**Supplementary Information**

**SI-Methods**

**1.0 Synthesis of drug molecules**

Synthesis of 1,20-bis(naphthalimido)eicosane (BNIPDi, 1): 1,20-Eicosanedicarboxylic acid (2.00 g, 5.85 mmol) was dissolved in SOCl\(_2\) (40 mL) and heated to reflux for 2.5 h until gas evolution had ceased completely. The solvent was evaporated and the solid residue was dissolved in anhydrous dioxan (20 mL). Concentrated aqueous solution of ammonia (25 mL) was added and the mixture was stirred for 1 h. The white precipitate was filtered, washed with water and dried in vacuo. The white solid was dissolved in dry tetrahydrofuran (25 mL) and a suspension of LiAlH\(_4\) (0.5 g, 15 mmol) in dry tetrahydrofuran (30 mL) was added at room temperature. The mixture was heated to reflux for 18 h. The reaction mixture was cooled, the excess LiAlH\(_4\) was quenched carefully with H\(_2\)O and the mixture was filtered to give a white waxy precipitate. The precipitate was dried in vacuo to give 1,20-diaminoeicosane (6.2 g 19.8 mmol) as a waxy white solid which was used without further purification. 1,8-Naphthalic anhydride (8.00 g, 40 mmol) was suspended in absolute ethanol (200 mL) with stirring. 1,20-Diaminoeicosane (6.2 g 19.8 mmol) was added and the mixture was heated to reflux for 15 h. The mixture was cooled and the precipitate formed was collected by filtration and dried. Silica gel column chromatography (ethyl acetate:petroleum ether (bp 40-60 °C) [1:1] as eluant) followed by recrystallized from absolute ethanol gave BNIPDi 1 (0.438 g, 11% overall) as a cream solid. \(^1\)H NMR (300 MHz CDCl\(_3\)): δ 8.62, (4H, d, J 7.4 Hz, ArH), 8.23, (4H, d, J 8.5 Hz, ArH), 7.78 (4H, d, J 8.5 Hz, ArH), 4.19 (4H, m, CH\(_2\)), 2.80 - 1.75 (36 H, m, CH\(_2\)). \(^13\)C NMR (300 MHz CDCl\(_3\)): 164.23 (C=O), 133.7 (Ar), 131.2 (Ar), 126.8 (Ar), 122.7 (Ar), 40.4 (CH\(_2\)), 31.7 (CH\(_2\)), 29.6 (CH\(_2\)), 29.4 (CH\(_2\)), 28.1 (CH\(_2\)), 27.5 (CH\(_2\)), 27.1 (CH\(_2\)), 21.1 (CH\(_2\)), 19.0 (CH\(_2\)), 14.2 (CH\(_2\)). BNIPDi has a molecular formula of C\(_{44}\)H\(_{52}\)N\(_2\)O\(_4\), predicted ionisation pattern: 673.4000 Da [M+H]\(^+\) and 674.4033 Da [M+2H]\(^+\). Observed data: 673.3994 Da [M+H]\(^+\) and 674.4028 Da [M+2H]\(^+\).

Synthesis of bis(naphthalimidopropyl)-1,12-diaminododecane (BNIPd, 2): 1,12-diaminododecane (2.0 g, 10 mmol) was dissolved in dry pyridine (40 mL) and the solution was cooled to 0 °C. Mesitylenesulfonyl chloride (4.37 g 20 mmol)
was added in portions. The mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The reaction mixture was poured on to iced water (200 mL) with vigorous stirring to obtain a viscous brown precipitate. The precipitate was filtered, washed with water and dilute aqueous hydrochloric acid, and dried. Recrystallisation from hot ethanol gave dimesitylated 1,12 diaminododecane 5 (2.76 g, 49 %) as a yellow solid. Mp: 102 °C. Dimesitylated 1,12 diaminododecane 5 (1.13 g, 2 mmol) was dissolved in anhydrous dimethylformamide (25 mL). para-toluenesulfonyloxypropynaphthalimide 8 (1.75 g, 4.5 mmol) was added followed immediately by caesium carbonate (3.5 g). The mixture was stirred at 85°C for 8 h. The reaction mixture was poured into iced water (500 mL) with vigorous stirring to give a solid precipitate. 2M aqueous hydrochloric acid (25 mL) was added with stirring to remove any remaining caesium carbonate. The precipitate was collected by filtration, washed with water and dried. Recrystallised from ethanol gave Di-mesityluted bis(naphthalimidopropyl)-1,12-diaminododecane (1.35 g, 65 %) as a white solid. Di-mesitylated bis(naphthalimidopropyl)-1,12-diaminododecane (1.05 g, 1 mmol) was dissolved in dry dichloromethane (20 mL). HBr as a 33% solution in acetic acid (3.85 mL) was added and the mixture stirred at room temperature under nitrogen for 18 h. The formed precipitate was filtered, washed with dry dichloromethane and dried in vacuo at 60 °C. BNIPd 2 (0.429 g, 66 %) was obtained as a pale orange solid. 1H NMR (300 MHz DMSO d6): δ 8.50, (8H, dd, ArH), 7.89 (4H, t, ArH), 4.12 (8H, t, CH2-N), 3.52 (28 H, m, CH2). 13C NMR (300 MHz DMSO d6): 163.6 (C=O), 134.4 (Ar), 130.7 (Ar), 127.2 (Ar), 122.1 (Ar), 46.7 (CH2), 44.8 (CH2), 36.9 (CH2), 28.8 (CH2), 28.4 (CH2), 25.9 (CH2), 25.5 (CH2), 24.5 (CH2).BNIPd was characterised using the peak observed for the free base. The free base has a molecular formula of C42H50N4O4, predicted ionisation pattern: of 675.3905 Da [M+H]+ and 676.3937 Da [M+2H]+. Observed data: 675.3885 Da [M+H]+ and 676.3921 Da [M+2H]+.

Synthesis of bis(naphthalimidopropyl) spermine (BNIPSpm, 3): Spermine (4.04 g, 20 mmol) was dissolved in dry pyridine (50 mL). The solution was cooled to 0°C. Mesitylenesulfonyl chloride (18.57 g, 85 mmol) was added in portions. The mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The
reaction mixture was poured on to iced water (200 mL) with vigorous stirring to obtain a viscous brown precipitate. The precipitate was filtered, washed with water and dilute aqueous hydrochloric acid, and dried. Recrystallisation from hot ethanol gave tetramesitylated spermine 6 (16.72 g, 90 %) as a yellow solid. Tetramesitylated spermine 6 (3.72 g, 4 mmol) was dissolved in anhydrous dimethylformamide. (50 mL). para-toluenesulfonyloxypropynaphthalimide 8 (3.31 g, 8.5 mmol) was added followed immediately by caesium carbonate (7 g). The mixture was stirred at 85°C for 8 h. The reaction mixture was poured into iced water (500 mL) with vigorous stirring to give a solid precipitate. 2M aqueous hydrochloric acid (50 mL) was added with stirring to remove any remaining caesium carbonate. The precipitate was collected by filtration, washed with water and dried. Recrystallisation from ethanol gave Tetra-mesitylated bis(naphthalimidopropyl) spermine (4.40 g, 78 %) as a pale pink solid. Tetra-mesitylated bis(naphthalimidopropyl) spermine (2.19 g, 1.5 mmol) was dissolved in dry dichloromethane (50 mL). HBr as a 33% solution in acetic acid (10 mL) was added and the mixture stirred at room temperature under nitrogen for 18 h. The formed precipitate was filtered, washed with dry dichloromethane and dried in vacuo at 60 °C. BNIPSpm 3 (0.604 g, 60 %) was obtained as an orange solid. ¹H NMR (300 MHz DMSO d₆): δ 8.51, (8H, dd, ArH), 7.90 (4H, t, ArH), 4.15 (4H, t, CH₂), 3.42 (28H, m, CH₂). ¹³C NMR (300 MHz DMSO d₆): 163.7 (C=O), 134.4 (Ar), 130.7 (Ar), 127.1 (Ar), 122.0 (Ar), 43.9 (CH₂), 24.5 (CH₂), 22.4 (CH₂). BNIPSpm was characterised using the peak observed for the free base. The free base has a molecular formula of C₄₀H₄₈N₆O₄, predicted ionisation pattern: 677.3810 Da [M+H]+ and 678.3841 Da [M+2H]+. Observed data: 677.3799 Da [M+H]+ and 678.3833 Da [M+2H]+.

Synthesis of bis(naphthalimidopropyl) 3,3′-butane-1,4-diylbisulfanediyl)dipropan-1-amine (BNIPds, 4): 1,4-butane dithiol (1.22 g, 10 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL) under nitrogen. The mixture was cooled to -78 °C. Triton B (1.67 g, 10 mmol) was added and the mixture stirred for 10 minutes. Acrylonitrile (1.06 g, 20 mmol) was added and the mixture was stirred at room temperature for 4 h. Water (20 mL) was added to the mixture and the mixture was extracted with diethyl ether (2 x 10 mL). The
combined organic extracts were washed with brine, dried over magnesium sulphate and filtered. The solvent was evaporated under reduced pressure to give 3,3’-(butane-1,4-diyl-disulfanediyl)dipropanenitrile (1.14 g, 51 %) as a yellow oil. 3,3’-(Butane-1,4diyldisulfanediyl)dipropanenitrile (1.32 g, 5.8 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL) under nitrogen. Borane-dimethylsulfide complex (2.5 mL, 33 mmol) was added and the mixture was heated to reflux for 24 h. The mixture was cooled to room temperature and an excess of methanol was added. The solvents and by products were evaporated under reduced pressure to give 3,3’-(butane-1,4-diyl-disulfanediyl)dipropan-amine (1.23 g, 90 %) as a viscous colourless oil. 3,3’-(butane-1,4-diyldisulfanediyl)dipropan-1-amine (2.36 g, 10 mmol) and sodium hydroxide (1.00 g, 25 mmol) were dissolved in water (50 cm3) and the solution stirred vigorously to 0° C. A solution of 2-mesitylenesulfonyl chloride (4.37 g, 20 mmol) in diethyl ether (30 mL) was added dropwise to the stirred solution over a period of 15 minutes. The mixture was stirred at 0° C for a further 30 minutes and then allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane (100 mL). The organic phase was washed with brine (2 x 50 mL), dried over magnesium sulfate and the solvent removed under reduced pressure to give dimesitylated 3,3’-(butane-1,4-diyl-disulfanediyl)dipropan-1-amine (4.19 g, 65%) as a pale yellow oil which crystallised on standing to give large pale yellow needles. Dimesitylated 3,3’-(butane-1,4-diyl-disulfanediyl)dipropan-1-amine (3.00 g, 5 mmol) was dissolved in anhydrous dimethylformamide (125 mL) under argon. N-(3-tosyloxypropyl)naphthalimide (4.30 g, 10.5 mmol) was added to the solution followed immediately by caesium carbonate (8.75 g). The mixture was stirred at 85 °C for 24 h. The reaction mixture was allowed to cool to room temperature and poured into iced water (1 L) with vigorous stirring to give a solid precipitate. 2M aqueous hydrochloric acid (100 mL) was added with stirring to remove any remaining caesium carbonate. The precipitate was collected by filtration, washed with water and dried in vacuo to give a sticky pale brown solid. Silica gel column chromatography (ethyl acetate:petroleum ether (bp 40-60 °C) [1:1] as eluant) followed by careful recrystallization from ethanol-dichloromethane gave dimesitylated bis(naphthalimidopropyl) 3,3’-butane-1,4-
Diyldisulfanediyl)dipropan-1-amine (2.47 g, 46%) as a pale cream solid. Dimesitylated bis(naphthalimidopropyl) 3,3'-butane-1,4-diyldisulfanediyl)dipropan-1-amine (4.06 g, 3.8 mmol) was dissolved in dry dichloromethane (120 mL) under argon. HBr as a 33% solution in acetic acid (20 mL) was added and the mixture stirred at room temperature for 18 h. The precipitate was filtered and washed with dry dichloromethane (50 mL) to give a yellow-orange solid. The precipitate was dried on the filter and then in vacuo at 60 °C to remove residual acetic acid to give BNIPds 4 (1.60 g, 59%) as a yellow-orange solid. 1H NMR (300 MHz DMSO d6): δ 8.50 (4 H, d, J 8.5 Hz, ArH), 8.48 (4 H, d, J 8.5 Hz, ArH), 7.89 (4 H, t, J 8.5 Hz, ArH), 4.13 (4H, t, J 6.0 Hz, CH2), 3.60-3.25 (8H, m, CH2), 3.05 (8H, m, CH2), 2.30-1.90 (24H, m, CH2). 13C NMR (300 MHz DMSO d6): 163.7 (C=O), 134.4 (Ar), 130.8 (Ar), 127.3 (Ar), 122.1 (Ar), 44.8 (CH2), 43.3 (CH2), 28.1 (CH2), 24.5 (CH2), 21.6 (CH2). BNIPds was analysed as the free base. The free base of BNIPds has a molecular formula of C40H46N4O4S2, predicted ionisation pattern: 711.3033 Da [M+H]+ and 712.3064 Da [M+2H]+. Observed data: 711.3027 Da [M+H]+ and 712.3061 Da [M+2H]+.
SI-Figure. 1. Mass spectra of A) BNIPDi, B) BNIPd, C) BNIPSpm and D) BNIPds.
SI-Figure 2. FTIR spectra of drug-HNP formulations. A) BNIPDi, B) BNIPd, C) BNIPSpm and D) BNIPds.

SI-Figure 3. Fluorescent emission spectra of drug-HNP formulations. A) BNIPDi, B) BNIPd, C) BNIPSpm and D) BNIPds.
**SI-Figure 4.** *In vitro* drug release of BNIPd and BNIPds from HNP surface at room temperature in water (n=3,±SE).

**SI-Figure 5.** *In vitro* evaluation on BxPC-3, Panc-1 and U937 cells. Cytotoxicity of A) HNP and B) gemcitabine over 24 h measured by MTT assay. C) Cellular uptake of gemcitabine after 1 h & 4 h and D) cytotoxicity measurement after incubation at varied temperature measured via MTT assay (n=3,±SE).
SI-Figure 6. AFM studies using Scan Asyst in air mode on fixed on A) Panc-1 and B) differentiated U937 cells after 24 h exposure to 1) control cells, and cells incubated with 2) HNPs, 3) gemcitabine 4) BNIPSpm and 5) HNP-BNIPSpm for 1 h.
### S1-Table 1. Size measurement of bisnaphthalimide drugs conjugated onto HNPs, using photon correlation spectroscopy and TEM imaging.

<table>
<thead>
<tr>
<th>Nanoparticle</th>
<th>Size, nm Recorded using PCS (n=3,±SD)</th>
<th>PDI</th>
<th>Size, nm Recorded using TEM (n=20,±SD)</th>
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<tbody>
<tr>
<td>HNP</td>
<td>1050 (330)</td>
<td>0.435</td>
<td>76 (7)</td>
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<tr>
<td>HNP-BNIPDi</td>
<td>830 (110)</td>
<td>0.312</td>
<td>72 (11)</td>
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<tr>
<td>HNP-BNIPdi</td>
<td>85 (16)</td>
<td>0.124</td>
<td>80 (16)</td>
</tr>
<tr>
<td>HNP-BNIPSpm</td>
<td>89 (25)</td>
<td>0.237</td>
<td>79 (15)</td>
</tr>
<tr>
<td>HNP-BNIPDi</td>
<td>75 (17)</td>
<td>0.222</td>
<td>79 (17)</td>
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