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**PRODRUGS TARGETING THE CENTRAL NERVOUS SYSTEM (CNS)**

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ABSTRACT

The classical approach for delivery of drugs into the central nervous system (CNS) is associated with adverse effects and it has many limitations. Therefore, extensive efforts have been done in searching and developing novel methods for achieving such delivery. This mini-review discusses the design and synthesis of selected targeting prodrugs for the treatment of conditions related to impairment in the CNS such as Parkinson's and Alzheimer's diseases. Such approaches include targeting prodrugs which are designed to interact with unique cellular conditions at the target site, especially the availability of certain enzymes and transporters at these sites. In addition, part of this mini-review is devoted to prodrugs design based on enzyme models that have been invoked to understand how enzymes

catalyze biotransformation. In this approach, the prodrugs design is done using quantum molecular orbital and molecular mechanics methods. The equations obtained from correlations of experimental and calculated rate values for some intramolecular processes are used to predict parameters for other intramolecular processes that can be utilized as prodrugs linkers. In this approach, there is no need for enzymes to catalyze the conversion of the prodrug to its active parent drug and the conversion rate of the prodrug is dependent only on those factors playing dominant role in the rate-limiting step of the process.

KEYWORDS: Prodrugs, Targeted prodrugs, CNS, Parkinson's disease, Dopamine, Alzheimer's disease, Intramolecularity, Enzyme models.

INTRODUCTION

During the last few decades the percentage of elderly population has drastically increased due to an improvement and advancement in the health care system in the developed world. This resulted in an increase in the conditions of CNS diseases such as Parkinson's and Alzheimer's which possess a serious public problem. An inefficient treatment for these neurodegenerative diseases is caused partly by the physiology of the CNS where the blood brain barrier (BBB) secures the entry of any foreign substance including medicines to the brain. Furthermore, the blood-cerebrospinal fluid barrier (BCSFB) is considered the second physiological barrier that separates the brain from its blood supply and controls the passage of endogenous and exogenous substances.

The BBB contains tight-junctions which only permit the transport of hydrophobic molecules to traverse it by diffusion or if the substance is a substrate for DBB carrier mediated transporters, also transcytosis takes place which can be absorptive mediated or receptor mediated transcytosis.^[1] The BBB presents an efficient structural and functional barrier for the delivery of therapeutics to the CNS. Due to its unique properties, passage across the BBB often becomes the main limiting factor for the delivery of potential CNS medicines into the brain parenchyma. In fact, it is estimated that more than 98% of drugs with small-molecular weight and practically 100% of drugs having large-molecular weight developed for the CNS diseases do not readily cross the BBB.^[2]

There are four factors that play a dominant role in the drugs' passage (free diffusion of molecules across the BBB) to the brain: hydrogen-bond donors, hydrogen-bond acceptors, molecular weight (MW) and partition coefficient (logP). The molecular weight of a drug is considered the most important parameter which determines free diffusion of molecules across the BBB. Studies have shown that most of the targeted drugs to the CNS have a molecular weight of 400-500 Da.^[3] It is believed that the pores created in the phospholipid bilayers are of limited size and allow only small molecules with a spherical volume that fit into these pores.^[4] The second factor determining the passage through BBB is the number of hydrogen-bond donors which the drug can make through its passage; each pair of hydrogen bonds decreases the permeability through DBB by one log of magnitude and it was demonstrated that drugs having up to five hydrogen-bond donors are capable of penetrating the BBB

whereas those possess higher hydrogen bonds are likely to be blocked from penetration.^[5-6] The third parameter determining the drug's passage via BBB is the drug's plasma pharmacokinetics; the drug's concentration in the brain is proportional to the BBB permeability coefficient (P_e) and the drug's plasma area under the curve (AUC). Generally, increasing the lipophilicity of a drug results in an increase of the P_e but a decrease in the plasma AUC, and these factors can have offsetting effects, resulting in little change in the drug's brain concentration.^[7]

For improving the bioavailability of a drug and increase its permeation through the DBB the prodrug approach has the potential and capability for achieving such goals.

The classical or traditional prodrugs approach aims to improve the physicochemical properties of a drug such as solubility and absorption by attaching the drug moiety to a non-toxic promoiety by a covalent bond. The resulting prodrug moiety is intended to be cleaved inside the body non-specifically or specifically by certain enzymes to give rise to the active parent drug. The promoiety can be hydrophilic aiming to increase the drug's solubility in gastro-intestinal tract (GIT) or hydrophobic aiming to enhance the drug's membrane permeability. These prodrugs suffer from non-specific activation at sites other than the active site resulting in related toxicities and low bioavailability.^[8-10]

On the other hand, targeted prodrugs are synthesized to deliver the desired drugs to a certain organ or tissues in the body, thus, overcoming problems associated with the classical prodrugs approach. The targeted prodrugs approach achieves its aim depending on the presence of unique cellular conditions at the desired target, especially the availability of certain enzymes and transporters. Targeted prodrugs in which a chemical moiety is attached to a parent drug to selectively target an activating enzyme or transporter is considered the main cornerstone for making efficient clinical profiles.

A successful targeting prodrug must be transported to its site rapidly, cleaved there selectively and retained at the site of action for a reliable time.^[11]

Targeting using both enzymes and transporters requires a great knowledge of the molecular structure and functionalities of those transporters and enzymes. When synthesizing a prodrug to target a specific site in the body, the prodrug must contain a chemical moiety that is specifically recognized by the aimed enzyme or transporter which is usually present exclusively or overexpressed at the desired site of action.^[12-15]

In the last few decades many advances have been made for achieving better CNS delivery. Among the approaches used are nanoparticles, liposomes, and some invasive strategies such as BBB disruption and intracerebral implants.^[16]

CNS targeting via prodrugs is considered a pharmacological strategy. Classical prodrugs are inactive chemical entities which are usually made to improve the physicochemical properties of a certain drug. Prodrugs become activated chemically or enzymatically giving rise to the active parent drug. When considering prodrugs to target CNS the first thing to come in mind is to link the active parent drug to a lipophilic moiety such as fatty acid, glyceride or phospholipids which yields a prodrug moiety with the capability to penetrate the BBB. Regardless of achieving a successful entry of the drug into the CNS via this approach many disadvantages are to be faced including poor selectivity, poor retention time and creation of toxic-reactive metabolites.^[17]

Another method used for CNS targeting is the vector mediated delivery. The principle of this method relies on using a non-transportable drug conjugated to BBB transport vector. The vector can be a modified protein or receptor specific antibody. The vector gains access to the brain through BBB transporters (for modified proteins) or via receptor mediated transcytosis (for monoclonal antibodies).^[18] The active parent drug can be conjugated to the vector via different methods such as chemical linkers, avidin-biotin technology, polyethylene glycol linkers and liposomes.^[19]

Furthermore, chemical delivery systems are also used in which at least one bond needs to be cleaved in order to release the active parent drug. Redox chemical delivery systems have shown a satisfactory efficiency in CNS targeting. This method consists of two steps: (i) target promoting moiety which is responsible for site specificity and (ii) modifier functions which enhance the system lipophilicity; these modifier functions are designed to prevent any chemical conversion to unwanted metabolites. Among these chemical delivery systems are those depending on an enzymatic oxidation reaction for the conversion of the lipophilic dihydropyridine to ionic pyridinium salt, thus retaining the drug in the brain for a longer time.^[16]

-1OPIATES PRODRUGS

Using the redox chemical delivery approach one system was applied for enkephalin delivery to the brain. Enkephalins are naturally occurring opioids used as analgesics and can replace

the currently used morphine and alkaloids derivatives and thus minimize their associated side effects.^[20] However, the use of this approach might encounter serious problems since enkephalins being proteins make them vulnerable to degradation by peptidases and in addition being high hydrophilic compounds limits their blood brain barrier (BBB) permeability.^[21]

A strategy to overcome and resolve this problem was achieved by utilizing the prodrug approach. An enkephalin prodrug was made with improved *in vivo* stability. This prodrug is δ opioid receptor-selective enkephalin analogue, Tyr-D-Ala-Gly-Phe-D-Leu (DADLE); it is a stable chemical entity however it cannot cross the BBB because of its hydrophilic character.^[22] For overcoming the barrier associated with the hydrophilic nature of this prodrug, brain-targeting chemical delivery system (BTCDS) for DADLE was made. This system is inactive on its own but is enzymatically activated in the brain by peptidases activation. This system consists of lipophilic 1, 4-dihydrotrigonellyl moiety which is attached to the N terminus of the active parent drug through a peptidic spacer. In the brain, oxidoreductases oxidize the dihydropyridine into the positively charged N-methylpyridinium thus retaining the drug in the brain for a longer time.^[23] Then the active parent drug is released followed the action of several peptidases especially the enzyme prolyloligopeptidase (POP) which removes the spacer from the oxidized BTCDS (Figure 1).^[24] *In vitro* studies on rats brain homogenates have shown increased half-life of the drug which was correlated with *in vivo* analgesic effects using tail-flick model.^[25]

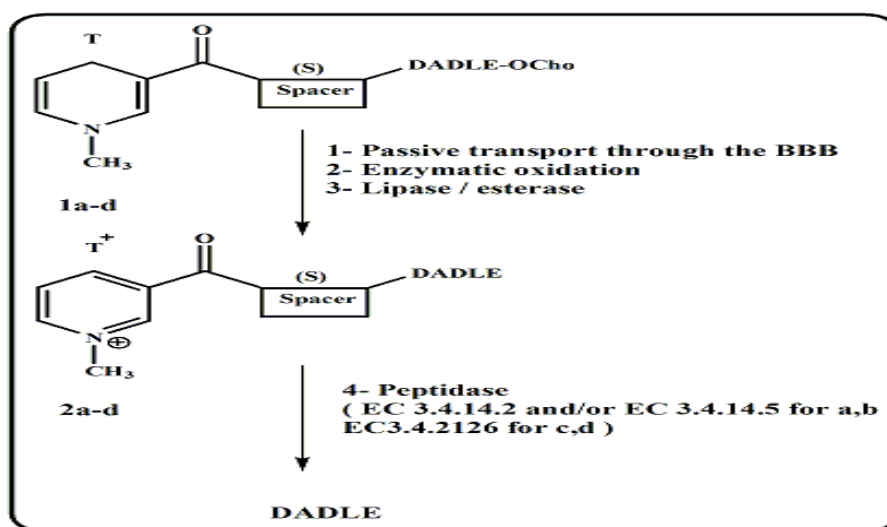


Figure 1: DADLE brain targeting delivery system. (a) DADLE (b) peptidic spacer (c) lipophilic 1, 4-dihydrotrigonellyl moiety (d) N-methylpyridine moiety.

Morphine, a member of the morphinan-framed alkaloids present in the poppy plant, is a potent opioid analgesic widely used for the treatment of acute and long-term treatment of severe pain. It is soluble in aqueous media, but has a poor solubility in lipids. In human, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are the major metabolites of morphine.^[26] On the other hand, codeine is considered a morphine prodrug since it undergoes oxidative demethylation by cytochrome P450 CYP2D6 to yield morphine (Figure 2). Detailed studies on the metabolism of codeine have showed that about 80% of the drug is converted to codeine-6-glucuronide, a metabolite that is pharmacologically active and, on a dose basis, elicits approximately 60% of the analgesic effect of codeine itself. Moreover, less than 5% of the codeine dose is generally converted to morphine. The remaining approximately 15% is demethylated by CYP3A4 to norcodeine, which is less potent than morphine. From these results, it has been proposed that codeine-6-glucuronide is the agent responsible for most of the analgesic effect of codeine, in which case codeine is might be considered as a prodrug of the glucuronide metabolite rather than of morphine.^[27] Therefore, cytochrome CYP2D6 is necessary for much of the analgesic effect of codeine. Most Caucasians convert codeine to morphine via CYP2D6 as other population around the world. However, approximately 7% - 10% of Caucasians have a genetic variant that produces limited CYP2D6 activity and slow metabolism of CYP2D6 substrates. In these cases, interconversion of codeine to morphine is reduced resulting in less analgesic efficacy. Upon administration of codeine dosage forms to these persons the expected extent of analgesia which is achieved will be drastically reduced.

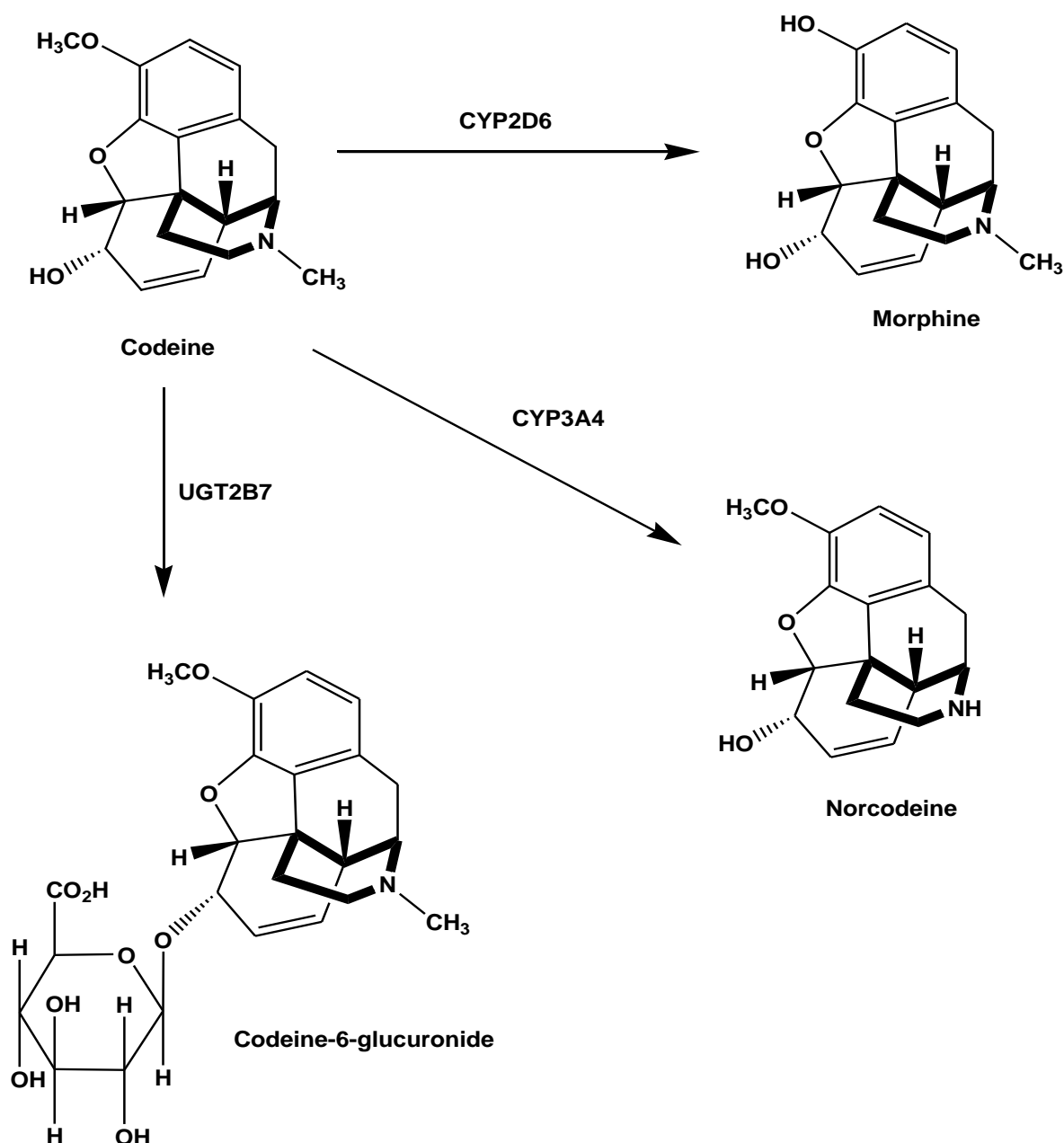


Figure 2: Conversion of codeine to its glucuronide and morphine metabolites with higher biological activity.

Wang et al. have synthesized two *N*-alkyl esters of morphine, morphine propionate and morphine enanthate as potential prodrugs for transdermal delivery of morphine (Figure 3). Both prodrugs were found to be more lipophilic than their parent drug. The *in vitro* skin permeation of morphine and its prodrugs, morphine propionate and morphine enanthate, showed that both prodrugs enhanced the transdermal delivery of morphine by 2- and 5-fold, respectively.^[28] The enhanced delivery might be due to the lipophilic nature of the prodrugs which enable permeation through membranes barriers especially BBB.

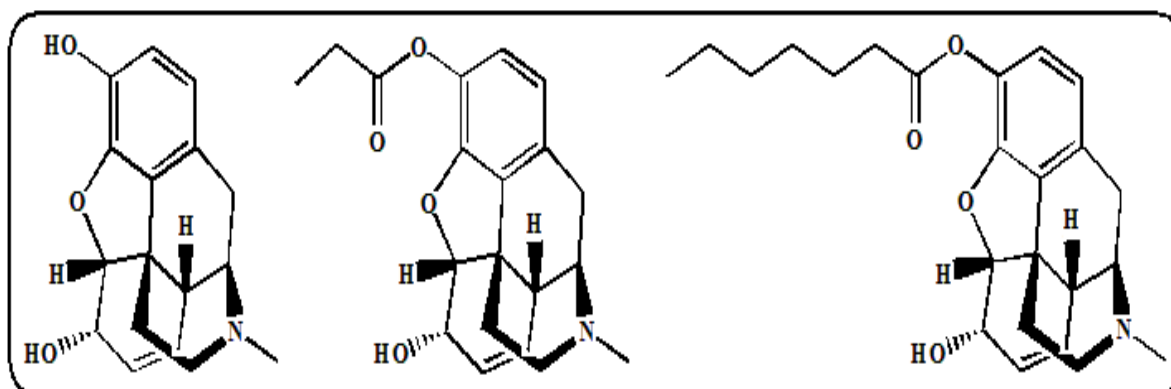


Figure 3: Chemical structures for *N*-alkyl esters of morphine, morphine propionate and morphine enanthate.

In another study conducted by Ward *et al.* on two newly synthesized ester prodrugs of morphine, Morphine Prodrug A and Morphine Prodrug B, which are esterase-sensitive prodrugs demonstrated that complexation with dendrimer allowed the solubilization of the prodrugs for *in vivo* applications without the necessity for salt. In addition, the structural features of the morphine prodrugs allowed the release of morphine in a controlled manner which extended the analgesic effect of morphine in an animal pain model from 2 hours for the control to 6 hours upon using Morphine Prodrug A (Figure 4).^[29]

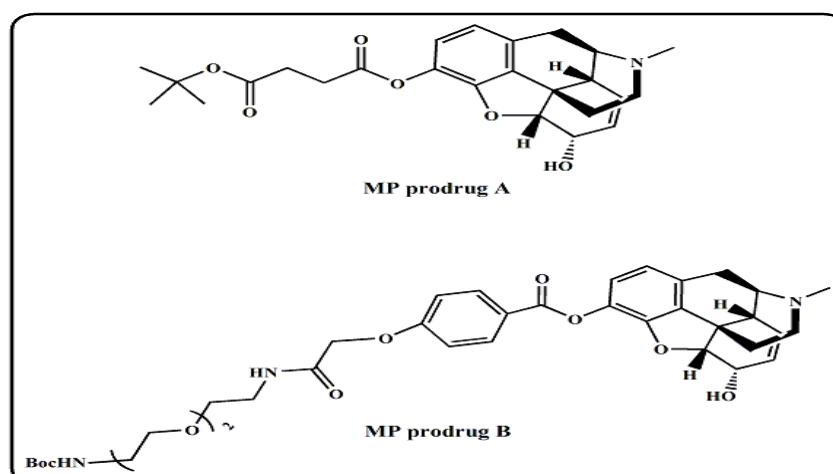


Figure 4: Chemical structures for morphine ester prodrugs, MP Prodrug A and MP Prodrug B.

The main obstacle of peptides delivery to the brain its hydrophilic character and sensitivity to cleavage by peptidases found within the capillary endothelium.^[30]

The esterase activation approach is considered as one of the main approaches to deliver drugs into the brain. Among the most promising examples of such approach is the one involves the

glycine derivative, thiorphan, a neutral endopeptidase inhibitor (Figure 5). The endopeptidase is a metalloenzyme responsible together with aminopeptidase N for the inactivation of endogenous enkephalins. The use of thiorphan encounters permeation restriction due to its inability to cross the BBB.^[31] On the other hand, some of its thiol derivatives such as *S*-acetylthiorphan (Figure 5), the monoacylated form of thiorphan, and acetorphan (Figure 5), the benzyl ester of *S*-acetylthiorphan, have proven to possess high analgesic effect, suggesting that their enhanced lipophilicity improves BBB permeation. Once these entities enter the brain they undergo hydrolysis catalyzed by esterase to the more active inhibitor thiorphan, **1**.^[32-33] Study that has been done by Fournie-Zaluski *et al.*^[34] revealed that the benzyl ester of acetorphan undergoes rapid hydrolysis in serum and therefore the metabolite *S*-acetylthiorphan is accountable for the BBB penetration.

Later on, based on the conclusions revealed from Fournie-Zaluski study Lambert and coworkers.^[35] have made a series of prodrugs consisting of amide pseudo triglycerides of *S*-acetylthiorphan in which the ester linkages in positions 1 and 3 of the glyceride have been replaced with amide linkages aiming to increase their metabolic stability. Pain tests have showed that these new compounds exhibited superior analgesic effects to those of thiorphan and *S*-acetylthiorphan, suggesting that they were acting as prodrugs.

More recent study in which the esterase activation was utilized to transport drugs through the BBB into the brain is the one reported by Krause *et al.*^[36] on azomethine prodrugs of (*R*)- α -methylhistamine (Figure 6). Krause's study demonstrated a correlation between lipophilicity and passive diffusion into the brain. The study also revealed that the release of the active parent drug is achieved after a chemical hydrolysis in which the carbon-nitrogen double bond is cleaved.

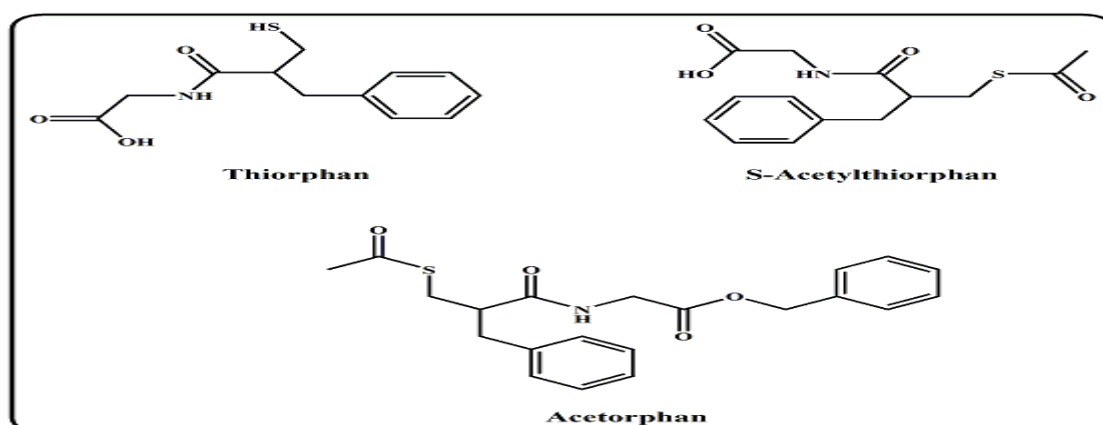


Figure 5: Chemical structures of thiorphan and prodrugs of thiorphan

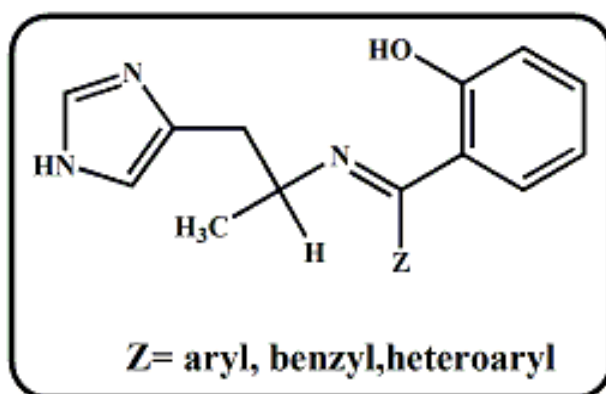


Figure 6: Chemical structures of azomethine prodrugs of (R)- α -methylhistamine.

-2GABAPENTIN PRODRUGS

Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, has similar chemical structure to GABA (Figure 7), and is used as anticonvulsant in various seizure models. Furthermore, gabapentin was approved for the treatment of trigeminal neuralgia, post herpetic neuralgia and other neuropathic pain status as it displays anti-nociceptive activity in various animal pain models.^[37-38] Gabapentin is also effective in improving restless legs syndrome (RLS) suggesting a potential role in treating this disease.^[37] Gabapentin's absorption occurs in the small intestine by a combination of diffusion and facilitated transports. Its transport from the gut is carried out by a saturable l-amino acid transport mechanism. The bioavailability of gabapentin varies inversely with dose as the carrier-dependent transport is saturable, and therefore the bioavailability of a 300-mg dose is approximately 60%, whereas that of a 600-mg dose is approximately 40%. Its C_{max} increases less than threefold as a result of the dose-dependent saturable absorption, when the dose is tripled from 300 to 900 mg.^[39]

However, more interestingly, XP13512 ((\pm)-1-((α -isobutanoyloxyethoxy) carbonyl]-aminomethyl)-1-cyclohexane acetic acid) (Figure 7) a novel transported prodrug of gabapentin was developed to overcome the pharmacokinetic deficiencies of gabapentin. XP13512 is a novel transported prodrug of gabapentin that is absorbed throughout the entire length of the intestine by high-capacity nutrient transporters. XP13512 is stable in gastrointestinal contents and is actively absorbed after oral dosing by high-capacity nutrient transporters present throughout the intestinal tract.^[40-41] Following absorption, the prodrug is rapidly converted to gabapentin by nonspecific esterases. During conversion to gabapentin, each molecule of XP13512 also generates one molecule of each of the following: carbon dioxide, acetaldehyde and isobutyrate.^[40-41]

Overall, XP13512 may provide enhanced absorption, more predictable gabapentin exposure, reduced interpatient variability, and decreased dosing frequency compared with commercial gabapentin. Therefore, XP13512 has the potential to become an important option for the management of long-term neuropathies and other conditions currently treated with oral gabapentin.^[40-41]

An alternative strategy was employed by Polli and coworkers where gabapentin was coupled to a natural substrate for a transporter to yield several novel prodrugs. These prodrugs were strategically designed to target hASBT with the same high affinity and high capacity as native bile acids. Among the five newly synthesized prodrugs, two were found to be potential prodrugs that may increase gabapentin absorption via hASBT uptake: CDCA-glu-gabapentin methyl ester and CDCA-gabapentin. The inhibition study with taurocholate revealed that the gabapentin conjugates are potent inhibitors, with strong interaction with the transporter. The K_m and V_{max} values for both prodrugs demonstrate high transporter affinity and capacity. The normalized V_{max} showed hASBT to possess higher transporter capacity for these two conjugates than for the native bile acid taurocholate. Furthermore, both prodrugs were chemically stable however; they underwent catalyzed-degradation to the active parent drug. Based on this study the researchers concluded that these two conjugates are novel prodrugs of gabapentin and can be designed to target hASBT.^[42]

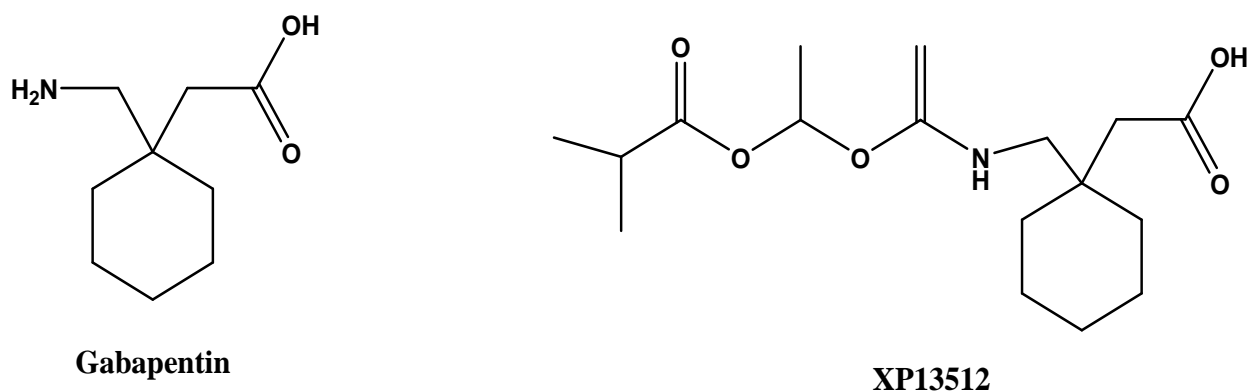


Figure 7: Chemical structures of gabapentin and XP13512.

-3DOPAMINE PRODRUGS

Dopamine is a neurotransmitter produced in the body and activates the five types of dopamine receptors– D1, D2, D3, D4, and D5 found in the brain. Dopamine is also a neurohormone released by the hypothalamus to inhibit the release of prolactin from the anterior lobe of the pituitary. The dopamine main functions are to regulate movement,

emotion, motivation, and the feeling of pleasure. Shortage of dopamine as a result of the death of dopamine neurons causes Parkinson's disease (PD), in which the ability to execute smooth and controlled movements is diminished. Since dopamine cannot cross the blood–brain barrier (BBB), it is not given as a drug for Parkinson's disease. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and dopa-responsive dystonia, levodopa (LD), which is the precursor of dopamine, is administered since it can cross the BBB.^[43-44]

The current therapy for PD is essentially symptomatic. L-dopa, the direct precursor of dopamine, is still the best choice of treatment for PD. However, long-term therapy with L-dopa is associated with significant adverse effects.^[45] PD patients have insufficient dopamine in specific regions of the brain, but since dopamine doesn't cross the BBB and its precursor LD does patients of this disease were given large doses of levodopa to compensate the deficiency of dopamine in the brain. However, because much of the LD is decarboxylated to dopamine in the periphery, high doses of LD are required, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.^[46] To minimize the conversion of LD to DA outside the CNS, LD is usually co-administered with peripheral inhibitors of amino acid decarboxylase such as carbidopa and benserazide.^[47-48] Although treatment with LD has minimized some side effects, other CNS adverse effects such as dyskinesia, on-off phenomenon and end-of-dose deterioration still remain.

It should be emphasized that the major factors causing the poor bioavailability of LD and inter- and intra-patient variations of plasma levels are the LD physicochemical properties such as the low water and lipid solubility which leads to unfavorable partition, and the high susceptibility to chemical and enzymatic degradation.^[47]

Recently, several attempts have been made to develop LD prodrugs with improved pharmacological and pharmacokinetic properties.^[47] For PD treatment, in addition to LD, DA agonists, antimuscarinic drugs, monoamine oxidase (MAO)-B and amantadine were utilized in Parkinson's disease.^[49-51] The following text describes the different prodrug approaches to enhance DP bioavailability and its concentrations in the brain.

3.1. Lipophilic LD prodrugs

A respected number of LD derivatives, such as ester, amide, dimeric and cyclic prodrugs, have been designed and made to increase LD lipophilicity:

3.1.1 Ester prodrugs

Nine ester derivatives of LD were the first to be synthesized as potentially LD prodrugs with enhanced bioavailability.^[52-60]

Although these prodrugs were as effective as their parent active drug, LD, in providing motor activity, however, none of them was significantly more potent or has longer duration than LD.^[58] On the other hand, two highly soluble ester prodrugs of LD and therapeutically efficient were synthesized, a methyl (Levomet, Chiesi Pharmaceuticals, Parma-Italy) and an ethyl ester (etilevodopa, TV-1203, Teva Pharmaceuticals, Petah Tikva-Israel).^[61] The ethyl ester, which is currently in Phase III clinical trials, could be given SC or IM for rigidity and to reverse akinesia. Studies showed that this prodrug was tolerated with only minor and negligible adverse effects.^[62] In addition, its physicochemical properties, such as water solubility and lipophilicity were found to be superior to those of LD and may hold promise for development of delivery strategies that would not be feasible with LD.

3.1.2 Amide prodrugs

Another approach which has been utilized to increase lipophilicity and thereby enhance the penetration through BBB to the brain is making LD amide prodrugs which are expected to undergo slower hydrolysis than their corresponding ester prodrugs. Novel LD amide prodrugs (**1** in Figure 8) for the treatment of PD and other similar conditions were patented.^[63] On the other hand, Jiang *et al.* have synthesized the LD amide prodrug **2** (Figure 8), and studied the *in vivo* (rats) release of LD from the prodrug after it underwent enzymatic hydrolysis following oral administration.^[64] The *in vivo* analysis for the amide prodrug and LD, respectively are: the C_{max} was 1980.7 ± 538.5 and 1936.6 ± 114.6 ng/ml, the T_{max} was 24.5 ± 3.5 and 4.5 ± 0.8 min, the area under curve (AUC) was $217,158.9 \pm 70,832.1$ and $94,469.5 \pm 7183.0$ ng/ml min and the $t_{1/2}$ was 56.5 ± 14.4 and 30.6 ± 1.6 h.

3.1.3 Dimeric prodrugs

Dimeric prodrugs can be made by direct attachment of two identical molecules or by linking the two identical molecules through a spacer.^[65-69] Felix and coworkers have made LD dimer prodrugs without spacer,^[70] while Di Stefano and coworkers have synthesized a number of dimeric prodrugs with different spacers.^[71-74] All the synthesized dimers were stable in aqueous buffer solution (pH 1.3 and 7.4) and in human plasma they liberate the LD in a slow release manner. Moreover, after *per os* administration, the DA concentration decreased much more slowly than that achieved with LD administration.

3.1.4 Cyclic prodrugs

A number of cyclic LD prodrugs were made by substituting the LD carboxyl and the amine groups in a cyclic skeleton. Based on this strategy, Cingolani and coworkers have prepared the 1-3-(3-hydroxy-4-pivaloyloxybenzyl)-2,5-diketomorpholine (**3** in Figure 8), in which the 2,5-diketomorpholine ring was essential for enhancing the stability toward GI hydrolysis and to liberate LD in human plasma after enzyme-catalyzed hydrolysis.^[75]

3.1.5 Chemical delivery system

Ishikura *et al.* has obtained a specific CDS for the brain delivery of LD (LD-CDS) by esterification of the protected carboxylic group of LD with a thiazolium moiety.^[76]

Ishikura brain delivery system is based on the redox ring closing reaction of *cis*-2-formylaminoethenylthio derivatives to quaternary thiazolium derivatives and the drug release was followed after hydrolysis of the ester bond. IV administration of these prodrugs and an equimolar dose of LD in rats revealed that while LD plasma levels did not show any difference between animals injected with prodrugs and those injected with LD, the LD levels in the whole brain were higher after prodrug administration compared with LD administration.

3.2 Lipophilic DA prodrugs

3.2.1 Ester prodrugs

DA is not used in PD treatment since it undergoes complete ionization at physiological pH, resulting in poor permeation across the BBB and other cell membranes. To overcome these problems, Casagrande *et al.* and Borgman *et al.* have prepared a number of lipophilic 3,4-O-diester prodrugs of DA as potential latentiated lipophilic derivatives of DA to be used in the therapy of PD, hypertension and renal failure.^[77-78] The results by Borgman *et al.* showed that O-acetylation was not enough to provide entry into the CNS while retaining intrinsic dopaminergic activity and N-alkylation of the DA molecule are also required.^[78]

3.2.2 Chemical delivery system

Similar to that done for LD, chemical drug delivery systems for brain-specific delivery have also been designed and made for DA.^[79] These prodrug devices were made joining DA with a pyridinium/dihydropyridine redox carrier.^[80-81] This carrier enables the prodrug entity to penetrate the BBB and then be oxidized to a quaternary precursor that is retained in the CNS, to provide a DA sustained release form.

3.2.3 Peptide transport-mediated prodrugs

2-Amino- N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide (DOPH), an amide prodrug of DA, was prepared by Giannola *et al.* (4 in Figure 8).^[82] upon condensation of DA with a neutral amino acid to interact with the BBB endogenous transporters and smoothly penetrate into the brain. DOPH underwent a slow cleavage by cerebral enzymes ($t_{1/2}$ 460 min) and produced free DA in the CNS; however, in human plasma it underwent a rapid hydrolysis ($t_{1/2}$ 28 min). In addition, chemical stability of DOPH showed the prodrug to be completely stable in the gastrointestinal tract and was able to permeate through a simulated intestinal mucosal membrane.

In another study, More and Vince synthesized prodrug (5 in Figure 8) in which DA is linked covalently via an amide bond to GSH.^[83] Compound 5 (Figure 8) showed high affinity for the GSH transporter at the BBB, liberated DA at the target site and showed a pretty good stability balance between the periphery and brain.

3.2.4 GLUT1 carrier-mediated prodrugs

Fernandez and coworkers designed and synthesized glycoconjugates in which the amino group of DA was attached to C-6, C-3 and C-1 of the sugar through a succinyl linker, carbamate bond, glycosidic and ester bonds. The prodrugs' affinity for the glucose carrier GLUT1 was tested using human erythrocytes.^[84-85] Upon incubation with brain extracts, several prodrugs liberated DA in rates that were found to be largely affected by the nature of the bond between DA and glucose. The glycosyl conjugates substituted at the C-6 position of the sugar were more potent inhibitors of glucose transport compared with C-1 and C-3 substituted prodrugs. In another study, Bonina *et al.* and Ruocco *et al.* have prepared sugar-DA prodrugs in which DA was attached to C-3 position of glucose (6 in Figure 8) and to C-6 of galactose (7 in Figure 8) by a succinyl spacer. Both of these prodrugs were found to be more active than LD in reversing reserpine-induced hypolocomotion in rats.^[86-87]

Although some success has been achieved using the different approaches by which prodrugs of DA and LD were utilized to provide DA in adequate concentrations and sustained release manner the prodrug chemical approach involving enzyme catalysis has many disadvantages related to many intrinsic and extrinsic factors that can affect the process. For instance, the activity of many prodrug-activating enzymes may be varied due to genetic polymorphisms, age-related physiological changes, or drug interactions, leading to variation in clinical effects.

Therefore, there is a need to synthesize new prodrugs for the treatment of Parkinson's disease having higher bioavailability than the current medications,^[88-94] and have the potential to release DA in a sustained manner via intramolecular chemical conversion without a need for enzyme catalysis.^[88]

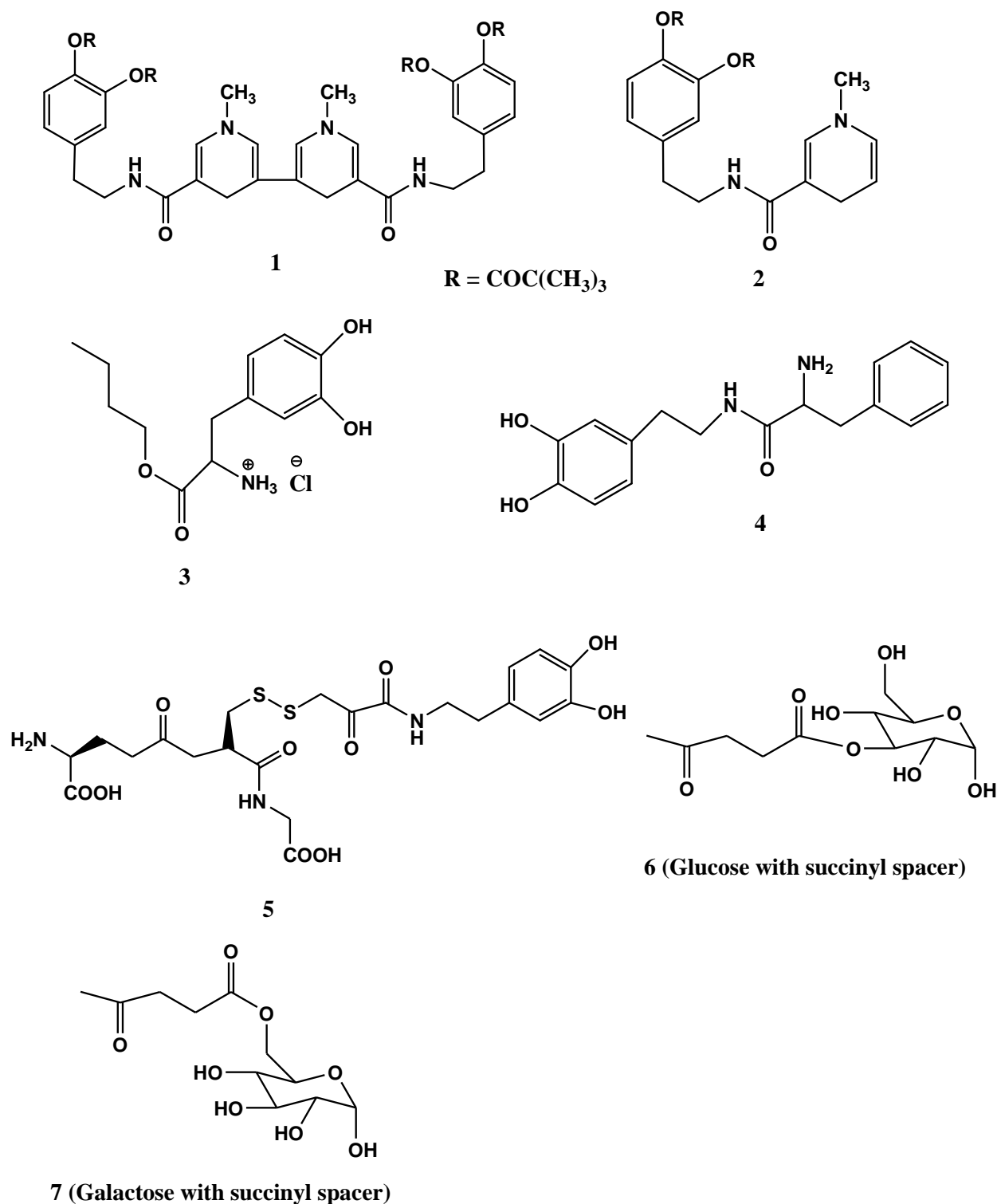


Figure 8: Chemical structures of compounds 1-7.

In the past seven years Karaman's group have explored a number of intramolecular processes to gain insight into enzyme catalysis and at the same time to utilize these enzyme models for the development of prodrug linkers with improved bioavailability over existing medications.^[95-144]

Few years ago we have designed and synthesized a number of DA prodrugs for the treatment of Parkinson's disease having the potential to be with a higher bioavailability than the current medications. The designed prodrugs have the following physicochemical properties: (i) soluble in physiological environment (ii) possess moderate hydrophilic lipophilic balance (HLB) (iii) release DA in a controlled manner, and (iv) undergo chemical cleavage to non-toxic by-products.^[88]

Utilizing enzyme models as potential linkers to be linked to amine-drugs, we have explored the proton transfer reaction in some of Kemp's acid amide derivatives, **8-18** (Figure 9).^[96] Based on the DFT calculations of the proton transfer mechanism of these acid amides, two dopamine prodrugs were proposed. As illustrated in Figure 10, **ProD 1** and **ProD 2** have a moderate HLB. In addition, in the blood circulation (pH 7.4) the dominant form of dopamine is the ionized form while prodrugs **ProD 1-2** are expected to exist in both forms, the ionic and the free acid. Thus, it is expected that prodrugs **ProD 1-2** may have a better bioavailability than DA because of improved absorption. Further, the designed prodrugs can be administered in a variety of dosage forms (i.e. enteric coated tablets) since they are expected to be soluble in organic and aqueous media due to the ability of the COOH to convert to COO⁻ in physiological environments of pH 5.0-7.4 (intestine and blood circulation).

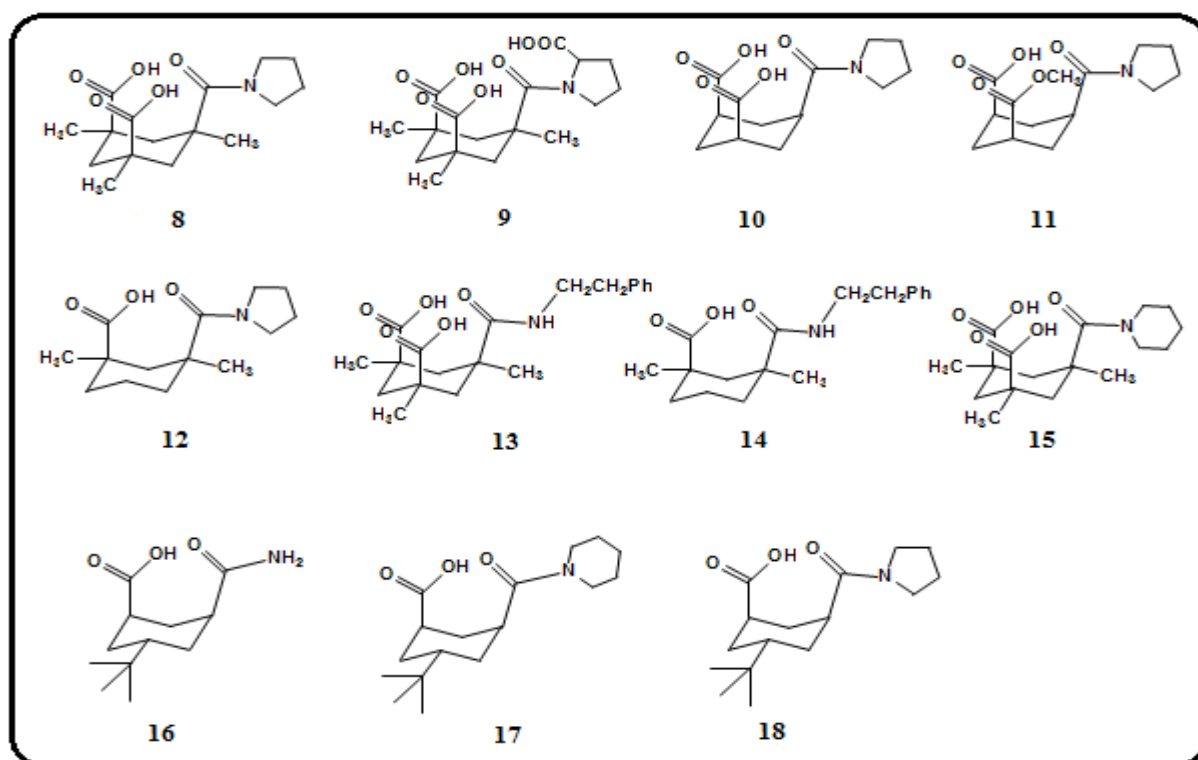


Figure 9. Chemical structures of Kemp's acid amides 8-18.

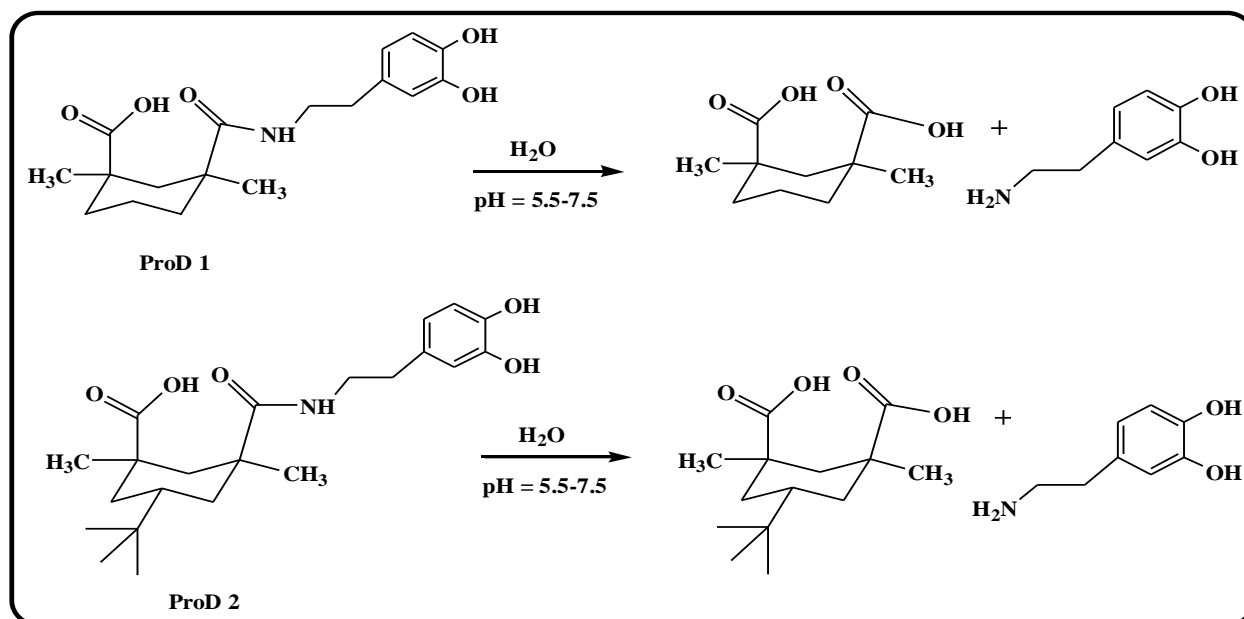


Figure 10: DA prodrugs ProD 1- ProD 2.

Moreover, the computational calculations predict a $t_{1/2}$ value of the cleavage reactions of **ProD 1- ProD 2** at pH 6 to be 12-20 hours, whereas at pH 7 the value is expected to be higher. The strategy to provide prodrugs for the treatment of Parkinson's disease with improved bioavailability consists of: (i) synthesis of Kemp's amide acid linker and linking it

with DA according to Menger's synthetic method [130]; (ii) *in vitro* kinetic studies of **ProD 1- ProD 2** in physiological environment (37 °C, pH = 6.0 in aqueous medium) and (iii) for the prodrugs that demonstrate desirable programmed release in the *in vitro* studies, *in vivo* pharmacokinetic studies should be carried out in order to determine the bioavailability and the duration of action of the tested prodrugs

SUMMARY AND CONCLUSIONS

In the past few years, researchers have shifted their attention towards developing targeted prodrugs to replace currently marketed drugs with poor bioavailability and insufficient clinical profiles. The targeted prodrugs approach has been accelerated after encouraging results which were emerged from a respected number of studies on targeted prodrugs that demonstrated better efficiency and higher safety profiles.

In this mini review targeted drugs delivery to the CNS using prodrugs is covered. Methods for targeting disease and selected newly synthesized prodrugs are reported in details. Many of the listed prodrugs in this mini review are still in clinical studies hoping to pass all clinical phases and be approved for marketing.

During the last two decades a significant advances have been for better delivery of drugs into the brain (CNS) Among these used methods are nanoparticles, liposomes, and some invasive strategies such as BBB disruption and intracerebral implants

Generally, prodrugs targeting the CNS are made by linking the active parent drug to a lipophilic moiety such as fatty acid, glyceride or phospholipids which is capable to permit BBB transmission. Regardless of the achievement of successful entry of the drug into the CNS via this method many disadvantages are to be faced including poor selectivity, poor retention and the creation of toxic/reactive metabolites.

An interesting strategy to solve the problems associated with the current targeting prodrugs is the one we suggested by us in which an active drug is linked to enzyme model (intramolecular chemical device) and upon an exposure of the prodrug moiety to the blood circulation within the brain it undergoes intramolecular chemical conversion (without any involvement of enzymes) to the active parent drug in a controlled manner. The conversion rate of the prodrug to its parent drug is solely determined on the chemical features of the linker (enzyme model.)

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