Supporting Information

Metabolically Stable Dibenzo[*b,e*]oxepin-11(6*H*)-ones as Highly Selective p38 MAP Kinase Inhibitors: Optimizing Anti-Cytokine Activity in Human Whole Blood

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General Information

All commercially available reagents and solvents were used without further purification. Melting points were determined with a Büchi melting point device, model B-545 and were thermodynamically corrected. ^{1}H NMR (200/400 MHz) and ^{13}C NMR (50/100 MHz) spectra were recorded on a Bruker Avance 200/400. Chemical shifts (δ) are reported in ppm from the solvent resonance. IR data were determined on a Perkin-Elmer Spectrum One spectrometer (ATR technique). Flash chromatography was performed using a LaFlash system (VWR) with Merck silica gel (PharmPrep® 60 CC 25-40 μm). The purity of the final compounds was determined by HPLC (Merck Hitachi L-6200 Intelligent Pump, Merck Hitachi AS-2000 Autosampler, Merck Hitachi L-4250 UV-VIS Detector) using a LiChrospher C18 column (5 μm), employing a gradient of 0.01 M KH_2PO_4 (pH 2.3) and methanol as solvent system with a flow rate of 1.0 mL/min and detection at 254 nm. Mass spectra were run on a Hewlett Packard HP 6890 Series GC-system equipped with a HP-5MS capillary column (0.25 μM film thickness 30 m x 0.25 mm) and a Hewlett Packard HP 5973 Mass selective detector (70 eV). HRMS (EI) (electron impact – high resolution mass spectroscopy) data were obtained from the department for mass spectrometry, Institute of Organic Chemistry, Eberhard-Karls-University Tübingen. All compounds were >95% pure. Metabolic and pharmacokinetic experiments were analyzed using a Micromass Quattro micro Triple quadrupole mass spectrometer coupled to JASCO HPLC system.

Synthesis of amino substituted dibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure B).

To a solution of the respective nitro compound in dry ethyl acetate, 50 mg of palladium on activated carbon were added at room temperature. The mixture was then stirred under a hydrogen atmosphere until TLC indicated complete conversion. After filtration over silica gel, the organic phase was evaporated and the resulting oil was purified via flash chromatography.

3-[(2-Amino-4-fluorophenyl)amino]-7-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (1c). Compound **1c** was prepared according to General Procedure B using **1k** (100 mg, 0.27 mmol). The reaction mixture was stirred under hydrogen atmosphere for 4.5 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 55 mg (60.4%), yellow solid. **HPLC**: t_R = 7.80 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.86 (s, 3 H, -OCH_3), 5.18 (s, NH_2, 2 H), 5.20 (s, 2 H, C^6H_2), 5.98 (d, *J*=2.02 Hz, 1 H, C^4H), 6.33 (m, 1 H, C^3'H), 6.45 (dd, *J*=8.97, 2.15 Hz, 1 H, C^5'H), 6.54 (m, 1 H, C^6'H), 6.95 (m, 1 H,C^2H), 7.27 (m, 2 H, C^8H, C^9H), 7.40 (d, *J*=7.83 Hz, 1 H, C^{10}), 7.89 (d, *J*=8.97 Hz, 1 H, C^1), 8.04 (s, NH, 1 H); **HRMS-EI**, *m*/*z* ($C_{21}H_{17}FN_2O_3$): calculated: 364.1223; found: 364.1231.

3-[(2-Amino-4-fluorophenyl)amino]-7-(2-morpholin-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (1e).

Compound **1e** was prepared according to General Procedure B using **1l** (100 mg, 0.20 mmol). The reaction mixture was stirred under hydrogen atmosphere for 8.5 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 60 mg (64.7%), yellow solid. **HPLC**: t_R = 3.98 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 2.47 (m, 4 H, $C^{3/5}{}_{morpholinyl}H_2$), 2.72 (t, *J*=5.18 Hz, 2 H, $C^2{}_{ethoxy}H_2$), 3.56 (t, *J*=3.92 Hz, 4 H, $C^{2/6}{}_{morpholinyl}CH_2$), 4.16 (t, *J*=5.43 Hz, 2 H, $C^1{}_{ethoxy}H_2$), 5.16 (s, -NH_2, 2 H), 5.21 (s, 2 H, C^6H_2), 5.99 (m, 1 H, C^5'H), 6.43 (m, 3 H, C^{4}H, C^3'H, C^{2}H) 6.95 (m, 1 H, C^6'H), 7.34 (m, 3 H, C^{8}H, C^{9}H, C^{10}H), 7.88 (m, 1 H, C^{1}H), 8.04 (s, -NH, 1 H); **HRMS-EI**, *m/z* ($C_{26}H_{26}FN_3O_4$): calculated: 463.1907; found: 463.1899.

3-[(2-Amino-4-fluorophenyl)amino]-8-(2-morpholin-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (2e).

Compound **2e** was prepared according to General Procedure B using **2n** (120 mg, 0.24 mmol). The reaction mixture was stirred under hydrogen atmosphere for 6 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 75 mg (67.4%), yellow solid. **HPLC**: t_R = 3.78 min, purity: 100%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.54 (m, 4 H, $C^{2/6}{}_{morpholinyl}H_2$), 2.80 (t, *J*=5.49 Hz, 2 H, t, *J*=5.62 Hz, 2 H, $C^2{}_{ethoxy}H_2$), 3.71 (m, 4 H, $C^{3/5}{}_{morpholinyl}H_2$), 4.16 (t, *J*=5.43 Hz, 2 H, $C^1{}_{ethoxy}H_2$), 5.03 (s, 2 H, C^6H_2), 5.75 (s, NH, 1 H), 6.09 (d, *J*=1.89 Hz, 1 H, C^1'H), 6.44 (m, 3 H, C^{4}H, C^5'H, C^6'H), 6.76 (m, 1 H, C^2), 6.96 (m, 2 H, C^{7}H, C^{9}H)), 7.95 (d, *J*=8.59 Hz, 1 H, C^{1}H), 8.17 (d, *J*=8.84 Hz, 1 H, C^{10}H); **HRMS-EI**, *m/z* ($C_{26}H_{26}FN_3O_4$): calculated: 463.1907; found: 463.1904.

9-Amino-3-[(2,4-difluorophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5a).

Compound **5a** was prepared according to General Procedure B using **28a**. The reaction mixture was stirred under hydrogen atmosphere for 6 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 25 mg (54.2%), yellow solid. **HPLC**: t_R = 6.81 min, purity: 98.4%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 4.98 (s, 2 H, -NH_2), 5.41 (s, 2 H, C^6H_2), 6.21 (s, 1 H, C^{4}H), 6.65 (m, 2 H, C^{2}H, C^6'H), 7.06 (m, 3 H; C^3'H, C^5'H, C^{8}H), 7.38 (m, 2 H, C^{10}H, C^{7}H), 7.95 (d, *J*=8.97 Hz, 1 H, C^{1}H) 8.62 (s, 1 H, NH); **HRMS-EI**, *m/z* ($C_{20}H_{14}F_2N_2O_2$): calculated. 352.1023; found: 352.1033.

9-Amino-3-[(2-amino-4-fluorophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5b).

Compound **5b** was prepared according to General Procedure B using **28b** (80 mg, 0.19 mmol). The reaction mixture was stirred under hydrogen atmosphere for 4 h and purified by flash chromatograph (SiO_2, hexane / ethyl acetate 1:1). Yield: 40 mg (60.3 %), yellow solid. **HPLC**: t_R = 5.57 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 4.94 (s, NH_2, 2 H), 5.17 (s, 2 H, C^6H_2), 5.36 (s, NH_2, 2 H), 5.97 (d, *J*=2.15 Hz, 1 H, C^{4}H), 6.43 (m, 3 H, C^3'H, C^5'H, C2H), 6.70 (dd, *J*=7.96, 2.40 Hz, 1 H, (C^7), 6.96 (m, 2 H, C^6'H, C^{8}H), 7.09 (d, *J*=8.08 Hz, 1 H, C^{10}H), 7.91 (d, *J*=8.97 Hz, 1 H, C^{1}H), 7.97 (s, 1 H, -NH); **HRMS-EI**, *m/z* (**$C_{20}H_{16}FN_3O_2$**): calculated: 349.1226; found: 349.1206.

9-Amino-3-[(2-aminophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5c).

Compound **5c** was prepared according to General Procedure B using **28c** (80 mg, 0.22 mmol). The reaction mixture was stirred under hydrogen atmosphere for 8 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 40 mg (54.5%), yellow oil. **HPLC**: t_R = 4.15 min, purity: 97.3%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 4.83 (s, 2 H, -NH_2), 4.95 (s, 2 H, C^6H_2), 5.39 (s, 2 H, -NH_2), 6.04 (d, *J*=2.02 Hz, 1 H, C^{4}H), 6.53 (m, 2 H, C^{2}H, C^3'H), 6.74 (m, 2 H, C^6'H, C^4'H), 6.95 (m, 3 H, C^5'H, C^{8}H, C^{10}H), 7.09 (d, *J*=8.08 Hz, 1 H, C^{7}H), 7.91 (d, *J*=8.97 Hz, 1 H, C^{1}H), 8.04 (s, 1 H, -NH); **HRMS-ESI**, *m/z* ($C_{20}H_{17}N_3O_2$) calculated: $[M + H]^+$ 322.1394; found: 322.1396.

9-Amino-3-[(3-aminophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5d).

Compound **5d** was prepared according to General Procedure B using **28d** (70 mg, 0.19 mmol). The reaction mixture was stirred under hydrogen atmosphere for 9 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 35 mg (54.5%), yellow oil. **HPLC**: t_R = 3.62 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 4.98 (s, 2

H, C^6H_2), 5.10 (s, 2 H, -NH_2), 5.40 (s, 2 H, NH_2), 6.27 (m, 2 H, $C^{4'}H$, $C^{2'}H$), 6.42 (m, 1 H, $C^{6'}H$), 6.49 (d, *J*=2.15 Hz, 1 H, $C^{2'}H$), 6.73 (m, 2 H, C^4H, C^8H), 6.95 (m, 2 H, $C^{10}H$, $C^{5'}H$), 7.11 (d, *J*=8.08 Hz, 1 H, C^7H), 7.94 (d, *J*=8.97 Hz, 1 H, C^1H), 8.63 (s, 1 H, NH); **HRMS-ESI**, *m/z* ($C_{20}H_{17}N_3O_2$) calculated $[M + H]^+$: 322.1394; found: 322.1394

9-Amino-3-[(2-fluorophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5e).

Compound **5e** was prepared according to General Procedure B using **28e** (80 mg, 0.20 mmol). The reaction mixture was stirred under hydrogen atmosphere for 5 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 45 mg (67.3%), yellow solid. **HPLC**: t_R = 6.51 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 4.99 (s, 2 H, C^6H_2), 5.43 (s, NH_2, 2 H), 6.33 (m, 1 H, C^2H), 6.71 (m, 2 H, $C^{3'}H$, $C^{6'}H$), 7.00 (d, *J*=2.02 Hz, 1 H, C^4H), 7.26 (m, 5 H, $C^{2'}H$, $C^{5'}H$, C^8H, $C^{10}H$), 7.98 (d, *J*=8.97 Hz, 1 H, C^1H), 8.71 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{20}H_{15}FN_2O_2$) calculated 334.1117; found 334.1127.

9-Amino-3-[(4-fluorophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5f).

Compound **5f** was prepared according to General Procedure B using **28f**. The reaction mixture was stirred under a hydrogen atmosphere for 3 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 45 mg (67.3%), yellow solid. **HPLC**: t_R = 6.84 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 4.99 (s, 2 H, C^6H_2), 5.42 (s, NH_2, 2 H), 6.42 (m, 1 H, C^4H), 6.70 (m, 2 H, C^2H, C^8H), 6.99 (m, 1 H, $C^{2'}H$), 7.19 (m, 5 H, $C^{3'}H$, $C^{5'}H$, , $C^{6'}H$, $C^{10}H$, C^7H), 7.97 (d, *J*=9.09 Hz, 1 H, C^1H), 8.84 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{20}H_{15}FN_2O_2$) calculated 334.1117; found 334.1124.

9-Amino-3-[(2,4,5-trifluorophenyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (5g).

Compound **5g** was prepared according to General Procedure B using **28g** (50 mg, 0.24 mmol). The reaction mixture was stirred under hydrogen atmosphere for 3 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 45 mg (60.9%), yellow solid. **HPLC**: t_R = 7.34 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 5.00 (s, 2 H, C^6H_2), 5.43 (s, NH_2, 2 H), 6.34 (s, 1 H, C^4H), 6.69 (m, 2 H, $C^{3'}H$, $C^{6'}H$), 6.99 (d, *J*=2.15 Hz, 1 H, C^2H), 7.12 (d, *J*=8.08 Hz, 1 H, C^8H), 7.55 (m, 2 H, ($C^{10}H$, C^7H), 7.98 (d, *J*=8.97 Hz, 1 H, C^1H), 8.74 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{20}H_{13}F_3N_2O_2$) calculated 370.0934; found 370.0929.

9-Amino-3-(2,4-difluorophenoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (6a).

Compound **6a** was prepared according to General Procedure B using **31** (100 mg, 0.26 mmol) . The reaction mixture was stirred under hydrogen atmosphere for 2 h and purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 65 mg (70.5%), yellow solid. **HPLC**: t_R = 8.13 min, purity: 98.5%; **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 5.13 (s, 2 H, C^6H_2), 5.53 (s, -NH_2, 2 H) 6.49 (s, 1 H, C^3H), 6.79 (m, 2 H, $C^{3'}H$, C^2H), 7.00 (m, 1 H, C^8H), 7.22 (m, 2 H, $C^{10}H$, $C^{5'}H$), 7.51 (m, 2 H, $C^{6'}H$, C^7H), 8.13 (d, *J*=9.09 Hz, 1 H, C^1H). **HRMS-EI**, *m/z* ($C_{20}H_{13}F_2NO_3$) calculated 353.0863; found 353.0869.

Synthesis of dihydroxy substituted dibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure C).

To a stirred solution of the respective 2,2-dimethyl-1,3-dioxolan-4-yl substituted compound in 50 ml methanol and 5 ml water, *p*-toluenesulfonic acid mono hydrate (50 mg, 0.50 mmol) was added. The mixture was then heated to reflux until TLC indicated complete conversion. After cooling to room temperature, the organic phase was evaporated. The resulting oil was purified via flash chromatography.

3-[(2,4-Difluorophenyl)amino]-7-{[(2*S*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (1i).

Compound **1i** was prepared according to General Procedure C using **1g** (75 mg, 0.16 mmol). The reaction mixture was heated to reflux temperature for 4 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 36 mg (52.6%), yellow solid. **HPLC**: t_R = 6.91 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.48 (m, 2 H, $C^3_{propoxy}$-H_2), 3.95 (m, 3 H, $C^2_{propoxy}H$, $C^1_{propoxy}H_2$), 5.29 (s, 2 H, C^6H_2), 6.24 (s, 1 H, C^4H), 6.59 (dd, *J*=8.84, 2.27 Hz, 1 H, C^2H), 7.10 (m, 1H, C^6'H), 7.35 (m, 5 H, C^3'H, C^5'H, C^8H, C^9H, $C^{10}H$), 7.93 (d, *J*=8.97 Hz, 1 H, C^1H), 8.70 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1231; found 427.1238.

3-[(2,4-Difluorophenyl)amino]-7-{[(2*R*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (1j).

Compound **1j** was prepared according to General Procedure C using **1h** (80 mg, 0.19 mmol). The reaction mixture was heated to reflux temperature for 5 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 43 mg (53.0%), yellow solid. **HPLC**: t_R = 6.93 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.49 (t, *J*=5.62 Hz, 2 H, $C^3_{propoxy}$-H_2), 3.97 (m, 3 H, $C^2_{propoxy}H$, $C^1_{propoxy}H_2$), 4.70 (t, *J*=5.62 Hz, -OH, 1 H), 5.05 (d, -OH, *J*=5.18 Hz, 1 H), 5.29 (s, 2 H, C^6H_2), 6.24 (m, 1 H, C^4H), 6.59 (dd, *J*=9.09, 1.89 Hz, 1 H, C^2H), 7.09 (m, 1 H, C^6'), 7.34 (m, 5 H, C^3', C^5', C^8, C^9, C^{10}), 7.93 (d, *J*=8.97 Hz, 1 H, C^1), 8.69 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1231; found 427.1224.

3-[(2,4-Difluorophenyl)amino]-8-{[(2*S*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (2l).

Compound **2l** was prepared according to General Procedure C using **2j** (75 mg, 0.16 mmol). The reaction mixture was heated to reflux temperature for 4 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 43 mg (66.2%), yellow solid. **HPLC**: t_R = 6.67 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.46 (m, 2 H, $C^3_{propoxy}H_2$), 3.94 (m, 3 H, $C^1_{propoxy}H_2$, $C^2_{propoxy}H$), 5.16 (s, 2 H, C^6H_2), 6.26 (s, 1 H, C^4H), 6.61 (dd, *J*=8.97, 1.26 Hz, 1 H, C^2H), 7.07 (m, 3 H, C^3'H, C^6'H, C^5'H), 7.39 (m, 2 H, C^7H, C^9H), 7.82 (d, *J*=8.34 Hz, 1 H, C^1H), 8.02 (d, *J*=8.97 Hz, 1 H, $C^{10}H$), 8.67 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated: 427.1231; found: 427.1217.

3-[(2,4-Difluorophenyl)amino]-8-{[(3*R*)-2,3-dihydroxybutyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (2m).

Compound **2m** was prepared according to General Procedure C using **2k** (60 mg, 0.12 mmol). The reaction mixture was heated to reflux temperature for 3 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 30 mg (56.6%), yellow solid. **HPLC**: t_R = 7.12 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 1.80 (m, 2 H, $C^2_{butoxy}H_2$), 3.64 (m, 1 H, $C^3_{butoxy}H$), 4.17 (m, 2 H, $C^4_{butoxy}H_2$), 4.63 (m, $C^1_{butoxy}H_2$), 5.14 (s, 2 H, C^6H_2), 6.26 (s, 1 H, C^4H), 6.61 (dd, *J*=8.97, 1.77 Hz, 1 H, C^2H), 7.07 (m, 3 H, C^7H, C^9H, C^3'H), 7.37 (m, 2 H, C^5'H, C^6'H), 7.82 (d, *J*=8.46 Hz, 1 H, $C^{10}H$), 8.02 (d, *J*=8.97 Hz, 1

H, C^1H), 8.67 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{24}H_{21}F_2NO_5$) calculated 441.1387; found 441.1371.

3-[(2,4-Difluorophenyl)amino]-9-{[(2*S*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (3h).

Compound **3h** was prepared according to General Procedure C using **3f** (80 mg, 0.19 mmol). The reaction mixture was heated to reflux temperature for 5 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 35 mg (44.6%), yellow solid. **HPLC**: t_R = 7.02 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.45 (m, 2 H, $C^3_{propoxy}H_2$), 3.84 (m, 2 H, $C^1_{propoxy}H_2$), 4.09 (m, 1 H $C^2_{propoxy}H$), 4.68 (t, -OH,*J*=5.68 Hz, 1 H), 4.97 (d, -OH, *J*=4.93 Hz, 1 H), 5.12 (s, 2 H, C^6H2), 6.22 (m, 1 H, C^4H) 6.60 (dd, *J*=9.22, 2.15 Hz, 1 H, C^2H) 7.11 (m, 2 H, $C^{6'}$, $C^{3'}$) 7.29 (m, 1 H, $C^{5'}$) 7.41 (m, 3 H, C^8H, C^{10}H, C^7H) 7.98 (d, *J*=8.84 Hz, 1 H, C^1H) 8.70 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1231; found 427.1223.

3-[(2,4-Difluorophenyl)amino]-9-{[(2*R*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (3i).

Compound **3i** was prepared according to General Procedure C using **3g** (100 mg, 0.21 mmol). The reaction mixture was heated to reflux temperature for 6 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 50 mg (56.4%), yellow oil. **HPLC**: t_R = 6.47 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.44 (m, 2 H, $C^3_{propoxy}H_2$), 3.84 (m, 2 H, $C^1_{propoxy}H_2$), 4.06 (m, 1 H, $C^2_{propoxy}H$), 4.68 (t, -OH, *J*=5.62 Hz, 1 H), 4.97 (d, -OH, *J*=5.05 Hz, 1 H), 5.12 (s, 2 H, C^6H_2), 6.22 (s, 1 H, C^4H), 6.60 (dd, *J*=8.53, 0.69 Hz, 1 H, C^2H), 7.11 (m, 2 H, $C^{6'}$, $C^{2'}$), 7.36 (m, 4 H, $C^{5'}$H, C^8H, C^{10}H, C^7H), 7.98 (d, *J*=8.72 Hz, 1 H, C^1H), 8.71 (s, NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1230; found 427.1222.

3-[(2,4-Difluorophenyl)amino]-10-{[(2*S*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (4e).

Compound **4e** was prepared according to General Procedure C using **4c** (80 mg, 0.17 mmol). The reaction mixture was heated to reflux temperature for 4 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 51 mg (71.2%), yellow oil. **HPLC**: t_R = 7.08 min, purity: 100%; **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 3.47 (m, 2 H, $C^3_{propoxy}H_2$), 3.75 (m, 1 H, $C^2_{propoxy}H$), 3.98 (m, 2 H, 1 H, $C^1_{propoxy}H_2$), 4.58 (t, -OH, *J*=4.93 Hz, 1 H),4.87 (d, -OH, *J*=4.55 Hz, 1 H), 5.08 (s, 2 H, C^6H_2), 6.21 (s, 1 H, C^4H), 6.58 (d, *J*=8.84 Hz, 1 H, C^2H), 7.07 (m, 2 H, $C^{3'}$H, $C^{6'}$H), 7.16 (d, *J*=8.59 Hz, 1 H, C^9H), 7.40 (m, 3 H, $C^{5'}$H, C^7H, C^8H), 7.72 (d, *J*=8.84 Hz, 1 H, C^1H), 8.57 (s, -NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1231; found 427.1203.

3-[(2,4-Difluorophenyl)amino]-10-{[(2*R*)-2,3-dihydroxypropyl]oxy}dibenzo[*b,e*]oxepin -11(6*H*)-one (4f).

Compound **4f** was prepared according to General Procedure C using **4c** (70 mg, 0.16 mmol). The reaction mixture was heated to reflux temperature for 3 h and purified by flash chromatography (SiO_2, dichloromethane / ethanol 95:5). Yield: 40 mg (60.5%), orange solid. **HPLC**: t_R = 7.11 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.45 (m, 2 H, $C^3_{propoxy}H_2$), 3.73 (m, 1 H, $C^2_{propoxy}H$), 3.96 (m, 2 H, $C^1_{propoxy}H_2$), 4.57 (t, -OH, *J*=5.68 Hz, 1 H), 4.86 (d, -OH, *J*=4.93 Hz, 1 H), 5.07 (s, 2 H, C^6H_2), 6.20 (s, 1 H, C^4H), 6.57 (dd, *J*=8.78, 1.71 Hz, 1 H, C^2H), 7.05 (m, 2 H, $C^{3'}$H, $C^{6'}$H), 7.15 (d, *J*=8.59 Hz, 1 H, C^9H), 7.39 (m, 3 H, $C^{5'}$H, C^7H, C^8H), 7.71 (d, *J*=8.72 Hz, 1 H, C^1H), 8.56 (s, -NH, 1 H); **HRMS-EI**, *m/z* ($C_{23}H_{19}F_2NO_5$) calculated 427.1231; found 427.1226.

Synthesis of *N*-morpholino substituted dibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure D).

The stated amount of aniline compound, *N*-(2-chloroethyl)morpholine hydrochloride, KI and K_2CO_3 was dissolved in acetonitrile (4ml) in a microwave vial. The vial was heated in a CEM Discover microwave at 110°C for 10 min. After cooling to room temperature, the mixture was hydrolyzed with water and extracted with ethyl acetate. After evaporating the organic phase, the resulting oil was purified via flash chromatography.

3-[(2,4-Difluorophenyl)amino]-9-[(2-morpholin-4-yl-ethyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (6b).

Compound **6b** was prepared according to General Procedure D using **30** (150 mg, 0.58 mmol), K_2CO_3 (160 mg, 1.16 mmol), *N*-(2-chloroethyl)morpholine hydrochloride (106 mg, 0.58 mmol) and KI (50 mg, 0.3 mmol). The resulting oil was purified by flash chromatography (SiO_2, dichloromethane / methanol 98:2). Yield: 85 mg (31.5%), yellow solid. **HPLC**: t_R = 5.26 min, purity: 100%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.48 (m, 4 H, $C^{2/6}{}_{morpholinyl}H_2$), 2.67 (t, *J*=5.62 Hz, 2 H, $C^{2}{}_{ethylamino}H_2$), 3.23 (t, *J*=5.75 Hz, 2 H, $C^{1}{}_{ethylamino}H_2$), 3.71 (m, 4 H, $C^{3/5}{}_{morpholinyl}H_2$), 5.05 (s, 2 H, $C^{6}H_2$), 6.44 (m, 1 H, $C^{4}H$), 6.61 (dd, *J*=8.91, 1.96 Hz, 1 H, $C^{2}H$), 6.84 (m, 3 H, $C^{6'}H$, $C^{3'}H$, $C^{5'}H$), 7.13 (m, 2 H, $C^{8}H$, $C^{10}H$), 7.35 (m, 1 H, $C^{7}H$), 8.17 (d, *J*=8.56 Hz, 1H, $C^{1}H$); **HRMS-ESI**, *m/z* ($C_{20}H_{17}N_3O_2$) calculated: $[M + H]^+$ 466.1937; found: 466.1940

3-[(2,4-Difluorophenoxy]-9-[(2-morpholin-4-yl-ethyl)amino]dibenzo[*b,e*]oxepin-11(6*H*)-one (6c).

Compound **6c** was prepared according to General Procedure D using **6a** (100 mg, 0.28 mmol), K_2CO_3 (78 mg, 0.56 mmol), *N*-(2-chloroethyl)morpholine hydrochloride (52 mg, 0.28 mmol) and KI (50 mg, 0.3 mmol). The resulting oil was purified by flash chromatography (SiO_2, dichloromethane / methanol 98:2). Yield: 34 mg (26.0%), yellow solid. **HPLC**: t_R = 6.38 min, purity: 99.5%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 2.57 (s, 4 H, $C^{3/5}{}_{morpholinyl}H_2$), 2.72 (s, 2 H t, *J*=5.62 Hz, 2 H, $C^{2}{}_{ethylamino}H_2$), 3.23 (s, 2 H $C^{1}{}_{ethylamino}H_2$), 3.74 (s, 4 H, $C^{2/6}{}_{morpholinyl}H_2$), 4.99 (s, 2 H, $C^{6}H_2$), 6.35 (s, $C^{4}H$), 6.62 (d, *J*=8.34 Hz, 1 H, $C^{2}H$), 6.73 (d, *J*=7.33 Hz, 1 H, $C^{3'}$), 6.86 (m, 2 H, $C^{8}H$, $C^{5'}H$), 7.05 (m, 3 H, $C^{10}H$, $C^{6'}H$, $C^{7}H$), 8.13 (d, *J*=9.09 Hz, 1 H, $C^{1}H$); **HRMS-EI**, *m/z* ($C_{26}H_{24}F_2N_2O_4$) calculated 466.1703; found 466.1688.

Synthesis of hydroxyl substituted 2-methylbenzoic acids (General Procedure E).

The aniline compound was dissolved in 200 ml H_2SO_4 (2.0%) and cooled to 0°C. The respective amount of $NaNO_2$ was dissolved in 20 ml H_2O and added dropwise to the reaction mixture and stirred for 30 min. After warming to room temperature, the solution was heated to reflux temperature for 30 min. After cooling down to room temperature, the solution was extracted with ethyl acetate and the organic phase was evaporated. The phenol compounds remain as orange solids.

5-Hydroxy-2-methylbenzoic acid (19a).

Compound **19a** was prepared according to General Procedure E using 5-amino-2-methylbenzoic acid (**18a**) (3.20 g, 21.17 mmol) and $NaNO_2$ (1.90 g, 27.50 mmol). Yield: 2.00 g (62.7%), orange solid. **$C_8H_8O_3$** (M_r = 152.14 g/mol); **mp** = 181.8 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.37 (s, 3 H, -CH_3), 6.82 (dd, *J*=8.27, 2.72 Hz, 1 H, C^4H), 7.06 (d, *J*=8.21 Hz, 1 H, C^3H), 7.22 (d, *J*=2.65 Hz, 1 H, C^6H), 9.43 (s, -OH, 1 H) 12.67 (s, -CO_2H, 1 H); **^{13}C NMR** (50 MHz, DMSO-d_6) δ [ppm] = 20.7 (-CH_3), 117.0 (C^6), 119.2 (C^4), 129.4 (C^3), 131.3 (C^2), 132.8 (C^1), 155.4 (C^5), 168.9 (CO_2H); **FT-IR (ATR, cm^{-1})** = 2925, 2606, 1682, 1656, 1307, 1276, 1245, 1222, 759.

6-Hydroxy-2-methylbenzoic acid (19b).

Compound **19b** was prepared according to General Procedure E using 6-amino-2-methylbenzoic acid (5.00 g, 32.90 mmol) and $NaNO_2$ (2.27 g, 36.18 mmol). Yield: 3.40 g (68.0%), orange solid. **$C_8H_8O_3$** (M_r= 152.14 g/mol); **mp** = 168.1 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.61 (s, 3 H, -CH_3), 6.78 (d, *J*=7.33 Hz, 1 H, C^5H), 6.88 (d, *J*=8.21 Hz, 1 H, C^3H),7.36 (m, 1 H, C^4H), 11.02 (s, -OH, 1 H); **^{13}C NMR** (50 MHz, DMSO-d_6) δ [ppm] = 24.0 (-CH_3), 110.8 (C^1), 115.8 (C^5), 123.2 (C^3), 135.4 (C^4), 142.9 (C^2), 163.7 (C^6), 176.1 (CO_2H); **FT-IR (ATR, cm^{-1})** = 2850, 1641, 1602, 1441, 1304, 1249, 1216, 902, 804, 718

Synthesis of substituted methyl-2-methylbenzoates (General Procedure F).

The benzoic acid is dissolved in 50 ml MeOH and 2ml $H_2SO_{4\ conc}$ and the solution was heated to reflux temperature for 6 hours. After cooling down to room temperature, the solution was evaporated. The resulting oil was dissolved in ethyl acetate and extracted with sodium hydroxide solution (10%). The organic phase was evaporated and the product remains as a colorless oil.

Methyl-3-methoxy-2-methylbenzoate (9a).

Compound **9a** was prepared according to General Procedure F using 3-methoxy-2-methylbenzoic acid (5.00 g, 30.1 mmol). Yield: 4.90 g (90.7%), colorless oil. **$C_{10}H_{12}O_3$** (M_r = 180.08 g/mol); **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.30 (s, 3 H, -CH_3), 3.80 (s, 6 H, 2*-OCH_3), 7.21 (m, 3 H, C^3H, C^4H, C^6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 12.8 (-CH_3), 52.2 (-O*C*H_3), 56.0 (-O*C*H_3), 114.0 (C^4), 121.6 (C^6, C^2), 126.8 (C^5), 131.7 (C^1), 158.0 C^3), 168.1 (CO_2Me); **FT-IR (ATR, cm^{-1})** = 3327, 2855, 1693, 1670, 1609, 1309, 1289, 1262, 1057, 713

Methyl-4-methoxy-2-methylbenzoate (9b).

Compound **9b** was prepared according to General Procedure F using 4-methoxy-2-methylbenzoic acid (5.00 g, 27.6 mmol). Yield: 5.02 g (93.3%), colorless oil. **$C_9H_9NO_4$** (M_r = 195.17 g/mol); **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.61 (s, 3 H, -CH_3), 3.87 (s, 3 H, -OCH_3), 7.62 (d, 1 H, *J*=8.48 Hz, C^3H), 8.29 (d, *J*=8.48 Hz, 1 H, C^4H), 8.52 (s, 1H, C^6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 21.4 (-CH_3), 52.9 (-OCH_3), 125.1 (C^6), 126.7 (C^4), 130.7 (C^1), 133.6 (C^3), 145.9 (C^2), 147.6 (C^5), 165.83 (CO_2Me);

Methyl-2-methyl-5-nitrobenzoate (9c).

Compound **9c** was prepared according to General Procedure F using 5-nitro-2-methylbenzoic acid (5.00 g, 30.1 mmol). Yield: 4.50 g (83.0%), colorless solid. **$C_{10}H_{12}O_3$** (M_r = 180.08 g/mol); **mp** = 72.3 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.50 (s, 3 H, -CH_3), 3.76 (s, 3 H, -OCH_3), 3.79 (s, 3 H-OCH_3), 6.84 (m, 2 H, C^3H, C^5H), 7.83 (d, *J*=8.72 Hz,

1 H, C^6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 22.0 (-CH_3), 51.8 (-OCH_3), 55.7 (-OCH_3), 111.7 (C^3), 117.2 (C^5), 121.5 (C^1), 132.9 (C^6), 142.5 (C^2), 162.4 (C^4), 167.0 (CO_2Me);

Synthesis of methoxy substituted methyl-2-methylbenzoates (General Procedure G).

The benzoic acid, iodomethan and K_2CO_3 were suspended in 50 ml DMF and heated to a temperature of 70°C for 16 hours. After cooling down to room temperature, the solution was hydrolyzed with water and extracted with ethyl acetate. After drying over Na_2SO_4, the organic phase was evaporated and the resulting oil was purified by flash chromatograph (SiO_2, hexane/ ethyl acetate 3:1).

Methyl-5-methoxy-2-methylbenzoate (20a).

Compound **20a** was prepared according to General Procedure G using **19a** (2.00 g, 13.1 mmol), K_2CO_3 (9.10 g, 66.2 mmol) and iodomethane (11.07 g, 78.5 mmol). Yield: 1.40 g (59.3%), yellow oil. **$C_{10}H_{12}O_3$** (M_r = 180.20 g/mol); **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.52 (s, 3 H, -CH_3), 3.82 (s, 3 H, -OCH_3), 3.90 (s, 3 H, -OCH_3), 6.96 (dd, *J*=8.40, 2.84 Hz, 1 H, C^4), 7.15 (m, 1 H, C^3), 7.45 (d, *J*=2.78 Hz, 1 H, C^6); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 20.6 (-CH_3), 51.7 (-OCH_3), 55.3 –OCH_3), 114.9 (C^4), 118.3 (C^3), 130.1 (C^6), 132.0 (C^1), 132.5 (C^2), 157.3 (C^5), 167.8 (CO_2Me);

Methyl-6-methoxy-2-methylbenzoate (20b).

Compound **20b** was prepared according to General Procedure G using **19b** (3.00 g, 19.7 mmol), K_2CO_3 (13.60 g, 98.6 mmol) and iodomethane (12.00 g, 85.1 mmol). Yield: 2.60 g (72.8%), yellow oil. **$C_{10}H_{12}O_3$** (M_r = 180.20 g/mol); **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.17 (s, 3 H, -CH_3), 3.74 (s, 3 H, -OCH_3), 3.79 (s, 3 H, -OCH_3), 6.83 (d, *J*=7.58 Hz, 1 H, C^5H), 6.90 (d, *J*=8.34 Hz, 1 H, C^3H), 7.28 (m, 1 H, C^4H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 19.0 (-CH_3), 52.3 (-OCH_3), 56.0 (-OCH_3), 109.2 (C^5), 122.4 (C^3), 123.8 (C^1), 130.7 (C^4), 135.8 (C^2), 156.2 (C^6), 168.2 (CO_2Me).

Synthesis of substituted methyl-2-bromomethylbenzoates (General Procedure H).

The benzoate was dissolved in 50 ml CCl_4 (50 ml) and heated to 72 °C. Then respective amount of NBS and AIBN were added. The mixture was heated to reflux for 3 hours. After cooling to room temperature, the organic phase was evaporated and the resulting oil was used in the next step without further purification.

Methyl-2-bromomethyl-3-methoxybenzoate (10a).

Compound **10a** was prepared according to General Procedure H using **8a** (4.90 g, 27.2 mmol), *N*-bromosuccinimide (4.84 g, 27.2 mmol) and AIBN (100mg, 0.60 mmol). Yield: not identified. **$C_{10}H_{11}BrO_3$** (M_r = 259.10 g/mol); **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 3.93 (s, 6 H, 2*-OCH_3), 5.05 (s, 2 H, Br-CH_2-), 7.07 (dd, *J*=8.21, 0.76 Hz, 1 H, C^4H), 7.34 (t, *J*=8.02 Hz, 1 H,C^5H), 7.52 (m, 1 H, C^6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 24.4 (CH_2-Br), 52.21 (-OCH_3), 56.1 (OCH_3), 114.5 (C^4), 122.8 (C^6), 127.5 (C^5), 129.2 (C^2), 130.6 (C^1), 157.8 (C^3), 167.1 (CO_2Me)

Methyl-2-bromomethyl-4-methoxybenzoate (10b).

Compound **10b** was prepared according to General Procedure H using **8b** (4.80 g, 26.7 mmol), *N*-bromosuccinimide (4.77 g, 26.7 mmol) and AIBN (100mg, 0.60 mmol). Yield: not identified. **$C_{10}H_{11}BrO_3$** (M_r = 259.10 g/mol)

Methyl-2-bromomethyl-5-nitrobenzoate (10c).

Compound **10c** was prepared according to General Procedure H using **8c** (5.00 g, 25.7 mmol), *N*-bromosuccinimide (4.60 g, 25.7 mmol) and AIBN (100mg, 0.60 mmol). Yield: not identified. **$C_9H_8BrNO_4$** (M_r = 274.07 g/mol)

Methyl-2-bromomethyl-5-methoxybenzoate (21a).

Compound **21a** was prepared according to General Procedure H using **20a** (1.10 g, 6.1 mmol), *N*-bromosuccinimide (1.09 g, 6.1 mmol) and AIBN (50 mg, 0.30 mmol). Yield: not identified. **$C_{10}H_{11}BrO_3$** (M_r = 259.10 g/mol); **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 3.93 (s, 6 H, 2*-OCH_3), 5.05 (s, 2 H, Br-CH_2-), 7.07 (dd, *J*=8.21, 0.76 Hz, 1 H, C^4H), 7.34 (t, *J*=8.02 Hz, 1 H,C^5H), 7.52 (m, 1 H, C^6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 24.4 (CH_2-Br), 52.21 (-OCH_3), 56.1 (OCH_3), 114.5 (C^4), 122.8 (C^6), 127.5 (C^5), 129.2 (C^2), 130.6 (C^1), 157.8 (C^3), 167.1 (CO_2Me)

Methyl-2-bromomethyl-6-methoxybenzoate (21b).

Compound **21b** was prepared according to General Procedure H using **20b** (2.00 g, 11.0 mmol), *N*-bromosuccinimide (1.97 g, 11.0 mmol) and AIBN (100 mg, 0.60 mmol). Yield: not identified. **$C_{10}H_{11}BrO_3$** (M_r = 259.10 g/mol); **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 3.85 (s, 3 H, -OCH_3), 3.96 (s, 3 H, -OCH_3), 4.50 (s, 2 H, C^6H_2), 6.90 (d, *J*=8.59 Hz, 1 H, C^5H), 7.02 (d, *J*=7.45 Hz, 1 H, C^3H), 7.35 (m, 1 H, C^4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 52.4 (-OCH_3), 56.0 (-OCH_3), 68.1 (CH_2Br), 111.5 (C^5), 119.0 (C^1), 122.2 (C^3), 131.0 (C^4), 136.4 (C^2), 156.8 (C^6), 167.4 (CO_2Me)

Synthesis of substituted phenoxyesters (General Procedure I).

The stated amount of benzyl bromide, K_2CO_3 and 3-chlorophenole were dissolved in acetone (50 ml) and heated to reflux for 4 hours. After cooling to room temperature, the mixture was evaporated and the resulting oil was dissolved in ethyl acetate and extracted with sodium hydroxide solution (10%). The organic phase was evaporated and the resulting oil was purified using flash chromatograph (SiO_2, hexane / ethyl acetate 3:1).

Methyl-2-[(3-chlorophenoxy)methyl]-3-methoxybenzoate (11a).

Compound **11a** was prepared according to General Procedure I using **10a** (5.00 g, 19.3 mmol), 3-chlorophenole (2.48 g, 19.3 mmol) and K_2CO_3 (2.67 g, 19.3 mmol). Yield: 4.06 g (68.6%), white solid; **$C_{16}H_{15}ClO_4$** (M_r = 306.75 g/mol); **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.71 (s, 3 H, -OCH_3), 3.84 (s, 3 H, -OCH_3), 5.28 (s, 2 H, -CH_2O-), 6.95 (m, 3 H, $C^{2'}$H, $C^{4'}$H, C^3H), 7.30 (m, 3 H, C^5H, C^4H, $C^{5'}$H), 7.48 (m, 1 H, C^6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 52.6 (-OCH_3), 56.6 (-OCH_3), 61.2 (-OCH_2-), 113.9 ($C^{6'}$), 114.7 ($C^{2'}$), 115.18 (C^4), 120.9 ($C^{4'}$), 121.9 (C^6), 123.8 (C^2), 130.4 (C^5), 131.2 ($C^{5'}$), 133.0 (C^1), 134.0 ($C^{3'}$), 158.1 (C^3), 160.0 $C^{1'}$), 167.8 (CO_2CH_3); **FT-IR (ATR, cm^{-1}):** 1713, 1587, 1458, 1276, 1242, 1068, 1004, 903, 749.

Methyl-2-[(3-chlorophenoxy)methyl]-4-methoxybenzoate (11b).

Compound **11b** was prepared according to General Procedure I using **10b** (3.00 g, 11.6 mmol), 3-chlorophenole (1.48 g, 11.6 mmol) and K_2CO_3 (1.61 g, 11.6 mmol). The crude yellow oil was used without further purification in the next step. Yield: not identified. **$C_{16}H_{15}ClO_4$** (M_r = 306.75 g/mol)

Methyl-2-[(3-chlorophenoxy)methyl]-5-nitrobenzoate (11c).

Compound **11c** was prepared according to General Procedure I using **10c** (2.74 g, 10.0 mmol), 3-chlorophenole (1.27 g, 10.0 mmol) and K_2CO_3 (1.39 g, 10.0 mmol). Yield: 1.80 g (55.9%), white solid; **$C_{15}H_{12}ClNO_5$** (M_r = 321.7 g/mol); **mp** = 143.4 °C; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.89 (s, 3 H, -OCH_3), 5.56 (s, 2 H, -CH_2O), 7.02 (m, 2 H, $C^{4'}$H, $C^{6'}$H), 7.11 (s, 1 H, $C^{2'}$H), 7.33 (m, 1 H, C5'H), 7.92 (d, 1H, J=8.58 Hz, C^3H), 8.46 (d, 1H, J=8.58Hz, C^4H), 8.62 (s, 1H, C^6H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 53.2 (-OCH_3), 67.7 (-OCH_2-), 114.6 ($C^{6'}$), 115.3 ($C^{2'}$), 121.6 ($C^{4'}$), 125.3 (C^6), 127.3 (C^4), 129.5 (C^3), 129.9 (C^1), 131.4 ($C^{5'}$), 134.2 ($C^{3'}$), 145.5 (C^2), 147.1 (C^5), 159.1 $C^{1'}$), 165.4 (*C*O_2CH_3); **FT-IR (ATR, cm^{-1}):** 1723, 1520, 1344, 1255, 1070, 1045, 902, 784, 735, 677.

Methyl-2-[(3-chlorophenoxy)methyl]-5-methoxybenzoate (22a).

Compound **22a** was prepared according to General Procedure I using **21a** (2.50 g, 9.7 mmol), 3-chlorophenole (1.24 g, 9.7 mmol) and K_2CO_3 (1.33 g, 9.7 mmol). Yield: 1.66 g (56.2%), white solid; **$C_{16}H_{15}ClO_4$** (M_r = 306.75 g/mol); **mp** = 55.7 °C; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.78 (s, 3 H, -OCH_3), 3.80 (s, 3 H, OCH_3), 5.31 (s, 2H, CH_2-O-), 6.97 (m, 3 H, $C^{2'}$H, $C^{6'}$H, $C^{4'}$H), 7.18 (m, 1 H, C^4H), 7.30 (m, 1 H, $C^{5'}$H), 7.38 (d, *J*=2.78 Hz, 1 H, C^6H), 7.54 (d, *J*=8.59 Hz, 1 H, C^3H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 52.6 (-OCH_3), 55.8 (–OCH_3), 68.0 (-CH_2-O), 114.1 ($C^{6'}$)', 115.1 $C^{2'}$), 115.7 (C^6), 118.1 (C^4), 121.1 ($C^{4'}$), 129.4 (C^1), 130.7 (C^3), 131.1 (C^2), 131.3 ($C^{5'}$), 134.1 ($C^{3'}$), 159.1 (C^5), 159.7 ($C^{1'}$), 167.1 (*C*O_2CH_3); **FT-IR (ATR, cm^{-1}):** 3090, 2923, 1717, 1288, 1218, 1078, 1030, 895, 828, 766.

Methyl-2-[(3-chlorophenoxy)methyl]-6-methoxybenzoate (22b).

Compound **22b** was prepared according to General Procedure I using **21b** (3.00 g, 11.6 mmol), 3-chlorophenole (1.49 g, 11.6 mmol) and K_2CO_3 (1.61 g, 11.6 mmol). Yield: 2.35 g (66.1%), yellow oil; **$C_{16}H_{15}ClO_4$** (M_r = 306.75 g/mol); **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.73 (s, 3 H, -OCH_3), 3.79 (s, 3 H, -OCH_3), 5.09 (s, 2 H, CH_2O), 6.91 (d, *J*=8.34 Hz, 1 H, $C^{6'}$), 7.02 (m, 2 H, $C^{2'}$H, C^5H), 7.12 (m, 2 H, $C^{4'}$H, C^7H), 7.29 (m, 1 H, $C^{5'}$H), 7.45 (m, 1 H, C^4H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 52.0 (-OCH_3), 55.9 (-OCH_3), 67.6 (-CH_2O), 111.8 (C^1), 113.8 ($C^{6'}$), 114.7 ($C^{2'}$), 120.6 (C^5), 120.9 (C^3), 122.3 (C^2), 130.8 ($C^{4'}$), 130.9 ($C^{5'}$), 133.7 (C^4), 135.0 ($C^{3'}$), 156.3 (C^6), 158.9 $C^{1'}$), 167.0 (*C*O_2CH_3).

Synthesis of substituted phenoxybenzoic acids (General Procedure J).

The stated amount of phenoxy ester and KOH were dissolved in MeOH (50 ml) / H_2O (2 ml) and heated to a temperature of 40°C for 4 hours. After cooling to room temperature, the mixture was evaporated and the resulting oil was dissolved in cooled water. After acidification with HCl solution (10%), the product precipitated as a white solid. The suspension was filtered and dried for 48 h in a exsiccator.

2-[(3-Chlorophenoxy)methyl]3-methoxybenzoic acid (12a).

Compound **12a** was prepared according to General Procedure J using **11a** (3.00 g, 9.8 mmol) and KOH (1.10 g, 19.6 mmol). Yield: 2.14 g (74.8%), white solid. **$C_{15}H_{13}ClO_4$** (M_r = 292.72 g/mol); **mp** = 147.3 °C; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 3.85 (s, 3 H, -OCH_3), 5.34 (s, 2 H, -CH_2O), 6.94 (d, *J*=8.34 Hz, 1 H, C6'H), 6.98 (d, *J*=8.08 Hz, 1 H, $C^{4'}$H), 7.05 (s, 1 H, $C^{2'}$H), 7.37 (m, 4 H, C^4H, C^5H, C^6H, $C^{5'}$H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 56.2 (-OCH_3), 60.9 (-OCH2-), 113.5 (C6'), 114.4 ($C^{2'}$), 114.4 (C^4), 120.4 ($C^{4'}$), 121.6 (C^6), 123.3 (C^2), 129.9 C^5), 130.8 ($C^{5'}$), 133.6 C^1), 134.1 ($C^{3'}$), 157.8 (C^3), 159.8 ($C^{1'}$), 168.6 (*C*O_2H); **FT-IR (ATR, cm^{-1}):** 1690, 1594, 1465, 1278, 1243, 1065, 999, 772, 750.

2-[(3-Chlorophenoxy)methyl]4-methoxybenzoic acid (12b).

Compound **12b** was prepared according to General Procedure J using **11b** (3.20 g, 10.4 mmol) and KOH (1.10 g, 19.6 mmol). Yield: 2.32 g (75.9%), white solid; **$C_{15}H_{13}ClO_4$** (M_r = 292.72 g/mol); **mp** = 133.0 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.82 (s, 3 H, -OCH3), 5.46 (s, 2 H,-CH2O-), 6.99 (m, 3 H, C6'H, C3H, C5H), 7.07 (s, 1 H, C2'), 7.16 (m, 1 H, C4'), 7.33 (m, 1 H, C5'), 7.96 (d, *J*=8.84 Hz, 1 H, C6), 12.73 (s, COOH, 1 H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 55.5 (-OCH_3), 67.8(-CH2O-), 91.7 (C3), 100.6 (C5), 108.7 (C2'), 112.2 (C6'), 113.7 (C4'), 120.8 (C1), 131.1 (C6), 133.2 (C5'), 133.7, 140.7 (C2), 159.2 (C4), 162.2 (C1'), 167.4 (COOH); **FT-IR (ATR, cm^{-1}):** 1678, 1596, 1569, 1292, 1237, 1153, 1046, 899, 773.

2-[(3-Chlorophenoxy)methyl]-5-nitrobenzoic acid (12c).

Compound **12c** was prepared according to General Procedure J using **11c** (3.52 g, 10.94 mmol) and KOH (0.61 g, 10.94 mmol). Yield: 2.45 g (73.3%), white solid; **$C_{14}H_{10}ClNO_5$** (M_r = 307.68 g/mol); **mp** = 164.4 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 5.58 (s, 2 H, CH_2O), 7.02 (m, 3 H, $C^{2'}$H, $C^{4'}$H, $C^{6'}$H), 7.33 (m, 1 H, $C^{5'}$H), 7.91(d, 1 H, J=8.58Hz, C^3H), 8.24 (d, *J*=8.58 Hz, 1 H, C^4H), 8.63 (s, 1 H, C^6); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 67.9 (CH_2O), 114.1 ($C^{6'}$), 115.3 (C^6), 115.9 ($C^{2'}$), 121.5 ($C^{4'}$), 125.5 (C^6), 127.0 (C^4), 129.4 (C^3), 130.9 (C^1), 131.4 ($C^{5'}$), 134.2 ($C^{3'}$), 145.7 (C^5), 159.2 ($C^{1'}$), 166.5 (CO_2H); **FT-IR (ATR, cm^{-1}):** 1723, 1613, 1522, 1347, 1256, 1233, 1071, 1047, 851, 734, 674.

2-[(3-Chlorophenoxy)methyl]-5-methoxybenzoic acid (23a).

Compound **23a** was prepared according to General Procedure J using **22a** (1.00 g, 3.3 mmol) and KOH (0.50 g, 8.9 mmol). Yield: 0.70 g (73.3%), white solid; **$C_{15}H_{13}ClO_4$** (M_r = 292.72 g/mol); **mp** = 126.5 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.79 (s, 3 H, -OCH_3), 5.34 (s, 2 H, CH_2O), 6.97 (m, 3 H, C2'H, C4'H, C6'H), 7.15 (dd, *J*=8.46, 2.91 Hz, 1 H, C3H), 7.30 (m, 1 H, C4), 7.40 (d, *J*=2.78 Hz, 1 H, C6), 7.51 (d, *J*=8.46 Hz, 1 H, C2'); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 55.8 (-OCH_3), 68.1 (CH_2O), 114.1 (C^2), 115.2 (C^6), 115.9 ($C^{6'}$), 117.8 (C^4), 121.0 ($C^{4'}$), 129.6 (C^1), 130.9 (C^3), 131.7 ($C^{3'}$), 134.1 (C^2), 159.0 (C^5), 159.8 ($C^{1'}$), 168.3 (CO_2H); **FT-IR (ATR, cm^{-1}):** 2837, 2547, 1690, 1572, 1295, 1276, 1230, 1048, 1037, 751.

2-[(3-Chlorophenoxy)methyl]-6-methoxybenzoic acid (23b).

Compound **23b** was prepared according to General Procedure J using **22b** (1.00 g, 3.3 mmol) and KOH (0.50 g, 8.9 mmol). Yield: 675 mg (70.5%), colorless oil; **$C_{15}H_{13}ClO_4$** (M_r = 292.72 g/mol), **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 3.80 (s, 3 H, -OCH_3) 5.08 (s, 2 H, CH_2O) 7.02 (m, 5 H, $C^{6'}$H, $C^{2'}$H, C^5H, C^7H, $C^{4'}$H) 7.31 (m, 1 H, C^7H) 7.41 (m, 1 H, $C^{5'}$) 13.01 (s, 1 H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 55.8 (-OCH_3), 67.6 (-CH_2O-), 111.7 (C^1), 113.8 ($C^{6'}$), 114.9 ($C^{2'}$), 120.5 (C^5), 120.9 (C^3), 124.2 (C^2), 130.2 ($C^{4'}$), 130.8 ($C^{5'}$), 133.6 (C^4), 134.1 ($C^{3'}$), 155.8 (C^6), 159.1 ($C^{1'}$), 167.9 (CO_2H); **FT-IR (ATR, cm^{-1}):** 3208, 2981, 1735, 1583, 1272, 1230, 1028, 778, 757, 675.

Synthesis of substituted 3-chlorodibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure K).

To a stirred solution of the benzoic acid in dichloromethane (40 ml), the thionyl chloride was added dropwise over 30 minutes at room temperature. After stirring another 60 minutes, $AlCl_3$ was added slowly and the mixture stirred for 30 minutes. After hydrolysis with water, the organic phase was extracted with sodium hydroxide solution (10%) and evaporated. The resulting oil was purified via flash chromatography.

3-Chloro-8-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (13b).

Compound **13b** was prepared according to General Procedure K using **12b** (2.50 g, 8.56 mmol), $SOCl_2$ (1.01 g, 8.56 mmol) and $AlCl_3$ (2.28 g, 17.15 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 3:1). Yield: 1.34 g (56.9%), white solid; **$C_{15}H_{11}ClO_3$** (M_r = 274.71 g/mol); **mp** = 120.8 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.87 (s, 3 H, -OCH_3), 5.29 (s, 2 H, C^6), 7.08 (m, 1 H, C^4), 7.15 (m, 1 H, C^2), 7.25 (m, 2 H, C^7, C^9), 7.84 (d, *J*=8.72 Hz, 1 H, C^{10}), 8.14 (d, *J*=9.35 Hz, 1 H, C^1); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 56.1 (-OCH_3), 73.7 (C^6), 113.8 (C^4), 115.0 (C^7), 120.6 (C^9), 123.1 (C^2), 124.9 (C^{11a}), 132.1 (C^{10a}), 132.3 (C^{10}), 133.7 (C^1), 138.8 (C^3), 139.6 (C^{6a}), 161.5 (C^8), 163.5 (C^{4a}), 187.1 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3070, 2947, 1591, 1281, 1193, 1122, 1019, 871, 749, 694.

3-Chloro-9-nitrodibenzo[*b,e*]oxepin-11(6*H*)-one (13c).

Compound **13c** was prepared according to General Procedure K using **12c** (2.70 g, 8.80 mmol), $SOCl_2$ (1.12 g, 8.80 mmol) and $AlCl_3$ (5.0 g, 35.0 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 3:1). Yield: 1.40 g (55.1%), white solid; **$C_{14}H_8ClNO_4$** (M_r = 289.67 g/mol); **mp** = 175.0 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 5.49 (s, 2 H, C^6H_2), 7.30 (m, 1 H, C^4H, C^2H), 7.90 (d, J=8.96 Hz,,1 H, C^1H), 8.13 (d, J=9.08Hz, 1 H, C^7H), 8.48 (m, 2 H, C^8H, C^{10}H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 72.7 (C^6), 120.8 (C^4), 123.5 (C^2), 123.9 (C^{11a}), 124.4 (C^8), 127.9 (C^{10}), 130.7 (C^7), 133.7 (C^1), 140.5 (C^{10a}), 140.7 (C^3), 142.4 (C^{6a}), 161.7 (C^{4a}), 187.3 (C^{11}); **FT-IR (ATR, cm^{-1}):** 1723, 1589, 1428, 1344, 1251, 1040, 1023, 881, 717, 682.

3-Chloro-10-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (24b).

Compound **24b** was prepared according to General Procedure K using **23b** (2.50 g, 8.56 mmol), $SOCl_2$ (1.01 g, 8.56 mmol) and $AlCl_3$ (2.28 g, 17.15 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 3:1). Yield: 1.45 g (61.8%), white solid; **$C_{15}H_{11}ClO_3$** (M_r = 274.71 g/mol); **mp** = 113.0 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.77 (s, 3 H, -OCH_3), 5.22 (s, 2 H, C^6H_2), 7.15 (m, 4 H, C^9H, C^4H, C^7H, C^2H), 7.54 (m, 1 H, C8H), 7.80 (d, *J*=8.34 Hz, 1 H, C^1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 56.0 (-OCH_3), 72.1 (C^6), 113.2 (C^9), 119.3 (C^4), 120.4 (C^7), 121.8 (C^2), 125.3 (C^{11a}), 129.0 (C^{10a}), 132.1 (C^8), 132.8 (C^1), 135.2, (C^3), 138.8 (C^{6a}), 156.7 (C^{10}), 159.6 (C^{4a}), 189.5 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3441,3014, 1662, 1593, 1472, 1271, 1091, 1001, 857, 800.

Synthesis of substituted 3-chlorodibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure L).

To a stirred solution of benzoic acid in DCM (40 ml), trifluoroacetic anhydride was added slowly at room temperature. After stirring for 30 minutes, the borontrifluorid etherate (0.2 ml) was added and the solution was stirred for another 30 minutes. After hydrolysis with water, the organic phase was extracted with sodium hydroxide solution (10%) and evaporated. The resulting oil was purified by flash chromatography.

3-Chloro-7-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (13a).

Compound **13a** was prepared according to General Procedure L using **12a** (2.00 g, 6.85 mmol), TFAA (4.50 g, 21.42 mmol) and BF_3-$O(Et)_2$ (0.2 ml). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 3:1). Yield: 1.12 g (59.7%), white solid; **$C_{15}H_{11}ClO_3$** (M_r = 274.71 g/mol); **mp** = 172.8 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 3.92 (s, 3 H, -OCH_3), 5.36 (s, 2 H,-CH_2O-), 7.08 (m, 3 H, C^2H, C^4H, C^8H), 7.40 (m, 2 H, C^9, C^{10}), 8.11 (d, *J*=9.09 Hz, 1 H, C^1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 55.9 (-OCH_3), 65.5 (-CH_2O-), 114.6 (C^4) , 120.3 C^8), 120.5 (C^2), 122.3 (C^{10}), 123.2 (C^{11a}), 123.7 (C^{10a}), 130.1 (C^9), 132.9 (C^1), 140.8 C^3), 142.4 (C^{6a}), 155.6 (C^7), 161.7 C^{4a}), 190.7 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3344, 2929, 1694, 1595, 1462, 1268, 1242, 1156, 1063, 766.

3-Chloro-9-methoxydibenzo[*b,e*]oxepin-11(6*H*)-one (24a).

Compound **24a** was prepared according to General Pprocedure L using **23a** (2.00 g, 6.85 mmol), TFAA (4.50 g, 21.42 mmol) and BF_3-$O(Et)_2$ (0.2 ml). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 3:1). Yield: 0.45 g (23.9%), white solid; **$C_{15}H_{11}ClO_3$** (M_r = 274.71 g/mol); **mp** = 105.1 °C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ [ppm] = 3.82 (s, 3 H, -OCH_3), 5.28 (s, 2 H, C^6H_2), 7.24 (m, 4 H, C^2H, C^4H, $C^{10}H$, C^8H), 7.51 (d, *J*=8.34 Hz, 1 H, C^7H), 8.08 (d, *J*=8.59 Hz, 1 H, C^1H); **^{13}C NMR** (100 MHz, DMSO-d$_6$): δ [ppm] = 55.5 (-OCH_3), 72.3 (C^6), 113.1 (C^4), 118.9 (C^{10}), 120.2 (C^8), 122.3 (C^2), 123.7 (C^{11a}), 127.9 (C^{10a}), 130.1 (C^7), 133.2 (C^1), 139.7 (C^{6a}), 141.0 (C^3), 159.7 (C^9), 161.3 (C^{4a}), 189.0 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3085, 2942, 1589, 1328, 1283, 1255, 1010, 878, 853, 766.

Synthesis of hydroxyl substituted 3-chloro-dibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure M).

A solution of 3-chloro-oxepin-11(6*H*)-one in dichloromethane (40ml) was cooled to a temperature of -20 °C under an argon atmosphere and BBr_3 was added slowly. The progress was monitored until TLC indicated complete conversion. After hydrolysis with water, the organic phase was evaporated. The resulting oil was purified by flash chromatography.

3-Chloro-7-hydroxydibenzo[*b,e*]oxepin-11(6*H*)-one (14a).

Compound **14a** was prepared according to General Procedure M using **13a** (1.70 g, 6.19 mmol) and BBr_3 (2.33 g, 9.28 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 830 mg (52.8%), colorless oil; **$C_{14}H_{19}ClO_3$** (M_r = 260.67 g/mol); **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 5.32 (s, 2 H, -CH_2O-), 7.22 (m, 5 H, C^2H, C^4H, C^8H, C^9, C^{10}), 8.00 (d, *J*=9.10 Hz, 1 H, C^1H), 10.35 (s, -OH, 1 H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 65.8 (-CH_2O-), 119.2 (C^{11a}), 120.3 (C^4), 120.4 (C^8), 121.6 (C^2), 122.5 (C^{10}), 124.1 (C^{10a}), 130.4 (C^9), 133.3 (C^1), 139.9 (C^3), 142.3 (C^{6a}), 154.4 (C^7), 161.6 (C^{4a}), 190.4 (C^{11}).

3-Chloro-8-hydroxydibenzo[*b,e*]oxepin-11(6*H*)-one (14b).

Compound **14b** was prepared according to General Procedure M using **13b** (1.50 g, 5.47 mmol) and BBr_3 (2.50 g, 10.0 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 630 mg (44.1%), white solid; **$C_{14}H_{19}ClO_3$** (M_r = 260.67 g/mol); **mp** = 254.1°C; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 5.22 (s, 2 H, C^6H_2), 6.89 (m, 2 H, C^7H, C^9H), 7.23 (m, 2 H, C^4H,C^2H), 7.76 (d, *J*=9.35 Hz, 1 H, $C^{10}H$), 8.14 (m, 1 H, C^1H), 10.58 (s, -OH, 1 H); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 73.9 (C^6), 115.0 (C^7), 116.3 (C^9), 120.6 (C^4), 123.0 (C^2), 125.1 (C^{11a}), 130.7 (C^{10a}), 132.6 (C^{10}), 133.7 (C^1), 139.1 (C^{6a}), 139.4 (C^3), 161.5 (C^8), 162.5 (C^{4a}), 186.8 (C^{11}).

3-Chloro-9-hydroxydibenzo[*b,e*]oxepin-11(6*H*)-one (25a).

Compound **25a** was prepared according to General Procedure M using **24a** (0.40 g, 1.46 mmol) and BBr_3 (0.73 g, 2.92 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 230 mg (60.4%), white solid; **$C_{14}H_{19}ClO_3$** (M_r = 260.67 g/mol); **mp** = 162.5 °C; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ [ppm] = 5.22 (s, 2 H, C^6H_2), 7.03 (m, 1 H, C^8H), 7.21 (m, 3 H, C^3H, C^2H, $C^{10}H$) 7.39 (d, *J*=8.34 Hz, 1 H, C1H, C^7H), 8.07 (d, *J*=8.34 Hz, 1 H, C^1H), 9.99 (s, OH, 1 H); **^{13}C NMR** (100 MHz, DMSO-d$_6$): δ [ppm] = 72.4 (C^6), 114.8 (C^4), 119.9 (C^{10}), 120.2 (C^8), 122.2 (C^2), 123.7 (C^{11a}), 126.3 (C^{10a}),

130.1 (C^7), 133.2 (C^1), 139.6 (C^{6a}), 141.0 (C^3), 158.0 (C^9), 161.3, (C^{4a}), 189.1 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3336, 1581, 1303, 1289, 1253, 1241, 1021, 873, 789, 771.

3-Chloro-10-hydroxydibenzo[*b,e*]oxepin-11(6*H*)-one (25b).

Compound **25b** was prepared according to General Procedure M using **24b** (1.50 g, 5.47 mmol) and BBr_3 (2.33 g, 9.28 mmol). The resulting oil was purified by flash chromatography (SiO_2, hexane / ethyl acetate 1:1). Yield: 860 mg (60.5%), white solid; **$C_{14}H_{19}ClO_3$** (M_r= 260.67 g/mol); **mp** = 145.4 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 5.14 (s, 2 H, C^6H_2), 6.84 (dd, *J*=7.20, 0.63 Hz, 1 H, C^9H), 7.11 (m, 3 H, C^4H, C^7H, C^2H), 7.47 (m, 1 H, C^8H), 8.35 (d, *J*=8.72 Hz, 1 H, C^1H), 12.50 (s, -OH, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 74.9 (C^6), 119.3 (C^9), 119.3 (C^4), 120.4 (C^7), 121.0 (C^{11a}), 123.3(C^2), 124.6 (C^{10a}), 133.8 (C^8), 135.5 (C^1), 137.0 (C^3), 141.6 (C^{6a}), 161.6 (C^{10}), 163.4 (C^{4a}), 191.4 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3073, 1590, 1256, 1205, 1165, 1089, 1013, 803, 772, 702.

Synthesis of 2,2-dimethyl-1,3-dioxolan-4-yl substituted 3-chlorodibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure N).

The stated amount of the phenole, K_2CO_3, and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate were dissolved in DMF (10 ml) under an argon atmosphere and heated to reflux for 6 hours. After cooling to room temperature, the solution was hydrolyzed with water and extracted with hexane. The organic phase was evaporated and the resulting oil was used in the next step without further purification.

3-(Chloro)-7-{2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (15c).

Compound **15c** was prepared according to General Procedure N using **14a** (200 mg, 0.77 mmol), [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-(Chloro)-7-{2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (15d).

Compound **15d** was prepared according to General Procedure N using **14a** (200 mg, 0.77 mmol), [(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-(Chloro)-8-{2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (16d).

Compound **16d** was prepared according to General Procedure N using **14b** (200 mg, 0.77 mmol), [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-Chloro-8-{2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (16e).

Compound **16e** was prepared according to General Procedure N using **14b** (200 mg, 0.77 mmol), [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl 4-methylbenzenesulfonate (432 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{21}H_{21}ClO_5$** (M_r = 388.84 g/mol)

3-(Chloro)-9-{2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (26b).

Compound **26b** was prepared according to General Procedure N using **25a** (200 mg, 0.77 mmol), [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-(Chloro)-9-{2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (26c).

Compound **26c** was prepared according to General Procedure N using **25a** (200 mg, 0.77 mmol), [(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-(Chloro)-10-{2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (27b).

Compound **27b** was prepared according to General Procedure N using **25b** (200 mg, 0.77 mmol), [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

3-(Chloro)-10-{2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (27c).

Compound **27c** was prepared according to General Procedure N using **25b** (200 mg, 0.77 mmol), [(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (440 mg, 1.44 mmol) and K_2CO_3 (200 mg, 1.44 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{19}ClO_5$** (M_r = 374.81 g/mol)

Synthesis of substituted 3-chloro-dibenzo[*b,e*]oxepin-11(6*H*)-ones (General Procedure O).

The stated amount of the phenol, K_2CO_3 and the halogen alkane were suspended in acetone (10ml) and heated to reflux for 6 hours under an argon atmosphere. After cooling to room temperature, the solution was evaporated and the resulting oil was dissolved in ethyl acetate and extracted twice with sodium hydroxide solution (10%). The organic phase was evaporated and the resulting oil was used in the next step without further purification.

3-Chloro-7-[(2-morpholin-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (15a).

Compound **15a** was prepared according to General Procedure O using **14a** (200 mg, 0.77 mmol), 4-(2-chloroethyl)morpholine hydrochlorid (150 mg, 0.79 mmol) and K_2CO_3 (400 mg, 2.87 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{20}ClNO_4$** (M_r = 374.83 g/mol)

3-Chloro-7-[(2-tetrahydro-2*H*-pyran-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (15b).

Compound **15b** was prepared according to General Procedure O using **14a** (200 mg, 0.77 mmol), 4-(2-bromoethyl)tetrahydro-2*H*-pyran (148 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77

mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{21}H_{21}ClO_4$** (M_r = 372.84 g/mol)

3-Chloro-8-[(2-morpholin-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (16a).

Compound **16a** was prepared according to General Procedure O using **14b** (200 mg, 0.77 mmol), 4-(2-chloroethyl)morpholine hydrochlorid (150 mg, 0.79 mmol) and K_2CO_3 (210 mg, 1.52 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{20}ClNO_4$** (M_r = 374.83 g/mol)

3-Chloro-8-[(2-tetrahydro-2*H*-pyran-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (16b).

Compound **16b** was prepared according to General Procedure O using **14a** (200 mg, 0.77 mmol), 4-(2-bromoethyl)tetrahydro-2*H*-pyran (150 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{21}H_{21}ClO_4$** (M_r = 372.84 g/mol)

3-Chloro-8-[(2-(dimethylamino)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (16c).

Compound **16c** was prepared according to General Procedure O using **14b** (200 mg, 0.77 mmol), *N*-(2-chlorethyl)-*N*,*N*-dimethylamin hydrochlorid (148 mg, 0.77 mmol) and K_2CO_3 (208 mg, 1.50 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{18}H_{18}ClNO_3$** (M_r = 331.79 g/mol)

3-Chloro-9-[(2-morpholin-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (26a).

Compound **26a** was prepared according to General Procedure O using **25a** (150 mg, 0.57 mmol), 4-(2-chloroethyl)morpholine hydrochlorid (113 mg, 0.59 mmol) and K_2CO_3 (210 mg, 1.52 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{20}ClNO_4$** (M_r = 374.83 g/mol), **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 2.57 (m, 4 H, $C^{3/5}{}_{Morpholino}H_2$), 2.80 (t, *J*=5.62 Hz, 2 H, $C^{2}{}_{Ethoxy}H_2$), 3.72 (m, 4 H, $C^{2/6}{}_{Morpholino}H_2$), 4.15 (t, *J*=5.62 Hz, 2 H, $C^{1}{}_{Ethoxy}H_2$), 5.11 (s, 2 H, C^6H2), 7.06 (m, 3 H, C^4H, C^8H, C^2H) 7.25 (m, 1 H, C^7H), 7.38 (d, *J*=2.65 Hz, 1 H, C^{10}H) 8.14 (d, *J*=9.09 Hz, 1 H, C^1H; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 53.9 ($C^{3/5}{}_{Morpholino}$), 57.3 8 $C^{2}{}_{Ethoxy}$), 66.0 ($C^{1}{}_{Ethoxy}$), 66.7 ($C^{2/6}{}_{Morpholino}$), 73.0 (C^6), 114.0 (C^4), 119.7 (C^{10}), 120.5 (C^8), 122.5 (C^2), 123.7 (C^{11a}), 127.9(C^{10a}), 129.3 (C^7), 133.2 (C^1), 140.9 (C^{6a}), 141.3 (C^3), 159.3 (C^9), 161.5 (C^{4a}), 189.5 (C^{11})

3-Chloro-9-[(2-(diethylamino)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (26d).

Compound **26d** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), *N*-(2-chlorethyl)-*N*,*N*-dimethylamin hydrochlorid (110 mg, 0.77 mmol) and K_2CO_3 (208 mg, 1.50 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{22}ClNO_3$** (M_r = 359.84 g/mol)

3-Chloro-9-[(2-tetrahydro-2*H*-pyran-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (26e).

Compound **26e** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), 4-(2-bromoethyl)tetrahydro-2*H*-pyran (150 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{21}H_{21}ClO_4$** (M_r = 372.84 g/mol)

3-Chloro-9-(2-cyclohexylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (26f).

Compound **26f** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), (2-bromoethyl)cyclohexane (147 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{21}H_{21}ClO_4$** (M_r = 370.86 g/mol)

2-[(3-Chloro-11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-9-yl)oxy]ethyl acetate (26g).

Compound **26g** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), 2-chloroethyl acetate (94 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{18}H_{15}ClO_5$** (M_r = 346.76 g/mol)

2-[(3-Chloro-11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-9-yl)oxy]ethyl acetate (26g).

Compound **26g** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), 2-chloroethyl acetate (94 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{18}H_{15}ClO_5$** (M_r = 346.76 g/mol)

3-[(3-Chloro-11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-9-yl)oxy]propyl acetate (26h).

Compound **26h** was prepared according to General Procedure O using **25a** (200 mg, 0.77 mmol), 3-chloropropyl acetate (105 mg, 0.77 mmol) and K_2CO_3 (108 mg, 0.77 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{19}H_{17}ClO_5$** (M_r = 360.78 g/mol)

3-Chloro-10-[(2-morpholin-4-yl)ethoxy]dibenzo[*b,e*]oxepin-11(6*H*)-one (27a).

Compound **27a** was prepared according to General Procedure O using **25b** (200 mg, 0.77 mmol), 4-(2-chloroethyl)morpholine hydrochlorid (150 mg, 0.79 mmol) and K_2CO_3 (400 mg, 2.87 mmol). The resulting yellow oil was used in the next step without further purification. Yield: not identified; **$C_{20}H_{20}ClNO_4$** (M_r = 374.83 g/mol)

***Tert*-butyl-2,4-difluorophenyl-(9-nitro-11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-3-yl)carbamate (29).**

Compound **29** was prepared using **28a** (370 mg, 0.96 mmol) and dimethylaminopyridine (236 mg, 1.94 mmol) in dichloromethane (50ml). After stirring for 30 minutes di-*tert*-butyl dicarbonate (236 mg, 1.94 mmol) was added and the progress was monitored until TLC indicated complete conversion. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash Chromatography. Yield: 220 mg (47.5%), white solid; **$C_{25}H_{20}F_2N_2O_6$** (M_r = 482.43 g/mol); **mp**. = 171.0°C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 1.30 (s, 9 H, (C(-CH_3)$_3$), 5.36 (s, 2 H, C^6H2), 6.85 (s, 1 H, $C^{3'}$H), 6.96 (d, *J*=8.84 Hz, 1 H, C^2H), 7.09 (m, 1 H, $C^{5'}$H), 7.41 (m, 2 H, C^4H, $C^{2'}$H), 7.80 (d, *J*=8.08 Hz, 1 H, C^7H), 8.02 (d, *J*=8.84 Hz, 1 H, C^1H), 8.42 (m, 2 H, C^8H, C^{10}H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 27.5 (-CH_3)$_3$, 72.2 (C^6), 82.2 (*C*(-CH_3)$_3$), 112.5 (C^4), 114.4 (C^2), 118.1(C^8), 121.0 (C^{11a}), 123.9 (C^{10}), 127.3 (C^7), 130.2 (C^1), 132.3 (C^{10a}), 142.3 (C^{6a}), 148.0 (C=O_{Boc}), 148.3 (C^9), 151.6 (C^3), 161.1 (C^{4a}), 186.4 (C^{11}), $C^{1'}$ – $C^{6'}$ not detected ; **FT-IR (ATR, cm^{-1}):** 1728, 1644, 1605, 1509, 1351, 1288, 1155, 1027, 819, 764.

Synthesis of the disubstituted dibenzo[*b,e*]oxepin-11(6*H*)-ones targeting the activation loop (General Procedure P).

The stated amount of amino derivative, X-Phos, Cs_2CO_3, halogen compound and $Pd(OAc)_2$ were dissolved in 10 ml of 1,4-dioxane and 2 ml of *t*-BuOH. The mixture was heated at 110°C under an atmosphere of argon until TLC indicated complete conversion. After cooling to room temperature, the mixture was filtrated and the solvent evaporated in vacuo. The remaining oil was purified using Flash chromatography (SiO_2 60).

***N*-(2-Fluoro-5-{[9-(2-morpholino-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-3-yl]amino}phenyl)benzamide (32a).**

Compound **32a** was prepared according to General Procedure P using 3-chloro-9-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (250 mg, 0.66 mmol), Cs_2CO_3 (700 mg, 2.14 mmol), *N*-(5-amino-2-fluorophenyl)benzamide (250 mg, 1.07 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h.

After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 35 mg (9.3%), yellow solid; **$C_{33}H_{30}FN_3O_5$** (M_r = 567.60 g/mol); **mp**. = 189.0°C; **HPLC**: t_R = 4.90 min, purity: 100%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.59 (m, 4 H, $C_{2/6morpholinyl}H_2$), 2.83 (t, *J* = 5.37 Hz, 2 H, $C_{2ethoxy}H_2$), 3.73 (m, 4 H, $C_{3/5morpholinyl}H_2$), 4.18 (t, *J* = 5,49 Hz, 2 H, $C_{1ethoxy}H_2$), 5.07 (s, 2 H, $C^{6''}H_2$), 6.45 (s, 1 H, $C^{4''}H$), 6.53 (m, 1 H, $C^{2''}H$), 6.64 (dd, *J*=8.97, 2.15 Hz, 1 H, $C^{8''}H$), 6.92 (m, 1 H, $C^{4'}H$), 7.05 (m, 2 H, $C^{3'}H$, $C^{6'}H$), 7.22 (m, 1 H, $C^{10''}H$), 7.50 (m, 4 H, C^3H, C^5H, $C^{1''}H$, $C^{7''}H$), 7.87 (m, 2 H, C^2H, C^6H), 8.33 (dd, *J*=6.88, 2.34 Hz, 1 H, C^4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 53.9 ($C^{3/5}_{Morpholinyl}$), 57.4 (C^2_{Ethoxy}), 65.8 ($C^{2/6}_{Morpholinyl}$), 66.7 (C^1_{Ethoxy}), 72.8 ($C^{6''}$), 102.9 ($C^{4''}$), 110.3 ($C^{2''}$), 113.9 ($C^{10''}$), 115.1 ($C^{8''}$), 115.1 (d, J=6.5 Hz, $C^{6'}$), 115.2 (d, J=20.6 Hz, $C^{3''}$), 117.1 (d, J=7.6 Hz, $C^{4''}$), 117.7 ($C^{11a''}$), 119.1 ($C^{7''}$), 127.0 (C^2, C^6), 127.13 (d, J=11.4 Hz, $C^{1'}$), 128.4 ($C^{10a''}$), 128.8 (C^3, C^5), 129.0 (C^1), 132.2 (C^4), 134.1 ($C^{1''}$), 136.6 (d, J=2.7 Hz), 141.8 ($C^{6a''}$), 149.3 (d, J=238.5 Hz, $C^{2'}$), 150.8 ($C^{3''}$), 159.0 ($C^{9''}$), 163.3 ($C^{4a''}$), 165.4 ($C{=}O_{Amid}$), 188.2 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3294, 1573, 1525, 1279, 1116, 856, 776, 708; **HRMS-EI**, *m/z*: calculated: 568.2242; found: 568.2241.

***N*-(4-Fluoro-3-{[9-(2-morpholino-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-3-yl]amino}phenyl)benzamide (32b).**

Compound **32b** was prepared according to General Procedure P using 3-chloro-9-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (250 mg, 0.66 mmol), Cs_2CO_3 (700 mg, 2.14 mmol), *N*-(3-amino-4-fluorophenyl)benzamide (250 mg, 1.07 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 45 mg (12.0%), yellow solid; **$C_{33}H_{30}FN_3O_5$** (M_r = 567.60 g/mol); **mp**. = 97.4°C; **HPLC**: t_R = 4.90 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d_6): δ [ppm] = 2.54 (m, 4 H, $C^{2/6}_{Morpholinyl}H_2$), 2.77 (t, *J*=5.24 Hz, 2 H, $C^2_{Ethoxy}H_2$), 3.70 (m, 4 H, $C^{3/5}_{Morpholinyl}H_2$), 4.10 (t, *J*=5.31 Hz, 2 H, $C^1_{Ethoxy}H_2$), 4.98 (s, 2 H, $C^{6''}H_2$), 6.37 (s, 1 H, $C^{2''}H$), 6.57 (d, *J*=1.89 Hz, 1 H, $C^{4''}H$), 6.67 (dd, *J*=8.97, 2.02 Hz, 1 H, $C^{8''}H$), 7.01 (m, 2 H, $C^{5'}H$, $C^{2'}H$), 7.15 (m, 1 H, $C^{6'}H$), 7.38 (m, 4 H, $C^{10''}H$, $C^{7''}H$, C^2H, C^5H), 7.80 (m, 3 H, C^4H, C^1H, C^6H), 8.09 (d, *J*=8.84 Hz, 1 H, $C^{1''}H$), 8.49 (s, 1H, -NH); **^{13}C NMR** (50 MHz, DMSO-d_6): δ [ppm] = 53.9 ($C^{3/5}_{Morpholinyl}$), 57.4 (C^2_{Ethoxy}), 65.7 ($C^{2/6}_{Morpholinyl}$), 66.7 (C^1_{Ethoxy}), 72.7 (C6''), 104.3 ($C^{4''}$), 111.1 ($C^{2''}$), 113.4 ($C^{10''}$), 113.9 ($C^{8''}$), 115.5 (d, J=7.6 Hz, $C^{6'}$), 115.9 (d, J=20.7 Hz, $C^{5'}$), 118.2 ($C^{11a''}$), 119.2 ($C^{7''}$), 127.1 (C^2, C^6), 128.2 ($C^{10a''}$), 128.5 (C^3, C^5), 128.6 (d, J=12.5 Hz, $C^{2'}$), 129.0 ($C^{3'}$), 131.7 (C^4), 133.9 ($C^{1''}$), 134.5 (C^1), 134.5 (d, J=2.3 Hz, $C^{1'}$), 141.6 ($C^{6a''}$), 149.3 ($C^{3''}$), 150.8 (d, J=240.7 Hz, $C^{4'}$), 159.0 ($C^{9''}$, 163.1 ($C^{4a''}$), 165.9 ($C{=}O_{Amid}$), 188.6 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3294, 1572, 1524, 1497, 1325, 1287, 1115, 1028, 855, 706; **HRMS-EI**, *m/z*: calculated: 568.2242; found: 568.2247.

***N*-(2-Fluoro-4-methyl-5-{[9-(2-morpholino-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo [*b*,*e*]oxepin-3-yl]amino}phenyl)thiophene-3-carboxamide (32c).**

Compound **32c** was prepared according to General Procedure P using 3-chloro-9-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (250 mg, 0.66 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol), *N*-(5-amino-2-fluoro-4-methylphenyl)thiophene-3-carboxamide (200 mg, 0.80 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 4 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 45 mg (11.4%), yellow oil; **$C_{32}H_{30}FN_3O_5S$** (M_r = 587.66 g/mol); **HPLC**: t_R = 4.87 min, purity: 95.3%; **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 2.19 (s, 3 H, $-CH_3$) 2.44 (m, 4 H, $C^{2/6}_{Morpholinyl}H_2$), 2.69 (t, *J*=5.05 Hz, 2 H, $C^2_{Ethoxy}H_2$), 3.58 (m, 4 H, $C^{3/5}_{Morpholinyl}H_2$), 4.14 (t, *J*=5.05 Hz, 2 H, $C^1_{Ethoxy}H_2$), 5.11 (s, 2 H, $C^{6''}H_2$), 6.17 (s, 1 H, $C^{4''}H$), 6.59 (d, *J*=9.10 Hz, 1 H, $C^{2''}H$), 7.15 (m, 1 H, $C^{3'}H$), 7.29 (m, 2 H, $C^{6'}H$, $C^{8''}H$), 7.41 (d, *J*=8.34 Hz,

1 H, $C^{7''}H$), 7.47 (d, *J*=7.33 Hz, 1 H, $C^{5}H$), 7.63 (m, 2 H, $C^{10''}H$, $C^{4}H$), 7.99 (d, *J*=8.84 Hz, 1 H, $C^{1''}H$), 8.36 (s, 1 H, $C^{1}H$), 8.45 (s, 1 H, NH), 9.90 (s, 1 H, NH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ [ppm] = 17.3 (-CH_3), 53.6 ($C^{3/5}$ $_{Morpholinyl}$), 56.9 (C^{2}_{Ethoxy}), 65.7 (C^{1}_{Ethoxy}), 66.1 ($C^{2/6}_{Morpholinyl}$), 72.1 ($C^{6''}$), 101.0 ($C^{4''}$), 109.3 ($C^{2''}$), 113.9 ($C^{10''}$), 115.8 ($C^{11a''}$), 117.6 (d, J=21.45 Hz, $C^{3'}$), 118.4 ($C^{8''}$), 123.1 ($C^{6'}$), 123.5 (d, J=13.24 Hz, $C^{4'}$), 127.0 ($C^{10''}$), 127.1 ($C^{7''}$), 128.4 ($C^{10a''}$), 129.6 (C^{4}), 130.1 (C^{5}), 132.1 (d, J=7.17 Hz, $C^{1'}$), 133.5 (C^{1}), 134.2 (d, J=2.13 Hz, $C^{5'}$), 136.9 (C^{1}), 141.5 ($C^{6a''}$), 152.6 (d, J=245.58 Hz), 152.9 ($C^{3''}$), 158.7 ($C^{9''}$), 160.8 ($C^{4a''}$), 163.0 ($C{=}O_{Amid}$), 186.8 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3297, 2922, 1569, 1520, 1279, 1255, 1115, 856, 776; **HRMS-EI**, *m/z*: calculated: 588.1963; found: 588.1968.

***N*-{5-[(9-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}-11-oxo-6,11-dihydrodibenzo [*b*,*e*]oxepin-3-yl)amino]-2-fluoro-4-methylphenyl}thiophene-3-carboxamide (32d).**

Compound **32d** was prepared according to General Procedure P using 3-chloro-9-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dibenzo[*b,e*]oxepin-11(6*H*)-one (150 mg, 0.40 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol), *N*-(5-amino-2-fluoro-4-methylphenyl)thiophene-3-carboxamide (200 mg, 0.80 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 50 mg (21.2%), yellow solid; **$C_{32}H_{29}F_2N_2O_6S$** (M_r = 588.46 g/mol); **mp**. = 120.8°C; **HPLC**: t_R = 8.20 min, purity: 95.3%; **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 1.31 (s, 3 H, -CH_3), 1.36 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.77 (m, 1 H, $C^{3}_{Propoxy}H$), 4.07 (m, 3 H, $C^{3}_{Propoxy}H$, $C^{1}_{Propoxy}H_2$), 4.42 (m, 1 H, $C^{1}_{Propoxy}H$), 5.12 (s, 2 H, $C^{6''}H_2$), 6.16 (s, 1 H, $C^{4''}H$), 6.58 (d, *J*=9.35 Hz, 1 H, $C^{2''}H$), 7.17 (dd, *J*=8.46, 1.89 Hz, 1 H, $C^{3'}H$), 7.26 (d, *J*=11.37 Hz, 1 H, $C^{6'}H$), 7.31 (m, 1 H, $C^{8''}H$), 7.44 (m, 2 H, $C^{10''}H$, $C^{7''}H$), 7.62 (m, 2 H, $C^{5}H$, $C^{4}H$), 7.98 (d, *J*=8.84 Hz, 1 H, $C^{1''}H$), 8.35 (s, 1 H, $C^{2}H$), 8.45 (s, NH, 1 H) 9.89 (s, NH, 1 H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ [ppm] = 17.7 (-CH_3), 25.7 (-$CH_{3Acetal}$), 26.9 (-$CH_{3Acetal}$), 66.0 ($C^{3}_{Propoxy}$), 69.4 ($C^{1}_{Propoxy}$), 72.4 ($C^{2}_{Propoxy}$), 74.0 ($C^{6''}$), 101.3 ($C^{4''}$), 109.2 (C_{Acetal}), 109.7 ($C^{2''}$), 114.2 ($C^{10''}$), 116.2 ($C^{8''}$), 118.0 (d, J=22.70 Hz, $C^{3'}$), 118.8 ($C^{11a''}$), 123.5 (d, J=1,79 Hz, $C^{6'}$), 123.8 (d, J=13.38 Hz, $C^{4'}$), 127.3 (C^{10a}), 127.5 ($C^{4'}$), 129.0 ($C^{7''}$), 130.0 (C^{4}), 130.5 (C^{5}), 132.4 (d, J=7.43 Hz, $C^{1'}$), 133.9 ($C^{1''}$), 134.5 (d, J=3.60 Hz, $C^{5'}$), 137.3 (C^{2}), 141.9 (C^{6a}), 153.0 (d, J=244.78 Hz, $C^{2'}$), 153.3 ($C^{3''}$), 159.0 ($C^{9''}$), 161.2 ($C^{4a''}$), 163.4 ($C{=}O_{Amid}$), 187.1 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3319, 2985, 1570, 1521, 1326, 1280, 1255, 1221, 1048, 1030, 841, 739; **HRMS-EI**, *m/z*: calculated: 588.1798; found: 588.1712.

***N*-{5-[(9-{[(2*R*)-2,3-Dihydroxypropyl]oxy}-11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-3-yl)amino]-2-fluoro-4-methylphenyl}thiophene-3-carboxamide (32e).**

Compound **32e** was prepared according to the following procedure: *N*-{5-[9-{[(4S]2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-11-oxo-6,11-dihydrodibenzo[b,e]oxepin-3-yl)amino]-2-fluoro-4-methylphenl}thiophene-3-carboxymide (40 mg, 0.07 mmol) were dissolved in 40 ml MeOH and 2 ml H_2O. Catalytic amounts of p-toulenesulfonic acid were added. After the reaction is completed, the solvent was removed in vacuo and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 24 mg (62.5%), yellow solid; **$C_{29}H_{25}FN_2O_6S$** (M_r = 548.52 g/mol); **mp**. = 178.9°C; **HPLC**: t_R = 6.46 min, purity: 100%; **^{1}H NMR** (400 MHz, DMSO-d_6): δ [ppm] = 2.19 (s, 3 H, -CH_3), 3.45 (m, 2 H, $C^{3}_{Propoxy}H_2$), 3.80 (m, 1 H $C^{1}_{Propoxy}H$), 3.92 (m, 1 H $C^{1}_{Propoxy}H$), 4.09 (m, 1 H $C^{2}_{Propoxy}H$), 4.67 (t, -OH, *J*=5.56 Hz, 1 H), 4.96 (d, -OH, *J*=5.05 Hz, 1 H), 5.12 (s, 2 H, $C^{6''}H_2$), 6.17 (s, 1 H, $C^{4''}H$), 6.58 (d, *J*=9.10 Hz, 1 H, $C^{2''}H$), 7.15 (m, 1 H, $C^{3'}$), 7.26 (d, *J*=11.12 Hz, 1 H, $C^{6'}H$), 7.32 (m, 1 H, $C^{8''}H$), 7.42 (d, *J*=8.08 Hz, 1 H, $C^{10''}H$), 7.46 (d, *J*=7.33 Hz, 1 H, $C^{7''}H$), 7.62 (m, 2 H, $C^{5}H$, $C^{4}H$), 7.99 (d, *J*=8.84 Hz, 1 H, $C^{1''}H$), 8.35 (s, 1 H, $C^{2}H$) 8.45 (s, NH, 1 H) 9.89 (s, NH, 1 H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ [ppm] = 17.3 (-CH_3), 62.6 ($C^{3}_{Propoxy}$), 69.8 ($C^{1}_{Propoxy}$), 70.0 ($C^{1}_{Propoxy}$), 72.1 ($C^{6''}$), 101.0 ($C^{4''}$), 109.3 ($C^{2''}$), 113.8 ($C^{10''}$), 115.9 ($C^{8''}$), 117.6 (d, J=20.7 Hz, $C^{3'}$), 118.5 ($C^{11a''}$), 123.2 $C^{6'}$, 123.5 (d, J=13.6 Hz, $C^{4'}$), 127.0

(C^{10a}), 127.1 ($C^{4'}$), 128.3 ($C^{7''}$), 129.6 (C^{4}), 130.1 (C^{5}), 132.1 (d, J=8.2 Hz, $C^{1'}$), 133.5 ($C^{1''}$), 134.2 (d, J=3.2 Hz, $C^{5'}$), 136.9 (C^{2}), 141.4 (C^{6a}), 152.6 (d, J=245.2 Hz, $C^{2'}$), 152.9 ($C^{3''}$), 159.0 ($C^{9''}$), 160.8 ($C^{4a''}$), 163.0 ($C{=}O_{Amid}$), 186.7 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3295, 2922, 1566, 1519, 1281, 1256, 1223, 1030, 859, 739; **HRMS-EI**, *m/z*: calculated: 548.1416; found: 548.1361.

***N*-(2-Fluoro-5-{[8-(2-morpholin-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-3-yl]amino}phenyl)benzamide (32f).**

Compound **32f** was prepared according to General Procedure P using 3-chloro-8-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (200 mg, 0.53 mmol), Cs_2CO_3 (700 m g, 2.14 mmol), *N*-(5-amino-2-fluorophenyl)benzamide (200 mg, 0.86 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 30 mg (10.0%), yellow solid; **$C_{33}H_{30}FN_3O_5$** (M_r = 567.60 g/mol); **mp**. = 77.7°C; **HPLC**: t_R = 4.63 min, purity: 100%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.56 (m, 4 H, $C^{2/6}{}_{Morpholinyl}H_2$), 2.81 (t, *J*=5.56 Hz, 2 H, $C^{2}{}_{Ethoxy}H_2$), 3.71 (m, 4 H, $C^{3/5}{}_{Morpholinyl}H_2$), 4.16 (t, *J*=5.62 Hz, 2 H, $C^{1}{}_{Ethoxy}H_2$), 5.05 (s, 2 H, C6''H_2), 6.59 (m, 3 H, C^{2}''H, -NH, C^{4} 'H), 6.78 (d, *J*=2.40 Hz, 1 H, C^{4}''H), 6.99 (m, 3 H, C^{3}'H, C^{7}''H, C^{8}''H) 7.50 (m, 3 H, C^{6}'H, C^{3}H, C^{5}H), 7.86 (m, 2 H, C^{1} ''H, NH), 7.96 (d, *J*=8.72 Hz, 1 H, C^{10}''H), 8.18 (m, 2 H, C^{2}H, C^{6}H), 8.28 (m, 1 H, C^{4}); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 54.0 ($C^{2/6}{}_{Morpholinyl}$), 57.3 ($C^{2}{}_{Ethoxy}$), 66.0 ($C^{3/5}{}_{Morpholinyl}$), 66.8 ($C^{1}{}_{Ethoxy}$), 73.9 ($C^{6''}$), 103.2 ($C^{4''}$), 110.5 ($C^{2''}$), 113.4 ($C^{7''}$), 114.4 ($C^{9''}$), 115.0 (C^{11a}), 115.2 (d, *J*= 20.4 Hz, $C^{3'}$), 117.0 (d, *J*=7.6 Hz, $C^{4'}$), 118.4 ($C^{6'}$), 127.0 (C^{2}, C^{6}), 127.2 (d, *J*=11.1 Hz, $C^{1'}$), 128.8 (C^{3}, C^{5}), 132.2 ($C^{10''}$), 132.3 (C^{4}), 133.1 ($C^{1''}$), 134.2 ($C^{10a''}$), 134.2 (C^{1}), 136.7 (d, *J*= 3.1 Hz, $C^{5'}$), 137.9 ($C^{6a''}$), 148.9 (d, *J*= 238.3 Hz, $C^{2'}$), 150.4 (C3''), 161.7 ($C{=}O_{Amid}$), 163.0 ($C^{8''}$), 165.4 ($C^{4a''}$), 186.7 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3302, 2857, 1598, 1525, 1263, 1228, 1114, 852, 702; **HRMS-EI**, *m/z*: calculated: 567.2168; found: 567.2167.

***N*-(4-Fluoro-3-{[7-(2-morpholin-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-3-yl]amino}phenyl)benzamide (32g).**

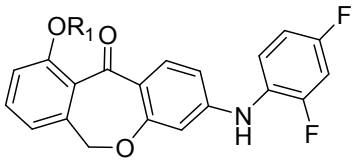
Compound **32g** was prepared according to General Procedure P using 3-chloro-7-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (200 mg, 0.53 mmol), Cs_2CO_3 (700 m g, 2.14 mmol), *N*-(3-amino-4-fluorophenyl)benzamide (200 mg, 0.86 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 40 mg (13.2%), yellow solid; **$C_{33}H_{30}FN_3O_5$** (M_r = 567.60 g/mol); **mp**. = 98.1°C; **HPLC**: t_R = 4.89 min, purity: 100%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ [ppm] = 2.54 (m, 4 H, $C^{3/5}{}_{Morpholinyl}H_2$), 2.81 (t, *J*=5.62 Hz, 2 H, $C^{2}{}_{Ethoxy}H_2$), 3.70 (m, 4 H, $C^{2/6}{}_{Morpholinyl}H_2$), 4.13 (m, 2 H, $C^{1}{}_{Ethoxy}H_2$), 5.26 (s, 2 H, C^{6}''H2), 6.25 (s, NH, 1 H), 6.65 (m, 2 H, C^{4}''H,C^{2}''H), 7.04 (m, 2 H, C^{5}'H, C^{8}''H), 7.39 (m, 6 H, C^{2}'H, C^{6}'H, C^{10}''H, C^{9}''H, C^{3}H, C^{5}H), 7.72 (m, 1 H, C^{1}''H), 7.83 (m, 2 H, C^{2}H, C^{6}H), 8.08 (d, *J*=8.72 Hz, 1 H, C^{4}H), 8.33 (s, NH, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ [ppm] = 53.9 ($C^{2/6}{}_{Morpholinyl}$), 57.4 ($C^{2}{}_{Ethoxy}$), 65.2 ($C^{3/5}{}_{Morpholinyl}$), 66.8 $C^{1}{}_{Ethoxy}$), 66.9 ($C^{6''}$), 104.2 ($C^{4''}$), 111.0 ($C^{2''}$), 113.1 ($C^{2'}$), 115.4 (d, *J*=7.2 Hz, $C^{6'}$), 115.5 ($C^{8''}$), 115.9 (d, *J*=20.6 Hz, $C^{5'}$), 118.3 (C^{11}a''), 121.1 ($C^{10''}$), 124.0 ($C^{10a''}$), 127.0 (C^{2}, C^{6}), 128.5 (C^{3}, C^{5}), 128.7 (d, *J*=11.8 Hz, $C^{3'}$), 129.7 ($C^{9''}$), 131.7 (C^{4}), 133.7 ($C^{1''}$), 134.4 (d, *J*=2,7 Hz, $C^{1'}$), 134.5 (C^{1}), 142.8 ($C^{6a''}$), 149.1 ($C^{3''}$), 154.7 ($C^{7''}$), 160.2 (d, *J*= 242.6 Hz, $C^{4'}$) 163.2 (C=OAmid), 165.9 ($C^{4a''}$), 189.5 (C^{11}); **FT-IR (ATR, cm^{-1}):** 3302, 2857, 1598, 1525, 1263, 1228, 1114, 852, 702; **HRMS-EI**, *m/z*: calculated: 567.2169; found: 567.2176.

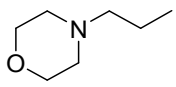
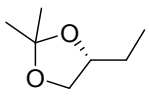
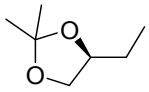
***N*-(3-{[7-(2-Morpholino-4-ylethoxy)-11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-3-yl]amino}phenyl)-3-furamide (32h).**

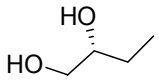
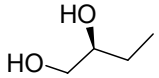
Compound **32h** was prepared according to General Procedure P using 3-chloro-7-(2-morpholino-4-ylethoxy)dibenzo[*b,e*]oxepin-11(6*H*)-one (200 mg, 0.53 mmol), Cs_2CO_3 (700

m g, 2.14 mmol), *N*-(3-aminophenyl)-3-furamide (200 mg, 1.0 mmol), X-Phos (100 mg, 0.11 mmol) and $Pd(OAc)_2$ (20 mg, 0.09 mmol). The mixture was heated to 110°C for 3 h. After hydrolysis with water the organic phase was evaporated and the resulting oil was purified by Flash chromatography (SiO_2 60, dichloromethane / ethanol 95+5). Yield: 35 mg (12.2%), yellow solid; **$C_{31}H_{29}N_3O_6$** (M_r = 539.57 g/mol); **mp**. = 194.8°C; **HPLC**: t_R = 4.31 min, purity: 100%; **^{1}H NMR** (200 MHz, DMSO-d$_6$): δ [ppm] = 2.47 (m, 4 H, $C^{3/5}{}_{Morpholinyl}H_2$), 2.74 (t, *J*=5.62 Hz, 2 H, $C^{2}{}_{Ethoxy}H_2$), 3.57 (m, 4 H, $C^{2/6}{}_{Morpholinyl}H_2$), 4.18 (t, *J*=5.68 Hz, 2 H, $C^{1}{}_{Ethoxy}H_2$), 5.28 (s, 2 H, $C^{6''}H_2$), 6.62 (d, *J*=2.15 Hz, 1 H, $C^{4''}H$), 6.85 (m, 2 H, $C^{2''}H$, $C^{2'}H$), 6.99 (m, 1 H, $C^{4}H$), 7.34 (m, 5 H, $C^{8''}H$, $C^{6'}H$, $C^{5'}H$, $C^{4'}H$, $C^{9''}H$), 7.75 (m, 2 H, ($C^{10''}$, $C^{5}H$), 7.97 (d, *J*=8.84 Hz, 1 H, $C^{1''}$), 8.38 (m, 1 H, $C^{2}H$), 9.01 (s, 1 H, -NH), 9.90 (s, 1 H, NH_{Amid}); **^{13}C NMR** (50 MHz, DMSO-d$_6$): δ [ppm] = 53.9 ($C^{2/6}{}_{Morpholinyl}$), 57.3 ($C^{2}{}_{Ethoxy}$), 65.1 ($C^{3/5}{}_{Morpholinyl}$), 66.6 ($C^{1}{}_{Ethoxy}$), 67.1 ($C^{6''}$), 102.6 ($C^{4''}$), 109.6 (C^{4}), 110.9 ($C^{2''}$), 111.6 ($C^{6'}$), 114.5 ($C^{2'}$), 115.6 ($C^{4'}$), 116.6 ($C^{8''}$), 116.8 ($C^{11a''}$), 120.8 ($C^{10''}$), 123.3 (C^{3}), 124.2 ($C^{10a''}$), 129.8 ($C^{9''}$), 130.3 ($C^{5'}$), 133.5 ($C^{1''}$), 140.1 (C^{6a}), 141.4 ($C^{1'}$), 142.6 ($C^{3''}$), 144.5 (C^{5}), 146.2 (C^{2}), 151.1 ($C^{3''}$), 155.0 ($C^{4a''}$), 160.8 ($C{=}O_{Amid}$), 163.3 (C^{3a}), 188.1 ($C^{11''}$); **FT-IR (ATR, cm^{-1}):** 3324, 2957, 1589, 1568, 1398, 1298, 1261, 1120, 1075, 759, 688; **HRMS-EI**, *m/z*: calculated: 539.2055; found: 539.2044.

Table S1. Biological activity of position 10-substituted 3-(2,4-difluorophenyl)amino-dibenzo[*b,e*]oxepin-11(6*H*)-ones **4a-f**. Variation of the hydrophilic residue R_1.



Compound	R_1	IC_{50} ± SEM p38α[a] [μM]	IC_{50} ± SEM TNF-α[b] [μM]
4a		0.280 ± 0.019	n. d.
4b		9.3% @10 μM	n. d.
4c		45.1% @10 μM	n. d.
4d		44.7% @10 μM	n. d.

4e		32.4% @10 μM	n. d.
4f		18.4% @10 μM	n. d.

[a] Results from three experiments.

[b] Results from four experiments except where otherwise stated. n. d.: not determined

Table S2. Data Collection and Refinement Statistics for p38α with compound **32a**[a]

	p38α_32a(4L8M)
Data collection	
Space group	$P2_12_12_1$
Celldimensions	
a, *b*, *c* (Å)	64.62, 72.95, 76,92
α, β, γ (°)	90.0, 90.0, 90.0
Resolution (Å)	50.0-2.10 (2.20-2.10)[a]
R_{sym}orR_{merge} (%)	2.9 (30.6)
I / σI	25.8 (5.2)
Completeness (%)	98.4 (97.7)
Redundancy	4.2 (4.3)
Refinement	
Resolution (Å)	48.4-2.10
No. reflections	21490
R_{work} / R_{free}	22.1 / 27.9
No. atoms	
Protein	2744
Ligand/ion	82
Water	43
B-factors	
Protein	49.0
Ligand/ion	52.7
Water	41.4

R.m.s. deviations	
Bond lengths (Å)	0.012
Bond angles (°)	1.488
Structure (PDB-ID code)	p38α_32a (4L8M)
Wavelength (Å)	0.978600
Temperature	90K
X-raysource	SLS X10SA
Ramachandran Plot:	
Residues in	
most favored regions	86.5%
additional allowed regions	12.5%
generously allowed regions	1.0%
disallowedregions	0.0%

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

Selectivity Screen.

Kinase Name	Kinase Family	Residual activity with 10 µM of compound 32e
CAMK2D	**CAMK**	**46**
p38-alpha	**CMGC**	**4**
p38-beta	**CMGC**	**1**
SLK	**STE**	**48**

PROQINASE Kinase WholePanelProfiler

Profiling of *32e* against 333 protein kinases

Residual activities (% of control)

Residual activity < 50 %

#	Kinase Name	Kinase Family*	Compound 32e 1.0E-05
1	ABL1 E255K	TK	103
2	ABL1 F317I	TK	100
3	ABL1 G250E	TK	101
4	ABL1 H396P	TK	96
5	ABL1 M351T	TK	103
6	ABL1 Q252H	TK	96
7	ABL1 T315I	TK	82
8	ABL1 wt	TK	94
9	ABL1 Y253F	TK	95
10	ABL2	TK	100
11	ACK1	TK	115
12	ACV-R1	TKL	105
13	ACV-R1B	TKL	80
14	ACV-RL1	TKL	100
15	AKT1	AGC	109
16	AKT2	AGC	123
17	AKT3	AGC	91
18	ALK	TK	105
19	AMPK-alpha1	CAMK	98
20	ARK5	CAMK	100
21	ASK1	STE	99
22	Aurora-A	OTHER	90
23	Aurora-B	OTHER	96
24	Aurora-C	OTHER	83
25	AXL	TK	105
26	BLK	TK	111
27	BMPR1A	TKL	101
28	BMX	TK	111
29	B-RAF V600E	TKL	112
30	B-RAF wt	TKL	118
31	BRK	TK	106
32	BRSK1	CAMK	99
33	BTK	TK	103
34	CAMK1D	CAMK	99
35	CAMK2A	CAMK	78
36	CAMK2B	CAMK	100
37	CAMK2D	CAMK	46
38	CAMK4	CAMK	93
39	CAMKK1	OTHER	88
40	CAMKK2	OTHER	97
41	CDC42BPA	AGC	99
42	CDC42BPB	AGC	80
43	CDK1/CycA	CMGC	97
44	CDK1/CycB1	CMGC	84
45	CDK1/CycE	CMGC	91
46	CDK2/CycA	CMGC	94
47	CDK2/CycE	CMGC	84
48	CDK3/CycE	CMGC	99
49	CDK4/CycD1	CMGC	107
50	CDK4/CycD3	CMGC	106
51	CDK5/p25NCK	CMGC	109
52	CDK5/p35NCK	CMGC	95
53	CDK6/CycD1	CMGC	97
54	CDK7/CycH/MAT1	CMGC	93
55	CDK8/CycC	CMGC	113
56	CDK9/CycK	CMGC	93
57	CDK9/CycT	CMGC	103
58	CHK1	CAMK	95
59	CHK2	CAMK	87
60	CK1-alpha1	CK1	97
61	CK1-delta	CK1	71
62	CK1-epsilon	CK1	78
63	CK1-gamma1	CK1	96
64	CK1-gamma2	CK1	91
65	CK1-gamma3	CK1	90
66	CK2-alpha1	OTHER	99
67	CK2-alpha2	OTHER	90
68	CLK1	CMGC	118
69	CLK2	CMGC	95
70	CLK3	CMGC	93
71	CLK4	CMGC	105
72	COT	STE	93
73	CSF1-R	TK	111
74	CSK	TK	116
75	DAPK1	CAMK	92
76	DAPK2	CAMK	86
77	DAPK3	CAMK	99
78	DCAMKL2	CAMK	91
79	DDR2	TK	101
80	DMPK	AGC	92
81	DNA-PK	ATYP	101
82	DYRK1A	CMGC	99
83	DYRK1B	CMGC	110
84	DYRK3	CMGC	97
85	DYRK4	CMGC	95
86	EEF2K	ATYPICAL	103
87	EGF-R d746-750	TK	107
88	EGF-R d747-749/A750P	TK	114
89	EGF-R d747-752/P753S	TK	115
90	EGF-R d752-759	TK	110
91	EGF-R G719C	TK	105
92	EGF-R G719S	TK	109
93	EGF-R L858R	TK	96
94	EGF-R L861Q	TK	114
95	EGF-R T790M	TK	111
96	EGF-R T790M/L858R	TK	103
97	EGF-R wt	TK	116
98	EIF2AK2	OTHER	96
99	EIF2AK3	OTHER	99
100	EPHA1	TK	108
101	EPHA2	TK	123
102	EPHA3	TK	105
103	EPHA4	TK	109
104	EPHA5	TK	136
105	EPHA7	TK	121
106	EPHA8	TK	101
107	EPHB1	TK	121
108	EPHB2	TK	103
109	EPHB3	TK	98
110	EPHB4	TK	115
111	ERBB2	TK	93
112	ERBB4	TK	124
113	ERK1	CMGC	91
114	ERK2	CMGC	85
115	FAK	TK	122
116	FER	TK	105
117	FES	TK	119
118	FGF-R1 V561M	TK	96
119	FGF-R1 wt	TK	114
120	FGF-R2	TK	136
121	FGF-R3 K650E	TK	92
122	FGF-R3 wt	TK	91
123	FGF-R4	TK	103
124	FGR	TK	103
125	FLT3 D835Y	TK	105
126	FLT3 ITD	TK	106
127	FLT3 wt	TK	90
128	FRK	TK	110
129	FYN	TK	120
130	GRK2	AGC	116
131	GRK3	AGC	98
132	GRK4	AGC	86
133	GRK5	AGC	112
134	GRK6	AGC	97
135	GRK7	AGC	93
136	GSG2	OTHER	93
137	GSK3-alpha	CMGC	93
138	GSK3-beta	CMGC	120
139	HCK	TK	102
140	HIPK1	CMGC	93
141	HIPK2	CMGC	111
142	HIPK3	CMGC	92
143	HIPK4	CMGC	112
144	HRI	OTHER	110
145	IGF1-R	TK	121
146	IKK-alpha	OTHER	96
147	IKK-beta	OTHER	92
148	IKK-epsilon	OTHER	91
149	INS-R	TK	95
150	INSR-R	TK	91
151	IRAK1	TKL	95
152	IRAK4	TKL	97
153	ITK	TK	97
154	JAK1	TK	94
155	JAK2	TK	96
156	JAK3	TK	106
157	JNK1	CMGC	89
158	JNK2	CMGC	75
159	JNK3	CMGC	89
160	KIT T670I	TK	145
161	KIT wt	TK	107
162	LCK	TK	124
163	LIMK1	TKL	105
164	LIMK2	TKL	98
165	LRRK2 G2019S	TKL	82
166	LRRK2 I2020T	TKL	94
167	LRRK2 R1441C	TKL	92
168	LRRK2 wt	TKL	97
169	LTK	TK	107
170	LYN	TK	102
171	MAP3K10	STE	100
172	MAP3K11	STE	114
173	MAP3K7/MAP3K7IP1	STE	80
174	MAP3K9	STE	101
175	MAP4K2	STE	98
176	MAP4K4	STE	85
177	MAP4K5	STE	82
178	MAPKAPK2	CAMK	79
179	MAPKAPK3	CAMK	79
180	MAPKAPK5	CAMK	95
181	MARK1	CAMK	89
182	MARK2	CAMK	85
183	MARK3	CAMK	95
184	MARK4	CAMK	95
185	MATK	TK	120
186	MEK1	STE	72
187	MEK2	STE	103
188	MEKK2	STE	92
189	MEKK3	STE	106
190	MELK	CAMK	88
191	MERTK	TK	110
192	MET D1228H	TK	100
193	MET D1228N	TK	101
194	MET F1200I	TK	108
195	MET M1250T	TK	98
196	MET wt	TK	104
197	MET Y1230A	TK	91
198	MET Y1230C	TK	88
199	MET Y1230D	TK	95
200	MET Y1230H	TK	105
201	MET Y1235D	TK	125
202	MINK1	STE	99
203	MKK6 S207D/T211D	STE	118
204	MKNK1	CAMK	83
205	MKNK2	CAMK	87
206	MST1	STE	74
207	MST2	STE	80
208	MST3	STE	90
209	MST4	STE	98
210	mTOR	ATYPICAL	92
211	MUSK	TK	107
212	MYLK	CAMK	74
213	MYLK2	CAMK	97
214	MYLK3	CAMK	95
215	NEK1	OTHER	106
216	NEK11	OTHER	109
217	NEK2	OTHER	90
218	NEK3	OTHER	90
219	NEK4	OTHER	98
220	NEK6	OTHER	101
221	NEK7	OTHER	88
222	NEK9	OTHER	108
223	NIK	STE	90
224	NLK	CMGC	95
225	p38-alpha	CMGC	4
226	p38-beta	CMGC	1
227	p38-delta	CMGC	79
228	p38-gamma	CMGC	68
229	PAK1	STE	97
230	PAK2	STE	91
231	PAK3	STE	91
232	PAK4	STE	96
233	PAK6	STE	101
234	PAK7	STE	89
235	PASK	CAMK	90
236	PBK	OTHER	109
237	PCTAIRE1	CMGC	93
238	PDGFR-alpha D842V	TK	93
239	PDGFR-alpha T674I	TK	97
240	PDGFR-alpha V561D	TK	93
241	PDGFR-alpha wt	TK	100
242	PDGFR-beta	TK	96
243	PDK1	AGC	97
244	PHKG1	CAMK	103
245	PHKG2	CAMK	84
246	PIM1	CAMK	105
247	PIM2	CAMK	100
248	PIM3	CAMK	88
249	PKA	AGC	88
250	PKC-alpha	AGC	124
251	PKC-beta1	AGC	116
252	PKC-beta2	AGC	94
253	PKC-delta	AGC	100
254	PKC-epsilon	AGC	108
255	PKC-eta	AGC	108
256	PKC-gamma	AGC	114
257	PKC-iota	AGC	91
258	PKC-mu	AGC	96
259	PKC-nu	AGC	102
260	PKC-theta	AGC	116
261	PKC-zeta	AGC	105
262	PLK1	OTHER	95
263	PLK3	OTHER	93
264	PRK1	AGC	97
265	PRK2	AGC	100
266	PRKD2	CAMK	105
267	PRKG1	AGC	113
268	PRKG2	AGC	97
269	PRKX	AGC	75
270	PYK2	TK	107
271	RAF1 Y340D/Y341D	TKL	104
272	RET V804L	TK	108
273	RET wt	TK	108
274	RET Y791F	TK	135
275	RIPK2	TKL	77
276	RIPK5	TKL	93
277	ROCK1	AGC	93
278	ROCK2	AGC	89
279	RON	TK	63
280	ROS	TK	110
281	RPS6KA1	AGC	92
282	RPS6KA2	AGC	88
283	RPS6KA3	AGC	87
284	RPS6KA4	AGC	82
285	RPS6KA5	AGC	66
286	RPS6KA6	AGC	98
287	S6K	AGC	95
288	S6K-beta	AGC	90
289	SAK	OTHER	77
290	SGK1	AGC	84
291	SGK2	AGC	91
292	SGK3	AGC	103
293	SLK	STE	48
294	SNARK	CAMK	114
295	SNF1LK2	CAMK	89
296	SNK	OTHER	95
297	SRC	TK	131
298	SRMS	TK	92
299	SRPK1	CMGC	106
300	SRPK2	CMGC	85
301	STK17A	CAMK	86
302	STK23	CAMK	87
303	STK25	STE	92
304	STK33	CAMK	92
305	STK39	STE	68
306	SYK	TK	103
307	TAOK2	STE	101
308	TAOK3	STE	103
309	TBK1	OTHER	88
310	TEC	TK	109
311	TGFB-R1	TKL	115
312	TGFB-R2	TKL	75
313	TIE2	TK	91
314	TRK-A	TK	112
315	TRK-B	TK	71
316	TRK-C	TK	140
317	TSF1	OTHER	91
318	TSK2	CAMK	94
319	TSSK1	CAMK	80
320	TTK	OTHER	85
321	TXK	TK	104
322	TYK2	TK	96
323	TYRO3	TK	115
324	VEGF-R1	TK	105
325	VEGF-R2	TK	94
326	VEGF-R3	TK	110
327	VRK1	CK1	99
328	WEE1	OTHER	90
329	WNK2	OTHER	109
330	WNK3	OTHER	96
331	YES	TK	136
332	ZAK	TKL	109
333	ZAP70	TK	109
	Selectivity Score (< 50 % residual activity):		**0,01**

*Classification of protein kinase families
(Manning et al. Science 6 December 2002: Vol. 298 no. 5600 pp. 1912-1934)
AGC: containing PKA, PKG and PKC families
CAMK: Calcium/Calmodulin-dependent protein kinases
CK1: Casein kinase 1 -like
CMGC: containing CDK, MAPK ,GSK3 and CLK families
TK: Tyrosine Kinase
TKL: Tyrosine Kinase-like
STE: Homologs of Yeast Sterile 7, Sterile 11, Sterile 20 Kinases

In Vitro Metabolism Studies. Pooled male and female liver microsomes of rats (RLMs) were purchased from Life Technologies GmbH (Darmstadt, Germany). These microsomes were characterized in protein and cytochrome P-450 content. Human CYP2B6R reductase bactosomes were purchased from tebu-bio GmbH (Offenbach, Germany).

All incubations (final total volume 1050 µl) were made in the presence of an NADPH-regenerating system, consisting of 5 mM Glucose 6-phosphate, 5 U/ml Glucose 6-phosphate dehydrogenase, and 1 mM $NADP^+$. The substrate (10 µM), NADPH regenerating system, and 3.8 mM $MgCl_2$ x 6 H_2O in 0.1 M Tris buffer (pH 7.4) were preincubated for 5 min in a shaking heating block at 37°C, 550 rpm, and the reaction was started by addition of microsomes (1 mg protein/ml or 0.578 pmol P450/ml). To follow the course of metabolism, 100 µl aliquots were withdrawn at different time points (0, 10, 20, 40, 60, 120 and 180 min) and transferred into an ice-cooled vial containing 100 µl internal standard at a concentration of 100 µg/mL. The samples were vortexed for 15 s and centrifuged (19800 relative centrifugal force/ 4°C/ 10 min). The supernatant was directly used for analysis. All incubations were conducted in triplicates; average mean values of these incubations are shown in the figures. In all incubations a limit of 1% organic solvent was not exceeded.[1,2]

Screening of Metabolites by LC-MS/MS Analysis. Metabolite formation was analyzed with a Jasco (Groß-Umstadt, Germany) HPLC system, consisting of a pump (PU-1580) and an autosampler from CTCAnalytics (HTSPal; Zwngen, Switzerland). The chromatographic separation was performed on a Phenomenex Synergi Polar RP column (150 x 4.6 mm; 5µm) with a precolumn of the same material. The injection volume was 30 µl. A binary gradient of 33 min with solvent A (H_2O/ ACN/ FA; 90/ 10/ 0.1%) and solvent B (ACN/ 0.1% FA) at a flow rate of 300 µl/min was used. The initial composition of 0% B was held for 3 min, followed by a linear gradient up to 95% B in 20 min, holding for 5 min, changing to 0% B in 1.5 min, and reequilibrating at the end. The detection was performed on a Micromass Quattro micro triple quadrupole mass spectrometer (Waters GmbH, Eschbronn) in the electrospray ionization-positve SRM/ MRM mode. Spray voltage was set to 2.9 kV and the heated capillary operated at 350°C. Desolvation gas flow worked at 200 l/hr. Metabolites were also identified by direct injection of the according reference material. Substrates and metabolites were quantified by internal standards as well as with calibration curves constructed from known concentrations of reference material.

Method validation parameters. The developed method was validated using spiked blank human plasma. The validation parameters were in accordance with the recommendations, defined by the EU and with the criteria in the literature.[3,4]

Pharmacokinetic study of the compound 3i in Black six C57 mice. The animal experimental part of this study was performed at Synovo GmbH (Tuebingen, Germany). The compound **3i** was administered to three male Black six C57 mice with a single oral gavage (p.o.) dose of 10 mg/kg body weight. The drug formulation was prepared by grinding 0.4 mg of 2M in a mortar. The drug was solved in a vehicle containing 10% DMSO and 90% of a hypromellose solution in H_2O (1%), 1% of citric acid, 1% of Tween 80 and PEG 400. A dose of 5 ml/kg was administered with continuous stirring of the suspension. All mice were following the same time schedule for blood sampling. A total of 9 samples were taken at time points 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h. Blood samples of 30 µL were drawn from the caudal vene into lithium-heparinized Eppendorf tubes. Blood samples were centrifuged for 10 min at 3000 rpm at 10 °C, and the plasma (approximately 15 µL) was transferred into Eppendorf tubes containing 15 µL of internal Standard (500 ng/mL). After centrifuging for 10 min at 19800 relative centrifugal force and 4 °C, the supernatant was transferred to into highperformance liquid chromatography vials and stored at -8 °C. Pharmacokinetic data were evaluated according to a two-compartmental pharmacokinetic model using WinNonlin 4.0.1 (Pharsight Corp., Mountain View, CA).

Derivatization of Plasma Samples. Samples were thawed to room temperature. To each vial, the derivatization reagent (50% v/v) 4-pyridinylboronic acid (10 mM in H_2O) was added. The derivatization was conducted at 70 °C for 40 min.

Online LC-SPE-MS/MS Analysis of Plasma Samples. For the quantitative analysis of the derivatized plasma samples, a fast and simple method was developed. The method is based on an online SPE in the first dimension to remove polar matrix elements coupled to a reversed-phase chromatography in the second dimension with a sensitive triple quadrupole mass spectrometric (MS) detection in the multiple reaction monitoring (MRM) mode. In this method, the compound **3i** is capable of being analyzed with an internal standard in 5 min without time-consuming offline extraction steps. Nine standard solutions (2.5, 5, 10, 50, 500, 1000 and 2500 ng/ml) were prepared by spiking human plasma of different donors. Blank human plasma samples were used to confirm the specificity of the method. All calibration standards were also derivatized as described above. Online SPE was performed on an Oasis HLB cartridge (Waters, Eschborn, Germany) with an isocratic clean-up flow of H_2O/Methanol/FA (90:10:0.1) at 2.5 ml/min. For the chromatographic separation, a Phenomenex Kinetex 2.6 µm C18 (50 x 2.1 mm) with a SecurityGuard ULTRA cartridge (Phenomenex, Aschaffenburg, Germany) was used with an isocratic elution of 60% solvent A (Water/Acetonitril/FA; 90:10:0.1) and 40% solvent B (Acetonitril/0.1% FA) at a flow rate of 0.15 ml/min. After each injection, the SPE cartridge was regenerated with an injection of 30 µL of Acetonitril. The detection was performed on a Micromass Quattro Micro triple quadrupole mass spectrometer (Waters, Eschbronn, Germany) in electrospray ionization-positive MRM mode. The linear range of the method extents from 2.5 ng/ml (limit of quantitation) to 2500 ng/ml. All metabolite areas of the MRM traces were related to the area of the 500 ng/ml internal standard.

References

(1) Chauret, N.; Gauthier, A.; Nicoll-Griffith, D. A. (1998) Effect of common organic solvents on in vitro cytochrome P450-mediated metabolic activities in human liver microsomes. *Drug Metab Dispos*, **1998**, *26*, 1-4.

(2) Busby, W. F.; Jr., Ackermann, J. M.; Crespi, C. L. Effect of methanol, ethanol, dimethyl sulfoxide, and acetonitrile on in vitro activities of cDNA-expressed human cytochromes P-450. *Drug Metab Dispos*, **1999**, 27:246-249.

(3) Anonymous, Commission decision (2002/657/EC) of 17. August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. *Official Journal of the European Community*, **2002**, L221.

(4) Anonymous, EMEA/CVMP/573/00-Final. Volume 8: notice to applicants, Veterinary medicinal products: establishment of maximum residue limits (MRLs) for residues of veterinary products in foodstuff of animal origin: development and validation of a proposed regulatory method, **2005**.