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Research Article

In Silico Approach in Predicting Bioactivity, ADMET, and Therapeutic Targets of Dexamethasone

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Abstract

Dexamethasone is a synthetic glucocorticoid widely used for its potent anti-inflammatory and immunosuppressive effects; however, its broad biological activity and potential adverse effects necessitate a comprehensive pharmacological evaluation. This study aimed to investigate the bioactivity profile, potential molecular targets, and ADMET properties of dexamethasone using an integrated *in silico* approach. Bioactivity prediction was performed using PASS Online, target identification was conducted via SwissTargetPrediction, and pharmacokinetic–toxicological profiling was evaluated using the pkCSM platform. The results revealed high probabilities for anti-inflammatory, antiallergic, and immunosuppressive activities, confirming the established therapeutic roles of dexamethasone. Multiple nuclear receptors, including the glucocorticoid, mineralocorticoid, androgen, and progesterone receptors, were identified as primary targets, providing mechanistic insight into both therapeutic effects and endocrine-related adverse outcomes. Additional targets related to inflammatory signaling, metabolic regulation, and G-protein–coupled receptors suggested broader pharmacological interactions. ADMET predictions indicated high intestinal absorption, moderate distribution, limited central nervous system penetration, manageable metabolic interactions, and low predicted toxicity risks.

Keywords: Dexamethasone, Target Prediction, PASS Online, ADMET, In Silico

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1 Introduction

Dexamethasone is a synthetic glucocorticoid that has been extensively used in clinical practice due to its potent anti-inflammatory, immunosuppressive, and anti-allergic properties [1]. It plays a crucial role in the management of a wide range of medical conditions, including autoimmune disorders, allergic reactions, inflammatory diseases, cerebral edema, and as an adjunct therapy in certain malignancies [2,3]. More recently, dexamethasone has gained global attention for its effectiveness in reducing mortality among hospitalized patients with severe inflammatory responses, such as those observed in acute respiratory distress syndromes [4]. Despite its widespread clinical use, dexamethasone therapy is often associated with significant adverse effects, particularly when administered at high doses or for prolonged periods, including immunosuppression, metabolic disturbances, osteoporosis, and adrenal suppression [5,6].

The pharmacological effects of dexamethasone are primarily mediated through its interaction with glucocorticoid receptors, leading to modulation of gene expression involved in inflammatory and immune responses [7]. However, emerging evidence suggests that dexamethasone may interact with multiple molecular targets beyond the classical glucocorticoid receptor pathway [8]. These off-target interactions can contribute not only to its therapeutic efficacy but also to its adverse drug reactions [9,10]. Therefore, a comprehensive understanding of dexamethasone's bioactivity profile and its interaction with various biological targets is essential to optimize its therapeutic use and minimize potential risks [11].

In addition to target interactions, the pharmacokinetic and toxicological characteristics of dexamethasone play a pivotal role in determining its clinical effectiveness and safety [12]. Parameters related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) significantly influence drug bioavailability, tissue distribution, and the likelihood of adverse effects [13,14]. Although dexamethasone has been used clinically for decades, systematic and integrative evaluations of its ADMET properties using modern computational approaches remain limited [15]. Such analyses are particularly important in the context of personalized medicine and rational drug use, where a deeper understanding of drug behavior at the molecular and systemic levels is required [16].

The rapid advancement of computational biology and bioinformatics has enabled the application of in silico methods as powerful tools in drug discovery and drug evaluation processes [17]. In silico approaches allow for the prediction of bioactivity, ADMET profiles, and potential therapeutic targets efficiently, cost-effectively, and ethically, reducing the reliance on extensive in vitro and in vivo experiments [18]. Techniques such as molecular target prediction, cheminformatics-based bioactivity modeling, and ADMET prediction platforms provide valuable insights into the molecular mechanisms of drugs and their safety profiles [19].

Applying an in silico approach to dexamethasone is particularly relevant, given its long-standing clinical use and the need to better understand its comprehensive pharmacological landscape [20,21]. By integrating bioactivity prediction, ADMET analysis, and therapeutic target identification, this study aims to provide a holistic overview of dexamethasone's molecular interactions and pharmacokinetic behavior [22]. Such an integrative analysis may uncover previously unrecognized targets, clarify mechanisms underlying adverse effects, and support the rational optimization of dexamethasone therapy [24].

Research employs an in silico approach to predict the bioactivity, ADMET properties, and potential therapeutic targets of dexamethasone [25]. The findings of this study are expected to contribute to a deeper molecular understanding of dexamethasone, support safer and more effective clinical use, and provide a scientific basis for future experimental and clinical investigations involving glucocorticoid-based therapies.

2 Method

This study employed a comprehensive in silico approach to predict the bioactivity profile, potential therapeutic targets, and ADMET properties of dexamethasone using established computational platforms. The overall workflow was designed to systematically integrate cheminformatics-based bioactivity prediction, molecular target identification, and pharmacokinetic–toxicological profiling in order to obtain a holistic understanding of dexamethasone's pharmacological characteristics. Dexamethasone was

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selected as the study compound due to its well-established clinical use and its relevance as a model glucocorticoid with complex pharmacodynamic and pharmacokinetic behavior. The chemical structure of dexamethasone was retrieved from a publicly available chemical database and verified to ensure structural accuracy before computational analysis. The compound structure was prepared in an appropriate digital format compatible with each in silico platform used in this study.

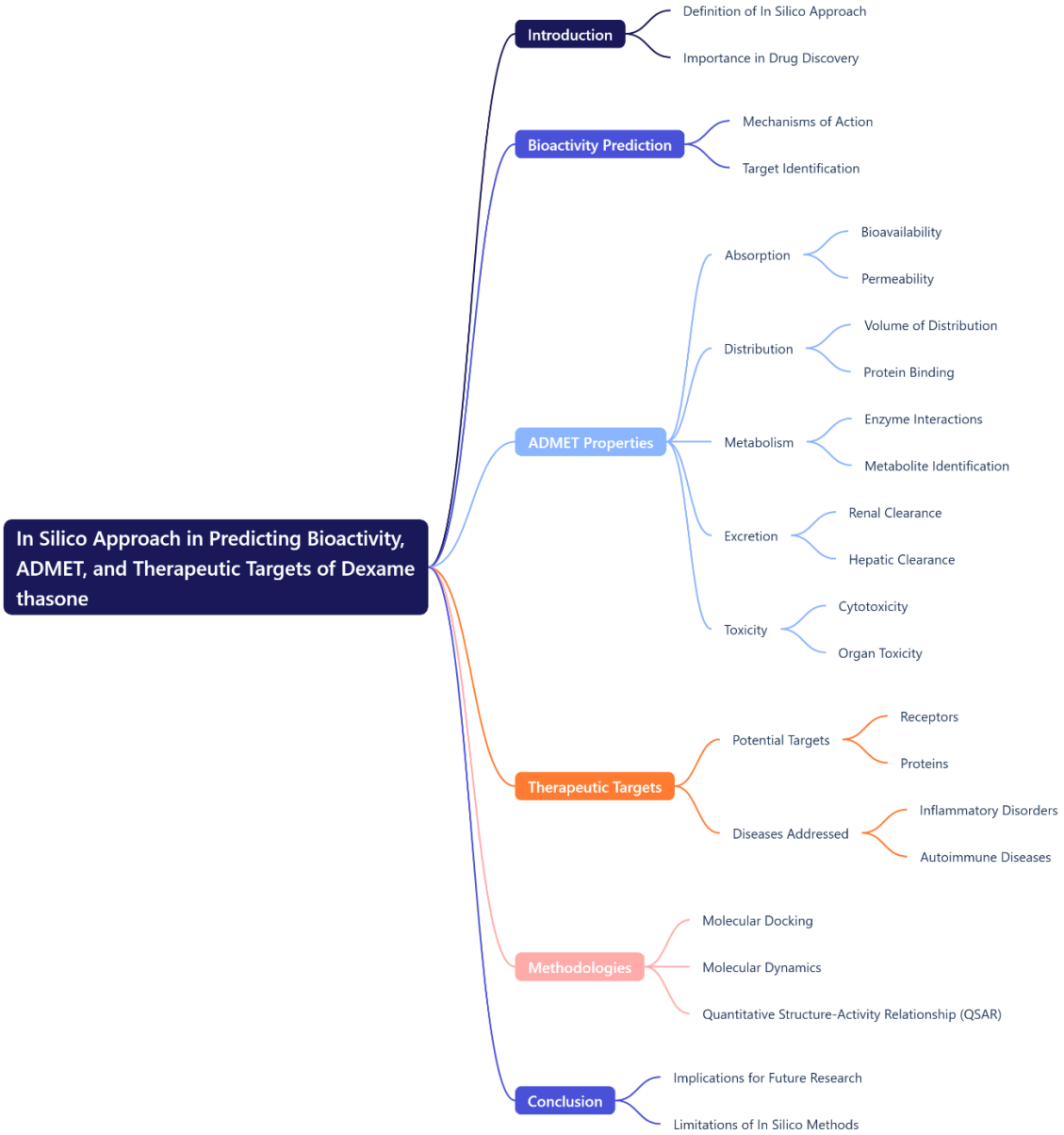

Figure 1. Mind Maps Reseach

Prediction of bioactivity was conducted using the Prediction of Activity Spectra for Substances (PASS) Online web server, which is accessible at https://www.way2drug.com/passonline/predict.php. PASS Online is a widely used computational tool that predicts the biological activity spectrum of a compound based on its chemical structure by employing structure–activity relationship models derived from a large database of biologically active substances. The simplified molecular-input line-entry system (SMILES) representation of dexamethasone was used as the input format for the PASS Online analysis. The SMILES string was carefully checked to avoid syntax errors that could influence prediction outcomes.

Once uploaded, the PASS Online server generated predictions of various biological activities expressed as probabilities of activity (Pa) and probabilities of inactivity (Pi). The predicted activities included pharmacological effects, biochemical mechanisms, and potential toxicological endpoints.

In this study, the predicted bioactivities were interpreted by focusing on activities with a Pa value greater than Pi, indicating a higher likelihood that the compound exhibits the predicted biological effect. Particular attention was given to bioactivities with higher Pa values, as these were considered more reliable predictions according to the PASS Online methodology. The predicted bioactivity spectrum was analyzed to identify anti-inflammatory, immunomodulatory, and glucocorticoid-related activities that are consistent with the known pharmacological profile of dexamethasone. Additionally, novel or less commonly reported activities were also documented to explore potential off-target effects or alternative therapeutic applications. The results obtained from PASS Online were systematically tabulated and categorized based on pharmacological relevance.

Target prediction analysis was performed using SwissTargetPrediction, an established in silico platform available at https://www.swisstargetprediction.ch/. This tool predicts potential protein targets of small molecules based on a combination of two-dimensional and three-dimensional similarity measures with known ligands. The chemical structure of dexamethasone was uploaded in SMILES format to the SwissTargetPrediction server. The organism of interest was specified as Homo sapiens to ensure that predicted targets were relevant to human biology. The platform then generated a ranked list of predicted targets, each associated with a probability score reflecting the likelihood of interaction between dexamethasone and the predicted protein.

The predicted targets were classified according to protein families, such as nuclear receptors, enzymes, kinases, and transcription factors. Special emphasis was placed on targets related to glucocorticoid signaling pathways, inflammatory mediators, and immune response regulators. The probability scores provided by SwissTargetPrediction were used to prioritize targets for further interpretation, with higher probability values indicating stronger confidence in the predicted interaction. Known targets, such as the glucocorticoid receptor, were used as internal validation references, while newly predicted targets were explored to understand potential off-target interactions. These predicted targets were analyzed in the context of their biological functions and therapeutic relevance.

ADMET prediction was conducted using the pkCSM web server, which is accessible at https://biosig.lab.uq.edu.au/pkcsm/prediction. pkCSM is a computational tool that predicts pharmacokinetic and toxicity properties of small molecules using graph-based signatures. The SMILES representation of dexamethasone was submitted to the pkCSM server to predict parameters related to absorption, distribution, metabolism, excretion, and toxicity. Absorption-related parameters included intestinal absorption and Caco-2 permeability, which provide insights into oral bioavailability. Distribution-related parameters included volume of distribution and blood–brain barrier permeability, which are important for understanding tissue distribution.

Metabolism-related predictions focused on interactions with cytochrome P450 enzymes, including potential inhibition or substrate characteristics. Excretion parameters included total clearance, which reflects the elimination behavior of the compound. Toxicity predictions included hepatotoxicity, cardiotoxicity, and mutagenicity indicators, which are critical for evaluating drug safety. The predicted ADMET values were interpreted based on established pharmacokinetic thresholds and compared with known clinical data on dexamethasone to assess consistency and reliability.

All predicted data obtained from PASS Online, SwissTargetPrediction, and pkCSM were integrated and analyzed descriptively. The integration aimed to correlate predicted bioactivities with potential molecular targets and ADMET properties to provide a comprehensive pharmacological profile of dexamethasone. This integrative analysis allowed for the identification of relationships between predicted biological effects, target interactions, and pharmacokinetic behavior. The methodology emphasizes reproducibility by clearly specifying the computational tools, input formats, and interpretation criteria used throughout the study. Overall, this in silico methodology provides a systematic and efficient framework for evaluating the bioactivity, target interactions, and ADMET characteristics of dexamethasone and may serve as a reference approach for similar pharmacological studies.

3 Result and Discussion

3.1 *Predicted Biological Activities of Dexamethasone Bioactivity*

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The PASS Online bioactivity prediction results provide a comprehensive overview of the potential pharmacological and biochemical activities of dexamethasone, reflecting both its well-established therapeutic effects and possible off-target interactions.

Table 1. PASS Online Prediction Results of Dexamethasone Bioactivity

).	Pa	Pi	Predicted Activity
1	0.985	0.003	Antiinflammatory
2	0.962	0.004	Antiallergic
3	0.958	0.000	Antiinflammatory, ophthalmic
4	0.942	0.002	Gonadotropin antagonist
5	0.940	0.004	CYP3A4 substrate
6	0.937	0.003	CYP3A substrate
7	0.931	0.004	CYP2C substrate
8	0.927	0.001	Antipruritic
9	0.926	0.004	Antiasthmatic
10	0.912	0.004	CYP2C9 substrate
11	0.906	0.002	Indanol dehydrogenase inhibitor
12	0.897	0.003	UDP-glucuronosyltransferase substrate
13	0.896	0.005	Antiarthritic
14	0.885	0.000	Antipruritic, allergic
15	0.883	0.004	Dermatologic
16	0.875	0.002	UGT2B substrate
17	0.870	0.002	Immunosuppressant
18	0.868	0.004	CYP3A inducer
19	0.846	0.004	UGT1A9 substrate
20	0.833	0.004	CYP3A1 substrate
21	0.822	0.000	Transcortin receptor antagonist
22	0.812	0.004	UGT1A substrate
23	0.812	0.006	CYP3A5 substrate
24	0.812	0.006	CYP3A4 inducer
25	0.807	0.001	UGT2B15 substrate
26	0.804	0.009	Prostaglandin E2 9-reductase inhibitor
27	0.802	0.001	Corticosteroid-like
28	0.791	0.000	Antipruritic, non-allergic
29	0.765	0.000	CYP3A5 inducer
30	0.756	0.004	UGT1A1 substrate
31	0.737	0.005	Autoimmune disorders treatment
32	0.737	0.008	CYP3A2 substrate
33	0.736	0.043	Testosterone 17β-dehydrogenase (NADP+) inhibitor
34	0.735	0.003	Androgen antagonist
35	0.732	0.002	Steroid-like
36	0.727	0.001	Glucocorticoid agonist
37	0.716	0.005	Antipsoriatic
38	0.711	0.005	UGT1A6 substrate
39	0.707	0.000	Arachidonic acid antagonist

The very high probability of activity (Pa) values observed for anti-inflammatory (Pa = 0.985), antiallergic (Pa = 0.962), and ophthalmic anti-inflammatory activities (Pa = 0.958) strongly confirm the classical clinical applications of dexamethasone. These findings align with its widespread use in managing inflammatory, allergic, and immune-mediated conditions, thereby supporting the validity of the *in silico*

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approach employed in this study. The extremely low Pi values further indicate a high confidence level for these predicted activities.

The prediction of antipruritic, antiasthmatic, antiarthritic, and antipsoriatic activities suggests that dexamethasone exhibits a broad anti-inflammatory spectrum affecting multiple inflammatory pathways and tissues. These results are consistent with the drug's capacity to suppress cytokine production, inhibit arachidonic acid metabolism, and downregulate inflammatory gene expression. Notably, the predicted antagonistic activity against arachidonic acid (Pa = 0.707) provides mechanistic insight into dexamethasone's ability to reduce prostaglandin and leukotriene synthesis, which are key mediators of inflammation and pain.

Several predictions related to endocrine modulation, such as glucocorticoid agonist (Pa = 0.727), gonadotropin antagonist (Pa = 0.942), and androgen antagonist (Pa = 0.735), highlight the steroid-like nature of dexamethasone. These activities help explain both its therapeutic benefits and endocrine-related adverse effects, including hormonal suppression during long-term therapy. The prediction of transcortin receptor antagonism (Pa = 0.822) further supports dexamethasone's high affinity for corticosteroid-binding proteins, influencing its distribution and bioavailability in systemic circulation.

The identification of multiple cytochrome P450-related activities, including CYP3A4 substrate (Pa = 0.940), CYP3A inducer (Pa = 0.868), and CYP3A4 inducer (Pa = 0.812), underscores the complexity of dexamethasone metabolism. These findings suggest a significant potential for drug–drug interactions, particularly with medications metabolized by CYP3A enzymes. Such interactions are clinically relevant and may necessitate dose adjustments or careful therapeutic monitoring. In addition, predictions involving UDP-glucuronosyltransferase (UGT) substrates, including UGT1A and UGT2B isoforms, indicate the importance of phase II metabolism in dexamethasone clearance.

The predicted inhibition of enzymes such as prostaglandin E2 9-reductase and testosterone 17β-dehydrogenase suggests possible biochemical interactions beyond primary glucocorticoid signaling. While these effects may contribute to therapeutic outcomes, they could also be associated with metabolic or hormonal side effects. The corticosteroid-like and steroid-like predictions further reinforce dexamethasone's classification as a potent synthetic steroid with wide-ranging biological effects. The PASS Online predictions illustrate that dexamethasone possesses a multifaceted bioactivity profile that extends beyond its primary anti-inflammatory action. The integration of these findings provides valuable insights into its pharmacological versatility, metabolic pathways, and potential adverse effects. Importantly, this *in silico* analysis supports the rational and cautious use of dexamethasone in clinical practice and highlights the need for personalized therapeutic strategies, particularly in patients receiving multiple medications or long-term corticosteroid therapy.

3.2 *Predicted* Target Class *of Dexamethasone Bioactivity*

The predicted molecular targets of dexamethasone reveal a complex and multifaceted pharmacological profile that extends beyond its classical role as a glucocorticoid receptor agonist

Table 2. Predicted Molecular Targets of Dexamethasone

No.	Target	Common Name	UniProt ID	Target Class
1	Androgen Receptor	AR	P10275	Nuclear receptor
2	Glucocorticoid Receptor	NR3C1	P04150	Nuclear receptor
3	Mineralocorticoid Receptor	NR3C2	P08235	Nuclear receptor
4	Progesterone Receptor	PGR	P06401	Nuclear receptor
5	Corticosteroid Binding Globulin	SERPINA6	P08185	Secreted protein

6	ADAM Metallopeptidase Domain 17	ADAM17	P78536	Protease
7	Fatty Acid-Binding Protein, Liver	FABP1	P07148	Fatty acid binding protein family
8	G-Protein Coupled Bile Acid Receptor 1	GPBAR1	Q8TDU6	Family A G protein-coupled receptor
9	Glutamine Synthetase	GLUL	P15104	Ligase
10	Interleukin-6	IL6	P05231	Secreted protein
11	Sex Hormone-Binding Globulin	SHBG	P04278	Secreted protein
12	Adenosine A1 Receptor	ADORA1	P30542	Family A G protein-coupled receptor
13	Adenosine A2A Receptor	ADORA2A	P29274	Family A G protein-coupled receptor
14	Adenosine Kinase	ADK	P55263	Enzyme
15	Anaplastic Lymphoma Kinase	ALK	Q9UM73	Kinase

The identification of multiple nuclear receptors, including the glucocorticoid receptor (NR3C1), mineralocorticoid receptor (NR3C2), androgen receptor (AR), and progesterone receptor (PGR), highlights the structural and functional versatility of dexamethasone as a synthetic steroid. Interaction with the glucocorticoid receptor remains the primary mechanism underlying its potent anti-inflammatory and immunosuppressive effects, achieved through transcriptional regulation of pro-inflammatory and anti-inflammatory genes. However, the predicted interactions with other steroid hormone receptors suggest potential cross-reactivity that may contribute to both therapeutic benefits and endocrine-related adverse effects, particularly during prolonged or high-dose therapy.

The involvement of the androgen receptor and progesterone receptor provides mechanistic insight into the hormonal disturbances often observed with chronic dexamethasone administration, such as alterations in reproductive hormone balance and metabolic regulation. Antagonistic or modulatory effects on these receptors may partially explain side effects including gonadal suppression, changes in secondary sexual characteristics, and metabolic dysregulation. Similarly, interaction with the mineralocorticoid receptor may influence electrolyte homeostasis and blood pressure regulation, contributing to fluid retention and hypertension in susceptible patients. These findings emphasize the importance of receptor selectivity in corticosteroid therapy and support the need for careful clinical monitoring.

The prediction of corticosteroid-binding globulin (SERPINA6) and sex hormone-binding globulin (SHBG) as targets further underscores the role of plasma transport proteins in modulating dexamethasone pharmacokinetics. Binding to these circulating proteins affects the free, biologically active fraction of the drug, thereby influencing its distribution, duration of action, and tissue-specific effects. Variations in binding protein levels among individuals may contribute to interpatient variability in therapeutic response and adverse effects, highlighting the relevance of personalized pharmacotherapy.

Beyond nuclear receptors, the identification of inflammatory and immune-related targets such as interleukin-6 (IL6) and ADAM17 provides additional insight into dexamethasone's immunomodulatory mechanisms. IL-6 is a key pro-inflammatory cytokine involved in acute and chronic inflammatory processes, and its modulation by dexamethasone is consistent with the drug's clinical efficacy in cytokine-driven inflammatory conditions. ADAM17, a metalloprotease involved in the shedding of cytokines and growth factors, represents a potential indirect target through which dexamethasone may regulate inflammatory signaling pathways, further amplifying its anti-inflammatory effects.

The prediction of G-protein-coupled receptors, including adenosine A1 (ADORA1), adenosine A2A (ADORA2A), and GPBAR1, suggests possible non-genomic actions of dexamethasone. These interactions may contribute to rapid cellular responses independent of transcriptional regulation, influencing immune cell activity, vascular tone, and metabolic processes. Modulation of adenosine

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receptors, in particular, may synergize with glucocorticoid signaling to suppress inflammatory responses and regulate immune cell activation.

Metabolic enzymes and binding proteins such as glutamine synthetase (GLUL), adenosine kinase (ADK), and fatty acid-binding protein 1 (FABP1) indicate that dexamethasone may influence cellular metabolism, energy homeostasis, and lipid handling. These interactions may underlie metabolic side effects such as hyperglycemia, dyslipidemia, and altered nitrogen metabolism observed during corticosteroid therapy. Additionally, the prediction of anaplastic lymphoma kinase (ALK) as a potential target raises the possibility of broader signaling pathway interactions, although the clinical relevance of this interaction requires further experimental validation. Predicted targets illustrate that dexamethasone exerts its pharmacological effects through a network of receptor-mediated, enzymatic, and signaling interactions.

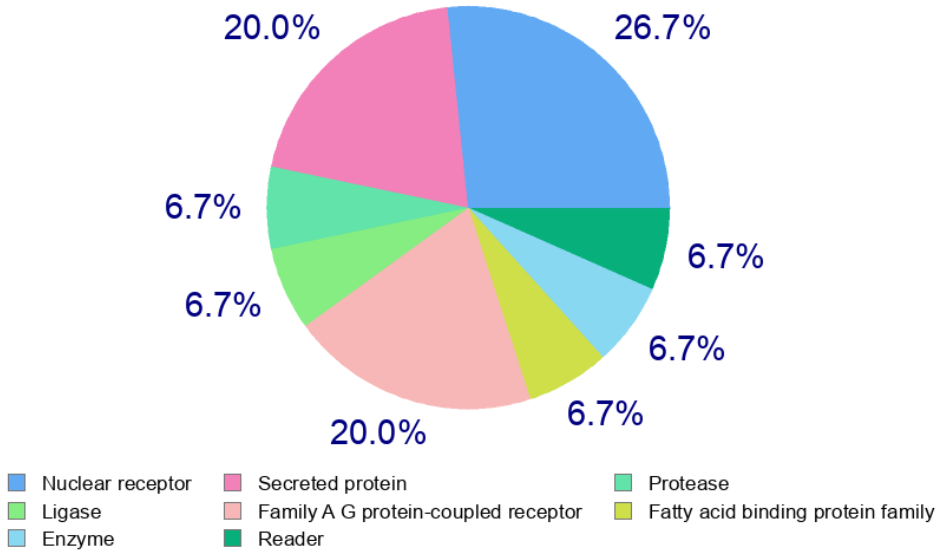

Figure 2. Percentase Target Class Dexamethasone

This *in silico* target profiling provides a valuable framework for understanding both the therapeutic efficacy and adverse effect profile of dexamethasone. The findings underscore the importance of integrative computational approaches in elucidating complex drug–target interactions and support the rational optimization of corticosteroid therapy in clinical practice.

3.3 *Predicted* Target Class *of Dexamethasone Bioactivity*

The predicted ADMET profile of dexamethasone provides important insights into its pharmacokinetic behavior and safety characteristics, which are highly relevant for its clinical use

Table 3. Predicted ADMET Properties of Dexamethasone Using pkCSM

Category	Property Model Name	Predicted Value	Unit
Absorption	Water solubility	−4.147	Log mol/L
Absorption	Caco-2 permeability	0.793	Log Papp (10^{-6} cm/s)
Absorption	Intestinal absorption (human)	81.31	% Absorbed
Absorption	Skin permeability	−3.972	Log Kp
Absorption	P-glycoprotein substrate	Yes	Categorical (Yes/No)

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Absorption	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	Volume of distribution (VDss, human)	−0.078	Log L/kg
Distribution	Fraction unbound (human)	0.381	Fu
Distribution	Blood–brain barrier permeability	−0.695	Log BB
Distribution	CNS permeability	−3.424	Log PS
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	No	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitor	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitor	No	Categorical (Yes/No)
Excretion	Total clearance	0.658	Log mL/min/kg
Excretion	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	No	Categorical (Yes/No)
Toxicity	Maximum tolerated dose (human)	0.097	Log mg/kg/day
Toxicity	hERG I inhibitor	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	No	Categorical (Yes/No)
Toxicity	Oral rat acute toxicity (LD_{50})	2.504	Log mol/kg
Toxicity	Oral rat chronic toxicity (LOAEL)	2.541	Log mg/kg_bw/day
Toxicity	Hepatotoxicity	No	Categorical (Yes/No)
Toxicity	Skin sensitisation	No	Categorical (Yes/No)
Toxicity	*Tetrahymena pyriformis* toxicity	0.299	Log µg/L
Toxicity	Minnow toxicity	2.535	Log mM

From an absorption perspective, dexamethasone exhibits relatively low aqueous solubility, as indicated by the predicted water solubility value of −4.147 log mol/L. This low solubility is characteristic of many steroidal compounds and may limit dissolution in aqueous environments; however, this limitation is offset by its high predicted intestinal absorption of 81.31%. This finding suggests that dexamethasone is efficiently absorbed through the gastrointestinal tract, supporting its effectiveness as an orally administered drug despite its poor solubility.

The predicted Caco-2 permeability value of 0.793 log Papp further supports good membrane permeability, indicating that dexamethasone can readily cross intestinal epithelial barriers. Additionally, the low skin permeability value (−3.972 log Kp) suggests limited transdermal penetration, which is consistent with the controlled absorption required for topical corticosteroid formulations. The prediction that dexamethasone is a P-glycoprotein substrate implies that efflux transporters may influence its absorption and bioavailability. However, the absence of P-glycoprotein inhibitory activity indicates a lower likelihood of transporter-mediated drug–drug interactions at the absorption level.

In terms of distribution, the predicted volume of distribution (VDss) value of −0.078 log L/kg suggests moderate tissue distribution, indicating that dexamethasone is neither highly confined to plasma nor extensively sequestered in peripheral tissues. The fraction unbound value of 0.381 indicates that a substantial proportion of dexamethasone remains bound to plasma proteins, such as corticosteroid-binding globulin and albumin, while still maintaining an adequate free fraction for pharmacological

activity. The predicted blood–brain barrier permeability (−0.695 log BB) and low CNS permeability (−3.424 log PS) suggest limited penetration into the central nervous system, which may reduce the risk of CNS-related adverse effects while still allowing sufficient therapeutic action in peripheral inflammatory conditions.

Metabolism predictions indicate that dexamethasone is not a substrate for CYP2D6 or CYP3A4 according to pkCSM, nor does it inhibit major cytochrome P450 isoforms including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. These findings suggest a relatively favorable metabolic interaction profile, with a lower risk of enzyme inhibition–mediated drug–drug interactions. Although clinical data indicate involvement of CYP3A pathways in corticosteroid metabolism, the absence of strong inhibitory effects supports the safe co-administration of dexamethasone with many commonly used medications, provided appropriate clinical monitoring is applied.

The predicted total clearance value of 0.658 log mL/min/kg reflects moderate systemic elimination, consistent with dexamethasone's known duration of action and dosing frequency. The prediction that dexamethasone is not a renal organic cation transporter 2 (OCT2) substrate suggests that renal transporter-mediated excretion is not a dominant elimination pathway, further supporting hepatic metabolism as the primary route of clearance.

Toxicity predictions reveal a generally favorable safety profile for dexamethasone. The absence of AMES toxicity indicates a low mutagenic potential, while the lack of predicted hERG I and II inhibition suggests a minimal risk of cardiotoxicity related to QT interval prolongation. The predicted maximum tolerated dose in humans and oral rat toxicity values indicate an acceptable safety margin, supporting its long-standing clinical use. Furthermore, the absence of predicted hepatotoxicity and skin sensitization aligns with clinical observations when dexamethasone is used appropriately.The predicted ADMET profile of dexamethasone demonstrates a balance between effective absorption, controlled distribution, manageable metabolism, and a favorable safety profile. These *in silico* findings support the rational clinical use of dexamethasone while highlighting the importance of dose optimization and monitoring, particularly in long-term therapy or polypharmacy settings. The integration of ADMET predictions with bioactivity and target analyses provides a comprehensive framework for understanding the therapeutic and safety characteristics of dexamethasone.

4. Conclusion

This study demonstrates that an integrated in silico approach provides a comprehensive understanding of the pharmacological profile of dexamethasone by simultaneously evaluating its predicted bioactivity, molecular targets, and ADMET characteristics. The PASS Online analysis confirmed the dominant anti-inflammatory, antiallergic, and immunosuppressive activities of dexamethasone with high probability values, while also revealing additional endocrine, metabolic, and enzyme-related activities that may contribute to both its therapeutic efficacy and adverse effect profile. These findings highlight the multifaceted biological actions of dexamethasone beyond its classical clinical indications.

The SwissTargetPrediction results identified a network of relevant molecular targets, particularly nuclear receptors such as the glucocorticoid, mineralocorticoid, androgen, and progesterone receptors, which collectively explain the drug's potent anti-inflammatory effects as well as its endocrine-related side effects. The involvement of inflammatory mediators, G-protein–coupled receptors, metabolic enzymes, and binding proteins further supports the complex mechanism of action of dexamethasone at both genomic and non-genomic levels. This target diversity emphasizes the importance of understanding off-target interactions when optimizing corticosteroid therapy.

The pkCSM-based ADMET prediction revealed favorable pharmacokinetic and safety characteristics, including high intestinal absorption, moderate distribution, limited central nervous system penetration, manageable metabolic interactions, and low predicted toxicity risks. These properties support the long-standing clinical use of dexamethasone while underscoring the need for careful dosing and monitoring, particularly during long-term treatment or in patients receiving multiple medications.

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