Metalloporphyrin mediated biomimetic oxidations. A useful tool for the investigation of cytochrome P450 catalyzed oxidative metabolism

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Dedicated to Professor Sándor Antus on his 60th birthday

(received 24 Nov 03; accepted 29 Feb 04; published on the web 02 Mar 04)

Abstract

This review summarizes the recent development on metalloporphyrin catalyzed biomimetic oxidations as applied for modeling cytochrome P450 mediated oxidative metabolic processes. Successful applications of metalloporphyrin-based models on known drugs, drug candidates and agrochemicals were reviewed.

Keywords: Metalloporphyrins, biomimetic oxidations, cytochrome P450, drugs

Contents

Introduction

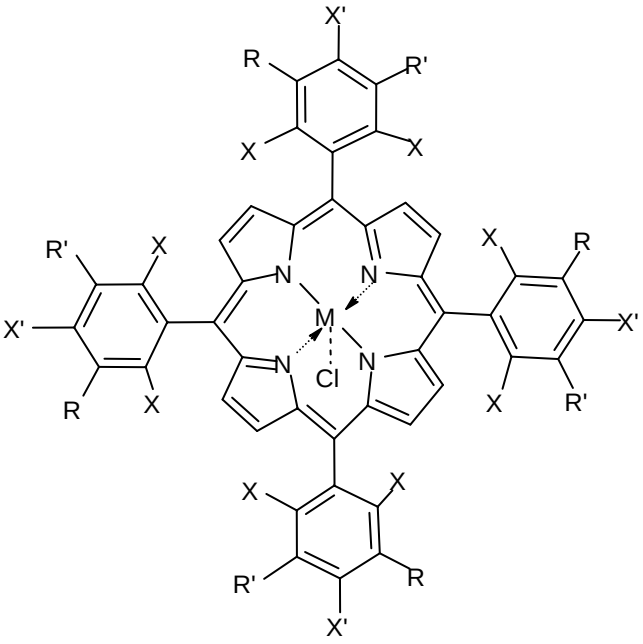
Cytochrome P450 is a member of the monoxygenase family of heme enzymes that plays an important role in metabolizing biomolecules and xenobiotics. The mechanism of its catalytic activity and structural functions have been the subject of extensive investigation in the field of biomimetic chemistry. The high-valent iron(IV)-oxo intermediate, formed by the reductive activation of molecular oxygen via peroxo-iron(III) and hydroperoxy-iron(III) intermediates by cytochrome P450,[1] is responsible for the in vivo oxidation of drugs and xenobiotics. This high-valent iron(IV)-oxo intermediate and probably other intermediates of the P450 catalytic cycle can be formed by the reaction of iron(III) porphyrins with different monooxygen donors and are responsible for the hydroxylation of hydrocarbons, epoxidation of olefins, oxidation of heteroatoms and the cleavage of C-C bonds in organic substrates. Although there are no any difference the activation state of the mainly used first row transition metalloporphyrins (Fe^{2+} or Mn^{2+} centered), difference of their substrate specificity and region selectivity was verified. Moreover the mainly used second row transition metal porphyrin complexes ruthenium (II) react with oxygen donors resulting *trans*-dioxo species which are mainly used for specific epoxidations of olefins. Besides of mechanistic studies these metalloporphyrin-based systems (Figure 1) can be used for the investigation of metabolic reactions of different substrates.[2]

The advantages of using model system to understand drug metabolism are as follows:

- chemical oxidations performed by biomimetic systems can lead to the formation of various metabolic products, are easy operate, and can yield products in sufficient amounts for isolation and further study,
- candidate metabolites are available in relatively large amounts and can be used to identify the real in vivo metabolites and provide sample for pharmacological testing,
- the mode of metabolism can be clarified, for example, unstable metabolites can be isolated under selected and controlled reaction conditions,
- the usage of experimental animals can be reduced.

In this review we focus the application of metalloporphyrin-based systems on known drugs, drug candidates and agrochemicals that mimic P450 catalyzed processes. The selection of small molecule substrates was based on a dual criteria:

- despite being a small molecule, has an aromatic ring, an aliphatic ring, and a N-containing heterocyclic ring moiety etc., which can be converted by a metabolic process,
- data are available on its in vitro and/or in vivo metabolism.



M =Fe, Mn

	X	X'	R	R'
TPP	H	H	H	H
TCl_8PP	Cl	H	H	H
$TCl_8\beta Cl_8PP$	Cl	H	Cl	Cl
$TCl_8\beta Br_8PP$	Cl	H	Br	Br
TCl_8SPP	Cl	H	H	SO_3H
TF_8PP	F	H	H	H
TCl_8SPP	F	H	H	SO_3H
$TF_{20}PP$	F	F	F	F
$TOMe_{12}PP$	OMe	OMe	H	H
$TPh_{12}PP$	Ph	Ph	H	H
TSPP	H	H	H	SO_3H

Figure 1

Discussion

IBPP (3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine, an antiasthma drug and cerebral vasodilator).

IBPP was oxidized by the TPPMnCl - NaOCl- bezalkonium chloride - 4'-imidazoyl-acetophenone (in CH_2Cl_2 at 0 ^oC) system to preferentially yield 6,7-epoxide which appeared to be an intermediated of main metabolite, 6,7-dihydro-6,7-diol, in vivo (human)[3] and in vitro,[4] which had not yet been isolated. Because of instability of the 6,7-epoxide in buffer solution, it was difficult to obtain appreciable amounts by dehydration with triphenylphosphine of 6,7-dihydro-6,7-diol. Novel epoxidation of the pyrazolo[1,5-a] pyridine ring was carried out by the chemical model system, metalloporphyrin-NaOCl (Figure 2). The monoepoxide and diepoxide were selectively prepared using TPPMnCl and $TF_8PPFeCl$[5], respectively.

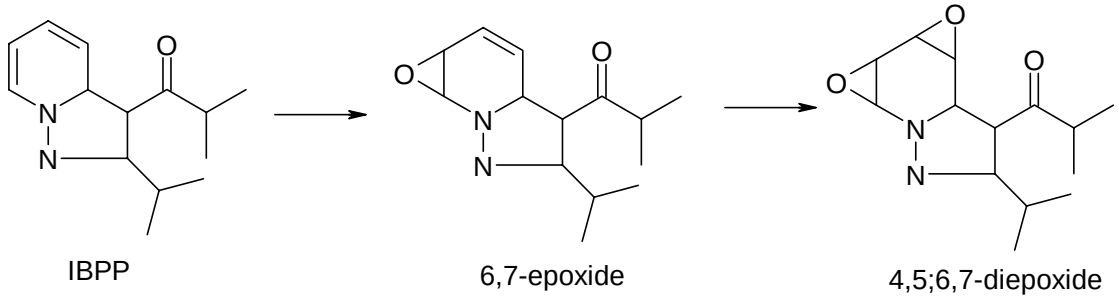


Figure 2

In the further study, the reaction profiles of IBPP in microsomes and various chemical models (TPPFeCl, TPPMnCl, $TF_8PPFeCl$, $TOMe_{12}PPFeCl$, $TPh_{12}PPFeCl$ / iodosybenzene (PhIO), NaOCl, *m*-chloroperbenzoic acid (mCPBA), Pt-colloid/H_2, O_2) were compared. A common reaction product (3-COOH) was obtained in the catalysts/Pt-colloid system and this product was also detected in the rat microsomal system. The α oxidation (2 α-OH, 3 α-OH and 2,3 α-diOH) of the side chains of IBPP and the ring hydroxylation (6,7-diOH) were the main pathways in both chemical model systems and microsomes. The reaction profile of IBPP in the metalloporphyrin model system was most similar to that in the rat or human microsomal system (Figure 3).[6]

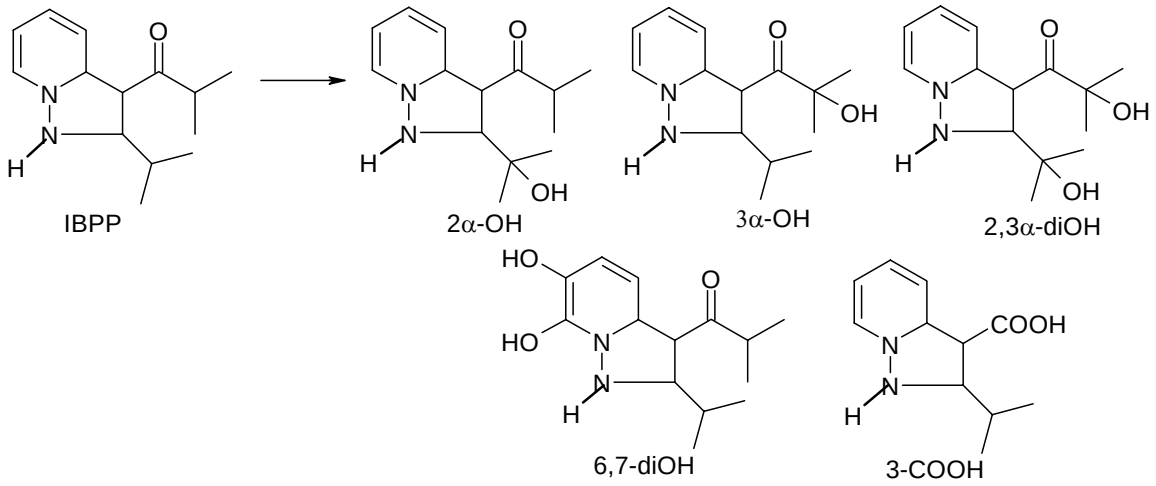


Figure 3

Phencyclidine (PCP, an anesthetic agent)

The major in vitro metabolites were identified from human liver microsomes as piperidine-4-hydroxyl and cyclohexane-4-hydroxyl derivatives.[7]

TPPFeCl catalyzed oxidation of PCP leads to the production of more of the piperidine ring-3-oxo compound than any other product if either iodosylxylene or cumene hydroperoxide is used as the oxidant (Figure 4). This product was quantified as the hydroxyl derivative after reduction by sodium borohydride because the piperidine-3-oxo compound is unstable.

Similarly to in vitro metabolism the TPPFeCl-Zn-acetic acid-O_2 system was found to hydroxylate preferentially the cyclohexane and piperidine rings. Hydroxylation of the aromatic ring was restricted to the meta position.[8]

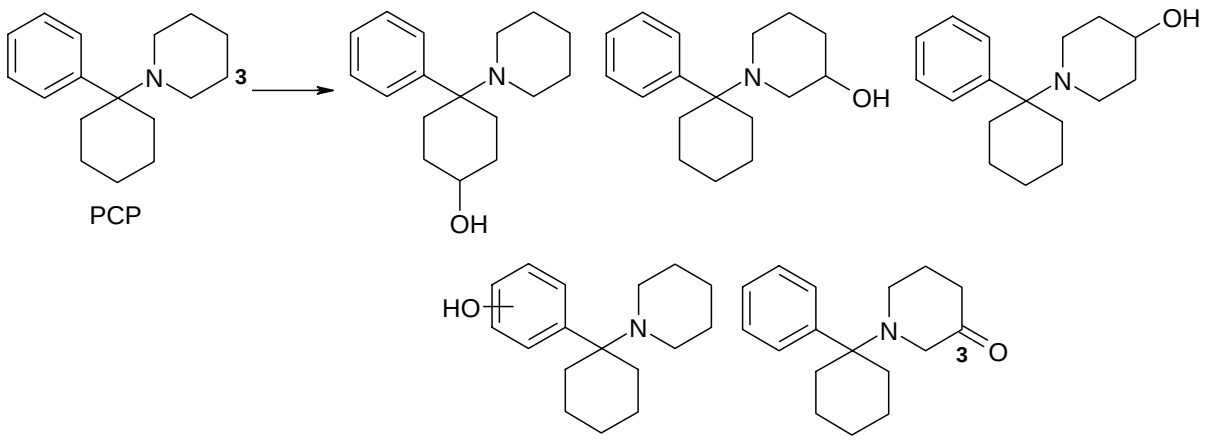


Figure 4

Nicotine

The major in vivo metabolites of nicotine in human are cotinine and 3'-hydroxycotinine (Figure 5).[9,10] In case of TPPFeCl/PhIO system, only one product was obtained, this was shown to be cotinine. When using TPPMnCl as catalyst with PhIO, the yield of cotinine was substantially increased. Cotinine was also oxidized by model systems. The TPPFeCl model only oxidized cotinine to 3-OH cotinine. When using TPPMnCl model, one further product was obtained. MS and NMR data indicated that it is isomeric with the keto-amide, which has been isolated as a urinary metabolite from Rhesus monkey.[11]

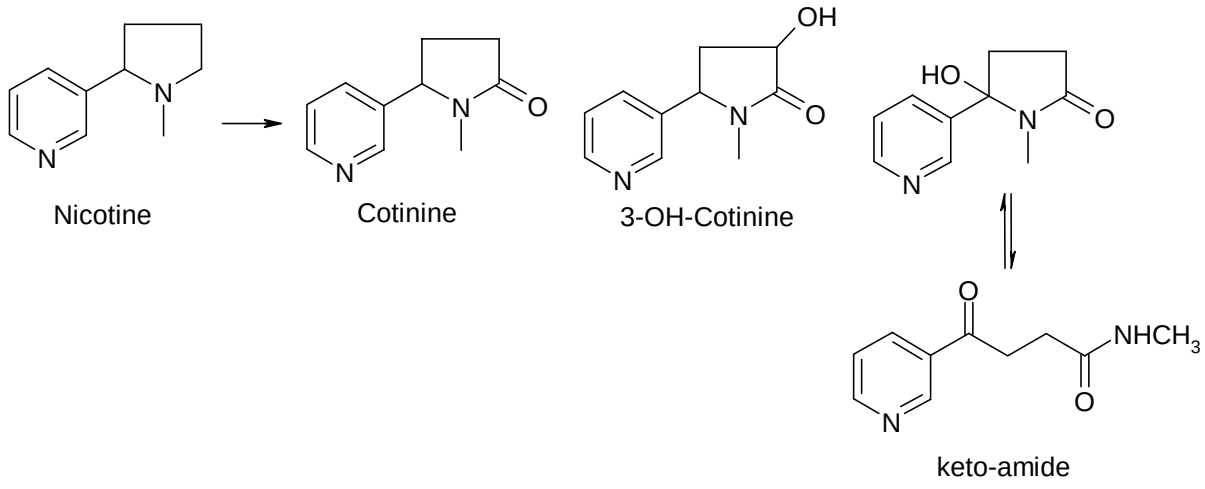


Figure 5

Androgens

The biotransformation of androgens to estrogens is catalyzed in vivo by microsomal cytochrome P450 aromatase.[12] CP450 is responsible for the in vivo oxidation of androst-4-en-3,17-dione to 19-hydroxyandrost-4-en-3,17-dione, androst-4-en-3,17,19-trione and estrone (Figure 6).[13] Oxidation of androst-4-en-3,17-dione by $TCl_8PPFeCl$/ CumOOH gave 19-hydroxyandrost-4-en-

3,17-dione and androst-4-en-3,17,19-trione. The same oxidation when carried out in the presence of *N*-methylimidazole (*N*-MeIm) gave increased amount of 19-hydroxyandrost-4-en-3,17-dione and androst-4-en-3,17,19-trione, furthermore estrone was obtained.

The reaction of $TCl_8PPFeCl$ with CumOOH is essentially slow but can be accelerated in the presence of *N*-MeIm. Firstly, *N*-MeIm axially ligates to the iron atom by displacing the chloride. Secondly, it acts as an acid-base catalyst for the heterolytic cleavage of the O-O bond of the porphyrin-Fe-O-O-Cumyl molecule to form iron(IV)-oxo intermediates.[14]

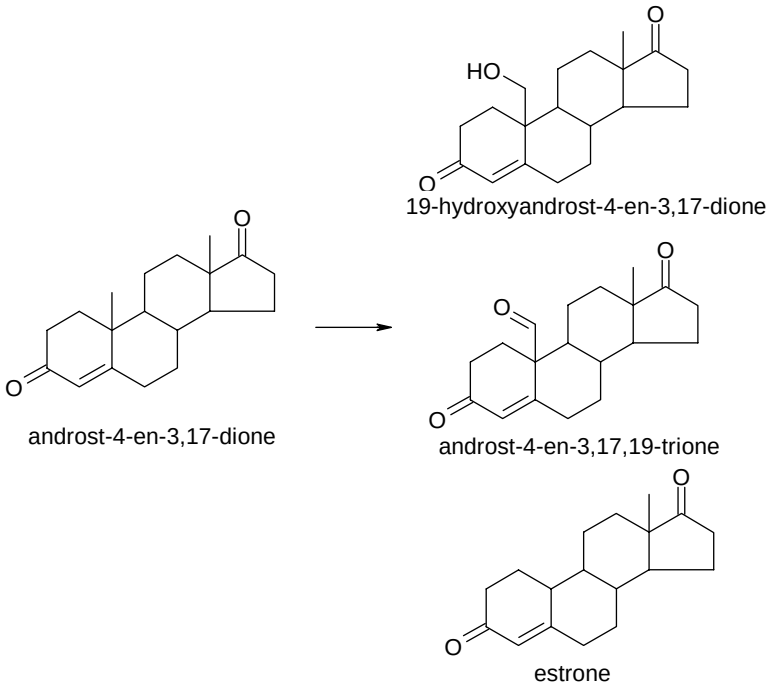


Figure 6

Acetaminophen (an analgesic and antipyretic drug)
N-acetyl-p-quinone-imine (NAPQI), the electrophilic metabolite of acetaminophen responsible for hepatic necrosis and renal damage, is believed to be an enzymatic oxidation product involving cytochrome P450 or/and systems like peroxidase or prostaglandin synthase.[15,16]

As metabolic reactions occur in biologically neutral aqueous medium, it could be more interesting to develop model systems active in physiological conditions. Therefore water-soluble metalloporphyrins and water-soluble oxygen donor ($KHSO_5$) were chosen for model reaction. Four water-soluble metalloporphyrins were tested: they were cationic (TMPyP) or anionic (TSPP) and metallated either by Mn or Fe. The nature of oxidation products of model reaction depends on the time and on the pH of reactions. TPPFeCl appeared as the most efficient catalytic system between pH7 and pH5; decreased activity at pH7 might be attribute to the generation of inactive μ-oxo iron porphyrin dimmers. The TPPMnCl was far less active, and the pH effect was opposite. TMPyPMn was more efficient at pH7, and the iron derivative more active at pH5. In

early step of the oxidation, the conversion of acetaminophen to NAPQI is apparently quantitative; then the polymerization process occur, giving nonstoichiometric amounts of NAPQI, 1,4-benzoquinone-monoimine (PQI), 1,4-benzoquinone (BQ) (Fig. 7.).[17]

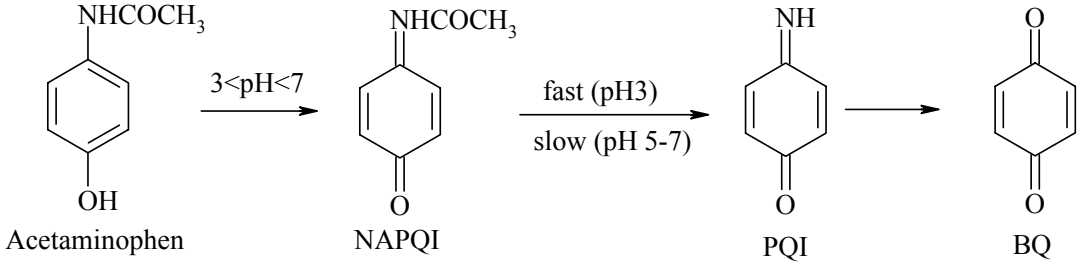


Figure 7

Tiagabine ((R)-1-(4,4-bis(3-methyl-2-thienyl)-3-butenyl)-3-piperidinecarboxylic acid hydrochloride, an anticonvulsant)

The major in vivo metabolite of tiagabine in human is 5-oxo-tiagabine, which is formed by oxidation in one of the thiophene rings of tiagabine (Figure 8).[18] The central double bond in tiagabine is hindered and relatively inert to epoxidation under a wide variety of reaction conditions. Treatment with H_2O_2, NaOCl or mCPBA did not yield significant amount of epoxide. The $TCl_8\beta Br_8PPFeCl$ and perfluoro TPPFeCl/NaOCl, H_2O_2 systems were very effective in achieving oxidation of the thiophene ring. This method is amenable to large scale synthesis of the major human metabolite of tiagabine.[19]

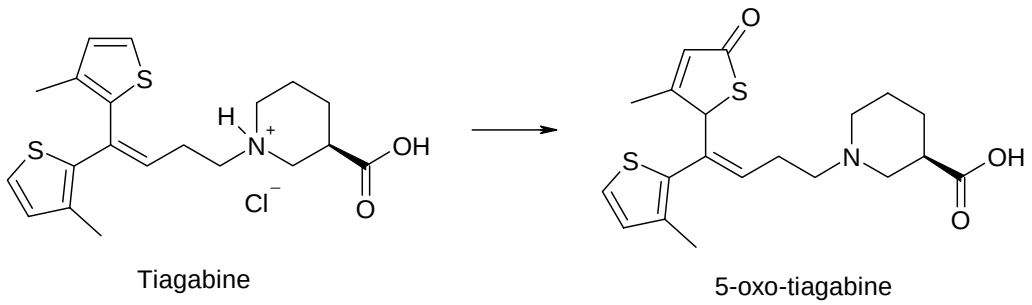


Figure 8

Lidocaine (a local anesthetic and antiarhytmic drug)

Its metabolism in human involves the oxidation of three parts of the molecule by three P450 isoenzymes: (i) an oxidative *N*-deethylation catalyzed by P450s of the 3A subfamily, which lead to corresponding secondary amine **1** and, sometimes, to metabolite **4** derived from reaction of **1** and acetaldehyde;[20,21] (ii) a hydroxylation of a benzylic methyl group, catalyzed by P450s of the 2B subfamily, with formation of the benzylic alcohol **2**;[22] and (iii) a hydroxylation of the

aromatic ring of lidocaine, mainly catalyzed by P450s of the 1A subfamily, leading to phenol **3** (Figure 9).[21]

The oxidation of lidocaine was carried out with various metalloporphyrin model systems $TCl_8PPMnCl$, $TC_8PPFeCl$, $TCl_8SPPMnCl$/ H_2O_2, PhIO, magnesium monoperoxyphthalate (MMP). Most model system oxidize lidocaine at its tertiary amine function which is very reactive towards the electrophilic metal-oxo active species. Model systems also give products from: (i) further oxidation of **1**; and (ii) combination of **1** with CH_3CHO and other electrophilic products derived from the oxidation of **1**. Oxidation of lidocaine at sites other than its amine function was obtained by performing the reaction in water at acidic pH with an oxidant and a stable Mn porphyrin soluble in water. These conditions lead to the formation of benzylic alcohol **2**. Metabolite **3** was never detected in biomimetic reactions. Finally, using metalloporphyrin model systems, metabolites **4**, **1** and **2** were prepared in relatively large amounts, which were sufficient to establish their structure. These systems are versatile and may be used in organic solvent and water. A proper choice of their components led to conditions of selective formation of **1**,**4**,**5** or **2**.[23]

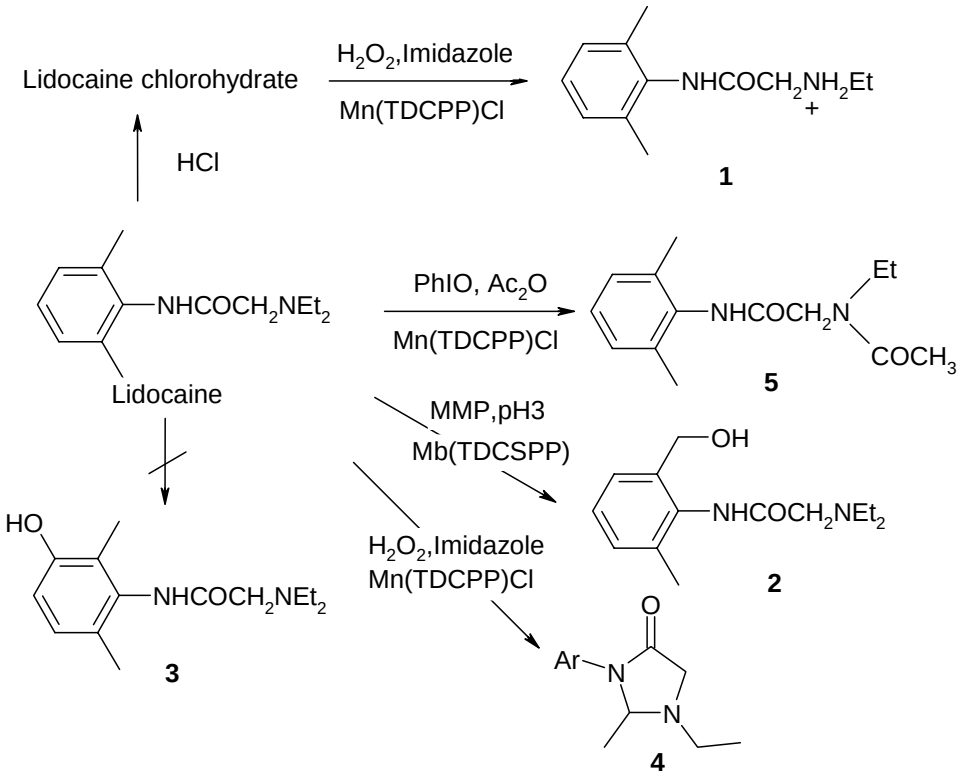


Figure 9

Odapipam (a dopamine D-1 receptor antagonist)

Four in vitro metabolites of odapipam were isolated from rat liver microsomes; *N*-desmethyl-odapipam, 1-hydroxy-odapipam and two isomers of 3'-hydroxy-odapipam.[24]

Oxidation of odapipam was carried out with $TF_{20}PPFeCl$. Cumene hydroperoxide was used as the source of exogenous oxygen. Products of model reaction were revealed complete identity with authentic reference samples of the major metabolites of odapipam previously isolated from urine of rats or characterized from rat liver microsomal incubations.[25]

The model reaction has been used to achieved *N*-demethylation, aliphatic hydroxylation and *N*-oxidation on odapipam (Figure 10).[26]

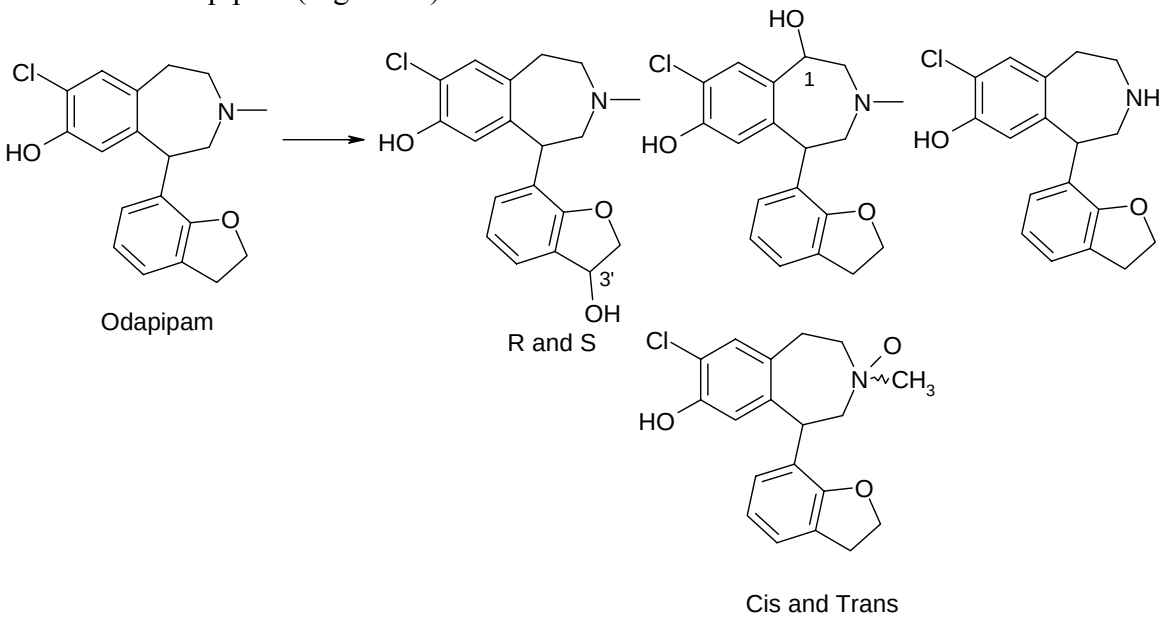


Figure 10

Aminopyrine

The major oxidative metabolites of aminopyrine in human are *N*-formyl-aminopyrine, aminopyrine and *N*-methylaminopyrine.[27]

Oxidation of aminopyrine was carried out with $TCl_8\beta Cl_8PPFe(SO_3H)_4$. PhIO was used as the source of exogenous oxygen. Products of model reaction revealed complete identity with authentic reference samples of the major metabolites of aminopyrine previously isolated from urine of rats or characterized from rat liver microsomal incubations. The model reaction has been used to achieved *N*-demethylation, aliphatic and aromatic hydroxylation and *N*-oxidation on aminopyrine (Figure 11).[28]

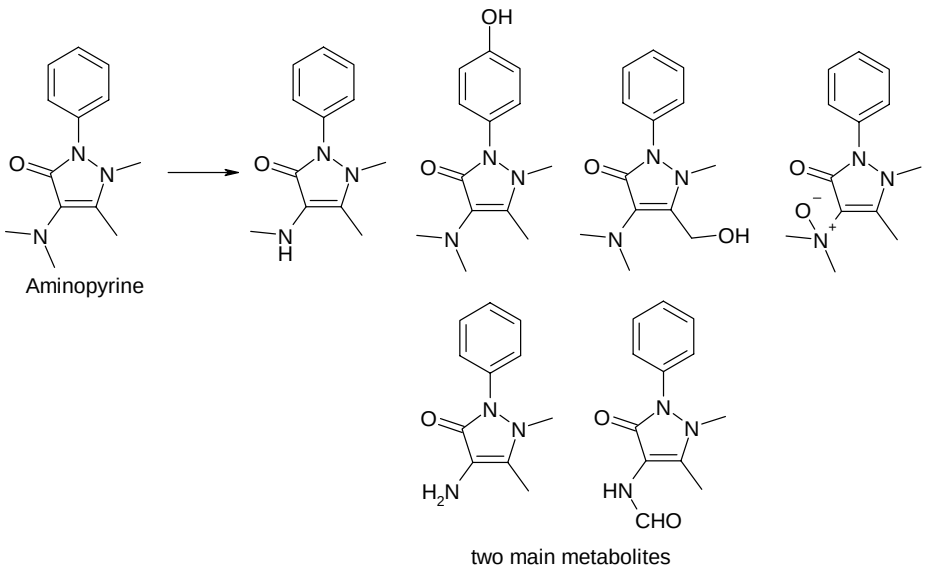


Figure 11

OPC-31260 (a vasopressin V2 receptor antagonist)

The *N*,*N*-dimethylalkylamine *N*-oxide **6** was efficiently demethylated using two kind of metalloporphyrins TPPFeCl, TPPMnCl with additives (imidazole, 1,2,4-triazole, tetrazole) to afford the corresponding secondary amine **7** which had been proposed as one of the metabolites of OPC-31260, in the rat, dog and human.[29] The study demonstrated the simple preparation method for secondary amine in high yield from the corresponding *N*,*N*-dimethylalkylamine *N*-oxide (Figure 12).[30]

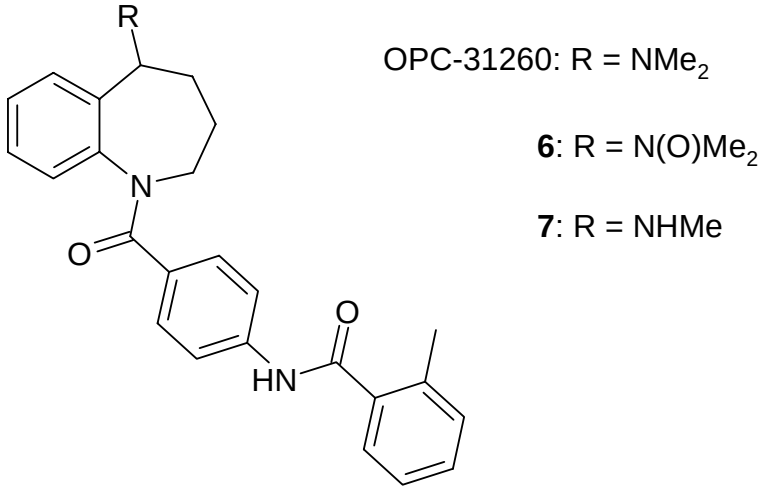


Figure 12

Denaverine hydrochloride (a spasmolytic drug)

Eleven metabolites of denaverine hydrochloride has been observed in rat studies. The identified metabolites are cleavage products of the ester and ether bond (**11**), of the oxidative N-demethylation (**9**), of cleavage of the ether bond and a further ring closure giving **12** of reductive cleavage of the ether bond resulting in **13** and **14**, and of transesterifications generating ethyl benzylate, methyl and ethyl *O*-(2-ethylbutyl)bezilate. The main metabolites are **11** and **12** (Figure 13).[31]

Different metalloprophyrins were used in non-aqueous $TF_{20}PPMnCl$, $TF_{20}PPFeCl$ and aqueous ($TF_8SPPMnCl$, $TF_8SPPFeCl$) medium in combination with imidazole or pyridine as co-catalysts. Iodosylbenzene was used to compare reaction profile with that of hydrogen peroxide. In the biomimetic systems **11** and its methyl ester were only found in small quantities. This proves the possibility of *O*-dealkylations with the biomimetic method, but the cleavage of the ether bond is clearly not favoured. The absence of **13** and **14** in the biomimetic reactions are not surprising, because they are products of reductive transformations. Another metabolite **9**, discovered in rat and human, was also found in moderate yields. Furthermore, **8** and its methyl ester **10** were obtained in biomimetic studies. From metabolism in rat only **10** and the ethyl ester of **8** are known.

Less than 1% of the applied dose of denaverine hydrochloride could be detected in metabolism studies in human. Besides unchanged denaverine hydrochloride, compounds **9** and **11** were detected. They are generated in chemical model systems, too.[32]

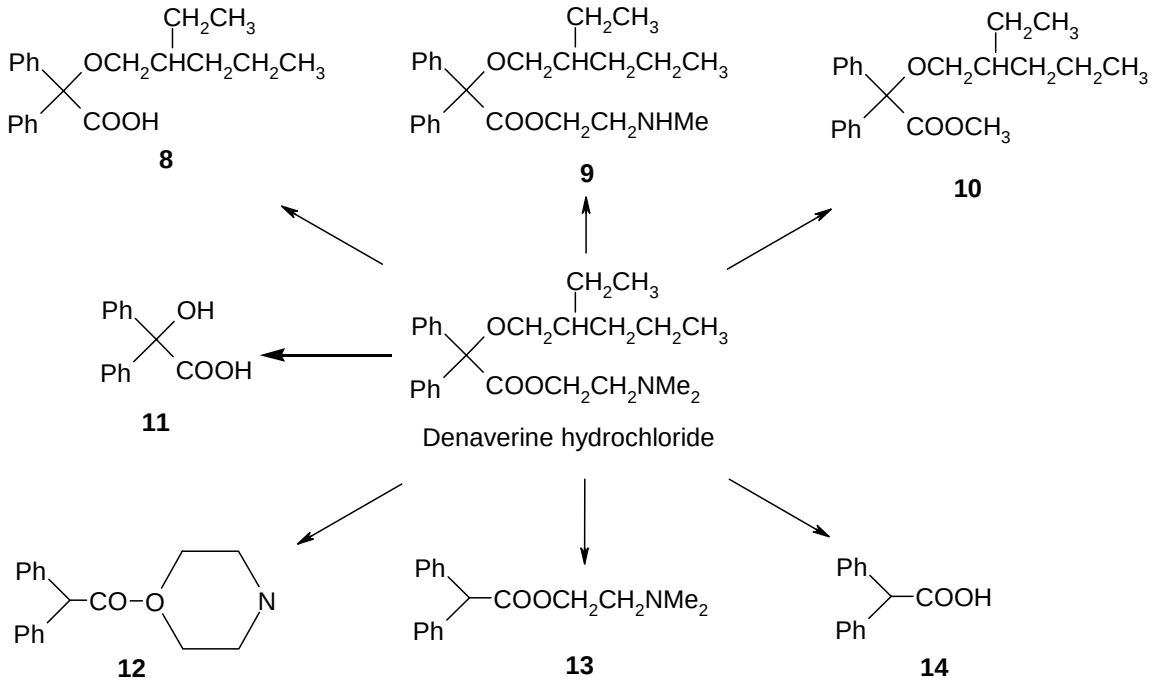


Figure 13

Diclofenac (an anti-inflammatory drug)

Metabolism of diclofenac in man leads to two hydroxylated products. The major metabolite results from 4′-hydroxylation of diclofenac, which catalyzed by cytochrome P450 2C9.[33] The minor metabolite results from 5-hydroxylation of the most electron-rich aromatic ring of the drug, which is catalyzed by several cytochromes P450, including 3A4, 2C8 and 2C19 (Figure 14).[34]

Oxidation of diclofenac was carried out with two kind of metalloporphyrins $TCl_8PPMnCl$ and $TCl_8PPFeCl$) in combination with CH_3COONH_4 as co-catalysts. H_2O_2 or t-BuOOH were used as the source of exogenous oxygen.

Results showed that the electrophilic species derived from reaction of iron porphyrin with oxygen atom donors regioselectively oxidize diclofenac at position 5. This is not surprising, as position 5 is para to an NH substituent on the more electron-rich aromatic ring of diclofenac and should be the most reactive one towards oxidants. The mechanism of formation of quinone-imine could either involve a *N*-oxidation of diclofenac with appearance of a cationic or radical species at position 5 within a quinone-imine type species and transfer of an OH group at this position, or direct 5–hydroxylation by an iron-oxo intermediate. Treatment of quinone-imine with a reducing agent such as sodium borohydride quantitatively led to 5-OH-diclofenac. The exclusive formation of quinone-imine in the TCl_8PP(Mn or Fe)Cl-tBuOOH systems and the appearance of small amounts of 4′-OH-diclofenac in the $TCl_8PPMnCl$-H_2O_2 system would indicate that different active species and mechanisms are involved in the two systems.[35]

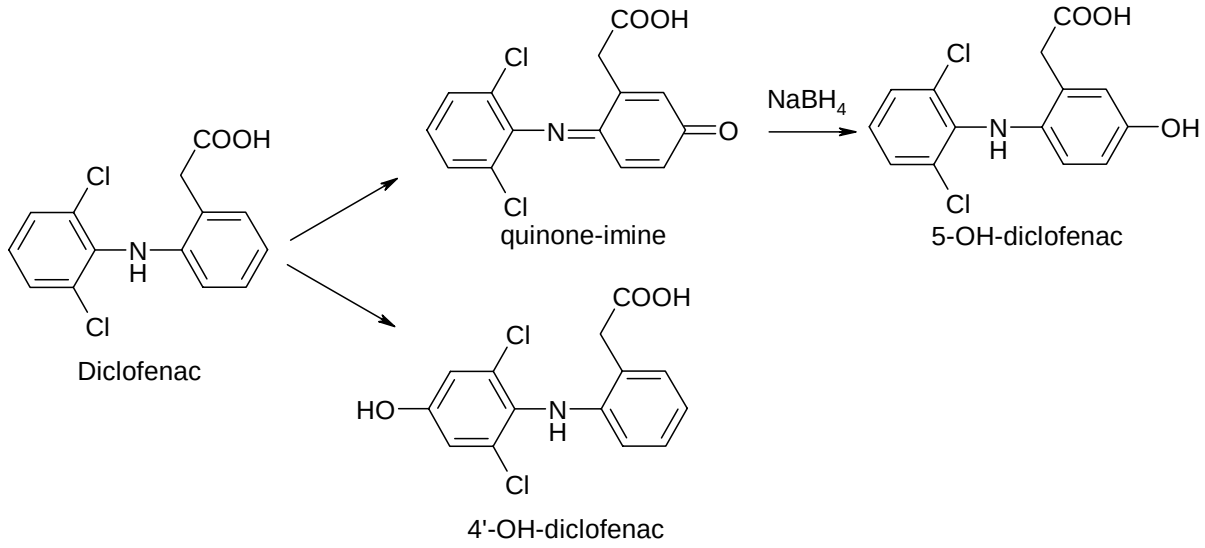


Figure 14

Etodolac (an anti-inflammatory agent)

The major primary oxidative metabolites of etodolac in man are 6-hydroxyetodolac, 7-hydroxyetodolac and 8-(1′-hydroxy)etodolac, whereas the major metabolite in rat is 4-oxoetodolac (Figure 15).[36]

The biomimetic oxidation of etodolac was studied with halogenated and perhalogenated iron(III) porphyrins in combination with *N*-methylimidazole as co-catalysts. Iodosylbenzene was used as the source of exogenous oxygen. The $TCl_8PPFeCl$ and TPPFeCl catalyzed reaction of etodolac catalyzed by gave 4-hydroxyetodolac and 4-oxoetodolac. In the presence of perhalogenated metalloporhyrins like $TF_{20}PPFeCl$ and $TCl_8\beta Cl_8PPFeCl$ and $TCl_8\beta Br_8PPFeCl$ the oxidation gave the increased amount of 4-hydroxy- and 4-oxoetodolac. Further the presence of strongly coordinating axial ligands like *N*-methylimidazole increased the yield of these metabolites. Although the aromatic ring hydroxylated and 8-ethyl hydroxylated metabolites are known but the pyrano ring hydroxylated metabolite, 4-hydroxyetodolac is not detected in the metabolism of etodolac in human or rat. The formation of 4-hydroxyetodolac may be explained by abstraction of hydrogen radical from the allylic 4-position of etodolac by the high valent oxo-iron(IV) porphyrins and subsequent recombination of etodolac radical with the hydroxyl radical or hydroxyl-iron(III) porphyrin present in the reaction medium ("oxygen rebound"). Further formation of 4-oxoetodolac can also be explained as over-oxidation of 4-hydroxyetodolac.[37]

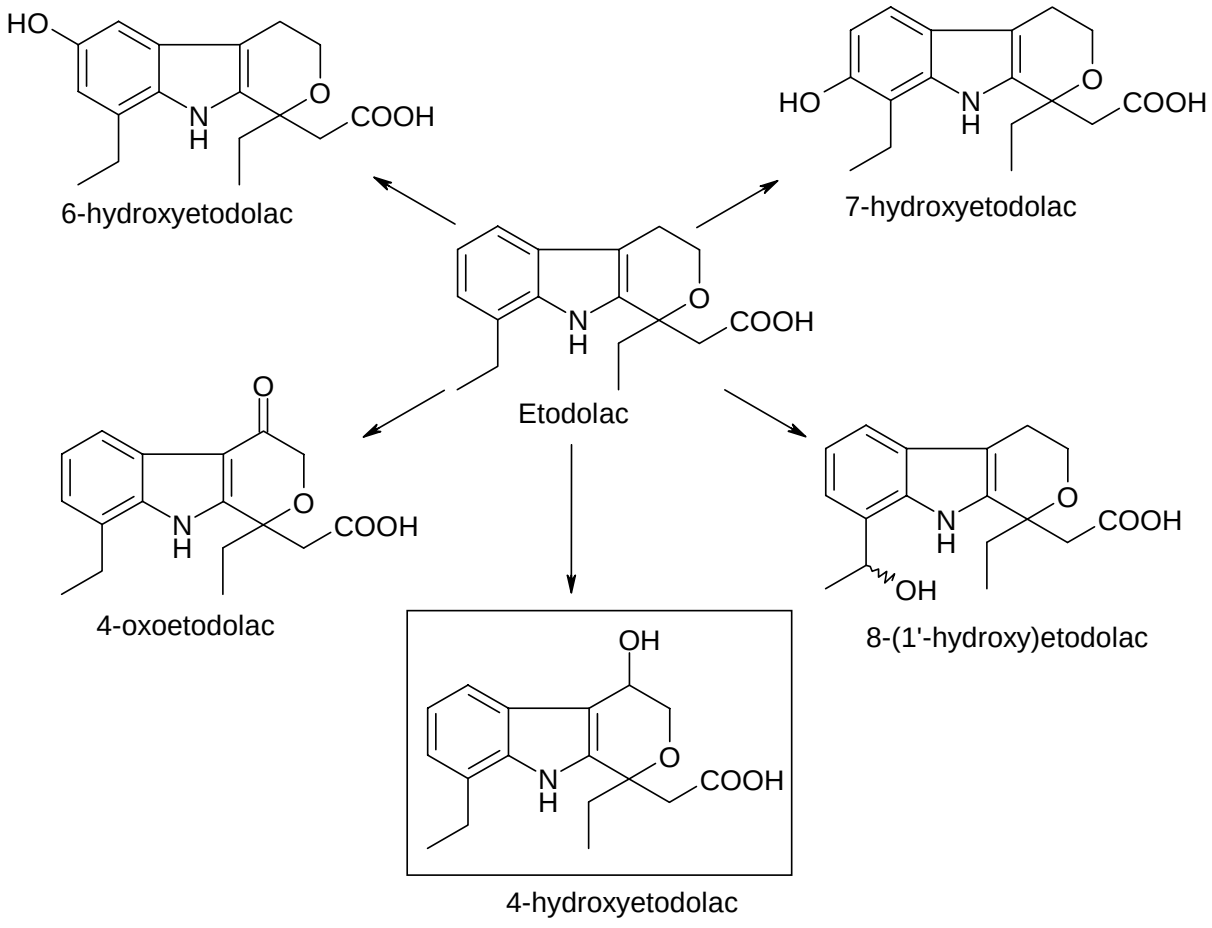


Figure 15

Carbofuran (an insecticide)

On the basis of radiolabeling studies, the major metabolite of carbofuran was identified as 3-hydroxycarbofuran, along with *N*-hydroxymethyl and 7-hydroxy analogues as minor components These compounds can be further transformed to the corresponding 3-keto, 3,7-dihydroxy, and 3-keto-7-hydroxy metabolites before conjugation and excretion (Figure 16).[38]

Biomimetic oxidation of carbofuran was firstly carried out using mCPBA, NaOCl, and H_2O_2 in the presence of $TCl_8PPFeCl$. Comparing the results with the metabolite profile measured in houseflies (*Musca domestica*), we found that in contrast to in vivo experiments, hydrolysis of carbamate side chain took place in all systems. In the case of NaOCl, due to the alkaline medium, this hydrolysis became dominant. In addition to the main product (3-keto-7-hydroxy-carbofuran) oxidation at the C3 center yielded the 3-keto metabolite as well. Oxidations associated with the simultaneous hydrolysis of the carbamate group led to the formation of products (3,7-hydroxy and 3-keto-*N*-hydroxymethyl) derived by multistep transformations.

Oxidation catalyzed by the most popular $TF_{20}PPFeCl$ were carried out to improve the performance of our model. Use of mCPBA as oxidant resulted in the almost selective formation of 3-keto-*N*-hydroxymethyl metabolite. Oxidation with H_2O_2, however, reproduced rather well the in vivo profile. Increased resistance of $TF_{20}PPFeCl$ against oxidative degradation may be responsible for differences between product distributions observed in $TCl_8PPFeCl$- and $TF_{20}PPFeCl$-catalyzed reactions.[39]

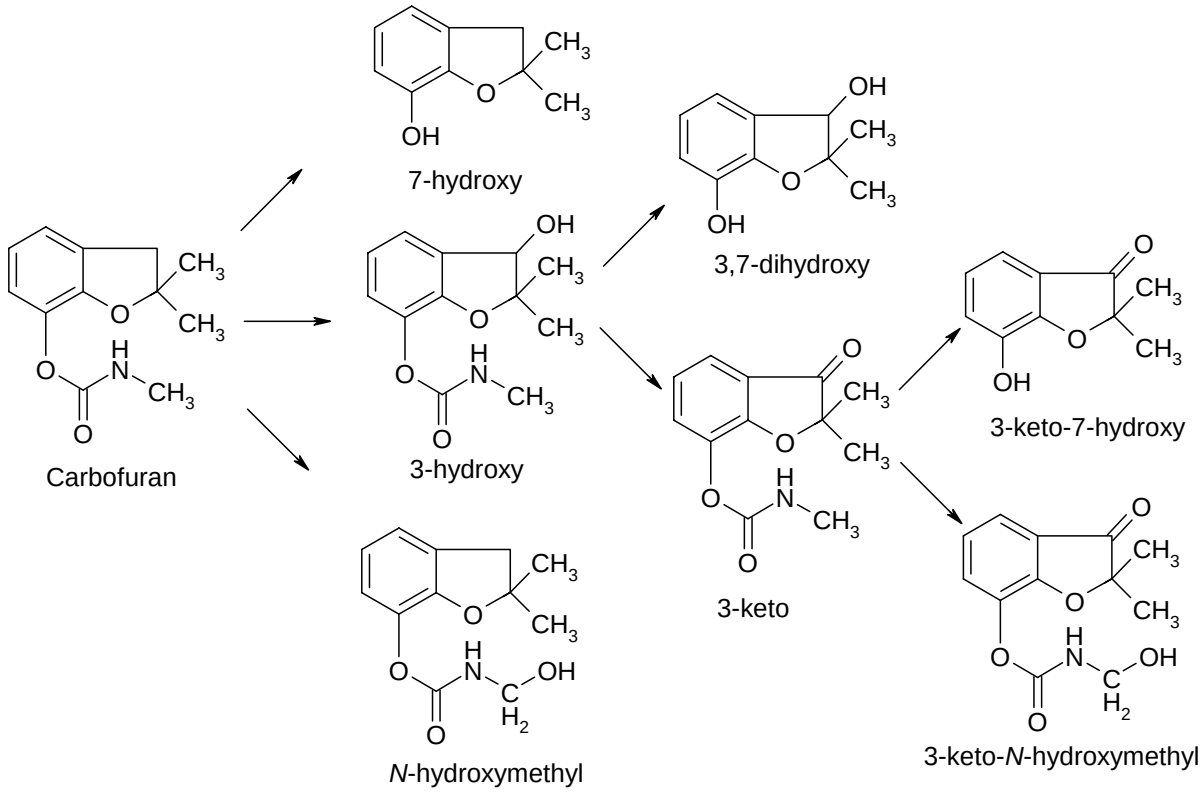


Figure 16

Examples collected to this review nicely demonstrate the usefulness of metalloporphyrin-based chemical models in metabolic studies. On the basis of literature data, as well as own experience we conclude that biomimetic oxidations can be considered a powerful medicinal chemistry tools when supporting pharmacokinetic studies.

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