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Novel steroid mimics: synthesis of tri- and tetra-substituted oxamides and oxoamides

Ian L. Jones, Daniel J. Schofield, Robert R. Strevens, Peter N. Horton, Michael B. Hursthouse and Nicholas C. O. Tomkinson*

School of Chemistry, Main Building, Cardiff University, Park Place, Cardiff CF10 3AT, UK

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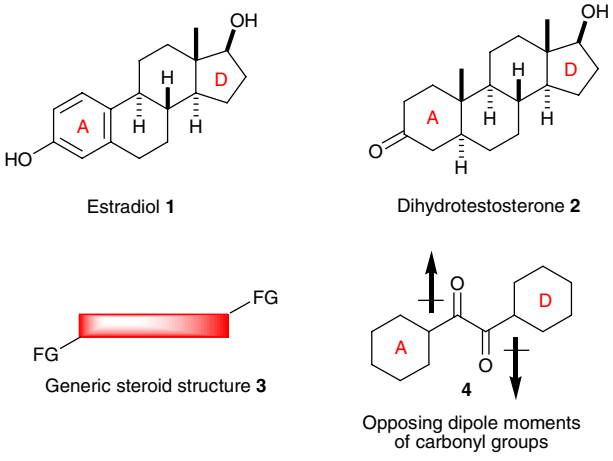
Abstract—A series of dicarbonyl compounds have been designed and prepared to mimic the rigid tetracyclic core of estradiol and dihydrotestosterone. Non-symmetrical tri- and tetra-substituted oxamides were prepared by the sequential addition of primary and secondary amines to phenyl cholorooxoacetate. Oxoamides were prepared via a Friedel–Crafts acylation/amide coupling protocol. Crystallographic data shows a good correlation between the structure of the dicarbonyl mimic and dihydrotestosterone complexed with the androgen receptor suggesting the molecular scaffolds may well prove versatile platforms for ligand design.

Steroids are a fundamental class of biological signalling molecule with profound chemical, clinical and scientific significance.[1] Their architectural and stereochemical complexity, however, render them an exceedingly difficult target for chemical synthesis.[2] The preparation of novel molecules which possess activity at steroid receptors but are chemically simpler and easier to prepare is therefore a major research target, and would provide a platform with which to approach the synthesis of new drugs for tackling important biological problems.

Steroids elicit their diverse biological actions via different functionality located around the periphery of their rigid tetracyclic core. For example, estradiol **1** and dihydrotestosterone **2** can be looked upon as two functional groups held in molecular space by a central nucleus (**3**). Regarding the steroid nucleus as this rigid molecular scaffold we have developed a series of chemically more accessible molecules based around a dicarbonyl motif **4** greatly simplifying the chemistry associated with their preparation. The rationale behind adopting these functional groups was the dipoles associated with the central carbonyl groups would oppose each other thereby placing the A- and D-ring mimics in the appropriate position to bind to the receptor.[3] It was also reasoned that restricted rotation about amide bonds could contribute favourably to receptor binding.[4] Herein we report synthetic strategies to prepare non-symmetrical tri- and tetra-substituted oxamides and oxoamides targeted towards the androgen and estrogen receptors.[5]



Treatment of 4-piperidinone (**5**) with ethyl chlorooxoacetate under basic reaction conditions gave adduct **6** in 56% isolated yield after purification by column chromatography (Scheme 1).[6] It was initially envisaged the D-ring mimic could be introduced via hydrolysis of the ester followed by standard amide coupling, however, under a variety of basic and acid conditions hydrolysis proved unsuccessful leading to no identifiable reaction

* Corresponding author. Tel.: +44 29 20874068; fax: +44 29 20874030; e-mail: tomkinsonnc@cardiff.ac.uk

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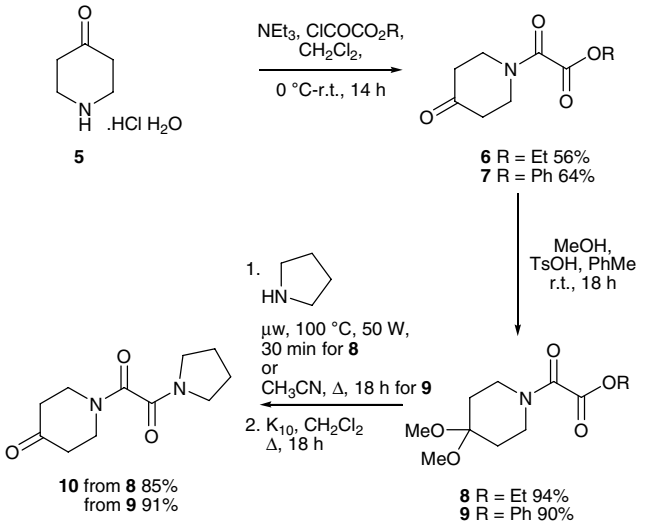


Scheme 1. Preparation of an oxamide.

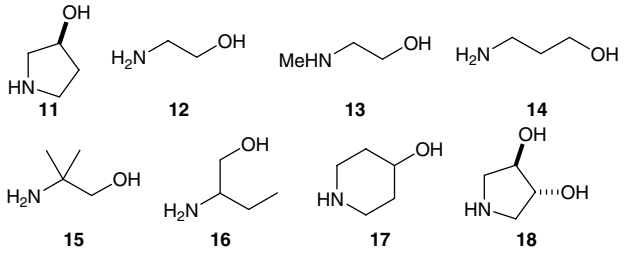
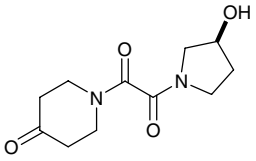
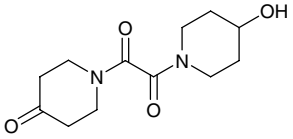
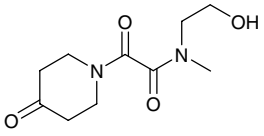
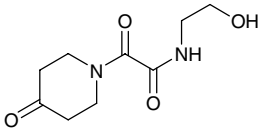
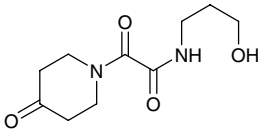
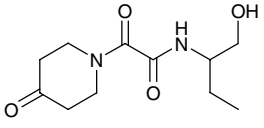
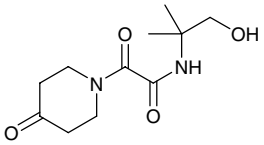


Figure 1. D ring mimics used.

products. Heating of **6** with pyrrolidine also led to decomposition of the starting material and no discernable product which we speculated was due to the cleavage of the A ring substitute. We therefore protected the ketone of **6** as its dimethyl ketal to give **8** (94%). Heating of **8** in the presence of pyrrolidine in a CEM microwave synthesiser for 30 min at 100 °C and an initial power of 50 W gave the corresponding amide **10** in 85% isolated

Table 1. Oxamides prepared

Entry	A-ring mimic	D-ring mimic	Product	Yield[a] (%)
1	**9**	**11**		94
2	**9**	**17**		91
3	**9**	**13**		29
4	**9**	**12**		60
5	**9**	**14**		57
6	**9**	**16**		87
7	**9**	**15**		41

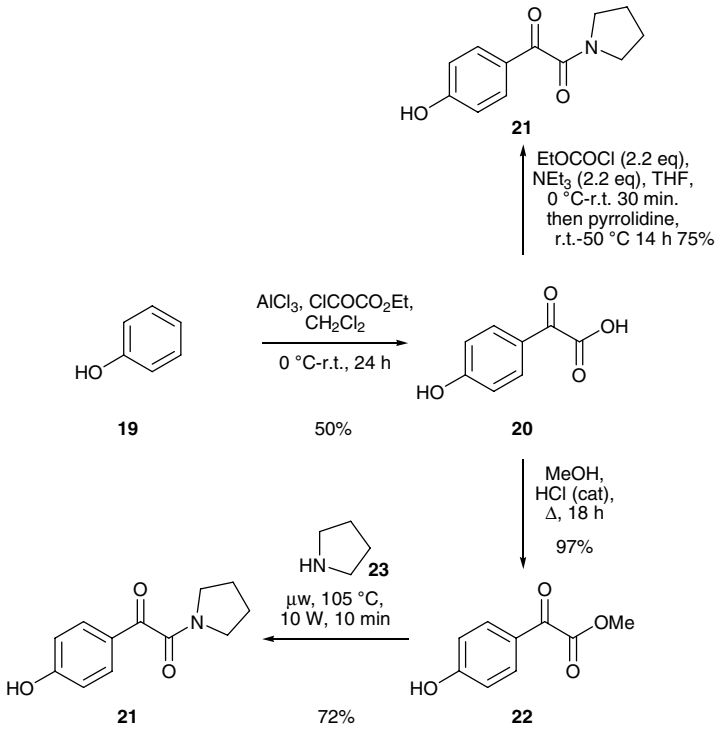
[a] Isolated yield after coupling in acetonitrile and hydrolysis with montmorillonite K 10.

yield after the hydrolysis of the ketal with Montmorillonite K 10.[7] Despite the convenience and simplicity of this route examination of alternative less nucleophilic amines in amide bond formation suggested that this would not prove to be a general method to access our target molecules. We therefore prepared the phenyl ester analogue **7** from piperidinone and phenyl chlorooxoacetate[8] in the belief that increasing the leaving group ability of the ester would lead to a more reactive substrate in the key amide bond forming process.[9] As observed previously, **7** was unstable to reaction with amines under forcing conditions, and again the ketone was protected as its dimethyl acetal **9** (90%). This was considerably more reactive in the key amide bond formation process which proceeded effectively under thermal conditions to give a representative dihydrotestosterone mimic **10** in an excellent 91% yield after the hydrolysis of the ketal.

Having developed a method to access the scaffold of our androgen mimics we set about altering the D-ring substitute to more appropriate alternatives and selected amines **11**–**18** as suitable candidates (Fig. 1). Adopting the procedure outlined in Scheme 1, **9** was reacted with each of amines **11**–**17** in refluxing acetonitrile overnight, the solvent removed and the crude reaction mixture hydrolysed with montmorillonite K 10 to give the desired mimic in 29–94% yields for the two steps after purification by column chromatography (Table 1). The reaction worked well for both secondary (entries 1–3) and primary (entries 4–7) amines and was unaffected by an increase in steric bulk around the nucleophilic nitrogen (entry 7). The transformation was tolerant of free hydroxyl groups in each case, which significantly added to the simplicity and efficiency of the synthesis. This provides a convenient, reliable and general method with which to access non-symmetrical oxamides which have previously been prepared from the symmetrical precursors oxalyl chloride,[10] diethyloxalate[11] and diisopropenyloxalate[12] (which frequently produce symmetrical dimer by-products), or in a controlled manner using bis-1-*H* benzotriazole chemistry developed by Katrizky et al.[13]

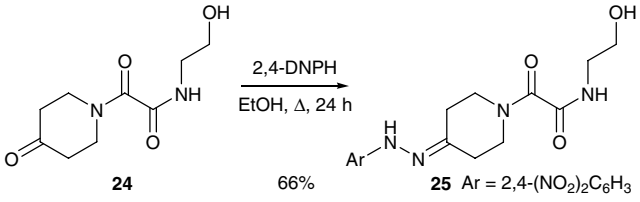
Having successfully prepared a novel series of potential androgenic mimics we turned our attention to an alternative scaffold that would target the estrogen receptor. In order to obtain a good binding with the estrogen receptor the aromatic A-ring is an essential pharmacophore, present in the majority of ligands reported to bind to all receptor sub-types.[14] We therefore decided to prepare a series of oxoamides via the sequence shown in Scheme 2.

Friedel–Crafts acylation of phenol (**19**) with ethyl chlorooxoacetate in the presence of aluminium trichloride led to carboxylic acid **20**, which was readily purified by crystallisation from chloroform. This acid could then be converted to the target mimics by one of two methods, crucially without the need for protection of the reactive phenol. Initially, products were accessed through mixed anhydride technology. Treatment of **20** with 2.2 equiv of ethyl chloroformate in the presence of triethylamine for 30 min followed by the addition of 2 equiv of pyrrolidine and heating the reaction mixture at 50 °C overnight gave the desired product **21** in 75% yield. Although this provided a convenient route to the target materials, purification frequently proved troublesome when the reaction of alternative amines was



Scheme 2. Preparation of oxoamides.

investigated and so a two step route was adopted which negated the need for an aqueous work-up within the reaction sequence. Methylation of carboxylic acid **20** under standard conditions (MeOH, $HCl_{(cat)}$, Δ, 18 h; 97%) followed by heating ester **22** in the presence of pyrrolidine in a CEM microwave synthesiser for 10 min at 105 °C and an initial power of 10 W gave the corresponding amide **21** in 72% isolated yield. Expansion of this work to encompass alternative amines led to a series of estrogen mimics in three synthetic steps starting from phenol (Table 2). The sequence proved to be general for both primary (entries 5–6) and secondary amines (entries 1–4 and 7) providing the products in moderate to excellent yield.



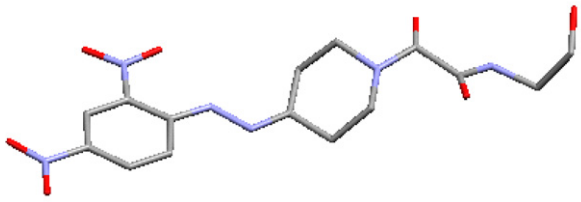
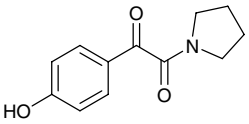
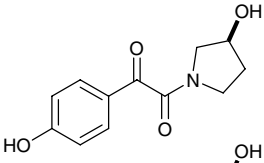
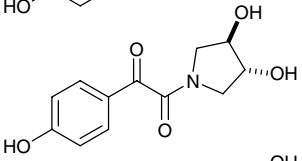
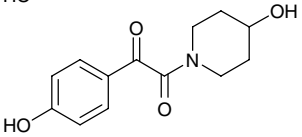
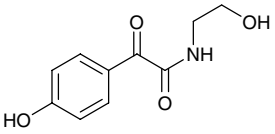
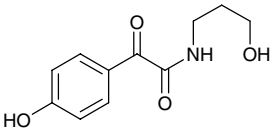
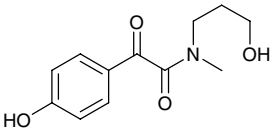


Figure 2. X-ray crystal structure of the 2,4-DNPH derivative of **24**.

We were unable to obtain direct crystallographic data of the compounds reported in Tables 1 and 2; however, the crystals suitable for X-ray analysis were obtained of the 2,4-dinitrophenyl hydrazine derivative of **24** (Fig. 2), which showed a series of interesting features.[15] An examination of the crystal structure clearly showed the A- and D-ring mimics held in positions similar to those of dihydrotestosterone **2**. The central dicarbonyl functionality behaved as predicted with the two carbonyl groups adopting a trans-conformation with the torsion angle between the two carbonyl oxygens being 167°. There was some disorder in the crystal structure of **25**, showing flexibility in the pseudo D-ring mimic however, this may well allow for **24** to adopt the required conformation on receptor binding. Measurement of the interatomic distance between the C-3 carbonyl oxygen and the C-17 hydroxyl group (steroid numbering) of dihy-

Table 2. Oxoamides prepared

Entry	A-ring mimic	D-ring mimic	Product	Yield (%)
1	**22**	**23**		72
2	**22**	**11**		48
3	**22**	**18**		54
4	**22**	**17**		37
5	**22**	**12**		27
6	**22**	**14**		30
7	**22**	**13**		25

drotestosterone when complexed to the androgen receptor showed an interatomic distance of 10.893 Å.[16] In **25**, the comparable distance between the hydrazone nitrogen and the hydroxyl group lies between 9.65 and 10.97 Å, suggesting that the interatomic distance between the ketone and hydroxyl in mimic **24** may well be able to demonstrate the same ligand–receptor interactions displayed by **2**.

In summary, we have developed two short, effective and convenient synthetic routes to a variety of non-symmetrical oxamides and oxoamides. Both key coupling procedures can be carried out in the presence of unprotected alcohol groups and without the need for an aqueous workup allowing for the reaction to be carried out in parallel on potentially water soluble substrates. Crystallographic data on the oxamide **25** has shown the dicarbonyl motif to preferentially adopt an antiparallel arrangement fixing the substituents within molecular space, which may also prove useful in the design of pharmacophores for alternative target receptors. The compounds reported are currently under biological evaluation and we will report our findings in due course.

Acknowledgements

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15. Crystal data for **25**: $C_{15}H_{18}N_6O_7$, crystallises from toluene as yellow rods. Triclinic, space group *P*-1, $a = 6.3978(4)$, $b = 10.3825(9)$, $c = 15.3945(13)$ Å, $\alpha = 70.443(3)$, $\beta = 81.209(5)$, $\gamma = 72.370(5)°$, 916.82(12) Å^3, $Z = 2$, $D_c = 1.428$ Mg m^{-3}, $M = 394.35$, $T = 120(2)$ K. 16461 Reflections collected, 3241 independent ($R_{int} = 0.0725$) which were used in calculations $R_1 = 0.1028$, $wR_2 = 0.2712$ for observed unique reflections [$F^2 > 2\sigma(F^2)$] and $R_1 = 0.1341$, $wR_2 = 0.2895$ for all 3241 unique reflections. The max. and min. residual electron densities on the final difference Fourier map were 0.663 and −0.406 e Å^{-3}, respectively. Crystallographic data (excluding structure factors) for structure **25** has been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication Number 620459. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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