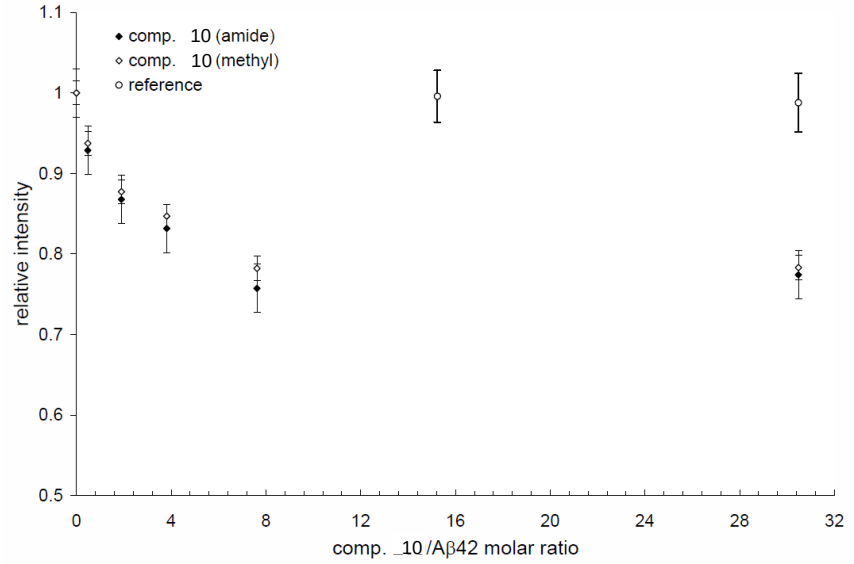
	cpd5	cpd6	cpd7	cpd10
IC_{50} [μM]	8.6±3.5	40.5±6.8	7.5±1.0	29±3.5

Sup. Fig. 2

A

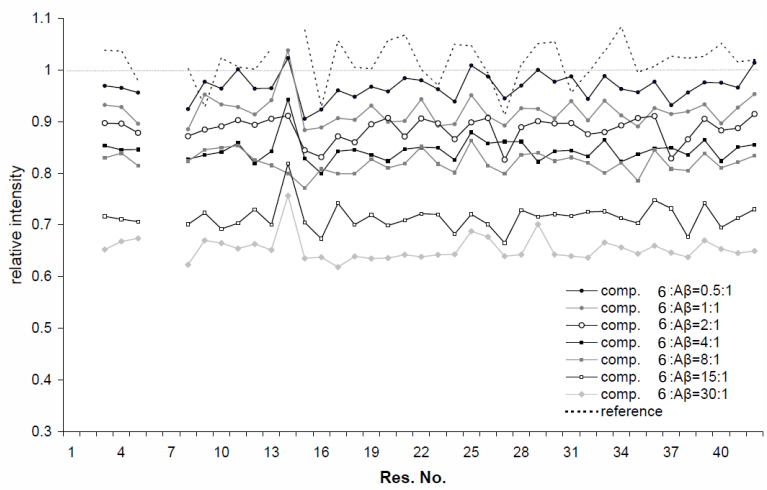

comp. 7 (amide)
comp. 7 (methyl)
reference
relative intensity
compound:Aβ42 molar ratio

B

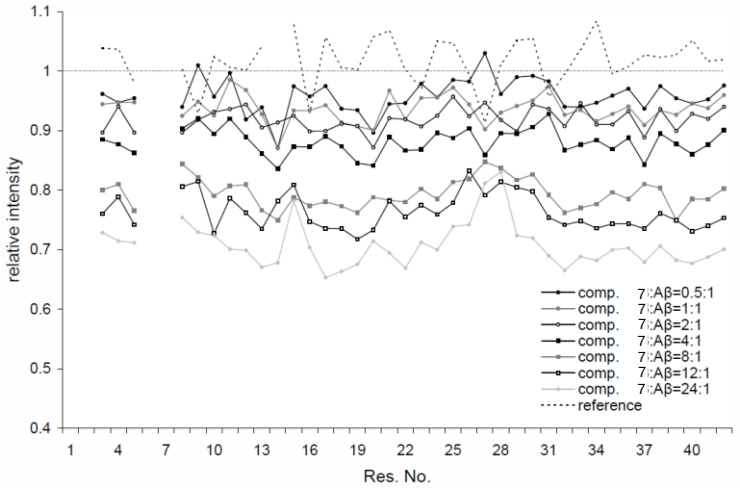

comp. 10 (amide)
comp. 10 (methyl)
reference
relative intensity
comp. 10 /Aβ42 molar ratio

Sup. Fig. 3

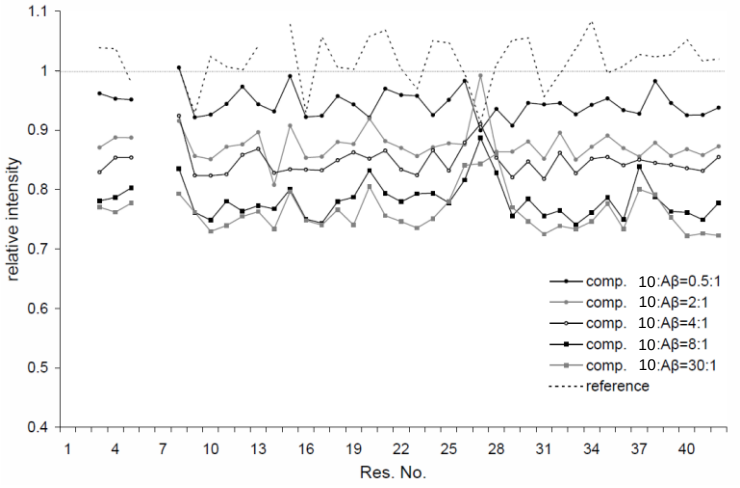
A


relative intensity
Res. No.
comp. 6:Aβ=0.5:1
comp. 6:Aβ=1:1
comp. 6:Aβ=2:1
comp. 6:Aβ=4:1
comp. 6:Aβ=8:1
comp. 6:Aβ=15:1
comp. 6:Aβ=30:1
reference

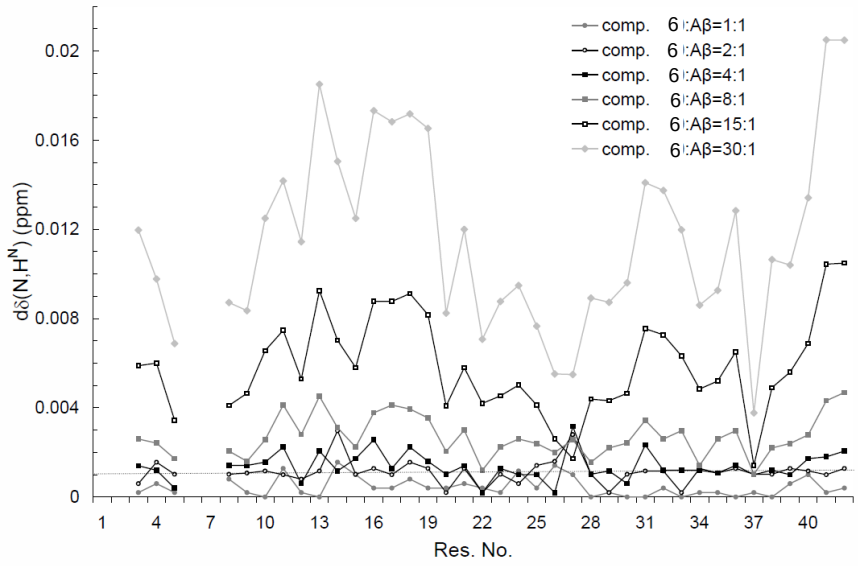
B


relative intensity
Res. No.
comp. 7:Aβ=0.5:1
comp. 7:Aβ=1:1
comp. 7:Aβ=2:1
comp. 7:Aβ=4:1
comp. 7:Aβ=8:1
comp. 7:Aβ=12:1
comp. 7:Aβ=24:1
reference

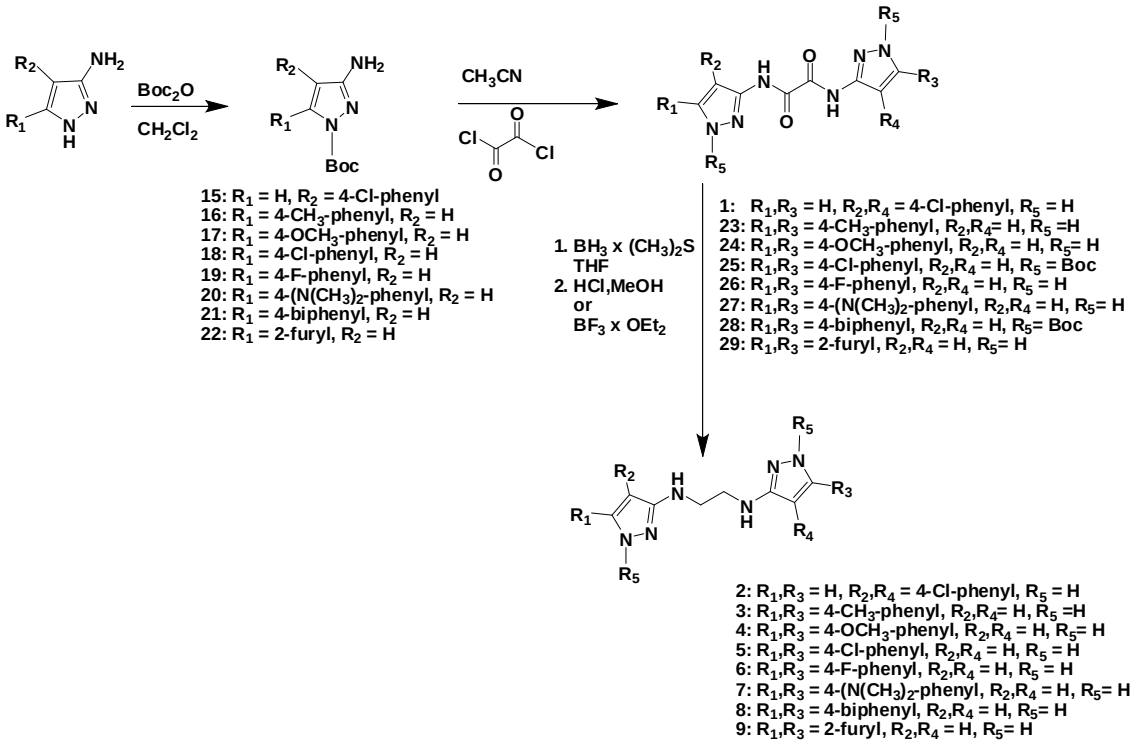
C


relative intensity
Res. No.
comp. 10:Aβ=0.5:1
comp. 10:Aβ=2:1
comp. 10:Aβ=4:1
comp. 10:Aβ=8:1
comp. 10:Aβ=30:1
reference

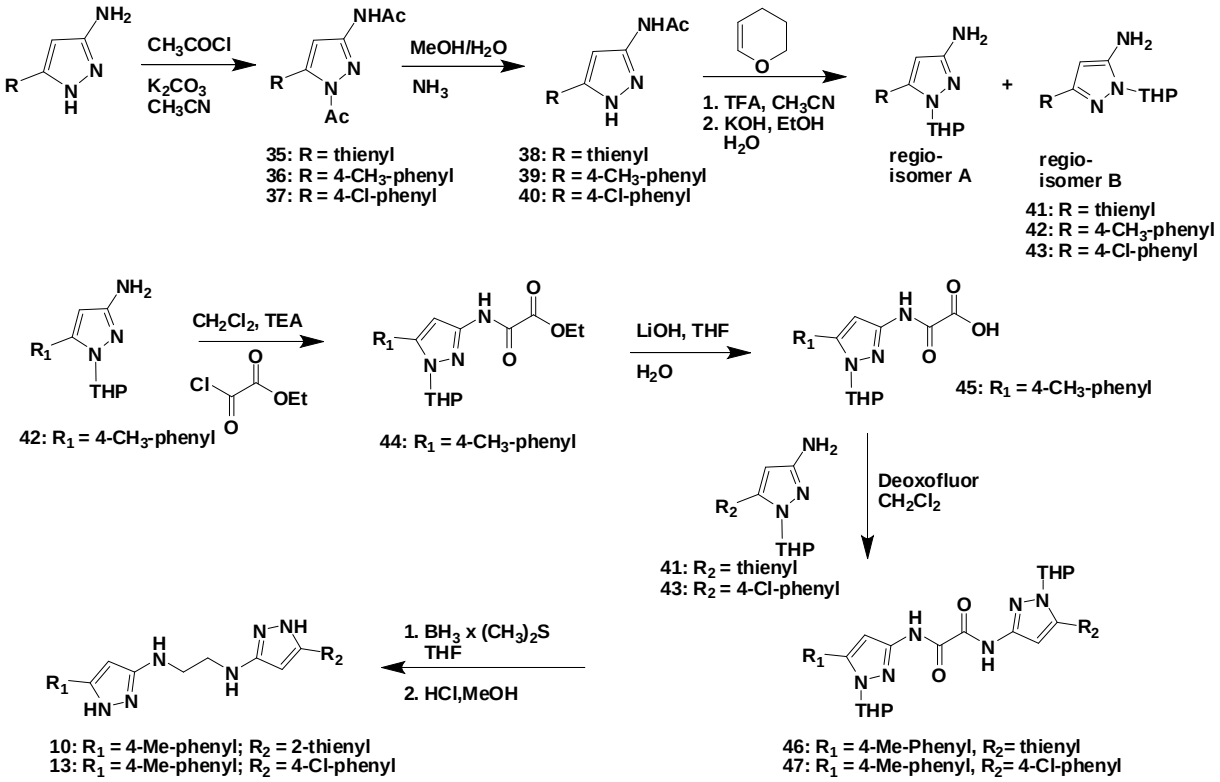
Sup. Fig. 4


comp. 6 :Aβ=1:1
comp. 6 :Aβ=2:1
comp. 6 :Aβ=4:1
comp. 6 :Aβ=8:1
comp. 6 :Aβ=15:1
comp. 6 :Aβ=30:1
dδ(N,H^N) (ppm)
0.02
0.016
0.012
0.008
0.004
0
1
4
7
10
13
16
19
22
25
28
31
34
37
40
Res. No.

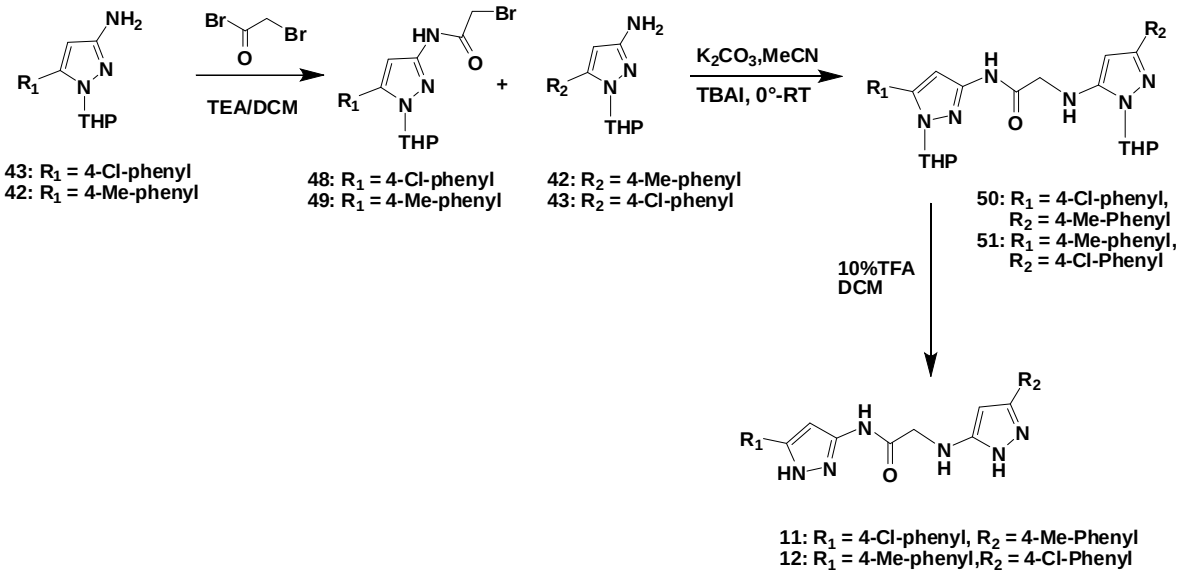
Sup. Fig. 5


Boc2O
CH2Cl2
CH3CN
15: R1 = H, R2 = 4-Cl-phenyl
16: R1 = 4-CH3-phenyl, R2 = H
17: R1 = 4-OCH3-phenyl, R2 = H
18: R1 = 4-Cl-phenyl, R2 = H
19: R1 = 4-F-phenyl, R2 = H
20: R1 = 4-(N(CH3)2-phenyl, R2 = H
21: R1 = 4-biphenyl, R2 = H
22: R1 = 2-furyl, R2 = H
1. BH3 x (CH3)2S
THF
2. HCl,MeOH
or
BF3 x OEt2
1: R1,R3 = H, R2,R4 = 4-Cl-phenyl, R5 = H
23: R1,R3 = 4-CH3-phenyl, R2,R4= H, R5 =H
24: R1,R3 = 4-OCH3-phenyl, R2,R4 = H, R5= H
25: R1,R3 = 4-Cl-phenyl, R2,R4 = H, R5 = Boc
26: R1,R3 = 4-F-phenyl, R2,R4 = H, R5 = H
27: R1,R3 = 4-(N(CH3)2-phenyl, R2,R4 = H, R5= H
28: R1,R3 = 4-biphenyl, R2,R4 = H, R5= Boc
29: R1,R3 = 2-furyl, R2,R4 = H, R5= H
2: R1,R3 = H, R2,R4 = 4-Cl-phenyl, R5 = H
3: R1,R3 = 4-CH3-phenyl, R2,R4= H, R5 =H
4: R1,R3 = 4-OCH3-phenyl, R2,R4 = H, R5= H
5: R1,R3 = 4-Cl-phenyl, R2,R4 = H, R5 = H
6: R1,R3 = 4-F-phenyl, R2,R4 = H, R5 = H
7: R1,R3 = 4-(N(CH3)2-phenyl, R2,R4 = H, R5= H
8: R1,R3 = 4-biphenyl, R2,R4 = H, R5= H
9: R1,R3 = 2-furyl, R2,R4 = H, R5= H

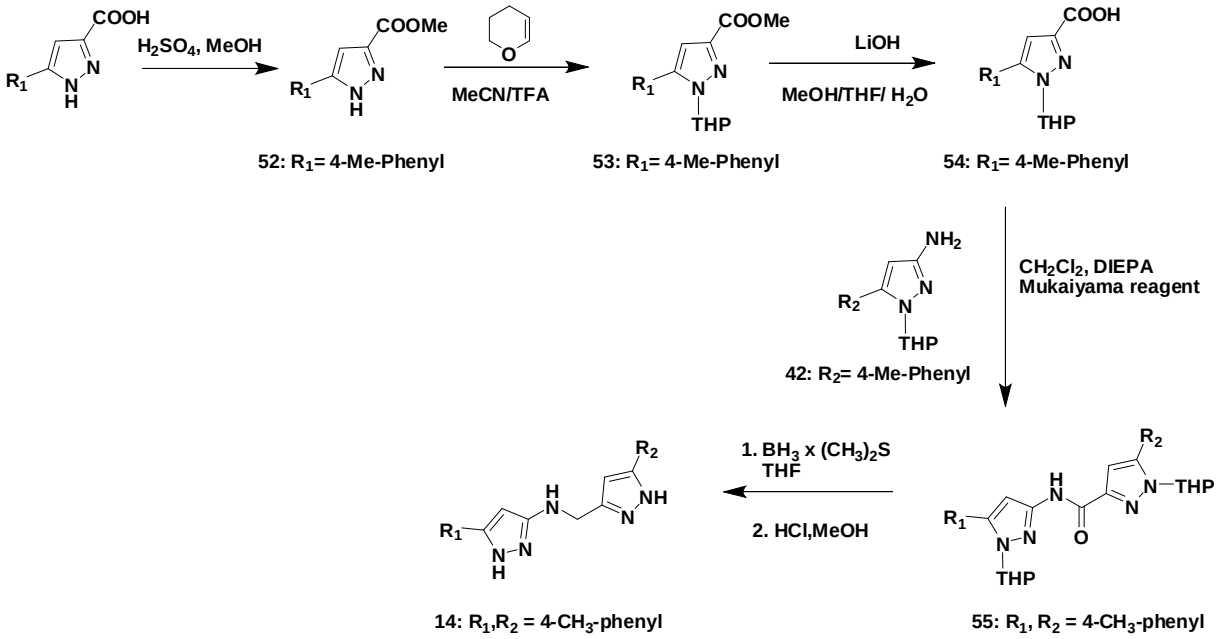
Sup. Fig. 6


CH3COCl
K2CO3
CH3CN
MeOH/H2O
NH3
1. TFA, CH3CN
2. KOH, EtOH
H2O
regio-isomer A
regio-isomer B
35: R = thienyl
36: R = 4-CH3-phenyl
37: R = 4-Cl-phenyl
38: R = thienyl
39: R = 4-CH3-phenyl
40: R = 4-Cl-phenyl
41: R = thienyl
42: R = 4-CH3-phenyl
43: R = 4-Cl-phenyl
CH2Cl2, TEA
LiOH, THF
H2O
42: R1 = 4-CH3-phenyl
44: R1 = 4-CH3-phenyl
45: R1 = 4-CH3-phenyl
Deoxofluor
CH2Cl2
41: R2 = thienyl
43: R2 = 4-Cl-phenyl
1. BH3 x (CH3)2S
THF
2. HCl,MeOH
10: R1 = 4-Me-phenyl; R2 = 2-thienyl
13: R1 = 4-Me-phenyl; R2 = 4-Cl-phenyl
46: R1 = 4-Me-Phenyl, R2= thienyl
47: R1 = 4-Me-phenyl, R2= 4-Cl-phenyl

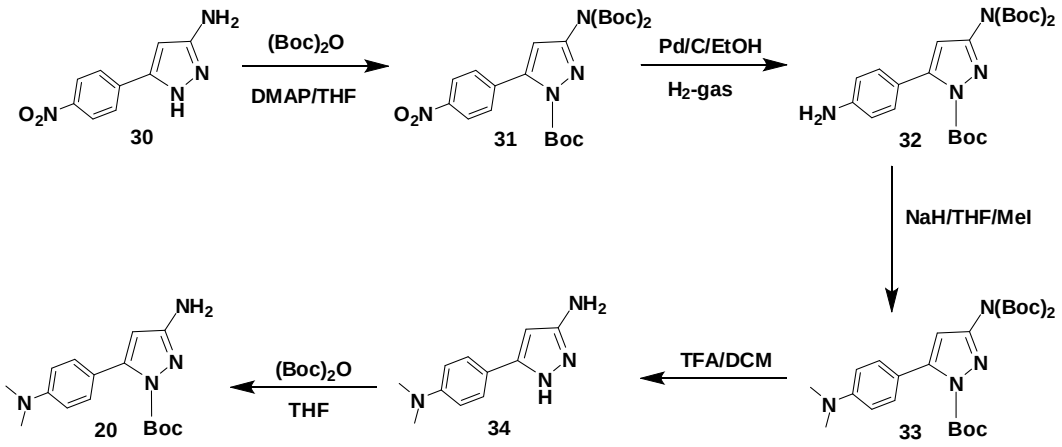
Sup. Fig. 7


43: R1 = 4-Cl-phenyl
42: R1 = 4-Me-phenyl
TEA/DCM
48: R1 = 4-Cl-phenyl
49: R1 = 4-Me-phenyl
42: R2 = 4-Me-phenyl
43: R2 = 4-Cl-phenyl
K2CO3,MeCN
TBAI, 0°-RT
50: R1 = 4-Cl-phenyl,
R2 = 4-Me-Phenyl
51: R1 = 4-Me-phenyl,
R2 = 4-Cl-Phenyl
10%TFA
DCM
11: R1 = 4-Cl-phenyl, R2 = 4-Me-Phenyl
12: R1 = 4-Me-phenyl,R2 = 4-Cl-Phenyl

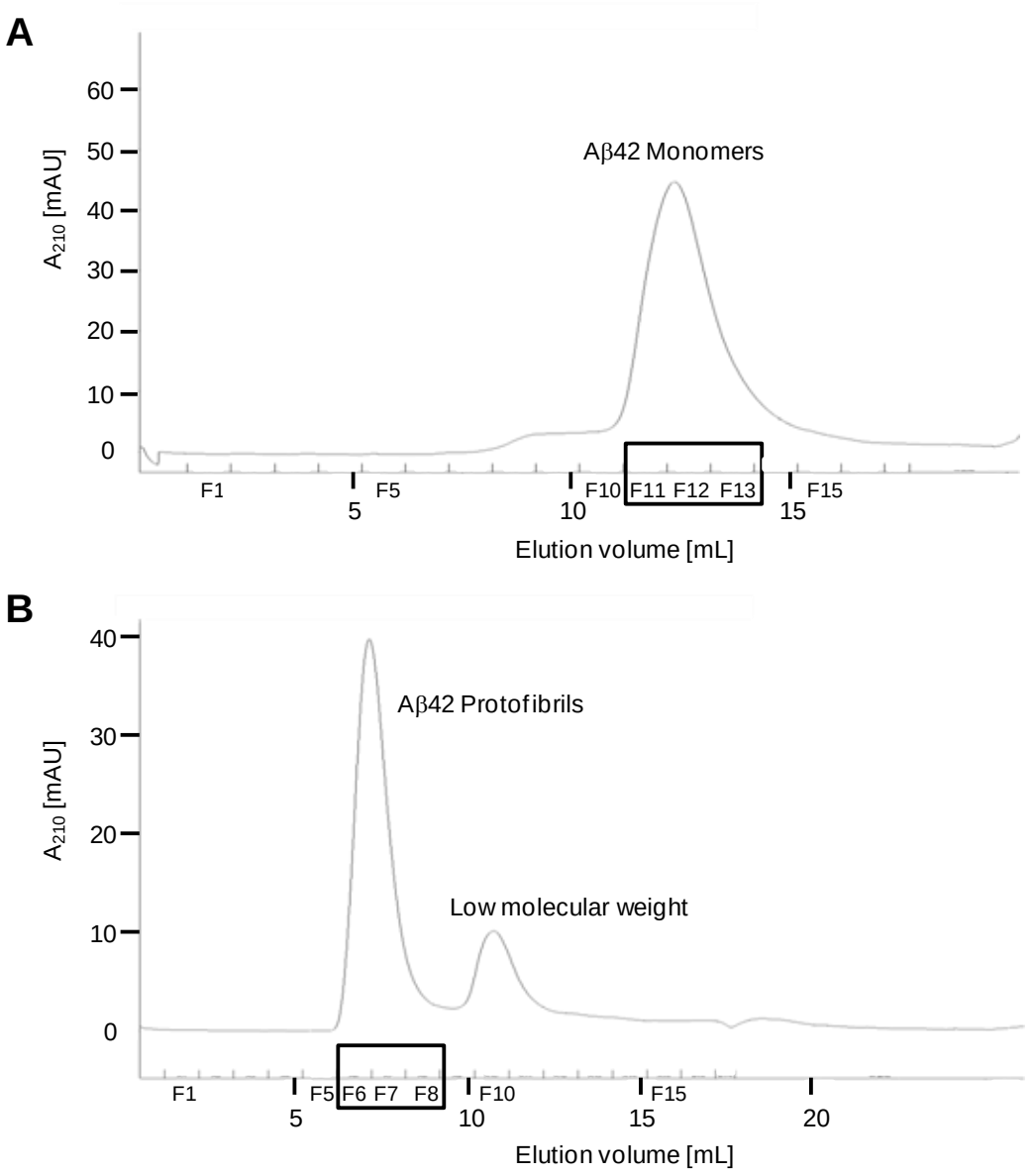
Sup. Fig. 8


COOH
H_2SO_4, MeOH
COOMe
MeCN/TFA
COOMe
LiOH
MeOH/THF/ H_2O
COOH
THP
52: R_1= 4-Me-Phenyl
53: R_1= 4-Me-Phenyl
54: R_1= 4-Me-Phenyl
NH_2
42: R_2= 4-Me-Phenyl
CH_2Cl_2, DIEPA
Mukaiyama reagent
1. BH_3 x $(CH_3)_2S$
THF
2. HCl,MeOH
14: R_1,R_2 = 4-CH_3-phenyl
55: R_1, R_2 = 4-CH_3-phenyl

Sup. Fig. 9


NH2
(Boc)2O
DMAP/THF
N(Boc)2
Pd/C/EtOH
H2-gas
O2N
30
31
Boc
H2N
32
NaH/THF/MeI
TFA/DCM
33
(Boc)2O
THF
34
20

Sup. Fig. 10


A
60
50
40
30
20
10
0
A210 [mAU]
Aβ42 Monomers
F1
F5
F10
F11 F12 F13
F15
5
10
15
Elution volume [mL]
B
40
30
20
10
0
A210 [mAU]
Aβ42 Protofibrils
Low molecular weight
F1
F5
F6 F7 F8
F10
F15
5
10
15
20
Elution volume [mL]

Supplementary Figure Legends

Sup. Fig. 1. Determination of the IC_{50} values of Aβ42 inhibition of fibrillization for compounds 5, 6, 7 and 10. The IC_{50} values were determined from the percent inhibition of aggregation values obtained at the end of the experiment. Thereafter these values were plotted against log of the inhibitor concentration. Fitting the data with a sigmoidal function in the Prism software (GraphPad Software, USA) the IC_{50} was obtained at the halfway of the percent inhibition of aggregation.

Sup. Fig. 2. Ligand-dependent conversion of Aβ42 into oligomers. (A) Intensity changes of proton signals in 1D ^{1}H NMR spectra of Aβ42 upon addition of compound 7 at various ratios. Changes in the methyl and backbone amide signals are shown separately. Reference values were obtained following addition of DMSO (without compound 7) at corresponding volumes. Note that backbone amide signals decay more strongly than the side chain methyl signals. (B) Intensity changes of proton signals in 1D ^{1}H NMR spectra of Aβ42 upon addition of compound 10 at various ratios. Changes in the methyl and backbone amide signals are shown separately. Reference values were obtained following addition of DMSO (without compound 10) at corresponding volumes.

Sup. Fig. 3. Residue-specific intensity changes of correlation peaks in 2D HSQC spectra of ^{15}N-labelled Aβ42 upon addition of compound 6 (A), compound 7 (B) and compound 10 (C) at the specified ratios. The reference values were obtained following addition of DMSO (without compounds) at the volume corresponding to the highest ligand/ Aβ42 ratio.

Sup. Fig. 4. Binding of compound 6 to monomeric Aβ42. Average backbone amide proton and nitrogen chemical shift deviations obtained from 2D [^{1}H,^{15}N]-HSQC spectra of ^{15}N-labelled Aβ42 at increasing compound 6/peptide ratios. The dotted line corresponds to the average uncertainty in the chemical shifts. Note that chemical shift deviations change roughly linearly with compound concentration, *i.e.* the binding is weak and far from saturation.

Sup. Fig. 5. Synthesis scheme to prepare compounds 1, 2, 3, 4, 5, 6, 7, 8 and 9.

Sup. Fig. 6. Synthesis scheme to prepare compounds 10 and 13.

Sup. Fig. 7. Synthesis scheme to prepare compounds 11 and 12.

Sup. Fig. 8. Synthesis scheme to prepare compound 14.

Sup. Fig. 9. Synthesis scheme to prepare building block 20.

Sup. Fig. 10. Preparation of Aβ42 monomers (A) and protofibrils (B). Aβ42 monomers eluted as a single peak after an elution volume of 11-13 ml (fractions F11 to F13). Aβ42 protofibrils eluted after an elution volume of 6-8 ml (fractions F6 to F8). The second peak contained low molecular weight Aβ42.

Supplementary Methods

Small molecule synthesis

The symmetrical compounds bearing an ethylenediamine linker unit were prepared from 4-, or 5- aryl substituted 3-aminopyrazoles. The 4- or 5-aryl substituted amino pyrazoles were treated with one equivalent of tert-butyl dicarbonate to afford the corresponding N^1-Boc-protected aminopyrazole building blocks (Fig. S5) as the basic ring NH group is more reactive than the aromatic amino group (1). The reaction of the N^1-Boc-protected aminopyrazole derivatives with oxalylchloride in acetonitrile without any base afforded the symmetrical final compound (**1**) containing an oxalyl linker. In most of the cases Boc deprotection also occurred during the reaction. Compounds where partial deprotection occurred were directly used in next reduction step. While doing the reaction in presence of triethyl amine base no deprotection of Boc group observed.
Reduction of the oxalyl moiety of the Boc-protected or unprotected symmetrical derivatives was achieved by treating the compounds with borane dimethylsulfide complex in tetrahydrofurane (2). After refluxing the reaction mixture for overnight, it was treated with concentrated HCl and refluxed for another 16 hours to decompose the borane complex. The free base was isolated upon adjusting the pH to 14 followed by extraction and subsequent purification on silica gel chromatography. Treating the free base with methanolic HCl afforded the symmetrical compounds (**2, 3, 4, 5, 6, 7, 8**) bearing an ethylenediamine linker as HCl-salts (Fig. S5). For the preparation of compound **7**, building block **20** was prepared (Fig. S9). Special reaction conditions were applied for the synthesis of compound **9**, as the furan moiety is sensitive to strong acids. The mild lewis acid BF_3xOEt_2 was used for *in situ* cleavage of the boran dimethyl sulfide complex during the reduction step and compound **9** was isolated as the free base.
To synthesize non-symmetrical compounds **10** and **13** having different aryl substituents at the 5-position of 3-aminopyrazoles, another set of building blocks **41, 42**, and **43** containing a THP-protecting group at the N^1-position of 3-aminopyrazole was prepared (Fig. S6). Reaction of 5-aryl substituted 3-aminopyrazoles with acetyl chloride afforded compounds being acylated at the N^1-position and at the 3 amino-group. A selective de-acylation of the N^1-position was achieved by treatment with aqueous ammonia solution at room temperature. Then the N^1-position was protected with the tetrahydropyrane (THP) moiety in the presence of trifluoroacetic acid. The cleavage of the acetyl group was achieved by refluxing the starting material under basic conditions (potassium hydroxide), to afford the 3-amino- N^1-THP protected building blocks **41**, **42**, and **43** as two regioisomers each. The 3-amino-N^1-THP protected building block **42** was treated with mono ethyl oxalyl chloride to afford the corresponding ester derivative (**44**). The mono ester reaction product was treated with lithium hydroxide to afford the corresponding free acid derivative **45**. The coupling reaction of the free acid derivative **45** with 3-amino-N^1-THP protected building blocks **41** and **43** was achieved via activation of the acid with Deoxo-Fluor (3) to afford the corresponding unsymmetrical 5-aryl substituted N^1-THP protected derivatives **46**, and **47**. The oxalyl moiety was reduced with borane dimethyl sulfide complex to the corresponding non-symmetrical 5-aryl substituted compounds (**10** and **13**) containing an ethylenediamine linker.
Another set of non-symmetrical compounds (Fig. S7) were prepared by reacting N^1-THP protected 5-aryl 3-aminopyrazole building blocks (**42** and **43**) with bromo acetyl bromide to afford the corresponding amide coupling derivatives **48** and **49**. The nucleophilic displacement of the bromide by different N^1-THP protected 5-aryl 3-aminopyrazole building blocks (**42** and **43**) under basic reaction conditions afforded to the corresponding the reaction products **50** and **51**. Cleavage of the THP-protecting groups was achieved by treatment with trifluoroacetic acid to afford the corresponding non-symmetric 5-aryl-substituted 3-aminopyrazole compounds (**11** and **12**) containing a linker with one amide bond.
Compound **14** containing a 5-tolyl-substituted 3-aminopyrazole linked via a C1-linker to a 5-tolyl pyrazole moiety (Fig. S8) was also prepared. Commercially available 5-tolyl-pyrazole-3-carboxylic acid was converted to its corresponding methyl ester **52**. THP-protection at the N^1-position of pyrazole, followed by the cleavage of the methyl ester **53** under basic conditions afforded the N^1-THP protected 5-tolyl-3-carboxylic acid pyrazole derivative **54**. Coupling of the pyrazole-3-carboxylic acid derivative **54**

to the N^1-THP protected 5-tolyl 3-aminopyrazole building block **42** mediated by Mukaiyama´s reagent (4) afforded the corresponding coupling product **55**. Reduction of the amide bond was achieved with borane dimethylsulfide complex to afford compound **14**.

Supplementary Results

General methods. All reagents and solvents were obtained from commercial sources and used without further purification. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DPX 400 MHz NMR spectrometer in deuterated solvents. Mass spectra (MS) were recorded on a Finnigan MAT TSQ 7000 spectrometer. Chromatography was performed using silica gel (Fluka: Silica gel 60, 0.063-0.2 mm) and suitable solvents as indicated in specific examples. Thin layer chromatography (TLC) was carried out on silica gel plates with UV detection.

*General procedure for the preparation of compound **1** having an oxalyl linker and substituents at the 4-position of 3-aminopyrazole*
*(N,N'-bis(4-(4-chlorophenyl)-1H-pyrazol-3-yl)oxalamide) (**1**)*
To a solution of compound **15** (0.5 g, 1.70 mmol) in anhydrous acetonitrile (20 ml) was added a solution of oxalyl chloride (2 M in CH_2Cl_2, 0.42 ml, 0.84 mmol). The resulting mixture was stirred under reflux for 30 min. The precipitate was filtrated and washed with acetonitrile and dichloromethane to obtain the product as a light yellow solid (0.186 g, 49 %); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.39 (d, J = 8.3 Hz, 4H), 7.47 (d, J = 8.3 Hz, 4H), 8.10 (s, 2H), 10.63 (s, 2H).

*Procedure for the preparation of compound **2** having a flexible (-CH_2-CH_2-) linker and substituents at the 4-position of 3-aminopyrazole*
*(N,N'-bis(4-(4-chlorophenyl)-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogen-chloride) (**2**)*
A solution of compound **1** (0.185 g, 0.42 mmol) in anhydrous DMF (6 ml) was refluxed with 3,4-dihydropyran (0.27 ml, 2.93 mmol) and trifluoroacetic acid (2 uL, 0.02 mmol) under inert atmosphere for 48 hrs. The solvent was evaporated and the excess of 3,4-dihydropyran was removed by chromatography on silica gel column (eluent: PE : EtOAc, 80:20). To a solution of THP-protected *N*,*N*'-bis(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)oxalamide in anhydrous THF (15 ml) was added drop wise borane dimethyl sulfide complex (0.28 ml, 2.94 mmol) and the reaction mixture was stirred under reflux for 16 h. The reaction was cooled down to 0 °C and MeOH (1 ml) was added and the mixture was stirred for 1h. Then conc. HCl (12 N) was added, until a pH < 2 was obtained, and the resulting mixture was stirred under reflux for 24 h. The mixture was cooled to room temperature, solvent was evaporated and residue was neutralized with 1M sodium hydroxide solution. The aqueous phase was extracted with $CHCl_3$ (5 x 20 ml), and after drying over Na_2SO_4, the solvent was evaporated. The residue was purified by chromatography on silica gel column (eluent: EtOAc) to obtain the free base as a white solid (0.058 g, 33 %). The free base (0.058 g, 0.14 mmol) was then dissolved in methanolic HCl (3 N, 2 ml) and precipitated by addition of Et_2O. The solid was filtered, washed with Et_2O and dried under vacuum to afford the product as white solid (0.061 g, 88 %). Mp = 228 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.46 (s, 4H), 7.44 (d, J = 8.3 Hz, 4H), 7.49 (d, J = 8.6 Hz, 4H), 8.23 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 42.80, 104.47, 128.40, 128.68, 129.67, 130.84, 131.83, 148.86. MS (ESI); *m/z* 413.34 (M+H).

*Procedure for the preparation of compounds **3-8** having a flexible (-CH_2-CH_2-) linker and substituents at the 5-position of 3-aminopyrazole*
To a suspension of the oxalyl-amide derivatives **23-29** (1 eq.) in dry THF or dioxane (30 ml) was added borane dimethylsulfide complex (6 eq.) and the reaction mixture was refluxed for 16h. Then, the solution was cooled to 0°C and added methanol (4 ml) and followed by concentrated HCl (4 ml). The resulting reaction mixture was further refluxed for 16h. Then the reaction mixture was cooled to room temperature and concentrated; the residue was diluted with (5ml) water and the aqueous phase pH was adjusted to

above 12 with NaOH and extracted with $CHCl_3$ (150 ml). The organic phase was washed with H_2O, brine solution, over Na_2SO_4 and concentrated under vacuum. The free base compound was dissolved in methanolic HCl (3N, 1 ml) and stirred for overnight. The precipitate was filtered and dried under vacuum to give corresponding hydrochloride salt.

*(N^1,N^2-bis(5-p-tolyl-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) (**3**)*
Yield 44 % (from **23**); Mp. 179 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 6H), 3.44 (s, 4H), 6.26 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.77 (d, *J* = 7.6 Hz, 4H); MS (ESI): *m/z* 373 (M+H).

*(N^1,N^2-bis(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) (**4**)*
Yield 19 % (from **24**); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.42 (s, 4H), 3.82 (s, 6H), 6.19 (s, 2H), 7.08 (d, *J* = 8.8 Hz, 4H), 7.81 (d, *J* = 8.4 Hz, 4H); MS (ESI): *m/z* 405 (M+H).

*(N^1,N^2-bis(5-(4-chlorophenyl)-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) (**5**)*
Yield 55 % (from **25**); Mp. 195 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.35 (s, 4H), 6.17 (s, 2H), 7.54 (d, *J* = 7.6 Hz, 4H), 7.78 (d, *J* = 7.6 Hz, 4H); MS (ESI) *m/z* 413 (M+H).

*(N^1,N^2-bis(5-(4-fluorophenyl)-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) (**6**)*
Yield 50 % (from **26**); Mp. 239-240 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.40 (s, 4H), 6.26 (s, 2H), 7.70 (d, *J* = 8.4Hz, 4H), 7.79 (d, *J* = 8.0 Hz, 4H); MS (ESI) *m/z* 381 (M+H).

*(N^1,N^2-bis(5-(4-(dimethylamino)phenyl)-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) (**7**)*
Yield 55 % (from **27**); Mp. 230-232 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.81 (d, *J* = 8.0 Hz, 4H), 7.03 (s, 4H), 6.1 (s, 2H), 3.46 (s, 4H), 3.01 (s, 12H); MS (ESI) *m/z* 431 (M+H)

*(N^1-(5-(biphenyl-4-yl)-1H-pyrazol-3-yl)-N^2-(3-(biphenyl-4-yl)-1H-pyrazol-5-yl)ethane-1,2-diamine dihydrogenchloride) (**8**)*
Yield 12 % (from **28**); Mp. 220-222 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.79 -7.93 (m, 12H), 7.41-7.51 (m, 8H), 3.44 (s, 4H); MS (ESI) *m/z* 497 (M+H)

*(N^1,N^2-bis-(5-(2-furyl)-1H-pyrazol-3-yl)ethane-1,2-diamine) (**9**)*
To a suspension of compound **29** (1.6 g, 2.8 mmol) in a mixture of dry THF/DCM (150/25 ml) was added borane dimethyl sulfide complex (1.6 ml, 17.3 mmol) and the reaction mixture was refluxed for 30 h to become a clear solution. The solution was cooled to 0°C and methanol (10 ml) was added followed by borane trifluoride diethyl etherate (20 ml). The resulting reaction mixture was further refluxed for 12 h, cooled to room temperature and concentrated. The white precipitation formed was filtered off. The filtrate was diluted with water (25 ml) and the pH of the aqueous phase was adjusted to 10 with using NaOH solution. The aqueous phase was extracted with $CHCl_3$ (4 x 50 ml), the organic phase was washed with brine solution, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude material was purified on silica gel column (EtOAc/MeOH, 98:2) to afford the product as white solid (0.77 g, 83 %); Mp. 214-216 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.16 (s, 4H), 6.12 (s, 2H), 6.71 (m, 2H), 7.10 (d, *J* = 3.2 Hz, 2H), 7.93 (s, 2H); MS (ESI): *m/z* 325 (M+H).

*(N-(5-(thiophen-2-yl)-1H-pyrazol-3-yl)-N'-(5-p-tolyl-1H-pyrazol-3-yl)ethane-1,2-diamine dihydrogenchloride) **(10)***
To a suspension of compound **46** (0.08 g, 0.14 mmol) in anhydrous THF (5 ml) was added drop-wise borane dimethylsulfide complex (0.95 ml, 1.00 mmol) and the reaction mixture was stirred under reflux for 16 h. The reaction mixture was cooled to 0°C, MeOH (0.7 ml) added and the mixture stirred for 45 min. Then conc. HCl was added until pH < 2 and the resulting mixture was stirred under reflux for 16 h. The reaction was cooled to room temperature, the solvent evaporated under vacuum and residue was

made alkaline by adding aqueous NaOH solution (1 M). The aqueous phase was extracted with chloroform (3 x 15 ml), the organic phase dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (EtOAc:MeOH, 98:2) to afford the free base as a solid. The free base (0.015 g, 0.042 mmol) was dissolved in methanolic HCl (3N, 1 ml) and precipitated by addition of Et_2O. The solid was filtered, washed with Et_2O and dried under vacuum to afford the product as white solid (0.018 g, 29 %). Mp. 148 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.70 (d, *J* = 7.6 Hz, 2H), 7.59 (m, 1H), 7.48 (m, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 3.6 Hz, 1H), 6.19 (s, 1H), 5.90 (s, 1H), 3.37 (dd, *J* = 4.4 Hz, *J* = 12.4 Hz, 4H), 2.36 (s, 3H); MS (ESI): *m/z* 365 (M+H).

(N^1-(5-(4-chlorophenyl)-1H-pyrazol-3-yl)-N2-(5-p-tolyl-1H-pyrazol-3-yl)ethane-1,2-diamine) ***(13)***
To a suspension of compound **47** (0.11 g, 0.18 mmol) in anhydrous THF (10 ml) was added drop-wise borane dimethylsulfide complex (0.125 ml, 1.31 mmol) and the reaction mixture was stirred under reflux for 16 h. The reaction mixture was cooled to 0°C, MeOH (0.7 ml) added and the mixture stirred for 45 min. Then conc. HCl was added until pH < 2 and the resulting mixture was stirred under reflux for 16 h. The reaction was cooled to room temperature, the solvent evaporated under vacuum and residue was made alkaline by adding aqueous NaOH solution (1 M). The aqueous phase was extracted with chloroform (3 x 15 ml), the organic phase dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (EtOAc:MeOH, 98:2) to afford the free base as a solid. The free base (0.015 g, 0.042 mmol) was dissolved in methanolic HCl (3 N, 1 ml) and precipitated by addition of Et_2O. The solid was filtered, washed with Et_2O and dried in vacuum to afford the product as white solid (0.018 g, 21 %). Mp. 182 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83 (d, *J* = 8.0Hz, 2H), 7.72 (d, *J* = 7.6Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.6Hz, 2H), 6.22 (s, 2H), 3.42 (s, 4H), 2.36 (s, 3H); MS (ESI): *m/z* 393 (M+H).

Procedure for the preparation of compounds ***11-12*** *having a (-CH_2-C(O)-) linker and substituents at the 5-position of 3-aminopyrazole*
(N-(5-(4-chlorophenyl)-1H-pyrazol-3-yl)-2-(5-p-tolyl-1H-pyrazol-3-ylamino)acetamide) ***(11)***
Compound **50** (0.064 g, 0.11mmol) was dissolved in dichloromethane (1 ml) and TFA (1 ml) was added. The reaction mixture was stirred for 16 h at room temperature. The precipitate was filtered off and dried under vacuum (0.013 g, 28 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.5 (brs, 2H), 7.72 (d, *J* = 8.4Hz, 2H), 7.63 (d, *J* = 8.0Hz, 2H), 7.49 (d, *J* = 8.4Hz, 2H), 7.30 (d, *J* = 8.0Hz, 2H), 6.87 (s, 1H), 6.20 (s, 1H), 4.0 (s, 2H), 2.35 (s, 3H); MS (ESI): *m/z* 407 (M+H).

(2-(5-(4-chlorophenyl)-1H-pyrazol-3-ylamino)-N-(5-p-tolyl-1H-pyrazol-3-yl)acetamide) ***(12)***
Compound **51** (0.058 g, 0.1 mmol) was dissolved in dichloromethane (1 ml) and TFA (1 ml) was added. The reaction mixture was stirred overnight at room temperature. The precipitate was filtered off and dried under vacuum (0.016 g, 39 %). Mp. 251°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.2 (s, 2H), 7.69 (d, *J* = 8.4Hz, 2H), 7.57 (d, *J* = 8.0Hz, 2H), 7.49 (d, *J* = 8.4Hz, 2H), 7.24 (d, *J* = 8.0Hz, 2H), 6.8 (s, 1H), 6.01 (s, 1H), 3.9 (s, 2H), 2.32 (s, 3H); MS (ESI): *m/z* 407 (M+H).

Procedure for the preparation of compound ***14*** *having a (-CH_2-) linker and substituents at the 5-position of 3-aminopyrazole*
(5-p-Tolyl-N-((5-p-tolyl-1H-pyrazol-3-yl)methyl)-1H-pyrazol-3-amine dihydrogenchloride) ***(14)***
To a suspension of compound **55** (0.14 g, 0.27 mmol) in anhydrous THF (10 ml) was drop-wise added borane dimethylsulfide complex (0.177 ml, 1.86 mmol). The reaction mixture was stirred under reflux for 16 h. The mixture was then cooled to 0°C, MeOH (0.5 ml) added and the mixture was stirred for 10 min. Then concentrated hydrochloric acid (12 N) was added until a pH < 2 was obtained, and the resulting mixture was stirred under reflux for 16 h. The reaction mixture was cooled to room temperature and the precipitate filtered off. To the aqueous phase and added an aqueous sodium hydroxide (1M). The aqueous phase was treated with aqueous sodium hydroxide (pH > 12) and then extracted with dichloromethane (3 x 10 ml). The organic phase was separated, dried over Na_2SO_4 and the solvent was evaporated under

vacuum. The residue was purified using a silica gel column (EtOAc) to afford the free base as white solid. The free base (0.027 g, 0.079 mmol) was treated with methanolic HCl (3 N, 1 ml). The solid was filtered off, washed with Et_2O and dried under vacuum to afford the product as white solid (0.032 g, 24 %). Mp. 132 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 6.30 (s, 1H), 4.42 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H).

*Synthesis of intermediates **15-29***

*(tert-butyl 3-amino-4-(4-chlorophenyl)-1H-pyrazole-1-carboxylate) (**15**)*

To a solution of commercially available 5-amino-4-(4-chlorophenyl)-pyrazole (1 g, 5.16 mmol) in a mixture of anhydrous CH_2Cl_2 (40 ml) and anhydrous THF (10 ml) was added drop-wise di-*tert*-butyl dicarbonate (1.25 ml, 5.44 mmol) and the reaction mixture was stirred for 16h at room temperature. The solution was concentrated under vacuum and the residue was purified on silica gel column (eluent: PE:EtOAc, 80:20) to afford the product as a white solid (1.31g, 2 regioisomers, 86 %). Major regioisomer (N^1-Boc): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.68 (*s*, 9H), 5.58 (*bs*, 2H), 7.31 (*d*, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.57 (s, 1H); Minor regioisomer (N^2-Boc): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H), 4.11 (bs, 2H), 7.39 (m, 4H), 7.94 (s, 1H).

*(tert-butyl 3-amino-5-p-tolyl-1H-pyrazole-1-carboxylate) (**16**)*

Yield 100 %; Mp. 147 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 9H), 2.36 (s, 3H), 5.32 (bs, 2H), 5.74 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.93, 27.61, 84.73, 85.96, 125.76, 128.68, 129.16, 138.27, 150.52, 153.70; MS (ESI): *m/z* 274 (M+H).

*(tert-butyl 3-amino-5-(4-methoxyphenyl)-1H-pyrazole-1-carboxylate) (**17**)*

Yield 90 %; Mp. 144-146 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.69 (s, 1H), 5.32 (brs, 2H), 3.82 (s, 3H), 1.67 (s, 9H); MS (ESI): *m/z* 290 (M+H).

*(tert-butyl 3-amino-5-(4-chlorophenyl)-1H-pyrazole-1-carboxylate) (**18**)*

Yield 87 %; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 9H), 5.35 (bs, 2H), 5.72 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H); MS (ESI): *m/z* 294 (M+H).

*(tert-butyl 3-amino-5-(4-fluorophenyl)-1H-pyrazole-1-carboxylate) (**19**)*

Yield 80 %; Mp. 156-157 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 5.6 Hz, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 5.71 (s, 1H), 1.68 (s, 9H); MS (ESI) *m/z* 278 (M+H).

*(tert-butyl 3-amino-5-(4-(dimethylamino)phenyl)-1H-pyrazole-1-carboxylate) (**20**)*

Using intermediate **34** and the procedure described for intermediate **15** afforded the title compound. Yield 78 %; Mp.146-147 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 5.71 (s, 1H), 5.32 (brs, 2H), 3.01 (s, 6H), 1.69 (s, 9H); MS (ESI) *m/z* 303 (M+H).

*(tert-butyl 3-amino-5-(biphenyl-4-yl)-1H-pyrazole-1-carboxylate) (**21**)*

Yield 64 %; Mp. 266-267 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0Hz, 4H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H) 5.82 (s, 1H), 5.37 (br s, 2H), 1.71 (s, 9H); MS (ESI): *m/z* 336 (M+H).

*(tert-butyl 3-amino-5-(furan-2-yl)-1H-pyrazole-1-carboxylate) (**22**)*

Yield 78 %; Mp. 135-136 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.44 (dd, *J* = 1.6 Hz, *J* = 3.6Hz, 1H), 5.66 (s, 1H), 5.40 (brs, 2H), 1.66 (s, 9H); MS (ESI) *m/z* 250 (M+H).

*Compounds **23-29** synthesized according to the procedure described for compound **1***

(N^1,N^2-bis(1-tert-butyloxycarbonyl-5-p-tolyl-1H-pyrazol-3-yl)-oxaldiamide) ***(23)***
Yield 56 %; Mp = >350 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 18H), 2.39 (s, 6H), 7.24 (d, *J* = 8.0 Hz, 4H), 7.80 (d, *J* = 7.6 Hz, 4H), 11,86 (bs, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.37, 27.98, 87.40, 96.21, 126.30, 128.64, 129.34, 139.40, 139.57, 154.28, 155.32.

(N^1,N^2-bis(1-tert-butyloxycarbonyl-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-oxaldiamide) ***(24)***
Yield 37.6 %; Mp. >350 °C.

(N,N'-bis(1-tert-butyloxycarbonyl-5- (4-chlorophenyl)pyrazol-3-yl)oxaldiamide) ***(25)***
Yield 35 %; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 18H), 7.34 (s, 2H), 7.41 (d, *J* = 8.8 Hz, 4H), 7.84 (d, *J* = 8.4 Hz, 4H), 11.86 (bs, 2H).

(N^1,N^2-bis(5-(4-fluorophenyl)-1H-pyrazol-3-yl) oxalamide) ***(26)***
Yield 63 %; Mp. > 350 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.81 (dd, *J* = 5.6 Hz, *J* = 8.0 Hz, 4H), 7.31 (t, *J* = 8.4 Hz, 4H), 6.92 (s, 2H).

(N^1,N^2-bis(5-(4-(dimethylamino)phenyl)-1H-pyrazol-3-yl) oxalamide) ***(27)***
Yield 96 %; Mp. > 350 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10. 8 (s, 2H) 7.62 (d, *J* = 8.0 Hz 4H), 6.88 (d, *J* = 8.0 Hz, 4H), 6.79 (s, 2H), 2.97 (s, 12H).

(N^1,N^2-bis(5-(furan-2-yl)-1H-pyrazol-3-yl)oxalamide) ***(29)***
Yield 89 %; Mp. > 350 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.0 (brs, 2H), 7.78 (d, *J* = 1.2 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.71 (s, 1H), 6.62 (dd, *J* = 2.0 Hz, *J* = 3.2 Hz 1H).

Synthesis of intermediates ***31-55***
(tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-5-(4-nitrophenyl)-1H-pyrazole-1-carboxylate) ***(31)***
To a solution of commercially available **30** (5-(4-nitrophenyl)-1H-pyrazol-3-amine; 3 g, 14.7 mmol) in THF (150 ml) was added di-tert-butyl dicarbonate (11.2 g, 51.45 mmol) followed by dimethyl-aminopyridine (0.150 g). The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue dissolved in dichloromethane (150 ml). The organic phase was washed with water, brine, dried over Na_2SO_4 and the solvent evaporated. The residue was purified using a silica gel column (EtOAc: PE, 80:20) to afford the product as white solid (6.2 g, 83 %); Mp. 154-155 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 1H), 1.65 (s, 9H), 1.44 (s, 18H); MS (ESI): *m/z* 506 (M+2H).

(tert-butyl-5-(4-aminophenyl)-3-(bis(tert-butoxycarbonyl)amino)-1H-pyrazole-1-carboxylate) ***(32)***
To a solution of compound **31** (0.5 g, 0.99 mmol) in EtOH (15 ml) was added Pd/C (10 % on charcoal) and the reaction mixture was stirred under H_2 balloon pressure for 6 h. Then, the reaction mixture was filtered off through a celite pad. The solvent was evaporated to afford the product as white solid (0.39 g, 83 %); Mp. 84-85 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.72 (d, *J* = 8.0 Hz, 2H) 6.73 (d, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 3.8 (brs, 2H), 1.63 (s, 9H), 1.42 (s, 18H); MS (ESI): *m/z* 475 (M+H).

(tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-5-(4-(dimethylamino)phenyl)-1H-pyrazole-1-carboxylate) ***(33)***
To solution of compound **32** (2.25 g, 4.74 mmol) in dry THF, was added NaH (0.6 g, 14.2 mmol). The resulting suspension was stirred for 10min, and added MeI solution (2 g, 14.2 mmol) and the reaction mixture was stirred at 70 °C (oil bath temp) for 2d. The reaction mixture was cooled to room temperature and carefully quenched with water. The aqueous phase was extracted with dichloromethane (150 ml). The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed. The crude product was purified on silica gel column (EtOAc: Petrolether, 75:25) to afford product as white solid

(0.85 g, 35 %). Mp. 64-65 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.46 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.82 (s, 1H), 4.72 (brs, 2H), 3.01 (s, 6H). MS (ESI): *m/z* 503 (M+H).

*(5-(4-(dimethylamino)phenyl)-1H-pyrazole-3-amine) (**34**)*
Compound **33** (0.15 g, 0.298 mmol) was dissolved in dichloromethane (5 ml) and an excess of TFA added. The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue re-dissolved in dichloromethane. The organic phase was washed with Na_2CO_3 solution, water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was crystallized from petrolether/ dichloromethane to afford the product as a solid (0.046 g, 76 %); Mp. 169-170 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.00 (m, 2H), 6.18 (s, 2H), 3.0 (s, 6H); MS (ESI) *m/z* 203 (M+H).

*(N-(1-acetyl-5-(thiophen-2-yl)-1H-pyrazol-3-yl)acetamide (**35**)*
To a suspension of commercially available 5-amino-3-(2-thienyl)pyrazole (3 g, 18.1 mmol) and potassium carbonate (8.8 g, 63.5 mmol) in anhydrous acetonitrile (40 ml) was added drop-wise acetyl chloride (3.9 ml, 54.5 mmol). The reaction mixture was refluxed for 16 h, the solvent evaporated under vacuum and the residue re-dissolved in chloroform. The organic phase was washed with 1 M HCl, sat. aq $NaHCO_3$, H_2O, brine, dried over Na_2SO_4 and the solvent concentrated under vacuum. The crude title compound was directly used in next step. MS (ESI): *m/z* 250 (M+H).

*(N-(1-acetyl-5-p-tolyl-1H-pyrazole-3-yl)acetamide) (**36**)*
To a suspension of commercially available 5-amino-3-(4-methylphenyl)pyrazole (5 g, 28,86 mmol) and potassium carbonate (14 g, 101.03 mmol) in anhydrous acetonitrile (100 ml) was added drop-wise acetyl chloride (6.16 ml, 86.60 mmol). The reaction was refluxed for 16 h, the solvent concentrated under vacuum and the residue re-dissolved in chloroform. The organic phase was washed with 1 M HCl, sat. aq $NaHCO_3$, H_2O, brine, dried over Na_2SO_4 and the solvent concentrated under vacuum. The crude title compound was directly used in next step.

*N-(1-acetyl-5-(4-chlorophenyl)-1H-pyrazol-3-yl)acetamide (**37**)*
To a suspension of commercially available 5-(4-chlorophenyl)-1H-pyrazol-3-amine (5 g, 26 mmol) and potassium carbonate (18.7 g, 135.13 mmol) in anhydrous acetonitrile (100 ml) was added drop-wise acetyl chloride (8.2ml, 115.8 mmol). The reaction was refluxed for 16 h, the solvent concentrated under vacuum and the residue re-dissolved in chloroform. The organic phase was washed with 1 M HCl, sat. aq $NaHCO_3$, H_2O, brine, dried over Na_2SO_4 and the solvent concentrated under vacuum to afford the product (5.56 g, 78 %); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.4 (s, 1H), 7.80 (d, *J* = 7.2Hz, 2H), 7.39 (d, *J* = 8.4Hz, 2H), 7.20 (s, 1H), 2.76 (s, 3H), 2.24 (s, 3H); MS (ESI): *m/z* 277 (M+H).

*(N-(5-(thiophen-2-yl)-1H-pyrazol-3-yl)acetamide) (**38**)*
Crude compound **35** was dissolved in a mixture MeOH/THF/H_2O (2:2:1, 80 ml) with 2 drops of an aqueous ammonia solution (33 %). The reaction mixture was stirred for 16 h and the solvents evaporated under vacuum. The crude product was directly used in next step. MS (ESI): *m/z* 208 (M+H).

*(N-(5-p-tolyl-1H-pyrazole-3-yl)acetamide) **(39)***
Crude compound **36** was dissolved in a mixture MeOH/THF/H_2O (2:2:1, 150 ml) with 2 drops of an aqueous ammonia solution (33 %). The reaction mixture was stirred for 16 h and the solvents evaporated under vacuum. The crude product was directly used in next step. MS (ESI): *m/z* 216 (M+H).

*(N-(5-(4-chlorophenyl)-1H-pyrazol-3-yl)acetamide) (**40**)*
Compound **37** (5.56 g, 20 mmol) was dissolved in a mixture MeOH/THF/H_2O (2:2:1, 125 ml) with 2 drops of an aqueous ammonia solution (33 %). The reaction mixture was stirred for 16 h and the solvents

evaporated under vacuum to afford the product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.4 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 8.4Hz, 2H), 7.20 (s, 1H), 2.76 (s, 3H), 2.22 (s, 3H); MS (ESI): *m/z* 236 (M+H).

(N-(5-(thiophen-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-acetamide) ***(41)***
A mixture of crude compound **38** (18.1 mmol), 3,4-dihydro-2*H*-pyran (4.1 ml, 44.7 mmol) and trifluoroacetic acid (0.026 ml, 0.35 mmol) in anhydrous acetonitrile (35 ml) was refluxed for 16 h. The solvent was evaporated and the residue was re-suspended in dichloromethane (35 ml). The organic phase was washed with H_2O, brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue (18.1 mmol) was dissolved in EtOH/H_2O (2:3, 60 ml), treated with potassium hydroxide (10 g, 178 mmol) and refluxed for 16 h. The reaction mixture was concentrated and then extracted with chloroform. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (PE-EtOAc, 7:3 to 5:5) to afford the product (0.6 g regioisomer A and 1.9 g regioisomer B, 83 % over 4 steps); regioisomer A: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 2.9 Hz, 1H), 7.19 (d, *J* = 4.85 Hz, 1H), 7.00 (t, *J* = 3.5 Hz, 1H), 5.74 (s, 1H), 5.37 (dd, *J* = 9.9 Hz, *J* = 3.2 Hz, 1H), 4.11 (m, 1H), 4.04 (bs, 2H), 3.67 (dt, *J* = 9.9 Hz, *J* = 2.9 Hz, 1H), 2.36 (m, 1H), 2.06 (m, 2H), 1.60-1.69 (m, 3H). MS (ESI): *m/z* 250 (M+H); regioisomer B: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 5.1 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 7.11 (dd, *J* = 3.5 Hz, *J* = 5.1 Hz, 1H), 5.80 (s, 1H), 5.23 (dd, *J* = 10.2 Hz, *J* = 2.2 Hz, 1H), 4.11 (m, 1H), 3.68 (bs, 2H), 3.62 (dt, *J* = 12.5 Hz, *J* = 1.9 Hz, 1H), 2.45 (m, 1H), 2.04 (m, 1H), 1.85 (m, 1H), 1.51-1.80 (m, 3H); MS (ESI): *m/z* 250.2 (M+H).

(N-(5-tolyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)acetamide) ***(42)***
A mixture of crude compound **39** (28.86 mmol), 3,4-dihydro-2*H*-pyran (6.7 ml, 72.15 mmol) and trifluoroacetic acid (0.043 ml, 0.58 mmol) in anhydrous acetonitrile (60 ml) was refluxed for 16 h. The solvent was evaporated and the residue was re-dissolved in dichloromethane (50 ml). The organic phase was washed with H_2O, brine, dried over Na_2SO_4 and the solvent evaporated under vacuum (MS (ESI): *m/z* 300 (M+H)). The residue (28.86 mmol) was dissolved in EtOH/H_2O (2:3, 100 ml), treated with potassium hydroxide (11g, 202 mmol) and refluxed for 16 h. The reaction mixture was concentrated and then extracted with chloroform. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 7:3 to 3:7) to afford the product (2.99 g, regioisomer A and 4.39 g, regioisomer B, 99 % over 4 steps). Regioisomer A: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 5.81 (s, 1H), 5.38 (dd, *J* = 8.9 Hz, *J* = 2.6 Hz, 1H), 4.01 (bm, 3H), 3.68 (dt, *J* = 11.5 Hz, *J* = 2.6 Hz, 1H), 2.38 (m, 1H), 2.35 (s, 3H), 2.03-2.14 (m, 2H), 1.62-1.71 (m, 3H). MS (ESI): *m/z* 258 (M+H); regioisomer B: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.69 (s, 1H), 5.03 (dd, *J* = 10.2 Hz, *J* = 2.5 Hz, 1H), 4.11 (m, 1H), 3.69 (bs, 2H), 3.54 (dt, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 2.46 (m, 1H), 2.41 (s, 3H), 1.70-1.79 (m, 2H),1.50-1.59 (m, 3H); MS (ESI): *m/z* 258 (M+H).

(S)-5-(4-chlorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-amine ***(43)***
A mixture of crude compound **40** (4.26g, 18.07), 3,4-dihydro-2*H*-pyran (4.1 ml, 45 mmol) and trifluoroacetic acid (0.026 ml, 0.35 mmol) in anhydrous acetonitrile (40 ml) was refluxed for 16 h. The solvent was evaporated and the residue was re-dissolved in dichloromethane (35 ml). The organic phase was washed with H_2O, brine, dried over Na_2SO_4 and the solvent evaporated under vacuum (MS (ESI): *m/z*: 320.38 (M+H)). The residue (5.9 g, 18.4 mmol) was dissolved in EtOH/H_2O (2:3, 100 ml), treated with potassium hydroxide (15g, 277 mmol) and refluxed for 16 h. The reaction mixture was concentrated and then extracted with chloroform. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 7:3 to 3:7) to afford the product (2.39 g, regioisomer A and 2.48 g, regioisomer B, 95 % for two isomers). Regioisomer A: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.8Hz, 2H), 7.30 (d, *J* = 8.4Hz, 2H), 5.80 (s, 1H), 5.37 (dd, *J* =2.8Hz, *J* = 11.6Hz, 1H), 3.9-4.03 (m, 2H), 3.65-3.71 (m, 1H), 2.35-2.44 (m, 1H), 2.07-2.14 (m, 2H), 1.60-1.74 (m, 4H); regioisomer B: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.41 (m, 4H), 5.71

(s, 1H), 4.95 (dd, *J* = 2.4H, *J* = 2.0Hz, *J* = 12.8Hz, 1H), 4.09-4.12 (m, 1H), 3.70 (brs, 2H), 3.49 (td, *J* = 2.0Hz, *J* = 11.6Hz, 1H), 2.40-2.49 (m, 1H), 1.99-2.04 (m, 1H), 1.67-1.79 (m 2H), 1.49-1.53 (m, 2H); MS (ESI): *m/z* 278 (M+H).

(Ethyl 2-oxo-2-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-ylamino)-acetate) ***(44)***
To a solution of compound **42** (0.5 g, 1.95 mmol) and triethylamine (0.81 ml, 5.83 mmol) in anhydrous dichloromethane (15 ml) was added mono ethyl oxalyl chloride (0.26 ml, 2.33 mmol). The reaction mixture was stirred at room temperature for 3 h and then washed with 1 M HCl, sat. aq $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), concentrated at reduced pressure and the crude was purified on silica gel column (PE:EtOAc, 9:1) to afford the product (0.4 g, 57 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.34 (bs, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.85 (s, 1H), 5.18 (d, *J* = 11.7 Hz, 1H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.58 (t, *J* = 10.5 Hz, 1H), 2.43 (m, 1H), 2.42 (s, 3H), 2.02 (m, 1H), 1.77 (m, 2H), 1.56 (t, *J* = 9.2 Hz, 2H), 1.41 (t, *J* = 7.63 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.13, 153.41, 145.33, 145.21, 139.10, 129.45, 128.93, 126.80, 98.16, 84.06, 68.02, 63.57, 30.03, 24.78, 22.93, 21.32, 13.99.

2-oxo-2-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-ylamino)acetic acid ***(45)***
To a solution of compound **44** (0.39 g, 1.1 mmol) in THF:water (1.1; 10 ml) was added LiOH (0.031 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated to afford the product (0.39 g, 100 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 2H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.19 (d, *J* = 10.2 Hz, 1H), 3.78 (s, 1H), 3.60 (t, *J* = 11.6 Hz, 1H), 2.46 (s, 3H), 2.39 (d, *J* = 11.1 Hz, 1H), 2.06 (d, J = 10.2 Hz, 1H), 1.97 – 1.69 (m, 3H), 1.56 (d, J = 12.0 Hz, 2H).

(N-(1-(tetrahydro-2H-pyran-2-yl)-5-(thiophen-2-yl)-1H-pyrazol-3-yl)-N2-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-yl)oxalamide) ***(46)***
A mixture of compound **45** (0.25 g, 0.76 mmol) and compound **41** (0.285 g, 1.14 mmol) in anhydrous dichloromethane (10 ml) was treated with Deoxo-Fluor (0.4 ml, 0.91 mmol) and kept at room temperature for 2 h. The reaction mixture was quenched with sat. aq $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 9:1) to afford the product as an oil (0.08 g, 20 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 9.67 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.13 (t, *J* = 4.0 Hz, 1H), 6.98 (s, 1H), 6.87 (s, 1H), 5.37 (d, *J* = 10.2 Hz, 1H), 5.19 (d, *J* = 9.1 Hz, 1H), 4.11 (t, *J* = 11.3 Hz, 2H), 3.65 (t, *J* = 11.7 Hz, 1H), 3.60 (t, *J* = 12.4 Hz, 1H), 2.45 (m, 2H), 2.42 (s, 3H), 2.03 (m, 1H), 1.87 (m, 1H), 1.77 (m, 4H), 1.59 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 156.78, 156.66, 145.38, 145.08, 144.98, 138.98, 138.31, 130.02, 129.37, 128.90, 128.18, 127.59, 127.47, 126.9199.10, 98.06, 84.15, 84.07, 67.78, 67.45, 29.88, 29.61, 24.77, 22.83, 22.70, 21.23.

N^1-(5-(4-chlorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-N2-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-yl)oxalamide ***(47)***
A mixture of compound **45** (0.18 g, 0.54 mmol) and compound **43** (0.228 g, 0.82 mmol) in anhydrous DCM (5 ml) was treated with Deoxo-Fluor (0.3 ml, 0.65 mmol) and kept at room temperature for 5 h. The reaction mixture was quenched with sat. aq $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 9:1) to afford the product as an oil (0.095 g, 30 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 2H), 7.42-7.48 (m, 6H), 7.26 (d, *J* = 6.8Hz, 2H), 6.90 (s, 1H), 6.86 (s, 1H), 5.17 (d, *J* = 10Hz, 1H), 5.10 (d, *J* = 10Hz, 1H), 4.10-4.13 (m, 4H), 3.57-3.60 (m, 2H), 2.41-2.46 (m, 4H); 1.72-1.80 (m, 4H), 1.52-1.55 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.7, 156.5, 145.3, 145.1,145.0, 144.0, 138.9, 135.1, 130.2, 129.3, 128.9, 128.9, 128.8, 128.1, 126.7, 98.3, 97.9, 84.1, 84.0, 67.8, 67.7, 60.3, 29.9, 29.7, 29.6, 24.7, 24.6, 22.8, 22.7, 21.2, 20.9, 14.1; MS (ESI): *m/z* 589 (M+H).

(2-bromo-N-(5-(4-chlorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)acetamide) ***(48)***
To a solution of compound **43** (0.200 g, 0.72 mmol), triethylamine (0.150 ml, 1.08 mmol) in dichloromethane (5 ml) was added bromoacetyl bromide (0.062 ml, 0.72 mmol) at 0 °C. The reaction mixture was then stirred for 3 h at room temperature. The solvent was evaporated under vacuum and residue was re-dissolved in chloroform (100 ml). The organic phase was washed with 1M HCl, $NaHCO_3$ solution, water, brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (EtOAc/petrol ether 10:90) to afford the product (0.03 g, 10 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.67 (s, 1H), 7.45 (m, 4H), 6.81 (s, 1H), 5.09 (dd, J = 2.0Hz, J = 12.4Hz, 1H), 4.12-4.18 (m, 1H), 4.01 (s, 2H), 3.57 (dt, J = 4Hz, J = 12Hz, 1H), 2.02-2.04 (m, 1H),1.73-1.79 (m, 2H), 1.53-1.60 (m, 2H); MS (ESI): *m/z*: 400 (M+H).

(2-bromo-N-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-yl)acetamid)e ***(49)***
To a solution of compound **42** (0.4 g, 1.55 mmol) and triethylamine (0.24 ml, 2.33 mmol) in dichloromethane (10 ml) was added 2-bromoacetyl bromide (0.31 ml, 1.55 mmol) at 0 °C. The reaction mixture was then stirred at 0 °C for 1.5 h. The reaction mixture was quenched with $NaHCO_3$ solution, diluted with dichloromethane (100 ml) and washed with water and brine. The organic phase was separated, dried over Na_2SO_4 and the solvent removed under vacuum, The residue was purified using a silica gel column (EtOAc: PE, 1:9) to afford the product as highly hygroscopic solid (0.22 g, 37 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.38 (d, *J* = 8.0Hz, 2H), 7.27 (d, *J* = 7.6Hz, 2H), 6.78 (s, 1H), 5.15 (dd, *J* = 2.0 Hz, *J* = 2.4Hz, *J* = 8.4Hz, 1H), 4.10-4.15 (m, 1H), 4.0 (s, 2H), 3.58 (td, *J* = 2.0Hz, *J* =11.6Hz, 1H), 2.41-2.44 (m, 5H), 1.73-1.78 (m, 2H), 1.51-1.55 (m, 2H); MS (ESI): *m/z* 380 (M^+).

(N-(5-(4-chlorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-2-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-ylamino)acetamide) ***(50)***
To a solution of compound **42** (112 mg, 0.44 mmol) in acetonitrile (2 ml) was added K_2CO_3 (0.12 g, 0.87mmol) and compound **48** (0.11 g, 0.29 mmol). The reaction mixture was stirred at room temperature for 16h. Then tetrabutylammoniumiodide (0.01 g, 0.029 mmol) was added and the reaction mixture was stirred for another 24 h at room temperature. The solvent was evaporated under vacuum and the residue dissolved in chloroform. The organic phase was washed with water, brine and dried over Na_2SO_4. The organic solvent was evaporated under vacuum and the residue purified using a silica gel column (EtOAc/PE, 3:7 to 6:4) to afford the product (0.064 g, 40 %).

(2-(5-(4-chlorophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-ylamino)-N-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-yl)acetamide) ***(51)***
To a solution of compound **43** (0.073 g, 0.26 mmol) in acetonitrile (3 ml) was added K_2CO_3 (0.073 g, 0.53 mmol) and compound **49** (0.2 g, 0.53 mmol). The reaction mixture was then stirred at room temperature overnight. Then tetrabutylammoniumiodide (0.019 g, 0.053 mmol) was added and stirring was continued for another 24 h at room temperature. The solvent was evaporated under vacuum and the residue dissolved in chloroform. The organic phase was washed with water, brine and dried over Na_2SO_4. The organic solvent was evaporated under vacuum and the residue purified using a silica gel column (EtOAc/PE, 3:7 to 6:4) to afford the product (0.05 g, 38 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 8H), 5.69-5.70 (m, 2H), 4.95-5.1(m, 2H), 4.08-4.11 (m, 4H), 3.52-3.55 (m, 4H), 2.41-2.51 (m, 7H), 1.67-1.79 (m, 4H), 1.46-1.56 (m, 4H).

(Methyl 5-p-tolyl-1H-pyrazole-3-carboxylate) ***(52)***
A mixture of commercially available 5-*p*-tolyl-1H-pyrazole-3-carboxylic acid (0.25 g, 1.24 mmol) and sulfuric acid (0.120 ml, 1.48 mmol) in methanol (5 ml) was refluxed for 16 h. The solvent was evaporated under vacuum and the residue suspended in dichloromethane. The mixture was filtered, the white solid washed with dichloromethane and dried under vacuum. The filtrate was washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under vacuum and the white solid was combined with the precipitate from the filtration to afford the product as white solid (0.22 g, 84 %). ^{1}H-NMR (400 MHz,

$CDCl_3$): δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 1H), 3.91 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 129.61, 125.45, 105.03, 52.02, 21.19.

(Methyl 1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazole-3-carboxylate) ***(53)***
A mixture of compound **52** (0.22 g, 1.03 mmol), 3,4-dihydro-2*H*-pyran (0.190 ml, 2.07 mmol) and trifluoroacetic acid (0.002 ml, 0.02 mmol) in anhydrous acetonitrile (3 ml) was refluxed for 2 h. The solvent was evaporated and residue was re-dissolved in dichloromethane (50 ml). The organic phase was washed with H_2O, brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 6:4) to afford the product (0.36 g, 68 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 1H), 5.25 (d, *J* = 10.0 Hz, 1H), 4.11 (m, 1H), 3.92 (s, 3H), 3.57 (t, *J* = 10.8 Hz, 1H), 2.61 (m, 1H), 2.41 (s, 3H), 2.03 (m, 1H), 1.82 (d, *J* = 8.06 Hz, 1H), 1.58-1.52 (m, 3H).

(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazole-3-carboxylic acid) ***(54)***
Compound **53** (0.36 g, 0.70 mmol) was dissolved in a mixture of MeOH/THF/H_2O (1:2:1, 4 ml). After the addition of excess lithium hydroxide, the reaction mixture was stirred for 16 h. The reaction mixture was diluted with water and washed with dichloromethane. The aqueous phase was separated and evaporated under vacuum to afford the product as white solid (0.2 g, quantitative). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 6.8Hz, 2H), 7.04 (d, *J* = 6.8Hz, 2H), 6.60 (s, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 3.89 (d, *J* = 8.4Hz, 1H), 3.35 (t, *J* = 10.8 Hz, 1H), 2.40 (m, 1H), 2.31 (s, 3H), 1.75 (m, 1H), 1.54 (m, 2H), 1.25 (m, 2H).

(*1-(tetrahydro-2H-pyran-2-yl)-N-(1-(tetrahydro-2H-pyran-2-yl)-5-p-tolyl-1H-pyrazol-3-yl)-5-p-tolyl-1H-pyrazole-3-carboxamide)* ***(55)***
To a solution of compound **54** (0.1 g, 0.34 mmol), 2-chloro-1-methylpyridinium iodide (0.12 g, 0.47 mmol) and *N,N'*-diisopropylethylamine (0.16 ml, 0.94 mmol) in dichloromethane (10 ml) was added 5-tolyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-amine (0.08 g, 0.31 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with water and extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified using a silica gel column (PE:EtOAc, 9:1) to afford the product (0.07 g, 43 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 0.5H), 9.34 (s, 0.5H), 7.43 (m, 4H), 7.28 (m, 4H), 6.95 (s, 0.5H), 6.94 (s, 0.5H), 6.90 (s, 1H), 5.24 (m, 2H), 4.15 (m, 2H), 3.60 (m, 2H), 2.45 (m, 2H), 2.42 (s, 6H), 1.80 (m, 2H), 1.56 (m, 4H), 1.25 (m, 4H).

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