Supplementary Information

Dibenzosuberones as p38 Mitogen-Activated Protein Kinase Inhibitors with Low ATP Competitiveness and Outstanding Whole Blood Activity

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1 Kinetics and crystal structure of 16e

Real-Time Kinetics of compound binding to p38α MAP kinase

Kinetics of the association of compound **16e** with p38α MAP kinase were determined using cuvettes and a JASCO FP-6500 fluorescence spectrophotometer (JASCO GmbH, Groß-Umstadt, Germany) as described previously.[1]

Crystallization and Structure Determination of p38α MAP kinase in complex with compound 16e.

Inactive (non-phosphorylated) human p38α MAP kinase was expressed and purified as described previously.[1] Compound **16e** was co-crystallized with p38α MAP kinase using crystallization conditions similar to those previously reported.[2] Briefly, 1 mM compound **16e** (prepared in DMSO) were pre-incubated with 14 mg/mL p38α MAP kinase (stored in 20 mM HEPES pH 7.1, 50 mM NaCl, 5 % glycerol (v/v), 1 mM DTT) for 1 h on ice to form the enzyme-inhibitor complex prior to crystallization. Co-crystals were grown in 24-well crystallization plates using the hanging-drop vapor diffusion method at 20 °C by mixing 1 µL of protein solution with 1 µL of reservoir solution (100 mM MES pH 6.0-6.3, 22-27 % PEG4000, 50 mM n-octly-β-D-glucopyranoside). Crystals were cryo protected by addition of 25 % PEG400 and subsequently flash frozen in liquid nitrogen.

Diffraction data were collected at the PX10SA beamline of the Swiss Light Source (PSI, Villingen, Switzerland). Images were processed with XDS and scaled using XSCALE.[3]

Structure Determination and Refinement of p38α with compound 16e.

The p38α-inhibitor complex structure was obtained by molecular replacement with PHASER[4], using a related p38α MAP kinase structure (Protein Data Bank entry 3QUE[5]) as a search model. Crystallographic refinement was performed with CNS[6] and Refmac5.[7] Model building and real space refinement was done using the program COOT.[8] The topology and library files for the ligand were generated with the Dundee PRODRG server.[9] The refined structure was validated with PROCHECK.[10] Detailed data, refinement and geometry statistics are provided in SI-Table 1. Figures were created with PyMOL[11].

SI-Table 1. Data Collection and Refinement Statistics for p38α with **16e**.

	p38α with **16e** (3UVQ)
Data collection	
Space group	$P2_12_12_1$
Cell dimensions	
a, *b*, *c* (Å)	66.09, 74.29, 77.73
α, β, γ (°)	90.00, 90.00, 90.00
Resolution (Å)	50.0-2.2 (2.30-2.20)[a]
R_{sym} or R_{merge} (%)	4.3 (34.1)
I / σI	33.23 (5.15)
Completeness (%)	99.7 (100.0)
Redundancy	5.06 (5.29)
Refinement	
Resolution (Å)	49.39-2.20
No. reflections	18972
R_{work} / R_{free}	23.6 / 31.8
No. atoms	
Protein	2720
Ligand/ion	59
Water	55
B-factors	

Protein	53.7
Ligand/ion	50.5
Water	49.5
R.m.s. deviations	
Bond lengths (Å)	0.015
Bond angles (°)	1.545

Structure (PDB-ID code)	p38α with **16e** (3UVQ)
Wavelength (Å)	1.000000
Temperature	90K
X-ray source	SLS X10SA
Ramachandran Plot:	
Residues in	
most favored regions	89.3%
additional allowed regions	10.1%
generously allowed regions	0.7%
disallowed regions	0.0%

[a]Diffraction data from one crystal was used to determine the complex structure. Values in parenthesis are referring to the highest resolution shell.

2 Analytical equipment and methods

Melting point	Büchi Melting Point B-545 (thermodynamic correction)
NMR-Spectroscopy	Bruker Advance 200 [*f* (^{1}H) = 200 MHz; *f* (^{13}C) = 50 MHz)
	Bruker Ultra Shield 400 [*f* (^{1}H) = 400 MHz; *f* (^{13}C) = 100 MHz)
	AVII + 400* [*f* (^{1}H) = 400 MHz; *f* (^{13}C) = 100 MHz)
IR- Spectroscopy	Nicolet 380 FT-IR (ATR)
HRMS (FT-ICR)	Bruker APEX II (electron spray ionisation)
GC-MS	Hewlett Packard HP 6890 Series GC-System; Hewlett Packard HP 5973 Mass Selective Detector GC-column: HP-5MS 5% phenylmethylsiloxane; carrier gas helium 6.0, flow 1,2 ml/min, temperature of injection 250 °C

GC method 160B270

Heating rate [K/min]	Final temperature [°C]	Time at temp. [min]
	160	1
10	240	5
15	270	15

GC method 160B270L

Heating rate [K/min]	Final temperature [°C]	Time at temp. [min]
	160	1
10	240	5
15	270	35

HPLC (method 2) LaChrome Ultra HPLC, Autosampler, Interface Module, Oven L2300, Pump L-216OU, Detector Diode Array C-2455U, Symmetry Column (150 mm × 4.6 mm; 5µm) (Waters). flow 1,5 ml/min. (standard method)

HPLC (method 1) Merck HPLC, Autosampler AS-2000, Interface Modul D-6000, Pump L-6200, Detector L4250, LiChrospher RP18 column (5µm), flow 1 ml/min. (compounds **18o**, **19a**, **16f**)

HPLC method

Zeit[min]	% MeOH	% 0,01 M, KH_2PO_4, pH 2,3
0-8	40 → 85	60 → 15
8-13	85	15
13-14	85 → 40	15 → 60
14-16	40	60

DC SiO_2 60 F_{254} – aluminium foils, Merck

Column chrom. La Flash System (VWR), FC 204 Fraction Collector, Pharmprep Si_{60} (25-40 µm, Merck); automated column chromatography

Solvents Dry solvents were purchased (stored over molecular sieve) and used for reaction mixtures. DCM was dried using $CaCl_2$

3 General procedures (synthesis)

General procedure A

The aryl carboxylic acid is suspended in THF / DCM under argon atmosphere and oxalyl chloride is added drop wise. Stirring continues after addition of one drop of DMF for 1 h at room temperature.

The reaction mixture is poured at 0°C into a mixture of the corresponding aniline, THF / DCM and triethylamine. Stirring continues over night at room temperature. Afterwards, the mixture is transferred in water and extracted with ethyl acetate / DCM. Solvents are removed in a rotary evaporator.

The crude product is either purified by recrystallization (ethyl acetate / hexane) or automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate).

General procedure B

The aryl carboxylic acid is suspended in THF / DCM under argon atmosphere and oxalyl chloride is added drop wise. Stirring continues after addition of one drop of DMF for 1 h at room temperature.

Triethylamine is added dropwise at 0°C and the mixture stirred for 15 min followed by addition of the corresponding aniline dissolved in THF / DCM. Stirring continues over night at room temperature. Afterwards, the mixture is transferred in water and extracted with ethyl acetate / DCM. Solvents are removed in a rotary evaporator.

The crude product is either purified by recrystallization (ethyl acetate / hexane) or automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate).

General procedure C

The nitro-compound is dissolved in a three-necked flask in ethyl acetate, followed by addition of Pd / C (10%). The reaction flask is evacuated and flushed 3-5 times with a balloon of H_2. An additional balloon of H_2 is connected and replaced as soon as the hydrogen is used up.

After complete conversion (1-5 h, monitored by TLC), coal is removed by filtration. Solvents are removed in a rotary evaporator.

General procedure D

Chlorsuberone, aniline, X-Phos, KO*tert*Bu, *tert*-BuOH and toluene are mixed in a three-necked flask under argon atmosphere, followed by addition of $Pd(OAc)_2$. The mixture is heated to 90-100°C for 15 min to 6 h. Complete conversion is determined by TLC.

The reaction mixture is poured into water and extracted with ethyl acetate or diethyl ether. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2). The product can be further purified by recrystallization.

General procedure E

Chlorsuberone, p-toluenesulfonic acid*H_2O, methanol and water are mixed under argon atomsphere in a three-necked flask and refluxed.

Reaction time 30 min – 3 h (monitored by TLC)

Solvents are removed in a rotary evaporator and the remainder taken up in $NaHCO_3$ solution (5%) and ethyl acetate. The product is extracted with ethyl acetate. The combined organic layers are washed with water. Solvents are removed in a rotary evaporator yielding the pure product.

4 Synthesis and analytical data

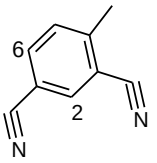
Compounds 10c and 15a-d are synthesized according to the methods described by Koeberle et al.[12]

Compound 14b is synthesized according to the methods described by Martz et al.[13]

Compounds 3-5 were synthesized according to a modified synthesis of Anzalone et al.[14]

Synthesis of compound 9 was previously described by another approach.[15]

4-Methyl-isophthalonitrile (3)



200 g (2.23 mol) CuCN in 100 g (0.62 mol) 2,4-dichlorotoluene and 500 ml N-methylpyrrolidone are mixed. The suspension is stirred for 7 days at 180°C, cooled to 110°C and poured carefully into 1500 ml of NH_3 (25%). The mixture is extracted 10 times with ethyl acetate. The organic layers are separated by decantation. Ethyl acetate is removed in a rotary evaporator. The crude product is normally used in the next step without removing remaining N-methylpyrrolidone.

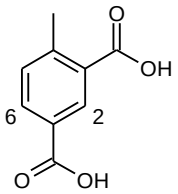
The crude product can be purified further by recrystallisation (ethyl acetate / hexane).

$C_9H_6N_2$ (Mr = 142.16)

Yield determined after step 3 (compound **5**)

^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.55 (s, 3 H, -CH_3), 7,68 (dd, 1H, J_1 = 0.6 Hz, J_2 = 8.1 Hz, C^5-H), 8.06 (dd, 1 H, J_1 = 1.8 Hz, J_2 = 8.1 Hz, C^6-H), 8.39 (d, 1 H, J = 1.8 Hz, C^2-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 20.7 (-CH_3), 110.2 (C^1), 113.6 (C^3), 116.6 (CN), 117.6 (CN), 131.9 (C^5), 136.7 (C^2), 136.7 (C^6), 147.6 (C^4)

4-Methyl-isophthalic acid (4)

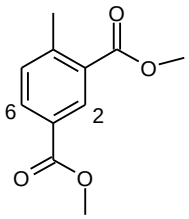


90 g (633 mmol) 4-methyl-isophthalonitrile (**3**), 120 g NaOH (powder), 500 ml diethylene glycol and 30 ml H_2O are mixed and refluxed for 5 d. Evaporated H_2O is replaced. The mixture is poured into 1000 ml of H_2O, the product is precipitated using HCl (concd) and filtered. Remaining diethylene glycol is removed by washing the crude product with water at pH 1. The yellow powder is dried in vacuo.

$C_9H_8O_4$ (Mr = 180.16)

Yield	determined after step 3 (compound **5**)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.58 (s, 3 H, -CH_3), 7.43 (d, 1 H, J = 7.8 Hz, C^5-H), 7.97 (d, 1 H, J = 7.8 Hz, C^6-H), 8.38 (s, 1 H, C^2-H), 12.98 (s, 2 H, -COOH)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 21.3 (-CH_3), 128.5 (C^1), 130.6 (C^3), 131.1 (C^5), 132.1 (C^2), 132.1 (C^6), 144.2 (C^4), 166.5 (-<u>C</u>OO-), 167.8 (-<u>C</u>OO-)

4-Methyl-isophthalic acid dimethyl ester (5)

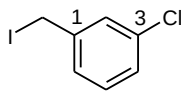


55 g (305 mmol) 4-methyl-isophthalic acid (**4**) are dissolved in 400 ml methanol. 10 ml H_2SO_4 are added and the mixture is refluxed for 6 h (monitored by TLC). Afterwards the mixture is poured into water and extracted with ethyl acetate. The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 95+5 to 90+10 in 1h).

$C_{11}H_{12}O_4$ (Mr = 208.22)

Yield	29 % (calculated for step 1-3)
GC-MS	Method 100B200; t_R = 10.98 min; m/z = 208 (14, M^+), 95 (100, 4-F-Phenyl), 89 (13)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.57 (s, 3 H, -CH_3), 3.71-3.99 (m, 6 H, -$COOCH_3$), 7.46 (d, 1 H, J = 8.1 Hz, C^5-H), 7.99 (d, 1 H, J = 7.8 Hz, C^6-H), 8.34 (s, 1 H, C^2-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 21.3 (-CH_3), 52.1 (-$COO\underline{C}H_3$), 52.2 (-$COO\underline{C}H_3$), 127.4 (C^1), 129.5 (C^3), 130.7 (C^5), 132.2 (C^2), 132.2 (C^6), 144.8 (C^4), 165.3 (-$\underline{C}OO$-), 166.3 (-$\underline{C}OO$-)

3-Chlorobenzyliodide (6)



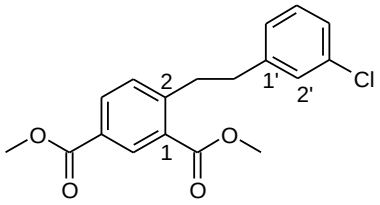
41 g 3-Chlorobenzylchloride are added to 180 ml acetone, mixed with 65 g NaI, and refluxed under argon for 2 h. The reaction mixture is poured into water and extracted with ethyl acetate. Solvents are removed in a rotary evaporator

yielding a black oil, which is used in the next step without further purification. Caution! Teargas.

C_7H_6Cl (Mr = 252.48)

Yield	61.5 g crude product (96 %)
GC-MS	method 100B200; 7,11 min; m/z (%): 254/252 (2/8, M^+), 127/125 (50/100, M^+-I), 89 (28)

4-[2-(3-Chloro-phenyl)-ethyl]-isophthalic acid dimethyl ester (7)



18 ml (45.0 mmol) n-BuLi (2.5 M in hexane) are added drop wise during 15 min to a mixture of 6.35 ml (45.2 mmol) diisopropylamine and 80 ml THF at 0°C. Stirring is continued for 15 min.

5 g (24.0 mmol) 4-methyl-isophthalic acid dimethyl ester (**5**), dissolved in 40 ml THF, are slowly added at -78°C. Stirring is continued for 1 h.

Subsequently 3-chlorobenzyliodide (**6**) is added (during 30 min). The reaction mixture is allowed to warm to 0°C during night.

After addition of NH_4Cl solution (sat.), the product can be extracted using ethyl acetate. Solvents are removed in a rotary evaporator.

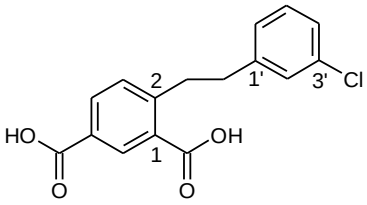
The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 95+5 to 90+10 in 1h).

$C_{18}H_{17}ClO_4$ (Mr = 332.79)

Yield	70 % -75 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 400 MHz): 2.85 (t, 2 H, J = 7.8 Hz, -CH_2-CH_2-), 3.24 (t, 2 H, J = 7.8 Hz, -CH_2-CH_2-), 3.87 (s, 6 H, -CH_3), 7,16 (d, 1 H, J = 7.3 Hz, $C^{6'}$-H), 7.22-7.35 (m, 3 H, $C^{2'}$/$C^{4'}$/$C^{5'}$), 7.53 (d, 1 H, J = 8.1 Hz,

	C^3-H), 8.04 (d, 1 H, J = 8.1 Hz, C^4-H), 8.37 (s, 1 H, C^6-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (f = 100 MHz): 35.4 (-CH_2-CH_2-), 36.4 (-CH_2-CH_2-), 52.3 (-CH_3), 52.3 (-CH_3), 126.0 ($C^{6'}$), 127.1 ($C^{4'}$), 127.8 (C^5), 128.2 (C^3), 129.6 (C^1), 130.1 ($C^{2'}$), 130.9 (C^6), 131.8 ($C^{5'}$), 132.3 (C^4), 132.9 ($C^{3'}$), 143.7 ($C^{1'}$), 147.9 (C^2), 165.3 (-COO-), 166.3 (-COO-)

4-[2-(3-Chloro-phenyl)-ethyl]-isophthalic acid (8)



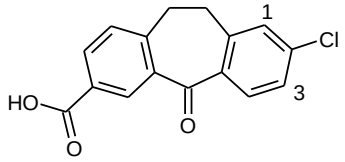
6 g (18.0 mmol) 4-[2-(3-Chloro-phenyl)-ethyl]-isophthalic acid dimethyl ester (**7**) are dissolved in 100 ml methanol and 5 ml H_2O. 10 g KOH are added and refluxed for 6 h (monitored by TLC). The reaction mixture is poured into water and extracted at pH 1 (HCl concd) using ethyl acetate. Solvents are removed in a rotary evaporator.

$C_{16}H_{13}ClO_4$ (Mr = 304.73)

Yield	> 95 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.86 (t, 2 H, J = 7.9 Hz, -CH_2-CH_2-), 3.26 (t, 2 H, J = 8.0 Hz, -CH_2-CH_2-), 7.15-7.35 (m, 4 H, $C^{6'/2'/4'/5'}$), 7,46 (d, 1 H, J = 8.1 Hz, C^3-H), 7.99 (d, 1 H, J = 7.8 Hz, C^4), 8.40 (s, 1 H, C^6-H), 13.14 (s, 2 H, COOH)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 35,6 (-CH_2-CH_2-), 36.5 (-CH_2-CH_2-), 125.9 ($C^{6'}$), 127.0 ($C^{4'}$), 128.2 (C^3), 128.8 (C^5), 130.1 ($C^{2'}$), 130.5 (C^1), 131.4 (C^6), 131.5 ($C^{5'}$),

132,1 (C^4), 132,9 ($C^{3'}$), 144.0 ($C^{1'}$), 147.4 (C^2), 166.5 (-COO-), 167.9 (-COO-)

8-Chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-carboxylic acid (9)



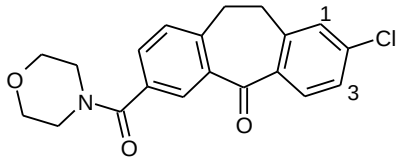
6.5 g (21.3 mmol) 4-[2-(3-chloro-phenyl)-ethyl]-isophthalic acid (**8**) are suspended in 150 ml DCM and heated to reflux temperature. 8.5 ml (117.2 mmol) $SOCl_2$ are added drop wise. The reaction mixture is refluxed until a clear solution is visible. It might be neccessary to add catalytic amounts of DMF.

15.53 g (116.5 mmol) $AlCl_3$ are added at 0°C. After 20 min the mixture is poured onto ice and stirred for 30 min. Extraction with DCM. Solvents are removed in a rotary evaporator.

$C_{16}H_{11}ClO_3$ (Mr = 286.72)

Yield	98 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 3.08-3.31 (m, 4 H, -CH_2-CH_2-), 7.35-7.54 (m, 3 H, $C^{1/3/9}$), 7.90 (d, 1 H, J = 8.5 Hz, C^4-H), 8.03 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 7.8 Hz, C^8), 8.44 (d, 1 H, J = 1.8 Hz, C^6-H), 13.0 (s, 1 H, -COOH)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.7 (C^{11}), 34.2 (C^{10}), 127.1 (C^3), 129.6 (C^1), 129.6 (C^9), 130.7 (C^6), 131.7 (C^7), 132.7 (C^4), 133.3 (C^8), 136.6 (C^{4a}), 137.8 (C^{5a}), 137.9 (C^2), 144.7 (C^{11a}), 147,2 (C^{9a}), 166.8 (-COO-), 192.8 (C^5)

2-Chloro-7-(morpholine-4-carbonyl)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (10a)

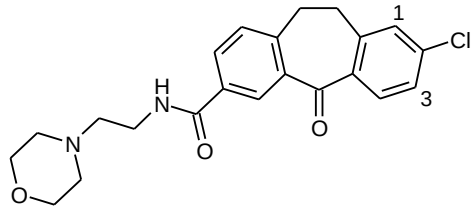


2.5 g (8.7 mmol) 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**9**) are dissolved in 10 ml DCM, 3 ml (41.4 mmol) $SOCl_2$ are added drop wise and refluxed for 1 h. The reaction mixture is poured into a solution of 21.2 ml (243.3 mmol) morpholine in 10 ml DCM at 0°C. Stirring is continued overnight at room temperature. Afterwards the mixture is poured into water and extracted with ethyl acetate. Solvents are removed in a rotary evaporator. The yellowish oil is washed with water and dried in vacuo.

$C_{18}H_{15}ClO_4$ (Mr = 355.82)

Yield	3.0 g (97 %)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 3.09-3.22 (m, 4 H, -CH_2-CH_2-), 3.51-3.83 (m, 8 H, Morpholine), 7.15-7.30 (m, 3 H, $C^{1/3/9}$-H), 7.46 (d, 1 H, J = 7.6 Hz, C^4-H), 7.92 (d, 1 H, J = 8.6 Hz, C^8-H), 7.97 (s, 1 H, C^6-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 34.6 (C^{10}), 34.7 (C^{10}), 66.9 (4 C, Morpholine), 127.1 (C^3), 129.3 (C^1), 129.6 (C^9), 129.9 (C^6), 131.4 (C^8), 132.7 (C^4), 134.0 (C^{4a}), 136.2 (C^{5a}), 138.2 (C^7), 138.8 (C^2), 143.5 (C^{9a}), 143.7 (C^{11a}), 169.4 (-COO-), 192.9 (C^5)

8-Chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (10b)



0.5 g (1.7 mmol) 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**9**) are suspended in 20 ml THF and 0.5 g CDI (3.1 mmol) are added. The mixture is stirred for 1.5 h at room temperature, 0.68 ml (5.2 mmol) 2-morpholin-4-yl-ethylamine is added, stirred over night, poured into water and extracted with ethyl acetate.

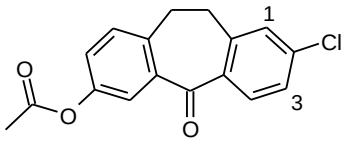
The combined organic layers are washed with water. Solvents are removed in a rotary evaporator.

$C_{18}H_{15}ClO_4$ (Mr = 398.89)

Yield	> 98%
GC-MS	method 160B270L; 43.21 min; m/z (%): 398 (0.2, M^+), 178 (11), 113 (23), 100 (100, N-Methylmorpholine)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.52 (t, 4 H, J = 4.6 Hz, $C^{2/6}$-$H_{Morpholinyl}$), 2.62 (t, 2 H, J = 5.9 Hz, N-C$\underline{H_2}$-CH_2-NH-CO-), 3.09-3.36 (m, 4 H, -CH_2-CH_2-), 3.51-3.64 (m, 2 H, N-CH_2-C$\underline{H_2}$-NH-CO-), 3.75 (t, 4 H, J = 4.6 Hz, $C^{3/5}$-$H_{Morpholinyl}$), 6.85 (s, 1 H, -CONH-) 7.23-7.29 (m, 1 H + $CDCl_3$, C^1-H), 7.30-7.39 (m, 2 H, $C^{3/9}$-H), 7.92-8.09 (m, 2 H, $C^{4/8}$-H), 8.35 (d, 1 H, J = 2.1 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 34.6 (C^{10}), 34.7 (C^{10}), 36.2 (-N-CH_2-$\underline{C}H_2$-NH-CO-), 53.4 (2 C, $C^{2/6}{}_{Morpholinyl}$), 57.0 (-N-$\underline{C}H_2$-CH_2-NH-CO-), 66.9 (2 C, $C^{3/5}{}_{Morpolinyl}$), 127.1 (C^3), 128.7 (C^1), 129.3 (C^9), 130.1 (C^6), 131.8

(C^{8}), 132.7 (C^{4}), 133.4 (C^{4a}), 136.3 (C^{7}), 138.0 (C^{5a}), 138.9 (C^{2}), 143.7 (C^{11a}), 145.1 (C^{9a}), 166.4 (-CONH-), 192.9 (C^{5})

Acetic acid 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-yl ester (10d)

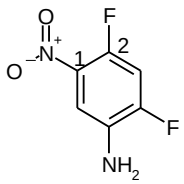


0.5 g (1.9 mmol) 2-chloro-7-hydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**10c**) is added to 30 ml of acetic anhydride. After addition of catalytic amounts of 4-DMAP, the mixture is heated to 100°C. After 10-20 minutes (monitored by TLC) the reaction mixture is poured onto ice and extracted with ethyl acetate. The organic layer is washed several times with water in order to remove remaining acetic acid.

$C_{17}H_{13}ClO_3$ (Mr = 300,74)

Yield — The crude product is used in the next step without further purification.

2,4-Difluoro-5-nitro-phenylamine (11a)



3.87 g (30.0 mmol) 2,4-difluoraniline are added drop wise to 10 ml H_2SO_4(concd). At 0°C a mixture of 3 ml H_2SO_4(concd) and 1,5 ml HNO_3 (65%) is slowly added and subsequently stirred for 1 h at 0°C.

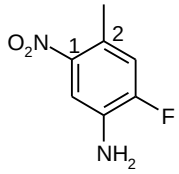
The reaction mixture is poured onto ice and alkalized. The yellow product precipitates, is filtered and washed with water. For higher purities the crude

product is solved in ethyl acetate and washed with water. Solvents are removed in a rotary evaporator.

$C_6H_4F_2N_2O_2$ (Mr = 174.11)

Yield	61 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 5.69 (s, 2 H, -NH_2), 7.44-7.54 (m, 2H, $C^{3/6}$-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 106.2 (t, J = 25.4 Hz, C^3), 110.7 (d, J = 7.3 Hz, C^6), 133.1 (dd, J_1 = 4.4 Hz, J_2 = 7.3 Hz, C^1), 134.1 (dd, J_1 = 2.5 Hz, J_2 = 14.2 Hz, C^5), 145.9 (dd, J_1 = 11.6 Hz, J_2 = 250.8 Hz, C^2), 152.6 (dd, J_1 = 10.2 Hz, J_2 = 250.8 Hz, C^4)

2-Fluoro-4-methyl-5-nitro-phenylamine (11b)



1.8 ml (1.99 g, 15.9 mmol) 2-fluoro-4-methyl-phenylamine are added drop wise to 30 ml of H_2SO_4(concd). At 0°C a mixture of 10 ml H_2SO_4(concd) and 5 ml HNO_3 (65%) are carefully added and stirring continued for 1 h at 0°C.

The reaction mixture is poured onto ice and alkalized. The product precipitates as black oil, which can be extracted using ethyl acetate. Solvents are removed in a rotary evaporator.

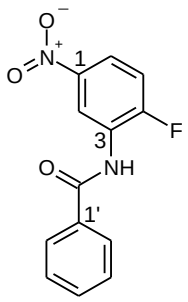
The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2).

$C_7H_7FN_2O_2$ (Mr = 170.14)

Yield	1.97 g (72 %)

^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.37 (s, 3H, -CH_3), 5.61 (s, 2 H, -NH_2), 7.15 (d, 1H, J = 11.9 Hz, C^3-H), 7.45 (d, 1H, J = 8.3 Hz, C^6-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 19.0 (-CH_3), 111.6 (t, J = 7.3 Hz, C^6), 118.5 (d, J = 20.4 Hz, C^3), 121.0 (dd J = 7.3 Hz, C^2), 135.5 (d, J = 14.5 Hz, C^5), 144.7 (dd, J = 2.2 Hz, C^1), 152.4 (d, J = 246.5 Hz, C^4)

N-(2-Fluoro-5-nitro-phenyl)-benzamide (13c)



The compound is synthesized according to the general procedure A.

2.2 g (18.0 mmol) benzoic acid, 20 ml THF, 1.6 ml (18.7 mmol) oxalyl chloride, 2.8 g (17.9 mmol) 5-nitro-2-fluoroaniline, 70 ml THF, 10 ml (72.1 mmol) triethylamine.

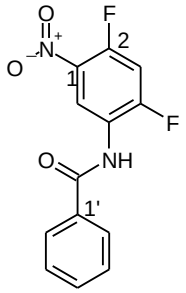
The crude product is purified by recrystallization (ethyl acetate / hexane).

$C_{13}H_9FN_2O_3$ (Mr = 260.23)

Yield	1.56 g (33 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 7.24-7.37 (m, 1 H, C^5-H), 7.50-7.69 (m, 3 H, $C^{3'/4'/5'}$-H), 7.87-7.97 (m, 2 H, $C^{2'/6'}$-H), 8.00-8.09 (m, 1 H, C^6-H), 8.17 (s, 1 H, -CONH-), 9.50 (d, 1 H, J = 6.8 Hz, C^2-H)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 117.1 (d, J = 23.3 Hz, C^5), 121.3 (d, J = 3.6 Hz, C^2), 122.0 (d, J = 9.5 Hz, C^6), 127.1 (d, J = 13.8 Hz, C^3), 127.9 (2 C, $C^{2'/6'}$), 128.5

(2 C, $C^{3'/5'}$), 132.2 ($C^{4'}$), 133.4 ($C^{1'}$), 143.7 (d, J = 2.2 Hz, C^{1}), 158.7 (d, J = 255.9 Hz, C^{4}), 165.8 (-CONH-)

N-(2,4-Difluoro-5-nitro-phenyl)-benzamide (13d)



The compound is synthesized according to the general procedure B.

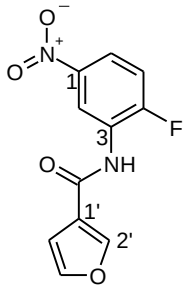
1.55 g (12.7 mmol) benzoic acid, 50 ml DCM, 2.2 ml (25 mmol) oxalyl chloride, 8.77 ml (63 mmol) triethylamine, 2.08 g (11.9 mmol) 2,4-difluoro-5-nitro-phenylamine (**11a**), 15 ml DCM.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2).

$C_{13}H_8F_2N_2O_3$ (Mr = 278.22)

Yield	0.59 g (18 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 Hz): 7.17 (t, 1 H, J = 5.0 Hz, C^3-H), 7.44-7.70 (m, 3 H, $C^{3'/4'/5'}$-H), 7.80-7.96 (m, 2 H, $C^{2'/6'}$-H), 8.05 (s, 1 H, -CONH-) 9.36 (t, 1H, J = 4.0 Hz, C^6-H)

Furan-3-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (13i)



The compound is synthesized according to the general procedure A.

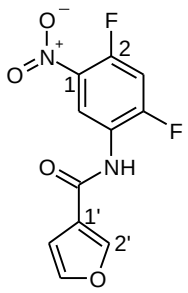
4.0 g (35.7 mmol) furan-3-carboxylic acid, 40 ml THF, 3.1 ml (36.1 mmol) oxalyl chloride, 5.6 g (35.9 mmol) 5-nitro-2-fluoroaniline, 150 ml THF, 30 ml (216.4 mmol) triethylamine.

The crude product is purified by recrystallization (ethyl acetate / hexane).

$C_{11}H_7FN_2O_4$ (Mr = 250.19)

Yield	0.5 g (6 %)
GC-MS	method 160B270; t_R = 9,05 min; m/z = 250 (34, M^+), 177 (100, M^+-CH_3-O), 149 (18, M^+-$COOCH_3$), 95 (100, 4-F-Phenyl)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 6.97-7.03 (m, 1 H, $C^{5'}$-H), 7.61 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 9.9 Hz, C^5-H) 7.82 (t, 1 H, J = 1.7 Hz, $C^{4'}$-H), 8.08-8.19 (m, 1 H, $C^{2'}$-H), 8.44-8.49 (m, 1 H, C^6-H), 8.64 (dd, 1 H, J_1 = 2.9 Hz, J_2 = 6.7 Hz, C^2), 10.20 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 109.2 ($C^{5'}$), 117.1 (d, J = 22.5 Hz, C^5), 121.1 (d, 3.6 Hz, C^2), 121.8 ($C^{1'}$), 121.9 (d, J = 10.2 Hz, C^6), 126.6 (d, J = 13.8 Hz, C^3), 143.7 (d, J = 2.2 Hz, C^1), 144.4 ($C^{4'}$), 146.6 ($C^{2'}$), 158.3 (d, J = 255.9 Hz, C^4), 160.7 (-CONH-)

Furan-3-carboxylic acid (2,4-difluoro-5-nitro-phenyl)-amide (13j)



The compound is synthesized according to the general procedure B.

0.95 g (8.5 mmol) furan-3-carboxylic acid, 50 ml DCM, 1.45 ml (16.9 mmol) oxalyl chloride, 5.86 ml (42.3 mmol) triethylamine, 1.34 g (7.7 mmol) 2,4-difluoro-5-nitro-phenylamine, 15 ml DCM.

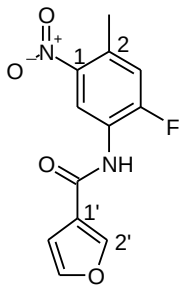
The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2).

The product is purified further by recrystallization (ethyl acetate / hexane).

$C_{11}H_6F_2N_2O_4$ (Mr = 268,18)

Yield	0,36 g (17 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 6.76 (s, 1 H, $C^{5'}$-H), 7.15 (t, 1 H, J = 10.1 Hz, C^3-H), 7.50-7.66 (m, 2 H, $C^{4'}$-H / -CONH-), 8.12 (s, 1 H, $C^{2'}$-H), 9.29 (t, 1 H, J = 8.0 Hz, C^6-H)

Furan-3-carboxylic acid (2-fluoro-4-methyl-5-nitro-phenyl)-amid (13k)



The compound is synthesized according to the general procedure B.

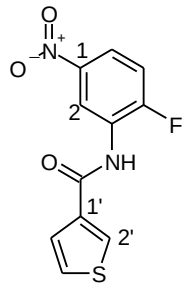
1.43 g (12.8 mmol) furan-3-carboxylic acid, 50 ml DCM, 2.17 ml (25.3 mmol) oxalyl chloride, 8.77 ml (63.3 mmol) triethylamine, 1.97 g (11.6 mmol) 2-fluoro-4-methyl-5-nitro-phenylamine (**11b**), 15 ml DCM.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2).

$C_{12}H_9FN_2O_4$ (Mr = 264.21)

Yield	0.6 g (19,6 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 2.60 (s, 3 H, -CH_3), 6.76 (s, 1 H, $C^{5'}$), 7.12 (d, 1 H, J = 11.1 Hz, C^3-H), 7.54 (d, 1 H, J = 1.5 Hz, $C^{4'}$-H), 7.64 (s, 1 H, -NH-), 8.11 (s, 1 H, $C^{2'}$-H), 9.16 (d, 1 H, J = 7.3 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 20.3 (-CH_3), 108.1 ($C^{5'}$), 118.4 (d, J = 21.8 Hz, C^3), 118.7 (d, J = 3.6 Hz, C^6), 118.7 ($C^{4'}$), 122.2 ($C^{1'}$), 124.8 (d, J = 10.9 Hz, C^5), 130.9 (d, J = 8.0 Hz, C^2), 144.5 (s, C^1), 145.7 ($C^{2'}$), 153.8 (d, J = 250.1 Hz, C^4), 160.3 (-CONH-)

Thiophene-3-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (13l)



The compound is synthesized according to the general procedure B.

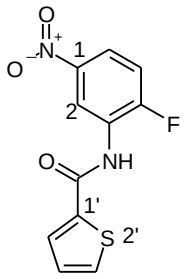
1.62 g (12.6 mmol) thiophene-3-carboxylic acid, 50 ml DCM, 2.17 ml (25.3 mmol) oxalyl chloride, 8.77 ml (63.3 mmol) triethylamine, 1.80 g (11.5 mmol) 2-fluoro-5-nitro-phenylamine, 15 ml DCM.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{11}H_7FN_2O_3S$ (Mr = 266.25)

Yield	0.70 g (22,9 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 7.22-7.34 (m, 1 H, C^5-H), 7.42-7.61 (m, 2 H, $C^{4'/5'}$-H), 7.87-8.23 (m, 3H, $C^{6/2'/}$-H / -NH-), 9.35-9.61 (m, 1 H, C^2-H)

Thiophene-2-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (13m)



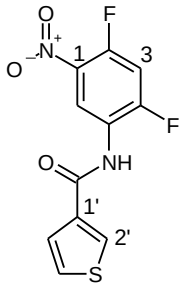
0.41 g (2.8 mmol) thiophene-2-carboxylic acid chloride, dissolved in 5 ml DCM, are added to a mixture of 0.44 g (2.8 mmol) 2-fluoro-5-nitroaniline and 0.39 ml (2.8 mmol) triethylamine in 5 ml DCM at 0°C. Stirring continues over night at room temperature. The reaction mixture is poured into water and extracted with DCM. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate).

$C_{11}H_7FN_2O_3S$ (Mr = 266.25)

Yield	15 %
^{1}H-NMR ($CDCl_3$)*	δ in ppm (*f* = 400 MHz): 7.19 (dd, 1 H, J_1 = 3.8 Hz, J_2 = 4.9 Hz, $C^{4'}$), 7.26-7.33 (m, 1 H + $CDCl_3$, C^5), 7.65 (dd, 1 H, J_1 = 1.1Hz, J_2 = 4.9 Hz, $C^{5'}$), 7.70 (dd, 1 H, J_1 = 1.1Hz, J_2 = 3.8 Hz, $C^{3'}$), 7.93-8.09 (m, 2 H, C^6 / -NH-), 9.41 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 3.8 Hz, C^2),

Thiophene-3-carboxylic acid (2,4-difluoro-5-nitro-phenyl)-amide (13n)



The compound is synthesized according to the general procedure B.

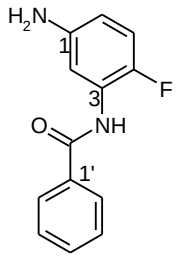
0.81 g (6.3 mmol) thiophene-3-carboxylic acid, 20 ml DCM, 1.08 ml (12.6 mmol) oxalyl chloride, 4.37 ml (31.5 mmol) triethylamine, 1.0 g (5.74 mmol) 2,4-difluoro-5-nitro-phenylamine (**11a**), 10 ml DCM.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 8+2). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{11}H_6F_2N_2O_3S$ (Mr = 284.24)

Yield	0.20 g (12 %)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 7.58-7.73 (m, 2 H, $C^{4'/5'}$-H), 7.85 (t, 1 H, J = 10.7 Hz, C^3-H), 8.41 (s, 1 H, $C^{2'}$-H), 8.52 (t, 1 H, J = 7.8 Hz, C^6-H), 10.27 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 107.3 (t, J = 26.2 Hz, C^3), 122.9 (dd, J_1 = 1.8 Hz, J_2 = 6.9 Hz, C^5), 123.5 (d, J = 3.6 Hz, C^6), 127.1 ($C^{5'}$), 127.2 ($C^{4'}$), 130.9 ($C^{2'}$), 133.0 (d, J = 7.3 Hz, C^1), 136.2 ($C^{1'}$), 152.6 (dd, J_1 = 12.7 Hz, J_2 = 261.4 Hz, $C^{2'}$), 158.4 (dd, J_1 = 11.3 Hz, J_2 = 258.5 Hz, $C^{4'}$), 161.0 (-CONH-)

N-(5-Amino-2-fluoro-phenyl)-benzamide (14c)



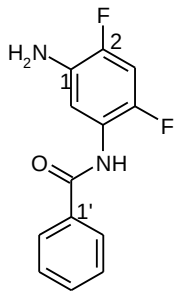
The compound is synthesized according to the general procedure C.

1.56 g (6.0 mmol) N-(2-fluoro-5-nitro-phenyl)-benzamide (**13c**), 0.4 g Pd / C (10%), 150 ml ethyl acetate.

$C_{13}H_{11}FN_2O$ (Mr = 230.24)

Yield	> 95 %
GC-MS	method 160B270; t_R = 9.94 min; m/z = 230 (63, M^+), 105 (100, OC-Phe), 77 (49, Benzene)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 3.66 (s, 2 H, -NH_2), 6.25-6.44 (m, 1 H, C^6-H), 6.87-7.00 (m, 1 H, C^5-H), 7.42-7.64 (m, 3 H, $C^{3'/4'/5'}$-H), 7.81-7.98 (m, 3 H, $C^{2/2'/6'}$-H), 8.04 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 111.3 (d, J = 7.3 Hz, C^6), 111.7 (C^2), 115.4 (d, J = 20.4 Hz, C^5), 125.5 (d, J = 13.1 Hz, C^3), 127.6 (2 C, $C^{2'/6'}$), 128.4 (2 C, $C^{3'/5'}$), 131.6 ($C^{4'}$), 134.2 ($C^{1'}$), 145.0 (C^1), 147.8 (d, J = 232.3 Hz, C^4), 165.2 (-CONH-)

N-(5-Amino-2,4-difluoro-phenyl)-benzamide (14d)



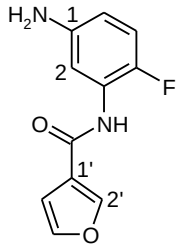
The compound is synthesized according to the general procedure C.

0.59 g (2.1 mmol) N-(2,4-difluoro-5-nitro-phenyl)-benzamide (**13d**), 0.4 g Pd / C (10%), 150 ml ethyl acetate.

$C_{13}H_{10}F_2N_2O$ (Mr = 248.23)

Yield	> 95 %
GC-MS	method 160B270L; t_R = 9,19 min; m/z = 248 (72, M^+), 105 (100, OC-Phe), 77 (62, Benzen)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 3.68 (s, 2 H, -NH_2), 6.86 (t, 1 H, J = 10.5 Hz, C^3-H), 7.41-7.65 (m, 3 H, $C^{3'/4'/5'}$-H), 7.80-8.09 (m, 4 H, $C^{2'/6'/6}$-H / -CONH-)

Furan-3-carboxylic acid (5-amino-2-fluor-phenyl)-amide (14i)



The compound is synthesized according to the general procedure C.

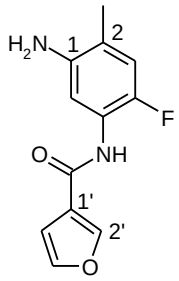
0.5 g (2.0 mmol) furan-3-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (**13i**), 0,4 g Pd / C (10%), 150 ml ethyl acetate.

$C_{11}H_9FN_2O_2$ (Mr = 220.20)

Yield	> 95 %

GC-MS	method 160B270L; t_R = 7.96 min; m/z = 220 (58, M^+), 95 (100, 4-F-Phenyl)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 5.07 (s, 2 H, -NH_2), 6.45 (d, 1 H, J = 8.6 Hz, C^6-H), 6.85 (d, 1 H, J = 6.6 Hz, C^5-H), 6.90-7.09 (m, 2 H, $C^{5'/2}$-H), 7.84 (d, 1 H, J = 1.5 Hz, $C^{4'}$-H), 8.42 (s, 1 H, $C^{2'}$-H), 9.60 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 109.2 ($C^{5'}$), 111.3 (d, J = 7.3 Hz, C^6), 111.6 (C^2), 115.4 (d, J = 21.1 Hz, C^5), 122.5 ($C^{1'}$), 124.9 (d, J = 13.1 Hz, C^3), 144.1 ($C^{2'}$), 144.9 (C^1), 145.9 ($C^{4'}$), 147.6 (d, J = 232.6 Hz, C^4), 160.2 (-CONH-)

Furan-3-carboxylic acid (5-amino-2-fluoro-4-methyl-phenyl)-amide (14k)



The compound is synthesized according to the general procedure C.

0.6 g (2.3 mmol) Furan-3-carboxylic acid (2-fluoro-4-methyl-5-nitro-phenyl)-amid (**13k**), 0.4 g Pd / C (10%), 150 ml ethyl acetate.

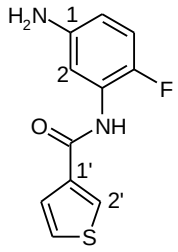
The crude product consists of **14k** and **14q**. They are separated by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 7+3).

$C_{12}H_{11}FN_2O_2$ (Mr = 234,23)

Yield	32 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.95 (s, 3 H, -CH_3), 4.74 (s, 2 H, -NH_2), 6.78 (d, 1 H, J = 7.1 Hz, C^6-H), 6.84 (d, 1

H, J = 11.1 Hz, C^3-H), 6.95 (s, 1 H, $C^{5'}$-H), 7.77 (s, 1 H, $C^{4'}$-H), 8.33 (s, 1 H, $C^{2'}$-H), 9.51 (s, 1 H, -NH-)

Thiophene-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (14l)



The compound is synthesized according to the general procedure C.

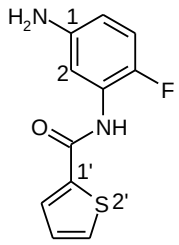
0.70 g (0.75 mmol) thiophen-3-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (**13l**), 0.4 g Pd / C (10%), 100 ml ethyl acetate.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 5+5).

$C_{11}H_7FN_2O_3S$ (Mr = 236.27)

Yield	32 %
^{1}H-NMR (DMSO-*d6*)*	δ in ppm (*f* = 400 MHz): 5.00 (s, 2 H, -NH_2), 6.35-6.42 (m, 1 H, C^6), 6.78 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 6.6 Hz, C^2-H), 6.90 (dd, 1 H, J_1 = 8.7 Hz, J_2 = 10.4 Hz, C^5-H), 7.57-7.66 (m, 2 H, $C^{4'/5'}$-H), 7.83 (dd, 1 H, J_1 = 1.1 Hz, J_2 = 5.0 Hz, $C^{5'}$-H), 8.32 (dd, 1 H, J_1 = 1.3 Hz, J_2 = 2.8 Hz, $C^{2'}$-H), 9.64 (s, 1 H, -NH-)

Thiophene-2-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (14m)



110 mg (0.41 mmol) thiophene-2-carboxylic acid (2-fluoro-5-nitro-phenyl)-amide (**13m**) and 0.47 g $SnCl_2*2H_2O$ are suspended in 7 ml of ethanol. The mixture is refluxed for 4 h (monitored by TLC) and subsequently stirred at room temperature over night.

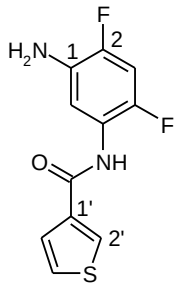
The ethanol is nearly completely removed in vacuo, 10 ml water are added and alkalized with NaOH solution. Extraction is accomplished with ethyl acetate. The organic layers are washed with water. Solvents are removed in a rotary evaporator.

The crude product is purified by column chromatography (SiO_2).

$C_{11}H_7FN_2O_3S$ (Mr = 236.27)

Yield	100 mg (> 95 %)
^{1}H-NMR (DMSO-*d6*)*	δ in ppm (*f* = 400 MHz): 5.01 (s, 2 H, $-NH_2$), 6.36-6.44 (m, 1 H, C^6), 6.76 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 6.7 Hz, C^2-H), 6.92 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 10.4 Hz, C^5-H), 7.20 (dd, 1 H, J_1 = 3.7 Hz, J_2 = 5.0 Hz, $C^{4'}$-H), 7.83 (dd, 1 H, J_1 = 1.1 Hz, J_2 = 5.0 Hz, $C^{5'}$-H), 7.97 (dd, 1 H, J_1 = 1.1 Hz, J_2 = 3.7 Hz, $C^{3'}$-H), 9.86 (s, 1 H, -NH-)

Thiophene-3-carboxylic acid (5-amino-2,4-difluoro-phenyl)-amide (14n)



240 mg (0.84 mmol) thiophene-3-carboxylic acid (2,4-difluoro-5-nitro-phenyl)-amide (**13n**), and 1.06 g $SnCl_2*2H_2O$ are suspended in 15 ml ethanol. The mixture is refluxed for 4 h (monitored by TLC) and subsequently stirred at room temperature over night.

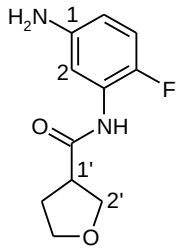
The ethanol is nearly completely removed in vacuo, 10 ml water are added and alkalized with NaOH solution. Extraction is accomplished with ethyl acetate. The organic layers are washed with water. Solvents are removed in a rotary evaporator.

The crude product is purified by column chromatography (SiO_2).

$C_{11}H_8F_2N_2OS$ (Mr = 254,26)

Yield	200 mg (93 %)
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 5.06 (s, 2 H, -NH_2), 6.93 (t, 1 H, J = 8.7 Hz, C^6-H), 7.11 (t, 1 H, J = 10.6 Hz, C^3-H), 7.51-7.70 (m, 2 H, $C^{4'/5'}$-H), 8.31 (s, 1 H, $C^{2'}$-H), 9.72 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 103.6 (t, J = 24.4 Hz, C^3), 121.1 (dd, J_1 = 3.6 Hz, J_2 = 24.4 Hz, C^1), 113.7 (d, 5.1 Hz, C^6), 126.9 ($C^{5'}$), 127.1 ($C^{4'}$), 129.8 ($C^{2'}$), 132.6 (dd, J_1 = 2.2 Hz, J_2 = 13.8 Hz, C^5), 137,1 ($C^{1'}$), 160.7 (-CONH-), not detected ($C^{2/4}$)

Tetrahydro-furan-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (14o)



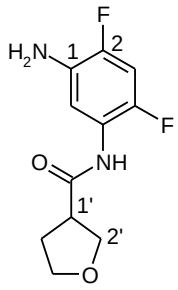
The compound is synthesized according to the general procedure C.

0.50 g (2.0 mmol) Furan-3-carboxylic acid (2-fluoro-5-nitro-phenyl)-amid (**13i**), 0.4 g Pd / C (10%), 150 ml ethyl acetate. Longer reaction times are needed than for compound **14i** (monitored by TLC).

$C_{11}H_{13}FN_2O_2$ (Mr = 224.24)

Yield	> 95 %
GC-MS	method 160B270; t_R = 13.15 min; m/z = 226 (68, M^+), 105 (100, 2-Methylaniline), 77 (42, Benzene)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 1.93-2.12 (m, 2 H, $C^{5'}$-H), 3.14-3.30 (m, 1 H, $C^{1'}$-H), 3.60-3.80 (m, 3 H, $C^{2'/4'}$-H), 3.84-3.98 (m, 1 H, $C^{2'}$-H), 6.14-6.36 (m, 1 H, C^6-H), 6.85 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 10.9 Hz, C^5), 7.09 (dd, 1 H, J_1 = 2.7 Hz, J_2 = 6.8 Hz, C^2), 9.50 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 30.3 ($C^{5'}$), 44.7 ($C^{1'}$), 68.1 ($C^{4'}$), 70.7 ($C^{2'}$), 109.7 (C^2), 110.2 (d, J = 6.9 Hz, C^6), 115.5 (d, J = 20.6 Hz, C^5), 126.2 (d, J = 12.6 Hz, C^3), 145.3 (d, J = 1.5 Hz, C^1), 172.2 (-CONH-), not detected (C^4)

Tetrahydro-furan-3-carboxylic acid (5-amino-2,4-difluoro-phenyl)-amide (14p)



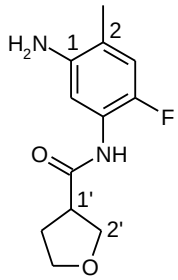
$C_{11}H_{12}F_2N_2O_2$ (Mr = 242.23)

The compound is synthesized according to the general procedure C.

0.60 g (2.2 mmol) furan-3-carboxylic acid (2,4-difluoro-5-nitro-phenyl)-amid (**13j**), 0.4 g Pd / C (10%), 150 ml ethyl acetate. Reaction time: 12 h

Yield	> 95 %
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 1.96-2,13 (m, 2 H, $C^{5'}$), 3.16-3.27 (m, 1 H, $C^{1'}$-H), 3.65-3.81 (m, 3 H, $C^{4'/2'}$-H), 3.92 (t, 1 H, J = 8.1 Hz, $C^{2'}$), 5.00 (s, 2 H, -NH_2), 7.06 (t, 1 H, J = 10.7 Hz, C^3-H), 7.21 (t, 1 H, J = 8.8 Hz, C^6-H), 9.55 (s, 1 H, -CONH-)

Tetrahydro-furan-3-carboxylic acid (5-amino-2-fluoro-4-methyl-phenyl)-amide (14q)



The compound is synthesized according to the general procedure C.

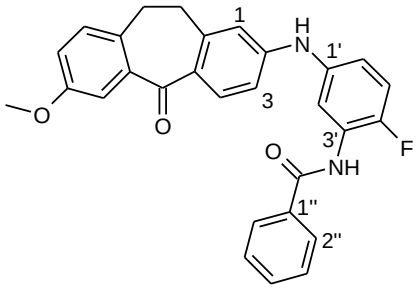
Furan-3-carboxylic acid (2-fluoro-4-methyl-5-nitro-phenyl)-amide (**13k**), 0.4 g Pd / C (10%), 150 ml ethyl acetate. The crude product consists of **14k** and **14q**.

They are separated by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 7+3).

$C_{12}H_{15}FN_2O_2$ (Mr = 238.26)

Yield	0.27 g (49 %)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.01 (s, 3 H, -CH_3), 3.17-3.27 (m, 1 H, $C^{5'}$), 3.35-3.55 (m, 2H, $C^{5'/1'}$-H), 3.60-3.81 (m, 3 H, $C^{4'/2'}$-H), 3.92 (t, 1 H, J = 8.1 Hz, $C^{2'}$), 4.69 (s, 2 H, -NH_2), 6.80 (d, 1 H, J = 11.4 Hz, C^3-H), 7.06 (d, 1 H, J = 7.0 Hz, C^6-H), 9.45 (s, 1 H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 16.9 (-CH_3), 30.0 ($C^{5'}$), 44.2 ($C^{1'}$), 67.7 ($C^{4'}$), 70.4 ($C^{2'}$), 109.7 (s, C^6), 116.0 (d, J = 21.1 Hz, C^3), 118.2 (d, J = 6.5 Hz, C^5), 123.3 (d, J = 12.4 C^2), 142.5 (s, C^1), 146.0 (d, J = 232.7 Hz, C^4), 171.6 (-CONH-)

N-[2-Fluoro-5-(7-methoxy-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino)-phenyl]-benzamide (16a)



The compound is synthesized according to the general procedure D.

0.50 g (1.8 mmol) 2-chloro-7-methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15a**), 0.45 g (2.0 mmol) N-(5-amino-2-fluoro-phenyl)-benzamide (**14c**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.17 g (0.36 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.1 g (9.8 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

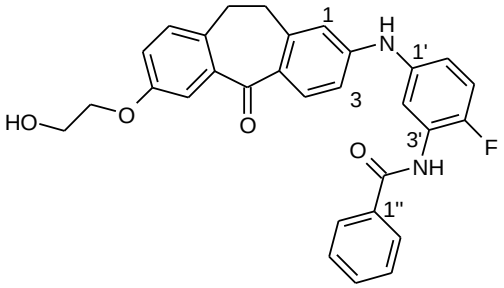
Reaction time: 3 h. Temperature: Reflux. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 7+3).

$C_{29}H_{23}FN_2O_3$ (Mr = 466.52)

Yield	0.25 g (30 %)
HRMS $[M+Na]^+$	489.158898 (calc. 489.15849)
Melting point	196°C
IR (ATR)	3283, 2927, 1660, 1557, 1497, 1288, 1267, 1218, 1048, 775, 713, 687, 615, 519 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 3.03 (s, 4 H, $-CH_2-CH_2-$), 3.77 (s, 3 H, $-CH_3$), 6.84 (d, 1 H, J = 2.2 Hz, C^1-H), 6.96 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 2.3 Hz, C^3-H) 7.00-7.11 (m, 2 H, $C^{6'/5'}$-H), 7.19-7.29 (m, 2 H, $C^{2'/8}$-H), 7.39 (d, 1 H, J = 2.8 Hz, C^6-H), 7.46-7.65 (m, 4 H, $C^{9/4/3''/5''}$-H), 7.89-8.03 (m, 3 H, $C^{2''/6''/4''}$-H), 8.84 (s, 1 H, -NH-), 10.10 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 33.4 (C^{10}), 36.4 (C^{11}), 55.5 ($-OCH_3$), 112.9 (C^3), 114.3 (C^6), 114.6 (C^1), 116.6 (d, J = 21.0 Hz, $C^{5'}$), 118.4 (d, 2 C, J = 7.2 Hz, $C^{6'/2'}$), 118.6 (C^8), 126.6 (d, J = 14.1 Hz, $C^{3'}$), 127.8 (C^{4a}), 128.2 (2 C, $C^{3''/5''}$), 128.8 (2 C, $C^{2''/6''}$), 130.6 (C^4), 132.2 (C^9), 133.9 ($C^{4''}$), 134.3 ($C^{1''}$), 134.6 (C^{5a}), 137.5 ($C^{1'}$) 140.1 (C^{9a}), 145.8 (C^2), 148.8 (C^{11a}), 158.1 (C^7), 165.8 (-CONH-), 190.7 (C^5), not detected ($C^{4'}$)

N-{2-Fluoro-5-[7-(2-hydroxy-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]-cycloheptен-2-ylamino]-phenyl}-benzamide (16b)



The compound is synthesized according to the general procedure D.

0.40 g (1.2 mmol) acetic acid 2-(8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptен-3-yloxy)-ethyl ester (**15b**), 0.46 g (2.0 mmol) N-(5-amino-2-fluoro-phenyl)-benzamide (**14c**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.20 g (0.42 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 0.80 g (7.1 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

Reaction time: 3 h. Temperature 90°C. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 6+4). The product is further purified by recrystallization (ethyl acetate / hexane).

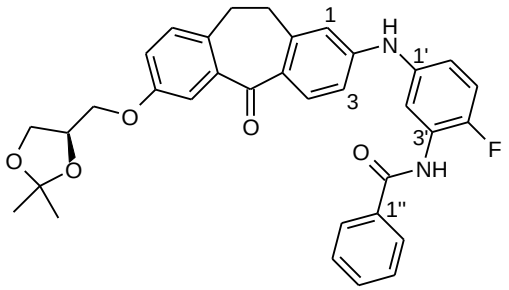
$C_{30}H_{25}FN_2O_4$ (Mr = 496.54)

Yield	10 % (Losses by recrystallization)
HRMS $[M+Na]^+$	519.168879 (calc. 519.16906)
Melting point	81°C
IR (ATR)	3290, 2922, 2359, 1660, 1567, 1524, 1496, 1354, 1262, 1354, 1262, 1211, 1116, 1047, 892, 813, 783, 703 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 3.02 (s, 4 H, -CH_2-CH_2-), 3.70 (t, 2 H, J = 4.8 Hz, OH-C<u>H$_2$</u>-CH_2-O-), 4.00 (t, 2 H, J = 4.9 Hz, OH-CH_2-C<u>H$_2$</u>-O-), 4.88 (s, 1 H, -OH), 6.84 (d, 1 H, J = 2.2 Hz, C^1-H), 6.95 (dd, 1 H, J_1 = 2.2 Hz, J_2 = 9.0 Hz, C^3-H), 7.01-7.12 (m, 2 H, $C^{6'/5'}$-

H), 7.17-7.31 (m, 2 H, $C^{2'/8}$-H), 7.39 (d, 1 H, J = 2.8 Hz, C^{6}-H), 7.44-7.66 (m, 4 H, $C^{9/4/3''/5''}$-H), 7.90-8.04 (m, 3 H, $C^{2''/6''/4''}$-H) 8.86 (s, 1 H, -NH-), 10.12 (s, 1 H, -CONH-)

^{13}C-NMR (DMSO-*d6*) δ in ppm (*f* = 50 MHz): 33.5 (C^{10}), 36.3 (C^{11}), 59.9 (OH-$\underline{C}H_2$-CH_2-O-), 70.0 (OH-CH_2-$\underline{C}H_2$-O-), 112.9 (C^{3}), 114.3 (C^{6}), 115.4 (C^{1}), 116.6 (d, J = 21.0 Hz, $C^{5'}$), 118.3 (d, 2 C, J = 7.6 Hz, $C^{2'/6'}$), 119.1 (C^{8}), 126.9 (d, J = 15.2 Hz, $C^{3'}$), 127.8 (C^{4a}), 128.2 (2 C, $C^{3''/5''}$), 128.8 (2 C, $C^{2''/6''}$), 130.6 (C^{4}), 132.2 (C^{9}), 133.9 ($C^{4''}$), 134.3 ($C^{1''}$), 134.6 (C^{5a}), 137.5 ($C^{1'}$) 140.0 (C^{9a}), 145.9 (C^{2}), 148.8 (C^{11a}), 157.5 (C^{7}), 170.4 (-CONH-), 190.7 (C^{5}), not detected ($C^{4'}$)

(*R*)-N-{5-[7-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-2-fluoro-phenyl}-benzamide (16c)



The compound is synthesized according to the general procedure D.

0.72 g (1.9 mmol) (*R*)-2-chloro-7-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15c**), 0.40 g (1.7 mmol) N-(5-amino-2-fluoro-phenyl)-benzamide (**14c**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.15 g (0.31 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.0 g (8.9 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

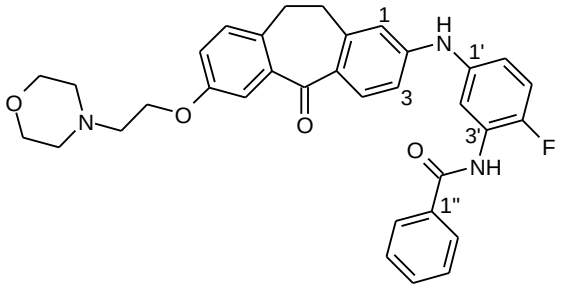
Reaction time: 3 h. Temperature: Reflux. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 6+4). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{34}H_{31}FN_2O_5$ (Mr = 566.63)

Yield	4 % (Losses by recrystallization)
HRMS $[M+Na]^+$	589.21102 (calc. 589.21092)
Melting point	176°C
IR (ATR)	3309, 2930, 2359, 1667, 1574, 1525, 1495, 1446, 1354, 1322, 1262, 1209, 1150, 1116, 1085, 1051, 973, 840, 784, 706, 651, 567, 452 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 1.29 (s, 3 H, $-CH_3$), 1.35 (s, 3 H, $-CH_3$), 3.02 (s, 4 H, $-CH_2-CH_2-$), 3.75 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 6.4 Hz, Dioxolane, 3.93-4.17 (m, 3 H, Dioxolane), 4.34-4.45 (m, 1 H, Dioxolane), 6.84 (d, 1 H, J = 1.8 Hz, C^1-H), 6.96 (dd, 1 H, J_1 = 8.9 Hz, J_2 = 2.1 Hz, C^3-H), 7.01-7.15 (m, 2 H, $C^{6'/5'}$-H), 7,16-7,34 (m, 2 H, $C^{2'/8}$-H) 7.40 (d, 1 H, J = 2.7 Hz, C^6-H), 7.44-7.67 (m, 4 H, $C^{9/4/3''/5''}$-H), 7.85-8.07 (m, 3 H, $C^{2''/6''/4''}$-H), 8.85 (s, 1 H, -NH-), 10.10 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 25.8 ($-CH_3$), 26.9 ($-CH_3$), 33.5 (C^{10}), 36.3 (C^{11}), 66.0 (C^3, Dioxolane), 69.2 (C^1, Dioxolane), 74.1 (C^2, Dioxolane, 109.2 ($\underline{C}(CH_3)_2$), 112.9 (C^3), 114.3 (C^6), 115.4 (C^1), 116.6 (d, J = 21.3 Hz, $C^{5'}$), 118.4 (2 C, d, J = 6.9 Hz, $C^{2'/6'}$), 119.1 (C^8), 126.6 (d, J = 13.3 Hz, $C^{3'}$), 127.7 (C^{4a}), 128.2 (2 C, $C^{3''/5''}$), 128.8 (2 C, $C^{2''/6''}$), 130.6 (C^4), 132.2 ($C^{4''}$), 133.9 (C^9), 134.3 ($C^{1''}$), 134.9 (C^{5a}), 137.5 (d, J = 2.7 Hz, $C^{1'}$) 140.1 (C^{9a}), 145.9 (C^2), 148.8 (C^{11a}), 157.2 (C^7), 165.8 (-CONH-), 190.6 (C^5), not detected ($C^{4'}$)

N-{2-Fluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-benzamide (16d)



The compound is synthesized according to the general procedure D.

0.74 g (2.0 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy-10,11-dihydrodibenzo[a,d]-cyclohepten-5-one (**15d**), 0.46 g (2.0 mmol) N-(5-amino-2-fluoro-phenyl)-benzamide (**14c**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.20 g (0.42 mmol) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-biphenyl, 0.80 g (7.1 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH. Reaction time: 3 h. Temperature: 90°C. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 1+9). The product is further purified by recrystallization (ethyl acetate / hexane).

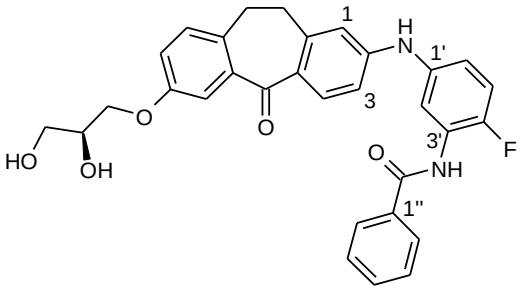
$C_{34}H_{32}FN_3O_4$ (Mr = 565.65)

Yield	3 % (Losses by recrystallization)
HRMS $[Na+H]^+$	566.245406 (calc. 566.2496)
Melting point	100°C
IR (ATR)	3308, 2922, 2358, 1667, 1573, 1525, 1495, 1446, 1354, 1321, 1263, 1210, 1147, 1113, 1033, 853, 783, 704, 452 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.45 (t, 4 H, J = 4.54 Hz, $C^{2/6}_{Morpholinyl}$-H), 2.67 (t, 2 H, J = 5.6 Hz, -N-C$\underline{H_2}$-CH_2-O-), 3.01 (s, 4 H, -CH_2-CH_2-), 3.55 (t, 4 H, J = 4.5 Hz, $C^{3/5}_{Morpholinyl}$-H), 4.08 (t, 2 H, J = 5.6 Hz, -N-CH_2-C$\underline{H_2}$-O-), 6.85 (d, 1 H, J = 1.8 Hz, C^1-H), 6.90-7.15 (m, 3 H, $C^{3/6'/5'}$-H), 7.14-7.32 (m, 2 H, $C^{2'/8}$-H), 7.40

(d, 1 H, J = 2.6 Hz, C^{6}-H), 7.44-7.67 (m, 4 H, $C^{9/4/3''/5''}$-H), 7.88-8.05 (m, 3 H, $C^{4''/2''/6''}$-H), 8.86 (s, 1 H, -NH-), 10.12 (s, 1 H, -CONH-)

^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 33.5 (C^{10}), 36.3 (C^{11}), 53.9 (2 C, $C^{2/6}{}_{Morpholinyl}$), 57.3 (-N-$\underline{C}H_2$-CH_2-O-), 65.8 (-N-CH_2-$\underline{C}H_2$-O-), 66.5 (2 C, $C^{3/5}{}_{Morpholinyl}$), 112.9 (C^{3}), 114.3 (C^{6}), 115.5 (C^{1}), 116.6 (d, J = 20,6 Hz, $C^{5'}$), 118.3 (d, 2 C, $C^{6'/2'}$), 119.1 (C^{8}), 126.6 (d, J = 13.7 Hz, $C^{3'}$), 127.8 (C^{4a}), 128.2 (2 C, $C^{3''/5''}$), 128.8 (2 C, $C^{2''/6''}$), 130.6 (C^{4}), 132.2 ($C^{4''}$) 133.9 (C^{9}), 134.3 ($C^{1''}$), 134.6 (C^{5a}), 137.5 ($C^{1'}$), 140.1 (C^{9a}), 145.8 (C^{2}), 148.8 (C^{11a}), 157.3 (C^{7}), 165.9 (-CONH-), 190.7 (C^{5}), not detected ($C^{4'}$)

(*S*)-N-{5-[7-(2,3-Dihydroxy-propoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-2-ylamino]-2-fluoro-phenyl}-benzamide (16e)



The compound is synthesized according to the general procedure E.

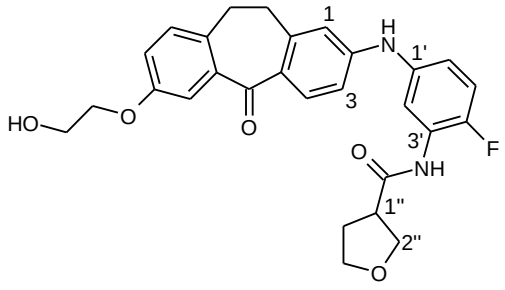
0.075 g (0.13 mmol) N-{5-[7-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-2-fluoro-phenyl}-benzamide (**16c**), 0.15 g (0.79 mmol) p-toluenesulfonic acid*H_2O, 40 ml methanol, 10 ml water. Reaction time: 3 h.

$C_{31}H_{27}FN_2O_5$ (Mr = 526.57)

Yield	>66 mg (0,13 mmol, > 95 %)
HRMS $[M+H]^+$	527.197433 (calc. 527.19768)

IR (ATR)	3352, 2922, 2358, 1644, 1593, 1524, 1502, 1480, 1422, 1338, 1276, 1154, 1092, 1044, 927, 856, 806, 785, 704, 685, 613, 589, 478 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 3.02 (s, 4 H, -CH_2-CH_2-), 3.44 (t, 2 H, J = 5.6 Hz, Diol), 3.70-4.10 (m, 3 H, Diol), 4.67 (t, 1 H, J = 5.7 Hz, -OH), 4.95 (d, 1 H, J = 4.80 -OH), 6.84 (d, 1 H, J = 2.2 Hz, C^{1}-H), 6.91-7.12 (m, 3 H, $C^{6'/3/5'}$-H), 7.16-7.33 (m, 2 H, $C^{2'/8}$-H), 7.41 (d, 1 H, J = 2.8 Hz, C^{6}-H), 7.46-7.67 (m, 4 H, $C^{9/4/3''/5''}$-H), 7.87-8.08 (m, 3 H, $C^{2''/6''/4''}$-H) 8.85 (s, 1 H, -NH-), 10.12 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 33.6 (C^{10}), 36.4 (C^{11}), 63.1 (Diol), 70.2 (Diol), 70.3 (Diol), 112.9 (C^{3}), 114.3 (C^{6}), 115.4 (C^{1}), 116.6 (d, J = 20.6 Hz, $C^{5'}$), 118.3 (d, 2 C, J = 5.7 Hz, $C^{2'/6'}$), 119.2 (C^{8}), 126.6 (d, J = 13.3 Hz, $C^{3'}$), 127.8 (C^{4a}), 128.2 (2 C, $C^{3''/5''}$), 128.8 (2 C, $C^{2''/6''}$), 130.6 (C^{4}), 132.2 (C^{9}), 133.9 ($C^{4''}$), 134.3 ($C^{1''}$), 134.6 (C^{5a}), 137.5 ($C^{1'}$) 140.0 (C^{9a}), 145.9 (C^{2}), 148.8 (C^{11a}), 157.6 (C^{7}), 165.8 (-CONH-), 190.7 (C^{5}), not detected ($C^{4'}$)

Tetrahydro-furan-3-carboxylic acid-{2-fluor-5-[7-(2-hydroxy-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16f)



The compound is synthesized according to the general procedure D.

0.67 g (1.9 mmol) acetic acid 2-(8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-yloxy)-ethyl ester (**15b**), 0.45 g (2.0 mmol)

tetrahydro-furan-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (**14o**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0,2 g (0.42 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.0 g (8.9 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

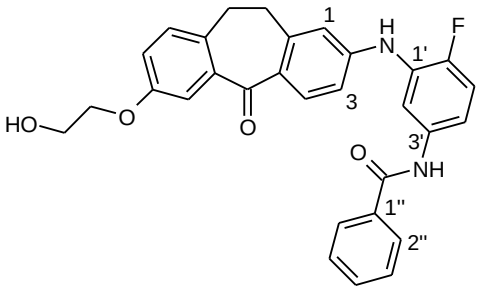
Reaction time: 3 h. Temperature: Reflux. Extraction wit diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 6+4). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{28}H_{27}N_2O_5$ (Mr = 490.54)

Yield	2 % (Losses by recrystallization)
HRMS $[M+Na]^+$	513.1801 (calc. 513.17962)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.06 (q, 2 H, J = 6.8 Hz, $C^{5''}$), 3.01 (s, 4 H, $-CH_2-CH_2-$), partially covered by H_2O (m, 1 H, $C^{1''}$), 3.64-4.06 (m, 8 H, OH-C<u>H</u>$_2$-C<u>H</u>$_2$-O- / $C^{2''/4''}$-H), 4.86 (t, 1 H, J = 5.6 Hz, -OH), 6.81 (d, 1 H, J = 1.9 C^1-H), 6.87-7.09 (m, 3 H, $C^{6'/3/5'}$-H), 7.13-7.27 (m, 2 H, $C^{2'/9}$-H) 7.39 (d, 1 H, J_1 = 2.7 Hz, C^6-H), 7.82 (dd, 1 H, J_1 = 2.3 Hz, J_2 = 6.9 Hz, C^8-H), 7.96 (d, 1 H, J = 8.7 Hz, C^4-H) 8.79 (s, 1 H, -NH-), 9.83 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 30.3 ($C^{5''}$), 33.5 (C^{10}), 36.3 (C^{11}), 44.7 ($C^{1''}$), 59.9 (OH-<u>C</u>H$_2$-CH$_2$-O-), 68.1 ($C^{4''}$), 70.0 (OH-CH$_2$-<u>C</u>H$_2$-O-), 70.7 ($C^{2''}$), 112.8 (C^3), 114.3 (C^6) 115.4 (C^1), 116.0 (d, J = 1.9 Hz, $C^{2'}$), 116.2 (d, J = 22.5 Hz, $C^{5'}$), 116.7 (d, J = 7.2 Hz, $C^{6'}$), 119.1 (C^8), 126.9 (d, J = 13.0 Hz, $C^{3'}$), 127.7 (C^{4a}), 130.6 (C^4), 133.9 (C^9), 134.5 (C^{5a}), 137.5 (d, J = 2.7 Hz, $C^{1'}$), 140.1 (C^{9a}), 145.8 (C^2), 148.9 (C^{11a}), 149.2 ($C^{4'}$) 157.5 (C^7), 172.7 (-CONH-), 190.6 (C^5)

N-{4-Fluoro-3-[7-(2-hydroxy-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]-cycloheptен-2-ylamino]-phenyl}-benzamide (16g)



The compound is synthesized according to the general procedure D.

0.67 g (1.9 mmol) acetic acid 2-(8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-yloxy)-ethyl ester (**15b**), 0.45 g (2.0 mmol) N-(3-amino-4-fluoro-phenyl)-benzamide (**14b**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.0 g (8.9 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

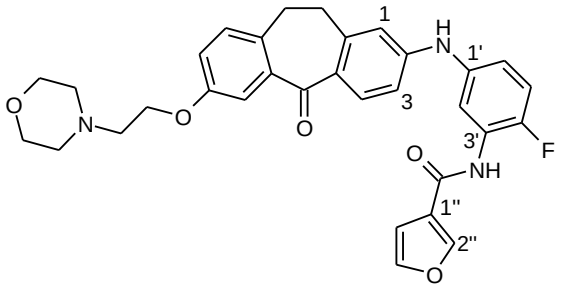
Reaction time: 3 h. Temperature: Reflux. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 6+4). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{30}H_{25}FN_2O_4$ (Mr = 496.54)

Yield	2 % (Losses by recrystallization)
HRMS $[M+Na]^+$	519.168788 (calc. 519.16906)
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 3.03 (s, 4 H, -CH_2-CH_2-), 3.77 (t, 2 H, J = 5.1 Hz, HO-C<u>H$_2$</u>-CH_2-O-), 4.00 (t, 2 H, J = 4.9 Hz, HO-CH_2-C<u>H$_2$</u>-O-), 4.86 (s, 1 H, -OH), 6.80 (d, 1 H, J = 1.9 Hz, C^1-H), 6.92 (dd, 1 H, J_1 = 1.8 Hz, J_2 = 8.8 Hz, C^3-H), 7.05 (dd, 1 H, J_1 = 2.8 Hz, J_2 = 8.4 Hz, $C^{4'}$-H), 7.20-7.32 (m, 2 H, $C^{6'/8}$-H), 7.39 (d, 1 H, J = 2.7 Hz, C^6-H), 7.45-7.60 (m, 4 H, $C^{3''/9/4/4''}$-H), 7.88-8.00 (m, 4 H, $C^{3''/5''/2''/6''}$-H), 8.67 (s, 1 H, -NH-), 10.28 (s, 1 H, -CONH-)

Furan-3-carboxylic acid {2-fluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptен-2-ylamino]-phenyl}-amide (16h)



The compound is synthesized according to the general procedure D.

0.75 g (2.0 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy-10,11-dihydrodibenzo[a,d]-cyclohepten-5-one (**15d**), 0.50 g (2.3 mmol) furan-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amid (**14i**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.15 g (0.31 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.10 g (10.2 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

Reaction time: 3 h. Temperature: Reflux. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 5+95). The product is further purified by recrystallization (ethyl acetate / hexane).

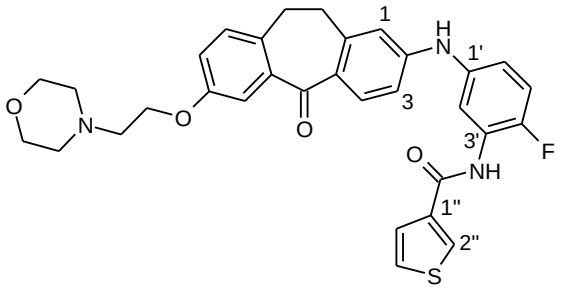
$C_{32}H_{30}FN_3O_5$ (Mr = 555.61)

Yield	0.05 g (4 %)
Purity	86 %
HRMS $[M+H]^+$	556.224635 (calc. 556.22423)
IR (ATR)	2920, 2851, 1660, 1568, 1525, 1495, 1454, 1353, 1260, 1212, 1112, 856, 821, 856, 821, 782, 748, 600, 451, 412 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): partially covered by DMSO (t, 4 H, $C^{2/6}_{Morpholinyl}$-H), 2.68 (t, 2 H, J = 5.6 Hz, -N-$C\underline{H_2}$-CH_2-O-), 2.96-3.08 (m, 4 H, -CH_2-$C\underline{H_2}$-), 3.56 (t, 4 H, J = 4.5 Hz, $C^{3/5}_{Morpholinyl}$-H), 4.10 (t, 2 H, J = 5.6 Hz, -N-CH_2-CH_2-O-), 6.83 (d, 1 H, J = 1.8 Hz, C^1-H), 6.91-7.09 (m, 7 H, $C^{6'/3/5'/5''}$-H), 7.18-7.28 (m, 2 H,

$C^{2'/9}$-H), 7.39 (d, 1 H, J = 2.8 Hz, C^{6}-H), 7.50 (dd, 1 H, J_1 = 3.0 Hz, J_2 = 6.5 Hz, C^{8}-H), 7.75-7.82 (m, 1 H, $C^{4''}$-H), 7.97 (d, 1 H, C^{4}-H, J = 8.8 Hz), 8,41 (s, 1 H, $C^{2''}$-H), 8.83 (s, 1 H, -NH-), 9.82 (s, 1 H, -CONH-)

^{13}C-NMR (DMSO-*d6*) δ in ppm (*f* = 50 MHz): 33.5 (C^{10}), 36.3 (C^{11}), 54.0 (2 C, $C^{2/6}_{Morpholinyl}$), 57.3 (-N-$\underline{C}H_2$-CH_2-O-), 65.9 (-N-CH_2-$\underline{C}H_2$-O-), 66.5 (2 C, $C^{3/5}_{Morpholinyl}$), 109.6 ($C^{5''}$), 112.9 (C^{3}), 114.3 (C^{6}), 115.5 (C^{1}), 116.6 (d, J = 21,3 Hz, $C^{5'}$), 118.1 (d, not clearly visible, $C^{6'}$), 118.2 (d, not clearly visible, $C^{2'}$), 119.1 (C^{8}), 122.7 ($C^{1''}$), 126.1 (d, J = 13.3 Hz, $C^{3'}$), 127.8 (C^{4a}), 130.6 (C^{4}), 133.9 (C^{9}), 134.6 (C^{5a}), 137.5 (d, J = 2,3 Hz, $C^{1'}$), 140.1 (C^{9a}), 144.6 ($C^{4''}$), 145.8 (C^{2}), 146.6 ($C^{2''}$), 148.8 (C^{11a}), 157.3 (C^{7}), 160.8 (-CONH-), 190.6 (C^{5}), not detected ($C^{4'}$)

Thiophene-3-carboxylic acid {2-fluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16i)



The compound is synthesized according to the general procedure D.

0.30 g (0.81 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.22 g (0.93 mmol) thiophene-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (**14l**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.5 g (13.4 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

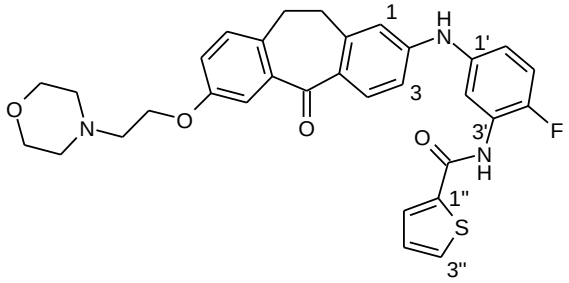
Reaction time: 30 min. Temperature 100°C. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 5+95). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{32}H_{30}FN_3O_4S$ (Mr = 571.68)

Yield	13 %
Melting point	122°C
HRMS $[M+H]^+$	572.201686 (calc. 572.20138)
IR (ATR)	2921, 2359, 1660, 1567, 1526, 1354, 1322, 1260, 1212, 1148, 1112, 1033, 852, 814, 783 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.59 (t, 4 H, J = 4.6 Hz, $C^{2/6}_{Morpholinyl}$-H), 2.81 (t, 2 H, J = 5.6 Hz, N-C$\underline{H_2}$-CH_2-), 2.99-3.20 (m, 4 H, -CH_2-CH_2-), 3.74 (t, 4 H, J = 4.6 Hz, $C^{3/5}_{Morpholinyl}$-H), 4.17 (t, 2 H, J = 5.6 Hz, N-CH_2-C$\underline{H_2}$-), 6.13 (s, 1 H, -NH-), 6.74 (d, 1 H, J = 2.4 Hz, C^1-H), 6.82-7.02 (m, 3 H, $C^{6'/3/5'}$-H), 7.03-7.18 (m, 2 H, $C^{2'/8}$-H), 7.38-7.46 (m, 1 H, $C^{4''}$-H), 7.47-7.54 (m, 1 H, C^9-H), 7.59 (d, 1 H, J = 2.5 Hz, C^6-H), 7.83-7.97 (m, 1 H, -CONH-), 8.02 (dd, 1 H, J_1 = 1.3 Hz, J_2 = 2.8 Hz, $C^{2''}$-H), 8.13 (d, 1 H, J = 8.7 Hz, C^4-H), 8.31 (dd, 1 H, J_1 = 2.5 Hz, J_2 = 6.8 Hz, $C^{5''}$-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 50 MHz): 33.8 (C^{10}), 36.3 (C^{11}), 53.9 (2 C, $C^{2/6}_{Morpholinyl}$), 57.5 (-N-$\underline{C}H_2$-CH_2-O-), 65.8 (-N-CH_2-$\underline{C}H_2$-O-), 66.8 (2 C, $C^{3/5}_{Morpholinyl}$), 113.2 (C^6), 114.5 (s, $C^{2'}$), 114.6 (C^3), 115.0 (C^1), 115.4 (C^{4a}), 116.2 (d, J = 7.2 Hz, $C^{6'}$), 119.5 (C^8), 125.9 (C^9), 127.0 (d, J = 11.0 Hz, $C^{5'}$), 127.1 ($C^{5''}$), 129.3 (d, J = 3.1 Hz, $C^{3'}$), 129.2 ($C^{4''}$), 129.9 (C^4), 134.0 ($C^{2''}$), 134.6 (C^{5a}), 137.1 (C^{9a}), 137.2 (s, $C^{1'}$), 139.9 ($C^{1''}$), 145.4 (C^2), 147.8 (C^{11a}), 148.5 (d, J = 238.1 Hz, $C^{4'}$), 157.2 (C^7), 160.8 (-CONH-), 191.8 (C^5)

Thiophene-2-carboxylic acid {2-fluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16j)



The compound is synthesized according to the general procedure D.

0.30 g (0.81 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.19 g (0.81 mmol) thiophene-3-carboxylic acid (5-amino-2-fluoro-phenyl)-amid (**14m**), 0.010 g (0.045 mmol) $Pd(OAc)_2$, 0.046 g (0.097 mmol) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-biphenyl, 0.266 g (2.37 mmol) KO*tert*Bu, 7.6 ml toluene, 1.5 ml *tert*-BuOH.

Reaction time: 30-60 min. Temperature 100°C.

The crude product is purified by column chromatography (SiO_2, DCM/ethanol 95+5).

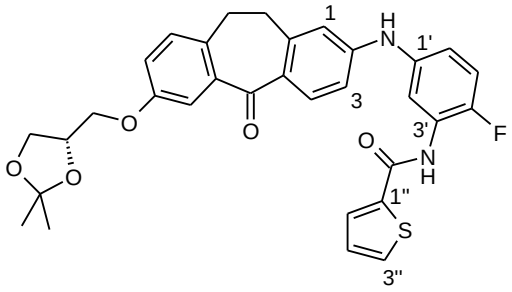
$C_{32}H_{30}FN_3O_4S$ (Mr = 571.68)

Yield	0.36 g crude product (80 %)
Melting point	161°C
HRMS $[M+H]^+$	572.201350 (calc. 572.201382)
IR (ATR)	3306, 2854, 1568, 1529, 1262, 1112, 852, 716 cm^{-1}
^{1}H-NMR (DMSO-*d6*)*	δ in ppm (*f* = 400 MHz): 2.38-2.55 (m, 4 H + DMSO, $C^{2/6}_{Morpholinyl}$), 2.68 (t, 2 H, J = 5.6 Hz, -N-$\underline{C}H_2$-CH_2-O-), 2.95-3.08 (m, 4 H, -CH_2-CH_2-), 3.56 (t, 4 H, J = 4.6 Hz, $C^{3/5}_{Morpholinyl}$), 4.10 (t, 2 H, J = 5.6 Hz, -N-CH_2-$\underline{C}H_2$-O-), 6.83 (d, 1 H, J = 1.9 Hz, C^1-H), 6.96 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 8.9 Hz, C^3-H), 7.17-7.10 (m, 2 H, $C^{5'/6'}$-H), 7.17-7.31 (m, 3 H, $C^{2'/8/9}$), 7.39 (d, 1 H, J = 2.8 Hz, C^6-H), 7.46 (dd, 1 H, J_1 = 2.5 Hz, J_2

= 6.5 Hz, $C^{4''}$-H), 7.87 (d, 1 H, J = 4.8 Hz, $C^{5''}$-H), 7.97 (d, 1 H, J = 8.7 Hz, C^{4}-H), 8.02 (d, 1 H, J = 3.2 Hz, $C^{3''}$-H), 8.83 (s, 1 H, -CONH-), 10.12 (s, 1 H, -NH-)

^{13}C-NMR (DMSO-*d6*) δ in ppm (*f* = 100 MHz): 33.2 (C^{10}), 35.9 (C^{11}), 53.6 (2 C, $C^{2/6}_{Morpholinyl}$), 57.0 (-N-$\underline{C}H_2$-CH_2-O-), 65.6 (-N-CH_2-$\underline{C}H_2$-O-), 66.2 (2 C, $C^{3/5}_{Morpholinyl}$), 112.5 (C^{6}), 114.0 (C^{3}), 115.1 (C^{1}), 116.3 (d, J = 21,1 Hz, $C^{5'}$), 118.0 (d, partially covered, $C^{6'}$), 118.1 (d, partially covered, $C^{2'}$), 118.7 (C^{8}), 125.7 (d, J = 13.1 Hz, $C^{3'}$), 127.5 (C^{4a}), 128.1 (C^{9}), 129.7 ($C^{4''}$), 130.2 (C^{4}), 132.1 ($C^{3''}$), 133.5 ($C^{5''}$), 134.2 (C^{5a}), 137.2 (d, J = 2,2 Hz, $C^{1'}$), 139.0 (C^{9a}), 139.7 ($C^{1''}$), 145.4 (C^{2}), 148.4 (C^{11a}), 150.8 (d, J = 239.9 Hz, $C^{4'}$), 156.9 (C^{7}), 160.0 (-CONH-), 190.3 (C^{5})

(*S*)-Thiophene-2-carboxylic acid {5-[7-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-2-fluoro-phenyl}-amide (16k)



The compound is synthesized according to the general procedure D.

(*S*)-2-chloro-7-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15e**), 0.10 g (0.43 mmol) thiophene-2-carboxylic acid (5-amino-2-fluoro-phenyl)-amide (**14m**), 0.005 g (0.023 mmol) $Pd(OAc)_2$, 0.024 g (0.050 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 0.14 g (1.25 mmol) KO*tert*Bu, 4 ml toluene, 0.8 ml *tert*-BuOH.

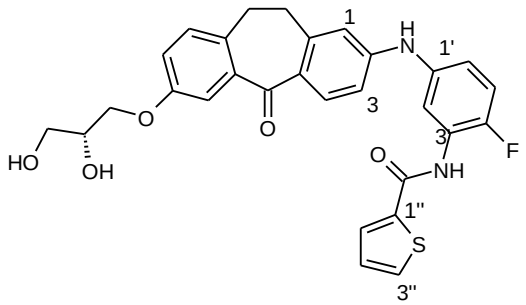
Reaction time: 15-30 min. Temperature: 100°C.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether(60-90)/ethyl acetate 6+4).

$C_{32}H_{29}FN_2O_5S$ (Mr = 572.66)

Yield	> 60 mg (26 %)
Melting point	123°C
HRMS $[M+Na]^+$	595.167768 (calc. 595.167342)
IR (ATR)	3308, 2931, 1567, 1531, 1494, 1269, 1210, 1050, 847, 715 cm^{-1}
^{1}H-NMR (DMSO-*d6*)*	δ in ppm (*f* = 400 MHz): 1.30 (s, 3 H, $-CH_3$), 1.35 (s, 3 H, $-CH_3$), 2.91-3.11 (m, 4 H, $-CH_2-CH_2-$), 3.69-3.82 (m, 1 H, Dioxolane), 3.95-4.12 (m, 3 H, Dioxolane), 4.33-4.46 (m, 1 H, Dioxolane), 6.84 (d, 1 H, J = 1.5 Hz, C^1-H), 6.96 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 8.7 Hz, C^3-H), 7.02-7.12 (m, 2 H, $C^{5'/6'}$-H), 7.16-7.33 (m, 3 H, $C^{2'/8/9}$), 7.40 (d, 1 H, J = 2.5 Hz, C^6-H), 7.46 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 6.7 Hz, $C^{4''}$-H), 7.87 (d, 1 H, J = 4.8 Hz, $C^{5''}$-H), 7.98 (d, 1 H, J = 8.8 Hz, C^4-H), 8.02 (d, 1 H, J = 3.6 Hz, $C^{3''}$-H), 8.84 (s, 1 H, -CONH-), 10.12 (s, 1 H, -NH-)

(*R*)-N-{5-[7-(2,3-Dihydroxy-propoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-2-ylamino]-2-fluoro-phenyl}-benzamide (16l)



The compound is synthesized according to the general procedure E.

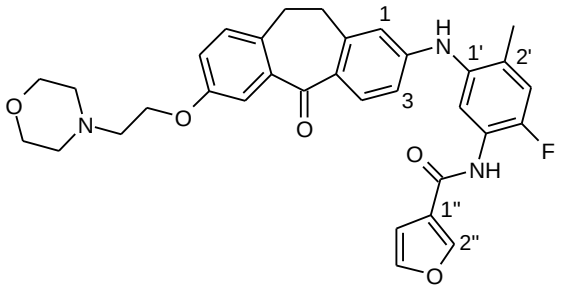
0,06 g (0,10 mmol) (*S*)-thiophene-2-carboxylic acid {5-[7-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-2-fluor-phenyl}-amid (**16k**), 0.1 g (0.53 mmol) p-toluenesulfonic acid*H_2O, 6 ml methanol, 1.5 ml water.

Reaction time: 90 min.

$C_{29}H_{25}FN_2O_5S$ (Mr = 532.60)

Yield	84 %
Melting point	amorphous solid
HRMS $[M+Na]^+$	555.136449 (calc. 555.136042)
IR (ATR)	3307, 1568, 1537, 1352, 1284, 850, 701 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.91-3.14 (m, 4 H, -CH_2-CH_2-), 3.45 (t, 2 H, J = 5.3 Hz, Diol), 3.72-4.15 (m, 3 H, Diol), 4.66 (t, 1 H, J = 5.4 Hz, -OH), 4.94 (d, 1 H, J = 4.8 -OH), 6.85 (s, 1 H, C^1-H), 6.97 (d, 1 H, J = 8.6 Hz, C^3-H), 7.02-7.13 (m, 2 H, $C^{6'/5'}$-H), 7.17-7.32 (m, 3 H, $C^{2'/8/9}$-H), 7.41 (s, 1 H, C^6-H), 7.46 (d, 1 H, J = 6.1 Hz, $C^{4''}$-H), 7.88 (d, 1 H, J = 4.8 Hz, $C^{5''}$-H), 7.99 (d, 1 H, J = 8.8 Hz, C^4-H), 8.03 (d, 1 H, J = 3.3 Hz, $C^{3''}$-H), 8.84 (s, 1 H, -NH-), 10.13 (s, 1 H, -CONH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.2 (C^{10}), 35.9 (C^{11}), partially covered by DMSO ($C^{2/6}_{Morpholinyl}$), 62.7 (-N-<u>C</u>H_2-CH_2-O-), 69.8 (-N-CH_2-<u>C</u>H_2-O-), 69.9 ($C^{3/5}_{Morpholinyl}$), 112.5 (C^6), 114.0 (C^3), 115.1 (C^1), 116.3 (d, J = 21.0 Hz, $C^{5'}$), 118.1 (s, 2 C, $C^{2'/6'}$), 118.8 (C^8), 125.7 (d, J = 13.8 Hz, $C^{3'}$), 127.5 (C^{4a}), 128.1 (C^9), 129.7 ($C^{4''}$), 130.2 (C^4), 132.1 ($C^{3''}$), 133.5 ($C^{5''}$), 134.2 (C^{5a}), 137.2 (C^{9a}), 139.0 (s, $C^{1'}$), 139.6 ($C^{1''}$), 145.5 (C^{11a}), 148.4 (C^2), 150.8 (d, J = 239.9 Hz, $C^{4'}$), 157.2 (C^7), 160.0 (-CONH-), 190.3 (C^5)

Furan-3-carboxylic acid {2-fluoro-4-methyl-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptен-2-ylamino]-phenyl}-amide (16m)



The compound is synthesized according to the general procedure D.

0.27 g (0.73 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.17 g (0.73 mmol) furan-3-carboxylic acid (5-amino-2-fluoro-4-methyl-phenyl)-amid (**14k**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-biphenyl, 1 g (8.9 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

Reaction time: 30 min. Temperature: 100°C. Extraction with ethyl acetate.

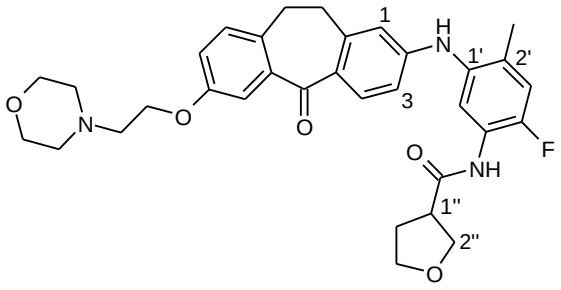
The crude product is purified by automated column chromatography (SiO_2, methanol/ethyl acetate 10+90). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{33}H_{32}FN_3O_5$ (Mr = 569.64)

Yield	10 %
Melting point	134°C
HRMS $[M+H]^+$	570.239723 (calc. 570.23988)
IR (ATR)	2921, 2359, 2342, 1661, 1568, 1520, 1455, 1410, 1354, 1320, 1271, 1195, 1162, 1114, 1033, 874, 826 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.22 (s, 1 H, $-CH_3$), 2.59 (t, 4 H, J = 4.6 Hz, $C^{2/6}_{Morpholinyl}$-H), 2.82 (t, 2 H, J = 5.7 Hz, -N-$C\underline{H_2}$-CH_2-O-), 2.99-3.22 (m, 4 H, $-CH_2-CH_2-$), 3.74 (t, 4 H, J = 4.6 Hz, $C^{3/5}$-$_{Morpholinyl}$-H), 4.17 (t, 2 H, J = 5.6 Hz, -N-CH_2-$C\underline{H_2}$-O-), 5.69 (s, 1 H, -NH-),

6.51 (d, 1 H, J = 2.3 Hz, $C^{6'}$-H), 6.67 (dd, 1 H, J_1 = 2.3 Hz, J_2 = 8.8 Hz, $C^{3'}$-H), 6.72 (d, 1 H, J = 1.2 Hz, C^{1}-H), 6.92-7.16 (m, 3 H, $C^{3/5''/8}$-H), 7.51 (t, 1 H, J = 1.7 Hz, $C^{4''}$-H), 7.54-7.63 (m, 2 H, $C^{6/2''}$-H), 8.05 (s, 1 H, -CONH-), 8.13 (d, 1 H, J = 8.8 Hz, C^{9}-H), 8.32 (d, 1 H, J = 7.6 Hz, C^{4}-H)

Tetrahydro-furan-3-carboxylic acid {2-fluoro-4-methyl-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16n)



The compound is synthesized according to the general procedure D.

0.27 g (0.73 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.23 g (0.94 mmol) tetrahydro-furan-3-carboxylic acid (5-amino-2-fluoro-4-methyl-phenyl)-amide (**14q**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-$2'$-,$4'$-,$6'$-triisopropyl-biphenyl, 1.0 g (8.9 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

Reaction time: 30 min. Temperature: 100°C. Extraction with diethylether.

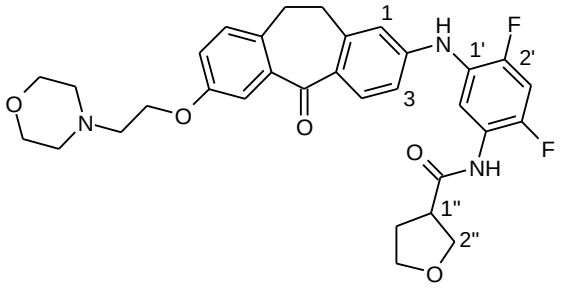
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 2+8). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{33}H_{36}FN_3O_5$ (Mr = 573.67)

Yield	31 %
Melting point	109°C
HRMS $[M+H]^+$	574.27118 (calc. 574.270633)

IR (ATR)	3290, 2858, 1681, 1567, 1520, 1495, 1454, 1409, 1354, 1322, 1268, 1194, 1148, 1113, 1053, 854, 783 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.12-2.33 (m, 5 H, -CH_3 / $C^{5''}$-H), 2.58 (t, 4 H, J = 4.6 Hz, $C^{2/6}_{Morpholinyl}$-H), 2.81 (t, 2 H, J = 5.7 Hz, -N-C$\underline{H_2}$-CH_2-O-), 3.00-3.11 (m, 5 H, $C^{1''}$ / -CH_2-CH_2-), 3.73 (t, 4 H, J = 4.5 Hz, $C^{3/5}_{Morpholinyl}$ -H), 3.82-4.10 (m, 4 H, $C^{4''/2''}$-H), 4.18 (t, 2 H, J = 5.7 Hz, -N-CH_2-C$\underline{H_2}$-O-) 5.74 (s, 1 H, -NH-), 6.47 (s, 1 H, C^{1}-H), 6.62 (dd, 1 H, J_1 = 2.3 Hz, J_2 = 9.0 Hz, C^{3}-H), 6.92-7.15 (m, 3 H, $C^{3'/6'/8}$-H), 7.57 (d, 1 H, J = 2.3 Hz, C^{6}-H), 7.66 (s, 1 H, -CONH-), 8.02-8.26 (m, 2 H, $C^{9/4}$-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 17.7 (-CH_3), 30.5 ($C^{5''}$), 33.9 (C^{10}), 36.4 (C^{11}), 46.6 ($C^{1''}$), 54.0 (2 C, $C^{2/6}_{Morpholinyl}$), 57.6 (-N-$\underline{C}H_2$-CH_2-O-), 65.9 (-N-CH_2-$\underline{C}H_2$-O-), 66.9 (2 C, $C^{3/5}_{Morpholinyl}$), 68.1 ($C^{4''}$), 70.9 ($C^{2''}$), 112.5 (d, J = 10.5 Hz, $C^{6'}$), 113.7 (C^{6}), 113.9 (C^{3}), 115.0 (C^{1}), 115.2 (C^{8}), 118.5 (d, J = 10.2 Hz, $C^{3'}$), 118.6 (C^{9}), 124.4 (d, J = 12.4 Hz, $C^{5'}$), 128.6 (C^{4a}), 129.9 (d, J = 7.2 Hz, $C^{2'}$), 134.2 (C^{4}), 134.5 (d, J = 11.6 Hz, $C^{1'}$), 134.7 (C^{5a}), 140.1 (C^{9a}), 145.6 (C^{11a}), 149.2 (C^{2}), 149.9 (d, J = 239.2 Hz, $C^{4'}$) 157.4 (C^{7}), 172.0 (-CONH-), 191.9 (C^{5})

Tetrahydro-furan-3-carboxylic acid {2,4-difluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16o)



The compound is synthesized according to the general procedure D.

0.47 g (1.3 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.30 g (1.3 mmol) tetrahydro-furan-3-carboxylic (5-amino-2,4-difluoro-phenyl)-amide (**14p**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-biphenyl, 1.0 g (8.9 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

Reaction time: 30 min. Temperature 100°C. Extraction with ethyl acetate.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 2+8). The product is further purified by recrystallization (ethyl acetate / hexane).

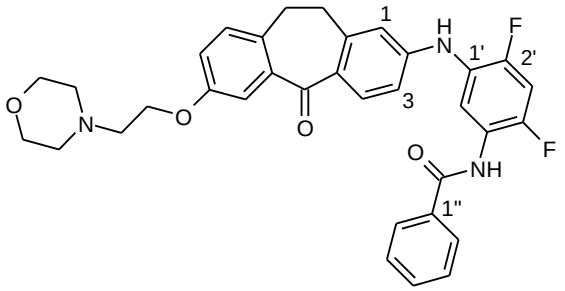
$C_{32}H_{33}F_2N_3O_5$ (Mr = 577.63)

Yield	36 %
Melting point	162°C
HRMS $[M+H]^+$	578.245571 (calc. 578.2461)
IR (ATR)	3270, 2951, 2850, 1671, 1604, 1628, 1526, 1495, 1456, 1407, 1351, 1328, 1269, 1196, 1147, 1113, 1062, 955, 922, 878, 858, 834, 817, 781, 750, 691, 601, 527 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 2.17-2.34 (m, 2 H, $C^{5''}$-H), 2.54-2.66 (m, 4 H, $C^{2/6}{}_{Morpholinyl}$-H), 2.83 (t, 2 H, J = 5.2 Hz, -N-C$\underline{H_2}$-CH_2-O-), 3.05-3.17 (m, 4 H, -CH_2-CH_2-), 3.66-3.80 (m, 4 H, $C^{3/5}{}_{Morpholinyl}$-H), 3.82-3.91

(m, 1 H, $C^{1''}$-H), 3.92-4.23 (m, 6 H, $C^{4''/2''}$-H / -N-CH_2-CH_2-), 5.95 (s, 1 H, -NH-), 6.78 (s, 1 H, C^{1}-H), 6.90 (d, 1 H, J = 8.6 Hz, C^{3}-H), 6.93-7.04 (m, 2 H, $C^{3'/8}$-H), 7.12 (d, 1 H, J = 8.3 Hz, C^{9}-H), 7.58 (s, 1 H, C^{6}-H), 7.65 (s, 1 H, -CONH-), 8.15 (d, 1 H, J = 8.8 Hz, C^{4}-H), 8.37 (t, J = 8.3 Hz 1 H, $C^{6'}$-H)

^{13}C-NMR ($CDCl_3$) δ in ppm (*f* = 100 MHz): 30.5 ($C^{5''}$), 33.9 (C^{10}), 36.3 (C^{11}), 46.6 ($C^{1''}$), 54.0 (2 C, $C^{2/6}_{Morpholinyl}$), 57.6 (-N-CH_2-CH_2-O-), 65.9 (-N-CH_2-CH_2-O-), 66.9 (2 C, $C^{3/5}_{Morpholinyl}$), 68.1 ($C^{4''}$), 70.8 ($C^{2''}$), 104.1 (t, J = 24.7 Hz, $C^{3'}$), 113.6 (C^{6}), 115.1 (C^{3}), 115.2 (C^{1}), 115.4 ($C^{6'}$), 119.7 (C^{8}), 122.5 (dd, J_1 = 3.6 Hz, J_2 = 10.9 Hz, $C^{5'}$), 125.1 (dd, J_1 = 2.9 Hz, J_2 = 12.4 Hz, $C^{1'}$), 130.0 (C^{4a}), 130.1 (C^{9}), 134.0 (C^{4}), 134.7 (C^{5a}), 139.9 (C^{9a}), 145.4 (C^{11a}), 146.9 (C^{2}), 157.4 (C^{7}), 172.1 (-CONH-), 192.2 (C^{5}), not detected ($C^{2'/4'}$)

N-{2,4-Difluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-benzamide (16p)



The compound is synthesized according to the general procedure D.

0.61 g (1.6 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0.53 g (2.1 mmol) N-(5-amino-2,4-difluoro-phenyl)-benzamide (**14d**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.3 g (11.6 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

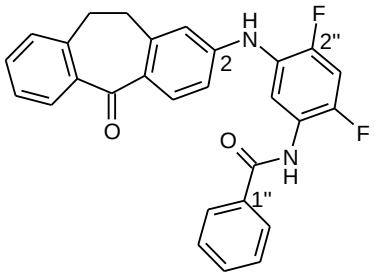
Reaction time: 30 min. Temperature 100°C. Extraction with diethyl ether.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 2+8). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{34}H_{31}F_2N_3O_4$ (Mr = 583.64)

Yield	17 %
Melting point	83°C
HRMS $[M+H]^+$	584.235069 (calc. 584.23554)
IR (ATR)	2922, 2359, 1661, 1582, 1532, 1435, 1355, 1269, 1205, 1148, 1114, 1033, 855, 784, 709, 650, 530 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.59 (t, 4 H, J = 4.6 Hz, $C^{2/6}_{Morpholinyl}$-H), 2.81 (t, 2 H, J = 5.6 Hz, N-C<u>H$_2$</u>-CH$_2$-), 2.98-3.28 (m, 4 H, -CH$_2$-CH$_2$-), 3.74 (t, 4 H, J = 4.5 Hz, $C^{3/5}_{Morpholinyl}$ -H), 4.17 (t, 2 H, J = 5.2 Hz, N-CH$_2$-C<u>H$_2$</u>-), 6.96 (s, 1 H, -NH-), 6.43 (d, 1 H, J = 2.4 Hz, C^1-H), 6.88-7.16 (m, 4 H, $C^{3'/3/8/9}$-H), 7.42-7.66 (m, 4 H, $C^{6''/3''/4''/5''}$-H), 7.81-7.93 (m, 2 H, $C^{6''/2''}$-H), 7.97 (s, 1 H, -CONH-), 8.16 (d, 1 H, J = 8.5 Hz, C^4-H), 8.57 (t, 1 H, J = 8.57 Hz, $C^{6'}$-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 50 MHz): 33.8 (C^{10}), 36.2 (C^{11}), 53.9 (2 C, $C^{2/6}_{Morpholinyl}$), 57.5 (-N-<u>C</u>H$_2$-CH$_2$-O-), 65.8 (-N-CH$_2$-<u>C</u>H$_2$-O-), 66.7 (2 C, $C^{3/5}_{Morpholinyl}$), 104.0 (t, J = 24.6 Hz, $C^{3'}$), 113.6 (C^6), 114.9 (C^3), 115.0 (C^1), 115.2 (not clearly visible, $C^{6'}$), 119.5 (C^8), 122.7 (dd, J_1 = 3.8 Hz, J_2 = 11.0 Hz, $C^{5'}$), 125.1 (dd, J_1 = 3.4 Hz, J_2 = 11.8 Hz, $C^{1'}$), 127.0 (2 C, $C^{2''/6''}$), 128.8 (2 C, $C^{3''/5''}$), 129.9 (C^9), 129.9 (C^{4a}), 132.2 (C^4), 133.9 ($C^{4''}$) 134.1 (C^{5a}), 134.6 (C^{9a}), 139.8 ($C^{1''}$), 145.3 (C^{11a}), 146.8 (C^2), 157.2 (C^7), 165.3 (-CONH-), 192.0 (C^5), not detected ($C^{2'/4'}$)

N-[2,4-Difluoro-5-(5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino)-phenyl]-benzamide (16q)



The compound is synthesized according to the general procedure D.

0.42 g (1,7 mmol) 2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15f**), 0.43 g (1,7 mmol) N-(5-amino-2,4-difluoro-phenyl)-benzamide (**14d**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 1.64 g (14.6 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

Reaction time: 60 min. Temperature: 100°C. Extraction with diethyl ether.

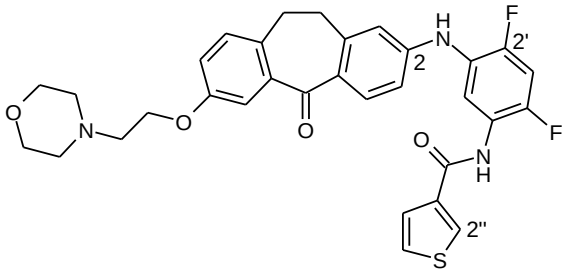
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{28}H_{20}F_2N_2O_2$ (Mr = 454.48)

Yield	20 mg (2,6 %)
HRMS $[M+H]^+$	455.156477 (calc. 455.156561)
IR (ATR)	3290, 1597, 1532, 1291, 1271, 756, 691, 534 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 2.89-3.21 (m, 4 H, -CH_2-CH_2-), 5.88 (s, 1 H, -NH-), 6.76 (s, 1 H, C^1-H), 6.85 (d, 1 H, J = 8.8 Hz, C^3-H), 6.94 (t, 1 H, J = 10.1 Hz, $C^{3'}$-H), 7.12 (d, 1 H, J = 7.3 Hz, C^9-H), 7.21-7.37 (m, 2 H, $C^{6'/7}$-H), 7.38-7.55 (m, 3 H, $C^{3''/5''/4}$-H), 7.73-7.85 (m, 2 H, $C^{8/4''}$-H), 7.85-7.98 (m, 2 H, $C^{2''/6''}$-H), 8.10 (d, 1 H, J = 8.6 Hz, C^6-H), 8.48 (t, 1 H, J = 8.2 Hz, -CONH-)

^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 33.7 (C^{10}), 35.1 (C^{11}), 103.1 (t, J = 24.4 Hz, $C^{3'}$), 112.8 (C^{3}), 114.2 ($C^{6'}$), 114.2 (C^{1}), 121.8 (dd, J_1 = 3.6 Hz, J_2 = 10.9 Hz, $C^{5'}$), 124.2 (dd, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 125.6 (C^{7}), 126.1 (2 C, $C^{2''/6''}$), 127.5 (C^{9}), 127.9 (2 C, $C^{3''/5''}$), 129.1 (C^{4a}), 129.7 (C^{6}), 130.9 (C^{4}), 131.3 ($C^{4''}$), 132.9 (C^{8}), 133.2 (C^{5a}), 138.4 ($C^{1''}$), 140.7 (C^{9a}), 144.4 (C^{11a}), 145.8 (C^{2}), 164.4 (-CONH-), 191.7 (C^{5}), not detected ($C^{2'/4'}$)

Thiophene-3-carboxylic acid {2,4-difluoro-5-[7-(2-morpholin-4-yl-ethoxy)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ylamino]-phenyl}-amide (16r)



The compound is synthesized according to the general procedure D.

0,29 g (0,78 mmol) 2-chloro-7-(2-morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**15d**), 0,20 g (0,79 mmol) thiophene-3-carboxylic acid (5-amino-2,4-difluor-phenyl)-amid (**14n**), 0,025 g (0,11 mmol) $Pd(OAc)_2$, 0,14 g (0,29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 0,40 g (3,6 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

Reaction time: 30 min. Temperature 100°C. Extraction with ethyl acetate.

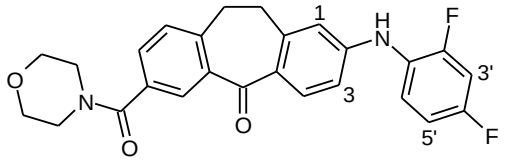
The crude product is purified by automated column chromatography (SiO_2, methanol/ethyl acetate 5+95). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{32}H_{29}F_2N_3O_4S$ (Mr = 589.68)

Yield	0.14 g (30 %)

Melting point	89°C
HRMS $[M+H]^+$	590.191584 (calc. 590.191960)
IR (ATR)	1585, 1532, 1417, 1270, 1115, 854, 741, 517 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.34-2.55 (m, 4 H + DMSO, $C^{2/6}_{Morpholinyl}$), 2.67 (t, 2 H, J = 5.6 Hz, -N-$\underline{C}H_2$-CH_2-O-), 2.86-3.15 (m, 4 H, -CH_2-CH_2-), 4.48-3.62 (m, 4 H, $C^{3/5}_{Morpholinyl}$), 4.09 (t, 2 H, J = 5.7 Hz, -N-CH_2-$\underline{C}H_2$-O-), 6.67 (s, 1 H, C^1-H), 6.79 (d, 1 H, J = 9.0 Hz, C^3-H), 7.00-7.09 (m, 1 H, $C^{3'}$-H), 7.15-7.26 (m, 1 H, $C^{6'}$-H), 7.35-7.68 (m, 5 H, $C^{8/6/9/4''/5''}$-H), 7.95 (d, 1 H, J = 8.8 Hz, C^4-H), 8.34 (s, 1 H, $C^{2''}$-H), 8.62 (s, 1 H, -CONH-), 9.97 (s, 1 H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.1 (C^{10}), 35.9 (C^{11}), 53.5 ($C^{2/6}_{Morpholinyl}$), 57.0 (-N-$\underline{C}H_2$-CH_2-O-), 65.6 (-N-CH_2-$\underline{C}H_2$-O-), 66.2 ($C^{3/5}_{Morpholinyl}$), 105.2 (t, J = 25.8 Hz, $C^{3'}$), 112.3 (C^6), 113.9 (C^3), 115.1 (C^1), 118.7 (C^8), 122.1 ($C^{5''}$), 127.0 (partially covered by $C^{4''}$, $C^{1'}$), 127.1 ($C^{4''}$), 127.6 (C^{4a}), 130.2 (C^9), 130.2 (C^4), 133.3 ($C^{2''}$), 134.2 (C^{5a}), 136.8 (C^{9a}), 139.7 ($C^{1''}$), 145.2 (C^{11a}), 148.8 (C^2), 156.9 (C^7), 160.9 (-CONH-), 190.5 (C^5), not detected ($C^{2'/4'/5'/6'}$)

2-(2,4-Difluoro-phenylamino)-7-(morpholine-4-carbonyl)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (16s)



The compound is synthesized according to the general procedure D.

1.24 g (3.5 mmol) 2-chloro-7-(morpholine-4-carbonyl)-10,11-dihydro-dibenzo-[a,d]cyclohepten-5-one (**10a**), 0.45 g (3.5 mmol) difluoroaniline, 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.24 g (0.50 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-

triisopropyl-biphenyl, 1.43 g (12.7 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

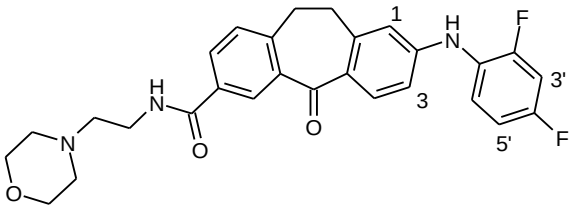
Temperature: 100°C. Reaction time: 2 h. Extraction with ethyl acetate.

The crude product is purified by automated column chromatography (SiO_2, ethyl acetate 100 %). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{26}H_{22}F_2N_2O_3$ (Mr = 448.47)

Yield	> 90 %
Melting point	160°C
HRMS $[M+Na]^+$	471.148925 (calc. 471.149070)
IR (ATR)	3268, 2918, 2857, 1588, 1505, 1434, 1246, 1102, 964, 855, 574 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 Hz): 2.89-3.17 (m, 4 H, -CH_2-CH_2-), 3.31-3.92 (m, 8 H, Morpholine), 6.50-6.65 (m, 2 H, $C^{1/3}$-H), 6.69-6.93 (m, 3 H, $C^{3'/5'/6'}$-H), 7.14-7,34 (m, 2 H, $C^{4/9}$-H), 7.45 (d, 1 H, J = 6.3 Hz, C^8-H), 7.96-8.15 (m, 2 H, C^6-H / -NH-)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 50 Hz): 34.6 (C^{10}), 35.9 (C^{11}), 66.8 (4 C, Morpholine), 104.7 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.3 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 113.0 (C^3), 114.0 (C^1), 124.4 (d, J = 8.8 Hz, $C^{6'}$), 124.9 (d, J = 11.6 Hz, $C^{1'}$), 128.6 (C^{4a}) 129.1 (C^9), 129.6 (C^6), 130.6 (C^8), 133.5 (C^{5a}), 134.1 (C^4), 139.2 (C^7), 143.6 (C^{11a}), 145.3 (C^2), 148.5 (C^{9a}), 155.5 (dd, J_1 = 11.6 Hz, J_2= 247.2 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.0 Hz, J_2 = 244.2 Hz, $C^{2'}$), 169.8 (-<u>C</u>OO-), 191.1 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (16t)



The compound is synthesized according to the general procedure D.

0.62 g (1.6 mmol) 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (**10b**), 0.22 g (1.,7 mmol) difluoraniline, 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 0.63 g (5.6 mmol) KO*tert*Bu, 10 ml toluene, 2 ml *tert*-BuOH.

Temperature: Reflux. Reaction time: 2 h. Extraction with diethyl ether.

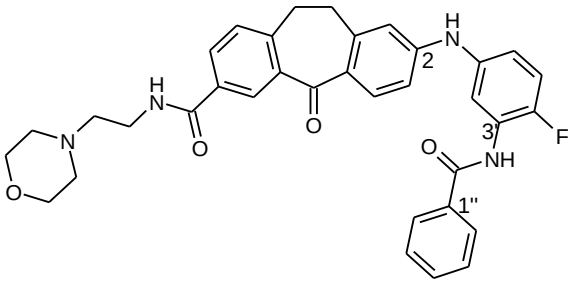
The crude product is purified by automated column chromatography (SiO_2, DCM/ethanol 95+5). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{28}H_{27}F_2N_3O_3$ (Mr = 491.54)

Yield	50 %
Melting point	78,3°C
HRMS $[M+H]^+$	492.209625 (calc. 492.209325)
IR (ATR)	3274, 2921, 1506, 1258, 1113, 846, 457 cm^{-1}
^{1}H-NMR (DMSO- *d6*)	δ in ppm (*f* = 200 MHz): 2.31-2.46 (m, 6 H, $C^{2/6}_{Morpholinyl}$-H / -N-C<u>H$_2$</u>-CH_2-NH-OC-), 2.94-3.19 (m, 4 H, -CH_2-CH_2-), 3.25-3.45 (m, 2 H + H_2O, -N-CH_2-C<u>H$_2$</u>-NH-OC-), 3.55 (t, 4 H, J = 4.6 Hz, $C^{3/5}_{Morpholinyl}$-H), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 8.7 Hz, C^3-H), 7.09-7.16 (m, 1 H, $C^{3'}$-H), 7.29-7,48 (m, 3 H, $C^{5'/6'/9}$-H), 7.90 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 7.8 Hz, C^8-H), 7.99 (d, 1 H, J = 8.7 Hz, C^4-H), 8,32 (d, 1 H, J =

	1.8 Hz, C^{6}-H), 8.51 (t , 1 H, J = 5.7 Hz, -CONH-), 8.58 (s, 1 H, -NH-)
^{13}C-NMR (DMSO- *d6*)	δ in ppm (*f* = 100 MHz): 33.8 (C^{10}), 35.4 (C^{11}), 36.5 (-N-CH_2-$\underline{C}H_2$-NH-OC-), 53.2 ($C^{2/6}_{Morpholinyl}$), 57.3 (-N-$\underline{C}H_2$-CH_2-NH-OC-), 66.1 ($C^{3/5}_{Morpholinyl}$), 104.9 (dd, J_1 = 23.6 Hz, J_2 = 26.6 Hz, $C^{3'}$), 111.8 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.3 (C^{3}), 113.5 (C^{1}), 124.8 (dd, J_1 = 3.0 Hz, J_2 = 11.6 Hz, $C^{1'}$), 126.2 (dd, J_1 = 3.0 Hz, J_2 = 9.4 Hz, $C^{6'}$), 127.1 (C^{4a}) 128.9 (C^{9}), 129.1 (C^{6}), 130.4 (C^{4}), 132.8 (C^{7}), 133.3 (C^{8}), 138.9 (C^{5a}), 144.5 (C^{11a}), 145.2 (C^{2}), 149.3 (C^{9a}), 155.7 (dd, J_1 = 12.8 Hz, J_2= 247.6 Hz, $C^{4'}$), 158.5 (dd, J_1 = 11.6 Hz, J_2 = 242.0 Hz, $C^{2'}$), 165.5 (-$\underline{C}$OO-), 190.4 (C^{5})

8-(3-Benzoylamino-4-fluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid-(2-morpholin-4-yl-ethyl)-amide (16u)



The compound is synthesized according to the general procedure D.

0.37 g (0.93 mmol) 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid-(2-morpholin-4-yl-ethyl)-amide (**10b**), 0.20 g (0.87 mmol) N-(5-amino-2-fluoro-phenyl)-benzamide (**14c**), 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2'-,4'-,6'-triisopropyl-biphenyl, 0.40 g (3.6 mmol) KO*tert*Bu, 15 ml toluene, 3 ml *tert*-BuOH.

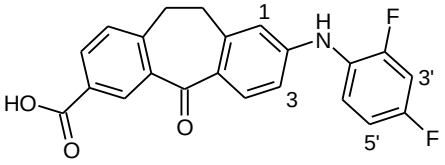
Temperature: 100°C. Reaction time: 30 min. Extraction with ethyl acetate.

The crude product is purified by automated column chromatography (SiO_2, DCM/ethanol 95+5). The product is further purified by recrystallization (ethyl acetate / hexane).

$C_{35}H_{33}FN_4O_4$ (Mr = 592,68)

Yield	0.04 g (7 %)
Melting point	disintegration
HRMS $[M+H]^+$	593.255492 (calc. 593.255860)
IR (ATR)	329, 1576, 1525, 1261, 1114, 861, 786, 706 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.27-2.62 (m, 6 H + DMSO, $C^{2/6}_{Morpholinyl}$-H / N-C$\underline{H_2}$-CH_2-NOC), 2.99-3.21 (m, 4 H, -CH_2-CH_2-), 3.24-3.48 (m, 2 H + H_2O, N-CH_2-C$\underline{H_2}$-NOC), 3.49-3.62 (m, 4 H, $C^{3/5}_{Morpholinyl}$-H), 6.86 (s, 1H, C^1-H), 6.93-7.44 (m, 4 H, $C^{3/6'/5'/2'}$-H), 7.47-7.62 (m, 4 H, $C^{4/3''/5''/4''}$-H), 7.86-8.06 (m, 4 H, $C^{9/2''/6''/8}$-H), 8.32 (d, 1 H, J = 1.1 Hz, C^6-H), 8.45-8.61 (m, 1 H, -CON$\underline{H}$-CH_2-), 8.89 (s , 1 H, -CONH-), 10.1 (s, 1H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.8 (C^{10}), 35.5 (C^{11}), 36.4 (-N-CH_2-$\underline{C}H_2$-NH-), 53.2 (2 C, $C^{2/6}_{Morpholinyl}$), 57.2 (-N-$\underline{C}H_2$-CH_2-NH-), 66.1 (2 C, $C^{3/5}_{Morpholinyl}$), 112.6 (C^3), 113.9 (C^1), 116.2 (d, J = 20.4 Hz, $C^{5'}$), 118.1 (d, J = 6.5 Hz, $C^{6'}$), 118.2 (s, $C^{1'}$), 126.2 (d, 1 H, J = 13.8 Hz, $C^{3'}$), 127.2 (C^{4a}), 127.8 (2 C, $C^{2''/6''}$), 128.4 (2 C, $C^{3''/5''}$), 128.9 (C^9), 129.1 (C^6), 130.4 (C^4) 131.8 (C^8), 133.5 ($C^{4''}$), 134.0 (C^7), 137.0 (C^{5a}), 137.1 ($C^{1''}$), 138.9 (C^2), 144.5 (C^{11a}), 148.7 (C^{9a}), 150.9 (d, J = 241.4 Hz, $C^{4'}$), 165.5 (2 C, -$\underline{C}$ONH-), 190.3 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (17)



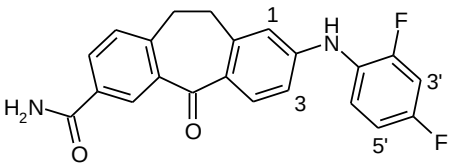
0.76 g (2.65 mmol) 2-(2,4-difluoro-phenylamino)-7-(morpholine-4-carbonyl)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (**16s**) are suspended in a mixture of 5 ml water and 50 ml HCl (37 %) and refluxed for 6 h.

After complete conversion (monitored by TLC) the reaction mixture is poured into 200 ml water and extracted with ethyl acetate. Solvents are removed in a rotary evaporator yielding the pure product.

$C_{22}H_{15}F_2NO_3$ (Mr = 379.37)

Yield	> 95 %
Melting point	237°C
HRMS $[M+H]^+$	380.109237 (calc. 380.109276)
IR (ATR)	3328, 2929, 1684, 1605, 1557, 1526, 1496, 1259, 1092, 763 cm^{-1}
^{1}H-NMR (DMSO- *d6*)	δ in ppm (*f* = 200 MHz): 3.03-3.18 (m, 4 H, $-CH_2-CH_2-$), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 8.7 Hz, C^3-H), 7.04-7.16 (m, 1 H, $C^{3'}$-H), 7.30-7.49 (m, 3 H, $C^{6'/5'/4}$-H), 7.95-8.03 (m, 2 H, $C^{9/8}$-H), 8.43 (d, 1 H, J = 1.64 Hz, C^6-H), 8.60 (s, 1 H, -NH-), 13.02 (s, 1H, -COOH)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid amide (18a)

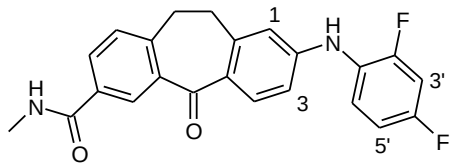


0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 10 ml THF. After addition of 0.13 g (0.80 mmol) CDI stirring is continued for 1.5 h at room temperature. Complete and immediate conversion is accomplished by adding 0.44 ml (5.80 mmol) NH_3 (25 %). The reaction mixture is acidified using HCl (dil.) and extracted with ethyl acetate. Solvents are removed in a rotary evaporator yielding the product.

$C_{22}H_{16}F_2N_2O_2$ (Mr = 378.38)

Yield	35%
Melting point	240°C
HRMS $[M+H]^+$	379.125693 (calc. 379.125261)
IR (ATR)	3374, 3204, 1676, 1649, 1607, 1503, 1394, 1359, 1145, 1095, 967, 866, 776, 684 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 200 MHz): 2.95-3.19 (m, 4 H, $-CH_2-CH_2-$), 3.42-3.74 (m, 2 H, $-NH_2$), 6.61 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 9.0 Hz, C^3-H), 7.00-7.19 (m, 1 H, $C^{3'}$-H), 7.26-7.52 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.93 (dd, 1H, J_1 = 7.9 Hz, J2 = 2.0 Hz, C^8-H), 7.96 (d, 1H, J = 8.6 Hz, C^4-H) 8.35 (d, 1H, J = 1.7 Hz, C^6-H), 8.57 (s, 1H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (f = 100 MHz): 33.8 (C^{10}), 35.4 (C^{11}), 104.9 (dd, 1 C, J_1 = 24.4 Hz, J_2 = 25.8 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 2.9 Hz, J_2 = 12.4 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.5 Hz, J_2 = 9.8 Hz, $C^{6'}$), 127.1 (C^{4a}), 128.8 (C^9), 129.6 (C^6), 130.6 (C^4) 132.6 (C^7), 133.3 (C^8), 138.9 (C^{5a}), 144.7 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 167.2 (-C(O)-NH-) 190.5 (C^5), not detected ($C^{2'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-carboxylic acid methylamide (18b)



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 15 ml THF and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h.

Afterwards solvents are removed in a rotary evaporator. The remaining substance is take up in 15 ml THF and added carefully to 25 ml methylamine (2.5 M in THF) at room temperature. The mixture is stirred over night, poured into 300 ml water and extracted with ethyl acetate. Solvents are removed in a rotary evaporator.

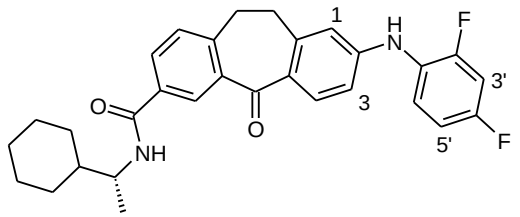
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{23}H_{18}F_2N_2O_2$ (Mr = 392.41)

Yield	71 %
Melting point	187°C
Purity	92 %
HRMS $[M+H]^+$	393.140870 (calc. 393.140911)
IR (ATR)	3291, 1506, 1259, 1140, 1115, 1095, 965, 847 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2,90-297 (m, 3 H, $-CH_3$), 2.98-3.18 (m, 4 H, $-CH_2-CH_2-$), 5.92 (s, 1 H, -NH-), 6.35 (s, 1 H, -CONH-), 6.59 (s, 1 H, C^1-H), 6.73-6.91 (m, 3 H, $C^{3/6'/3'}$-H), 7.20-7.34 (m, 2 H, $C^{5'/9}$-H), 7.90 (d, 1 H, J = 7.8 Hz, C^8-H), 8.07 (d, 1 H, C^4-H), 8.24 (s, 1 H, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 50 MHz): 26.8 ($-CH_3$), 34.7 (C^{10}), 35.8 (C^{11}), 104.8 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 4.0 Hz, J_2 = 22.2 Hz, $C^{5'}$), 113.3 (C^3), 114.6 (C^1), 123.9 (dd, J_1 = 2.5 Hz, J_2 = 9.1 Hz, $C^{6'}$), 124.8 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, $C^{1'}$), 128.4 (C^9), 129.2 (C^{4a}), 129.5 (C^6), 131.3 (C^4), 133.0 (C^7), 134.2 (C^8), 138.8 (C^{5a}), 145.1

(C^{11a}), 145.3 (C^{2}), 148.0 (C^{9a}), 167.3 (-CONH-), 191.4 (C^{5}), not detected ($C^{2'/4'}$)

_(R)_-8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (1-cyclohexyl-ethyl)-amide (18c)



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 20 ml DCM and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h. The remainig substance is taken up in 15 ml DCM and carefully added to a solution of 6.36 g (50.0 mmol) *(R)*-1-cyclohexylethylamine in 25 ml DCM at room temperature. The mixture is stirred over night, poured into 300 ml water and extracted with DCM. Solvents are removed in a rotary evaporator.

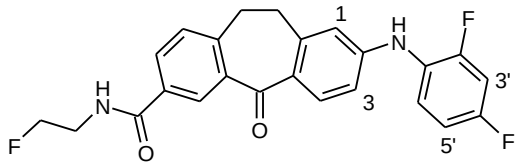
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{30}H_{30}F_2N_2O_2$ (Mr = 488.58)

Yield	58 %
Melting point	173°C
HRMS $[M+H]^+$	511.216856 (calc. 511.216756)
IR (ATR)	3273, 2922, 2850, 1506, 1257, 1139, 1095, 964, 845 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 0.87-1.01 (m, 2 H, Cyclohexane), 1.03-1.25 (m, 6 H, Cyclohexane, $-CH_3$), 1.33-1.48 (m, 1 H, Cyclohexane), 1.54-1.79 (m, 5 H, Cyclohexane), 2.98-3.15 (m, 4 H, $-CH_2-CH_2-$), 3.78-3.88 (s, 1 H, -CH-NH-), 6.62 (s, 1 H, C^1-H), 6.76 (d, 1 H, J = 6.8 Hz, C^3-H), 7.01-7.17 (m, 1 H, $C^{3'}$-H), 7.27-7.49 (m, 3 H, $C^{5'/6'/9}$-H), 7.90 (d, 1 H, J =7.8 Hz, C^8-H), 7.99 (d, 1 H, J = 8.8 Hz, C^4-H), 8.24 (d, 1 H, J = 8.6 Hz, -CONH-), 8.30 (s, 1 H, C^6-H), 8.59 (s, 1 H, -NH-)

^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 17.6 (-CH_3), 25.7 (2 C, $C^{3/5}$ Cyclohexane), 26.0 (C^6 Cyclohexane), 29.0 (C^4 Cyclohexane), 29.2 (C^2 Cyclohexane), 33.7 (C^{10}), 35.4 (C^{11}), 42.3 (C^1 Cyclohexane), 49.3 (-CH-NH-Cyclohexane), 104.9 (dd, J_1 = 24.4 Hz, J_2 = 26.5 Hz, $C^{3'}$), 111.8 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.2 (C^3), 113.5 (C^1), 124.7 (dd, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{6'}$), 126.2 (dd, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{1'}$), 127.1 (C^{4a}), 128.7 (C^9), 129.1 (C^6), 130.5 (C^4), 133.2 (C^8), 133.3 (C^7), 138.8 (C^{5a}), 144.3 (C^{11a}), 145.3 (C^2), 149.3 (C^{9a}), 155.7 (dd, J_1 = 6.2 Hz, J_2 = 247.2 Hz, $C^{4'}$), 158.5 (dd, J_1 = 12.0 Hz, J_2 = 241.7 Hz, $C^{2'}$), 165.0 (-CONH-), 190.6 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2-fluoroethyl)-amide (18d)



0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 10 ml THF and activated by addition of 0.13 g (0.80 mmol) CDI during 1.5 h at room temperature.

After addition of 0.16 g (2.5 mmol) 2-fluoroethylamine hydrochloride stiring is continued over night at room temperature.

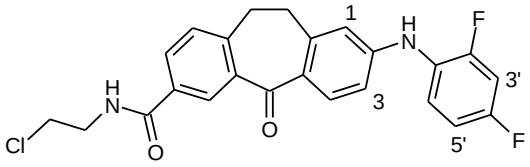
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{24}H_{19}F_3N_2O_2$ (Mr = 424.43)

Yield	37 %
Melting point	183°C
HRMS $[M+H]^+$	425.147082 (calc. 425.147139)
IR (ATR)	3287, 2968, 1662, 1603, 1578, 1546, 1508, 1361, 1310, 1262, 1139, 1115, 966, 842, 782, 731, 678 cm^{-1}

^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 200 MHz): 2.91-3.23 (m, 4 H, -CH_2-CH_2-), 3.43-3.73 (m, 2H, C^1-H_{Ethyl}), 4.53 (dt, 2H, J_1 = 48,0 Hz, J_2 = 5,2 Hz, C^2-H_{Ethyl}), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 9,6 Hz, C^3-H), 7.04-7.19 (m, 1 H, $C^{3'}$-H), 7.25-7.54 (m, 3 H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.84-8.09 (m, 2 H, C^8-H, C^4-H), 8.36 (s, 1 H, C^6-H), 8.57 (s, 1 H, -NH-), 8.80 (t, 1 H, J = 5,4 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (f = 100 MHz): 33.8 (C^{10}), 35.4 (C^{11}), 39.1 (C^1_{Ethyl}), 82.1 (C^2_{Ethyl}), 105.0 (dd, 1 C, J_1 = 24.4 Hz, J_2 = 26.6 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 22.2 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 2.6 Hz, J_2 = 11.3 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.6 Hz, J_2 = 9.8 Hz, $C^{6'}$), 127.1 (C^{4a}), 128.9 (C^9), 129.2 (C^6), 130.4 (C^4) 132.4 (C^7), 133.4 (C^8), 138.9 (C^{5a}), 144.8 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 155.7 (dd, 1C, J_1 = 246,1 Hz, J_2 = 12,7 Hz, $C^{2'}$), 158.5 (dd, 1C, J_1 = 241,0 Hz, J_2 = 10,5 Hz, $C^{4'}$) 165.8 (-C(O)-NH-), 190.4(C^5), not detected ($C^{2'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (2-chloroethyl)-amid (18e)



Compound (**18e**) is prepared in a similar manner as compound (**18d**).

0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), in 10 ml THF, 0.13 g (0.80 mmol) CDI, 0.12 g (1.5 mmol) 2-chloro-ethylamine.

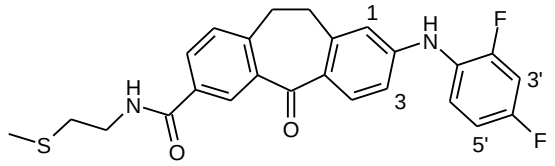
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 6+4).

$C_{24}H_{19}ClF_2N_2O_2$ (Mr = 440.88)

Yield	47 %
Melting point	179°C

HRMS $[M+Na]^+$	463.099612 (calc. 463.099533)
IR (ATR)	3479, 3255, 1647, 1603, 1522, 1507, 1281, 1356, 1140, 1118, 965, 838, 789, 708 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.97-3.18 (m, 4 H, $-CH_2-CH_2-$), 3.48-3.64 (m, 2H, C^1-H_{Ethyl}), 3.66-4.0 (m, 2H, C^2-H_{Ethyl}), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 8.3 Hz, C^3-H), 7.01-7.18 (m, 1 H, $C^{3'}$-H), 7.27-7.51 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.92 (dd, 1H, J_1 = 7.77 Hz, J_2 = 1.6 Hz, C^8-H), 7.99 (d, 1H, J = 8.7 Hz, C^4-H) 8.34 (d, 1H, J = 1.78 Hz, C^6-H), 8.58 (s, 1H, -NH-), 8.83 (t, 1H, J = 5,4 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.9 (C^{10}), 35.2 (C^{11}), 38.0 (C^1_{Ethyl}), 61.6 (C^2_{Ethyl}), 111.9 (dd, 1 C, J_1 = 5.1 Hz, J_2 = 21.1 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 126.4 (dd, 1 C, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 126.8 (C^{4a}), 127.7 (C^9), 129.3 (C^6), 131.6 (C^4) 132.5 (C^7), 133.4 (C^8), 139.3 (C^{5a}), 143.5 (C^{11a}), 145.3 (C^2); 149.6 (C^{9a}), 165.2 (-C(O)-NH-) 190.0 (C^5), not detected ($C^{1'/2'/3'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2-methylsulfanyl-ethyl)-amide (18f)



Compound (**18f**) is prepared in a similar manner as compound (**18d**).

0.30 g (0.79 mmol) 8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), in 10 ml THF, 0.19 g (1.17 mmol) CDI, 0.22 g (2.4 mmol) 2-methylsulfanyl-ethylamine.

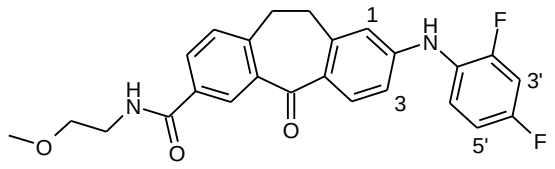
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{25}H_{22}F_2N_2O_2S$ (Mr = 452.53)

Yield	20 %
Melting point	161 °C

HRMS $[M+Na]^+$	475.126466 (calc. 475.126226)
IR (ATR)	3310, 3064, 2916, 1633, 1603, 1578, 1507, 1354, 1194, 1139, 1114, 1093, 963, 846, 785, 760, 695 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.08-2.14 (s, 3H, $-CH_3$), 2.64 (t, 2H, C^1-H_{Ethyl}), 2.95-3.19 (m, 4 H, $-CH_2-CH_2-$), 3.35-3.57 (m, 2H, C^2-H_{Ethyl}), 6.62 (s, 2 H, C^1-H), 6.69-6.82 (m, 2 H, C^3-H), 6.97-7.18 (m, 2 H, $C^{3'}$-H), 7.28-7.53 (m, 6H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.91 (dd, 1H, J_1 = 2,0 Hz, J_2 = 7,8 Hz, C^8-H), 7.99 (d, 1H, J = 8,7 Hz, C^4-H) 8.58 (m, 1H, C^6-H) 8.63 (m, 1H, -NH-), 8.69 (t, 1H, J = 5,2 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 14.5 ($-CH_3$), 30.7 (C^1-H_{Ethyl}), 32.6 (C^2-H_{Ethyl}), 33.8 (C^{10}), 35.4 (C^{11}), 104.9 (dd, 1 C, J_1 = 24.4 Hz, J_2 = 26.4 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 9.8 Hz, $C^{6'}$), 127.1 (C^{4a}), 128.9 (C^9), 129.1 (C^6), 130.4 (C^4) 132.6 (C^7), 133.4 (C^8), 138.9 (C^{5a}), 144.7 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 155.7 (dd, 1 C, J_1 = 12.4 Hz, J_2 = 246.5 Hz, $C^{1'}$), 158.5 (dd, 1 C, J_1 = 11.6 Hz, J_2 = 242.1 Hz, $C^{1'}$) 165.4 (-C(O)-NH-) 190.4 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2-methoxyethyl)-amide (18g)



Compound (**18g**) is prepared in a similar manner as compound (**18d**).

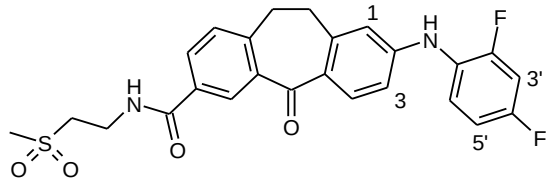
0.30 g (0.79 mmol) 8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 10 ml THF, 0.19 g (1.17 mmol) CDI, 0.18 g (2.4 mmol) 2-methoxy-ethylamine

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 45+55).

$C_{25}H_{22}F_2N_2O_2S$ (Mr = 436.46)

Yield	12 %
Melting point	155°C
HRMS $[M+H]^+$	437.167515 (calc. 437.167125)
IR (ATR)	3259, 3069, 2935, 1647, 1603, 1566, 1502, 1355, 1196, 1112, 1094, 964, 855, 826, 751, 694 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 200 MHz): 2.95-3.18 (m, 4 H, $-CH_2-CH_2-$), 3.25 (s, 3H, $-O-CH_3$), 3.39-3.53 (m, 4H, $C^{1,2}$-H_{Ethyl}), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 8.7 Hz, C^3-H), 6.98-7.20 (m, 1 H, $C^{3'}$-H), 7.24-7.55 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.91 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.2 Hz, C^8-H), 7.99 (d, 1H, J = 8.7 Hz, C^4-H), 8.22-8.44 (m, 1H, C^6-H), 8.48-8.75 (m, 2H, -NH-, Amid)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (f = 100 MHz): 33.8 (C^{10}), 35.4 (C^{11}), 38.9 (C^1_{Ethyl}), 57.9 ($-CH_3$), 70.4 (C^2_{Ethyl}), 104.9 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 127.1 (C^{4a}), 128.9 (C^9), 129.2 (C^6), 130.4 (C^4) 132.7 (C^7), 133.3 (C^8), 138.9 (C^{5a}), 144.6 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 155.7 (dd, 1C, J_1 = 246,5 Hz, J_2 = 12,4 Hz, $C^{4'}$), 158.5 (dd, 1C, J_1 = 241,7 Hz, J_2 = 11,3 Hz, $C^{2'}$), 165.6 (-C(O)-NH-), 190.5 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid-(2-methanesulfonyl-ethyl)-amide (18h)



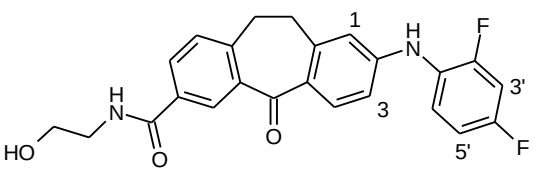
0.1 g (0.22 mmol) **18f** are dissolved in 2 ml THF and 0.3 ml (16 mmol) water. 0.27 g (0.44 mmol) potassium monopersulfate (Oxone®) in 0.5 ml (23.7 mmol) water (cooled to 0°C) are added at 0°C under heavy stirring.

Complete conversion is monitored by HPLC. The reaction mixture is extracted with ethyl acetate. Solvents are removed in a rotary evaporator.

$C_{25}H_{22}F_2N_2O_4S$ (Mr = 484.53)

Yield	64 %
Melting point	175°C
HRMS $[M+Na]^+$	507.116223 (calc. 507.116055)
IR (ATR)	3332, 2929, 1639, 1581, 1510, 1356, 1261, 1128, 1096, 964, 848, 786, 762, 697 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 400 MHz): 2.94-3.18 (m, 7H,-CH_3, -CH_2-CH_2-), partially covered by H_2O (m, 2H, C^2-H_{Ethyl}), 3.61-3.80 (m, 2H, C^1-H_{Ethyl}), 6.63 (s, 1 H, C^1-H), 6.77 (d, 1 H, J = 8,6 Hz, C^3-H), 7.03-7.17 (m, 1 H, $C^{3'}$-H), 7.30-7.49 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.92 (d, 1H, J = 7,8 Hz, C^8-H), 8.00 (d, 1H, J = 8,8 Hz, C^4-H), 8.35 (s, 1H, C^6-H), 8,59 (s, 1H, -NH-), 8.83 (t, 1H, J = 2,7 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (f = 100 MHz): 33.4 (C^{10}), 33.8 (C^{11}), 35.3 (C^1_{Ethyl}), 40.7 (-CH_3), 52.9 (C^2_{Ethyl}), 104.9 (dd, 1 C, J_1 = 24.4 Hz, J_2 = 26.6 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 127.1 (C^{4a}), 129.0 (C^9), 129.1 (C^6), 130.4 (C^4) 132.3 (C^7), 133.4 (C^8), 138.9 (C^{5a}), 144.9 (C^{11a}), 145.5 (C^2); 149.4 (C^{9a}), 155.7 (dd, 1 C, J_1 = 246.5 Hz, J_2 = 12.4 Hz, $C^{2'}$), 158.5 (dd, 1 C, J_1 = 242.1 Hz, J_2 = 11.6 Hz, $C^{4'}$), 165.8 (-C(O)-NH-), 190.4(C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid-(2-hydroxyethyl)-amide (18i)



Compound (**18i**) is prepared in a similar manner as compound (**18d**).

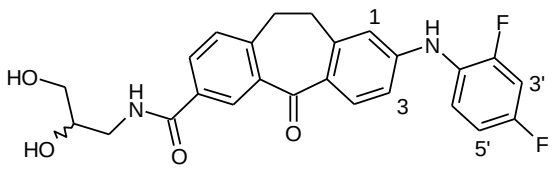
0.30 g (0.79 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 10 ml THF, 0.19 g (1.17 mmol) CDI, 0.15 g (2.4 mmol) 2-aminoethanol.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 1+9).

$C_{24}H_{20}F_2N_2O_3$ (Mr = 422.44)

Yield	42 %
Melting point	183°C
HRMS $[M+H]^+$	423.151134 (calc. 423.151475)
IR (ATR)	3274, 2929, 1741, 1644, 1604, 1547, 1506, 1411, 1355, 1263, 1212, 1095, 1051, 967, 892, 861, 843, 758, 692 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 400 MHz): 2.93-3.17 (m, 4H, $-CH_2-CH_2-$), 3.31-3.37 (m, 2 H, C^1-H_{Ethyl}), 3.49-3.66 (m, 2H, C^2-H_{Ethyl}), 6.64 (s, 1 H, C^1-H), 6.77 (d, 1 H, J = 8,6 Hz, C^3-H), 7.03-7.16 (m, 1 H, $C^{3'}$-H), 7.28-7.51 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.94 (d, 1H, J = 4,1 Hz, C^8-H), 8.01 (d, 1H, J = 4,4 Hz, C^4-H), 8.36 (s, 1H, C^6-H), 8.54 (d, 1H, J = 2,6 Hz, Amid), 8.58 (s, 1H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 33.8 (C^{10}), 35.4 (C^{11}), 42.3 (C^1_{Ethyl}), 59.8 (C^2_{Ethyl}), 104.9 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 112.3 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 22.2 Hz, $C^{5'}$), 112.3 (C^3), 113.6 (C^1), 124.9 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 127.3 (C^{4a}), 128.8 (C^9), 129.2 (C^6), 130.4 (C^4) 132.9 (C^7), 133.3 (C^8), 138.9 (C^{5a}), 144.5 (C^{11a}), 145.2 (C^2); 149.3 (C^{9a}), 155.7 (dd, 1 C, J_1 = 12.4 Hz, J_2 = 247.2 Hz, $C^{4'}$), 158.5 (dd, 1 C, J_1 = 11.6 Hz, J_2 = 242.1 Hz, $C^{2'}$),165.7 (-C(O)-NH-), 190.5 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2,3-dihydroxy-propyl)-amine (18j)



0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 5 ml DMF and activated by addition of 0.13 g (0.80 mmol) CDI during 1.5 h at room temperature.

After addition of 0.072 g (0.79 mmol) 3-aminopropane-1,2-diol stirring is continued over night for 4 h at 120°C. The reaction mixture is poured into water an extracted using ethyl acetate. Solvents are removed in a rotary evaporator.

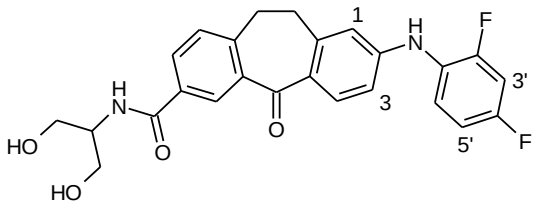
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 1+9).

$C_{25}H_{22}F_2N_2O_4$ (Mr = 452.15)

Yield	8.4%
HRMS $[M+Na]^+$	475.143713 (calc. 475.14398)
IR (ATR)	3278, 2925, 1737, 1601, 1553, 1507, 1358, 1114, 1097, 964, 835, 783, 761, 694 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.97-3.16 (m, 4 H, -CH_2-CH_2-), 3.17-3.72 partially covered by H_2O (m, 5 H, -C<u>H</u>$_2$-C<u>H</u>(OH)-C<u>H</u>$_2$-OH), 4.56 (t, 1 H, J = 5.81 Hz ,-CH_2-O<u>H</u>), 4.80 (d, 1 H, , J = 4.92 Hz, -CH-O<u>H</u>), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 10.2 Hz, C^3-H), 7.03-7.17 (m, 1 H, $C^{3'}$-H), 7.30-7.49 (m, 3 H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.92 (dd, 1 H, J_1 = 7,9 Hz J_2 = 1.8 Hz, C^8-H), 7.99 (d, 1 H, J = 8.7 Hz, C^4-H) 8.33 (d, 1H, J = 1.3 Hz, C^6-H), 8.48 (t, 1 H, J = 5.2 Hz, Amide), 8.57 (s, 1 H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 34.1 (C^{10}), 35.8 (C^{11}), 43.4 (C^1_{propyl}), 64.3 (C^3_{propyl}), 70.2 (C^2_{propyl}), 105.3 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.7 Hz, $C^{3'}$), 112.2 (dd, 1 C, J_1 = 3.8 Hz, J_2 = 21.7 Hz, $C^{5'}$), 112.7 (C^3), 113.9 (C^1), 125.2 (dd, 1 C, J_1 = 3.8 Hz, J_2 = 12.2 Hz, $C^{1'}$), 126.6 (dd, 1 C, J_1 = 3.2 Hz, J_2

= 9.7 Hz, $C^{6'}$), 127.5 (C^{4a}), 129.2 (C^{9}), 129.6 (C^{6}), 130.8 (C^{4}) 133.2 (C^{7}), 133.7 (C^{8}), 139.2 (C^{5a}), 144.9 (C^{11a}), 145.6 (C^{2}); 149.7 (C^{9a}), 166,3 (-C(O)-NH-), 190.8 (C^{5}), not detected ($C^{2'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (2-hydroxy-1-hydroxymethyl-ethyl)-amide (18k)



Compound (**18k**) is prepared in a similar manner as compound (**18j**).

0.14 g (0.37 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 5 ml DMF, 0.12g (0.74 mmol) CDI, 0.2 g (2.15 mmol) 2-aminopropan-1,3-diol

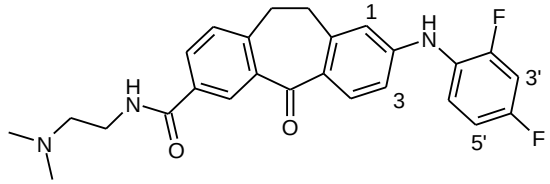
The crude product is purified by automated column chromatography (SiO_2, DCM/EtOH, 93+7)

$C_{25}H_{22}F_2N_2O_4$ (Mr = 452.46)

Yield	68%
HRMS $[M+Na]^+$	475.143841 (calc. 475.14398)
IR (ATR)	3293, 2928, 1737, 1627, 1603, 1508, 1354, 1259, 1095, 1039, 964, 846, 761 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.96-3.17 partially covered by H_2O (m, 4 H, $-CH_2-CH_2-$), 3.46-3.58 (m, 5 H, Isopropyl), 6.62 (s, 1 H, C^{1}-H), 6.75 (d, 1 H, J = 8.2 Hz, C^{3}-H), 7.03-7.18 (m, 1 H, $C^{3'}$-H), 7.29-7.5 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^{9}-H), 7.93 (dd, 1H, J_1 = 7.8 Hz, J2 = 2.0 Hz, C^{8}-H), 7.99 (d, 1H, J = 8.8 Hz, C^{4}-H) 8.07 (d, 1H, J = 8.2 Hz, Amide), 8.33 (d, 1H, J = 1.8 Hz, C^{6}-H), 8.58 (s, 1 H, -NH-), -OH not detected
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 34.1 (C^{10}), 35.8 (C^{11}), 54.3 ($C^{2}_{isopropyl}$), 60.1 ($C^{1}_{isopropyl}$), 60.8 ($C^{3}_{isopropyl}$), 105.3 (dd, 1

C, J_1 = 23.8 Hz, J_2 = 26.7 Hz, $C^{3'}$), 112.2 (dd, 1 C, J_1 = 3.4 Hz, J_2 = 22.1 Hz, $C^{5'}$), 112.7 (C^3), 113.9 (C^1), 125.2 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.6 (dd, 1 C, J_1 = 3.4 Hz, J_2 = 9.5 Hz, $C^{6'}$), 127.5 C^{4a}), 128.6 (C^9), 129.1 (C^6), 129.6 (C^4) 131.0 (C^7), 133.4 (C^8), 133.7 (C^{5a}), 144.8 (C^{11a}), 145.6 (C^2); 149.7 (C^{9a}), 165,0 (-C(O)-NH-) 191.0 (C^5), not detected ($C^{2'/4'}$)

8-(2,4-Difluor-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-carbonsäure(2-dimethylaminoethyl)-amid (18l)



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 10 ml DCM and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h. The remainig substance is taken up in 15 ml DCM and carefully added to a solution of 4.7 g (53.3 mmol) Dimethylethylendiamin in 10 ml DCM at 0°C. The mixture is stirred over night at room temperature, poured into 300 ml water and extracted with DCM. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2, DCM/EtOH, 95+5). The product is further purified by recrystallization (ethyl acetate / hexane).

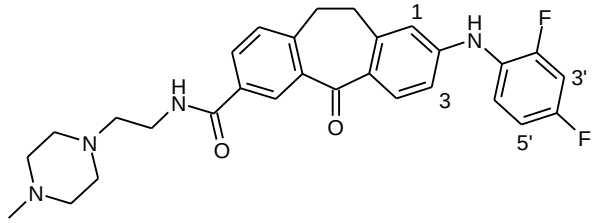
$C_{26}H_{25}F_2N_3O_2$ (Mr = 449.50)

Yield	2 %
Melting point	116°C
IR (ATR)	3266, 2941, 1636, 1636, 1603, 1578, 1506, 1407, 1354, 1258, 1139, 1095, 964, 844, 760, 728 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.15 (s, 6H, -N(CH_3)$_2$), .2.31-2.43 (m, 2 H, C^2-H_{Ethyl}), 2.31-2.43 (m, 2 H, C^1-H_{Ethyl}), 2.95-3.17 (m, 1 H, -H_2-CH_2-), partially covered by $H_2$0 (m, 1 H, C^2-

H_{Ethyl}), 6.61 (s, 2 H, C^1-H), 6.75 (d, 1 H, J = 8.6 Hz, C^3-H), 6.97-7.19 (m, 1 H, $C^{3'}$-H), 7.28-7.52 (m, 3 H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.83-8,07 (m, 2 H, C^8-H, C^4-H), 8.25-8.38 (m, 1 H, C^6-H), 8.43-8.59 (m, 1 H, Amid), 8.68 (s, 1 H, -NH-)

^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 34.2 (C^{10}), 35.8 (C^{11}), 37.8 (C^1_{Ethyl}), 45.6 (-N(CH_3)$_2$), 58.5 (C^2_{Ethyl}), 105.8 (dd, 1 C, J_1 = 24.9 Hz, J_2 = 27.5 Hz, $C^{3'}$), 112.7 (C^3), 113.9 (C^1), 127.4 (C^{4a}), 129.3 (C^9), 129.5 (C^6), 130.7 (C^4) 133.2 (C^7), 133.7 (C^8), 139.2 (C^{5a}), 144.9 (C^{11a}), 145.7 (C^2); 149.7 (C^{9a}), 165.8 (-C(O)-NH-) 190.8 (C^5), not detected ($C^{1'/2'/4'/5'/6'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide (18m)



Compound (**18m**) is prepared in a similar manner as compound (**18d**).

0.2 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 0.13 g (0.80 mmol) CDI, 0.23 g (1.58 mmol) 1-(2-aminoethyl)-4-methyl-piperazine.

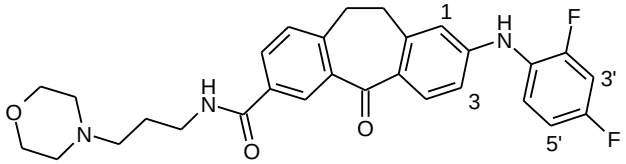
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{29}H_{30}F_2N_4O_2$ (Mr = 504.58)

Yield	83 %
Melting point	60°C
HRMS $[M+H]^+$	505.240605 (calc. 505.240959)
IR (ATR)	3269, 3071, 2937, 2805, 1633, 1603, 1580, 1505, 1355, 1216, 1140, 1115, 1095, 965, 854, 785, 680 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2.00-2,19 (m, 3H, -CH_3), 2.18-2.46 (m, 10H, $C^{2,3,5,6}_{Piperazine}$, C^1-H_{Ethyl}), 2.85-3.17 (m, 4H, -

	CH_2-CH_2-), 3.28-.3.44 (m, 1H, C^2-H_{Ethyl}), 6.62 (s, 1 H, C^1-H), 6.77-6.87 (m, 1 H, C^3-H), 6.92-7.21 (m, 1 H, $C^{3'}$-H), 7.25-7.56 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.83 (dd, 1H, J_1 = 1,3 Hz, J_2 = 7,83 Hz, C^8-H), 7.99 (d, 1H, J = 8,7 Hz C^4-H), 8.32 (s, 1 H, C^6-H), 8.41-8.55 (m, 1H, Amid), 8.58 (s, 1H, -NH-)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 34.1 (C^{10}), 35.8 (C^{11}), 37.3 ($C^1{}_{Ethyl}$), 46.1 ($-CH_3$), 53.0 ($C^2{}_{Piperazine}$, $C^6{}_{Piperazine}$), 55.1 ($C^2{}_{Ethyl}$), 57.3 ($C^3{}_{Piperazine,}$ $C^5{}_{Piperazine}$), 105.3 (dd, 1 C, J_1 = 24.2 Hz, J_2 = 26.5 Hz, $C^{3'}$), 112.2 (dd, 1 C, J_1 = 3.4 Hz, J_2 = 21.3 Hz, $C^{5'}$), 112.7 (C^3), 113.9 (C^1), 125.2 (dd, 1 C, J_1 = 4.0 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.6 (dd, 1 C, J_1 = 3.4 Hz, J_2 = 9.9 Hz, $C^{6'}$), 127.5 (C^{4a}), 129.2 (C^9), 129.5 (C^6), 130.7 (C^4) 133.2 (C^7), 133.7 (C^8), 139.3 (C^{5a}), 144.9 (C^{11a}), 145.6 (C^2); 149.7 (C^{9a}), 165.5 (-C(O)-NH-), 190.4(C^5), not detected ($C^{2'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid (3-morpholin-4-yl-propyl)-amide (18n)



Compound (**18n**) is prepared in a similar manner as compound (**18l**).

0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene-3-carboxylic acid (**17**), 10 ml DCM, 1.25 ml (17.2 mmol) $SOCl_2$, 15 ml DCM, 2.0 g (13.9 mmol) 3-Morpholin-4-yl-propylamine, 8 ml (57.7 mmol) triethylamine, 10 ml DCM.

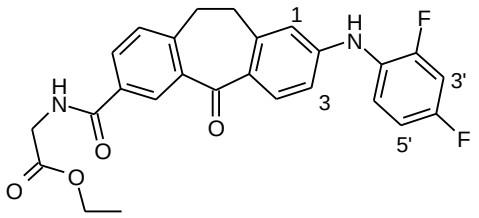
The crude product is purified by automated column chromatography (SiO_2, DCM/EtOH, 87+13).

$C_{29}H_{29}F_2N_3O_3$ (Mr = 505.57)

Yield	45%
Melting point	61°C

HRMS $[M+H]^+$	506.225411 (calc. 506.22497)
IR (ATR)	3277, 2925, 2854, 1718, 1636, 1603, 1504, 1439, 1355, 1259, 1140, 1113, 965, 916, 846, 785, 762, 728 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 2,92-4,04 partially covered by H_2O (m, 18 H, $-CH_2-CH_2-$, $C^{1,2,3}$-H_{Propyl}, $C^{2,3,5,6}$-$H_{Morpholine}$), 6.62 (s, 1 H, C^1-H), 6.74 (d, 1 H, J = 8.8 Hz, C^3-H), 7.00-7.19 (m, 1 H, $C^{3'}$-H), 7.27-7.49 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.92 (dd, 1H, J_1 = 7.8 Hz, J_2 = 2.0 Hz, C^8-H), 7.98 (d, 1H, J = 8.7 Hz, C^4-H) 8.33 (d, 1H, J = 1.9 Hz, C^6-H), 8.59 (s, 1H, -NH-), 8.73 (t, 1H, J = 5.5 Hz, Amid)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 24.1 (C^2_{Propyl}), 34.1 (C^{10}), 35.8 (C^{11}), 37.0 (C^1_{Propyl}), 51.6 (C^3_{Propyl}), 54.6 (2 C, $C^2_{Morpholine}$, $C^6_{Morpholine}$), 63.9 (2 C, $C^3_{Morpholine}$, $C^5_{Morpholine}$), 105.3 (dd, 1 C, J_1 = 24.2 Hz, J_2 = 26.5 Hz, $C^{3'}$), 112.2 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.5 Hz, $C^{5'}$), 112.7 (C^3), 113.7 (C^1), 125.1 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.6 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 9.7 Hz, $C^{6'}$), 127.4 (C^{4a}), 129.3 (C^9), 129.5 (C^6), 130.8 (C^4) 132.9 (C^7), 133.7 (C^8), 139.3 (C^{5a}), 145.1 (C^{11a}), 145.7 (C^2); 149.7 (C^{9a}), 166.1 (-C(O)-NH-) 190.8 (C^5), not detected ($C^{2'/4'}$)

{[8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-3-carbonyl]-amino}-acetic acid ethyl ester (18o)



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 10 ml DCM and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h and subsequently added to a suspension of 1.46 g (10.5 mmol) glycin ethyl ester*HCl in 13.2 ml (95.2 mmol) triethylamine and 10 ml DCM at 0°C. Stirring continues for 3 h

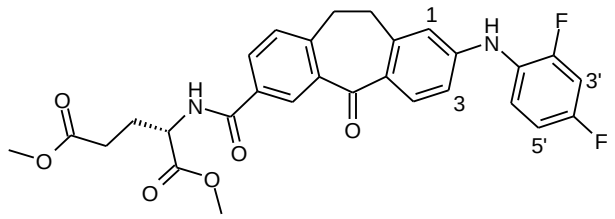
at room temperature. Afterwards the reaction mixture is poured in 300 ml water and extracted with DCM. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 2+8).

$C_{26}H_{22}F_2N_2O_4$ (Mr = 464.47)

Yield	12 %
Melting point	amorphous solid
HRMS $[M+H]^+$	465.162378 (calc. 465.162040)
IR (ATR)	3308, 2929, 1733, 1507, 1259, 1194, 1094, 964, 845 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 1,31 (t, 3 H, J = 7.1 Hz, $-CH_3$), 3.03-3.23 (m, 4 H, $-CH_2-CH_2-$), 4.19-4.31 (m, 4 H, $-C\underline{H_2}-NH-$ / $-C\underline{H_2}-CH_3-$), 5.97 (s, 1 H, -NH-), 6.66 (d, 1 H, J = 2.0 Hz, C^1-H), 6.81-7.00 (m, 4 H, $C^{3/6'/3'}$-H / -CONH-), 7.28-7.43 (m, 2 H, $C^{5'/9}$-H), 7.95 (dd, 1 H, J_1 = 7.9 Hz, J_2 = 2.0 Hz, C^8-H), 8.14 (d, 1 H, J = 8.9 Hz, C^4-H), 8.39 (d, 1 H, J = 1.8 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 14.1 ($-CH_3$), 34.7 (C^{10}), 35.8 (C^{11}), 41.9 ($-NH-CH_2-$), 61.6 ($-O-CH_2-$), 104.8 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 113.3 (C^3), 114.6 (C^1), 123.9 (dd, J_1 = 2.2 Hz, J_2 = 9.5 Hz, $C^{6'}$), 124.8 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, $C^{1'}$), 128.9 (C^9), 129.1 (C^{4a}), 129.4 (C^6), 131.2 (C^4), 132.2 (C^7), 134.2 (C^8), 139.1 (C^{5a}), 145.3 (C^{11a}), 145.4 (C^2), 148.1 (C^{9a}), 155.3 (dd, J_1 = 12.0 Hz, J_2= 246.1 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.3 Hz, J_2 = 244.6 Hz, $C^{2'}$), 166.7 (-CONH-), 170.0 (-COO-), 191.3 (C^5)

***(S)*-2-{[8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carbonyl]-amino}-pentanedioic acid dimethyl ester (18p)**



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-difluor-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carbonxylic acid (**17**) are dissolved in 10 ml DCM and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h and subsequently added to a suspension of 2.21 g (10.4 mmol) L-glutamic acid dimethyl ester*HCl in 6.6 ml (47.6 mmol) triethylamin and 10 ml DCM at 0°C. Stirring continues over night at room temperature. Afterwards the reaction mixture is poured into 300 ml water and extracted with DCM. Solvents are removed in a rotary evaporator.

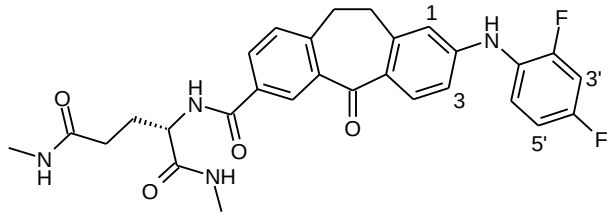
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 2+8).

$C_{29}H_{26}F_2N_2O_6$ (Mr = 536.54)

Yield	42 %
Melting point	amorphous solid
HRMS $[M+Na]^+$	559.165236 (calc. 559.165114)
IR (ATR)	3308, 2951, 1732, 1603, 1581, 1508, 1258, 1199, 1095, 847 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.11-2.21 (m, 1 H, Glu), 2.28-2.37 (m, 1 H, Glu), 2.45-2.56 (m, 2 H, Glu), 3.07-3.24 (m, 4 H, -CH_2-CH_2-), 3.70 (s, 3 H, -CH_3), 3.79 (s, 3 H, -CH_3), 6.68 (d, 1 H, J = 2.1 Hz, C^1), 6.83-7.00 (m, 3 H, $C^{3/3'/6'}$), 7.06 (d, 1 H, J = 7.5 Hz, -CONH-), 7.28-7.44 (m, 2 H, $C^{5'/9}$), 7.95 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 8.0 Hz, C^8), 8.17 (d, 1 H, J = 8.7 Hz, C^4-H), 8.39 (d, 1 H, J = 2.0 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 27.3 (C^3 Glu), 30.2 (C^4 Glu), 34.7 (C^{10}), 35.8 (C^{11}), 51.9 (-CH_3), 52.3 (-CH_3), 52.6 (C^2 Glu), 104.8 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 =

3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 113.2 (C^3), 114.6 (C^1), 123.8 (dd, J_1 = 2.2 Hz, J_2 = 8.7 Hz, $C^{6'}$), 124.9 (dd, J_1 = 3.3 Hz, J_2 = 11.3 Hz, $C^{1'}$), 128.9 (C^9), 129.3 (C^{4a}), 129.4 (C^6), 131.2 (C^4), 132.2 (C^7), 134.2 (C^8), 139.2 (C^{5a}), 145.2 (C^{11a}), 145.5 (C^2), 148.0 (C^{9a}), 155.3 (dd, J_1 = 11.6 Hz, J_2= 246.5 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.3 Hz, J_2 = 244.6 Hz, $C^{2'}$), 166.4 (-CONH-), 172.3 (-COO-), 173.5 (-COO-) 191.3 (C^5)

_(S)_-2-{[8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carbonyl]-amino}-pentandioic acid bis-methylamide (18q)



Compound (**18q**) is prepared in a similar manner as compound (**18d**).

0.3 g (0.79 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**)**,** 10 ml THF, 0.19 g (1.17 mmol) CDI, 0.32 g (1.85 mmol) (2-amino-pentanedioic acid bis-methylamide).

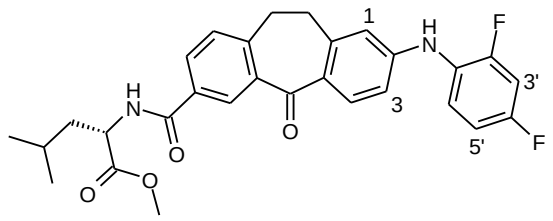
The crude product is purified by automated column chromatography (SiO_2, methanol/ethyl acetate 2+8). The product is further purified by washing using ethyl acetate.

$C_{29}H_{28}F_2N_4O_4$ (Mr = 534.57)

Yield	12 %
Melting point	56°C
HRMS $[M+H]^+$	535.214984 (calc. 535.215138)
IR (ATR)	3298, 2938, 1608, 1566, 1508, 1356, 1274, 1262, 1138, 1098, 966, 927, 841, 786, 690 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (f = 200 MHz): 1.81-2,23 (m, 4H, C^3-$H_{Glutamic\ acid}$, C^4-$H_{Glutamic\ acid}$), 2.49-2.64 (m, 6H, -CH_3), 2.92-3.18 (m, 4H, -CH_2-CH_2-), 4.24-4.46 (m, 1H, C^2-$H_{Glutamic\ acid}$), 6.62 (s, 1 H, C^1-H), 6.75 (d, 1 H, J = 9,8 Hz, C^3-H), 7.02-7.17

	(m, 1 H, $C^{3'}$-H), 7.28-7.51 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^{9}-H), 7.63-7.77 (m, 1H, N^{1}-H_{Amid}), 7.77-7.89 (m, 1H, N^{2}-H_{Amid}) 7.90-8.07 (m, 2H, C^{8}-H, C^{4}-H), 8.37 (s, 1H, C^{6}-H), 8.52-8.65 (m, 2H, -NH-, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 50 MHz): 25.8 ($-CH_3$), 26.0 ($-CH_3$), 27.8 ($C^{3}_{\text{Glutamic acid}}$), 32.4 ($C^{4}_{\text{Glutamic acid}}$), 34.1 ($C^{10}$), 35.8 ($C^{11}$), 53.8 ($C^{2}_{\text{Glutamic acid}}$), 105.3 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.3 Hz, $C^{3'}$), 112.2 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 21.9 Hz, $C^{5'}$), 112.7 (C^{3}), 113.9 (C^{1}), 125.2 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 12.0 Hz, $C^{1'}$), 126.6 (dd, 1 C, J_1 = 3.2 Hz, J_2 = 9.7 Hz, $C^{6'}$), 127.5 (C^{4a}), 129.0 (C^{9}), 129.9 (C^{6}), 131.1 (C^{4}) 132.8 (C^{7}), 133.7 (C^{8}), 139.3 (C^{5a}), 145.0 (C^{11a}), 145.6 (C^{2}); 149.7 (C^{9a}), 165.5 (-C(O)-NH-), 172.1 ($C^{1}_{\text{Glutamic acid}}$), 172.4 ($C^{5}_{\text{Glutamic acid}}$) 190.9($C^{5}$), not detected ($C^{2'/4'}$)

_(S)_-2{[8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carbonyl]-amino}4-methyl-pentanoic acid methyl ester (18r)



Compound (**18r**) is prepared in a similar manner as compound (**18d**).

0.20 g (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 10 ml THF, 0.13 g (0.80 mmol) CDI, 0.29 g (1.58 mmol) L-leucine methyl ester hydrochlorid.

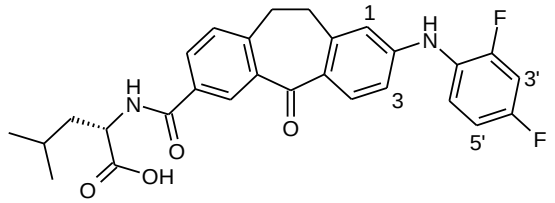
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 75+25).

$C_{29}H_{28}F_2N_2O_4$ (Mr = 506.55)

Yield	37 %
Melting point	94°C
HRMS $[M+H]^+$	507.208947 (calc. 507.208990)

IR (ATR)	3287, 2959, 1659, 1602, 1578, 1545, 1507, 1360, 1262, 1139, 1115, 966, 842, 783, 731 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 0.77-0.98 (m, 6H, -$(CH_3)_2$), 2.97-3.20 (m, 4 H, -CH_2-CH_2-), 3.63 (s, 3H, -O-CH_3), 4.40-4.62 (m, 1H, C^2-H_{Pentyl}), 1.48-1.88 (m, 3H, C^3-H_{Pentyl}, C^4-H_{Pentyl}), 6.62 (s, 1 H, C^1-H), 6.76 (d, 1 H, J = 9.8 Hz, C^3-H), 7.02-7.20 (m, 1 H, $C^{3'}$-H), 7.28-7.51 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 7.89-8.07 (m, 2H, C^8-H, C^4-H), 8.37 (d, 1H, J = 2,0 Hz, C^6-H), 8.58 (s, 1H, -NH-), 8.83 (d, 1H, J = 7,2 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 21.1 (2 C, -$(CH_3)_2$), 24.4 (C^3_{Pentyl}), 33.8 (C^{10}), 35.4 (C^{11}), 38.9 (C^2_{Pentyl}), 50.9 (C^1_{Pentyl}), 51.8 (-O-CH_3), 105.0 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.8 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 22.4 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.8 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.7 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.5 Hz, J_2 = 10.5 Hz, $C^{6'}$), 127.0 (C^{4a}), 128.9 (C^9), 129.4 (C^6), 130.7 (C^4) 132.0 (C^7), 133.3 (C^8), 139.0 (C^{5a}), 144.9 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 165.9 (-C(O)-NH-), 173.0(C^5), not detected ($C^{2'/4'}$)

_(S)_-2-{[8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carbonyl]-amino}-4-methylpentanoic acid (18s)



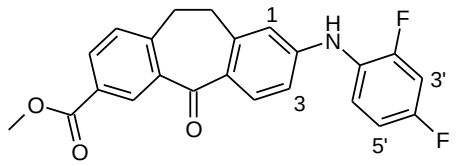
0.06 g (0.12 mmol) (**18r**) are dissolved in 10 ml methanol. 0.5 g potassium hydroxide and 1 ml water are added. The reaction mixture is refluxed until complete conversion can be observed (monitored by TLC). Afterwards the mixture is acidified and extracted with ethyl acetate. Solvents are removed in a rotary evaporator.

$C_{28}H_{26}F_2N_2O_4$ (Mr = 492.53)

Yield	28 %
Melting point	149°C

HRMS $[M+H]^+$	493.193660 (calc. 493.193340)
IR (ATR)	3310, 2956, 1720, 1604, 1580, 1510, 1355, 1262, 1216, 1141, 1115, 1097, 965, 847, 786, 728, 678 cm^{-1}
^{1}H-NMR (DMSO-*d6*)	δ in ppm (*f* = 200 MHz): 0.83-0.97 (m, 6H, -$(CH_3)_2$), 1.39-1.89 (m, 3H, C^3-H_{Pentyl}, C^4-H_{Pentyl}), 2.95-3.17 (m, 4H, -CH_2-CH_2-), 4.29-4.59 (m, 1H, C^2-H_{Pentyl}), 6.62 (s, 1H, C^1-H), 6.75 (d, 1 H, J = 9.6 Hz, C^3-H), 6.97-7.19 (m, 1H, $C^{3'}$-H), 7.27-7.53 (m, 3H, $C^{5'}$-H, $C^{6'}$-H, C^9-H), 8.32-8.41 (m, 2H, C^8-H, C^4-H), 8.32-8.41 (m, 1H, C^6-H), 8.57 (s, 1H, -NH-), 8.66 (d, 1H, J = 7,9 Hz, Amide)
^{13}C-NMR (DMSO-*d6*)	δ in ppm (*f* = 100 MHz): 24.5 (C^3_{Pentyl}), 33.9 (C^{10}), 35.6 (C^{11}), 38.9 (C^2_{Pentyl}), 50.9 (C^1_{Pentyl}), 51.85 (-O-CH_3), 104.9 (dd, 1 C, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.9 (dd, 1 C, J_1 = 3.6 Hz, J_2 = 22.4 Hz, $C^{5'}$), 112.3 (C^3), 113.5 (C^1), 124.5 (dd, 1 C, J_1 = 3.3 Hz, J_2 = 12.7 Hz, $C^{1'}$), 126.2 (dd, 1 C, J_1 = 2.5 Hz, J_2 = 10.5 Hz, $C^{6'}$), 127.0 (C^{4a}), 128.9 (C^9), 129.4 (C^6), 130.7 (C^4) 132.0 (C^7), 133.3 (C^8), 139.0 (C^{5a}), 144.9 (C^{11a}), 145.3 (C^2); 149.3 (C^{9a}), 165.8 (-C(O)-NH-), 173.0(C^5), not detected ($C^{2'/4'}$)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid methyl ester (19a)



200 mg (0.51 mmol) 8-(2,4-difluor-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-carboxylic acid (**17**) are dissolved in 50 ml methanol and 1 ml H_2SO_4 (98 %) is added. The mixture is refluxed for 3 h.

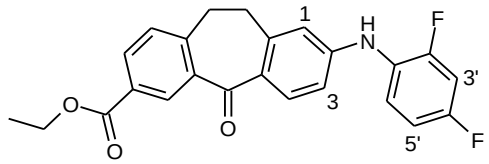
After complete conversion (monitored by TLC), the reaction mixture is poured into 300 ml water and extracted with ethyl acetate. The combined organic layers are washed with NaOH (dil.). Solvents are removed in a rotary evaporator.

The crude product is purified by recrystallization (ethyl acetate / hexane).

$C_{23}H_{17}F_2NO_3$ (Mr = 393.39)

Yield	> 90 %
Melting point	155°C
HRMS $[M+H]^+$	394.124888 (calc. 394.124926)
IR (ATR)	3376, 1718, 1603, 1504, 1242, 1131, 962, 832, 760 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 3.06-3.23 (m, 4 H, -CH_2-CH_2-), 3.92 (s, 3 H, -CH_3), 6.00 (s, 1 H, -NH-), 6.66 (d, 1 H, J = 2.4 Hz, C^1-H), 6.81-6.99 (m, 3 H, $C^{3/6'/3'}$-H), 7.25-7,41 (m, 2 H, $C^{5'/9}$-H), 8.06 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 8.0 Hz, C^8-H), 8.16 (d, 1 H, J = 8.7 Hz, C^4-H), 8,66 (d, 1 H, J = 1.8 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 34.8 (C^{10}), 35.7 (C^{11}), 52.1 (-CH_3), 104.8 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 4.0 Hz, J_2 = 22.2 Hz, $C^{5'}$), 113.3 (C^3), 114.6 (C^1), 123.9 (dd, J_1 = 2.6 Hz, J_2 = 9.0 Hz, $C^{6'}$), 124.9 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, $C^{1'}$), 128.9 (C^9) 129.0 (C^{4a}), 129.2 (C^7), 132.3 (C^6), 132.6 (C^4), 134.1 (C^8), 139.5 (C^{5a}), 145.1 (C^{11a}), 146.4 (C^2), 148.0 (C^{9a}), 155.3 (dd, J_1 = 12.0 Hz, J_2= 246.0 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.2 Hz, J_2 = 241.7 Hz, $C^{2'}$), 166.5 (-COO-), 191.0 (C^5)

8-(2,4-Difluor-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-3-carbonsäure ethyl ester (19b)



Compound (**19b**) is prepared in a similar manner as compound (**19a**).

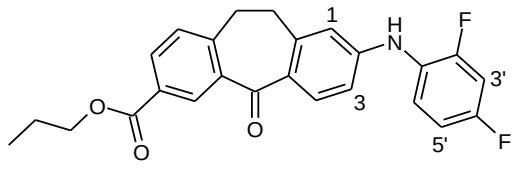
300 mg (0,79 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carbonxylic acid (**17**), 50 ml ethanol, 1 ml H_2SO_4 (98 %)

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 7+3).

$C_{24}H_{19}F_2NO_3$ (Mr = 407.42)

Yield	> 90 %
Melting point	148°C
HRMS $[M+H]^+$	408.140857 (calc. 408.140576)
IR (ATR)	3373, 1713, 1602, 1560, 1504, 1095, 961, 832, 759, 692, 449 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 1.40 (t, 3 H, J = 7.1 Hz, -CH_3), 3.06-3.26 (m, 4 H, -CH_2-CH_2-), 4.39 (q, 2 H, J = 7.2 Hz, -O-CH_2-), 5.89 (s, 1 H, -NH-), 6.68 (d, 1 H, J = 2.1 Hz, C^1-H), 6.82-7.01 (m, 3 H, $C^{3/6'/3'}$-H), 7.25-7.44 (m, 2 H, $C^{5'/9}$-H), 8.08 (dd, 1 H, J_1 = 7.9 Hz, J_2 = 1.8 Hz, C^8-H), 8.19 (d, 1 H, J = 8.7 Hz, C^4-H), 8.66 (d, 1 H, J = 1.8 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 14.3 (-CH_3), 34.7 (C^{10}), 35.8 (C^{11}), 61.1 (-O-CH_2-), 104.8 (dd, J_1 = 24.0 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 113.4 (C^3), 114.7 (C^1), 123.7 (dd, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 124.9 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, $C^{1'}$), 128.9 (C^{4a}), 129.3 (C^9), 129.3 (C^7), 132.2 (C^6), 132.6 (C^4), 134.2 (C^8), 139.5 (C^{5a}), 145.2 (C^{11a}), 146.2 (C^2), 147.9 (C^{9a}), 155.2 (dd, J_1 = 12.0 Hz, J_2= 246.1 Hz, $C^{4'}$), 158.7 (dd, J_1 = 10.9 Hz, J_2 = 244.3 Hz, $C^{2'}$), 166.1 (-COO-), 191.5 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid propyl ester (19c)



Compound (**19c**) is prepared in a similar manner as compound (**19a**).

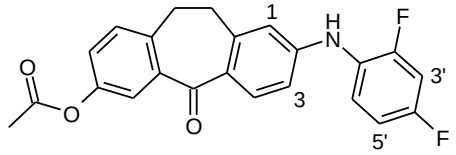
300 mg (0.79 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**), 50 ml n-propanol, 0.5 ml H_2SO_4 (98 %).

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 85+15).

$C_{25}H_{21}F_2NO_3$ (Mr = 421.45)

Yield	> 90 %
HRMS $[M+H]^+$	422.156290 (calc. 422.156226)
IR (ATR)	3372, 2969, 1714, 1604, 1560, 1504, 1355, 1240, 1129, 962, 834, 759, 692 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 1.03 (t, 3 H, J = 7.4 Hz, $-CH_3$), 1.69-1.92 (m, 2 H, $-C\underline{H_2}-CH_3$) 3.04-3.29 (m, 4 H, $-CH_2-CH_2-$), 4.30 (t, 2 H, J = 7.0 Hz, $-O-CH_2-$), 6.68 (d, 1 H, J = 2.2 Hz, C^1-H), 6.82-7.03 (m, 3 H, $C^{3/6'/3'}$-H), 7.22-7.46 (m, 2 H, $C^{5'/9}$-H / -NH-), 8.08 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 1.9 Hz, C^8-H), 8.19 (d, 1 H, J = 8.8 Hz, C^4-H), 8.66 (d, 1 H, J = 1.8 Hz, C^6-H)

Acetic acid 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]-cycloheptен-3-yl ester (19d)



Under argon atmosphere 0.57 g (1.9 mmol) acetic acid 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-yl ester **(10d)** 0.26 g (2.0 mmol) 2,4-difluoraniline, 0.05 g (0.22 mmol) $Pd(OAc)_2$, 0.14 g (0.29 mmol) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-biphenyl, 2.6 g (8.0 mmol) Cs_2CO_3 and 15 ml of toluene are added to a three-necked flask. The mixture is heated to 100°C. After 3 h (monitored by TLC), the reaction mixture is poured into water and extracted with ethyl acetate. Solvents are removed in a rotary evaporator.

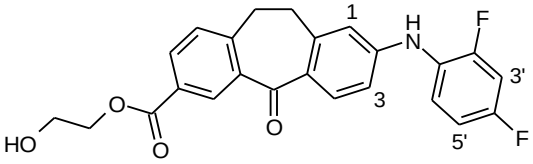
The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 7+3).

$C_{23}H_{17}F_2NO_3$ (Mr = 393.39)

Yield	4 %

HRMS $[M+H]^+$	394.124859 (calc. 394.124926)
IR (ATR)	3316, 2935, 1766, 1604, 1531, 1498, 1193, 11139, 850, 554 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.32 (s, 1 H, $-CH_3$), 3.08-3.20 (m, 4 H, $-CH_2-CH_2-$), 5.86 (s, 1 H, -NH-), 6.67 (d, 1 H, J = 2.4 Hz, C^1-H), 6.80-7.00 (m, 3 H, $C^{3/6'/3'}$-H), 7.11-7.26 (m, 2 H, $C^{5'/9}$-H), 7.30-7.44 (m, 1 H, C^8-H), 7.77 (d, 1 H, J = 2.4 Hz, C^6-H), 8.14 (d, 1 H, J = 8.8 Hz, C^4-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 21.0 ($-CH_3$), 34.3 (C^{10}), 35.9 (C^{11}), 104.8 (dd, J_1 = 23.2 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$), 113.3 (C^3), 114.6 (C^1), 123.6 (dd, J_1 = 2.9 Hz, J_2 = 9.5 Hz, $C^{6'}$), 123.8 (C^6), 125.0 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, $C^{1'}$), 125.1 (C^8) 129.5 (C^{4a}), 130.0 (C^9), 134.2 (C^4), 139.4 (C^{5a}), 140.1 (C^{9a}), 145.3 (C^{11a}), 147.7 (C^2), 149.4 (C^7), 155.1 (dd, J_1 = 11.6 Hz, J_2= 245.8 Hz, $C^{4'}$), 158.6 (dd, J_1 = 11.3 Hz, J_2 = 244.6 Hz, $C^{2'}$), 169.5 (-COO-), 190.9 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid 2-hydroxy-ethyl ester (19e)



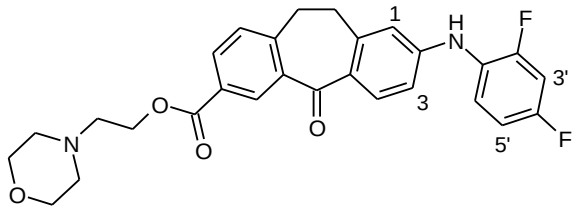
Under argon atmosphere 100 mg (0.26 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) is dissolved in 10 ml DCM gelöst and 0.5 ml (6.9 mmol) $SOCl_2$ are added. The mixture is refluxed for 1 h and subsequently carefully added to a solution of 5 g ethylene glycole in 10 ml DCM at 0°C. Stirring continues over night at room temperature. Afterwards the reaction mixture is poured into 200 ml water and is extracted with DCM. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 5+5).

$C_{24}H_{19}F_2NO_4$ (Mr = 423.42)

Yield	0.05 g (39 %)
Melting point	136°C
Purity	93 %
HRMS $[M+H]^+$	424.135194 (calc. 424.135491)
IR (ATR)	3482, 3267, 1716, 1603, 1528, 1249, 1124, 1061, 860, 760 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 400 MHz): 3.00-3.30 (m, 4 H, -CH_2-CH_2-), 3.98 (t, 2 H, J = 4.6 Hz, -COO-CH_2-C<u>H_2</u>-O-), 4.48 (t, 2 H, J = 4.6 Hz, -COO-C<u>H_2</u>-CH_2-O-), 5.88 (s, 1 H, -NH-), 6.67 (d, 1 H, J = 2.3 Hz, C^1-H), 6.78-7.03 (m, 3 H, $C^{3/6'/3'}$-H), 7.23-7.46 (m, 2 H, $C^{5'/9}$-H), 8.09 (dd, 1 H, J_1 = 2.0 Hz, J_2 = 7.8 Hz, C^8-H), 8.17 (d, 1 H, J = 8.8 Hz, C^4-H), 8.68 (d, 1 H, J = 1.9 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 34.8 (C^{10}), 35.7 (C^{11}), 61.4 (-COO-CH_2-<u>C</u>H_2-O-), 66.8 (-COO-<u>C</u>H_2-CH_2-O-), 104.8 (dd, J_1 = 23.2 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 4.0 Hz, J_2 = 22.2 Hz, $C^{5'}$), 113.4 (C^3), 114.6 (C^1), 123.8 (dd, J_1 = 2.2 Hz, J_2 = 9.5 Hz, $C^{6'}$), 124.8 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, $C^{1'}$), 128.6 (C^{4a}), 129.0 (C^9), 129.2 (C^7), 132.3 (C^6), 132.8 (C^4), 134.2 (C^8), 139.5 (C^{5a}), 145.2 (C^{11a}), 146.6 (C^2), 147.9 (C^{9a}), 155.3 (dd, J_1 = 12.0 Hz, J_2= 246.1 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.6 Hz, J_2 = 244.3 Hz, $C^{2'}$), 166.4 (-<u>C</u>OO-), 191.4 (C^5)

8-(2,4-Difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene-3-carboxylic acid 2-morpholin-4-yl-ethyl ester (19f)



Under argon atmosphere 200 mg (0.53 mmol) 8-(2,4-difluoro-phenylamino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-3-carboxylic acid (**17**) are dissolved in 50 ml of DCM and 1.25 ml (17.2 mmol) $SOCl_2$ are added. The mixture is refluxed for 1h. 1.08 g (8.2 mmol) 2-morpholin-4-yl-ethanol is added at room temperature and stirring continued over night. Afterwards the reaction mixture is poured in 200 ml of water and extracted with DCM. Solvents are removed in a rotary evaporator.

The crude product is purified by automated column chromatography (SiO_2, petroleum ether (60-90)/ethyl acetate 1+9).

$C_{28}H_{26}F_2N_2O_4$ (Mr = 492.53)

Yield	26 %
Melting point	145°C
HRMS $[M+H]^+$	493.193321 (calc. 493.193340)
IR (ATR)	3372, 2956, 2854, 1711, 1605, 1558, 1505, 1258, 1117, 962, 834, 759, 694 cm^{-1}
^{1}H-NMR ($CDCl_3$)	δ in ppm (*f* = 200 MHz): 2.71-2.85 (m, 4 H, $C^{2/6}_{Morpholinyl}$-H), 2.97 (t, 2 H, J = 5.4 Hz, -N-CH_2-$C\underline{H_2}$-O-), 3.08-3.25 (m, 4 H, -CH_2-CH_2-), 3.85 (t, 4 H, J = 4.6 Hz, $C^{3/5}_{Morpholinyl}$-H), 4.60 (t, 2 H, J = 5.6 Hz, -N-CH_2-$C\underline{H_2}$-O-), 5.92 (s, 1 H, -NH-), 6.67 (d, 1 H, J = 2.3 Hz, C^1-H), 6.83-7.00 (m, 3 H, $C^{3/6'/3'}$-H), 7.28-7,44 (m, 2 H, $C^{5'/9}$-H), 8.07 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 7.8 Hz, C^8-H), 8.17 (d, 1 H, J = 8.7 Hz, C^4-H), 8,64 (d, 1 H, J = 1.8 Hz, C^6-H)
^{13}C-NMR ($CDCl_3$)	δ in ppm (*f* = 100 MHz): 34.8 (C^{10}), 35.7 (C^{11}), 53.5 (2 C, $C^{2/6}_{Morpholinyl}$), 56.9 (2 C, $C^{3/5}_{Morpholinyl}$), 61.5 (-N-$\underline{C}H_2$-CH_2-O-), 66.0 (-N-CH_2-$\underline{C}H_2$-O-), 104.8 (dd, J_1 = 23.2 Hz, J_2 = 26.2 Hz, $C^{3'}$), 111.4 (dd, J_1 = 3.6 Hz, J_2 = 21.8 Hz, $C^{5'}$),

113.3 (C^{3}), 114.6 (C^{1}), 123.9 (dd, J_1 = 2.6 Hz, J_2 = 9.0 Hz, $C^{6'}$), 124.8 (dd, J_1 = 3.6 Hz, J_2 = 12.4 Hz, $C^{1'}$), 128.6 (C^{4a}) 129.1 (C^{9}), 129.2 (C^{7}), 132.3 (C^{6}), 132.7 (C^{4}), 134.2 (C^{8}), 139.5 (C^{5a}), 145.2 (C^{11a}), 146.7 (C^{2}), 148.0 (C^{9a}), 155.3 (dd, J_1 = 12.0 Hz, J_2= 246.0 Hz, $C^{4'}$), 158.8 (dd, J_1 = 11.0 Hz, J_2 = 245.0 Hz, $C^{2'}$), 165.7 (-<u>C</u>OO-), 191.2 (C^{5})

5 Selectivity data

SI-Table 2. Selectivity data of **16u** and **18j**.

Compound Name,KINOMEscan Gene Symbol,Entrez Gene Symbol,Percent Control,Compound Concentration (nM)	
16u,AAK1,AAK1,100,1000	18j,AAK1,AAK1,100,1000
16u,ABL1(E255K)-phosphorylated,ABL1,97,1000	18j,ABL1(E255K)-phosphorylated,ABL1,95,1000
16u,ABL1(F317I)-nonphosphorylated,ABL1,80,1000	18j,ABL1(F317I)-nonphosphorylated,ABL1,81,1000
16u,ABL1(F317I)-phosphorylated,ABL1,78,1000	18j,ABL1(F317I)-phosphorylated,ABL1,93,1000
16u,ABL1(F317L)-nonphosphorylated,ABL1,100,1000	18j,ABL1(F317L)-nonphosphorylated,ABL1,100,1000
16u,ABL1(F317L)-phosphorylated,ABL1,100,1000	18j,ABL1(F317L)-phosphorylated,ABL1,100,1000
16u,ABL1(H396P)-nonphosphorylated,ABL1,86,1000	18j,ABL1(H396P)-nonphosphorylated,ABL1,92,1000
16u,ABL1(H396P)-phosphorylated,ABL1,90,1000	18j,ABL1(H396P)-phosphorylated,ABL1,96,1000
16u,ABL1(M351T)-phosphorylated,ABL1,93,1000	18j,ABL1(M351T)-phosphorylated,ABL1,99,1000
16u,ABL1(Q252H)-nonphosphorylated,ABL1,79,1000	18j,ABL1(Q252H)-nonphosphorylated,ABL1,98,1000
16u,ABL1(Q252H)-phosphorylated,ABL1,96,1000	18j,ABL1(Q252H)-phosphorylated,ABL1,100,1000
16u,ABL1(T315I)-nonphosphorylated,ABL1,100,1000	18j,ABL1(T315I)-nonphosphorylated,ABL1,100,1000
16u,ABL1(T315I)-phosphorylated,ABL1,100,1000	18j,ABL1(T315I)-phosphorylated,ABL1,100,1000
16u,ABL1(Y253F)-phosphorylated,ABL1,100,1000	18j,ABL1(Y253F)-phosphorylated,ABL1,98,1000
16u,ABL1-nonphosphorylated,ABL1,85,1000	18j,ABL1-nonphosphorylated,ABL1,93,1000
16u,ABL1-phosphorylated,ABL1,95,1000	18j,ABL1-phosphorylated,ABL1,97,1000
16u,ABL2,ABL2,99,1000	18j,ABL2,ABL2,92,1000
16u,ACVR1,ACVR1,90,1000	18j,ACVR1,ACVR1,99,1000
16u,ACVR1B,ACVR1B,99,1000	18j,ACVR1B,ACVR1B,95,1000
16u,ACVR2A,ACVR2A,73,1000	18j,ACVR2A,ACVR2A,83,1000
16u,ACVR2B,ACVR2B,83,1000	18j,ACVR2B,ACVR2B,100,1000
16u,ACVRL1,ACVRL1,76,1000	18j,ACVRL1,ACVRL1,77,1000
16u,ADCK3,CABC1,100,1000	18j,ADCK3,CABC1,100,1000
16u,ADCK4,ADCK4,94,1000	18j,ADCK4,ADCK4,100,1000
16u,AKT1,AKT1,79,1000	18j,AKT1,AKT1,78,1000
16u,AKT2,AKT2,100,1000	18j,AKT2,AKT2,100,1000

16u,AKT3,AKT3,77,1000	18j,AKT3,AKT3,100,1000
16u,ALK,ALK,100,1000	18j,ALK,ALK,100,1000
16u,AMPK-alpha1,PRKAA1,95,1000	18j,AMPK-alpha1,PRKAA1,99,1000
16u,AMPK-alpha2,PRKAA2,100,1000	18j,AMPK-alpha2,PRKAA2,100,1000
16u,ANKK1,ANKK1,100,1000	18j,ANKK1,ANKK1,100,1000
16u,ARK5,NUAK1,92,1000	18j,ARK5,NUAK1,100,1000
16u,ASK1,MAP3K5,100,1000	18j,ASK1,MAP3K5,100,1000
16u,ASK2,MAP3K6,70,1000	18j,ASK2,MAP3K6,93,1000
16u,AURKA,AURKA,100,1000	18j,AURKA,AURKA,100,1000
16u,AURKB,AURKB,22,1000	18j,AURKB,AURKB,100,1000
16u,AURKC,AURKC,59,1000	18j,AURKC,AURKC,100,1000
16u,AXL,AXL,100,1000	18j,AXL,AXL,100,1000
16u,BIKE,BMP2K,94,1000	18j,BIKE,BMP2K,100,1000
16u,BLK,BLK,100,1000	18j,BLK,BLK,100,1000
16u,BMPR1A,BMPR1A,81,1000	18j,BMPR1A,BMPR1A,88,1000
16u,BMPR1B,BMPR1B,100,1000	18j,BMPR1B,BMPR1B,100,1000
16u,BMPR2,BMPR2,100,1000	18j,BMPR2,BMPR2,100,1000
16u,BMX,BMX,97,1000	18j,BMX,BMX,100,1000
16u,BRAF,BRAF,100,1000	18j,BRAF,BRAF,100,1000
16u,BRAF(V600E),BRAF,100,1000	18j,BRAF(V600E),BRAF,100,1000
16u,BRK,PTK6,100,1000	18j,BRK,PTK6,100,1000
16u,BRSK1,BRSK1,100,1000	18j,BRSK1,BRSK1,100,1000
16u,BRSK2,BRSK2,100,1000	18j,BRSK2,BRSK2,100,1000
16u,BTK,BTK,100,1000	18j,BTK,BTK,100,1000
16u,BUB1,BUB1,73,1000	18j,BUB1,BUB1,86,1000
16u,CAMK1,CAMK1,91,1000	18j,CAMK1,CAMK1,71,1000
16u,CAMK1D,CAMK1D,98,1000	18j,CAMK1D,CAMK1D,100,1000
16u,CAMK1G,CAMK1G,93,1000	18j,CAMK1G,CAMK1G,100,1000
16u,CAMK2A,CAMK2A,89,1000	18j,CAMK2A,CAMK2A,100,1000
16u,CAMK2B,CAMK2B,98,1000	18j,CAMK2B,CAMK2B,99,1000
16u,CAMK2D,CAMK2D,81,1000	18j,CAMK2D,CAMK2D,100,1000
16u,CAMK2G,CAMK2G,90,1000	18j,CAMK2G,CAMK2G,100,1000
16u,CAMK4,CAMK4,100,1000	18j,CAMK4,CAMK4,100,1000
16u,CAMKK1,CAMKK1,100,1000	18j,CAMKK1,CAMKK1,99,1000

16u,CAMKK2,CAMKK2,79,1000	18j,CAMKK2,CAMKK2,100,1000
16u,CASK,CASK,94,1000	18j,CASK,CASK,89,1000
16u,CDC2L1,CDK11B,85,1000	18j,CDC2L1,CDK11B,100,1000
16u,CDC2L2,CDC2L2,100,1000	18j,CDC2L2,CDC2L2,100,1000
16u,CDC2L5,CDK13,93,1000	18j,CDC2L5,CDK13,100,1000
16u,CDK11,CDK19,85,1000	18j,CDK11,CDK19,99,1000
16u,CDK2,CDK2,100,1000	18j,CDK2,CDK2,100,1000
16u,CDK3,CDK3,100,1000	18j,CDK3,CDK3,100,1000
16u,CDK4-cyclinD1,CDK4,96,1000	18j,CDK4-cyclinD1,CDK4,100,1000
16u,CDK4-cyclinD3,CDK4,99,1000	18j,CDK4-cyclinD3,CDK4,100,1000
16u,CDK5,CDK5,94,1000	18j,CDK5,CDK5,89,1000
16u,CDK7,CDK7,97,1000	18j,CDK7,CDK7,100,1000
16u,CDK8,CDK8,100,1000	18j,CDK8,CDK8,100,1000
16u,CDK9,CDK9,91,1000	18j,CDK9,CDK9,68,1000
16u,CDKL1,CDKL1,89,1000	18j,CDKL1,CDKL1,100,1000
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16u,CHEK1,CHEK1,81,1000	18j,CHEK1,CHEK1,90,1000
16u,CHEK2,CHEK2,100,1000	18j,CHEK2,CHEK2,100,1000
16u,CIT,CIT,100,1000	18j,CIT,CIT,90,1000
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16u,CLK4,CLK4,100,1000	18j,CLK4,CLK4,100,1000
16u,CSF1R,CSF1R,100,1000	18j,CSF1R,CSF1R,100,1000
16u,CSF1R-autoinhibited,CSF1R,100,1000	18j,CSF1R-autoinhibited,CSF1R,100,1000
16u,CSK,CSK,93,1000	18j,CSK,CSK,100,1000
16u,CSNK1A1,CSNK1A1,54,1000	18j,CSNK1A1,CSNK1A1,100,1000
16u,CSNK1A1L,CSNK1A1L,61,1000	18j,CSNK1A1L,CSNK1A1L,100,1000
16u,CSNK1D,CSNK1D,5.8,1000	18j,CSNK1D,CSNK1D,96,1000
16u,CSNK1E,CSNK1E,0.75,1000	18j,CSNK1E,CSNK1E,89,1000
16u,CSNK1G1,CSNK1G1,82,1000	18j,CSNK1G1,CSNK1G1,100,1000
16u,CSNK1G2,CSNK1G2,82,1000	18j,CSNK1G2,CSNK1G2,100,1000

16u,CSNK1G3,CSNK1G3,35,1000	18j,CSNK1G3,CSNK1G3,69,1000
16u,CSNK2A1,CSNK2A1,99,1000	18j,CSNK2A1,CSNK2A1,75,1000
16u,CSNK2A2,CSNK2A2,100,1000	18j,CSNK2A2,CSNK2A2,100,1000
16u,CTK,MATK,69,1000	18j,CTK,MATK,85,1000
16u,DAPK1,DAPK1,85,1000	18j,DAPK1,DAPK1,91,1000
16u,DAPK2,DAPK2,85,1000	18j,DAPK2,DAPK2,83,1000
16u,DAPK3,DAPK3,82,1000	18j,DAPK3,DAPK3,88,1000
16u,DCAMKL1,DCLK1,72,1000	18j,DCAMKL1,DCLK1,100,1000
16u,DCAMKL2,DCLK2,100,1000	18j,DCAMKL2,DCLK2,100,1000
16u,DCAMKL3,DCLK3,100,1000	18j,DCAMKL3,DCLK3,100,1000
16u,DDR1,DDR1,100,1000	18j,DDR1,DDR1,100,1000
16u,DDR2,DDR2,100,1000	18j,DDR2,DDR2,100,1000
16u,DLK,MAP3K12,100,1000	18j,DLK,MAP3K12,100,1000
16u,DMPK,DMPK,80,1000	18j,DMPK,DMPK,96,1000
16u,DMPK2,CDC42BPG,88,1000	18j,DMPK2,CDC42BPG,73,1000
16u,DRAK1,STK17A,100,1000	18j,DRAK1,STK17A,100,1000
16u,DRAK2,STK17B,100,1000	18j,DRAK2,STK17B,100,1000
16u,DYRK1A,DYRK1A,100,1000	18j,DYRK1A,DYRK1A,100,1000
16u,DYRK1B,DYRK1B,88,1000	18j,DYRK1B,DYRK1B,98,1000
16u,DYRK2,DYRK2,100,1000	18j,DYRK2,DYRK2,92,1000
16u,EGFR,EGFR,64,1000	18j,EGFR,EGFR,78,1000
16u,EGFR(E746-A750del),EGFR,100,1000	18j,EGFR(E746-A750del),EGFR,100,1000
16u,EGFR(G719C),EGFR,12,1000	18j,EGFR(G719C),EGFR,70,1000
16u,EGFR(G719S),EGFR,20,1000	18j,EGFR(G719S),EGFR,62,1000
16u,"EGFR(L747-E749del, A750P)",EGFR,100,1000	18j,"EGFR(L747-E749del, A750P)",EGFR,85,1000
16u,"EGFR(L747-S752del, P753S)",EGFR,99,1000	18j,"EGFR(L747-S752del, P753S)",EGFR,100,1000
16u,"EGFR(L747-T751del,Sins)",EGFR,70,1000	18j,"EGFR(L747-T751del,Sins)",EGFR,59,1000
16u,EGFR(L858R),EGFR,100,1000	18j,EGFR(L858R),EGFR,84,1000
16u,"EGFR(L858R,T790M)",EGFR,91,1000	18j,"EGFR(L858R,T790M)",EGFR,100,1000
16u,EGFR(L861Q),EGFR,67,1000	18j,EGFR(L861Q),EGFR,72,1000
16u,EGFR(S752-I759del),EGFR,52,1000	18j,EGFR(S752-I759del),EGFR,78,1000
16u,EGFR(T790M),EGFR,100,1000	18j,EGFR(T790M),EGFR,100,1000
16u,EIF2AK1,EIF2AK1,98,1000	18j,EIF2AK1,EIF2AK1,86,1000
16u,EPHA1,EPHA1,95,1000	18j,EPHA1,EPHA1,100,1000

16u,EPHA2,EPHA2,92,1000	18j,EPHA2,EPHA2,97,1000
16u,EPHA3,EPHA3,100,1000	18j,EPHA3,EPHA3,100,1000
16u,EPHA4,EPHA4,85,1000	18j,EPHA4,EPHA4,71,1000
16u,EPHA5,EPHA5,93,1000	18j,EPHA5,EPHA5,93,1000
16u,EPHA6,EPHA6,100,1000	18j,EPHA6,EPHA6,100,1000
16u,EPHA7,EPHA7,100,1000	18j,EPHA7,EPHA7,100,1000
16u,EPHA8,EPHA8,99,1000	18j,EPHA8,EPHA8,98,1000
16u,EPHB1,EPHB1,100,1000	18j,EPHB1,EPHB1,100,1000
16u,EPHB2,EPHB2,100,1000	18j,EPHB2,EPHB2,100,1000
16u,EPHB3,EPHB3,86,1000	18j,EPHB3,EPHB3,85,1000
16u,EPHB4,EPHB4,100,1000	18j,EPHB4,EPHB4,91,1000
16u,EPHB6,EPHB6,100,1000	18j,EPHB6,EPHB6,100,1000
16u,ERBB2,ERBB2,90,1000	18j,ERBB2,ERBB2,100,1000
16u,ERBB3,ERBB3,88,1000	18j,ERBB3,ERBB3,88,1000
16u,ERBB4,ERBB4,83,1000	18j,ERBB4,ERBB4,100,1000
16u,ERK1,MAPK3,93,1000	18j,ERK1,MAPK3,88,1000
16u,ERK2,MAPK1,90,1000	18j,ERK2,MAPK1,85,1000
16u,ERK3,MAPK6,97,1000	18j,ERK3,MAPK6,77,1000
16u,ERK4,MAPK4,99,1000	18j,ERK4,MAPK4,92,1000
16u,ERK5,MAPK7,95,1000	18j,ERK5,MAPK7,93,1000
16u,ERK8,MAPK15,86,1000	18j,ERK8,MAPK15,95,1000
16u,ERN1,ERN1,94,1000	18j,ERN1,ERN1,100,1000
16u,FAK,PTK2,100,1000	18j,FAK,PTK2,100,1000
16u,FER,FER,92,1000	18j,FER,FER,95,1000
16u,FES,FES,100,1000	18j,FES,FES,100,1000
16u,FGFR1,FGFR1,100,1000	18j,FGFR1,FGFR1,100,1000
16u,FGFR2,FGFR2,100,1000	18j,FGFR2,FGFR2,100,1000
16u,FGFR3,FGFR3,100,1000	18j,FGFR3,FGFR3,100,1000
16u,FGFR3(G697C),FGFR3,88,1000	18j,FGFR3(G697C),FGFR3,100,1000
16u,FGFR4,FGFR4,93,1000	18j,FGFR4,FGFR4,100,1000
16u,FGR,FGR,83,1000	18j,FGR,FGR,83,1000
16u,FLT1,FLT1,82,1000	18j,FLT1,FLT1,100,1000
16u,FLT3,FLT3,97,1000	18j,FLT3,FLT3,100,1000
16u,FLT3(D835H),FLT3,100,1000	18j,FLT3(D835H),FLT3,100,1000

16u,FLT3(D835Y),FLT3,100,1000	18j,FLT3(D835Y),FLT3,99,1000
16u,FLT3(ITD),FLT3,93,1000	18j,FLT3(ITD),FLT3,87,1000
16u,FLT3(K663Q),FLT3,98,1000	18j,FLT3(K663Q),FLT3,100,1000
16u,FLT3(N841I),FLT3,100,1000	18j,FLT3(N841I),FLT3,100,1000
16u,FLT3(R834Q),FLT3,100,1000	18j,FLT3(R834Q),FLT3,100,1000
16u,FLT3-autoinhibited,FLT3,100,1000	18j,FLT3-autoinhibited,FLT3,100,1000
16u,FLT4,FLT4,100,1000	18j,FLT4,FLT4,100,1000
16u,FRK,FRK,100,1000	18j,FRK,FRK,100,1000
16u,FYN,FYN,98,1000	18j,FYN,FYN,93,1000
16u,GAK,GAK,100,1000	18j,GAK,GAK,6.8,1000
16u,"GCN2(Kin.Dom.2,S808G)",EIF2AK4,84,1000	18j,"GCN2(Kin.Dom.2,S808G)",EIF2AK4,80,1000
16u,GRK1,GRK1,100,1000	18j,GRK1,GRK1,100,1000
16u,GRK4,GRK4,100,1000	18j,GRK4,GRK4,97,1000
16u,GRK7,GRK7,100,1000	18j,GRK7,GRK7,100,1000
16u,GSK3A,GSK3A,39,1000	18j,GSK3A,GSK3A,37,1000
16u,GSK3B,GSK3B,100,1000	18j,GSK3B,GSK3B,100,1000
16u,HASPIN,GSG2,100,1000	18j,HASPIN,GSG2,100,1000
16u,HCK,HCK,83,1000	18j,HCK,HCK,100,1000
16u,HIPK1,HIPK1,100,1000	18j,HIPK1,HIPK1,100,1000
16u,HIPK2,HIPK2,87,1000	18j,HIPK2,HIPK2,100,1000
16u,HIPK3,HIPK3,100,1000	18j,HIPK3,HIPK3,92,1000
16u,HIPK4,HIPK4,100,1000	18j,HIPK4,HIPK4,99,1000
16u,HPK1,MAP4K1,100,1000	18j,HPK1,MAP4K1,100,1000
16u,HUNK,HUNK,98,1000	18j,HUNK,HUNK,100,1000
16u,ICK,ICK,100,1000	18j,ICK,ICK,100,1000
16u,IGF1R,IGF1R,100,1000	18j,IGF1R,IGF1R,97,1000
16u,IKK-alpha,CHUK,100,1000	18j,IKK-alpha,CHUK,100,1000
16u,IKK-beta,IKBKB,100,1000	18j,IKK-beta,IKBKB,100,1000
16u,IKK-epsilon,IKBKE,100,1000	18j,IKK-epsilon,IKBKE,100,1000
16u,INSR,INSR,98,1000	18j,INSR,INSR,100,1000
16u,INSRR,INSRR,100,1000	18j,INSRR,INSRR,100,1000
16u,IRAK1,IRAK1,95,1000	18j,IRAK1,IRAK1,100,1000
16u,IRAK3,IRAK3,100,1000	18j,IRAK3,IRAK3,100,1000
16u,IRAK4,IRAK4,100,1000	18j,IRAK4,IRAK4,89,1000

16u,ITK,ITK,95,1000	18j,ITK,ITK,96,1000
16u,JAK1(JH1domain-catalytic),JAK1,78,1000	18j,JAK1(JH1domain-catalytic),JAK1,70,1000
16u,JAK1(JH2domain-pseudokinase),JAK1,100,1000	18j,JAK1(JH2domain-pseudokinase),JAK1,100,1000
16u,JAK2(JH1domain-catalytic),JAK2,100,1000	18j,JAK2(JH1domain-catalytic),JAK2,100,1000
16u,JAK3(JH1domain-catalytic),JAK3,100,1000	18j,JAK3(JH1domain-catalytic),JAK3,100,1000
16u,JNK1,MAPK8,99,1000	18j,JNK1,MAPK8,81,1000
16u,JNK2,MAPK9,48,1000	18j,JNK2,MAPK9,38,1000
16u,JNK3,MAPK10,100,1000	18j,JNK3,MAPK10,8.2,1000
16u,KIT,KIT,100,1000	18j,KIT,KIT,100,1000
16u,KIT(A829P),KIT,95,1000	18j,KIT(A829P),KIT,100,1000
16u,KIT(D816H),KIT,98,1000	18j,KIT(D816H),KIT,100,1000
16u,KIT(D816V),KIT,96,1000	18j,KIT(D816V),KIT,100,1000
16u,KIT(L576P),KIT,100,1000	18j,KIT(L576P),KIT,100,1000
16u,KIT(V559D),KIT,100,1000	18j,KIT(V559D),KIT,100,1000
16u,"KIT(V559D,T670I)",KIT,90,1000	18j,"KIT(V559D,T670I)",KIT,97,1000
16u,"KIT(V559D,V654A)",KIT,100,1000	18j,"KIT(V559D,V654A)",KIT,100,1000
16u,KIT-autoinhibited,KIT,100,1000	18j,KIT-autoinhibited,KIT,100,1000
16u,LATS1,LATS1,100,1000	18j,LATS1,LATS1,100,1000
16u,LATS2,LATS2,100,1000	18j,LATS2,LATS2,100,1000
16u,LCK,LCK,89,1000	18j,LCK,LCK,92,1000
16u,LIMK1,LIMK1,99,1000	18j,LIMK1,LIMK1,100,1000
16u,LIMK2,LIMK2,76,1000	18j,LIMK2,LIMK2,52,1000
16u,LKB1,STK11,80,1000	18j,LKB1,STK11,67,1000
16u,LOK,STK10,100,1000	18j,LOK,STK10,100,1000
16u,LRRK2,LRRK2,100,1000	18j,LRRK2,LRRK2,100,1000
16u,LRRK2(G2019S),LRRK2,100,1000	18j,LRRK2(G2019S),LRRK2,90,1000
16u,LTK,LTK,100,1000	18j,LTK,LTK,100,1000
16u,LYN,LYN,100,1000	18j,LYN,LYN,100,1000
16u,LZK,MAP3K13,98,1000	18j,LZK,MAP3K13,100,1000
16u,MAK,MAK,100,1000	18j,MAK,MAK,100,1000
16u,MAP3K1,MAP3K1,100,1000	18j,MAP3K1,MAP3K1,100,1000
16u,MAP3K15,MAP3K15,56,1000	18j,MAP3K15,MAP3K15,78,1000
16u,MAP3K2,MAP3K2,100,1000	18j,MAP3K2,MAP3K2,100,1000
16u,MAP3K3,MAP3K3,100,1000	18j,MAP3K3,MAP3K3,100,1000

16u,MAP3K4,MAP3K4,100,1000	18j,MAP3K4,MAP3K4,100,1000
16u,MAP4K2,MAP4K2,100,1000	18j,MAP4K2,MAP4K2,100,1000
16u,MAP4K3,MAP4K3,90,1000	18j,MAP4K3,MAP4K3,92,1000
16u,MAP4K4,MAP4K4,89,1000	18j,MAP4K4,MAP4K4,77,1000
16u,MAP4K5,MAP4K5,75,1000	18j,MAP4K5,MAP4K5,67,1000
16u,MAPKAPK2,MAPKAPK2,100,1000	18j,MAPKAPK2,MAPKAPK2,87,1000
16u,MAPKAPK5,MAPKAPK5,100,1000	18j,MAPKAPK5,MAPKAPK5,100,1000
16u,MARK1,MARK1,100,1000	18j,MARK1,MARK1,100,1000
16u,MARK2,MARK2,86,1000	18j,MARK2,MARK2,92,1000
16u,MARK3,MARK3,100,1000	18j,MARK3,MARK3,100,1000
16u,MARK4,MARK4,100,1000	18j,MARK4,MARK4,100,1000
16u,MAST1,MAST1,76,1000	18j,MAST1,MAST1,100,1000
16u,MEK1,MAP2K1,100,1000	18j,MEK1,MAP2K1,98,1000
16u,MEK2,MAP2K2,99,1000	18j,MEK2,MAP2K2,100,1000
16u,MEK3,MAP2K3,100,1000	18j,MEK3,MAP2K3,100,1000
16u,MEK4,MAP2K4,82,1000	18j,MEK4,MAP2K4,99,1000
16u,MEK5,MAP2K5,100,1000	18j,MEK5,MAP2K5,98,1000
16u,MEK6,MAP2K6,98,1000	18j,MEK6,MAP2K6,100,1000
16u,MELK,MELK,98,1000	18j,MELK,MELK,92,1000
16u,MERTK,MERTK,100,1000	18j,MERTK,MERTK,100,1000
16u,MET,MET,100,1000	18j,MET,MET,100,1000
16u,MET(M1250T),MET,100,1000	18j,MET(M1250T),MET,100,1000
16u,MET(Y1235D),MET,73,1000	18j,MET(Y1235D),MET,87,1000
16u,MINK,MINK1,100,1000	18j,MINK,MINK1,100,1000
16u,MKK7,MAP2K7,100,1000	18j,MKK7,MAP2K7,100,1000
16u,MKNK1,MKNK1,92,1000	18j,MKNK1,MKNK1,100,1000
16u,MKNK2,MKNK2,100,1000	18j,MKNK2,MKNK2,100,1000
16u,MLCK,MYLK3,100,1000	18j,MLCK,MYLK3,100,1000
16u,MLK1,MAP3K9,100,1000	18j,MLK1,MAP3K9,100,1000
16u,MLK2,MAP3K10,100,1000	18j,MLK2,MAP3K10,100,1000
16u,MLK3,MAP3K11,100,1000	18j,MLK3,MAP3K11,87,1000
16u,MRCKA,CDC42BPA,100,1000	18j,MRCKA,CDC42BPA,100,1000
16u,MRCKB,CDC42BPB,99,1000	18j,MRCKB,CDC42BPB,100,1000
16u,MST1,STK4,100,1000	18j,MST1,STK4,100,1000

16u,MST1R,MST1R,87,1000	18j,MST1R,MST1R,80,1000
16u,MST2,STK3,100,1000	18j,MST2,STK3,100,1000
16u,MST3,STK24,98,1000	18j,MST3,STK24,100,1000
16u,MST4,MST4,83,1000	18j,MST4,MST4,100,1000
16u,MTOR,MTOR,81,1000	18j,MTOR,MTOR,98,1000
16u,MUSK,MUSK,100,1000	18j,MUSK,MUSK,100,1000
16u,MYLK,MYLK,98,1000	18j,MYLK,MYLK,88,1000
16u,MYLK2,MYLK2,100,1000	18j,MYLK2,MYLK2,100,1000
16u,MYLK4,MYLK4,100,1000	18j,MYLK4,MYLK4,99,1000
16u,MYO3A,MYO3A,90,1000	18j,MYO3A,MYO3A,100,1000
16u,MYO3B,MYO3B,100,1000	18j,MYO3B,MYO3B,97,1000
16u,NDR1,STK38,98,1000	18j,NDR1,STK38,100,1000
16u,NDR2,STK38L,93,1000	18j,NDR2,STK38L,100,1000
16u,NEK1,NEK1,100,1000	18j,NEK1,NEK1,100,1000
16u,NEK11,NEK11,100,1000	18j,NEK11,NEK11,95,1000
16u,NEK2,NEK2,88,1000	18j,NEK2,NEK2,100,1000
16u,NEK3,NEK3,100,1000	18j,NEK3,NEK3,100,1000
16u,NEK4,NEK4,100,1000	18j,NEK4,NEK4,100,1000
16u,NEK5,NEK5,100,1000	18j,NEK5,NEK5,89,1000
16u,NEK6,NEK6,100,1000	18j,NEK6,NEK6,100,1000
16u,NEK7,NEK7,100,1000	18j,NEK7,NEK7,100,1000
16u,NEK9,NEK9,100,1000	18j,NEK9,NEK9,100,1000
16u,NIM1,MGC42105,100,1000	18j,NIM1,MGC42105,100,1000
16u,NLK,NLK,66,1000	18j,NLK,NLK,85,1000
16u,OSR1,OXSR1,100,1000	18j,OSR1,OXSR1,100,1000
16u,p38-alpha,MAPK14,0,1000	18j,p38-alpha,MAPK14,0.05,1000
16u,p38-beta,MAPK11,0,1000	18j,p38-beta,MAPK11,0,1000
16u,p38-delta,MAPK13,99,1000	18j,p38-delta,MAPK13,85,1000
16u,p38-gamma,MAPK12,14,1000	18j,p38-gamma,MAPK12,100,1000
16u,PAK1,PAK1,100,1000	18j,PAK1,PAK1,100,1000
16u,PAK2,PAK2,100,1000	18j,PAK2,PAK2,100,1000
16u,PAK3,PAK3,100,1000	18j,PAK3,PAK3,100,1000
16u,PAK4,PAK4,100,1000	18j,PAK4,PAK4,100,1000
16u,PAK6,PAK6,100,1000	18j,PAK6,PAK6,94,1000

16u,PAK7,PAK7,100,1000	18j,PAK7,PAK7,100,1000
16u,PCTK1,CDK16,98,1000	18j,PCTK1,CDK16,96,1000
16u,PCTK2,CDK17,92,1000	18j,PCTK2,CDK17,93,1000
16u,PCTK3,CDK18,100,1000	18j,PCTK3,CDK18,88,1000
16u,PDGFRA,PDGFRA,100,1000	18j,PDGFRA,PDGFRA,100,1000
16u,PDGFRB,PDGFRB,100,1000	18j,PDGFRB,PDGFRB,99,1000
16u,PDPK1,PDPK1,95,1000	18j,PDPK1,PDPK1,100,1000
16u,PFCDPK1(P.falciparum),CDPK1,100,1000	18j,PFCDPK1(P.falciparum),CDPK1,100,1000
16u,PFPK5(P.falciparum),MAL13P1.279,100,1000	18j,PFPK5(P.falciparum),MAL13P1.279,100,1000
16u,PFTAIRE2,CDK15,100,1000	18j,PFTAIRE2,CDK15,83,1000
16u,PFTK1,CDK14,100,1000	18j,PFTK1,CDK14,92,1000
16u,PHKG1,PHKG1,100,1000	18j,PHKG1,PHKG1,98,1000
16u,PHKG2,PHKG2,89,1000	18j,PHKG2,PHKG2,96,1000
16u,PIK3C2B,PIK3C2B,100,1000	18j,PIK3C2B,PIK3C2B,100,1000
16u,PIK3C2G,PIK3C2G,100,1000	18j,PIK3C2G,PIK3C2G,100,1000
16u,PIK3CA,PIK3CA,100,1000	18j,PIK3CA,PIK3CA,100,1000
16u,PIK3CA(C420R),PIK3CA,100,1000	18j,PIK3CA(C420R),PIK3CA,100,1000
16u,PIK3CA(E542K),PIK3CA,100,1000	18j,PIK3CA(E542K),PIK3CA,99,1000
16u,PIK3CA(E545A),PIK3CA,95,1000	18j,PIK3CA(E545A),PIK3CA,100,1000
16u,PIK3CA(E545K),PIK3CA,100,1000	18j,PIK3CA(E545K),PIK3CA,100,1000
16u,PIK3CA(H1047L),PIK3CA,100,1000	18j,PIK3CA(H1047L),PIK3CA,100,1000
16u,PIK3CA(H1047Y),PIK3CA,100,1000	18j,PIK3CA(H1047Y),PIK3CA,100,1000
16u,PIK3CA(I800L),PIK3CA,91,1000	18j,PIK3CA(I800L),PIK3CA,100,1000
16u,PIK3CA(M1043I),PIK3CA,100,1000	18j,PIK3CA(M1043I),PIK3CA,100,1000
16u,PIK3CA(Q546K),PIK3CA,100,1000	18j,PIK3CA(Q546K),PIK3CA,100,1000
16u,PIK3CB,PIK3CB,93,1000	18j,PIK3CB,PIK3CB,100,1000
16u,PIK3CD,PIK3CD,89,1000	18j,PIK3CD,PIK3CD,91,1000
16u,PIK3CG,PIK3CG,100,1000	18j,PIK3CG,PIK3CG,100,1000
16u,PIK4CB,PI4KB,100,1000	18j,PIK4CB,PI4KB,100,1000
16u,PIM1,PIM1,98,1000	18j,PIM1,PIM1,92,1000
16u,PIM2,PIM2,100,1000	18j,PIM2,PIM2,100,1000
16u,PIM3,PIM3,92,1000	18j,PIM3,PIM3,100,1000
16u,PIP5K1A,PIP5K1A,88,1000	18j,PIP5K1A,PIP5K1A,83,1000
16u,PIP5K1C,PIP5K1C,75,1000	18j,PIP5K1C,PIP5K1C,100,1000

16u,PIP5K2B,PIP4K2B,100,1000	18j,PIP5K2B,PIP4K2B,100,1000
16u,PIP5K2C,PIP4K2C,71,1000	18j,PIP5K2C,PIP4K2C,100,1000
16u,PKAC-alpha,PRKACA,81,1000	18j,PKAC-alpha,PRKACA,96,1000
16u,PKAC-beta,PRKACB,100,1000	18j,PKAC-beta,PRKACB,99,1000
16u,PKMYT1,PKMYT1,86,1000	18j,PKMYT1,PKMYT1,100,1000
16u,PKN1,PKN1,100,1000	18j,PKN1,PKN1,100,1000
16u,PKN2,PKN2,90,1000	18j,PKN2,PKN2,100,1000
16u,PKNB(M.tuberculosis),pknB,100,1000	18j,PKNB(M.tuberculosis),pknB,100,1000
16u,PLK1,PLK1,100,1000	18j,PLK1,PLK1,100,1000
16u,PLK2,PLK2,93,1000	18j,PLK2,PLK2,94,1000
16u,PLK3,PLK3,69,1000	18j,PLK3,PLK3,87,1000
16u,PLK4,PLK4,100,1000	18j,PLK4,PLK4,100,1000
16u,PRKCD,PRKCD,100,1000	18j,PRKCD,PRKCD,94,1000
16u,PRKCE,PRKCE,67,1000	18j,PRKCE,PRKCE,95,1000
16u,PRKCH,PRKCH,100,1000	18j,PRKCH,PRKCH,100,1000
16u,PRKCI,PRKCI,100,1000	18j,PRKCI,PRKCI,100,1000
16u,PRKCQ,PRKCQ,100,1000	18j,PRKCQ,PRKCQ,90,1000
16u,PRKD1,PRKD1,100,1000	18j,PRKD1,PRKD1,66,1000
16u,PRKD2,PRKD2,88,1000	18j,PRKD2,PRKD2,82,1000
16u,PRKD3,PRKD3,100,1000	18j,PRKD3,PRKD3,100,1000
16u,PRKG1,PRKG1,100,1000	18j,PRKG1,PRKG1,100,1000
16u,PRKG2,PRKG2,100,1000	18j,PRKG2,PRKG2,97,1000
16u,PRKR,EIF2AK2,100,1000	18j,PRKR,EIF2AK2,100,1000
16u,PRKX,PRKX,100,1000	18j,PRKX,PRKX,100,1000
16u,PRP4,PRPF4B,100,1000	18j,PRP4,PRPF4B,100,1000
16u,PYK2,PTK2B,100,1000	18j,PYK2,PTK2B,100,1000
16u,QSK,KIAA0999,90,1000	18j,QSK,KIAA0999,100,1000
16u,RAF1,RAF1,99,1000	18j,RAF1,RAF1,93,1000
16u,RET,RET,95,1000	18j,RET,RET,100,1000
16u,RET(M918T),RET,100,1000	18j,RET(M918T),RET,100,1000
16u,RET(V804L),RET,100,1000	18j,RET(V804L),RET,100,1000
16u,RET(V804M),RET,100,1000	18j,RET(V804M),RET,100,1000
16u,RIOK1,RIOK1,96,1000	18j,RIOK1,RIOK1,100,1000
16u,RIOK2,RIOK2,100,1000	18j,RIOK2,RIOK2,100,1000

16u,RIOK3,RIOK3,100,1000	18j,RIOK3,RIOK3,100,1000
16u,RIPK1,RIPK1,100,1000	18j,RIPK1,RIPK1,95,1000
16u,RIPK2,RIPK2,74,1000	18j,RIPK2,RIPK2,92,1000
16u,RIPK4,RIPK4,100,1000	18j,RIPK4,RIPK4,100,1000
16u,RIPK5,DSTYK,83,1000	18j,RIPK5,DSTYK,100,1000
16u,ROCK1,ROCK1,100,1000	18j,ROCK1,ROCK1,100,1000
16u,ROCK2,ROCK2,100,1000	18j,ROCK2,ROCK2,100,1000
16u,ROS1,ROS1,99,1000	18j,ROS1,ROS1,100,1000
16u,RPS6KA4(Kin.Dom.1-N-terminal),RPS6KA4,72,1000	18j,RPS6KA4(Kin.Dom.1-N-terminal),RPS6KA4,100,1000
16u,RPS6KA4(Kin.Dom.2-C-terminal),RPS6KA4,100,1000	18j,RPS6KA4(Kin.Dom.2-C-terminal),RPS6KA4,100,1000
16u,RPS6KA5(Kin.Dom.1-N-terminal),RPS6KA5,100,1000	18j,RPS6KA5(Kin.Dom.1-N-terminal),RPS6KA5,99,1000
16u,RPS6KA5(Kin.Dom.2-C-terminal),RPS6KA5,75,1000	18j,RPS6KA5(Kin.Dom.2-C-terminal),RPS6KA5,95,1000
16u,RSK1(Kin.Dom.1-N-terminal),RPS6KA1,100,1000	18j,RSK1(Kin.Dom.1-N-terminal),RPS6KA1,100,1000
16u,RSK1(Kin.Dom.2-C-terminal),RPS6KA1,95,1000	18j,RSK1(Kin.Dom.2-C-terminal),RPS6KA1,68,1000
16u,RSK2(Kin.Dom.1-N-terminal),RPS6KA3,99,1000	18j,RSK2(Kin.Dom.1-N-terminal),RPS6KA3,94,1000
16u,RSK2(Kin.Dom.2-C-terminal),RPS6KA3,100,1000	18j,RSK2(Kin.Dom.2-C-terminal),RPS6KA3,100,1000
16u,RSK3(Kin.Dom.1-N-terminal),RPS6KA2,93,1000	18j,RSK3(Kin.Dom.1-N-terminal),RPS6KA2,84,1000
16u,RSK3(Kin.Dom.2-C-terminal),RPS6KA2,80,1000	18j,RSK3(Kin.Dom.2-C-terminal),RPS6KA2,94,1000
16u,RSK4(Kin.Dom.1-N-terminal),RPS6KA6,100,1000	18j,RSK4(Kin.Dom.1-N-terminal),RPS6KA6,100,1000
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16u,SGK,SGK1,100,1000	18j,SGK,SGK1,100,1000
16u,SgK110,SgK110,100,1000	18j,SgK110,SgK110,100,1000
16u,SGK3,SGK3,80,1000	18j,SGK3,SGK3,100,1000
16u,SIK,SIK1,100,1000	18j,SIK,SIK1,100,1000
16u,SIK2,SIK2,83,1000	18j,SIK2,SIK2,100,1000
16u,SLK,SLK,93,1000	18j,SLK,SLK,100,1000
16u,SNARK,NUAK2,100,1000	18j,SNARK,NUAK2,100,1000
16u,SNRK,SNRK,98,1000	18j,SNRK,SNRK,100,1000
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16u,SRMS,SRMS,100,1000	18j,SRMS,SRMS,100,1000
16u,SRPK1,SRPK1,100,1000	18j,SRPK1,SRPK1,100,1000
16u,SRPK2,SRPK2,86,1000	18j,SRPK2,SRPK2,80,1000

16u,SRPK3,SRPK3,100,1000	18j,SRPK3,SRPK3,98,1000
16u,STK16,STK16,92,1000	18j,STK16,STK16,92,1000
16u,STK33,STK33,100,1000	18j,STK33,STK33,100,1000
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16u,STK39,STK39,83,1000	18j,STK39,STK39,100,1000
16u,SYK,SYK,94,1000	18j,SYK,SYK,89,1000
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16u,TAOK2,TAOK2,100,1000	18j,TAOK2,TAOK2,100,1000
16u,TAOK3,TAOK3,100,1000	18j,TAOK3,TAOK3,100,1000
16u,TBK1,TBK1,100,1000	18j,TBK1,TBK1,100,1000
16u,TEC,TEC,100,1000	18j,TEC,TEC,100,1000
16u,TESK1,TESK1,88,1000	18j,TESK1,TESK1,100,1000
16u,TGFBR1,TGFBR1,100,1000	18j,TGFBR1,TGFBR1,100,1000
16u,TGFBR2,TGFBR2,81,1000	18j,TGFBR2,TGFBR2,84,1000
16u,TIE1,TIE1,100,1000	18j,TIE1,TIE1,100,1000
16u,TIE2,TEK,100,1000	18j,TIE2,TEK,100,1000
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16u,TNK2,TNK2,100,1000	18j,TNK2,TNK2,100,1000
16u,TNNI3K,TNNI3K,92,1000	18j,TNNI3K,TNNI3K,100,1000
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16u,TRKC,NTRK3,100,1000	18j,TRKC,NTRK3,100,1000
16u,TRPM6,TRPM6,98,1000	18j,TRPM6,TRPM6,100,1000
16u,TSSK1B,TSSK1B,98,1000	18j,TSSK1B,TSSK1B,100,1000
16u,TTK,TTK,77,1000	18j,TTK,TTK,85,1000
16u,TXK,TXK,100,1000	18j,TXK,TXK,100,1000
16u,TYK2(JH1domain-catalytic),TYK2,100,1000	18j,TYK2(JH1domain-catalytic),TYK2,100,1000
16u,TYK2(JH2domain-pseudokinase),TYK2,100,1000	18j,TYK2(JH2domain-pseudokinase),TYK2,100,1000
16u,TYRO3,TYRO3,78,1000	18j,TYRO3,TYRO3,70,1000

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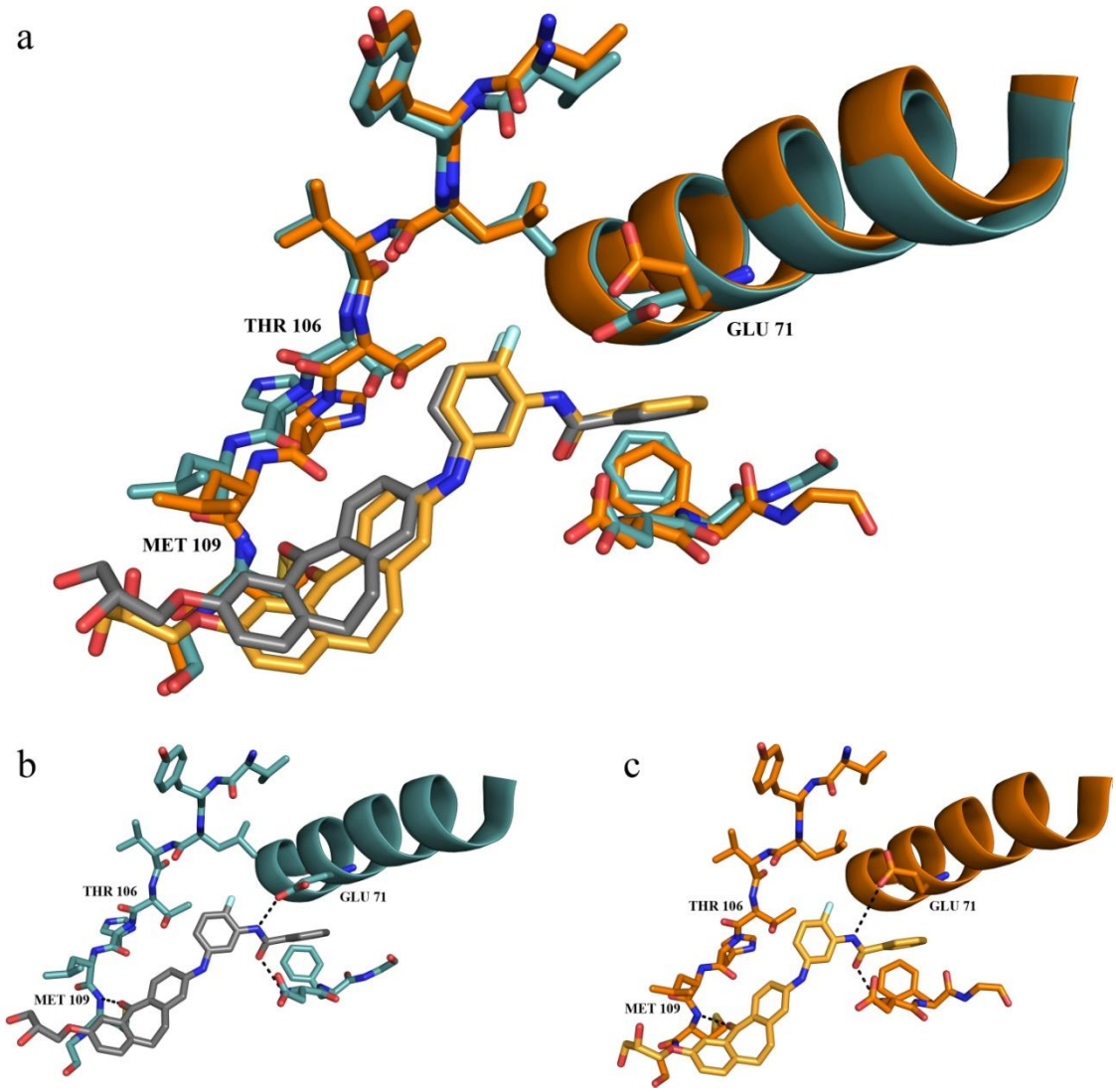
16u,ULK2,ULK2,100,1000	18j,ULK2,ULK2,100,1000
16u,ULK3,ULK3,100,1000	18j,ULK3,ULK3,100,1000
16u,VEGFR2,KDR,100,1000	18j,VEGFR2,KDR,100,1000
16u,VRK2,VRK2,100,1000	18j,VRK2,VRK2,100,1000
16u,WEE1,WEE1,100,1000	18j,WEE1,WEE1,94,1000
16u,WEE2,WEE2,100,1000	18j,WEE2,WEE2,100,1000
16u,WNK1,WNK1,86,1000	18j,WNK1,WNK1,100,1000
16u,WNK3,WNK3,85,1000	18j,WNK3,WNK3,100,1000
16u,YANK1,STK32A,100,1000	18j,YANK1,STK32A,100,1000
16u,YANK2,STK32B,100,1000	18j,YANK2,STK32B,100,1000
16u,YANK3,STK32C,100,1000	18j,YANK3,STK32C,100,1000
16u,YES,YES1,96,1000	18j,YES,YES1,100,1000
16u,YSK1,STK25,100,1000	18j,YSK1,STK25,100,1000
16u,YSK4,YSK4,100,1000	18j,YSK4,YSK4,100,1000
16u,ZAK,ZAK,95,1000	18j,ZAK,ZAK,100,1000
16u,ZAP70,ZAP70,100,1000	18j,ZAP70,ZAP70,100,1000

6 Molecular modeling



SI-Figure 1. Depictions of crystal structures 3UVQ and **16e** docked into 3UVP. (a) Superposition of 3UVQ (green: protein, grey: ligand) and pose of **16e** docked into the binding site of 3UVP (orange: protein, light orange: ligand). The RMSD of both ligands is 0.91 Å (0.69 Å without the flexible substituent R5) (b) Crystal structure 3UVQ featuring key interactions of **16e** with the binding site of p38α. (c) Docking pose of **16e** within the binding site of 3UVP. Hinge binding to Met109 and hydrogen bonds to Glu71 and Asp168 were features suggested in the binding mode, which were confirmed by crystal structure 3UVQ.

Methods

Computational Procedure

The protein structure of 3UVP was prepared using the protein preparation wizard of Schroedinger 9.0 at default parameters.[16] The docking was carried out using the Induced Fit workflow. The binding site was defined by the respective co-crystallized ligand. Glide re-docking was set to extra precision (XP).

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