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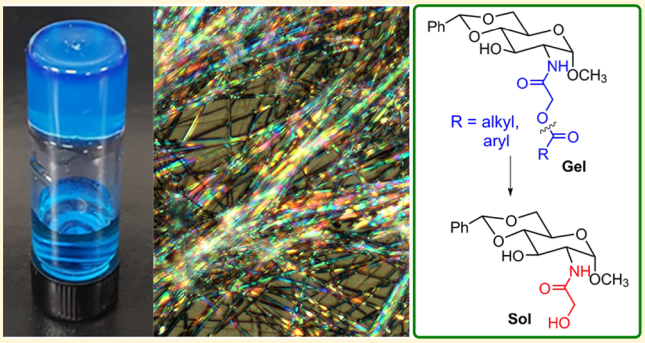
Synthesis and Characterization of Hybrid Glycolipids as Functional Organogelators and Hydrogelators

Joedian Morris, Paige Kozlowski, and Guijun Wang*

Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, Virginia 23529, United States

Supporting Information

ABSTRACT: Carbohydrate-based low-molecular-weight gelators are useful and versatile compounds for the preparation of soft materials. Using *N*-acetyl-D-glucosamine as the starting material, we synthesized and characterized 15 glycolipids containing an amide with different ester functional groups. These include aliphatic derivatives with varying chain lengths and aromatic derivatives. Most of the hybrid amide-esters have molecular weights less than 500 D. These glycolipids were found to be effective gelators for several organic solvents, water, and aqueous solutions. Two efficient hydrogelators were also obtained at low concentrations. A few representative gels were characterized using optical microscopy, atomic force microscopy, and rheology to obtain information on their morphology and gel stability. Three gelators were also used to encapsulate naproxen sodium and toluidine blue. The sustained release of the drug from the gel to the aqueous phase was monitored by UV−vis spectroscopy. These gelators have structural flexibility that can be stimuli responsive. The esters can be hydrolyzed and several gels were converted to solutions under basic conditions. These rationally designed gelators could be utilized as stimuli-responsive smart materials with controlled release properties.



INTRODUCTION

Low-molecular-weight gelators (LMWGs) or molecular gelators are useful compounds for the preparation of soft gel-like materials. The resulting gels are reversible and are called physical gels or supramolecular gels, which are composed of cross-linked networks with the solvents as the main component of the gels.[1−5] The interactions that govern the intricate supramolecular network formed by these gelators are non-covalent interactions. These include hydrogen bonding, van der Waals forces, $\pi-\pi$ stacking, CH$-\pi$ interactions, and hydrophobic effects.[6−9] Many different classes of natural products have been reported as molecular gelators, for instance, oligopeptides, carbohydrate derivatives, and cholesterol derivatives. Compounds containing functional groups such as urea, urethane, amide, aromatic, and long-chain alkyl groups are found to be effective organogelators and hydrogelators.[10,11] They have shown applications in a variety of research fields including environmental applications, biomedical research, and catalysts for synthesis.[12−19] Among the different classes of gelators, we are more interested in using sugars as the building blocks due to their biocompatibility and biodegradability. Carbohydrate derivatives have been utilized extensively as scaffolds for biomaterials with different functions. One important facet of carbohydrates is the presence of multiple functional groups that can form hydrogen bonds, which are necessary for supramolecular systems and self-assembly.[20−22] The versatile hydrogels and organogels obtained from carbohydrate derivatives have shown remarkable applications in a variety of research fields.[21,23−25] These include but are not limited to biomedical applications such as drug delivery, tissue engineering, and enzyme immobilization.[25−27] Several LMWGs and other supramolecular gelators have shown applications in environmental chemistry for pollutant removal, phase selective gelation, and oil spill clean ups.[28−35] Gelators containing functional groups that are responsive toward different stimuli including acids and bases or enzymes are useful new materials with stimuli-responsive properties.[36] For instance, phosphatase responsive gelators have shown remarkable applications as anticancer agents with a new mode of action, physical gelation.[37,38]

We have been working on the selective functionalization of sugar templates that are suitable for gelation and molecular self-assemblies and obtained several different classes of sugar-based LMWGs.[39−45] Most of the gelators form physical gels composed of up to ∼2 wt % gelator and ∼98% solvents. The structures of a few examples are shown in Figure 1. Certain alkyl derivatives of the 2-*O*-ester from glucose, esters **1** were gelators for several solvents. The amide derivatives **2** were more effective gelators for a wide range of functional groups, many amides formed gels in mixtures of dimethyl sulfoxide

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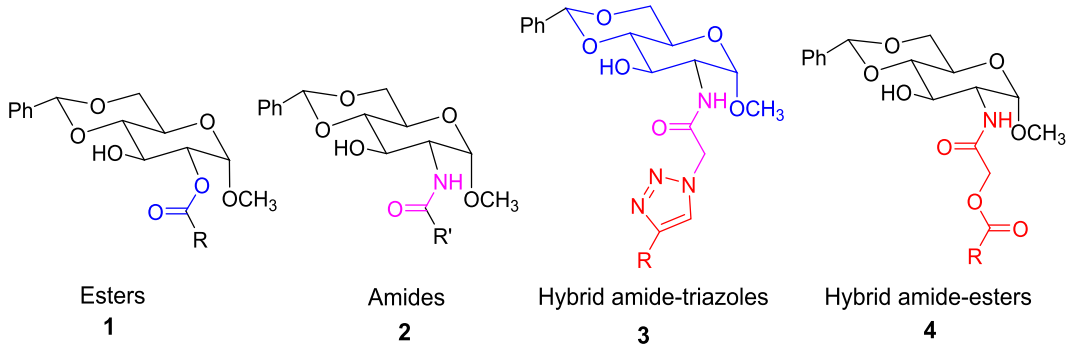
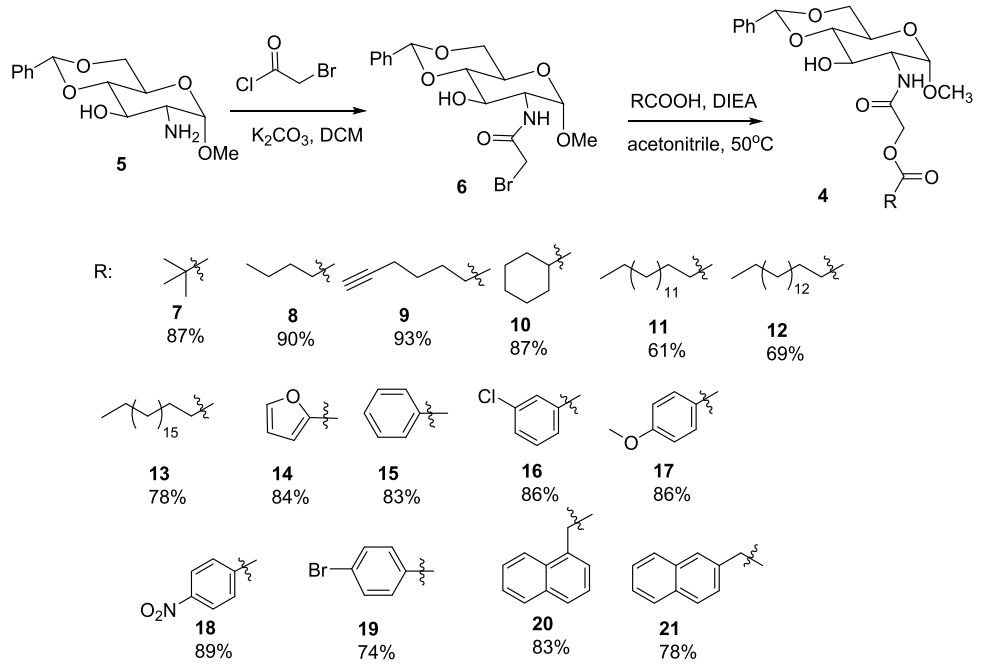


Figure 1. Structures of several sugar-based gelators and the structure of a new class of hybrid amide ester gelator system **4**.

Scheme 1. Synthesis of Hybrid Amide and Ester Derivatives



(DMSO) and water or ethanol and water, and a few formed hydrogels.[39,40,43,45] Recently, we reported a hybrid system **3**,[41] in which a triazole functional group was introduced to the amide **2**; these compounds were found to be extremely effective gelators, and more compounds formed hydrogels in comparison to the simple amide derivatives **2**. The hybrid system **4** combines ester functions with the amide functional group, and this system should lead to effective LMWGs since the modification will not affect the molecular assemblies much while adding additional hydrogen-bonding acceptors to the molecules. In addition, the ester functional group is base responsive and could be cleaved either under basic conditions or using lipase enzymes. Therefore, compounds with the general structure **4** could lead to a new class of functional and stimuli-responsive gelators. These different glycolipids could be useful as stimuli-responsive gelators and in drug-delivery studies.

RESULTS AND DISCUSSION

The synthesis of the series of esters is shown in Scheme 1. The starting material amino compound **5** was prepared from *N*-acetyl-D-glucosamine.[40,41] The compound **5** was treated with bromo-acetyl chloride or bromo-acetyl bromide to afford the headgroup **6**, and then the bromo group was displaced by different carboxylates via S_N2 reactions to obtain a series of esters **4**. To probe the structural impact toward gelation properties, a series of different alkyl and aryl carboxylate esters were synthesized and characterized. An important feature for these compounds is that they can be synthesized in a very straightforward manner with readily available carboxylic acids, which are abundant starting materials with many different structures available. The structure and gelation relationship studies allow us to design new and effective gelators using a sugar template. As shown in Scheme 1, the representative primary, secondary, and tertiary aliphatic esters **7**−**13** and aromatic derivatives **14**−**21** were synthesized. Their gelation properties were screened, and the results are shown in Table 1. The minimum gelation concentrations (MGCs) are also included for the gels formed by the compounds.

All 15 compounds formed gels in several of the tested solvents; the only compound that did not perform as well as the others was the *t*-butyl ester. The branched ester derivative formed gels only in ethylene glycol and glycerol at higher concentrations. The linear short-chain pentyl ester **8** was the most versatile gelator, forming gels in 10 out of the 11 tested solvents. It also formed a hydrogel at 0.14 wt %. The longer

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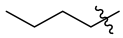
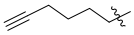
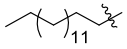
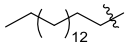
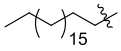
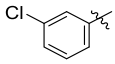
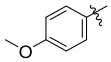
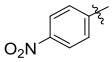
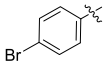
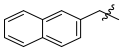
Table 1. Gelation Test Results of Compounds 7−21[a]

Cpd. #	Structure	Tol	*i*-PrOH	EtOH	EG	Glycerol	TEG	EtOH :H_2O (1:2)	EtOH :H_2O (1:1)	DMSO :H_2O (1:2)	DMSO :H_2O (1:1)	H_2O
7		PG	P	P	$G20_O$	$G20_O$	S	P	P	P	P	I
8		$G6.7_C$	$G6.7_O$	$G10_O$	$G10_C$	$G2.5_C$	S	$G2.9_T$	$G10_O$	$G2.5_T$	$G5.0_C$	$G1.4_O$
9		$G6.7_C$	$G20_O$	S	S	$G5.0_C$	S	$G6.7_O$	$G10_O$	$G10_O$	$G10_O$	$G2.9_O$
10		$G4.0_C$	$G6.7_O$	S	$G10_C$	$G10_T$	S	$G5.0_O$	$G5.0_O$	$G5.0_O$	$G4.0_T$	P
11		$G6.7_C$	$G10_O$	P	$G4.0_O$	$G10_C$	$G4.0_O$	P	P	S	S	I
12		$G20_C$	$G20_O$	I	$G5.0_T$	$G10_C$	$G10_C$	I	P	I	I	I
13		$G3.3_C$	$G6.7_O$	$G6.7_O$	$G10_T$	$G20_C$	$G5.0_T$	P	P	P	P	I
14		$G6.7_C$	$G20_T$	$G10_O$	$G10_T$	$G20_C$	S	$G20_O$	$G6.7_O$	$G5.0_O$	$G5.0_O$	I
15		$G10_C$	$G5.0_T$	$G20_O$	$G5.0_T$	$G3.3_T$	$G20_C$	I	$G6.7_O$	I	$G6.7_O$	I
16		$G4.0_C$	$G20_O$	$G10_O$	$G3.3_T$	$G6.7_C$	$G20_T$	I	$G1.5_O$	$G1.4_T$	$G1.4_T$	I
17		$G10_C$	$G2.5_T$	$G4.0_T$	$G1.7_T$	$G10_C$	$G20_C$	I	$G1.3_T$	$G1.3_O$	$G1.3_T$	I
18		$G20_C$	$G2.5_T$	$G20_O$	$G4.0_C$	$G10_C$	S	P	P	$G2.2_T$	$G2.5_O$	I
19		$G20_C$	$G6.7_O$	$G10_O$	$G20_O$	S	S	I	$G4.0_O$	I	I	I
20		$G10_O$	P	PG	$G20_O$	$G6.7_O$	S	I	P	$G5.0_O$	$G20_O$	I
21		$G10_C$	$G20_O$	P	$G10_T$	$G5.0_T$	S	I	$G20_O$	$G5.0_O$	$G5.0_O$	I

[a]All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are minimum gelation concentrations (MGCs) in mg/mL; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque; Hex, hexane; Tol, toluene; EG, ethylene glycol; TEG, triethylene glycol. All tested compounds were soluble in tetrahydrofuran, and most were insoluble in hexane.

alkyl derivative heptynoate **9** formed gels in eight of the tested solvents but typically required higher concentrations for gelation in comparison to the pentanoate **8**. Compound **9** also formed a hydrogel at 0.29 wt %. The hydrogelators **8** and **9** formed hydrogels at low concentrations, which should allow them to be useful for entrapment of drug molecules and other applications. The cyclohexyl ester **10** was also a versatile gelator for toluene, isopropanol, and aqueous mixtures of ethanol or DMSO. For the linear aliphatic derivatives, increasing the chain length in compounds **11**, **12**, and **13** to 15, 16, and 19 carbons, respectively, increased the hydrophobicity of the compounds; they formed gels only in organic solvents but not in water and the aqueous solutions. The longest-chain ester **13** was the most efficient gelator for toluene, forming a gel at 3.3 mg/mL. All aromatic ester derivatives were gelators for at least four of the tested solvents; among these, the 2-furan ester **14**, benzoate **15**, 3-chlorobenzoate **16**, and 4-methoxybenzoate **17** were the most versatile gelators, forming gels in eight or nine of the tested solvents. They were effective for aqueous mixtures of DMSO or ethanol, with the chloro- or methoxy-substituted aryl derivatives being the most efficient in DMSO and water mixtures. The 4-nitrobenzoate derivative **18** performed well too; however, the bulkier 4-bromobenzoate **19** was not as effective as the rest. The addition of another aromatic ring as in the 1- or 2-naphthalene derivatives **20** and **21** diminished gelation slightly. It is interesting to observe that the stereoisomers gave different gelation properties, with the 2-naphthylacetate **21** being more proficient in comparison to the 1-naphthylacetate **20**. Most of the gels were opaque or translucent with a few being transparent. A few representative gel photos are shown in Figure 2.

The gels were characterized using optical microscopy to obtain molecular assembly morphologies. A few selected

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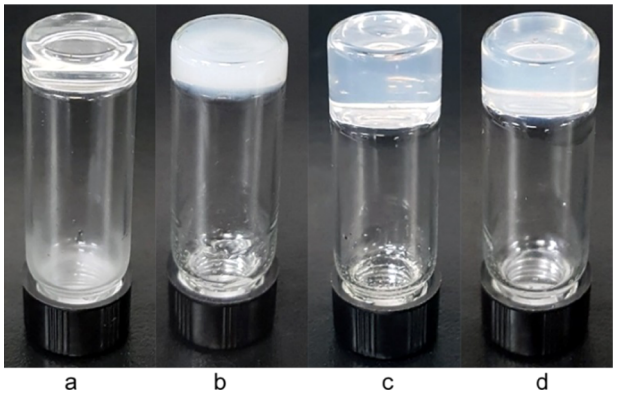

Figure 2. (a) Clear gel of compound **9** in glycerol at 5.0 mg/mL; (b) opaque gel of compound **10** in DMSO/H_2O (v/v 1:2) at 5.0 mg/mL; (c) translucent gel of compound **16** in DMSO/H_2O (v/v 1:2) at 1.4 mg/mL; (d) translucent gel of compound **18** in DMSO/H_2O (v/v 1:2) at 2.2 mg/mL.

samples are shown in Figure 3. The series of compounds formed effective gels in many solvents; typically, the gels exhibited fibrous morphologies. The gel of compound **9** in EtOH/H_2O (v/v 1:2) exhibited fibrous aggregates (Figure 3a). The gel of compound **10** in EtOH/H_2O (v/v 1:2) showed long fibrous networks with densely aligned birefringent fibers (Figure 3b). The gels in DMSO/H_2O (v/v 1:2) also showed similar fibrous features (Figure 3c–e). The furan derivative **14** formed long uniform fibers with lengths of more than 100 μm (Figure 3c), and the gel of compound **16** showed similar birefringent long fibrous networks with lengths of more than 200 μm (Figure 3d). The gel of compound **20** showed shorter fibers with a length of less than 100 μm (Figure 3e). Figure 3f shows the morphology of the wet gel formed by compound **18** with toluidine blue (TBO); clusters of fibers were arranged around fan-shaped assemblies.

To further characterize the surface morphological properties, atomic force microscopy (AFM) studies were carried out for several gelators. These are shown in Figures 4 and S32–S34 in the Supporting Information. Figure 4a shows the AFM images of the hydrogel formed by compound **9**, which exhibited long fibrous assemblies. The DMSO/H_2O (v/v 1:2) gel formed by compound **16** showed shorter and thinner fibrous aggregates (Figure 4b), and the gel formed by compound **18** in DMSO/

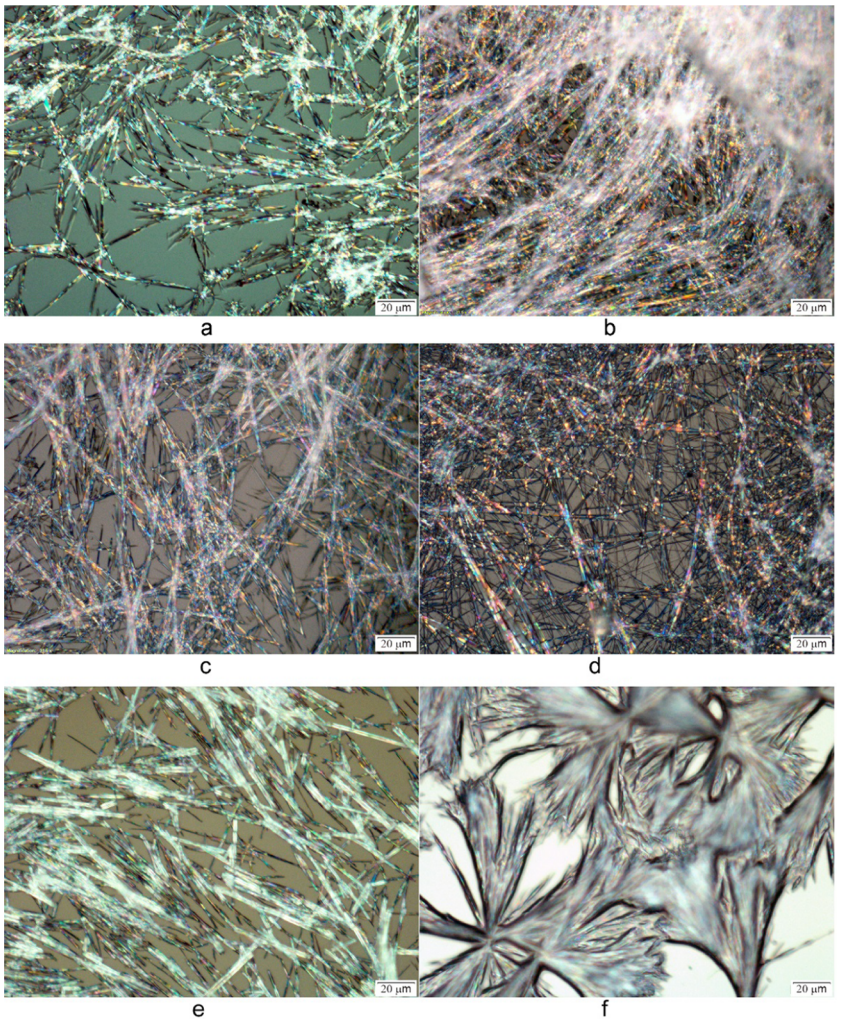

Figure 3. Optical micrographs of gels: (a) compound **9** in EtOH/H_2O (v/v 1:2) at 6.7 mg/mL; (b) compound **10** in EtOH/H_2O (v/v 1:2) at 4.0 mg/mL; (c) compound **14** in DMSO/H_2O (v/v 1:2) at 5.0 mg/mL; (d) compound **16** in DMSO/H_2O (v/v 1:2) at 1.4 mg/mL; (e) compound **20** in DMSO/H_2O (v/v 1:2) at 5.0 mg/mL, (f) compound **18** in DMSO/H_2O (v/v 1:8) at 2.25 mg/mL (for the gel only; the gel volume was 2 mL) and toluidine blue (TBO) dye at 0.031 mg/mL. The scale bar is 20 μm for all images.

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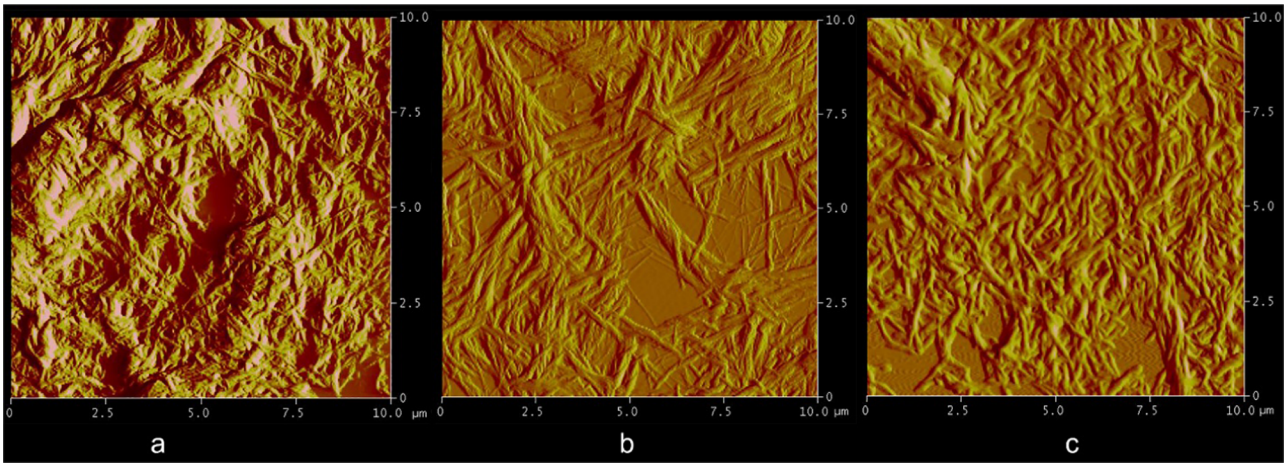

Figure 4. AFM phase images for several gels: (a) hydrogel formed by compound **9** at 2.9 mg/mL; (b) compound **16** in DMSO/H_2O (v/v 1:2) at 1.4 mg/mL; (c) compound **18** in DMSO/H_2O (v/v 1:8) at 2.25 mg/mL and toluidine blue (TBO) dye at 0.031 mg/mL.

H_2O (v/v 1:8) and in the presence of toluidine blue showed twisted ribbonlike morphologies (Figure 4c). The AFM images illustrated more detailed structural information of the assemblies in comparison to the optical micrographs. Additional AFM images including both the height and phase images are included in the Supporting Information.

To analyze the mechanical properties and stability of the gels, several rheological experiments were performed on the hydrogels and organogels formed by the gelators. The results can be seen in Figures 5 and S2–S7 in the Supporting Information. The amplitude sweep experiments were carried out first to obtain the linear viscoelastic range that would be needed to carry out the frequency sweep. As shown in Figure 5, the storage modulus (G') was greater than the loss modulus (G'') for all gels analyzed, which validated that the gels were stable with viscoelastic properties. The hydrogel formed by compound **8** has larger G' (more than 100 kPa) values than the gel formed by compound **9**, which means that the hydrogel of **8** is relatively stronger when both gelators are at their MGCs. The rheological properties of the DMSO/H_2O (v/v 1:2) gels for compounds **10**, **16**, **17**, **18**, and **20** are also included in Figure 5. Among these, the gel of cyclohexyl ester **10** exhibited the highest G' (more than 100 kPa) values, followed by that of compound **18**. The G'/G'' ratios for the gels formed by compounds **8**–**10**, **16**–**19**, and **20** are included in Tables S4–S8 in the Supporting Information.

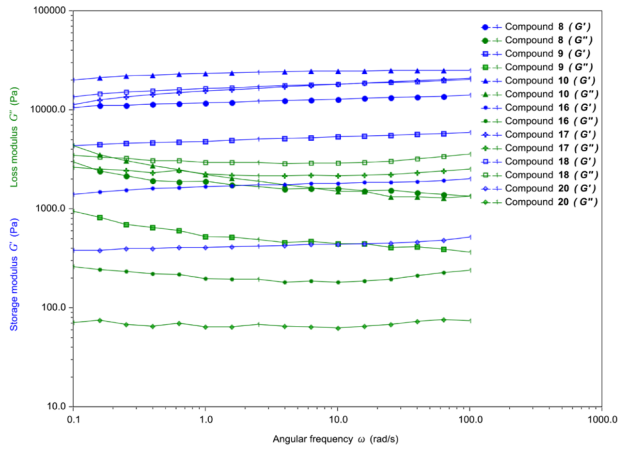

Figure 5. Rheological properties of the hydrogels of compound **8** (H_2O, 1.4 mg/mL) and compound **9** (H_2O, 2.9 mg/mL) and the gels in DMSO/H_2O (v/v 1:2) for compounds **10**, **16**, **17**, **18**, and **20**. The concentrations of the gelators are as follows: compound **10** (5.0 mg/mL), compound **16** (1.4 mg/mL), compound **17** (1.3 mg/mL), compound **18** (2.2 mg/mL), and compound **20** (5.0 mg/mL).

To further analyze the thermal stability of gels, the melting points of a few representative gels in DMSO/H_2O (v/v 1:2) were measured and, these are listed in Table 2. The median melting temperature can represent the relative thermal stability of these gels. The melting temperatures of the gels seem to be structure dependent, with aromatic esters (**16** and **20**) having higher melting points than the aliphatic esters (**8** and **10**). The melting behavior of the gels was affected by the strength of the interactions within the intricate network, whereby the gels with stronger intermolecular forces should have a higher melting point than others.

For applications in biological systems, the hydrogelators for pure water or hydrogels with a small amount of DMSO are preferable. Therefore, the gelation properties of compounds **16**, **17**, and **18** were studied in different proportions of DMSO and water. The results are summarized in Tables S1–S4 and Figure S1. All three gelators formed gels in DMSO/H_2O at 1:1 and 1:2 ratios. Upon serial dilution, compound **18** formed gels in DMSO/H_2O at ratios of 1:3, 1:4, 1:5, 1:6, 1:7, and 1:8. Compound **18** formed a gel at a 1:8 volume ratio of DMSO/water at 2.2 mg/mL. The *p*-methoxybenzoate **17** also formed gels at 12.5% DMSO in water at 2.5 mg/mL, but the 3-chlorobenzoate **16** formed gels only in 25% DMSO aqueous solution at 5.0 mg/mL.

Based on these results, the gels formed by compound **8** in water and compound **17** in DMSO/H_2O (v/v 1:5) were chosen for naproxen entrapping and release studies. These two gelators represented the two general classes of esters, aliphatic and aromatic esters. Compound **8** was an effective hydrogelator; therefore, its properties for encapsulating drugs or other compounds would be important. Compound **17** represented aromatic ester derivatives, and it may interact with aromatic-group-containing compounds more strongly. Naproxen sodium was used as the model drug, which represents compounds containing aryl and carboxylate functional groups. The release profile of naproxen from the gel matrix and the approximate release percentages are shown in

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Table 2. Melting Points of the Gels in DMSO/H_2O (v/v 1:2)[a]

Compound	R	Concentration mg/mL	Molar concentration (mM)	T_1 °C	T_2 °C	T_3 °C
8		2.5	5.9	34.0	58.0	92.8
10		5.0	11.1	40.9	54.9	113.9
16		1.4	3.0	57.3	65.5	126.1
20		5.0	10.1	60.5	93.0	124.0

[a] T_1, initial melting temperature; T_2, the temperature at which half of the gel has melted; T_3, the temperature at which melting of the gel finished.

Figures 6 and 7. Naproxen was slowly released from the hydrogel of ester **8** in about 2−3 days. After 72 h, almost all of

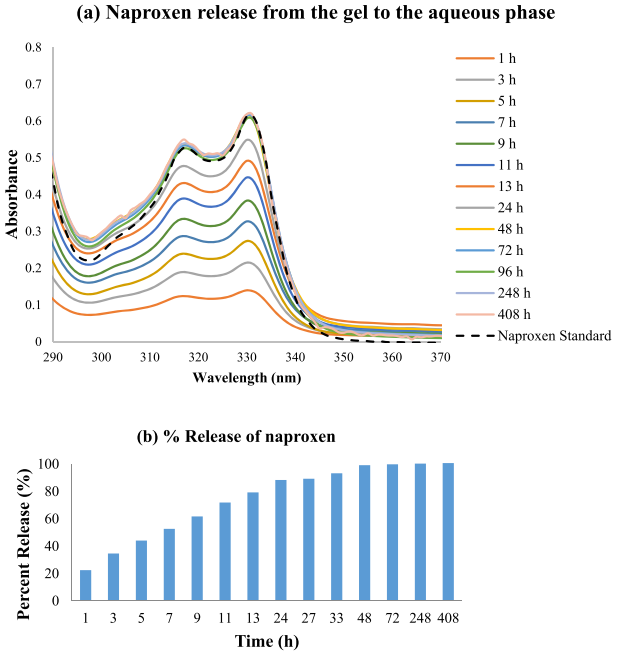

Figure 6. (a) UV−vis spectra and (b) release profile of naproxen sodium at different time intervals from the hydrogel of compound **8**. The hydrogel was prepared using 2.8 mg of compound **8** and 0.5 mg of naproxen sodium in 2.0 mL of water. Then, 2.0 mL of water (pH 7) was placed on top of the gel; the UV absorption of the aqueous phase was measured and shown in (a). The naproxen release percentage was estimated using the absorbance at 330 nm for the aqueous phase versus the standard.

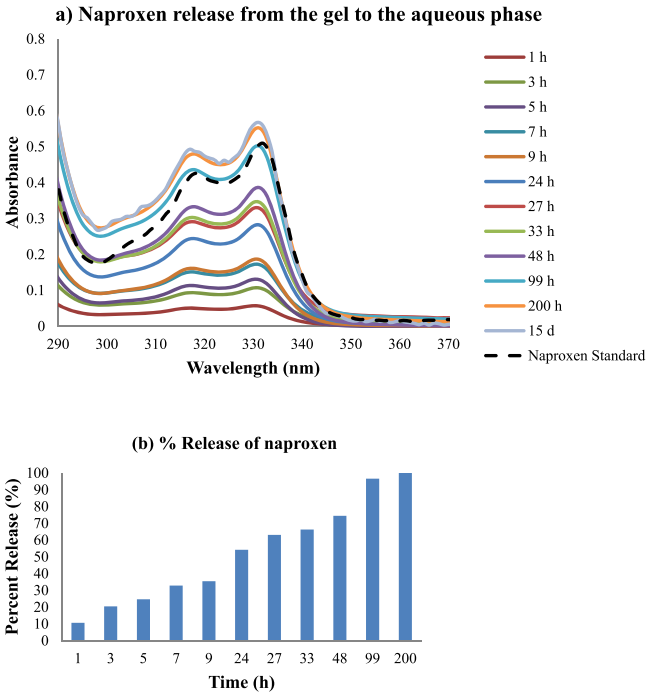

Figure 7. UV−vis spectra and release profile of naproxen sodium at different times for the gel formed by compound **17** in DMSO/H_2O (v/v 1:5). The gel was prepared using 5.0 mg of compound **17** and 0.5 mg of naproxen sodium in 2.0 mL of DMSO/H_2O (v/v 1:5) solution. Then, 2.0 mL of water (pH 7) was placed on top of the gel. The percent release was calculated using the absorbance of the aqueous phase versus the standard at 330 nm.

the naproxen sodium was released from the gel and the naproxen concentration reached equilibrium in the solution and gel phase. The gel was quite stable even after 18 days but slowly dissolved as the time progressed; after 30 days, the gel was almost fully dissolved and turned into a solution.

Naproxen release was slower for the gel formed by compound **17** in DMSO/H_2O (v/v 1:5) as shown in Figures 7 and S9 in the Supporting Information. A similar steady release was seen for the gel matrix formed by compound **17**, and it took about one day for half of the naproxen to diffuse from the gel to the aqueous phase. It is interesting that the gel was very stable and remained intact even up to 28 days in the presence of the added water! This result indicated that the gelators could be useful as soft materials for applications requiring stable gels. Compound **17** was used to form a gel with added chloramphenicol as well; the UV−vis spectra recorded at different time intervals for chloramphenicol are included in Figure S11 of the Supporting Information.

The effective gelators **8**−**21** are simple ester derivatives that were synthesized from glucosamine, and they should be biocompatible for certain applications. To test whether they can interact with ionic compounds, toluidine blue (TBO) dye was used as an example and the aromatic ester **18** was selected

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for the study. Compound **18** formed a stable co-gel in the presence of TBO (molar ratio 1:1) at 4.0 mg/mL of compound **18** and 2.4 mg/mL of TBO in DMSO/H_2O (v/v 1:8) (Supporting Information page S44). This result indicated that the gelator molecules could interact with the dye and form stable gel networks. To analyze whether the gel can absorb the dye from aqueous solutions, a gel of compound **18** in DMSO/H_2O (v/v 1:8) was prepared and an equal volume of toluidine blue solution was added on top of the gel. A few selected photos are shown in Figure S12 of the Supporting Information. The TBO dye was slowly absorbed by the gel; at 28 h, the dye almost diffused to the bottom of the gel, and after 72 h, the gel phase showed a homogenous blue color from the dye. The gel trapped with the TBO dye was very stable and showed very little degradation after 9 days. The sample was left with the aqueous phase on top of the gel, and this was still intact after 6 months! This extraordinary stability could be utilized for different applications where gel stability is desirable.

Toluidine blue and other phenothiazines form dimers or higher-order aggregations in aqueous solutions, and the photophysical behavior of the dyes is important for their applications.[46] The TBO dye exhibited strong dimer absorption at a wavelength of λ_{max} 590 nm and monomer absorption at λ_{max} 626 nm. Both are in the long-wavelength regions without an overlap with the molecular gelators, which allows for a more accurate measurement of the dye concentration. The absorption of toluidine blue into the gel phase was measured at different time intervals; the UV−vis spectra of the TBO left in the aqueous phase were recorded and are included in Figure 8 and Supporting Information pages S44−S46. The dimer was the major form of toluidine blue in solution; before placing the dye solution on top of the gel, only a small amount of the monomer was present. After 2 days, the most dominant peak was the monomer at approximately 626 nm. This indicated that the dimer was absorbed into the three-dimensional network of the gel more preferentially than the monomer and the presence of the gelators resulted in the reduction of dimerization of the TBO in the aqueous phase. It is possible that the gelator was able to absorb the dimeric form of TBO due to $\pi-\pi$ interactions and hydrophobic forces between the aryl rings of the dye and the molecular gelator. The observation is interesting since it can decrease the dimerization of the dye and confirm that the gel can interact well with cationic compounds or charged ions. The dye-absorbing properties can be further studied for the gelators as biosorbents and for the removal of dyes from a mixture of solvents or aqueous environments.

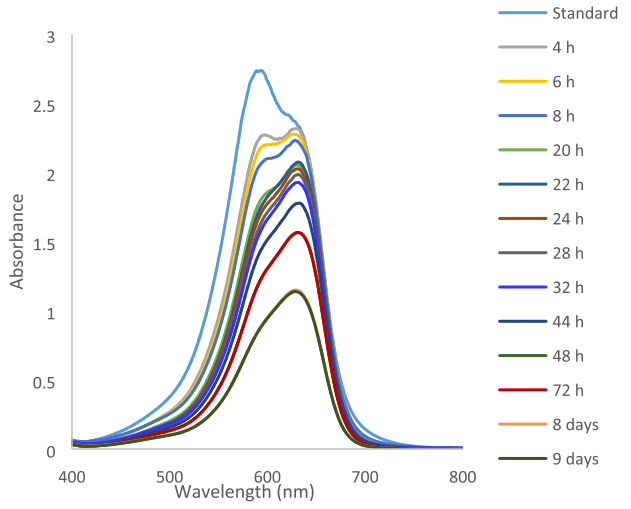

Figure 8. UV−vis spectra of toluidine blue solution above the gel of compound **18** at different time intervals. The standard corresponds to the initially added 2.0 mL of a 0.1 mM solution of the toluidine blue dye.

These esters are excellent gelators, and the resulting gels can be stimuli responsive if treated with a base or a suitable enzyme to hydrolyze the ester functional group. The stability toward basic conditions for several representative gels was analyzed. As shown in Scheme 2, we treated the gels formed by gelators **8**, **16**, and **17** in DMSO/H_2O (v/v 1:2, 8.0 mg/mL) with basic solutions (pH 12 and pH 13 solutions). Under pH 13 aqueous solutions, the gels turned to liquid within 1 h for compounds **8** and **16**; the gel formed by compound **17** in the DMSO water mixture turned to liquid after a 4 h treatment of the basic solution, which showed more stability toward base hydrolysis than compounds **8** and **16**. The resulting solution was extracted, and compound **22** was obtained as the product of the cleavage. This compound was also prepared by a different method and tested for gelation properties. As shown in Table S4, the diol was soluble in most of the tested solvents including ethanol, isopropanol, ethanol and water mixtures, and DMSO and water mixtures. It formed a partial gel in water at 20.0 mg/mL and became soluble in water at lower concentrations.

At milder basic conditions, the gels formed by compounds **8** and **16** were stable up to 7 h after exposure to the base solution (pH 12) and started showing decomposition after that. The gel formed by compound **17**, however, was more stable; no sign of degradation was observed after 13 days under similar conditions. We also did the naproxen trapping and release monitoring study for this compound. In the presence of the pH 12 solution, the gel was stable up to 7 days and no significant decomposition was observed (Figure S30). The base-triggered conversion of the lipid to the corresponding hydroxyl compound **22** indicated that the gels can be chemically converted to solutions. The chemical trigger could be replaced by an enzymatic trigger using a lipase under neutral conditions. These will be studied in the future together with other applications of these gelators.

CONCLUSIONS

In summary, a series of D-glucosamine-derived amide-esters were prepared, and they were effective LMWGs especially for organic solvents and mixtures of polar organic solvents with water. Both aliphatic and aromatic esters performed very well in organic solvents including toluene and isopropanol, ethylene glycol, and glycerol. Short-chain linear aliphatic esters were also effective hydrogelators, whereas long-chain and aromatic esters were not soluble in water. Single-ring aromatic esters including furan and substituted benzoic esters were efficient gelators for organic solvents, DMSO water mixtures, and ethanol water mixtures. The short-chain linear alkyl and cyclohexyl derivatives and aromatic derivatives were more effective than the long-chain and *t*-butyl ester derivatives. Optical microscopy and atomic force microscopy studies showed that the morphologies of the different gels were mostly fibrous networks. The rheological studies for the gelators confirmed their stability and viscoelastic behavior. The steady release of naproxen sodium from the gels of compounds **8** and **17** demonstrated their potential to be used in medical

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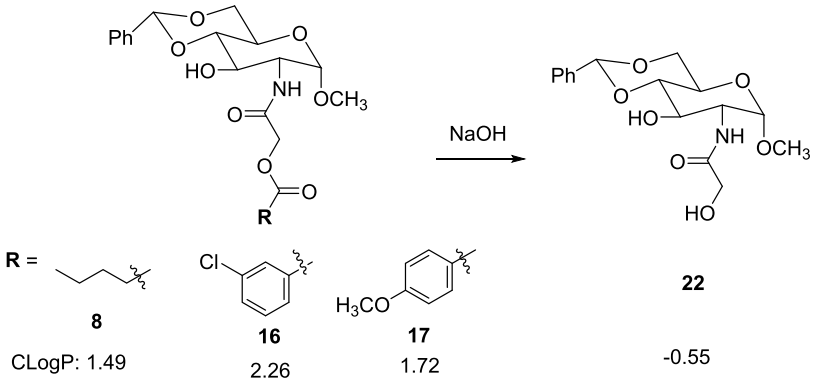
Scheme 2. Cleavage of the Ester in Basic Conditions and the clog *P* Values



applications as drug-delivery systems. Moreover, the gels formed by the esters can be cleaved under basic conditions and result in a more water-soluble diol. The stimuli-responsive gelators have the potential to be utilized as controlled delivery carriers for various applications. These amide and ester hybrids demonstrated success in the structure-based design to obtain stimuli-responsive soft gel materials. The gelators were synthesized in a straightforward manner from glucosamine derivatives and carboxylic acids, and the structure−gelation relationship obtained from the study would be useful for the design of other carbohydrate-based gelators.

EXPERIMENTAL SECTION

General Methods and Materials. Reagents and solvents were used as they were received from the suppliers. All purifications were carried out using flash chromatography on a 230−400 mesh silica gel with a gradient of solvent systems. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Stuart automatic melting point apparatus SMP40. Rheology measurements were done using an HR-2 Discovery Hybrid Rheometer from TA instruments and a 25 mm Peltier plate. UV−vis experiments were done using a Thermo Scientific Evolution 201 UV−Visible spectrophotometer.

Optical Microscopy. A thin slice of the gel was transferred onto a clean glass slide and then left to air-dry for a day or so. The gel was then observed under an Olympus BX60M optical microscope using an Olympus DP73-1-51 high-performance 17MP digital camera with pixel shifting and Peltier cooling. The program used to acquire and store the images was CellSens Dimension 1.11.

Atomic Force Microscopy. The representative gels were prepared approximately 12 h before being placed on the slides. A thin slice of the gel was transferred onto a clean glass slide and then left to air-dry for a day or so before being observed under an atomic force microscope (AFM). AFM measurements were carried out using a Veeco Dimension 3100 atomic force microscope using tapping mode. The tips used were Nanosensors silicon AFM probes with a resonant frequency of 340−500 kHz and a force constant of 20−45 N m^{-1}.

Gelation Test. Approximately 2 mg of the desired compound was placed in a one-dram vial and 0.1 mL of the gelation solvent or solution was transferred inside the vial to attain a concentration of 20 mg/mL. The vial was then heated until the gelator dissolved fully; sometimes, the mixture was sonicated to help with dissolving the compound and the mixture was left to cool for approximately 15 min or longer for the gel to form. After this period, if the solution was clear, this was recorded as soluble; if the solid reappeared, this was recorded as a precipitate; if the sample formed a gel, then the vial was inverted; if no solvent was flowing, this indicated that a stable gel was formed; otherwise, this was recorded as unstable gel. If gelation occurs, another 0.1 mL is added and the method is repeated until an unstable gel is formed. The minimum gelation concentration (MGC), the concentration prior to unstable gelation, was recorded.

Naproxen Trapping and Release Studies. Naproxen sodium was dissolved in the desired solvent, and this was used to prepare the gel first. For compound **8**, naproxen sodium (2.5 mg) was dissolved in 10.0 mL of H_2O and 2.0 mL of this solution was used to prepare the gel using compound **8** (2.8 mg). The gelator concentration was 1.4 mg/mL, and the initial naproxen sodium concentration was 0.25 mg/mL. The gel was left at room temperature for ∼12 h, and then 2.0 mL of water (pH 7) was placed on top of the gel. The UV absorbance of the aqueous phase was taken at different time intervals by transferring the solution to a cuvette and then cautiously returning it to the vial after the measurement. The final naproxen concentration should be 0.125 mg/mL in both aqueous and gel phases if equilibrium has been achieved.

A similar protocol was used for other gelators. For compound **17**, naproxen sodium (2.5 mg) was dissolved in 10.0 mL of DMSO/H_2O (v/v 1:5), and 2.0 mL of this solution was used to make the gel with compound **17** (5.0 mg). The gelator concentration was 2.5 mg/mL, and the initial naproxen concentration was 0.25 mg/mL. The gel was left at room temperature for 12 h, and then 2 mL of water (pH 7) was placed on top of the gel and the absorbance was taken at different time intervals.

Toluidine Blue Dye Absorption Studies. A 0.1 mM solution of toluidine blue was prepared by dissolving 6.2 mg of the TBO dye in 200 mL of water. From this solution, 2.0 mL was placed on top of the gel for the study. The gel was prepared using 4.5 mg of compound **18** in 2.0 mL of DMSO/H_2O (v/v 1:8). The absorbance was taken at different time intervals of the aqueous solution on top of the gel.

General Procedure for the Synthesis of Esters 7−21. Compound **6** was synthesized by a previously reported literature procedure.[37] In a 50 mL round-bottom flask equipped with a drying tube, the headgroup, compound **6** (about 100 mg, 0.25 mmol, 1 equiv) was dissolved in 4 mL of anhydrous acetonitrile. The carboxylic acid (1−1.5 equiv) was then added to the flask, followed by *N*,*N*-diisopropylethylamine (DIEA) (2.0 equiv). The reaction mixture was stirred for about 6 h at 50 °C, and thin-layer chromatography (TLC) and ^{1}H NMR spectroscopy were used to monitor the progress of the reaction. If the reaction was not complete, the reaction mixture was stirred for a longer time. After the starting material was fully converted to the product, the reaction mixture was cooled and concentrated on a rotavap to remove the solvent. The crude product was worked up with dichloromethane (DCM) and 2% cold $NaHCO_3$ solution and then with water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed to obtain the crude product. Then, the crude product was purified by flash chromatography on silica gel using a gradient of dichloromethane and methanol. The quantities of reagents and characterization data are given below; detailed procedures are not given unless different conditions were used.

Synthesis of Compound 7. Compound **6** (81.7 mg, 0.20 mmol, 1 equiv), trimethylacetic acid (26.5 mg, 0.26 mmol, 1.3 equiv), and DIEA (0.071 mL, 0.40 mmol, 2 equiv) were added. The reaction mixture was stirred for 6 h at which the ^{1}H NMR spectrum showed full conversion. The crude product was purified by column

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chromatography using hexane/EtOAc from 9:1 to 3:7 to give the desired product as a white solid (75 mg, 87%), R_f = 0.46 in 3% MeOH/DCM, mp 176.0−178.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.39−7.33 (m, 3H), 6.44 (d, J = 8.9 Hz, 1H), 5.57 (s, 1H), 4.72 (d, J = 3.9 Hz, 1H), 4.66 (d, J = 15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.32−4.21 (m, 2H), 3.92 (t, J = 9.6 Hz, 1H), 3.86−3.74 (m, 2H), 3.60 (t, J = 9.1 Hz, 1H), 3.40 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 168.4, 137.0, 129.2, 128.3, 126.3, 102.0, 98.7, 81.8, 70.5, 68.0, 62.7, 62.4, 55.3, 53.5, 38.8, 27.1. Liquid chromatography−mass spectrometry (LC−MS) m/z calcd for $C_{21}H_{30}NO_8$ $[M + H]^+$ 424.2, found 424.2.

Synthesis of Compound ***8***. Compound **6** (103.1 mg, 0.26 mmol), valeric acid (0.04 mL, 0.37 mmol, 1.4 equiv), and DIEA (0.09 mL, 0.52 mmol) were added. The reaction mixture was stirred for 8 h at which the ^{1}H NMR spectrum showed full conversion. The crude product was purified by column chromatography using pure DCM to 1.5% MeOH/DCM to afford the desired product as a clear solid (97.7 mg, 90%), R_f = 0.55 in 3% MeOH/DCM, mp 165.0−167.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.41−7.34 (m, 3H), 6.42 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.59 (d, J = 15.5 Hz, 1H), 4.32−4.23 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.86−3.74 (m, 2H), 3.60 (t, J = 9.1 Hz, 1H), 3.41 (s, 3H), 2.44 (t, J = 7.4, 2H), 1.71−1.62 (m, 2H), 1.45−1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.2, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.8, 62.8, 62.4, 55.4, 53.5, 33.7, 26.9, 22.2, 13.6. LC−MS m/z calcd for $C_{21}H_{30}NO_8$ $[M + H]^+$ 424.2, found 424.2.

Synthesis of Compound ***9***. Compound **6** (77.5 mg, 0.19 mmol, 1 equiv), 6-heptynoic acid (27.2 mg, 0.22 mmol, 1 equiv), and DIEA (68 μL, 0.39 mmol, 2 equiv) were added. The reaction mixture was stirred at 60 °C for 6 h at which the ^{1}H NMR spectrum and TLC showed full conversion. The crude product was purified by column chromatography using pure DCM to 3% MeOH/DCM to afford the desired product as a white solid (79.9 mg, 93%), R_f = 0.4 in 3% MeOH/DCM, mp 167.0−169.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.39−7.34 (m, 3H), 6.39 (d, J = 8.9 Hz, 1H), 5.56 (s, 1H), 4.75 (d, J = 3.8 Hz, 1H), 4.64 (d, J =15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 4.32−4.23 (m, 2H), 3.95 (m, 1H), 3.85−3.74 (m, 2H), 3.62−3.56 (m, 1H), 3.42 (s, 3H), 2.47 (t, J = 7.4 Hz, 2H), 2.24 (td, J = 7.0, 2.6 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.86−1.77 (m, 2H), 1.65−1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.0, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 83.7, 81.9, 70.3, 68.9, 68.8, 62.9, 62.4, 55.4, 53.6, 33.4, 27.7, 23.8, 18.1. LC−MS m/z calcd for $C_{23}H_{30}NO_8$ $[M + H]^+$ 448.2, found 448.2.

Synthesis of Compound ***10***. Compound **6** (94.4 mg, 0.23 mmol, 1 equiv), cyclohexanecarboxylic acid (39.3 mg, 0.31 mmol, 1.3 equiv), and DIEA (0.08 mL, 0.46 mmol, 2 equiv) were added. The reaction mixture was stirred for 7 h at which the ^{1}H NMR spectrum and TLC showed full conversion. The crude product was purified via column chromatography using hexane/EtOAc from 8.5:1 to 2:8 to produce the desired product as a white solid (91.4 mg 87%), R_f = 0.40 in 3% MeOH/DCM, mp 174.0−176.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.46 (m, 2H), 7.40−7.33 (m, 3H), 6.42 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.66 (d, J = 15.7 Hz, 1H), 4.58 (d, J = 15.7 Hz, 1H), 4.32−4.21 (m, 2H), 3.94 (t, J = 9.4 Hz, 1H), 3.86−3.73 (m, 2H), 3.60 (t, J = 9.1 Hz, 1H), 3.41 (s, 3H), 2.43 (m, 1H), 2.02−1.91 (m, 2H), 1.84−1.74 (m, 2H), 1.73−1.63 (m, 1H), 1.57−1.44 (m, 2H), 1.41−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 168.4, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.6, 68.8, 62.6, 62.4, 55.3, 53.6, 42.9, 29.0, 28.9, 25.6, 25.3, 25.27. LC−MS m/z calcd for $C_{23}H_{32}NO_8$ $[M + H]^+$ 450.2, found 450.2.

Synthesis of Compound ***11***. Compound **6** (100.7 mg, 0.25 mmol, 1 equiv) and palmitic acid (68.7 mg, 0.27 mmol, 1 equiv), followed by DIEA (0.09 mL, 0.52 mmol, 2 equiv), were added. The reaction mixture was left to stir for 7 h at which TLC and the ^{1}H NMR spectrum demonstrated full conversion. The crude product was purified via column chromatography using hexane/acetone to produce the desired product as a white solid (88.3 mg 61%). R_f = 0.63 in 3% MeOH/DCM, mp 138.0−140.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.40−7.34 (m, 3H), 6.42 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.64 (d, J = 15.2 Hz, 1H), 4.59 (d, J = 15.2 Hz, 1H), 4.32−4.23 (m, 2H), 3.94 (t, J = 9.3 Hz, 1H), 3.86−3.73 (m, 2H), 3.60 (t, J = 9.1 Hz, 1H), 3.42 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 1.73−1.62 (m, 2H), 1.41−1.14 (m, 24 H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.2, 137.0, 129.2, 128.3, 126.3, 102.0, 98.7, 81.9, 70.3, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 24.8, 22.7, 14.1. LC−MS m/z calcd for $C_{32}H_{52}NO_8$ $[M + H]^+$ 578.4, found 578.3.

Synthesis of Compound ***12***. Compound **6** (101 mg, 0.25 mmol, 1 equiv), heptadecanoic acid (68 mg, 0.25 mmol, 1 equiv), and DIEA (80 μL, 0.47 mmol, 2 equiv) were added. The reaction mixture was stirred for 24 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 2% MeOH/DCM to yield the desired product as a white solid (101 mg, 69%), R_f = 0.5 in 3% MeOH/DCM, mp 142.0−144.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.46 (m, 2H), 7.39−7.34 (m, 3H), 6.41 (d, J = 8.9 Hz, 1H), 5.57 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.64 (d, J =15.6 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.31−4.24 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.85−3.75 (m, 2H), 3.64−3.57 (m, 1H), 3.41 (s, 3H), 2.43 (t, J = 7.6 Hz, 2H), 1.72−1.62 (m, 2H), 1.39−1.21 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.2, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.9, 29.7, 29.6, 29.4, 29.34, 29.25, 29.1, 24.8, 22.7, 14.1. LC−MS m/z calcd for $C_{33}H_{53}NO_8Na$ $[M + Na]^+$ 614.4, found 614.4.

Synthesis of Compound ***13***. Compound **6** (100.1 mg, 0.25 mmol, 1 equiv), eicosanoic acid (80.3 mg, 0.26 mmol, 1 equiv), and DIEA (0.09 mL, 0.52 mmol, 2 equiv) were added. The reaction mixture was stirred for 7 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using 100% DCM to 1.5% MeOH/DCM to give the desired product as a white solid (122 mg, 78%), R_f = 0.50 in 3% MeOH/DCM, mp 145.0−147.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.46 (m, 2H), 7.40−7.33 (m, 3H), 6.40 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.64 (d, J = 15.5 Hz, 1H), 4.59 (d, J = 15.5 Hz, 1H), 4.33−4.22 (m, 2H), 3.93 (t, J = 9.4 Hz, 1H), 3.85−3.73 (m, 2H), 3.59 (t, J = 9.1 Hz, 1H), 3.41 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H), 1.73−1.61 (m, 2H), 1.40−1.15 (m, 32H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.2, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.2, 29.1, 24.8, 22.7, 14.1.

Synthesis of Compound ***14***. Compound **6** (97 mg, 0.24 mmol, 1 equiv), 2-furoic acid (27 mg, 0.240 mmol, 1 equiv), and DIEA (78 μL, 0.45 mmol, 2 equiv) were added. The reaction mixture was stirred for 24 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 3% MeOH/DCM to afford the desired product as a white solid (87 mg, 84%), R_f = 0.35 in 5% MeOH/DCM, mp 229.0−231.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + d_4-MeOH) δ 7.61 (m, 1H), 7.50−7.41 (m, 2H), 7.36−7.29 (m, 3H), 7.28 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 6.54 (m, 1H), 5.53 (s, 1H), 4.79 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 3.8 Hz, 1H), 4.28−4.14 (m, 2H), 3.86 (t, J = 9.7 Hz, 1H), 3.81−3.70 (m, 2H), 3.56 (m, 1H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + d_4-MeOH) δ 167.7, 157.2, 147.1, 143.4, 137.0, 129.2, 128.2, 126.2, 119.3, 112.2, 101.9, 98.8, 81.9, 69.5, 68.8, 62.8, 62.6, 55.4, 53.6. LC−MS m/z calcd for $C_{21}H_{24}NO_9$ $[M + H]^+$ 434.1, found 434.1.

Synthesis of Compound ***15***. Compound **6** (102.7 mg, 0.26 mmol, 1 equiv), benzoic acid (48.8 mg, 0.40 mmol, 1.5 equiv), and DIEA (0.09 mL, 0.52 mmol, 2 equiv) were added. The reaction mixture was stirred for 7 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 1.5% MeOH/DCM to give the desired product as a white solid (95.5 mg, 83%), R_f = 0.38 in 3% MeOH/DCM, mp 223.0−225.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0, 2H), 7.67−7.58 (m, 1H), 7.54−7.43 (m, 4H), 7.40−7.32 (m, 3H), 6.56 (d, J = 9.0 Hz, 1H), 5.56 (s, 1H), 4.90 (d, J = 15.6 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.74 (d, J = 3.2 Hz, 1H), 4.36−4.23 (m, 2H), 3.95 (t, J = 9.5 Hz, 1H), 3.86−3.72 (m, 2H), 3.61 (m,

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1H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 165.2, 137.1, 133.8, 129.7, 129.2, 128.7, 128.3, 126.3, 102.0, 98.8, 81.8, 70.4, 68.8, 63.4, 62.5, 55.4, 53.7. LC−MS m/z calcd for $C_{23}H_{26}NO_8$ $[M + H]^+$ 444.2, found 444.2.

Synthesis of Compound ***16***. Compound **6** (80.4 mg, 0.20 mmol, 1 equiv), 3-chlorobenzoic acid (39.3 mg, 0.22 mmol, 1 equiv), and DIEA (0.07 mL, 0.40 mmol, 2 equiv) were added. The reaction mixture was stirred for 7 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 1% MeOH/DCM to afford the desired product as a white solid (82.3 g, 86%), R_f = 0.43 in 3% MeOH/DCM, mp 233.0−235.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 1H), 8.00−7.94 (m, 1H), 7.64−7.59 (m, 1H), 7.52−7.42 (m, 3H), 7.40−7.34 (m, 3H), 6.50 (d, J = 9.1 Hz, 1H), 5.57 (s, 1H), 4.86 (br s, 2H), 4.76 (d, J = 3.8 Hz, 1H), 4.34−4.24 (m, 2H), 3.96 (t, J = 9.6 Hz, 1H), 3.86−3.73 (m, 2H), 3.61 (m, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 164.0, 137.0, 134.9, 133.8, 130.7, 130.1, 129.7, 129.3, 128.3, 127.9, 126.3, 102.0, 98.7, 81.8, 70.6, 68.8, 63.7, 62.5, 55.4, 53.6. LC−MS m/z calcd for $C_{23}H_{25}ClNO_8$ $[M + H]^+$ 479.1, found 479.1.

Synthesis of Compound ***17***. Compound **6** (80.3 mg, 0.20 mmol, 1 equiv), 4-methoxybenzoic acid (31.4 mg, 0.21 mmol, 1 equiv), and DIEA (0.071 mL, 0.41 mmol, 2 equiv) were added. The reaction mixture was stirred for 6 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 1% MeOH/DCM to give the desired product as a white solid (81 mg, 86%), R_f = 0.5 in 5% MeOH/DCM, mp 236.0−238.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.9 Hz, 2H), 7.52−7.46 (m, 2H), 7.40−7.33 (m, 3H), 6.97 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.79 (d, J = 15.5 Hz, 1H), 4.74 (d, J = 3.9 Hz, 1H), 4.33−4.23 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.89 (s, 3H), 3.85−3.73 (m, 2H), 3.61 (m, 1H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.9, 164.1, 137.1, 131.9, 129.3, 128.3, 126.3, 114.0, 102.0, 98.8, 81.8, 70.6, 68.8, 63.2, 62.4, 55.5, 55.4, 53.6. LC−MS m/z calcd for $C_{24}H_{28}NO_9$ $[M + H]^+$ 474.2, found 474.2.

Synthesis of Compound ***18***. Compound **6** (100.2 mg, 0.26 mmol, 1 equiv), 4-nitrobenzoic acid (42.7 mg, 0.26 mmol, 1 equiv), and DIEA (0.09 mL, 0.52 mmol, 2 equiv) were added. The reaction mixture was stirred for 23.5 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 1% MeOH/DCM to yield the desired product as a white solid (108.6 g, 89%), R_f = 0.38 in 5% MeOH/DCM, mp 241.0−243.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 7.52−7.45 (m, 2H), 7.40−7.32 (m, 3H), 6.35 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 4.90 (br s, 2H), 4.77 (d, J = 3.8 Hz, 1H), 4.36−4.24 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.84−3.74 (m, 2H), 3.65−3.55 (m, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 163.6, 151.0, 137.0, 134.3, 130.9, 129.3, 128.3, 126.3, 123.8, 102.0, 98.7, 81.8, 70.4, 68.8, 63.9, 62.5, 55.4, 53.6. LC−MS m/z calcd for $C_{23}H_{25}N_2O_{10}$ $[M + H]^+$ 489.2, found 489.2.

Synthesis of Compound ***19***. Compound **6** (103 mg, 0.26 mmol, 1 equiv), 4-bromobenzoic acid (51 mg, 0.25 mmol, 1 equiv), and DIEA (81 μL, 0.47 mmol, 2 equiv) were added. The reaction mixture was stirred for 8 h at which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 2% MeOH/DCM to obtain the desired product as a white solid (98 mg, 74%), R_f = 0.3 in 3% MeOH/DCM, mp 221.0−223.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.91 (m, 2H), 7.66−7.61 (m, 2H), 7.51−7.45 (m, 2H), 7.40−7.33 (m, 3H), 6.47 (d, J = 8.9 Hz, 1H), 5.56 (s, 1H), 4.87 (d, J = 15.3 Hz, 1H), 4.82 (d, J = 15.3 Hz, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.31−4.24 (m, 2H), 3.94 (dd~t, J = 9.6 Hz, 1H), 3.83−3.73 (m, 2H), 3.64−3.55 (m, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.6, 137.0, 132.1, 131.2, 129.3, 129.1, 128.3, 127.8, 126.3, 102.0, 98.7, 81.8, 70.3, 68.8, 63.5, 62.5, 55.4, 53.7. LC−MS m/z calcd for $C_{23}H_{25}NO_8Br$ $[M + H]^+$ 522.1, found 522.1.

Synthesis of Compound ***20***. Compound **6** (75.0 mg, 0.19 mmol, 1 equiv) dissolved in *N*,*N*-dimethylformamide (3 mL), 1-napthylacetic acid (56.7 mg, 0.30 mmol, 1.6 equiv), and potassium carbonate (53.7 mg, 0.39 mmol, 2 equiv) were added. The reaction mixture was stirred for 12 h at rt after which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 3% MeOH/DCM to afford the desired 1-naphthylacetate product as a white solid (78.8 mg, 83%), R_f = 0.50 in 3% MeOH/DCM, mp 183.0−185.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.91 (m, 1H), 7.88−7.82 (m, 1H), 7.64−7.44 (m, 6H), 7.44−7.35 (m, 3H), 5.84 (d, J = 9.2 Hz, 1H), 5.53 (s, 1H), 4.65 (d, J =15.6 Hz, 1H), 4.55 (d, J = 15.6 Hz, 1H), 4.54 (d, J = 3.8 Hz, 1H), 4.25 (m, 1H), 4.22 (d, J =15.6 Hz, 1H), 4.18 (d, J = 15.6 Hz, 1H), 4.07 (td, J = 9.5, 3.8 Hz, 1H), 3.77−3.62 (m, 2H), 3.51−3.42 (m, 1H), 3.37 (m, 1H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.5, 137.1, 134.0, 131.9, 129.7, 129.3, 129.0, 128.5, 128.3, 128.2, 126.8, 126.3, 126.2, 125.6, 123.5, 101.9, 98.5, 81.7, 69.7, 68.8, 63.1, 62.3, 55.2, 53.1, 39.1. LC−MS m/z calcd for $C_{28}H_{30}NO_8$ $[M + H]^+$ 508.2, found 508.2.

Synthesis of Compound ***21***. Compound **6** (131.3 mg, 0.33 mmol, 1 equiv) dissolved in *N*,*N*-dimethylformamide (3 mL), 2-naphthylacetic acid (94.5 mg, 0.51 mmol, 1.5 equiv), and DIEA (0.11 mL, 0.63 mmol, 2 equiv) were added. The reaction mixture was stirred for 24 h at rt after which the ^{1}H NMR spectrum and TLC confirmed full conversion. The crude product was purified by column chromatography using pure DCM to 2% MeOH/DCM to afford the desired 2-naphthylacetate product as a white solid (129.5 mg, 78%), R_f = 0.4 in 3% MeOH/DCM, mp 154.0−156.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.75 (m, 4H), 7.57−7.33 (m, 8H), 6.00 (d, J = 8.9 Hz, 1H), 5.51 (s, 1H), 4.66 (d, J =15.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 4.58 (d, J = 3.8 Hz, 1H), 4.23 (dd, J = 10.2, 4.7 Hz, 1H), 4.10 (m, 1H), 3.91 (br s, 2H), 3.71 (t, J = 10.2 Hz, 1H), 3.60 (m, 1H), 3.49−3.40 (m, 2H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.6, 137.2, 133.5, 132.6, 130.7, 129.3, 128.7, 128.3, 128.1, 127.7, 127.6. 127.0, 126.6, 126.3, 101.9, 98.5, 81.7, 69.6, 68.8, 63.0, 62.3, 55.1, 53.3, 41.5. LC−MS m/z calcd for $C_{28}H_{30}NO_8$ $[M + H]^+$ 508.2, found 508.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.9b02347.

Copies of ^{1}H and ^{13}C NMR spectra of compounds **7**−**22**; 2D NMR spectra of compounds **7**, **8**, **11**, **17**, **18**, and **20**; gelation analysis in DMSO/H_2O at different ratios for compounds **16**−**18**; rheological data and amplitude experiments; UV−vis spectra of compounds **8**, **17**, and **18**; additional information and photos for naproxen drug release, chloramphenicol release studies, and toluidine blue absorption studies; base-catalyzed hydrolysis of gels formed by compounds **8**, **16**, and **17**; Fourier transform infrared spectra of compounds **7**−**21**; and AFM images for gels formed by compounds **9**, **16**, and **18** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g1wang@odu.edu. Tel: (757) 683-3781. Fax: (757) 683-4628.

ORCID

Guijun Wang: 0000-0001-7473-0004

Notes

The authors declare no competing financial interest.

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