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Sugar isoxazole based hydrogelators and their applications as reusable hydrogels for dye removal†

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A series of eleven new *N*-acetyl glucosamine isoxazole derivatives were synthesized and analyzed for their self-assembling properties. These glycoconjugates are gelators for several solvents and eight compounds are able to form hydrogels, representing the first class of isoxazole based molecular hydrogelators. The metallogel formation and dye removal application were also studied.

The self-assembly of small molecules through non-covalent interactions may lead to the formation of supramolecular gels. These compounds are referred to as low molecular weight gelators (LMWGs) or molecular gelators. Among these, the low molecular weight hydrogelators (LMHGs) are especially interesting due to their biocompatibility and potential biomedical and environmental applications.^{1,2} Using certain structural templates, effective LMWGs can be designed by balancing and adjusting various intermolecular forces such as hydrogen bonding, hydrophobic interactions, π - π stacking, and van der Waals forces. Among the many classes of compounds that are able to form supramolecular gels, carbohydrate derivatives have gained great attention due to their unique structures.³ Heterocycle functionalized carbohydrate derivatives are useful for the formation of self-assembled networks and for the formation of LMWGs. We have found that triazole functional group is useful for the design of LMWGs through our previous work with peracetylated glucose and glucosamine triazole derivatives (Fig. 1A and B).^{4,5} Eight glucose triazole derivatives **A** are organogelators and one is a hydrogelator.⁴ Twelve glucosamine triazole derivatives **B** are organogelators and seven are hydrogelators.⁵ The beta-glucosyl derivatives with triazole functional group linked through a 2 carbon spacer were also reported, some of the

compounds are organogelators but the structure flexibility tend to make the molecules more soluble and less prone to form gels.⁶ Isoxazoles are five membered ring heterocycles which can be synthesized *via* 2+3 cycloaddition reactions.^{7,8} We envisioned that the nitrogen and oxygen containing isoxazole heterocycle could be used for the design of sugar based molecular gelators through modification of template **B**. The five membered ring isoxazole exhibits strong dipole moment and can participate in hydrogen bonding through its nitrogen and oxygen, and the hetero-aromaticity contributes to π - π interactions. However, isoxazole based LMWGs are much less studied for gelation in comparison to triazole derivatives. Several isoxazole based organogelators have been reported.^{9–11} A few rigid aromatic isoxazoles have been shown to form organogels but not hydrogels.^{12–14} Certain isoxazole based organogelators were studied for phase selective oil gelation for oil spill cleanup.^{9,15} Isoxazoles have important biological activities and several glycosyl isoxazole conjugates have been synthesized due to their potential biological activities.^{16–18} In the different applications of LMWGs, absorbing various dyes and drug molecules can have environmental applications.^{19–21} Using sugar based gelators for dye absorptions have practical utilities since they are biocompatible.^{22–25} LMWGs in particular those form gels in the presence of metal ions may have additional utilities. These metallogels have exhibited unique properties and have been explored for catalysis,^{26–31} environmental applications of removal toxic metal or dyes,^{32–34} and for preparation of new materials.^{35,36} To the best of our knowledge, isoxazole based hydrogelators have not been reported yet, and isoxazole sugar conjugates have not been studied for their molecular self-assembly and formation of supramolecular gels.

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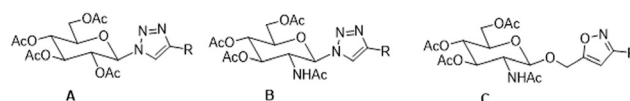
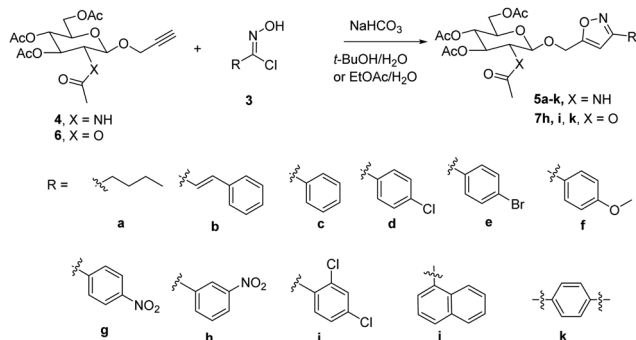


Fig. 1 Structures modifications of triazole heterocycle derivatives to isoxazole derivatives.

Communication



Scheme 1 Synthesis of sugar isoxazole derivatives **5a–5k**, and **7h**, **7i**, and **7k**.

To expand the structures of sugar derivatives for effective molecular gelators, we synthesized a series of isoxazole derivatives from *N*-acetyl-D-glucosamine with the general structure **C** and expect that they will be able to form hydrogels due to the structure similarity to the triazole based hydrogelators **B**. The systematic structure and gelation correlation can allow us to obtain a novel class of isoxazole based LMWGs.

The isoxazole compounds **C** were synthesized using cycloaddition reactions of chloroximes with propargylated sugar head-groups (Scheme 1). The chloroximes **3** were prepared from the corresponding aldehyde **1** in two steps by forming hydroxylamines **2** and followed by *N*-chlorosuccinimide (NCS) oxidation (Scheme S1, ESI†). Most of these compounds contain aromatic functional groups. In addition, three per-acetylated glucose derivatives, **7h**, **7i**, and **7k** were also synthesized (Scheme S2, ESI†).

After these compounds were obtained, they were tested in a panel of solvents and the results are shown in Table 1. The gels are translucent to opaque, several representative images are shown in Fig. 2. All glucosamine derivatives (**5a–5k**) were able to form gels in at least one of the selected test solvents, and remarkably, all compounds were found to be gelators for glycerol, forming clear or translucent gels. These compounds also formed gels in glycerol/ H_2O , $\text{DMSO}/\text{H}_2\text{O}$, or $\text{EtOH}/\text{H}_2\text{O}$

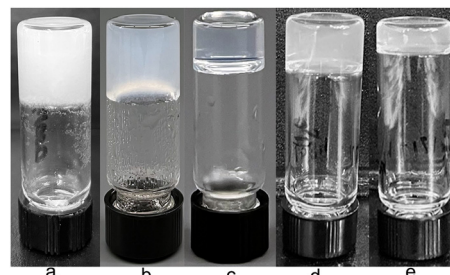


Fig. 2 Gel appearances are opaque in (a); translucent in (b), (d), and (e); clear in (c). (a) **5d** in water at 1.1 mg mL^{-1} , (b) **5e** in water at 1.2 mg mL^{-1} ; (c) **5e** in glycerol at 2.0 mg mL^{-1} , (d) **5h** in H_2O at 2.0 mg mL^{-1} , (e) **5h** in $\text{EtOH}:\text{H}_2\text{O}$ (v/v 1:2) at 5.0 mg mL^{-1} .

mixed solvents. Four compounds formed stable gels in toluene, they are not effective gelators for isopropanol and ethanol. We were delighted to find that these compounds tend to form hydrogels, eight compounds formed stable gels in water. The most efficient hydrogelators are the 4-chlorophenyl derivative **5d**, 4-bromophenyl derivative **5e**, and 3-nitrophenyl derivative **5h**, forming hydrogels at 1.1 , 1.2 , and 2.0 mg mL^{-1} concentrations, respectively. All substituted phenyl isoxazoles are effective gelators in water, $\text{DMSO}/\text{H}_2\text{O}$ (1:2) mixture, and in glycerol. These structural features enable them to form hydrogels can be a useful template for the design of effective low molecular weight hydrogelators. The non-substituted phenyl derivative **5c** and naphthyl derivative **5j** did not form hydrogels, the substituent on the phenyl ring contributed to intermolecular interactions more positively to enable gelation. The dimer **5k** on the other hand is not as effective gelator comparing to the monomeric isoxazole derivatives. It mainly formed gels in glycerol and $\text{EtOH}/\text{H}_2\text{O}$ (1:1) mixture and partial gel like particles for the other solvents. This can be attributed to strong intermolecular forces from both isoxazole ring.

The glucose derivatives **7h** and **7k** mostly formed precipitates in the tested solvents. In comparison to the gelation properties of the glucosamine derivative **5h**, compound **7h** formed partial gels in glycerol and in water at 30 mg mL^{-1} .

Table 1 Gelation properties of the isoxazole derivatives

No	Tol	IPA	EtOH	Glycerol	EtOH:H ₂ O (1:1)	EtOH:H ₂ O (1:2)	DMSO:H ₂ O (1:1)	DMSO:H ₂ O (1:2)	Gly:H ₂ O (1:1)	H ₂ O
5a	S	S	S	G6.7 _C	S	S	G20 _O	G20 _O	G2.5 _O	G20 _O
5b	PG	P	S	G6.7 _T	PG	PG	G20 _O	G20 _O	G2.2 _O	G10 _O
5c	P	P	PG	G20 _T	PG	PG	PG	G20 _O	G4.0 _O	PG
5d	PG	S	P	G6.7 _C	G10 _T	G2.8 _T	G20 _O	G5.0 _O	G2.8 _O	G1.1 _O
5e	G20 _C	PG	G20 _O	G2.0 _C	G5.0 _O	G5.0 _O	G5.0 _O	G5.0 _O	G1.6 _O	G1.2 _T
5f	PG	P	P	G10 _T	P	P	PG	G10 _O	G2.5 _O	G5.0 _O
5g	G5.0 _T	G10 _O	G6.7 _O	G4.0 _T	G10.0 _O	G5.0 _O	G6.7 _T	G6.7 _O	G1.6 _O	G3.3 _O
5h	G10 _C	PG	PG	G6.7 _C	G20 _O	G2.0 _T	G10 _O	G2.8 _T	G1.2 _O	G2.0 _T
5i	G4.0 _C	P	P	G5.0 _T	P	G20.0 _O	G10.0 _O	G10.0 _O	G3.3 _O	G4.0 _O
5j	P	S	P	G20.0 _O	P	P	P	P	G2.8 _O	I
5k	I	PG	PG	G3.3 _C	PG	G2.5 _T	PG	P	I	I
5gf	G13.0 _T	P	P	G2.5 _T	G5.0 _O	G3.3 _T	G10 _O	G7.8 _O	N/A	G5.6 _O
7h	P	P	P	PG	P	P	P	P	N/A	P
7k	P	P	P	P	P	P	P	P	N/A	I

All compounds were tested starting from 20 mg mL^{-1} . G, stable gel at rt, the numbers are minimum gelation concentrations (MGC) in mg mL^{-1} ; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque. **5gf** is a 1:1 mixture of **5g** and **5f**.

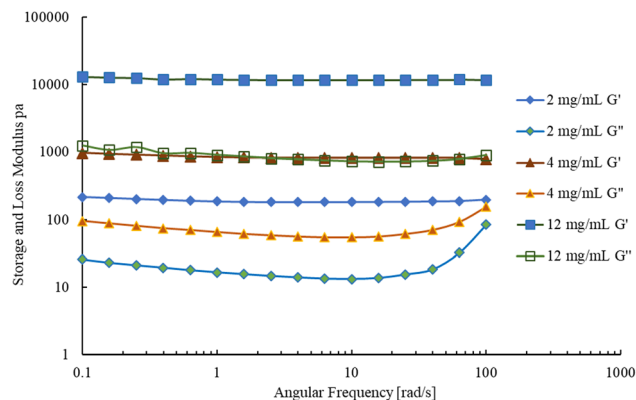


Fig. 3 Rheology properties of the hydrogels formed by **5h** at 2.0, 4.0 and 12.0 mg mL⁻¹.

The dimeric glucose derivative **7k** didn't form gels in any tested solvents. This trend indicates that 2-acetamido group is essential for the gelation properties. The ¹H NMR spectra of compound **5h** at different concentrations showed that the amide NH signal shifted when concentration is increased, which is attributed to the intermolecular hydrogen bonding, as shown in Fig. S2 (ESI[†]).

The rheological properties of several hydrogels formed by gelator **5d** and **5h** are analyzed at different gelation concentrations. The *p*-chlorophenyl derivative **5d** at gelation concentrations in water at 1.1 mg mL⁻¹, 2.2 mg mL⁻¹, and 4.4 mg mL⁻¹ (Fig. S3, ESI[†]) and the 3-nitrophenyl derivative **5h** at 2.0, 4.0 and 12.0 mg mL⁻¹ (Fig. 3) were measured. For all hydrogels, the storage moduli *G'* are greater than the loss moduli *G''* for all frequencies and the storage moduli *G'* exhibited concentration dependence. At higher concentrations, the storage and loss moduli have higher values, indicating that the gels' stiffness and mechanical strengths are concentration dependent.

Compound **5d** formed hydrogel at 0.11 wt%, this gelator was analyzed for its potential of gelation for metal ions. Several metal ions were tested, it was able to form stable gels in the presence of Ni²⁺, Zn²⁺, Cu²⁺, Hg²⁺, and Pb²⁺, the gels are typically opaque as shown in Fig. S1 (ESI[†]). We also found that a two-component system formed by the 4-methoxyphenyl derivative **5f** and 4-nitrophenyl derivative **5g** (1 : 1 molar ratio) were effective gelators in several solvents (Table 1, **5gf**). This result indicates that the gelator molecule can be used to entrap a different small molecule and still maintain the molecular assembling structure.

The gel morphology was characterized using optical microscopy and scanning electron microscopy (SEM). A few representative images are shown in Fig. 4, 5 and Fig. S61, S62 (ESI[†]). Typically, the gels formed long fibrous networks. The Cl-compound **5d** showed long tubular fibers which are highly birefringent (Fig. 4a), the metallo gels formed by this compound exhibited fibrous network as well, but typically narrower or smaller fibers, the additions of the metal ions didn't affect the hydrogelation. The hydrogel of **5d** in the presence of zinc ions and copper ions exhibited long and narrow fibrous network (Fig. 4b and c). The SEM of hydrogels mostly exhibited fibrous network as well.

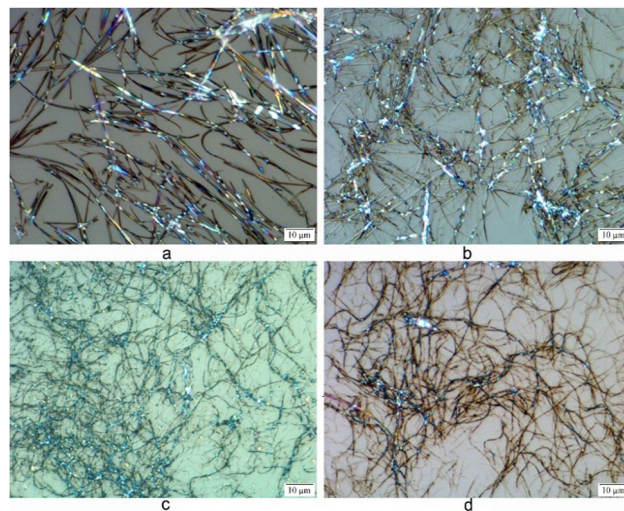


Fig. 4 Optical micrographs of a few hydrogels. (a)–(c) Compound **5d** in water at 1.1 mg mL⁻¹, (b) with Zn(OAc)₂·2H₂O, (c) with Cu(OAc)₂, (d) compound **5e** in water at 1.2 mg mL⁻¹.

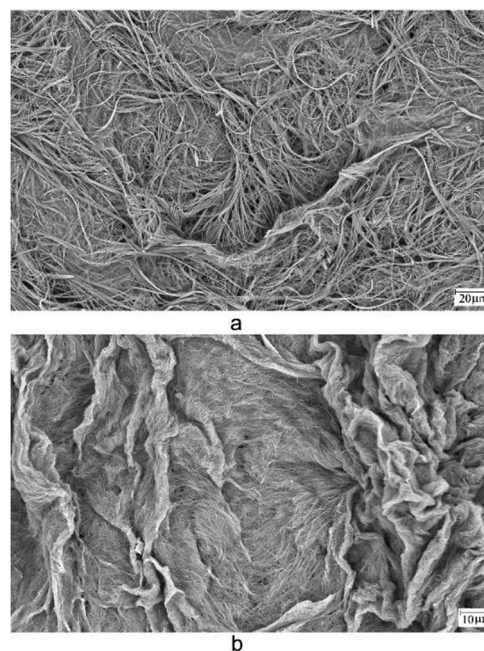


Fig. 5 The scanning electron micrographs of the hydrogels formed by: (a) compound **5d** at 1.1 mg mL⁻¹; (b) a mixture of compound **5f** and **5g** at 5.6 mg mL⁻¹.

Compounds **5d** and **5h** were evaluated for applications in dye removal from aqueous solutions. The hydrogel was prepared in a syringe column and dye solution was eluted from the gel. UV-vis spectroscopy was used to analyze the amount of dyes passing through the column. The hydrogel formed by **5d** at 4.4 mg mL⁻¹ was used for the dye removal experiment. The gel column was shown to absorb 98% of the toluidine blue dye (Fig. S16 and S17, ESI[†]), and approximately 96% of the rhodamine B dye (Fig. S18 and S19, ESI[†]). Gelator **5h** was also used

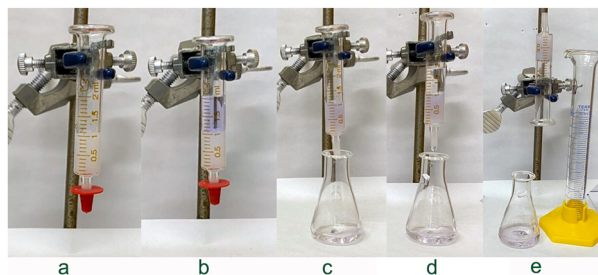


Fig. 6 (a) Initial gel, 1.0 mL gel of **5h** in $8.0 \text{ mg mL}^{-1} \text{ H}_2\text{O}$; (b) 1.0 mL dye mixture was added on top of the gel; (c) gel column after passing dye; (d) after dye solution finished eluting, the gel was eluted with 1.0 mL of DI water; (e) inverted gel column after the completion of the experiment.

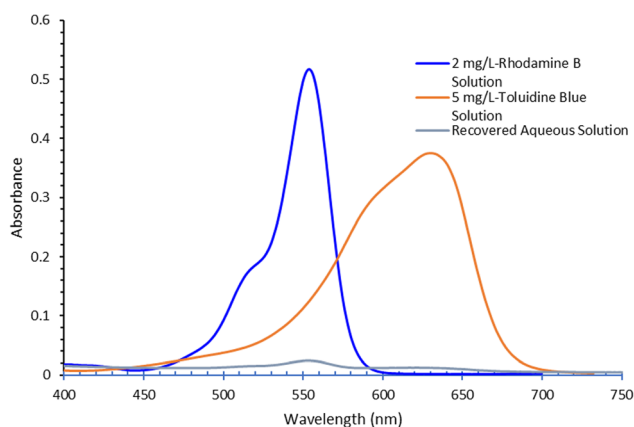


Fig. 7 UV-vis spectra of eluted liquid from the gel column of **5h** and the initial dye solutions, about 79% RB and 82% TB were removed from the mixture.

for the absorption of three dyes, including toluidine blue (TB), crystal violet (CV), and rhodamine B (RB). The gel formed by **5h** was stable to act as filtering matrix for the removal of the dyes. As shown in Fig. S20–S23 (ESI[†]), the dye absorption studies for TB and RB were analyzed first separately. Then a mixture the two dyes were tested using the hydrogel of **5h** at 8.0 mg mL^{-1} , the results are shown in Fig. 6, 7 and Fig. S24, ESI[†].

Besides the mixed dye experiment, we also studied the reusability of the gel column by sequentially loading three different dyes. First, CV solution was loaded to the gel, after washing with water, RB, and lastly TB was added and eluted (Fig. S25–S30, ESI[†]). The gel column was stable after the eluting and washing cycles and was re-used for all three dyes. The same hydrogel of **5h** (1.0 mL , 8.0 mg mL^{-1}) was shown to be able to remove about 58% CV, 56% RB, and 82% TB.

In summary, we have synthesized and characterized a series of isoxazole glycoconjugates. The isoxazole glucosamine derivatives are effective LMWGs for at least one of the selected test solvents, and several of the derivatives are gelators for multiple solvents. Eight compounds are hydrogelators. Compound **5d** formed stable hydrogels as well as in the presence of different metal ions at 0.11 wt%. The gelators **5d** and **5h** were able to form gel columns for dye absorption. An advantage of using

hydrogels for dye removal is that the water is an environmental benign solvent comparing to organic solvents. The hydrogels formed by **5h** was used for multiple dyes and showed effectiveness in removal of dyes from aqueous solution. The gel column can be reused several times demonstrating the reusability of the gels for dye absorption. Future studies will further evaluate these novel isoxazole derivatives for their biomedical and environmental applications.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- X. Du, J. Zhou, J. Shi and B. Xu, *Chem. Rev.*, 2015, **115**, 13165–13307.
- B. O. Okesola and D. K. Smith, *Chem. Soc. Rev.*, 2016, **45**, 4226–4251.
- J. Morris, J. Bietsch, K. Bashaw and G. Wang, *Gels*, 2021, **7**, 24.
- H. P. R. Mangunuru, J. R. Yerabolu, D. Liu and G. Wang, *Tetrahedron Lett.*, 2015, **56**, 82–85.
- H. P. R. Mangunuru, J. R. Yerabolu and G. Wang, *Tetrahedron Lett.*, 2015, **56**, 3361–3364.
- P. Sharma, A. Chen, D. Wang and G. Wang, *Chemistry*, 2021, **3**, 935–958.
- F. Hu and M. Szostak, *Adv. Synth. Catal.*, 2015, **357**, 2583–2614.
- A. V. Galenko, A. F. Khlebnikov, M. S. Novikov, V. V. Pakalnis and N. V. Rostovskii, *Russ. Chem. Rev.*, 2015, **84**, 335–377.
- S. K. Singh, P. Saha, S. Dey and S. Nandi, *ACS Omega*, 2020, **5**, 8613–8618.
- Q. Jin, J. Li, L. Zhang, S. Fang and M. Liu, *CrystEngComm*, 2015, **17**, 8058–8063.
- T. Haino, Y. Hirai, T. Ikeda and H. Saito, *Org. Biomol. Chem.*, 2013, **11**, 4164–4170.
- M. Tanaka, T. Ikeda, J. Mack, N. Kobayashi and T. Haino, *J. Org. Chem.*, 2011, **76**, 5082–5091.
- T. Haino, M. Tanaka and Y. Fukazawa, *Chem. Commun.*, 2008, 468–470, DOI: [10.1039/b715871h](https://doi.org/10.1039/b715871h).
- T. Ikeda, K. Hirano and T. Haino, *Mater. Chem. Front.*, 2018, **2**, 468–474.
- C.-C. Tsai, Y.-T. Cheng, L.-C. Shen, K.-C. Chang, I. T. Ho, J.-H. Chu and W.-S. Chung, *Org. Lett.*, 2013, **15**, 5830–5833.
- A. Mishra, B. B. Mishra and V. K. Tiwari, *RSC Adv.*, 2015, **5**, 41520–41535.
- J. Luginina, V. Rjabovs, S. Belyakov and M. Turks, *Tetrahedron Lett.*, 2013, **54**, 5328–5331.

- 18 M. S. Le Pors, I. A. Barri, L. E. Riafrecha, G. A. Echeverria, O. E. Piro and P. A. Colinas, *ChemistrySelect*, 2022, 7, e202104379.
- 19 C. Jian, N. Tao, L. Xu, M. Liu, X. Huang, W. Gao and H. Wu, *ACS Sustainable Chem. Eng.*, 2019, 7, 11062–11068.
- 20 J. Bietsch, M. Olson and G. Wang, *Gels*, 2021, 7, 134.
- 21 J. Liu, J. Li, P. Lin, N. Zhang, X. Han, B. Zhang and J. Song, *Chem. Commun.*, 2016, 52, 13975–13978.
- 22 C. Narayana, R. K. Upadhyay, R. Chaturvedi and R. Sagar, *New J. Chem.*, 2017, 41, 2261–2267.
- 23 X. Guan, K. Fan, T. Gao, A. Ma, B. Zhang and J. Song, *Chem. Commun.*, 2016, 52, 962–965.
- 24 A. Mitra, V. Sarkar and B. Mukhopadhyay, *ChemistrySelect*, 2017, 2, 9958–9961.
- 25 G.-R. Huang, X.-W. Shi, Y.-M. Wu, B.-P. Cao, H. Okamoto and Q. Xiao, *New J. Chem.*, 2023, 47, 84–91.
- 26 H. Wu, J. Zheng, A. L. Kjoniksen, W. Wang, Y. Zhang and J. Ma, *Adv. Mater.*, 2019, 31, e1806204.
- 27 T. T. Zhao, Z. W. Jiang, S. J. Zhen, C. Z. Huang and Y. F. Li, *Microchim. Acta*, 2019, 186, 1–8.
- 28 Q. Lin, T. T. Lu, X. Zhu, B. Sun, Q. P. Yang, T. B. Wei and Y. M. Zhang, *Chem. Commun.*, 2015, 51, 1635–1638.
- 29 K. Gayen, K. Basu, D. Bairagi, V. Castelletto, I. W. Hamley and A. Banerjee, *ACS Appl. Bio Mater.*, 2018, 1, 1717–1724.
- 30 B. Li, X. Zhou, X. Liu, H. Ye, Y. Zhang and Q. Zhou, *Chem. – Asian J.*, 2019, 14, 1582–1589.
- 31 G. Wang, D. Wang, J. Bietsch, A. Chen and P. Sharma, *J. Org. Chem.*, 2020, 85, 16136–16156.
- 32 Z. Gao, J. Sui, X. Xie, X. Li, S. Song, H. Zhang, Y. Hu, Y. Hong, X. Wang, J. Cui and J. Hao, *AIChE J.*, 2018, 64, 3719–3727.
- 33 E. Saha and J. Mitra, *ACS Appl. Mater. Interfaces*, 2019, 11, 10718–10728.
- 34 N. Malviya, R. Ranjan, C. Sonkar, S. M. Mobin and S. Mukhopadhyay, *ACS Appl. Nano Mater.*, 2019, 2, 8005–8015.
- 35 A. Garai, A. Goswami and K. Biradha, *Chem. Commun.*, 2022, 58, 11414–11417.
- 36 X. Yu, Z. Wang, Y. Li, L. Geng, J. Ren and G. Feng, *Inorg. Chem.*, 2017, 56, 7512–7518.