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RESEARCH ARTICLE

Applied Research: Conceptual Study of Cellular Membrane Organic Compounds Enzymatic Synthesis towards Promedicine of Dopamine and Cocaine Penetration into the Cytoplasm

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Abstract

In order to better understand how dopamine and cocaine penetrate the cellular cytoplasm, I have detailed significant mechanisms regarding the synthesis of the cellular membrane organic compoundsin connection with the dopamine and cocaine penetration into the cytoplasm. I suitably also applied organicchemistry knowledge to properly explain organic reactions occurring between dopamine as well as cocaine and the main chemical cellular components such as glycoproteins, glycolipids together with phospholipids.Specifically, biological substances are reactive organic entities such as glycoproteins, glycolipids or phospholipids,which contain functional groups and for that reason they can behave as acids, bases, electrophiles or nucleophiles towards dopamine and cocaine depending on the reaction conditions like enzymes acting as natural catalysts.

Keywords: Promedicine, Dopamine, Cocaine, Glycoproteins, Glycolipids, Phospholipids, Enzymatic Synthesis.

1. Introduction

1.1 Objective

The main objective of this article is to propose an appropriate conceptualstudy of enzymatic organic reactions, which naturally take place into living beings, notably animals, plants and microorganisms. Indeed, dopamine, cocaine, glycoproteins, glycolipids, and phospholipids have been chosen to serve as an illustration of these kinds of natural enzymatic organic reactions. In this perspective, enzymatic organic reactions are chemical reactions that are activated or catalyzed by specific enzymes. That means, enzymes combine with appropriate substrates to place them in closer position to corresponding reactive entities so that they can react properly. Indeed, in this conceptual study as said earlier, dopamine and cocaine have been selected as adequatereactive entities to understand how they react with cellular membrane chemical constituents in order to resemble as them, and then easily cross the selective cellular membrane. A such ability is due to their chemical properties essentially, they may be have as nucleophiles, electrophiles, acids or bases.

1.2 Cellular Membrane Organic Compounds

The cellular membrane is essentially constituted by proteins and lipids, which are bounded to a glycosyl as well as aphosphate group and consequently they are simply known as glycoproteins, glycolipids and phospholipids.[1-4]These organic compounds surround

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the cytoplasm or an intracellular fluid environment containing diverse organelles.[5]

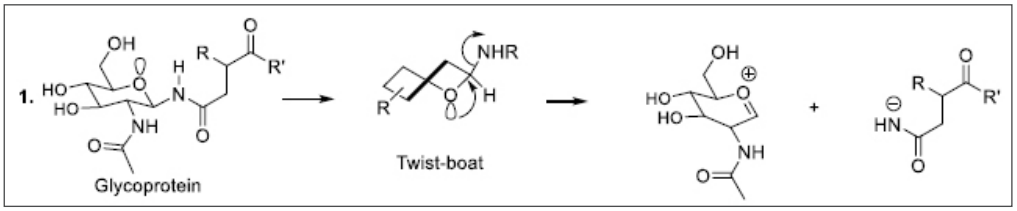
2. Enzymes

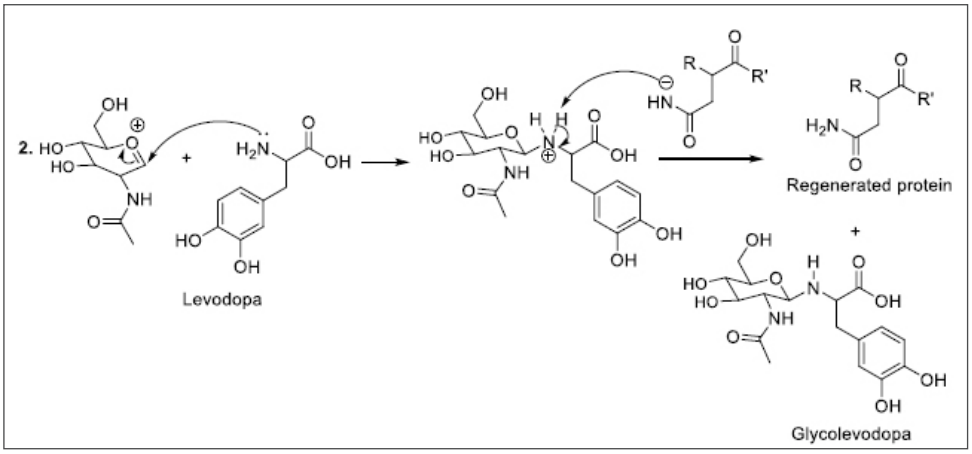
2.1 Chemical Behaviour

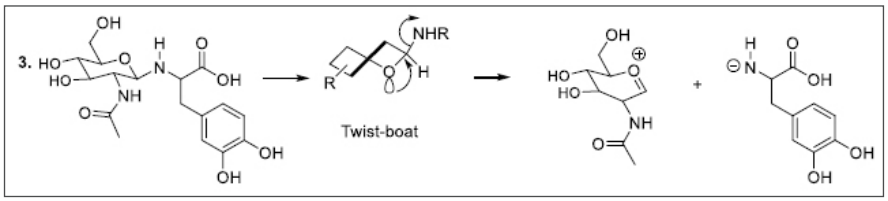
Enzymes are proteins, which catalyze organic reactions into the leaving beings inside the cell (intracellular environment) or outside the cell (extracellular environment) because they intracellularly secreted and they can diffuse through the cellular membrane to reach the extracellular environment to fulfill their catalytic role.[6-18]The intracellular enzymes diffuse easily through the cellular membrane due to the similarity of their derived products (analogous products) with glycoproteins, glycolipids and phospholipids known as the essential cellular membrane constituents.[6-18]

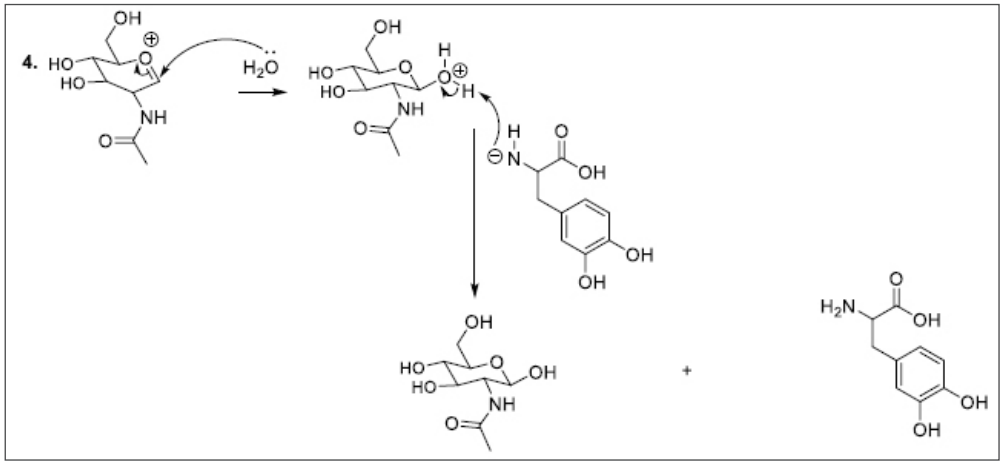
The organic compounds analogous model proposed in this conceptual study is comprehensively supported by the intracellular enzymenaturalbehaviour because enzymes are secreted into the cell and they can cross the cellular membrane in order to catalyse reactions in the extracellular environment.This analogous model is also supported by the prodrug concept, which means a promedicine is a derivative or analogous of a parent medicinal organic compound that will be hydrolysed to release the active parent medicine into the cell.[6-12]In this aqueous condition reaction, it has been revealed that levodopa is a promedicine of the dopamine.[6-12]Being very polar dopamine cannot be administrated as such. That is why, the levodopa (L-3.4-Dihydroxyphenylalanine) is administrated in the place of dopamine because it is an amino acid susceptible to be recognised by a specific cellular membrane receptor (bearer protein), which facilitates the promedicine to passe through the cellular membrane, and as soon as the levodopa is integrated into the cell, the decarboxylase will catalyze the departure of the carboxylic group to provide the desired dopamine into the cell (Scheme 1,reactions1-2). Indeed, the experimental observations has shown that cysteine and aspartate residues are essentially involved in the enzymatic activities of the decarboxylase (Scheme 1, reaction 3).[13-14]

Regarding the reaction mechanism, the glycoprotein equatorial isomer will adopt the twist-boat conformation to align in an opposite direction the leaving group and the intra cyclic oxygen free double electrons in order to easily promote the departure of the leaving group (Scheme 1, reaction 1). The levodopa pro medicine will now react with the carbo oxonium ion to furnish the corresponding products (Scheme 1, reaction 2). The successive following mechanism stages indicate the regeneration of decarboxylase as well as the expected dopamine into the intracellular environment (Scheme 1, reactions 3-6).

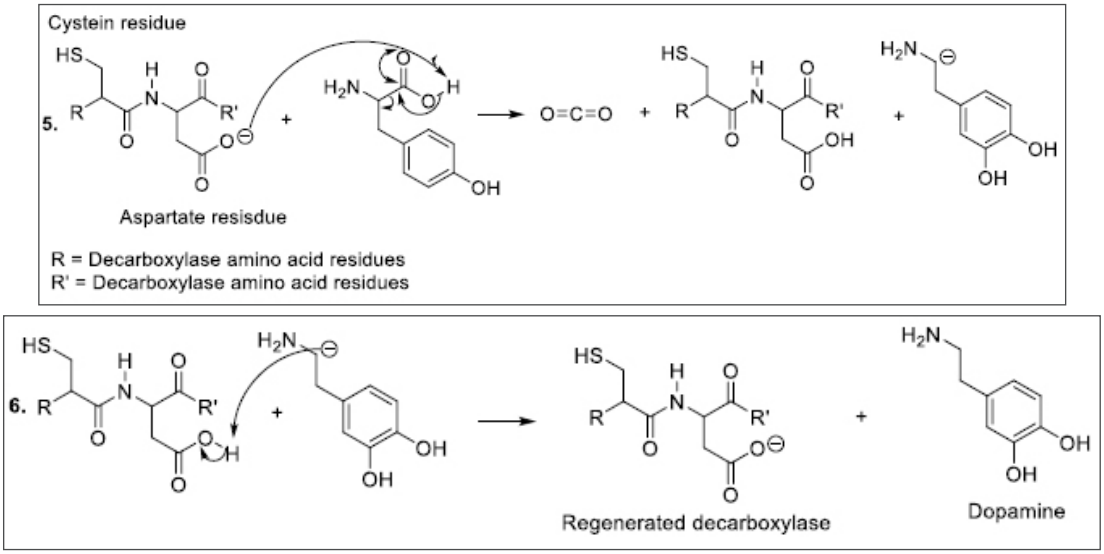








Scheme 1a

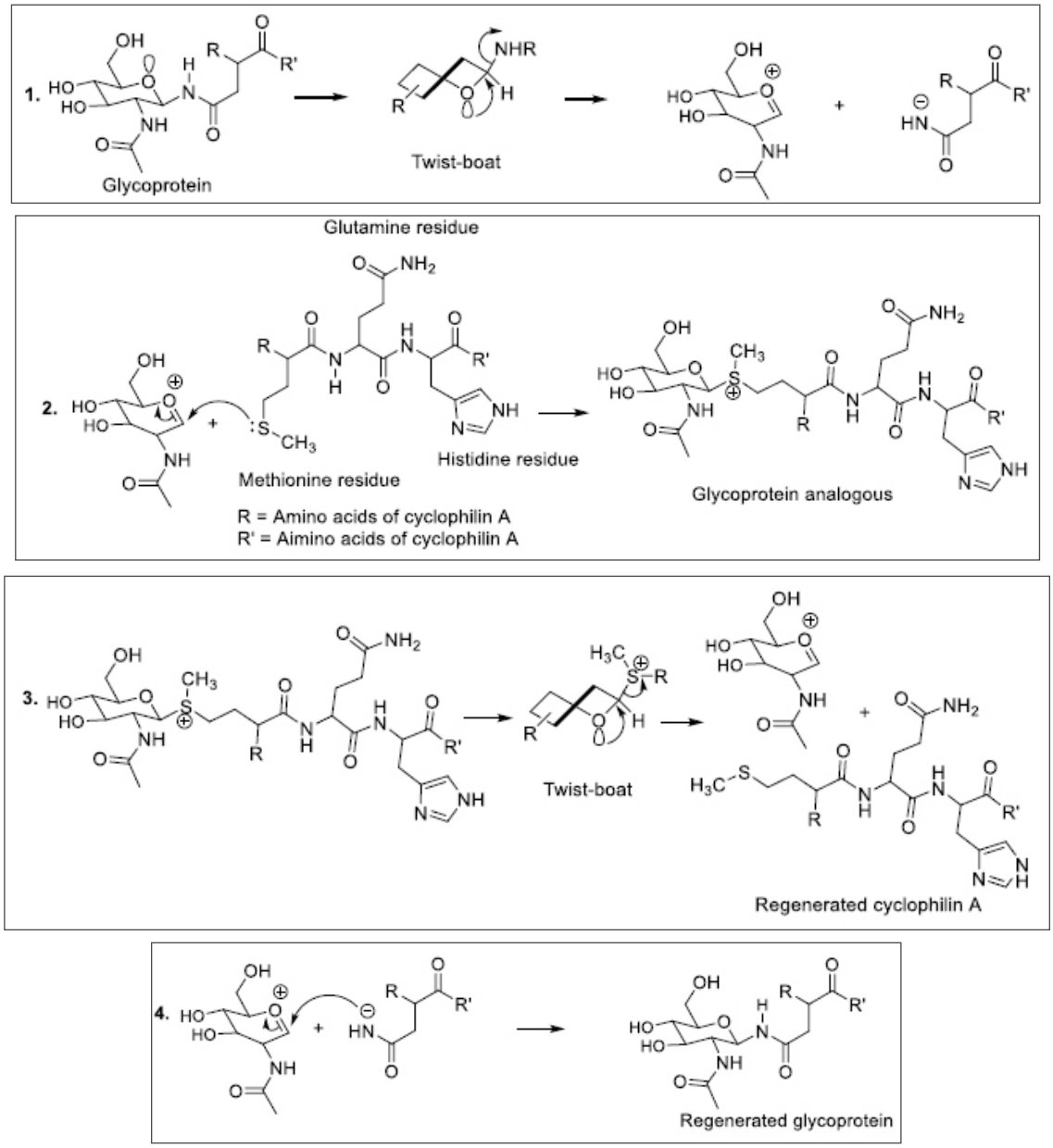


Scheme 1b

In other words, it has been reported that the movement of the intracellular enzymes induces their catalysis responsibility, notably the human cyclophilin A intracellular enzyme that is secreted into the cell and can act out the cell as an organic catalyst.[15-27]The experimental observations reveal that among active site amino acids of this enzyme, Methionine, Glutamine and Histidine have been shown to serve as active site amino acids to exhibit the interactions between cyclophilin A intracellular enzyme with glycoproteins, glycolipids and phospholipids when the enzyme move outside the cellular membrane.[15-27]It should be noted that when organic compounds are closely together, their nucleophilic or bases atoms connect with the appropriate electrophilic acceptors. For instance,when the intracellular enzymespass through the cellular membrane to catalyze the outside cellular membrane reactions.

2.2 Cyclophilin a Reaction with Cellular Memebrane Glycoprotein

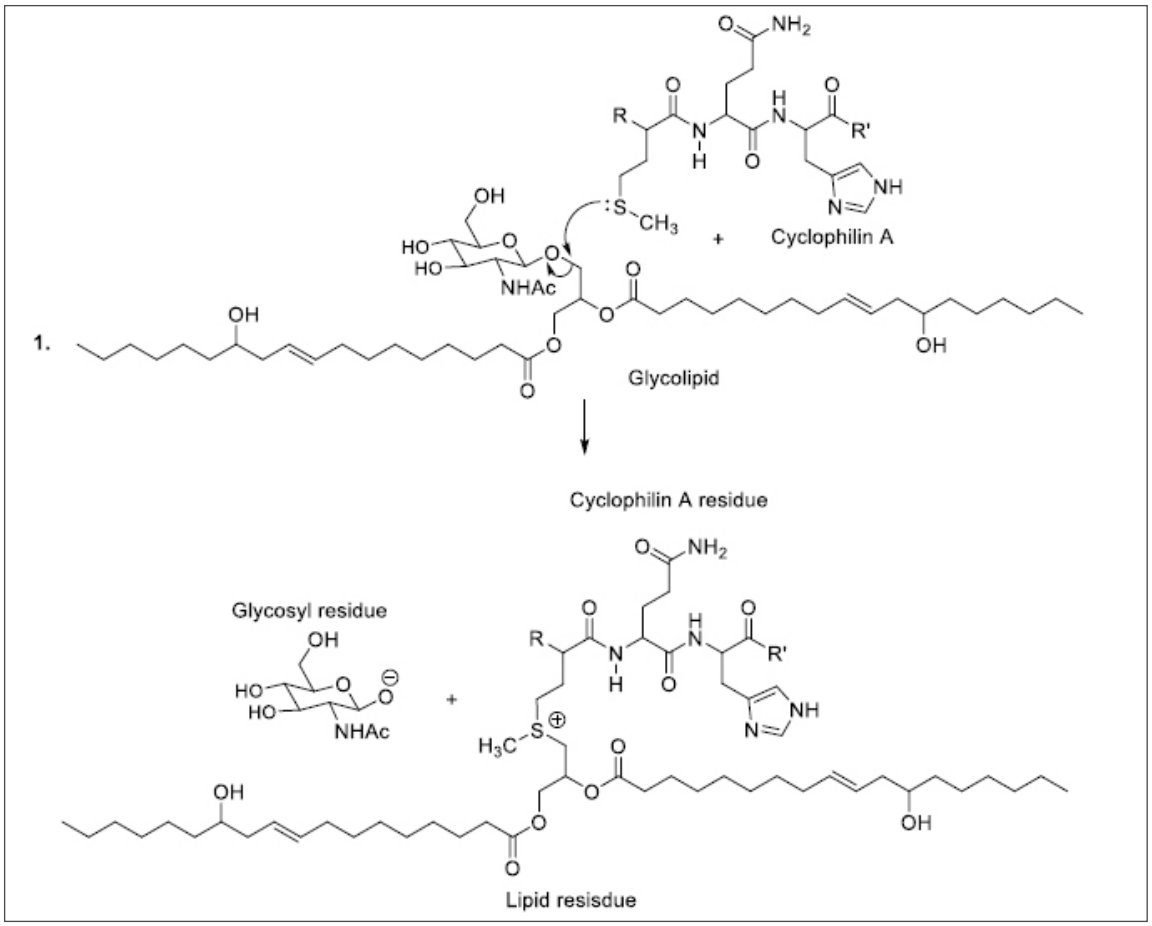
The reaction between glycoproteinstarts with chair conformation modification of the glycoproteinto better eliminate the equatorial leaving group in adopting the twist-boat conformation (Scheme 2, reaction 1). This change of conformation is because in the twist-boat conformation, the leaving group is aligned in an opposite position with respect to the free electrons pair upon the intra cyclic oxygen atom, and this position favors the easily departure of the leaving group (Scheme 2, reaction 1). The resulting products such as the cyclic oxonium ion will react with the cyclophilin A enzyme to furnish the glycoprotein analogous, which in a good shape to reach the extracellular environment due to its similarity with the cellular membrane glycoprotein. In the same perspective, the conjugate base of the protein moisture into the glycoprotein substrate will also react with the cyclic oxonium ion to generate the substrate glycoprotein (Scheme 2, reaction 4).



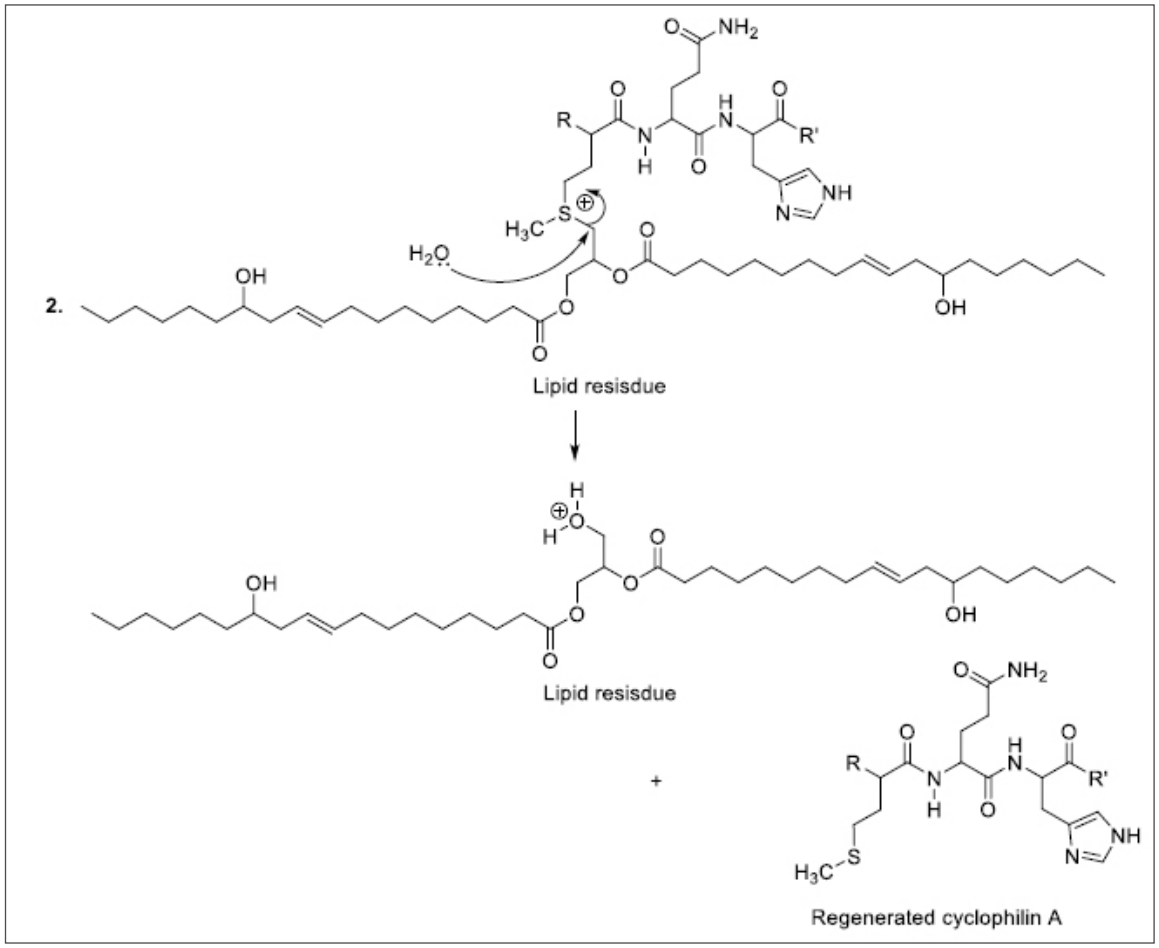
Scheme 2

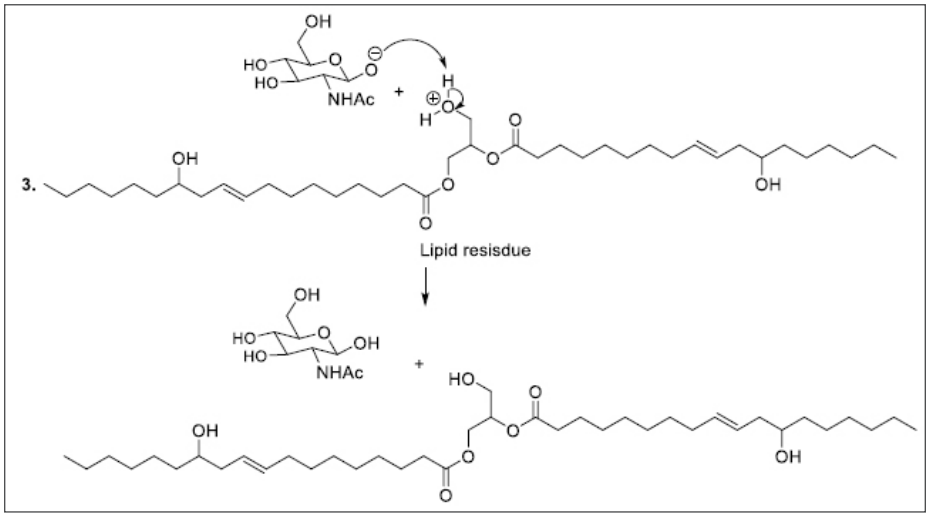
2.3 Cyclophilin a Reaction with Cellular Memebrane Glycolipids

The plausible reaction between cyclophilin A and cellular membrane glycolipid is the substitution of glycosyl moisture by cyclophilin Ato produce a complex compound bearing a cyclophilin A ion residue and a lipid residue including a glycosyl ion residue, which is analogous to glycolipid parent (Scheme 3, reaction 1). Indeed, due to the similarity of the obtained complex compound with the parent glycolipid, the cyclophilin A can now move trough the cellular membrane to reach the extracellular medium where it will act as an extracellular enzymeafter being freed due to the hydrolysis of the analogous compoundsubstrate (Scheme 3, reaction 2). In the same perspective, the glycosyl moisture or the glycan one will be also regenerated from the deprotonation reaction of the lipid ion portion (Scheme 3, reaction 3). Being free in an extracellular environment, the cyclophilin A will catalyze the addition of the regenerated glycan to the lipid residue to regenerate the glycolipid parent (Scheme 3). Indeed, the regenerated cyclophilin A will deprotonate the lipid residue to provide a strong nucleophilic lipid residue and the corresponding cyclophilin A conjugate acid (Scheme 3, reaction 4). In the same circumstances, the cyclophilin A conjugate acid will protonate the regenerated glycan to obtain the glycan conjugate acid, which will adopt an appropriate twist-boat conformation to promote the departure of the leaving group or a molecule of water (Scheme 3, reactions 5-6). The resulting carbo oxonium anion will then reaction with the strong nucleophilic lipid residue to regenerate the corresponding glycolipid (Scheme 3, reaction 7).

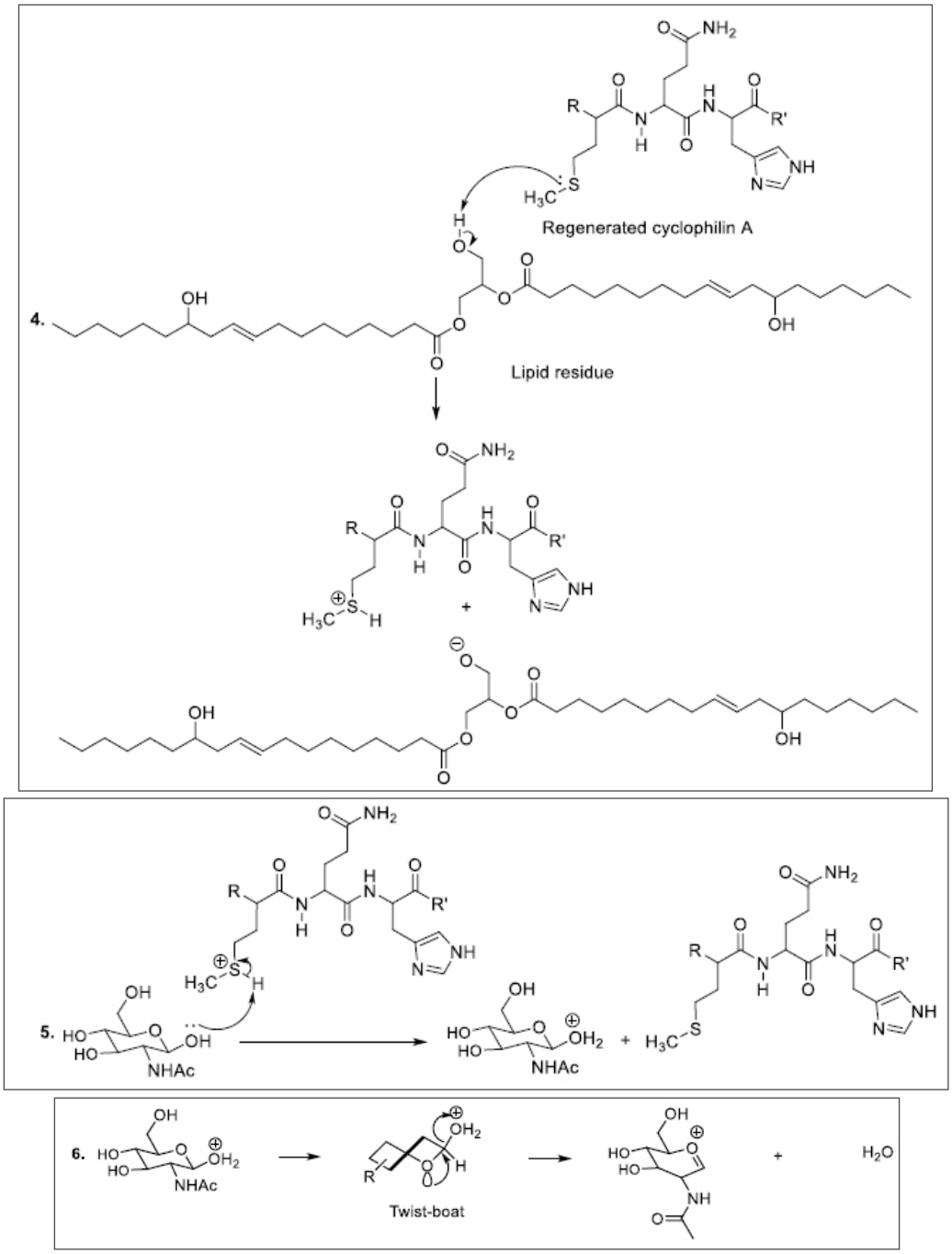

1.
Cyclophilin A
Glycolipid
Cyclophilin A residue
Glycosyl residue
Lipid resisdue

Scheme 3a

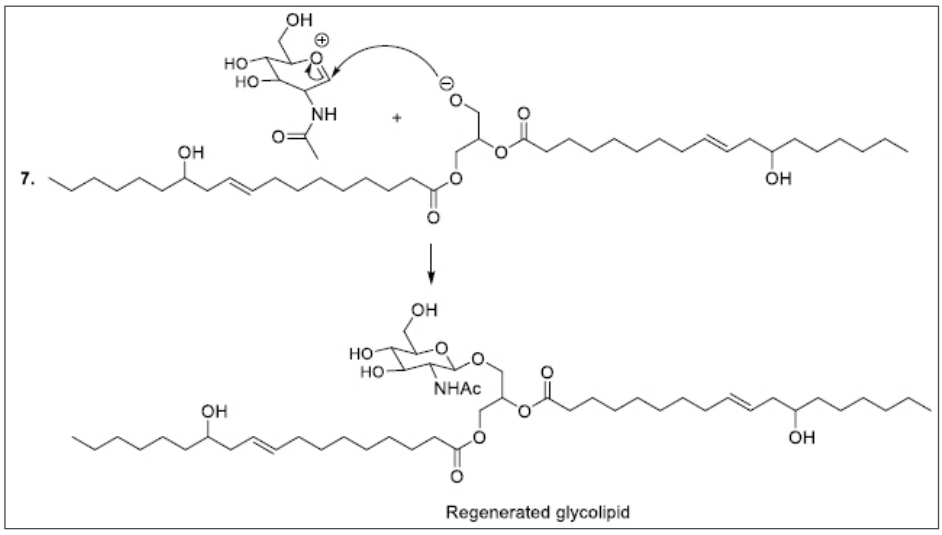

2.
Lipid resisdue
Lipid resisdue
Regenerated cyclophilin A



Scheme 3b



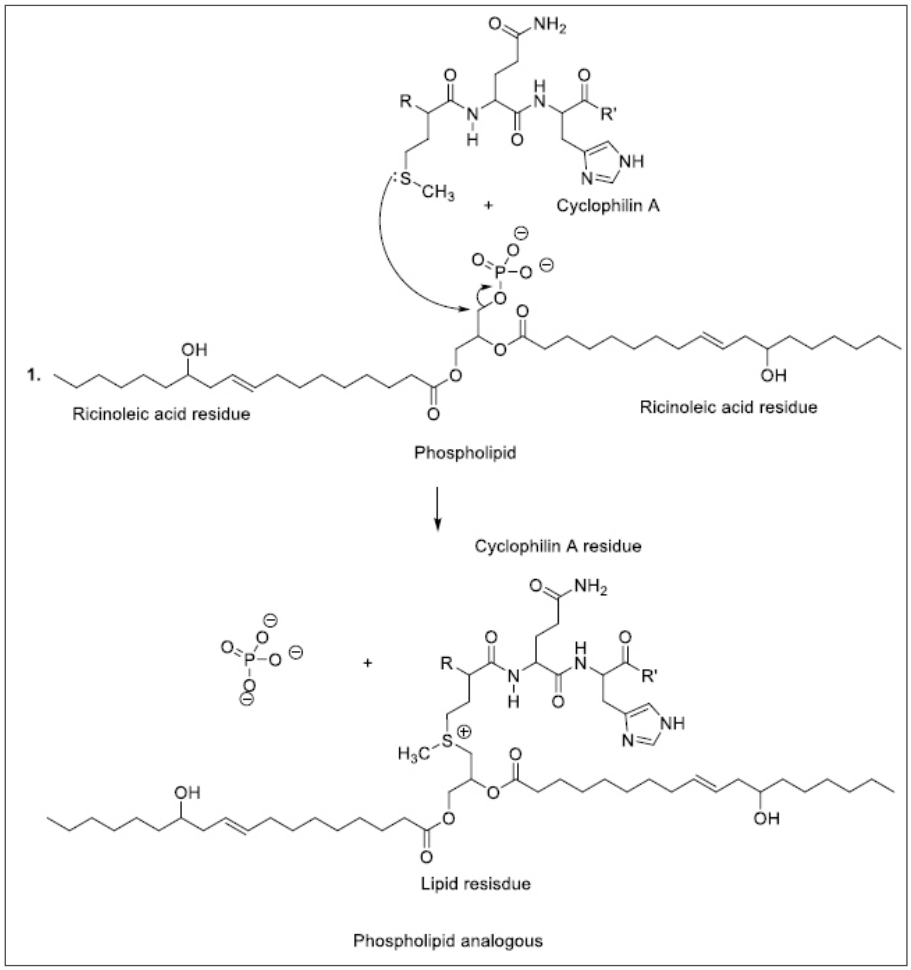
Scheme 3c



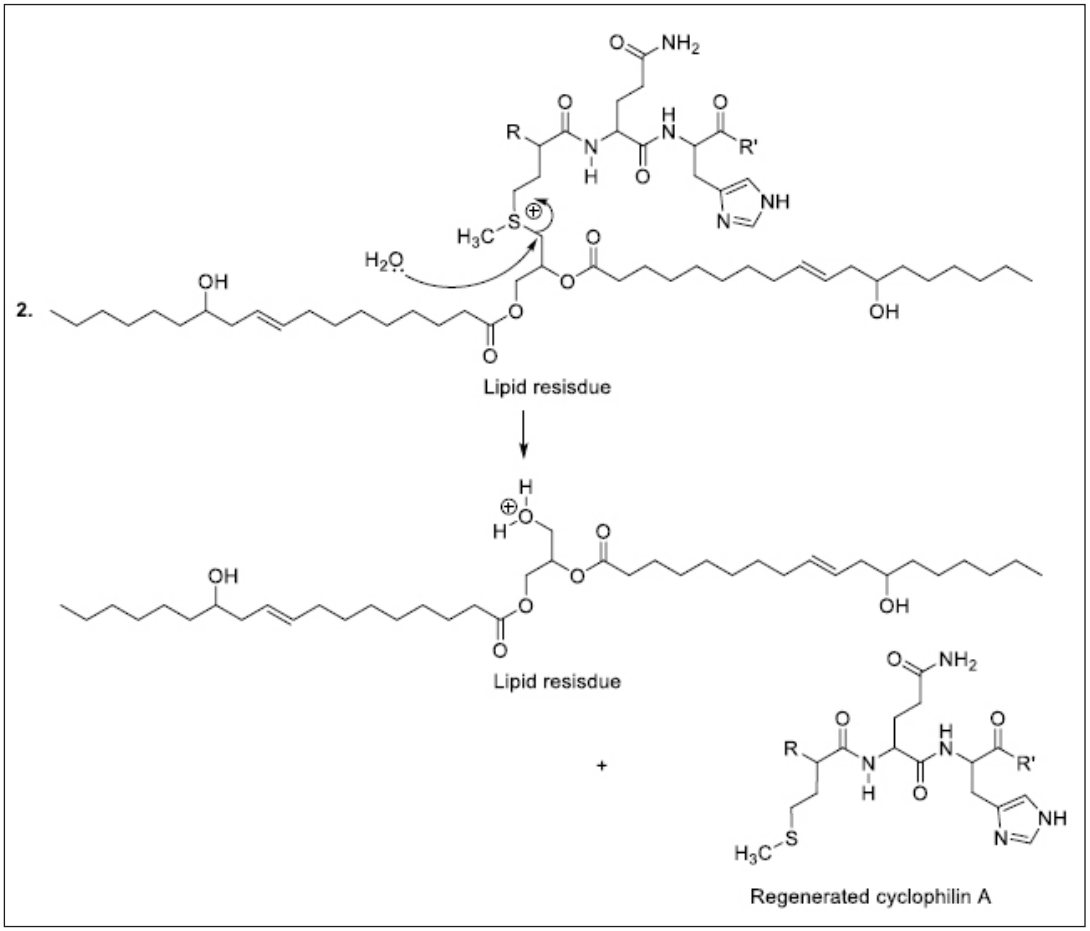
Scheme 3d

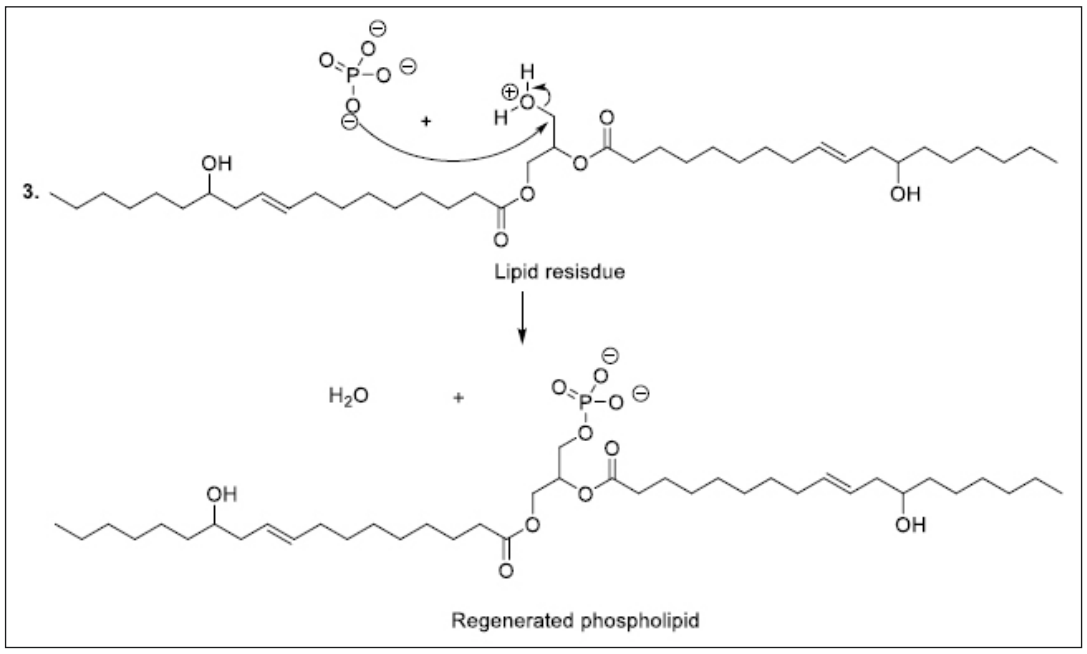
2.4 Cyclophilin a Reaction with Cellular Memebrane Phospholipid

The phospholipid structure showing its functional groups determines its reactivity towards nucleophilic functional groups, particularly the thiol group of the cyclophilin A (Scheme 4, reactions 1). In this situation, the thiol group of the cyclophilin A will donate two free electrons to an adequate electrophile in order todisplace the phosphate leaving group and produce a corresponding analogous compound (Scheme 4, reactions 1). Consequently, the obtained analogous compound has acquired the ability to cross over the cellular membrane and to arrive in the extracellular environmentdue to its similarity with the phospholipid parent (Scheme 4, reactions 1). The extracellular analogous compound will be therefore hydrolyzed to regenerate the cyclophilin A, which will now freely exert its catalytic activities (Scheme 4, reaction2). In the same context, the phosphate group conjugate base will remove a molecule of water from the lipid residue conjugate acid to regenerate the phospholipid parent (Scheme 4, reaction 3).



Scheme 4a





Scheme 4b

3. Cellular Membrane Organic Compound Enzymatic Synthesis

3.1 Glycoprotein Synthesis

Golgi apparatus is a cellular organelle in which glycoproteins synthesis occur. It is important to recall that glycoproteins are proteins upon which a carbohydrate (glycan) residu has been aconnected with the assistance of a specific enzyme known as glycosyl transferase. This enzyme catalyzes not only glycoproteins synthesis but also the synthesis of glycolipids or fatty acids which are esterified to glycerol on whicha glycan residue has also been attached (Figure 1).[28-34]

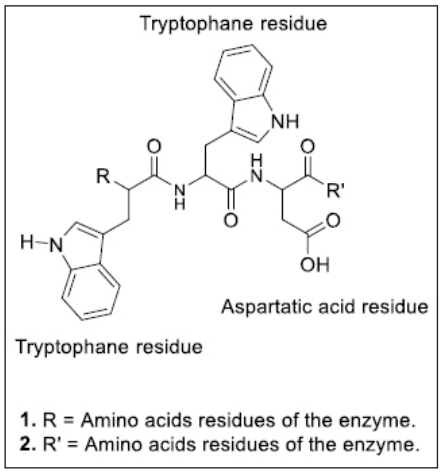
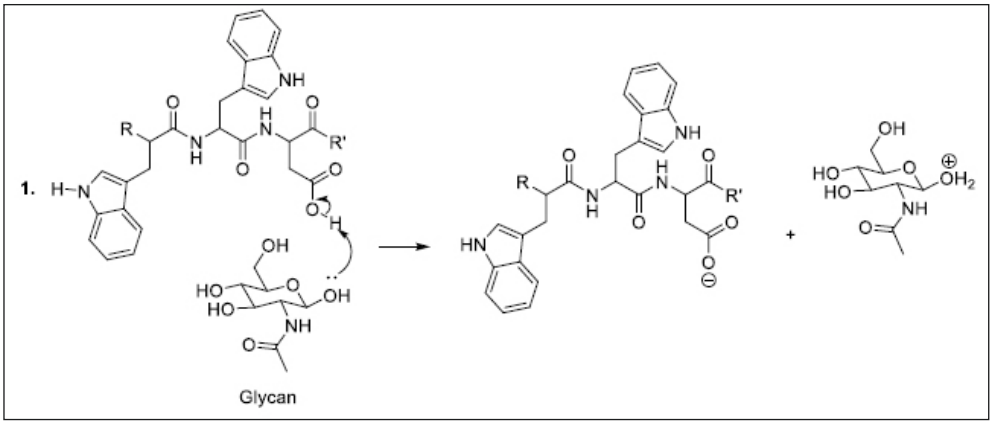
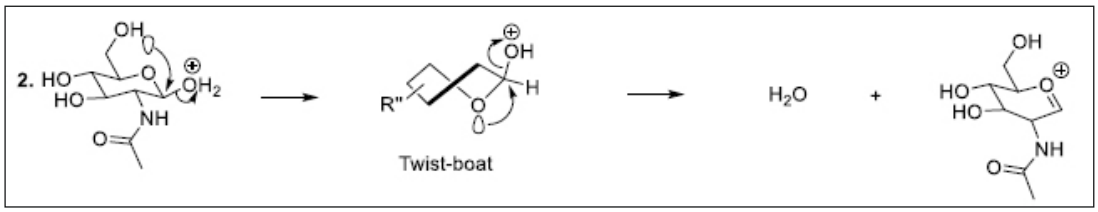
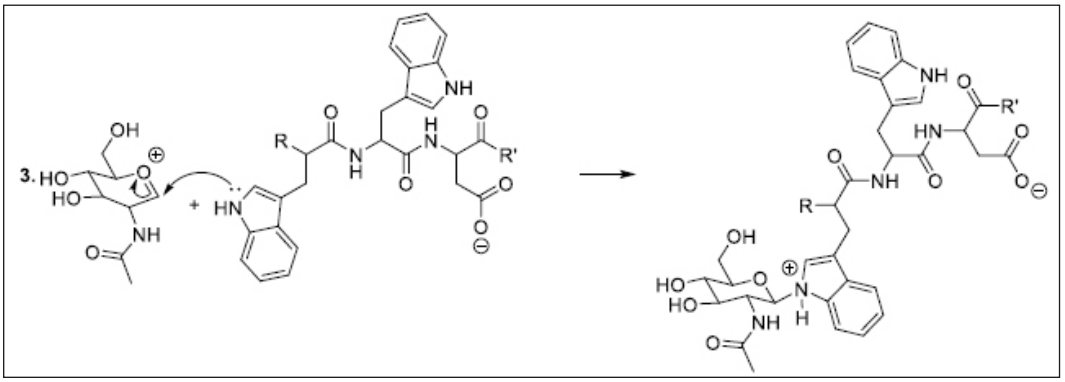


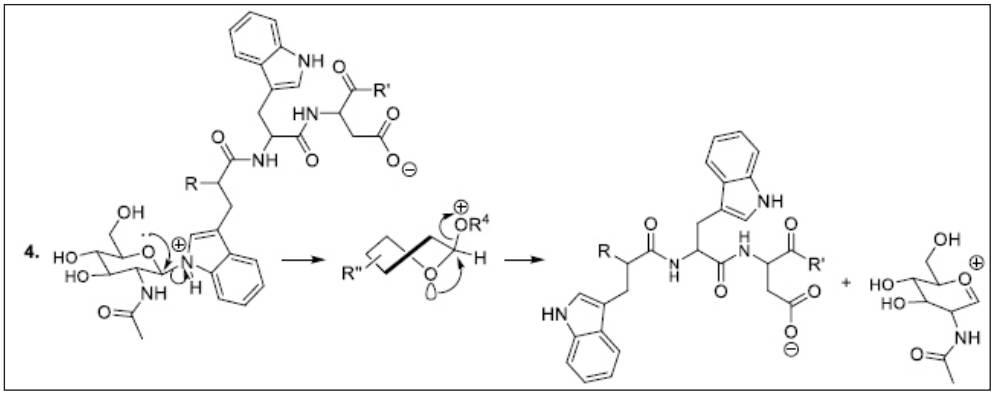
Figure 1

The experimental observations have demostrated that in the eucaryotes organisms, the formation of glycoproteins implies the addition of glycosyl moisture to the lateral chaine of the asparagine amide group (Scheme 5).In this circumstance, the enzyme aspartic acid residue donates a proton glycan hydroxyl group to produce the enzyme conjugate base and the corresponding glycan conjugate acid, which adopts the twistconformation to align the oxygen atom free double electrons into an opposite position to the leaving group. Therefore, the glycan conjugate acid disintegrates to generate a molecule of water and a cyclic oxo carbonium ion (Scheme5, reaction 1-2). Indeed, the cyclic oxo carbonium ion behaves as an electrophile in accepting the free double electrons located on the nitrogen of the enzyme aspartic acid residue to furnish the complex enzyme-substrate, which will also align the oxygen free double electrons in an opposite position to the leaving group in twist conformation to afford a carbo oxonium ion (Scheme5, reaction 3-4).

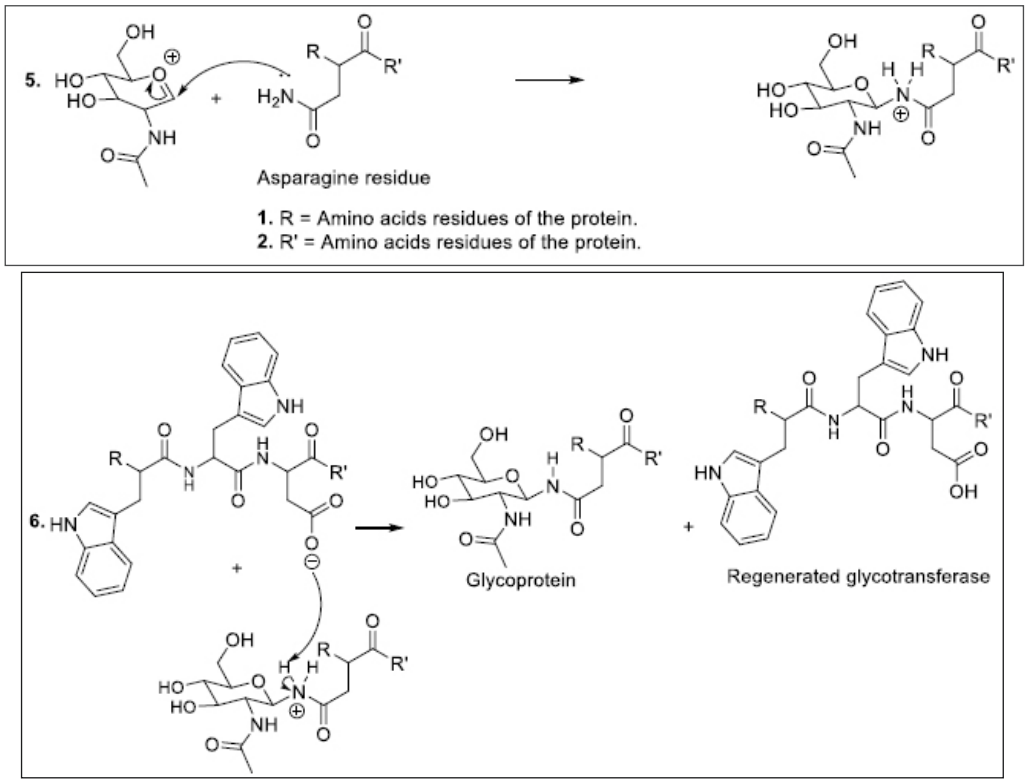








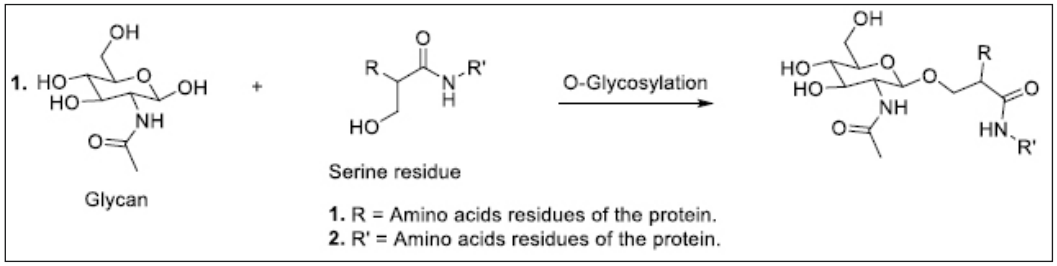
Scheme 5a

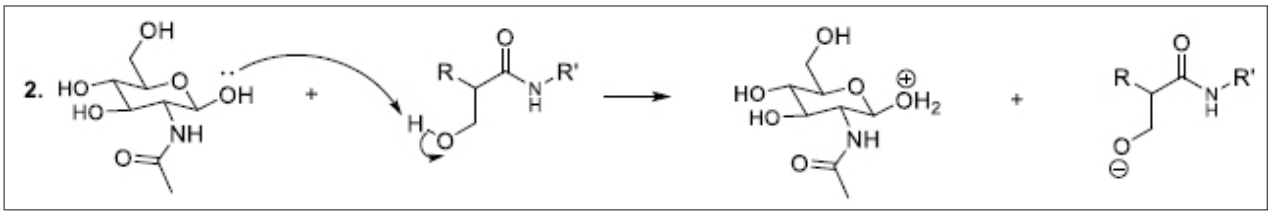


Scheme 5b

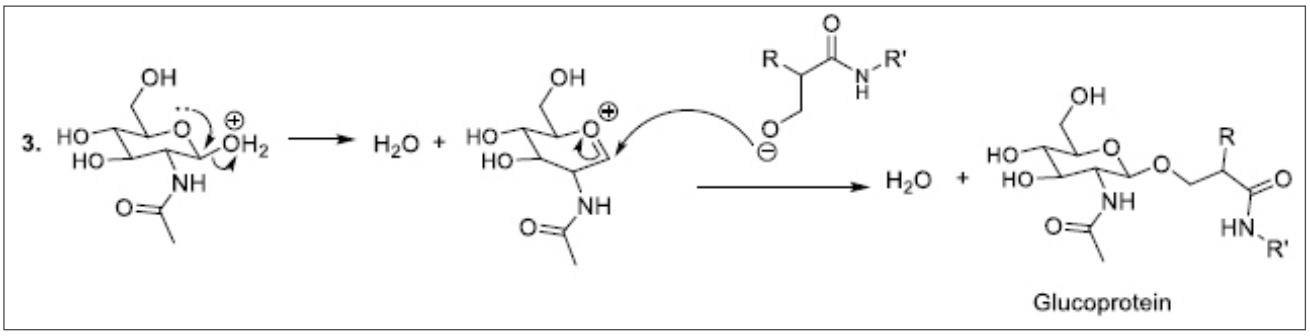
The nucleophilic addition on the carbo oxonium ion and the protonation of the resulting intermediate product leads to the formation of glycoprotein including the enzyme regeneration (Scheme5, reactions 5-6). It is important to mention that the glycan carbon anomeric equatorial stereochemistry has not been modified or is maintained in theglycoprotein because it has been reported that the glucosyltransferases can inverse or preserve the starting product stereochemistry in the final product.[28-34]

The serine hydroxyl group glycosylation or O-glycosylation reaction follows the same pathway as for the asparagine residue (Scheme 5).[35-37] Indeed, the glycan hydroxyl group acts as a nucleophile to accept a serine residue proton to generate a glycan conjugate acid and a serine protein conjugate base (Scheme 6, reaction 2). The following step is the displacement of a molecule of water to afford a carbo oxonium ion derived from a glycan conjugate acid, and the rection of a serine protein conjugate base (nucleophile) with a carbo oxonium ion (electrophile) to furnish the expected glycoprotein (Scheme 6, rection 3).





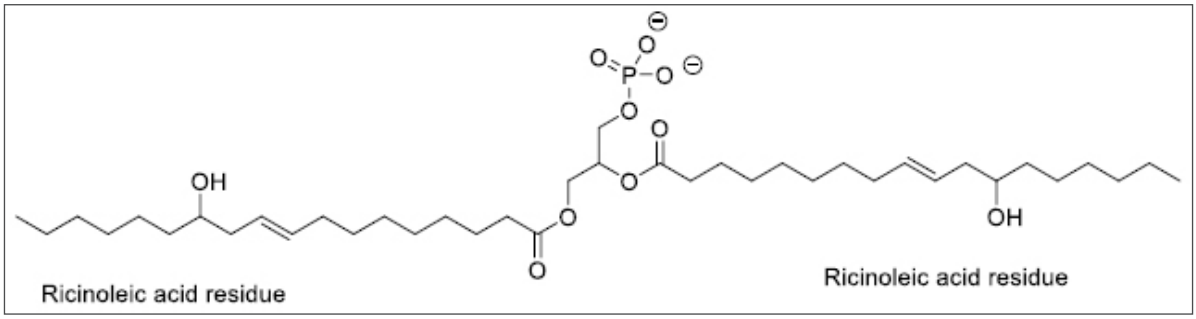
Scheme 6a



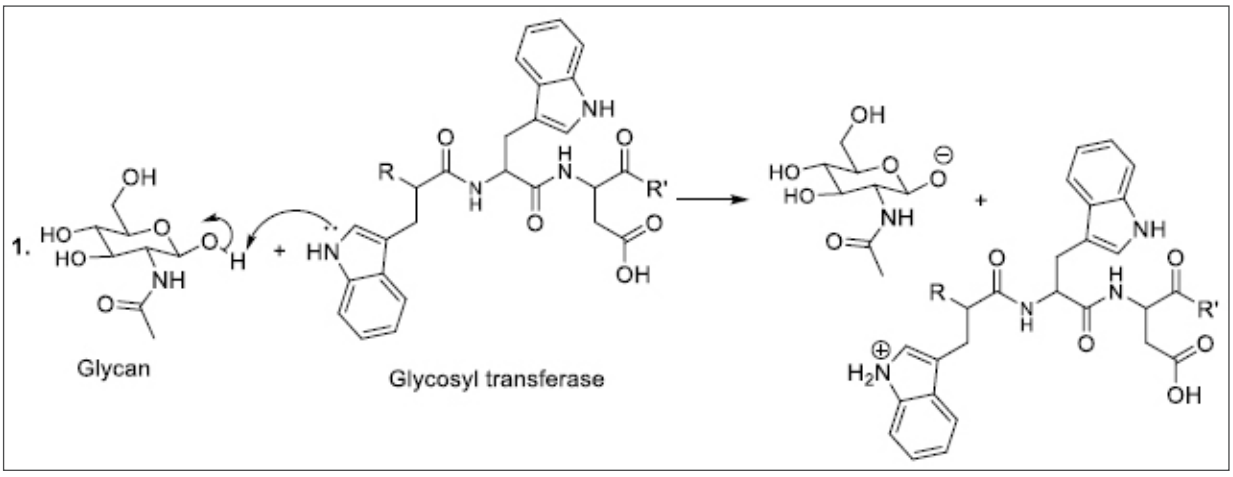
Scheme 6b

3.2 Glycolipid Synthesis

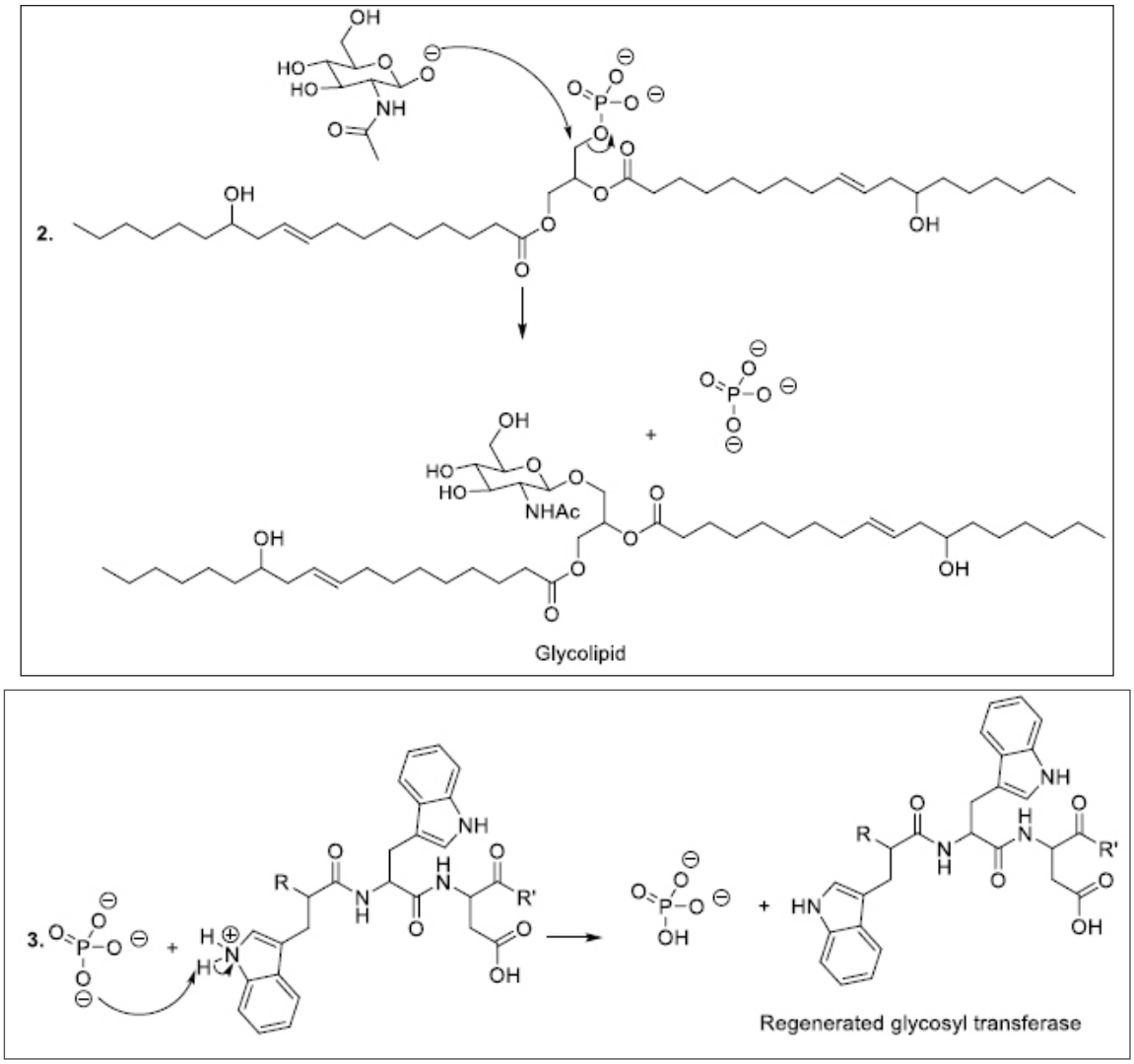
It is important to recall that phospholipids are organic compounds containing a phosphate group linked to glycerol and two fatty acids esterified to glycerol (Figure 2).[38-41]



It has been observed that the synthesis of glycolipids also occurs in the Golgi apparatus.[38-41]Indeed, the enzyme accepts a proton from glycan anomeric carbon hydroxyl group to produce a conjugate base and the enzyme conjugate acid (Scheme 7, reaction 1). This step is followed by the nucleophilic addition of the glycan conjugate base to phospholipid substrate, and this addition reaction facilates the departure of the phosphate leaving group and the production of the excpected glycolipid as well as the regeneration of the enzyme or glycosyl transferase(Scheme7, reactions2-3).



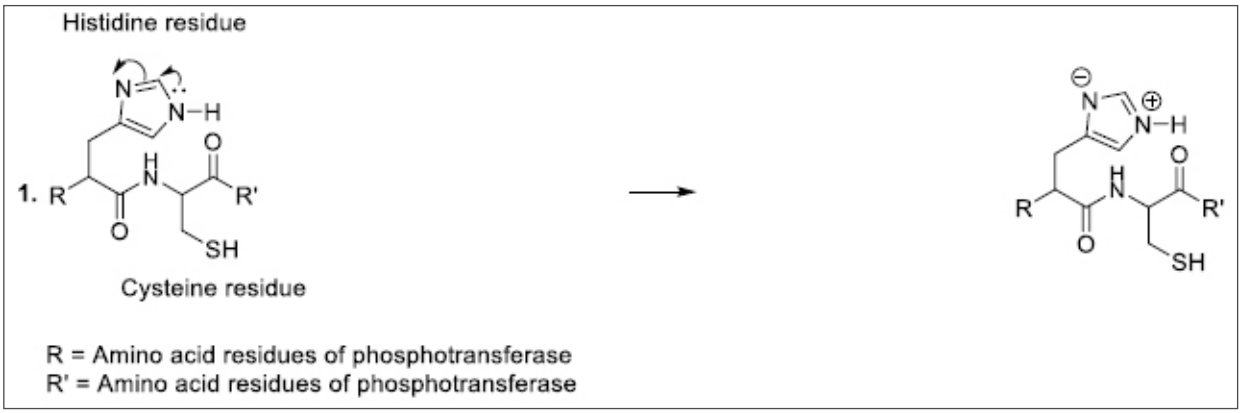
Scheme 7a

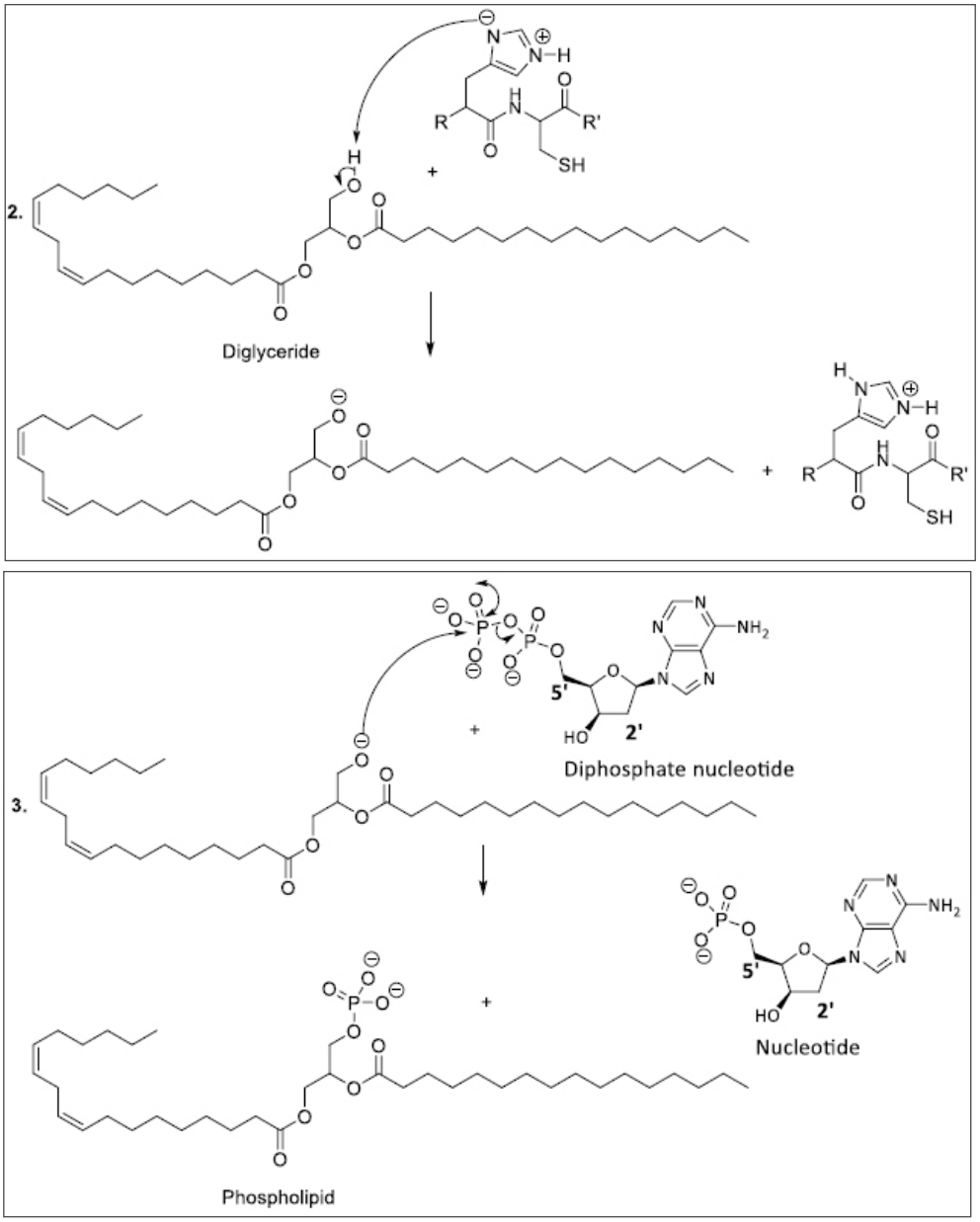


Scheme 7b

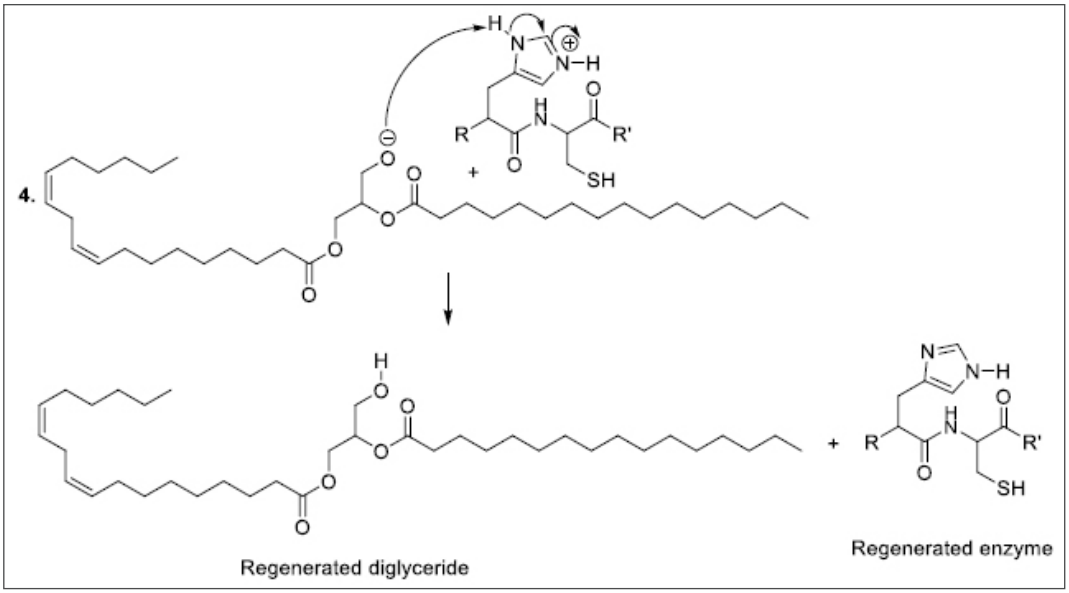
3.3 Phospholipid Synthesis

The phospholipid synthesis is derived from the combination of the diglyceride and the phosphorylation specific enzyme as reactive entities. In this regard, the experimental observations have shown that cysteine and histidine residues are the root of the phosphotransferase catalytic activities.[42-43] Indeed, due to the structure of the said enzyme, the free pair of electrons located on the intra cyclic nitrogen atom will move towards the other intra cyclic nitrogen atom to produce a conjugate base (Scheme 8, reaction 1). This later will removea proton from diglyceride to afford the corresponding an alkoxide ion, which is a very good nucleophile to induce the departure of the leaving group in order to generate the expected phospholipid (Scheme 8, reactions 2-3). The following reaction stage will accomplish the regeneration of the diglyceride including the phosphotransferase enzyme (Scheme 8, reaction 4).





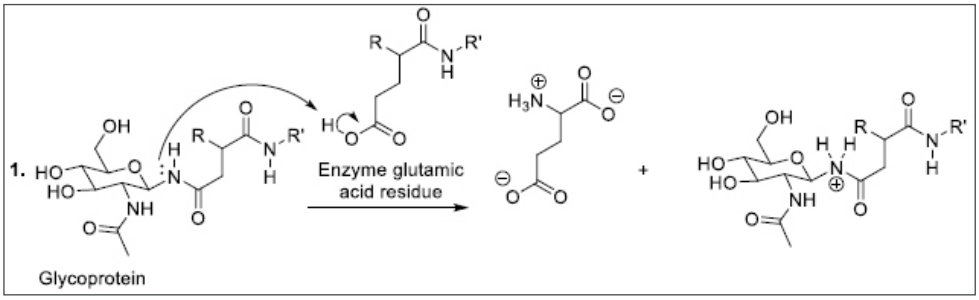
Scheme 8a



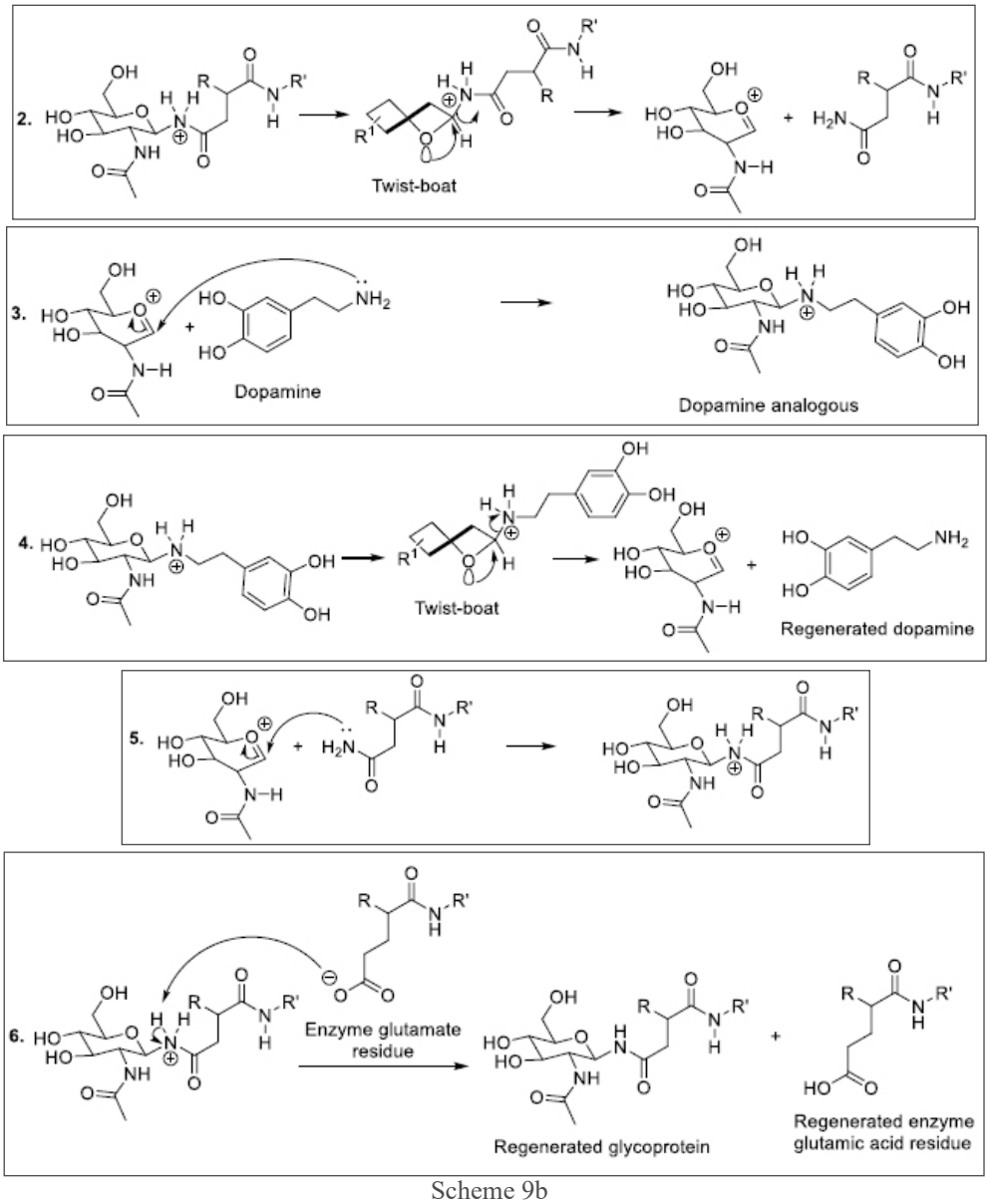
Scheme 8b

4. Dopamine Penetration into Cellular Cytoplsm

According to the experimental observations, it has been revealed that dopamine binds to a glycoprotein of the human platelet membrane.[44]Dopamine is a hormone or an organic substance, which plays an essential role in order to maintain the normal functionality of the human organism.[45-50] Particularly it is responsible for the nervous cell adequate effectiveness. Indeed, a dopamine produced by a specific neurone will move toward another nervous cell to connect or react with its cellular membrane constituents reversibly due to a specific enzyme (Scheme 9). The resulting dopamine analogous can now diffuse or cross the nervous cellular membrane in order to attend the cellular cytoplasm into which dopamine will be released, and it will proceed with its action (Scheme 9, reactions 4-5). It is important to mention that the substrate glycoprotein or a transporter also known as an intracellular receptor of the extracellular dopamine as well as the enzyme will be furthermore regenerated into the cellular cytoplasm (Scheme 9, reactions 6-7).

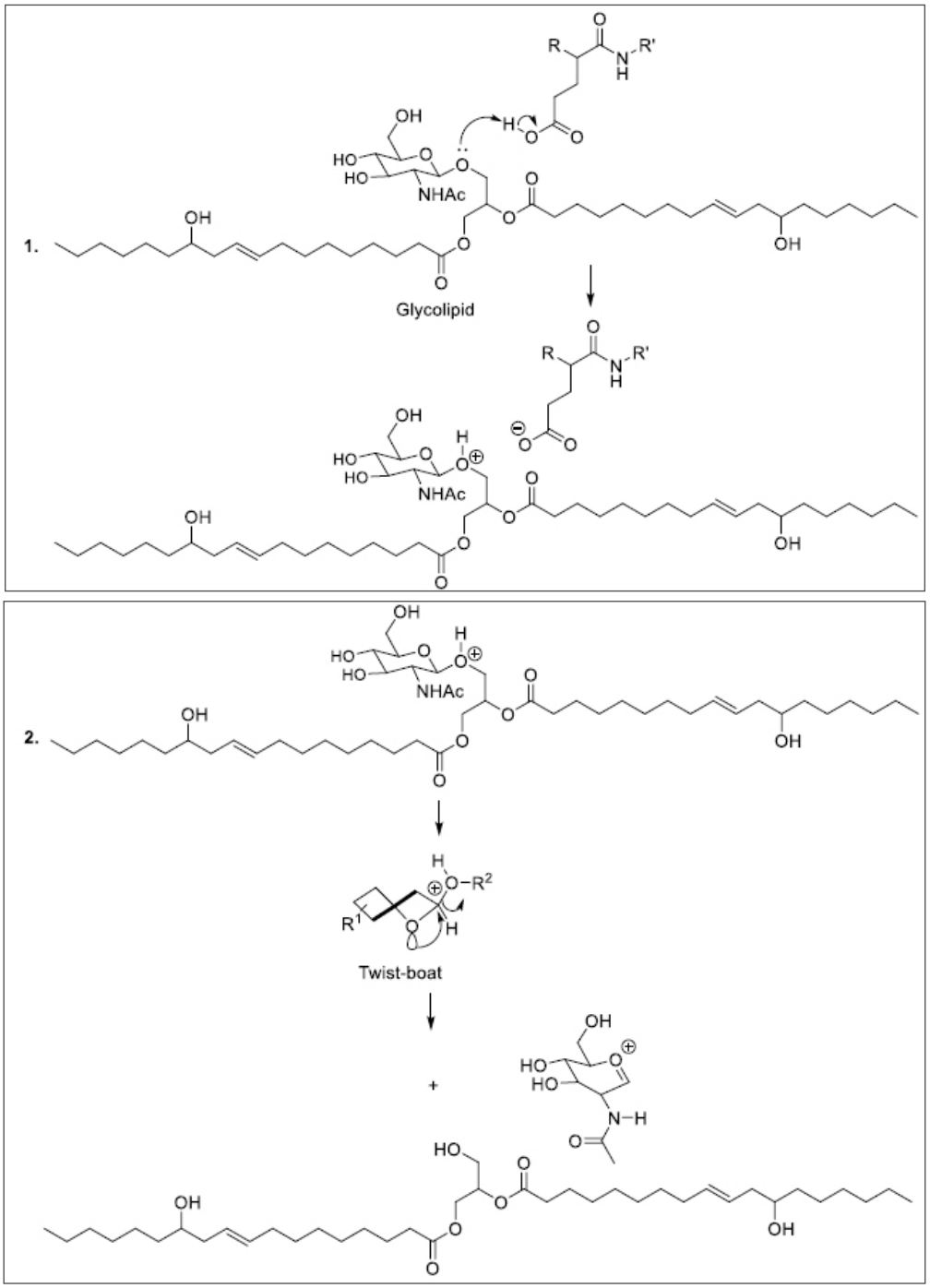


Scheme 9a

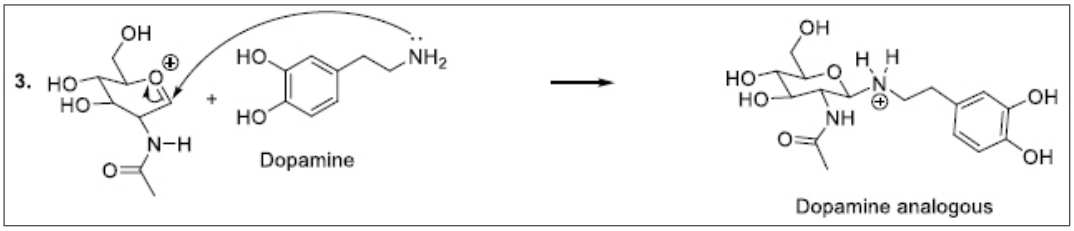


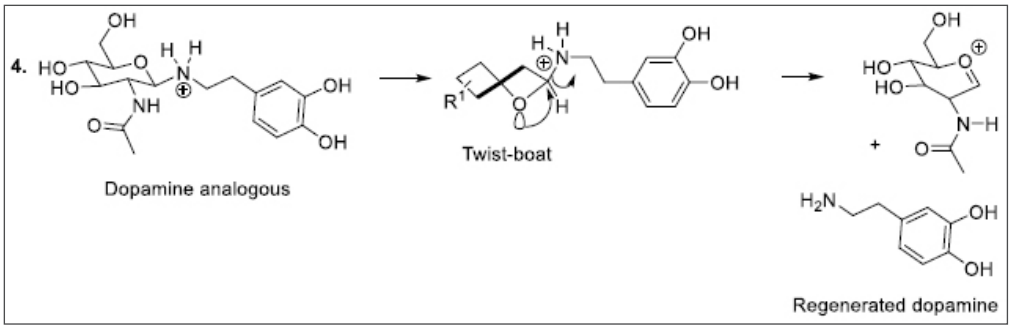
Scheme 9b

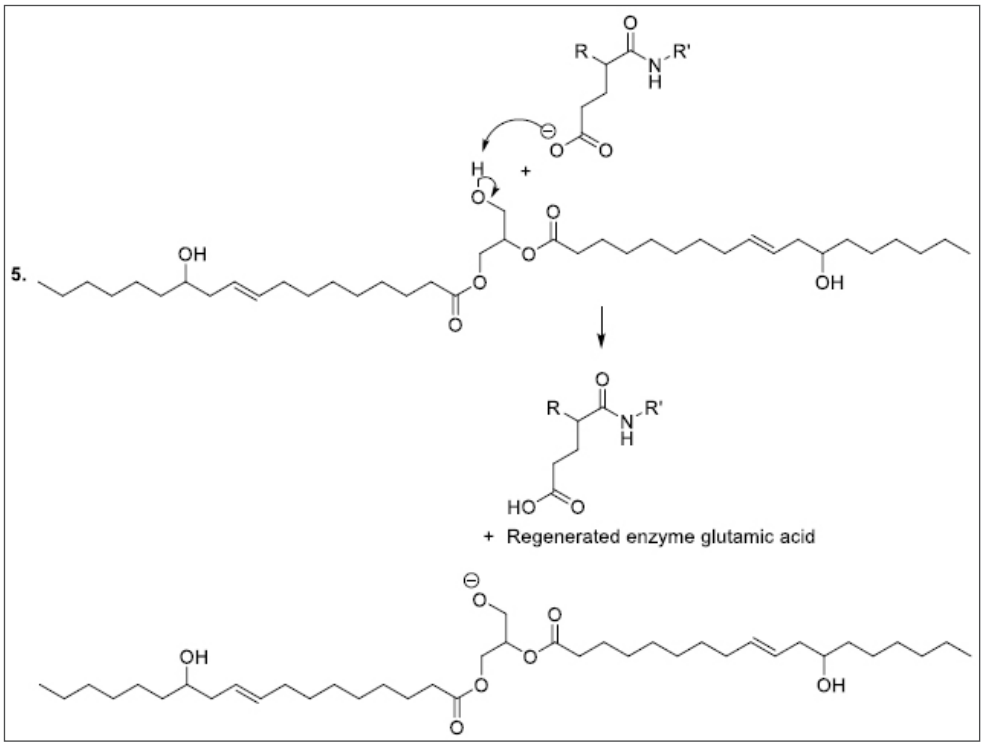
Dopamine combinesalso with glycolipid, another chemical cellular membrane constituent, to generate a dopamine analogous, which can easily penetrate the cellular cytoplasm. It is important to recall that the structure of an organic compound determines its reactivity. In other words, a particular organic compound utilizes its functional groups to react as acid, base, nucleophile or electrophile with an appropriate reactive chemical entity. For example, dopamine structure shows hydroxyl groups (OH), which can behave as electrophiles or nucleophiles,and an amine group(NH_2) that can react as nucleophile (Scheme 10, reaction 3).



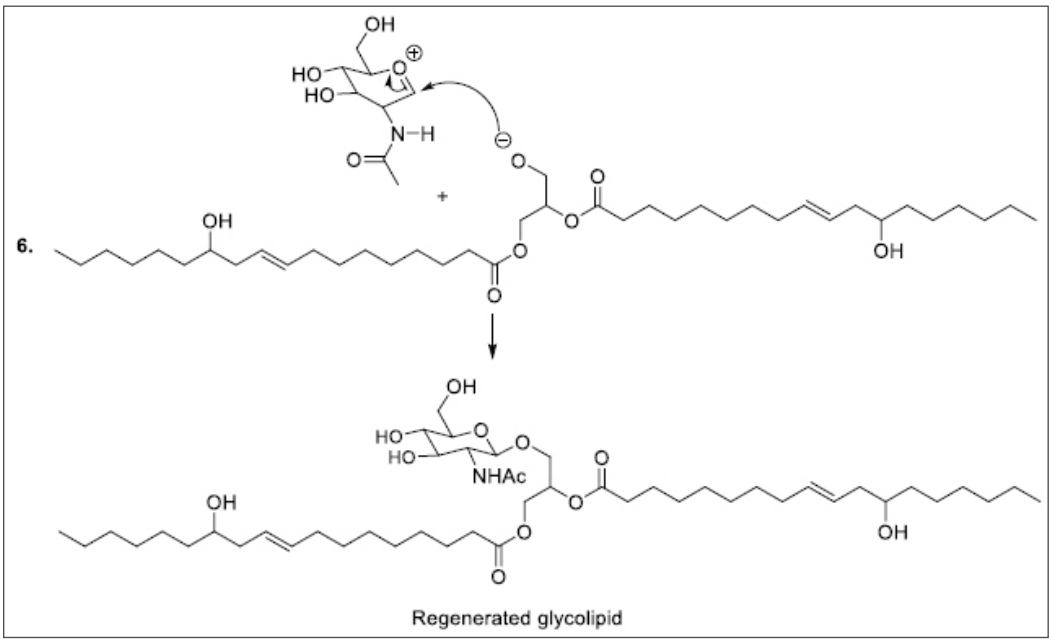
Scheme 10a







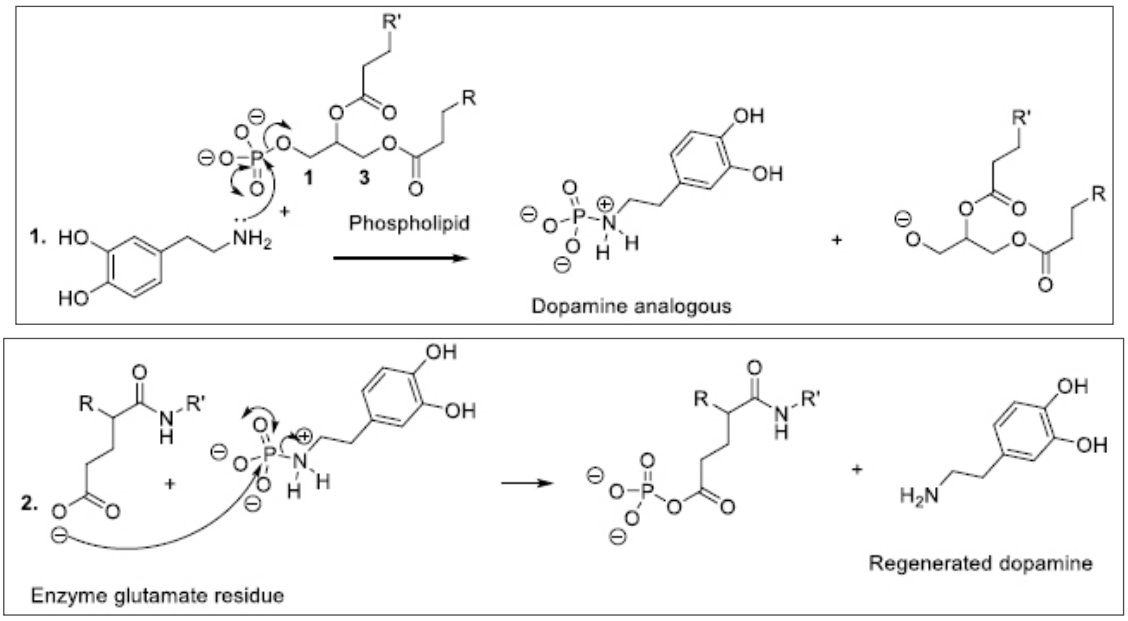
Scheme 10b



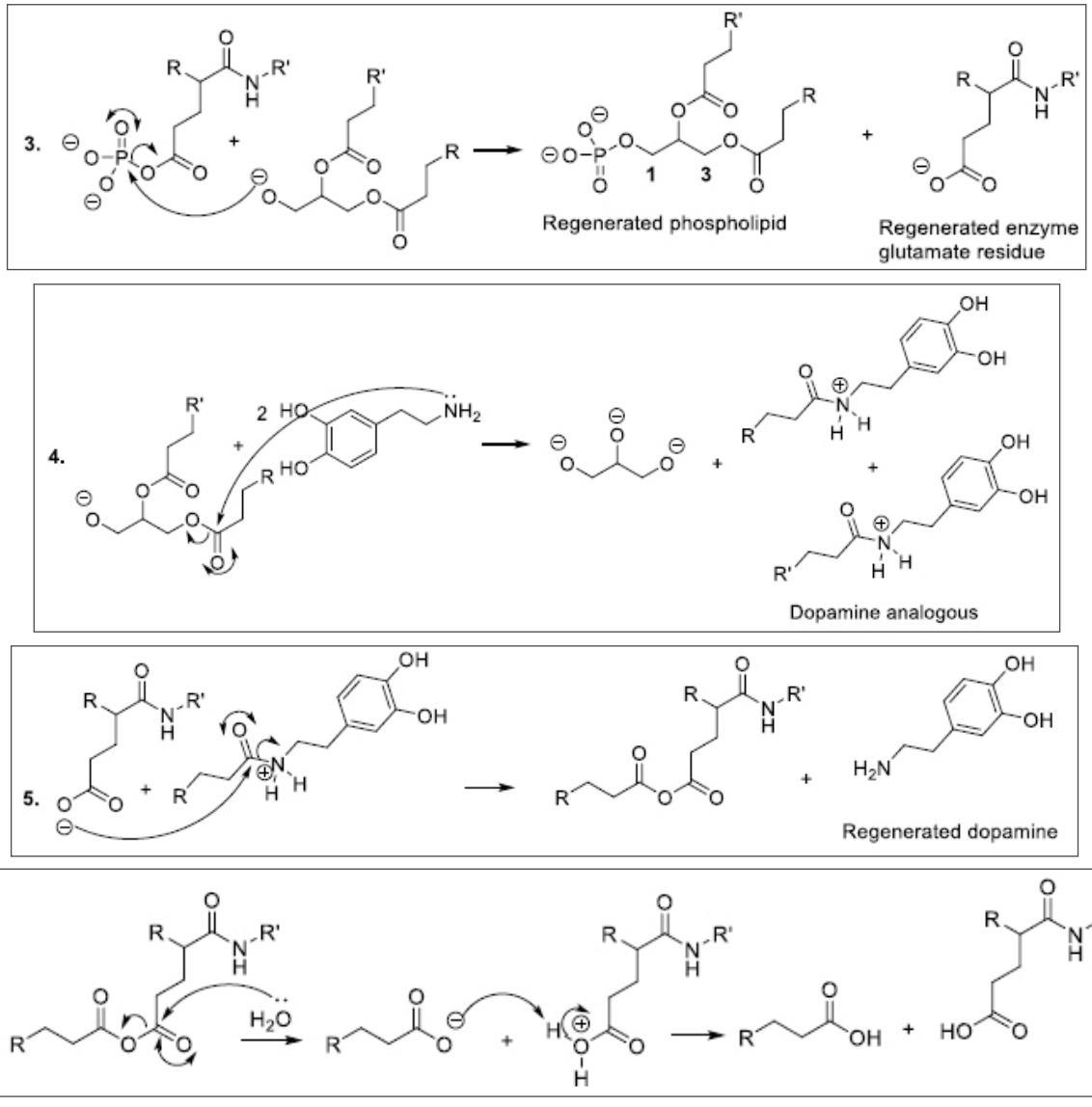
Scheme 10c

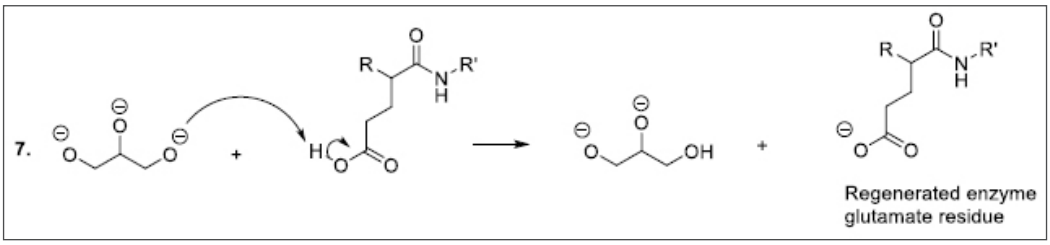
Similarly, dopamine will react with phospholipid, especially with phosphate group to produce a dopamine analogous, which can now move easily into the cellular membrane to reach the cytoplasm environment (Scheme 11, reaction 1). Dopamine can also react with carbonyl group of the phospholipid

ester moisture to afford the corresponding dopamine analogous (Scheme 11, reaction 4). The following steps are the regeneration of dopamine, enzyme and phospholipid because these enzymatic reactions are reversible (Scheme 11).



Scheme 11a

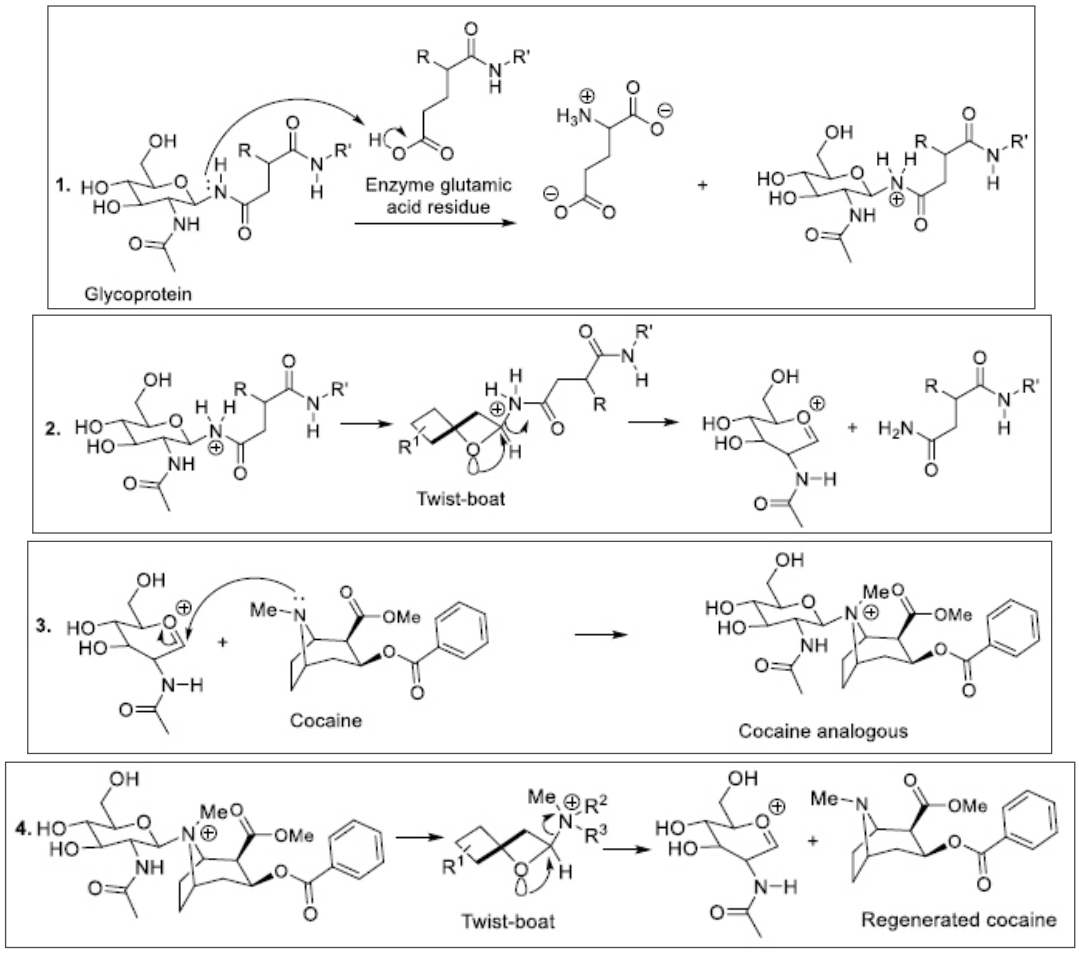




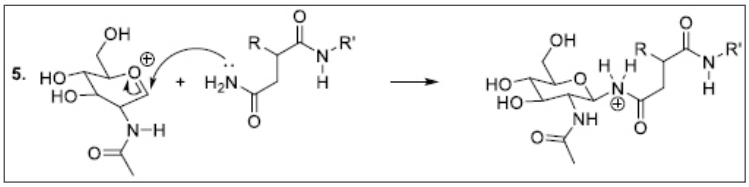
Scheme 11b

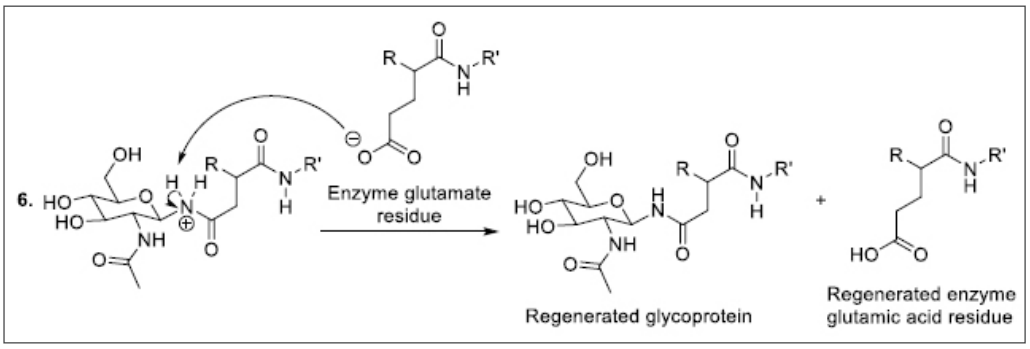
5. Cocaine Penetration into Cellular Cytoplasm

Cocaine is an organic compound containing a nitrogen atom in its structure. It is originally extracted from coca plants.[51-54] It inhibits the dopamine absorption. Indeed, excessive consumption of cocaine constitutesa significant problem for the society because it prevents dopamine reabsorption into the presynaptic neurons.[51-54] Consequently, dopamine accumulates in the synapse because cocaine has more rapidly reacted with dopamine transporters that form the cellular membrane.[51-54]Cocaine and dopamine are in competitive fashion into the synapse towards cellular membrane chemical components such as glycoproteins, glycolipids and phospholipids so as the reaction between cocaine and cellular membrane chemical constituents is prompt comparing to that with dopamine (Scheme 12).[55]As said earlier, It is essential to mention that extra cellular organic compounds such as cocaine must diffuse or cross the cellular membrane in order to attend the cellular cytoplasm. For that reason, the analogous cocaine bearing the glycol amide moisture will easily pass through the cellular membrane to attend the cytoplasm where cocaine and glycoprotein will be regenerated (Scheme 12, reactions 5-7).



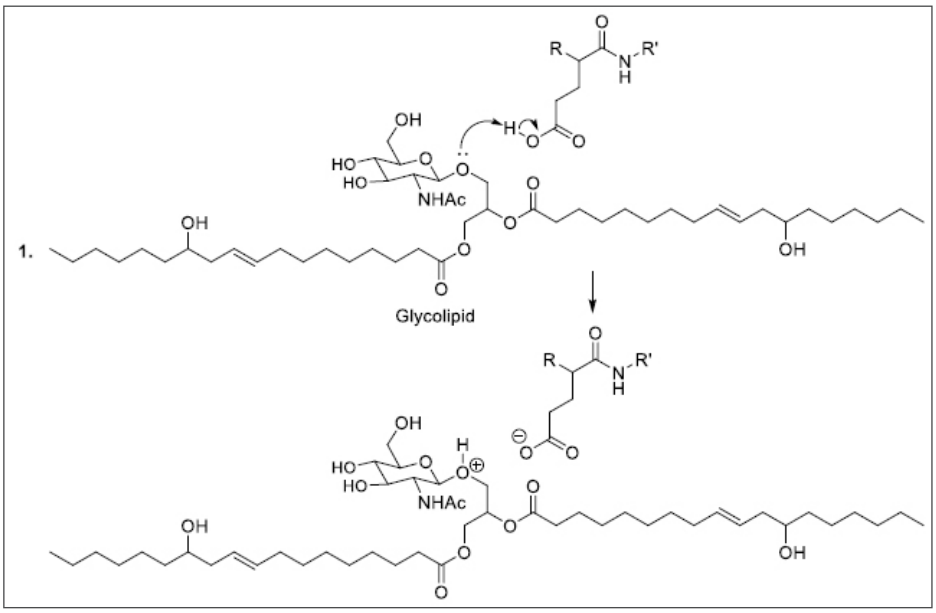
Scheme 12a



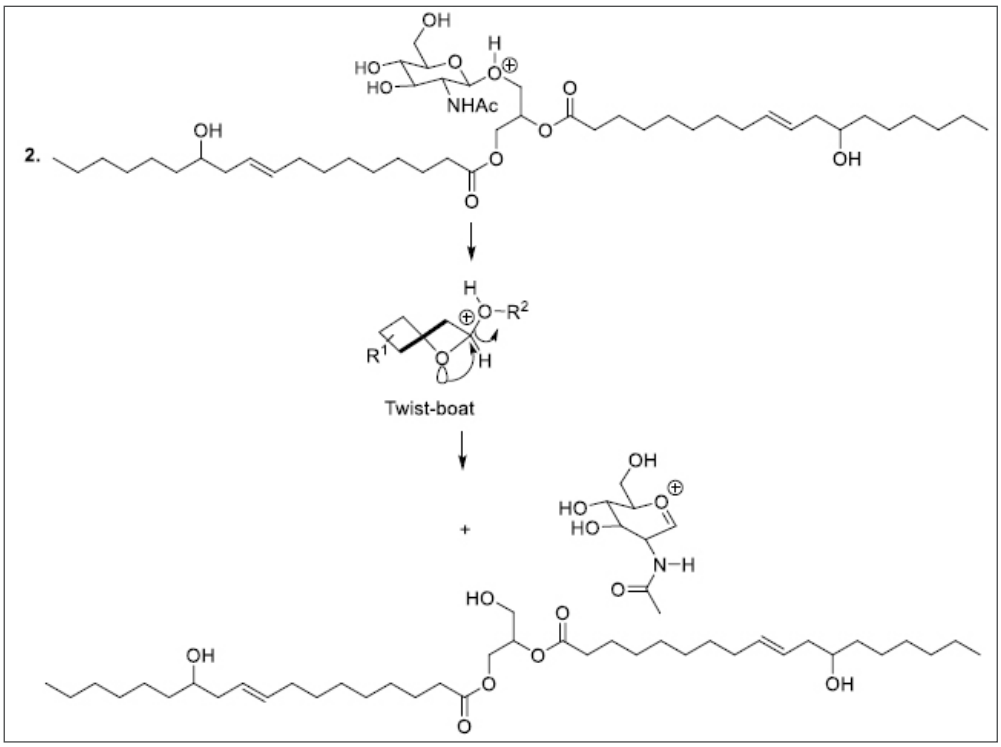


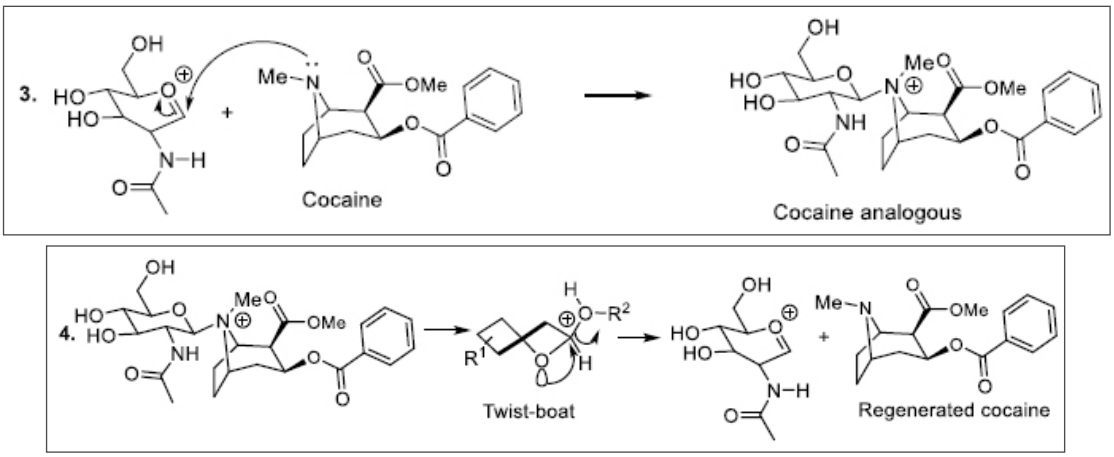
Scheme 12b

In the case of glycolipid, cocaine behaves as a nucleophile to displace the glycol amide portion of glycolipid to produce a phospholipid analogous, which will now easily diffuse through the cellular membrane up to the cytoplasm where the glycolipid will be regenerated as well as the cocaine (Scheme 13, reactions 4-6).

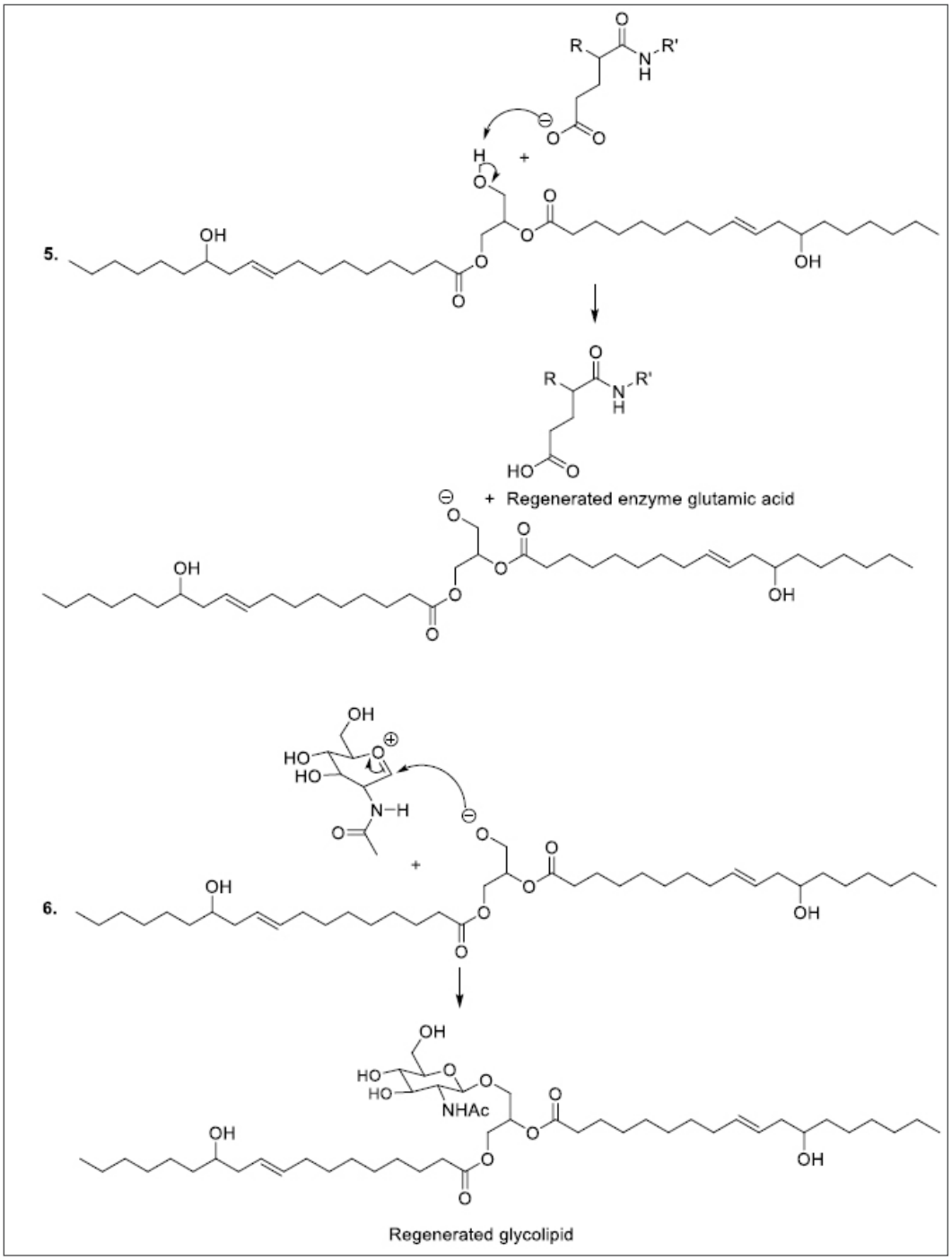


Scheme 13a



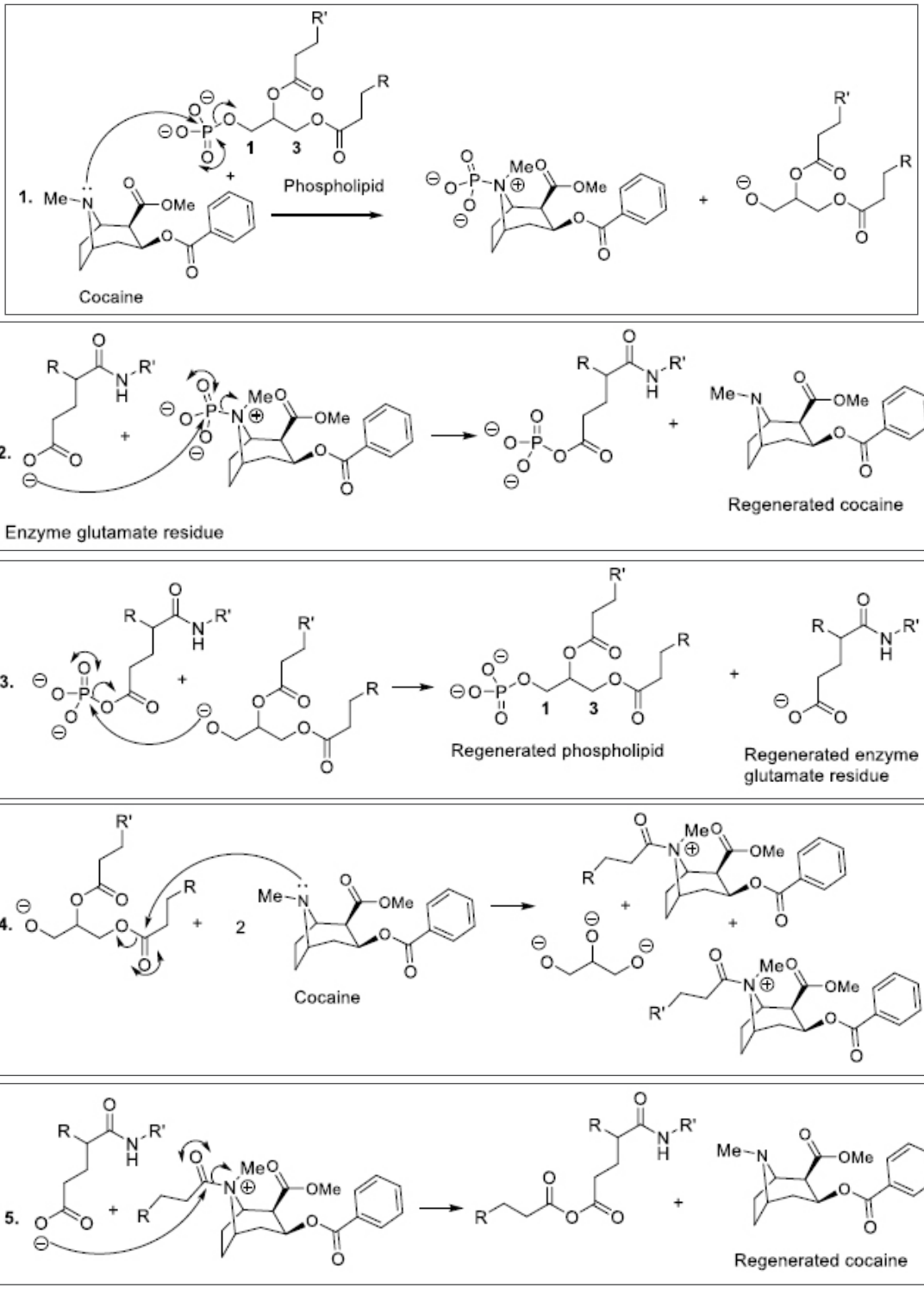


Scheme 13b

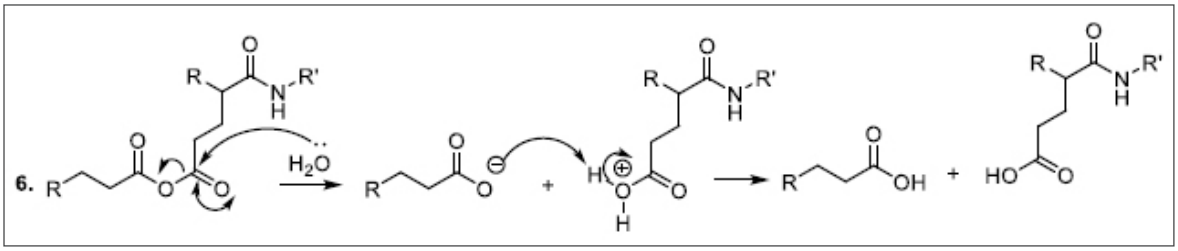


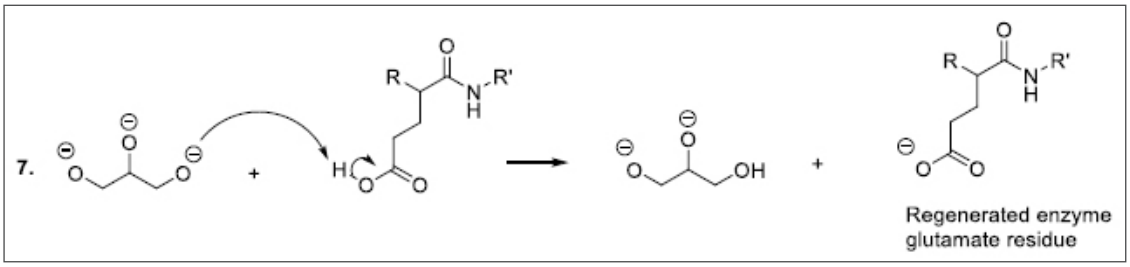
Scheme 13c

The nucleophilic addition of cocaine to phospholipid in order to displace a living group is an acceptable reaction in organic chemistry (Scheme 14, reaction 1). Therefore, the resulting intermediate compound bearing a phosphate group now diffuse smoothly through the cellular membrane up to the cytoplasm where the cocaine and the phospholipid will be regenerated (Scheme 14, reactions 2-3).



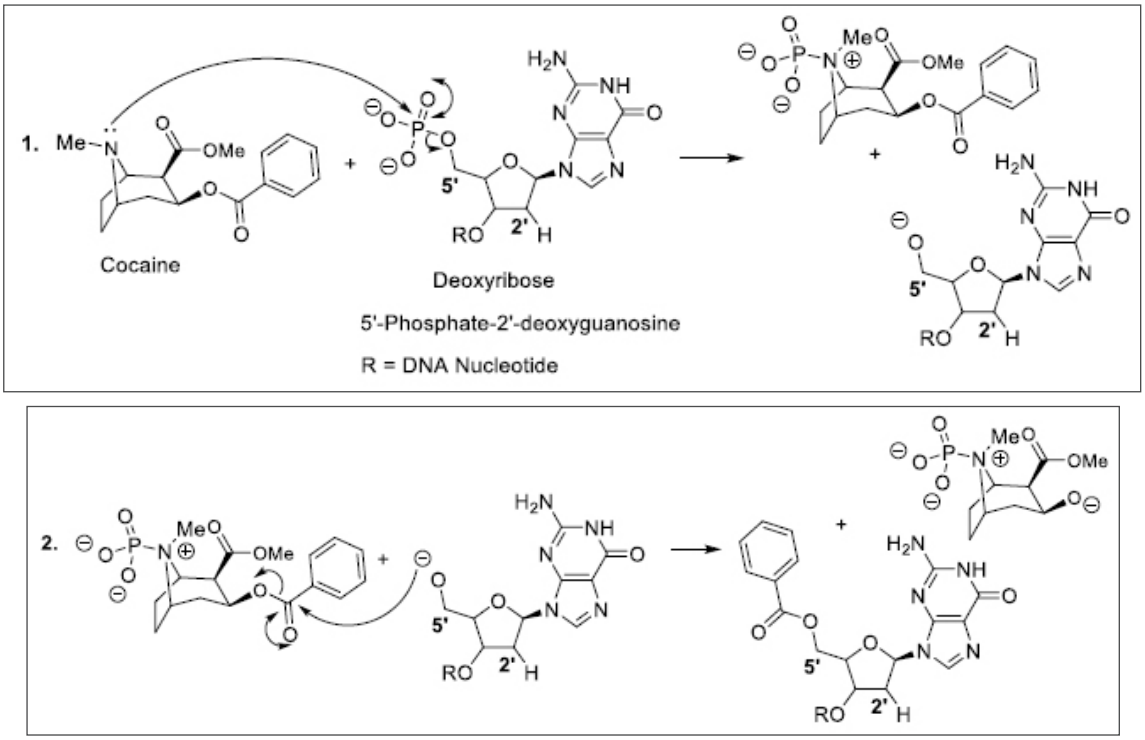
Scheme 14a





Scheme 14b

When the cocaine is now available into the cellular cytoplasm, it can destabilize the cellular metabolism because it can behave as nucleophile towards cellular electrophilic substances due to its nitrogen atom (Scheme 15, reaction 1). The cocaine can also behave as electrophile towards cellular nucleophile components due to its carbonyl groups (Scheme 15, reaction 2). For example, cocaine can react with deoxyribonucleic acid (DNA) (Scheme 15, reaction 2).



Scheme 15

6. Conclusion

I have applied organic basic knowledge to synthesize cellular membrane organic compounds, which promote the dopamine as well as cocaine penetration means into the cellular cytoplasm in proposing principal organic reactions between them and cellular membrane organic substances such as glycoproteins, glycolipids and phospholipids. Indeed, through this theoretical model based on experimentally approved organic notions, people can now understand how extracellular compounds diffuse through the cellular membrane to reach cytoplasm. In the same perspective, I have also hereby demonstrated the detailed reaction mechanisms, which help to comprehensively understand the introduction of dopamine and cocaine into the cellular cytoplasm where the two organic molecules will affect negatively the normal functionality of the addicted individual to cocaine.

In other words, the proposed rection mechanisms are acceptable in organic chemistry because in according to the functional groups of dopamine and cocaine, these two organic molecules can act as nucleophiles to concede electrons to the acceptors or to the poor chemical entities (electrophiles). They can also behave as electrophiles to accept electrons from the rich chemical entities (nucleophiles). In other words, the structure of dopamine and cocaine determines their reactivities or chemical properties towards cellular chemical constituents.

Conflict of Interest Statement

I declare that I do not have a conflict of interest regarding the publication of this paper.

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