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# Soft Glucocorticoids: Eye-Targeted Chemical Delivery Systems (CDSs) and Retrometabolic Drug Design: A Review

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## 1. Introduction

Steroids play a vital role in human physiology and medicine. Glucocorticoids have dominated the class of anti-inflammatory agents quite successfully over other drugs since their introduction to dermatology more than fifty years ago. Later they have been developed both as topical and systemic anti-inflammatory agents. From studies it has been found that glucocorticoids normally release their anti-inflammatory effects mainly through the modulation of the cytosolic glucocorticoid receptor (GR) at the genomic level [1, 2]. The activated glucocorticoid-GR complex formed *via* binding of glucocorticoid with the GR in the cytoplasm, migrates to the nucleus, where it upregulates the expression of anti-inflammatory proteins and repress the expression of pro-inflammatory proteins. In some recent work, it has been reported that the activated glucocorticoid-GR complex has also been found to initiate nongenomic effects like inhibition of vasodilation, vascular permeability and migration of leukocytes [1, 3]. Glucocorticoids also mediate anti-inflammatory activity through membrane-bound GR-mediated nongenomic effects and also through direct non specific interaction with cellular membranes [3, 4]. Since GR is involved in a plethora of signalling pathways, more than 5000 genes are expressed or suppressed following glucocorticoid exposure [4, 5]. Therefore long term use or high dosages of glucocorticoids could result in adverse drug reactions (ADRs) like increased Intraocular Pressure (IOP) [6, 7] in ocular therapeutics. Glucocorticoids- induced ocular hypertension is of great concern in ophthalmic therapeutics as it can lead to secondary iatrogenic open-angle glaucoma. Glaucoma is a group of eye diseases characterized by progressive optic nerve cupping with visual field loss leading to bilateral blindness. It has been reported that glaucoma is estimated to affect more than 50 million people worldwide as defined by the World Health Organization (WHO) [8].

However, the use of corticosteroids has become more and more restricted and unacceptable because most of these agents are found to be associated with severe side effects, including percutaneous absorption and cutaneous atrophy [9]. Also allergic contact dermatitis is an unexpected adverse effect in most of these corticosteroids. On the other hand because of their high efficacy, their use is inevitable to give them the status of life saving drugs. The severe side effects associated with these glucocorticoids, has led to the pharmaceutical industry to make a productive effort towards the introduction of new generation of topical corticosteroids with specific substituents in their parent molecules to make them safer in comparison to the old generation glucocorticoids [10].

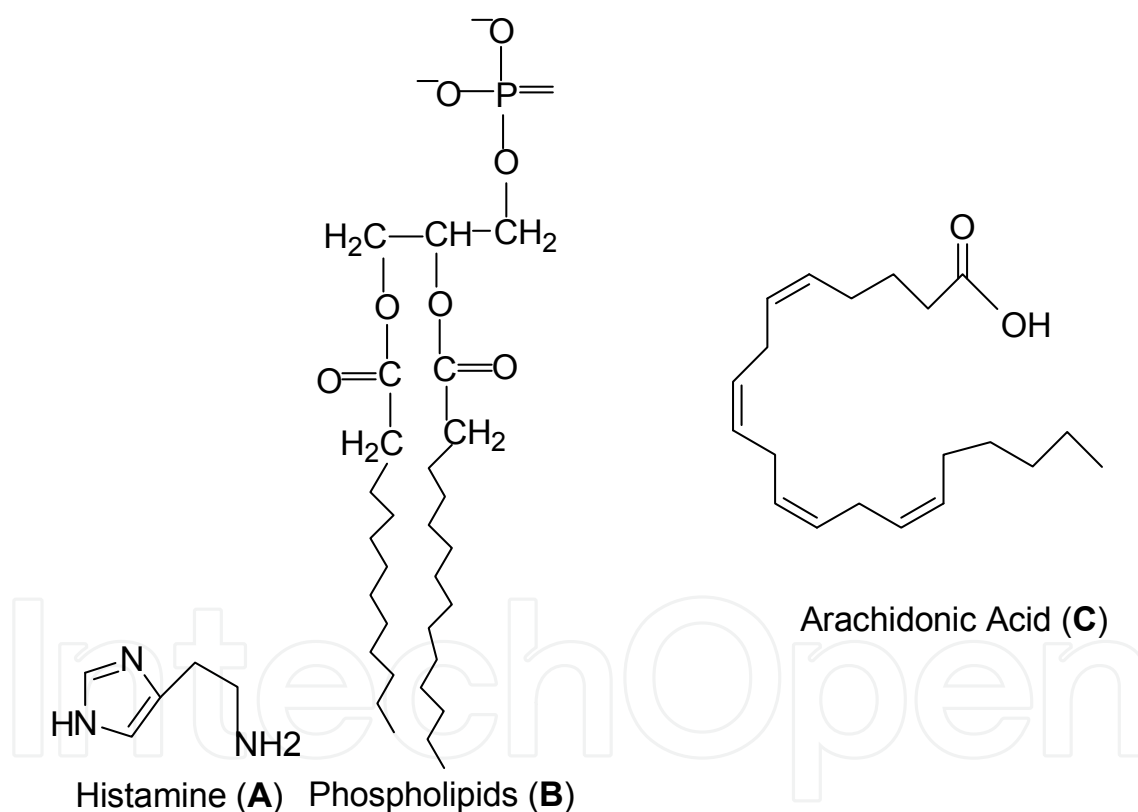
The effectiveness of hydrocortisone was first demonstrated by Sulzberger and Witten during 1950 [11] and soon after the new and more effective fluorinated hydrocortisones were introduced in the market during 1960 [12]. Further R&D works on these glucocorticoids led to introduction of super potent corticosteroids in the 1970s and 1980s. Cornell and Stoughton [13] had proposed a potency rating of these topically applied glucocorticoids in 1984, based primarily on the vasoconstrictor assay or skin-blanching of corticosteroid preparations. Again based upon the consensus of the United States Pharmacopoeia (USP) Dermatology Advisory Panel, a classification of the potency ranking for these glucocorticoids had been done as low, medium, high and very high [14]. New generation of glucocorticoids do not cause much cutaneous atrophy or systemic absorption in human body. Molecular configuration of these new corticosteroids tends to display a rapidly declining concentration gradient in the skin. Many of these new generation glucocorticoids are developed through the concept of prodrugs – a tool for improving physiochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. Thus prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic or chemical transformation *in vivo* to release the active parent drug, which could then exert the desired pharmacological effect. These new generation glucocorticoids primarily act in the top layers of the skin where the most important mediators of the inflammatory reactions are [10, 14] found.

As for these new generation glucocorticoids, the action in the deeper layer is considerably diminished making them having less systemic side effects [14]. European and North American based clinical studies have shown that the new generation corticosteroids with their improved risk- benefit ratio are as effective as products currently available in the market [15]. These new generation glucocorticoids are highly effective in treating plethora of disease including psoriasis, allergies, asthma, rheumatoid arthritis and lupus [2-8, 14,15].

Again the application of anti-inflammatory agents in ophthalmic therapeutic is a challenging task because of severe complications arising out of the currently used anti-inflammatory agents. The eye is vulnerable to damage from low level of intraocular inflammation. The blood-aqueous and blood-retinal barriers generally limit penetration of protein and cells from peripheral circulation, while regulatory molecules and cells in the eye actively suppress immunological responses [16]. The fact that ocular inflammatory conditions and surgical trauma induce changes in the blood- aqueous and blood-retinal barriers [16-18], due to which immune cells and mediators of inflammation could enter the

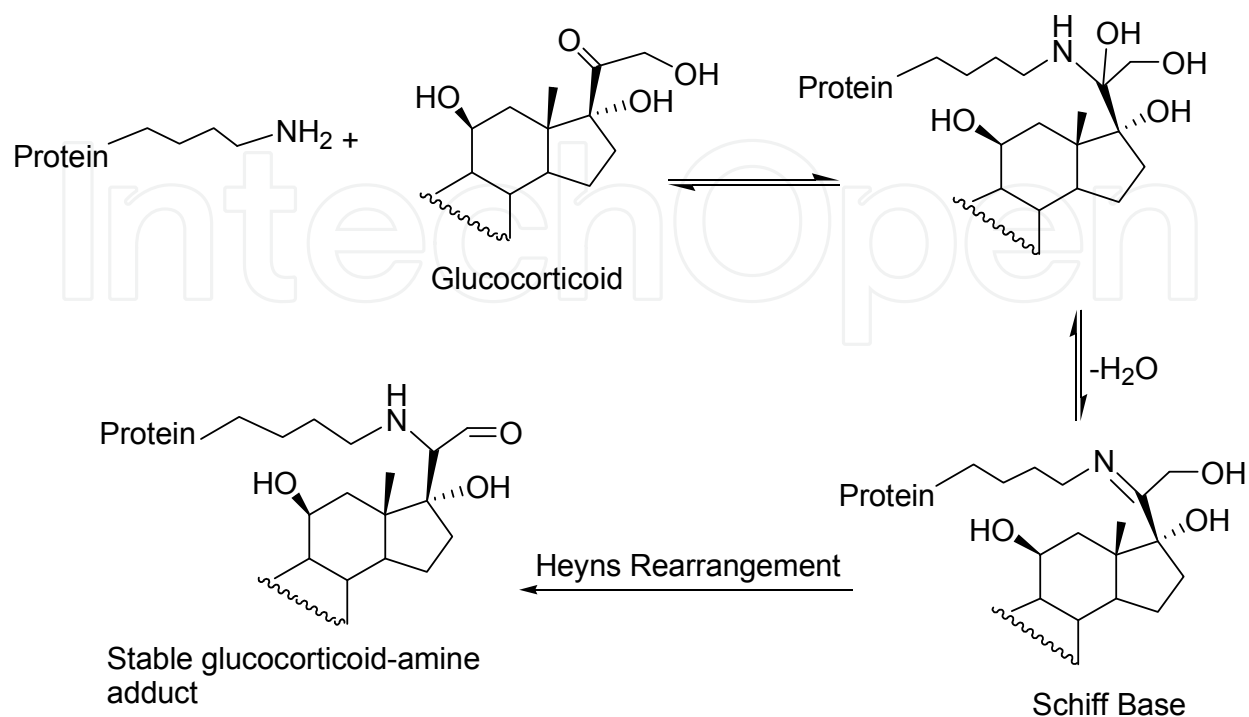
eye, resulting in the development of symptoms of ocular inflammation such as redness, pain, swelling and itching [19]. Ocular inflammation is a serious problem, negligence of which may lead to temporary or permanent blindness [20].

Clinical studies suggest that topical glucocorticoids are effective in the management of anterior segment inflammation. They impart a number of potent anti-inflammatory effects [21]. They are found to suppress cellular infiltration, capillary dilation, proliferation of fibroblasts, collagen deposition leading to scar formation; they also stabilize intracellular and extracellular membranes. Glucocorticoids increase the synthesis of lipocortins which block *phospholipase A<sub>2</sub>* and also inhibit Histamine (A) synthesis in mast cells. A critical step in the inflammatory cascade is the inhibition of *phospholipase A<sub>2</sub>* that inhibits the transformation of Phospholipids (B) to Arachidonic acid (C). Glucocorticoids are also found to increase the enzyme histaminase and modulate transcription factors present in mast cell nuclei [21, 22]. The formation of cataract is also one of the severe adverse drug reactions (ADRs) associated with glucocorticoids when used for ocular problems.



It has been reported by Manabe *et al* [23] that the mechanism of steroid-induced cataract formation is chemically based and possibly not related to the downstream effects of glucocorticoid receptor (GR) activation. At present the most accepted hypothesis of this mechanism is likely to involve non-enzymatic formation of Schiff base intermediates between the steroid C-20 ketone group and nucleophilic groups such as  $\beta$ -amino groups of lysine residues of proteins (Figure 1). Schiff base formation is followed by a Heyns rearrangement [23] involving the nearby C-21 hydroxyl group of the glucocorticoid molecule furnishing stable amine-linked adducts. This covalent binding results in the

destabilization of the protein structure allowing further oxidation leading to steroid-induced cataract formation [23].



**Figure 1.** Mechanism of steroid-induced cataract formation due to the synthesis of the stable steroid-amine adduct between the C-20 carbonyl group of glucocorticoids and nucleophilic group such as  $\beta$ -amino groups of lysine residues of proteins via formation Schiff Base

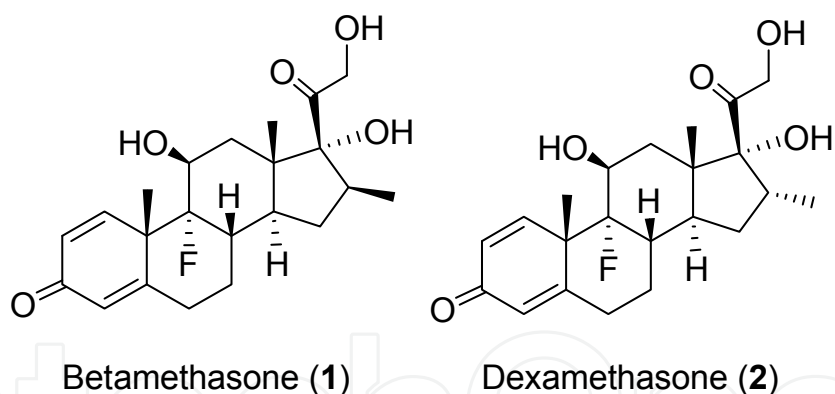
R&D work in understanding the mechanism of action of steroids, both for their anti-inflammatory effects and adverse drug reactions (ADRs) has led to the development new generation glucocorticoids mainly through prodrug design approach to find use in treating plethora of diseases as mentioned earlier. All these new generation glucocorticoids are not designed for ophthalmic therapeutics. Hence a real breakthrough in the field of ophthalmic therapeutic could be achieved only by specifically designing new drug entities to incorporate the eye targeting possibility into their chemical structure [24,25]. Chemical Delivery Systems (CDSs) and Retrometabolic drug design principles have led to development of a new but unique class of glucocorticoids which are safe and effective in treating a wide variety of ocular inflammatory conditions including giant papillary conjunctivitis, seasonal allergic conjunctivitis, and uveities as well as in the treatment of ocular inflammation and pain following cataract surgery. This new and unique class of glucocorticoids are now known as soft glucocorticoids which are associated with highly minimized ADRs to justify terming them as 'soft drugs' [24, 26].

It is pertinent to note that, this important drug design based on Chemical Delivery Systems (CDSs) and Soft drug (SD) approaches integrate the specific pharmacological, metabolic, and targeting requirements for ophthalmic therapeutics. A number of glucocorticoid soft drugs and soft  $\beta$ -blockers have been developed this way for clinical trials. Their potential is already documented by the results obtained with several soft drugs designed within this

framework. Glucocorticoid soft drugs such as Loteprednol Etabonate, and Etiprednol Dicloacetate and  $\beta$ -blockers such as Betaxoxime, and Adaprolol are some of the new chemical entities developed as soft drugs for ocular applications. Besides, many of these soft drugs have already reached the clinical development phase in various ophthalmic areas and one of them Loteprednol Etabonate has already been marketed [24]. Herein we review the important aspects of the development of new generation glucocorticoids through prodrug approach with special reference to the development of the first and second generation glucocorticoid soft drugs by the application chemical delivery systems (CDSs) and retrometabolic drug design approaches towards ophthalmic therapeutics. A few examples of soft ocular  $\beta$ -blockers have also been cited to know more about the retrometabolic drug design approach in depth as have been put forwarded by Bodor and his co-workers (24).

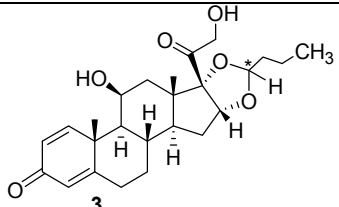
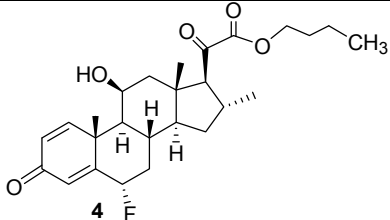
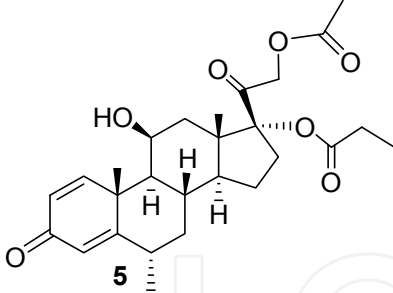
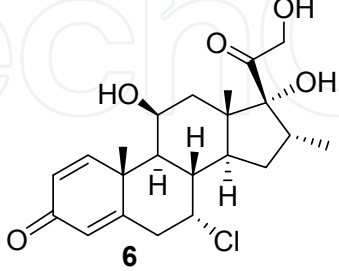
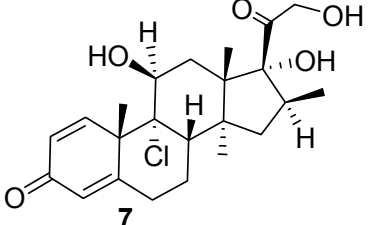
## 2. New generation glucocorticoids: Prodrugs

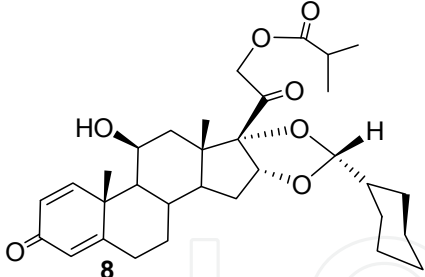
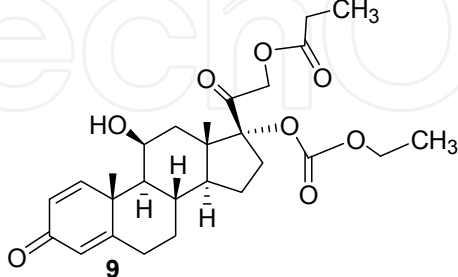
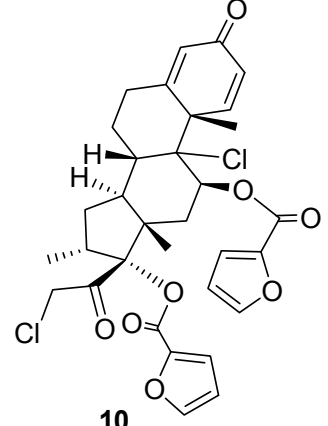
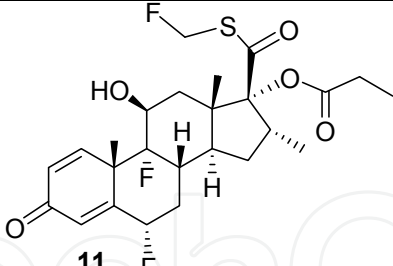
As discussed earlier several numbers of new entities of glucocorticoids have been developed during the last two decades. Many of them are already in market for their high efficacy and less systemic side effects. These new generation corticosteroids were developed with modifications made in the basic glucocorticoid molecules, *viz.*, Betamethasone **1** or Dexamethasone **2** extensively used during early stage of glucocorticoids therapy. The main object of synthesizing these modified glucocorticoids was to get better skin penetration, slower enzyme degradation, and greater affinity for cytosol receptors [5].



Even then in some cases it was observed that the changes that increased potency, also led sometimes to more systemic side effects. As per clinical investigations by various workers, these new generation glucocorticoids have been found to act *via* hepatic or extra hepatic biotransformation. These results in lesser systemic side effects and hence are much safer drugs to be used specially by adults and non-erythrodermic patients. However, while systemic side effects are of concern, cutaneous side effects are generally common involving problems such as striae formation, atrophy, purpura, peri-oral dermatitis, steroid rosacea, hypertrichosis and steroid acne [2,6]. Most of the side effects associated even with these new generation glucocorticoids are basically related to the duration and potency of the application, the manner of application, the presence of penetration-enhancing substances and the state of skin barrier. Besides these, the anatomic site and the age of the patient could also adversely influence the side effect profile [2, 6]. In both drug discovery and

development, prodrug design approach helped to maximize the amount of an active drug to reach its target through changing the physicochemical, pharmacokinetics or biopharmaceutical properties of the drug. Therefore the term prodrug refers to a pharmacologically inactive compound which is converted to an active drug by metabolic biotransformation which may occur prior, during or after absorption or at specific target sites within the body because of their specific molecular configurations [28-30]. The labile 'prodrug' corticosteroids such as 17-Prednicarbate, Alclometasone, Methylprednisolone aceponate, Fluticasone Propionate and Fluocortin butylester are some of these new generation glucocorticoids which are developed through prodrug approach [2,6]. Based on the molecular configuration of these new generation glucocorticoids, they are classified into several categories [Table1] [2, 6].

| Molecular Configurations | Structures   | Names                            |
|--------------------------|--|----------------------------------|
| Asymmetric acetonides    |  <p>3</p>   | Budesonide (3)                   |
| C-21-Carboxylesters      |  <p>4</p>  | Fluocortin butylester (4)        |
|                          |  <p>5</p> | Methylprednisolone aceponate (5) |
|                          |  <p>6</p> | Alclometasone dipropionate( 6)   |
|                          |  <p>7</p> | Beclomethasone (7)               |

|                        |  |                                      |
|------------------------|--|--------------------------------------|
|                        |  <p style="text-align: center;"><b>8</b></p>    | Ciclesonide ( <b>8</b> )             |
| C-17 –Prednicarbonates |  <p style="text-align: center;"><b>9</b></p>    | 17-Prednicarbate ( <b>9</b> )        |
| Carbothiates           |  <p style="text-align: center;"><b>10</b></p>  | Mometasone furoate ( <b>10</b> )     |
|                        |  <p style="text-align: center;"><b>11</b></p> | Fluticasone propionate ( <b>11</b> ) |

**Table 1.** Classification of new generation glucocorticoids on the basis of their molecular configurations

Chemical stability is another criteria for classification of these new generation corticosteroids. Based on this, most of these newer drugs can be regarded as prodrugs because immediately after application to the system, they undergo metabolism and acyl-exchanges to form the active molecule to fight the ailment in the system. As mentioned earlier, all these glucocorticoids have been developed through prodrugs design approach in order to maximize the amount of an active drug reaching its target through changing the physicochemical, biopharmaceutical or pharmacokinetic properties of drugs. Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect [28-30]. Most of the new generation corticosteroids have been found belonging to the class of molecules

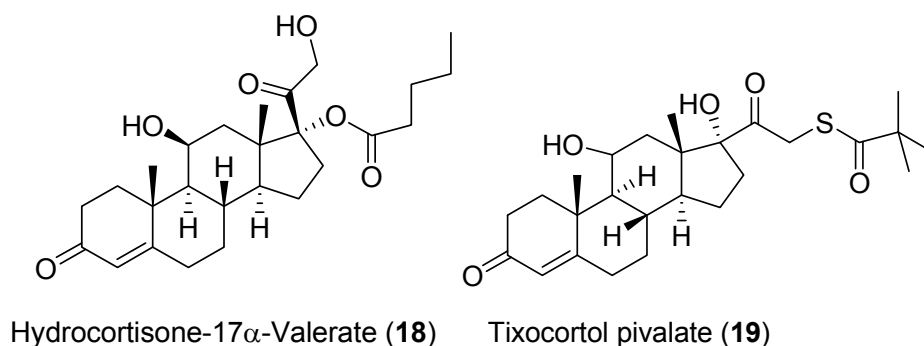
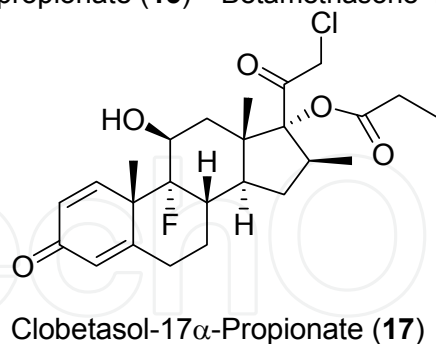
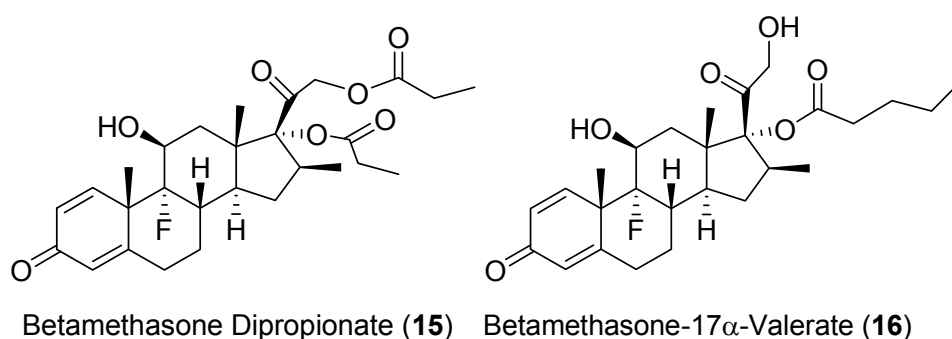
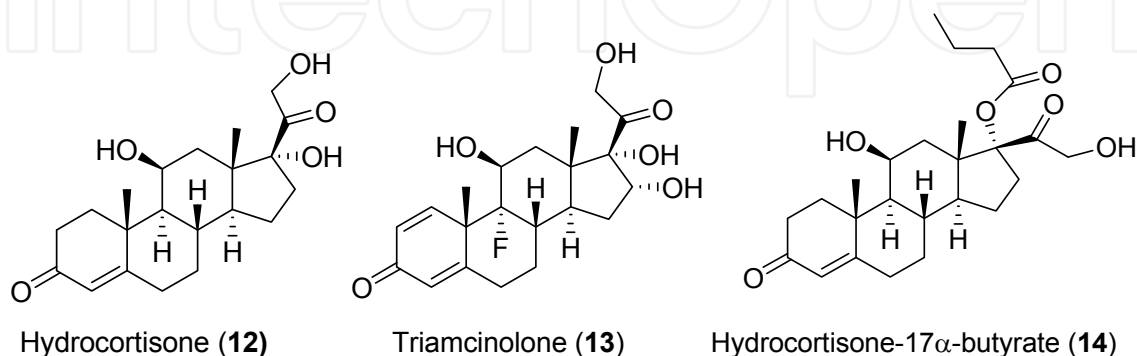


having high potency. By introducing various substituents at different positions, changes or modifications were made on the parent hydrocortisone molecules, such as Betamethasone (1) and Dexamethasone (2) in order to get better skin penetration, slower enzymatic degradation and greater affinity for the cytosol receptor for these molecules to reduce or eliminate their systemic side effects [6]. The systemic side effects of these new corticosteroids are reduced due to rapid biotransformation while applying them for treatment of atopic dermatitis. However it is pertinent to note that there are still risks of having potential hypothalamus and pituitary axis (HPA) suppression with some of these new generation glucocorticoids while treating young children and erythrodermic patients. Clinical safety has been demonstrated in most of these newer corticosteroids with restricted duration of treatment up to six weeks [2, 6]. Even then skin atrophy and some telangiectasia have been observed in some patients. A large number of reports of contact allergic reactions associated with these new generation glucocorticoids were still of great concern. To explain the increased allergenicity, data from clinical studies and literature were reviewed to define precisely some of the more important groups of cross-reacting molecules [31]. **Table 2** represents the various allergy groups of these newer glucocorticoids based on their molecular structures and configurations. Clinical studies have revealed that Tixocortol pivalate (19) has been identified as a good screening agent for the Group A [32]. Budesonide (3) is in fact a 1:1 mixture of two diastereomers (R- and S- isomer). The R-isomer has been found to be a marker for the Group B while the S-isomer for the Group D. Glucocorticoid members of Group C cause minimized contact sensitivity and do not cross react with other groups. As shown in **Table 2**, Group D has been divided in two sub-groups D<sub>1</sub> and D<sub>2</sub> based on recent studies [2, 33] with respect to their mode of substitutions.

| Group          | Molecular configuration                       | Characteristics of substituent  |
|----------------|---|---|
| A              | Hydrocortisone (12) type                      | No substitution in D ring, except a short chain ester on C-17 or C-21 or a thioester on C-21                                  |
| B              | Triamcinolone (13) type                       | C-16,C-17- <i>cis</i> -ketal or -diol structure   |
| C              | Betamethasone (1) type                        | C-16 methyl substitution, no side chain on C-17; possible side chain at C-21.   |
|                | Fluocortin Butylester (4)                     |   |
| D              | Hydrocortisone-17 $\alpha$ -butyrate(14) type | Long chain ester at C-17 and/or C-21 with or without C-16 methyl substitution.  |
| D <sub>1</sub> | Betamethasone Dipropionate(15)                | Long chain ester at C-17 and/or C-21 with C-16 methyl substitution; halogen substituent in ring B                             |
|                | Betamethasone 17 $\alpha$ -Valerate (16)      |   |
|                | Clobetasol 17 $\alpha$ -Propionate (17)       |   |
|                | Mometasone Furoate (10)                       |   |
|                | Fluticasone Propionate (11)                   |   |
| D <sub>2</sub> | Hydrocortisone-17 $\alpha$ -butyrate(14)      | Long chain ester at C-17; possibly a side chain at C-21; no methyl substitution at C-16 and no halogen substituent in ring B. |
|                | Hydrocortisone 17 $\alpha$ -Valerate (18)     |   |
|                | 17-Prednicarbate (9)                          |   |
|                | Methylprednisolone Aceponate (5)              |   |

**Table 2.** Allergy Groups of new generation corticosteroids based on their molecular structures and configurations

To the Group D<sub>1</sub>, belong not only the old generation glucocorticoid molecules like Betamethasone dipropionate (**15**), Betamethasone-17 $\alpha$ -valerate (**16**) and Clobetasol 17 $\alpha$  propionate (**17**) but also new generation corticosteroids such as Mometasone furoate (**10**) and Fluticasone propionate (**11**). These glucocorticoids are found to possess very less systemic side effects and so can be used safely even in case of patients who are allergic to other corticosteroids. To the Group D<sub>2</sub> belong Hydrocortisone-17 $\alpha$ -valerate (**18**) and Hydrocortisone-17 $\alpha$ -butyrate (**14**) as well as the labile new generation glucocorticoids like 17-Prednicarbate (**9**) and Methylprednisolone Aceponate (**5**). They are sometimes found to cause allergic reactions.



S-isomer of Budesonide (3) is the marker for this Group D<sub>2</sub>, but they can cross react with the Group A. **Table 3** illustrates the safety profile, potency, side effects and allergy groups of some of the new generation glucocorticoids along with their manufactures.

| Product                         | Manufacturer                                | Safety profile  | Potency        | Side effect  | Allergygroup   |
|---------------------------------|---|---|----------------|--|----------------|
| Budesonide(3)                   | Astra, Entcort                              | A Stable asymmetric acetone undergoing rapid biotransformation in liver with less systemic side effects   | High potency   | May be problem with contact sensitivity                                      | B              |
| Mometasone Furoate (10)         | Schering-Plough, Elocom                     | A stable chlorinated topical glucocorticoid with low penetration with high biliary excretion, and also low resorption in the circulation with fast biotransformation in the liver resulting in rare local systemic side effect. | High potency   | Very rare contact hypersensitivity   | D <sub>1</sub> |
| Fluocortin butylester(4)        | Schering Corp.- Essex, Varlane              | Biotransformation into the non- active fluocortolone-21- acid in skin.  | Medium potency | Rare contact hyper-sensitivity   | C              |
| Alclometasone dipropionate(6)   | Schering-Plough, Aclovate, Glaxo- - welcome | A labile prodrug metabolizing to inactive compound  | High potency   | Occasional Contact hyper-sensitivity   | D <sub>2</sub> |
| 17-Prednicarbate( 9)            | Hoechst-Roussel, Dermatop Emollient         | A labile prodrug glucocorticoid, converting to prednisolone in the skin   | High potency   | Contact hyper-sensitivity is observed. Also can cross-react with the Group A | D <sub>2</sub> |
| Methylprednisolone aceponate(5) | Schering Corp. Essex, Advantan              | A labile prodrug. Get transformed into methyl prednisolone in the skin and into nonactive derivatives in the liver  | High potency   | Contact hyper-sensitivity is not rare  | D <sub>2</sub> |

|                             |   |   |              |                                       |                |
|-----------------------------|---|---|--------------|---------------------------------------|----------------|
| Fluticasone propionate (11) | Cutivate, Glaxo Wellcome                            | A fluorinated topical glucocorticoid. Readily metabolized in the liver resulting in a locally potent steroid drug with a low HPA inhibitory potency | High potency | Contact hypersensitivity is very rare | D <sub>1</sub> |
| Beclomethasone(7)           | Schwitz Biotech, Havione Farmacencias, Portugal     | A chlorinated topical corticosteroid. Readily metabolized in the liver resulting in a locally potent steroid with a low HPA inhibitory potency      | High potency | Contact hypersensitivity is very rare | D <sub>1</sub> |
| Ciclesonide (8)             | Brand Name: Alvesco, Taj Pharmaceuticals Ltd. India | A triamcinolone type Glucocorticoid with low HPA inhibitory potency   | High Potency | Contact hypersensitivity is rare      | D <sub>1</sub> |

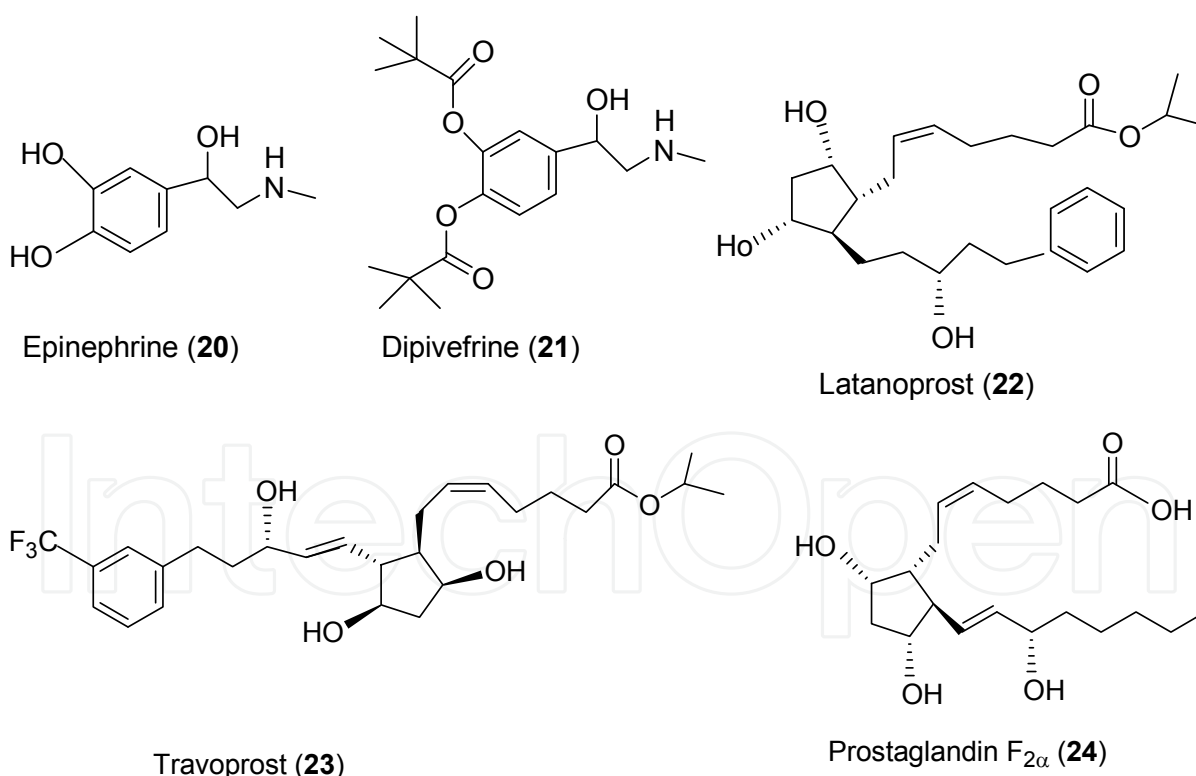
**Table 3.** Some of the marketed new generation glucocorticoids and their allergy groups:

Continuous efforts are still being sought after by pharmaceutical companies worldwide to develop and market more and more safer glucocorticoids as anti-inflammatory agents, because clinical investigations on some already marketed newer glucocorticoids have revealed that many of them are still prone to cause allergic reactions and other systemic side effects specially on prolonged use. However, glucocorticoids are still regarded as life saving drugs dominating over the other anti-inflammatory agents for the treatment of a number of diseases including psoriasis, allergies, acute asthma, rheumatoid arthritis and lupus.

*Eye-targeted Chemical Delivery Systems (CDSs) and retrometabolic drug design: Soft  $\beta$ -Blockers and Soft Glucocorticoids*

Soft corticosteroids or Soft glucocorticoids can be termed as a unique class of new generation glucocorticoids that are designed specifically for ophthalmic therapeutics [24-27]. The new generation glucocorticoids developed by prodrug approach as described earlier have brought revolution in treating a plethora of disease including psoriasis, allergies, asthma, rheumatoid arthritis and lupus because of their minimized systemic side effects. However, these new generation glucocorticoids are still not useful for ophthalmic applications due to their association with adverse drug reactions (ADRs) including elevation of intraocular pressure (IOP) and steroid-induced cataract formation [23] in ophthalmic applications. For the therapeutic treatment of most of ocular problems, topical

administration undoubtedly seems preferred mode, because for systemically administered drugs, only a very small fraction of the total dose will reach the eye from the general circulatory system. Even distribution for this fraction to the inside of the eye is further hindered by the blood-retinal barrier (BRB), which is almost as effective as blood-brain barrier (BBB) in restricting the passage of xenobiotics from the blood stream [34]. Therefore despite its apparent accessibility, the eye, in fact, is well protected against the absorption of foreign materials, including drug molecules, by the eyelids, by flow of tears, and also by the permeability barriers imposed by the cornea on one side and the blood-retinal barrier on the other side as mentioned above [24]. Because of this a significant portion of the applied drug is absorbed through nasolacrimal duct and the mucosal membranes of the nasal, oropharyngeal, and gastrointestinal tract to pass to the system. It has been found that no more than 2% of medication introduced topically to the eye is adsorbed [35-37]. Again clinical studies by various workers reveal that the main biological barrier for penetration to the eye is represented by the cornea. The relatively lipophilic corneal epithelium tissue having low porosity and high tortuosity due to tight annular junctions, is the primary barrier for hydrophilic drugs, where as the middle stromal layer consisting mainly of water interspersed with collagen fibrils( major thickness of cornea), is the main barrier for the lipophilic drugs [38-41]. All these facts result not only in a low net eye drug delivery, but also in substantial systemic availability of ophthalmic drugs after



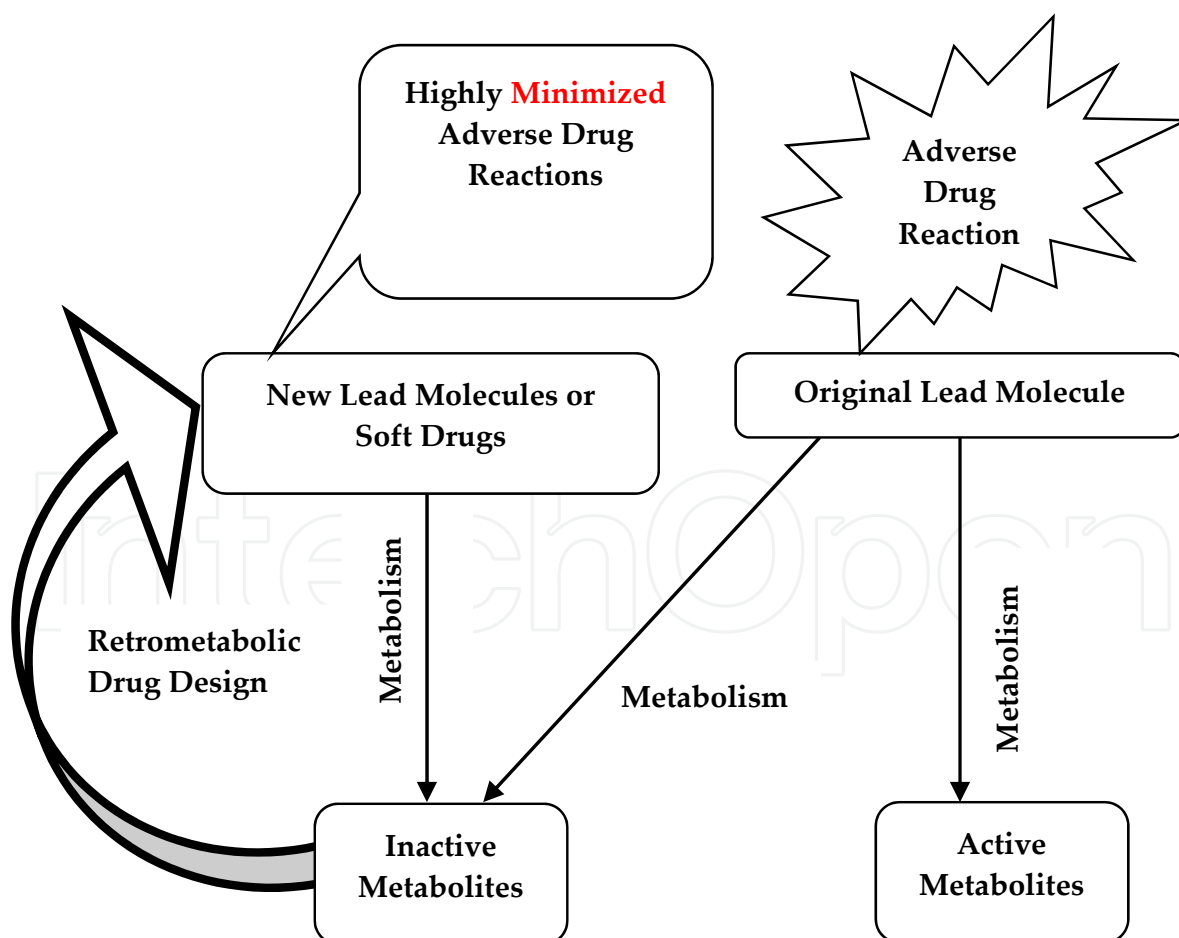
topical administration giving systemic side effects [42]. Moreover as mentioned earlier, existing ophthalmic drugs are actually not developed for ocular applications, they were intended for other therapeutic areas which were later converted to ocular applications following their high efficacy. This further has decreased the likelihood of achieving eye-specific delivery along with reduced systemic side effects. In view of this, various drug

design approaches have been tried to eliminate the problems of low ocular delivery and potential for substantial systemic side effects [6, 43]. It has been found that prodrug approach here had some limitations. Prodrugs are pharmacologically not active (or may be weakly active) compounds that results from transient chemical modifications of biologically active species, so that they are metabolically transformed into effective drugs following administration [28-30, 44-47]. Compared with the original structures, prodrug structures incorporate chemical modifications to get improvement in some deficient physiological properties, such as membrane permeability or water solubility or to overcome some other problems like rapid elimination, bad taste, a formulation difficulty etc. After administration, the prodrug because of its improved characteristics, is more systemically or locally available than the parent drug. However the prodrug must undergo chemical or biochemical conversion to the active form before exerting its biological effect. Some of the marketed ophthalmic prodrugs include Dipivefrine (**21**)-the dipivalate ester prodrug of epinephrine (**20**), latanoprost (**22**) and travoprost (**23**) -isopropyl ester prodrugs that are prostaglandin F<sub>2α</sub> (**24**) analogs [24].

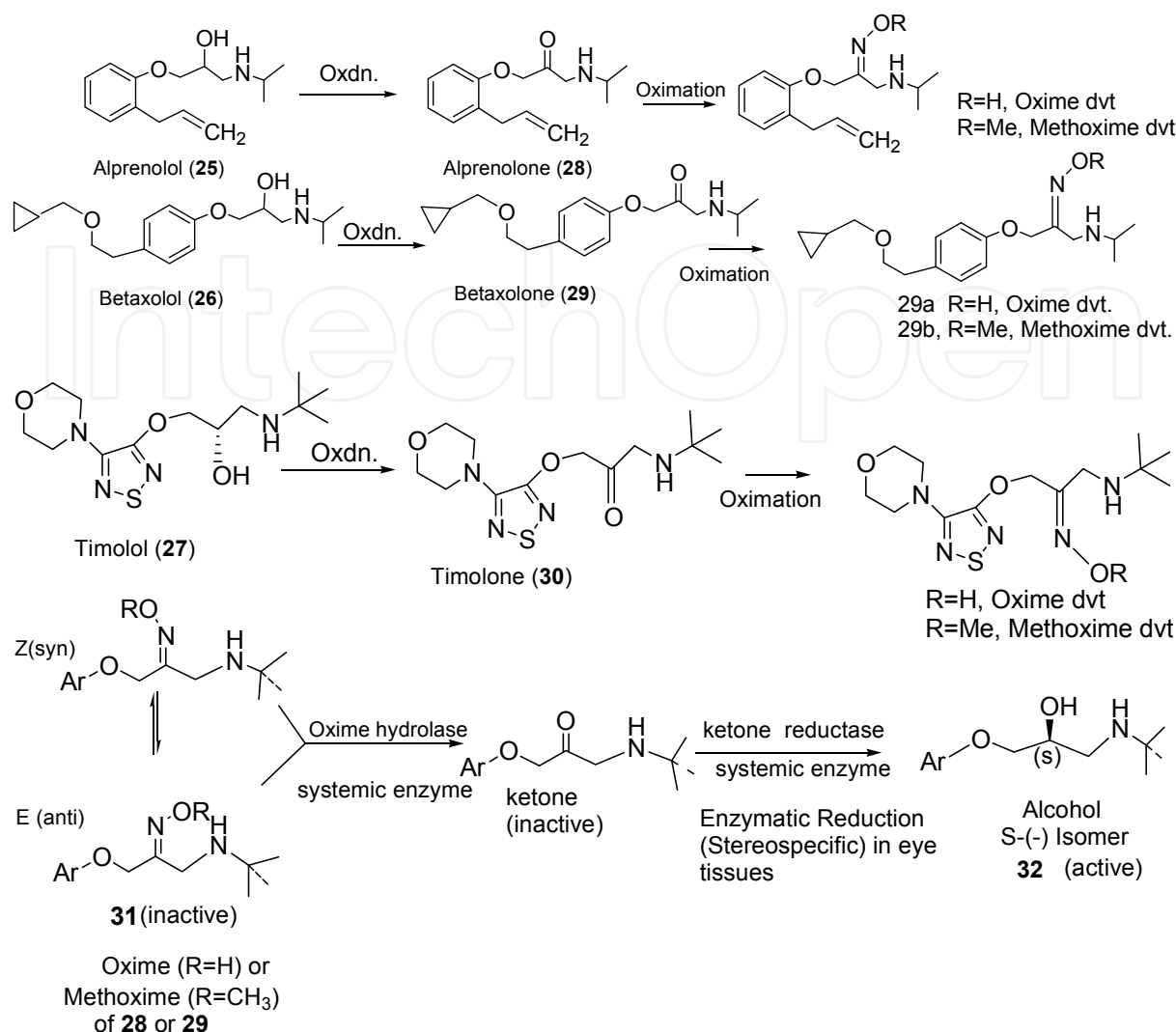
#### *Retrometabolic Drug Design:*

Because of the adverse drug reactions (ADRs) associated even with the new generation glucocorticoids in ocular treatment, the real breakthrough in the area of ophthalmic therapeutics could be achieved only by specifically designing new drugs with their ophthalmic applications in mind, so that the possibility of eye targeting with reduced systemic side effects is already incorporated in their chemical structures. In an effort to minimize ADRs and other complications associated with glucocorticoids, Bodor and his colleagues for the first time have developed the concept of retrometabolic drug design for ophthalmic therapeutics to introduce a new and unique class of glucocorticoids now known as soft corticosteroids or soft glucocorticoids that helped in developing glucocorticoid soft drugs for ophthalmic use [24, 48-50]. Soft  $\beta$ -blockers are also falling in this soft drug category. The concept of soft drugs has been originated from the pioneer work of Prof. N Bodor and his co-workers at the Center for Drug Discovery, University of Florida, Health Science Center, Gainesville, FL 32610-0497, USA [24, 48-50]. The possibility of developing these soft drugs has been extensively studied along the lines of retro- metabolic drug design for two important classes of ophthalmic drugs,  $\beta$ - blockers and glucocorticoids [24]. The underlying principle of retrometabolic drug design involves synthesizing analogs of lead molecules or reference molecules, starting from one of the known inactive metabolites of that lead compound. The inactive metabolite is then converted to an isosteric or isoelectronic analog with structural modifications designed for a rapid and predictable metabolism back to the original inactive metabolite after exerting the desired therapeutic effect at the site (**Figure 2**) [24, 26]. These analogs or soft drugs were predicted to have therapeutic potential similar to that of the lead compound, but because of the structural modifications provided by the design, any active drug remaining after attainment of the therapeutic effect would be metabolically deactivated, thus reducing adverse drug reactions (ADRs) [24, 26, 48-51]. According to Prof Bodor, in developing soft drugs the goal is not to avoid metabolism but rather to control and direct it. Inclusion of a metabolically sensitive moiety into the parent drug molecule can make possible the design and prediction of the major metabolic pathway

preventing the formation of undesired toxic, active, or high-energy intermediates. It is desired that, if possible, inactivation should take place as the result of a single, low-energy and high-capacity step that gives the inactive species subject to rapid elimination. Most critical metabolic pathways in a biological system are mediated by *oxygenases*, a consequence of the fact that the normal reaction of an organism to a foreign material is to burn it up as food [52]. However *oxygenases* exhibit not only interspecies, but also inter-individual and are subject to inhibition and induction (24) and because the rates of hepatic *mono-oxygenases* reactions are at least two orders of magnitude lower than the slowest of the other enzymatic reactions [53,54], it is usually desirable to avoid oxidative pathways as well as these slow, easily saturable *oxidases*. In view of this, the design of soft drugs must be based on moieties activated by hydrolytic enzymes. Rapid metabolism could be more reliably performed by these ubiquitously distributed *esterases*. Bodor et al (26) suggested that it is desirable not to rely exclusively on metabolism by organs such as kidney or liver to have an additional advantage because blood flow and enzyme activities in these organs can be fatally damaged in critically ill patients. However, the increase in the therapeutic index can only be achieved if the drug is stable enough to reach its receptor site to deliver the desired effect, and any free drug remaining thereafter should be metabolized to minimize ADRs [24].



**Figure 2.** Retrometabolic drug design approach: Synthesis of new lead molecules (Soft drugs) based on an inactive metabolite of an original lead molecule



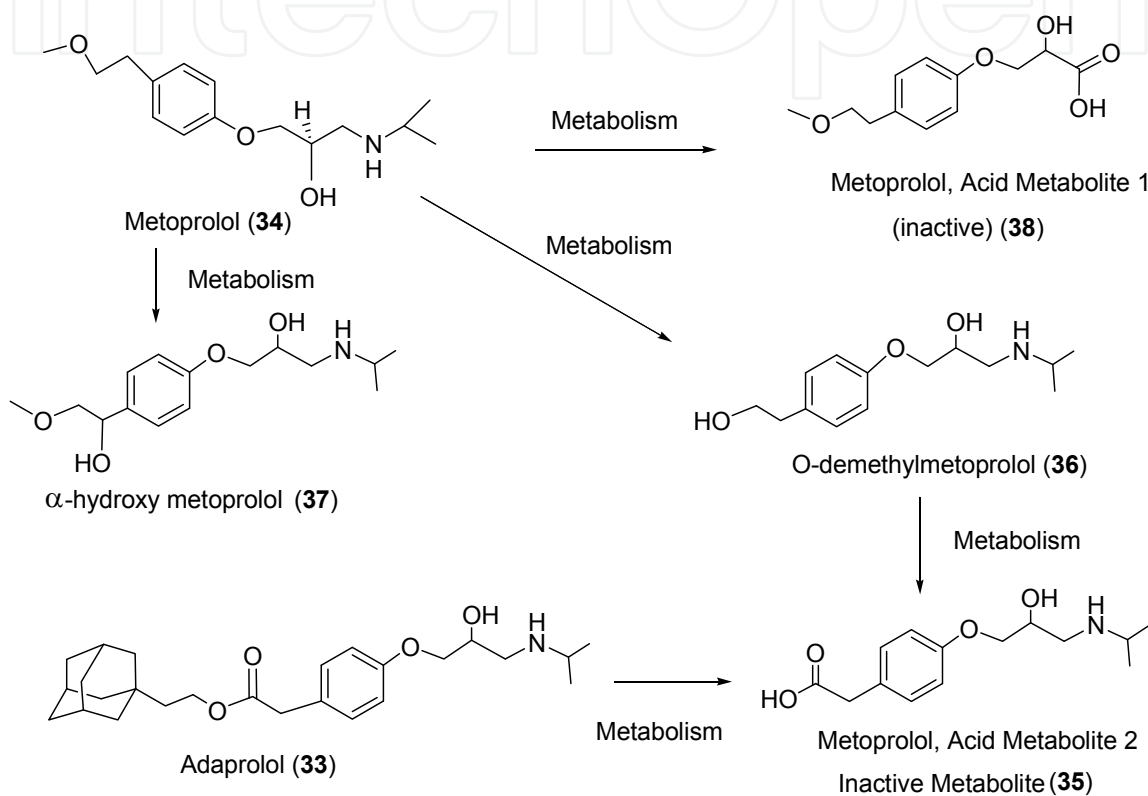
**Figure 3.** Site- and Stereospecific delivery of  $\beta$ -adrenergic antagonists to the eye through sequential activation of their oximes and alkyl oximes.

#### Soft- $\beta$ -Blockers:

As because soft drug design is a general concept, typically applied soft drugs that show local activity with reduced systemic side effects could become potential therapeutics for any ocular diseases [24]. During the last three decades, Bodor and his colleagues have applied retrometabolic drug design to a variety of therapeutic agents such as  $\beta$ -blockers, antimicrobials, analgesics, and acetyl cholinesterase (ACE) inhibitors and were successful in developing retrometabolically designed compounds with market potential. As for example, in addition to the oxime or methoxime  $\beta$ -blocker analogs, the development of soft  $\beta$ -blockers could represent another possible route toward improved and safer antiglaucoma agents [54-62]. Several oxime and methoxime analogs of known  $\beta$ -Adrenergic blockers such as Alprenolol (25), Betaxolol (26), Timolol (27) etc. were synthesized from their respective ketone derivatives, *viz.*, Alprenolone (28), Betaxolone (29), Timolone (30) and studied clinically [54-62]. They are potential drugs which have been developed applying general retrometabolic drug design principle and can be recognized as site-specific enzymatic



chemical delivery systems (CDSs) [54-62]. In these compounds, a  $\beta$ -amino oxime or alkyloxime function replaces the corresponding  $\beta$ -amino alcohol pharmacore part of the original molecules (**Figure 3**). These oxime or alkyloxime derivatives (**31**) are found to exist in Z (syn) or E (anti) configuration. They are hydrolyzed within the eye by enzymes located in the iris-ciliary body and subsequently again by reductive enzymes present there producing only the active S- (-) stereoisomeric alcohol (**32**) of the corresponding  $\beta$ -blockers [54]. For aryl  $\beta$ -amino alcohol-type  $\beta$ -adrenergic agonists and antagonists, most of the activity has been known to be



**Figure 4.** Inactive Metabolite-based Soft Drug Design: Comparison of the structure and metabolism of the soft  $\beta$ -blocker Adaprolol (**23**) with that of the traditional  $\beta$ -blocker Metoprolol (**24**).

present with the S- (-) stereoisomer [63-65], possibly because this isomer allows better interaction of all three important functionalities (aromatic, amino and  $\beta$ -hydroxyl moieties) with the  $\beta$ -adrenoceptor. In fact these oxime and alkyloxime derivatives have been found to exhibit significant intraocular pressure (IOP) lowering activity, but even their intravenous administration did not produce the active  $\beta$ -blocker metabolically; as a result they are void of any cardiovascular activity, which has been found to be a major drawback of classical antiglaucoma agents [26].

According to Bodor and his team [24], the oxime-type CDS approach clearly demonstrates the site-specific or site-enhanced drug delivery through sequential, multi-step enzymatic and/or chemical transformations through a targetor moiety that is converted into a biologically active function by enzymatic reactions which take place primarily at the site of action as a result of differential distribution of some enzymes found in the eye [24].

Again as Prof. Bodor and his team suggest [24,26], soft drugs (SDs) represent a different, conceptually opposite targeting concept; whereas eye-targeting CDSs, represented here by the above discussed oxime analogs, are inactive compounds designed to achieve the targeted effects *via* a multi-step activation process by enzymes found at their intended site of action. However soft drugs represented by  $\beta$ -blockers or glucocorticoids are active compounds designed to achieve the targeted effects *via* a single-step inactivation process involving enzymes found ubiquitously in the systemic circulation. Because in this class, inactive metabolite based soft drugs can be achieved introducing the hydrolytically sensitive functionality at a flexible pharmacophore region, there is considerable freedom for structural modifications. As a result, transport and metabolism properties are easier to control. From the various soft  $\beta$ -blockers developed along these lines by Bodor and Buchwald [24], Adaprolol (33), an adamantane ethyl ester was selected as a potential candidate for a new topical antiglaucoma agent [24]. The metabolism of the well-known  $\beta$ -blocker Metoprolol (34) has been compared with that of the soft  $\beta$ -blocker Adaprolol which has been designed starting from one of Metoprolol's inactive acid metabolite (35), *viz.*, phenyl acetic acid (Figure 4). Its other metabolites include  $\alpha$ -hydroxymetoprolol (36) and O-Dimethylmetoprolol (37) both of which are active. Another inactive metabolite includes the acid derivative 38. Adaprolol was chosen because of the fact that if membrane transport (lipophilicity) and relative stability are important for pharmacological activity as they are needed to achieve right corneal permeability, then the ester group should be relatively lipophilic and should provide ester stability [66-70]. In clinical trials Adaprolol (33) indeed produced prolonged and significant IOP-reduction while hydrolyzed relatively fast [67, 68]. Therefore, it was possible to separate local activity from undesired systemic cardiovascular or pulmonary activity, a characteristic highly desirable in development of antiglaucoma therapy [24]. Adaprolol (33) could be now a potent antiglaucoma soft  $\beta$ -blocker to replace the traditional  $\beta$ -blocker Metoprolol (34). Further clinical studies confirmed that Adaprolol is not only effective in reducing intraocular pressure (IOP) but also has a safer cardiovascular profile than Timolol (27) because unlike Timolol, Adaprolol did not reduce the systolic blood pressure [24].

#### *Glucocorticoid Soft Drugs: Ophthalmic Therapeutics*

Along the line of soft  $\beta$ -blockers, development of soft anti-inflammatory glucocorticoids represents a promising and successful ophthalmic drug design area initiated by Bodor and his colleagues [24,26]. Inflammation in the eye could result from surgery, injury, infection, conjunctivitis, or uveitis-conditions that can cause severe discomfort even leading to loss of vision. As mentioned earlier, topical glucocorticoids represent an important class of molecules to treat ocular inflammations and allergies as they are the most effective anti-inflammatory compounds offering the broadest range of treatment. However a number of contradictions limit their usefulness severely [12]. In addition to the general systemic side effects or adverse drug reactions (ADRs) associated with these glucocorticoids, they also cause several ocular complications such as IOP-elevation resulting steroid-induced glaucoma, induction of cataract formation and other secondary complications [12, 71]. In this context design of soft anti-inflammatory glucocorticoids has been one of the most active

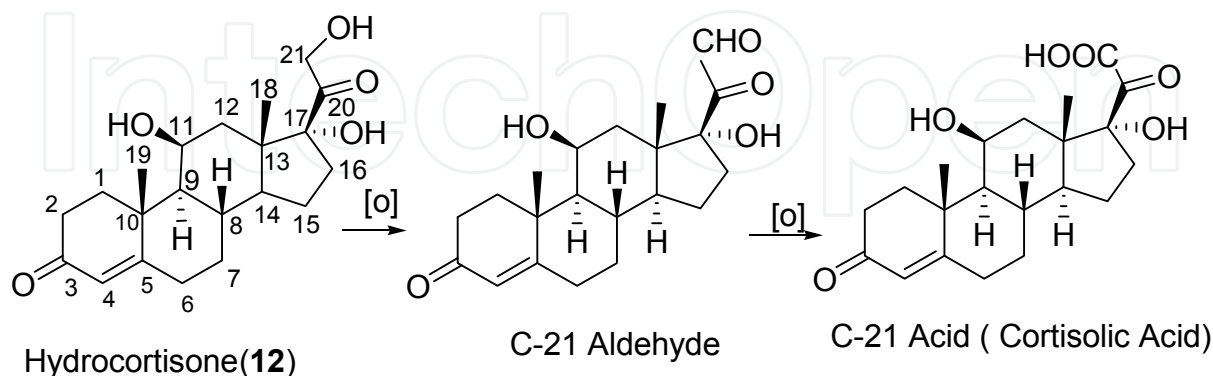
and productive fields of soft drug design. Ophthalmic use of glucocorticoids usually causes increased intraocular pressure (IOP) as a result of increased resistance to aqueous humour outflow. The design of soft anti-inflammatory glucocorticoids has been one of the most important and most successful areas of Soft Drug design. Although the soft nature of such drugs are mainly associated with fast hydrolytic degradation, in fact it is not necessarily be so as Bodor and his co-workers suggested [24]. Too much rapid hydrolysis may in fact result in weak activity. The desired increase of therapeutic index can be obtained only if the drug is sufficiently stable to reach the receptor sites at the target organ to produce the desired effect, but the free, non-protein-bound drug undergoes facile hydrolysis to avoid undesired systemic side effects. Therefore to develop a soft drug and hence separating successfully the desired local activity from systemic toxicity, an adequate balance between intrinsic activity, solubility/lipophilicity, tissue distribution, protein binding and rate of metabolic deactivation have to be achieved. In the case of slow, sustained release to the general circulatory system from delivery site, even a relatively slow hydrolysis could result in a very low, almost steady-state systemic concentration [24]. Based on these concepts of eye-targeting chemical delivery systems (CDSs) and retrometabolic drug design approaches, Bodor and his group was successful in developing glucocorticoid soft drugs for ophthalmic therapeutics having potential market value.

*First Generation Cortienic Acid (39)-based Glucocorticoid Soft Drugs: Loteprednol Etabonate (41) and its Analogs (42):*

*Synthesis of Dug molecules and Structure-Activity Studies:*

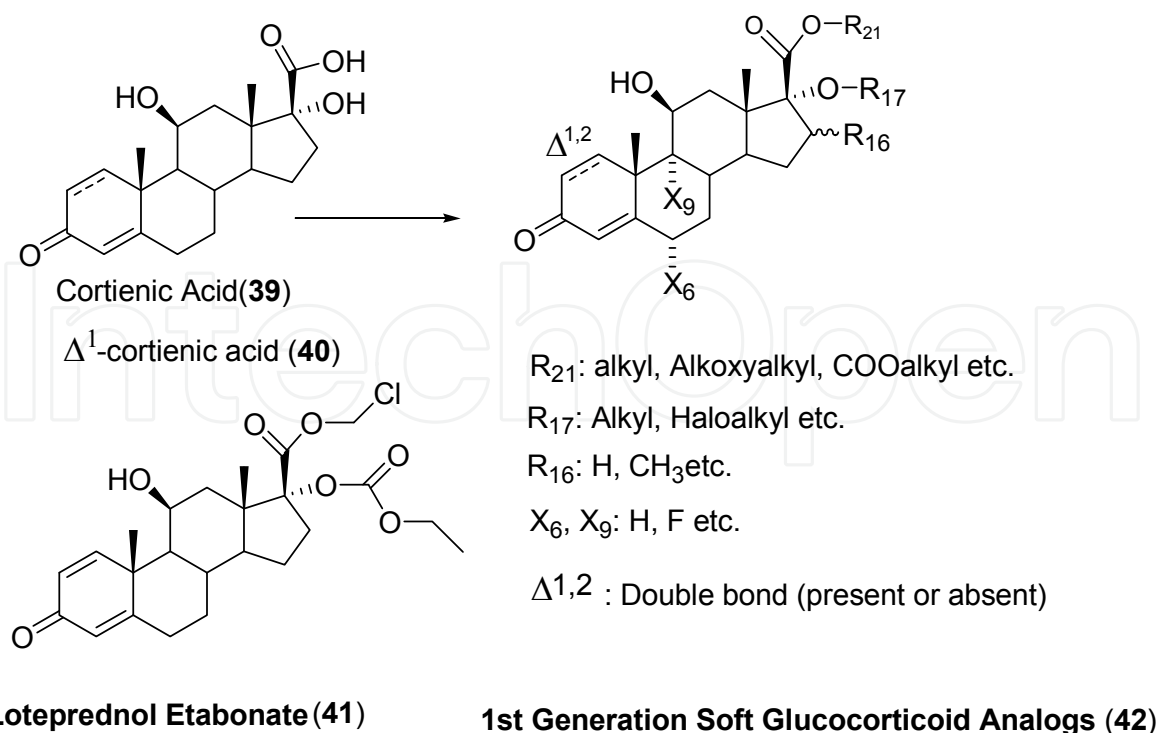
As already mentioned, Bodor and his colleagues [24, 26] have applied retrometabolic drug design approach to a variety of therapeutic agents such as  $\beta$ - blockers, antimicrobials, analgesics, and acetyl cholinesterase (ACE) inhibitors and were successful in developing retrometabolically designed molecules reaching towards market application. They had designed a number of analogs starting with  $\Delta^1$ -cortienic acid (40), the primary metabolite of prednisolone that lacks corticosteroid activity [25]. Hydrocortisone can undergo a variety of oxidative and reductive metabolic conversions [72] by local *esterases* within the system. Thus oxidation of its dihydroxyacetone side chain leads to the formation of cortienic acid *via* 21-dehydrocortisol (21-aldehyde) and cortisolic acid (21-acid) [Figure 5]. Cortienic acid (39) is an ideal lead molecule for the inactive metabolite soft drug (SD) approaches because it is lack of corticosteroid activity and therefore is major metabolite excreted in human urine. To get the new lead compounds, the pharmacophore moieties of the  $17\alpha$ -hydroxyl and  $17\beta$ -carboxy substituents of the lead compound had to be restored by suitable isosteric/isoelectronic substitution containing esters or other types of functions that could restore the anti-inflammatory potency of the original corticosteroid while at the same time incorporating hydrolytic features to ensure metabolism. Other structural considerations included the presence or absence of double bond at C-1 position, presence of  $6\alpha$  or  $9\alpha$  fluorine, and  $16\alpha$  &  $16\beta$  -methyl group (Figure 6). More than hundred possible drug molecules were synthesized and tested in pre-clinical anti-inflammatory models [5]. Structure-activity studies by Bodor and his group [24] of these molecules have confirmed

that the best substituent for maximal therapeutic activity included a haloester at 17 $\beta$ -position and a carbonate or ether moiety at 17 $\alpha$ -position. Incorporation of 17 $\alpha$  carbonates or ether was preferred over 17 $\alpha$ -esters to increase stability and to prevent potential formation of mixed anhydrides by reaction of a 17 $\alpha$  ester with a 17 $\beta$  acid functionality and subsequent potential for lens protein binding leading to steroid-induced cataract formation.



**Figure 5.** Oxidative metabolism of hydrocortisone by local esterases into C-21 Aldehyde and C-21 Acid (Cortisolic Acid)

Therefore in addition to the C-20 ketone functionality of prednisolone being replaced to eliminate the possibility of Schiff base intermediates, other chemical features associated with cataractogenesis were also eliminated by the proposed design. The carbonates were expected to be less reactive than the corresponding esters due to the lower electrophilicity of the carbonyl carbon [24].



**Figure 6.** Design of 1<sup>st</sup> Generation Cortienic acid-based Glucocorticoid Soft Drugs (42) with their Glucocorticoid Soft Drug representative Loteprednol Etabonate (LE)(41)

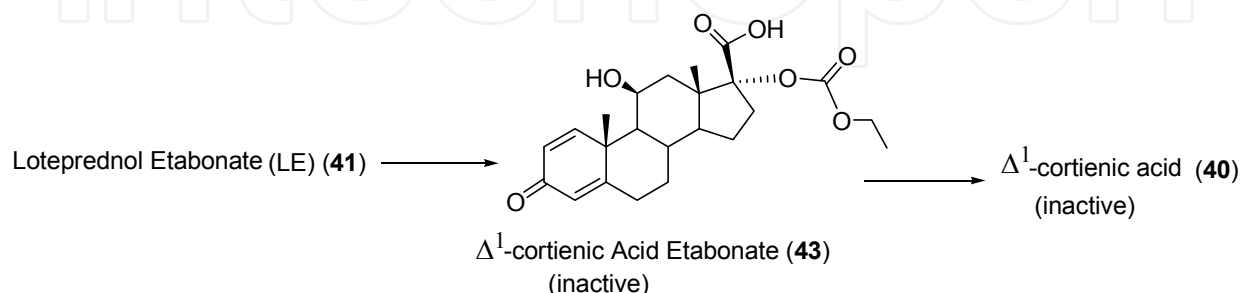
Loteprednol Etabonate (LE) namely chloromethyl- 17 $\alpha$ -[(ethoxycarbonyl) oxy]-11 $\beta$ -hydroxy-3-oxoandrosta-1, 4-diene-17  $\beta$  -carboxylate (**41**), was the most promising drug candidate among the various cortienic acid-based derivatives synthesized by Bodor and his group (**Figure 6**). In Loteprednol Elaborate (**41**), a metabolically labile ester function occupies 17  $\beta$  - position, while a stable carbonate group occupies 17 $\alpha$ -position. The ester is hydrolyzed to an inactive carboxylic acid,  $\Delta^1$ -cortienic acid etabonate (**43**), and then into  $\Delta^1$ -cortienic acid (**40**) in biological systems after exerting the desired therapeutic effect, thereby minimizing the likelihood of toxicity [**Figure 7**]. As a result of the predictable conversion of Loteprednol Etabonate into an inactive metabolite in the eye following topical administration, this glucocorticoid has a low propensity for undesirable toxicity while possessing increased anti-inflammatory activity. In fact Loteprednol Etabonate (**41**) has been found to be 1.5 times more potent than the parent anti-inflammatory agent dexamethasone [24].

*Loteprednol Etabonate (41) and its Clinical Investigations in Ophthalmic Therapeutics:*

Clinical study confirmed that Loteprednol Etabonate and some of the other soft glucocorticoids synthesized, provided a significant improvement of the therapeutic index, determined as the ratio between the anti-inflammatory activity and the thymus evolution activity [24]. In addition, binding studies using rat lung cytosolic corticosteroid receptors exhibited that the receptor binding affinity of LE and some of its analogs even exceeded that of the most potent glucocorticoids known[24]. Loteprednol Etabonate (**41**) is the one of the first-generation cortienic acid-based glucocorticoid soft drugs to get approved by Food and Drug Administration (FDA), USA for use in all inflammatory and allergy-related ophthalmic disorders, including inflammation after cataract surgery, uveitis, allergic conjunctivitis, and giant papillary conjunctivitis (GPC) [73-76]. Clinical tests on LE (**41**) by various groups of workers suggest it to be a potent glucocorticoid soft drug for ocular therapeutics. LE has also been selected for development as a potent glucocorticoid soft drug based on various considerations including the therapeutic index, availability, synthesis, and 'softness' (the rate and easiness of metabolic deactivation). LE is now the active ingredient of a number of ophthalmic preparations available in the market (*Lotemax, Alrex, Zylet etc.*) [73, 74, 76].

Loteprednol Etabonate (**41**) has been found to be highly lipophilic which is 10 times greater than that of Dexamethasone (**2**), a characteristic that could increase its efficacy by enhancing penetration through biological membranes [24,26]. Competitive binding studies with rat lung type II GRs confirmed that binding affinity of LE was more than 4 times that of Dexamerhasone [77]. A vasoconstriction test in humans used to assess the bioavailability exhibited that LE could produce a blanching response similar to that of Betamethasone 17 $\alpha$ -valerate (**16**) to confirm its good penetration properties and strong potency [11]. Bodor and his group, have reported the therapeutic index of LE having more than 20-fold better than that of other glucocorticoids including Hydrocortisone 17 $\alpha$ -butyrate (**14**), Betamethasone 17 $\alpha$ -valerate (**16**) and Clobetasol 17 $\alpha$ -propionate (**17**) based on their cotton pellet glaucoma test and thymolysis potency [9]. LE (**41**) has been rightly selected on the basis of considerations including Therapeutic Index (TI) which is the ratio between the median toxic dose (TD<sub>50</sub>) and the median effective dose (ED<sub>50</sub>), availability, synthesis and the rate and

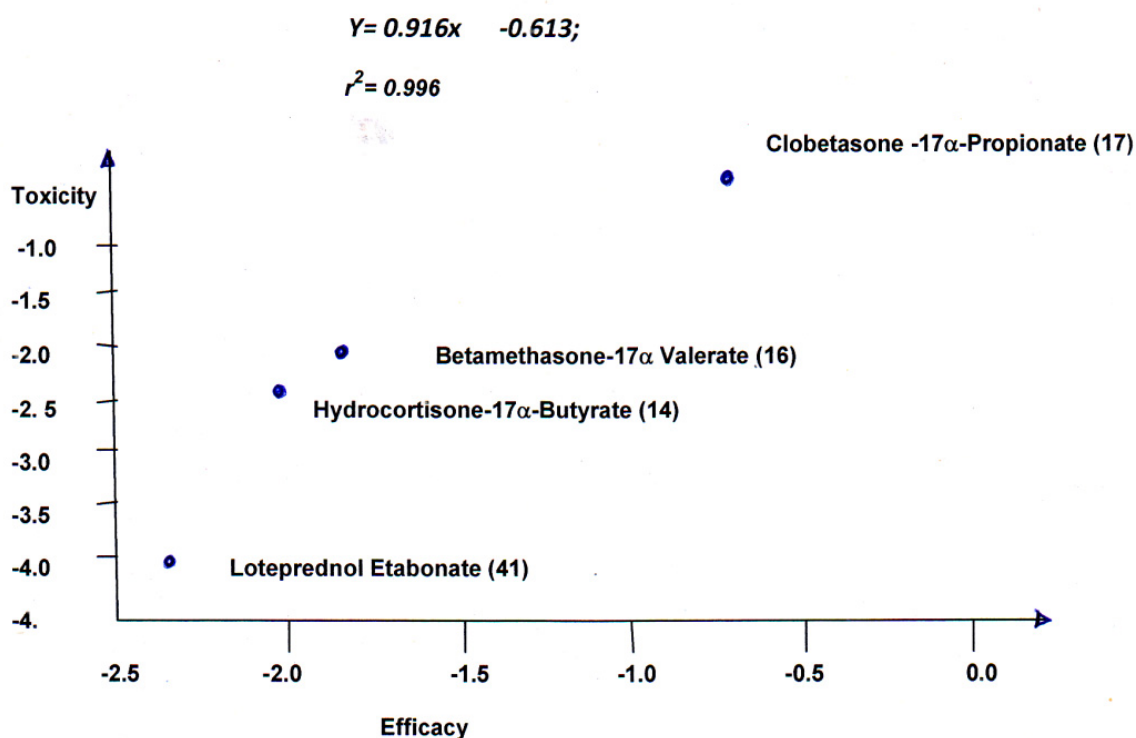
easiness of metabolic deactivation (Softness)[24]. In traditional glucocorticoids such as Hydrocortisone 17 $\alpha$ -butyrate (**14**), Betamethasone 17 $\alpha$ -valerate (**16**) and Clobetasol 17 $\alpha$ -propionate (**17**), efficacy and toxicity are closely correlated ( $r^2 = 0.996$ ) applying the relationship between the anti-inflammatory and thymus involution activities [24] determined in the cotton pellet granuloma test (**Figure 8**). In these glucocorticoids, the reported results [24] have shown that TI have been found to be almost similar regardless of their intrinsic activities; however glucocorticoid soft drug Loteprednol Etabonate (**41**) owing to its softness and improved toxicity profile, provides a significant improvement (24) (**Table 4**).



**Figure 7.** Metabolism of Loteprednol Etabonate (**41**) to  $\Delta^1$ -Cortienic acid etabonate (**43**) and then to  $\Delta^1$ -Cortienic acid (**40**).

Loteprednol Etabonate (LE) is predictably metabolized by local *esterases* into its inactive metabolite  $\Delta^1$ -cortienic acid (**40**) which has been confirmed through animal studies [20]. Clinical studies by Druzgala *et al* [78] have confirmed that the highest concentration of LE was found in cornea, followed by the iris/ciliary body and aqueous humour. The cornea also showed the highest ratio of metabolite to Loteprednol Etabonate (**41**), indicating that the cornea was the prime site of metabolism, while aqueous humour concentrations of LE were nearly 100-fold lower. This finding suggested that Loteprednol Etabonate may exert a decreased IOP effect as compared to other glucocorticoids [78]. Further a comparison of the IOP-elevating activity of Loteprednol Etabonate with that of Dexamethasone (**2**) in rabbits confirmed a lack of IOP effect with LE [79, 80]. LE was found to have a terminal half-life ( $t_{1/2}$ ) of 2.8 hrs in dogs following intravenous administration [81]. Further when absorbed systemically, LE was found to be metabolized to  $\Delta^1$ -cortienic acid etabonate (**43**) and then to  $\Delta^1$ -cortienic acid (**40**) (**Figure 7**) and have been found to be eliminated rapidly through the bile and urine [26, 81, 82]. So far numerous preclinical tests were carried out on Loteprednol Etabonate (**41**) including more recent ones by Comstock and DeCory [20, 83]. Most of these clinical studies have confirmed that Loteprednol Etabonate achieves the required balance between the solubility/lipophilicity, ocular tissue distribution, receptor binding, and subsequent rate of metabolic deactivation as have been outlined by Bodor when he conceptualized for the first time the retrometabolic drug design.

Since the design of this glucocorticoid soft drug LE by Bodor and his group, various ophthalmic suspension formulation of LE *viz.*, a 0.2% suspension, a 0.5% suspension and a combination suspension of LE 0.5% plus tobramycin 0.3%, have been developed and clinically tested in various ocular inflammatory conditions and postoperative ocular inflammation.



**Figure 8.** Literature reported [24] graph showing the relationship between the Efficacy [ $\log 1/ED_{50}$  ( $\mu\text{g/pellet}$ )] and Toxicity [ $\log 1/TD_{50}$  ( $\mu\text{g/pellet}$ )] of Hydrocortisone-17  $\alpha$ -Butyrate (14: 0.1%), Betamethasone-17  $\alpha$ -Valerate (16: 0.12%), Clobetasone-17  $\alpha$ -Propionate (17: 0.1%) and Loteprednol Etabonate (41: 0.1%). Relative TI being computed with Betamethasone-17  $\alpha$ -Valerate (16) as reference.

| Glucocorticoids                                  | Therapeutic Index (TI)<br>$TD_{50}/ED_{50}$ | Relative Therapeutic Index<br>(Rel TI) $TI/TI_{BMV}$ |
|--|---|--|
| Loteprednol Etabonate (41)                       | 56.2  | 22.5   |
| Clobetasone-17 $\alpha$ -Propionate (17)         | 3.8   | 1.5  |
| Hydrocortisone-17 $\alpha$ -Butyrate (14)        | 3.1   | 1.3  |
| Betamethasone-17 $\alpha$ -Valerate<br>(BMV: 16) | 2.5   | 1.0  |

**Table 4.** Literature reported Therapeutic Index (TI) and Relative Therapeutic Index (Rel. TI) of some glucocorticoids and Loteprednol Etabonate (41). Relative Therapeutic Index was computed with Betamethasone-17 $\alpha$  -Valerate (BMV)(16) as the reference.

Ocular diseases against which LE formulations were clinically tested included Giant Papillary Conjunctivitis, Prophylaxis of Seasonal Allergic Conjunctivitis, Seasonal Allergic Conjunctivitis, Anterior Uveitis, Blepharokerato Conjunctivitis, and Keratoconjunctivitis sicca etc. All these studies confirmed the clinical anti-inflammatory potency of LE and lack of significant IOP after its use [20]. Again two identical placebo-controlled trials examined the safety and efficacy of LE in treating post operative inflammation following cataract surgery with intraocular lens implantation [92]. Ilyas *et al* [93] have studied the long term safety of LE 0.2% by conducting a retrospective review of more than 350 seasonal and

perennial conjunctivitis patients who used LE 0.2% on a daily basis for extended periods of time. The results showed the absence of significant ADRs as there were no reports of posterior subcapsular opacification with quite insignificant IOP in most of the patients. In fact there was no observation of IOP elevation greater than 4mm Hg over base line at any period of time.

Besides, safety and efficacy of LE ophthalmic ointment 0.5% in the treatment of inflammation and pain following cataract surgery was studied in two randomized, multicentre, double-masked, parallel group, vehicle-controlled studies [20]. A very fewer LE ointment-treated patients needed rescue medication and most of them did not showed any ocular adverse event. Clinical trials on gel formulation of LE in treatment of ocular inflammation and pain after cataract surgery have been taken up more recently [20]. It is because of the high lipophilic nature of LE, gel formulation could provide improved product homogeneity over a suspension formulation to enhance its more consistent clinical response.

LE has been designed by Bodor and his group with a C-20 ester rather than a C-20 ketone and so LE is unable to form covalent adduct with lens protein, the main reason behind steroid-induced cataract formation as discussed earlier. Global market research indicates that an estimated more than 20 million LE units have been distributed globally. Clinical studies suggest the rapid metabolism of LE into inactive metabolites in conjunction with the lack of C-20 carbonyl functionality have resulted in LE – to become a unique glucocorticoid soft drug with significantly less, if any, potential for promoting steroid-induced cataract formation.[20]. LE has now been proved as a safe and effective treatment for contact lens-associated GPC, seasonal allergic conjunctivitis, postoperative inflammation or uveitis. Retrospective study established that even long time (>1 year) use of LE caused no reported adverse effects. .

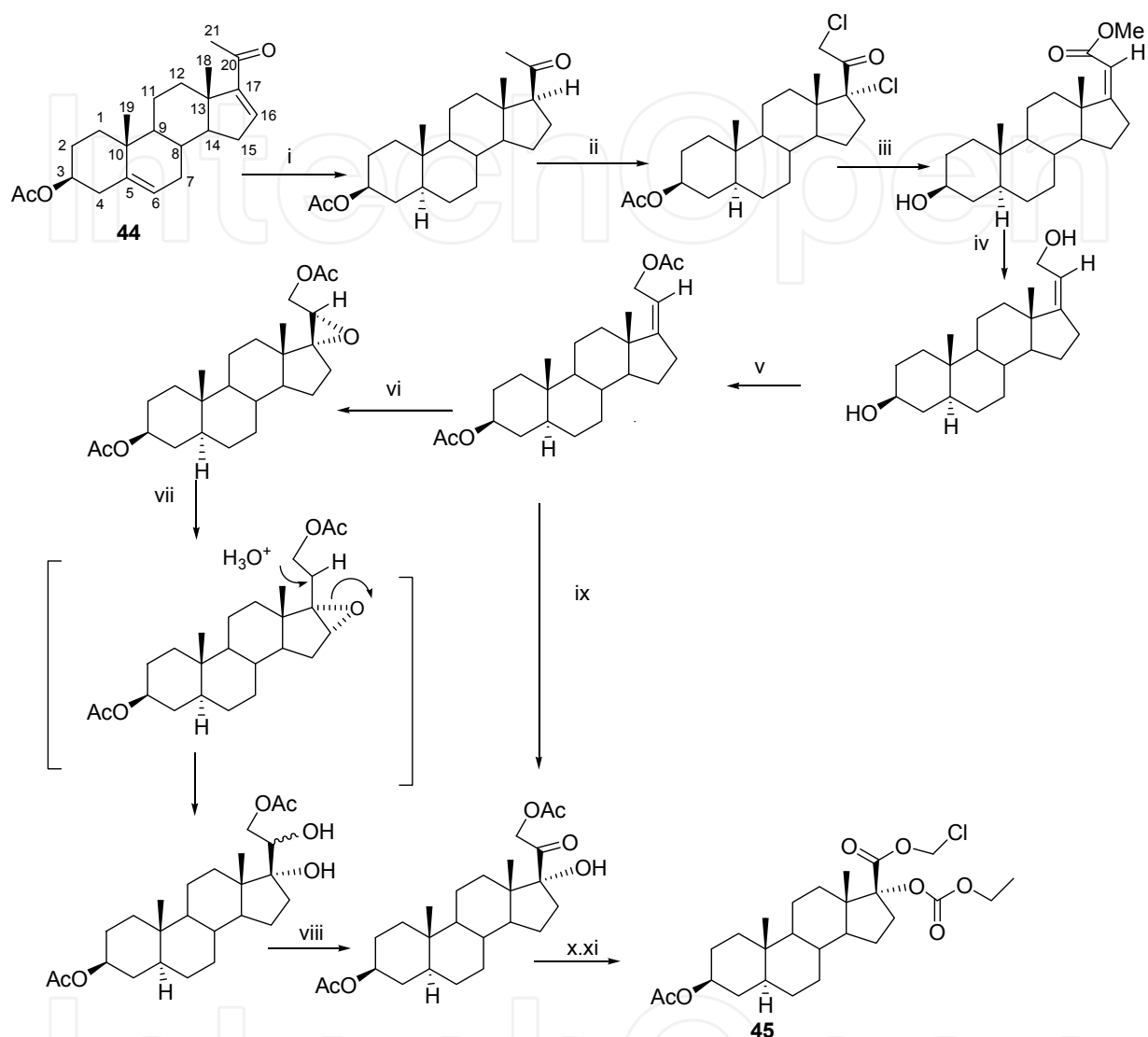
*Synthesis of the Side Chain of Loteprednol Etabonate (41) directly from 20-Oxopregnane (44) to furnish an Analog (45) of LE:*

Based on promising results from animal studies, further clinical trials on Loteprednol Etabonate (41) are also going on for a safer treatment of gastrointestinal inflammation and other diseases such as asthma, rhinitis, and dermatological problems [76,82,84-86]. Success story of this retrometabolically designed glucocorticoid soft drug Loteprednol Etabonate has drawn attention to pharmaceutical industries as well as people working in steroid field worldwide. The authors of this chapter [87], recently, have reported a facile synthesis of the side chain of this potent ocular glucocorticoid soft drug, starting directly from 20-oxopregnanes, *viz.*, 3 $\beta$ -acetoxy-pregn-5(6),16(17)-diene-20-one (16- dehydropregnenolone acetate i.e. 16-DPA) (44)- a potent steroid drug intermediate, utilizing their recently developed metal mediated halogenation technique as a key reaction [88,89 ] to furnish the final product –an analog (45) of Loteprednol Etabonate (41) with the requisite side chain [Scheme 1].

The present methodology paves a useful and productive way to construct the side chain of this important glucocorticoid soft drug directly from 20-oxopregnanes *via* its C-21



functionalization in much simpler and easier way with their newly developed metal mediated halogenation technique, which avoids application of harsh and tedious reaction conditions associated with this conversion [90, 91].



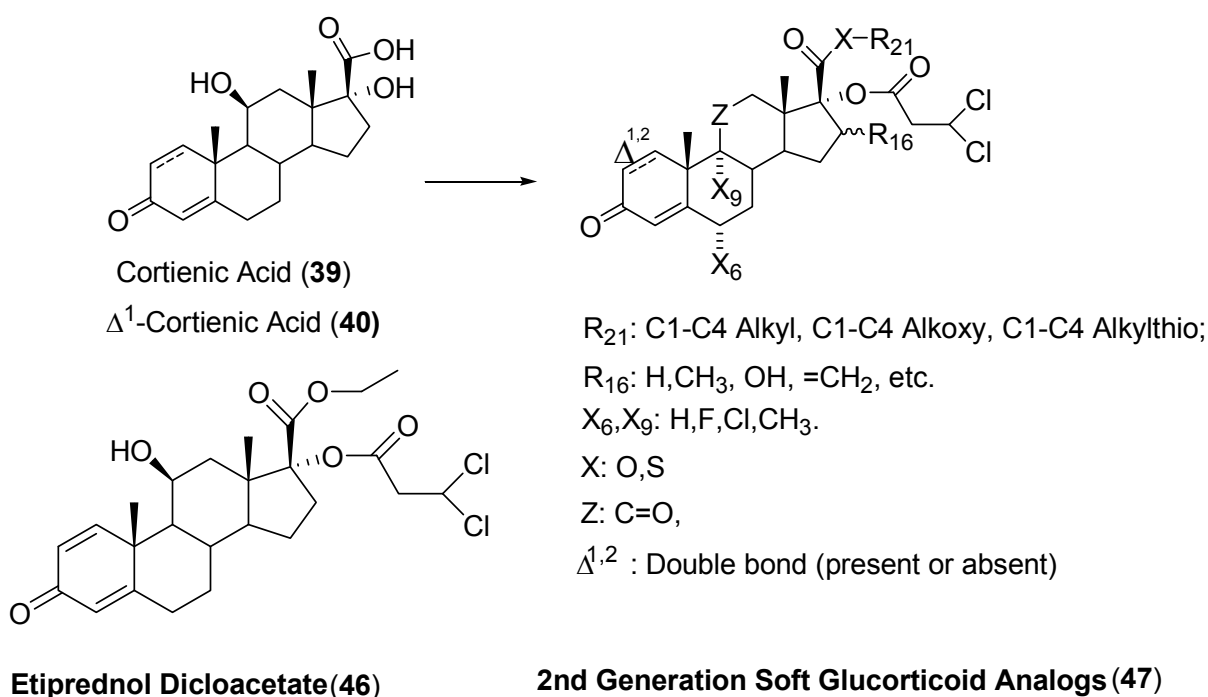
**Scheme 1.** Reagents and conditions: (i)  $\text{H}_2$ , Pd-C, 95% (ii)  $\text{MnO}_2$ -TMSCl/AcCl-AcOH, 81% (iii) 3% KOH, MeOH- $\text{H}_2\text{O}$ , 75% (iv)  $\text{LiAlH}_4$ , THF, 88% (v) CAN, AcOH, 75% (vi) *m*-CPBA,  $\text{CHCl}_3$ , 62% (vii)  $\text{H}_2\text{SO}_4$ , acetone- $\text{H}_2\text{O}$ , 48% (viii) Jones reagent, 57% (ix)  $\text{OsO}_4$  -  $\text{H}_2\text{O}_2$ , rt., 50% (x)  $\text{NaIO}_4$ , Ethyl chloroformate, 70% (xi) Chloromethyl iodide, 75% .

*Second-generation Corticoid Acid (39)-based Glucocorticoid soft drugs: Etiprednol dicloacetate (46) and its Analogs (47):*

*Synthesis of Drug molecules and Structure-Activity Studies:*

Based on their retrometabolic drug design approach, Nicholas Bodor [94] have more recently introduced another new class of soft glucocorticoids with  $17\alpha$ -dichloroester substituent. These are now known as the second generation soft glucocorticoids (**Figure 9**). This is said to be a unique design as no known glucocorticoid has been found to contain a

halogen substituent at the  $17\alpha$  position. Nevertheless, the pharmacophore portions of these second-generation cortienic acid-based soft glucocorticoids, having the halogen atoms at  $17\alpha$  position, can be positioned so as to provide excellent overlap with those of the traditional glucocorticoids [24, 95]. It has been conceived the idea that dichlorinated substituents seem required for activity and sufficiently soft nature. Molecular configuration suggests that with dichlorinated substituents, one of the chlorine atom would necessarily point in the direction needed for pharmacophore overlap, whereas with monochlorinated substituents, steric hindrance might force the lone chlorine atom to point away from this desired direction. Secondly experimentally it has been found that as compared with the unsubstituted ester, dichloro substituents could cause ~20 fold increase in the second-order rate constant  $k_{cat}/K_M$  of enzymatic hydrolysis in acetate esters, on the other hand monochloro



**Figure 9.** Design of 2<sup>nd</sup> Generation Cortienic Acid-based Soft Glucocorticoids Soft Drugs (47) and their Glucocorticoid Soft Drug representative Etiprednol Dicloacetate (ED)(46)

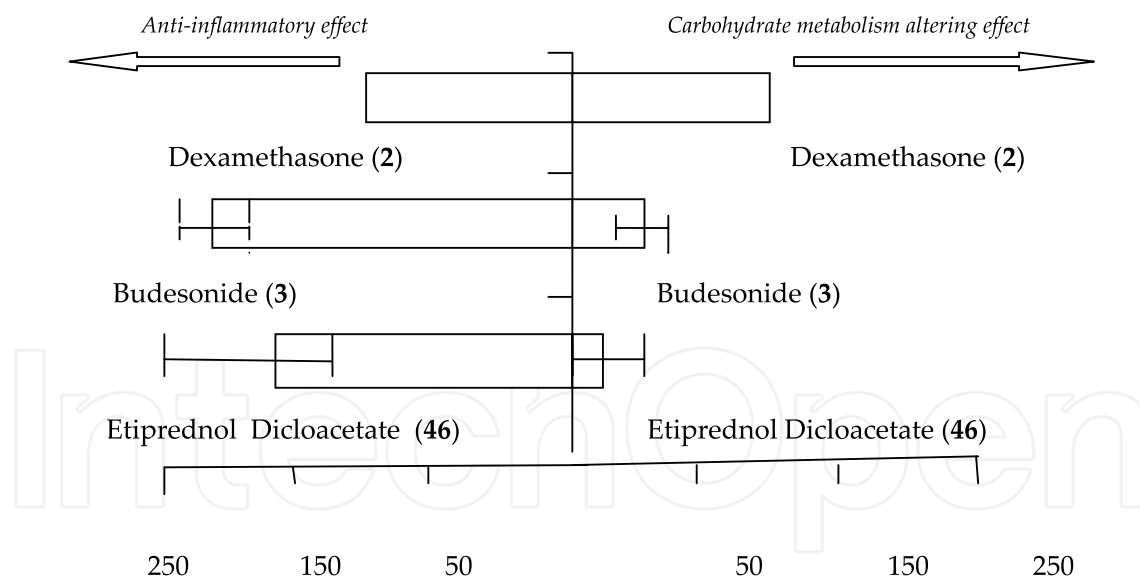
substituent did not cause any change [96]. Unlike first generation soft glucocorticoids, in the second generation of this soft steroid series, hydrolysis primarily cleaves the  $17\alpha$ - ester group and not the  $17\beta$ -ester group. The corresponding metabolites are also not active. From large no of compounds synthesized in this series, Etiprednol Dicloacetate (ED) (46) had been selected for development as a potent ocular glucocorticoid soft drug [24].

#### *Etiprednol Dicloacetate (46) and its Clinical Investigations in Ophthalmic Therapeutics:*

In animal and in human clinical trials, in accordance with its soft nature, Etiprednol Dicloacetate (46) was found to have low systemic toxicity [94, 97-99]. Etiprednol Dicloacetate had also shown better receptor binding capacity than Loteprednol Etabonate and was found to be more effective than Budesonide (3) in various asthma models [24]. Further No Observable Adverse Effect Level (NOAEL) of ED after oral administration for 28 days was

found to be 2mg/kg in rats and dogs, and about 40 times higher than that of Budesonide [97].

The comparison of the transrepressing and transactivating activity of Etiprednol Dicolacetate (46) and Budesonide(3) were done by measuring their inhibition in interleukin(IL)-1 $\beta$  production of a simulated human monocyte cell line and by evaluating glucocorticoid-induced increase in the activity of tyrosine-amino-transferase ( TAT) of a rat hepatoma cell line respectively [99] and the measured activities were expressed relative to Dexamethasone (2) From the results it was found that ED (46) possesses less transactivating activity with a preserved transrepressing activity, and hence ED is to be called as a dissociated glucocorticoid. Dissociation of transactivating ( carbohydrate metabolism altering) and transrepressing ( anti-inflammatory) activity found in Etiprednol Dicloacetate(ED) is a fruitful advantage in subsequent help in separating the most beneficial anti-inflammatory activity from the undesired side effects or adverse drug reactions (ADRs).A comparison of transrepression ( anti-inflammatory effect) and transactivation (carbohydrate metabolism altering) effects of dexamethasone (2), used as 100% reference, Budesonide (3) and Etiprenol Dicloacette (46) determined on an average of two experiments for concentrations of  $10^{-7}$  (98) is depicted in **Figure 10** [24]. Hence this productive effort in developing dissociated glucocorticoids can be termed as one of the novel and sought after mechanistic approaches towards the development of newer glucocorticoid soft drugs [24, 100,101].



**Figure 10.** Literature reported [24] tentative comparison of transrepression (anti-inflammatory effect) and transactivation (carbohydrate metabolism altering) effects of dexamethasone (2)(used as 100% reference), Budesonide (3) and Etiprednol Dicloacetate (46)

### 3. Conclusion

Since the introduction of glucocorticoids in drug industry more than a half century ago, new series of glucocorticoids have been introduced for site specificity as well as for minimizing

systemic side effects. At the initial stage, several new generation glucocorticoids were developed using prodrug design approach involving changes or modifications made in glucocorticoid molecules introducing specific substituents at various specific positions of the basic glucocorticoid skeletons to obtain better skin penetration, slower enzyme degradation and greater affinity for the cytosol receptor. The term prodrug refers to a pharmacologically inactive molecule that is converted to an active drug by metabolic biotransformations that may occur prior, during or after adsorption or at specific target sites within the body. This approach has given several potent new generation glucocorticoids such as Budesonide (3), 17-Prednicarbate (9), Fluticasone propionate (11), Methyl prednisolone aceponate (5), Beclomethasone (7) etc towards successful treatment of plethora of diseases including psoriasis, allergies, asthma, rheumatoid arthritis and lupus, with significantly minimized systemic side effects. However, all these old and new generation glucocorticoids are effective in reducing anterior segment inflammation only and not suitable for ophthalmic therapeutics as they are found to be associated with Adverse Drug Reactions (ADRs) including elevation of Intraocular Pressure (IOP) and steroid-induced cataract formation in case of ophthalmic therapeutics as they were not designed for ocular treatment. Successful eye-specific therapeutic agents can only be achieved by suitable drug-design approaches which thoroughly can integrate the specific pharmacological, metabolic, and targeting requirements of ophthalmic drugs. Chemical Delivery Systems (CDSs) and Retrometabolic Soft Drug Design approaches initiated by Prof. Nicholas Bodor and his group at the Center for Drug Discovery, University of Florida, Health Science Center, USA, are found to be quite successful with a major break through for this purpose providing flexible and generally applicable solutions. Their potential is indeed well illustrated by the results obtained with a number of soft  $\beta$ -blockers and glucocorticoid soft drugs designed within this framework towards ophthalmic therapeutics. Soft  $\beta$ -blockers, *viz.*, Betaxoxime (29a), Adaprolol (33) and Glucocorticoid Soft drugs *viz.*, Loteprednol Etabonate (41) and Etiprednol Dicloacetate (46) are some of the soft drugs developed by this retrometabolic drug design approach which have already reached the clinical development phase in various ophthalmic areas and one of them Loteprednol Etabonate (LE) is already being in the market as a promising glucocorticoid soft drug in ophthalmic therapeutics. Not only that, based on clinical results from animal studies, LE now also finds place in safer treatment of gastrointestinal inflammations and other diseases such as asthma, rhinitis and dermatological problems. Moreover dissociation of transactivating and transrepressing activity found in the second generation glucocorticoid soft drug, *viz.*, Etiprednol Dicloacetate (ED) could open up a novel and promising mechanistic pathways towards the development of more and more potent glucocorticoid soft drugs in future.

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