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Selective Glucocorticoid Receptor Modulator: A Novel Class of Anti-inflammatory Compounds

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Authors' contributions

This work was carried out in collaboration between both authors. Author MAA contributed to idea development, design and drafting of the manuscript. Author MA contributed to idea development and design, supervision and submission of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Glucocorticoids exert a wide range of physiological effects. They effectively control various inflammatory and autoimmune diseases and play an important role in organ transplantation. Glucocorticoids are associated with unfavorable side effects that restrict their utilization. The most undesirable side effects are related to the transactivation of target genes. On the other hand, the transrepression of the genes is also responsible for the anti-inflammatory and immunomodulator of glucocorticoids.
Principal Findings: The separation between these two processes through alteration in glucocorticoid receptor resulting in a compound with similar GCs benefit activity with fewer side effects. This review will discuss the molecular mechanism and summarizes the most common compounds and their beneficial effect in preclinical experiments.
Conclusion: Several compounds that possess this feature are tested in preclinical experiments with promising results. These compounds are expected to be a better alternative to GCs drugs in the management of different diseases with a high degree of effectiveness.

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1. INTRODUCTION

Glucocorticoids (GCs) are steroidal hormones that are released and synthesized in the adrenal gland and controlled by the hypothalamic-pituitary-adrenal axis [1]. GCs have an important role in maintaining hemostasis in many body organs. Several types of steroid hormones are associated with different functions. In general, steroid hormones can be categorized into two major classes; the adrenocorticosteroids and adrenal androgens. Furthermore, the adrenocorticosteroids are sub-classified into glucocorticoids (GCs) and mineralocorticoids (MCs) [2]. In humans, GCs are mainly produced as a form of a hormone called cortisol, which plays a role in the regulation of metabolism, cardiovascular function, growth and immunity [3].

In general, GCs are mediated through Glucocorticoid Receptors (GR). GCs bind GR to form an active GCs/GR complex. Following this interaction, the ligand-GR receptor migrates into the nucleus and interacts with Glucocorticoids Response Element (GRE) or other transcriptional factors and thus, enhances the transcriptional of anti-inflammatory genes (transactivation) [4]. It has been documented that transactivation process is responsible for the most adverse effects of GCs such as hyperglycemia, muscle atrophy and osteoporosis [5,6]. On the other hand, GCs/GR complex inhibits the transcription of proinflammatory genes (transrepression) which result in the suppression of many pro-inflammatory cytokines and inflammatory mediators such as Interleukin-6 (IL-6), Interleukin-12 (IL-12), Tomer Necrosis Factor (TNF), and prostaglandin E2 [7-11]. This transrepression activity of GR is a different pathway that responsible for the anti-inflammatory effect of the GCs with fewer and less severe side effects [12,13].

Therapeutic use of exogenous GCs is considered an effective treatment of various inflammatory and autoimmune diseases such as asthma, rheumatoid arthritis, systemic lupus erythematosus, nephrotic syndrome, ulcerative colitis, and ocular inflammation [14]. GCs are one of the major drugs that have a significant impact in reducing organ or graft rejection following transplant therapy. These drugs are also important in the treatment of allergic reactions and anaphylactic shock [15]. Moreover, GCs are used to treat different kinds of disorders such as dermatological disorders (e.g. acute contact dermatitis, erythema multiforme, herpes zoster), adrenal endocrine disorders (e.g. adrenocortical insufficiency and congenital adrenal hyperplasia) [16], neoplastic diseases (e.g. acute and chronic leukemias, Hodgkin's disease), and neurologic conditions (e.g. cerebral edema, brain tumor, acute spinal cord injury) [15].

Several side effects associated with GCs treatments have been reported especially with high dose or chronic use. The most common side effects are diabetes, skin atrophy, osteoporosis, glaucoma, peptic ulcer muscle wasting, hypertension, behavioral alterations, and inhibition of wound repair [17,18]. More than two weeks of GCs treatment can cause the suppression of the hypothalamic-pituitary-adrenal axis, which in turn prevent the natural production of GCs in the adrenal gland if GCs treatment is abruptly stopped [4]. It might take from 2-12 months to restore this axis to work properly after its suppression with GCs treatment [4]. Several symptoms of GCs withdrawal may appear including anorexia, lethargy, postural hypotension, and muscle pain [4].

GCs is essential in the management of a variety of diseases with high efficacy profile, however, it has a wide range of side effects that restrict its utilization. For these reasons, it was important to discover new therapeutic approaches that aim to maintain the same pharmacological effect of GCs while minimizing the unwanted side effects. One of these approaches takes advantage of the pharmacological compounds that capable to dissociate transactivation from transrepression on GR known as selective glucocorticoid receptor agonists or modulators (SEGRAs) or (SEGRMs) [15,18]. This review will cover and summarize the most common types of these compounds.

2. MOLECULAR MECHANISM OF GLUCOCORTICOID RECEPTOR

Glucocorticoid receptor (GR) presents mainly intracellular of many human cells [15] and consists of the N-terminal domain responsible for the transactivation process, DNA binding domain, and C-terminal ligand-binding domain [15]. While the mineralocorticoids receptor (MR) mainly present in secretory organs such as the kidney colon, salivary, and sweat glands [19].

Additionally, during the splicing of GR protein, different isoforms will be generated, not all of these isoforms are functionally active [15]. Different mechanisms of action are described [20,1] to explain the therapeutic effect of glucocorticoids. During the absence of GCs, the inactive cytosolic GR bind to Heat Shock Proteins (HSPS). However, GCs is a lipophilic molecule that can diffuse the cell membrane and binds with cytoplasmic GR [15]. After GCs bind to the ligand-binding domain at GR to form an active GC/GR complex. This complex is translocated and binds to specific DNA binding sites referred to as glucocorticoid-responsive components (GRE) or binding other transcriptional factors [4]. The GR binding as a homodimer with GREs mediating transcription of anti-inflammatory genes such as Interleukin-10 (IL-10), Interleukin-4 (IL-4), and transforming growth factor- *β* (TGF-*β*). (this process called Transactivation) [11,21]. It has been documented that, transactivation process is responsible for the most adverse effects of GCs [5] such as hyperglycemia, muscle atrophy, and osteoporosis [6]. GC/GR complex, on the other hand, either interacts as a monomer directly by combining with these transcription factors[7] or GC/GR homodimer binding with Negative GRE (nGRE) mediating repression in transcription factors [8,9] (this process called Transactivation). These factors regulate the expression of pro-inflammatory genes. As a result, translocation is inhibited [10] together with the suppression of many pro-inflammatory cytokines and inflammatory mediators such as IL-6, IL-12, TNF, and prostaglandin E2 [11]. The transrepression activity of GR on the transcription factors is responsible for the anti-inflammatory effect of the GCs with few side effects. Also, there are coregulator factors that could induce or inhibit the transcription of different genes. GCs can regulate the expression of about10-20% of the genes in human cells. The physiological effect of GCs mainly resulted from the protein synthesis after transcribing of mRNA of target genes [4]. Unfortunately, GCs (specific cortisol) can bind to MR with the same affinity as the aldosterone. However, this effect could be abolished in tissue that has 11β-Hydroxysteroid dehydrogenase type 2 enzyme responsible for the biotransformation of cortisol into cortisone [4]. Consequently, the affinity toward the MR was significantly reduction in cortisone compared with the cortisol [4].

On the other hand, the non-genomic mechanism is complex and not fully understood [22]. The interaction of GCs by non-genomic results in rapid immunosuppressive and anti-inflammatory is compared with the regulation of transcription of a specific gene [20,22]. Several mechanisms could explain the process of non-genomic interactions include GCs interacts with lipid membrane resulting in a change in physicochemical properties [23], interaction with GR receptor, which related to the classical GR receptor, located at the cell membrane, interaction with other cell membrane receptor which is a G-coupled protein signal through of Cyclic adenosine monophosphate (Camp) [24], or others [25,26,27,28]. Morgan et al. showed there is a GR isoform present in the mitochondria and also plays a role in regulating cell energy, and metabolism in a ligand-independent manner [29].

The affinity of the SEGRMs ligand such as Abbott-Ligand (AL-438) and ORG-214007 forward GR have been shown a higher binding affinity than prednisolone [15]. Additionally, the LGD-5552 compound binds to the GR receptor with high efficacy and potency demonstrated through competitive binding assay [30] Furthermore, Compound A (CpdA) exhibit a high binding affinity for GR compared with dexamethasone [17]. Also, study has been demonstrated the ability of compounds CpdA and ZK-216348 to induce nuclear translocation of GR in a similar to dexamethasone. The nuclear level of CpdA was reduced compared to dexamethasone [31].

The separation between transactivation and transrepression for these compounds could explain by several mechanisms on GR. According to crystallography analysis, compound 10 was able to bind on the second meta channel on GRs lead to potential separation in transrepression and transactivation activity [32]. Another crystal structure study has been shown compound 10 has a novel structure conformation change following binding at ligand-binding domain at GR receptor [33] enhances the selectivity toward transrepression more than transactivation. Additionally, the Dimeric binding of GCs with GR at a DNA binding site is associated with an increased transcriptional of anti-inflammatory proteins [9,34]. However, the monomeric binding to GR also showed repress the proinflammatory genes either through binding to negative Glucocorticoids response element (nGRE) or direct combines with transcriptional factors nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) or Activator protein 1

(AP-1) [35,36]. Animal models induced loss in GR dimerization is achieved either GR dimerization-deficient (GR^{dim}) mice [37] or through using monomeric ligand such as CpdA [38]. A study showed a significantly reduction side effect profile of dexamethasone together with maintaining the anti-inflammatory activity. Diabetogenic and osteoporosis of GCs were tested in the animal models mentioned before. The diabetogenic neither shown in GR^{dim} mice using dexamethasone nor with CpdA treated mice which explains that some side effects of GCs required GR dimerization. Unexpectedly, osteoporosis appears in GR^{dim} mice [39,40] and not induced with CpdA in both *in-vivo* and *in-vitro* models [41,42]. Loss of GRs dimerization in GR^{dim} mice has been shown to prevent the development of gastrointestinal side effects of dexamethasone [43]. However, dexamethasone still induces muscle atrophy to a similar degree in GR^{wt} and GR^{dim} mice [44]. Besides, CpdA inhibits skin irritation and hyperplasia together with an increase rather than decrease skin epidermal thickness [45].

SEGRAs or SEGRMs bind to the glucocorticoid receptors (GRs) which undergoes a conformational change in structure, this leads to GR induce transrepression more than transactivation of the target gene [15]. It is a hypothesis that the anti-inflammatory activity is linked to the transrepression mechanism of glucocorticoids receptor while the side effect such as hyperglycemia and muscle wasting mediate by the transactivation of glucocorticoids receptors. However, some side effects such as osteoporosis mediated by both mechanisms [46, 47]. Therefore, these compounds retain the therapeutic effects of glucocorticoids with fewer side effects that appear with chronic treatment or high doses of classic glucocorticoids.

3. SELECTIVE GLUCOCORTICOID RECEPTOR AGONISTS SEGRAS

Compounds that can bind and activate a partial part of the effect refer to dissociation Selective glucocorticoid receptor agonists or SEGRAs or SEGRMs [15]. According to chemical structure, compounds that have a steroidal nucleus referred to by SEGRAs and consider the first generation. While, the term SGRMs is used for a non-steroidal compound [48,15]. The anti-inflammatory activity of these compounds was tested in many preclinical animal studies.

3.1 Compound A

Compound A is a non-steroid plant-derived phenyl aziridine precursor, it has an affinity to GR non-dimer binding, it does not activate the GRE gene indicated to dissociated activity [17], and unable to produce transactivation of the inflammatory genes [6]. A study has been shown CpdA has a narrow therapeutic index that is a restriction uses for research purposes [49,15]. Additionally, the narrow therapeutic index was demonstrated through induced apoptosis by enhanced production of a reactive breakdown product known as aziridines at a concentration ≥ of 15 μM [50]. [31]. Reuter et al. compared CpdA with dexamethasone in mice to treat experimentally induced inflammatory bowel disease (IBD). The experimental resulting CpdA exerts potent anti-inflammatory action with no major side effects experienced related to conventional GCs such as glucocorticoid resistance, diabetes, and suppression of the hypothalamic-pituitary-adrenal axis [50,51]. Also, the expression of A mitogen-activated protein kinase (MAPK) and Annexin-1 was measured as a result of the biomarker of the transactivation process. These biomarkers were significantly reduction in SEGRAs (CpdA and ZK-216348) compared with Dexamethasone [31]. Another cell type shown these two SEGRAs compounds induce LDH after the concentration reach and above 15 μM [31]. Also, these SEGRAs products did not inhibit the migration of cells and subsequently enhance the wound closure compared to Dexamethasone [31].

Furthermore, CpdA was evaluated for the treatment of inner ear disorders and ototoxic effects in guinea pigs [52]. The experiment revealed it has a promising new therapeutic application for the treatment of inner ear disorders effect with a minimum metabolic side effect. Additionally, CpdA was tested in experimental autoimmune neuritis (EAN) [53]. EAN is a helper T cell-mediated autoimmune disease in the peripheral nervous system. Interestingly, CpdA attenuates inflammation and suppressed EAN, and concomitantly stops the progression of neuropathic pain. CpdA did not elevate the blood glucose level in rats when compared to a classical GCs prednisolone [53]. Indeed, CpdA did not inhibit the proliferation of osteoclast activity [54]. Also, the cells' lack of GR did not inhibit proliferation even by dexamethasone [54]. Besides, CpdA has exhibited an anti-inflammatory effect through it can prevent ovalbumin induces airway

hyperresponsiveness and decrease inflammatory cells to infiltration. Also, these effects depend on present a sufficient level of GR [55].

3.2 RU Compounds

These compounds are considered prototyping of dissociated receptors discovered by Roussel Uclaf [6]. They are synthetic steroidal compounds such as RU- 24782 [6]. Belvisi et al. provide evidence of these compounds have a potent GR affinity with dissociated of the transrepression more than transactivation. However, RU-24858 failed to improve the side effects *in-vivo* model compared with prednisolone and budesonide [56]. Coghlan et al. [57] confirmed RU-486, GR antagonist, did not elevate blood glucose as similar to the control group. However, prednisolone significantly elevated blood glucose [57].

3.3 ZK Compounds

ZK are non-steroidal compounds with the GR-dissociation effect. The *in-vitro* model described this compound as SEGRA after decreased the Interleukin-8 (IL-8) with a 2-fold lower potency and affinity in cells line as transrepression evaluation. However, it around 60-fold and 300 fold less than prednisolone and dexamethasone respectively in tyrosine aminotransferase (TAT), transactivation assessment, in hepatoma cells [13]. In the human cell line, ZK-216348 showed the same result [13]. Additionally, human leukemia cells showed a reduction in IL-8 (2-fold) and TAT (60-fold) expression compared with prednisolone [6]. Also, the anti-inflammatory effects of CpdA and ZK-216348 were assessed in cytokine-stimulated cells, these compounds and dexamethasone-induced significant reduction of P65 after cytokine-stimulated cells indicated the transrepression activity. Additionally, the anti-inflammatory activity determined by shown the SEGRAs and dexamethasone a significantly decreased in nuclear P65 protein expression together with enhancing cytosolic inhibitor of the NF-κB (IkB-a). Furthermore, these SEGRAs compounds were concentration-dependent inhibit of IL-8 [31]. On the other hand, both compounds showed less transactivation potency and effectively inhibited NF-κB activity and IL-8 secretion. Furthermore, SEGRAs showed fewer side effects regarding the wound healing process [31]. However, *in-vivo* rats study, topical application of ZK-216348 showed less anti-inflammatory activity ear inflammation induced by croton oil in rats model. While mice showed similar efficacy of prednisolone [13]. Indeed, markedly superior in hyperglycemia, skin atrophy, and thyme involution. On the other hand, Hypothalamus-pituitary Adrenal axis suppression in both agents [13]. Also, ZK had a less potent effect on the osteoblast cell line suggesting a reduced effect on bone [42]. Additionally, Reuter et al. compared ZK-216348 with dexamethasone in mice to treat experimentally induced inflammatory bowel disease (IBD). The experiment results showed ZK-216348 possesses potent anti-inflammatory action with no major side effects experienced during the use of conventional GCs, like glucocorticoid resistance, diabetes, and suppression of hypothalamic pituitary adrenal axis activity [51].

Another ZK-245186 (also known as Mapracorat or BOL-303242-X) has, similar to ZK-216348, in affinity to GR with a dissociated profile. Neither elevated in blood glucose nor spleen involution. The efficacy was demonstrated in Lipopolysaccharide (LPS)-induced secretion of cytokines mediators [58]. Also, *in-vivo* showed this compound has potent anti-inflammatory activity against contact dermatitis [58]. Together, ZK-245186 has low bioavailability and a shorter half-life. Thus, these properties make it a good candidate as a topical anti-inflammatory in contact dermatitis [58]. In 2016 published research, the effect of ZK-245186 was tested against another conventional GCs (triamcinolone acetonide) using a skin inflammation model in dogs [59]. The obtained results showed that it has anti-inflammatory potency comparable to conventional GCs with a minimum side effect on the skin. Indeed, the anti-inflammatory effect of ZK-245186 in various primary human ocular cells were tested [60]. The new compound showed comparable efficacy to GCs (dexamethasone) or (triamcinolone acetonide) [60]. A study also demonstrated the NF-κB and AMPK signaling are involved in the mechanism of the anti-inflammatory activity of this compound. Together, it has been improved the safety profile by decrease the intraocular pressure through decrease the protein level of myocilin in monkey trabecular meshwork cells compared with dexamethasone [61]. Another study uses different primary human ocular cells to demonstrate the anti-inflammatory activity of ZK-2452186. Also, it was tested on sensitized guinea pigs 2 hours after subjected to allergic conjunctivitis with the objectives of investigating its activity in decreasing ocular clinical signs and

determining the mechanism of action in reducing the inflammatory mediators [62]. Mapracorat possesses more efficacy than dexamethasone and has better anti-allergic activity demonstrated the late phase of the disease [62]. The animal study demonstrated that the transgenic mice treated with dexamethasone intraocular versus normal mice, a study showed the mice resistance to develop glaucoma significantly compared to normal mice [63]. In line with the results of the above-mentioned experiments, mapracorat demonstrated an anti-inflammatory effect *in-vitro* by inhibiting cytokine secretion and T cell proliferation [64]. Besides, this efficacy was also documented *in-vivo*, in mice and rats, for the topical treatment of inflammatory dermatitis. The compound possesses a good safety profile compared to the classical GCs, (mometasone furoate) and (methylprednisolone acetate) [64]. ZK-245186 is introduced in clinical trials for Atopic Dermatitis as well as in ophthalmic applications [58, 65].

The strong transrepression and weak transactivation properties of other SEGRAs compound called ZK-209614 were reported *in-vitro* assays [66]. This compound also showed both anti-inflammatory and anti-allergic actions when given as eye drops without elevating the intraocular pressure [66].

3.4 Abbott-Ligand

Abbott-Ligand (AL-438) is a non-steroidal compound that has a higher affinity for GR receptors compared with classical GCs. It could be an effective alternative anti-inflammatory agent to GCs, especially in children without growth retardation seen with GCs [67]. Also, AL-438 showed less phosphorylation of S211 and S226 in GR compared with classical GCs. Activated of these residuals by GCs resulting to inhibit the maximum transrepression effect on NF-κB and AP-1 promoter [68]. Additionally, it has more efficiently repressed the AP-1 gene [69].

Coghlan et al [57] demonstrated that AL-438 protects the osteoblast activity in cancellous bone with a small inhibition bone formation in cortical bone in the arthritis rats model [57]. Furthermore, AL-438 did not inhibit osteocalcin in the human osteoblast cell line [57] In contrast to prednisolone, AL-438, and RU-486 (non-selective GR antagonist) treated groups the blood glucose remains with a normal range similar to control groups. Also, these compounds prevent hyperglycemia in pretreated animals with prednisolone [57]. The molecular mechanism of GC-induced hyperglycemia could be through an increase in the transcriptional of peroxisomal proliferator-activated receptor γ coactivator-1 (PGC-1). However, a study showed the AL-438/GR complex could attenuate GR binding to the PGC-1 cofactor [57].

3.5 LGD-5552

LGD-5552 is a non-steroidal SEGRMs and has an affinity for MR receptors with the antagonized property. Miner et al. tested LGD-5552 activities *in-vitro* and *in-vivo* models. According to *in-vitro*, LGD-5552 has a high affinity to GR receptor-like prednisolone and less than dexamethasone. It showed repression of the transcriptional factors of the inflammatory gene with a similar extent to dexamethasone. However, LGD-5552 increases the transactivation of the PEPCK gene at a dose ≥ of 1.0 μM. In contrast to prednisolone, LGD-5552 prevents the PDK4 gene transcription at any dose [70]. While *in-vivo*, LGD-5552 has a similar benefit anti-inflammatory effect in arthritis induced by collagen [30] Freund's complete adjuvant intradermally [71], acute and chronic models of inflammation [6], and experimentally encephalitis induced by autoimmune multiple sclerosis model [71]. Interestingly, LGD-5552 did not alter the percentage of the body fat, and bone formation rate except at high dose (30mg/kg) [30]. Additionally, elevated in the main arterial blood pressure was unchanged at low dose LGD-5553 groups (1 & 3 mg/kg). While on the high dose, LGD-5553, elevated main arterial blood pressure with a less potent compared to prednisolone [71] this might exhibit through antagonized of MR. Furthermore, prednisolone significantly reducing body weight could be secondary to decrease muscle mass or suppression of appetite in rats [72, 73]. However, LGD-5553 is a less potent inhibition of the reduction of body weight compared to prednisolone. Also, it showed less impact on growth which might be a potential benefit in the children population [71]. Also, a study showed suppression of the adrenal gland in rats by both agents, LGD-5553 10-fold less potent at inhibiting the size of the adrenal gland compared to prednisolone [71]. Interestingly, LGD-5553 has a good pharmacokinetic profile after the oral administration compared to prednisolone in Sprague Dawley rats [71] and it could be a better GCs alternative [6].

It still needs more to be investigated, what is the effect of other SEGRMs, such as AL-438, PF-

802, Org-214007-0, and LGD-5552 on muscle and skin metabolism [74].

3.6 Ginsenoside Rg1

Ginsenoside Rg1 is a natural compound that has structural similarity to GCs and function related to binding with the GR receptor [75,76]. It considers another SEGRAs compound, was compared *in-vivo* study with GCs (dexamethasone) [77]. Ginsenoside Rg1 demonstrated a better therapeutic index in inhibition of acute and chronic inflammation without causing hyperglycemia or osteoporosis as seen with dexamethasone [77]. A recent study proved the anti-inflammatory effect without tissue regeneration of Ginsenoside Rg1 on the zebrafish model [78]. These results are related to the selective GR agonist action of Ginsenoside Rg1 [78].

4. GLUCOCORTICOID RESISTANCE

Resistance to GCs treatment is the most common GCs related problem resulting in either disease progression or an increase in the GCs dose [79]. The resistance could be inherited [80] or acquired. However, the acquired can develop by downregulation of GR receptors after continuous or repeated administration of the ligands [81,82,83]. Indeed, drug tolerance is primarily controlled by the cytosolic free GR density [38]. The reduction of receptor density achieved either decrease the de novo synthesis of the GR or increase the receptor degradation [83]. There were a few data describe the implication of GR dimerization on GCs resistance. Arthritis induced mice study has been shown dexamethasone-induced significant downregulation in GR compared with GR^{dim} mice [84]. Moreover, CpdA prevented downregulation of GR proteins or mRNA levels [38]. Also, ZK-216348 prevented the downregulation of GR protein level, despite no data on dimerization [50, 38]. In conclusion: a study has been shown downregulating the GR receptor achieved follow dimerization of the receptors. It is approved by using dimerization promoting ligands lead to a significant downregulation of the receptors, by increase the rate of turnover and decrease the half-life. On the other hand, prevent of dimerization of either GR^{dim} or CpdA leads to severely restricted receptor turnover. Also, the half-life of GR after binding to CpdA was very similar to that of unliganded GR. The mechanism of CpdA induced resistance differs from dimerization deficit GR^{dim} mice [85].

5. CONCLUSION

Although the pharmacological efforts of the last decade have led to an increase in new and selective GR modulators. This selectivity leads to the discovery of new compounds known as SEGRAs or SEGRMs that favor and retains the positive anti-inflammatory and anti-allergic effects of GCs drugs while reducing the adverse effects, their basic mechanism largely remains unknown, so it justifies further research in this field. Several compounds that possess this feature are tested in preclinical experiments with promising results. In the near future, these compounds are expected to be a better alternative to GCs drugs in the management of different diseases with a high degree of effectiveness.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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