Electronic Supplementary Information (ESI)

Quinoides and VEGFR2 TKIs influencing the fate of hepatocellular carcinoma and its cancer stem cells

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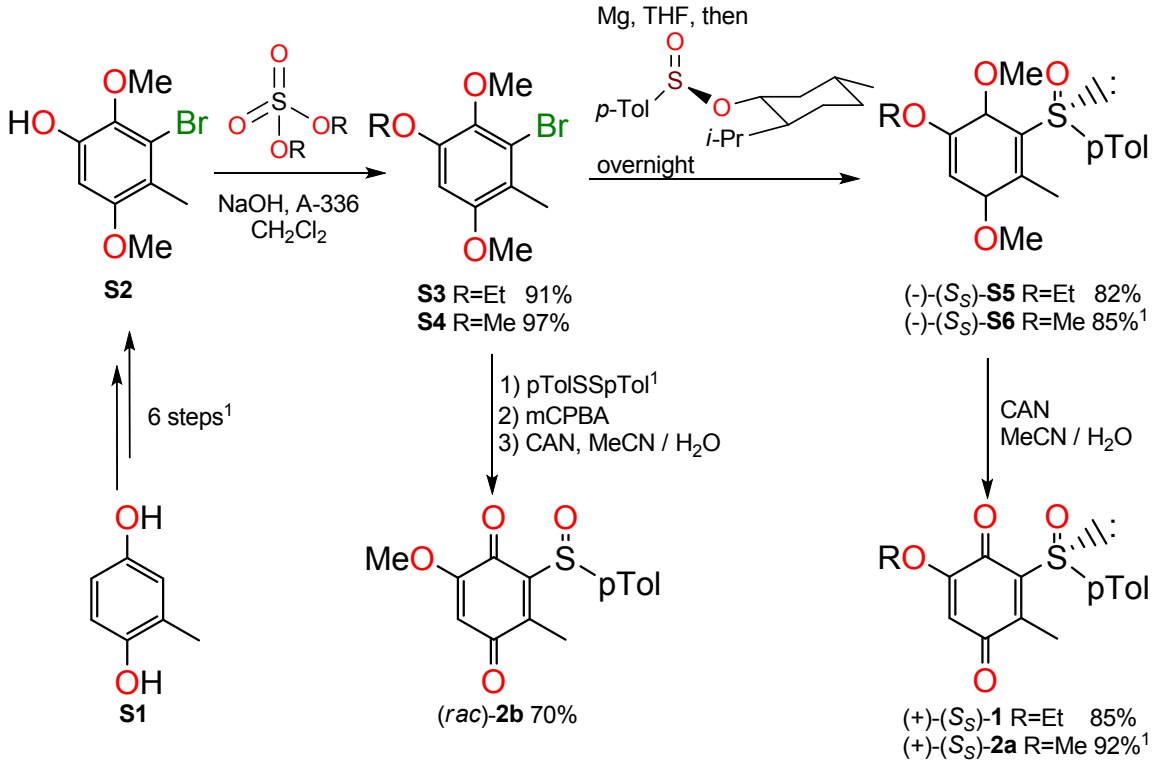
1. Synthesis of quinones 1-5

All quinones **1-5** were prepared enantiomerically pure. Enantiomeric excess (ee) was determined as > 98 % by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$ as NMR chiral shift reagent. For this purpose, the racemic mixture of each compound was prepared according to the procedure described for (*rac*)-**2b**.[1] By addition of the NMR chiral shift reagent, a splitting of the quinonic proton (5.8 - 6.0 ppm for **1**, **2** and **4**; 6.7 - 7.0 ppm for **3** and **5**); appeared, allowing the ee determination without any ambiguity. Absolute configuration of quinones **1**, **2a**, **3** was determined by comparison of optical rotation with previously described $[\alpha]_D^{20}$.[1,2]

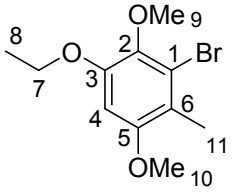


Scheme 1. Synthesis of quinoides **1, 2a, 2b**.

(+)-(S_S)-**2a**, (*rac*)-**2b**, **S4** and 1-bromo-2,5-dimethoxy-3-hydroxy-6methyl benzene **S2** were prepared according to our previous paper.[1]

Preparation of (+)-(S_S)-1

1-Bromo-2,5-bis(methoxy)-3-ethoxy-6-methylbenzene S3



FW: 275.14 g mol^{-1}

$C_{11}H_{15}O_3Br$

1-Bromo-2,5-dimethoxy-3-hydroxy-6-methyl benzene **S2** 12.035 g (48.7 mmol, 1.00 mol eq) was dissolved in CH_2Cl_2 200 mL and stirred with an aqueous solution of sodium hydroxide (3.250 g, 81.3 mmol, 1.67 mol eq). 1.12 mL (990 mg, 2.45 mmol, 0.05 mol eq) of Aliquat® 336 (Starks' catalyst, quaternary ammonium salts: tricaprylylmethylammonium chloride, trioctylmethylammonium chloride from Sigma-Aldrich) were added in the mixture followed by 12.6 mL (15.08 g, 97.86 mmol, 2.00 mol eq) of diethyl sulfate. The mixture was vigorously stirred until disappearance of starting phenol controlled by TLC. Then, 2.00 g of solid NaOH were added and the mixture was stirred at room temperature overnight. Aqueous phase was extracted with 2×200 mL of CH_2Cl_2 and the combined organic phases were washed with brine (2×100 mL), dried over $MgSO_4$, filtered off and evaporated to give 14.5 g of crude which was flash chromatographied on silica gel (hexane / Et_2O, 3 / 2) to afford 12.2 g (44.3 mmol, 91 %) of **S3** as white crystals.

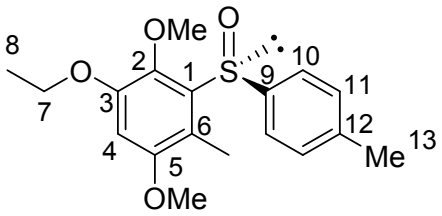
R_F: 0.60 (cyclohexane / Et_2O, 3 / 1).

M.p.: 63 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.39 (s, 1H, C^4H), 4.11 (q, 2H, J = 7.0 Hz, C^7H_2), 3.79 (s, 3H, C^9H_3), 3.78 (s, 3H, $C^{10}H_3$), 2.24 (s, 3H, C^6H_3), 1.41 (t, 3H, J = 7.0 Hz, C^8H_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 154.2 (C_q), 151.3 (C_q), 140.3 (C_q), 121.5 (C_q), 119.2 (C_q-Br), 96.7 (C^4H), 66.7 (C^7H_2), 60.5. (-OCH_3), 56.4 (-OCH_3), 15.3 ($C^{11}H_3$), 9.4 (C^8H_3).

2,5-Dimethoxy-3-ethoxy-6-methyl-1 [(*S*)-4-methylbenzenesulfinyl]benzene (-)-(S_S)-S5



FW: 334.20 g mol^{-1}

$C_{18}H_{20}O_4S$

A THF solution (30.0 mL) of bromotoluene **S3** (5.00 g, 18.2 mmol, 1.00 mol eq) was added dropwise under argon to an anhydrous THF (30.0 mL) suspension of magnesium slurry (460 mg, 1.05 mol eq). When the formation of the Grignard reagent was completed, the solution was cooled to 0 °C and cannulated to a THF (50.0 mL) solution of 5.60 g of (-)-menthyl *p*-tolylsulfinate (19.2 mmol, 1.05 mol eq) under argon at 0 °C. The solution was allowed to warm up to room temperature and quenched with a saturated solution of NH_4Cl (100 mL). Aqueous phase was extracted three times with diethyl ether (100 mL) and the combined organic phases were treated with brine (200 mL), dried over magnesium sulfate, filtered off and concentrated to afford a waxy solid which after trituration with Et_2O (100 mL) delivered 4.98g of (-)-(SS)-**S5** as white needles (14.9 mmol, 82 %).

M.p.: 134°C.

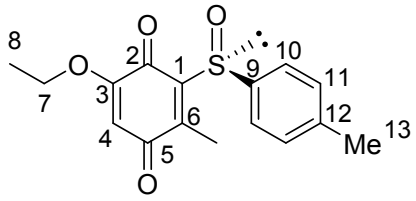
$[\alpha]_D^{20}$: -167.1 (c = 1.21, acetone).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (dd, 4H, *J* = 8.0 Hz, 2 × C^{10}*H* and 2 × C^{11}*H*), 5.96 (s, 1H, C^4*H*), 4.08 (q, 2H, *J* = 7.0 Hz, C^7*H*$_2$), 3.84 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, -OC*H*$_3$), 2.51 (s, 3H, C^{13}*H*$_3$), 2.39 (s, 3H, C^6*H*$_3$), 1.49 (t, 3H, *J* = 7.0 Hz, C^8*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 154.6 (C_q), 151.0 (C_q), 141.7 (C_q), 141.0 (C_q), 139.3 (C_q), 137.5 (C_q), 129.6 (2 × C^{11}*H*), 124.7 (2 × C^{10}*H*), 119.7 (C_q), 100.9 (C^4*H*), 65.7 (C^{7}H$_2$), 61.7 (-OCH_3), 56.2 (-OCH_3), 21.2 (-CH_3), 9.9 (-CH_3), 9.4 (-CH_3).

Microanalysis: for $C_{18}H_{20}O_4S$, calculated: C: 64.65, H: 6.63, O: 19.14; found: C: 64.61, H: 6.68, O: 19.24.

3-Ethoxy-6-methyl-1-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-1,3-diene-2,5-dione (+)-(S_S)-1



FW: 304.18 g mol^{-1}

$C_{16}H_{16}O_4S$

Into a 500 mL flask, 3.00 g of sulfoxide (-)-(S_S)-**S5** (9.00 mmol, 1.0 mol eq) were dissolved in 150 mL of MeCN. A solution of 13.82 g of CAN (25.2 mmol, 2.80 mol eq) dissolved in 100 mL of distilled water was quickly poured on the sulfoxide solution. After 20 minutes, a TLC analysis indicates the complete conversion of the starting material. MeCN was evaporated and the aqueous residue was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated to give 2.325 g (7.64 mmol, 85 %) of (+)-(S_S)-**1** as light orange needles after crystallization in hot methanol.

M.p.: 142.0 °C.

$[\alpha]_D^{20}$: +460.6 (c = 1, dichloromethane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (dd, 4H, A_2B_2 J = 8.0 Hz, Dn=103 Hz, 2 × C^{10}H and 2 × C^{11}H), 5.93 (s, 1H, C^4H), 3.97 (q, 2H, J=7.0 Hz, C$^7H_2$), 2.51 (s, 3H, C$^{13}H_3$), 2.4 (s, 3H, C$^6H_3$), 1.46 (t, 3H, J=7.0 Hz, C$^8H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 185.5 (C=O), 179.4 (C=O), 157.2 (C_q), 148.1 (C_q), 144.6 (C_q), 141.8 (C_q), 139.6 (C_q), 130.2 (2 × C^{10}H), 125.1 (2 × C^9H), 108.3 (C^4H), 65.7 (C$^7H_2$), 21.5 (CH_3), 13.9 (CH_3), 9.5 (CH_3).

Microanalysis: for $C_{16}H_{16}O_4S$, calculated: C: 63.14, H: 5.30, O: 21.03; found: C: 63.21, H: 5.39, O: 21.20.

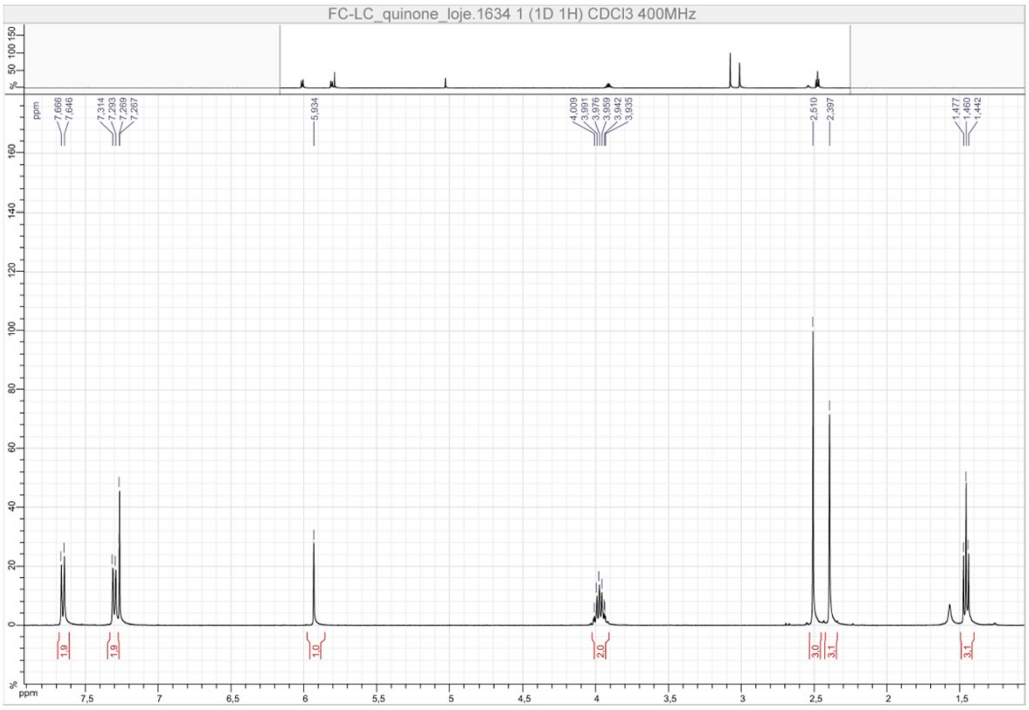


Fig. 1. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**1**.

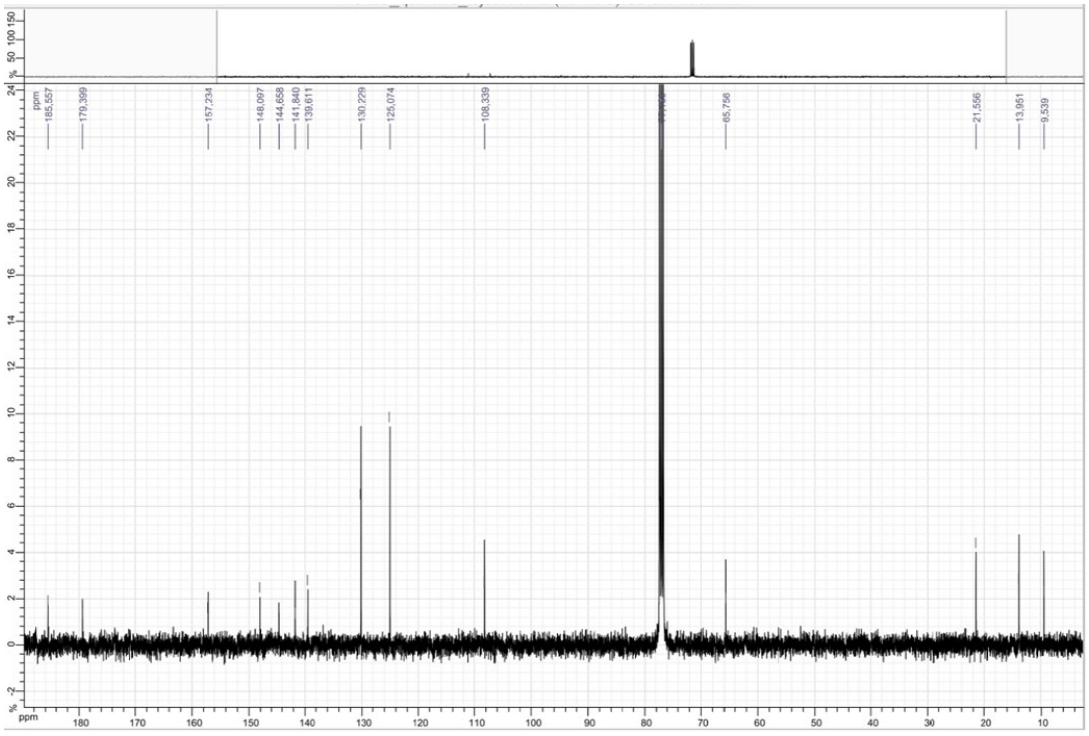
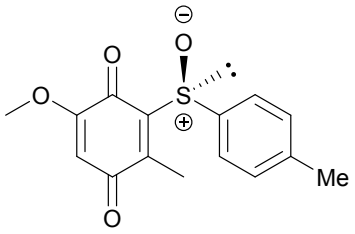


Fig. 2. ^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**1**.

Characteristics of quinone (+)-(S_S)-2a



FW: 290.33 g mol^{-1}

$C_{15}H_{14}O_4S$

M.p.: 130 - 132 °C.

$[\alpha]_D^{20}$: +469 ° (c = 1.0, CH_2Cl_2).

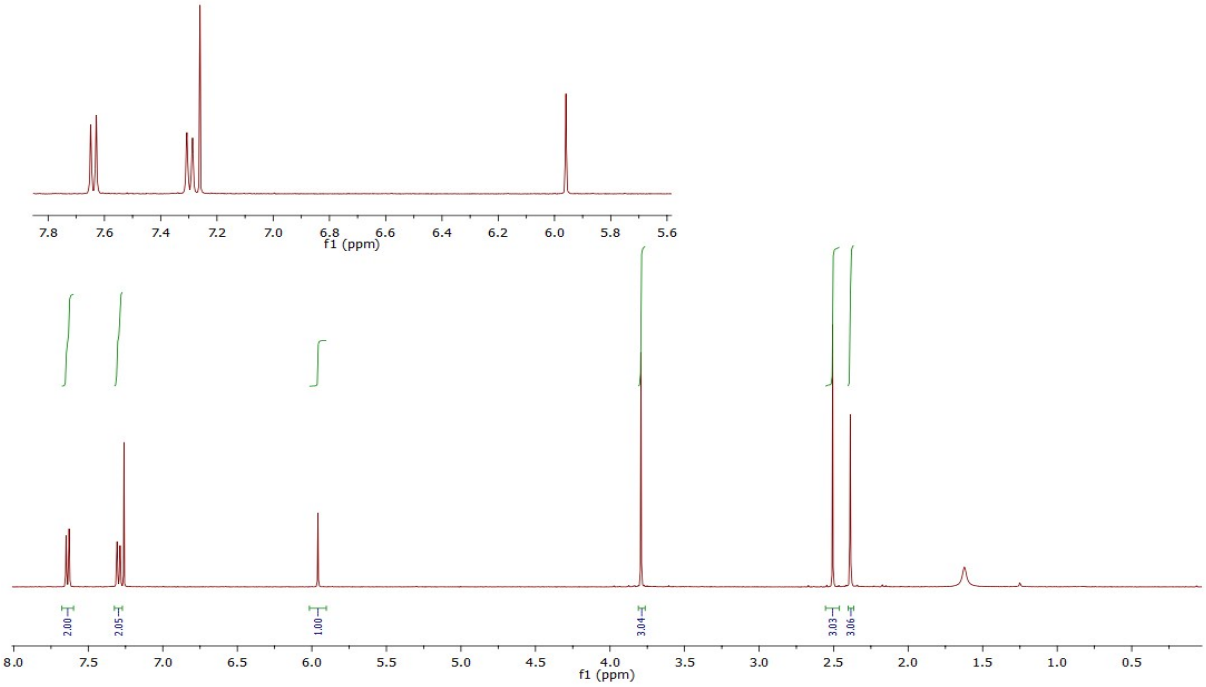


Fig. 3. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**2a**.

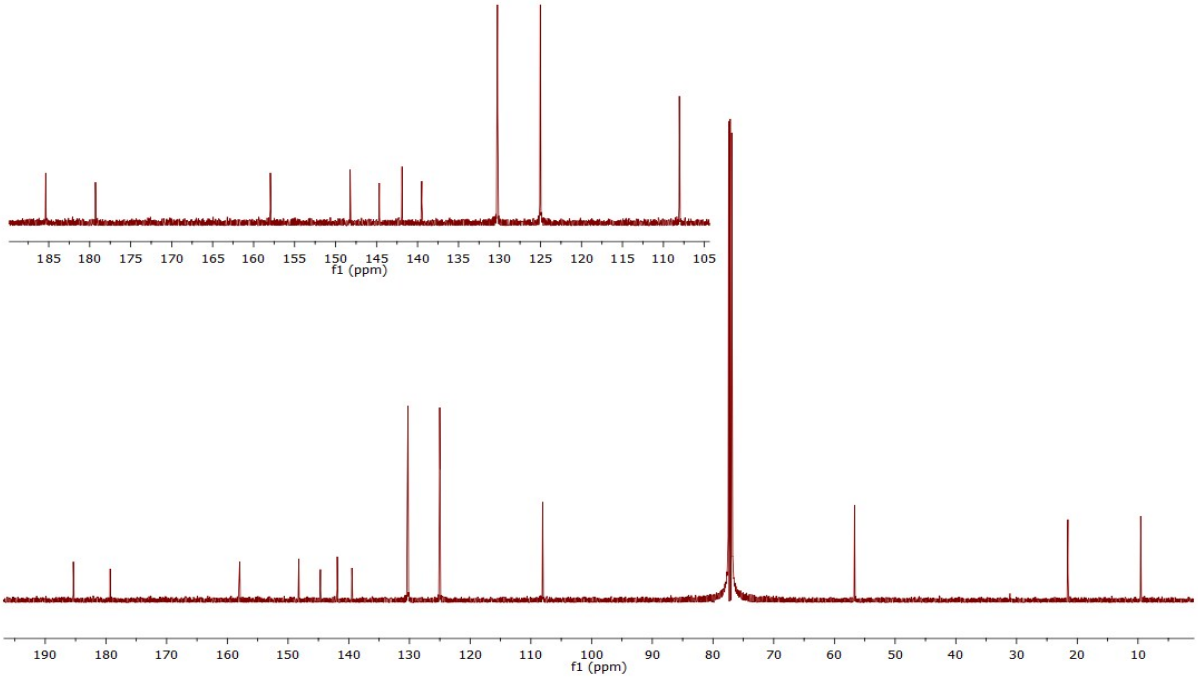
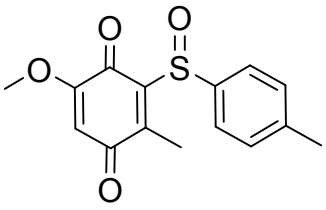


Fig. 4. ^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**2a**.

Characteristics of racemic quinone 2b



FW: 290.33 g mol^{-1}

$C_{15}H_{14}O_4S$

M.p.: 130.0 - 130.5 °C.

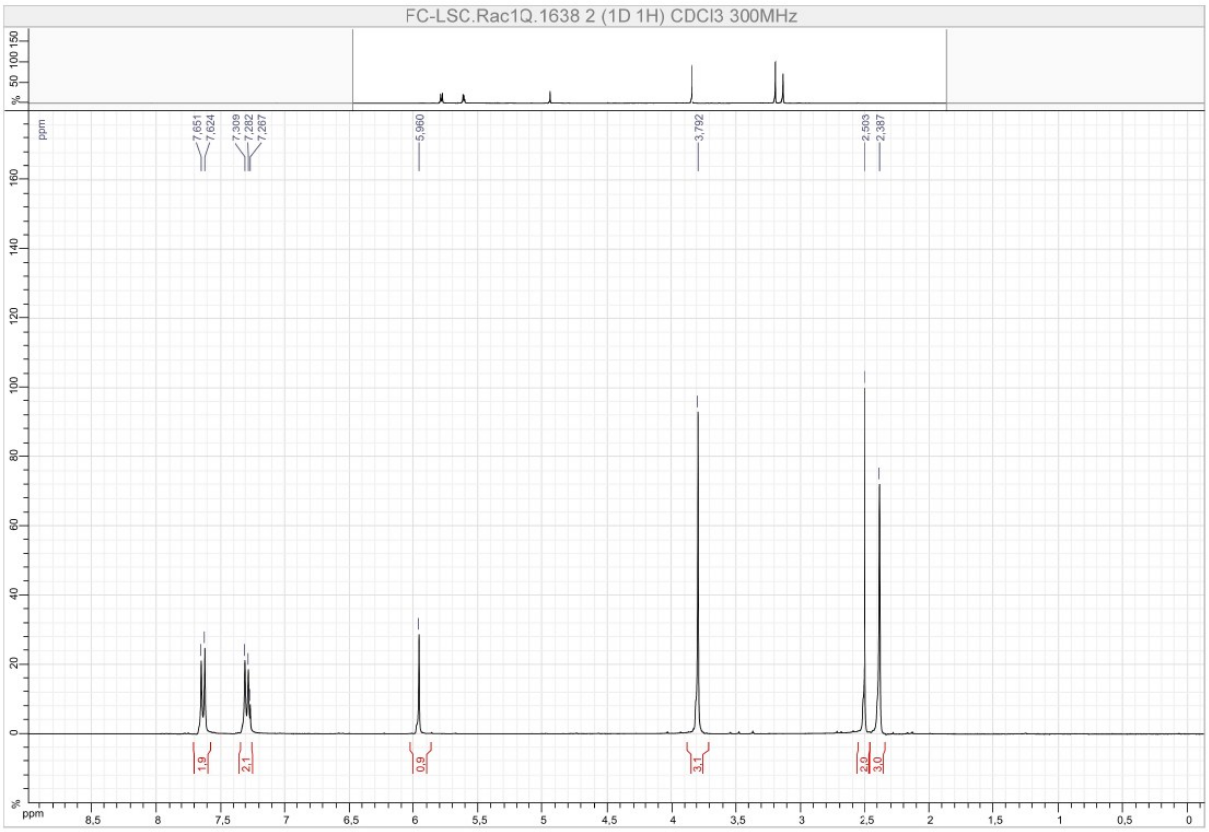


Fig. 5. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of racemic compound **2b**.

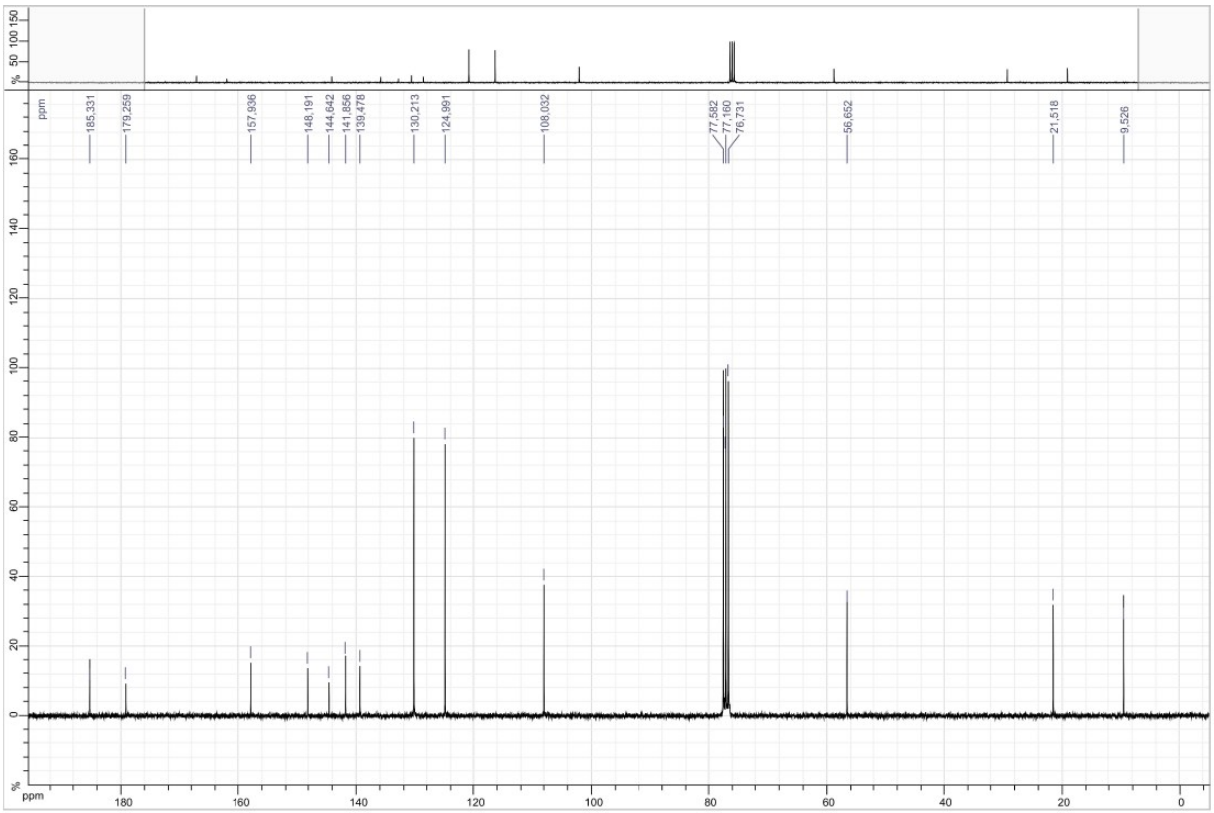
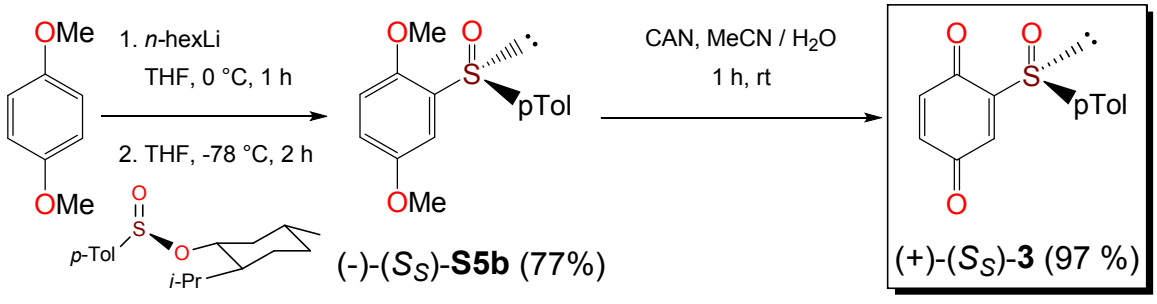


Fig. 6. ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum of racemic compound **2b**.

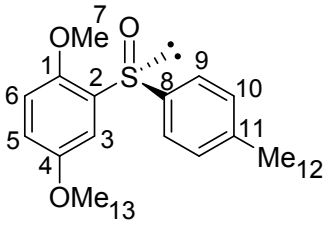
Preparation of quinone (+)-(S_S)-3

Compound **(+)-(S_S)-3** has been prepared from 1,4-dimethoxybenzene in two reaction steps according the **Scheme 2**.



Scheme 2. Synthesis of quinone **(+)-(S_S)-3**.

(−)-(*S*)-1,4-Dimethoxy-2-(*p*-tolylsulfinyl)benzene (-)-(S_S)-**S5b**



FW: 276.38 g mol^{-1}

$C_{15}H_{16}O_3S$

The protocol of Carreño and Brimble *et al.* have been used with slight modifications.[2,3]

Into a 250 mL two-neck flask under argon atmosphere, 2.059 g (15.0 mmol, 1.00 mol eq) of 1,4-dimethoxybenzene was dissolved in 60.0 mL of anhydrous THF. The solution was cooled down to 0 °C and 6.00 mL of a 2.50 M *n*-hexyllithium solution in hexane (15.0 mmol, 1.00 mol eq) was added dropwise. The solution was stirred for one hour at 0 °C, then cooled down to -78 °C and quickly cannulated over a solution of 4.483 g of (-)-menthyl *p*-tolylsulfinate (15.0 mmol, 1.00 mol eq) in 40.0 mL of anhydrous THF (also cooled down to -78 °C). The mixture was stirred for two hours at -78 °C. The solution was allowed to warm up to room temperature and quenched with 100 mL of distilled water. The phases were separated and the aqueous phase was extracted with dichoromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated. The crude was purified by chromatography on silica gel (cyclohexane / EtOAc, 9 / 1 → 8 / 2 → 7 / 3) to give 3.188 g (11.5 mmol, 77 %) of (−)-(*S*)-1,4-dimethoxy-2-(*p*-tolylsulfinyl)benzene ((-)-(S_S)-**S5b**) as a white solid.

R_F: 0.54 (cyclohexane / EtOAc, 5 / 5).

$[\alpha]_D^{20}$: -21 ° (c = 1.0, $CHCl_3$).

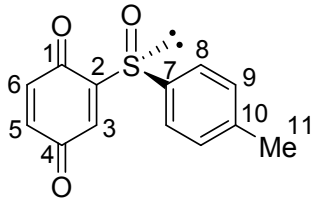
M.p.: 75 - 77 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, 2H, *J* = 8.1 Hz, 2 × C^9H), 7.48 (d, 1H, *J* = 3.1 Hz, C^3H), 7.21 (d, 2H, *J* = 8.1 Hz, 2 × $C^{10}H$), 6.90 (dd, 1H, *J* = 8.9; 3.1 Hz, C^5H), 6.77 (d, 1H, *J* = 8.9 Hz, C^6H), 3.82 (s, 3H, C^7H_3), 3.72 (s, 3H, $C^{13}H_3$), 2.34 (s, 3H, $C^{12}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 154.7 (C^4_q), 149.7 (C^1_q), 142.4 (C^8_q), 141.5 (C^{11}_q), 134.1 (C^2_q), 129.8 (2 × C^{10}H), 125.5 (2 × C^9H), 118.1 (C^5H), 112.7 (C^6H), 108.7 (C^3H), 56.3 (C^7H_3), 56.1 ($C^{13}H_3$), 21.5 ($C^{12}H_3$).

IR: ν (cm^{-1}) 1267 (O-C^{ar}), 1210 (O-C^{ar}), 1029 (sulfoxide).

(+)-(*S*)-2-(*p*-Tolylsulfinyl)cyclohexa-2,5-diene-1,4-dione (+)-(S_S)-3



FW: 246.30 g mol^{-1}

$C_{13}H_{10}O_3S$

This molecule (+)-(S_S)-**3** was synthesized according to Carreño *et al.* protocol.[2]
Into a 500 mL flask, 2.520 g (9.12 mmol, 1.00 mol eq) of (*S*)-1,4-dimethoxy-2-(p-tolylsulfinyl)benzene (-)-(S_S)-**S5b** was dissolved in 100 mL of MeCN. A solution of 12.627 g of CAN (23.03 mmol, 2.50 mol eq) in 100 mL of distilled water was added at once over the sulfoxide solution and stirred for one hour at room temperature. MeCN was then evaporated and the aqueous residue was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated to yield 2.183 g (8.86 mmol, 97 %) of the desired sulfinylquinone (+)-(S_S)-**3**. Recrystallization from hot diethyl ether gave blood red needles.

R_F: 0.63 (cyclohexane / EtOAc, 5 / 5).

$[\alpha]^{20}_D$: +1011 ° (c = 1.0, $CHCl_3$).

M.p.: 124 - 126 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 (d, 2H, *J* = 8.1 Hz, 2 × C^8H), 7.43 (d, 1H, *J* = 2.5 Hz, C^3H), 7.29 (d, 2H, *J* = 8.1 Hz, 2 × C^9H), 6.79 (dd, 1H, *J* = 10.1; 2.5 Hz, C^5H), 6.71 (d, 1H, *J* = 10.1 Hz, C^6H), 2.39 (s, 3H, $C^{11}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 185.2 (C^4_q), 183.71 (C^1_q), 155.4 (C^2_q), 143.1 (C^{10}_q), 138.3 (C^7_q), 137.5 (C^5H), 136.6 (C^6H), 131.7 (C^3H), 130.4 (2 × C^9H), 125.9 (2 × C^8H), 21.6 ($C^{11}H_3$).

IR: ν (cm^{-1}) 1657 (C=O), 1273 (O-C^{ar}), 1057 (sulfoxide).

HRMS (ESI+): for $[M+H]^+$ calc.: 247.0429, found: 247.0423.

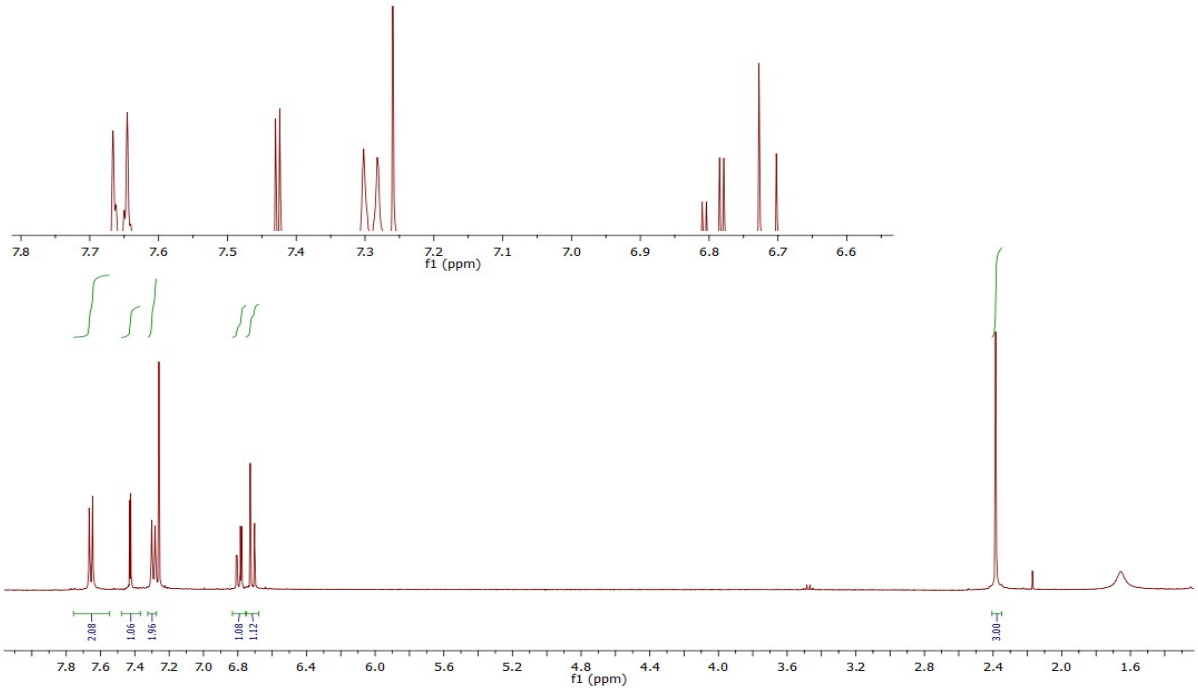


Fig. 7. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound (+)-(S_s)-**3**.

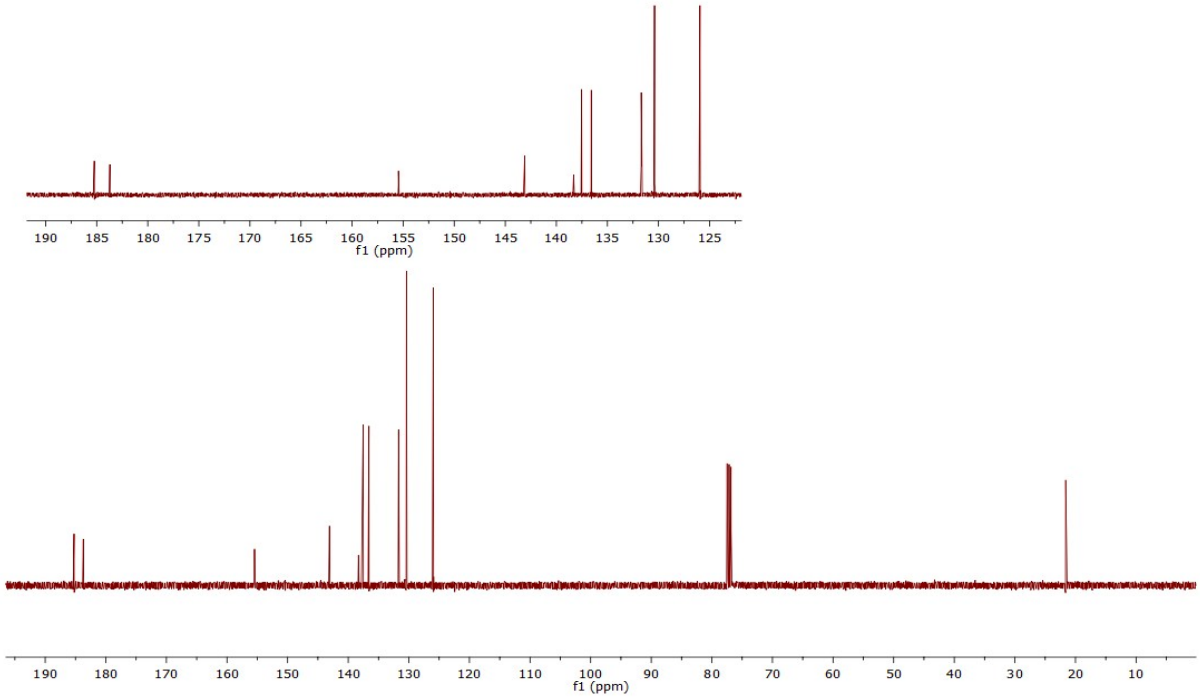
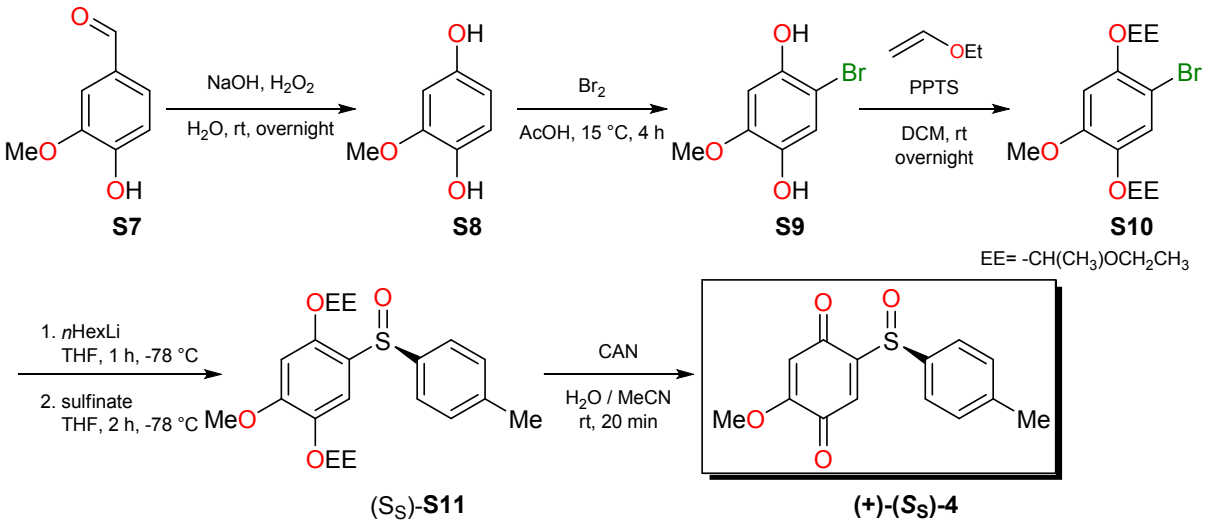


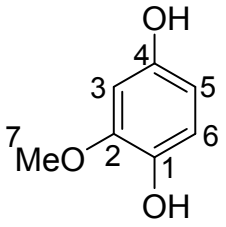
Fig. 8. ^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**3**.

Preparation of (+)-(S_S)-4



Scheme 3. Synthesis of qionoide (+)-(S_S)-**4**.

2-Methoxy-1,4-dihydroxybenzene S8



FW: 140.15 g mol^{-1}

$C_7H_8O_3$

Compound **S8** was obtained using a modified version of Ferreira *et al.* protocol.[4]

Into a 100 mL two-neck flask, a solution of 1.574 g of NaOH (39.4 mmol, 1.20 mol eq) in 40.0 mL of distilled water was used to dissolve 5.163 g of vanillin (**S7**) (33.9 mmol, 1.00 mol eq). Through a dropping funnel, 3.30 mL of H_2O_2 (37 %, 40.6 mmol, 1.20 mol eq) diluted with 20.0 mL of distilled water is added dropwise to the phenolate solution. The mixture directly turned dark and was stirred overnight at room temperature. The solution was acidified with 20.0 mL of HCl (10.0 %) and extracted with ethyl acetate. The organic phase was washed with a saturated solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered off and evaporated to provide a dark oil which was chromatographied on silica gel (cyclohexane / EtOAc, 8 / 2) to give 3.633 g of **S8** as a white solid (25.9 mmol, 76 %).

R_F: 0.43 (cyclohexane / EtOAc, 5 / 5).

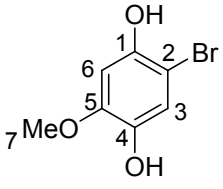
M.p.: 85.0 - 86.0 °C.

^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) 7.71 (s, 1H, O*H*), 6.85 (s, 1H, O*H*), 6.63 (d, 1H, *J* = 8.5 Hz, C^6*H*), 6.46 (d, 1H, *J* = 2.5 Hz, C^3*H*), 6.27 (dd, *J* = 8.5; 2.5 Hz, C^5*H*), 3.80 (s, 3H, C$^7H_3$).

^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) 151.5 (C^1_q), 148.8 (C^2_q), 140.4 (C^4_q), 115.8 (*C*^{6}H), 107.3 (*C*^{5}H), 101.1 (*C*^{3}H), 56.07 (*C*$^7H_3$).

IR: ν (cm^{-1}) 3500 - 3100 (OH), 1290 (O-C^{ar}), 1244 (O-C^{ar}), 1218 (O-C^{ar}), 1034 (O-CH_3).

2-Bromo-4-methoxy-1,4-dihydroxybenzene S9



FW: 219.04 g mol^{-1}

$C_7H_7O_3Br$

The compound **S9** was synthesized according to Keana *et al.* protocol.[5]

Into a 500 mL two-neck flask, equipped with a dropping funnel, under argon atmosphere, 3.506 g of hydroquinone **S8** (25.0 mmol, 1.00 mol eq) was dissolved in 150 mL of glacial acetic acid. The solution was cooled down using an iced-water bath. 1.30 mL of bromine (25.3 mmol, 1.00 mol eq), dissolved in 30 mL of glacial acetic acid, were added dropwise through the dropping funnel. The mixture was stirred for four hours. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was washed with saturated solutions of $Na_2S_2O_3$, $NaHCO_3$ and brine, successively, then dried over $MgSO_4$, filtered off and evaporated. The crude was purified by recrystallization in hot toluene (80 °C) to give 4.582 g (20.9 mmol, 83 %) of **S9**.

R_F: 0.46 (cyclohexane / EtOAc, 5 / 5).

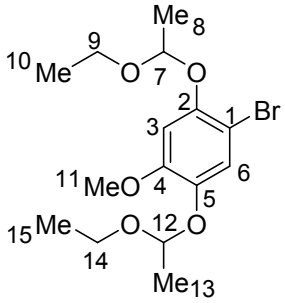
M.p.: 120 - 122 °C.

^{1}H-NMR (400 MHz, acetone-d_6): δ (ppm) 7.95 (s, 1H, O*H*), 7.38 (s, 1H, O*H*), 6.93 (s, 1H, C^3*H*), 6.64 (s, 1H, C^6*H*), 3.78 (s, 3H, C^7*H*$_3$).

^{13}C-NMR (100 MHz, acetone-d_6): δ (ppm) 147.9 (C^5_q), 146.9 (C^1_q), 140.6 (C^4_q), 118.2 (*C*^{3}H), 101.3 (*C*^{6}H), 98.9 (C^2_q), 55.5 (*C*^{7}H$_3$).

IR: ν (cm^{-1}) 3500 - 3000 (OH), 1274 (O-C^{ar}), 1198 (O-C^{ar}), 1165 (O-C^{ar}), 1038 (O-CH$_3$), 820 (C^{ar}-Br).

1-Bromo-2,5-bis(1-ethoxyethoxy)-4-methoxybenzene S10



FW: 363.00 g mol^{-1}

$C_{15}H_{23}O_5Br$

Into a 100 mL two-neck flask under argon atmosphere, 1.415 g of hydroquinone **S9** (6.46 mmol, 1.00 mol eq) were suspended into 25.0 mL of anhydrous dichloromethane. To that suspension, 3.40 mL of ethyl vinyl ether (35.6 mmol, 5.50 mol eq) was added dropwise and, after five minutes, 42.0 mg of PPTS (0.167 mmol, 0.025 mol eq) were added. The solid solubilized after ca 30 minutes. The reaction was stirred overnight at room temperature and a solution of saturated $NaHCO_3$ was added to quench the reaction. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phases were gathered and dried over $MgSO_4$, then filtered off and the solvents were evaporated. The crude product was purified by filtration over a silica gel pad, using a cyclohexane / diethyl ether mixture in 4 / 1 ratio as eluent. The solvents are evaporated to give 2.344 g (6.46 mmol, quantitative yield) of **S10** as yellow oil.

R_F: 0.55 (cyclohexane / EtOAc, 7 / 3).

A mixture of diastereoisomers:

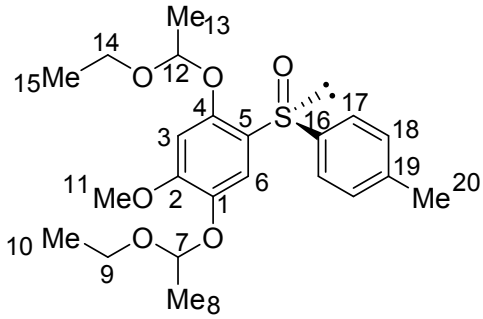
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 (s, 1H), 6.75 (s, 1H), 5.28 (m, 1H), 5.21 (m, 1H), 3.91-3.71 (m, 3H), 3.78 (s, 3H, C$^{11}H_3$), 3.67-3.50 (m, 3H), 1.47 (d, 3H, J = 5.4 Hz), 1.42 (d, 3H, J = 5.3 Hz), 1.21-1.15 (m, 6H, C$^8H_3$ + C$^{13}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 151.0 (C^4_q), 149.01+149.0 (C^2_q or C^5_q), 141.5+141.5 (C^2_q or C^5_q), 124.0 (C^6H), 105.1+105.1 (C^3H), 104.22 (C^1_q), 101.9+101.9 (C^7H or C^{12}H), 101.7+101.7

(C^7H or C^{12}H), 62.4+62.3 (C^9H_2 or $C^{14}H_2$), 61.8+61.8 (C^9H_2 or $C^{14}H_2$), 56.1 ($C^{11}H_3$), 20.3+20.3 (C^8H_3 or $C^{13}H_3$), 20.3+20.2 (C^8H_3 or $C^{13}H_3$), 15.4 ($C^{10}H_3$ or $C^{15}H_3$), 15.3 ($C^{10}H_3$ or $C^{15}H_3$).

IR: ν (cm^{-1}) 1198 - 1040 (multiple peaks corresponding to ether groups), 988 - 891 (multiple peaks corresponding to acetal groups), 820 (C^{ar}-Br).

1,4-Bis(1-ethoxyethoxy)-2-methoxy-5 [(*S*)-4-methylbenzenesulfinyl]benzene (S_S)-S11



FW: 422.22 g mol^{-1}

$C_{22}H_{30}O_6S$

Into a 100 mL two-neck flask under argon atmosphere, 1.60 mL of a 2.50 M *n*-hexyllithium solution in hexane (4.00 mmol, 1.00 mol eq) were dissolved in 15 mL of anhydrous THF and cooled down to -78 °C. A solution of 1.423 g of bromide **S10** (3.919 mmol, 1.00 mol eq), dissolved in 25.0 mL of anhydrous THF, was added dropwise to the lithium solution. The golden mixture was stirred for one hour at -78 °C. Into a 250 mL two-neck flask under argon atmosphere, 1.399 g of (-)-menthyl *p*-tolylsulfinate (4.76 mmol, 1.20 mol eq) was dissolved in 45.0 mL of anhydrous THF and cooled down to -78 °C. The lithium solution was quickly cannulated over the sulfinate solution and the final mixture was stirred for two hours at -78 °C. The solution was allowed to warm up to room temperature and was quenched with distilled water. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered off and evaporated. The crude product was purified by chromatography on silica gel (cyclohexane / EtOAc, 9 / 1 → 8 / 2) to give 916 mg (2.17 mmol, 55 %) of **S11** as golden oil.

R_F: 0.50 (cyclohexane / EtOAc, 4 / 6).

A mixture of diastereoisomers:

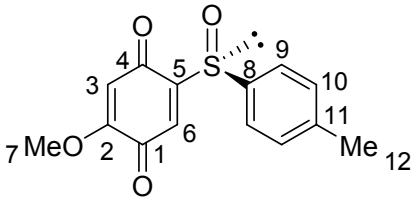
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62-7.51 (m, 2H, 2 × C^{17}*H*), 7.32-7.26 (m, 2H, C^{18}*H*), 6.93+6.89+6.70 (3 × s, 1H, C^{6}*H*), 6.42+6.41+6.40 (3 × s, 1H, C^{3}*H*), 5.37-5.27 (m, 1H, C^{7}*H* or C^{12}*H*), 5.24-5.14 (m, 1H, C^{7}*H* or C^{12}*H*), 3.91-3.72 (m, 5H, C$^{11}H_3$ + C$^{9}H_2$ or C$^{14}H_2$), 3.67-3.45 (m, 2H, C$^{9}H_2$ or C$^{14}H_2$), 2.37 (s, 3H, C$^{11}H_3$), 1.45-1.09 (m, 12H, C$^{8}H_3$ + C$^{10}H_3$ + C$^{13}H_3$ + C$^{15}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 154.0+153.9+153.8 (C_q^2), 149.0+148.9+148.8 +148.7 (C_q^{Ar}), 142.8+148.8+148.78+148.76 (C_q^{Ar}), 141.3+141.3+141.3+141.2 (C_q^{Ar}), 141.11+141.09 (C_q^{Ar}), 129.6 (2 × $C^{p\text{Tol}}$H), 125.7+126.6 (C^{6}H), 125.2 (2 × $C^{p\text{Tol}}$H), 115.5+ 115.3+115.1+114.6 (C_q^{Ar}), 101.99+101.97 (C^{3}H), 101.7+101.60+101.57+101.54 (C^{7}H or C^{12}H), 100.4+100.3+100.17+100.16 (C^{7}H or C^{12}H), 62.62+62.58+62.3+62.2 ($C^{9}H_2$ or $C^{14}H_2$), 61.2+61.1+60.3+60.2 ($C^{9}H_2$ or $C^{14}H_2$), 56.11+56.10+56.08 ($C^{11}H_3$), 21.4 ($C^{20}H_3$), 20.5+20.4+20.3 ($C^{8}H_3$ or $C^{13}H_3$), 19.82+19.80+19.6+19.5 ($C^{8}H_3$ or $C^{13}H_3$), 15.23+15.18+15.14 ($C^{10}H_3$ + $C^{15}H_3$).

IR: ν (cm^{-1}) 1197 - 1081 (multiple peaks corresponding to ether groups), 1046 (sulfoxide), 994 - 906 (multiple peaks corresponding to acetal groups).

2-Methoxy-5-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-2,5-diene-1,4-dione

(+)-(S_S)-4



FW: 276.16 g mol^{-1}

$C_{14}H_{12}O_4S$

Into a 50 mL flask, 604 mg of sulfoxide (S_S)-**S11** (1.43 mmol, 1.00 mol eq) were dissolved in 15.0 mL of MeCN. A solution of 2.178 g of CAN (3.97 mmol, 2.80 mol eq) dissolved in 10.0 mL of distilled water was quickly poured on the sulfoxide solution. After 20 minutes, a TLC analysis indicates the complete conversion of the starting material. The MeCN was evaporated

and the aqueous residue was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated to give 375 mg (1.297 mmol, 95.0 %) of (+)-(S_S)-**4** a light orange solid.

R_F: 0.20 (cyclohexane / TBME, 5 / 5).

$[\alpha]_D^{20}$: +428.8 ° (c = 1.0, $CHCl_3$).

M.p.: 121-123 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 (d, 2H, *J* = 8.1 Hz, 2 × C^9H), 7.34 (s, 1H, C^6H), 7.29 (d, 2H, *J* = 8.1 Hz, $C^{10}H$), 5.85 (s, 1H, C^3H), 3.81 (s, 3H, C^7H_3), 2.38 (s, 3H, $C^{12}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 183.7 (C_q^1), 179.7 (C_q^4), 159.7 (C_q^2), 156.5 (C_q^5), 149.9 (C_q^{11}), 138.5 (C_q^8), 130.4 (2 × C^{10}H), 129.7 (C^6H), 126.0 (2 × C^9H), 107.6 (C^3H), 56.9 (C^7H_3), 21.6 ($C^{12}H_3$).

IR: ν (cm^{-1}) 1676 (C=O), 1634 (C=O), 1190 (O-C^{ar}), 1079 (O-CH_3 or sulfoxide), 1055 (O-C^{ar} or sulfoxide).

HRMS (ESI+): for $[M+H]^+$ calc.: 277.0535, found: 277.0529.

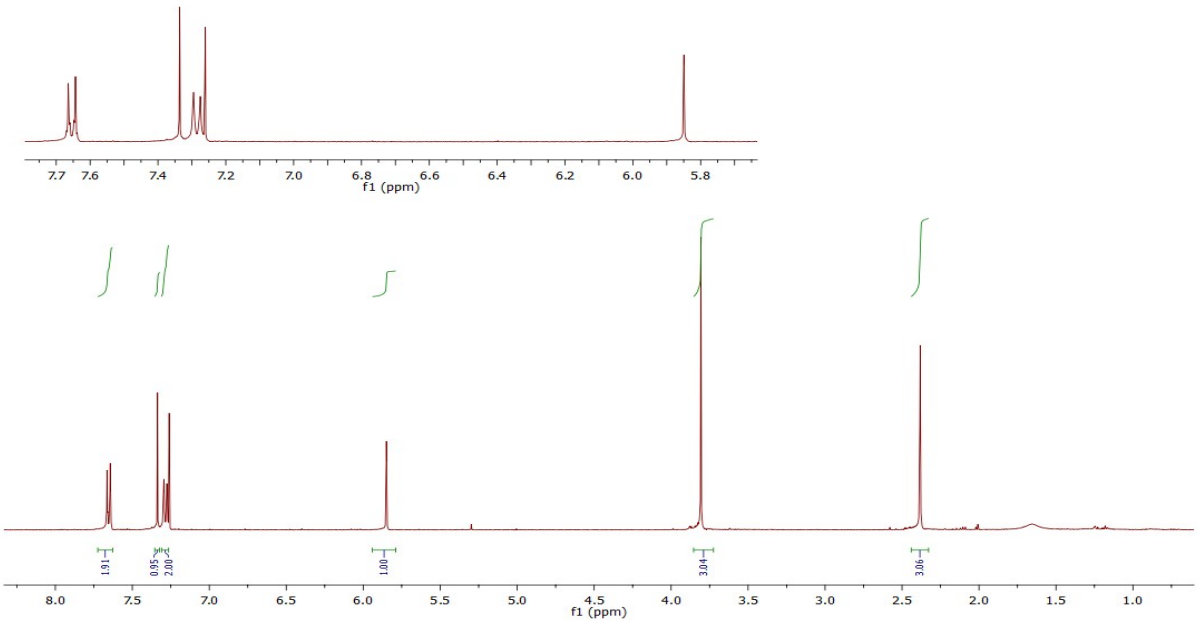


Fig. 9. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**4**.

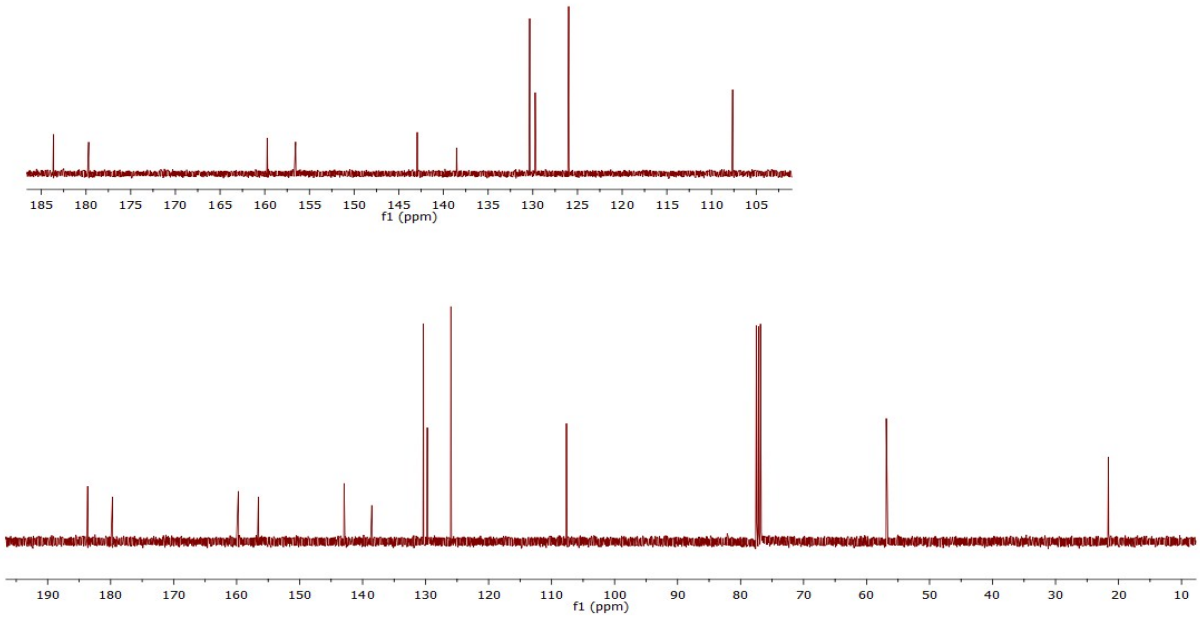
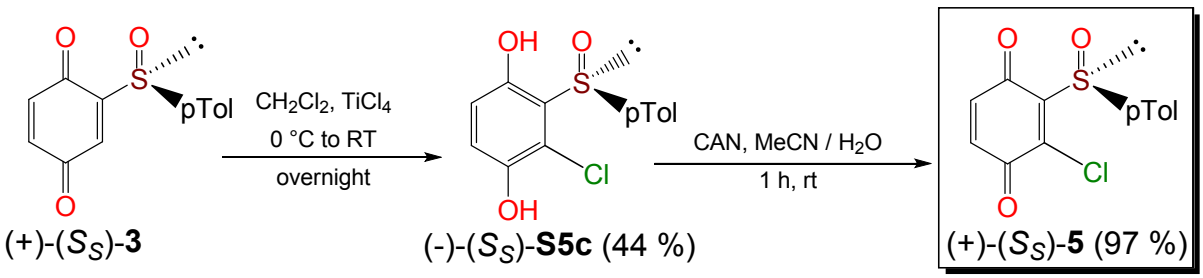


Fig. 10. ^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**4**.

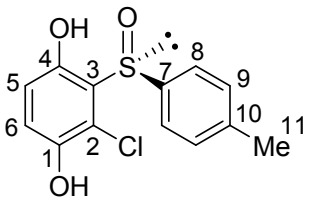
Preparation of (+)-(S_S)-5

Compound **(+)-(S_S)-5** has been prepared from **(+)-(S_S)-3** in two reaction steps according the **Scheme 4**.



Scheme 4. Synthesis of quinone **(+)-(S_S)-3**.

(−)-2-Chloro-3-[(*S*)-4-methylbenzenesulfinyl]benzene-1,4-diol (-)-(S_S)-S5c



FW: 282.76 g mol^{-1}

$C_{13}H_{11}O_3SCl$

The title compound **S4** was cited by Carreño *et al.* although no experimental procedure was given.[6]

Into a 250 mL two-neck flask under argon atmosphere, 1.996 g (8.10 mmol, 1.00 mol eq) of (+)-(S_S)-**3** was dissolved in 150 mL of anhydrous dichloromethane and cooled down to 0 °C and 2.5 mL of $TiCl_4$ (22.8 mmol, 2.80 mol eq) was added dropwise. The dark red solution was allowed to warm up to room temperature and was stirred overnight. Hydrolysis was performed by addition of 100 mL of a saturated solution of sodium potassium tartrate and a vigorous stirring for five hours. The phases are separated and the aqueous phase was extracted with dichloromethane. Organic phases are gathered and washed with a saturated solution of $Na_2S_2O_3$ and brine, successively. The organic phase was then dried over $MgSO_4$, filtered off and evaporated. The crude was purified by chromatography on demetallated silica gel (cyclohexane / EtOAc, 9 / 1 → 8 / 2) to give 1.001 g (3.54 mmol, 44 %) of (-)-(S_S)-**S5c** a pale yellow solid.

R_F: 0.60 (cyclohexane / EtOAc, 5 / 5).

$[\alpha]_D^{20}$: -95 ° (c = 1.0, acetone).

M.p.: 173 - 176 °C.

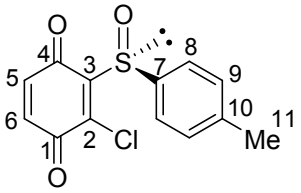
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 10.87 (s, 1H, O*H*), 7.74 (d, 2H, *J* = 8.1 Hz, 2 × C^8*H*), 7.32 (d, 2H, *J* = 8.1 Hz, 2 × C^9*H*), 7.01 (d, 1H, *J* = 9.2 Hz, C^5*H* or C^6*H*), 6.78 (d, 1H, *J* = 9.2 Hz, C^5*H* or C^6*H*), 5.30 (s, 1H, O*H*), 2.40 (s, 3H, C^{11}H$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 154.6 (C_q^{Ar}), 145.0 (C_q^{Ar}), 143.3 (C_q^{Ar}), 139.7 (C_q^{Ar}), 130.5 (2 × *C*^{8}H or 2 × *C*^{9}H), 126.2 (2 × *C*^{8}H or 2 × *C*^{9}H), 120.6 (*C*^{5}H or *C*^{6}H), 120.4 (C_q^{Ar}), 119.7 (*C*^{5}H or *C*^{6}H), 115.8 (C_q^{Ar}), 21.7 (*C*^{11}H$_3$).

IR: ν (cm^{-1}) 3400 - 2800 (OH), 1286 (C^{ar}-OH), 1207 (C^{ar}-OH), 966 (sulfoxide), 805 (C^{ar}-Cl).

(+)-2-Chloro-3-[(*S*)-4-methylbenzenesulfinyl]cyclohexa-2,5-diene-1,4-dione

(+)-(S_S)-5



FW: 280.74 g mol^{-1}

$C_{13}H_9O_3SCl$

The title compound was cited by Carreño *et al.* although no experimental procedure was given.[6]

Into a 100 mL flask, 602 mg (2.13 mmol, 1.00 mol eq) of sulfinylhydroquinone (-)-(S_S)-**S5c** were dissolved in 40.0 mL of MeCN. A solution of 2.942 g of CAN (5.37 mmol, 2.50 mol eq) in 40.0 mL of distilled water was added at once over the sulfoxide solution. After one hour, the MeCN was evaporated and the aqueous residue was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered off and evaporated to give 578 mg (2.06 mmol) of sulfinylquinone (+)-(S_S)-**5** (97 %). Recrystallization from a hot mixture of pentane and toluene afforded blood red needles.

R_F: 0.41 (cyclohexane / EtOAc, 5 / 5).

$[\alpha]_D^{20}$: +638 ° (c = 1.0, $CHCl_3$).

M.p.: 138 - 140 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, 2H, *J* = 8.2 Hz, 2 × C^8H), 7.33 (d, 2H, *J* = 8.2 Hz, 2 × C^9H), 6.91 (d, 1H, *J* = 10.1 Hz, C^5H or C^6H), 6.78 (d, 1H, *J* = 10.1 Hz, C^5H or C^6H), 2.40 (s, 3H, $C^{11}H_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 181.3 (C^{1}_{q} or C^{4}_{q}), 177.9 (C^{1}_{q} or C^{4}_{q}), 146.3 (C^{2}_{q} or C^{3}_{q}), 143.7 (C^{2}_{q} or C^{3}_{q}), 142.6 (C^{10}_{q}), 138.0 (C^{7}_{q}), 137.3 ($C^{5}H$ or $C^{6}H$), 136.0 ($C^{5}H$ or $C^{6}H$), 130.3 (2 × C^{9}H), 125.2 (2 × C^{8}H), 21.6 ($C^{11}H_3$).

IR: ν (cm^{-1}) 1676 (C=O), 1652 (C=O), 1063 (sulfoxide), 836 (C-Cl).

HRMS (ESI+): for $[M+H]^+$ calc.: 281.0039, found: 281.0034

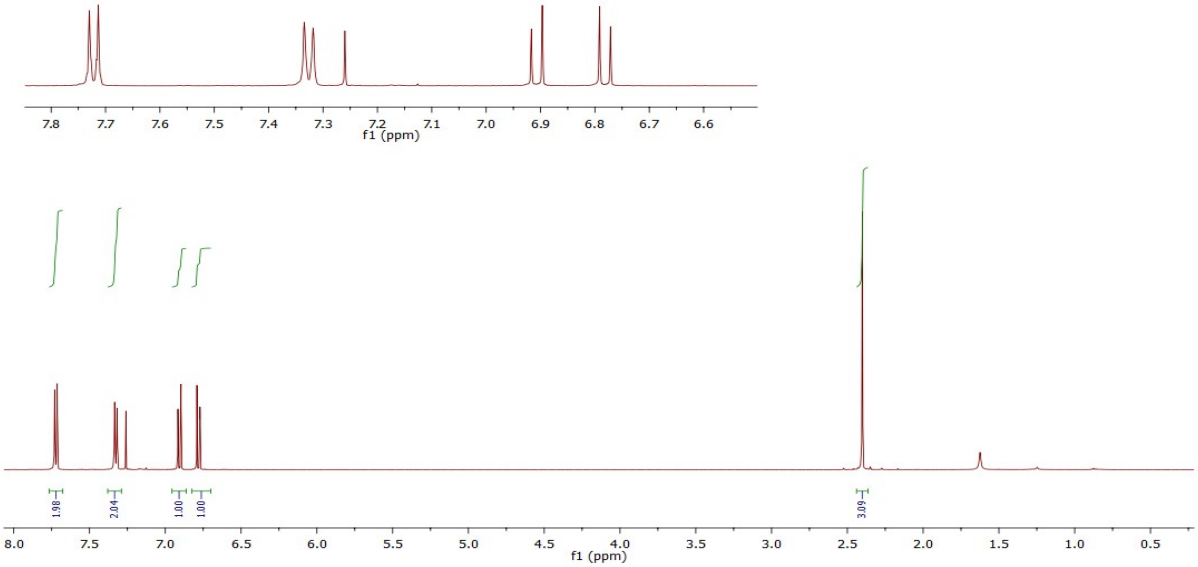


Fig. 11. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**5**.

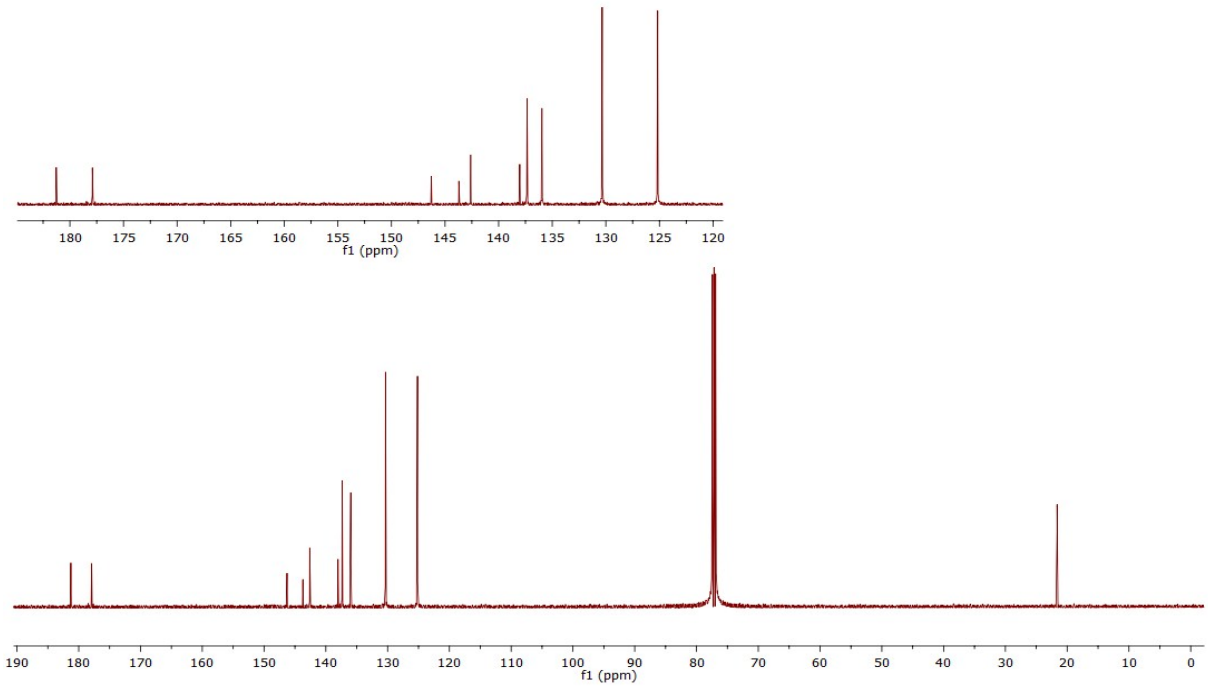
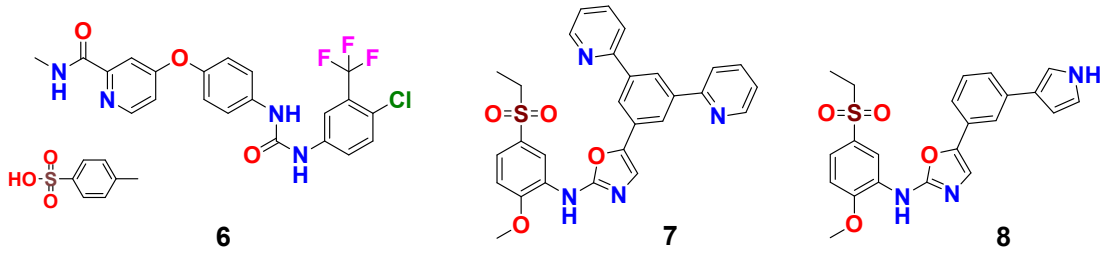


Fig. 12. ^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound (+)-(S_S)-**5**.

2. Availability of VEGFR2 TKIs 6,7 and 9



6

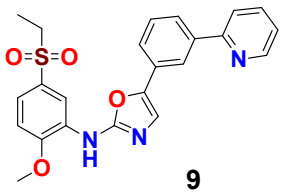
IC_{50} = 8.5 nM (VEGFR2 TK), BM03014
sorafenib tosylate
(Nexavar®, Bayer, FDA 2005)

7

IC_{50} = 15 nM (VEGFR2 TK)
BM06614 (Biomagi)

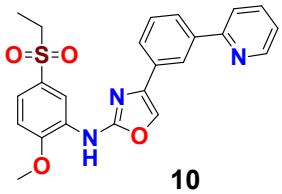
8

IC_{50} = 18 nM (VEGFR2 TK)
BM02814 (Biomagi)



9

IC_{50} = 22 nM (VEGFR2 TK), BM02514
AAZ (PDB: 1Y6A)
(GlaxoSmithKline, 2005)



10

IC_{50} = 564 uM (VEGFR2 TK), BM02614
N-regio of **AAZ** (Biomagi)

Fig. 13. The structures of tested TKIs **6-10**.

Sorafenib tosylate 6

Compound **6** is an active component of the commercial drug Nexavar® and was obtained from Bayer, Inc.

5-(Bispyridinylphenyl)oxazol-2-amine 7

Synthesis and physico-chemical properties of **7** was described by us recently.[7]

5-(Pyridinylphenyl)oxazol-2-amine 9 (AAZ)

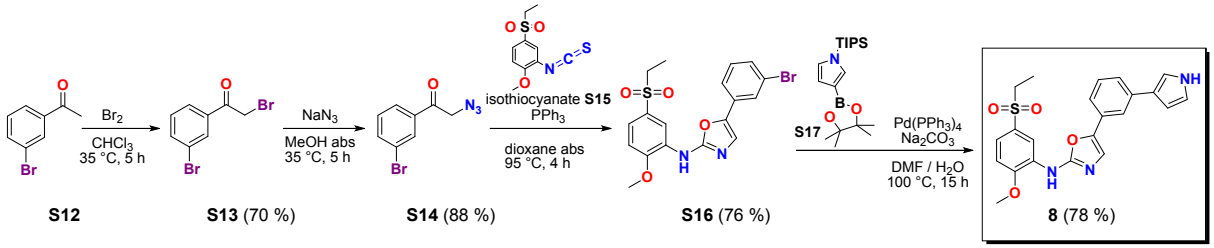
Compound **9** is known also under its ligand name **AAZ** from X-ray structure in complex with VEGFR2 TK (PDB: 1Y6A) described in PDB database.[8] Compound **9** was developed as VEGFR2 TK inhibitor by GlaxoSmithKline. Its synthesis and physico-chemical properties are described in the literature by Harris et al.[9] Compound **9** was prepared according their procedure.

3. **Synthesis of VEGFR2 TKIs** 8 **and** 10

Compounds **8** and **10** were prepared according the reaction conditions depicted on a **Scheme 5** and **6**.

Preparation of 5-(pyrrolylphenyl)oxazol-2-amine 8

4-(Ethylsulfonyl)-2-isothiocyanato-1-methoxybenzene (**S15**) was prepared according the procedure described by Harris at al.[9] Synthesis and characteristics of **S17** are given in supplementary material to our recent publication Vojtičková et al.[10]



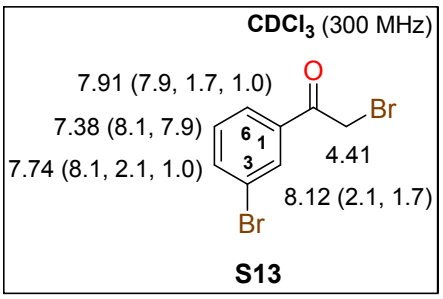
Scheme 5. Synthetic pathway to oxazol-2-amine **8**.

Synthesis of dibromoacetophenone S13

Novelty: Synthesis of **S13** was previously described in a literature with 78 % yield.[11] ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectral analysis were published.[12]

A solution of 3.60 g (18.1 mmol, 1.00 mol eq) of 1-(3-bromophenyl)ethanone (**S12**) in 30.0 ml of $CHCl_3$ was heated to 35 °C and 2.89 g (18.1 mmol, 1.00 mol eq) of Br_2 in 10.0 ml $CHCl_3$ was added dropwise within 1.5 h. After addition the mixture was stirred at the same temperature for 3.5 h. After the complete consumption of the starting material **S12** (TLC analyze), the mixture was cooled down to rt and extracted with 10 ml of H_2O and 2 × 10.0 ml of $NaHCO_3$ aq saturated solution. Combined organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product a pale yellow oil was purified by crystallization from EtOH yielding 3.50 g (12.6 mmol, 70 %) of 2-bromo-1-(3-bromophenyl)ethanone (**S13**).

M.p.: 49.0 - 51.0 °C [EtOH] (lit. M.p.: 51-52 °C).12 White crystalline solid material.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, 1H, J(2,4) = 2.1 Hz, J(2,6) = 1.7 Hz, H-C(2)), 7.91 (ddd, 1H, J(5,6) = 7.9 Hz, J(2,6) = 1.7 Hz, J(4,6) = 1.0 Hz, H-C(6)), 7.74 (ddd, 1H, J(4,5) = 8.1 Hz, J(2,4) = 2.1 Hz, J(4,6) = 1.0 Hz, H-C(4)), 7.38 (dd, 1H, J(4,5) = 8.1 Hz, J(5,6) = 7.9 Hz, H-C(5)), 4.41 (s, 2H, -$COCH_2$Br).

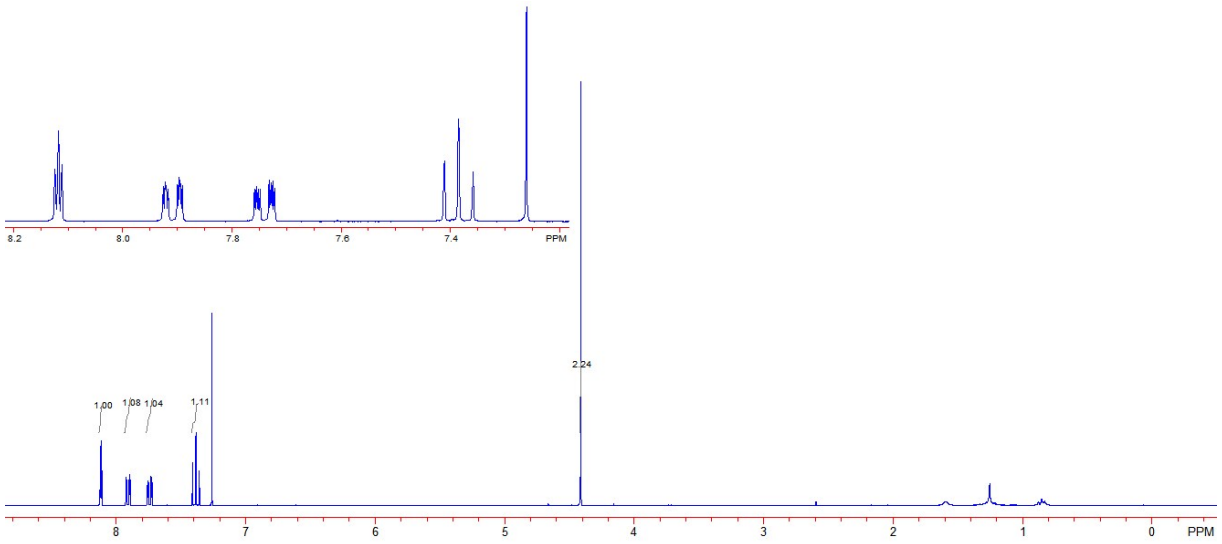


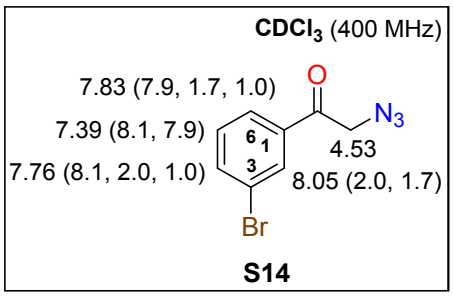
Fig. 14. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of compound **S13**.

Synthesis of azidoacetophenone S14

Novelty: Synthesis of **S14** was described in the literature with 91 % yield.[13] ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectral analysis were also published.[13]

To a solution of 500 mg (1.80 mmol, 1.00 mol eq) 2-bromo-1-(3-bromophenyl)ethanone (**S13**) in 5.0 ml of MeOH abs, 234.2 mg (3.60 mmol, 2.00 mol eq) NaN_3 was added portionwise and the reaction mixture was stirred for 5 h at 35 °C under Ar. After consumption of starting material **S13** (TLC analysis) the mixture was cooled down to rt and evaporated under vacuum. A solid residue was partitioned between 30 mL of EtOAc and 30 mL of water, organic layer was separated and water layer extracted with 3 × 5.0 ml EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by crystallization from a mixture EtOH / pentane to yield 380 mg (1.58 mmol, 88 %) of 2-azido-1-(3-bromophenyl)ethanone (**S14**).

M.p.: 71.0-74.0 °C [EtOH / pentane] (lit. M.p.: 51-53 °C [Hex / EtOAc]).13 Yellow crystalline solid material.



^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, 1H, J(2,4) = 2.0 Hz, J(2,6) = 1.7 Hz, H-C(2)), 7.83 (ddd, 1H, J(5,6) = 7.9 Hz, J(2,6) = 1.7 Hz, J(4,6) = 1.0 Hz, H-C(6)), 7.76 (ddd, 1H, J(4,5) = 8.1 Hz, J(2,4) = 2.0 Hz, J(4,6) = 1.0 Hz, H-C(4)), 7.39 (dd, 1H, J(4,5) = 8.1 Hz, J(5,6) = 7.9 Hz, H-C(5)), 4.53 (s, 2H, -$COCH_2$N3).

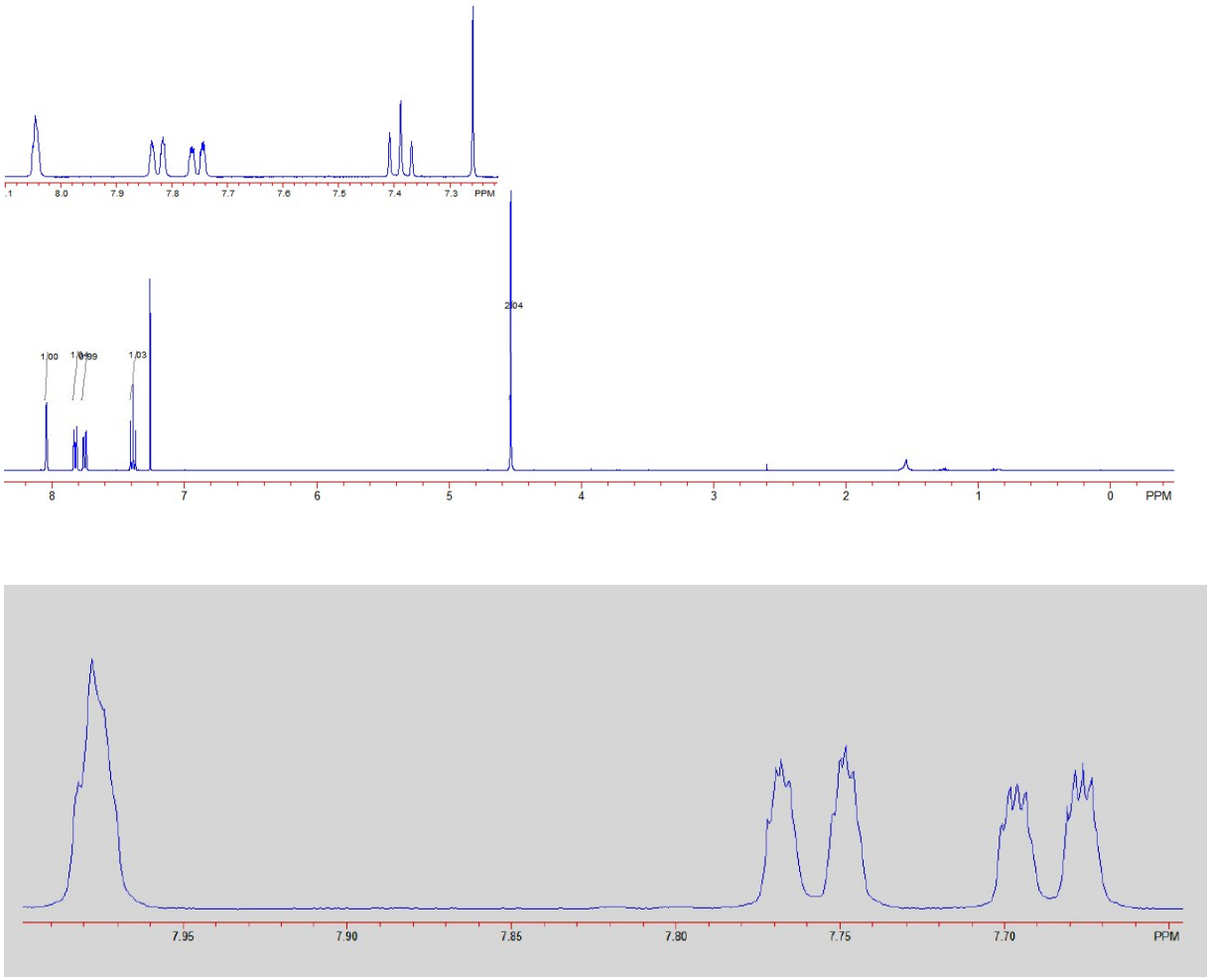


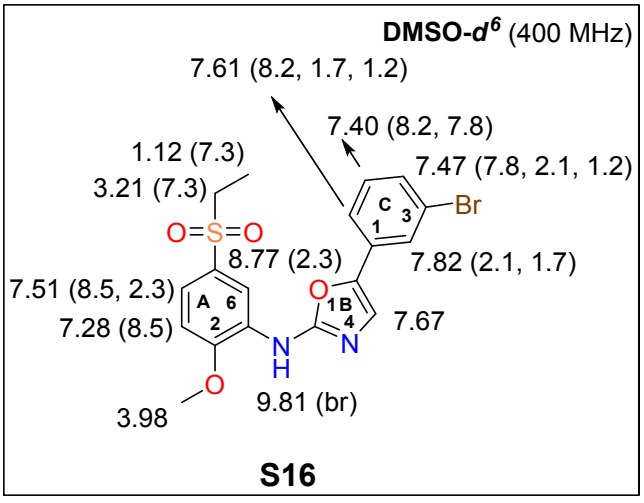
Fig. 15. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of compound **S14** and its expanded aromatic part to show also a presence of small interactions.

Synthesis of 5-(bromophenyl)oxazol-2-amine S16

Novelty: Synthesis of compound **S16** was previously described in the literature in 35 % yield. ^{1}H-, ^{13}C-NMR, IR spectral analysis and elemental analysis were previously published in the literature.[9]

A mixture of 930 mg (3.90 mmol, 1.00 mol eq) of azide **S14**, 1.00 g (3.90 mmol, 1.00 mol eq) of 4-(ethylsulfonyl)-2-isothiocyanato-1-methoxybenzene (**S15**)[9] and 1.00 g (3.90 mmol, 1.00 mol eq) of PPh_3 were dissolved in 25 ml of dioxane abs under Ar. The obtained solution was placed into the preheated 95 °C oil bath for 4 h. After consumption of the starting material **S14** (TLC analysis), the mixture was evaporated and a solid resting material partitioned with 25 ml EtOAc and 4 × 5 ml of brine (sat aq solution of NaCl). The organic layer was dried over Na_2SO_4, filtrated and evaporated under reduced pressure. The crude product was purified by Flash liquid chromatography (Hex / EtOAc, 1 / 3) and crystallized from Hex / EtOAc to yield 1.30 g (3.00 mmol, 76 %) of 5-(3-bromophenyl)-*N*-(5-(ethylsulfonyl)-2-methoxyphenyl) oxazol-2-amine (**S16**).

M.p.: 177-178 °C [Hex / EtOAc]. (lit. M.p.: 182-183 °C [Hex / EtOAc]).[9] Pale yellow solid material.



^{1}H-NMR (400 MHz, DMSO-d^6): δ 9.81 (br s, 1H, -NH-), 8.77 (d, 1H, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(6)), 7.82 (dd, 1H, $J(C_2,C_4)$ = 2.1 Hz, $J(C_2,C_6)$ = 1.7 Hz, H-C_C(2)), 7.67 (s, 1H, H-C_B(4)),

7.61 (ddd, 1H, $J(C_5,C_6)$ = 8.2 Hz, $J(C_2,C_6)$ = 1.7 Hz, $J(C_4,C_6)$ = 1.2 Hz, H-C_C(6)), 7.51 (dd, 1H, $J(A_3,A_4)$ = 8.5 Hz, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(4)), 7.47 (ddd, 1H, $J(C_4,C_5)$ = 7.8 Hz, $J(C_2,C_4)$ = 2.1 Hz, $J(C_4,C_6)$ = 1.2 Hz, H-C_C(4)), 7.40 (dd, 1H, $J(C_5,C_6)$ = 8.2 Hz, $J(C_4,C_5)$ = 7.8 Hz, H-C_C(5)), 7.28 (d, 1H, $J(A_3,A_4)$ = 8.5 Hz, H-C_A(3)), 3.98 (s, 3H, -OCH_3), 3.21 (q, 2H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2C\underline{H}_2CH_3$), 1.12 (t, 3H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2CH_2C\underline{H}_3$).

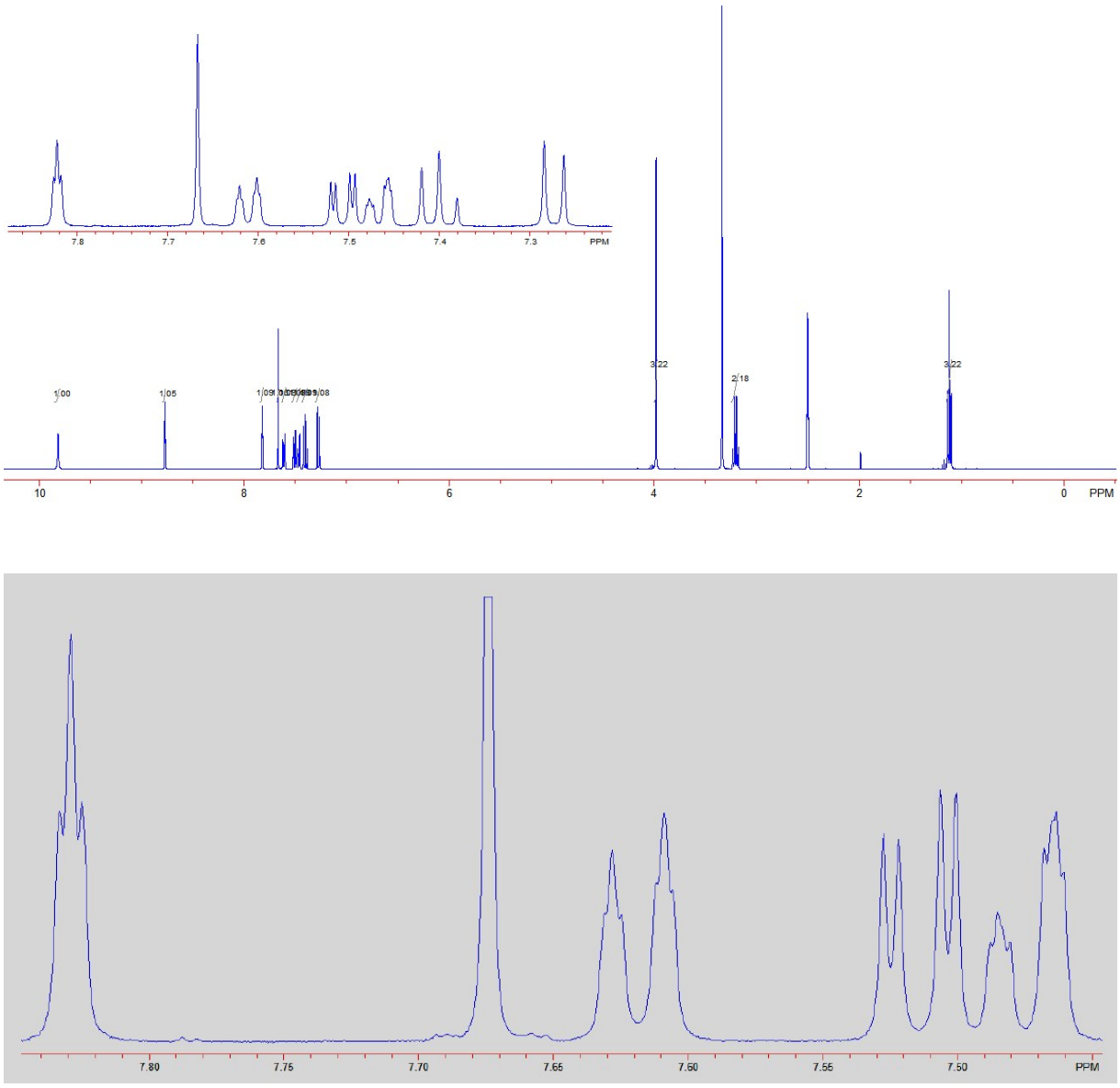


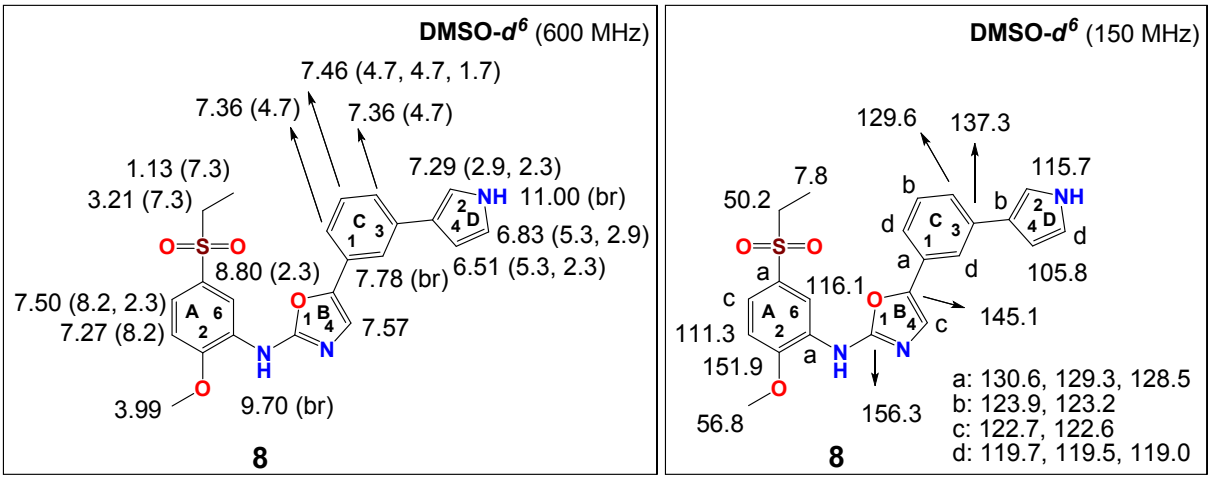
Fig. 16. ^{1}H-NMR (400 MHz, DMSO-d^6) spectrum of compound **S16** and its expanded aromatic part to show also a presence of small interactions.

Synthesis of 5-(pyrrolylphenyl)oxazol-2-amine 8

Novelty: Synthesis of compound **8** has not been previously described in the literature.

A mixture of 60.0 mg (0.14 mmol, 1.00 mol eq) of **S16**, 71.8 mg (0.21, 1.50 mol eq) of pinacolboronate **S17** and 15.8 mg (0.01 mmol, 0.10 mol eq) $Pd(PPh_3)_4$ was placed in a sealed tube and suspended in 5.0 ml DMF and 29.0 mg (0.27 mmol, 2.00 mol eq) Na_2CO_3 in 2.0 ml water. Then the suspension was deoxygenated by Ar (needle bubbling through a mixture) for 10 min, sealed, stirred and heated at 100 °C for 15 h. The reaction was cooled down to rt, diluted with 10 ml of EtOAc and extracted by 3 × 5.0 ml of brine. The organic layer was separated, dried over Na_2SO_4, filtrated and evaporated under reduced pressure. The crude product was purified by Flash liquid chromatography (Hex / EtOAc, 1 / 9) and triturated with Hex / EtOAc to yield 45.0 mg (0.11 mmol, 78 %) of 5-(3-(1*H*-pyrrol-3-yl)phenyl)-*N*-(5-(ethylsulfonyl)-2-methoxyphenyl)oxazol-2-amine (**8**).

M.p.: 230-250 °C (decomp.) [Hex / EtOAc]. Pale yellow solid material.



^{1}H-NMR (300 MHz, DMSO-d^6): δ 11.00 (br s, 1H, -NH- from pyrrol), 9.70 (br s, 1H, -NH-), 8.80 (d, 1H, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(6)), 7.78 (br s, 1H, H-C_C(2)), 7.57 (s, 1H, H-C_B(4)), 7.50 (dd, 1H, $J(A_3,A_4)$ = 8.2 Hz, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(4)), 7.46 (ddd, 1H, $J(C_4,C_5)$ = $J(C_5,C_6)$ = 4.7 Hz, $J(C_2,C_5)$ = 1.7 Hz, H-C_C(5)), 7.36 (d, 2H, $J(C_4$ or $C_6,C_5)$ = 4.7 Hz, H-C_C(4 or 6)), 7.29 (dd, 1H, $J(D_2,D_5)$ = 2.9 Hz, $J(D_2,D_4)$ = 2.3 Hz, H-C_D(2)), 7.27 (d, 1H, $J(A_3,A_4)$ = 8.2 Hz, H-C_A(3)), 6.83 (dd, 1H, $J(D_4,D_5)$ = 5.3 Hz, $J(D_2,D_5)$ = 2.9 Hz, H-C_D(5)), 6.51 (dd, 1H, $J(D_4,D_5)$

= 5.3 Hz, $J(D_2,D_4)$ = 2.3 Hz, H-C_D(4)), 3.99 (s, 3H, -OCH_3), 3.21 (q, 2H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2C\underline{H}_2CH_3$), 1.13 (t, 3H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2CH_2C\underline{H}_3$).

^{13}C-NMR (150 MHz, DMSO-*d*^{6}): δ 156.3 (C_B(2)), 151.9 (C_A(2)), 145.1 (C_B(5)), 137.3 (C_C(3)), 130.6, 129.3, 128.5, 129.6 (C_C(4)), 123.9, 123.2, 122.7, 122.6, 119.7, 119.5, 119.0, 116.1 (C_A(6)), 115.7 (C_D(2)), 111.3 (C_A(3)), 105.8 (C_D(4)), 56.8 (-OCH_3), 50.2 (-$SO_2\underline{C}H_2CH_3$), 7.8 (-$SO_2CH_2\underline{C}H_3$). The exact carbon assignments are based on HSQC 2D NMR spectrum analysis.

IR (neat, ν/cm^{-1}): 3415 (w -NH-), 3348 (w -NH-), 1613 (m), 1577 (s), 1529 (m), 1501 (w), 1488 (w), 1433 (m), 1347 (w), 1294 (m), 1259 (m -OCH_3), 1227 (w), 1185 (w), 1171 (w), 1137 (m), 1122 (s -SO_2-), 1074 (m), 1047 (m), 1018 (m), 968 (w), 925 (w), 888 (w), 880 (w), 813 (m), 794 (w), 779 (s -SO_2-), 732 (s), 713 (s), 684 (s), 656 (m), 635 (w).

ESI-MS *m/z*: positive mode 424 $[M + H]^+$, negative mode (100 %), 422 $[M - H]^-$ (100 %).

Anal. calcd for $C_{22}H_{21}N_3O_4S$ (423.48): C, 62.40; H, 5.00; N, 9.92; S, 7.57; found: C, 62.13; H, 5.11; N, 9.62; S, 7.36.

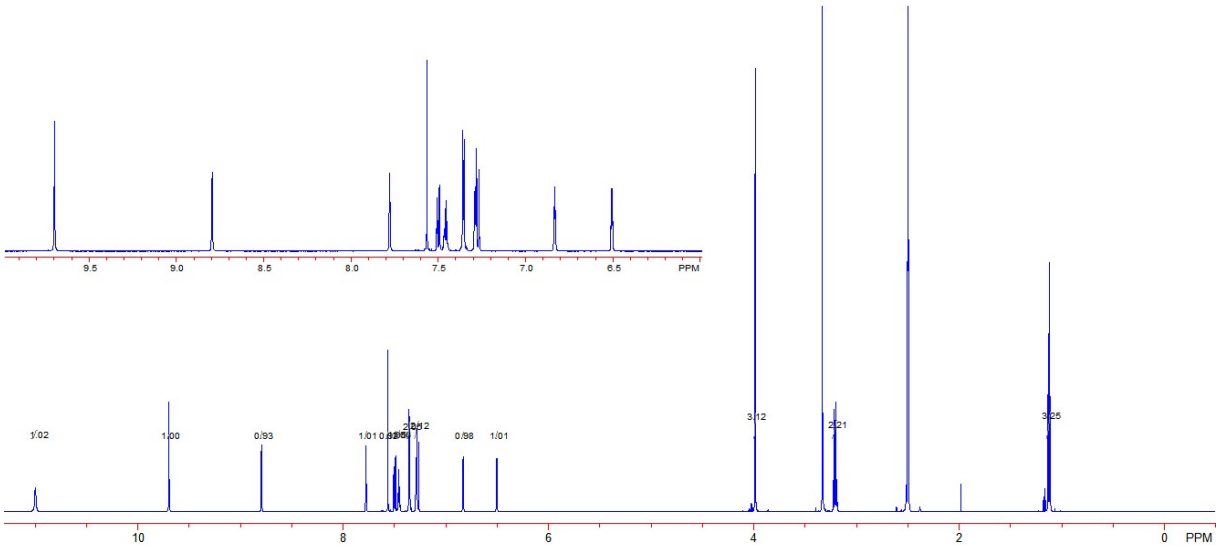


Fig. 17. ^{1}H-NMR (300 MHz, DMSO-*d*^{6}) spectrum of compound **8**.

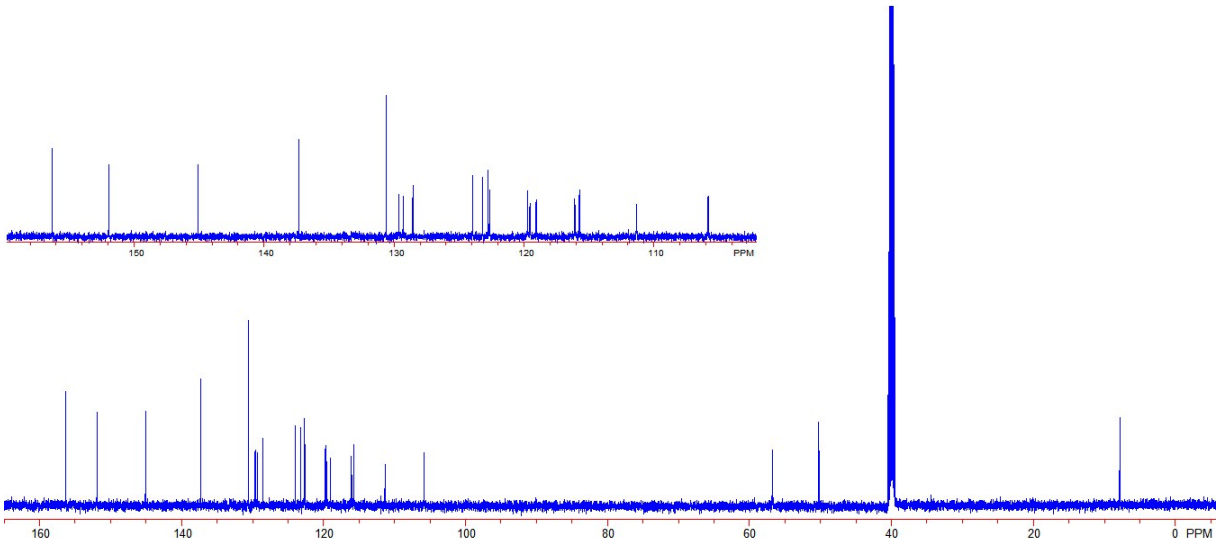
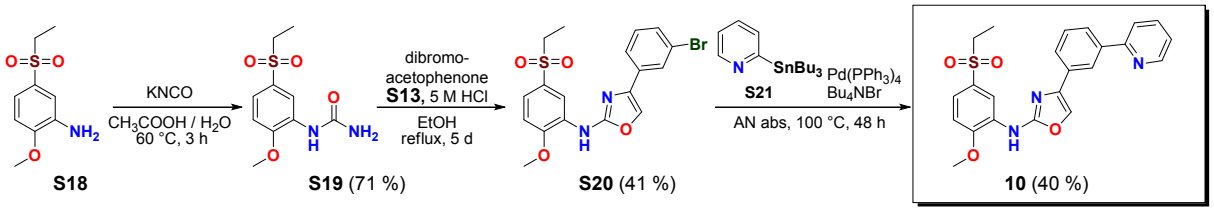


Fig. 18. ^{13}C-NMR (150 MHz, DMSO-d^6) spectrum of compound **8**.

Preparation of 4-(pyridinyphenyl)oxazol-2-amine 10

Compound **S18** was prepared according a procedure described in the literature Murár et. al.[14]



Scheme 6. Synthetic pathway to oxazol-2-amine **10**.

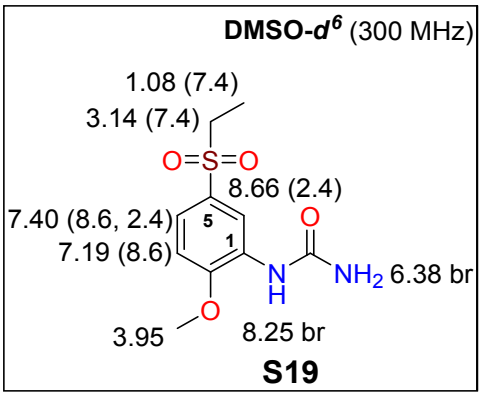
Synthesis of *N*-arylurea S19

Novelty: The synthesis of compound **S19** (58 % yield), ^{1}H-NMR, ^{13}C-NMR, IR spectral analysis were previously published in the literature.[15]

To solution of 100.0 mg (0.46 mmol, 1.00 mol eq) aniline **S18** in 2.0 ml of CH_3COOH and 4.0 ml of H_2O, another solution of 75.4 mg (0.93, 2.00 mol eq) KNCO in 1.0 ml of H_2O was added within 10min and the resulting mixture heated at 60 °C for 3 h. Then the reaction was poured into a mixture of ice and H_2O and neutralized by $NaHCO_3$ (sat aq solution). The water layer was extracted by EtOAc (3 × 10 ml), the organic phase separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by crystallization

from H_2O / EtOH yielded 85.0 mg (0.33 mmol, 71 %) of 1-(5-(ethylsulfonyl)-2-methoxyphenyl)urea (**S19**).

M.p.: 196.0 – 197.0 °C [water / EtOH]. (Lit. M.p.: 198 - 199 °C [EtOAc]). Light brown solid material.



^{1}H-NMR (300 MHz, DMSO-d^6): δ 8.66 (d, 1H, J(4,6) = 2.4 Hz, H-C(6)), 8.25 (br s, 1H, -N<u>H</u>CONH$_2$), 7.40 (dd, 1H, J(3,4) = 8.6 Hz, J(4,6) = 2.4 Hz, H-C(4)), 7.19 (d, 1H, J(3,4) = 8.6 Hz, H-C(3)), 6.38 (br s, 2H, -NHCON<u>H</u>$_2$), 3.95 (s, 3H, -OCH$_3$), 3.14 (q, 2H, J(CH$_2$CH$_3$) = 7.4 Hz, -COOC<u>H</u>$_2$CH$_3$), 1.08 (t, 3H, J(CH$_2$,CH$_3$) = 7.4 Hz, -COOCH$_2$C<u>H</u>$_3$).

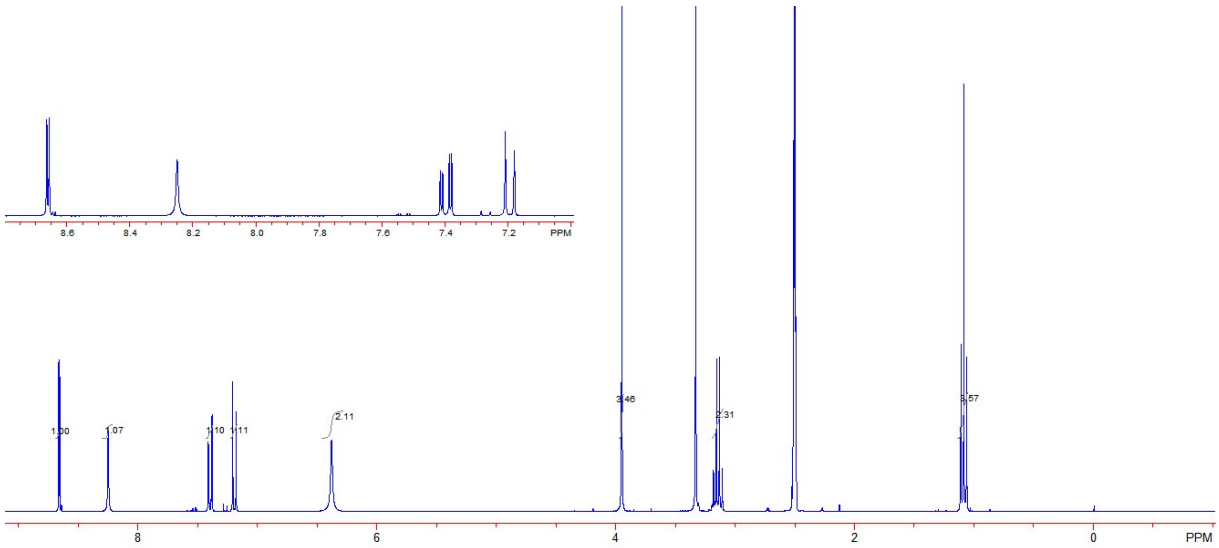


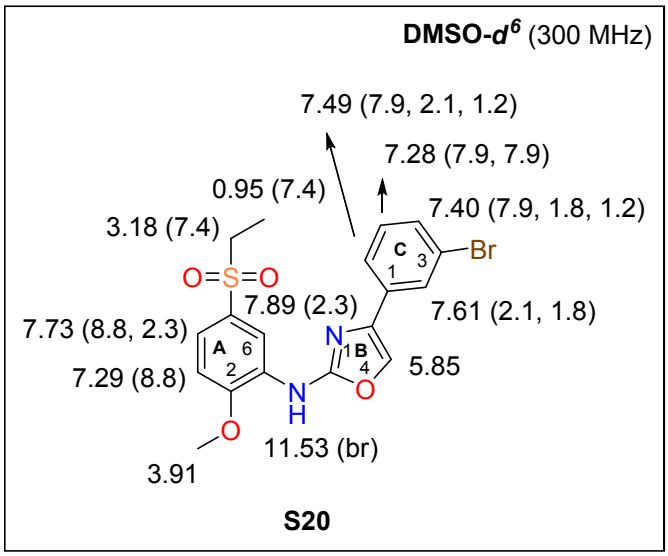
Fig. 19. ^{1}H-NMR (300 MHz, DMSO-d^6) spectrum of compound **S19**.

Synthesis of 4-(bromophenyl)oxazol-2-amine S20

Novelty: The synthesis of compound **S20** in 47 % yield, ^{1}H-NMR, ^{13}C-NMR, IR spectral analysis were previously published in the literature.[15]

To a solution of 1.86 g (7.20 mmol, 1.00 mol eq) urea **S19** and 2.00 g (7.20 mmol, 1.00 mol eq) of acetophenone **S13** in 30 ml of EtOH, 1.5 ml (3.6 mmol, 0.5 mol eq) of 5 M HCl was added. The reaction was refluxed for 3 d and afterwards the second portion of 1.00 g (3.6 mmol, 0.50 mol eq) of acetophenone **S13** added and refluxed for another 2 d. The mixture was concentrated under vacuum and the solid residue dissolved in 30 ml EtOAc. Organic phase was extracted with 2 × 10 ml $NaHCO_3$ (saturated aq solution) and 10 ml of water. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by Flash liquid chromatography (Hex / EtOAc, 1 / 3) yielding 1.30 g (3.00 mmol, 41 %) of 4-(3-bromophenyl)-*N*-(5-(ethylsulfonyl)-2-methoxyphenyl)oxazol-2-amine (**S20**).

M.p.: 217.0 - 218.0 °C [Hex / EtOAc]. (Lit. M.p.: 206 - 208 °C [EtOH]).[15] White solid material.



^{1}H-NMR (300 MHz, DMSO-d^6): δ 11.53 (br s, 1H, NH), 7.89 (d, 1H, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(6)), 7.73 (dd, 1H, $J(A_3,A_4)$ = 8.8 Hz, $J(A_4,A_6)$ = 2.3 Hz, H-C_A(4)), 7.61 (dd, 1H, $J(C_2,C_6)$ = 2.1 Hz, $J(C_2,C_4)$ = 1.7 Hz, H-C_C(2)), 7.49 (ddd, 1H, $J(C_5,C_6)$ = 7.9 Hz, $J(C_2,C_6)$ = 2.1 Hz, $J(C_4,C_6)$ = 1.2 Hz, H-C_C(6)), 7.40 (ddd, 1H, $J(C_4,C_5)$ = 7.9 Hz, $J(C_2,C_4)$ = 1.8 Hz, $J(C_4,C_6)$ =

1.2 Hz, H-C_C(4)), 7.29 (d, 1H, $J(A_3,A_4)$ = 8.8 Hz, H-C_A(3)), 7.28 (dd, 1H, $J(C_5,C_6)$ = 7.9 Hz, $J(C_4,C_5)$ = 7.9 Hz, H-C_C(5)), 5.85 (s, 1H, H-C_B(4)), 3.91 (s, 3H, -OCH_3), 3.18 (q, 2H, $J(CH_2,CH_3)$ = 7.4 Hz, -$SO_2C\underline{H}_2CH_3$), 0.95 (t, 3H, $J(CH_2,CH_3)$ = 7.4 Hz, -$SO_2CH_2C\underline{H}_3$).

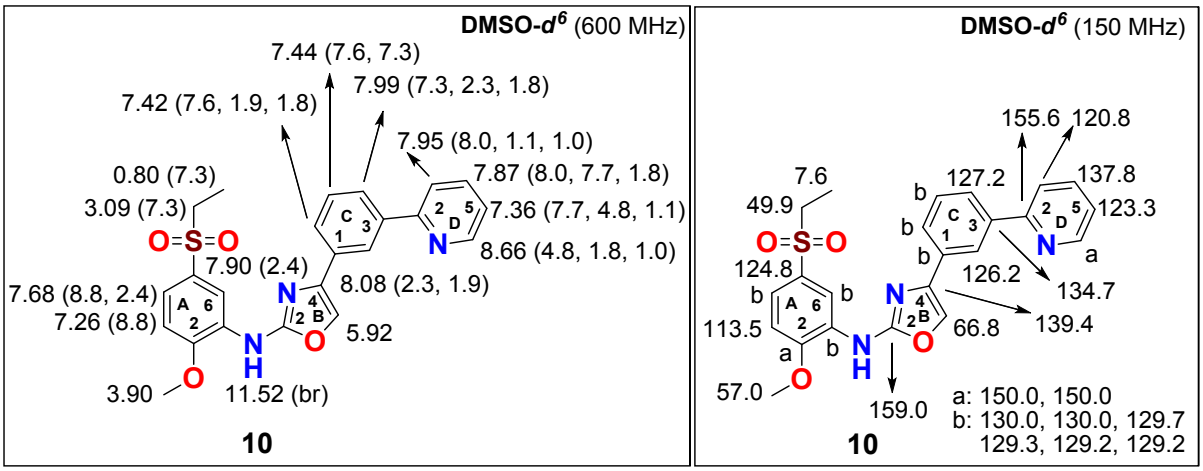
Fig. 20. ^{1}H-NMR (300 MHz, DMSO-d^6) spectrum of compound **S20**.

Synthesis of 4-(pyridinylphenyl)oxazol-2-amine 10

Novelty: Synthesis of compound **10** has not been previously described.

A mixture of 50.0 mg (0.11 mmol, 1.00 mol eq) **S20**, 13.2 mg (0.01 mmol, 0.10 mol eq) of $Pd(PPh_3)_4$ and 80.1 mg (0.25 mmol, 2.18 mol eq) of Bu_4NBr were placed in a glass tube and suspended in 3.5 ml of MeCN abs. Then 151.1 mg (0.41, 3.60 mol eq) of tributylstanyl reagent **S21** (Sigma-Aldrich) was added, the glass tube sealed and the mixture stirred at 100 °C for 48 h. Afterwards the reaction was cooled down to rt, diluted with 10 ml EtOAc, quenched with 10 ml of 1.00 M KF aq. solution and stirred for 3 h. The organic layer was separated, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The crude product was purified by Flash liquid chromatography (Hex / EtOAc, 1 / 3) and triturated by Hex / EtOAc yielding 20.0 mg (0.05 mmol, 40 %) of *N*-(5-(ethylsulfonyl)-2-methoxyphenyl)-4-(3-(pyridin-2-yl)) oxazol-2-amine (**10**).

M.p.: 138.0 - 140.0 °C [H / EtOAc]. White solid compound.



^{1}H-NMR (600 MHz, DMSO-d^6): δ 11.52 (br s, 1H, -NH-), 8.66 (ddd, 1H, $J(D_5,D_6)$ = 4.8 Hz, $J(D_4,D_6)$ = 1.8 Hz, $J(D_3,D_6)$ = 1.0 Hz, H-C_D(6)), 8.08 (dd, 1H, $J(C_2,C_4)$ = 2.3 Hz, $J(C_2,C_6)$ = 1.9 Hz, H-C_C(2)), 7.99 (ddd, 1H, $J(C_4,C_5)$ = 7.3 Hz, $J(C_2,C_4)$ = 2.3 Hz, $J(C_4,C_6)$ = 1.8 Hz, H-C_C(4)), 7.95 (ddd, 1H, $J(D_3,D_4)$ = 8.0 Hz, $J(D_3,D_5)$ = 1.1 Hz, $J(D_3,D_6)$ = 1.0 Hz, H-C_D(3)), 7.90 (d, 1H, $J(A_4,A_6)$ = 2.4 Hz, H-C_A(6)), 7.87 (ddd, 1H, $J(D_3,D_4)$ = 8.0 Hz, $J(D_4,D_5)$ = 7.7 Hz, $J(D_4,D_6)$ = 1.8 Hz, H-C_D(4)), 7.68 (dd, 1H, $J(A_3,A_4)$ = 8.8 Hz, $J(A_4,A_6)$ = 2.4 Hz, H-C_A(4)), 7.44 (dd, 1H, $J(C_5,C_6)$ = 7.6 Hz, $J(C_4,C_5)$ = 7.3 Hz, H-C_C(5)), 7.42 (ddd, 1H, $J(C_5,C_6)$ = 7.6 Hz, $J(C_2,C_6)$ = 1.9 Hz, $J(C_4,C_6)$ = 1.8 Hz, H-C_C(6)), 7.36 (ddd, 1H, $J(D_4,D_5)$ = 7.7 Hz, $J(D_5,D_6)$ = 4.8 Hz, $J(D_3,D_5)$ = 1.1 Hz, H-C_D(5)), 7.26 (d, 1H, $J(A_3,A_4)$ = 8.8 Hz, H-C_A(3)), 5.92 (s, 1H, H-C_B(4)), 3.90 (s, 3H, -OCH_3), 3.09 (q, 2H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2C\underline{H}_2CH_3$), 0.80 (t, 3H, $J(CH_2,CH_3)$ = 7.3 Hz, -$SO_2CH_2C\underline{H}_3$).

^{13}C-NMR (150 MHz, DMSO-d^6): δ 159.0 (C_B(2)), 155.6 (C_D(2)), 2 × 150.0, 139.4 (C_B(4)), 137.8 (C_D(4)), 134.7 (C_C(3)), 2 × 130.0, 129.7, 129.3, 2 × 129.2, 127.2 (C_C(4)), 126.2 (C_C(2)), 124.8 (C_A(5)), 123.3 (C_D(5)), 120.8 (C_D(3)), 113.5 (C_A(3)), 66.8 (C_B(5)), 57.0 (-OCH_3), 49.9 (-$SO_2C\underline{H}_2CH_3$), 7.6 (-$SO_2CH_2C\underline{H}_3$). The exact carbon assignments are based on HSQC 2D NMR spectrum analysis.

IR (neat, ν/cm^{-1}): 2925, (w, -NH-), 2704 (w), 1771 (w), 1721 (s), 1593 (w), 1567 (w), 1504 (m, aromatics), 1477 (w), 1438 (m, aromatics), 1415 (m, aromatics), 1388 (m), 1307 (m, -SO_2-), 1262 (m, -SO_2-), 1182 (w), 1136 (s), 1091 (w), 1040 (w), 1018 (m), 1005 (w), 923 (w), 864 (w), 824 (w), 800 (w), 782 (m), 766 (m), 757 (m), 731 (s), 716 (m), 696 (m), 631 (m).

Anal. calcd for $C_{23}H_{21}N_3O_4S$ (435.50): C, 63.43; H, 4.86; N, 9.65; S, 7.36; found: C, 63.13; H, 4.68; N, 9.59; S, 7.34.

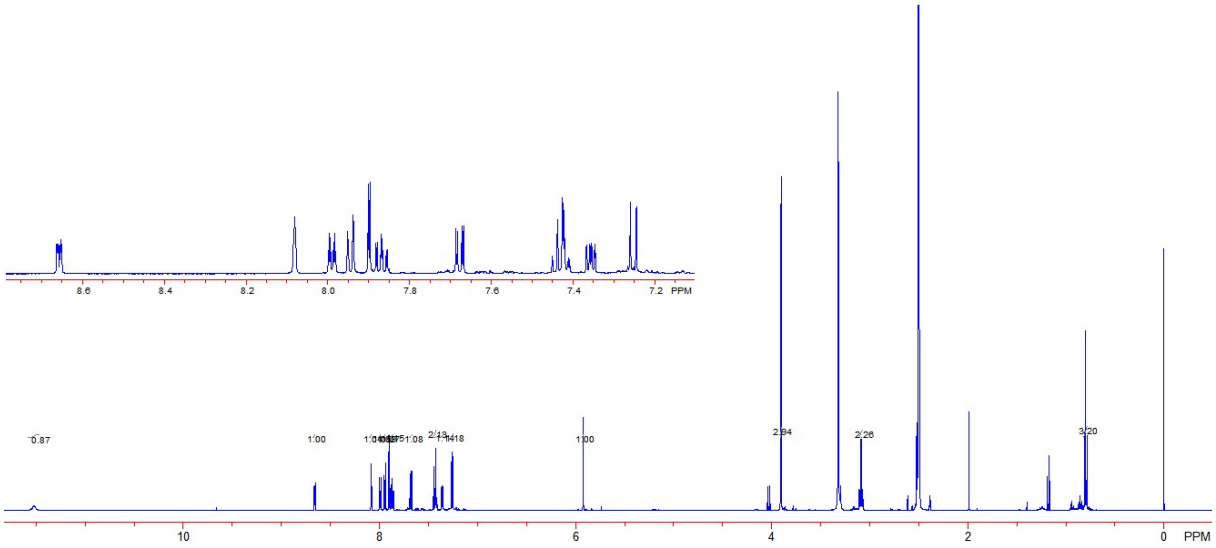


Fig. 21. ^{1}H-NMR (600 MHz, DMSO-d^6) spectrum of compound **10**.

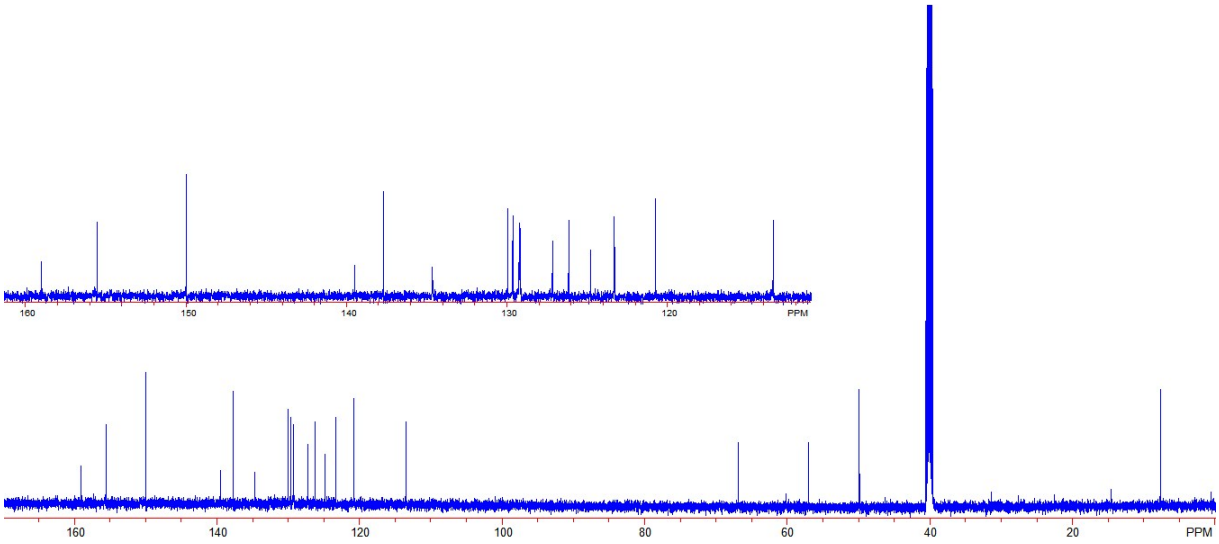


Fig. 22. ^{13}C-NMR (150 MHz, DMSO-d^6) spectrum of compound **10.**

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