**Supporting information**

**Linifanib – A Multi-Targeted Receptor Tyrosine Kinase Inhibitor and a Low Molecular Weight Gelator**

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S1. Synthesis and analysis of linifanib (1) and its analogues (2-9)

Synthesis of 4-ido-1H-indazol-3-amine

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\text{I} & \quad \text{H} \\
\text{N} & \quad \text{H}
\end{align*}
\]

1a


Synthesis of 1-(2-fluoro-5-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{N} \\
\text{H} & \quad \text{F} \\
\text{O} & \quad \text{B} & \quad \text{O}
\end{align*}
\]

1b


**Synthesis of linifanib (1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-fluoro-5-methylphenyl)urea)**

**Synthesis of 1-(2-methoxyphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea**

To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg, 2 mmol) in DCM (10 ml) at 0 °C (water ice bath) 2-methoxyphenyl isocyanate (298 mg, 2 mmol) was added. The whole solution was allowed to stir overnight. Then, the solution was evaporated under vacuum and purified by flush column chromatography (20-80 % EtAOc/hexane) to get the title compound as a white solid (600 mg, 80 %). MS: m/z (HRMS) calculated for C_{20}H_{23}BN_{2}O_{4} 369.1907 [M+H], MS found: 369.1861 [M+H]. \(^{1}\)H NMR (400
The same procedure was used in preparation of urea boronates of the linifanib analogues by the addition of the corresponding isocyanate to the aniline.

**Synthesis of 1-(4-(3-amin-1H-indazol-4-yl)phenyl)-3-(2-methoxyphenyl)urea**

The 4-iodo-1H-indazol-3-amine 1a (259 mg, 1 mmol), urea boronate 2a (441 mg, 1.2 mmol) and Na2CO3 (260 mg, 2.4 mmol) were suspended in dimethoxyethane/water (36:12) mixture. The Palladium was then added and the reaction was allowed to stir at 85 °C overnight. TLC indicated complete conversion of the starting material. The solution was cooled, evaporated, extracted twice with ethyl acetate/water twice and dried over MgSO4. The EtOAc extract was concentrated down and purified by flash column chromatography (20-80 % MeOH/DCM) to get the product (150 mg, 40 %). MS: m/z (HRMS) calculated for C21H19N5O2 374.1538 [M+H], MS found: 374.1601 [M+H]. 1H NMR (400 MHz, DMSO-d6): δ 3.9 (s, 3H), 4.34 (s, 2H), 6.79 (dd, J = 1.95 Hz, J = 5.91 Hz, 1H), δ 6.95 (m, 2H), δ 7.04 (d, J = 7.95 Hz, 2H), δ 7.26 (s, 1H), δ 7.4 (d, J = 8.56 Hz, 2H), δ 7.61 (d, J = 8.60 Hz, 2H), δ 8.18 (d, 1H), δ 8.32 (s, 1H), δ 9.50 (s, 1H), δ 11.71 (s, 1H). 13C NMR (125 MHz, DMSO-d6): δ 31.24, 33.56, 35.40, 56.25, 79.10, 79.45, 79.76, 111.20, 118.18, 118.76, 119.52, 120.50, 121.02, 122.30, 126.75, 128.88, 129.10, 129.79, 132.99, 139.88, 148.12, 152.85.
The same method was used in preparation of linifanib analogues by the reaction between the 4-iodo-1H-indazol-3-amine with its corresponding urea boronate.

**Synthesis of 1-phenyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea**

![Chemical structure of 3a](image)


**Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-phenylurea**

![Chemical structure of 3](image)


**Synthesis of 1-(2-chlorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea**
By the method outlined for compound 2a, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg, 2 mmol) and 2-chlorophenyl isocyanate (307 mg, 2 mmol) were reacted together in DCM to give 1-(2-chlorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (692 mg, 93 %). MS: m/z (HRMS) calculated for C_{19}H_{22}BClN_{2}O_{3} 373.1412 [M+H], MS found: 372.9811 [M+H]. ^1H NMR (400 MHz, CHCl$_3$-d$_1$): δ 1.37 (s, 12H), 6.93 (s, 1H), 7.02 (t, J = 7.72 Hz, 1H), 7.22 (s, 1H), 7.28 (s, 1H), 7.36 (dd, J = 1.48 Hz, J = 7.95 Hz, 1H), 7.41 (s, 1H), 7.23 (s, 1H), 7.80 (s, 1H), 7.82 (s, 1H), 8.17 (s, 1H), 8.20 (s, 1H).

Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-chlorophenyl)urea

By the method outlined for compound 2, the 4-iodo-1H-indazol-3-amine 1a (259 mg, 1 mmol), urea boronate 8 (453 mg, 1.2 mmol) were reacted to give 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-chlorophenyl)urea (139 mg, 37 %). MS: m/z (HRMS) calculated for C$_{20}$H$_{16}$ClN$_{5}$O 378.1043 [M+H], MS found: 378.1006 [M+H]. ^1H NMR (400 MHz, DMSO-d$_6$): δ 4.34 (s, 2H), 6.80 (dd, J = 2.28 Hz, J = 5.52, 1H), 7.05 (t, J = 7.74 Hz, 1H), 7.26 (m, 2H), 7.32 (t, 1H), δ 7.42 (d, J = 8.53 Hz, 2H), 7.48 (d, J = 1.51 Hz, J = 8.00 Hz, 1H), 7.62 (d, J = 8.65 Hz, 2H), 8.20 (dd, 1H), 8.40 (s, 1H), 9.59 (s, 1H), 11.73 (s, 1H). ^13C NMR (125
MHz, DMSO-d$_6$): $\delta$ 60.20, 109.10, 118.50, 119.60, 121.84, 122.49, 123.83, 126.72, 128.10, 129.70, 129.85, 133.40, 135.91, 136.41, 139.48, 152.29.

**Synthesis of 1-(2-cyanophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea**

![Image](5a)

By the method outlined for compound 2a, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg, 2 mmol) and 2-cyanophenyl isocyanate (288 mg, 2 mmol) were reacted together in DCM to give 1-(2-cyanophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (654 mg, 90 %). MS: m/z (HRMS) calculated for C$_{20}$H$_{22}$BN$_3$O$_3$ 364.1754 [M+H], MS found: 363.9423 [M+H]. $^1$H NMR (400 MHz, CHCl$_3$-d$_1$): $\delta$ 1.37 (s, 12H), 7.13 (t, $J$ = 7.65 Hz, 1H), 7.49 (d, $J$ = 8.48 Hz, 2H), 7.59 (d, $J$ = 7.60 Hz, 2H), 7.80 (d, $J$ = 8.42 Hz, 2H), 7.81 (s, 1H), 8.39 (s, 1H), 8.42 (s, 1H).

**Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-cyanophenyl)urea**

![Image](5)

By the method outlined for compound 2, the 4-iodo-1H-indazol-3-amine 1a (259 mg, 1 mmol), urea boronate 10 (442 mg, 1.2 mmol) were reacted to give 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-cyanophenyl)urea (158 mg, 43 %). MS: m/z (HRMS) calculated for
C_{21}H_{16}N_{6}O 369.1385 [M+H], MS found: 369.1461 [M+H].  \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): \textsuperscript{\delta} 4.34 (s, 2H), 6.79 (dd, J = 1.98 Hz, J = 5.69 Hz, 1H), 7.05 (t, J = 7.62 Hz, 1H), \textsuperscript{\delta} 7.27 (m, 2H), 7.32 (m, 1H), 7.42 (d, J = 8.66 Hz, 2H), 7.48 (dd, J = 1.51 Hz, J = 8.08 Hz, 1H), 7.62 (d, J = 8.64 Hz, 2H), 8.20 (dd, J = 1.39 Hz, J = 8.27 Hz, 1H), 8.38 (s, 1H), 9.58 (s, 1H), 11.72 (s, 1H, NH). \textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}): \textsuperscript{\delta} 60.22, 114.76, 115.76, 119.85, 122.88, 123.01, 126.92, 128.04, 129.62, 129.90, 130.33, 135.62, 139.44, 140.33, 150.70, 162.70.

Synthesis of 1-(2-fluorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea

\[\text{6a}\]


Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2-fluorophenyl)urea

**Synthesis of 1-(2,4-difluorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea**

By the method outlined for compound 2a, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg, 2 mmol) and 2,4-difluorophenyl isocyanate (310 mg, 2 mmol) were reacted together in DCM to give 1-(2,4-difluorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (710 mg, 95 %). MS: m/z (HRMS) calculated for C_{19}H_{21}BF_{2}N_{2}O_{3} 375.1613 [M+H], MS found: 375.1327 [M+H]. ^1H NMR (400 MHz, CHCl$_3$-d$_1$): δ 1.35 (s, 12H), 7.06 (m, 3H), 7.19 (s, 2H), 7.37 (d, J = 8.50 Hz, 2H), 7.77 (s, 1H), 8.07 (s, 1H).
Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2,4-difluorophenyl)urea

By the method outlined for compound 2, the 4-iodo-1H-indazol-3-amine 1a (259 mg, 1 mmol), urea boronate 14 (449 mg, 1.2 mmol) were reacted to give 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(2,4-difluorophenyl)urea (197 mg, 52 %). MS: m/z (HRMS) calculated for C20H15F2N5O 380.1244 [M+H], MS found: 380.1337 [M+H]. ¹H NMR (400 MHz, DMSO-d₆): δ 4.33 (s, 2H), 6.79 (dd, J = 2.07 Hz, J = 5.87 Hz, 1H), 7.08 (t, J = 7.93 Hz, 1H), 7.27 (m, 2H), 7.33 (m, 1H), 7.41 (d, J = 8.52 Hz, 2H), 7.59 (d, J = 8.65 Hz, 2H), 8.12 (m, 1H), 8.57 (s, 1H), 9.18 (s, 1H), 11.72 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 104.01, 104.26, 104.51, 109.12, 111.05, 111.42, 111.63, 118.43, 119.57, 126.74, 129.88, 133.40, 135.90, 139.48, 142.54, 148.62, 152.84.

Synthesis of 1-(3-fluoro-2-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea

By the method outlined for compound 2a, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (238 mg, 2 mmol) and 2-methyl-3-fluorophenyl isocyanate (302 mg, 2 mmol) were
reacted together in DCM to give 1-(3-fluoro-2-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (710 mg, 95 %). MS: m/z (HRMS) calculated for C_{20}H_{24}BFN_{2}O_{3} 371.1864 [M+H], MS found: 371.1778 [M+H]. ^1H NMR (400 MHz, CHCl₃-d₁): δ 1.36 (s, 12H), 2.17 (s, 3H), 6.52 (s, 1H), 6.80 (s, 1H), 6.93 (t, J = 8.38 Hz, 1H), 7.19 (m, 1H), 7.36 (d, J = 8.62 Hz, 3H), 7.75 (s, 1H), 7.77 (s, 1H).

**Synthesis of 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(3-fluoro-2-methylphenyl)urea**

![8]

By the method outlined for compound 2, the 4-ido-1H-indazol-3-amine 1a (259 mg, 1 mmol), urea boronate 16 (444 mg, 1.2 mmol) were reacted to give 1-(4-(3-amino-1H-indazol-4-yl)phenyl)-3-(3-fluoro-2-methylphenyl)urea (197 mg, 52 %). MS: m/z (HRMS) calculated for C_{21}H_{18}FN_{5}O 376.1495 [M+H], MS found: 375.9643 [M+H]. ^1H NMR (400 MHz, DMSO-d₆): δ 2.18 (s, 3H), 4.34 (s, 2H), 6.79 (dd, J = 2.03 Hz, J = 5.83 Hz, 1H), 6.87 (t, J = 8.83 Hz, 1H), 7.19 (m, 1H), 7.27 (m, 2H), 7.41 (d, J = 8.56 Hz, 2H), 7.61 (d, J = 8.56 Hz, 2H), 7.72 (d, J = 8.28 Hz, 1H), 8.16 (s, 1H), 9.21 (s, 1H), 11.72 (s, 1H). ^13C NMR (125 MHz, DMSO-d₆): δ 19.9, 109.02, 109.81, 111.01, 115.31, 117.52, 118.39, 119.51, 126.70, 127.23, 129.81, 133.19, 135.92, 139.70, 142.55, 148.59, 152.99, 159.84, 162.23.

**Synthesis of 2-(3,5-difluorophenyl)acetyl chloride**

![ClC\(\text{O}\)F]
To a solution of 2-(3,5-difluorophenyl)acetic acid (344 mg, 2 mmol) in dichloromethane (2 mL) was added thionyl chloride (218 μL, 3 mmol) and dimethylformamide (16 μL, 0.2 mmol) and the mixture stirred at room temperature for 3 hours. The solvent was removed under vacuum to give 2-(3,5-difluorophenyl)acetyl chloride as a yellow oil, which was used without further purification.

**Synthesis of 2-(3,5-difluorophenyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide**

![Chemical Structure](image)

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (438 mg, 2 mmol) in dichloromethane (20 mL) cooled with an ice-water bath was added triethylamine (418 μL, 3 mmol) and 2-(3,5-difluorophenyl)acetyl chloride 9a (217 μL, 2 mmol). The mixture was stirred overnight, washed with water, dried (MgSO4), filtered, and concentrated to give the product as a white solid (708 mg, 95%). MS: m/z (HRMS) calculated for C20H22BF2NO3, 374.1660 [M+H], MS found: 374.1731 [M+H]. 1H NMR (400 MHz, CHCl3-d1): δ 1.35 (s, 12H), 3.75 (s, 2H), 6.90 (m, 2H), 7.37 (m, 1H), 7.54 (d, J = 8.28 Hz, 2H), 7.62 (m, 1H), 7.75 (s, 1H), 7.77 (s, 1H).

**Synthesis of N-(4-(3-amino-1H-indazol-4-yl)phenyl)-2-(2,4-difluorophenyl)acetamide**
The 4-iodo-1H-indazol-3-amine 1a (259 mg, 1 mmol), acetamide 9b (373 mg, 1 mmol) and Na₂CO₃ (78 mg, 0.7 mmol) were suspended in dimethoxyethane/water (36:12) mixture. The Palladium was then added and the reaction was allowed to stir at 85 °C overnight. TLC indicated complete conversion of the starting material. The solution was cooled, evaporated, extracted twice with ethyl acetate/water twice and dried over MgSO₄. The EtOAc extract was concentrated down and purified by flash column chromatography (20-80 % MeOH/DCM) to get the product as light brown solid (210 mg, 56 %). MS: m/z (HRMS) calculated for C₂₁H₁₆F₂N₄O 379.1292 [M+H], MS found: 379.1398 [M+H]. ¹H NMR (400 MHz, DMSO-d₆): δ 3.77 (s, 2H), 4.30 (s, 2H), 6.69 (m, 1H), 6.78 (q, 1H), 7.13 (m, 3H), 7.42 (d, J = 8.60 Hz, 2H), 7.47 (d, J = 6.86 Hz, 1H), 7.73 (d, J = 8.60 Hz, 2H), 10.37 (s, 1H), 11.72 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 36.23, 104.05, 109.16, 111.00, 111.57, 111.77, 114.14, 119.39, 119.58, 126.69, 129.77, 129.90, 133.43, 134.56, 135.82, 139.09, 142.55, 148.57, 168.48.
S2. Preparation of gels and vial inversion

Gels were prepared for both linifanib (1) and its analogues (compounds 2-9) as shown in Table 1

Table 1: Amounts of compound, DMSO and water required for gel preparation

<table>
<thead>
<tr>
<th>Final concentration % (w/v)</th>
<th>Compound (mg)</th>
<th>DMSO µL</th>
<th>Water µL</th>
<th>Final volume µL</th>
<th>% (v/v) DMSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.5</td>
<td>25</td>
<td>475</td>
<td>500</td>
<td>5</td>
</tr>
<tr>
<td>0.5</td>
<td>2.5</td>
<td>50</td>
<td>450</td>
<td>500</td>
<td>10</td>
</tr>
<tr>
<td>0.5</td>
<td>2.5</td>
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<td>425</td>
<td>500</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>2.5</td>
<td>100</td>
<td>400</td>
<td>500</td>
<td>20</td>
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<tr>
<td>0.5</td>
<td>2.5</td>
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<td>500</td>
<td>25</td>
</tr>
<tr>
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<td>350</td>
<td>500</td>
<td>30</td>
</tr>
<tr>
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<td>500</td>
<td>40</td>
</tr>
<tr>
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<td>2.5</td>
<td>230</td>
<td>250</td>
<td>500</td>
<td>50</td>
</tr>
</tbody>
</table>

Note: The 0.25 % and 0.125 % (w/v) were prepared by using 1.25 mg and 0.625 mg of the weight of compound respectively.

The compounds were measured into individual vials (Fisherbrand screw top wide opening 9mm short thread 2 mL, 12 mm x 32 mm). DMSO was then added and the vials were heated up to 60 °C in a bespoke heating mantle for a period of time to ensure solubilisation. Pre-heated (70 °C) purified water was added before removal of the vials from the heating block and then allowed to cool down to room temperature.

S3. Rheological measurements were performed using an Anton Paar modular compact rheometer MCR302 equipped with a temperature controlled peltier. Cup and vane accessories were used to complete all amplitude sweeps (see K. J. Skilling et al., Gelation properties of
self-assembling N-acyl modified cytidine derivatives. *Journal of Materials Chemistry B* 2, 8412 (2014) for further details). All gels were prepared in a similar manner as described in S3 above to make a 2 ml volume in sterilin vials. All strain amplitude measurements were performed in the range of 0.01 % – 100 % strain and at a frequency of 10 rad s⁻¹. All measurements were performed on three replicate samples.

![Graph showing strain amplitude data of analogue 3 gels](image)

**Figure 11:** Strain amplitude data of analogue 3 gels at 0.25% (w/v)) in 5% (v/v) DMSO/water. Storage modulus (G’) and loss modulus (G’’) shown.
Figure 2: Strain amplitude data of linifanib gels at different concentrations (0.0625 to 1.25% (w/v)) in 5% (v/v) DMSO/water. Only storage modulus ($G'$) shown.
Figure 3: Storage modulus (G’) versus linifanib concentration (% (w/v) in 0.5% (v/v) DMSO/water. All measurements were carried out in triplicate and the mean calculated. Slope = 1.86 to 2 decimal places.

S4. Transmission electron microscope (TEM) imaging was undertaken using a JEOL JEM – 2000FXII transmission electron microscope. 4 μL of sample was placed on a carbon coated copper grid (300 mesh, Agar Scientific) for 30 seconds. The sample was blotted with Whatman 50 filter paper, the grid was then inserted in the microscope through a sample holder and a high vacuum was applied. Images were subsequently taken at an accelerating voltage of 100 kV.