



## Review Article

### Oxidation: The Most Common Pathway for the Prodrugs Bio Precursors Activation

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#### ABSTRACT

Oxidation of inactive prodrug (that their mode of action is not via linkage carrier, but occur through modification of their molecules which are called the bio precursor) to active parent drug design is generally via the methods modification strategies that aim to improve the physicochemical and pharmacological properties of drugs such as increases bioavailability, water solubility and/or duration of action.

These prodrugs need metabolically or chemical transformation reactions to change to their active drugs, these chemical reactions are generally formed by phase I reactions through proton activation, elimination activation, oxidative activation, reductive activation and phosphorylation activation or decarboxylation activation.

The goal of this review is to study the up-to-date advances in the prodrug's oxidative activation such as N- and O- oxidative dealkylation, oxidative deamination, N-oxidative and S-oxidative important strategies to produce the parents' active drugs. Oxidation reactions are of great importance and most cancerous diseases begin with these reactions.

**Keywords:** prodrug, oxidative activation, linkage carrier, drug bioavailability.

## INTRODUCTION

The prodrugs whose mechanisms are not via linkage carrier, but occur through modification of their molecules are precursor prodrugs. These prodrugs need metabolically or chemical transformations reactions to change their active drugs, these chemical reactions are generally formed by phase I reactions (Kokil and Rewatkar, 2010):

1. Proton activation.
2. Elimination activation
3. Oxidative activation.
4. Reductive activation.
5. Phosphorelation activation.
6. Decarboxylation activation.

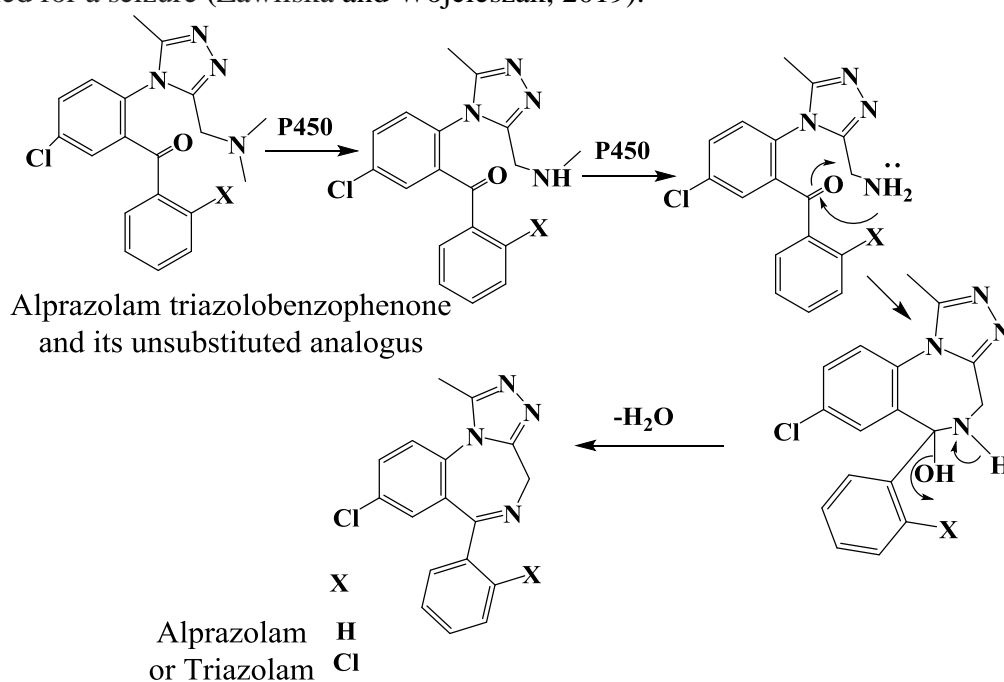
The review of this paper included the oxidative activation which is the most common pathway for the prodrugs Bioprecursors activations using the extremely multipurpose oxidative catalysts of the human genome encodes 57 cytochrome P450 (CYP450) enzymes. (Guengerich, 2005).

There are Four Types of Oxidative Activations of Prodrugs:

1. N- and O- oxidative dealkylation.
2. Oxidative deamination.
3. N-Oxidative
4. S-Oxidative

### 1. N- and O- Oxidative Dealkylation Activations:

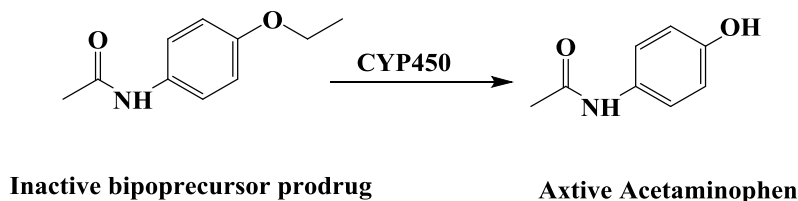
Alprazolam and triazolam are central nervous system depressants, (anxiolytics) drugs which are triazolobenzodiazepines analogs, Fig. (1) (Beale and Block, 2011). They were injectable water-soluble prodrugs but were never developed for medical use. In Spain at 2014 they were first identified for a seizure (Zawilska and Wojcieszak, 2019).



**Fig.1:N-Dealkylation oxidative activation of Alprazolam triazolobenzophenone and its unsubstituted analogus (open ring benzodiazepines)**

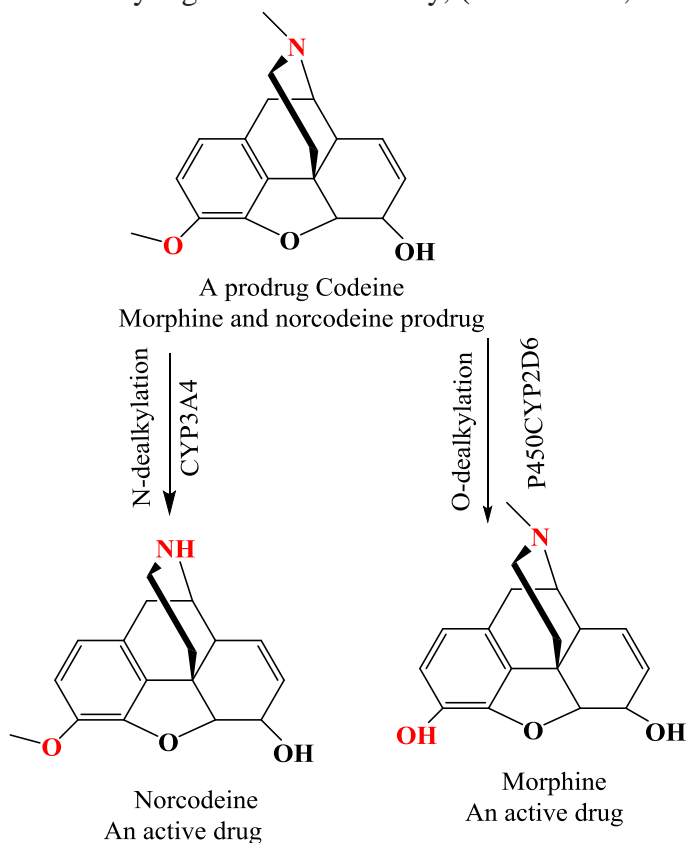
An example of O-dealky, was the activation of precursor prodrug phenacetin to acetaminophen a NSAID drug with a further affinity to inhibit COX2 enzyme, (Gralak *et al.*, 2000).

Fig. (2). Note that, it was withdrawn from medicinal use as dangerous in the 1970s (Liu *et.al.*, 2020).



**Fig. 2: The equation of O-dealkylation activation of bioprecursor prodrug phenacetin to acetaminophen**

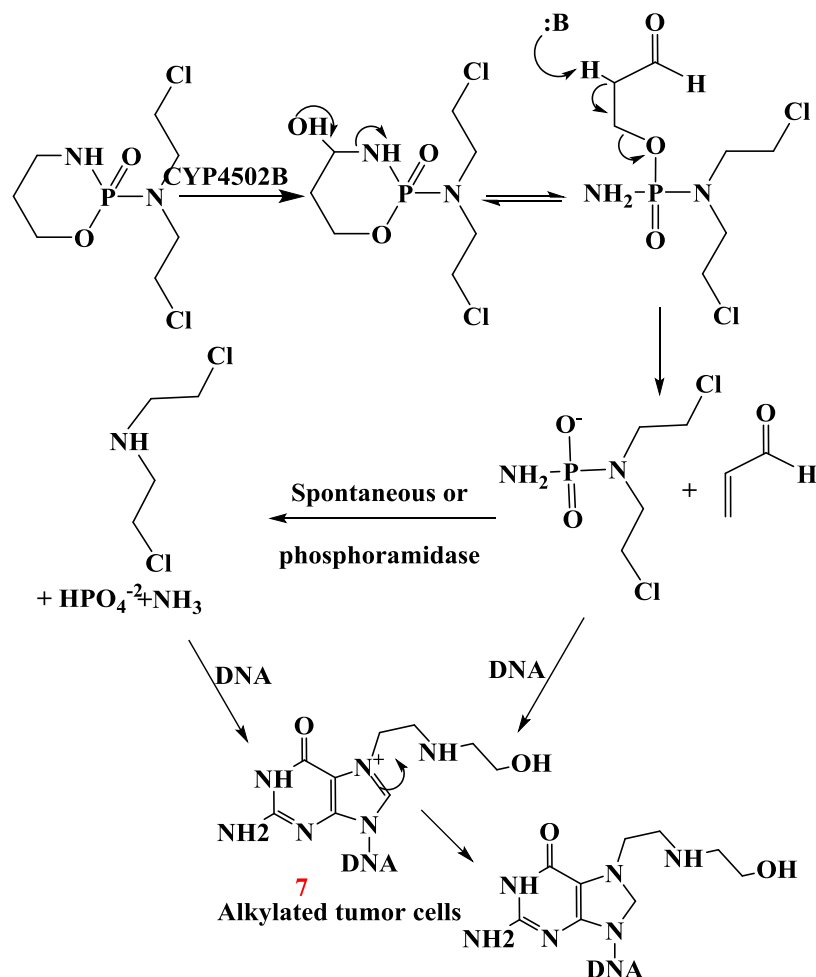
An example of O and N-dealkylation was revealed by codeine, which is a morphine and norcodeine prodrug which O-demethylated by cytochrome P450CYP2D6 to give the primer (of 20 times more active than the prodrug) or N-demethylated by cytochrome CYP3A4 to give the later (the same action as the prodrug), this therapeutic scenario is complicated by the fact that O-demethylation to morphine plays a greater role in individuals with the extensive metabolizer phenotype associated with abnormally high CYP2D6 activity, (Koren *et al.*, 2006), Fig. (3).



**Fig. 3: Codeine prodrug O and N-dealkylation**

## 2. Oxidative Deamination Activations:

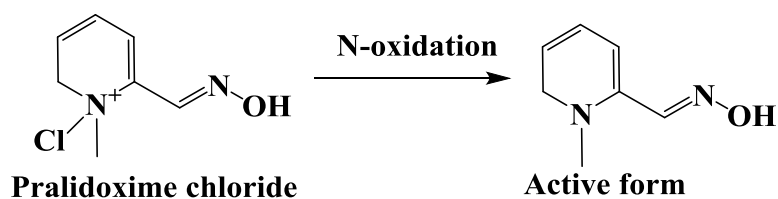
The importance of this strategy was the activation of many bio precursor prodrugs of antineoplastic agents such as the chemotherapeutic and the immune system suppressant alkylating agent cyclophosphamide (nitrogen mustard precursor prodrug) which oxidative deamination by liver enzyme CYP450<sub>2B</sub> (i.e hydroxylate first to 4-hydroxycyclophosphamide then free of the bis-(2-chloroethyl moiety)), then the intermediate form was bind to nitrogen at position 7 of DNA quinine ring spontaneously or by the help of phosphor amidase enzyme in tumor cells , which causes them to death, the suggested mechanism is shown in Fig. (4), (Kobayashi *et al.*, 1999).



**Fig. 4: The suggested mechanism of cyclophosphamide O--Deamination**

### 3. N-Oxidative activations:

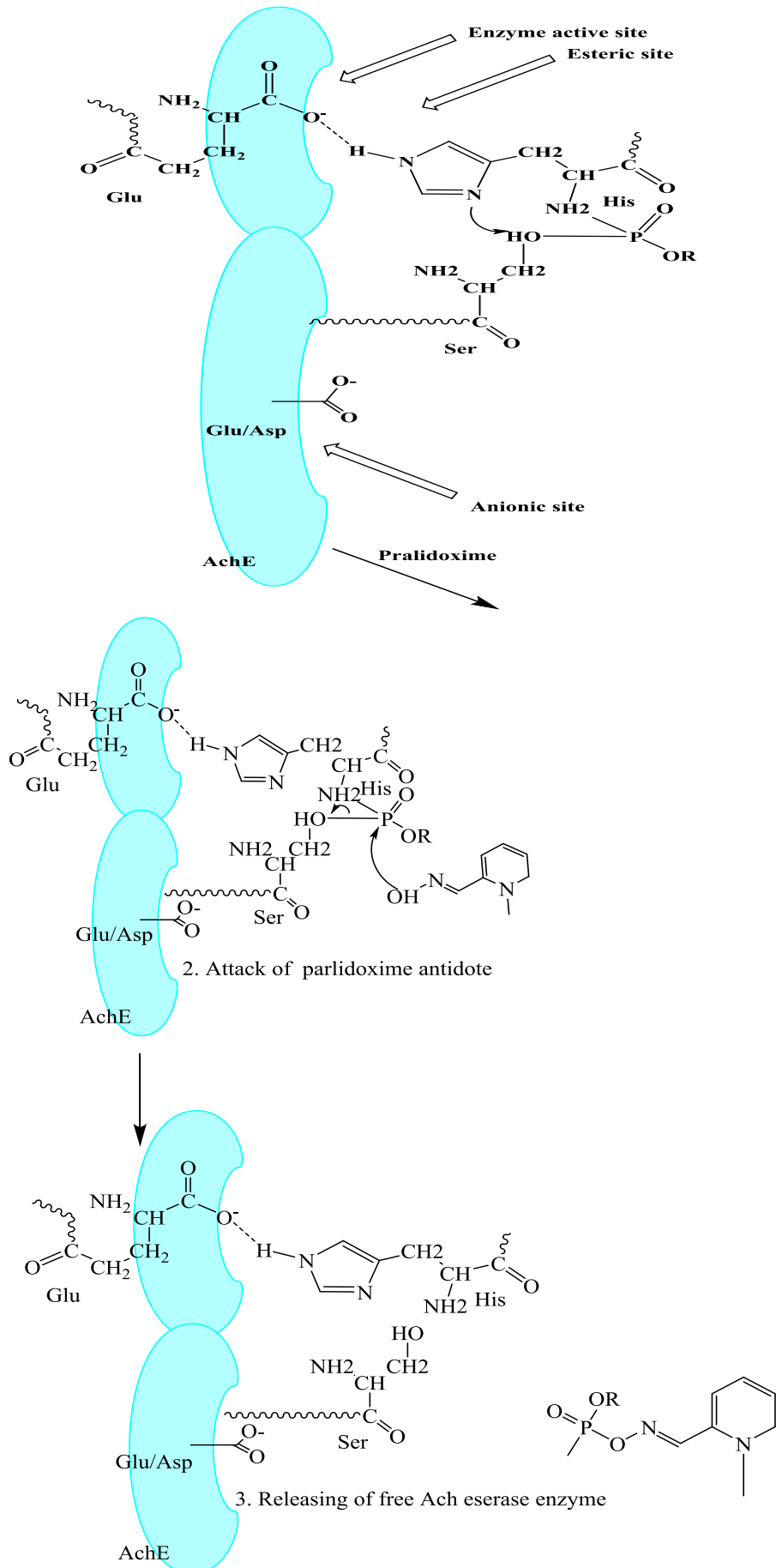
An important example of N-oxidative activation of precursor prodrugs is the pralidoxime chloride (2PAM), this prodrug is activated to its parent drug pralidoxime via N-oxidation, this is the antidote of organophosphorus poisoning which binds to the hydroxy component (the esteric site) of the active site of the acetylcholinesterase enzyme, thereby blocking its activity, this pralidoxime binds to the other half (the unblocked, anionic site) of the active site and then displaces the phosphate from the serine residue and thus reactivates the acetylcholine esterase and regenerates the fully functional enzyme. The problem here is that the active drug pralidoxime is unable to cross the BBB as its prodrug chloride salt does as shown in Figs. (5), (Kushwaha *et al.*, 2016).



In active prodrug (able to cross the BBB)      Active prodrug (able to cross the BBB)

**Fig. 5: N- Oxidation activation of Pralidoxime chloride**

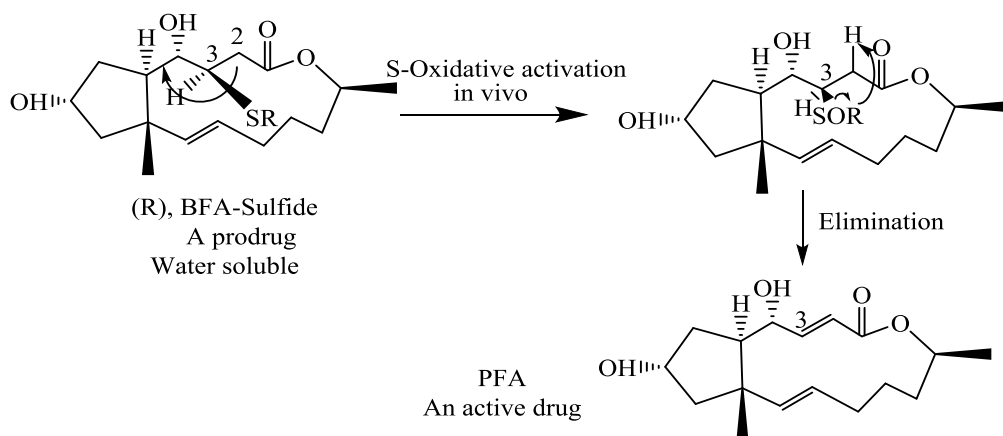
The mechanism of pralidoxime antidote for organophosphorus poisoning which is suggested by this paper is shown in Fig. (6).



**Fig. 6: Mechanism of pralidoxime antidote for organophosphorus poisoning**

#### 4. S-Oxidative activations:

Many prodrugs resolved the problems of parent active drugs rapidly cleared and poor bioavailability by their converted to sulfide derivatives which were recognized by their aqueous solubilities, and there simply converted back to the active parent drugs through S-oxidation, a good example is an antitumor and antiviral antibiotic Brefeldin A (BFA). So as to recover BFA water solubility Cushman and coworkers change the C2–C3 alkene functional group of BFA with various sulfide moieties to produce a latent leaving group via in vivo oxidation, the newly generated stereocenters at C3 and sulfur were determined to be (*R*) and (*S*), respectively, (Peak, 2018), Fig. (7).



**Fig. 7: S-Oxidative activation of BFA-Sulfide**

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## الأكسدة: المسار الأكثر شيوعًا لتنشيط السلانف الحيوية للعقاقير الأولية

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### الملخص

إن أكسدة العقاقير الأولية غير النشطة (والتي لا تتم طريقة عملها عن طرائق الناقل الرابط، ولكنها تحدث من خلال تعديل جزيئاتها التي تسمى السلانف الحيوية) لتصميم الدواء الأم النشط بشكل عام عن طريق استراتيجيات تعديل الطرائق التي تهدف إلى تحسين الصفات الفيزيائية والكيميائية والدوائية. خصائص الأدوية مثل زيادة التوافر البيولوجي والذوبان في الماء و / أو مدة التأثير.

تحتاج هذه العقاقير الأولية إلى تفاعلات تحويلات استقلابية أو كيميائية للتغيير إلى عقاقيرها النشطة، وتتشكل هذه التفاعلات الكيميائية عمومًا عن طريق تفاعلات المرحلة الأولى من خلال تنشيط البروتون، وتفعيل الإزالة، والتنشيط التأكسدي، والتفعيل الاختزالي، وتفعيل الفسفرة، أو تنشيط نزع الكربوكسيل.

الهدف من هذه المراجعة هو دراسة التطورات الحديثة في تنشيط أكسدة العقاقير الأولية مثل إزالة الألكلة المؤكسدة للنتروجين والاكسجين، نزع الأمين المؤكسد، N-مؤكسد والكبريت المؤكسد الاستراتيجيات الهامة لإنتاج العقاقير الفعالة. تفاعلات الأكسدة لها أهمية كبيرة وتبدأ معظم الأمراض السرطانية بهذه التفاعلات.

الكلمات الدالة: العقاقير الأولية، التنشيط بالاكسدة، الناقل الرابط، التوافر الحيوي.