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Article

Using drug chemical structures in the education of pharmacology and clinical therapeutics key concepts

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Medicinal chemistry made it possible for pharmacists to propose pharmacodynamics and pharmacokinetics explanations of many existing drugs. Moreover, medicinal chemistry education provides pharmacy students with a reasonable understanding of drug physicochemical properties, mechanism of action (MOA), side effects, metabolism and structure-activity relationship (SAR). This paper highlights the importance of these medicinal chemistry key elements in understanding other pharmacy core courses, mainly pharmacology and clinical therapeutics. Such elements can be utilized as a tool for pharmacists while training or counseling their patients on the use of their treatments. Different new examples from the literature have been incorporated in this paper to show how chemical structures of existing drugs can provide essential information about main concepts in the education of pharmacology and clinical therapeutics, and the key structural elements for the discovery and development of other same class drugs.

Keywords: Medicinal chemistry. Structure. Pharmacy students. Pharmacology. Clinical therapeutics.

INTRODUCTION

In 1974 IUPAC (International Union of Pure and Applied Chemistry) gave the following definition of medicinal chemistry: "*Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemist is not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification and synthesis of the metabolic products of these drugs and related compounds*".(Wermuth *et al.*, 1998) Tremendous advances in both medicinal chemistry and clinical therapeutics have enabled chemists to understand the fascinating relationship between the chemistry of drugs and their biology in the human body. (Fernandes 2018) Medicinal chemistry courses are fundamental courses for undergraduate pharmacy students that combine chemistry, especially organic chemistry, pharmacology and clinical therapeutics.(Currie *et al.*, 1994; Alsharif, Destache, Roche, 1999) A comprehensive understanding of the drug chemical structure including functional groups, bonds, substructures, stereochemistry and specific structural features enable pharmacy students to understand the key concepts of pharmacology and clinical therapeutics.(Alsharif, Theesen, Roche, 1997; Krueger, 2013) Thus, linking these structural drug features to its physicochemical properties can enable pharmacy students to understand the pharmacokinetic and pharmacodynamic properties for each category of drug.(Satyanarayanajois, 2010; Brito, 2011) Overall,

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understanding medicinal chemistry of drug classes along with the pharmacological principles empowers pharmacy students to understand clinical therapeutic courses, in addition to the efficient use of existing drugs on the market and the design of new drugs.(Alsharif *et al*., 2006) This explains why medicinal chemistry courses are essential for pharmacy education, being a key component in the pharmacy curriculum.(Ferreira 2010; Das *et al*., 2018)

It has been acknowledged that it is important to emphasize the significance of medicinal chemistry to provide essential knowledge and critical-thinking skills of other core pharmacy courses such as pharmacology and clinical therapeutics. (Das *et al*., 2018) Herein, using different examples of existing drugs from the literature, we highlight the importance of relating the drug structural features to its pharmacokinetic and pharmacodynamic performance. Medicinal chemistry educators can benefit from linking the concepts discussed in this paper with the chemical structures of different drug classes to improve the ability of students to explain these concepts from a structural analysis concept. The aim of this paper is to determine the significance of medicinal chemistry scope in teaching key concepts of drug pharmacokinetic and pharmacodynamic profiles to pharmacy students.

METHODS

In the construction of this paper, different examples of existing drugs found in the literature were discussed in order to show the importance of medicinal chemistry in the education of pharmacology and clinical therapeutic courses. The scope of each example was defined in preparation for the students or practitioner predictions about similar drugs. Each example was related to a key concept of these core courses, linking it to the chemical structure of a drug. These concepts included the mechanism of action, side effects, oral bioavailability, onset of action, and duration of action. Different structural features and properties were identified and interpreted in a way that could be applied by students and practitioners to explain many other examples of different drugs for such major concepts. Then, unique examples of drugs with similar molecular features were discussed to help the reader to predict their bioactivity based on their understanding of these concepts. Predictions were made as to which of the new molecules have or lack the particular clinical feature being assessed. Answers to the prediction and validation examples were finally summarized at the end of the paper. Authors performed literature evaluation after each prediction set to show that the predictions made were correct on the basis of the proposed medicinal chemistry rationale.

RESULTS AND DISCUSSION

Mechanism of Action

It is known that different structural elements of a drug are required for its interaction with the target and will define its mechanism of action.(Ramsay *et al*., 2018) The drug structure mimics an endogenous ligand of the human body which results in a similar mode of action. On the other hand, for many other cases, drugs in the same class can have the same structural skeleton, .(Salahudeen, Nishtala, 2017) This means that the chemical structure of a drug can provide information about its mechanism of action.

Scope: Rotigotine, for example, is a dopamine receptor agonist used for the treatment of idiopathic Parkinson's disease.(Waters, 2013; Benitez *et al*., 2014) Rotigotine, 1, shows agonistic activity on all dopamine receptors which is clearly resulted from a significant similarity to the structure of dopamine (DA, 2), the endogenous ligand for this family of dopamine receptors (Figure 1). *Pharmacophore identification*: Both dopamine, 2, and rotigotine, 1, have *meta* hydroxyl aromatic ring ethylamine group. The amine may or may not be substituted. The pharmacophore is 3-(2-aminoethyl)phenol, 3 (Figure 1). *Predictions*: Now, structures 4, 5, and 6 act at the dopaminergic receptor (Figure 2). However, taking the defined pharmacophore of the *meta*-hydroxyl aromatic ring ethylamine in both dopamine and rotigotine, can we predict which of the three drugs have the maximum potential use in idiopathic Parkinson's disease?

The above given example clarifies that certain elements of a drug structure are, therefore, clearly

involved in its action as these elements interact with the drug target. As a result, many details of a drug mechanism of action could be interpreted based on its structure.

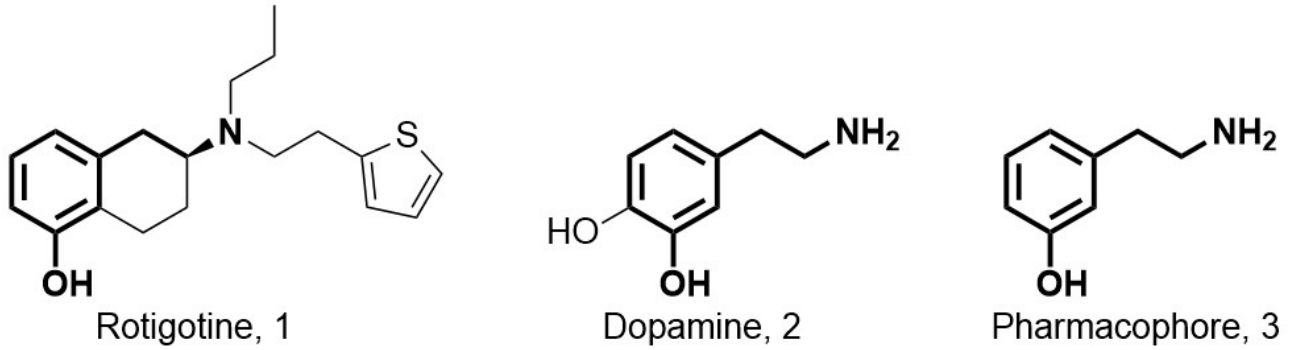


FIGURE 1 - Rotigotine, 1, has a significant structural similarity to dopamine, 2, (the pharmacophore, 3, shown in bold) that explains its agonistic mode of action.

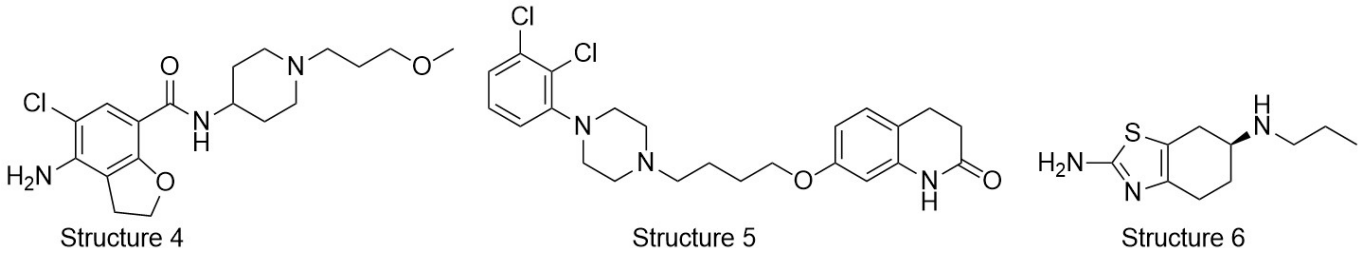


FIGURE 2 - Derivatives that act on the dopaminergic receptor.

Side Effects

Structural features for most drugs can influence their side effects profile.(Tatonetti, Liu, Altman, 2009) For most drugs, specific substructures called toxicophoric groups are linked to their side effects. (Tatonetti, Liu, Altman, 2009; Kalgutkar *et al.*, 2008) Toxicophoric groups are either reactive themselves or can be bioactivated to reactive metabolites that can modify body macromolecules and result in potential side effects.

Scope: Carbamazepine (7, CBZ) for example has a toxicophoric group that is bioactivated to a highly reactive metabolite which causes specific side effects (Figure 3).(Higuchi *et al.*, 2012) CBZ, 7 is an iminostilbene antiepileptic drug that is widely used to treat certain types of seizures and nerve pain.(Schmidt, Elger, 2004) CBZ, 7 is oxidized by the cytochrome P-450 system to a chemically reactive epoxide metabolite, 8, that causes serious idiosyncratic reactions such as hepatotoxicity (Figure 3).(Higuchi *et al.*, 2012) This metabolic step is followed by a hydroxylation to 10,11-dihydroxy CBZ inactive metabolite, 9. The human body has defense mechanisms to such reactive species including glutathione conjugation (10, Figure 3). However, these mechanisms are only partially protective, for example glutathione can be depleted which will allow the drugs to bind to a nucleophilic site in proteins and nucleic acids (11, Figure 3).

Identification: In contrast; oxcarbazepine (12, OXC), another iminostilbene antiepileptic drug, is not likely to cause idiosyncratic hepatotoxicity (Figure 4).(Abou-Khalil, 2007) Structurally, the 10,11-double bond of CBZ is replaced by a 10-carbonyl group in OXC. OXC, 12, is reduced *in vivo* to 10-monohydroxy OXC, 13, which is the main active metabolite, then to the inactive 10,11-dihydroxy OXC metabolite, 14. Therefore, it is clear that OXC risk of hepatotoxicity is much less (at around 0.1 to 1%) (Schmidt, Elger, 2004; Abou-Khalil, 2007).

Predictions: Structure 15 is another carbamazepine derivative where toxicity could be predicted based on the knowledge of toxicophoric groups and metabolism of such derivatives (Figure 5). As a result, can a student or practitioner predict the risk of hepatotoxicity for this structure?

As shown through these examples, understanding the chemical structure of drugs and identifying its toxicophoric groups provides an indication of their toxicity and assists drug development avoiding the presence of these groups. Thus, structural modifications of drugs in the same category can result in avoiding potential side effects.(Tatonetti, Liu, Altman, 2009)

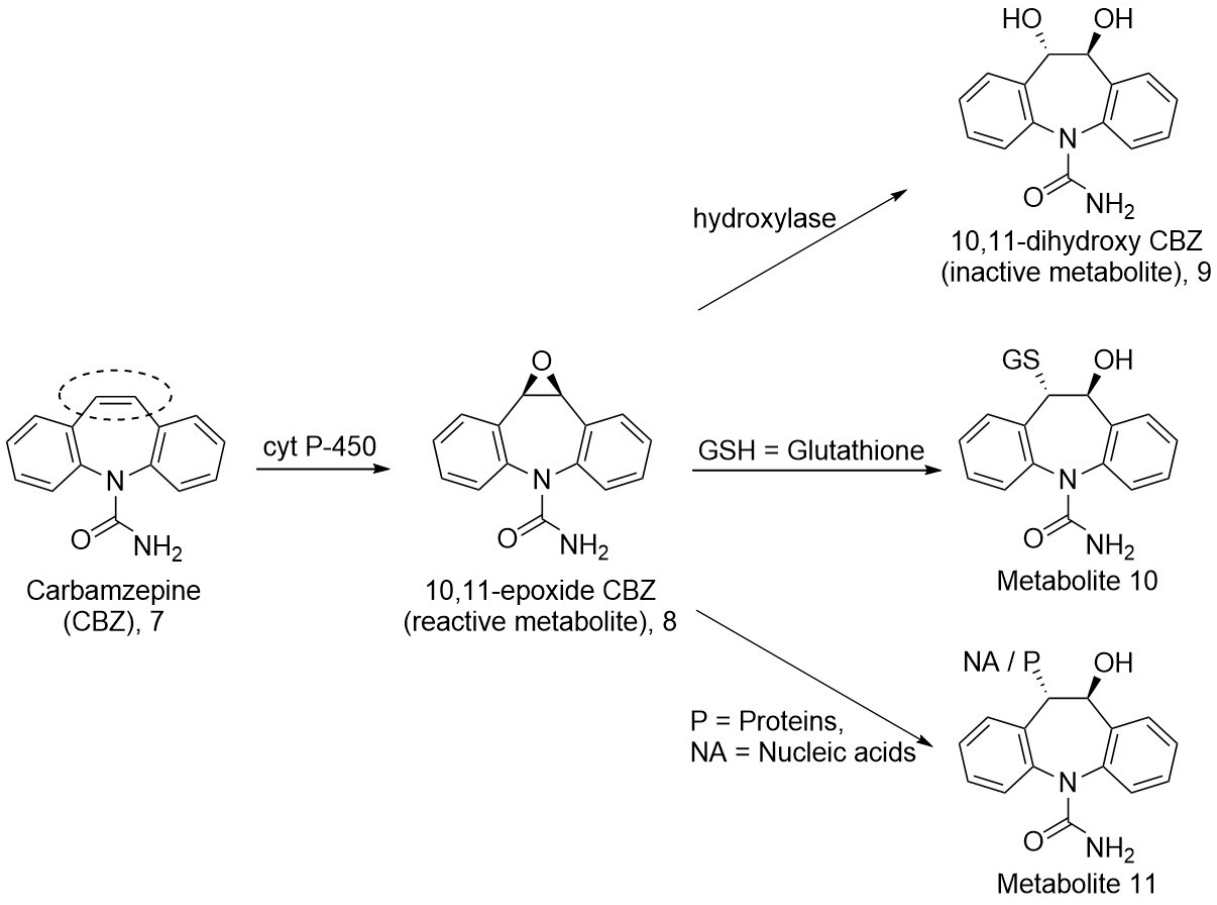


FIGURE 3 - Metabolic transformations for carvamazepine, 7.

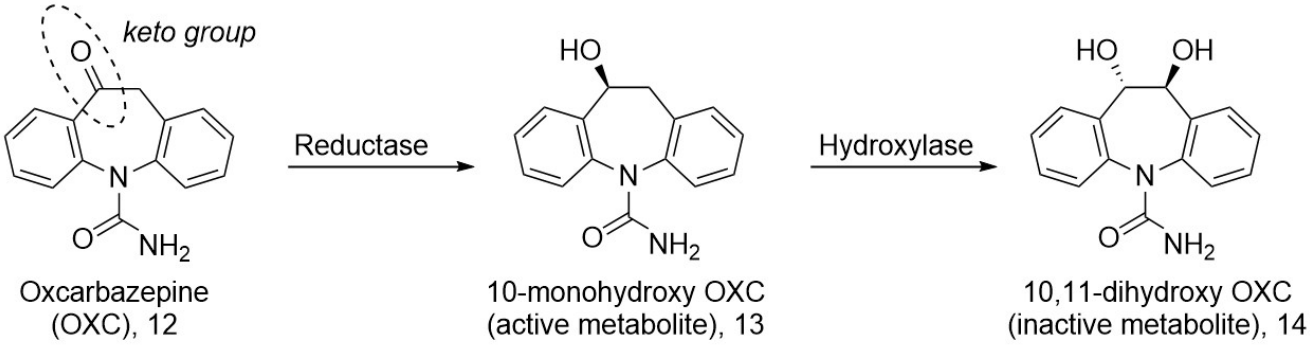
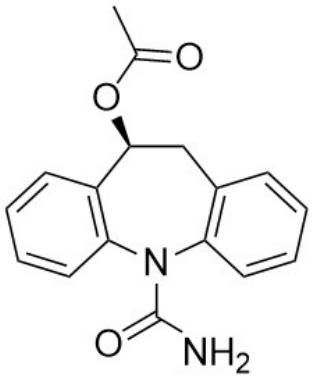


FIGURE 4 - Metabolic transformations for oxcarbazepine, 12.



Structure 15

FIGURE 5 - Structure 15, a carbamazepine derivative.

Oral Bioavailability

One of the essential requirements for orally administered drugs is to gain an adequate systemic amount of the oral doses to achieve the full benefit of the drug. (Aungst, 2017) In addition to a proper drug dosing the drug molecular size, dissolution rate, dosage form, first-pass metabolism, and solubility of drugs in gastrointestinal fluids, oral bioavailability of a drug is highly influenced by its structural properties such as ionization and acidity/basicity character.(Veber *et al*., 2002)

Scope: Neuroaminidase (NA) inhibitors are a class of antiviral drugs.(Gubareva, Webster, Hayden, 2001) The FDA has approved two inhibitors from this class for clinical use, zanamivir and oseltamivir. Zanamivir, 16, has a poor oral bioavailability (F% ~ 2%) resulting from the presence of a zwitterionic species in the human body (Figure 6).(Gupta *et al*., 2011)

Identification: The zwitterion of zanamivir, 17, formed from the guanidinium cationic and carboxylate anionic groups at the physiological pH, has no lipophilicity, and thus is poorly absorbed. The poor oral bioavailability limits zanamivir's clinical use in treating influenza infections despite being effective. However, oseltamivir, the ethyl ester of oseltamivir carboxylate, 18, is bioavailable upon oral administration (F% >75%) (Figure 6).(Gupta *et al*., 2011) This enhanced oral bioavailability is due to three reasons: first, the dihydropyran oxygen in zanamivir is replaced by a methylene isostere, which increases the compound lipophilicity. The second reason is the masking effect of the carboxylate group with the introduction of an ethyl; therefore, the compound does not form a zwitterion. Besides that, the highly hydrophilic guanidinium group results in the low oral bioavailability of zanamivir compared to the less hydrophilic ammonium group in oseltamivir ester.(Shie, Fang, 2019) The guanidine group is more basic than the amine group with pK_a values of 11.3 and 9.3 respectively.(Schade *et al*., 2015) As a result; it is preferable to form zwitterionic species in zanamivir that results in lower absorption and bioavailability.

Predictions: Taking a closer look at the other two neuroaminidase inhibitors, laninamivir and peramivir (19 and 20; Figure 7). Trying to interpret the two structures based on their solubility and lipophilicity and their similarities and differences from the previous NA inhibitors, a student or practitioner can predict their oral bioavailability.

Successful functioning of an oral drug depends on its physicochemical properties such as the solubility and lipophilicity, which determine the extent of its absorption through its unionized form.(Aungst, 2017) Thus, by understanding the different structural properties, such as the polarity and ionization, pharmacy students can better predict the oral bioavailability of drugs.

Onset of Action

Different drug properties, such as the absorption and distribution, can influence drug onset of action. (Ludbrook, Upton, 2002) Similarly, for prodrugs, the metabolic activation contributes to its onset of action and consistency of activity.(Rautio *et al*., 2008) A prodrug undergoes a metabolic transformation *in vivo* in order to be activated. The resulting active metabolite can then afford the desired pharmacological activity.(Rautio *et al*., 2008) As for a drug, the metabolic transformation of a prodrug depends specifically on its chemical structure. (Baillie *et al*., 2016) Some prodrugs need two-steps of metabolic activation which would inevitably affect the onset of action for the active drug.

Scope: Clopidogrel, 21, is a well-known tetrahydro thienopyridine antiplatelet that was approved in 1997 as a $P2Y_{12}$ irreversible antagonist that prevents thrombotic episodes in patients with cardiovascular diseases (Figure 8).(Hagihara *et al*., 2009; Norgard, Abu-Fadel, 2009) Clopidogrel is a prodrug that needs three-cytochrome P450 (CYP-450) oxidative metabolic steps to afford the active metabolite.(Dansette *et al*., 2015) The first step is the formation of *oxo*-clopidogrel metabolite, 22, followed by the formation of thiolactone sulfoxide, 23. The third step is a ring cleavage to result in the active metabolite, 24. The active metabolite prevents the platelet function by irreversibly binding to a cysteine residue of the $P2Y_{12}$ receptor to afford structure 25.(Hagihara *et al*., 2009) Prasugrel, 26, is another tetrahydro thienopyridine $P2Y_{12}$ antagonist that was approved by the FDA in 2009 (Figure 9).(Norgard, Abu-Fadel, 2009) Prasugrel is a prodrug that is structurally similar to the initial *oxo*-metabolite which is oxidatively obtained from clopidogrel, 21.(Dansette *et al*., 2015) It needs only two CYP-450 oxidative activation steps after the rapid hydrolysis of the ester to afford the active metabolite, 29.

Identification: This metabolic activation explains why a 60 mg loading dose of prasugrel, 26, has shown a more rapid onset of action than a 300 mg loading dose of clopidogrel, 21, taking about 30 minutes for prasugrel and 1.5 hours for clopidogrel to start their action post administration. (Brandt *et al*., 2007; Weerakkody *et al*., 2007).

Predictions: Looking at ticlopidine, 31, another thienopyridine used in clinical practice, an onset of action could be predicted based on its structure and comparing it to the known thienopyridine antiplatelets (Figure 10).

The above example illustrates how the structures of drugs and their metabolic activation have an important effect on their onset and consistency of action. Overall, the drug chemical structure affects its absorption, bioactivation, and distribution which in turn determines its onset of action.(Ludbrook, Upton, 2002)

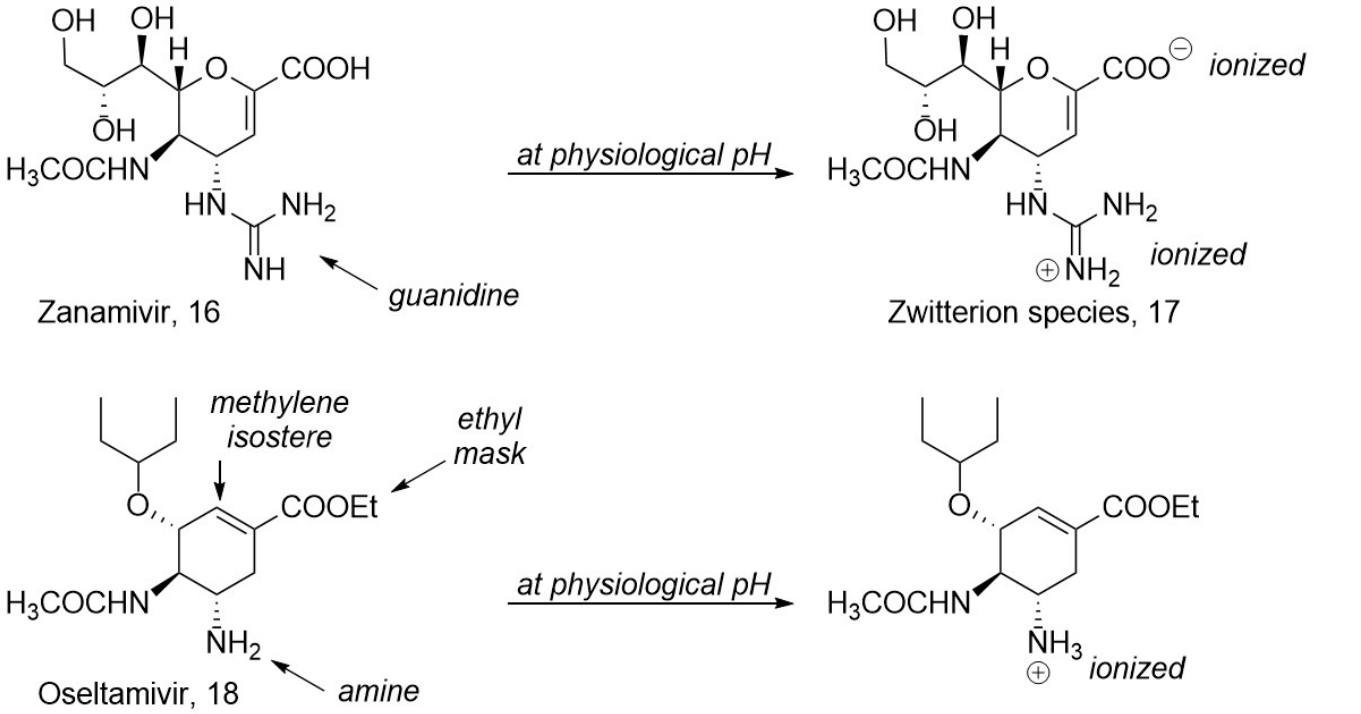


FIGURE 6 - Oseltamivir, 18, is available upon oral administration however; zanamivir, 16, is not as a result of forming a zwitterion in human body, 17.

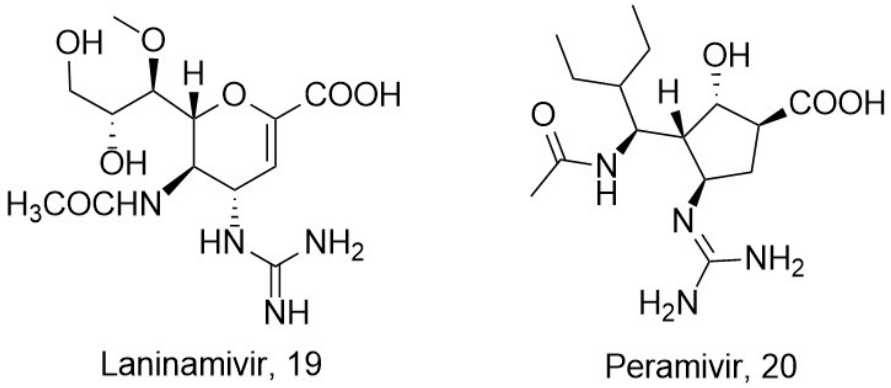


FIGURE 7 - Laninamivir, 19, and peramivir, 20, NA inhibitors.

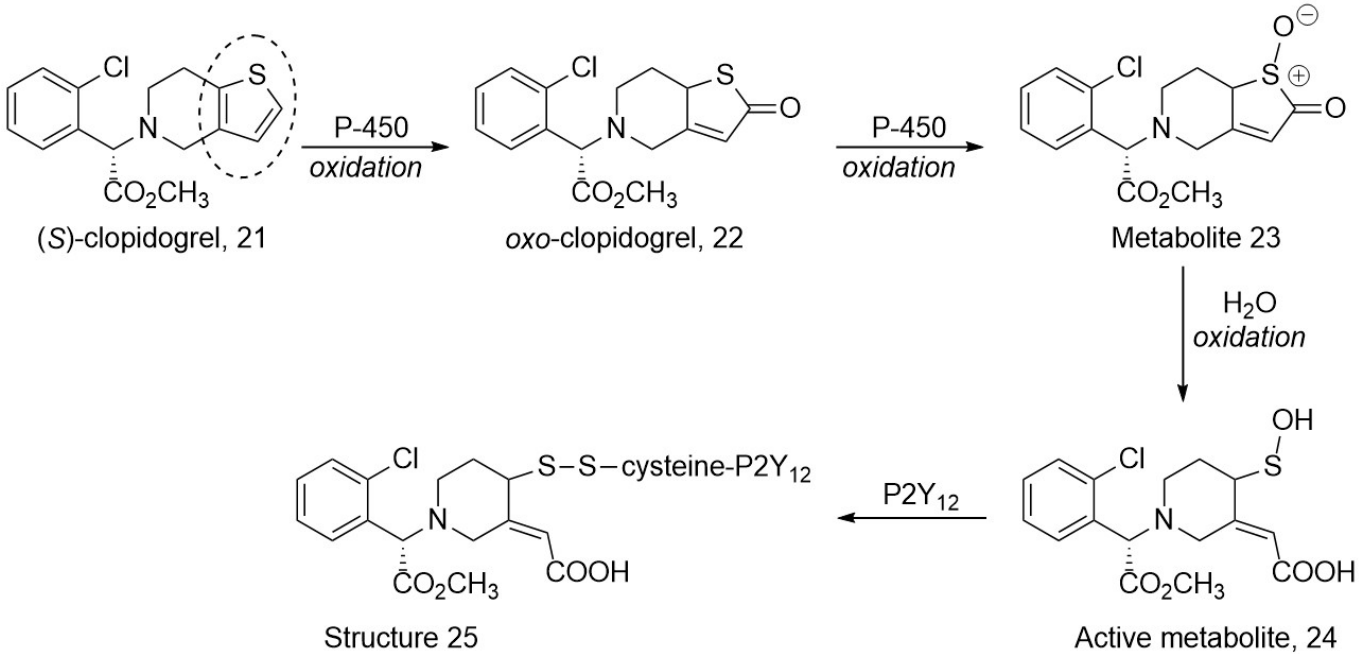


FIGURE 8 - Clopidogrel, 21, needs three-oxidative metabolic steps to be activated.

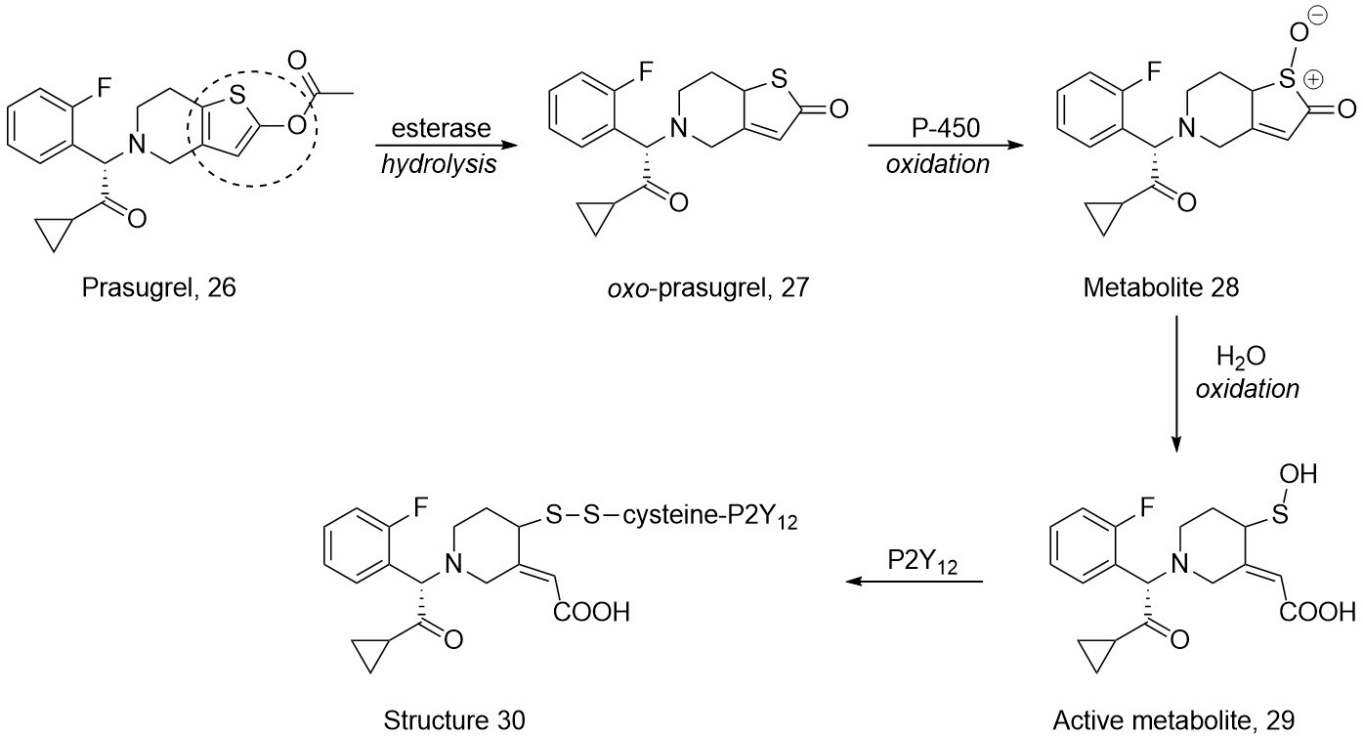
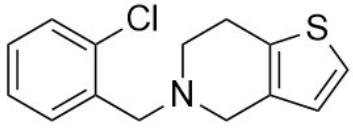


FIGURE 9 - Prasugrel, 26, is a clopidogrel analogue that needs only two-oxidative metabolic steps to be activated.



Ticlopidine, 31

FIGURE 10 - ticlopidine, 31, a thienopyridine antiplatelet.

Duration of Action

Structural features of a drug largely influence its metabolic and/or chemical stability, which is directly linked to the drug's duration of action.(Masimirembwa, Bredberg, Andersson, 2003) Specific metabolic and chemical degradation pathways are associated with specific functional groups in the structure of the drug, that consequently results in altering its chemical structure in the human body.

Scope: Atracurium, 32, for example is an isoquinoline non-depolarizing neuromuscular blocker that is used for muscle relaxation through anesthesia.(Lee, 2001) Atracurium's structure contains two quaternary ammonium groups separated by a bridge with two ester functionalities (Figure 11). A bisquaternary structure is essential for the neuromuscular blocking activity and a distance of around 1-1.4 nm in between these two quaternary nitrogens is also important for this activity. (Bowman, 2006) This allows these nitrogens to form ionic interactions with the anionic centers at the nicotinic receptor. Moreover; the two carbonyls in the bridge in-between the two nitrogens engage in hydrogen bonding with the active site.(Lee, 2003) About 70% of the drug undergoes Hofmann elimination at the physiological pH, leaving a tertiary benzylisoquinoline inactive product. This chemical instability results in its short duration of action, which is approximately 40 minutes, that is desired to allow for a fast recovery after anesthesia.(Appiah-Ankam, Hunter, 2004)

Identification: Mivacurium, 33, is a newer isoquinoline neuromuscular blocker that is similar to atracurium, 32; however, its structure is modified to not undergo Hofmann elimination with retention of its pharmacological activity. (Lee, 2001) On the other hand, mivacurium, 33, is rapidly

inactivated by the action of plasma cholinesterases on the ester functionalities, which are more easily approachable, compared to atracurium, 32, resulting in approximately 15 minutes of duration of action (Figure 12).

Predictions: Now, in a trial to predict the duration of action of another isoquinoline, doxacurium (34, Figure 13), being a bis-quaternary ammonium molecule that is larger than atracurium as it has two more methoxy groups on the terminal isoquinoline rings. Based on that, can we predict its duration of action?

Hence, different drugs in the same class could have different duration of actions due to having different substructures. For a drug development process, a drug may be modified with substructures that undergo chemical or biological transformations in the human body in order to end up with a drug structure providing the desired duration without losing or changing its activity.

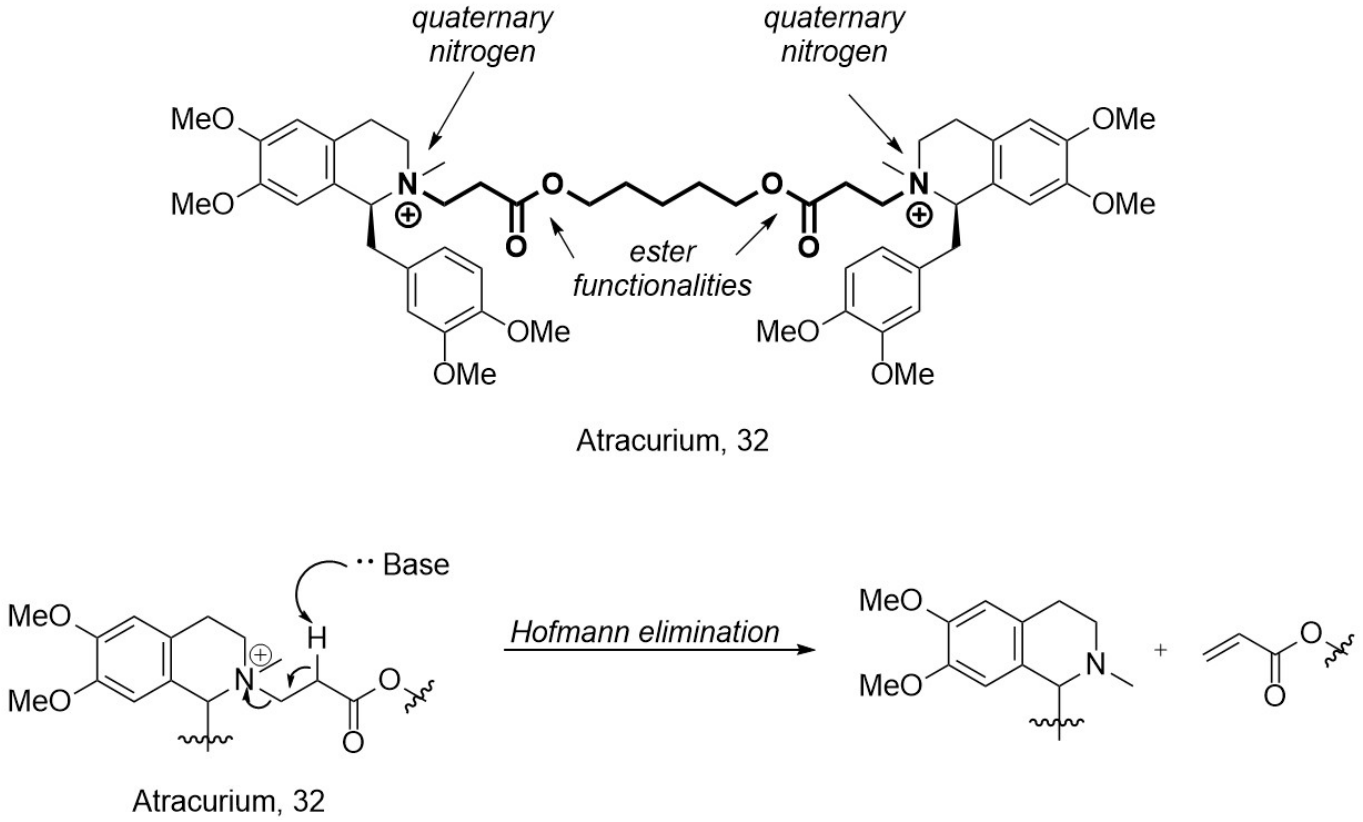


FIGURE 11 - Atracurium, 32, undergoes Hofmann to an inactive product.

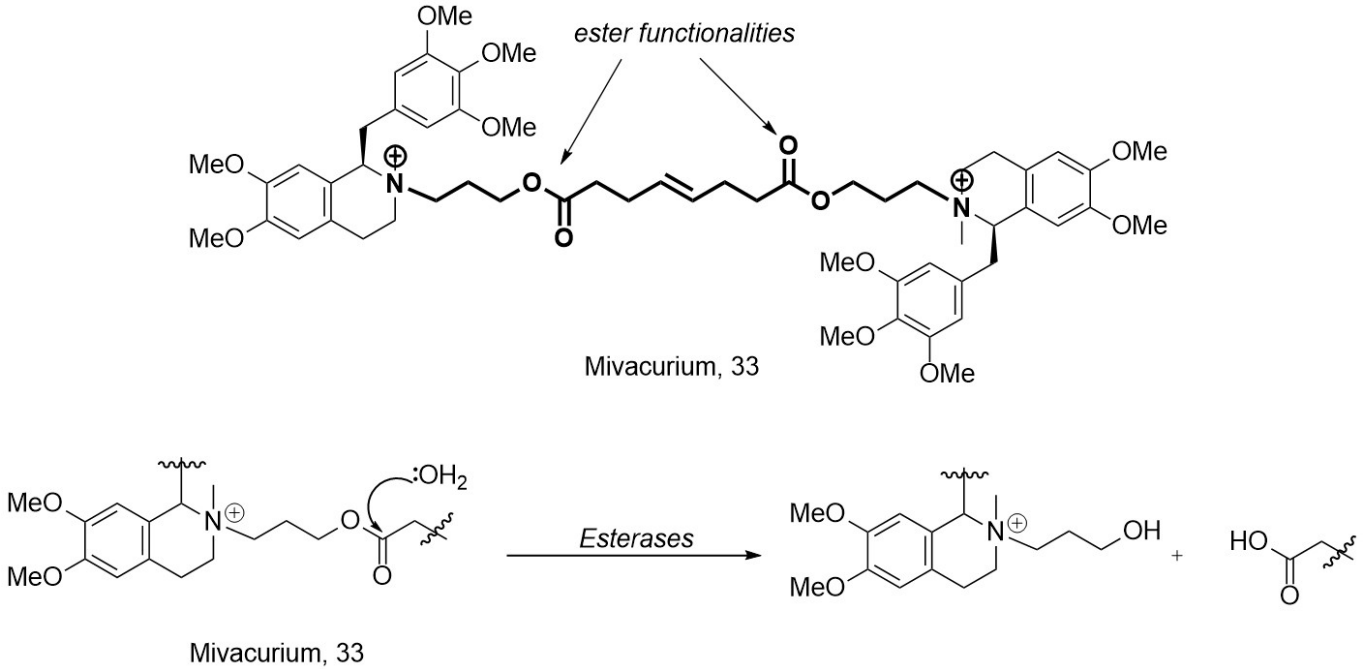


FIGURE 12 - Mivacurium, 33, rapidy undergoes an ester hydrolysis to yield an inactive product.

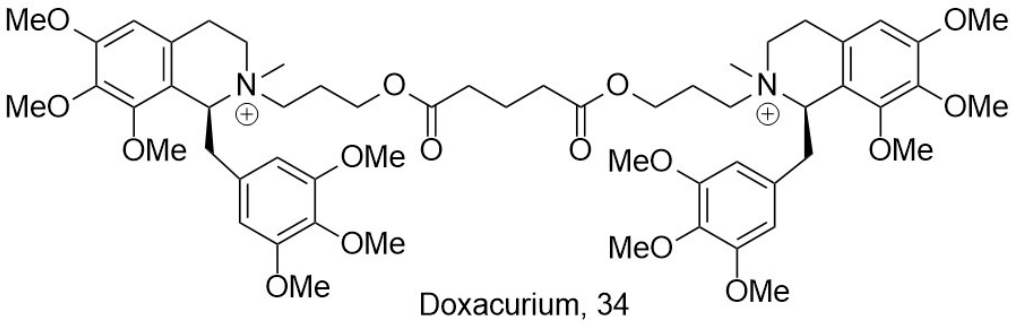


FIGURE 13 - Doxacurium, 34, an analogue for atracurium, 32.

ANSWERS FOR THE PREDICTIONS AND VALIDATION

Mechanism of Action

It would take the student or practitioner little effort to note that only structure 6 offers the best match with the nitrogen atom having distance and spatial arrangement from the aromatic ring most resembling the pharmacophore for dopamine, 2, and rotigotine, 1, (Figure 14). Instead the *meta* hydroxyl was replaced with an amine group that could have the same binding effect to the target. Structures 4, 5, and 6 consist of prucalopride (potent prokinetic), aripiprazole (antipsychotic), and pramipexole (antiparkinsonian) respectively. (Wong, Manabe, Camilleri, 2010; Chernoloz, El Mansari, Blier, 2012; Varela *et al*., 2014)

Side Effects

Structure 15 has obviously no double bond at the 10,11 position as in CBZ, 7, however it is an ester derivative of OXC, 12, (Figure 15). A student or practitioner can predict and as shown; this carbamazepine derivative will be hydrolyzed by esterase to give the 10-hydroxy active metabolite, 35, then to the dihydroxy metabolite, 36, same as OXC. As an expectation, it will have a low hepatotoxicity. Validated from literature this drug, known

as elicarbazepine, has a very low hepatotoxicity that is below the 1%. (Björnsson, 2008)

Oral Bioavailability

It could be predicted that although peramivir, 20, has a slightly better bioavailability than laninamivir, 19, due to having less polar atoms or groups, however; both drugs possess poor bioavailability as reported in literature (laninamivir; F% ~ 15% and peramivir; F% < 3%).(Li *et al.*, 2017) The reason is that these NA inhibitors, same as zanamivir, 16, form zwitterion easily with their guanidinium cationic and carboxylate anionic groups at the physiological pH, thus expressing lack of lipophilicity nature, and resulting in poor absorption by passive diffusion.

Onset of Action

Ticlopidine, 31, is clearly shown to have a delayed onset of action as it more highly mimics clopidogrel (Figure 17). In fact, ticlopidine undergoes extensive and multiple oxidative metabolisms into many inactive metabolites. Ticlopidine active metabolite, 39, was deduced only after prasugrel and clopidogrel, and its onset of action is known to be much more delayed, taking about 24 to 48 hours post administration of ticlopidine (250 mg loading dose). (Farid, Kurihara, Wrighton, 2010)

Duration of Action

It could be predicted that doxacurium, 34, would have a slower inactivation and longer duration of action than atracurium, 32, and mivacurium, 33. This has been reported in literature with a duration of action about 80 minutes, as this drug does not undergo Hofmann elimination and its two ester functionalities are more hindered by the aryl groups to be hydrolyzed than in mivacurium, 33 (Figure 18). (Appiah-Ankam, Hunter 2004)

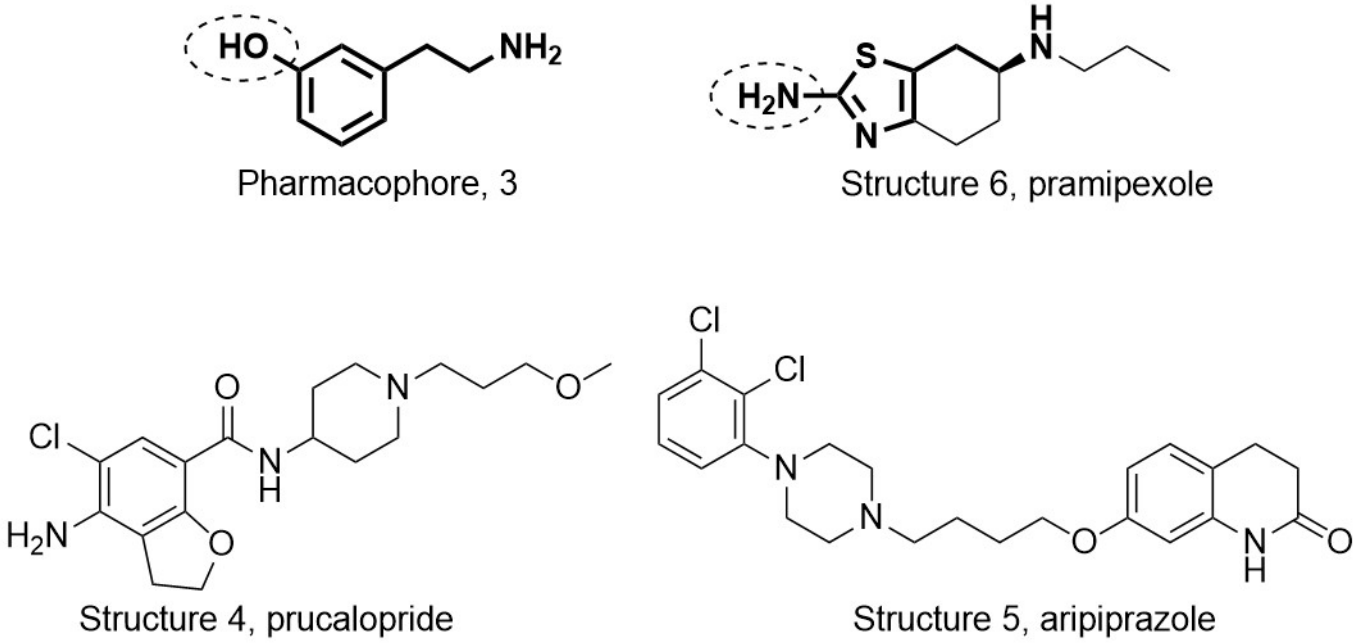


FIGURE 14 - Structure 6, pramipexole, has a significant structural similarity to the pharmacophore, 3, (shown in bold) that explains its agonistic mode of action.

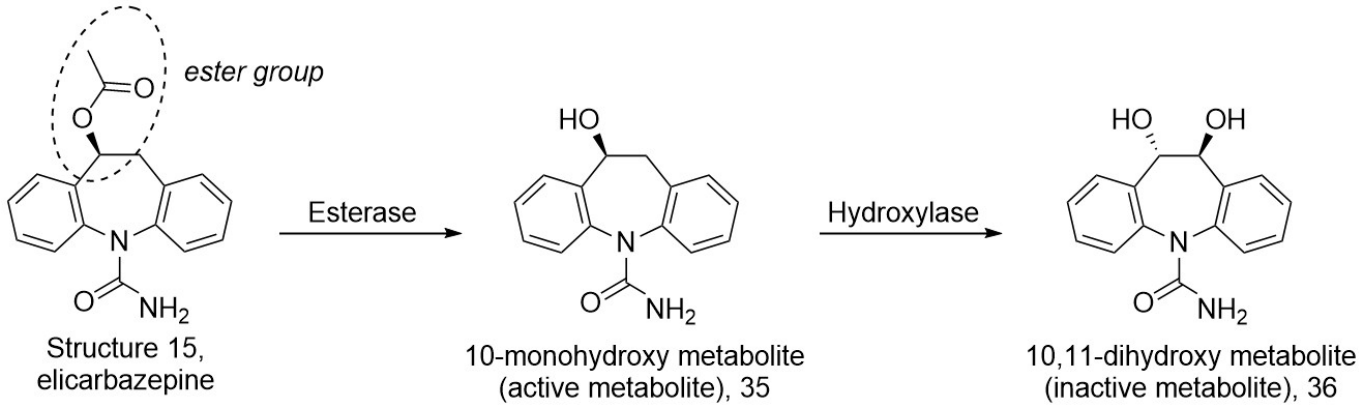


FIGURE 15 - Metabolic transformations for structure 15 (elicarbazepine).

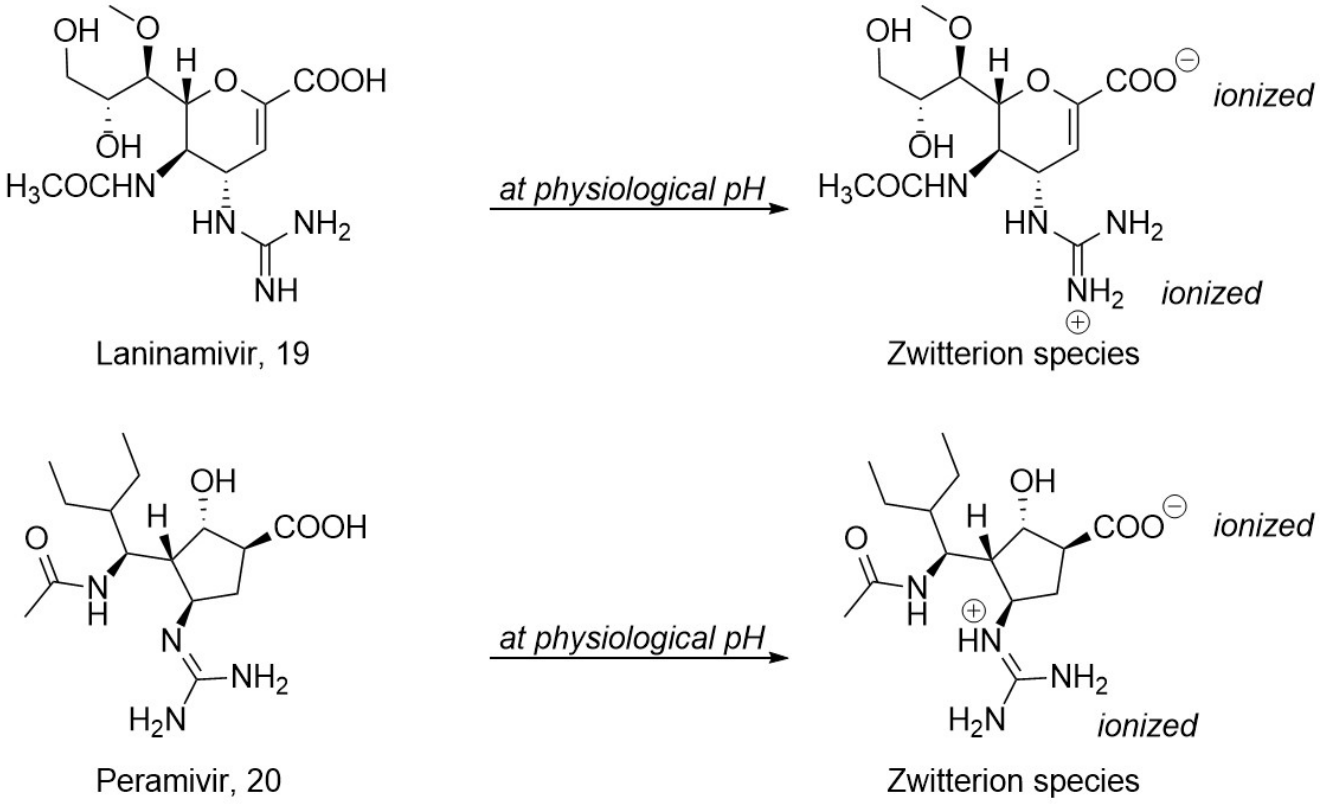


FIGURE 16 - Laninamivir, 19, and peramivir, 20, from zwitterionic species in human body.

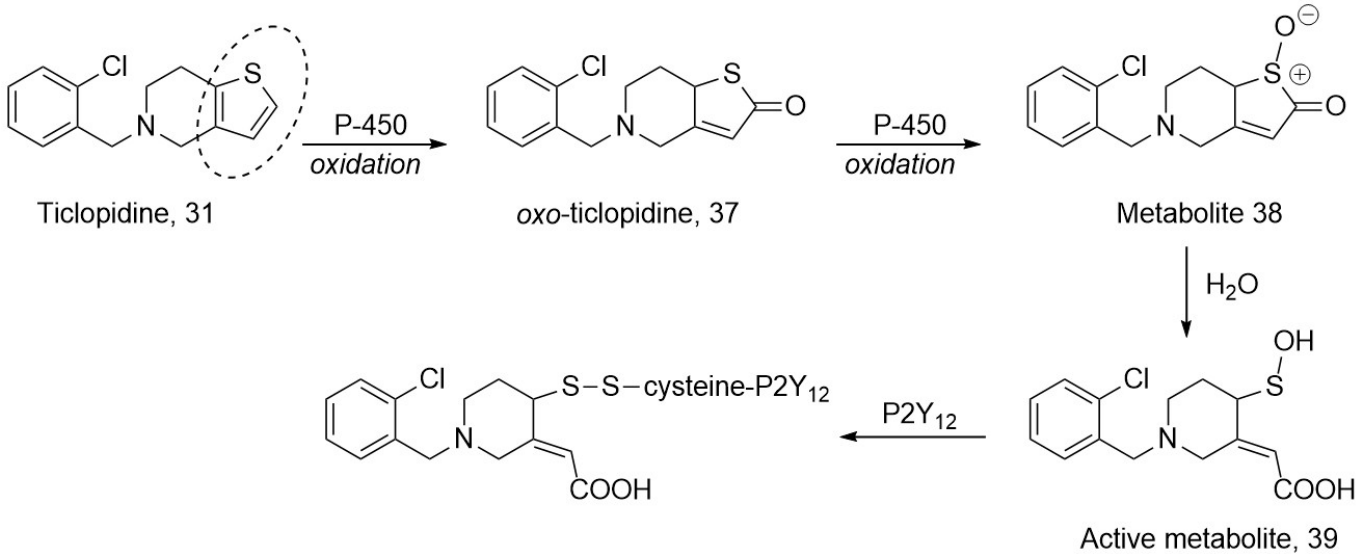


FIGURE 17 - Ticlopidine, 31, metabolic activation.

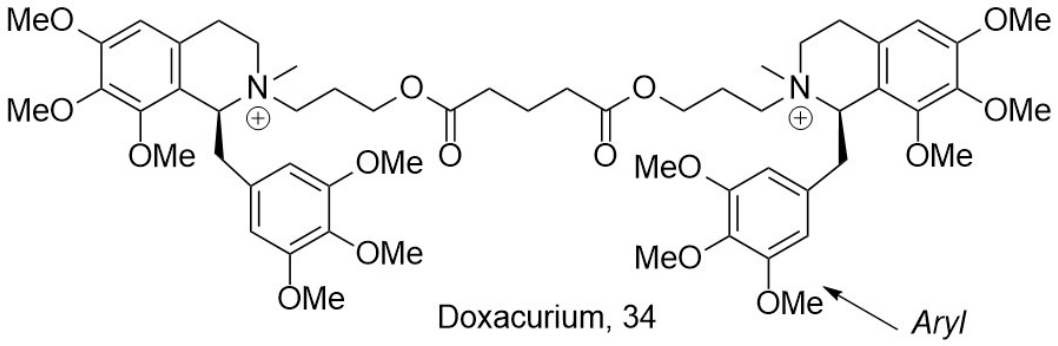


FIGURE 18 - Doxacurium, 34, an analogue for atracurium, 32.

CONCLUSION

This paper illustrated the significance of the inclusion of medicinal chemistry in pharmacy education by using key concepts in pharmacology and clinical therapeutic courses provided to pharmacy students. There is a comprehensible relationship between the chemical structures and the pharmacokinetic and pharmacodynamic performance of drugs. This model can be helpful for medicinal chemistry educators to teach pharmacy students how to clarify the principal pharmacological concepts of drugs based on the chemical structures. Evidently, medicinal chemistry knowledge is important for the interpretation of existing drugs' properties and the discovery and development of new pharmaceutical agents. Thus, learning medicinal chemistry courses and incorporating the skills explained above represent an essential component of pharmacy students' education. Moreover, medicinal chemistry can help pharmacy practitioners and other healthcare providers better predict and explain drug actions, and hence make optimal pharmacotherapy selections. The next step to this work would be to conduct randomized controlled trials involving students and practitioners assessing their performance while incorporating specific medicinal chemistry modules in explaining different drug action. A practice-based chemistry-driven diagnosis service is also called for. Such a service can be trialed via a randomized fashion providing evidence of pharmacist and patient counselling benefits with regards to diagnosis, and management and identifying medication-related problems.

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