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STRUCTURE–ACTIVITY RELATIONSHIP (SAR) ANALYSIS OF GLUCOCORTICOIDS AND THEIR PHARMACOKINETIC PROPERTIES

Afruza Axmadovna Narziyeva

Lecturer in instrumental methods of drug analysis

Department of General Subjects

Asia International University

Bukhara, Uzbekistan

Abstract: Glucocorticoids are steroid hormones produced in the adrenal cortex that play a vital role in regulating metabolism, inflammatory processes, and immune responses in the human body. Both natural glucocorticoids (such as cortisol) and their synthetic derivatives are widely used in pharmacology. They possess anti-inflammatory, antiallergic, immunosuppressive properties and are life-saving drugs in shock conditions.

One of the most important factors determining the activity of glucocorticoids is their chemical structure. Therefore, studying their structure–activity relationship (SAR) is one of the key areas in medicinal chemistry. Through SAR analysis, it becomes possible to understand how small structural modifications in the molecule affect biological activity, thereby enabling the design of new and more effective therapeutic agents. Glucocorticoids (GCs) are widely used to treat a variety of autoimmune and inflammatory diseases; however, systemic delivery of GCs is associated with side-effects that affect essentially every organ system .“One of the most important factors determining the activity of glucocorticoids is their chemical structure. … In this review, we summarize current data on design of GC side-effects in animals over the past years.“. Glucocorticoids (GCs) are steroid hormones that play a role in physiological processes and are widely used as immunosuppressive and anti-inflammatory agents […] however, their clinical use is restricted due to a wide range of complications associated with their long-term topical and systemic use.“

Keywords: Glucocorticoids, steroid hormones, SAR analysis, cortisol, prednisolone, dexamethasone, anti-inflammatory, chemical structure, pharmacological activity.

General Structural Features of Glucocorticoids. Glucocorticoids are 21-carbon steroids possessing a pregnane skeleton, with a basic nucleus composed of a cyclopentanoperhydrophenanthrene system. This system consists of four rings (A, B, C, and D), and the functional groups attached to these rings determine the biological activity of the compound.

The main natural representative is hydrocortisone (cortisol). Its structure contains 11β-hydroxyl, 17α-hydroxyl, 3-keto, and a 4–5 double bond, all of which are essential for glucocorticoid activity.

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Structure–Activity Relationship (SAR) Analysis: The SAR analysis of glucocorticoids demonstrates how **chemical modifications** in their molecular structure influence **pharmacological properties**.

C11 position –OH group: This group is essential for glucocorticoid activity. If replaced by a keto group (as in cortisone), the compound becomes inactive.

C1–C2 double bond: This structural change increases anti-inflammatory activity while reducing sodium-retaining effects.

C6 and C9 positions: Substitution with methyl or fluorine atoms enhances activity (e.g., dexamethasone).

C16 position: The addition of CH_3 or OH groups reduces mineralocorticoid activity.

C17 and C21 positions: The presence of –OH or –acetate groups determines the rate of absorption and duration of action.

Table 1

Drug	Structural Modification	Relative Glucocorticoid Activity	Mineralocorticoid Activity	Duration	Remarks
Prednisolone	Δ^1 double bond	4–5	++	Intermediate	Enhanced potency
Methylprednisolone	6–CH_3	5–6	+	Intermediate	Stronger anti-inflammatory
Triamcinolone	9–F, 16–OH	5	+	Intermediate	No salt retention
Dexamethasone	9–F, 16–CH_3	25–30	0	Long	Very potent
Betamethasone	9–F, 16–CH_3 (isomer)	25–30	0	Long	Isomeric form
Prednisolone	Δ^1 double bond	4–5	++	Intermediate	Enhanced potency

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Table 1. Properties of Glucocorticoids Changing with Structural Modifications

As can be seen from the table, with the establishment of the structure of the produced glucocorticoids, their relative activity increases, mineralocorticoid activity decreases, and their potency increases, i.e., their control increases.

The binding of glucocorticoids to proteins
Glucocorticoids in blood plasma are mainly bound to proteins. Their main carrier proteins are: albumine and transcortin

Table 2

Drug	Protein Binding (%)	Major Binding Protein
Cortisol	90–95%	Transcortin, Albumin
Prednisolone	70–90%	Transcortin
Dexamethasone	65–75%	Albumin
Betamethasone	60–70%	Albumin
Methylprednisolone	75–85%	Transcortin, Albumin

Table 2. Indicators of the binding of glucocorticoids to blood proteins

The table show the duration of action and activity level of glucocorticoids in the body depend on their degree of protein binding. The lower the binding, the faster and more potent the effect, but the drug is also eliminated from the body more quickly. The portion that is strongly bound to proteins is pharmacologically inactive; only the free fraction (5–10%) can enter cells and interact with receptors. The level of transcortin increases during pregnancy, liver diseases, or under the influence of estrogens, which reduces the amount of the drug in its free form.

Biotransformation of Glucocorticoids: Glucocorticoids have lipophilic properties, which allow them to easily pass through cell membranes. They mainly accumulate in the liver, adrenal glands, and adipose (fat) tissues.

Table 3

Drug	**Vd (L/kg)**	**Description**
Cortisol	0.5–0.6	Moderate distribution
Prednisolone	0.6–0.8	Efficient tissue penetration

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Dexamethasone	0.9–1.1	High tissue concentration

Table 3. Biotransformation of Glucocorticoids

Glucocorticoids undergo extensive biotransformation in the liver, where they are metabolized mainly through reduction, hydroxylation, and conjugation reactions such as glucuronidation and sulfation.
These metabolic pathways convert active glucocorticoids into water-soluble inactive metabolites, which are then excreted primarily via the kidneys. The rate of metabolism depends on the chemical structure of the compound, the type of substitution at specific carbon positions, and the individual's liver enzyme activity.

Elimination (Excretion) of Glucocorticoids: Glucocorticoids undergo biotransformation in the liver. Their metabolites are excreted through the kidneys via glucuronidation or sulfation pathways. The average half-life (T½). The **average half-life (T½)** of glucocorticoids varies depending on the specific compound — short-acting ones (like cortisol) have a shorter half-life, while long-acting ones (like dexamethasone or betamethasone) persist longer in the body.

Pharmacological Properties: Glucocorticoids are steroid hormones that exert powerful anti-inflammatory, immunosuppressive, anti-allergic, and metabolic effects. Their actions are mediated through specific intracellular receptors that regulate gene transcription Anti-inflammatory effect:Glucocorticoids inhibit phospholipase A_2 activity, reducing the synthesis of prostaglandins and leukotrienes. This decreases inflammation, redness, swelling, and pain. Immunosuppressive effect:They suppress the proliferation and activity of immune cells (T-lymphocytes, macrophages), reducing the immune response. This makes them useful in autoimmune and transplant-related conditions.Anti-allergic effect:Glucocorticoids reduce histamine release and capillary permeability, alleviating symptoms of allergic reactions.Metabolic effects:Carbohydrate metabolism: Increase gluconeogenesis and blood glucose levels.Protein metabolism: Promote protein catabolism (breakdown) in muscles and skin.Lipid metabolism: Redistribute fat — increasing deposition in the face, neck, and trunk (characteristic of Cushing's syndrome in prolonged use)Electrolyte and water balance:Some glucocorticoids cause sodium retention and potassium excretion, leading to water retention.Effect on the central nervous system:They can influence mood and behavior — high doses may cause euphoria, insomnia, or irritability

Conclusion: Glucocorticoids are among the most important steroid preparations in pharmacology. Their efficacy is directly related to structural modifications of the molecule. Structure–activity relationship (SAR) analysis shows that the presence of a 1–2 double bond, a 9-fluoro group, and a 16-methyl group increases glucocorticoid activity while reducing mineralocorticoid effects. Modified derivatives such as prednisolone, methylprednisolone, dexamethasone, and betamethasone are therefore more effective than cortisol.Thus, SAR analysis serves as an important scientific basis for the development of new generations of glucocorticoids. A higher degree of protein binding leads to longer duration of action and slower

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elimination, whereas drugs with lower protein binding (e.g., dexamethasone) have a greater free fraction and stronger pharmacological activity. As the volume of distribution increases, the drug penetrates more deeply into the central nervous system and peripheral tissues. The rate of metabolism depends largely on liver function.

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