IJPSR (2011), Vol. 2, Issue 4 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 November, 2010; received in revised form 28 January, 2011; accepted 03 March, 2011

MUTUAL PRODRUGS- A SWOT ANALYSIS

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Keywords:

Pharmacokinetics,

Bio conversion,

Docking,

Mechanisms

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ABSTRACT

Mutual prodrug is a form of prodrug in which two pharmacologically active agents are attached to each other in such a way that each drug acts as a promoiety/carrier for each other and vice versa. The association may be "synergistic" if the carrier shows the same biological action as that of parent drug or may provide "additional" benefit if it shows new pharmacological action which is lacking in parent drug. The mutual prodrug concept has shown its marked therapeutic gain in case of well-accepted and useful drugs with minor undesirable properties and in those active compounds that suffer from severe limitations, like lack of site specificity, poor bioavailability or lack of particular activity. Now a days *Anticancer, cardiovascular, antiviral, antipsychotic and anti-inflammatory drugs* are best utilizing the concept of mutual prodrug designing for their better effect. In this paper, we have reviewed mechanism of activation, contribution of mutual prodrug approach in different therapeutic areas and the development in this field during the last few decades including a list of patents. This review not only describes various design approaches, methods of synthesis, pharmacological evaluations for mutual prodrugs, but has also highlighted the emerging fields of docking studies and their relevance to the pharmacokinetics of mutual prodrugs.

INTRODUCTION: The concept of a "mutual prodrug" is relatively new in medicinal chemistry, pharmaceutics, and drug delivery. A mutual prodrug is composed of two drug compounds that are covalently linked, for example, by an ester linkage. A mutual prodrug is an association in a unique molecule of two, usually synergistic, drugs attached to each other, one drug being the carrier for the other and vice versa [1].

Classification of mutual prodrug: Depending upon their constituents and composition, *Mutual prodrugs* can be classified as,

- Carrier- linked mutual prodrug. It can be further subdivided into two types:
  - Bipartate carrier- linked mutual prodrug
  - Tripartate carrier- linked mutual prodrug
- Bio-precursor mutual prodrugs or Chemical activation prodrugs.

Carrier- linked mutual prodrug is bipartate or tripartate where a synergistic drug acts as the carrier. Bipartate mutual prodrug is having a pharmacologically active carrier drug which is directly attached to parent drug where as in case of tripartate mutual prodrugs; the carrier drug is not linked directly to the parent drug but instead through a linker so it allows for decreased steric hindrance during enzymatic cleavage that may occur with bipartate prodrugs. Here Carrier drug is enzymatically cleaved from linker in first step then linker is spontaneously cleaved from parent Drug.

Bio- precursor mutual prodrugs produce their effects after in vivo chemical modification of their inactive form. Bioprecursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs.

Objective/ Reasons of Mutual Prodrug: Mutual prodrug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. The main objectives of a mutual prodrug designing are:

- To bring both active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.
- To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness
- To avoid the practice of clinically co-administering two drugs in order to enhance pharmacological activity or prevent clinical side effects. Simultaneous administration does not guarantee equivalent absorption or transportation to site of action. So, mutual prodrug concept is useful when two synergistic drugs need to be administered at the same site at the same time. Mutual prodrugs are synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities.

Selection criteria for Mutual Prodrug synthesis: Some important factors such as therapeutic combinations of candidate drugs and probable linkage between drugs may form the basis of selection criteria for mutual prodrug synthesis. The significant parameters which are to be considered before synthesis of mutual prodrug are summarized below:

a) The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or from different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act

on different biological targets with different mechanisms of action.

b) The candidates for making mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at investigational stage) in various therapeutic areas provided each of those drugs possesses the requisite functional group(s). There are a number of therapeutic areas where such combination therapy is applied routinely and successfully.

c) The linkage between the first and second component should be a cleavable linkage. For example, the linkage may be hydrolyzable and/or may be enzymatically cleavable. Preferably, the linkage should be cleavable under physiological conditions, such as those present in a mammalian body, particularly a human body.

Mechanism of activation: Like a prodrug, a mutual prodrug is converted into the component active drugs within the body through enzymatic and/or non-enzymatic reactions.

1. ***In vivo*** **metabolic activations of bioprecursor mutual prodrugs:**

a) Oxidative Activation

- *N*- and *O*-Dealkylation
- Oxidative Deamination
- N-Oxidation
- Epoxidation

b) Reductive Activation

- Azo- Reduction
- Sulfoxide Reduction
- Disulfide Reduction
- Bioreductive Alkylation
- Nitro Reduction

c) Nucleotide Activation
d) Phosphorylation Activation
e) Decarboxylation Activation

2. **Intramolecular activation:** Active Drug as the cyclic product of intramolecular activation is one of the important approach proposed to explain the activation of some mutual prodrugs. This approach found application in explaining the release the parent drugs from carbamate mutual prodrugs in aqueous buffer (pH 6-11) and plasma (pH 7.4) through intramolecular reactions due to a hydroxyl nucleophile [2].

Strengths- advantages of making Mutual Prodrug:

1. Help in reduction of Side-effects of Parent Drugs
2. Produces synergistic effect
3. Give additional biological action as that of parent drug.
4. Reduction in dose due to synergistic effect
5. Improve pharmacokinetics of Parent drug

Weaknesses- Limitations of mutual prodrug design: Even if mutual prodrug design has proven highly beneficial in overcoming various undesirable properties of drugs, it can also give rise to a large number of newer difficulties, especially in the assessment of pharmacological, pharmacokinetic, toxicological and clinical properties [3].

i. **Problems at the pharmacological level**: These compounds cannot be submitted to preliminary in vitro screening tests like binding studies, reuptake of neurotransmitter and enzyme inhibition measurement because bioactivation to their active species is necessary.
ii. **Problems at the toxicological level**: Even though mutual prodrugs are derived from well-known active principles, they have to be regarded as new entities. In a review by Gored, he has cited certain toxicity mechanisms like

formation of toxic metabolite of total prodrug which is not produced by the parent drugs, consumption of vital constituent during prodrug activation process, generation of a toxic derivative, release of a pharmacokinetic modifier which may cause enzyme induction or alter drug excretion.

iii. **Problems at the pharmacokinetic Studies:** The mutual prodrug may not be an ideal substrate for the activating enzymes. So, it is necessary to consider modifying the carrier with electron withdrawing or donating groups *to* facilitate the hydrolysis. Pharmacokinetic studies may lead to numerous misinterpretations. When mutual prodrug and parent molecules are being compared, one must take into account the differences in their respective time courses of action. The maximum activity may appear later for mutual prodrug than for parent compounds, so area under the curve should be compared as it presents a better criterion for comparison.

iv. **Problems at the clinical stage:** The predictive value of animal experiments is also questionable. The active doses of two mutual prodrugs of the same parent drugs may appear to be same in rats but may be quite different in clinical investigations.

Opportunities - Patents filed in the area of Mutual prodrug: Following patents have been claimed in the area of mutual prodrugs of different therapeutic categories during previous decade.

- Monophosphates as Mutual Prodrugs of Anti-Inflammatory Signal Transduction Modulators (AISTM's) and Beta-Agonists for the Treatment of Pulmonary Inflammation and Bronchoconstriction [4]
- Mutual prodrugs and methods to treat cancer [5]
- Glucosamine and glucosamine/anti-inflammatory mutual prodrugs, compositions, and methods [6]
- Mutual prodrug of amlodipine and atorvastatin [7]
- Prodrugs containing Bio- Cleavable Linkers [8]
- Monophosphates as mutual prodrugs of muscarinic receptor antagonists and β-agonists for the treatment of COPD and chronic bronchitis [9]
- Hepatoprotectant acetaminophen mutual prodrugs [10]

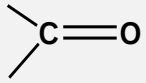
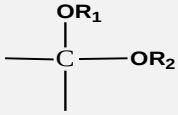
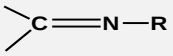
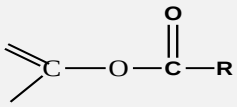
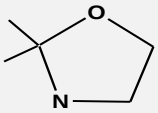
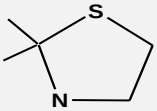
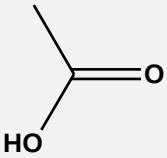
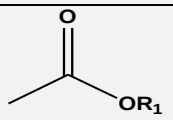
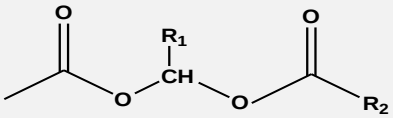
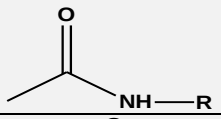
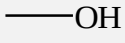
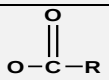
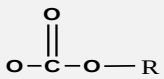
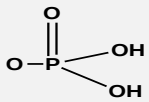
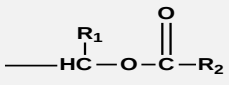
Methodologies used for Mutual prodrug Synthesis: Synthesis of Mutual prodrug is basically a concept of designing drug through conjunction of two different pharmacophores having similar or different pharmacological activities. Before synthesizing mutual prodrugs, following queries arises regarding the linkage between two pharmacologically active drugs:

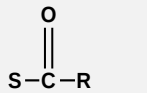
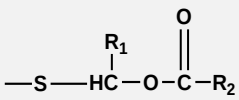
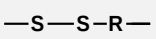
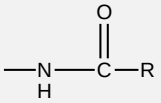
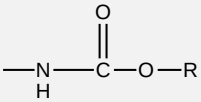
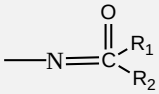
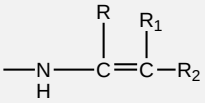
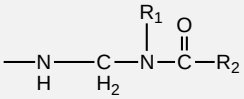
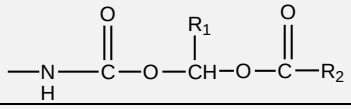
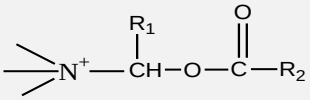
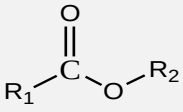
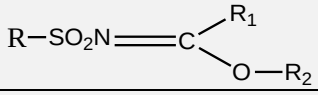
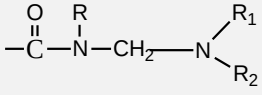
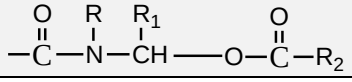
- What types of groups are the easiest to link to a carrier drug?
- What types of groups are the easiest to cleave from a carrier drug?

These are suitably answered by study of nature of functional groups forming a suitable linkage or bond between two drugs which get easily hydrolyzed by suitable enzymes. Mutual Prodrug forms of various functional groups are shown in **table 1**. There are so many methodologies followed to synthesize mutual prodrug depending upon the functional group attached to parent drug or carrier drug. Among them some are given below:

- Esterification
- Amidation
- Using spacer technique
- Azo linkage for example Sulfasalazine
- Enzymatic Regioselective methodology
- Elaborate protection/deprotection and separation strategies
- Multi-step chemical reaction synthesis

TABLE 1: MUTUAL PRODRUG FORMS OF VARIOUS FUNCTIONAL GROUPS

Functional Group	Mutual Prodrug Form
	 Ketals
	 Imines
	 Enol esters
	 Oxazolidines
	 Thiazolidines
	 Ester
	 α-acycloxyalkyl ester
	 Amides
	 Esters
	 Carbonate ester
	 Phosphate esters
	Ethers
	 α- acyloxyalkyl ethers

—SH		Thioester
		α- acyloxyalkyl ethers
		Disulphides
—NH_2		Amides
		Carbamates
		Imines
		Enamines
		N-Mannich bases
		N-acyloxy alkoxy carbonyl derivatives
		N-acyoxyalkyl derivatives
		N-sulfonyl imidates
—SO_2NH_2	—SO_2NH—CH_2O—R	N-sulfonyl imidates
NH-Acidic group		N-mannich bases
Hetrocyclic amine		N-acyloxyalkyl derivatives

Methods of Evaluation of Mutual Prodrug:

Solubility Measurement: The solubility measurement of mutual prodrug is carried out by placing an excess amount of mutual prodrug in separate vials containing different solvents like 10 ml deionized water, n-hexane, phosphate buffer of different pH etc and then stirring at 37^{o}C for 24 hours. The solutions are centrifuged for 5 min at 9000 rev/min and the supernatant is filtered with cellulose acetate membrane filters. The mutual prodrug concentration in each filtrate is determined by suitable analytical technique like HPAE-PAD/UV spectroscopy/HPLC after the appropriate dilution.

Determination of Partition Coefficients: By shaking flask method partition coefficient of mutual prodrugs can easily be determined.

In vitro **Hydrolytic study in different Buffers:** Hydrolysis studies are carried out in aqueous buffer so as to study whether the mutual prodrug hydrolyzes in an aqueous medium and to what extent or not, suggesting the fate of mutual prodrug in the system. Mutual prodrugs may also be subjected to *in vitro* hydrolysis in simulated gastric fluid (SGF) at pH 1.2, simulated intestinal fluid (SIF) at pH 7.4 and SIF+ 80 % human plasma at pH 7.4. The kinetics of hydrolysis is monitored by the increase of free drug concentration with time and the order of the reaction and half-life (*t*1/2) are calculated. The rate of hydrolysis is calculated using the equation:

$$kH = (2.303/t) \log (a/a–x)$$

Where, kH represents the hydrolysis constant, 't' is the time in min, 'a' is the initial conjugate concentration, 'x' is the amount of Mutual prodrug hydrolyzed and '(a–x)' is the amount of the remaining prodrug. The graph between % cumulative amounts of drug release after hydrolysis versus time is also plotted to study the *in vitro* hydrolysis of mutual prodrug in SGF, SIF and 80% plasma. For better absorption, mutual prodrug should not hydrolyze appreciably in these fluids. Jyoti Rawat *et al*., (2007) studied *in vitro* hydrolysis of mutual prodrugs of isoniazid, *p*-amino salicylic acid and ethambutol [11].

In vivo **enzymatic hydrolysis *:*** An *in vivo* study are conducted to determine the plasma concentration drug time profile using suitable analytical technique like UV spectrophotometeric determination, HPLC etc. In this study all mutual prodrugs and individual drugs are administered to animals and after particular intervals drug concentrations can be determined in serum. The reactions are initiated by adding stock solution of mutual prodrug in suitable solvent to preincubated 80% human plasma with isotonic phosphate buffer (pH 7.4) and incubated at 37^{o}C. At appropriate time intervals the plasma reaction are withdrawn and deproteinized by mixing with acetonitrile. After centrifugation for 10 min at 104 rpm, clear supernatant is analyzed by suitable analytical technique like HPLC.

In vitro **biological activity:** *In vitro* transport (diffusion) is evaluated by Franz cell diffusion experiments using shed snakeskin. Shed snakeskin is widely recognized as a sufficient model membrane to human skin for preliminary permeability studies due to the similarity in its composition to the human stratum corneum. Benorylate (4-acetamido phenyl-O-acetylsalicylate) hydrolysis in vitro by human plasma and by human liver microsomes and cytosol has been investigated by F M Williams *et al*. (1989) [12].

Chemical stability (kinetics of chemical hydrolysis): A Mutual prodrug should be chemically stable so that it can be formulated in an appropriate pharmaceutical dosage form with optimum half life. At the same time, it should be biolabile to regenerate the parent drug molecules

to exhibit therapeutic activity. For this purpose the kinetics of chemical hydrolysis is studied at 37^{o}C using buffer solutions of different pH. Different pharmacokinetic parameters obtained/ calculated during this study like rate constant, order of reaction and half-life helps in determining the chemical stability of mutual prodrug. The chemical stability of mutual prodrug is also studied at various temperatures.

Protein binding studies: Protein binding of mutual prodrug is studied by preparing a solution of the mutual prodrug in phosphate buffered saline (PBS, pH 7.4). 100mL of this solution is placed in a beaker. The cellophane membrane firstly washed with distilled water and then with buffer solution (pH 7.4) is tied at the opening end of a dialysis tube; the dialysis tube containing (6 %) egg albumin is dipped into the drug solution and covered. The whole assembly is placed on a magnetic stirrer and set at low revolutions per minute. The temperature must be maintained at 37 ± 0.5°C. After each 1 h, 1mL of the PBS containing drug solution is replaced with fresh 1mL of PBS. The withdrawn sample is further diluted with 1mL phosphate buffer and the concentration of the mutual prodrug is estimated using a suitable analytical technique.

In vivo **pharmacokinetic study:** Tissue homogenates are used for *in vivo* pharmacokinetic study.

Biochemical studies: Suitable markers are used to determine biological activity of mutual prodrug. For example for evaluating anti-inflammatory activity of mutual prodrug TNF- alpha, IL-1 β and IL-6 etc are used. Biochemical evaluation was carried by M. Madhukar *et al*. (2010) by using various peripheral markers of oxidative stress including lipid peroxidation (MDA levels), myeloperoxidase activity (MPO levels), superoxide dismutase activity (SOD) and catalase activity to study the effect of mutual prodrug of 4-biphenylacetic acid and quercetin tetramethyl ether (BPAeQTME) [13].

In vivo **Pharmacological evaluations:** Mutual prodrugs are pharmacologically evaluated by selecting suitable animal models. Some of the activities are given below:

Anticancer activity: Anticancer activity is evaluated on different cell lines. For example Evaluation of anticancer activity of mutual prodrug of Retinoic and Butyric Acids was carried out via study of ED_{50} for differentiation induction, IC50 values for inhibition of Lewis lung (3LLD122) and pancreatic ($PaCa_2$) carcinoma cell line colony formation by Nudelman A. *et al.* (2000). [14]

Anti-inflammatory, Analgesic, and Ulcerogenic Activities: The pharmacological effects of mutual prodrugs of NSAIDs include the evaluation of anti-inflammatory, analgesic, and ulcerogenic Activities. The most commonly used methods for measuring peripheral analgesic activity are the writhing tests in mice (various modifications) and the RANDALL-SELITTO- test in rats, Carrageennan-induced paw edema bioassay for anti-inflammatory and the examination of gastric mucosa by means of magnifying lens or microscope. Ulcer scores are measured by the method of Kunchandy *et al*., for ulcerogenic study [15].

In case of mutual prodrugs of NSAIDs in which carrier moiety is showing additional pharmacologic effect as compared to parent drug then that specific pharmacological effect of carrier or promoiety is also studied, for example Chlorzoxazone esters of acidic NSAIDs as Mutual prodrugs were evaluated for their muscle relaxation activity in addition of anti-inflammatory, analgesic and ulcerogenic activity by A. Z. Abdel-Azeem *et al*. (2009) [16].

Antipsychotic: d- amphetamine- induced hyper-activity model is most preferable model used to evaluate Antipsychotic activity of mutual prodrug. Nudelman *et al*. evaluated the mutual prodrug esters of GABA and perphenazine in rat models for antipsychotic activity which displayed a significant decrease of catalepsy associated with increased prolactin blood levels [17].

Neuropathic pain: A rat model of chronic sciatic nerve constriction injury (CCI) is a selective model for *in vivo* evaluation of neuropathic pain relief activity of mutual prodrug. Shi W *et al*. investigated Gabapentin-pregabalin mutual Prodrugs which were found effective in reversing tactile allodynia in CCI rats [18].

Mutual prodrugs of different therapeutic categories: There are so many mutual prodrugs which are basically designed for specific purpose like to decrease the dose of parent drug if carrier moiety is also of same pharmacological action, to show additional effect than parent drug which is required for specific diseased condition, to improve pharmacokinetic profile, to decrease side effects, to shorten as well as prolong action and to alter bioactivation etc. Mutual prodrugs belonging to different therapeutic area are listed in **table 2**.

TABLE 2: EXAMPLES OF MUTUAL PRODRUGS BELONGING TO THERAPEUTIC AREAS

Therapeutic Area	Mutual Prodrug	Purpose
Antitubercular Drugs	Mutual prodrugs of isoniazid, *p*-amino salicylic acid and ethambutol. [11]	To eliminate the problem of fast metabolism, toxicity and local irritation and reduction of therapeutic doses.
Antipsychotic	Mutual prodrug ester of GABA and perphenazine. [17]	To minimize the extrapyramidal effects
Analgesic in Neuropathic pain	Gabapentin-Pregabalin Mutual Prodrugs. [18]	To show better effectiveness in reversing tactile allodynia in CCI rats
Anticancer	Mutual prodrugs All-*trans*-Retinoic Acid and Histone Deacetylase Inhibitors. [5]	To show differential antiproliferative potencies in both MDA-MB-231 and PC-3 cell lines.
	5-Fluorouracil / Cytarabine Mutual Prodrugs. [19]	To show synergistic effect therefore help in reduction of dose as well as toxicity
Anti viral Agents	Mutual prodrugs of 2′, 3′-dideoxyinosine with 3-octadecyloxy-propane-1, 2-diol. [20]	To show synergistic effect with different mechanisms and to release the parent drugs at desired site of action.
Pulmonary Inflammation and Bronchoconstriction	Mutual Prodrugs of Anti-Inflammatory Signal Transduction Modulators (AISTM's) and Beta-Agonists. [4]	For producing synergistic effects with different mechanism of action in the treatment of Pulmonary inflammation and Bronchoconstriction
Cardiovascular drugs	Mutual prodrugs of Amlodipine and Atorvastatin. [7]	For the treatment of arthrosclerosis, angina pectoris, combined hypertension and hyperlipidaemia and the management of cardiac risk
Non –steroidal Anti-inflammatory Drugs (NSAIDS)	Benorylate (Mutual prodrug of paracetamol and aspirin). [12]	For Reduction of Gastro- intestinal side effects and ulcerogenicity of NSAIDs
	4-biphenylacetic acid and quercetin tetramethyl ether (BPA-QTME). [13]	
	Chlorzoxazone esters of acidic NSAIDs. [16]	
	Indomethacin–flavonoid Mutual prodrug. [21]	
	Aminoalcohol ester analogues of Indomethacin. [22]	
	Coupling with amino acids. [23-24]	
	Paracetamol (acetaminophen) esters of some acidic NSAIDs. [25]	
	Naproxen propyphenazone mutual prodrugs. [26]	

	Mutual prodrugs of NSAIDs and natural antioxidants. [27]	
	Conjugation of NSAIDs with H_2 antagonist. [28]	
	Chemically coupling a nitric oxide (NO) releasing moiety to the parent NSAID. [29]	
	Glucosamine conjugate prodrug of NSAIDs. [6]	To show additional Antiarthritic activity
	Colon-specific mutual prodrug of 5-aminosalicylic acid (5-ASA) and sulfapyridine.[30]	To enhance site-specific delivery of NSAIDs
	Aceclofenac colon specific mutual amide prodrug. [31]	

Threats: Inadequate animal model selection, *in vitro* screening testing like binding studies, pharmacokinetic behavior and toxic metabolite formation are some threats associated with the mutual prodrug concepts.

Docking: Docking of the mutual prodrugs into active site of receptor is conducted in order to predict the affinity and orientation of prodrug at the enzyme active site. It is very much helpful in predicting the ligand- enzyme interactions at the active sites. Suitable software can be used for this purpose.

A. Z. Abdal Azeem *et al*. (2009) performed Docking studies of non-steroidal anti-inflammatory drugs and their mutual prodrug esters with chlorzoxazone by MOE (Molecular Operating Enviroment) using murine COX-2 co-crystallized with SC-558 (PDB ID: 1CX2) as a template. The recent determination of the three-dimensional co-crystal structure of murine COX-2 complexed with SC-558 has led to the development of a model for the topography of NSAIDs binding site in human COX-2.

This might enable the prediction of the orientation and interaction of parent drugs and their ester prodrugs into COX-2 active site. They performed 100 docking iterations for each ligand and the top scoring configuration of each of the ligand-enzyme complexes was selected on energetic ground. The output of docking simulation was the scoring function which reflects the binding free energy dG in kcal/mol (S), value proportional to the sum of Gaussian R1R2exp (⁻0.5d2), where R1 and R2 are the radii of atoms in Angstrom Å and d is the distance between the pair in Å (ASE) a linear combination of (S, ASE, Econf) where Econf is an estimated self-energy of the ligand in kcal/mol (E) [16].

CONCLUSION: Separation of therapeutic effects from toxicity is a valuable goal in the drug development process. Mutual prodrug design is a part of the general drug discovery process, in which a unique combination of therapeutically active substances is observed to have desirable pharmacological effects. In human therapy mutual prodrug designing has given successful results in overcoming undesirable properties like absorption, nonspecificity, poor bioavailability and GIT toxicity. Thus, mutual prodrug approach offers a wide range of options in drug design and delivery. The mutual prodrug approach outlined in this review article may provide relevant information to researchers involved in improving the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness otherwise.

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