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High thermal stability, pH responsive organogels of 2H-benzo[d]1,2,3-triazole derivatives as pharmaceutical crystallization media

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2H-benzo[d]1,2,3-triazole derivatives with a range of chemical functionalities showed significant organogel formation, particularly bis-amide derivative 4e which gave robust thermally stable gels, in a range of solvents down to 0.1 wt\%. The gelators proved responsive under pH stimuli or to the presence of metal cations. The gels also proved to be useful vehicles to crystallize pharmaceutical drugs, resulting in a change in polymorphic outcome in the case of sulfathiazole compared to the solution crystallization outcome.

Despite the fact that a plethora of LWM organogels have been reported and recent work has uncovered some trends in gelation tendency,\textsuperscript{5} it is still difficult to predict the molecular structure of a promising gelator and in what solvents a gel may be formed.\textsuperscript{6} The discovery of gelators remains serendipitous and usually involves screening of different solvent systems potentially compatible with gelation. It is clear that without consideration of the solvent properties, the development of new types of molecular gels will be challenging. Consideration of specific solvent properties such as dipole moment, dielectric constant, refractive index, solvachromatic shift or Hildebrand solubility parameter, can bring us closer to understanding the mechanism of gelation, but this analysis still falls short of explicitly predicting gelation behaviour.\textsuperscript{7} A new method has been reported to help predict the behaviour of a known gelator.\textsuperscript{8} Based on the previous behaviour of the gelator in a wide range of solvents, it is possible to define a solubility sphere and one (or more) gelation spheres bearing in mind the Hansen solubility parameters.\textsuperscript{9} If the untested solvent parameters fall in the solubility sphere or in the gelation sphere, then this solvent will be able to either dissolve the gelator or allow the formation of a gel, respectively. While this approach depends on the quality of the available solubility data set, it represents a useful tool to reduce the number of tests in gelation behaviour studies. However, many other factors such as steric effects, rigidity, polarity and aggregation rate may affect the aggregation tendency. For this reason, control over the gelation process as well as the discovery of new types of organogelators remain important challenges. Of particular recent interest are gelators that exhibit a response to external stimuli leading to switchable gelation behaviour or tunable rheology.\textsuperscript{10} Such programmability, however, further complicates the gelation landscape.

One interesting recent application of organogels is as media for the crystallization of pharmaceutical compounds. The control of drug
solid form and hence properties such as bioavailability and dissolution rate is vitally important in the pharmaceutical industry.\textsuperscript{11} Polymorphic form, crystal morphology and particle size can highly influence a material's solubility, compressibility, friability, melting point, hygroscopy, bulk density and dissolution rate.\textsuperscript{12,13} Furthermore, polymorphism control may offer the transformation of an amorphous or poorly crystalline active pharmaceutical ingredient (API) into a readily handled, stable crystalline solid and understanding of the solid form landscape is tremendously important in obtaining regulatory approval.\textsuperscript{14} Because they offer a potential alternative nucleation pathway, gels can give rise to novel polymorphs and hence modify drug solid state properties. The gel environment can also potentially influence crystal habit, particle size and enantiomorphism.\textsuperscript{15,16,17}

There are some recent studies in which triazole and benzimidazole derivatives as organogels have been described.\textsuperscript{18,19,20} Benzotriazole derivatives possess significant potential in a number of applications.\textsuperscript{21} Benzotriazole is a moderate electron acceptor moiety which can be easily modified by the introduction of different substituents on the nitrogen in the 2-position modulating the electron acceptor properties, and the carbon atoms at the 4 and 7 positions in the benzene-derived ring are very reactive, so it is possible to introduce different groups to modulate the chemical structure and as a consequence its properties. A convenient functionalization of the benzotriazole moiety has afforded derivatives with application as optical waveguides,\textsuperscript{22} organic field-effect transistors,\textsuperscript{23} and in bioimaging.\textsuperscript{24} In this work, we report a series of novel 2H-benzo[d]1,2,3-triazole derivatives that function as LMW organogelators and the application of their gels as drug crystallization media.

**Results and Discussion**

**Synthesis**

Benzotriazoles 4 were prepared by the synthetic approach described by Höger from 1-nitro-2-nitrosobenzene and 3,5-bis(trifluoromethyl)aniline.\textsuperscript{25} Bromination of benzotriazoles 1 afforded the dibromobenzotriazole 2 in good yield (Scheme 1). A double Sonogashira C–C cross-coupling reaction between dibromobenzotriazole 2 and arylacetylenes 3 using reusable Pd-EnCat TPP30, 1,5-diazabicyclo[5.4.0]undecene-5-ene (DBU), Cul and microwave irradiation afforded the arylalkynylbenzotriazoles of type 4 within 20 minutes in good yields. This sustainable procedure for the preparation of triazole and benzotriazole derivatives has been widely employed in our research group.\textsuperscript{22,26} All compounds gave satisfactory characterisation data.

![Scheme 1. Synthesis of the possible gelators 4.](image-url)

Derivative 3b was commercially available and was used without previous purification. Derivatives 3a, 3c, 3d and 3e were synthesized according to literature procedures as described below.

For the synthesis of the acetylenic derivative 3a, the procedure described by Ma et al. was followed.\textsuperscript{27} The synthesis of the derivative takes place by a Sonogashira reaction between the halogenated derivative and ethynyltrimethylsilane followed by deprotection of the SiMe\textsubscript{3} group with K\textsubscript{2}CO\textsubscript{3} in MeOH/THF (Scheme S1 in SI). The alkynyl derivative 3c was prepared by N-alkylation of 4-bromobenzamide\textsuperscript{28}, following by the formation of the triple bond and later deprotection with the procedure described for 3a. (Scheme S2 in SI). Derivative 3d was prepared by reaction between commercially available 4-ethynylaniline, and 3,4,5-tris(dodecyloxy)benzoic acid following the procedure described by Tian.\textsuperscript{29} (Scheme S3 in SI). Synthesis of derivative 3e proved more challenging than the other compounds. First, hydrolysis of methyl 3,4,5-tris(dodecylxoy)benzoate in basic media gave 3,4,5-tris(dodecylxoy)benzoic acid\textsuperscript{30}, followed by the formation of the acid chloride\textsuperscript{30} and the amide group by reaction with diethylenediamine.\textsuperscript{30} Finally, reaction with 4-((trimethylsilyl)ethynyl)benzoic acid and deprotection gave the final product (Scheme 2).
Gelation tests

Gelation tests were carried out for compounds of type 4 using thirty different solvents and at different concentrations (2% wt, 1% wt. and 0.5% wt). Gelators were dissolved in 0.5 mL of the respective solvent through gentle heating followed by sonication for 1 min until complete dissolution. The vials were then kept undisturbed at room temperature. The vials were checked after 4, 24, 48 and 72 hours using the simple tube inversion test to assess the flow properties of the resulting mixture. Results are collected in Tables S1-S15 in the Supporting Information. The outcomes of the gelation tests showed that compound 4b did not give gels in any solvent and in any concentration. Compound 4c gelled partially at concentrations of 2% wt. and 1% wt. in 1,4-butanediol but after inversion for 20-30 seconds the gel broke down and began to flow. On the other hand, 4a, 4d and 4e gave gels in a range of solvents. Compound 4a gave opaque gels in four solvents (1,4-butanediol, 2-propanol, 1-pentanol and methanol) at a concentration of 2% wt. (Figure 1a) and in two solvents (1,4-butanediol and 1-pentanol) at 1% wt. (Figure S1 in Supporting Information). Compound 4d behaved similarly to 4c, giving a partial gel in 1,4-butanediol as well as gels in DMF and diethylene glycol (Figure 1b). Finally, 4e proved to be a highly effective gelator even at low concentration in a range of solvents. For example, gels of 4e at a concentration of 1% wt. are shown in Figure 1c. This compound proved to be particularly effective at gelling even relatively polar alcohol solvents and its gelation ability is likely to be linked to the presence of the additional amide group in conjunction with the relative hydrophobicity of the molecule resulting in hydrophobically insulated, multiple hydrogen bonded stacks of molecules.

The CGC for 4a ranges between 0.7% wt. in the case of 1-pentanol and 1.7% wt. in the case of methanol. The CGC values for 4d are relatively high (between 1.5 and 1.8%). In contrast, the CGCs for 4e proved to be very low, consistent with the additional hydrogen bonding functionality. In ethanol this gelator gives gels at a concentration of only 0.1% wt. (Figure 2) and hence may be regarded as a ‘supergelator’. The CGC values are generally found to be low in alcoholic solvents, perhaps reflecting a solvophobic effect from the highly lipophilic substituents coupled with strong self-association from the amide groups. Similar effects are noted for tris(amide) derivatives.

The gel to sol phase transition temperature, ($T_{g-s}$) was assessed using the dropping ball method. Gels derived from 4a are stable,
(e.g., 1-pentanol $T_{sol} \ 105^\circ C$ at a concentration of 2% wt, Table 2, entry 1). As expected the gel stability decreases with concentration (Table 2, Entries 1-6). Compound 4d has a relatively low $T_{sol}$ between 45 and 53 $^\circ C$ highlighting the relatively weak self-association of the gelator molecules and the generally poor gelation properties of this compound (Table 2, entries 7-8).

The outcomes shown in Table 2 indicate the highly effective gelator properties of compound 4e in particular, with $T_{sol}$ values well above the solvent boiling point in many cases. Gels of 4e apparently do not follow the trend of decreasing gel stability with concentration, and as a consequence, the $T_{sol}$ does not decrease with concentration. Surprisingly, the stability of these gels is the same at every concentration and every solvent in the range 0.5 – 2 % wt. The strong hydrogen bonds between the protons of N-H groups and interdigitation between the long alkyl chains may explain the strength of these gels and the high values of $T_{sol}$.

Table 2. Critical gel-to-sol transition temperatures ($T_{sol}$) for 4a, 4d and 4e at different concentrations.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration (%wt)</th>
<th>$T_{sol}$ (°C)</th>
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<tr>
<td>4a</td>
<td>1</td>
<td>1-pentanol</td>
<td>2</td>
<td>105</td>
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<tr>
<td></td>
<td>2</td>
<td>2-propanol</td>
<td>2</td>
<td>74</td>
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<tr>
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<td>3</td>
<td>Methanol</td>
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<td>65</td>
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<tr>
<td></td>
<td>4</td>
<td>1,4-butanediol</td>
<td>2</td>
<td>76</td>
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<tr>
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<td>1-pentanol</td>
<td>1</td>
<td>62</td>
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<tr>
<td></td>
<td>6</td>
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<td>1</td>
<td>50</td>
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<tr>
<td>4d</td>
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<td>DMF</td>
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<td>45</td>
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<tr>
<td></td>
<td>8</td>
<td>Diethylene glycol</td>
<td>2</td>
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<td>4e</td>
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<td>12</td>
<td>Methanol</td>
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<tr>
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<td>DMF</td>
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<td>1,4-butanediol</td>
<td>0.5</td>
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</table>

The morphology of the supramolecular aggregates as dried xerogels was examined by SEM.\[35,36\] As a general rule, small-molecule supramolecular gels exhibit an interconnected fibrous morphology.\[37\] SEM images of xerogels from ethanol of 4e are shown in Figure 3a. In contrast, 4b xerogels showed a spheroidal morphology (Figure 3b), consistent with the lack of gelation by this compound.

![Figure 3](image)

Oscillatory rheology measurements revealed the viscoelastic state of the gel materials.\[38,39\] Frequency and stress sweep experiments, showed that for all gels the elastic modulus, $G'$, is at least an order of magnitude greater than the viscous modulus, $G''$, confirming the solid-like behaviour of the materials.

Rheology experiments were used to compare gels at the same concentration (2% wt) in different solvents, and to compare the stability of different gels of the same solvent at different concentrations. The yield stresses ($\sigma$) for each gel were determined showing the point where the gels broke down. As a general rule, high values of yield stress indicate a higher stability of the gel.\[40\]

Gels of 4a and 4e proved to be particularly robust, for example 4a or 4e exhibit $\sigma$ more than 1000 Pa in both cases (Figure 4c, S8 and S10). In contrast, 4d gives much weaker gels with yield stresses of around 20 and 40 Pa in DMF and diethylene glycol, respectively (Figure 4b and S9). While all of these compounds possess a trialkoxyaryl motif the additional amide groups in 4e apparently results in more robust fibre formation. In the case of 4a the gels are opaque suggesting larger, more crystalline particles and the high yield stress may represent the presence of large solid particles rather than an elastic gel network. This difference is also reflected in the higher $\sigma$ values for 4e compared to 4a in 1,4-butanediol (1585 vs 914 Pa)
Figure 4. Stress sweep experiments at a concentration of 2% wt. for a) 4a in 1,4-butanediol ($\sigma$= 914 Pa), b) 4d in DMF ($\sigma$= 20 Pa), c) 4e in 1,4-butanediol ($\sigma$= 1585 Pa).

We also compared the gels of 4e in ethanol, at various concentrations (2% wt, 1% wt. and 0.5 %wt) (Figure S11 in SI). Consistent with the $T_{gel}$ measurements the stability of the gel decreases with concentration. In general, when the concentration is decreased, the number of inter-fibre interactions decrease due to the lower fibre density, resulting in weakening of the gel.

Stimuli response

Responsive gels are of significant current interest as advanced materials. Given the potential importance of the balance between hydrophobic and hydrogen bonding interactions in gels of the most effective gelator 4e the influence of pH on its gelation properties was examined. Gels in ethanol at 2% wt. of 4e were treated with a solution of 0.1 M NaOH (pH=13). This resulted in the transformation of the gel into a sol suggesting potential disruption of the hydrogen bonded network because of deprotonation or increased ionic strength. When the base-treated gel was acidified with a strong acid at the same concentration (0.1 M HCl, pH=1), the gel recovers its structure (Figure 5) suggesting reprotonation and lending weight to the important role of hydrogen bonding in this system.

Figure 5. pH response of 4e.

The influence of a range of metal ions on gel formation of compound 4e was examined by adding 0.2 M of different metal salts (Cu$^{2+}$, Co$^{2+}$ and Zn$^{2+}$ as the sulfate salts and Na$^+$ and Li$^+$ as chlorides) to hot solutions of the gelator, followed by cooling. When treated with Cu$^{2+}$, Co$^{2+}$ and Zn$^{2+}$ sulfates the gels did not form, however in the presence of Na$^+$ and Li$^+$ the gels remained stable (Figure 6). A possible explanation is the greater affinity of the transition metal ions for the gelator amide carbonyl oxygen atoms or triazole nitrogen atoms.

Figure 6. Response of gels of 4e (2% wt. in Ethanol) to the addition of 0.2 M solutions of metal salts.

Gel phase crystallization of pharmaceutical drugs

One important potential application of low molecular weight organogels is as media for the crystallization of active pharmaceutical ingredients (APIs). Organogels of 4e were examined as potential crystallization media for pharmaceutical APIs. A range of representative APIs were chosen based on their known polymorphism and chemical diversity; namely theophylline, sulfathiazole, sulfamerazine and niflumic acid (Figure 7).
Figure 7. Structure of the different compounds used for crystallization within the gel.

A series of crystallization experiments was performed to optimize the crystallization conditions. The optimized conditions for gelation are found to be 10 mg/mL drug concentration at 0.1% gelator concentration. A mixture of gelator and drugs in a particular solvent was warmed followed by sonication to give a gel of the API solution. Samples in open vials were then left undisturbed at room temperature over periods of several weeks to allow crystallization. In many cases, no crystallization was observed. The experiments were repeated three times with the same results in all cases. The vials were checked visually for crystallization and crystalline products were analysed by X-ray powder and single crystal diffraction. No significant difference on crystallization outcome between gel and a solution phase control experiment under the same conditions was observed for theophylline, sulfamerazine and niflumic acid. The experiments resulted in the known Form II in the case of theophylline in ethanol, the Pna21 polymorph in the case of sulfamerazine and P21/n form in the case of niflumic acid. Microscopic images of theophylline and sulfathiazole crystals obtained through gel crystallization using gelator 4e, shows a cluster of needle-shaped crystals slightly bigger in size than those obtained from solution crystallization. In the case of niflumic acid a change in crystal habit was observed inside the gels in methanol in comparison to the solution crystallization (Figure 8). In the gel phase crystallization block shaped crystals were observed, whereas from solution crystallization in methanol resulted in needle type crystals. In the gel phase crystallization of sulfathiazole a change from polymorphic Form II in solution to room temperature kinetic Form I was observed in the presence of the gel (Figure 9). Polymorphic form was confirmed by unit cell determination on representative crystals (Figure S12). This interesting outcome suggests that the gelator either inhibits crystallization of Form II or increases the nucleation rate of Form I.

Conclusions

Derivatives of 2H-benzo[d]1,2,3-triazole 4a, 4d, and 4e gave a number of organogels in specific solvents. Compound 4e in particular proved to be an effective gelator of a wide range of solvents even at low concentrations, in some cases acting as a supergelator (e.g. ethanol, critical gelation concentration 0.1 %wt). These gels also displayed high thermal stability and significant mechanical resistance. Gels of 4e were used in the crystallization of the pharmaceutical drugs theophylline, sulfathiazole, sulfamerazine and niflumic acid. In the case of sulfathiazole the gel induces a change in the polymorphic form observed in comparison to solution crystallization under the same conditions. These gels offer significant scope for expanding the rage of current polymorph discovery methods particularly in the pharmaceutical industry.

Experimental

General

All reagents were used as purchased. Reactions with air-sensitive materials were carried out under an argon atmosphere. Flash chromatography was performed using silica gel (Merck, Kieselgel 60, 230–240 mesh or Scharlau 60, 230–240 mesh). Analytical thin layer chromatography (TLC) was performed using aluminium-coated Merck Kieselgel 60 F254 plates. NMR spectra were recorded on a Varian Unity 500 (1H: 500 MHz; 13C: 125 MHz) spectrometer at 298 K using deuterated solvents as an internally referenced against the residual protic solvent signal. Chemical shifts (δ) are denoted in
ppm. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

SEM images were obtained on a JEOL JSM 6335F microscope working at 10 kV. The samples for SEM imaging were prepared by a controlled precipitation using the appropriate solvent or by slow diffusion by using mixtures of solvents, depending on their solubility properties (see the corresponding figure caption for a detailed description). The corresponding solid was deposited onto a glass substrate and the remaining solvent was slowly evaporated.

IR spectra were recorded on a IR Shimadzu, FTIR IR Affinity 1S WL C/Lab solution, with a zinc selenide crystal and ATR device. For drop-milling test to calculate \( T_{\text{m}} \), a small metal ball with a diameter of 1 cm was used for the experiments.

Rheological measurements were performed with an advanced rheometer AR 2000 from TA Instruments which was equipped with a cooling system (Julabo C). A 20 mm plain plate geometry (stainless steel) was used. First strain sweep measurements were carried out to estimate the strain in % at which reasonable torque values were given (about 10 times of the transducer resolution limit). Afterwards, frequency sweep measurements and time sweep measurements from 0.1 to 4000 Pa were performed.

Gel phase crystallizations were performed by adding 10 mg of the drug in a vial containing 0.1% wt. of the gelator in a particular solvent. The vials were warmed followed by sonication to obtain a gel of the API solution. Crystals start appearing 2-3 days as observed by microscopy. Crystals were characterized by determining the unit cell parameter.

General synthetic procedure for derivatives 4

A mixture of 2-(3,5-bis(trifluoromethyl)phenyl)-4,7-dibromo-2H-benzo[d][1,2,3]triazole (2) (0.100 g, 0.200 mmol), the corresponding acetylene derivative (3) (0.4 mmol), DBU (0.061 g, 0.400 mmol), CuI (0.002 g, 0.010 mmol) and Pd-EncatTM TCPP30 (0.018 g, 0.007 mmol) was charged under argon to a dried microvial. CH2CN (1 mL) was added. The vessel was closed and irradiated at 130 °C for 20 min. The crude reaction product was purified by chromatography, eluting with hexane/ethyl acetate to give an analytically pure products 4.

2-(3,5-bis(trifluoromethyl)phenyl)-4,7-bis(3,4,5-tris(dodecylxyloxy)phenyl)ethyl)benzene [triazole (4a)]. From 1,2,3-tris(dodecylxyloxy)-5-ethylbenzene (3a) (0.266 g, 0.400 mmol), derivative 4a (0.201 g, 61%) was obtained as an orange solid by chromatography eluting with hexane/ethyl acetate (98/2). P.f.: 156-158°C. 1H-NMR (CDCl3 ppm): 9.01 (s, 2H, =O-Ph), 7.96 (s, 1H, p-N-Ph), 7.63 (s, 2H, H-benzotriazolyl), 6.91 (s, 4H, o-Ph), 4.01 (t, 12H, -OCH2), 1.61-2.12 (m, 120 H, -CH2), 0.93 (s, 18H, -CH3). 13C-NMR (CDCl3 ppm): 147.0, 141.2, 139.5, 138.3, 131.9, 131.3, 124.7, 123.6, 123.1, 122.0, 115.5, 102.2, 93.3, 92.8, 31.9, 29.6, 29.3, 25.9, 22.7, 14.0. HRMS calculated for (C120H185F33N10O14) M+ 1636.21 found 1636.78. Elemental analysis: C, 74.80; H, 9.89; F, 6.96; N, 2.58; O, 5.88.

IRMS spectra were recorded on a FTIR Shimadzu, FTIR IR Affinity 1S WL C/Lab solution, with a zinc selenide crystal and ATR device. For drop-milling test to calculate \( T_{\text{m}} \), a small metal ball with a diameter of 1 cm was used for the experiments.
Alkyl derivatives 3

1,2,3-tris(dodecylxoyl)-5-ethylbenzene (3a): A brown solid (0.389 g, 72%) was obtained and identified as 3a. HMR (CDCl3, 500 MHz): 6.69 (s, 2H, o-H), 3.93-3.96 (m, 6H, 3x-OCH3), 2.98 (s, 1H, iCH), 1.71-1.80 (m, 6H, 3xCH2), 1.44-1.47 (m, 6H, 3xCH2), 1.26-1.34 (m, 48H, -CH2), 0.87-0.89 (m, 9H, 3xCH3) ppm. 13C-NMR (CDCl3, 125 MHz): 141.1, 127.1, 126.2, 29.3, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 30.3, 31.8, 31.9, 69.1, 73.5, 75.7, 84.0, 110.7, 116.4, 139.6, 152.9 ppm. HRMS calculated for (C24H32O)M* 654.60 found 654.74.

N-dodecyl-4-ethylbenzamide (3c): A black solid (0.060 g, 97%) was obtained and identified as 3c. HMR (CDCl3, ppm): 7.80 (s, 1H, NH), 7.65-7.63 (d, 2H, m-Ph), 7.54-7.52 (d, 2H, o-Ph), 3.85-3.83 (t, 12H, -OCH2), 3.04 (s, 1H, iCH), 1.41-1.25 (m, 120H, -CH2), 0.91 (s, 18H, -CH3). 13C-NMR (CDCl3, ppm): 153.1, 125.9, 144.9, 133.1, 132.4, 132.7, 126.1, 126.2, 123.4, 74.1, 69.5, 31.9, 30.3, 29.8, 29.7, 29.6, 29.4, 29.3, 26.1, 22.7, 14.2. HRMS calculated for (C24H34NO)M* 313.24 found 313.47.

3,4,5-tris(dodecylxoyl)-N-(4-ethylbenzoyl)benzamide (3d): A white solid (0.080 g, 48%) was obtained and identified as 3d. HMR (CDCl3, ppm): 7.76 (s, 1H, NH), 7.63-7.61 (d, 2H, m-Ph), 7.54-7.51 (d, 4H, o-Ph), 7.04 (s, 2H, o-PhOC2H5), 4.04-4.02 (t, 12H, -OCH2), 2.92 (s, 1H, iCH) 1.41-1.25 (m, 120H, -CH2), 0.91 (s, 18H, -CH3). 13C-NMR (CDCl3, ppm): 153.1, 125.9, 144.9, 133.1, 132.4, 132.7, 126.2, 123.4, 74.1, 69.5, 31.9, 30.3, 29.8, 29.7, 29.6, 29.4, 29.3, 26.1, 22.7, 14.2. HRMS calculated for (C30H46NO2)M* 773.63 found 773.99.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

Graphical Abstract

High thermal stability, pH responsive organogels of 2H-benzo[d]1,2,3-triazole derivatives as pharmaceutical crystallization media

Iván Torres-Moya, Basanta Saikia, Pilar Prieto, José R. Carrillo and Jonathan W. Steed

2H-benzo[d]1,2,3-triazole derivatives give rise to a supergelator that results in the crystallization of kinetic Form I sulfathiazole