Advances in Contemporary Research

Retrometabolism based drug targeting- Soft drug approach

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Despite considerable progress in medicinal chemistry in the last century, rational drug design that allows the development of effective pharmaceutical agents with minimal side effects is still an elusive goal. The primary causes for side effects are the generalized effect of drug on receptors present throughout the body and uncontrolled drug metabolism. Thus, it has become evident that targeting and metabolism considerations should be an integral part of any drug design process and that the focus should be on increasing activity as well as therapeutic index of the potential drug candidate. Various ideas have been suggested over the years to come up with an ideal approach to drug design. In this review, we shall be dealing with one such approach, that is, the soft drug approach. A soft drug is pharmacologically active as such, and it undergoes a predictable and controllable metabolism to nontoxic and inactive metabolites. The main concept of soft drug design is to avoid oxidative metabolism as much as possible and to use hydrolytic enzymes to achieve predictable and controllable drug metabolism. The discussion shall present an overview on the need for the development of soft drugs, associated terminologies and the different classes of soft drugs.

Keywords: Rational drug design, drug targeting, retrometabolism, soft drugs, predictable metabolism

Need for Drug Targeting

During the last few years, medicinal chemistry has witnessed significant progress in several fields including elucidation of biochemical mechanism of drug action, high throughput screening, combinatorial chemistry, etc. Unfortunately, there has not been a proportionate increase in the number of new approved drugs. The main reason for the low success rate of most of these promising drug candidates is that even though a great deal of attention is paid to increasing efficacy, toxicity concerns are often ignored. Toxicity concerns come to light only during clinical trials. Large percentage of drugs having good activity have been discarded when they showed unacceptable toxicity or unavoidable side effects[1].

Side effects are a result of intrinsic receptor affinity, which is also responsible for drug action. In addition, although localized drug action is desired in most cases, the corresponding receptors are present throughout the body. This leads to generalized action of the drug[1-3].

Drug (D) metabolism can generate analog metabolites that have structures and activities similar to the original drug, but have different pharmcokinetic properties; other metabolites $(M_1 \ldots M_k)$ including inactive ones (M_i) and potentially reactive intermediates $(I_1^* \ldots I_n^*)$ that can be responsible for various kinds of cell damage by forming toxic species[4,5]. The resultant toxicity will be the sum total of the toxicities due to the parent drug as well as toxicities of individual drug metabolites (Eqn. 1)

$$T(D) = T_i(D) + T(D_1 \ldots D_m) + T(M_1 \ldots M_k) + T(I_1^* \ldots I_n^*) \qquad \ldots 1$$

This brings us to the conclusion that rational drug design should incorporate drug targeting and metabolism considerations in addition to aiming for an increase in drug activity right from the inception stage.

Drug Targeting Approaches

Drug targeting can be achieved by the following three approaches [3]:

a) **Physical Targeting**: This includes the concept of controlled and sustained drug release. The focus of this type of targeting is to modify drug delivery without affecting specificity.

b) **Biological Targeting**: This involves use of drug-monoclonal antibody complex for site directed drug delivery.

c) **Chemical Targeting**: This concept involves modifications in the chemical nature of drug

molecule itself. Chemical targeting has been found to be most rewarding amongst the 3 approaches. Chemical targeting itself can be divided into three different approaches:

(i) **Hard Drug Approach**: Hard drug approach, based on Ariens's theoretical drug design concept of non- metabolizable drugs was introduced in 1972[6,7]. Hard drugs do not undergo any metabolism and hence, avoid the problems caused by reactive intermediates. A few successful examples of hard drugs include bisphosphonates and ACE inhibitors[6].

The discovery of bisphosphonates was based on earlier studies of inorganic pyrophosphate by Fleisch and his coworkers[8]. Pyrophosphates were seen to bind very strongly to calcium phosphate. *In vitro* studies showed that pyrophosphates inhibited formation of calcium phosphate crystals and also the dissolution of these crystals. However, pyrophosphates did not exhibit these properties *in vivo*[6]. The *in-vivo* failure of pyrophosphates to inhibit bone resorption was attributed to it's rapid enzymatic hydrolysis before reaching the site of action. These findings led to a search for analogs that would display properties similar to pyrophosphate, but would also resist enzymatic hydrolysis. Thus bisphosphonates were developed. Bisphosphonates resemble the structure of pyrophosphates, the only difference being that the P-O-P bond in pyrophosphate is replaced by P-C-P in bisphosphonates[6,11]. Bisphosphonates inhibit bone resorption and are resistant to enzymatic hydrolysis. The structure of alendronate, an example of bisphosphonate is given below (**Figure 1**). Due to their poor lipophilicity, the bisphosphonates are not metabolized *in vivo*[9-12]. In general, these compounds are very safe with no significant systemic toxicity.

Though the concept of hard drugs sounds good theoretically, practically it is difficult to achieve non-metabolizable drugs. It is well recognized that the body can attack and alter chemically quite stable structures. Therefore, even if a drug is 95% excreted unchanged, the unaccounted small portion can cause toxicity[6,13]. Considering the broad substrate specificities and the versatilities of cytochrome P-

450s and other drug-metabolizing enzymes, designing drug candidates that are metabolically inert may not always be feasible[6]. Besides, in order to achieve non-metabolizable quality, one has to go to pharmacokinetic extremes in drug design[1].

(ii) **Prodrug Approach**: A prodrug is a pharmacologically inactive derivative of a parent drug molecule, which requires spontaneous, i.e., non-enzymatic or enzymatic transformation within the body in order to release active drug [14-19]. The rationale behind the prodrug approach is that a molecule with optimum structural configuration and physicochemical properties for eliciting desired therapeutic response at it's target site does not necessarily possess the best molecular form for it's delivery to the site of action. Eg.: Most drugs diffuse poorly through the stratum corneum because of unfavourable physicochemical properties. Several studies have demonstrated a biphasic solubility profile for absorption through the skin, i.e., in order to diffuse through the skin a compound should possess adequate water as well as lipid solubility. This can often be achieved by the prodrug approach. Nalidixic acid is a promising agent for the treatment of psoriasis, but it's physicochemical properties are sub optimal for efficient topical absorption. By esterification of carboxylic acid group by O- acyloxymethylation, the prodrug derivatives, both being more lipid and water-soluble have been obtained. The double esters are enzymatically hydrolyzed to nalidixic acid during transport through skin[15]. The structure of nalidixic acid and it's prodrug derivatives are shown in the **Figure 2**.

Even in case of prodrugs, toxicity concerns cannot be completely ruled out. The metabolism of the prodrugs after it reaches the site of action is not controlled. There is every possibility that adverse drug reactions as a result of reactive intermediates can occur.

(iii) **Retrometabolism Based Drug Targeting**: A combination of classical Structure Activity Relationship (SAR) based drug discovery approaches with structure metabolism relationships is termed as *retrometabolism based drug design approach*

$$O=\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-O-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}=O \qquad\qquad O=\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-\overset{\overset{\displaystyle R'}{|}}{\underset{\underset{\displaystyle R''}{|}}{C}}-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}=O$$

Pyrophosphate   Geminal biphosphonate
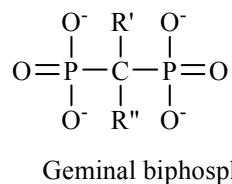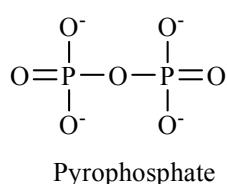
Figure 1 — Comparative structures of pyrophosphate and bisphosphonate

R   =   H   (Nalidixic acid)

R   =   —CH$_2$O—C(=O)—CH$_3$

R   =   —CH$_2$O—C(=O)—CH$_2$CH$_3$
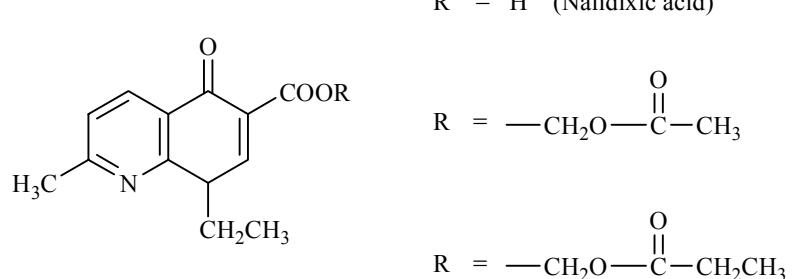
Figure 2 — Nalidixic acid and it's prodrug derivatives

Retrometabolism based drug targeting involves two drug design approaches, namely:

a) Chemical Delivery Systems (CDS): Chemical Delivery Systems are defined[23] as chemical compounds that are produced by synthetic chemical reactions forming covalent bonds between the drug and specifically designed 'carrier' and other moieties. CDSs consist of biologically inert molecule containing the drug in an appropriately modified form that requires several enzymatic steps during it's conversion to active drug, and that enhances drug targeting to a particular organ or site[20-24]. CDSs comprises of drug complexed with targetor and modifiers. Targeting is achieved by removal of modifiers and finally targetor by sequential metabolic cleavages.

Major CDSs can be divided into three classes [3]:
a) Enzymatic physical chemical based targeting
b) Site specific enzyme activated targeting
c) Receptor based chemical targeting

Eg.: Brain targeting CDS[25]: Brain targeted CDSs are designed to deliver drugs specifically to the brain. This type of CDS takes advantage of the unique properties of the Blood Brain Barrier. Brain targeted CDS is based on the idea that a highly lipophilic compound is rapidly absorbed by the brain and once it enters the brain it is converted into a hydrophilic molecule which is incapable of leaving the brain. Thus the drug becomes 'locked–in'. To obtain such a CDS, the drug is chemically modified to introduce the protective function and targetor moiety (T). In principle, many targetor moieties are possible but in practice, the one based on 1,4-dihydrotrigonelline system, in which the lipophilic 1,4 dihydro form (T) is converted *in vivo* to the hydrophilic quaternary form

(T*), proved the most useful. Many brain targeting CDSs have already been explored; estradiol- CDS is undergoing clinical trials[26]. The schematic representation of 'lock-in' mechanism of estradiol CDS is shown in **Figure 3**.

b) *Soft Drugs*: Soft drugs can be defined as new, active therapeutic agents often isosteric/ isoelectronic analogs of lead compound, with chemical structure specifically designed to allow predictable metabolism into inactive metabolites after exerting desired therapeutic effect[27-32] (**Figure 4**).

The two approaches are opposite to each other, **CDS**- inactive by design, activated strategically at site of action; **Soft Drugs**- active, novel drugs exert their desired activity at applied site, they will be destroyed metabolically in a timely fashion, and so they cannot affect other sites in the body.

One other difference between the 2 approaches is that in case of CDSs, various enzymes including oxidative and reductive enzymes are involved whereas oxidative processes are preferentially avoided in soft drug design.

Soft Drugs

Soft drugs are new active therapeutic agents obtained by building into the molecule a detoxification route in addition to activity. Desired activity is generally local and these agents are administered or applied at or near the site of action. Therefore, in most cases they produce pharmacological activity locally but their distribution away from the site results in immediate metabolic deactivation that prevents any kind of toxicity. The aim for designing soft drugs is not to avoid metabolism but to control and direct it.

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* Tapfer M K, Sebestyer L, Kurucz I & Bodor N, *Pharmacol Biochem Behav*, 77, **2004**, 443

ᵞ Bodor N & Buchwald P, in *Burger's Medicinal Chemistry and Drug Discovery*, Vol. 2, Drug discovery and development, 6th edition; Abraham D J; Wiley, New York, 2, **2003**, 533

Tapfer M K, Sebestyer L, Kurucz I & Bodor N, *Pharmacol Biochem Behav*, 77, **2004**, 443

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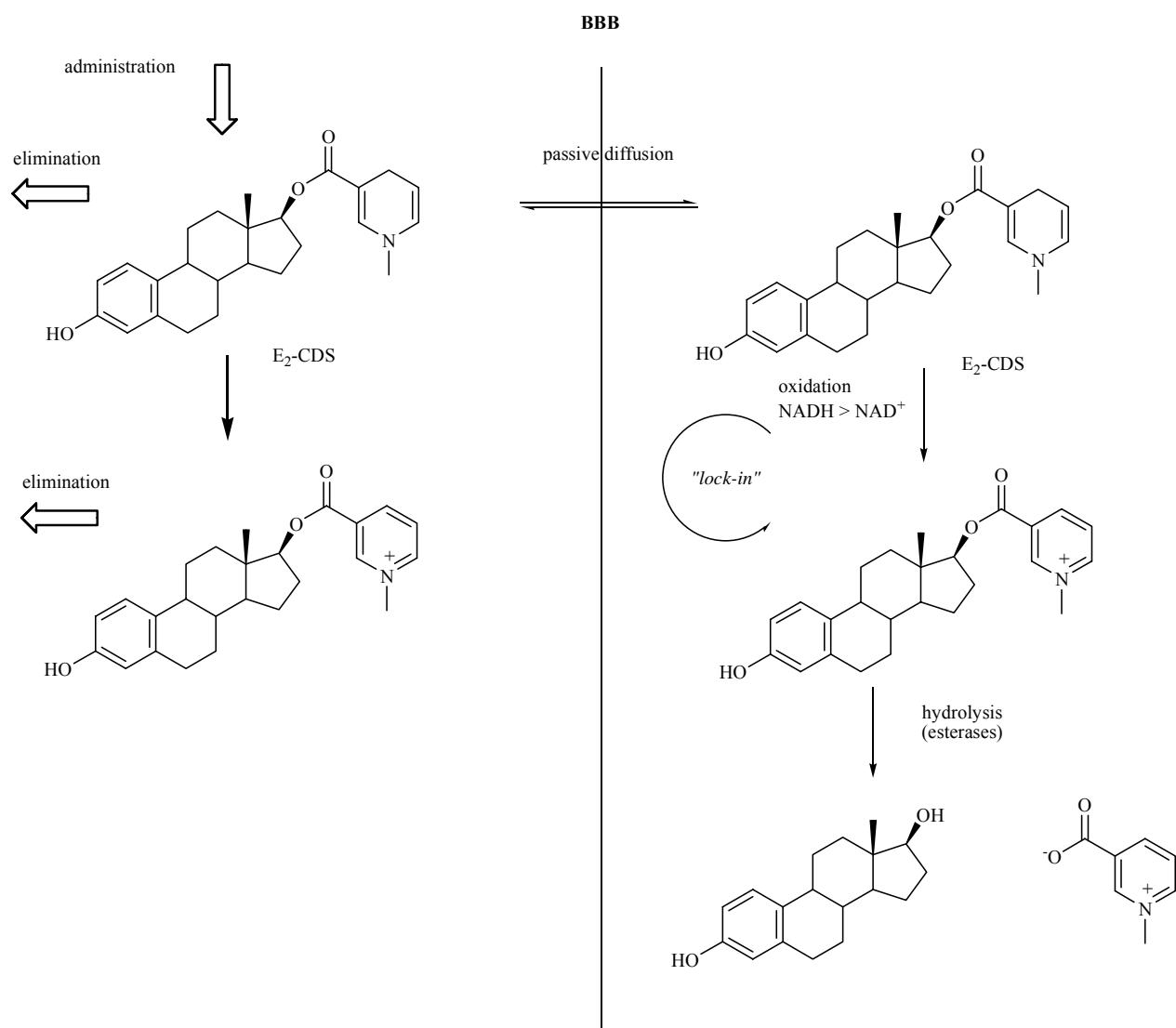
Figure 3 — Schematic representation of 'lock-in' mechanism for estradiol-CDS

The rational design of soft drugs can be divided into the following steps:

i) Identification of drug toxicity problem; ii) Determination of metabolic pathways of drug in the body; iii). Identification of pharmacophore in the molecule; iv) Modification of the parent molecule in such a way that it shows good therapeutic efficacy at site of action but undergoes metabolism in a controlled and predictable manner to form inactive non toxic moiety when distributed away from this site.

Several criteria should be considered in the design of a soft drug:

i) Pharmacophore of the drug: The participation of restrictive pharmacophore regions in formation of soft drugs is the deciding factor for the degree of freedom

one has in structural modifications. If they are not involved, there is more freedom for structural modifications; ii) Resulting soft drugs should be isosteric/ isoelectronic with parent drug moiety; iii) As far as possible, oxidative routes of metabolism for soft drug to be converted to non-toxic metabolite should be avoided. Inspite of being the mediator in the most critical metabolic pathways, oxygenases are generally not preferred because they show a great deal of interspecies and inter individual variability. Oxygenases are also subject to induction and inhibition; iv) If possible, inactivation should take place as a result of a single, low energy and high capacity step that yields inactive species subject to rapid elimination. The preferred route of metabolism

retrometabolic
design

SD

$\|$

M_i

D

M_1 .... M_k

D_1 .... D_m

I_1 .... I_n

IC_1
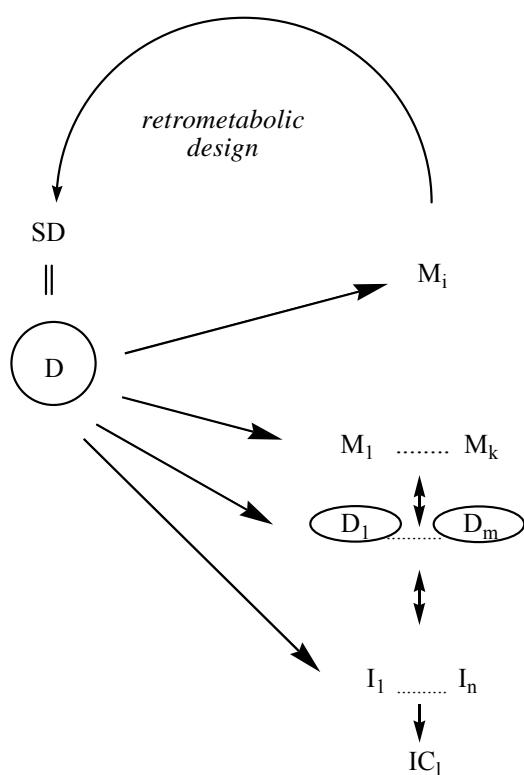
Figure 4 — The retrometabolic design loop, including soft drug design. A schematic representation of possible metabolic pathways for drugs in general is also included.

for soft drugs is hydrolytic cleavage. Hydrolytic cleavage does not rely entirely on kidneys or liver. Thus metabolism of these soft drugs is not altered in case of impairment of these organs.

Soft Drug Approaches

Bodor has classified and defined soft drug design under 5 broad categories[1]. We will discuss them one by one.

1. Inactive Metabolite Based Soft Drugs

Inactive metabolite based soft drugs are active, therapeutic agents which are designed using an inactive metabolite of active parent drug. These soft drugs are isosteric/ isoelectronic analogs of the parent drug. These drugs are converted to the inactive metabolite in one step via a carefully controlled metabolic conversion after the desired effect has been achieved.

Some of the classes of drugs, which have been explored for soft drug design based on this approach, are:

a Soft β blockers[32,37]: Adaprolol, Esmolol

b Soft corticosteroids: Glucocorticoid γ Lactones[35,36], Loteprednol Etabonate[37-39]], Etiprednol dicloacetate [40,41].

c Soft opioid Analgetics: Remifentanil[42]

d We will restrict ourselves to a detailed account of one of the more successful classes of inactive metabolite based soft drugs i.e., soft cortico-steroids.

Soft Corticosteroids

Corticosteroids have very good anti-inflammatory action but they are generally contra-indicated for use in treatment of ocular inflammations, a in addition to general systemic side effects, they also produce elevation of intra ocular pressure (IOP), i.e., they cause glaucoma and cataract. Glaucoma is caused as a result of increased resistance to aqueous humor outflow[43]. Hypothesis given for the steroid induced cataract[44] is the formation of Schiff bases between steroid C_{20} ketone group and nucleophilic groups of lysine residues of proteins. This is followed by Heyns rearrangement[45] involving adjacent C_{21} hydroxyl group. This results in destabilization of protein structures and thus, cataract[46-49]. The mechanism of steroid induced cataract is depicted in **Figure 5**.

First Generation Cortienic acid based soft steroids

Loteprednol etabonate is a soft steroid, which received FDA approval on March 9, 1998, as the active ingredient of two ophthalmic preparations- Lotemax and Alrex[50-52]. Loteprednol Etabonate is the only corticosteroid receiving FDA approval for all anti-inflammatory and allergy related ophthalmic disorders, including post surgical inflammation, uveitis, allergic conjunctivitis, etc. It resulted from classic inactive metabolite based soft drug approach[52-57].

Hydrocortisone undergoes a variety of oxidative and reductive conversions[58]. Cortienic acid is an ideal lead for inactive metabolite approach because it lacks corticosteroids activity and is a major metabolite excreted in the urine of man. To obtain active compounds, the important pharmacophores found in 17α and 17β side-chains had to be restored. The structure of hydrocortisone and it's inactive metabolite, cortienic acid, which is the lead molecule for soft drug is shown in **Figure 6**.

A haloester in the 17β position[54] and novel carbonate or ether[59] substitution were found as critical functions for activity. A 17α ester instead of a carbonate would have led to interaction between 17α
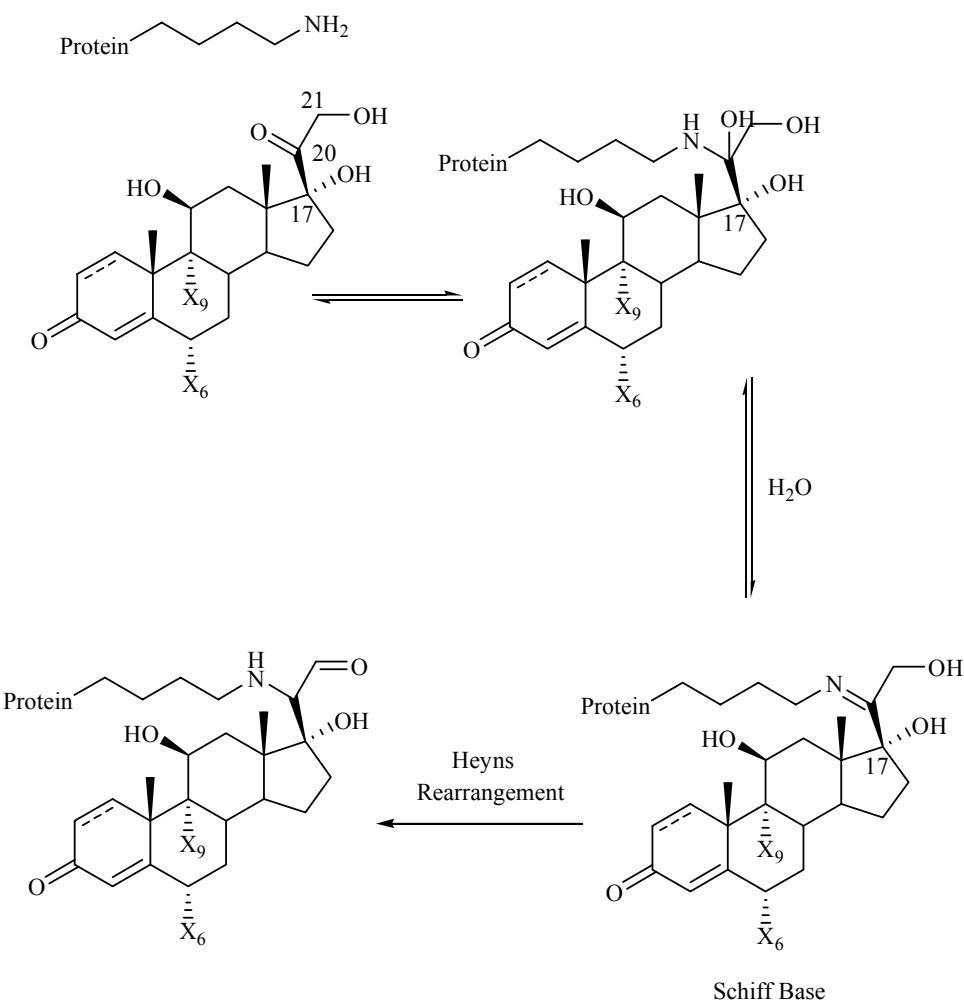
Figure 5 ― Mechanism of steroid induced cataract

hyrocortisone
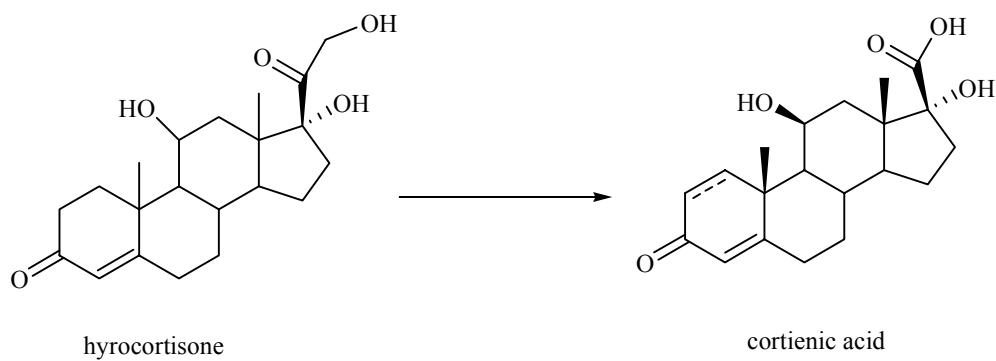
cortienic acid

Figure 6 ― Hydrocortisone and it's inactive metabolite, cortienic acid

Sr. no.	Corticosteroid	Therapeutic Index
1	Loteprednol Etabonate	24.0
2	Betamethasone 17 α valerate	1.0
3	Clobetasol 17 α propionate	1.5

ester with 17β acid function to give a mixed anhydride, which is potentially toxic. A variety of 17β esters were synthesized. Because this position is an important pharmacophore that is sensitive to modifications, freedom of choice was limited. For e.g., although chloromethyl or fluromethyl esters

showed very good activity, the chloroethyl demonstrated very weak activity. Simple alkyl esters were inactive. Consequently, the 17 β- chloromethyl esters were held constant and 17 α carbonates with different substituents on steroid skeleton were varied for further investigation. Loteprednol Etabonate was selected for development because of considerable improvements in therapeutic index in comparison to traditionally used corticosteroids[32].]

Recently, loteprednol has been proven to be effective in the management of allergic rhinitis (400 μg once daily). Loteprednol etabonate has found to be effective in reducing rhinorrhea, nasal congestion, nasal itching and improving nasal flow[60]. In conclusion, loteprednol as the first representative of soft steroids elicits marked anti-inflammatory effects, but has no impact on endocrine responses. It may represent a promising new therapy in the treatment of allergic rhinitis and asthma[53].

The general structure of designed soft corticosteroid classes, design process and metabolism are summarized in **Figure 7**.

Second generation cortienic acid based soft steroids

A new class of soft steroids has been developed which is unique in design owing to the presence of halogen substituents at 17 α position. Pharmacophore portions of this class of drugs overlap with that of traditional corticosteroids [61].

Dichlorination is required for the following reasons: i) With dichlorinated substituents, one chlorine atom will necessarily point in the direction needed for pharmacophore overlap but with monochlorinated substituents steric hindrance forces the lone chlorine atom to point away from desired direction; ii) Dichloro substituents result in nearly 20 fold increase in second order rate constant K_{Cat}/K_M of enzymatic hydrolysis in comparison to unsubstituted ester [62].

In second generation soft steroids cleavage occurs at 17 α positioned ester unlike first generation soft steroids. Metabolites formed are inactive. From second generation series Etiprednol Dicloacetate was selected for further development. It was found to have low toxicity in animal models and human clinical trials[40,41,63,64].

R_1 = alkyl, haloalkyl, etc.
R_2 = alkyl, alkoxyalkyl, COOalkyl, etc.
R_{16} = H, CH$_3$
X_9, X_6 = H, F

R_1 = C$_1$-C$_4$ alkyl, C$_1$-C$_4$ alkoxy, C$_1$-C$_4$ alkylthio
R_{16} = H, CH$_3$, OH, = CH$_2$, etc.
X = O, S
Z = C=O,-CHOH,-CHCl

cortienic acid

Loteprednol Etabonate

Etiprednol Dicloacetate

Figure 7 — Design of first and second-generation soft steroids based on the known inactive metabolite cortienic acid

Soft corticosteroids can also be used as anti-asthamatics. Although, the current generation of anti asthamatic drugs show virtually no oral bio-availability, some of the active drug reaches other tissues via absorption through lungs resulting in adverse effects such as osteoporosis and suppression of the hypothalamic-pituitary-adrenocortical axis. Considerable efforts have been carried out for the development of ester derivatives of corticosteroids, which can undergo rapid hydrolysis to form inactive metabolite. But the disadvantage with these ester soft drugs is that they undergo premature hydrolysis in the lung itself due to the presence of lung esterases and thus do not show significant activity. Itrocinonode is one such example. However, it has been recently discovered that glucocorticoid lactone soft drugs display sufficient activity and stability in the human lung. It also undergoes rapid hydrolysis in the plasma to form inactive metabolite. This property is a result of hydrolysis in plasma being mediated by human serum paraoxonase, an esterase that is confined to plasma and liver[35]. The structure and metabolism of glucocorticoid lactone is depicted in **Figure 8**.

2. Soft Analogs

Compounds classified as soft analogs are close structural analogs of known active drugs (lead compounds), but they have a moiety that is susceptible to metabolic, preferentially hydrolytic degradation built into their structure[1,2]. These analogs are characterized by following basic features: i) They are close structural analogs; the whole molecules are isosteric/isoelectronic with basic drug; ii) The metabolically soft spot is built in non-critical part of the molecule, which results in little or no effect on transport, affinity, and activity of the drug; iii) The built-in metabolism is the major or preferentially the only metabolic route; iv) The rate of the predicted metabolism can be controlled by molecular manipulations; v) The resulting products are non-toxic or of very low toxicity.

The predicted metabolism does not require enzymatic processes leading to highly active intermediates.

We can illustrate the use of this approach by citing the example of soft antimicrobials.

The general structure of these soft antimicrobials is represented in **Figure 9.**

The disadvantage of majority of traditional antimicrobial agents is the development of bacterial resistance against them. Long chain quaternary ammonium compounds exert antibacterial activity against both gram-positive and gram-negative bacteria, as well as against some pathogenic species of fungi and protozoa. These quaternary compounds, in general have toxic effects towards mammalian cells. In animals and humans, they are considered too
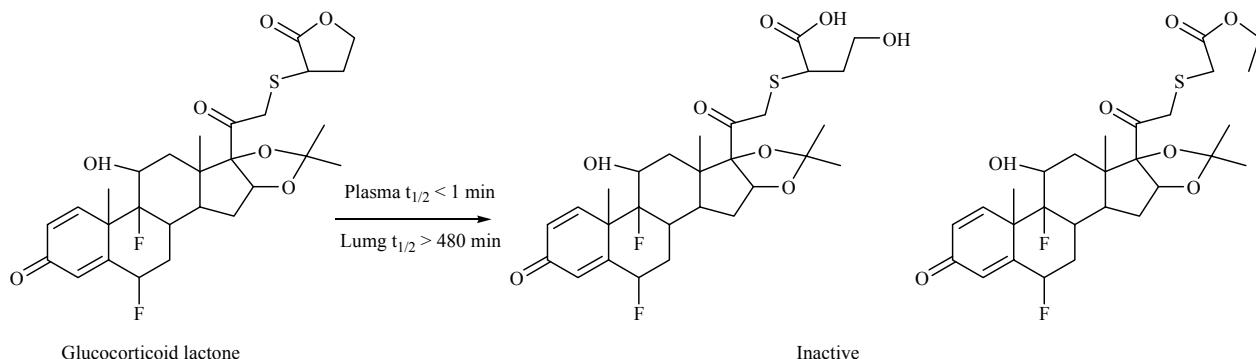
Figure 8 — Glucocorticoid lactone and it's metabolism.
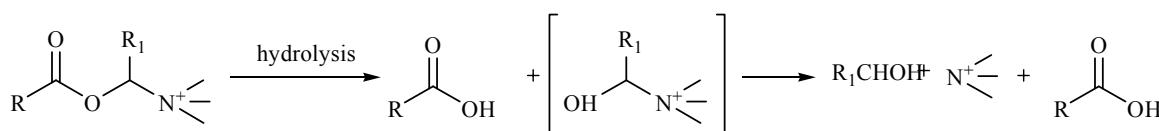
R = straight or branched alkyl or aralkyl
R_1= H, alkyl, aryl, etc.

N^+⧸— = tertiary or unsaturated amine

Figure 9 — The general hydrolytic deactivation mechanism of soft quaternary salts through a very short-lived intermediate to an acid, an amine, and an aldehyde.

toxic for systemic applications, but acceptable for topical applications. The sustained toxicity and environmental impact of these antibacterial compounds are related to their chemical stability[13]. They do not undergo metabolism easily leading to their accumulation in the body. To overcome these limitations, a series of chemically labile derivatives of long chain quaternary ammonium compounds, so called soft analogs have been synthesized and tested *in vitro* and *in vivo*.

These soft quaternary agents are converted to non-toxic moieties after they exert their antimicrobial effects via chemical or enzymatic hydrolysis.

The main features of this compound are the close structural similarity to the corresponding quaternary salts (isosteric) and the hydrolytic sensitivity of the ester portion, leading to simultaneous destruction of both- the quaternary head and surfactant character.

Cetylpyridinium Analogs; Soft Quaternary Salts[65]

The simplest example of useful true soft analogs is provided by the isosteric analogs of *cetylpyridinium chloride*, shown in **Figure 10**. Hard and soft compounds possess comparable antimicrobial activity measured by their contact germicidal efficacy, but soft compounds undergo facile hydrolytic cleavage, leading to their deactivation. Because of this, the soft drug **3** is about 40 times less toxic than hard drug. **1**.

A series of quarternary ammonium compounds that are esters of betaine and fatty alcohols with hydrocarbon chain lengths of 10-18 carbon atoms were tested with respect to antimicrobials activities and rates of hydrolysis (**Figure 11**)[66]. The anti-microbials activity was found to be comparable to cetyltrimethylammonium bromide and their hydroly-sis products are normal human metabolites. Hence, they can be used as disinfectants and antiseptics for food and body surfaces.
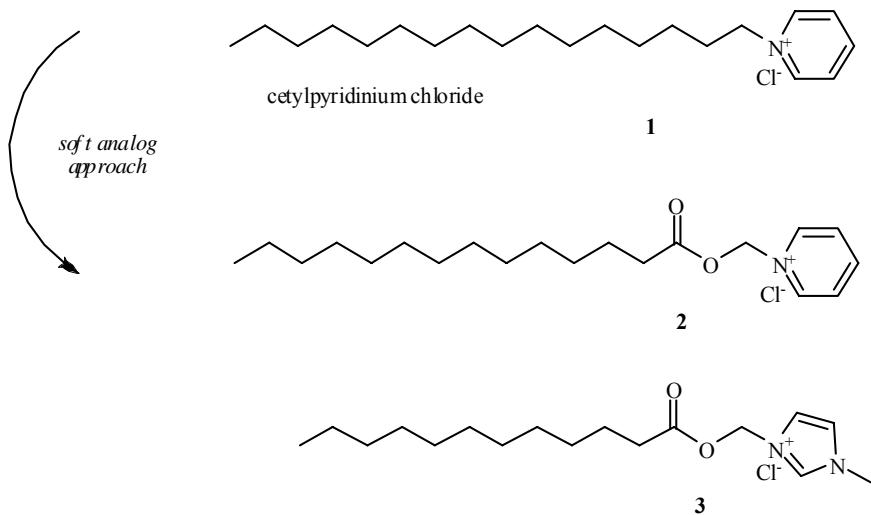

**Figure 10** — Cetylpyridinium chloride and soft analog antimicrobials

$$R \quad = \quad (CH_2)_9CH_3$$
$$(CH_2)_{11}CH_3$$
$$(CH_2)_{13}CH_3$$
$$(CH_2)_{15}CH_3$$
$$(CH_2)_{19}CH_3$$
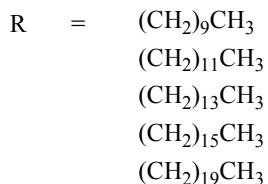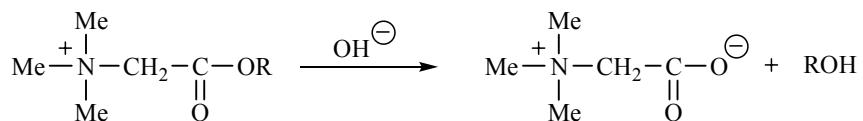
Figure 11 — Chemical structure and hydrolysis of soft antimicrobials betaine esters

$X = Cl$
$Y = Cl$ or H
$R = alkyl$, etc.
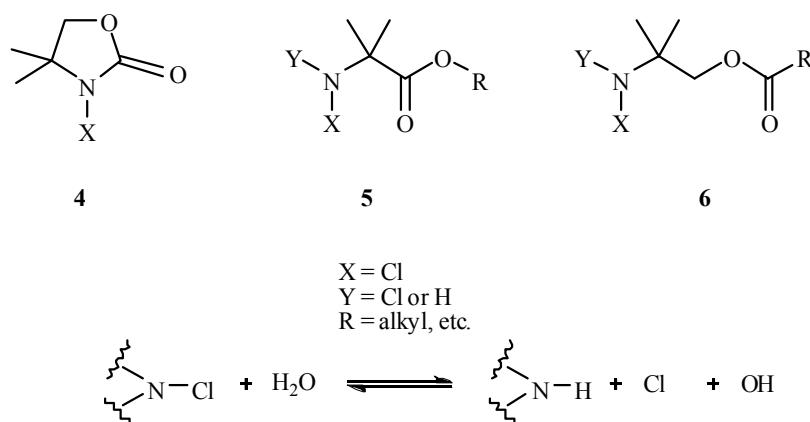
Figure 12 — General structures of representative low chlorine potential,
soft N chloramines antimicrobials and their mechanisms of action.

Another example of soft analogs is soft anticholinergics[67].

3. Active Metabolite Based Soft Drugs[42]

Active metabolite-based soft drugs are metabolic products of a drug resulting from oxidative conversions that retain significant activity of the same kind as the parent drug. The oxidative metabolic transformations in human body are slow and saturable. This results in formation of drug intermediates or drug metabolites having varied selectivity, binding, distribution and elimination properties. Some of these metabolites show significant activity. Thus at any given time, a mixture of drugs and active intermediates/ metabolites are present in varying concentrations that result in complex, uncontrollable situations, making safe and effective dosing almost impossible. In agreement with the basic soft drug design principles, careful selection of an active metabolite can yield a potent drug that will undergo a one step deactivation process, given that it is already at the highest oxidation state. For example, if sequential oxidative metabolic conversion of a drug takes place such as the quite common hydroxyalkyl → oxo → carboxy sequence, in which the carboxy function is generally the inactive form, some previous oxidative metabolite (preferably, one just before deactivation) could be the best choice for a drug.

There are examples of active metabolites used as a source of new drug candidates because of better safety profiles; for e.g.,

- Oxyphenbutazone, the active *p*-hydroxy metabolite of phenylbutazone
- Oxazepam, the common active metabolite of chlordiazepoxide, halazepam, chlorazepate and diazepam.

4. Activated Soft Drugs

Activated soft drugs are not analogs of known drugs, but are derived from non-toxic chemical compounds activated by introduction of a group that provides pharmacological action[1]. During expression of activity, the inactive starting molecule is regenerated as a result of hydrolytic process.

An example of activated soft compound is provided by N-chloramine antimicrobials. During an effort to identify locally active antimicrobial agents of low toxicity, N-chloramines based on amino acids, amino alcohol esters and amides serve as a source of positive chlorine, which was assumed to be primarily responsible for antimicrobial activity. However, when the chloramine is lost, before or after penetration through microbial cell walls, the non-toxic initial amine is regenerated. **Figure 12** illustrates some of these low chlorine potential, soft chloramines. Structure **4** in **Figure 12** proved to be a particularly effective bactericide in a water treatment plant.

5. Pro-Soft Drugs

As their name implies, pro-soft drugs are inactive pro-drugs of a soft drug of any of the above classes including endogenous soft molecules. They are converted enzymatically into the active soft drug, which is subsequently enzymatically deactivated. Soft drugs, as any other drug can be the subject of pro-drug design resulting in pro-soft drugs.

Pro soft drugs combine the advantages of pro drugs as well as soft drugs. Their design in the form of prodrugs results in targeted drug delivery to the site of action and soft drug properties renders easy, controllable conversion to non-toxic metabolites.
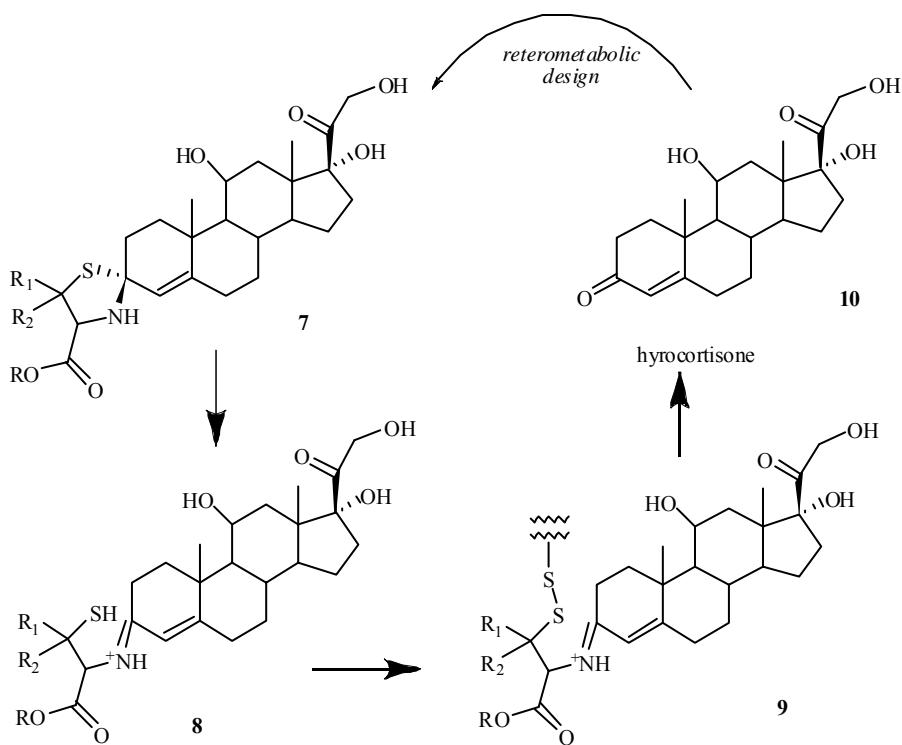
Figure 13 — Hydrocortisone can be regarded as a natural soft drug,
and spirothiazolidine derivatives serves as pro-soft drug for controlled release.

Derivatives of natural hormones and other biologically active agents such as neurotransmitters have well developed mechanisms for their disposition and therefore can be considered natural soft drugs (hydrocortisone, dopamine, etc). Because their metabolism is usually fast and their transport is specific, local or site specific delivery is developed for them. Compounds designed for such purposes can also be considered pro-soft drugs.

A possible example for sustained chemical release at the site of application for hydrocortisone **10**, a natural soft drug is shown in **Figure 13**.

The 4, 5-unsaturated 3-ketone group, being essential for binding and activity, is a good target for modification. Spirothiazolidine derivatives **7** were selected because they would be subject to biological cleavage of the imine formed after spontaneous cleavage of the carbon-sulphur bond[68,69].

Spirothiazolidines of hydrocortisone acetate were about 3-4 times more potent than hydrocortisone derivatives when tested for topical anti-inflammatory activity. Meanwhile, they delivered significantly less hydrocortisone transdermally than did either the unmodified hydrocortisone or hydrocortisone acetate. These results are consistent with local tissue binding through a disulphide bridge, as suggested in figure.

The opening of the spirothiazolidine ring of **7** as shown in structure **8** allows trapping of the steroid with disulphide bridging **9** at the site of application. Hydrolysis releases the active component **10** only locally[70].

Conclusion

Soft drug design approaches are a result of an attempt to synthesizing safer drugs without compromising on therapeutic efficacy. As we have mentioned earlier, the reason for the failure of most of the promising drug candidates at the clinical trials is their unacceptable toxicity. Thus, inspite of huge investments by pharmaceutical industries in the field of drug discovery technologies with an aim to increase productivity, satisfactory results have not been obtained. In order to keep pace with increasing demand for newer drugs, pharmaceutical companies are exploring newer strategies for drug discovery. One such method is drug repositioning which involves exploring new uses for existing drugs has gained tremendous popularity. The advantage with this is that the safety of the drugs has already been proved. The authors would like to propose that in addition to drug repositioning, soft drug design approaches could be used effectively for retrieving

old drug candidates, which showed good efficacy, but were abandoned solely as a result of their toxicity. Modifications of these molecules could result in therapeutically effective and safe drugs; a few examples of already marketed soft drugs are loteprednol etabonate, esmolol and remifentanil.

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References

1 Bodor N & Buchwald P, in *Burger's Medicinal Chemistry and Drug Discovery*. Vol. 2, *Drug discovery and development*, 6th Edn; edited by D J Abhraham (Wiley: New York), 2, **2003**, 533.
2 Bodor N, *Med Res Rev*, 20, **2000**, 58.
3 Bodor N, *NIDA Res Monogr*, 154, **1995**, 1.
4 Gillette J R, *Drug Metab Rev*, 10, **1979**, 59.
5 Picot A & Macherey A C, in *The practice of Medicinal Chemistry* edited by. C G Wermuth (Academic, London), **1996**, 643.
6 Lin J H & Lu A Y, *Pharmacol Rev*, 49, **1997**, 403.
7 Ariens E J & Simonis A M, *Strategy in Drug Research* (Elsevier, Amsterdam), **1982**, 165.
8 Fleisch H Russel, R G & Straumann F, *Nature*, 212, **1966**, 901.
9 Lin J H, Duggan D E & Chen, *Drug Metab Dispos*, 19, **1991**, 926.
10 Lin J H, *Bone*, 18, **1996**, 75.
11 Purohit M N, Pujar G V & Mayur Y C, *Ind J Pharm Educ*, 39(1), **2005**, 14.
12 Fleisch H, *Endocrine Reviews,* 19, **1998**, 80.
13 Bodor N, *J Med Chem*, 23, **1980**, 469.
14 Stella V J, edited by T Higuchi & V J Stella, *Prodrugs as novel drug delivery systems*. (DC, Washington); *Am Chem Soc*), **1975**, 1.
15 Bundgaard H, *Design of Prodrugs*, (Elsevier Science, Amsterdam) **1985**.
16 Wermuth C G, Gaignault J C, edited by C G Wermuth, *The practice of Medicinal Chemistry* (Academic, London.) **1996**, 671.
17 Bodor N & Kaminskii J J, *Annu Rep Med Chem*, 22, **1987**, 303.
18 Balant L P & Doelker E in *Burger's Medicinal Chemistry and drug discovery*, (Wiley Interscience, New York), 1, **1995**, 949.
19 Stella V J, editor. Themed issue, *Adv Drug Deliv Rev*, 19, **1996**, 111.
20 Bodor N, *Adv Drug Res*, 13, **1984**, 255.
21 Bodor N, Farag H H & Brewster M E, *Science*, 214, **1981**, 1370.
22 Bodor N, *Ann NY Acad Sci,* 507, **1981**, 289.
23 Bodor N & Brewster M E, *Handbook of Experimental Pharmacology*, 100, **1991**, 231.

24 Bodor N & Buchwald P, *Adv Drug Deliv Res*, 36, **1999**, 229.
25 Bodor N. & Farag H, *J Med Chem,* 26, **1983**, 313.
26 Tapfer M K, Sebestyer L, Kurucz I & Bodor N, *Pharmacol Biochem Behav*, 77, **2004**, 423.
27 Bodor N, , *Design of Biopharmaceutical properties through prodrugs and analogs*, edited by E B Roche (Washington, DC, Acad Pharm. Sci), **1977**, 98.
28 Bodor N, *Trends Pharmacol Sci*, **1982**, 53.
29 Bodor N, *Med Res Rev,* 3, **1984**, 449.
30 Bodor N, *Chemtech*, 14, **1984**, 28.
31 Bodor N & Buchwald P, *Pharmacol Ther*, 76, **1997,** 1.
32 Bodor N, *J Control Release*, 1, 62, **1999**, 209.
33 Masson Mar & Thorsteinsson T, *J Med Chem*, 46, **2003**, 4173.
34 Bodor N & Oshiro Y Loftson, *Pharm Res*, 3, **1984**, 120.
35 Keith Biggadike, Ian Uings & Stuart N Farrow, *The Proceedings of American Thoracic Society,* 1, **2004**, 352.
36 Bengt Axelsson & Ralph Brattsand, *Prog Respir Res*, Basel, Karger, 31, **2001**, 94.
37 Bodor N & Buchwald P, *The AAPS journal,* **2005**, 7 (4) Article 79, E820.
38 Bodor N, *Pharmazie*, 55, **2000**, 163.
39 Szelenyi I., R Hermann & U Petzold, *Pharmazie*, 59, **2004**, 409.
40 Kurucz I, Nemeth K & Mezaros S, *Pharmazie*, 59, **2004**, 412.
41 Kurucz I, Toth S & Nemeth K, *J Pharmacol Exp Ther,* 307 **2003**, 83.
42 Bodor N & Buchwald P, *Mol. Biotechnology*, 26, **2004**, Vol. 26, 123.
43 Raizman M, *Arch Ophthalmol*, 114, **1996**, 1000.
44 Dickerson J E Jr, Dotzel E & Clark A F, *Exp Eye Res*, 65, **1997**, 507.
45 Heyns K & Koch W, *Naturforsch [B]*, 7B, **1952**, 486.
46 Bucala R, Fishman J & Cerami A, *Proc Natl Acad Sci USA*, 79, **1982**, 3320.
47 Manabe S, Bucala R. & Cerami A, *J Clin Invest*, 74, **1984**, 1803.
48 Bucala R., Gallati M., Manabe S, Cotlier E & Cerami A, *Exp Eye Res*, 40, **1985**, 853.
49 Urban R C Jr & Cotlier E, *Surv Ophthalmol*, 31, **1986**, 102.
50 Noble S & Goa K L, *Biodrugs*, 10, **1998**, 329.
51 Howes J F, *Pharmazie*, 55, **2000**; 178.
52 Bodor N & Buchwald P, In *Inhaled steroids in asthma, Optimizing effects in Airways* (Marcel Dekker, New York), 163, **2002**, 541.
53 Bodor N & Vagra M, *Exp Eye Res*, 50, **1990**, 183.
54 Druzgala P, Hochhaus G & Bodor N, *J Steroid Biochem*, 38, **1991**, 149.
55 Bodor N, Loftsson T & Wu W M, *Pharm Res*, 9**, 1992**, 1275.
56 Bodor N, Murakami T & Wu W M, *Pharm Res*, 12, **1995**, 869.
57 Bodor N, Murakami T, Wu W M. & Engel S, *Pharm Res*, 12, **1995**; 875.
58 Monder C & Bradlow H L, *Recent Prog Horm Res*, 36, **1980**, 345.
59 Druzgala P & Bodor N, *Steroids*, 56, **1991**, 490.
60 Krug N, Hohlfeld J M, Geld Macher H., Larbig M., Heermann R., Lavallee N., Nguyen D T, Petzold U & Hermann R, *Allergy,* 60, **2005**, 354.
61 Buchwald P & Bodor N, *Pharmazie*, 59, **2004**, 396.
62 Barton P, Laws A P & Page M I., *J Chem Soc*, *Perkin Trans 2*. **1994**, 2021

63 Bodor N, *US patent 5 981 517*, **1999**.

64 Milklos A, Magyar Z & Kiss E, *Pharmazie*, 57, **2002**, 142.

65 Bodor N, *US patent 3998815*, **1976**.

66 Lindstedt M, Allenmark S, Thompson R A & Edebo L, *Antimicrob Agents Chemother*, 34, **1990**, 1949.

67 Bodor N, *J Med Chem*, 23, **1980**, 474.

68 Bodor N & Sloan K B, *J. Pharm Sci*, 71, **1982**, 514.

69 Schubert W M & Motoyama Y, *J Am Chem Soc*, 111, **1989**, 3783.

70 Bodor N, Sloan K B & Little R J, *Int J Pharm*, 10, **1982**, 307.