Tunable degradation of PEG-like polymers based on imine and oxime bonds

Joe Collins,^a Zeyun Xiao,^{a*} Luke A. Connal^{ab*}

^a School of Chemical Engineering, University of Melbourne, Parkville, Melbourne, Victoria, Australia, 3010

^b Research School of Chemistry, Australian National University, Canberra, Australian Capital Territory, Australia, 2601

* luke.connal@unimelb.edu.au

* xiao.z@unimelb.edu.au

Abstract

Hydrolytically degradable PEG-like polymers with number average molecular weight (M_n) between 3.9 – 10.9 kDa were prepared using oxime and/or imine chemistry. Oxime-based polymers were found to be reasonably hydrolytically stable, retaining 75% of the initial M_n after 5 days at pH 7.4. In contrast, the corresponding imine-based polymer degraded completely after 4 hours. By blending the oxime and imine bonds, polymers with tuneable, two-stage degradation profiles could be prepared. Finally, progesterone, a biomolecule of interest, was successfully conjugated to the end of the polymer (confirmed by ¹H-NMR analysis). The comparatively high hydrolytic stability of the oxime-based polymer and simple means of functionalization demonstrates the potential of oxime chemistry as a new tool for the development of PEG-like biodegradable materials.

Introduction

Polyethylene glycol (PEG) is the most widely used polymer for drug delivery applications as it has been reported to increase drug circulation time in the body, solubilise hydrophobic molecules and can be easily conjugated onto biomolecules and surfaces.¹ A wide range of PEG-ylated therapeutics have been approved by the USA and Europe and are currently used to treat a variety of conditions such as Leukaemia (Oncaspar®), gout (Krystexxa®), anaemia/renal failure (Mircera®), hepatitis B and C (PEGASYS®).¹ Additionally, PEG-functional materials have been developed for diagnostic/imaging applications.² The number average molecular weight (M_n) of the PEG polymer used in treatments normally ranges from 5 – 40 kDa,¹ though recent reports have shown that PEG with M_n as low as 400 Da can have positive therapeutic effects.³ Recently however, the biodegradability and non-immunogenic effects of PEG have been questioned with reports finding PEG to be non-biodegradable, capable of eliciting an immune response after repeated injections/use, and to cause toxic effects through bioaccumulation and crystallization.^{4,5} Additionally, PEG-ylation has been shown to inactivate proteins and biomolecules.^{6,7} Therefore, developing a degradable PEG for pro-drug formulations, in which the degradation of the PEG triggers the reactivation of the biomolecule, is of significant interest.⁵ In light of this, polymers such as polypeptides and poly(2-oxazoline)s have been investigated as PEG-alternatives.^{4,5,8,9} These polymers however do not possess the same positive properties as PEG in terms of drug delivery and ease of

synthesis. Ideally, a degradable PEG-based polymer could be prepared which would retain the attributes of PEG while possessing biodegradable properties in order to reduce or remove the reported side effects caused by PEG bioaccumulation.

The polyether backbone of PEG is very hydrolytically stable, hence, to build degradability into PEG backbones a new approach is required. Hawker and co-workers instilled methylene ethylene oxide units to render PEG copolymers degradable.¹⁰ Other chemistries have been introduced into the PEG backbone to achieve degradability such as hemiacetal,¹¹ ester,^{12,13} and urethane.¹⁴ These materials suffer from drawbacks such as complex and time consuming synthesis with no simple means of tuning the degradation profile other than by varying the degree of incorporation of the degradable bond.

Oximes, imines and hydrazones all have varying degrees of hydrolytic stability. The oxime bond possess greater hydrolytic stability than imines and hydrazones,¹⁵ but has been shown to slowly degrade under physiologically relevant conditions.^{16,17} Imine and hydrazone chemistry has been widely used in materials science for the development of dynamic/functional polymers,^{18,19} self-healing hydrogels,^{20,21} and new, 3D-printable materials.²² Oxime chemistry, traditionally finding widespread use in bioconjugation,^{23–25} has remained under-used for materials science applications until very recently.^{26–31} The slow rate of hydrolysis of oxime bonds combined with the bioorthogonal properties indicates the potential of oxime-based materials for applications requiring high hydrolytic stability while maintaining a slow rate of biodegradation, such as drug delivery.

Herein, we report oxime and/or imine linked PEG-like polymers (*Mn* 3.9 – 10.9 kDa) with tuneable, sustained degradation under biologically relevant conditions (pH 7.4). The polymer degradation products (1.0 kDa PEG monomers) are below the size limit for PEG crystallization and should also be easily removed from the body through renal filtration. The high hydrolytic stability of the oxime bond was evidenced by slow polymer degradation at pH 7.4 with only 25% loss in *Mn* being observed after 5 days. The corresponding imine-based polymer however degraded completely after only 4 hours indicating the much greater hydrolytic stability of oxime bonds compared to imine. A range of PEG-like polymers were prepared by blending oxime and imine bonds to create a set of materials with two-stage degradation profiles. Finally, progesterone, an illustrative biomolecule of interest, was conjugated onto the oxime-based PEG-like polymer to represent the potential of these materials as new polymers for degradable PEG-like bioconjugates.

Results and Discussion

PEG-like polymers incorporating hydrolytically cleavable oxime and/or imine bonds were prepared through the polycondensation of PEG-1k monomers terminated with benzaldehyde or amine/hydroxylamine functionality (Scheme 1). To prepare water soluble polymers, PEG monomers of 1000 Da (PEG-1k, approximately 22 ethylene glycol repeat units) were required. Early investigations using difunctional tetraethylene glycol monomers (4 ethylene glycol repeat units) resulted in water insoluble polymers (data not shown).

Scheme 1 (A) Representation of oxime/imine PEG-like co-polymers. Degradation occurs in two stages. Firstly, rapid imine hydrolysis at pH 7.4 yields partially degraded oligomers within 4 hrs. Following this, slow oxime degradation occurs with polymers remaining stable for longer than 5 days. (B) Synthesis of hydrolytically degradable oxime/imine-based PEG-like polymers. Polycondensation between difunctional hydroxylamine PEG1k (**PEG1k_{ONH2}**) and dibenzaldehyde functional PEG1k (**PEG1k_{C=O}**) results in an oxime-based PEG-like polymer (**PEG_{ox}**). Similarly, polycondensation between difunctional amine PEG1k (**PEG1k_{NH2}**) and dibenzaldehyde functional PEG1k (**PEG1k_{C=O}**) results in an imine-based PEG-like polymer (**PEG_{im}**). Blending **PEG1k_{ONH2}** with **PEG1k_{NH2}** results in polymers with both imine and oxime bonds (**PEG_{oxX/imY}**, where X and Y indicate the relative fraction of oxime and imine in the polymer).

The difunctional PEG-1k benzaldehyde monomer (**PEG1k_{C=O}**) was prepared through a simple carbodiimide coupling between dihydroxy PEG-1k and 4-formyl benzoic acid. Amine/hydroxylamine PEG-1k monomers (**PEG1k_{NH2}** / **PEG1k_{ONH2}** respectively) were prepared by first functionalizing dihydroxy PEG-1k with phthalimide/N-hydroxy phthalimide respectively, followed by deprotection with hydrazine (see SI for experimental details, Figures S1-S5).

To achieve efficient imine formation polymer synthesis was undertaken at 110°C using a Dean-Stark apparatus. Oxime formation does not require heating to such temperatures but to maintain a comparable and standard synthetic procedure oxime polymer synthesis was also undertaken following the above-mentioned conditions. In this way PEG-like polymers could be prepared comprising 100% oxime (**PEG_{ox}**), 100% imine (**PEG_{im}**) or a variation in composition of each (**PEG_{oxX/imY}**, where X and Y indicate the relative fraction of oxime and imine in the polymer). ¹H-NMR analysis of **PEG_{ox}** confirmed successful polymer formation as a singlet peak at 8.12 ppm appeared corresponding to the oxime proton (Figure S7). Similarly, a singlet peak at 8.33 ppm was observed in the ¹H-NMR spectrum of **PEG_{im}** corresponding to the imine proton (Figure S7). For samples **PEG_{ox75/im25}**, **PEG_{ox50/im50}** and **PEG_{ox25/im75}** both oxime and imine singlet peaks at 8.12 and 8.33 ppm, respectively, were observed confirming the successful formation of polymers containing both oxime and imine bonds (Figure S7).

The un-catalysed polymerizations resulted in polymers with *M_n* ranging between 3.9 – 5.7 kDa (Table 1, Figures S8-S12). The addition of aniline, reported to catalyse oxime formation,^{32,33} increased **PEG_{ox}** molecular weight to above 10 kDa (Table 1, Figure 1). The catalysed **PEG_{ox}** polymer, as well as a number of the uncatalysed polymers, have molecular

weights within the range of currently used PEG-ylated therapeutics (5 – 40 kDa).¹ Therefore, these polymers hold potential as new PEG-ylating agents with clinically relevant molecular weights.

	<i>M_n</i> (kDa)	<i>Đ</i>
PEG_{ox} ^a	10.9	1.9
PEG_{ox}	5.7	1.8
PEG_{ox} (ONH ₂ capped) ^{a,b}	5.3	2.1
PEG_{ox75/im25}	4.4	1.8
PEG_{ox50/im50}	3.9	1.6
PEG_{ox25/im75}	5.0	2.2
PEG_{im}	4.1	2.5

Table 1 Polymer characterization. Molecular weights and dispersity were calculated relative to PEG standards. All reactions were undertaken at a concentration of 150 mmolL⁻¹ in DMF at 110°C. ^a Reaction undertaken with aniline (40 mol %) as catalyst. ^b Reaction undertaken with a slight excess of **PEG1k_{ONH2}** (1.1 eq. compared to **PEG1k_{C=O}**) to prepare polymers terminated with hydroxylamine functionality.

Figure 1 GPC trace of **PEG_{ox}** with a calculated molecular weight of 10.9 kDa, *Đ* 1.9. Synthesis was undertaken at 150 mmolL⁻¹ in DMF at 110°C with aniline (40 mol %) as catalyst. Molecular weight and dispersity was calculated relative to PEG standards.

In order to be applicable for biomedical applications polymers must degrade under physiological conditions (pH 7.4). Therefore, we examined the hydrolytic stability of the imine/oxime PEG-like polymers using a pH 7.4 phosphate buffer at room temperature. The most hydrolytically stable polymer, **PEG_{ox}**, demonstrated a slow and sustained degradation over a 5 day period. After 5 days **PEG_{ox}** retained 75% of its initial molecular weight (Figure 2, red squares). In comparison, **PEG_{im}** degraded completely after only 4 hours (Figure 2, purple circles). The stark difference in hydrolytic stability between imine and oxime bonds is demonstrated here clearly. We could predict from this that imine-based materials degrade too rapidly to be applicable for biomedical applications requiring medium-to-long circulation

times. Oxime bonds however display a much higher hydrolytic stability and therefore hold promise for such applications. Additionally, these materials show an accelerated rate of degradation under slightly acidic conditions, such as those found in lysosomes and endosomes (pH 5 – 7), as has been previously reported for oxime-based materials.^{34,35}

In aiming for the preparation of polymers with tuneable degradation profiles we synthesized a range of polymers with varying compositions of imine and oxime bonds. Interestingly, as the imine bonds in **PEG_{im}** were found to degrade very rapidly at pH 7.4 (<4hrs), the **PEG_{ox75/im25}**, **PEG_{ox50/im50}** and **PEG_{ox25/im75}** co-polymers exhibited tuneable and predictable degradation profiles. In all cases a fast initial loss of molecular weight was observed which corresponds closely to the fraction of imine bonds present in the polymer. **PEG_{ox75/im25}** which has 25% imine bonds quickly loses 21% of its initial mass, through imine hydrolysis, which is followed by a slow loss of mass from 79% to 64% over the 5 day period (Figure 2, green triangles). This slower degradation kinetics reflects the oxime hydrolysis which proceeds at a slower rate than imine hydrolysis. The same trend of a fast initial mass loss, corresponding to imine hydrolysis, followed by slow oxime hydrolysis is also observed for **PEG_{ox50/im50}** and **PEG_{ox25/im75}**. In each case the initial mass loss is almost proportional to the fraction of imine bonds in the polymer, 40% for **PEG_{ox50/im50}** and 55% for **PEG_{ox25/im75}**. Oxime hydrolysis then proceeds very slowly with **PEG_{ox50/im50}** only degrading from 60% to 59% and **PEG_{ox25/im75}** degrading from 45% to 42% over 5 days (Figure 2, blue crosses and orange stars respectively). These degradation profiles indicate that the **PEG_{oxX/imY}** co-polymers are formed of a stable oxime-linked polymer core with block-like imine-linked polymer capping each end. This triblock-like structure likely forms *in-situ* as a result of the differences in the rate of oxime and imine formation. As the rate oxime formation is much more rapid than imine formation at the start of the reaction a core of oxime linked polymer is produced. Once the hydroxylamine monomer has been exhausted, amine monomers then attach to the oxime core and form imine-linked polymer blocks on each end. The oxime/imine co-polymers reported here display a two stage degradation profile achieved by integrating two chemistries with different reaction rates and different hydrolytic stabilities.

Figure 2 Polymer degradation at pH 7.4 recorded over 5 days. Polymer molecular weights, measured via GPC and calculated relative to polystyrene standards, are recorded as a percentage of original mass. The most hydrolytically stable polymer, the 100% oxime-based **PEG_{ox}** (red squares), degrades slowly and retains 75% of its initial mass after 5 days. In

comparison, the least hydrolytically stable polymer, the 100% imine-based **PEG_{im}** (purple circles), degrades completely after 4 hours. The oxime/imine co-polymers **PEG_{ox75/im25}**, **PEG_{ox50/im50}** and **PEG_{ox25/im75}** (green triangles, blue cross, and orange stars, respectively) show a fast initial degradation caused by rapid imine hydrolysis and the percent mass loss corresponds closely to the percent incorporation of imine bonds in the polymer. Following this, slow oxime hydrolysis is observed over the following 5 days.

For drug delivery applications polymers must be easily conjugated to molecules of interest. We identified progesterone as a representative drug-like molecule to demonstrate the ability to prepare drug-**PEG_{ox}** conjugates for potential applications in drug delivery. Previously, progesterone has been reported to be functionalised with small molecules due to the accessible carbonyl bonds that can react with hydroxylamines.^{36–38} Successful conjugation of progesterone to a hydroxylamine-terminated **PEG_{ox}** allowed for the preparation of **PEG_{ox}-progesterone** conjugates (**PEG_{ox}-Prog**).

In order to prepare **PEG_{ox}** polymers end-capped with the hydroxylamine functionality required for progesterone conjugation polymer synthesis was undertaken using a slight excess of **PEG1k_{ONH2}** (1.1 eq. compared to **PEG1k_{C=O}**). Crude ¹H-NMR analysis revealed the complete disappearance of the benzaldehyde peak at 10.07 ppm indicating the ends of the polymer are terminated with hydroxylamine functionality (Figure S13). With aniline as catalyst a 5.3 kDa hydroxylamine-functional polymer could be prepared. Conjugation with progesterone was undertaken at 40°C with catalytic TFA (1-2 drops), with successful **PEG_{ox}-Prog** synthesis occurring within 3 hours. **PEG_{ox}-Prog** precipitation into hexane realised the isolation of the pure product. ¹H-NMR analysis revealed the expected **PEG_{ox}-Prog** polymer peaks as the oxime singlet at 8.12 ppm (Figure 3, peak a), two doublets at 8.06 and 7.74 ppm corresponding to the aromatic benzaldehyde protons (Figure 3, peaks b and c), two triplets at 4.47 and 4.33 ppm corresponding to the terminal ethylene glycol ethyl groups adjacent to the oxime and ester groups respectively (Figure 3, peaks d and e), as well as a large singlet peak at 3.64 ppm corresponding to the ethylene glycol chain (Figure 3, peak h). Additionally, characteristic peaks confirming progesterone conjugation were identified. As previously reported, under mild conditions, oxime formation on progesterone occurs only at the C3 ketone site and causes a characteristic splitting of the adjacent H4 proton peak into two singlet peaks caused by the formation of the two oxime isomers (*E* and *Z*).^{36,38} This is observed in the ¹H-NMR spectra of **PEG_{ox}-Prog** in which the H4 peak of progesterone is split from a singlet at 5.73 ppm into two singlets at 5.74 and 6.41 ppm indicating successful oxime formation at the C3 ketone site (Figure 3, peaks 4). Furthermore, a multiplet at 4.15 ppm appears which was not previously seen in the unfunctionalized **PEG_{ox}** polymer. This multiplet can be assigned to the ether protons adjacent to the terminal oxime bonds conjugating the progesterone molecule to the **PEG_{ox}** polymer (Figure 3, peak f).

To confirm the molecular weight of the polymer and degree of progesterone functionalization, the integrations of the H4 progesterone peaks can be compared to one of the triplet peaks of the **PEG_{ox}** polymer. As the integration is calculated to be 1:4 we can use this to calculate a number of repeat units per polymer. A molecular weight of slightly over 4.4 kDa was calculated which matches closely with the molecular weight measured by GPC (5.3 kDa) and we can therefore confirm successful conjugation of progesterone to **PEG_{ox}**.

¹H-NMR analysis also confirmed that progesterone conjugation only occurs at the C3 ketone site of progesterone. Oxime formation at the second ketone site of progesterone, C20, would result in a shift of the adjacent H21 proton peak as the ketone group is reacted to an oxime.

As no shift in protons H21 was observed upon **PEG_{ox}-Prog** formation we can conclude that oxime formation has occurred at only the C3 ketone site on progesterone.

Figure 3 ^1H -NMR spectrum of **PEG_{ox}-Prog**. The successful conjugation of progesterone to **PEG_{ox}** is confirmed by the splitting of proton H4 into two singlet peaks and the appearance of multiplet f, both of which are only seen if oxime formation occurs at the C3 ketone of progesterone.

In summary, the successful preparation of degradable PEG-like oxime/imine based polymers has been reported. The use of aniline, an effective catalyst for oxime formation, resulted in the synthesis of 10.9 kDa oxime polymers (**PEG_{ox}**) which were found to possess high hydrolytic stability. In a pH 7.4 aqueous buffer **PEG_{ox}** was found to only degrade to 75% of its initial molecular weight after 5 days. This indicates the potential of oxime chemistry for applications such as drug delivery which requires high hydrolytic stability with degradation times over the course of days to weeks. In contrast, the corresponding imine-based polymer (**PEG_{im}**) degraded completely after 4 hours. This provides a clear indication of the relative hydrolytic stabilities of oxime and imine bonds. The combination of imine and oxime bonds allowed for the preparation of polymers with predictable degradation profiles (**PEG_{ox75/im25}**, **PEG_{ox50/im50}** and **PEG_{ox25/im75}**). Finally, progesterone, a model molecule of interest, was successfully conjugated onto the **PEG_{ox}** polymer, confirmed by ^1H -NMR analysis. The slow, sustained hydrolytic degradation of the reported polymers, together with a facile means of conjugation, highlight the potential of oxime chemistry as a new tool for the preparation of biodegradable, functional polymers.

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References

- P. L. Turecek, M. J. Bossard, F. Schoetens and I. A. Ivens, *J. Pharm. Sci.*, 2016, **105**, 460–475.
- E. D. Pressly, R. Rossin, A. Hagooly, K. I. Fukukawa, B. W. Messmore, M. J. Welch, K. L. Wooley, M. S. Lamm, R. A. Hule, D. J. Pochan and C. J. Hawker, *Biomacromolecules*, 2007, **8**, 3126–3134.
- B.-L. Ma, Y. Yang, Y. Dai, Q. Li, G. Lin and Y.-M. Ma, *RSC Adv.*, 2017, **7**, 2435–2442.
- S. Lowe, N. M. O'Brien-Simpson and L. A. Connal, *Polym. Chem.*, 2015, **6**, 198–212.
- K. Knop, R. Hoogenboom, D. Fischer and U. S. Schubert, *Angew. Chemie - Int. Ed.*, 2010, **49**, 6288–6308.
- M. J. Roberts and J. Milton Harris, *J. Pharm. Sci.*, 1998, **87**, 1440–1445.
- S. Zalipsky, *Adv. Drug Deliv. Rev.*, 1995, **16**, 157–182.
- M. Barz, R. Luxenhofer, R. Zentel and M. J. Vicent, *Polym. Chem.*, 2011, **2**, 1900.
- B. D. Ulery, L. S. Nair and C. T. Laurencin, *J. Polym. Sci. Part B Polym. Phys.*, 2011, **49**, 832–864.
- 0 P. Lundberg, B. F. Lee, S. A. Van Den Berg, E. D. Pressly, A. Lee, C. J. Hawker and N. A. Lynd, *ACS Macro Lett.*, 2012, **1**, 1240–1243.
- 1 B. Reid, S. Tzeng, A. Warren, K. Kozielski and J. Elisseeff, *Macromolecules*, 2010, **43**, 9588–9590.
- 2 A. S. Sawhney, C. P. Pathak and J. A. Hubbell, *Macromolecules*, 1993, **26**, 581–587.
- 3 D. Liu and C. W. Bielawski, *Macromol. Rapid Commun.*, 2016, **37**, 1587–1592.
- 4 Y. L. Luo, C. H. Zhang, F. Xu and Y. S. Chen, *Polym. Adv. Technol.*, 2012, **23**, 551–557.
- 5 J. Kalia and R. T. Raines, *Angew. Chemie - Int. Ed.*, 2008, **47**, 7523–7526.
- 6 B. Liu, H. Chen, X. Li, C. Zhao, Y. Liu, L. Zhu, H. Deng, J. Li, G. Li, F. Guo and X. Zhu, *RSC Adv.*, 2014, **4**, 48943–48951.
- 7 Y. Jin, L. Song, Y. Su, L. Zhu, Y. Pang, F. Qiu, G. Tong, D. Yan, B. Zhu and X. Zhu, *Biomacromolecules*, 2011, **12**, 3460–3468.
- 8 E. R. L. Brisson, Z. Xiao, L. Levin, G. V Franks and L. A. Connal, *Polym. Chem.*, 2016, **7**, 1945–1952.
- 9 E. R. L. Brisson, Z. Xiao, G. V. Franks and L. A. Connal, *Biomacromolecules*, 2017, **18**, 272–280.
- 0 A. Chao, I. Negulescu and D. Zhang, *Macromolecules*, 2016, **49**, 6277–6284.
- 1 N. Boehnke, C. Cam, E. Bat, T. Segura and H. D. Maynard, *Biomacromolecules*, 2015, **16**, 2101–2108.
- 2 M. Nadgorny, Z. Xiao and L. A. Connal, *Mol. Syst. Des. Eng.*, , DOI:10.1039/C7ME00023E.
- 3 S. Ulrich, D. Boturyn, A. Marra, O. Renaudet and P. Dumy, *Chem. - A Eur. J.*, 2014, **20**, 34–41.
- 4 K. L. Christman, R. M. Broyer, E. Schopf, C. M. Kolodziej, Y. Chen and H. D. Maynard, *Langmuir*, 2011, **27**, 1415–1418.
- 5 A. P. Esser-Kahn, V. Trang and M. B. Francis, *J. Am. Chem. Soc.*, 2010, **132**, 13264–13269.
- 6 J. Collins, Z. Xiao, M. Müllner and L. A. Connal, *Polym. Chem.*, 2016, **7**, 3812–3826.
- 7 J. Collins, M. Nadgorny, Z. Xiao and L. A. Connal, *Macromol. Rapid Commun.*, 2017, **38**, 1600760.
- 8 J. Collins, Z. Xiao, A. Espinosa-Gomez, B. P. Fors and L. A. Connal, *Polym. Chem.*, 2016, **7**, 2581–2588.
- 9 R. K. Iha, B. A. van Horn and K. L. Wooley, *J. Polym. Sci. Part A Polym. Chem.*,

- 2010, **48**, 3553–3563.
- 0 W. Liu, C. Zhang, H. Zhang, N. Zhao, Z. Yu and J. Xu, *J. Am. Chem. Soc.*, 2017, **139**,
8678–8684.
- 1 S. Mukherjee, W. L. A. Brooks, Y. Dai and B. S. Sumerlin, *Polym. Chem.*, 2016, **7**,
1971–1978.
- 2 A. Dirksen, T. M. Hackeng and P. E. Dawson, *Angew. Chemie Int. Ed.*, 2006, **45**,
7581–7584.
- 3 A. Dirksen and P. E. Dawson, *Bioconjug. Chem.*, 2008, **19**, 2543–2548.
- 4 B. Liu, H. Chen, X. Li, C. Zhao, Y. Liu, L. Zhu, H. Deng, J. Li, G. Li, F. Guo and X.
Zhu, *RSC Adv.*, 2014, **4**, 48943–48951.
- 5 Y. Jin Song, L., Su, Y., Zhu, L., Pang, Y., Qiu, F., Tong, G., Yan, D., Zhu, B., Zhu,
X., *Biomacromol.*, 2011, **12**, 3460–3468.
- 6 C. W. Bennett, J. Collins, Z. Xiao, D. Klinger and L. A. Connal, *Chem. - An Asian J.*,
2017, **12**, 1456–1460.
- 7 M. Mitsuma, A. Kambegawa, S. Okinaga and K. Arai, *J. steroid Biochem.*, 1987, **28**,
83–88.
- 8 M. Adamczyk, Y. Y. Chen, J. Grote and P. G. Mattingly, *Steroids*, 1999, **64**, 283–290.

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Author/s:

Collins, J;Xiao, Z;Connal, LA

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