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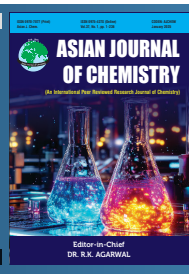

Synthesis and Molecular Docking study of Beclomethasone Dipropionate Derivatives as Glucocorticoid Receptor Inhibitors

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The present study involved the synthesis of four beclomethasone dipropionate (BDP) derivatives with structural modifications at the C9, C11 and C21 carbon atoms and changing the substituents with halogen (Cl & Br) and alkyl moieties. The synthesis was achieved through a series of stepwise reactions and the derivatives were characterized by mass & ^{1}H NMR spectral data and by HPLC analysis. *In silico* molecular docking studies demonstrated that all the synthesized BDP derivatives (**5**, **7**, **9** and **12**) exhibited favourable binding interactions with the glucocorticoid receptor (GR). The docking results revealed that all the BDP derivatives were in good agreement, particularly compound **5**, which had strong binding affinity with the GR protein, comparable to the co-crystal. Based on the results, it was found that all BDP derivatives and its acts as drug-like molecules.

Keywords: Beclomethasone dipropionate, Molecular docking, Glucocorticoid receptor.

INTRODUCTION

Corticosteroids are widely accepted globally due to their potent anti-inflammatory and immunosuppressive properties, making them pharmacologically significant [1]. These compounds like betamethasone, mometasone, beclomethasone and dexamethasone, play crucial roles in dermatology and allergy treatment [2-5] (Fig. 1). Among these, beclomethasone-17,21-dipropionate (BDP) stands out because of its anti-inflammatory potency for asthma management [6]. The lipophilicity and topical anti-inflammatory activity of BDP are enhanced by selective propionylation at the C17 and C21 hydroxyl groups, as compared to beclomethasone [7]. Despite the therapeutic benefits of BDP, it has a few limitations, including low systemic toxicity, reduced bioavailability and low oral absorption (~1%) [8-10]. This limited bioavailability may compromise therapeutic outcomes, necessitating the use of higher doses or combination therapies [11].

The structural modifications to corticosteroids improve receptor affinity, selectivity and therapeutic outcomes. In this regard, synthetic corticosteroids like mometasone furoate exhibit enhanced binding to the glucocorticoid receptor (GR) and higher efficacy compared to cortisol with the introduction of a furoate group at the C-17α position [12,13] (Fig. 1). Similarly, the structural changes in fluticasone and budesonide such as addition of 21α esters and C1-C2 double bonds, respectively, enhance GR selectivity and reduce interactions with mineralocorticoid receptors (MRs) [14]. Such structural modifications may improve efficacy and effectiveness in the anti-inflammatory treatment. On the other hand, the synthesis of such modified corticosteroids remains challenging. For example, Welideniya *et al.* [15] reported the scalability challenges in BDP synthesis, including inconsistent yields and byproduct formation, underscoring the need for process optimization. Despite these advancements, the synthesis of such modified corticosteroids remains challenging.

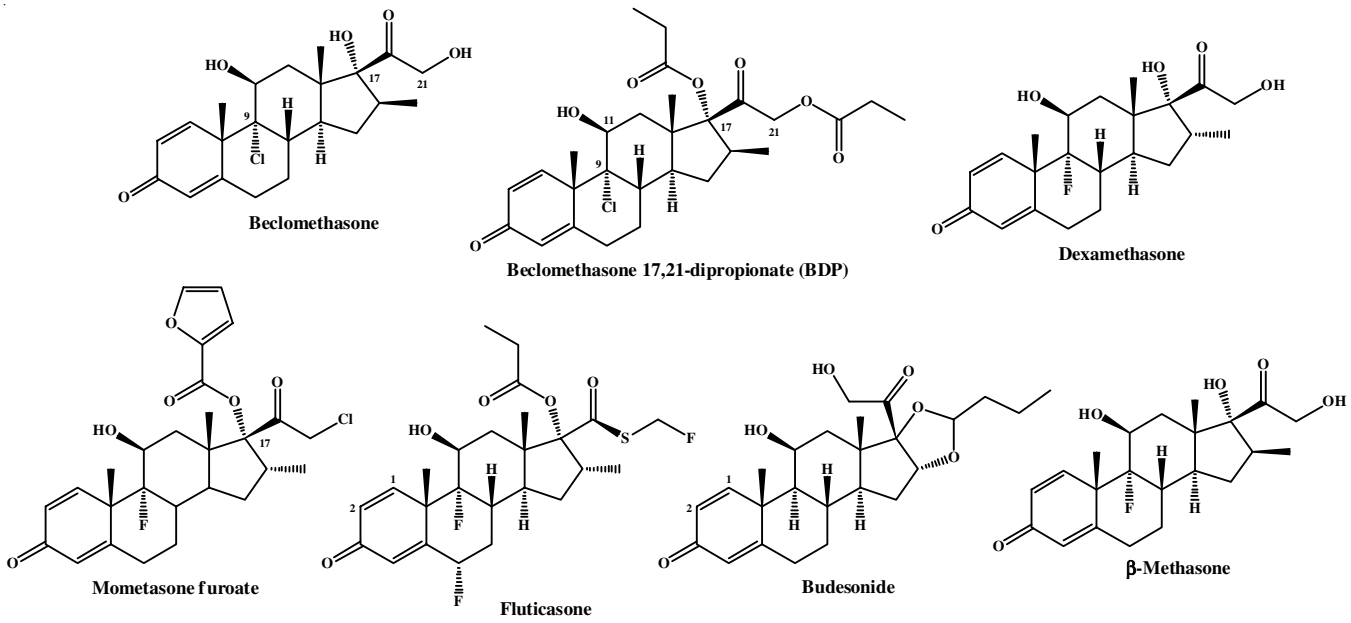


Fig. 1. Chemical structures of some corticosteroids

Based on these findings, four BDP derivatives with structural modifications at the C9, C11 and C21 carbons and changing the substituents with halogen (Cl & Br) and alkyl moieties were synthesized . The structures of BDP derivatives are confirmed by mass & NMR spectral data and HPLC analysis. Additionally, *in silico* the molecular docking studies have been carried out to investigate interactions of such BDP derivatives in the context of human glucocorticoid receptors (GR). BDP and co-crystal ligand are compared with docking scores, Glide energy and hydrogen bonding interactions with active site regions. These studies is to help design next-generation corticosteroids with improved efficacy, safety profiles and optimized therapeutic outcomes.

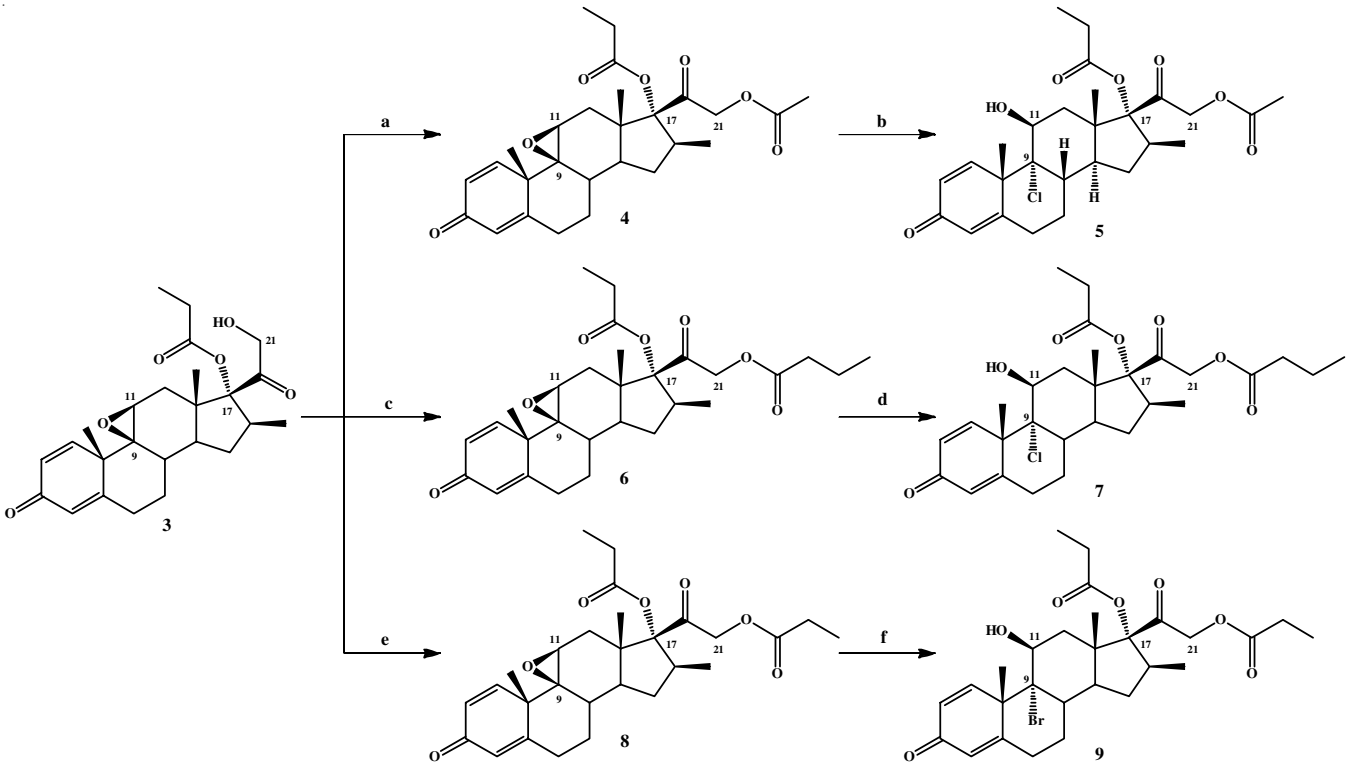
EXPERIMENTAL

All solvents and chemicals were procured from Bldpharm, Chemscene and Hyma without further purification. Thin-layer chromatography (TLC) was performed on Merck silica gel (DC Alurolle Kieselgel 60 F_{254}, 0.2 mm layer) plates in the solvent system. ^{1}H NMR spectra were recorded on a Bruker Avance NEO (NanoBay)-300 MHz spectrometer using DMSO-d_6 or Chloroform-*d* as solvent. Electron impact mass spectra (EI) were obtained using a (LS/MS-APCl) Agilent 1100 MSD spectrometer at 100 eV. Compound purities were determined by HPLC analysis. The HPLC system was equipped with quaternary gradient pumps, an auto-sampler and auto-injector (Shimadzu LC2010CHT, Japan) connected to photo diode array detector controlled with LC solution software (Shimadzu, Japan). A LUNA C18 column, of 250 × 4.6 mm, 5 µ and the mobile phase was used as per the USP monograph method. The eluent was monitored at a wavelength of 254 nm with a flow rate of 1.0 mL/min. All the BDP derivatives were dissolved in mobile phase as diluents and the sample was sonicated for about 5 min; the sample was further filtered through 0.2 µm syringe filter and then injected into HPLC.

Betamethasone 9,11-epoxide (**1**) and beclomethasone dipropionate (BDP) were selected as the starting materials for synthesizing the BDP derivatives due to its low cost and wide availability. Compounds **2** and **3** were synthesized by the reported procedures [16].

Synthesis of 21-(acetyloxy)-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (5): A dry clean round-bottom flask was used to dissolve compound **3** (6.0 g, 14.01 mmol) in 20 mL of dichloromethane. 4-Dimethylaminopyridine (0.17 g, 1.40 mmol) and pyridine (1.35 mL, 16.81 mmol) were added to the reaction mixture at room temperature under an argon atmosphere. After the addition was over, acetic anhydride (1.49 mL, 16.81 mmol) was added dropwise to the reaction mixture and stirred for 20 h. The solution was then poured into water and the organic layer was washed with 1.0 M HCl. The separated organic layer was dried over anhydrous Na_2SO_4. The solvent was removed using a rotary evaporator to obtain the crude product. The crude solid was purified by recrystallization from acetone/pet. ether (2:1) to afford compound **4** in 90% yield (**Scheme-I**). MS (ESI) *m/z* 471.5 $[M+H]^+$.

A dry, clean round-bottom flask was used to dissolve compound **4** (5.0 g, 10.63 mmol) in 50 mL of dichloromethane. The reaction mixture was cooled to 0 ºC and 3 M HCl (25 mL) was added while maintaining the solution temperature below 0 ºC. Then, the temperature of reaction mixture was raised to room temperature and stirring was continued with same for 2 h. Afterward, the reaction mixture was neutralized with 20 mL of saturated $NaHCO_3$ solution and stirred for an additional 2 h. The resulting precipitate was filtered, washed multiple times with deionized water and subsequently washed with cold methylene chloride to obtain product **5** as white solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.19 (d, *J* = 10.2 Hz, 1H), 6.34 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.09 (s, 1H), 4.83 (d, *J* = 16.5, 1H), 4.58 (br. s, 1H), 4.28 (d, *J* = 16.5 Hz, 1H), 2.83



(a) Acetic anhydride, pyridine, DMAP, DCM, 30 °C, 20 h; (b) 3 M HCl (aq.) 30 °C, 2 h; (c) Butyric anhydride, pyridine, DMAP, DCM, 30 °C, 24 h; (d) 3 M HCl (aq.) 30 °C, 2 h; (e) Propionic anhydride, pyridine, DMAP, DCM, 30 °C, 20 h; (f) 70% HBr (aq.) 30 °C, 2 h

Scheme-I: Synthetic routes of compounds **4**-**9**

(dd, *J* = 14.1, 3.3 Hz, 1H), 2.69-2.61 (m, 2H), 2.45-2.37 (m, 3H), 2.27-2.22 (m, 2H), 2.20-2.14 (m, 4H), 1.94-1.83 (m, 4H), 1.75-1.65 (m, 1H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.22-1.17 (m, 5H), 0.99 (s, 3H); MS (ESI) *m/z* 507.1 $[M+H]^+$; HPLC: Retention time (RT) = 11.443 min, purity = 95.01%.

9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxo-17-(propanoyloxy)pregna-1,4-dien-21-yl butanoate (7): A dry, clean round-bottom flask was used to dissolve compound **3** (4.0 g, 7.88 mmol) in 20 mL of dichloromethane. 4-Dimethylaminopyridine (100 mg, 0.78 mmol) and pyridine (0.75 mL, 9.46 mmol) were added to the reaction mixture at room temperature under an argon atmosphere. After the addition was over, butyric anhydride (1.55 mL, 9.46 mmol) was added dropwise to the reaction mixture and stirred for 24 h. The solution was then poured into water and the organic layer was washed with 1M HCl. The separated organic layer was dried over anhydrous Na_2SO_4. The solvent was removed using a rotary evaporator to obtain the crude product. The crude solid was purified by recrystallization from acetone/pet. ether (2:1) to afford compound **6** in 80% yield. MS (ESI) *m/z* 499.6 $[M+H]^+$.

Compound **6** (1.0 g, 2.0 mmol) was taken in a round-bottom flask and the reaction mixture was cooled to 0 ºC and 3M HCl (3.35 mL, 10 mmol) was slowly added to the flask, maintaining the solution temperature below 0 ºC. The reaction mixture was allowed to warm to room temperature for 2 h. The reaction mixture was then neutralized with 20 mL of saturated $NaHCO_3$ solution until neutral conditions were reached and stirred for 1 h. The precipitate obtained was filtered and washed with deionized water (three times), followed by washing it with ethyl acetate to obtain product **7** as white solid (**Scheme-I**). Yield: 70%; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.30 (d, *J* = 9.9 Hz, 1H), 6.24 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.99 (s, 1H), 5.70 (d, *J* = 5.4Hz, 1H), 4.71 (d, *J* = 16.8 Hz, 1H), 4.45 (d, *J* = 17.1 Hz, 2H), 2.75-2.58 (m, 3H), 2.45-2.32 (m, 6H), 2.19-2.06 (m, 2H), 1.89-1.80 (m, 2H), 1.71-1.69 (m, 1H), 1.64-1.50 (m, 6H), 1.23 (d, *J* = 7.2 Hz, 4H), 1.18-1.14 (m, 1H), 1.04 (t, *J* = 8.4, 7.5 Hz, 3H), 0.91 (q, 6H); MS (ESI) *m/z* 535.1 $[M+H]^+$; HPLC: Retention time (RT) = 12.457 min, purity: 99.53%.

Synthesis of 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate (9): In a dry, clean round-bottom flask, compound **3** (1.0 g, 2.23 mmol) was dissolved in 20 mL of dichloromethane. 4-Dimethylaminopyridine (28 mg, 0.23 mmol) and pyridine (0.23 mL, 2.80 mmol) were added to the reaction mixture at room temperature under an argon atmosphere. After the addition, propionic anhydride (0.36 mL, 2.80 mmol) was added dropwise to the reaction mixture and stirred for 20 h. The solution was then poured into water and the organic layer was washed with 1.0 M HCl. The separated organic layer was dried over anhydrous Na_2SO_4. The solvent was removed using a rotary evaporator to obtain the crude product. The crude solid was purified by recrystallization from acetone/pet ether (2:1) to afford compound **8** in 85% yield; MS (ESI) *m/z* 485.5 $[M+H]^+$.

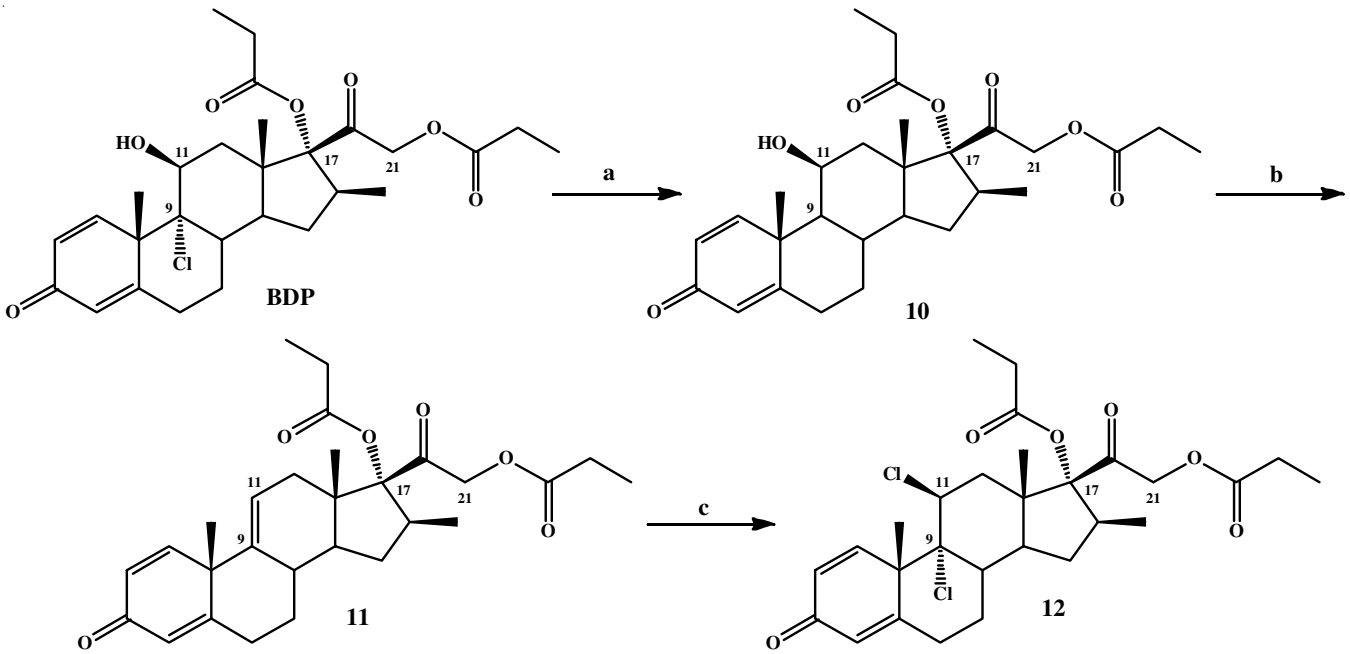
Compound **8** (500 mg, 1.03 mmol) was taken in a round-bottom flask and cooled to 0 ºC in a nitrogen atmosphere and 70% aqueous HBr (10 mL) was slowly added to the flask, maintaining the solution temperature at 30 ºC. The reaction mixture was allowed to stay at the same temperature for another

2 h. The reaction mixture was then neutralized with 40 mL of saturated $NaHCO_3$ solution and stirred for another 1 h. The precipitate obtained was filtered and washed with deionized water, followed by washing with ethyl acetate and methyl *tert*.-butyl ether to afford product **9** as white solid (**Scheme-I**). Yield: 70%; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.31 (s, 1H), 7.33 (d, *J* = 10.2 Hz, 1H), 6.24 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.98 (s, 1H), 5.72 (d, *J* = 5.7 Hz, 1H), 4.71 (d, *J* = 16.8 Hz, 1H), 4.62 (d, *J* = 2.4 Hz, 1H), 4.45 (d, *J* = 17.1 Hz, 1H), 2.82 (dd, *J* = 16.5, 7.5 Hz, 1H), 2.72-2.58 (m, 1H), 2.46-2.36 (m, 4H), 2.34-2.05 (m, 4H), 1.93-1.82 (m, 2H), 1.76 (dd, *J* =13.5, 1.8 Hz, 1H), 1.65 (s, 3H), 1.58-1.48 (m, 1H), 1.27-1.22 (m, 3H), 1.06 (t, *J* =15, 7.5 Hz, 6H), 0.87 (s, 3H); MS (ESI) *m/z* 565.2 $[M+H]^+$; HPLC: Retention time (RT) = 12.060 min, purity: 97.80%.

Synthesis of 9,11β-dichloro-16β-methyl-3,20-dioxo-pregna-1,4-diene-17,21-diyl dipropanoate (12): Beclomethasone dipropionate (2.0 g, 3.83 mmol) was taken in a round-bottom flask and dissolved in 5 mL DMF. The reaction mixture was cooled to 0 ºC and thioglycolic acid (0.32 mL, 4.60 mmol) was added to flask, maintaining the solution temperature below 0 ºC. After 10 min of interval time, 10% aqueous $CrCl_2$ solution (40 mL) was added. The reaction mixture was allowed to warm to 50-55 ºC for 2 h. The reaction mixture was then neutralized with 20 mL of saturated $NaHCO_3$ solution. The organic layers were separated, washed with a saturated NaCl solution and dried with Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on a silica gel column; elution with DCM and methanol (10%) affords compound **10** as white solid (**Scheme-II**). Yield: 50%; MS (ESI) *m/z* 487.60 $[M+H]^+$.

Compound **10** (1.0 g, 2.05 mmol) and pyridine (0.20 mL, 2.46 mmol) were dissolved in DMF (5 mL) at 0 ºC followed by the addition of methane sulfonyl chloride (0.24 mL, 3.08 mmol) dropwise in a round bottom flask. The reaction mixture was stirred at room temperature under argon atmosphere for 1 h; after that the temperature was increased to 90 ºC for another 12 h. After the completion of the reaction, quenched the reaction mixture with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous $NaSO_4$ and the solvent was removed under reduced pressure to obtain the crude product. The crude product was recrystallized by using the *n*-hexane and ethyl acetate (1:1) system to obtain compound **11** (**Scheme-II**). Yield: 60%; MS (ESI) *m/z* 469.59 $[M+H]^+$.

Compound **11** (500 mg, 0.92 mmol) dissolved in chlorobenzene (5.0 mL) at 0 ºC was added to pyridine (0.15 mL, 1.85 mmol) in a round-bottom flask followed by the slow dropwise addition of sulfuryl chloride solution (0.20 mL, 1.39 mmol) for 30 min. The reaction mixture was then allowed to stir at room temperature for an additional 2 h. Then the reaction mixture was quenched with saturated $NaHCO_3$ solution (pH 8). The reaction mixture was extracted with DCM, the organic layer dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using DCM and methanol eluent (10%) to obtain compound **12** as white solid (**Scheme-II**). Yield: 58%; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.27 (d, *J* = 10.2 Hz, 1H), 6.27 (dd, *J* = 8.7, 1.2 Hz, 1H), 6.00 (s, 1H), 5.07 (d, *J* = 2.4 Hz, 1H), 4.75 (d, *J* = 17.1 Hz, 1H), 4.38 (d, *J* = 16.8 Hz, 1H), 3.09 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.87-2.77 (m, 1H), 2.72-2.58 (m, 1H), 2.45 -2.37 (m, 5H), 2.25-2.08 (m, 3H), 1.94-1.86 (m, 2H), 1.70 (s, 3H), 1.58-1.45 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.15-1.11 (m, 1H), 1.04 (q, 6H), 0.96 (s, 3H); MS (ESI) *m/z* 539.2 $[M+H]^+$; HPLC: Retention time (RT) = 12.980 min, purity: 99.70%.



(a) Thioglycolic acid, 10% aq. $CrCl_2$, DMF, 50-55 °C, 2 h; (b) Methanesulfonyl chloride, pyridine, 90 °C, 12 h; (c) Sulfuryl chloride, pyridine, chlorobenzene, 30 °C, 2 h

Scheme-II: Synthesis of compounds **10**-**12**

In silico molecular docking studies

Protein preparation: The three-dimensional structure of the glucocorticoid receptor (GR) was retrieved from the Protein Data Bank (PDB) (PDB id: 1M2Z) [17] and structure was imported to the Maestro workspace, the protein was pre-processed and missing loops were added using the prime module of the Schrödinger suite. The process of hydrogen bond optimization was done using an H-bond optimizer. Water molecules beyond 3.0 Å were removed from the protein structure. The crystal structure of the protein was subjected to minimization of the structural energy and relaxed for the lowest energy conformational state using Optimized Potentials for Liquid Simulations (OPLS-2005) from the Schrödinger suite of tools [18].

Ligand preparation: The ligand preparation was done with Ligprep 2.5 from the Schrödinger suite, which allows for the hydrogen for the ligand, conversion of two-dimensional (2D) to a three-dimensional (3D) structure, realistic bond lengths and bond angles, low-energy structure with correct chiralities, ionization states, tautomers, stereochemistry and ring conformations [19]. Ionization states were generated at pH 7.0 ± 2.0 using an inbuilt Epik module in the Schrödinger suite. Stereoisomers were generated with unassigned stereo genic centers, with a maximum of 32 stereoisomers per ligand. Optimized Potentials for Liquid Stimulations Force Fields (OPLS-2005) were used for minimization; only the lowest energy conformation was kept for each ligand.

Induced fit docking (IFD) method: Glucocorticoid receptor (GR) complex structure was carried out in the molecular docking studies. The active site residual information obtained from the crystal structure of the GR. In order to keep the receptor as flexible for docking studies, a molecular docking protocol called induced fit docking (IFD) were used [20]. The IFD docking studies were carried out in three consecutive steps. In first step, the receptor was kept as rigid and ligands were freely allowed to interact with the receptor. The scaled-down van der Waals (vdW) radii. A vdW scaling of 0.5 was used for both the ligand and the protein. In second step, Prime was used to generate the induced-fit protein–ligand complexes. Each of the structures from the previous step was subjected to side-chain and backbone refinements. All residues with at least one atom located within 4.0 Å of each corresponding ligand pose were included in the Prime refinement. The refined complexes were ranked by Prime energy and the receptor structures within 30 kcal mol^{-1} of the minimum energy structure were put through to a final round of Glide docking and scoring [21]. Finally, the obtained binding poses were evaluated through the Glide empirical scoring function.

RESULTS AND DISCUSSION

Four BDP derivatives, namely beclomethasone 21-(acetyloxy)-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (**5**), 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxo-17-(propanoyloxy)-pregna-1,4-dien-21-yl butanoate (**7**), 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate (**9**) and 9,11β-dichloro-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate (**12**), were synthesized as outlined in **Schemes I-II**. The formation of these compounds has been confirmed by mass, NMR spectral data and purity levels were determined using HPLC analysis. To the best of our knowledge, only the crystal structure was reported for compound **9** from 17α,21-dihydroxy-16β-methylpregna-1,4,9-triene-3,20-dionedipropionate as a key starting material was reacted with 1,3-dibromo-5,5-dimethylhydantoin.

BDP derivatives **5**, **7** & **9** were synthesized from commercially available 16-β-methyl epoxide (**1**) in the steps shown in **Scheme-I**. Step-1 involves the treatment of compound **1** with triethyl orthopropionate in the presence of *p*-toluenesulfonic acid in DMF at 80 ºC for 5 h, which results in the formation of cyclic intermediate **2**. This intermediate was then reacted with aqueous solution of $AlCl_3$ for 12 h to produce the key intermediate, beclomethasone 21-hydroxy 17-propionate (**3**) [16], in the quantitative yields. Further reactions of compound **3** with acetic anhydride, butyric anhydride and propionic anhydride in the presence of pyridine yield epoxide intermediates **4**, **6** and **8**. Of these, compounds **4** and **6** were hydrolyzed by 3 M HCl to give compounds **5** & **7**, respectively. In addition, compound **9** was synthesized by the treatment of compound **8** with 70% aqueous HBr at room temperature, yielding brominated derivative **9**. The synthesis of 1-chlorobeclomethasone 17,21-dipropionate (**12**) involves a 9-deschlorination process starting from BDP. The BDP was reacted with thioglycolic acid in the presence of 10% aqueous $CrCl_2$ solution at 50 ºC for 2 h yielding 9-deschlorination compound **10**. It was then subjected to mesylation and followed by the elimination using methane sulfonyl chloride in the presence of pyridine to give compound **11** with a 60% yield. The synthesis of compounds **10** and **11** was carried out from the modification of the reported procedures [22,23]. Finally, compound **11** was reacted with sulfuryl chloride in chlorobenzene, leading to the formation of 11-chloro beclomethasone-17,21-dipropionate (**12**) with a yield of 58%.

All compounds **2**-**12** and their product formation were confirmed from TLC analysis and its observed required $[M + H]^+$ ion peak in the mass spectra. For compounds **5**, **7**, **9** and **12**, the $[M + H]^+$ values were observed at *m/z* 507.1, 535.1, 565.2 and 539.2, respectively. Particularly, the presence of Cl in compounds **5**, **7** & **12** and Br in compound **9**, was confirmed by its characteristic isotopic patterns consistent with their calculated molecular weight.

In the ^1H NMR spectral data of compound **5**, the introduction of the acetate group at C21 is confirmed by the observation of new signals for the acetate methyl group at δ 2.20-2.14 ppm. Further for compound **7**, the butyrate entry at C21 is confirmed by the observation of the terminal methyl signal at δ 1.04 ppm. For compound **9**, the substitution of Cl to Br on the C9 carbon results in a significant downfield shift of olefinic protons at δ 8.31 ppm due to the electron-withdrawing effect of Br. In compound **12**, the chemical shift of the olefinic proton shifts to deshielded region at δ 7.27 ppm as a result of the substitutions of Cl at C9 & C11 carbons. These specific observations support the structural conformation of BDP derivatives. Furthermore, the HPLC results of compounds **5**, **7**, **9** and **12** show

that the synthesized BDP derivatives have high purity levels, ranging from 95% to 99%.

Molecular docking study: Molecular docking studies were performed on synthesized BDP derivatives (**5**, **7**, **9** and **12**) to investigate their binding affinity. It shows that adding propionate esters at C17 and C21 increased the lipophilicity and potency of BDP, thus to verify this, the docking studies were conducted on beclomethasone and BDP. The crystal structure of glucocorticoid receptor, complexed with dexamethasone (co-crystal ligand), was obtained from the Data Bank.

Docking results were evaluated based on the docking score, glide energy and hydrogen bonds, with parameters are listed in Table-1. Compound **5** having strong docking score and glide energy (-14.89 and -73.50 kcal/mol) is significantly higher than other compounds, even compared to BDP. ASN564 having hydrogen bond interaction its bifurcated with the hydroxy atom and keto group, respectively. And one more bifurcation of methoxy group was having strong interaction with ARG611 & GLN570, respectively. The docking score and glide binding energies for similar cocrystal values of -15.82 and-63.91 kcal/mol, respectively. The docking score and binding energy for BDP were -14.32 and -72.30 kcal/mol, respectively, which are similar to those of the co-crystal (–15.82 and -63.91 kcal/mol).

To analyze the strong binding affinity of protein-ligand interactions, hydrogen bond interactions were analyzed for all compounds. The synthesized BDP derivatives (**5**, **7**, **9** and **12**) formed strong hydrogen bonds with the active site residues of the target protein, with the key amino acids of GLN570, ASN564 and GLN642, respectively. Among these, GLN642 played a crucial role in hydrogen bonding interactions in the active site region of the glucocorticoid receptors for all the compounds, including beclomethasone, BDP and the cocrystal, along with the other aminoacids such as ASN564, THR739 and GLN570, respectively.

The BDP derivatives exhibit favourable key hydrogen bond interactions and binding energetics. Furthermore, the obtained docking results of BDP derivatives are comparable to those of standard drug and co-crystal. The detailed protein-ligand interactions, including key residues involved in the intermolecular interactions, are shown in Fig. 2. The BDP derivatives form hydrogen bonds within the active site of the glucocorticoid receptor. Among all the docked compounds, compound **5** demonstrated the most significant binding contribution through both non-bonded and hydrogen bonding interactions. Thus, the present results show that the synthesized BDP derivatives have a significant potential for inhibiting and binding to the glucocorticoid receptor.

Conclusion

Four BDP derivatives were synthesized and its structures were confirmed using mass & NMR spectral data and purity by HPLC analysis. *In silico* molecular docking studies revealed, all the synthesized derivatives bind effectively within the ligand-binding domain of glucocorticoid receptor. Among the synthesized compounds, compound **5** has shown the most significant binding contribution through hydrogen bonding

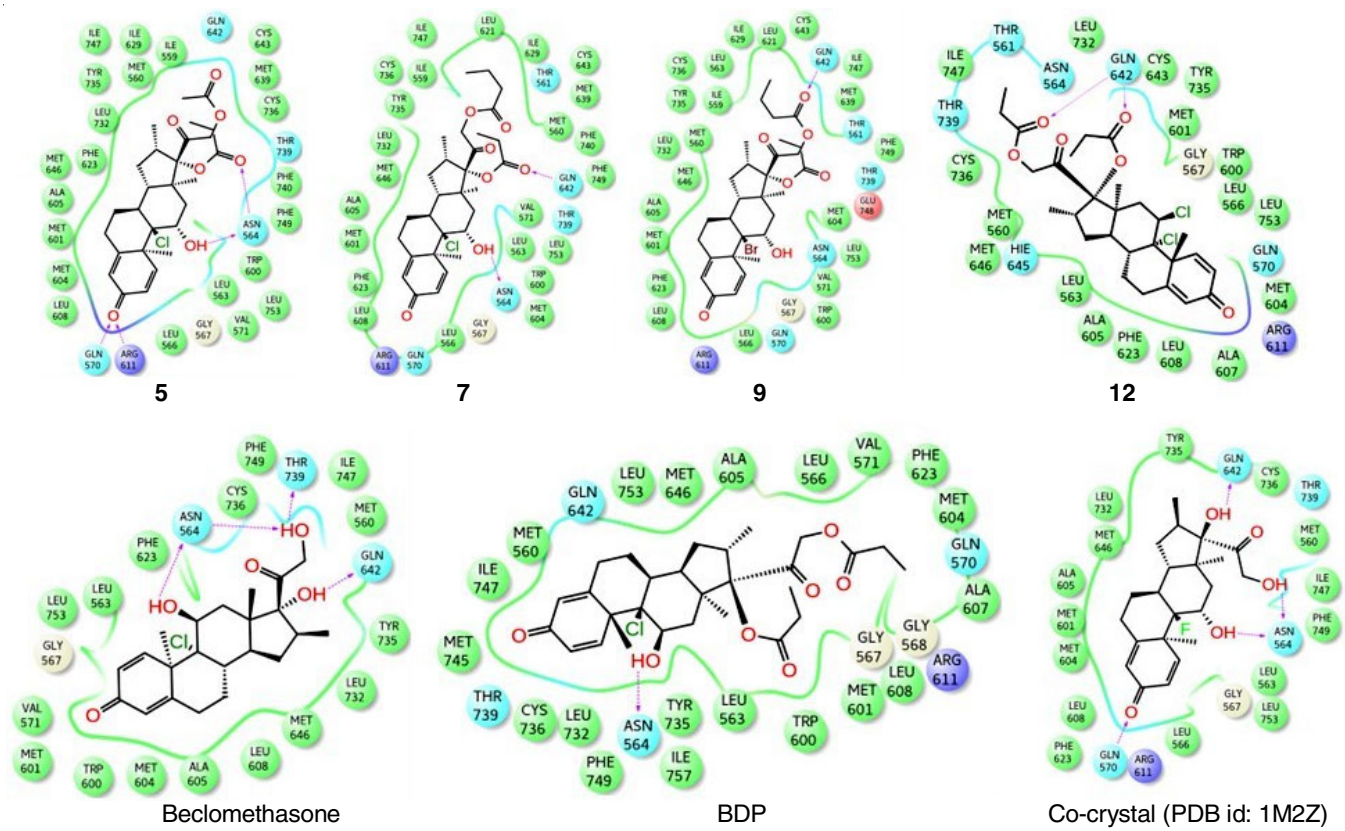


Fig. 2. Key interacting residues involved in the intermolecular interactions of co-crystallized inhibitor of glucocorticoid receptor (PDB: 1M2Z) with the BDP derivatives, beclomethasone and BDP

TABLE-1
DOCKING RESULTS OF COMPOUNDS AGAINST HUMAN GLUCOCORTICOID RECEPTOR

Compounds	Docking score (kcal/mol)	Glide energy (kcal/mol)	Hydrogen bond interactions
5	-14.89	-73.50	**GLN570**, **ASN564**, ARG611
7	-14.44	-75.88	**GLN642**, **ASN564**
9	-14.62	-70.22	**GLN642**
12	-14.75	-63.16	**GLN642**
Beclomethasone	-14.06	-63.33	**GLN642**, **ASN564**, THR739
BDP	-14.32	-72.309	**ASN564**
Cocrystal	-15.82	-63.91	**GLN570**, **ASN564**, **GLN642**

interactions. Overall, beclomethasone dipropionate analogs show promise as potential lead compounds targeting the glucocorticoid receptor.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M. De Bock and P. Sienaert, *World J. Biol. Psych.*, **25**, 161 (2024); https://doi.org/10.1080/15622975.2024.2312572
2. B. Brazzini and N. Pimpinelli, *Am. J. Clin. Dermatol.*, **3**, 47 (2002); https://doi.org/10.2165/00128071-200203010-00005
3. D.H. Kim, H.J. Lee, C.W. Park, K.H. Kim, K.H. Lee, B.I. Ro and S.H. Cho, *Ann. Dermatol.*, **25**, 17 (2013); https://doi.org/10.5021/ad.2013.25.1.17
4. J.S. Vilsvik, A.O. Jenssen and R. Walstad, *Clin. Exp. Allergy*, **5**, 291 (1975); https://doi.org/10.1111/j.1365-2222.1975.tb01865.x
5. E. Nucera, A. Buonomo, E. Pollastrini, T. De Pasquale, M. Del Ninno, C. Roncallo, D. Schiavino and G. Patriarca, *Dermatology*, **204**, 248 (2002); https://doi.org/10.1159/000057891
6. G.D. Raphael, R.Q. Lanier, J. Baker, L. Edwards, K. Rickard and W.R. Lincourt, *J. Allergy Clin. Immunol.*, **103**, 796 (1999); https://doi.org/10.1016/S0091-6749(99)70422-7
7. A. Miller-Larsson, P. Jansson, A. Runström and R. Brattsand, *Am. J. Respir. Crit. Care Med.*, **162**, 1455 (2000); https://doi.org/10.1164/ajrccm.162.4.9806112
8. K. Nishimura, H. Koyama, A. Ikeda, M. Tsukino, T. Hajiro, M. Mishima and T. Izumi, *Chest*, **115**, 31 (1999); https://doi.org/10.1378/chest.115.1.31
9. G. Nicolini, N. Scichilone, A. Bizzi, A. Papi and L.M. Fabbri, *Ther. Clin. Risk Manag.*, **4**, 855 (2008); https://doi.org/10.2147/TCRM.S3126
10. A. Ahmet, H. Kim and S. Spier, *Allergy Asthma Clin. Immunol.*, **7**, 13 (2011); https://doi.org/10.1186/1710-1492-7-13
11. A. Renner, K. Marth, R. Breyer-Kohansal and W. Pohl, *Respir. Med.*, **207**, 107097 (2023); https://doi.org/10.1016/j.rmed.2022.107097
12. Y. He, W. Yi, K. Suino-Powell, X.E. Zhou, W.D. Tolbert, X. Tang, J. Yang, H. Yang, J. Shi, L. Hou, H. Jiang, K. Melcher and H.E. Xu, *Cell Res.*, **24**, 713 (2014); https://doi.org/10.1038/cr.2014.52
13. F. Spada, T.M. Barnes and K.A. Greive, *Australas. J. Dermatol.*, **59**, e168 (2018); https://doi.org/10.1111/ajd.12762
14. G. Caramori, S. Mumby, G. Girbino, K.F. Chung and I.M. Adcock, in eds.: M.J. Parnham, F.P. Nijkamp and A.G. Rossi, Nijkamp and Parnham's Principles of Immunopharmacology, Springer International Publishing, Cham, pp. 661-688 (2019).
15. D.T. Welideniya, A.S. Jayathilaka, A.D. Acharige, K.A.U. Samanthi, U.K. Wanninayake, W. Rajapaksha, C.C. Fernando, M. Hewadikaram, S.S. Perera, J. Buddhika, P. Gunasekara, V. Karunaratne, G.A.J. Amaratunga and D.S. Gunasekera, *Steroids*, **177**, 108948 (2022); https://doi.org/10.1016/j.steroids.2021.108948
16. H. Wang, Z. Niu, Q. Wang, H. Li and J. Su, China Patent CN111944002 (2020).
17. R.K. Bledsoe, V.G. Montana, T.B. Stanley, C.J. Delves, C.J. Apolito, D.D. McKee, T.G. Consler, D.J. Parks, E.L. Stewart, T.M. Willson, M.H. Lambert, J.T. Moore, K.H. Pearce and H.E. Xu, *Cell*, **110**, 93 (2002); https://doi.org/10.1016/S0092-8674(02)00817-6
18. L.L.C. Schrödinger, Schrodinger release 2014-2; New York, NY: Schrödinger, LLC (2014).
19. T. Halgren, *Chem. Biol. Drug Des.*, **69**, 146 (2007); https://doi.org/10.1111/j.1747-0285.2007.00483.x
20. R.A. Friesner, J.L. Banks, R.B. Murphy, T.A. Halgren, J.J. Klicic, D.T. Mainz, M.P. Repasky, E.H. Knoll, M. Shelley, J.K. Perry, D.E. Shaw, P. Francis and P.S. Shenkin, *J. Med. Chem.*, **47**, 1739 (2004); https://doi.org/10.1021/jm0306430
21. H. Wang, R. Aslanian and V.S. Madison, *J. Mol. Graph. Model.*, **27**, 512 (2008); https://doi.org/10.1016/j.jmgm.2008.09.002
22. J.E. Huber and J.A. Fleming, 9α-Dehalogenation Process, US Patent, US5426198 (1995).
23. M.J. Green, H.J. Shue, E.L. Shapiro and M.A. Gentles, German patent CH637406 (1983).