Synthesis of Unsymmetrical Mono- and Bissquaramides with (3-Aminopropyl)triethoxysilane (APTES) or Dopamine Moieties

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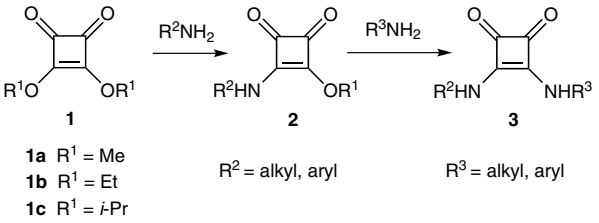
Abstract: A simple and efficient synthesis of unsymmetrical mono- and bissquaramides derivatives and their corresponding methyltrialkyl ammonium salts was achieved in moderate yields from diethyl squarate via sequencial reactions.

Key words: squaramides, bissquaramides, modular synthesis, ammonium iodide salt, receptors

Squaric acid (3,4-dihydroxi-3-cyclobutene-1,2-dione), also known as 'quadric acid', and its derivatives have attracted considerable attention since the parent compound was first reported in 1959 by Cohen and co-workers.[1] A squaric acid derivative, the squaramide, has been recognized to offer the potential to act as a hydrogen-bond donor, hydrogen-bond acceptor, or both hydrogen-bond donor–acceptor. The ability of squaramides to act as hydrogen-bond donors to anionic species has been also investigated.[2] In this way, some abiotic squaramide receptors have been reported to successfully bind carboxylate anions working in water, a highly competitive medium for hydrogen bonding. In spite of the large capacity that squaramides have to behave as hydrogen-bond donors and acceptors, these binding units have not been used in conjunction with magnetic iron nanoparticles as new hybrid nanomaterials with potential to be employed for establishing intermolecular noncovalent forces, for example, in supramolecular chemistry or for bioconjugation. For us, squaramide tetraalkylammonium salts are very important binding units due to their high ability to favorably interact with several oxoanions as nitrate, sulfate,[3] and carboxylates, for example, as acetate, benzoate, oxalate, tartrate, trimesoate, tricarballate, citrate, and folates.[4]

The aim of this communication is to present the preparation, via modular synthesis under mild experimental conditions, of several unsymmetrical mono- and bissquaramides with dopamine or triethoxysilane amine ready to be coupled to iron nanoparticles.

Dopamine (3,4-dihydroxyphenylethylamine) and (3-aminopropyl)triethoxysilane (APTES) are the linkers most frequently used to tie iron nanoparticles to another compound through the Fe–O bond. It has been demonstrated[5] that chatecols form strong bonds with metal oxide nanoparticles. Aminosilanes are widely used as coupling agents because of their bifunctional nature and the nucleophilicity of the NH_2 group which will be beneficial for the coupling with the squarate molecule. On the other hand, the most widely used substrates for the synthesis of modular squaramides are mono- or dialkoxysquarate [dimethyl (**1a**), diethyl (**1b**), or diisopropyl squarate (**1c**)] derivatives by amine condensation (Scheme 1). Usually this reaction is carried out in organic media or buffer aqueous solution, in high yield at room temperature for several hours with a slight excess of the amine, to generate the corresponding symmetrical squaramide **3** ($R^1 = R^2$).



Scheme 1 General route of the synthesis of squaramides

Although it is possible to synthesize unsymmetrical squaramides **2** when the reaction is carried out with one equivalent of a primary or secondary amine, symmetrical squaramides **3** may also be produced. To minimize this undesired side reaction, the reaction is usually carried out in diethyl ether, as in this medium, the formation of disquaramides is disfavored, due to the precipitation of the mixed squaramate **2**. Accordingly, for the introduction of a second different alkylamine or arylamine, it suffices to dissolve the mixed squaramate **2** in an alcoholic solvent, typically ethanol or methanol, and to add another equivalent of a different alkylamine or arylamine. Other solvents such as dichloromethane, chloroform, dimethyl sulfoxide, or even aqueous basic buffer solution, can be used.

Scheme 2 depicts the preparation of simple squaramides **5** and **7** with APTES moieties. Our synthetic plan starting from the parent compound squaramide **4** readily provides the desired products from the condensation of the diethoxysquarate **1b** with the *N*,*N*-dimethyl-1,3-diaminopropane in diethyl ether in good yield.[6] The introduction of this amine compound provides an excellent binding unit, and more specifically the corresponding trimethylalkyl ammonium iodide salt.

The preparation of the unsymmetrical ethoxysilane squaramide **5** is readily achieved by combination of

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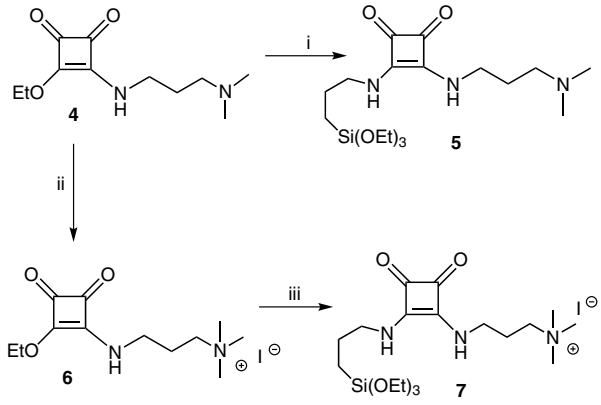
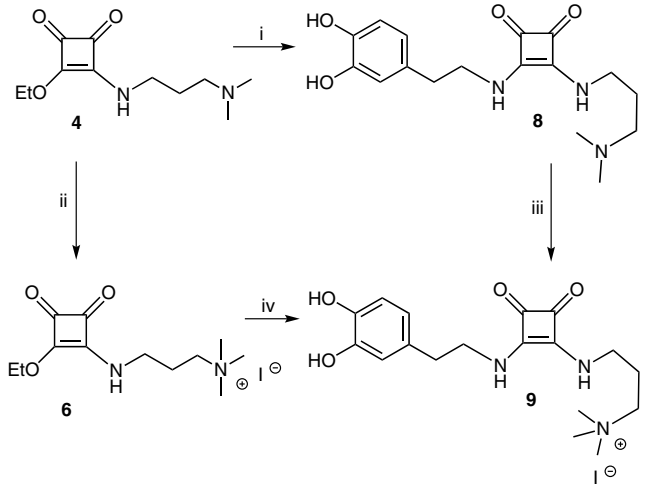


Scheme 2 Synthesis of unsymmetrical aliphatic monosquaramides **5** and **7**. *Reagents and conditions*: i) APTES, EtOH, r.t., 56%; ii) MeI, acetone, DMF, 90 °C, 80%; iii) APTES, EtOH, r.t., 85%.



Scheme 3 Synthesis of unsymmetrical aliphatic monosquaramides **8** and **9**. *Reagents and conditions*: i) dopamine, EtOH, Na_2CO_3, $Na_2S_2O_4$, pH 7, r.t., 40%; ii) MeI, acetone, DMF, 90 °C, 80%; iii) MeI, acetone, DMF, 90 °C, 50%; iv) dopamine, EtOH, Na_2CO_3, $Na_2S_2O_4$, pH 7, r.t., 50%.

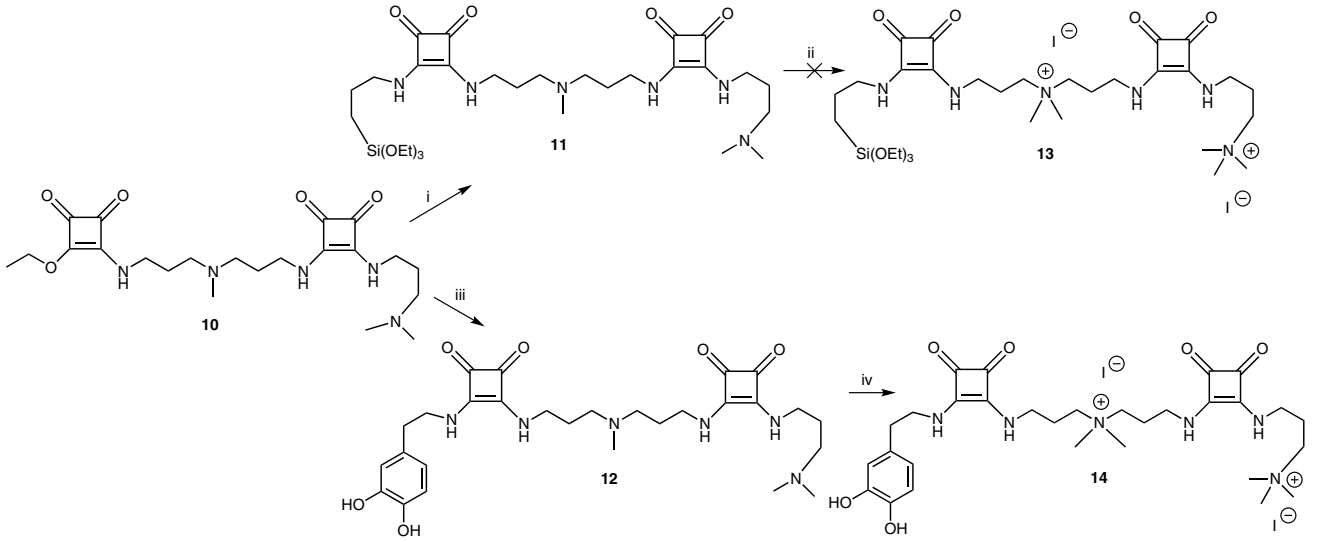
squaramide **4** with the corresponding commercially primary amine, APTES. To avoid hydrolysis[7] of the alkyltriethoxysilane group, we preferably use anhydrous ethanol as solvent as we observed exchange of ethoxy groups, ethoxy for hydroxy, under standard conditions involving extended periods of reaction, typically 12 hours, at a high pH value.

The unsymmetrical squaramide **8** was obtained by condensation of squaramide **4** with dopamine in moderate yield (Scheme 3). To minimize the ready but undesirable formation of the dopaquinone (DOQ),[8] an excess of solid sodium dithionite (1.5 equiv) was added[9] to prevent the oxidation of the catechol moiety of the dopamine. To generate the amine from the commercially dopamine hydrochloride salt, an excess of solid of sodium carbonate (4 equiv) was added, and the reaction mixture was protected from air and light, maintaining the experimental assembly under an argon atmosphere in the dark.

To obtain the unsymmetrical trimethylalkyl ammonium squaramide iodide salts **7**[10] and **9**, the squaramide **6** was initially formed by methylation of **4** with methyl iodide[11] in acetone–DMF. In fact, the preparation of squaramide ammonium iodide salt **9** from **8** by direct methylation is also possible, without protecting the aromatic hydroxyl group, because the pH is not appropriate for the formation of the dimethoxy ether of the catechol residue of the dopamine.

The preparation of unsymmetrical bissquaramides can proceed in two ways. One consists of modifying the previously synthesized the squaramate–squaramide **10** (Scheme 4). Alternatively, the commercially available diethyl squarate **1b** can be used as a starting material, to introduce the different substitution by a sequential modular synthesis (Scheme 5 and Scheme 6).

Some time ago, we reported the preparation of mixed bissquaramate **10**.[12] From this compound the bissquaramides **11** and **14** can be obtained by two different routes



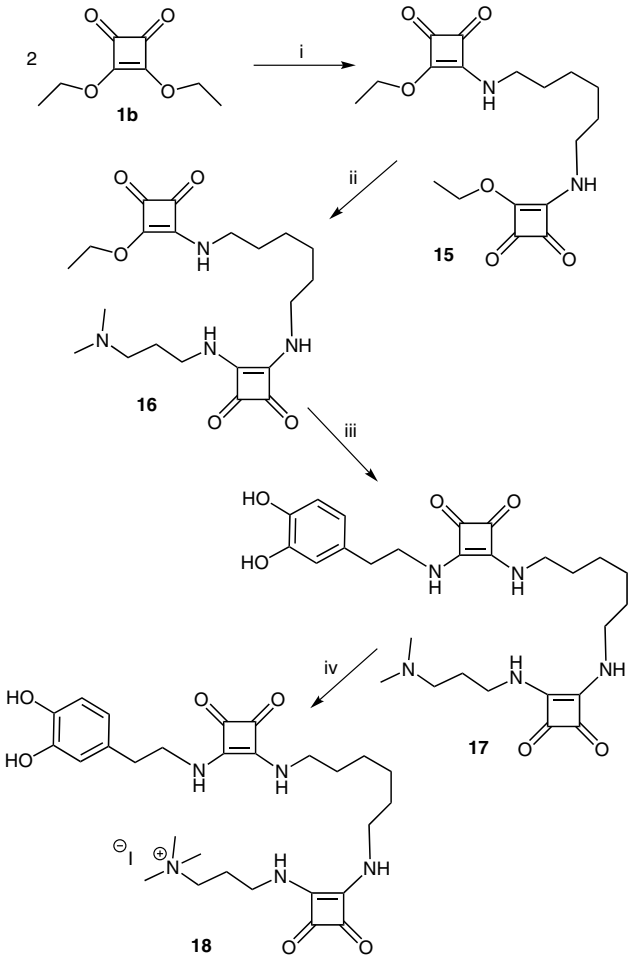
Scheme 4 Synthesis of unsymmetrical aliphatic bissquaramides **11** and **14**. *Reagents and conditions*: i) APTES, EtOH, r.t., 98%; ii) MeI, acetone, DMF, 90 °C; iii) dopamine, EtOH, Na_2CO_3, $Na_2S_2O_4$, pH 7, r.t., 70%; iv) MeI, acetone, DMF, 90 °C, 17%.

(Scheme 4). The synthetic approach and experimental conditions are similar to the ones described above. It is worth mentioning that in the methylation of bissquaramide triethoxysilane **11**, the compound obtained was not the expected squaramide **13**. In fact, the best way to obtain the squaramide functionalized with both groups – triethoxysilane and tetraalkyl ammonium iodide – consists in initially preparing the iodide ammonium tetraalkyl squarate and then adding the (3-aminopropyl)triethoxysilane as described above for the preparation of squaramide **9** from **8**.

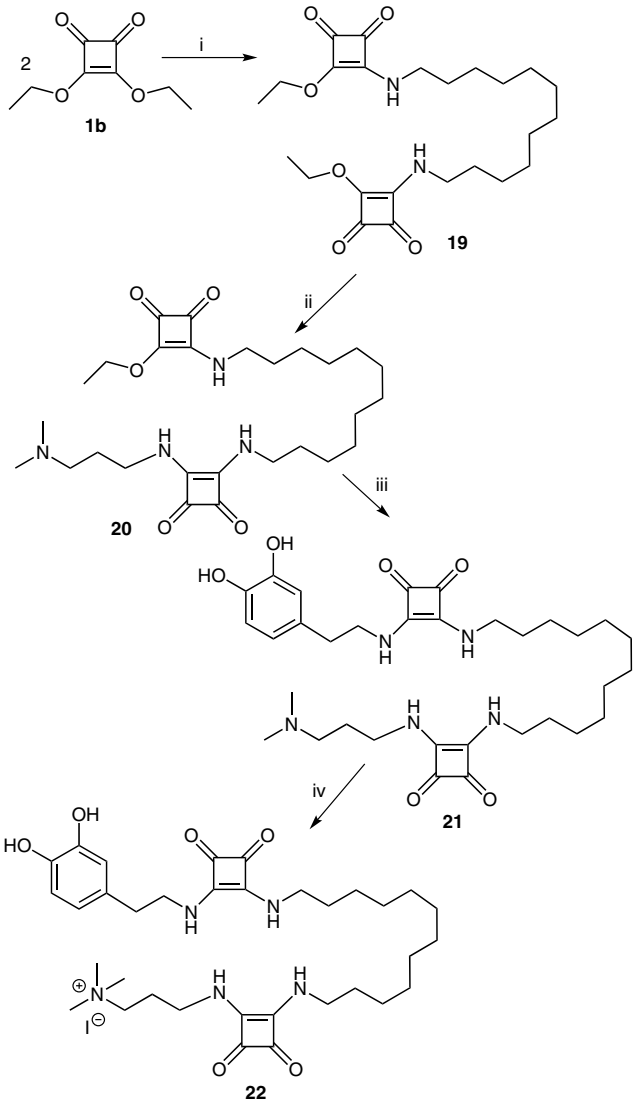
Schemes 5 and 6 show the synthetic approaches for the preparation of bissquaramides **18** and **22**, with a long chain (6 and 12 methylene groups) from the commercial diethoxysquarate **1b**[13] and 1,6-diaminohexane (1,6-hexamethylenediamine) or 1,12-diaminododecane (dodecamethylenediamine) in methanol. The key step for the synthesis of the bissquaramide **18**[14] (with 6 methylene groups) is the preparation of the intermediate unsymmetrical mixed bissquaramate **16**. This process is carried out by condensation of a slight molar excess of the symmetrical bissquaramide **15** with 3-(dimethylamino)-1-propylamine in a 2:1 mixture (v/v) of chloroform and acetonitrile.

The appropriate choice of solvents in this step was important, because in this mixture the reactants were soluble while the reaction products were insoluble, preventing the undesired formation of the squaramide resulting of the double attack of the first amine. A 63% yield of material of adequate purity by ^{1}H NMR spectroscopy was thus obtained. Finally, the condensation of **16** with dopamine hydrochloride produced the desired bissquaramide **17** in good yield (77%).

An analogous process was followed to obtain the unsymmetrical bissquaramide **22**. Just as in the preparation of bissquaramide **18**, the key step was the condensation of the 3-(dimethylamino)-1-propylamine with bissquaramate **19** to obtain unsymmetrical mixed bissquaramate **20**. In this case, the experimental conditions were similar: a



Scheme 5 Synthesis of unsymmetrical bissquaramides **17** and **18**. *Reagents and conditions*: i) 1,6-diaminehexane, EtOH, r.t., 91%; ii) 3-(dimethylamine)-1-propylamine, $CHCl_3$–MeCN, r.t., 63%; iii) dopamine, MeOH, Na_2CO_3, $Na_2S_2O_4$, pH 7, r.t., 77%; iv) MeI, DMF, 153 °C, 30%.



Scheme 6 Synthesis of unsymmetrical bissquaramides **21** and **22**. *Reagents and conditions*: i) 1,12-diaminedodecane, MeOH, r.t., 80%; ii) 3-(dimethylamine)-1-propylamine, $CHCl_3$, r.t., 66%; iii) dopamine, MeOH, Na_2CO_3, $Na_2S_2O_4$, pH 7, r.t., 92%; iv) MeI, DMF, 153 °C, 32%.

slight excess of **19** in chloroform. The bissquaramide **21** was synthesized by condensation of **20** and dopamine hydrochloride in methanol in good yield (77%) as a white solid. Finally, the ammonium salts **18** and **22** are obtained by methylation with methyl iodide in DMF.

In summary, unsymmetrical mono- and bissquaramides, with catechol or ethoxysilane groups, have been synthesized by modular condensation under mild conditions in moderate to high yields for each synthetic step, with the added advantage that no chromatography is required. Repeated washing of the crude reaction material with organic solvent yields material of high purity as indicated by spectroscopic analysis.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Caution**: This compound has been found, in some individuals, to be irritating upon contact with the skin.

(14) **Typical Procedure for the Synthesis of Unsymmetrical Bissquaramide**

Reaction of Diethyl Squarate 1b with 1,6-Diaminehexane

A solution of 1,6-diaminehexane (0.35 g, 3 mmol) in ethanol (50 mL) was added drop-wise to a stirred solution of **1b** (1.5 g, 8.8 mmol) in ethanol (10 mL). The reaction mixture was stirred overnight at room temperature under an atmosphere of argon. The resulting white solid **15** was isolated by centrifugation after decanting the supernatant and washed with ether (3 × 10 mL) and cold ethanol (3 × 10 mL). Finally, the precipitate **15** was dried under vacuum; yield: 0.99 g (91%). m.p. = 163–164 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.81 (br, *J* = 5.6 Hz, NH), 8.60 (br, *J* = 5.6 Hz, NH), 4.65 (q, *J* = 7 Hz, 4 H), 3.45 (q, *J* = 6.1 Hz, 2 H), 3.27 (q, *J* = 6.6 Hz, 2 H), 1.50 (m, *J* = 6.3 Hz, 4 H), 1.36 (t, *J* = 6.3 Hz, 6 H), 1.28 (m, 4 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.32, 182.99, 177.90, 177.35, 173.58, 173.20, 69.69, 44.63, 44.30, 31.20, 30.69, 26.24, 16.57 ppm. IR (KBr): 3284, 2944, 1804, 1703, 1598, 1517, 1461, 1388, 1340, 1288, 1106, 1043, 1009, 817 cm^{-1}. HRMS–ES(+): *m*/*z* calcd for $C_{18}H_{24}N_2O_6Na$: 387.1533; found: 387.1532.

Reaction of 15 with 3-(Dimethylamine)-1-propylamine:

A solution of 3-(dimethylamine)-1-propylamine (115 μL, 0.9 mmol) in ethanol (50 mL) was added dropwise to a stirred solution of **15** (0.5 g, 1.37 mmol) in a mixture of ethanol (10 mL) and acetonitrile (5 mL). The reaction mixture was stirred overnight at room temperature under an atmosphere of argon. After this period, a white precipitated was collected from the reaction mixture by centrifugation, washed with ether (3 × 5 mL) and with cold acetonitrile (3 × 5 mL) to give **16**; yield: 24 mg (63%). m.p. = 183–185 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.79 (br, *J* = 5.6 Hz, 1 H), 8.58 (br, *J* = 5.6 Hz, 1 H), 7.32 (br, 1 H), 4.63 (q, *J* = 6.9 Hz, 2 H), 3.47 (t, *J* = 6.1 Hz, 4 H), 3.32 (t, *J* = 6.9 Hz, 2 H), 2.25 (t, *J* = 6.9 Hz, 2 H), 2.12 (s, 6 H), 1.65 (m, *J* = 7.5 Hz, 2 H), 1.51 (m, 4 H), 1.36 (t, *J* = 6.9 Hz, 3 H), 1.27 (m, 4 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 189.85, 182.96, 182.53, 177.51, 176.89, 173.05, 172.67, 168.33, 69.20, 56.40, 45.36, 44.22, 43.88, 43.63, 42.00, 31.19, 30.73, 30.38, 28.85, 25.65, 16.30 ppm. IR (KBr): 3171, 2942, 1803, 1703, 1639, 1584, 1518, 1432, 1357 cm^{-1}. HRMS–ES(+): *m*/*z* calcd for $C_{21}H_{32}N_4O_5Na$: 443.2270; found: 443.2276.

Reaction of 16 with Dopamine: To a mixture of sodium carbonate (400 mg, 3.6 mmol) and sodium dithionite (200 mg, 0.59 mmol) was added methanol (10 mL). A solution of dopamine hydrochloride (0.17 g, 0.88 mmol) in methanol (5 mL) was added drop-wise to the stirred mixture. Immediately, a solution of **16** (0.25 g, 0.59 mmol) in methanol (55 mL) and DMSO (10 mL) was added into the above solution drop-wise too. The pH of the mixture was adjusted to 7 by adding 2 drops of 1 M NaOH. The reaction mixture was stirred for 2 h at room temperature under an atmosphere of argon and in the absence of light. After this

period, the solution was filtered and the resulting solution was stirred overnight in the same conditions. The product was obtained by evaporating the solvent under vacuum. The white solid **17** was washed with cold methanol (5 × 10 mL) and acetone (2 × 10 mL); yield: 0.24 g (77%). m.p. = 243–245 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.79 (br, *J* = 5.6 Hz, 1 H), 8.70 (br, *J* = 5.6 Hz, 1 H), 7.70 (br, 2 NH), 7.38 (br, 2 NH), 6.64 (dd, *J* = 8.2, 4.2 Hz, 2 H), 6.48 (d, *J* = 7.9 Hz, 1 H), 3.49 (t, *J* = 6.6 Hz, 8 H), 2.67 (t, *J* = 6.7 Hz, 2 H), 2.49 (t, *J* = 7.2 Hz, 2 H), 2.26 (s, 6 H), 1.72 (m, *J* = 5.9 Hz, 2 H), 1.52 (m, 4 H), 1.31 (m, 4 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 183.45, 168.84, 146.10, 144.66, 130.21, 120.36, 117.10, 116.49, 56.11, 45.82, 44.88, 44.06, 37.43, 31.51, 28.66, 26.30 ppm. IR (KBr): 3170, 2931, 1799, 1641, 1582, 1432, 1357 cm^{-1}. MALDI–TOF/TOF(+): *m*/*z* calcd for $C_{27}H_{37}N_5O_6Na$: 550.2636; found: 550.2646.

Reaction of 17 with MeI: Methyl Iodide (0.24 mL, 3.80 mmol) was added via syringe to a solution of **17** (0.50 g, 0.95 mmol) in DMF (7 mL). The mixture was heated under reflux at 153 °C for 12 h, after which it was cooled to room temperature. 30 mL of acetone were added and the solution was placed in an ice-cold water bath to obtain the product. The resulting brown solid was isolated by centrifugation after decanting the supernatant and purified by washing with cold methanol (3 × 10 mL) and cold acetone (3 × 10 mL). Finally, the precipitate **18** was dried under vacuum; yield: 0.19 g (30%). m.p.= 229–231 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.77 (br, 1 H), 8.68 (br, 1 H), 7.41 (br, 4 NH), 6.63 (dd, *J* = 7.9, 3.5 Hz, 2 H), 6.47 (d, *J* = 8.1 Hz,1 H), 3.64 (t, 2 H), 3.47 (m, 6 H), 3.10 (s, 9 H), 2.65 (t, *J* = 7.1 Hz, 2 H), 1.97 (m, 1 H), 1.82 (m, 1 H), 1.50 (m, 4 H), 1.30 (m, 4 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 182.21, 167.79, 145.08, 143.74, 129.31, 119.33, 116.06, 115.48, 54.38, 54.19, 44.86, 43.17, 36.41, 30.65, 25.41 ppm. IR (KBr): 3171, 1800, 1645, 1583, 1434, 1384, 1357, 1284, 1116, 617 cm^{-1}. MALDI–TOF/TOF(+): *m*/*z* calcd for $C_{28}H_{40}N_5O_6$: 542.2973; found: 542.3003.

