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Synthesis and biological activity of benzamide DNA minor groove binders

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ABSTRACT

A range of di- and triaryl benzamides were synthesised to investigate the effect of the presence and nature of a polar sidechain, bonding and substitution patterns and functionalisation of benzylic substituents. These compounds were tested for their antiproliferative activity as well as their DNA binding activity. The most active compounds in all assays were unsymmetrical triaryl benzamides with a bulky or alkylating benzylic substituent and a polar amino sidechain.

DNA minor groove binders (MGB's) are a diverse group of compounds, of both natural (e.g., distamycin **1a**)[1] and synthetic (e.g., tallimustine **1b**)[2] origins (Fig. 1).[3] Although wide-ranging in nature, they all have a concave-shaped aromatic framework that can fit in to the minor groove of DNA in addition to containing groups that are capable of hydrogen bonding.[4]

Distamycin **1a** is a naturally occurring MGB isolated from *Streptomyces distallicus*, and despite having little antitumor activity and low cytotoxicity owing to their reversible binding to DNA, **1a** has been a lead compound in the synthesis of DNA MGB's,[1] with a large number of polypyrrolic analogues synthesised, a notable of example of which is **1b**.[2,5] Unfortunately, there are significant problems associated with polypyrrole MGB's; due to their electron rich nature there are limited reaction conditions that they can withstand and that can be used to functionalise them. Also, added substituents on the nitrogen have been known to undergo unwanted intramolecular cyclisation, negating the benefits these substituents could provide to activity.[3,6] Additionally, to construct MGB's with appropriate curvature, only substitution at the 2- and 4-positions would provide compounds with the desired curvature. A strategy to overcome these problems is to synthesise benzamide derived MGB's. The synthesis of benzamide derivatives (e.g., **2**) is known,[7] however these benzamide derivatives are either simple symmetrical diaryl derivatives or triaryl amides, none with alkylating functional groups; there is little literature precedent for the synthesis of non-symmetrical and more complicated symmetrical oligoamides with various additional functionalities. Herein we report the synthesis and biological evaluation of complex diaryl and symmetrical and unsymmetrical triaryl benzamide MGB's. These structures have been chosen to explore various structural features that can be incorporated in to benzamide MGB's, including the effect of the presence and nature of a polar sidechain, bonding and substitution patterns and functionalisation of benzylic substituents.

We envisioned that complex symmetric triaryl benzamide MGB's could be formed through the coupling of a symmetric diacid chloride **3**. To incorporate benzylic substitution into the resultant triaryl oligoamide that could be functionalised or allow for conjugation to other bioactive molecules, we wished to synthesise an appropriate aniline for the coupling; aniline **4**, with an easily removable TBDMS (*tert*-butyldimethylsilyl) group was thought to be suitable for this purpose. To provide **4**, dinitrobenzyl alcohol **5** was mono-reduced using Zinin reduction procedures,[8] and then both the resultant amine and alcohol groups were acetylated to give diacetate **6** (Scheme 1). Diacetate **6** was then selectively hydrolysed with sodium hydroxide in ethanol to provide an alcohol which was then protected to give aniline **4** in a very high yield of 97% over two steps.[9] With required aniline **4** in hand, we next sought to achieve dicoupling of **3** and **4**. After screening various reaction conditions, we found that using K_2CO_3 (5.4 equiv) in THF at rt efficiently produced the desired triaryl benzamide in an excellent 96% yield, which was then deprotected with TBAF (tetra-*n*-butylammonium fluoride) to provide diol **7** in a high yield.

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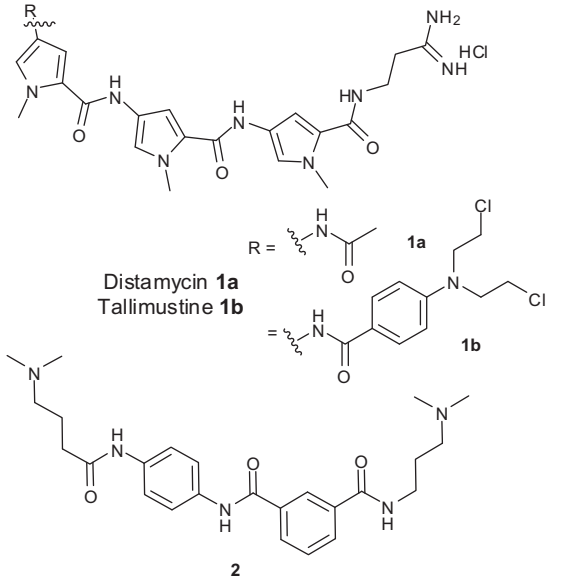
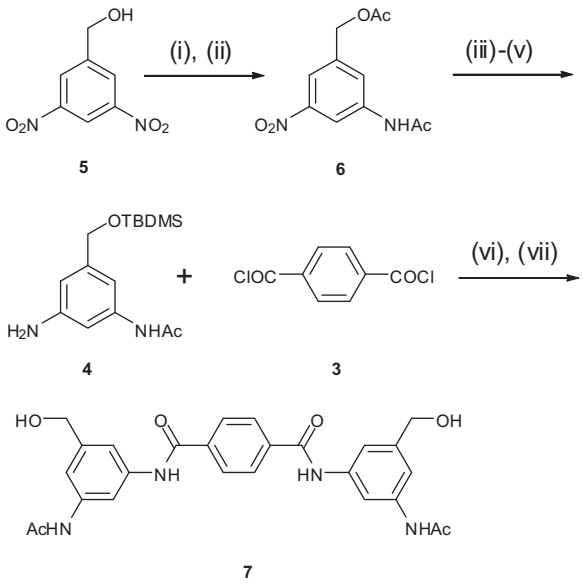
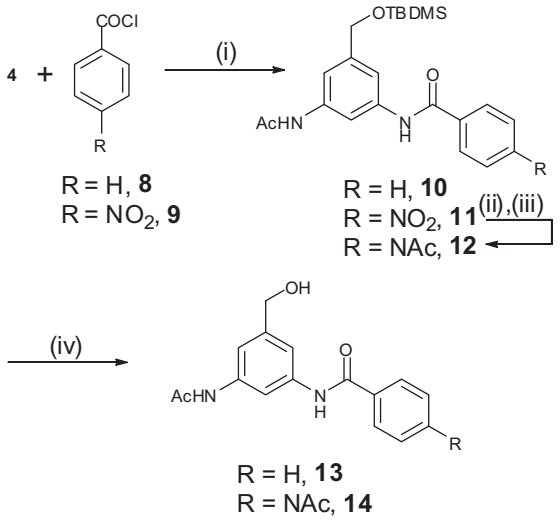


Figure 1. Distamycin **1a**, tallimustine **1b** and benzamide **2**.



Scheme 1. Reagents, conditions and yields: (i) $(NH_4)_2S$, MeOH, reflux then rt, 6 h then 20 h, 81%; (ii) Ac_2O, Et_3N, DMF, rt, 24 h, 99%; (iii) NaOH, EtOH, rt, 3 h, 98%; (iv) TBDMSCl, imidazole, DMF, rt, 5 h, 99%; (v) 10% Pd/C, H_2, MeOH, rt, 3 h, quant; (vi) K_2CO_3, THF, rt, 30 min, 96%; (vii) TBAF, THF, rt, 24 h, 97%.

In order to study the effect of an increased number of aryl groups on the binding of these compounds, we decided to synthesise a range of diaryl benzamides so they could be compared to triaryl benzamides. We first sought to produce simple benzamides with no additional sidechains (Scheme 2) and then follow this with exploration into the addition of polar sidechains to the MGB compounds, which should increase the solubility and binding capabilities of these compounds. Synthesising diaryl benzamides that lack these functionalities would allow the determination of their effect on the biological activity. Aniline **4** was reacted with benzoyl chlorides **8** and **9** to give benzamides **10** and **11** (Scheme 2). The nitro group in **11** was then reduced in quantitative yield to provide benzamide **12**. Finally, deprotection of the TBDMS groups in **10** and **12** gave diaryl benzamides **13** and **14** in high yields.



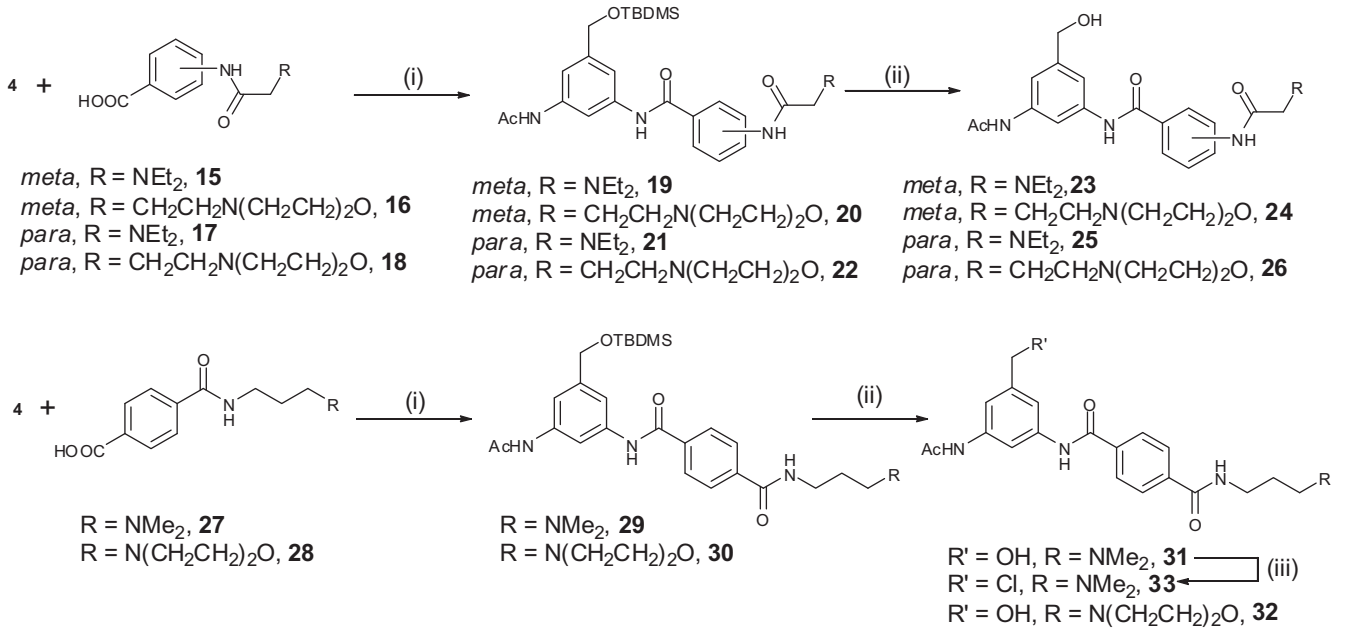
Scheme 2. Reagents, conditions and yields: (i) pyridine, rt, 16 h, 84% **10**, 77% **11**; (ii) 10% Pd/C, H_2, MeOH, rt, 3 h, quant; (iii) Ac_2O, Et_3N, DMF, rt, 24 h, 89%; (iv) TBAF, AcOH, THF, rt, 24 h, 84% **13**, 93% **14**.

After successfully synthesising simplified benzamides **13** and **14**, we wished to adapt our methods to produce diaryl benzamides with additional sidechains, which as stated above, should aid in solubility and binding of the resultant MGB's. Aniline **4** was coupled[11] with *meta* and *para* regioisomers of various previously prepared[10] benzamides **15**–**18** to provide benzamides **19**–**22** which were then deprotected to provide alcohols **23**–**26**. Synthesising both *meta* and *para* substituted benzamides would allow us to investigate the effect of curvature on the activity.

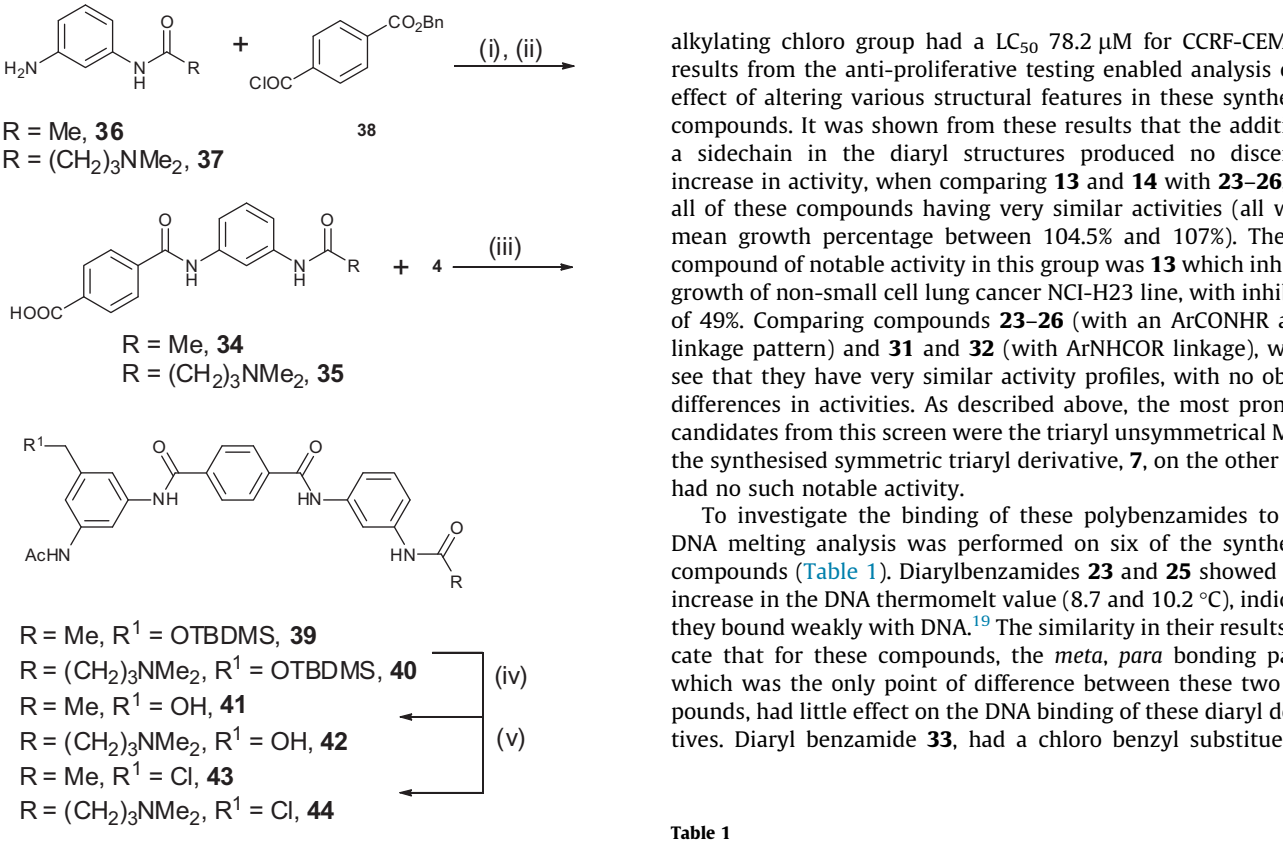
Additionally, we sought to investigate the effect of altering the pattern of amide bonding (from ArNHCOR to ArCONHR); we anticipated that this alteration would have a strong effect on the electronic character in the molecule which could also play an important role in the solubility and activity of the compounds. Once again aniline **4** was used; it was coupled[11] to benzoic acids **27** and **28**[10] to provide benzamides **29**[12] and **30** in very good yields of 96% (**29**) and 80% (**30**). Silyl group deprotection with TBAF gave alcohols **31** and **32**. Alcohol **31** was further functionalised to the mesylate which was immediately converted[13] to the corresponding chloride **33**,[14] an alkylating agent, in 96% over two steps (see Scheme 3).

In addition to the symmetrical triaryl benzamide synthesised earlier, we also sought to construct various unsymmetrical triaryl compounds to further explore the activity of these larger compounds. The acid coupling partners **34** and **35** were synthesised through the coupling of amides **36**[15] and **37**[7b] which contain a polar amino sidechain, with acid chloride **38** followed by hydrogenolysis to give **34** and **35**. Benzoic acids **34** and **35** were then coupled[11] with aniline **4** to provide triaryl benzamides **39** and **40**[16] which were then deprotected to provide alcohols **41** and **42**. Chloride derivatives **43** and **44**[17] were also synthesised from alcohols **41** and **42** in very high yields of 91% and 97%, respectively, over two steps (see Scheme 4).

With various classes of benzamide MGB's synthesised, we next sought to investigate their biological activities and the effect of various structural changes on their activity. As part of the National Cancer Institute's Developmental Therapeutics Program, 15 of the synthesised compounds were selected to be tested for their antiproliferative activity against 60 human tumour cell lines.[18] The compounds were not toxic to all cell lines and instead generally showed very high selectivity for certain cell lines, particularly leukaemia lines K-562, CCRF-CEM, MOLT-4 and SR lines (see Support-



Scheme 3. Reagents, conditions and yields: (i) DIC (*N*,*N*′-diisopropylcarbodiimide), HOBt (hydroxybenzotriazole), DMAP (4-dimethylaminopyridine), DMF, rt, 16 h, 92% **19**, 26% **20**, 73% **21**, 47% **22**, 96% **29**, 80% **30**; (ii) TBAF, THF, rt, 24 h, 84% **23**, 66% **24**, 54% **25**, 93% **26**, 94% **31**, 71% **32**; (iii) MsCl, Et_3N, DMF, rt, 2 h, then NaCl, 60 °C, 30 min, 96%.



Scheme 4. Reagents, conditions and yields: (i) K_2CO_3, THF, rt, 30 min; (ii) 10% Pd/C, H_2, MeOH, rt, 5 h, 79% (2 steps) **34**, 94% (2 steps) **35**; (iii) DIC, HOBt, DMAP, DMF, rt, 18 h, 95% **39**, 26% **40**; (iv) TBAF, THF, rt, 24 h, 91% for **41**, $Et_3N{\cdot}3HF$, THF, rt, 24 h, 61% for **42**; (v) MsCl, Et_3N, DMF, rt, 2 h, then NaCl, 60 °C, 30 min, 91% **43**, 97% **44**.

ing information for full screen data). Owing to this, the most active compounds, **40** and **44**, both triaryl benzamides, were selected for 5-dose testing. In these tests, **44**, the triaryl benzamide with an alkylating chloro group had a LC_{50} 78.2 μM for CCRF-CEM. The results from the anti-proliferative testing enabled analysis of the effect of altering various structural features in these synthesised compounds. It was shown from these results that the addition of a sidechain in the diaryl structures produced no discernible increase in activity, when comparing **13** and **14** with **23**–**26**, with all of these compounds having very similar activities (all with a mean growth percentage between 104.5% and 107%). The only compound of notable activity in this group was **13** which inhibited growth of non-small cell lung cancer NCI-H23 line, with inhibition of 49%. Comparing compounds **23**–**26** (with an ArCONHR amide linkage pattern) and **31** and **32** (with ArNHCOR linkage), we can see that they have very similar activity profiles, with no obvious differences in activities. As described above, the most promising candidates from this screen were the triaryl unsymmetrical MGB's, the synthesised symmetric triaryl derivative, **7**, on the other hand, had no such notable activity.

To investigate the binding of these polybenzamides to DNA, DNA melting analysis was performed on six of the synthesised compounds (Table 1). Diarylbenzamides **23** and **25** showed slight increase in the DNA thermomelt value (8.7 and 10.2 °C), indicating they bound weakly with DNA.[19] The similarity in their results indicate that for these compounds, the *meta*, *para* bonding pattern which was the only point of difference between these two compounds, had little effect on the DNA binding of these diaryl derivatives. Diaryl benzamide **33**, had a chloro benzyl substituent, as

Table 1
ΔT_m and C_{50} values of selected ligands bound with poly AT DNA

Compound	$\Delta T_m \pm 1$ (°C)	C_{50} value
23	8.7	>1 mM
25	10.2	—
31	—	>1 mM
33	21.6	506 μM
40	47.2	5.0 μM
42	30.7	117.6 μM
44	38.7	9.9 μM

opposed to a hydroxyl group for the other diaryl benzamides tested in this assay, as well as an different amide linkage and longer tether to the amine on the sidechain. Compound **33** did have an increased thermomelt value compared to **23** and **25** (21.6 °C). Triaryl benzamides (compounds **40**, **42** and **44**) showed far greater DNA binding activity than the diaryl compounds, as can be seen by the increase in DNA thermomelt values (47.2, 30.7 and 38.7 °C for **40**, **42** and **44**). All tested triaryl benzamides differed only in the benzyl substituent; it can be seen from the reported results that **40** (with an OTBDMS group) binds strongest to DNA, followed by **44** with a chloro substituent. Of the triaryl benzamides, **42** bound the weakest, indicating that the hydroxyl group is not as favourable for DNA binding activity as the other test substituents.

Owing to the ability of ethidium bromide to bind with DNA, ethidium displacement assays have been used to study the binding activities of minor groove binding agents,[7,20] whereby ethidium displacement from DNA by the minor groove binder can be measured through fluorescence. To further quantify the extent of DNA binding of these synthesised compounds, an ethidium displacement assay was used; we report the C_{50} (amount of ligand required to displace ethidium from DNA, with a resultant 50% drop in fluorescence intensity)[21] of six selected compounds. As with the DNA melt assay, diaryl benzamides (**23**, **31** and **33**) were the least active in displacing ethidium, diaryl benzamides **23** and **31** had $C_{50} > 1$ mM. Diaryl benzamide **33**, which differs from **31** only in the chloro substituent (as opposed to a hydroxy group in **31**) had a C_{50} 506 μM; this indicates that the chloro substituent has a marked effect on the ethidium displacement activity. Once again, **40**—a triaryl benzamide with a bulky OTBDPS benzylic substituent was the most active (C_{50} 5.0 μM). Also correlating to the DNA melt assay, triaryl benzamide with a chloro substituent, **44**, was the second most active compound tested (C_{50} 9.9 μM). These two compounds were far more active than **42** (C_{50} 117.6 μM), which differs only from **40** and **44** by the benzylic substituent (hydroxyl for **42**). These results once again indicate that triaryl benzamides have an increased activity over their diaryl counterparts and chloro and the bulky OTBDMS benzylic substituents are desirable for greater activity over compounds with an alcohol group.

In summary, a range of di- and triaryl benzamide MGB's were synthesised. These compounds differed from each other in the presence and nature of a polar sidechain, bonding and substitution patterns and functionalisation of benzylic substituents. These compounds were tested for their antiproliferative activity as well as their DNA binding activity. The most active compounds in all assays were triaryl benzamides **40** and **44**, with a bulky and alkylating chloro benzylic substituent, respectively, and a polar amino sidechain. The alcohol that is formed from the deprotection of **40** can be used as an additional site of modification, as shown be the subsequent of chloride **44**. Based on these results, we aim to further explore compounds similar to **40** and **44**, and will report our results in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.12.090.

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9. See Supporting information for further experimental details on the synthesis of aniline **4**.
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11. *General procedure for the coupling of acid and aniline:* To a solution of acid (1 equiv) in dry DMF (5 mL/mmol), was added aniline (0.5 equiv) and catalytic amount of DMAP (1–2 mg) and the mixture was stirred for 5–10 min under an atmosphere of nitrogen. DIC (1 equiv) was then added dropwise and the resulting solution stirred for 2 min, followed by the addition of HOBt (1 equiv). The mixture was then stirred for 18 h at room temperature, before the DMF was removed in vacuo. The residue was diluted with methanol (10 mL), water (2 mL) and potassium carbonate (1 equiv). Silica gel was added to form a slurry. The solvent was then removed in vacuo to give the crude product adhered to silica. This silica was then loaded and purified by flash chromatography. In some cases repeated chromatography was needed to purify the product.
12. *Data for* **29**: R_f (MeOH/NH_3 9:1) = 0.13; IR ν_{max}(NaCl)/cm^{-1}: 3429, 2952, 1670, 1620, 1551, 1459, 1374, 1287; ^{1}H NMR (400 MHz, CD_3OD): δ 0.10 (6H, s, OSi(CH_3)$_2$), 0.94 (9H, s, OSiC(CH_3)$_3$), 1.81 (2H, p, J = 7.3 Hz, $CH_2CH_2CH_2$), 2.10 (3H, s, NHCOCH_3), 2.26 (6H, s, N(CH_3)$_2$), 2.43 (2H, t, J = 7.6 Hz, NCH_2), 3.41 (2H, t, J = 7.0 Hz, CONHCH_2), 4.69 (2H, s, ArCH_2O), 7.36 (1H, s, Ar-H), 7.42 (1H, s, Ar-H), 7.86–90 (3H, m, Ar-H), 7.96 (2H, d, J = 8.3 Hz, Ar-H); ^{13}C NMR (100 MHz, CD_3OD): δ −5.5 (OSi(CH_3)$_2$), 18.2 (OSiC(CH_3)$_3$), 23.8 (NHCOCH_3), 25.3 (OSiC(CH_3)$_3$), 25.7 ($CH_2CH_2CH_2$), 38.3 (CONHCH_2), 44.2 (N(CH_3)$_2$), 56.8 (NCH_2), 66.7 (ArCH_2O), 110.8 (Ar-C), 113.8 (Ar-C), 114.0 (Ar-C), 127.0 (Ar-C), 127.4 (Ar-C), 136.7 (Ar-C), 137.3 (Ar-C), 138.3 (Ar-C), 138.6 (Ar-C), 142.7 (Ar-C), 165.9, 167.2 and 169.6 (NHCOAr, CONHCH$_2$ and NHCOCH$_3$); m/z (FAB$^+$) 527 (MH$^+$, 72%), 469 (MH$^+$-C_4H_9, 7%), 450 (100%), 265 (20%); HRMS found (FAB$^+$); MH$^+$ 527.3058, $C_{28}H_{43}N_4O_4Si$ requires 527.3054.
13. *General procedure for the conversion of benzylic alcohol to chloride:* To a solution of alcohol (1 equiv) and triethylamine (1.5 equiv) in dry DMF (4 mL/mmol alcohol) at 0 °C was added methanesulfonyl chloride (1.5 equiv) in dry DMF (3 mL/mmol alcohol) and the resulting solution stirred at room temperature for 2 h. Sodium chloride (10 equiv) was added and the mixture was heated at 60 °C for 30 min. The solvent was then removed in vacuo. The crude product was then purified by flash chromatography to furnish the pure product.
14. *Data for* **33**: IR ν_{max}(NaCl)/cm^{-1}: 3266, 3067, 1642, 1616, 1544, 1455, 1286; ^{1}H NMR (400 MHz, CD_3OD): δ 2.08 (2H, p, J = 7.3 Hz, $CH_2CH_2CH_2$), 2.15 (3H, s, NHCOCH_3), 2.94 (6H, s, N(CH_3)$_2$), 3.25 (2H, t, J = 7.6 Hz, NCH_2), 3.53 (2H, t, J = 6.9 Hz, CONHCH_2), 4.62 (2H, s, ArCH_2Cl), 7.47 (1H, t, J = 1.6 Hz, Ar-H), 7.54 (1H, t, J = 1.6 Hz, s, Ar-H), 7.99–8.02 (5H, m, Ar-H); ^{13}C NMR (100 MHz, CD_3OD): δ 24.0 (NHCOCH_3), 26.1 ($CH_2CH_2CH_2$), 37.7 (CONHCH_2), 43.6 (N(CH_3)$_2$), 46.8 (ArCH_2Cl), 56.8 (NCH_2), 113.8 (Ar-C), 117.5 (Ar-C), 118.0 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 138.1 (Ar-C), 139.0 (Ar-C), 140.3 (Ar-C), 140.4 (Ar-C), 144.0 (Ar-C), 167.8, 169.6 and 171.8 (NHCOAr, CONHCH$_2$ and NHCOCH$_3$); m/z (ESI$^+$): 431 (MH$^+$, 100%), 413 (29%), 381 (20%), 251 (5%), 292 (21%); HRMS found (ESI$^+$): MH$^+$ 431.1829 $C_{22}H_{28}N_4O_3$ requires 431.1839.
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16. *Data for* **40**: R_f (MeOH/NH_3 9:1) = 0.81; IR ν_{max}(solid)/cm^{-1}: 3287, 2929, 1652, 1606, 1540, 1417, 1254; ^{1}H NMR (400 MHz, CD_3OD): δ 0.09 (6H, s, OSi(CH_3)$_2$), 0.92 (9H, s, OSiC(CH_3)$_3$), 1.83 (2H, p, J = 7.6 Hz, $CH_2CH_2CH_2$), 2.09 (3H, s, NHCOCH_3), 2.24 (6H, s, N(CH_3)$_2$), 2.34–2.39 (4H, m, NCH_2, NHCOCH_2), 4.66 (2H, s, ArCH_2O), 7.24 (1H, t, J = 8.2 Hz, Ar-H), 7.32 (1H, br s, Ar-H), 7.34 (1H, br s, Ar-H), 7.39 (1H, d, J = 8.0 Hz, Ar-H), 7.42 (1H, s, Ar-H). 7.90 (1H, br s, Ar-H), 7.91 (1H, t, J = 1.8 Hz, Ar-H), 7.95 (4H, m, Ar-H); ^{13}C NMR (100 MHz, CD_3OD): δ −5.0 (OSi(CH_3)$_2$), 19.3 (OSiC(CH_3)$_3$), 24.0 ($CH_2CH_2CH_2$), 24.1 (NHCOCH_3), 26.5 (OSiC(CH_3)$_3$), 35.7 (NHCOCH_2), 45.3 (N(CH_3)$_2$), 59.9 (NCH_2), 66.0 (ArCH_2O), 112.8 (Ar-C), 114.2 (Ar-C), 115.4 (Ar-C), 115.8 (Ar-C), 117.6 (Ar-C), 118.0 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 130.1 (Ar-C), 139.0 (Ar-C), 139.1 (Ar-C), 140.0 (Ar-C), 140.2 (Ar-C), 140.3 (Ar-C), 140.4 (Ar-C), 144.1 (Ar-C), 167.8, 167.9, 172.7 and 173.9 (NHCOAr, NHCO, CONH and NHCOCH$_2$); m/z (ESI$^+$): 646 (MH$^+$, 100%), 532 (6%), 384 (22%); HRMS found (ESI$^+$): MH$^+$ 646.3428, $C_{35}H_{48}N_5O_5Si$ requires 646.3425.
17. *Data for* **44**: R_f (MeOH/NH_3 9:1) = 0.74; IR ν_{max}(solid)/cm^{-1}: 3260, 2930, 1649, 1606, 1544, 1450, 1416, 1287; ^{1}H NMR (400 MHz, CD_3OD): δ 2.10 (3H, s,

NHCOCH_3), 2.10 (2H, pentet, J = 8.0 Hz, $CH_2CH_2CH_2$), 2.59 (2H, t, J = 8.0 Hz, NHCOCH_2), 2.74 (6H, s, N(CH_3)$_2$), 3.24 (2H, t, J = 8.0 Hz, NHCOCH_2), 4.61 (2H, s, ArCH_2Cl), 7.30 (1H, t, J = 8.0 Hz, Ar-H), 7.39 (1H, d, J = 8.0 Hz, Ar-H), 7.44 (1H, d, J = 8.0 Hz, Ar-H), 7.47 (1H, br s, Ar-H), 7.55 (1H, br s, Ar-H), 8.03–8.04 (5H, m, Ar-H), 8.13 (1H, t, J = 4.0 Hz, Ar-H); ^{13}C NMR (100 MHz, CD_3OD): δ 21.4 ($CH_2CH_2CH_2$), 24.1 (NHCOCH_3), 35.4 (NHCOCH_2), 43.6 (N(CH_3)$_2$), 46.9 (ArCH_2Cl), 58.6 (NCH_2), 113.8 (Ar-C), 114.4 (Ar-C), 117.5 (Ar-C), 117.6 (Ar-C), 118.0 (Ar-C), 118.2 (Ar-C), 128.9 (Ar-C), 129.0 (Ar-C), 130.1 (Ar-C), 138.9 (Ar-C), 139.0 (Ar-C), 140.1 (Ar-C), 140.2 (Ar-C), 140.4 (Ar-C), 140.6 (Ar-C), 167.8, 167.8, 171.8 and 172.7 (NHCOAr, NHCO, CONH and NHCOCH$_2$); m/z (ESI$^+$): 550 (MH$^+$, 100%), 546 (4%); HRMS found (ESI$^+$): MH$^+$ 550.2213, 552.2199, $C_{29}H_{33}^{35}ClN_5O_4$ and $C_{29}H_{33}^{37}ClN_5O_4$ requires 550.2221, 552.2192.

18. See Supporting information for full NCI report sheets.
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