A fragment based click chemistry approach towards hybrid G-quadruplex ligands: design, synthesis and biophysical evaluation

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ABSTRACT

A library of hybrid oxazole–triazole based compounds containing contiguously linked aromatic units were synthesised as G-quadruplex binding ligands. The design of these ligands was based upon combining features of our first generation of G-quadruplex bis-triazole ligands and the natural product telomestatin. The syntheses and biophysical studies of these ligands are described.

In recent years numerous G-quadruplex binding ligands have been identified, the vast majority possessing a large aromatic/heteroaromatic unit, usually locked into a planar disposition. These aromatic moieties π-stack onto the terminal tetraplex of the quadruplex providing extra stabilisation, and can even induce folding into the higher order structures. Side chains, which have a positive charge or that can become protonated at physiological pH, are another common feature, and provide points for electrostatic interactions with the negatively charged phosphate residues in the grooves. However, ligands that selectively target specific G-quadruplex structures are limited, presenting a significant challenge for further development.

We have previously reported the synthesis and biological evaluation of a family of triazole based quadruplex binding ‘click’ ligands (e.g., Scheme 1), which showed strong G-quadruplex stabilising effects, telomerase inhibition and anti-cancer activity. The design of these compounds was inspired by the non-fused complex polycyclic aromatic structure of telomestatin (2), a very potent telomerase inhibitor isolated from Streptomyces annulatus.

We proposed that the 1,4-triazole moiety would serve as a suitable mimic of the oxazole functionality of telomestatin (2), and could be readily installed using the powerful CuAAC click reaction, thus facilitating the synthesis of libraries of potential ligands. Indeed, the ‘click’ ligands (e.g., 1) displayed impressive selectivity for G-quadruplex structures over duplex DNA, comparative to that of telomestatin (2). Although 2 is an incredibly potent and selective quadruplex binder, it is also a complex synthetic target requiring lengthy syntheses, whereas our ligands were readily accessible in significant quantities.
We have since developed a second generation of tristriazole ligands (3), which were designed in order to examine whether G-quadruplexes could be stabilised by end-on hydrogen atom–π interactions. However, whilst the loss of effective π–π binding interactions by the inclusion of such tetrahedral centres was not balanced by potential hydrogen–π bonding interactions, the quadruplex/duplex selectivity of the ligands once again remained high, suggesting that the rotational freedom of non-fused polyaromatic systems is important with regard to selectivity.

Taking these two factors into consideration, we have designed a third generation of ligands, again based on a non-fused polyaromatic system but excluding excessive conformational flexibility. Since π-stacking interactions had proven to be particularly important, we opted to increase the number of heteroaromatic units in the ligand cf. 1, in an attempt to maximise binding between electron-rich ligand heterocycles and guanine residues. The general design of these hybrid ligands was to incorporate the oxazole motifs of telomestatin (2), and the 1,4-triazole and side chain functionalities present in our first generation (e.g., 1) (Scheme 1). Keeping in mind the proposed use of click chemistry, we opted to target a series of triazole-centred ligands (e.g., 4) flanked by phenoxazoles (Scheme 1). Syntheticlly, the ligands would be accessed through a CuAAC reaction of the corresponding alkynes and azides.

2. Results and discussion

The synthesis of our library began using the procedure of Scanlan et al., with a Sonogashira reaction of 4-bromobenzoamide 7 with ethynyltrimethylsilane to give 8 in 88% yield (cf. 53% Scanlan, Scheme 2).17 Typical Blumlein–Lewy oxazole synthesis conditions (8, ethyl bromopyruvate, EtOH, reflux) provided oxazole 9 in low yield (<30%). Hence, we opted for the two-step procedure described by Panek,18 which provided the oxazole 9 in good overall yield. The TMS-protected alkynyl was then unmasked and the ester hydrolysed in one step to afford the acid 10, which was converted to the acid chloride 11 by treatment with (COCl)2/DMF. Compound 11 was subsequently reacted with various N,N-dialklyldiamines to afford the alkynle coupling partners 12–17 for the ensuing click reaction.

The complementary azide coupling partners were accessed via an analogous route. Hence, 4-aminobenzoamide 18 was converted to the corresponding azide, which was then subjected to the same oxazole forming conditions as before to give 19 (Scheme 2). Hydrolysis of 19 was followed by conversion to the acid chloride 20, to which a series of N,N-dialklyldiamines were added providing the amides 21–26. Finally, the azide 5 and alkyl 6 coupling partners were reacted together, under our previously developed microwave conditions,19 to deliver the new library of hybrid triazole–bisoxazole ligands 27–35 in good yield (69–87%, Scheme 2).

The ability of these compounds to stabilise G-quadruplex and double helix DNA was investigated using a high-throughput FRET (fluorescence resonance energy transfer) assay.20 Table 1 shows the effect of different concentrations of compounds 27–35 on the melting temperature (Tm) of two labelled oligomers in 60 mM potassium cacodylate buffer at pH 7.4. The G-quadruplex forming human telomeric (h-Tel) sequence (5′-FAM-d(GGG[TAGGG][TTAGGG][TTAGGG][TTAGGG]); TAMRA-3′) and the F10T (ds) sequence (5′-FAM-dTATAGCTATA-HEG-TATAGCTATA-TAMRA-3′)—a hairpin double helix labelled oligomer with an internal hexaethylenglycol (HEG) linker.

At a concentration of 4 μM several ligands, 31, 34 and 35, showed moderate to good stabilisation of the G-quadruplex with excellent selectivity over duplex DNA. Ligand 30 was by far the best binder (ΔTm=15°C) but it did not discriminate between duplex and quadruplex DNA quite as effectively as 31, 34 and 35, which is essential for development as potential therapeutics. The ligands with side chains containing three methylene units (n/n′=2) were uniformly stronger quadruplex binders than the analogous ligands with side chains containing two methylene units (n/n′=1) i.e., 27 cf. 30, 28 cf. 31, 29 cf. 32, 33 cf. 34. This may be due to the fact that the longer arms allow more effective positioning of the protonated amines for interaction with the phosphate backbone, or simply due to providing more interactions with the guanine quartet. It appears that the smaller ammonium ions interact more effectively than larger analogues, regardless of the length of the side chain, i.e., 27 cf. 29 and 30 cf. 32, suggesting that there is a pocket with some steric constraints where the protonated amines and phosphate backbone interact. At a concentration of 1 μM the ligands were quite poor at binding G-quadruplex forming DNA, the unsymmetrical ligand 35 being the only ligand to show any real affinity for h-Tel. Although these ligands show comparable quadruplex binding ability to some previously reported ligands,24 they were rather disappointing bearing in mind our first generation of ligands, i.e., 1 (Scheme 1), which exhibited ΔTm=−18°C at a concentration of 1 μM for the h-Tel G-quadruplex forming sequence.

However, one critical feature was prominent from these studies; the selectivity of the ligands for quadruplex DNA over duplex DNA remained consistently high, even at higher concentrations of the

![Scheme 1. Rational design and retrosynthesis of new hybrid G-quadruplex ‘click’ ligands.](image-url)
ligands. Although non-specific binding of the ligands to quadruplex DNA cannot be ruled out, it is noteworthy that this series of non-fused polyaromatic ligands have displayed excellent selectivity for quadruplex DNA over duplex DNA. In this context perhaps ligand 35 is most interesting, which displayed complete selectivity for quadruplex DNA over duplex DNA, even at a concentration of 4 mM, and showed a small amount of stabilisation of h-Tel at a concentration of 1 mM.

3. Conclusion

In summary, we have prepared a small library of hybrid G-quadruplex binding ligands inspired by the natural product telomestatin and our first generation ‘click’ ligands. These non-fused polycyclic ligands comprised both triazole and oxazole functionality with pendant side chains and demonstrated modest, yet selective, affinity for the intramolecular h-Tel G-quadruplex.

We undertook SAR studies, which further confirmed the advantageous nature of designing ligands with non-fused polyaromatic motifs with regard to selectivity of the ligand for quadruplex DNA over duplex DNA. We believe that these results provide important information that will aid in the design of new G-quadruplex binding ligands that could potentially lead to novel cancer therapeutics.

4. Experimental section

4.1. General

High Resolution Mass Spectra were recorded on VG micron Autospec or Bruker microTOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin–Elmer 1600 series or Bruker Tensor 27. 1H and 13C NMR spectra were recorded on a Bruker AV(III) 400, Bruker AV 400, Bruker DPX 400 (400 MHz (1H) and 100 MHz (13C)) spectrometers. Coupling constant are given in hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), br s (broad signal), t (triplet), q (quartet), quint (quintet), m (multiplet). Thin layer chromatography was performed on Merck precoated silica gel aluminium plates (60 F254) and visualised using UV absorption and/or an appropriate stain. Column chromatography was performed using Merck silica gel 60 (230–400 mesh), Petrol ethers refer to petroleum ethers 40–60 °C. Anhydrous THF was distilled from sodium wire/benzophenone and anhydrous CH2Cl2 from CaH2 immediately prior to use. MeCN and CHCl3 were distilled from CaH2 and stored over.
activated 4 Å MS. Toluene was dried by passing the solvent over an activated alumina column, which was pressurised with dry N2. Anhydrous DMF was purchased and used as received. Microwave reactions were conducted on a CEM Discover Explorer microwave reactor in sealed tubes with stirring at a constant temperature for the indicated time. Preparative HPLC was performed with an Agilent Technologies 1200 series system using a reverse phase column (YMC Co., Ltd., YMC-Pack R&D ODS-A, 100×20 mm I.D., particle size S-5 μm, 12 nm). Analytical HPLC was carried out on using the same instrument as for preparative HPLC, using a reverse phase column (YMC Co., Ltd., YMC-Pack R&D ODS-A, 100×4.6 mm I.D., particle size S-5 μm, 12 nm). Solvents were HPLC grade purchased from Fischer Scientific.

4.1.1. 4-(Trimethylsilyl)ethylbenzamide (8). To a solution of 4-bromobenzamide 7 (8.00 g, 40.2 mmol) and ethynyl-trimethylsilane (16.8 mL, 121 mmol) in degassed (Ar bubbled for 3/4 h) Et2NH (240 mL) under an Ar atmosphere were added PdCl2(PPh3)2 (1.42 g, 2.02 mmol, 5 %) and Cul (152 mg, 0.804 mmol, 2 mol %). After 2 days the solvent was evaporated and the residue was suspended in EtOAc, which was then filtered through Celite. The filtrate was then washed with H2O (100 mL) and brine (80 mL) before being dried (MgSO4), filtered and concentrated. The product was purified by flash chromatography (1:1, EtOAc/petrol ethers) to give the title compound 8 as an off-white solid (6.63 g, 30.6 mmol, 76%). δF 16 (400 MHz, CDCl3) 7.78 (2H, d, J 8.6), 7.56 (2H, d, J 8.6), 6.10 (1H, br s), 5.75 (1H, br s), 0.28 (9H, s); δC (101 MHz, CDCl3) 168.9, 132.8, 132.1, 127.2, 126.9, 103.9, 97.4, –0.2; HRMS ESI+ calculated for C12H16NOSi [M+H]+ 218.1001, found 218.0992.

4.1.2. Ethyl 2-(4-(trimethylsilyl)phenyl)oxazole-4-carboxylate (9). The amide 8 (6.63 g, 30.6 mmol) was dissolved in dry THF (125 mL) under N2. NaHCO3 (8.98 g, 107 mmol) and ethyl bromopyruvate (3.90 mL, 31.0 mmol) were added, after which the reaction was heated to reflux overnight. After 16 h ethyl bromopyruvate (3.90 mL, 31.0 mmol) was added and the reaction refluxed a further 7 h. The reaction was cooled to room temperature and filtered through Celite washing with EtOAc. The filtrate was concentrated then redissolved in dry THF (125 mL) under N2 and cooled to 0 °C. Trifluoroacetic anhydride (12.9 mL, 91.8 mmol) was added dropwise and the reaction was allowed to come to room temperature slowly. The mixture was stirred overnight before being cooled to 0 °C, then a saturated solution of NaHCO3 (100 mL) was added carefully. The reaction was neutralised by the careful addition of solid NaHCO3 and the THF was evaporated in vacuo. The crude oxazole was extracted with EtOAc (3×250 mL), which was washed with brine (150 mL), dried (MgSO4), filtered and concentrated. The oxazole was recrystallised from EtOAc/petrol to give 9 as light orange needles (5.90 g, 38.4 mmol). The mother liquors were purified by flash chromatography (9:1, petrol/EtOAc) to give the title compound 9 as a pale yellow solid (2.30 g, 8.91 mmol, total 47.3 mmol, 64% over three steps). δF 0.16 (1:1, petrol ethers/EtOAc); δF (400 MHz, CDCl3) 7.78 (2H, d, J 8.6), 7.56 (2H, d, J 8.6), 6.10 (1H, br s), 5.75 (1H, br s), 0.28 (9H, s); δC (101 MHz, CDCl3) 168.9, 132.8, 132.1, 127.2, 126.9, 103.9, 97.4, –0.2; HRMS ESI+ calculated for C12H16O3N2Si [M+H]+ 281.0651, found 281.0651.

4.1.4. Ethyl 2-(4-azidophenyl)oxazole-4-carboxylate (19). 4-Aminobenzamide 18 (10.0 g, 73.4 mmol) was suspended in THF (600 mL) and cooled to 0 °C then concd HCl (35 mL) was added dropwise followed by t-BuONa (22.0 mL, 186 mmol). The reaction was stirred for 2 h then NaOH (14.2 g, 218 mmol) was added in one portion. H2O (150 mL) was then added very carefully and after ½ h the reaction was warmed to room temperature and was stirred overnight. The solvents were removed in vacuo and the crude brown solid was used directly in the next step without further purification.

4.1.5. 2-(4-Azidophenyl)oxazole-4-carbonyl chloride (20). The azide 19 (9.87 g, 38.3 mmol) was dissolved in THF/H2O (4.3:1, 160 mL) and cooled to 0 °C. LiOH (1.39 g, 57.9 mmol) in H2O (30 mL) was added slowly then the reaction was stirred ½ h before being warmed to room temperature. After a further 1 ½ h H2O was added until all the solids had dissolved then the pH was adjusted to ~2 with 10% HCl. The mixture was extracted with EtOAc repeatedly (150 mL portions) until all the solids had dissolved. The organics were combined, dried (MgSO4), filtered and concentrated. The crude material was used directly in the next step.

The crude acid was suspended in anhydrous CH2Cl2/THF (7:1, 173 mL) under an Ar atmosphere with anhydrous DMF (0.2 mL) and cooled to 0 °C. COCl2 (3.70 mL, 44.0 mmol) was added slowly, and after 1 h the reaction was allowed to come to room temperature slowly and was stirred overnight. The solvents were removed in vacuo and the crude brown solid was used directly in the next step without further purification.
4.2. General procedure for the synthesis of amines: 12–17; 21–26

The crude acid chloride (20, 0.35 M solution in anhydrous CHCl₃ plus half the volume of CH₂Cl₂ wash) was added to the desired primary amine (2 equiv, 0.7 M solution in CH₂Cl₂) under an Ar atmosphere at 0 °C. After ½ h the reaction was warmed to room temperature and stirred overnight. A saturated solution of NaHCO₃ (3–½ volume of the reaction) was added and the mixture was stirred vigorously for 10 min. The layers were then separated and the aqeous layer was extracted with EtOAc (3–½ volume of the reaction). The organics were combined, dried (Na₂SO₄), filtered and concentrated, and the product was purified by flash chromatography CH₂Cl₂/MeOH to afford the product.

4.2.1. N-(2-(Dimethylamino)ethyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (12). Off-white solid (546 mg, 52% over three steps). Rₛ 0.22 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3413, 3301, 3010, 2826, 2109, 1927, 1661, 1599; δₛ (400 MHz, CDCl₃) 6.23 (1H, s), 7.07 (2H, d, J 8.6), 7.55 (2H, d, J 8.6), 4.70 (1H, br s), 3.57 (2H, app q, J 5.5), 3.25 (1H, s), 2.51 (2H, t, J 6.1); 2.57 (5H, s); δc (101 MHz, CDCl₃) 166.0, 165.5, 141.0, 137.7, 132.5, 126.7, 82.9, 79.8, 58.0, 45.4, 36.7; HRMS ESI⁺ calculated for C₁₆H₁₈N₃O₂ 284.1389 [MH⁺], found 284.1407.

4.2.2. N-(2-(Pyrrolidin-1-yl)ethyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (21). Yellow solid (1.30 mmol, 83% over three steps). Rₛ 0.23 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3413, 3011, 2826, 2130, 2097, 1661, 1611, 1600; δₛ (400 MHz, CDCl₃) 8.22 (1H, s), 8.07 (2H, d, J 8.8), 7.49 (1H, br s), 7.15 (2H, d, J 6.8), 3.64 (2H, m), 2.81 (2H, br s), 2.70 (4H, br s); δc (101 MHz, CDCl₃) 167.0, 170.4, 142.8, 140.7, 137.5, 128.3, 123.4, 119.5, 58.1, 54.5, 54.1, 37.9, 23.6; HRMS ESI⁺ calculated for C₁₆H₁₉N₃O₂ 310.1413 [MH⁺], found 310.1419.

4.2.3. N-(2-(Pyrrolidin-1-y1)-ethyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (22). Pale yellow solid (1.73 mmol, 85% over three steps). Rₛ 0.23 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3413, 3006, 2809, 2130, 2097, 1661, 1611, 1600; δₛ (400 MHz, CDCl₃) 8.24 (1H, s), 8.07 (2H, d, J 8.8), 7.49 (1H, br s), 7.15 (2H, d, J 6.8), 3.64 (2H, m), 2.81 (2H, br s), 2.70 (4H, br s); δc (101 MHz, CDCl₃) 167.0, 170.4, 142.8, 140.7, 137.5, 128.3, 123.4, 119.5, 58.1, 54.5, 54.1, 37.9, 23.6; HRMS ESI⁺ calculated for C₁₆H₁₉N₃O₂ 310.1413 [MH⁺], found 310.1419.

4.2.4. N-(3-(Dimethylamino)propyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (14). Off-white solid (1.27 mmol, 74% over three steps). Rₛ 0.25 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3413, 3301, 3004, 2809, 2109, 1927, 1662, 1599; δₛ (400 MHz, CDCl₃) 8.27 (1H, s), 8.04 (2H, d, J 8.4), 7.62 (2H, d, J 8.4), 4.78 (1H, br s), 3.67 (2H, br s), 3.24 (2H, m), 2.92–2.62 (6H, m), 1.90 (4H, br s); δc (75 MHz, CDCl₃) 166.0, 165.0, 141.0, 137.7, 132.5, 126.6, 126.4, 124.7, 82.9, 79.8, 57.3, 54.4, 36.0, 26.1, 24.4; HRMS ESI⁺ calculated for C₁₆H₂₃N₃O₂ 298.1556 [MH⁺], found 298.1564.

4.2.5. N-(3-(Dimethylamino)propyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (15). Light orange solid (1.40 mmol, 81% over three steps). Rₛ 0.13 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3416, 3301, 3005, 2824, 2109, 1926, 1663, 1599; δₛ (400 MHz, CDCl₃) 8.20 (1H, s), 8.09 (1H, br s), 7.90 (2H, d, J 8.5), 7.64 (2H, d, J 8.5), 3.60 (2H, app q, J 5.8), 3.26 (1H, s), 2.58 (2H, t, J 6.3), 2.48 (4H, br s), 1.64 (4H, m), 1.49 (2H, m); δc (101 MHz, CDCl₃) 160.5, 160.4, 140.8, 137.9, 132.5, 126.7, 126.3, 124.7, 82.8, 79.8, 58.1, 45.5, 38.4, 26.6; HRMS ESI⁺ calculated for C₁₇H₂₅N₃O₂ 298.1556 [MH⁺], found 298.1564.

4.2.6. N-(3-(Piperidin-1-yl)propyl)-2-(4-ethynylphenyl)oxazole-4-carboxamide (24). Pale yellow solid (1.71 mmol, 85% over three steps). Rₛ 0.28 (9:1, CH₂Cl₂/MeOH); Rₓmax/cm 1 3413, 2941, 2130, 2097, 1660, 1611, 1600; δₛ (400 MHz, CDCl₃) 8.22 (1H, s), 8.03 (2H, d, J 8.8), 7.52 (1H, br s), 7.13 (2H, d, J 8.8), 3.55 (2H, m), 2.57 (2H, t, J 6.3), 2.47 (4H, br s), 1.64 (4H, m), 1.48 (2H, m); δc (101 MHz, CDCl₃) 160.7, 166.0, 142.7, 140.6, 137.6, 128.2, 123.4, 119.5, 57.3, 54.2, 36.0, 26.1, 24.4; HRMS ESI⁺ calculated for C₁₇H₂₅N₃O₂ 314.1726 [MH⁺], found 314.1755.

4.3. General procedure for click reactions

The alkyne (1 equiv) and azide (1 equiv) were dissolved in t-BuOH (0.3 M) then CuSO₄ 5H₂O (5 mol %) was added followed by
sodium ascorbate (0.25 equiv) dissolved in H2O (equal volume to t-BuOH). The reaction was heated to 100 °C in the microwave for 25 min then it was cooled to room temperature and diluted with H2O (4 volumes). The suspension was filtered and washed with a small amount of methanol then EtOAc. The residue was dissolved in CH2Cl2/MeOH (9:1), dried (Na2SO4), filtered and concentrated. A sample was purified by prep HPLC for analysis and biological evaluation (see SD for details).

3.8. 1,4-Bis-[N-(2-(dimethylamino)ethyl)-2-(4-phenyloxazole-4-carboxamide)]-1,2,3-triazole (27). Pale yellow/orange solid (0.232 mmol, 87%). rmax/cm−1 1674; δH (400 MHz, MeOD) 8.90 (1H, s), 8.47 (1H, s), 8.44 (1H, s), 8.09 (2H, d, J = 8.5), 7.87–8.00 (6H, m), 3.80 (4H, br s), 3.45 (4H, br s), 3.04 (12H, s); δC (101 MHz, MeOD) 162.6, 162.5, 162.1, 160.4, 147.1, 142.2, 141.9, 138.2, 136.7, 136.5, 132.3, 127.7, 126.7, 126.3, 125.9, 125.6, 119.8, 118.9, 2.5 ± 0.7, 2.4 ± 0.5, 2.3 ± 0.4; HRMS ESI+ calculated for C39H36N10O6 584.2734 [MH]+, found 584.2730.

3.9. 1,4-Bis-[N-(2-(piperidin-1-yl)ethyl)-2-(4-phenyloxazole-4-carboxamide)]-1,2,3-triazole (28). Light orange solid (0.266 mmol, 81%). rmax/cm−1 1672; δH (400 MHz, MeOD) 8.76 (1H, s), 8.39 (1H, s), 8.36 (1H, s), 7.96 (2H, d, J = 8.5), 7.74–7.88 (6H, m), 3.68–3.88 (8H, br s), 3.46 (4H, br s), 3.15 (4H, s), 2.16 (4H, br s), 2.03 (4H, br s); δC (101 MHz, MeOD) 162.5, 162.3, 162.1, 161.0, 160.3, 147.6, 142.2, 141.8, 138.1, 136.7, 136.5, 132.2, 127.6, 126.7, 126.2, 125.8, 125.6, 119.6, 118.7, 2.5 ± 0.4, 2.5 ± 0.4, 2.5 ± 0.3, 2.2 ± 0.2; HRMS ESI+ calculated for C40H38N10O6 624.3360 [MH]+, found 624.3360.

3.10. 1,4-Bis-[N-(2-(piperidin-1-yl)ethyl)-2-(4-phenyloxazole-4-carboxamide)]-1,2,3-triazole (29). Pale yellow solid (0.214 mmol, 77%). rmax/cm−1 1672; δH (400 MHz, MeOD) 9.04 (1H, s), 8.42 (1H, s), 8.39 (1H, s), 8.33 (1H, s), 7.84–8.11 (8H, m), 3.50 (4H, br s), 3.25 (4H, br s), 2.96 (12H, s), 2.16 (4H, s), 1.10 (4H, s); δC (101 MHz, MeOD) 162.0, 162.1, 160.1, 160.3, 147.0, 141.8, 141.5, 138.1, 136.9, 136.8, 136.6, 133.6, 124.7, 127.8, 126.8, 126.4, 126.0, 125.7, 119.9, 119.0, 2.5 ± 0.5, 2.5 ± 0.3, 2.3 ± 0.2, 2.2 ± 0.2; HRMS ESI+ calculated for C40H38N10O6 624.3360 [MH]+, found 624.3360.

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Supplementary data

Supplementary data pertaining to this article including NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.10.066.

References and notes


