

Success Stories of Enolate Form of Drugs

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ABSTRACT

Stereochemistry of clinical agents play a key role in their success to become drugs. Tautomerism is a structural isomerism, playing a key role in the orientation of organic compounds and also found significant in distinctive base pairing in nucleic acids. Keto-enol form usually occurs and found prominently among different types of tautomers. The enol form ionizes in the physiological solution into enolate and alter the biological activity. So, how this enolate form brings modification in pharmacokinetics and pharmacodynamics of a drug is very important and quite interesting to know. As this form is ionic in nature so it increases the interaction with the concerning receptors, enzymes, ion channels or functional proteins. In this review we cover and compile success, role and the significance of the enolate form of clinical agents which succeed to become drugs!

Keywords: Stereochemistry, tautomerism, Keto-Enol Tautomerism

INTRODUCTION

Usually therapeutic molecule has some sort of structural peculiarity in terms of its stereo-geometric forms. The stereo-geometric forms give rise to various geometric forms known as isomers. Isomers are mainly present in paired form and can be of different types: Cis-Trans, R-S, Syn-Anti, E-Z or tautomers^[1]. These tautomers are the constitutional isomers that can be easily interconvert into their forms through a concerning phenomena, called tautomerization and this sort of isomerism is known as tautomerism^[2].

Tautomerism is a kind of isomerization resulted from the intramolecular migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. However, this isomerism is a special case of structural isomerism and also found significant in distinctive base pairing in nucleic acid^[3].

In tautomerism, there is chemical equilibrium between the tautomers and the proportionality of tautomers depend on several factors preferentially solvent, temperature, and pH of the solution^[4,5]. Tautomerism can be of different types, elucidated in the following section.

Most common tautomeric pairs are:

Amide - imidic acid, e.g., Nitrile hydrolysis

Anomers of reducing sugars in solution interconvert through an intermediate open chain form.

Enamine - enamine, e.g., during pyridoxal phosphate-catalyzed enzymatic reactions and has biological significance in some diseases.^[6,7]

Enamine - imine

Ketene - ynol, e.g., for ethenone, (triphenylphosphoranylidene) ethenone

Keto-enol, e.g., especially in ketones

Lactam - lactim, antimetabolites drugs (purine and pyrimidine analogs and penicillins)

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Among tautomers, *keto-enol* form is most studied and common, which can be easily seen in a number of FDA approved drugs. The ionic form of *enol* is enolates possessing an alkene ($C=C$) with a hydroxyl group ($-OH$ group) located on one of the carbon atom of the same alkene, see in fig.1.

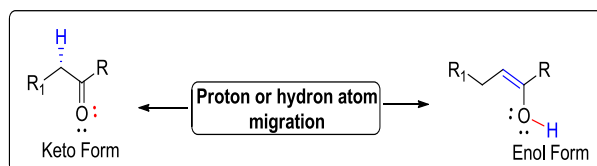


Fig.1. Enolate formation: *Keto* form interconverted into *enol* form via proton migration, which is followed by the abstraction of a proton (deprotonation) to achieve the ionic form of enol, "enolate".

This property of forming keto-enol form is exclusively attributed by the ketones, aldehyde and α -unsaturated alcohols. This type of tautomers often occurs in nature and even in the human body which is prominently manifested via acid or base-assisted catalysis. Usually it has been observed that the '*keto*' form of the compound is more stable, but in certain physiological conditions, the '*enol*' form can also be the stable in nature.

KETO-ENOL TAUTOMERISM

Keto-enol tautomerism refers to a chemical equilibrium between *keto* form (ketone or an aldehyde) and an *enol* (an alcohol with conjugated unsaturation). Simply it clearly indicates the interconversion relationship between "*enol* and *keto* forms are said to be tautomers^[8]. The interconversion of the two forms involves the migration of a proton and the shifting of bonding electrons (see in fig.2.); hence, the isomerism qualifies as tautomerism and therefore mainly affected by the pH of the medium.

Mechanistically, a compound containing a carbonyl group ($C=O$) is normally in rapid equilibrium with an *enol* tautomer, which contains a pair of doubly bonded carbon atoms adjacent to a hydroxyl ($-OH$) group ($C=C-OH$, linear representation of *enol* form). In general, the *keto* form predominates at equilibrium for most ketones. Furthermore, the deprotonated intermediate-II in the inter-conversion of the two forms, referred as an enolate anion^[9], which is significant in carbonyl chemistry, see in fig. 2.

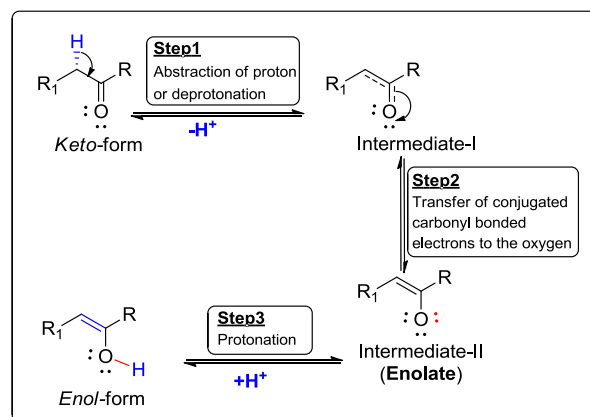


Fig.2. Mechanistic pathway of enolate formation.

keto-enol tautomerization governs thermodynamically but favored in *keto* form as compared to *enol* form. This can illustrate by classical example of vinyl alcohol and acetaldehyde.^[10]

What makes enolates so much interesting and how they are important in biological systems? Enolates are the ionic product of *enol* form. In other words, it is deprotonated form having oxygen atom with un-bonded electron pair which finally makes it a strong nucleophile and having ability to bring necessary physiological reactions.

ENOLATE IMPLICATION IN MEDICINAL CHEMISTRY

Enolate implication in Antiepileptic Drug

Antiepileptic drug act against convulsions, tremors, seizures and neuro-electrophysiological disorders where patient become motionless like a statue.^[11]

Hydratoin

Hydratoin is canonical class of antiepileptics which contain phenytoin, mephenytoin, ethotoin (See fig.2.). Out of these, phenytoin is effective against all types of partial and tonic-clonic seizures but failed against the absence seizures^[12]. Its superior neuro-pharmacological role exerted antiseizure activity without causing general CNS depression. But in toxic doses, it aggravate the excitatory signs while lethal dosing causes a type of decerebrate rigidity^[13]. Its mechanism of action revealed a special mechanism which restrict the repetitive firing of action potentials, evoked by a sustained depolarization and mediated by a slowing rate of recovery of voltage-activated Na⁺ channels from inactivation^[13].

Phenytoin is majorly (95%) metabolized by hepatic cytochrome enzymes. The principal metabolite is *para*-hydroxyphenol derivative which is inactive and its concentration cause saturation in further metabolism of the remaining drug. Whereas the intravenous use is restricted by its low aqueous solubility. Its water soluble prodrug, Fosphenytoin, achieve the higher status of success as it can rectify the limitation of intravenous use as it reaches in blood, it then rapidly converted into phenytoin by erythrocytes and phosphatases in liver. Fosphenytoin have higher affinity for plasma proteins, primarily albumin and this binding is saturable in respect to displaced phenytoin from binding sites. Fosphenytoin is useful for adults with partial or generalized seizures when intravenous or intramuscular administration is indicated. Suggestively the water solubility or intravenous accessibility of these drugs can be attributed by ability of the hydratoin scaffold to form the enolate (see in fig.3.)^[14-16].

Table.1. Generic names and different types of modification in the hydration scaffold.

Generic Name	Substituent's		
	R ₁	R ₂	R ₃
Phenytoin, USP	C ₆ H ₅ -	C ₆ H ₅ -	H
Mephenytoin	C ₆ H ₅ -	C ₂ H ₅ -	CH ₃ -
Ethotoin	C ₆ H ₅ -	H	C ₂ H ₅ -

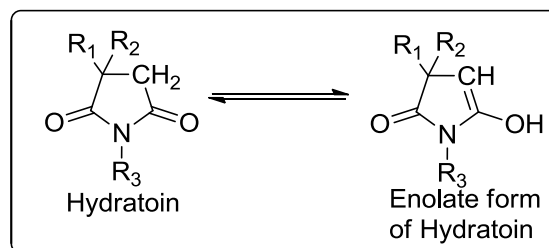


Fig.3. Hydratoin and its enolate form.

Enolates Implication as Hypnotics and Sedatives

Phenobarbital

Phenobarbital is acidic in nature as compare to the water therefore it protonates water and itself gets ionize in enolate form.^[17] This enolate form (see Fig.4.) increases aqueous solubility and affect its dissolution rate which lastly improve its bioavailability^[18].

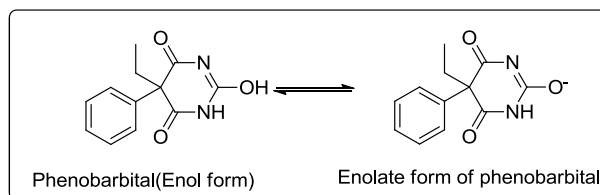


Fig.4. Enolate form of Phenobarbital.

Enolate Implication as Drug metabolite Amphetamines and Heterocyclic amines

Structural features especially the α -substitution in the primary amine metabolize by *N*-hydroxylation. But it is observed that amphetamines and heterocyclic amines also undergo *N*-hydroxylation to *N*-hydroxyamphetamine^[17] in *in-vitro* screening^[19] (see in fig.5).

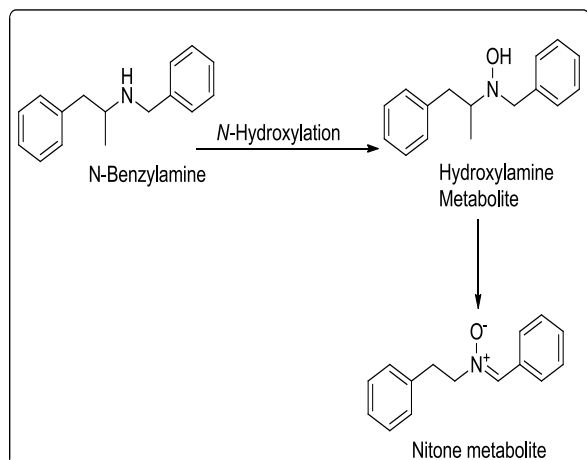


Fig.5. Metabolism of *N*-Benzylamphetamine.

While, phenmetrazine acts as a sympathomimetic and have relative activities like dopamine and norepinephrine. After its oral administration, 70% of the drug is excreted within 24 hours and approximately 19% of that is excreted as the unmetabolised form and the rest as various metabolites. This metabolism is preferentially governed by the enolate formation and there is possibility of the other metabolites to form the enolates, see in fig.6.^[20-21]

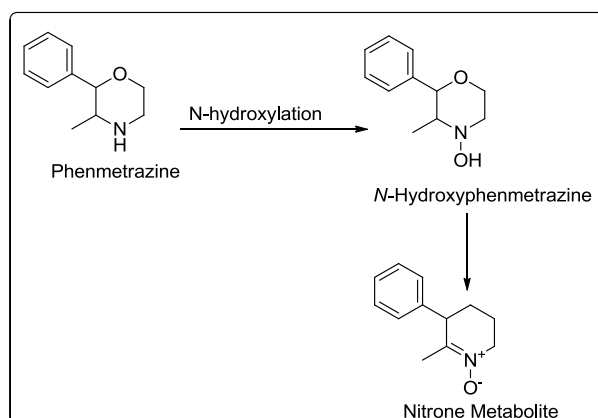


Fig.6. Metabolism of Phenmetrazine

Secondary Aromatic amines

In some special cases, secondary aromatic amines metabolism produce toxicity where *N*-hydroxy derivative forms and oxidize ferrous form of haemoglobin to its higher oxidative

form (ferric form).^[17] This oxidized ferric state of haemoglobin (called methemoglobin or ferrihaemoglobin) can no longer possess the ability to transport the oxygen and lastly leading to serious complications like hypoxia or anemia (see fig.7. depicting such type of metabolism)^[22-23]

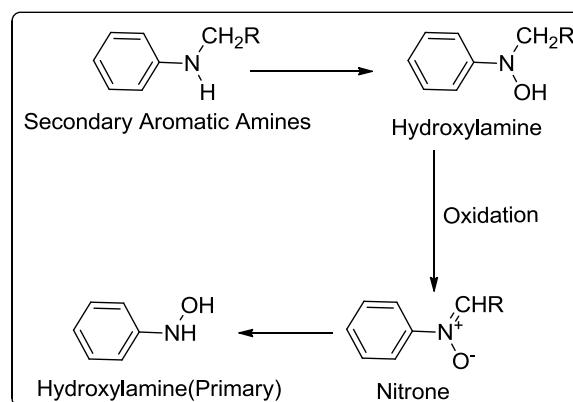


Fig.7. Metabolism of secondary amines.

Enolate Implication as Diuretic

Amiloride

The metabolism assisted conversion of amiloride into its water soluble enolate form which excrete predominantly *via* renal route (see in fig.8.)^[24] This means that the enolate form encompass the solubility profile and also attribute to its diuretics action.^[25-26]

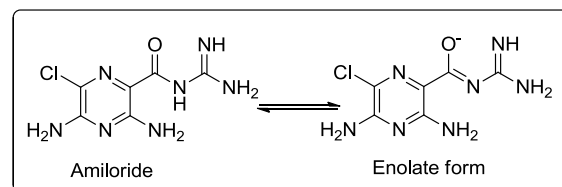


Fig.8. Amiloride and its enolate form.

Enolates Implication in Congestive heart Failure

Amrinone and Milrinone

The most valuable use of enolate form can be seen in amrinone and milrinone, which are especially prescribed in short-term support of the circulation in advanced heart failure. Usually they are present in salt form in parental

dosage, but when dissolved with water for injection, they rapidly get converted into their enolate form, which increases their solubility and absorption (see in fig. 9 and 10). Structurally both the drugs are bi-pyridine derivatives and relatively selective inhibitor of phosphodiesterase-3 isoform. These drugs cause direct stimulation of myocardial contractility, acceleration of myocardial relaxation, balanced arterial and venous dilation with a consequent fall in systemic and pulmonary vascular resistances, left and right heart filling pressures. All these effects together increase the cardiac output, stimulates the myocardial contractility and the decrease in left ventricular afterload.

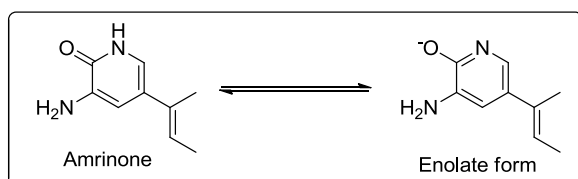


Fig.9. Enolate form of Amrinone.

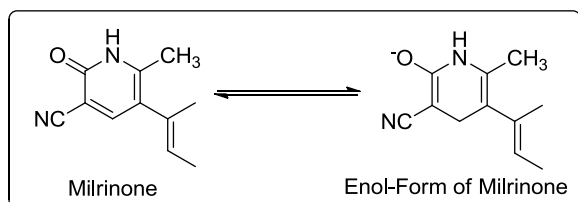


Fig.10. Milrinone and its enolate form.

Enolate Implication as Anti Hyperlipidemics

Atorvastatin

Atorvastatin has a long half-life ($T^{1/2}$) which gives it an edge over the other drugs of the same class. Moreover, it is marketed in combination with the Ca^{2+} -channel blocker (amlodipine), for patients with hypertension or angina^[27] and also directed in case of hypercholesterolemia.^[28-29] The story behind its long $T^{1/2}$, hides in its structure peculiarity where its amide bond get ionize in the physiological solution and improvise bioavailable fraction and therapeutic efficacy (see fig. 11).

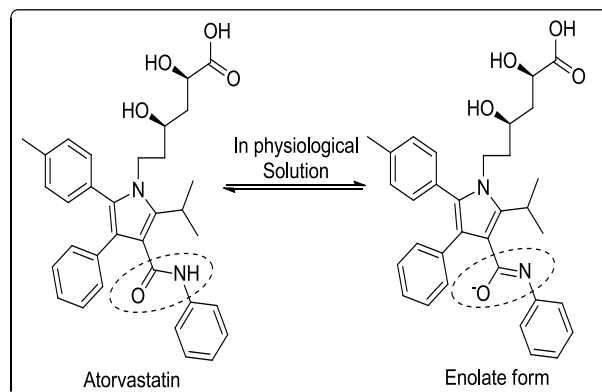


Fig.11. Atorvastatin and its enolate form.

Enolates Implication as Anti arrhythmic Drug

Disopyramide

Disopyramide has a specialty in its mode of action where it exerts its electrophysiological effects quite similar like quinidine, but also pose different adverse effects. It is directed in maintaining the sinus rhythm in patients with atrial flutter or atrial fibrillation or to prevent recurrence of ventricular tachycardia or ventricular fibrillation.^[17-30] These actions are mainly governed by its racemate form. The *in-vitro* electrophysiological actions of its S-(+)-disopyramide form are similar to those of quinidine whereas R-(-)- enantiomer produces similar Na^+ channel blocking effects but are shortly terminated^[31-32].

Unlike quinidine, racemic disopyramide exert prominent anticholinergic actions and therefore cause unpleasant side effects. Its rate of excretion depends on the concentration ratio between unchanged versus changed drug concentration, which is mainly manifested by the amide-enolate form (fig.12).

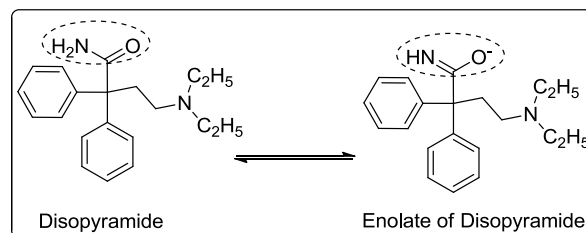


Fig.12. Disopyramide and its enolate form.

Enolates Implication as Anti-Hypertensive Drug Hydralazine

Hydralazine causes direct relaxation of arteriolar smooth muscle *via* altering the intracellular Ca^{2+} concentrations. Most of hydralazine's pharmacological effects are confined to the cardiovascular physiology^[33]. Low systemic bioavailability is the major shortcoming of this drug besides of its well absorption from the gastrointestinal tract.

Firstly its benzylic oxidation brings a product which is quite susceptible for acetylation and also possess the ability of tautomerism and to form enolate isomer. Thereafter, Hydralazine gets *N*-acetylated in the bowel and/or the hepatic portal system.^[34] This acetylated compound is inactive in nature. However, hydralazine rapidly combines with circulating α -keto acids to form hydrazones, and the major metabolite recovered from the plasma is hydralazine pyruvic acid hydrazone.^[35] This metabolite has a longer $T^{1/2}$ than hydralazine but does not appear to be very active. The rate of acetylation is an important determinant of hydralazine bioavailability. Although its $T^{1/2}$ in plasma is ~ 1 hour, but the duration of the hypotensive effect of hydralazine can long last as 12 hours. There is no clear explanation for this discrepancy, suggestively it can be concurred by its ability to form the tautomer/enolate form (for depicting its metabolism pathway, see in fig.13)^[36]

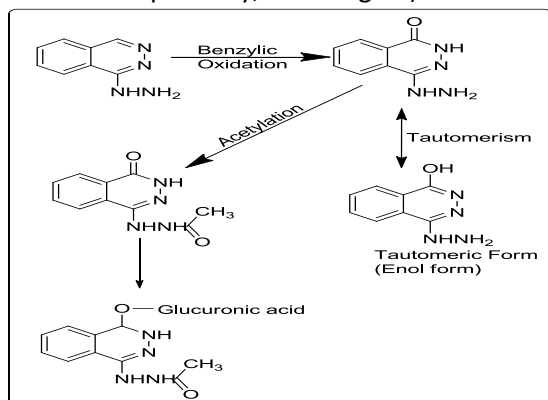


Fig.13. Metabolism of Hydralazine hydrochloride.

Enolates Implication as Anti-Hyperglycemic Drug Repaglinide

Diabetes categorizes as third disease which cause fatality in the world-wide. But present circumstances are so critical that it cause patient more prone towards the cancer.^[37] Moreover there are many drugs for the treatment of diabetes. Repaglinide is one of them which is an oral insulin secretagogue of the meglitinide class.^[38] Like sulfonylureas, it stimulates insulin release by closing ATP-dependent K^{+} -channels in pancreatic cells. It is absorbed rapidly from gastrointestinal tract and attains peak blood levels within 1 hour after oral administration. These features permit multiple preprandial uses as compared with the classical once or twice-daily dosing of sulfonylureas^[17]. It is metabolized mainly in liver to inactive derivatives and should be used cautiously in patients with hepatic and renal insufficiency. The major shortcoming of this drug is hypoglycemia^[39]. Its pharmacokinetic parameters are altered by its enolate form which can be easily achieving higher level in physiological solution and affect its metabolism and excretion (see in fig.14).

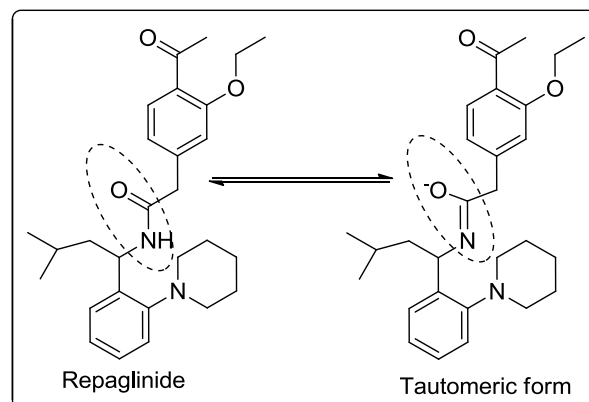


Fig.14. Repaglinide and it tautomeric form.

Enolates Implication as Antithyroid Drugs Thiouracil

Initially, thiouracil discovered great success as anti-thyroid agent but its severe metabolic side effects and less selectivity, creates a dawn in the path of its success^[17]. Moreover some reports highlight its structural feature which makes it more prone towards the isomerization and unwanted adverse effects. Thiouracil present in *enol* form shows tautomerism via *keto*-form, see in fig.15.

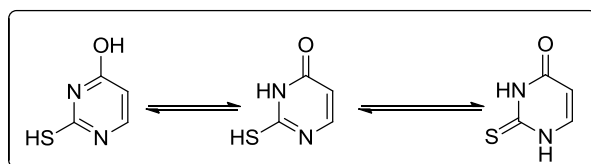


Fig.15. Different forms of Thiouracil.

Propylthiouracil

propylthiouracil is another antithyroid drug having shorter T_{1/2} and prescribed in severe hyperthyroid states, even a 500-mg dose of propylthiouracil must be dosed every 6-8 hours to yield complete thyroid inhibition^[17]. The drug is concentrated in the thyroid and its metabolites mainly excreted in the urine. Propylthiouracil has ability to cross the placenta^[40] and mammary epithelial cells and can often found in milk^[41]. This awkward

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presence in these places disclosed the possible role of enolate form which increases its hydrophilicity and assist in cellular transportation to reach to placenta and mammary ducts (in fig. 16).

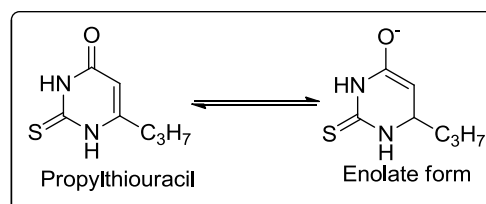


Fig.16. Propylthiouracil and its enolate form.

CONCLUSION

The implication of enolates in the medicinal chemistry brings new interface in rational drug discovery and drug designing. This form is an intermediary and short lived, so need of proper assessment is required to track the mode of mechanism of enolate forming drugs. Therefore the possibility of enolate formation during the drug action helps to the researcher in understanding the novel mechanism inside the physiology of the body. However, proper studies help in teasing the pharmacokinetics of drugs in order to improve their ADMET profile.

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