Tetrahedron 65 (2009) 3990–3997

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An 'inside-out' approach to suramin analogues

Ross P. McGeary [a,b,*], Andrew J. Bennett [a], Quoc B. Tran [a], Johannes Prins [c], Benjamin P. Ross [a,b]

[a] The University of Queensland, School of Chemistry and Molecular Biosciences, QLD 4072, Australia
[b] The University of Queensland, School of Pharmacy, QLD 4072, Australia
[c] The University of Queensland, Diamantina Institute for Cancer, Immunology and Metabolic Medicine, QLD 4072, Australia

ARTICLE INFO

Article history:
Received 26 November 2008
Received in revised form 25 February 2009
Accepted 12 March 2009
Available online 21 March 2009

Keywords:
Suramin
Sulfonic acid
Acylation
Urea

ABSTRACT

An approach to the synthesis of suramin analogues has been realised, which avoids synthetic problems associated with conventional routes. The use of isobutyl ester protecting groups for sulfonic acids was crucial to the success of the strategy, because these were able to be cleanly deprotected with sodium iodide, yielding the sodium salts of the corresponding sulfonic acids.

1. Introduction

Suramin **1** is a symmetric polysulfonated polyaromatic urea, which has been used since 1920 to treat trypanosome-caused onchocerciasis (African river blindness) and African trypanosomiasis (African sleeping sickness). It has also been trialled extensively for the treatment of a number of diseases, including HIV-AIDS and hormone-refractory prostate cancer. Suramin's clinical uses have recently been reviewed; a large number of analogues have been tested, and Figure 1 shows a summary of suramin's structure–activity relationships.[1]

The synthesis of suramin and its analogues invariably involves an 'outside-in' approach, beginning with sulfonated aromatic terminal groups and building the molecule up by sequential nitro group reductions followed by amide-forming reactions, culminating in the synthesis of the central urea functionality using phosgene (Fig. 1).[2–5] This approach has the disadvantages that: (i) the sulfonated starting materials are very poorly soluble in organic solvents and this solubility problem is carried through all subsequent synthetic steps; and (ii) phosgene is a significant hazard. We sought to overcome these problems by devising an 'inside-out' approach to the synthesis of suramin analogues, beginning with the central aromatic urea moiety, and constructing the symmetrical molecules in a bidirectional manner. In this way, we expected that we could avoid the use of highly toxic urea-forming reagents, and delay the incorporation of sulfonate groups until the last step in the synthesis. Herein we report the synthesis of two suramin analogues, **2** and **6**, using this methodology.

2. Results and discussion

Retrosynthetic analysis of suramin analogue **2** leads to 4-nitroaniline **5** via symmetric nitroaryl ureas **3** and **4** (Fig. 2), whereas retrosynthesis of **6** leads to 3-nitroaniline **9** via ureas **7** and **8** (Fig. 3).

2.1. Synthesis of the symmetrical dinitrourea 4

Synthesis of the bis(4-nitrophenyl)urea **4** was first attempted by heating 4-nitroaniline **5** with urea in aqueous acetic acid (Scheme 1), using conditions previously demonstrated for aniline itself.[6] Unfortunately, the desired urea product **4** was obtained only in poor yield after prolonged reaction times. An improved synthesis of **4** began with the acyl azide **10**, which underwent Curtius rearrangement in refluxing toluene to give the unisolated isocyanate **11**. Addition of nitroaniline **5** to the toluene solution of **11**, along with a catalytic amount of acid, then gave the desired urea **4** in good yield.

2.2. Synthesis of 13 and attempted synthesis of 2

Diamino-urea **12** was obtained in excellent yield by catalytic hydrogenation of **4** in DMF solution at atmospheric pressure and room temperature (Scheme 2). The reaction of **12** with 3-nitrobenzoyl chloride then afforded intermediate **3** in good yield, and this was again hydrogenated to the extended diamino-urea **13**.

* Corresponding author. Tel.: +61 7 33653955.
E-mail address: r.mcgeary@uq.edu.au (R.P. McGeary).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.03.033

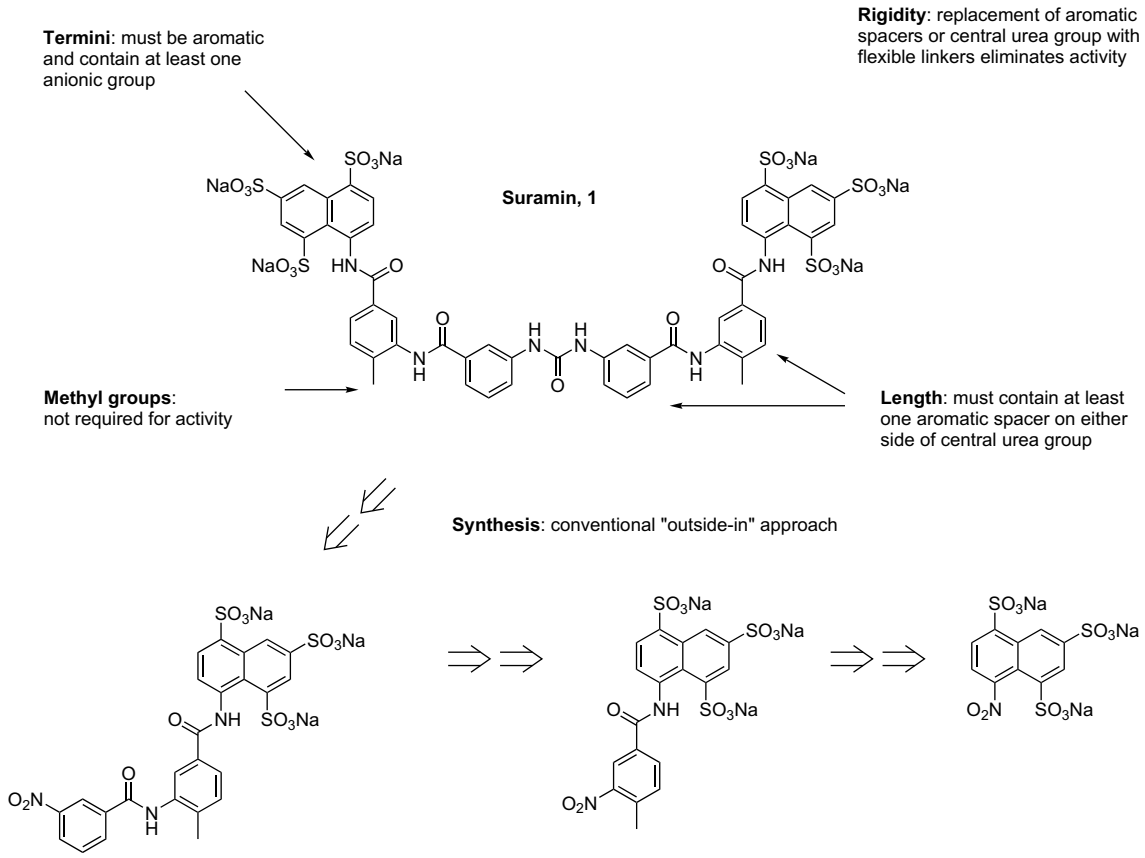


Figure 1. Summary of structure–activity relationships, and conventional synthetic approach to suramin **1** and its analogues.

Unfortunately, all attempts to couple **13** with 4-carboxybenzenesulfonic acid potassium salt, following literature precedent for aromatic amines[7,8] were unsuccessful, leading only to recovery of starting material.

2.3. Model reactions with sulfonyl chloride–acid chloride 14

Having failed to prepare **2** by the route shown in Scheme 2, we devised an alternate approach, requiring the selective acylation of the diamine **13** with the sulfonyl chloride–acid chloride **14** and subsequent hydrolysis of the sulfonyl chloride groups to the sulfonic acids. Since literature precedent for such chemoselectivity between an aromatic sulfonyl chloride and an aromatic acid chloride was scant,[9] we trialled the reaction of **14** with aniline (Scheme 3). We were disappointed to find that treatment of **14** with 1 equiv of aniline at room temperature resulted in reaction at both the sulfonyl chloride and acid chloride groups of **14**, leading to the formation of the corresponding anilide–sulfonamide. However,

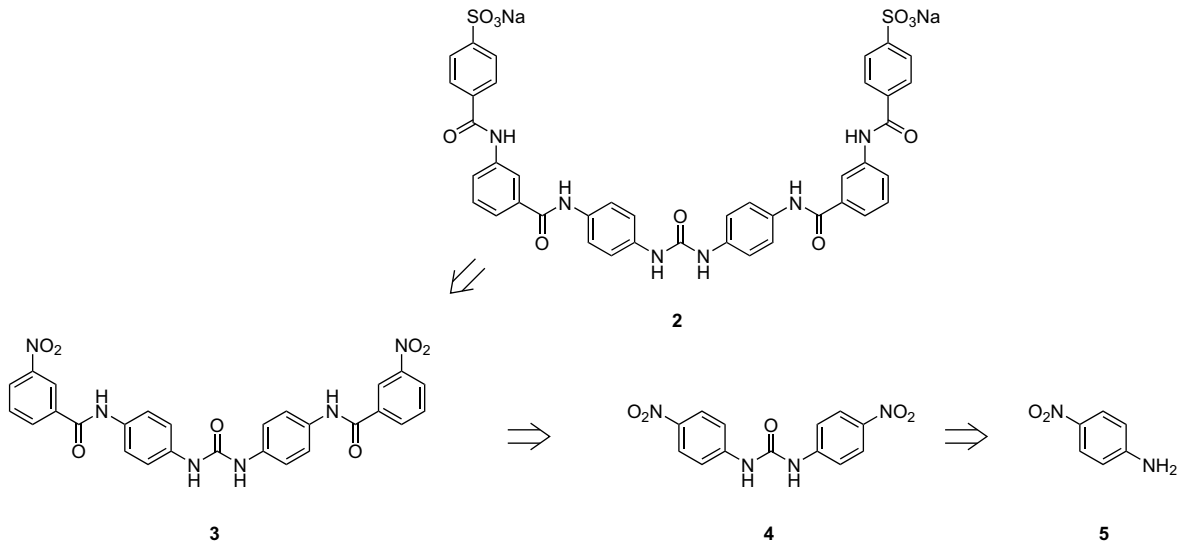


Figure 2.

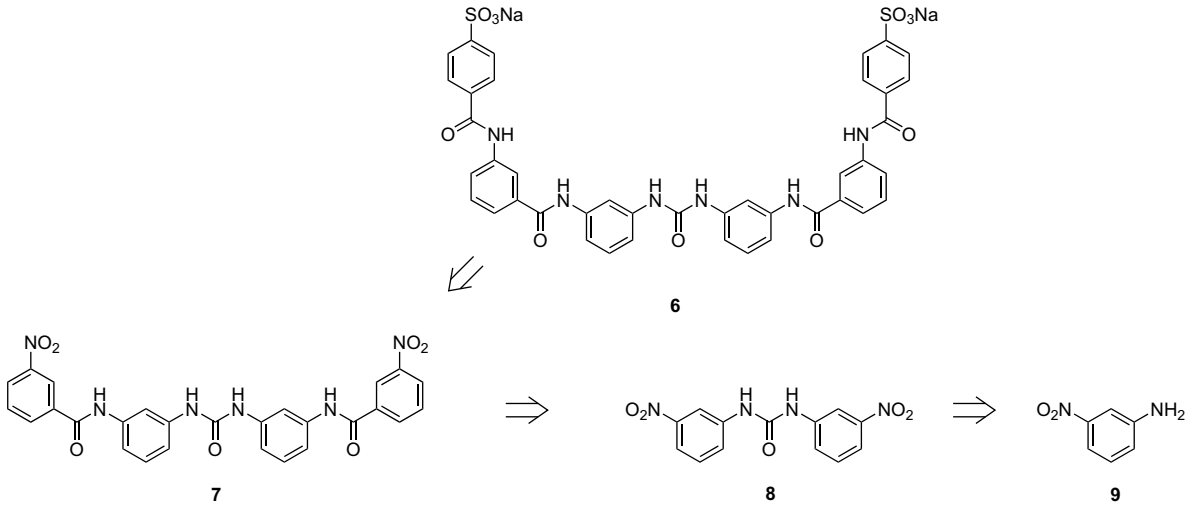
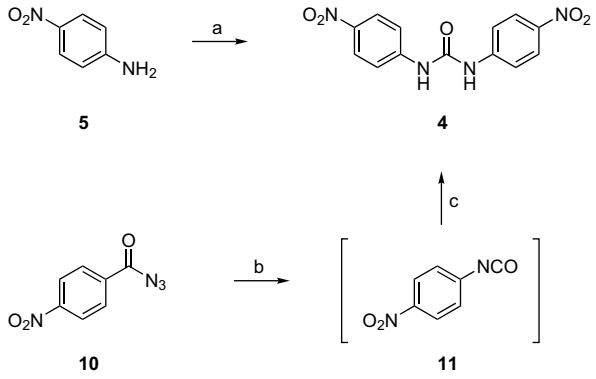


Figure 3.



Scheme 1. Reagents and conditions: (a) $(NH_2)_2CO$, AcOH, H_2O, 130 °C, 45 h (18%); (b) PhMe, Δ, 30 min; (c) **5**, TsOH (cat.), DMF, 125 °C, 135 min (70% from **10**).

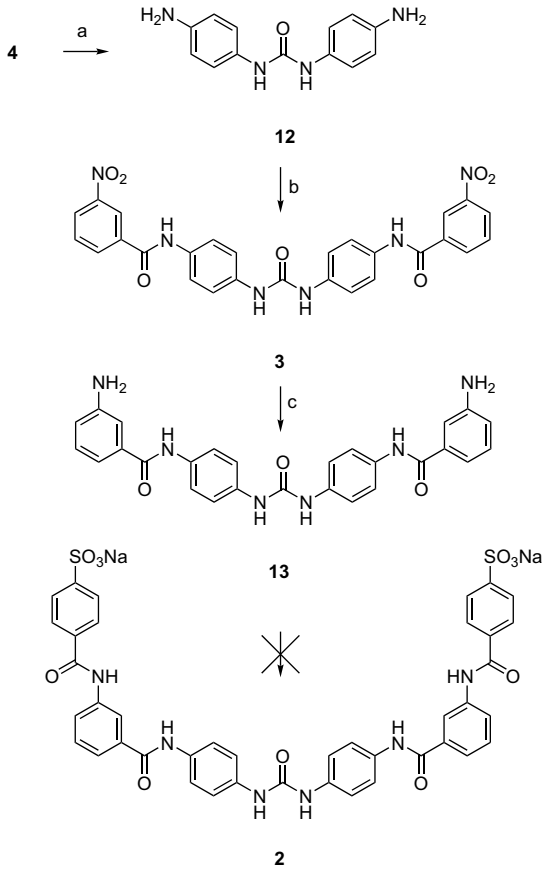
when the reaction was performed at −78 °C, a good yield of the anilide–sulfonyl chloride **15** was obtained. Further, when **15** was warmed in water, the corresponding sulfonic acid **16** was obtained quantitatively.

2.4. Synthesis of the acid forms of 2 and 6

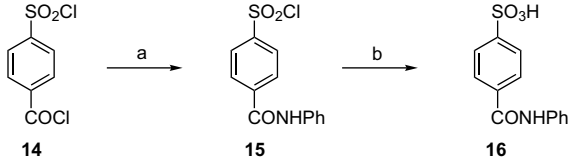
Encouraged by these trial reactions, we next treated diamine **13** with acid chloride **14** and base in cold THF and obtained the presumed bis-sulfonyl chloride as a highly hygroscopic solid, which was not isolated (Scheme 4). Attempts to hydrolyse this material in neat water were unsuccessful, but hydrolysis did occur in aqueous DMF solution. Spectral data of the material obtained after workup showed it to consist largely of the expected bis-sulfonic acid **2**, but this compound proved extremely difficult to purify, due to its poor solubility in aqueous and organic solvents. A sample was subjected to preparative RP-HPLC, which afforded pure **2**, but the amount of material isolated was very low. Similar results occurred when using the same approach to synthesise the acid form of **6**. Clearly, an alternate approach was required to produce pure **2** and **6** in reasonable quantities.

2.5. Model reactions with isobutyl sulfonate ester–acid chloride 19

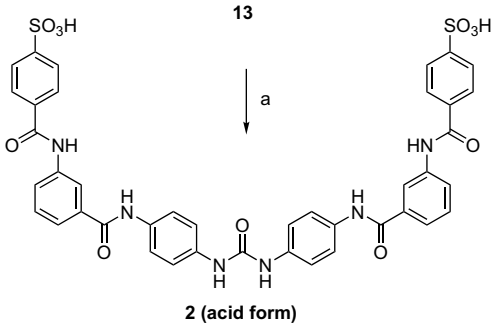
Given that the purification of **2** as its free sulfonic acid had proved problematical, we undertook a strategy whereby the



Scheme 2. Reagents and conditions: (a) H_2/Pd/C, DMF, 24 h (94%); (b) 3-nitrobenzoyl chloride, Et_3N, THF, 12 h (81%); (c) H_2/Pd/C, DMF, 12 h (87%).



Scheme 3. Reagents and conditions: (a) $PhNH_2$, Et_3N, THF, −78 °C (70%); (b) H_2O, 75 °C, 18 h (100%).

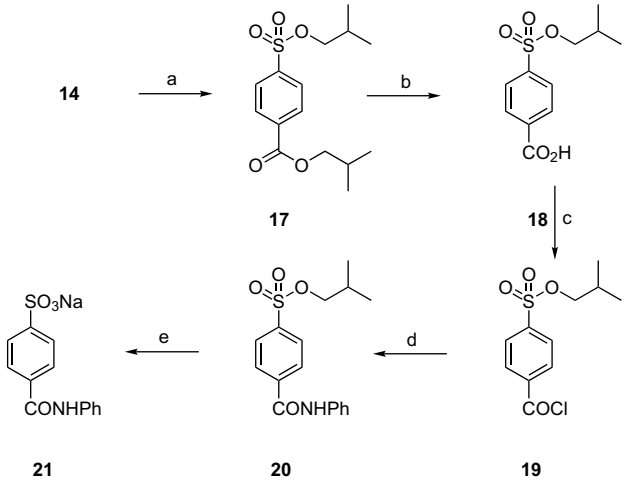


Scheme 4. Reagents and conditions: (a) (i) **14**, Et_3N, THF, −78 °C; (ii) H_2O, DMF.

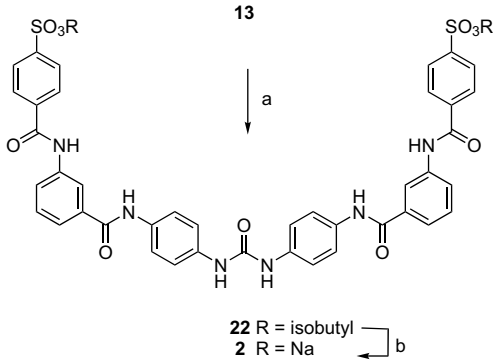
sulfonate salts of the desired targets would be revealed in the final synthetic step, without the need for purification of the products. We envisaged that treatment of a suitable sulfonate ester with iodide anion would liberate a volatile iodoalkane and simultaneously form the sulfonate salt. This strategy has been used previously with isopropyl,[10–12] isobutyl[13] and neopentyl[12,14] esters of sulfonic acids. We found that the isobutyl esters performed best, as demonstrated in the trial reactions shown in Scheme 5. Conversion of **14** to the diester **17** was achieved with isobutanol in the presence of base and a catalytic amount of DMAP. This diester could be selectively hydrolysed with LiOH in aqueous THF to give the carboxylic acid **18**, which was converted to its corresponding acid chloride **19** using thionyl chloride. Reaction of **19** with aniline provided anilide **20** and the sulfonate ester group of this was then cleanly deprotected by treatment with sodium iodide in hot acetone to give the sulfonic acid, sodium salt **21**, which precipitated from solution in excellent yield without the need for purification.

2.6. Synthesis of the disodium salt 2

Having established that the isobutyl sulfonate ester of **20** could be readily removed with iodide ion, we then applied this methodology to the synthesis of target **2**, as shown in Scheme 6. Acylation of diamine **13** with the acid chloride **19** gave disulfonate ester **22**, and this was smoothly deprotected with sodium iodide in refluxing 2-butanone, which precipitated the pure disodium salt **2**, in almost quantitative yield.



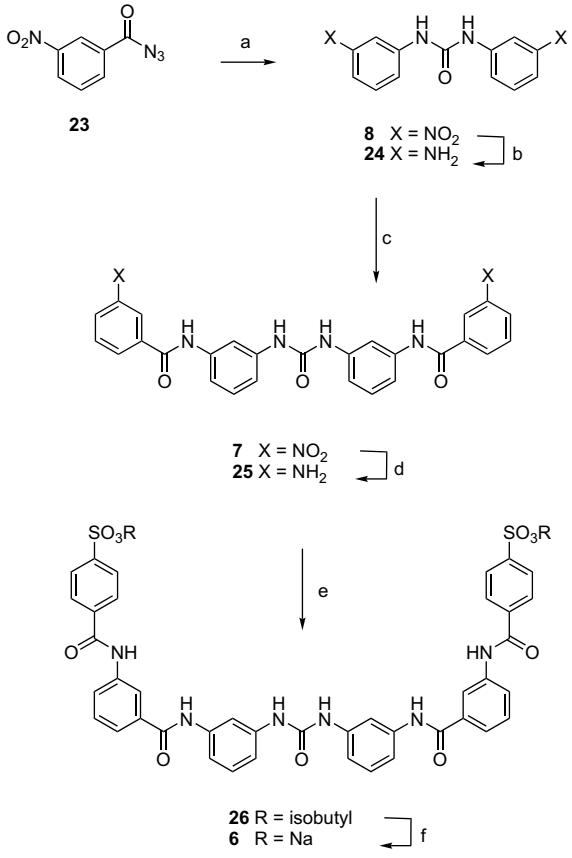
Scheme 5. Reagents and conditions: (a) isobutanol, DMAP (cat.), Et_3N, CH_2Cl_2 (82%); (b) LiOH, H_2O, THF (90%); (c) $SOCl_2$, DMF (cat.), Δ (100%); (d) $PhNH_2$, Et_3N, THF (54%); (e) NaI, Me_2CO, Δ, 32 h (86%).



Scheme 6. Reagents and conditions: (a) **19**, Et_3N, THF, 18 h (73%); (b) NaI, 2-butanone, Δ, 48 h (99%).

2.7. Synthesis of the disodium salt 6

Similar methodology, as outlined in Scheme 7, was then used to prepare suramin analogue **6**. 3-Nitrobenzoyl azide **23** was converted to the corresponding isocyanate in hot toluene, and this reacted with 3-nitroaniline **9** to give bis(3-nitrophenyl)urea **8**. Reduction of the nitro groups of **8** led to the air-sensitive diamine **24**, which was immediately acylated with 3-nitrobenzoyl chloride to give the dinitro intermediate **7**. Hydrogenation of **7** gave the diamine **25**, which was treated with the acid chloride **19** to give the disulfonate ester **26**. Finally, deprotection of **26** with sodium iodide then yielded the disodium disulfonate salt target **6** in excellent yield without the need for purification.



Scheme 7. Reagents and conditions: (a) (i) PhMe, Δ, 40 min; (ii) **9**, TsOH (cat.), Δ, 3.5 h (89%); (b) H_2/Pd/C, DMF, 24 h; (c) 3-nitrobenzoyl chloride, Et_3N, THF, 12 h (42%); (d) H_2/Pd/C, DMF, 36 h (91%); (e) **19**, Et_3N, THF, 18 h (89%); (f) NaI, Me_2CO, Δ, 6 days (84%).

3. Conclusions

A general 'inside-out' approach to the synthesis of suramin analogues **2** and **6** has been developed that avoids conventional methodologies requiring phosgene to form the final urea functionality. Beginning with bis(nitroaryl)ureas, iterative reduction and acylations were employed to build up the symmetrical molecules bidirectionally. A key to this strategy was the use of the isobutyl ester protecting group for sulfonic acids, which underwent deprotection with sodium iodide to liberate the pure sodium salts of the sulfonic acids in the final synthetic step.

4. Experimental

4.1. General

NMR spectra were acquired on a Bruker AV300, AV400 or AV500 spectrometer. Chemical shifts are given in parts per million (ppm) on a δ scale using: (i) D_2O calibrated at δ 4.67 for ^1H spectra and δ 49.50 (based on the addition of a single drop of methanol) for ^{13}C spectra; (ii) $(CD_3)_2SO$ calibrated at δ 2.49 for ^1H spectra and δ 39.50 for ^{13}C spectra; and (iii) $CDCl_3$ calibrated at δ 7.24 for ^1H spectra and δ 77.0 for ^{13}C spectra. The following abbreviations were used to indicate the peak multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Coupling constants (J) are given in hertz. Carbons and protons were assigned with the assistance of COSY, DEPT, HSQC and HMBC spectra. Mass spectral data was performed on a Finnigan AP1-3 sprayer, a PE SCIEX API3000 mass spectrometer or an Applied Biosystems Qstar Pulsar electrospray qtof mass spectrometer in either positive or negative electrospray ionisation mode. Infrared spectra were recorded on a Perkin–Elmer Spectrum 2000 FTIR spectrometer. Melting points were measured with a Stuart capillary apparatus and are uncorrected. Compounds **2** and **6** (acid forms) were purified and analysed on a Shimadzu HPLC system (SCL-10A Controller, SPD-10A UV detector, LC10AT pump). The mobile phase consisted of solvent A: 0.1% trifluoroacetic acid in water; solvent B: 0.1% trifluoroacetic acid in 90% acetonitrile/10% water. Purification was performed using a Merck C18 LiChroSphere semi-preparative column (10 μm, 10×250 mm) with detection at 255 nm. The eluent composition was 0% B then a linear gradient to 100% B over 35 min at a flow rate of 6 mL/min. Fractions (ca. 5 mL) of the eluent were collected and examined for the desired product by ESI-MS. The purity of fractions containing the desired product was examined using a Merck LiChroSphere column (5 μm, 4×250 mm) with detection at 255 nm. The eluent composition was as for the purification method. Column chromatography was carried out using Merck 230–400 mesh silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF_{254}$.

4.2. 4-Nitrobenzoyl azide (10)

Following the general procedure of Munch-Petersen,[15] a solution of 4-nitrobenzoyl chloride (5.05 g, 27.21 mmol) in dry acetone (13 mL) was added dropwise over 1 h to a stirred solution of sodium azide (2.86 g, 44.1 mmol) in water (13 mL) at 0 °C under an atmosphere of argon. A solid precipitated immediately. The suspension was stirred for a further 30 min before water (13 mL) was added and stirring was continued for 30 min. The solid was collected, washed with water and air-dried to yield **10** as almost colourless crystals (4.78 g, 92%), mp 67–69 °C (lit.[16] mp 68–69 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (2H, dt, J 9.1, 2.1), 8.18 (2H, dt, J 9.1, 2.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.2, 135.7, 130.5, 123.8.

4.3. *N,N′*-Bis(4-nitrophenyl)urea (4)

4.3.1. Method A[6]

4-Nitroaniline **5** (105 mg, 0.76 mmol) and urea (23 mg, 0.38 mmol) were dissolved in acetic acid (3 mL) and water (3 mL). The solution was stirred for 45 h at 130 °C. After cooling, additional water (15 mL) was added and a precipitate formed immediately. This was collected and washed with 5% aqueous HCl and water and dried in vacuo to yield **4** as a pale yellow solid (21 mg, 18%), mp 299–305 °C (lit.[17] mp>300 °C); ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.7 (2H, br s, NH), 8.20 (4H, d, J 9.2), 7.71 (4H, d, J 9.2); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 151.7, 145.8, 141.4, 125.1, 118.0.

4.3.2. Method B

4-Nitrobenzoyl azide **10** (4.53 g, 5.1 mmol) was dissolved in dry toluene (50 mL) and the solution was heated under reflux under an atmosphere of argon for 30 min. The solution was allowed to cool before a solution of 4-nitroaniline **5** (3.27 g, 6.5 mmol) in DMF (165 mL) was added, along with a single crystal of toluene-4-sulfonic acid. The mixture was heated at 125 °C for 135 min. Upon cooling yellow crystals formed, which were collected and washed with toluene. The solid was triturated with water and washed with acetone to yield **4** (4.98 g, 70%), with mp and NMR spectra identical to the material prepared above.

4.4. *N,N′*-Bis(4-aminophenyl)urea (12)

N,N′-Bis(3-nitrophenyl)urea **4** (113 mg, 0.38 mmol) was suspended in DMF (5 mL) and 5% palladium on carbon (22 mg) was added. The flask was fitted with a balloon of hydrogen gas and the mixture was stirred for 24 h. The mixture was filtered through Celite® and the catalyst was washed with DMF. The solvent was evaporated to give **12** as a purple powder (86 mg, 94%). This material sublimed at 213–217 °C (lit.[18] mp sublimes above 200 °C); ESI-MS m/z 243.6 $[M+H]^+$, 485.7 $[2M+H]^+$; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 7.90 (2H, s, NH), 7.02 (4H, d, J 8.8), 6.47 (4H, d, J 8.8), 4.70 (4H, br s, NH_2); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 153.3, 143.6, 129.1, 120.4, 114.1; HRMS $[M+H]^+$ calcd for $C_{13}H_{15}N_4O$: 243.1240, found: 243.1250.

4.5. *N,N′*-Bis(4-(3-nitrobenzoyl)aminophenyl)urea (3)

N,N′-Bis(4-aminophenyl)urea **12** (0.86 g, 3.5 mmol) was added to a solution of 3-nitrobenzoyl chloride (1.31 g, 7.1 mmol) in dry THF (10 mL) under an atmosphere of argon, then triethylamine (2.0 mL, 14 mmol) was added dropwise. The suspension was allowed to warm to room temperature and stirring was continued for 12 h. The solid was collected, washed with water and then THF, and air-dried to yield **3** as a red powder (1.55 g, 81%), mp>300 °C; ESI-MS m/z 541.7 $[M+H]^+$; ν_{max} 3278, 1642, 1604, 1533, 1512, 1222 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.48 (2H, s, NH), 8.79–8.78 (2H, m), 8.71 (2H, s, NH), 8.44–8.39 (4H, m), 7.83 (2H, t, J 8.0), 7.68 (4H, d, J 8.9), 7.46 (4H, d, J 9.0); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 162.9, 152.6, 147.8, 136.4, 136.1, 134.1, 132.8, 130.2, 126.0, 122.3, 121.3, 118.4; HRMS $[M+H]^+$ calcd for $C_{27}H_{21}N_6O_7$: 541.1466, found: 541.1469.

4.6. *N,N′*-Bis(4-(3-aminobenzamido)phenyl)urea (13)

Urea **3** (253 mg, 0.47 mmol) was suspended in DMF (5 mL) and 5% palladium on carbon (68 mg) was added. The flask was fitted with a balloon of hydrogen gas and the mixture was allowed to stir for 12 h. The mixture was filtered through Celite®, the catalyst was washed with DMF and the filtrate was evaporated. The residue was triturated with cold water and then dried in vacuo to yield **13** as a colourless solid (196 mg, 87%), mp 201 °C (dec); ESI-MS m/z 481.4

$[M+H]^+$; ν_{max} 3278, 1641, 1603, 1532, 1222 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 9.93 (2H, s, NH), 8.54 (2H, s, NH), 7.65 (4H, d, *J* 8.9), 7.39 (4H, d, *J* 8.9), 7.16–7.04 (6H, m), 6.73 (2H, br d, *J* 7.74), 5.31 (4H, br s, NH_2); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 166.0, 152.6, 148.7, 136.0, 135.4, 133.6, 128.7, 120.9, 118.4, 116.6, 114.7, 113.0; HRMS $[M+H]^+$ calcd for $C_{27}H_{25}N_6O_3$: 481.1988, found: 481.1990.

4.7. 4-(Chlorosulfonyl)benzoyl chloride (14)

The potassium salt of 4-sulfobenzoic acid (1.05 g, 4.4 mmol) was added to thionyl chloride (10 mL) along with one drop of DMF. The suspension was refluxed under argon for 4 h. Upon cooling a precipitate formed, which was filtered off, then the filtrate was evaporated and co-evaporated with toluene (25 mL) to yield **14** as colourless crystals (1.01 g, 97%), mp 53–57 °C (lit.[19] mp 58 °C); ν_{max} 1776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (2H, d, *J* 8.7), 8.18 (2H, d, *J* 8.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.1, 138.6, 132.3, 127.7.

4.8. 4-Phenylcarbamoyl-benzenesulfonyl chloride (15)

Aniline (78 mg, 0.84 mmol) was added dropwise to the solution of 4-(chlorosulfonyl)benzoyl chloride **14** (241 mg, 1.01 mmol) and triethylamine (103 mg, 1.01 mmol) in dry THF at −78 °C under argon. The mixture was then allowed to warm to room temperature over 1 h. The precipitate, which formed was removed by filtration and the filtrate was evaporated. The residue was redissolved in wet THF (10 mL) and the solution was stirred for 15 min and evaporated again. The residue was dissolved in $CHCl_3$ (50 mL) and the solution was washed with saturated $NaHCO_3$ (3×50 mL), 5% HCl (1×50 mL) and brine (1×50 mL), then dried ($MgSO_4$), filtered and evaporated to yield **15** as a faintly red powder (173 mg, 70%), mp 153–155 °C (lit.[20] mp 157–158 °C); ESI-MS *m*/*z* 294 $[M-H]^-$, 296 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* 8.6), 8.06 (2H, d, *J* 8.6), 7.91 (1H, s, NH), 7.61 (2H, br d, *J* 8.0), 7.38 (2H, t, *J* 8.2), 7.20 (1H, t, *J* 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 146.5, 141.1, 137.1, 129.3, 128.5, 127.5, 125.5, 120.5.

When the same reaction was conducted at room temperature, the product obtained in quantitative yield was *N*-phenyl-4-(*N*-phenylsulfamoyl)benzamide: mp 243–244 °C (lit.[19] mp 254–255 °C); ESI-MS *m*/*z* 375 $[M+Na]^+$; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.39 (1H, s, NH), 10.38 (1H, s, NH), 8.03 (2H, d, *J* 8.6), 7.88 (2H, d, *J* 8.6), 7.72 (2H, d, *J* 7.6), 7.36–7.31 (2H, m), 7.27–7.21 (2H, m), 7.13–7.01 (4H, m); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 164.3, 141.9, 138.9, 138.8, 137.4, 129.2, 128.6, 128.5, 126.7, 124.3, 124.0, 120.3, 120.2.

4.9. 4-Phenylcarbamoyl-benzenesulfonic acid (16)

A suspension of 4-phenylcarbamoyl-benzenesulfonyl chloride **15** (53 mg, 0.18 mmol) in water (5 mL) was heated at 75 °C for 18 h. The solution was filtered, evaporated and then co-evaporated with toluene to yield **16**[20] as a colourless powder (49 mg, 100%), mp 170 °C (dec); ESI-MS *m*/*z* 276 $[M-H]^-$; ν_{max} 3289, 1651, 1604, 1536, 1498, 1340, 1205 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.79–7.73 (4H, m), 7.40–7.34 (2H, m), 7.33–7.24 (2H, m), 7.16–7.08 (1H, m); ^{13}C NMR (125 MHz, D_2O) δ 168.9, 146.2, 137.3, 137.2, 129.8, 128.7, 126.6, 126.5, 123.1.

4.10. *N,N′*-Bis(4-(3-(4-sulfobenzamido)benzamido)phenyl)-urea (2) (diacid form)

Urea **13** (171 mg, 0.36 mmol) was suspended in dry THF (10 mL) at −78 °C under argon. 4-(Chlorosulfonyl)benzoyl chloride **14** (180 mg, 0.76 mmol) was added and allowed to dissolve before triethylamine (158 mg, 1.56 mmol) was added dropwise. The mixture was stirred at −78 °C for 45 min, then it was allowed to warm to room temperature over 2 h. The solvent was evaporated and then the residue was suspended in water and collected (184 mg). The solid was dissolved in DMF (5 mL) and water (1 mL) and the solution was heated for 12 h at 60 °C. The solvent was evaporated and the residue was dissolved in water by sonication for 2 h and heating at 65 °C for 2 h [although a significant portion remained undissolved (78 mg)]. The dissolved portion was purified by preparative RP-HPLC. The fractions containing pure product were pooled and lyophilised to yield the target compound as a colourless powder (5 mg, 2%); analytical RP-HPLC t_R=17.5 min, purity 95% (255 nm), mp>300 °C; ESI-MS *m*/*z* 847 $[M-H]^-$; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.45 (2H, s, NH), 10.19 (2H, s, NH), 8.61 (2H, s, NH), 8.31–8.29 (2H, m), 8.02–8.00 (2H, m), 7.95 (4H, d, *J* 8.5), 7.73 (4H, d, *J* 8.5), 7.69–7.66 (6H, m), 7.50 (2H, t, *J* 8.0), 7.43 (4H, d, *J* 9.0); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 165.2, 165.1, 152.6, 151.3, 139.2, 135.7, 135.6, 134.4, 133.4, 128.5, 127.3, 125.5, 123.2, 122.6, 121.0, 119.9, 118.4; HRMS $[M+H]^+$ calcd for $C_{41}H_{33}N_6O_{11}S_2$: 849.1643, found: 849.1589.

4.11. Isobutyl 4-(isobutoxysulfonyl)benzoate (17)

Isobutanol (3.0 mL, 2.41 g, 33 mmol) and a catalytic amount of DMAP were added to a solution of 4-(chlorosulfonyl)benzoyl chloride **14** (4.02 g, 16.8 mmol) and triethylamine (10 mL, 7.3 g, 72 mmol) in dry CH_2Cl_2 under argon at 0 °C. The mixture was allowed to warm to room temperature with stirring over 4 h. The solvent was evaporated and the residue was purified by silica flash column chromatography (15% ethyl acetate in petroleum ether), R_f 0.31, to yield **17** as a colourless oil (4.34 g, 82%); ESI-MS *m*/*z* 337 $[M+Na]^+$; ν_{max} 2965, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* 8.5), 7.96 (2H, d, *J* 8.5), 4.13 (2H, d, *J* 6.5), 3.82 (2H, d, *J* 6.5), 2.03–2.13 (1H, m, *J* 6.5), 1.89–1.98 (1H, m, *J* 6.5), 1.01 (6H, d, *J* 7.0), 0.88 (6H, d, *J* 7.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 139.9, 135.0, 130.2, 127.8, 76.7, 71.7, 27.9, 27.8, 19.0, 18.4; HRMS $[M+Na]^+$ calcd for $C_{15}H_{22}NaO_5S$: 337.1080, found: 337.1088.

4.12. 4-(Isobutoxysulfonyl)benzoic acid (18)

A solution of $LiOH\cdot H_2O$ (0.519 g, 12.4 mmol) in water (16 mL) was added to a stirred solution of isobutyl 4-(isobutoxysulfonyl)benzoate **17** (3.18 g, 10.1 mmol) in THF (16 mL). After 4 h the pH was reduced to ca. 2 by the dropwise addition of 5% HCl. The THF was evaporated and the suspension was extracted with CH_2Cl_2 (3×200 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated to yield **18** as a colourless solid (2.36 g, 90%), mp 161 °C (dec); ESI-MS *m*/*z* 281 $[M+Na]^+$; ν_{max} 2549, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (2H, d, *J* 8.7), 8.0 (2H, d, *J* 8.7), 3.85 (2H, d, *J* 6.5), 1.89–2.02 (1H, m, *J* 6.7), 0.89 (6H, d, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 141.0, 133.8, 131.0, 128.0, 76.5, 28.1, 18.5; HRMS $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_5S$: 281.0454, found: 281.0459.

4.13. 4-Isobutoxysulfonyl-benzoyl chloride (19)

A solution of 4-(isobutoxysulfonyl)benzoic acid **18** (0.511 g, 1.98 mmol) and one drop of DMF in thionyl chloride (5 mL) was heated under reflux for 2 h. The solvent was evaporated and then co-evaporated with dry toluene (3×30 mL) to give **19** as an unstable dark oil (0.547 g, 100%); ν_{max} 1776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* 6.5), 8.01 (2H, d, *J* 6.5), 3.90 (2H, d, *J* 6.5), 2.04–1.91 (1H, m), 0.91 (6H, d, *J* 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 142.3, 137.4, 131.8, 128.3, 77.3, 28.1, 18.5.

4.14. Isobutyl 4-(phenylcarbamoyl)benzenesulfonate (20)

Aniline (145 μL, 0.148 g, 1.59 mmol) was added to a solution of 4-(isobutoxysulfonyl)benzoyl chloride **19** (0.488 g, 1.76 mmol) and triethylamine (0.311 g, 3.08 mmol) in dry THF (10 mL) at 0 °C under

argon. After stirring overnight at room temperature, the suspension was evaporated and the residue was purified by silica flash column chromatography (20% ethyl acetate in petroleum ether), R_f 0.20, to give **20** as a yellow solid (0.286 g, 54%), mp 118–121 °C; ESI-MS *m*/*z* 356 $[M+Na]^+$; ν_{max} 3362, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (1H, s, NH), 7.98 (2H, d, *J* 8.5), 7.91 (2H, d, *J* 8.5), 7.65 (2H, d, *J* 8.0), 7.36 (2H, t, *J* 8.0), 7.17 (2H, t, *J* 7.5), 3.82 (2H, d, *J* 6.5), 1.90–1.96 (1H, m, *J* 6.5), 0.88 (6H, d, *J* 7.0); ^{13}C NMR (125 MHz) δ 164.1, 139.9, 138.7, 137.1, 129.1, 128.1, 128.0, 125.1, 120.3, 77.1, 28.0, 18.4; HRMS $[M+Na]^+$ calcd for $C_{17}H_{19}NNaO_4S$: 356.0927, found: 356.0920.

4.15. 4-(Phenylcarbamoyl)benzenesulfonic acid sodium salt (21)

A solution of isobutyl 4-(phenylcarbamoyl)benzenesulfonate **20** (0.057 g, 0.17 mmol) and sodium iodide (0.039 g, 0.26 mmol) in dry acetone (1 mL) was heated under reflux for 32 h. The resulting precipitate was collected and washed thoroughly with acetone to give **21** as a colourless solid (0.043 g, 86%), mp>300 °C; ESI-MS *m*/*z* 276 $[M-Na]^-$; ν_{max} 1648 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.22 (1H, s, NH, exchanged with D_2O), 7.29 (2H, d, *J* 8.5), 7.77 (2H, d, *J* 7.7), 7.72 (2H, d, *J* 8.3), 7.33 (2H, t, *J* 7.7), 7.08 (1H, t, *J* 7.3); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.1, 151.0, 139.1, 134.8, 128.5, 127.2, 125.5, 123.6, 120.4; HRMS $[M-Na^+]$ calcd for $C_{13}H_{10}NO_4S$: 276.0336, found: 276.0329.

4.16. *N,N′*-Bis(4-(3-((4-isobutoxysulfonyl)benzamido)-benzamido)phenyl)urea (22)

The diamine **13** (0.095 g, 0.20 mmol) was added to a solution of **19** (0.117 g, 0.42 mmol) in dry THF (5 mL) at 0 °C under argon. Triethylamine (0.080 mL, 0.57 mmol) was added and the reaction was allowed to warm to room temperature while stirring overnight. The resulting precipitate was collected, sonicated in saturated $NaHCO_3$ (3 mL) for 2 min and then this was repeated in 5% HCl solution (3 mL) and finally washed with water and THF to yield **22** as a light yellow solid (0.139 g, 73%), mp 240 °C (dec); ESI-MS *m*/*z* 983 $[M+Na]^+$; ν_{max} 3296, 1642, 1604, 1532, 1515, 1438, 1225 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.71 (2H, s, NH), 10.19 (2H, s, NH), 8.61 (2H, s, NH), 8.30 (2H, s), 8.24 (4H, d, *J* 8.6), 8.09 (4H, d, *J* 8.6), 8.02 (2H, d, *J* 8.0), 7.74 (2H, d, *J* 8.0), 7.69 (4H, d, *J* 9.0), 7.53 (2H, t, *J* 7.9), 7.45 (4H, d, *J* 9.0), 3.91 (4H, d, *J* 6.3), 1.93–1.85 (2H, m), 0.84 (12H, d, *J* 6.8); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.0, 164.2, 152.6, 139.6, 138.9, 137.9, 135.9, 135.7, 133.3, 129.0, 128.7, 127.7, 123.3, 122.9, 121.1, 120.0, 118.4, 76.9, 27.5, 18.2; HRMS $[M+Na]^+$ calcd for $C_{49}H_{48}N_6NaO_{11}S_2$: 983.2715, found: 983.2711.

4.17. *N,N′*-Bis(4-(3-(4-sulfobenzamido)benzamido)phenyl)-urea disodium salt (2)

A suspension of **22** (0.089 g, 0.10 mmol) and sodium iodide (0.082 g, 0.55 mmol) in dry 2-butanone (1 mL) was heated under reflux for 2 days. The resulting precipitate was collected, resuspended in 2-butanone (3×2 mL) and filtered to give **2** as a colourless solid (0.810 g, 99%), mp>300 °C; ESI-MS *m*/*z* 915 $[M+Na]^+$; ν_{max} 3280, 1641, 1604, 1537, 1486, 1437, 1224 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.44 (2H, s, NH), 10.18 (2H, s, NH), 8.64 (2H, s, NH), 8.31 (2H, s), 8.02 (2H, d, *J* 7.8), 7.97 (4H, d, *J* 8.3), 7.76 (4H, d, *J* 8.3), 7.69 (6H, d, *J* 8.7), 7.50 (2H, t, *J* 7.9), 7.45 (4H, d, *J* 8.9); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.2, 165.1, 152.6, 152.2, 139.2, 135.7, 135.6, 135.4, 133.4, 128.6, 127.3, 125.5, 123.2, 122.6, 121.0, 119.9, 118.4.

4.18. 3-Nitrobenzoyl azide (23)[15]

A solution of 3-nitrobenzoyl chloride (5.09 g, 27.5 mmol) in dry acetone (13 mL) was added dropwise over a period of 30 min to a stirred solution of sodium azide (3.08 g, 46.9 mmol) in water at 0 °C under an atmosphere of argon. The suspension was stirred for a further 30 min before water (13 mL) was added and stirring was continued for 1 h. The solid was collected, washed with water and air-dried to yield **23** as almost colourless crystals (4.74 g, 90%), mp 65–67 °C (lit.[15] mp 67 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (1H, t, *J* 2.0), 8.44 (1H, ddd, *J* 8.2, 2.3, 1.1), 8.34–8.31 (1H, m), 7.67 (1H, t, *J* 8.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.4, 134.8, 132.2, 130.0, 128.5, 124.3.

4.19. *N,N′*-Bis(3-nitrophenyl)urea (8)[21]

A solution of 3-nitrobenzoyl azide **23** (4.74 g, 24.7 mmol) in dry toluene (50 mL) was heated under reflux under an atmosphere of argon for 40 min. The solution was allowed to cool before a suspension of 3-nitroaniline **9** (3.42 g, 24.8 mmol) in toluene (150 mL) was added followed by the addition of a crystal of toluene-4-sulfonic acid. The suspension was heated at 120 °C for 3.5 h; upon cooling the solid was collected, washed with toluene and dried in vacuo to yield **8** as yellow crystals (6.65 g, 89%), mp 247–251 °C (lit.[21] mp 256–258 °C); ESI-MS *m*/*z* 325 $[M+Na]^+$; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.39 (2H, s, NH), 8.55 (2H, t, *J* 2.1), 7.86–7.84 (2H, m), 7.77–7.75 (2H, m), 7.58 (2H, t, *J* 8.2); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 152.4, 148.1, 140.6, 130.1, 124.7, 116.7, 112.5.

4.20. *N,N′*-Bis(3-(3-nitrobenzamido)phenyl)urea (7)

Urea **8** (2.04 g, 6.80 mmol) was suspended in DMF (30 mL) and 5% palladium on carbon (166 mg) was added. The flask was fitted with a balloon of hydrogen gas, and the mixture was allowed to stir for 60 h. The mixture was filtered through Celite®, the catalyst was washed with DMF and the solvent was evaporated to yield the air-sensitive *N,N′*-bis(3-aminophenyl)urea **24**. Dry THF (10 mL) and triethylamine (3.75 mL, 26.9 mmol) were added and the mixture was cooled to 0 °C. A solution of 3-nitrobenzoyl chloride (2.51 g, 13.6 mmol) in dry THF was added dropwise to the mixture under an atmosphere of argon. The suspension was allowed to warm to room temperature and stirring was continued for 12 h. The mixture was filtered and evaporated. The residue was triturated firstly in $CHCl_3$ and then in saturated $NaHCO_3$ before the solid was collected and washed with water, then acetone, to yield **7** as a yellow solid (1.54 g, 42%), mp 170 °C (dec); ESI-MS *m*/*z* 541.7 $[M+H]^+$, 558.6 $[M+NH_4]^+$; ν_{max} 3417, 3309, 1684, 1640, 1604, 1539, 1511, 1438, 1345 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.59 (2H, s, NH), 8.79 (2H, s, NH), 8.79 (2H, s), 8.44–8.40 (4H, m), 8.04 (2H, m), 7.84 (2H, t, *J* 8.0), 7.40 (2H, br d, *J* 7.5), 7.29–7.24 (4H, m); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 163.8, 152.7, 148.0, 140.2, 139.3, 136.5, 134.4, 130.5, 129.3, 126.4, 122.7, 114.6, 114.4, 110.8; HRMS $[M+Na]^+$ calcd for $C_{27}H_{20}N_6NaO_7$: 563.1286, found: 563.1311.

4.21. *N,N′*-Bis(3-(3-aminobenzamido)phenyl)urea (25)

Compound **7** (0.403 g, 0.75 mmol) was suspended with 5% palladium on carbon (100 mg) in DMF (15 mL). The flask was fitted with a balloon of hydrogen gas, and the mixture was allowed to stir for 36 h. The resulting solution was filtered through Celite®, the catalyst was washed with DMF (40 mL) and the solvent was evaporated. The residue was triturated with cold water (10 mL), collected and dried in vacuo to yield **25** as a colourless solid (0.325 g, 91%), mp 221 °C (dec); ESI-MS *m*/*z* 503 $[M+Na]^+$; ν_{max} 3281, 1637, 1604, 1538, 1515, 1489, 1438 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.04 (2H, s, NH), 8.64 (2H, s, NH), 7.92 (2H, s), 7.34 (2H, d, *J* 8.0), 7.27 (2H, d, *J* 8.1), 7.21 (2H, t, *J* 8.0), 7.13 (2H, t, *J* 7.8), 7.08 (2H, s), 7.06 (2H, d, *J* 7.7), 6.74 (2H, d, *J* 7.9), 5.30 (4H, br s, NH_2); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 166.4, 152.3, 148.6, 139.8, 139.7, 136.0, 128.7, 128.6, 116.7, 114.8, 113.9, 113.2, 113.0, 110.1; HRMS $[M+H]^+$ calcd for $C_{27}H_{25}N_6O_3$: 481.1988, found: 481.1990.

4.22. *N,N′*-Bis(3-(3-(4-sulfobenzamido)benzamido)phenyl)-urea (6) (diacid form)

Urea **7** (103 mg, 0.19 mmol) was suspended in DMF (5 mL) and 5% palladium on carbon (25 mg) was added. The flask was fitted with a balloon of hydrogen gas, and the mixture was allowed to stir for 12 h. The mixture was filtered through Celite®, the catalyst was washed with DMF and the solvent was evaporated to yield the crude **25**. Dry THF (10 mL) was added and the mixture was cooled to −78 °C. 4-(Chlorosulfonyl)benzoyl chloride **19** (103 mg, 0.43 mmol) was added to the mixture and allowed to dissolve before triethylamine (95 mg, 0.94 mmol) was added dropwise under an atmosphere of argon. The mixture was stirred at −78 °C for 45 min before it was allowed to warm to room temperature over 2 h. The solvent was evaporated, and the residue was triturated with water to give a colourless solid (56 mg). This was then dissolved in a DMF/water solution (5 mL DMF, 1 mL water) and the solution was heated for 12 h at 60 °C. The solvent was evaporated and then the residue was dissolved in water by sonication for 2 h [a significant portion remained undissolved (15 mg)]. The dissolved portion was purified by preparative RP-HPLC. The fractions containing pure product were pooled and the solution was lyophilised to yield **6** as a colourless powder (3 mg, 2%); analytical RP-HPLC t_R=18.4 min, purity 97% (255 nm), mp>300 °C; ESI-MS *m*/*z* 423 $[M-2H]^{2-}$; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.46 (2H, s, NH), 10.28 (2H, s, NH), 8.70 (2H, s, NH), 8.32–8.29 (2H, m), 8.01 (2H, br d, *J* 8.7), 7.98–7.92 (6H, m), 7.73 (4H, d, *J* 8.2), 7.68 (2H, br d, *J* 7.9), 7.50 (2H, t, *J* 7.9), 7.38 (2H, br d, *J* 8.0), 7.31 (2H, br d, *J* 8.5), 7.24 (2H, t, *J* 8.0); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 165.6, 165.3, 152.3, 151.3, 139.9, 139.6, 139.2, 135.7, 134.4, 128.9, 128.6, 127.4, 125.5, 123.3, 122.8, 120.0, 114.0, 113.5, 110.1; HRMS $[M+H]^+$ calcd for $C_{41}H_{33}N_6O_{11}S_2$: 849.1643, found: 849.1592.

4.23. *N,N′*-Bis(3-(3-((4-isobutoxysulfonyl)benzamido)-benzamido)phenyl)urea (26)

The diamine **25** (0.24 g, 0.50 mmol) was added to a solution of **19** (0.372 g, 1.34 mmol) in dry THF (6 mL) at 0 °C under argon. Triethylamine (0.185 mL, 1.33 mmol) was added and the reaction was allowed to warm to room temperature while stirring overnight. The resulting precipitate was collected, sonicated in saturated $NaHCO_3$ (5 mL) for 2 min and then this was repeated in 5% HCl solution (5 mL) and finally washed with water and THF to yield **26** as a light yellow solid (0.427 g, 89%), mp 260 °C (dec); ESI-MS *m*/*z* 983 $[M+Na]^+$; ν_{max} 3279, 1638, 1604, 1537, 1515, 1487, 1435, 1287 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.73 (2H, s, NH), 10.28 (2H, s, NH), 8.75 (2H, s, NH), 8.31 (2H, s), 8.24 (2H, d, *J* 8.5), 8.09 (2H, d, *J* 8.6), 8.03 (2H, d, *J* 7.9), 7.99 (2H, s), 7.75 (2H, d, *J* 8.1), 7.53 (2H, t, *J* 8.0), 7.39 (2H, d, *J* 7.2), 7.28 (2H, d, *J* 8.3), 7.25 (2H, t, *J* 8.0), 3.91 (6H, d, *J* 6.0), 1.85–1.93 (2H, m, *J* 7.0), 0.84 (12H, d, *J* 6.5); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.4, 164.2, 152.3, 139.9, 139.6, 138.8, 137.9, 135.8, 129.0, 128.8, 128.7, 127.7, 123.4, 123.1, 120.1, 114.1, 113.6, 110.2, 76.9, 27.5, 18.2; HRMS $[M+Na]^+$ calcd for $C_{49}H_{48}N_6NaO_{11}S_2$: 983.2715, found: 983.2709.

4.24. *N,N′*-Bis(3-(3-(4-sulfobenzamido)benzamido)phenyl)-urea disodium salt (6)

A suspension of **26** (0.035 g, 36.5 μmol) and sodium iodide (0.022 g, 0.15 mmol) in dry acetone (1 mL) was heated under reflux for 6 days. The resulting precipitate was collected, resuspended in acetone (3×2 mL) and filtered to give **6** as a cream solid (0.027 g, 84%), mp>300 °C; ESI-MS *m*/*z* 915 $[M+Na]^+$; ν_{max} 3279, 1638, 1604, 1537, 1516, 1487, 1437, 1225 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.45 (2H, s, NH), 10.26 (2H, s, NH), 9.00 (2H, s, NH), 8.32 (2H, s), 8.03 (2H, d, *J* 8.05), 7.98 (4H, d, *J* 8.75), 7.95 (2H, s), 7.76 (4H, d, *J* 8.7), 7.70 (2H, d, *J* 7.9), 7.50 (2H, t, *J* 7.95), 7.40 (2H, d, *J* 8.0), 7.31 (2H, d, *J* 8.75), 7.24 (2H, d, *J* 8.0); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.5, 165.2, 152.4, 151.1, 140.1, 139.5, 139.2, 135.7, 134.5, 128.8, 128.6, 127.3, 125.6, 123.3, 122.7, 120.0, 114.0, 113.5, 110.2.

Acknowledgements

We thank Adipogen Pharmaceuticals Pty Ltd for providing a scholarship to A.J.B. through the UnIChe Project at The University of Queensland.

References and notes

1. McGeary, R. P.; Bennett, A. J.; Tran, Q. B.; Cosgrove, K. L.; Ross, B. P. *Mini-Rev. Med. Chem.* **2008**, *8*, 1384–1394.
2. Kassack, M. U.; Braun, K.; Ganso, M.; Ullmann, H.; Nickel, P.; Boing, B.; Muller, G.; Lambrecht, G. *Eur. J. Med. Chem.* **2004**, *39*, 345–357.
3. Kreimeyer, A.; Mueller, G.; Kassack, M.; Nickel, P.; Gagliardi, A. R. T. *Arch. Pharm.* **1998**, *331*, 97–103.
4. Biasoli, G.; Botta, M.; Ciomei, M.; Corelli, F.; Grandi, M.; Manetti, F.; Mongelli, N.; Paio, A. *Med. Chem. Res.* **1994**, *4*, 202–210.
5. Nickel, P.; Haack, H. J.; Widjaja, H.; Ardanuy, U.; Gurgel, C.; Duewel, D.; Loewe, H.; Raether, W. *Arzneim.-Forsch.* **1986**, *36*, 1153–1157.
6. Coxon, B.; Fatiadi, A. J.; Schaffer, R.; Cohen, A.; Hertz, H. S. *Org. Magn. Reson.* **1980**, *13*, 187–192.
7. Yan, L.; Muller, C. E. *J. Med. Chem.* **2004**, *47*, 1031–1043.
8. Hayallah, A. M.; Sandoval-Ramirez, J.; Reith, U.; Schobert, U.; Preiss, B.; Schumacher, B.; Daly, J. W.; Muller, C. E. *J. Med. Chem.* **2002**, *45*, 1500–1510.
9. Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653–3661.
10. Musicki, B.; Widlanski, T. S. *Tetrahedron Lett.* **1991**, *32*, 1267–1270.
11. Musicki, B.; Widlanski, T. S. *J. Org. Chem.* **1990**, *55*, 4231–4233.
12. Wrobel, J.; Green, D.; Jetter, J.; Kao, W.; Rogers, J.; Claudia Perez, M.; Hardenburg, J.; Deecher, D. C.; Lopez, F. J.; Arey, B. J.; Shen, E. S. *Bioorg. Med. Chem.* **2002**, *10*, 639–656.
13. Xie, M.; Widlanski, T. S. *Tetrahedron Lett.* **1996**, *37*, 4443–4446.
14. Roberts, J. C.; Gao, H.; Gopalsamy, A.; Kongsjahju, A.; Patch, R. J. *Tetrahedron Lett.* **1997**, *38*, 355–358.
15. Munch-Petersen, J. *Org. Synth.* **1953**, *33*, 53–55.
16. Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2002**, *43*, 1345–1346.
17. Curtis, N. J. *Aust. J. Chem.* **1988**, *41*, 585–595.
18. Bouanane, A.; Lochon, P.; Neel, J. *Bull. Soc. Chim. Fr.* **1974**, 641–648.
19. Imai, Y.; Okunoyama, H. *J. Polym. Sci., Part A: Polym. Chem.* **1972**, *10*, 2257–2264.
20. Tagiev, B. A.; Mel'nikova, E. P.; Vansheidt, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 1669–1675.
21. Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426.