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The Medicinal Chemistry of Glucocorticoid Receptor Modulators

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Preface

Since the discovery of cortisone as a treatment for rheumatoid arthritis over 70 years ago, glucocorticoid receptor modulators (GRM) have become a mainstay of modern medicine, most notably their use to treat inflammatory, allergic and autoimmune disorders. This book discusses the numerous medicinal chemistry approaches that have been explored to optimize this compound class. These have included advances that have increased the potency at the glucocorticoid receptor, optimized the selectivity versus the other mineral acid receptors, minimized the systemic exposure of the GRM, enabled topical applications, attempts to identify selective glucocorticoid receptor modulators (SGRM) that would maximize the beneficial transrepression functional component while minimizing the unwanted transactivation and the targeted delivery of the GRM to the disease area or cell type. In addition, the application of computational approaches has been applied to extensive quantitative structure-activity analyses of cortisol-based GRMs while virtual screening of homology models or using publicly available crystal structures of the glucocorticoid receptor have successfully identified non-steroidal GRMs that offer excellent starting points for medicinal chemistry optimization. Finally, the targeted delivery of the GRM to the site of disease has been explored with numerous targeting modalities that include approaches for targeting specific organs like the kidney with C21 peptide analogues of dexamethasone, hydrazone analogues of the C3 carbonyl to enable localized pH-dependent delivery of the therapeutically active GRM, and α-TNF antibody drug conjugates with a GRM payload to target immune cells.

Worcester, USA — Adrian Hobson

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About the Author

Adrian Hobson PhD FRSC is a senior research fellow at Abbvie and an adjunct professor of Chemistry at Clark University in Worcester, USA. With 30 years of experience as a medicinal chemist, he started his journey at Boots Pharmaceuticals, Nottingham UK, where he worked on anti-depressants and anti-psychotics and the Special Synthesis group making metabolites and possible impurities. After the company was acquired by BASF in 1994, he formed the High Speed Analoging team, working there for 6 years until he transferred to the BASF Bioresearch Corporation at Worcester, USA, where he formed a new High Speed Analoging team to support both oncology and immunology. He spent the next 12 years working in medicinal chemistry on kinase, GPCR and NHR targets including selective glucocorticoid receptor modulators. When AbbVie split from Abbott, Dr. Hobson switched his attention to immunology antibody drug conjugates, where he has pioneered the use of glucocorticoid receptor modulators (GRM) as a payload for antibody drug conjugates.

Chapter 1
Introduction

Glucocorticoids along with mineralocorticoids make up the corticosteroid class of compounds. In addition to binding the glucocorticoid receptor, glucocorticoids also bind to other members of the nuclear receptor family including the androgen receptor (AR), estrogen receptor (ER), mineralocorticoid receptor (MR) and progesterone receptor (PR) [1] During the past 70 years glucocorticoid receptor modulator agonists (GRM) have become a major therapeutic class [2] being the primary therapeutic for multiple diseases including rheumatoid arthritis, asthma, psoriasis and certain cancers. Much of this interest has been driven by the positive anti-inflammatory effects of glucocorticoids [3] which are attributed to their capacity to reduce the expression of pro-inflammatory genes such as NF-kB. The term transrepression is used to describe these beneficial effects. While their therapeutic benefit is without question, their use for chronic dosing has been limited by unwanted side effects, with the side effects attributed to transactivation [4].

In September 1948 Hench, Kendall and Reichstein gave cortisone to patients with severe rheumatoid arthritis which resulted in amazing results. In recognition of this work in 1950 the trio were awarded the Nobel Prize for Physiology or Medicine. Almost immediately medicinal chemists around the world became interested in cortisone and since then there has been constant interest in this class of compound. During the many medicinal chemistry programs to enhance glucocorticoids the areas of focus have included:

(a) Increasing potency at glucocorticoid receptor versus mineral acid receptors.
(b) Minimizing systemic exposure of the GRM.
(c) Enabling topical applications.
(d) Design of selective glucocorticoid receptor modulators (SGRM) that maximize the transrepression functional component while minimizing unwanted transactivation.
(e) Targeted delivery of the GRM to the disease area or cell type.

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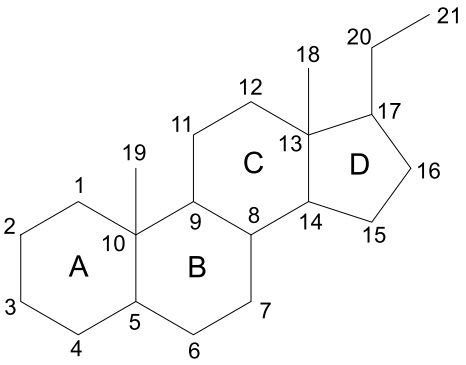
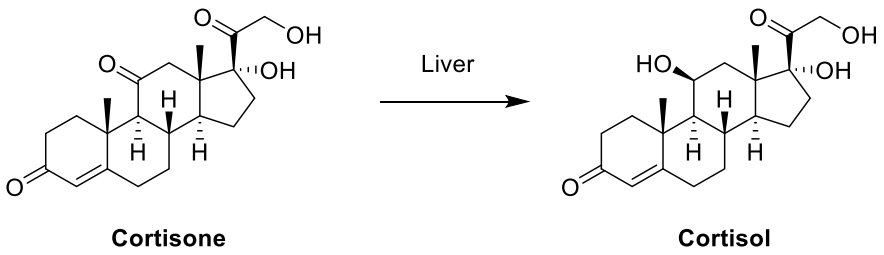


Fig. 1.1 Corticosteroid nomenclature



Scheme 1.1 Cortisone is converted in the liver to Cortisol

The name cortisone was derived by Kendall from a shortened version of its full chemical name of 17-hydroxy-11-dehydrocorticosterone and this clearly identifies cortisone as a member of the corticosteroid class of compounds. This class of compound comprises the 4-ring skeleton (Fig. 1.1) found in cholesterol from which corticosteroids are derived in nature.

Cortisone is a naturally occurring corticosteroid. The key structural features are carbonyl on carbons 3, 11 and 20, hydroxyl on carbons 17 and 21 and an unsaturated A-ring, with a double bond between carbons 4 and 5. Of these the carbonyl on carbon 11 is of particular note. Cortisone is an inactive prodrug that requires conversion to the C11 hydroxy analogue cortisol [5, 6] (also known as hydrocortisone) which is responsible for the biological activity (Scheme 1.1). Enzymic conversion of inactive cortisone to active cortisol is primarily facilitated by 11β-hydroxysteroid dehydrogenase in the liver. Sulzberger [7, 8] demonstrated a major advantage of cortisol was that it is effective when administered both topically and systemically whereas cortisone which requires activation in the liver was only effective following systemic administration. Therefore topical application of cortisol offered a route of administration that minimized the unwanted side effects associated with cortisone treatment.

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Chapter 2
Cortisol Based Glucocorticoids

Synthesis of cortisol would confirm the need for the C11 hydroxyl and Wendler [1, 2] published the first synthesis of cortisol. As this was an area of high interest other groups also published their syntheses including an improved synthesis by Wendler and a comprehensive review by Rosenkranz and Sondheimer [3] highlighting many elegant synthetic approaches. However, the major benefit of synthetic access to cortisol was that it now enabled extensive SAR exploration of both cortisone and cortisol. Optimization of cortisone/cortisol was required due to the many adverse effects like salt and water retention that were a result of their mineralcorticoid activity [4].

The first structural modification and probably the most impactful was increased unsaturation of the A-ring with the introduction of a double bond between carbons 1 and 2 [5]. It was shown that cortisone and cortisol could be converted to prednisone (also known as metacortandracin) and prednisolone [6] (also known as metacortandralone) respectively using Corynebacterium simplex [7]. Prednisone is a prodrug being converted to the more potent prednisolone by reduction of the C11 carbonyl in the liver [8] (Scheme 2.1). Both prednisone and prednisolone had enhanced glucocorticosteroid activity of up to five times that of cortisone and equally as important displayed reduced mineralocorticoid activity and have been profiled extensively [9]. The magnitude of the impact introducing the double bond to the A-ring can be judged by the fact that there are at least 33 marketed glucocorticoid drugs that incorporate it.

Halogenated analogues of cortisol at carbon 9 were secured through a 4-step synthesis (Scheme 2.2) starting from the C21 acetate of cortisol [10, 11]. The most promising halogen was identified as fluorine in fludrocortisone [12] for which the anti-inflammatory activity was enhanced relative to cortisol. Unfortunately, halogenation at C9 had an even greater impact on mineralocorticoid activity with large increases in both salt and water retention [13]. Combining the A-ring unsaturation and fluorination of carbon 9 in a single molecule resulted in isoflupredone (Fig. 2.1). This was never marketed as a drug and has been investigated for veterinary applications [14, 15]. Incorporation of fluorine to carbon 6 of isoflupredone and butyrate

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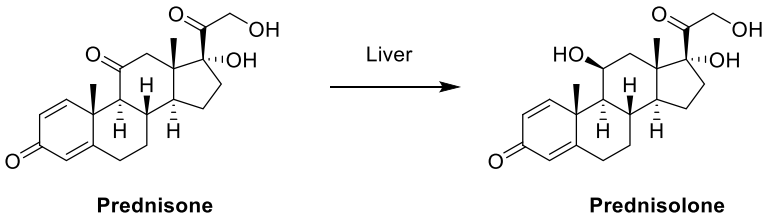
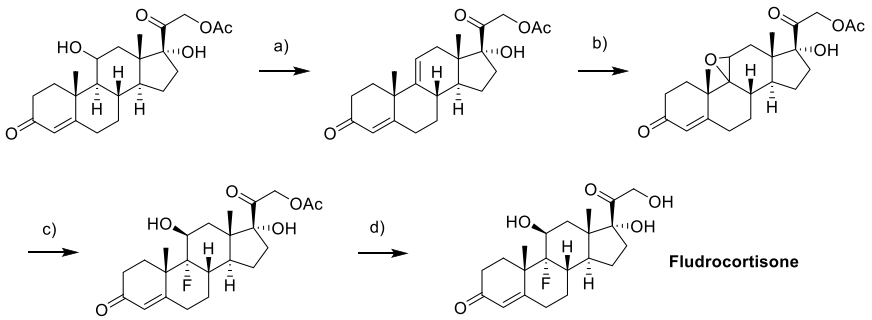


Scheme 2.1 Prednisone is converted in the liver to prednisolone



Scheme 2.2 Synthetic route to Fludrocortisone. Reagents and conditions: **a** $POCl_3$, pyridine; **b** (i) $CH_3CONHBr$, (ii) CH_3CO_2Na; **c** HF; **d** Base

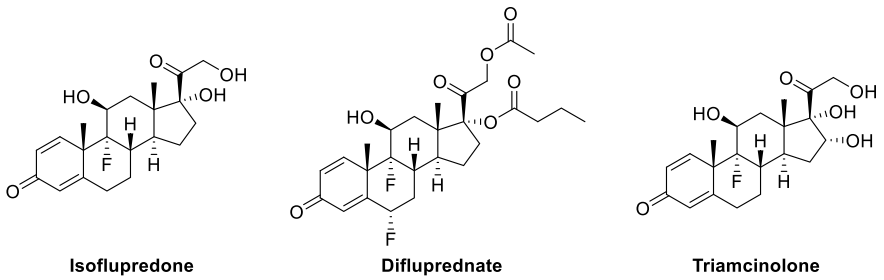


Fig. 2.1 C6/C9/C16/C17 analogues of prednisolone

and acetate to C17 and C21 hydroxyls respectively afforded difluprednate which compares favourably to prednisolone acetate for the treatment of anterior uveitis [16].

Investigation of the substitution at carbon 16 afforded triamcinolone [17] which is the 16-hydroxy analogue of isoflupredone. In the rat electrolyte assay triamcinolone was shown to exhibit no sodium retention properties while being about 13 times more active than cortisol in the rat liver glycogen assay and was advanced to the clinic [18]. Further SAR identified the C16/C17 dimethyl ketal glucocorticoids exemplified by triamcinolone acetonide (Fig. 2.2). Triamcinolone acetonide was synthesized by

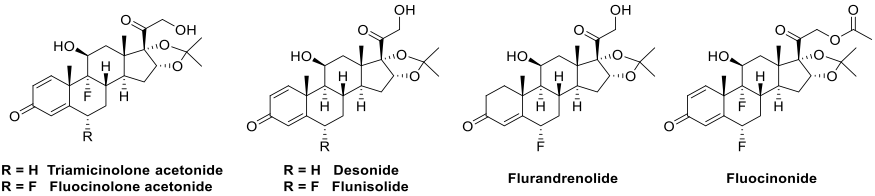


Fig. 2.2 C16/C17 Dimethyl ketal glucocorticoids

agitating triamcinolone in acetone in the presence of a trace amount of perchloric acid at ambient temperature [19]. Unlike most cyclic ketals the acetonide was shown to be stable after refluxing in acidified aqueous methanol for 4 h. Triamcinolone showed considerably greater glucocorticoid and anti-inflammatory activity than 6α-methyl-9α-fluoroprednisolone which was the most potent glucocorticoid described at the time. Studies also showed triamcinolone acetonide was a highly active therapeutic agent when applied topically compared to both cortisol and fludrocortisone [20]. To rationalize the increased potency of triamcinolone acetonide compared to dexamethasone a crystal structure of GR in complex with triamcinolone acetonide was solved. The C16/C17 acetonide is oriented essentially at 90° from the steroid skeleton and the compound occupies additional space of the binding pocket generating additional hydrophobic interactions which are likely responsible for both the increased potency and affinity [21].

Synthesis of the fluocinolone acetonide was achieved starting from readily available 16α,17α-oxido-Δ^5-pregnene-3b,21-diol-20-one 21-acetate [22] and achieved in 14-steps [23]. In addition, improved syntheses have been developed [24, 25]. Fluocinolone acetonide exhibited 100-fold the anti-inflammatory activity of hydrocortisone without any sodium retention clearly identifying the 6α-fluoro as a key structural modification to drive potency. Flunisolide is the 6α-fluoro isomer of triamcinolone and is often prescribed for allergic rhinitis [26]. After both oral and intravenous administration, it is rapidly metabolized to the 6β-hydroxy metabolite offering an explanation for the clinical observation that neither intranasal nor inhalation administration cause a significant reduction in adrenal function [27]. As expected desonide, the des-fluoro analogue of fluocinolone acetonide, is less potent and is used to treat atopic dermatitis [28].

Flunisolide and flurandrenolide are closely related C16/C17 hydroxyl dimethyl ketals and both have the 6α-fluoro substituent (Fig. 2.2). Flurandrenolide has the cortisol ring structure while flunisolide has the prednisolone ring structure with the double bond between carbons 1 and 2 in the A-ring. Studies on the metabolic pathways of inhaled acetonide based glucocorticoids have been studied to identify differences in rates of clearance [29]. They have been used as topical anti-inflammatory therapies, for example, for the treatment of allergic rhinitis [30]. Desonide is the des-fluoro analogue of fluocinolone acetonide and despite the absence of the C6α fluorine desonide still displays comparable potency to triamcinolone acetonide [31] and has been used in the treatment of steroid-responsive dermatoses. Acetylation of the C21