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A Scalable and Versatile Synthesis of Oxime-Based Hormone Dimers and Gels for Sustained Release

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Abstract: Well-defined steroid hormone dimers and organogels were produced via a facile and scalable synthesis using oxime click chemistry. The versatile synthetic procedure extends to a wide range of hormones and linker groups exemplified here through the synthesis of cortisol- and progesterone-dimers linked via hydrophobic, hydrophilic or functional groups. This method was also extended to the synthesis of cortisone-based organogels. Owing to the dynamic nature of the oxime bond, the hormone-based materials are degradable via acidic hydrolysis and transoximation representing new materials for the controlled release of steroid hormones.

Steroid hormones act to regulate many essential cellular processes such as growth, development and wound healing.^[1] Progesterone, cortisone and cortisol, three important, naturally occurring steroid hormones, play key roles in the immune system and pregnancy cycle as well as blood pressure and blood glucose concentration regulation.^[2] Therapeutically, progesterone is used in hormone replacement therapy and in the treatment of premenstrual syndrome^[3] whilst cortisol and cortisone derivatives are used to treat inflammation and autoimmune disorders.^[4] The typical administration routes for these hormones (orally, topically or through injection) often lead to low bioavailability, short half-life, unwanted side effects and withdrawal symptoms thereby reducing the therapeutic efficacy.^[5] Consequently, alleviating such problems is not only of high interest to improve the therapeutic application but also of significant commercial value since the global hormone replacement therapy market was estimated to be worth over US \$3.7 billion in the US alone in 2013.^[6]

Developing prodrug constructs of steroid hormones has emerged as a promising strategy to address these challenges. Especially, the family of dimeric and oligomeric hormone molecules has received significant attention due to their unique chemical activity including micellar behavior,^[7] antimicrobial properties^[8] and catalysis.^[9] To further expand this class of molecules to new therapeutics, prodrug constructs should fulfil the following criteria. First, the materials should contain biodegradable linker groups to enable the release of the native hormone molecules. Second, the synthesis should be achieved via a simple and scalable procedure that results in high product

yield under mild conditions.

Upon approaching both tasks simultaneously we were drawn to the oxime ligation, achieved through the addition of aldehydes or ketones to hydroxylamines. While the oxime ligation has been previously overlooked as a dynamic covalent chemistry, it displays great potential for the synthesis of stimuli-responsive materials similar to that of imine, hydrazine, thiol and others reviewed previously.^[10] The oxime reaction, an example of click chemistry, occurs extremely rapidly in high yields,^[11] is biorthogonal^[12] and degradable,^[13] due to its dynamic covalent properties. Classically, oxime chemistry has found great success in bioconjugation^[12] but has more recently been applied for polymer and hydrogel synthesis, surface patterning and for the development of degradable and self-healing materials.^[14] The greater hydrolytic stability of oxime bonds compared to imine bonds has been well documented^[15] and the lability of imine bonds has been previously exploited in our group to achieve dynamic amino-acid functional polymers.^[16] We believe that this enhanced stability will give oxime-based materials a longer residence time in the body and prove valuable for long term/sustained hormone release.

Herein we report the facile synthesis of a suit of well-defined steroid hormone dimers through the use of oxime click chemistry. Key to this approach is the selective reaction at only one ketone group on the hormones. Dimers were formed using cortisol or progesterone with a variety of linkers: propyl, tetraethylene glycol (TEG) or alkyne-functionalized groups, (Scheme 1) and product purification was achieved through simple precipitation. The versatility of the reported procedure extends its use to a range of steroid hormones and linker groups, beyond those demonstrated here, and the simple preparation/purification indicates scalability. This method can easily be extended to more complex material architectures by exploiting multiple ketone groups on hormone molecules for oxime functionalization. In particular, cortisone, a tri-ketone functional hormone, was used to successfully synthesize a range of new, hormone-releasing gels. Owing to the dynamic nature of the oxime bond, the hormone dimers and hormone gels were found to degrade in an acidic environment thereby creating a new platform for controlled and sustained hormone delivery. These novel materials hold potential for a wide range of pharmaceutical applications such as chronic wound healing, contraception and hormone replacement therapy.

To engineer the controlled hormone release from the prodrug dimers, it is mandatory to access a well-defined dimeric structure. For this, the difference in the reactivity of the ketone groups (C3 and C20, Scheme 1) of steroid hormones was exploited. This site-selective reactivity, first reported in the 1950's by Herr *et al.*, is possibly due to steric hindrance crowding the C20 ketone making oxime formation unfavorable under mild conditions or through electronic effects acting to promote oxime formation at the C3 ketone. This difference in

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Scheme 1. Synthesis of hormone dimers **CD-1,2,3** and **PD-1**. Dimer synthesis is selective at the C3 ketone and applies to a range of di-ketone functional hormones (demonstrated here by the use of cortisol and progesterone). Together with the different linker functionalities, hydrophilic, hydrophobic and functional this method allows for the production of a variety of dimeric hormone materials.

reactivity has previously been used for the precise functionalization of steroid hormones at the C3 ketone.^[17] Following this approach, well-defined dimers are easily accessible by the site selective reaction of the C3 ketone groups with bis-hydroxylamine linkers. The wide variety of naturally occurring di-ketone functional hormones together with the facile preparation of linker chains from various di-hydroxy terminated species allows for the synthesis of a suite of dimeric hormone molecules. To demonstrate the potential of this method, oxime-linked cortisol dimers were prepared with TEG (**CD-1**), propyl (**CD-2**) or alkyne-functional (**CD-3**) linkers and TEG-linked progesterone dimers (**PD-1**) were also prepared (Scheme 1). These linkers were selected to demonstrate the ability to form dimers with hydrophobic, hydrophilic or functional materials. Of interest is the addition of the alkyne which provides a handle for post-functionalization via the copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction. Dimer synthesis was undertaken in methanol at room temperature and achieved acceptable yields, 25–68 % after a reaction time of 4 hours (see Supplementary Information (SI) for experimental detail). Of high commercial interest, dimer purification was achieved through simple precipitation into water indicating the scalable potential of the procedure.

The well-defined dimeric structure was confirmed via ¹H-NMR experiments on **CD-1**. Proton peaks arising from the cortisol molecule can be seen clearly; two doublets at 4.60 and 4.24 ppm can be assigned to the four H-21 protons and the broad singlet at 4.37 ppm can be assigned to four H-11 protons. Additionally two multiplets and a strong singlet peak at 4.13, 3.71 and 3.65 ppm with integrations of four, four and eight, respectively, can be assigned to protons Ha, Hb and Hc of the TEG linker (Figure 1A). The proton integrations in the ¹H-NMR spectrum of **CD-1** suggest a 2:1 ratio of cortisol:TEG which can only arise from a dimeric structure.

To verify the selective conjugation of C3 ketone over the C20 ketone ¹H-NMR was further employed. The synthesis of monofunctional 3-carboxymethyl oxime (CMO) hormones and difunctional 3,20-CMO hormones has been previously reported.^[17a] The following ¹H-NMR observations for the monofunctional 3-CMO hormone were made: an upfield shift of proton H4 and no shift in proton H21. The upfield shift for proton H4 is evidence of oxime formation at C3 while proton H21 remain unchanged which suggests no oxime formation at C20. In the case of the difunctional 3,20-CMO derivative, a strong upfield shift of H21 was observed caused by the new oxime bond at C20.^[17a] This previously reported ¹H-NMR analysis

Figure 1. (A) ¹H-NMR spectrum of cortisol dimer **CD-1**. (B) NOESY spectra of native cortisol and **CD-1** showing the coupling between protons H-4 and H-6 and confirming the splitting of proton H-4 upon dimerization.

reflects the exact changes seen in the ¹H-NMR spectrum of **CD-1**. The two H21 doublets at 4.60 and 4.24 ppm do not shift upon dimerization indicating no oxime formation at C20. However, proton H4 shifts upfield from a singlet at 5.66 ppm to two singlets at 6.33 and 5.67 ppm indicating oxime formation at C3. These results strongly suggest the proposed dimeric structure is linked through an oxime bond at the C3 position only.

Interestingly, the formation of **CD-1** resulted in splitting of proton H-4 from a singlet at 5.66 ppm in the native cortisol to two singlet peaks at 6.33 and 5.67 ppm in **CD-1** (Figure 1A). Similarly, H19 shifts from a singlet at 1.47 ppm with an integration of six to two singlets at 1.34 and 1.38 ppm, each with an integration of 3. It is suggested that the splitting of the proton peaks may result from the arising stereochemistry (*Syn* or *Anti*) caused by the nucleophilic attack of the hydroxylamine toward the carbonyl carbon, dependent on whether the reaction occurs from above or below the plane of the steroid ring.

The splitting of proton H-4 caused by the dimerization of cortisol was further confirmed through nuclear Overhauser effect spectroscopy (NOESY) of **CD-1**. Proton H-4 was found to be coupled to a single proton, H-6, in the native cortisol (Figure 1B).

Figure 2. (A) **CD-1** degradation via transoximation with TFA/acetone. (B) ¹H-NMR spectra following **CD-1** degradation in the presence of 50 eq. TFA at room temperature over 28 days. The attenuation of the split H-4 **CD-1** proton peaks (6.33 and 5.67 ppm) and reappearance of the native cortisol H-4* proton peak (5.66 ppm) allows the rate of **CD-1** degradation and cortisol release to be estimated. (C) Graph indicating the rates of **CD-1** degradation under different reaction conditions (50 or 500 eq. of acetone and/or TFA at room temperature or 40°C).

Upon dimerization, the two peaks at 6.33 and 5.67 ppm were also found to couple only with proton H-6, suggesting that the peaks can be assigned to proton H-4 and that the proton peak is being split into two upon dimerization. This splitting is seen in all dimers **CD-2,3** and **PD-1**.

¹³C-NMR was also employed to confirm the successful conjugation through C3. ¹³C-NMR analysis of cortisol shows peaks at 212.92 and 202.47 ppm for carbons 20 and 3 respectively. Upon dimerization, ¹³C-NMR analysis of **CD-1** revealed that peak C20 did not change chemical shift while carbon 3 shifted downfield. This further suggests that oxime formation occurred at C3 alone. Additionally, carbon peaks corresponding to the TEG linker group appeared between 65–75 ppm in the ¹³C-NMR of **CD-1** confirming the incorporation of the TEG linker (see SI for ¹³C-NMR spectra).

¹H-, ¹³C-NMR and high resolution ESI-MS analysis of **CD-2**, **CD-3** and **PD-1** was used to confirm their structures. The resulting spectra, and those of cortisol and progesterone, can be seen in the SI.

In summary, the ¹H- and ¹³C-NMR experiments indicate suggest the successful preparation of steroid hormone dimers coupled via oxime linkages on the C3 position of the respective hormone. The dynamic nature of the oxime bond was utilized here to develop steroid releasing prodrugs. Oxime degradation via transoximation or acidic hydrolysis has been well documented.^[13] For the prepared hormone dimers, this reversibility can be used to achieve degradation of the oxime linkage and release of the respective steroid hormone. Unfortunately, the hydrophobic properties of the hormone dimers and their consequential insolubility prevented the use of aqueous buffer solutions during the degradation experiments. Hence, accurate measurement of pH was not possible. To overcome this limitation, degradation experiments were undertaken in deuterated methanol and followed by ¹H-NMR. These experiments serve as a first basic understanding of the degradation profile and to demonstrate the general potential of these materials for hormone release. The degradation of **CD-1** via transoximation with TFA and acetone was investigated,

with degradation affording the release of cortisol and the biocompatible TEG linker (Figure 2A). The effect of varying the TFA and acetone concentration on the rate of **CD-1** degradation was investigated and **CD-1** degradation at elevated temperatures (40°C) was examined to approximate the thermal conditions of the human body. The degradation reactions were monitored by ¹H-NMR spectroscopy. Here, the attenuation of the split H-4 proton peaks (5.67 ppm and 6.33 ppm) in **CD-1** and the corresponding reappearance of the native cortisol H-4 singlet peak (5.66 ppm) allows the degradation of **CD-1** and the release of the native cortisol to be monitored (Figure 2B). At the most benign reaction conditions (50 eq. TFA, RT), the degradation of **CD-1** occurred slowly with approximately 40% degradation observed after 28 days (Figure 2B and Figure 2C, black trace). The rate of **CD-1** degradation could be enhanced via a transoximation reaction achieved through the addition of a competing monofunctional ketone. The addition of acetone (50 eq.) increased **CD-1** degradation from 40% to 45% after 28 days (Figure 2C, red trace). Importantly, it was found that increasing the temperature from room temperature to 40°C significantly increased **CD-1** degradation from 40% to 70% in the presence of 50 eq. TFA and to 80% in the presence of 50 eq. acetone and 50 eq. TFA over a 28 day period (Figure 2C, blue and purple traces respectively).

The very high hydrolytic stability of the oxime bond was demonstrated here as rapid and complete degradation of **CD-1** was only achieved when high acid and ketone equivalents (500 eq. of acetone and TFA at 40°C) were used. In this case, **CD-1** degradation was greater than 95% complete after 2 days. (Figure 2C, orange trace). Whilst the ¹H-NMR peaks for proton H-4 were well defined for samples containing 50 eq. of TFA, the addition of higher equivalents of TFA (500 eq.) led to peak overlap in the ¹H-NMR spectra. Therefore, determination of **CD-1** degradation rates for samples with 500 eq. of TFA required an alternate analysis. Upon degradation of **CD-1**, the multiplet peaks at 4.13 and 3.71 ppm, corresponding to the TEG chain protons adjacent to the oxime bond, shift to 4.10 and 3.67 ppm respectively and become well-defined triplets. This change in the

Figure 3. (A) Synthesis of cortisone gel **CtG-1**. (B) Degradation of **CtG-1**. When exposed to 50 eq. of TFA at room temperature **CtG-1** undergoes only partial gel-sol transition after 10 weeks. When exposed to 500 eq. TFA at room temperature however, the gel-sol transition is complete within 1hr.

^1H -NMR spectrum offers an alternative means to estimate the rate of **CD-1** degradation. For ^1H -NMR analysis of **CD-1** degradation under the various reaction conditions see Figures S1-9.

While the reaction conditions used above do not mimic physiological conditions, these experiments were used to indicate the degradability of the oxime bond and the potential of the hormone-dimers as new hormone-releasing materials. As the oxime bond has been shown to be reversible under physiological conditions (slow at pH 7 with increased rates at pH 5)^[18] we believe that these materials hold relevance as new routes for hormone release in the body. We envision the reported materials to be applied as hydrophobic therapeutics similar to current DEPO medications. DEPO treatment involves the injection of an insoluble drug/material under the skin/muscle which slowly degrades to afford drug release. Currently, hormone-based DEPO therapeutics are used for contraception and hormone replacement therapy and can remain in the body for up to three years.^[19]

While these experiments clearly reveal the potential of the new dimeric hormone prodrugs to release cortisol from well-defined small molecules, the synthetic procedure easily allows the expansion of this strategy to a wider range of hormones and materials. To demonstrate the versatility of this concept, the synthesis of oxime crosslinked hormone gels was investigated using the tri-ketone functional hormone cortisone. Cortisone-gel synthesis is represented here using TEG bishydroxylamine (**CtG-1**, Figure 3) and required the addition of TFA at 40°C with a cortisone:TEG bis-hydroxylamine molar ratio of 1:3.

Degradation of **CtG-1** due to oxime hydrolysis was achieved through the addition of TFA in a similar procedure as for the degradation of **CD-1**. After 8 weeks with 50 eq. of acid **CtG-1** had only experienced a partial gel-sol transition. In contrast, degradation with 500 eq. acid led to a complete gel-sol transition in less than one hour (Figure 3b).

These results demonstrate the potential of the oxime click ligation for the facile preparation of new, degradable hormone-based dimers and macroscopic gel materials, therefore setting the basis for sustained release applications. The dimers show great potential for large-scale applications due to their simple, one step purification method. This work could be further explored to produce a range hormone prodrugs with different physical properties and reactivity.

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Keywords: oxime • hormone • dimer • organogel • degradable

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