Electronic Supplementary Information (ESI)

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

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Contents

1. Synthesis of quinones 1-5 ...................................................................................................2
Preparation of (+)-(S\textsubscript{S})-1 .........................................................................................3
Characteristics of quinone (+)-(S\textsubscript{S})-2a ........................................................................7
Characteristics of racemic quinone 2b .......................................................................................9
Preparation of quinone (+)-(S\textsubscript{S})-3 .............................................................................10
Preparation of (+)-(S\textsubscript{S})-4 ..........................................................................................14
Preparation of (+)-(S\textsubscript{S})-5 .......................................................................................21
2. Availability of VEGFR2 TKIs 6,7 and 9..........................................................................25
3. Synthesis of VEGFR2 TKIs 8 and 10 ...............................................................................26
Preparation of 5-(pyrrolylphenyl)oxazol-2-amine 8 .............................................................26
Preparation of 4-(pyridinyphenyl)oxazol-2-amine 10 ..........................................................34
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.$^1,2$

![Scheme 1](image)

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<sub>S</sub>)-1

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

\[
\begin{align*}
&\text{FW: } 275.14 \text{ g mol}^{-1} \\
&C_{11}H_{15}O_3\text{Br}
\end{align*}
\]

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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> and the combined organic phases were washed with brine (2×100 mL), dried over MgSO<sub>4</sub>, filtered off and evaporated to give 14.5 g of crude which was flash chromatographed on silica gel (hexane / Et<sub>2</sub>O, 3 / 2) to afford 12.2 g (44.3 mmol, 91%) of S3 as white crystals.

**R<sub>f</sub>:** 0.60 (cyclohexane / Et<sub>2</sub>O, 3 / 1).

**M.p.:** 63 °C.

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): δ (ppm) 6.39 (s, 1H, C<sup>4</sup>H), 4.11 (q, 2H, J = 7.0 Hz, C<sup>7</sup>H<sub>2</sub>), 3.79 (s, 3H, C<sup>9</sup>H<sub>3</sub>), 3.78 (s, 3H, C<sup>10</sup>H<sub>3</sub>), 2.24 (s, 3H, C<sup>6</sup>H<sub>3</sub>), 1.41 (t, 3H, J = 7.0 Hz, C<sup>8</sup>H<sub>3</sub>).

**<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>): δ (ppm) 154.2 (C<sub>q</sub>), 151.3 (C<sub>q</sub>), 140.3 (C<sub>q</sub>), 121.5 (C<sub>q</sub>), 119.2 (C<sub>q</sub>-Br), 96.7 (C<sup>4</sup>H), 66.7 (C<sup>7</sup>H<sub>2</sub>), 60.5. (-OCH<sub>3</sub>), 56.4 (-OCH<sub>3</sub>), 15.3 (C<sup>11</sup>H<sub>3</sub>), 9.4 (C<sup>8</sup>H<sub>3</sub>).
2,5-Dimethoxy-3-ethoxy-6-methyl-1 [(S)-4-methylbenzenesulfinyl]benzene
(-)-(S₅)-S₅

FW: 334.20 g mol⁻¹
C₁₈H₂₀O₄S

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 NH₄Cl (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 Et₂O (100 mL) delivered 4.98 g of (-)-(SS)-S₅ as white needles (14.9 mmol, 82 %).

M.p.: 134°C.

[α]D²⁰ -167.1 (c = 1.21, acetone).

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.34 (dd, 4H, J = 8.0 Hz, 2 × C¹⁰H and 2 × C¹¹H), 5.96 (s, 1H, C⁴H), 4.08 (q, 2H, J = 7.0 Hz, C⁷H₂), 3.84 (s, 3H, -OCH₃), 3.78 (s, 3H, -OCH₃), 2.51 (s, 3H, C¹³H₃), 2.39 (s, 3H, C⁶H₃), 1.49 (t, 3H, J = 7.0 Hz, C⁸H₃).

¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 154.6 (C₉), 151.0 (C₉), 141.7 (C₉), 141.0 (C₈), 139.3 (C₈), 137.5 (C₈), 129.6 (2 × C¹¹H), 124.7 (2 × C¹⁰H), 119.7 (C₉), 100.9 (C⁴H), 65.7 (C⁷H₂), 61.7 (-OCH₃), 56.2 (-OCH₃), 21.2 (-CH₃), 9.9 (-CH₃), 9.4 (-CH₃).
**Microanalysis:** for C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>S, 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 (++)-\((S)_5\)-1**

\[
\begin{align*}
\text{FW: } & 304.18 \text{ g mol}^{-1} \\
C_{16}H_{16}O_4S
\end{align*}
\]

Into a 500 mL flask, 3.00 g of sulfoxide (++)-(S)<sub>5</sub>-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<sub>4</sub>, filtered off and evaporated to give 2.325 g (7.64 mmol, 85 %) of (++)-\((S)_5\)-1 as light orange needles after crystallization in hot methanol.

**M.p.:** 142.0 °C.

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

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): \(\delta\) (ppm) 7.47 (dd, 4H, A<sub>2</sub>B<sub>2</sub>, \(J = 8.0\) Hz, Dn=103 Hz, 2 \(\times \) C<sup>10</sup>H and 2 \(\times \) C<sup>11</sup>H), 5.93 (s, 1H, C<sup>4</sup>H), 3.97 (q, 2H, \(J\) = 7.0 Hz, C<sup>7</sup>H<sub>2</sub>), 2.51 (s, 3H, C<sup>13</sup>H<sub>3</sub>), 2.4 (s, 3H, C<sup>6</sup>H<sub>3</sub>), 1.46 (t, 3H, \(J\) = 7.0 Hz, C<sup>8</sup>H<sub>3</sub>).

**<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>): \(\delta\) (ppm) 185.5 (C=O), 179.4 (C=O), 157.2 (C<sub>q</sub>), 148.1 (C<sub>q</sub>), 144.6 (C<sub>q</sub>), 141.8 (C<sub>q</sub>), 139.6 (C<sub>q</sub>), 130.2 (2 \(\times \) C<sup>10</sup>H), 125.1 (2 \(\times \) C<sup>9</sup>H), 108.3 (C<sup>4</sup>H), 65.7 (C<sup>7</sup>H<sub>2</sub>), 21.5 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 9.5 (CH<sub>3</sub>).
Microanalysis: for C\textsubscript{16}H\textsubscript{16}O\textsubscript{4}S, calculated: C: 63.14, H: 5.30, O: 21.03; found: C: 63.21, H: 5.39, O: 21.20.

**Fig. 1.** \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) spectrum of compound (+)-(S\textsubscript{3})-1.

**Fig. 2.** \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) spectrum of compound (+)-(S\textsubscript{3})-1.
Characteristics of quinone (+)-(S$_S$)-2a

**FW**: 290.33 g mol$^{-1}$

**C$_{15}$H$_{14}$O$_4$S**

**M.p.:** 130 - 132 °C.

$[\alpha]_{D}^{20}$: +469 ° (c = 1.0, CH$_2$Cl$_2$).

**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$_2$)-2a.
Characteristics of racemic quinone 2b

FW: 290.33 g mol\(^{-1}\)

C\(_{15}\)H\(_{14}\)O\(_4\)S

M.p.: 130.0 - 130.5 °C.

Fig. 5. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) spectrum of racemic compound 2b.
Preparation of quinone (+)-(S\textsubscript{S})-3

Compound (+)-(S\textsubscript{S})-3 has been prepared from 1,4-dimethoxybenzene in two reaction steps according the Scheme 2.

Scheme 2. Synthesis of quinone (+)-(S\textsubscript{S})-3.
(−)-(S)-1,4-Dimethoxy-2-(p-tolylsulfinyl)benzene (−)-(S(S)S)-S5b

\[
\text{FW: } 276.38 \text{ g mol}^{-1}
\]

\[
\text{C}_{15}\text{H}_{16}\text{O}_{3}\text{S}
\]

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)S)-S5b) as a white solid.

\(R_f\): 0.54 (cyclohexane / EtOAc, 5 / 5).

\([\alpha]_{D}^{20}\): -21 ° (c = 1.0, CHCl\(_3\)).

\textbf{M.p.:} 75 - 77 °C.

\(\text{\textsuperscript{1}H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (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 ($C^5_4$), 149.7 ($C^5_3$), 142.4 ($C^8_4$), 141.5 ($C^11_3$), 134.1 ($C^2_4$), 129.8 (2 × $C^{10}_3$), 125.5 (2 × $C^9_3$), 118.1 ($C^5_3$), 112.7 ($C^6_3$), 108.7 ($C^3_3$), 56.3 ($C^7_3$), 56.1 ($C^{13}_3$), 21.5 ($C^{12}_3$).

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

$(+)-(S)$-2-(p-Tolylsulfinyl)cyclohexa-2,5-diene-1,4-dione $(+)-(S)_3$-3

This molecule $(+)-(S)_3$-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 $(−)-(S)_3$-$S_5b$ 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 $(+)-(S)_3$-3. Recrystallization from hot diethyl ether gave blood red needles.

$R_f$: 0.63 (cyclohexane / EtOAc, 5 / 5).

$[a]_D^{20}$: $+1011$° (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 × $C^8_3$), 7.43 (d, 1H, $J = 2.5$ Hz, $C^3_3$), 7.29 (d, 2H, $J = 8.1$ Hz, 2 × $C^9_3$), 6.79 (dd, 1H, $J = 10.1$; 2.5 Hz, $C^5_3$), 6.71 (d, 1H, $J = 10.1$ Hz, $C^6_3$), 2.39 (s, 3H, $C^{11}_3$).
\(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 185.2 (C\(_4\)), 183.71 (C\(_5\)), 155.4 (C\(_6\)), 143.1 (C\(_7\)), 138.3 (C\(_8\)), 137.5 (C\(_9\)), 136.6 (C\(_10\)), 131.7 (C\(_1\)), 130.4 (2 × C\(_2\)), 125.9 (2 × C\(_3\)), 21.6 (C\(_11\))

**IR:** \(\nu\) (cm\(^{-1}\)) 1657 (C=O), 1273 (O-C\(_\text{ar}\)), 1057 (sulfoxide).

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

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Fig. 7. \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) spectrum of compound (+)-(S)-3.
**Preparation of (+)-(S₈)-4**

![Chemical diagram](attachment:chemical_diagram.png)

**Scheme 3.** Synthesis of qionoide (+)-(S₈)-4.
2-Methoxy-1,4-dihydroxybenzene S8

\[
\text{FW: 140.15 g mol}^{-1}
\]

\[
\text{C}_7\text{H}_8\text{O}_3
\]

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\(_2\)O\(_2\) (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\(_2\)S\(_2\)O\(_3\), dried over MgSO\(_4\), filtered off and evaporated to provide a dark oil which was chromatographed on silica gel (cyclohexane / EtOAc, 8 / 2) to give 3.633 g of S8 as a white solid (25.9 mmol, 76 %).

\[
\text{R}_f: 0.43 \text{ (cyclohexane / EtOAc, 5 / 5).}
\]

\[
\text{M.p.: 85.0 - 86.0 °C.}
\]

\(^1\text{H-NMR (400 MHz, acetone-}d_6\text{): }\delta \text{ (ppm) 7.71 (s, 1H, O}H\text{), 6.85 (s, 1H, O}H\text{), 6.63 (d, 1H, }J = 8.5 \text{ Hz, }C^6\text{H), 6.46 (d, 1H, }J = 2.5 \text{ Hz, }C^3\text{H), 6.27 (dd, }J = 8.5; 2.5 \text{ Hz, }C^5\text{H), 3.80 (s, 3H, }C^7\text{H}_3\text{).}
\]

\(^13\text{C-NMR (100 MHz, acetone-}d_6\text{): }\delta \text{ (ppm) 151.5 (}C_1^4\text{), 148.8 (}C_3^2\text{), 140.4 (}C_3^4\text{), 115.8 (}C^6\text{H), 107.3 (}C^3\text{H), 101.1 (}C^3\text{H), 56.07 (}C^7\text{H}_3\text{).}
\]

\text{IR: }\nu \text{ (cm}^{-1}\text{) 3500 - 3100 (OH), 1290 (O-C}^\text{ar}\text{), 1244 (O-C}^\text{ar}\text{), 1218 (O-C}^\text{ar}\text{), 1034 (O-CH}_3\text{).}
2-Bromo-4-methoxy-1,4-dihydroxybenzene S9

FW: 219.04 g mol⁻¹
C₇H₇O₃Br

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 Na₂S₂O₃, NaHCO₃ and brine, successively, then dried over MgSO₄, 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.

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

M.p.: 120 - 122 °C.

¹H-NMR (400 MHz, acetone-d₆): δ (ppm) 7.95 (s, 1H, OH), 7.38 (s, 1H, OH), 6.93 (s, 1H, C₃H), 6.64 (s, 1H, C₆H), 3.78 (s, 3H, C₇H₃).

¹³C-NMR (100 MHz, acetone-d₆): δ (ppm) 147.9 (C₅), 146.9 (C₀), 140.6 (C₄), 118.2 (C₃H), 101.3 (C₆H), 98.9 (C₀), 55.5 (C₇H₃).

IR: ν (cm⁻¹) 3500 - 3000 (OH), 1274 (O-C₆H), 1198 (O-C₆H), 1165 (O-C₆H), 1038 (O-CH₃), 820 (C₆H-BR).
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$^8$H$_3$ + C$^{13}$H$_3$).

$^{13}$C-NMR (100 MHz, CDCl$_3$): δ (ppm) 151.0 (C$^4$), 149.01+149.0 (C$^2$ or C$^5$), 141.5+141.5 (C$^2$ or C$^5$), 124.0 (C$^6$H), 105.1+105.1 (C$^3$H), 104.22 (C$^8$), 101.9+101.9 (C$^7$H or C$^{12}$H), 101.7+101.7
(C\textsuperscript{7}H or C\textsuperscript{12}H), 62.4+62.3 (C\textsuperscript{8}H\textsubscript{2} or C\textsuperscript{14}H\textsubscript{2}), 61.8+61.8 (C\textsuperscript{9}H\textsubscript{2} or C\textsuperscript{16}H\textsubscript{2}), 56.1 (C\textsuperscript{11}H\textsubscript{3}), 20.3+20.3 (C\textsuperscript{8}H\textsubscript{3} or C\textsuperscript{13}H\textsubscript{3}), 20.3+20.2 (C\textsuperscript{9}H\textsubscript{3} or C\textsuperscript{14}H\textsubscript{3}), 15.4 (C\textsuperscript{10}H\textsubscript{3} or C\textsuperscript{15}H\textsubscript{3}), 15.3 (C\textsuperscript{10}H\textsubscript{3} or C\textsuperscript{15}H\textsubscript{3}).

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

**1,4-Bis(1-ethoxyethoxy)-2-methoxy-5 [(S)-4-methylbenzenesulfinyl]benzene (S\textsubscript{S})-S\textsubscript{11}**

![Chemical structure of 1,4-Bis(1-ethoxyethoxy)-2-methoxy-5 [(S)-4-methylbenzenesulfinyl]benzene (S\textsubscript{S})-S\textsubscript{11}](image)

\[\text{FW: } 422.22 \text{ g mol}^{-1}\]

\[\text{C}_{22}\text{H}_{30}\text{O}_{6}\text{S}\]

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 S\textsubscript{10} (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 \(\rightarrow\) 8 / 2) to give 916 mg (2.17 mmol, 55 %) of S\textsubscript{11} as golden oil.

**R\textsubscript{F}:** 0.50 (cyclohexane / EtOAc, 4 / 6).
A mixture of diastereoisomers:

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (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, $C^{11}H$), 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$_3$): $\delta$ (ppm) 154.0+153.9+153.8 ($C^2_\text{a}$), 149.0+148.9+148.8 +148.7 ($C^2_\text{ar}$), 142.8+148.8+148.78+148.76 ($C^4_\text{a}$), 141.3+141.3+141.3+141.2 ($C^4_\text{ar}$), 141.11+141.09 ($C^4_\text{q}$), 129.6 (2 × $C^\text{Tol}_H$), 125.7+126.6 ($C^6_H$), 125.2 (2 × $C^\text{Tol}_H$), 115.5+115.3+115.1+114.6 ($C^7_\text{a}$), 101.99+101.97 ($C^7_H$), 101.7+101.60+101.57+101.54 ($C^{12}H$ 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 ($C^9_H_3$ or $C^{13}H_3$), 19.82+19.80+19.6+19.5 ($C^{10}H_3$ or $C^{13}H_3$), 15.23+15.18+15.14 ($C^{10}H_3 + C^{15}H_3$).

IR: $\nu$ (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

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$_3$): $\delta$ (ppm) 7.66 (d, 2H, $J = 8.1$ Hz, 2 $\times$ C$_9^g$H), 7.34 (s, 1H, C$_6^g$H), 7.29 (d, 2H, $J = 8.1$ Hz, C$_{10}^{10}$H), 5.85 (s, 1H, C$_3^g$H), 3.81 (s, 3H, C$_7^g$H$_3$), 2.38 (s, 3H, C$_{12}^{12}$H$_3$).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 183.7 (C$_1^q$), 179.7 (C$_3^q$), 159.7 (C$_4^q$), 156.5 (C$_5^q$), 149.9 (C$_8^q$), 138.5 (C$_9^q$), 130.4 (2 $\times$ C$_{10}^{10}$H), 129.7 (C$_6^g$H), 126.0 (2 $\times$ C$_9^g$H), 107.6 (C$_3^g$H), 56.9 (C$_7^g$H$_3$), 21.6 (C$_{12}^{12}$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).


**Fig. 9.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of compound (+)-(S$_S$)-4.
Preparation of (+)-(S₅)-5

Compound (+)-(S₅)-5 has been prepared from (+)-(S₅)-3 in two reaction steps according the Scheme 4.

(--)-2-Chloro-3-[(S)-4-methylbenzenesulfinyl]benzene-1,4-diol (-)-(S₅)-S₅c

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 (+)-(S₅)-3 was dissolved in 150 mL of anhydrous dichloromethane and cooled down to 0 °C and 2.5 mL of TiCl₄ (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 Na₂S₂O₃ and brine, successively. The organic phase was then dried over MgSO₄, 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 (-)-(S₅)-S₅c a pale yellow solid.

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

[α]D²⁰: -95 ° (c = 1.0, acetone).

M.p.: 173 - 176 °C.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 10.87 (s, 1H, OH), 7.74 (d, 2H, J = 8.1 Hz, 2 × C₈H), 7.32 (d, 2H, J = 8.1 Hz, 2 × C₈H), 7.01 (d, 1H, J = 9.2 Hz, C₅H or C₆H), 6.78 (d, 1H, J = 9.2 Hz, C₅H or C₆H), 5.30 (s, 1H, OH), 2.40 (s, 3H, C₁₁H₃).

¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 154.6 (C₈), 145.0 (C₈), 143.3 (C₈), 139.7 (C₈), 130.5 (2 × C₈H or 2 × C₉H), 126.2 (2 × C₈H or 2 × C₉H), 120.6 (C₅H or C₆H), 120.4 (C₅H or C₆H), 119.7 (C₅H or C₆H), 115.8 (C₅H or C₆H), 21.7 (C₁₁H₃).
**IR:** $\nu$ (cm$^{-1}$) 3400 - 2800 (OH), 1286 (C$^{\equiv}$-OH), 1207 (C$^{\equiv}$-OH), 966 (sulfoxide), 805 (C$^{\equiv}$-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$_9$O$_3$SCl

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 sulfanylquinone (+)-(S$_S$)-5 (97 %). Recrystallization from a hot mixture of pentane and toluene afforded blood red needles.

$\textbf{R_F}$: 0.41 (cyclohexane / EtOAc, 5 / 5).

$\textit{[a]}^D_20: +638$ ° (c = 1.0, CHCl$_3$).

**M.p.:** 138 - 140 °C.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.72 (d, 2H, $J$ = 8.2 Hz, 2 × C$^8$H), 7.33 (d, 2H, $J$ = 8.2 Hz, 2 × C$^9$H), 6.91 (d, 1H, $J$ = 10.1 Hz, C$^5$H or C$^6$H), 6.78 (d, 1H, $J$ = 10.1 Hz, C$^5$H or C$^6$H), 2.40 (s, 3H, C$^{11}$H$_3$).
$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 181.3 (C$_q$ or C$_s$), 177.9 (C$_q$ or C$_s$), 146.3 (C$_q$ or C$_s$), 143.7 (C$_q$ or C$_s$), 142.6 (C$_q$), 138.0 (C$_q$), 137.3 (C$_5$H or C$_6$H), 136.0 (C$_5$H or C$_6$H), 130.3 (2 $\times$ C$_9$H), 125.2 (2 $\times$ C$_8$H), 21.6 (C$_{11}$H$_3$).

IR: $\nu$ (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$_3$)-5.
2. Availability of VEGFR2 TKIs 6, 7 and 9

IC$_{50}$ = 8.5 nM (VEGFR2 TK), 6
BM03014
sorafenib tosylate
(Nexavar®, Bayer, FDA 2005)

IC$_{50}$ = 15 nM (VEGFR2 TK), 7
BM06614 (Biomagi)

IC$_{50}$ = 18 nM (VEGFR2 TK), 8
BM02814 (Biomagi)

IC$_{50}$ = 22 nM (VEGFR2 TK), 9
BM02514
AAZ (PDB: 1Y6A)
(GlaxoSmithKline, 2005)

IC$_{50}$ = 564 uM (VEGFR2 TK), 10
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-(Ethylsulfanyl)-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.](image-url)
Synthesis of dibromoacetophenone S13

Novelty: Synthesis of S13 was previously described in a literature with 78 % yield.\textsuperscript{11} \textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, IR and HRMS spectral analysis were published.\textsuperscript{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\textsubscript{3} was heated to 35 °C and 2.89 g (18.1 mmol, 1.00 mol eq) of Br\textsubscript{2} in 10.0 ml CHCl\textsubscript{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\textsubscript{2}O and 2 × 10.0 ml of NaHCO\textsubscript{3} aq saturated solution. Combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{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).\textsuperscript{12} White crystalline solid material.

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \textsuperscript{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\textsubscript{2}Br).

\begin{center}
\begin{tikzpicture}
\node[anchor=center] at (0,0) {S13};
\node[anchor=center] at (1.5,0.75) {CDCl\textsubscript{3} (300 MHz)};
\node[anchor=center] at (0,0.5) {7.91 (7.9, 1.7, 1.0)};
\node[anchor=center] at (0,0.25) {7.38 (8.1, 7.9)};
\node[anchor=center] at (0,0) {7.74 (8.1, 2.1, 1.0)};
\node[anchor=center] at (2.5,0) {Br};
\node[anchor=center] at (2.5,-0.25) {8.12 (2.1, 1.7)};
\node[anchor=center] at (2.5,-0.5) {4.41};
\end{tikzpicture}
\end{center}
Synthesis of azidoacetophenone S14

Novelty: Synthesis of S14 was described in the literature with 91 % yield. $^{13}$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$_2$SO$_4$, 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.
1H-NMR (400 MHz, CDCl₃): 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, -COCH₂N₃).

Fig. 15. 1H-NMR (400 MHz, CDCl₃) 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\(_2\)SO\(_4\), 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\(_6\)): \(\delta\) 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\(_B(4)\)), 7.40 (8.2, 7.8), 7.47 (7.8, 2.1, 1.2), 7.47 (7.8, 2.1, 1.7), 7.82 (2.1, 1.7), 7.67, 7.51 (8.5, 2.3), 7.28 (8.5), 3.98, 1.12 (7.3), 3.21 (7.3), 8.77 (2.3), \(\delta \) 9.81 (br)
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, $J(C_4,C_6) = 8.2$ 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$_2$CH$_2$CH$_3$), 1.12 (t, 3H, $J(CH_2,CH_3) = 7.3$ Hz, -SO$_2$CH$_2$CH$_3$).

**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(PPh₃)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) Na₂CO₃ 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 Na₂SO₄, 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-(1H-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.

\[\text{H-NMR (300 MHz, DMSO-d}_6\text{): } \delta 11.00 \text{ (br s, } 1\text{H, -NH from pyrrol), } 9.70 \text{ (br s, } 1\text{H, -NH-),}
8.80 \text{ (d, } 1\text{H, } J(A_4,A_6) = 2.3 \text{ Hz, H-C}(A(6)),
7.78 \text{ (br s, } 1\text{H, H-C}(C(2)),
7.57 \text{ (s, } 1\text{H, H-C}(B(4)),
7.50 \text{ (dd, } 1\text{H, } J(A_3,A_4) = 8.2 \text{ Hz, } J(A_4,A_6) = 2.3 \text{ Hz, H-C}(A(4)),
7.46 \text{ (ddd, } 1\text{H, } J(C_4,C_5) = J(C_5,C_6) = 4.7 \text{ Hz, H-C}(C_5),
7.36 \text{ (d, } 2\text{H, } J(C_4 \text{ or } C_6,C_5) = 4.7 \text{ Hz, H-C}(C(4 \text{ or } 6)),
7.29 \text{ (dd, } 1\text{H, } J(D_2,D_3) = 2.9 \text{ Hz, } J(D_2,D_4) = 2.3 \text{ Hz, H-C}(D(2)),
7.27 \text{ (d, } 1\text{H, } J(A_3,A_4) = 8.2 \text{ Hz, } J(A_3,A_5) = 4.7 \text{ Hz, H-C}(A(3))
6.83 \text{ (dd, } 1\text{H, } J(D_4,D_5) = 5.3 \text{ Hz, } J(D_2,D_3) = 2.9 \text{ Hz, H-C}(D(5)),
6.51 \text{ (dd, } 1\text{H, } J(D_4,D_5)
\]
= 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$_2$CH$_2$CH$_3$), 1.13 (t, 3H, $J$(CH$_2$,CH$_3$) = 7.3 Hz, -SO$_2$CH$_2$CH$_3$).

$^{13}$C-NMR (150 MHz, DMSO-$d^6$): $\delta$ 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$_2$CH$_2$CH$_3$), 7.8 (-SO$_2$CH$_2$CH$_3$). The exact carbon assignments are based on HSQC 2D NMR spectrum analysis.

IR (neat, $\nu$/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$_3$O$_4$S (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.
Preparation of 4-(pyridinylphenyl)oxazol-2-amine 10

Compound S18 was prepared according a procedure described in the literature Murár et al.\textsuperscript{14}

\begin{equation*}
\text{Scheme 6. Synthetic pathway to oxazol-2-amine 10.}
\end{equation*}

Synthesis of N-arylurea S19

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

To solution of 100.0 mg (0.46 mmol, 1.00 mol eq) aniline S18 in 2.0 ml of CH\textsubscript{3}COOH and 4.0 ml of H\textsubscript{2}O, another solution of 75.4 mg (0.93, 2.00 mol eq) KNCO in 1.0 ml of H\textsubscript{2}O was added within 10 min and the resulting mixture heated at 60 \textdegree C for 3 h. Then the reaction was poured into a mixture of ice and H\textsubscript{2}O and neutralized by NaHCO\textsubscript{3} (sat aq solution). The water layer was extracted by EtOAc (3 \times 10 ml), the organic phase separated, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude product was purified by crystallization.
from H$_2$O / 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.

![Diagram of molecule S19]

$^1$H-NMR (300 MHz, DMSO-$d^6$): $\delta$ 8.66 (d, 1H, $J(4,6) = 2.4$ Hz, H-C(6)), 8.25 (br s, 1H, -NHCONH$_2$), 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, -NHCONH$_2$), 3.95 (s, 3H, -OCH$_3$), 3.14 (q, 2H, $J(CH_2CH_3) = 7.4$ Hz, -COOCH$_2$CH$_3$), 1.08 (t, 3H, $J(CH_2CH_3) = 7.4$ Hz, -COOCH$_2$CH$_3$).

![NMR spectrum]

**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 $2 \times 10$ ml NaHCO$_3$ (saturated aq solution) and 10 ml of water. The combined organic layer was dried over Na$_2$SO$_4$, 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.

![Chemical Structure](image)

$^1$H-NMR (300 MHz, DMSO-d$_6$): $\delta$ 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, $J(C_4,C_6) = 7.9$ 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, $J(C_4,C_6) = 2.3$ Hz, H-C$_A$(4))
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\(_2\)CH\(_2\)CH\(_3\)), 0.95 (t, 3H, \(J(CH_{2},CH_{3}) = 7.4\) Hz, -SO\(_2\)CH\(_2\)CH\(_3\)).

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\(_4\)NBr 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\(_2\)SO\(_4\), 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.
**1H-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$_5$) = 1.8 Hz, J(D$_3$,D$_4$) = 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$_2$CH$_2$CH$_3$), 0.80 (t, 3H, J(CH$_2$,CH$_3$) = 7.3 Hz, -SO$_2$CH$_2$CH$_3$).

**13C-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$_2$CH$_2$CH$_3$), 7.6 (-SO$_2$CH$_2$CH$_3$). 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 $\text{C}_{23}\text{H}_{21}\text{N}_{3}\text{O}_{4}\text{S}$ (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. $^1\text{H}-\text{NMR}$ (600 MHz, DMSO-$d^6$) spectrum of compound 10.

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

8. RCSB Protein Data Bank http://www.rcsb.org/pdb/explore/explore.do?structureId=1Y6 (accessed 8.07.2016)
Acknowledgements

Liver Cancer stem cell studies and DCK supported by TUBITAK grant# 113S540, COST Actions: CM1106, CA15135, VEGA 1/0634/13, APV SK-FR-2015-0014 and Biomagi, Ltd. for aggressiveness factors AF and NA_F proposal is also acknowledged. Sorafenib tosylate (6) was obtained as a gift from Bayer, Inc.