Archives of Toxicology (2022) 96:2145–2246
https://doi.org/10.1007/s00204-022-03304-3

REVIEW ARTICLE

Roles of selected non-P450 human oxidoreductase enzymes in protective and toxic effects of chemicals: review and compilation of reactions

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Received: 25 March 2022 / Accepted: 26 April 2022 / Published online: 1 June 2022

Abstract
This is an overview of the metabolic reactions of drugs, natural products, physiological compounds, and other (general) chemicals catalyzed by flavin monooxygenase (FMO), monoamine oxidase (MAO), NAD(P)H quinone oxidoreductase (NQO), and molybdenum hydroxylase enzymes (aldehyde oxidase (AOX) and xanthine oxidoreductase (XOR)), including roles as substrates, inducers, and inhibitors of the enzymes. The metabolism and bioactivation of selected examples of each group (i.e., drugs, "general chemicals," natural products, and physiological compounds) are discussed. We identified a higher fraction of bioactivation reactions for FMO enzymes compared to other enzymes, predominately involving drugs and general chemicals. With MAO enzymes, physiological compounds predominate as substrates, and some products lead to unwanted side effects or illness. AOX and XOR enzymes are molybdenum hydroxylases that catalyze the oxidation of various heteroaromatic rings and aldehydes and the reduction of a number of different functional groups. While neither of these two enzymes contributes substantially to the metabolism of currently marketed drugs, AOX has become a frequently encountered route of metabolism among drug discovery programs in the past 10–15 years. XOR has even less of a role in the metabolism of clinical drugs and preclinical drug candidates than AOX, likely due to narrower substrate specificity.

Keywords Flavin-containing monooxygenase · Monoamine oxidase · NAD(P)H quinone oxidoreductase · Molybdenum hydroxylases · Xenobiotics · Natural products · Bioactivation

Introduction

In our previous reports, we analyzed the properties and participation of human enzymes in the metabolism of physiological and xenobiotic compounds, including natural products (Rendić and Guengerich 2012, 2015, 2021). The analysis showed an overwhelming participation of the cytochrome P450 (P450, CYP) enzymes (~95%) in the metabolism of the compounds. P450 enzymes catalyze a great number of metabolic reactions and have important effects on the biological activities (physiologic, therapeutic, and/or toxic) of xenobiotics such as drugs, natural products, "general chemicals" (e.g., pesticides, pro-carcinogens, various environmental chemicals), and physiological compounds. In addition to P450s, other enzymes such as microsomal flavin-containing monooxygenase (FMO), monoamine oxidase (MAO), and aldehyde oxidase (AOX) enzymes participate in the metabolism of these compounds, although to a lower extent (~2%, 1%, and 2%, respectively). Other oxidoreductase enzymes participate to an extent of < 1% (Rendić and Guengerich 2012, 2015). The mechanism, kinetics, and metabolic properties of P450 enzymes (Guengerich 2022) and oxidative metabolism, and the gene regulation of non-cytochrome P450 enzymes have been discussed recently (Pang et al. 2022). In the present paper, we discuss mechanisms and metabolic properties of human FMO, MAO, NAD(P)H quinone oxidoreductase (NQO), molybdenum-containing hydroxylases (AOX and xanthine oxidoreductase (XOR) enzymes) in the oxidation of drugs, physiological and natural products, and other (general) chemicals as substrates and inhibitors of these enzymes, in

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the context of their participation in the metabolism of the compounds and also possible toxic effects that might result from oxidation and reduction reactions.

The review is divided into four parts, addressing these four sets of enzymes. Only the human enzymes are discussed and data are only presented for these. The experimental data are presented in tables, and the published kinetic values were categorized according to the values and effects presented in Table 1.

Results and discussion

Flavin-containing monooxygenase (FMO)

As reported previously, FMOs participate in ~ 2% of reactions involved in the metabolism of xenobiotics, natural products, and physiological compounds (Rendić and Guengerich 2015). There is a higher fraction of FMO enzymes involved in the metabolism of general chemicals when compared to the metabolism of drugs, natural products, or physiological compounds. The reactions catalyzed by FMO enzymes are predominately detoxication reactions and include N-, S-, P-, and Se-atom oxygenations, depending on the substrate structure (Table 2).

In some cases, FMOs are involved in the activation of substrates to toxic products. When calculating the participation of FMO enzymes in activation reactions, we found that FMOs participate in ~ 1% in the reactions, catalyzed predominately by FMO1 and FMO3 and related to the formation of *N*- or *S*-oxides. These results show equal participation of FMO enzymes in detoxication reactions and the formation of potentially toxic products. For comparison, P450 enzymes participate in ~ 66% of reactions involving the formation of toxic products and in 95% of the overall oxidations and reductions of xenobiotics and natural products (Rendić and Guengerich 2012, 2015).

Enzymes

In the literature, different terminology has been used for these enzymes: FMO(s), FAD-containing amine oxidases, microsomal oxygenases containing flavin, and

Table 1 Values and limits used for evaluation of kinetic data*

Inhibition, IC_{50} (K_i), μM	Very weak inhibition	> 100
	Weak inhibition	> 30
	Intermediate inhibition	1–30
	Strong inhibition	< 1
	Very strong inhibition	< 0.010
Percent inhibition, %	Very strong inhibition	≥ 99
	Strong inhibition	> 90
	Intermediate inhibition	50–90
	Weak inhibition	20–50
	Very weak	10–20
	No inhibition or very weak inhibition	< 10
Percent of control activity, %	Very strong inhibition	< 1
	Strong inhibition	< 10
	Intermediate inhibition	10–50
	Weak inhibition	50–80
	Very weak inhibition	80–90
	No inhibition or very weak inhibition	> 90
K_m, μM	High K_m	> 50
	Intermediate K_m	2–50
	Low K_m	< 2
Efficiency (specificity constant), k_{cat}/K_m, min^{-1} uM^{-1}	Low efficiency	< 0.02
	Intermediate efficiency	0.02–2
	High efficiency	> 2
V_{max}, mmol/min/mg protein	High (activity)	> 5
	Intermediate (activity)	1–5
	Low (activity)	< 1
	Very low (activity)	< 0.01

*Adapted from FDA guidance document (Food and Drug Administration 2021) (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

Table 2 Examples of substrates, products, and reactions catalyzed by FMO enzymes

N-oxygenations substrates (products)	*S*-oxygenations substrates (products)	*Se*-oxygenations substrates (products)	*P*-oxygenations substrates (products)
Hydroxylamines (nitrones)	Aminothiol (sulfinate)	Selenides, Se conjugates (Se-oxygenated)	Phosphines (*P*-oxides)
Secondary amines (hydroxylamines)	Disulfides (thiosulfinate)		
Imine and arylamines (*N*-oxides)	Thioamides (sulfoxides, sulfones)		
Hydrazines (*N*-hydroxy hydrazine)	Thiocarbamates (sulfines)		
Primary amines (hydroxylamines and oximes)	Thiocarbamides (sulfoxides, sulfones)		
Tertiary amines (*N*-oxides)	Thioethers (*S*-oxides)		
	Thiols, thioketones (*S*-oxides)		
	Sulfide (sulfoxides)		
	Sulfoxide (sulfones)		

mixed-function microsomal amine oxidases. The enzyme was discovered by the late Prof. Daniel Ziegler, who worked with the enzyme from swine, and frequently scientists simply referred to this as "Ziegler's Enzyme" for many years (Pettit et al. 1964; Ziegler 1988, 2002; Ziegler and Pettit 1966). The enzymes are found in the endoplasmic reticulum of most organs and tissues, predominately in the liver and in the lungs, kidneys, digestive tract, brain, and others (Dannan and Guengerich 1982).

The human FMO enzymes are characterized by the following features: FMO enzymes contain 1 mol FAD/mol enzyme, $M_r \sim 65$ kDa, and about 535 amino acids. In humans, 11 FMO genes have been identified, encoding five active FMOs (FMO1–5) and six pseudogenes. FMOs are differentially distributed in organs, and the amino acid sequences of the orthologous forms of the enzymes in different animal species are 80–90% similar (Cashman 2004; Henderson et al. 2014; Hines 2006; Huang et al. 2021; Koukouritaki et al. 2002; Krueger et al. 2009; Nagashima et al. 2009; Phillips and Shephard 2017, 2020; Shimizu et al. 2011, 2015; Ziegler 1988).

The most frequently represented reactions catalyzed by FMO enzymes are *N*- and *S*-oxygenations (Elfarra 1995; Furnes and Schlenk 2004; Krause et al. 2003), although some oxygenations are known for phosphorus and selenium atoms (Hodgson and Levi 1992; Jones et al. 2017; Rooseboom et al. 2001) (Table 2).

FMO1 is the major form expressed in the neonatal liver and kidneys and small intestine of adults. FMO2 is the most abundant in human lungs and is expressed in the liver and kidneys at a minor level. The non-functional variant FMO2*2 is predominant in humans, but in some ethnic groups that have been studied (Afro- and Hispanic-Americans) the variant FMO2*1 is present (Krueger et al. 2005). The developmental expression pattern for human hepatic FMO1 and FMO3 shows that relatively high levels of FMO1 expression are observed throughout prenatal development, in particular during the embryonic period, but FMO3 is essentially absent in the fetal liver. In the human liver, FMO3 is the most abundant enzyme and predominantly oxidizes tertiary amines, including a large number of clinically important drugs and amines ingested in food. FMO3 is a highly polymorphic enzyme, and polymorphism is related to a rare hereditary disorder of the inability to metabolize trimethylamine (a disorder called trimethylaminuria) (Phillips et al. 1995). FMO3 enzymes have been associated with some clinically relevant drug–drug or drug–chemical interactions because a large number of clinically important drugs (as well as natural products, e.g., indoles, tyramine, trimethylamine) possess amine structures. FMO4 is present at a low level in multiple tissues (e.g., liver, kidneys, brain). FMO5 is highly expressed in the adult human liver.

There are significant differences between individuals and ethnic groups in both expression and functional activity. Genetic polymorphism in the human *FMO* genes (in major part associated with the *FMO3* gene) may lead to changes in *N*- and/or *S*-oxygenations of drugs, xenobiotics, and endogenous substances.

Following the P450s (Rendić 2002; Rendić and Di Carlo 1997), FMOs are the most important enzymes involved in the monooxygenation of amine-containing xenobiotics or amines that are formed during the biotransformation of drugs, general chemicals, natural products, and physiological compounds (Rendić and Guengerich 2015). Reactions catalyzed by FMO enzymes have been generally considered as detoxications but there are exceptions to this rule. All FMO enzymes possess the structural features by which FAD and NADPH are bound. Important endogenous roles for the FMO family have been suggested, including the regulation of cellular stress resistance and major cellular metabolic activities that involve central carbon metabolism (Huang et al. 2021; Krueger and Williams 2005).

Typical substrates include aliphatic, basic amines and some aromatic primary amines, secondary amines, tertiary amines, *N*-arylamides, heteroaromatic amines, hydroxylamines, and hydramines (e.g., metamizole, *N*,*N*-dimethylaniline). Substrates of FMOs (e.g., *N*-alkyl arylamines including *N*-methylaniline and *N*,*N*-dimethylaniline) can be substrates for both FMO and P450 enzymes, depending on the structural and electronic properties of substituents and basicity of the amines. FMO enzymes predominantly catalyze *N*-oxidation of most of the cyclic and acyclic secondary amines (Hanson et al. 2010) (Tables 3, 4, 5), while P450s tend to catalyze *N*-dealkylation reactions because of the chemical mechanisms involved (Seto and Guengerich 1993).`

FAD, NADPH, and O_2 are required for the FMO catalyzed reactions, but the FAD is tightly bound to the enzyme and does not need to be added (i.e., acts as a prosthetic group instead of a cofactor (Dixon and Webb 1964)). Of the human FMO enzymes, FMO3 is the prominent enzyme that converts nucleophilic heteroatom-containing chemicals, drugs, and xenobiotics to more polar materials, which are generally more efficiently excreted in the urine. The substrate specificity for FMO3 is distinct from that of FMO1. Of the five FMO families, FMO1 and FMO3 are the most prevalent in drug metabolism in humans (Fig. 1, Table 3). A similar participation pattern of the enzymes was found for general chemicals (Table 4). For natural products and physiological compounds, the most prominent enzymes were FMO3 and FMO1, followed by FMO2 and FMO4, with low participation of FMO5 (Table 5).

In general, FMO enzymes have not been reported to be very inducible. However, induction of FMO4 and FMO5 cDNA has been reported in human hepatocytes by the drug rifampicin (Rae et al. 2001), and the tricyclic antidepressants imipramine and chlorpromazine were reported to upregulate recombinant FMO3 catalyzed methimazole *S*-oxidation in a concentration-dependent manner (Adali et al. 1998, 1999; Cherrington et al. 1998) (Table 3). In addition, FMO5 mRNA was upregulated in HepG2 cells by the natural product (herbal medicine) St. John's wort and its active component hyperforin, as well as by the synthetic progestin R5020 in a breast cancer cell line that stably expresses B-receptors (YB cells) (Miller et al. 1997).

Inhibition of FMO3 was reported by dietary indoles such as indole-3-carbinol (contained in Brussels sprouts (Cashman et al. 1999a)) and decreased expression and activity of FMO3 was observed for endogenously formed nitric oxide (Ryu et al. 2004) (Table 6).

The potential for adverse reactions due to drug–drug interactions is less likely for drugs predominately metabolized by FMO than for P450 enzymes. However, physiological factors can influence FMO function, and this may have clinical implications (Cashman and Zhang 2006; Ryu et al. 2004). For instance, in the case of mammalian FMO3, which does not appear to be very inducible (vide supra), inter-individual variations in FMO3-dependent metabolism of drugs, other chemicals, and endogenous compounds are more likely to be caused by genetic and ethnic polymorphisms (Cashman 2002b; Cashman et al. 2000; Cashman and Zhang 2002; Hisamuddin and Yang 2007). However, human FMO enzymes can activate drugs (e.g., antibiotics, antibacterial, antitubercular, CNS stimulants), natural products, and general chemicals to toxic products, resulting in adverse reactions (Table 7).

Reactions

Human FMO3 *N*-oxygenates primary, secondary, and tertiary amines but only human FMO1 is highly efficient at *N*-oxygenating tertiary amines. Both human FMO1 and FMO3 *S*-oxygenate many nucleophilic sulfur-containing substrates, and in some cases, reactions proceed with high stereoselectivity (Cashman 2000).

N-oxygenations

The *N*-oxygenation reactions of primary amines catalyzed by FMO enzymes, which occur without splitting the C–N bond, can result in the formation of toxic nitroso compounds. The reaction usually creates potentially toxic hydroxylamines in the first step, which can be further oxidized into oxime and nitroso compounds (Fig. 2) (e.g., sulfamethoxazole and amphetamine *N*-oxidation). *N*-Oxygenations of secondary amines, e.g., cyclic and acyclic secondary amines, are catalyzed by FMO enzymes, and those of *N*-alkyl- and *N*-aryl amines are generally catalyzed by both FMO and P450 enzymes (e.g., *N*-methylamphetamine, Tables 3, 7).

S-oxygenations

Compounds containing a sulfur atom as a part of the structure are present in physiological compounds such as amino acids and derivatives (e.g., cysteine, methionine, glutathione), lipids, and enzyme cofactors (e.g., biotin, thioredoxin, lipoic acid, coenzyme A) and in natural products (e.g., the toxin amanitin and various compounds isolated from onions, radishes, and watercress). The characteristic odor and healing properties of plants of the genus Allium are attributed to sulfur-containing compounds. A number of drugs and general chemicals (e.g., solvents, insecticides) are substrates for *S*-oxygenation.

S-Oxygenation reactions (Fig. 3) occur by mechanisms similar to *N*-oxygenation (vide infra), catalyzed by FMO enzymes (also called sulfoxidases). In addition, P450s may be involved (Rendić 2002). Substrates in these reactions include thiocarbamides, thiones, thioamides, sulfides

Table 3 Examples of drugs as substrates in oxygenation reactions catalyzed by human FMO enzymes

Drug	Enzyme*	Atom affected	Comments	PMID numbers	References
ABT-418	FMO3	*N′*-	Stereoselective *N′*-oxidation, substrate for P450 and AOX enzymes	8654204	(Rodrigues et al. 1995)
Albendazole	FMO3	*S*-	Intermediate K_m, sulfoxide and sulfone formation, also catalyzed by multiple P450s	10759686, 30117405, 23959307	(Giri et al. 2018; Rawden et al. 2000; Wu et al. 2013)
Almotriptan	FMO3	*N*-	*N*-Oxide formation, minor reaction in overall metabolism, also substrate for multiple P450 enzymes, MAO A, and ADH enzymes	12642466	(Salva et al. 2003)
Amphetamine	FMO3	*N*-	Hydroxylamine and *trans*:*cis* oxime 5:1 formation, activation to toxic product(s)	10027866	(Cashman et al. 1999b)
Amphetamine hydroxylamine	FMO3	*N*-	Oxime formation through dioxygenated intermediate, stereoselective for the *trans*-oxime formation	10027866	(Cashman et al. 1999b)
Arbidol	**FMO1,** FMO3, FMO5	*S*-	FMOs minor enzymes in overall metabolism, P450 3A4 as the major enzyme	23357765	(Deng et al. 2013)
N-(3*R*)-1-Azabicyclo[2.2.2]oct-3-ylfuro[2,3-*c*]pyridine-5-carboxamide	**FMO1,** FMO3	*N*-	Forms *N*-oxide at the quinuclidine nitrogen, also formed by P450 2D6	17446264, 20642449	(Shaffer et al. 2007; Shilliday et al. 2010)
Benzydamine	FMO1, **FMO3**, FMO4, FMO5	*N*-	High K_m and activity, suggested as test/marker substrate, contribution to microsomal metabolism	11012553, 11136294, 16719388, 17142560, 17531949, 24821112, 25760532, 25760531 28145791, 28784689, 32213186	(Gao and Zheng 2020; Jones et al. 2017; Lang and Rettie 2000; Schlenk et al. 2002; Shimizu et al. 2015; Störmer et al. 2000; Taniguchi-Takizawa et al. 2015; Yamazaki et al. 2014; Yamazaki-Nishioka et al. 2018; Yeung et al. 2007; Yeung and Rettie 2006)
Se-Benzyl-L-seleno-cysteine	**FMO1,** FMO3	*Se*-	k_{cat}/K_m for selenoxidation 3.8-fold higher for FMO1 than for FMO3	11170516	(Rooseboom et al. 2001)
C-1311	FMO1, FMO3	*N*-	Major enzymes	21555506, 21859392	(Fedejko-Kap et al. 2011; Potega et al. 2011)
Cediranib	**FMO1,** FMO3	*N*-	Intermediate K_m for FMO1	20634336	(Schulz-Utermoehl et al. 2010)
Chlorpromazine	**FMO1,** FMO3, FMO4	*N*-	*N*,*S*-Dioxide formation, also substrate for multiple P450s (S-oxidation and *N*-demethylation)	9750169, 10445381	(Adali et al. 1998, 1999)

Table 3 (continued)

Drug	Enzyme*	Atom affected	Comments	PMID numbers	References
Cimetidine	FMO1, **FMO3**	*S*-	Enantioselective for (-)-*S*-oxide FMO1 and for (+)-*S*-oxide FMO3	7720103, 8104117, 9305407, 19283698, 11465082	(Cashman 2000; Cashman et al. 1995, 1993a; Hai et al. 2009; Overby et al. 1997)
Clomiphene	FMO3	*N*-	Intermediate K_m	28137602 32197603, 29959872	(Catucci et al. 2018, 2020, 2017)
Clozapine	FMO3	*N*-	High K_m, minor contribution to microsomal metabolism, also catalyzed by P450s 1A2 and 3A4	9107553, 9840430, 28784689	(Fang et al. 1998; Jones et al. 2017; Tugnait et al. 1997)
Danusertib	FMO3	*N*-	High K_m, intermediate catalytic efficiency	23358255	(Catucci et al. 2013)
Dapsone	FMO1, **FMO3**	*N*-	Arylhydroxylamine formation, activation to toxic metabolite(s)	16857727	(Vyas et al. 2006)
Dasatinib	FMO3	*N*-	Minor enzyme in overall metabolism	18556438, 32197603	(Catucci et al. 2020; Wang et al. 2008)
N,*N*-Dimethylamphetamine	**FMO1,** FMO3	N-	Intermediate K_m, enantioselective for *L*- *N*-oxide formation (FMO1)	19552509, 23640382	(Lee et al. 2013; Lee et al. 2009a, b)
5,6-Dimethylxanthenone-4-acetic acid (DMXAA)	FMO3	C6-methyl	Low activity, intermediate K_m, also catalyzed by P450 1A2	12365199	(Zhou et al. 2002)
Diphenhydramine	FMO3	*N*-	Also catalyzed by P450s 2D6 and 3A4	25003501	(Cruciani et al. 2014)
Ethionamide	FMO1, FMO2, FMO3	S-	High K_m, sulfinic acid formation from sulfenic acid product, activation to toxic product(s)	16544950, 18930751	(Henderson et al. 2008; Qian and Ortiz de Montellano 2006)
Fenbendazole	FMO	*S*-	Sulfoxide formation, also catalyzed by multiple P450 enzymes	23959307	(Wu et al. 2013)
GSK 5182	FMO1, FMO3	*N*-	High regio-selectivity for (*Z*)-isomer of substrate	32197603, 25451157	(Catucci et al. 2020; Joo et al. 2015)
3-Hydroxynabumetone	FMO5	Carbon–carbon cleavage by Baeyer–Villiger oxidation	6-Methoxy-2-naphthyl acetic acid, active metabolite formation	28783300 33146575	(Fiorentini et al. 2017; Matsumoto et al. 2021)
Imipramine	**FMO1**, FMO3, FMO5	*N*-	Also substrate for multiple P450s	9711811, 10445381, 9750169	(Adali et al. 1998, 1999; Cherrington et al. 1998)
Itopride	FMO1, **FMO3**	*N*-	Major contribution to microsomal metabolism	10997945, 28255999, 25760532, 28784689	(Jones et al. 2017; Mushiroda et al. 2000; Shimizu et al. 2015; Zhou et al. 2017)
K11777, K77	FMO3	*N*-	High K_m	11038163	(Jacobsen et al. 2000)

Table 3 (continued)

Drug	Enzyme*	Atom affected	Comments	PMID numbers	References
Ketoconazole, *N*-deacetyl	FMO1, FMO3	*N*-	Hepatotoxic metabolite(s) formation, activation to toxic product(s)	10950853, 27422753	(Fukami et al. 2016; Rodriguez and Miranda 2000)
L-775,606	FMO3	*N*-	Minor reaction in overall metabolism	10659950, 33290197	(Prueksaritanont et al. 2000; Taniguchi-Takizawa et al. 2021)
MK-0457	FMO1, **FMO3**, FMO5	*N*-	Also catalyzed by P450 3A4	17537870	(Ballard et al. 2007)
Methimazole, thiamazole	**FMO1,** FMO2, FMO3, FMO4, FMO5	*S*-	Intermediate to high K_m, high activity, low activity for FMO5	15922018, 10445381, 29959003, 9711811, 8702731, 9305407, 9711811 10901713 24821112, 14976351, 11744609, 17050781, 9344459, 9010587	(Adali et al. 1999; Cherrington et al. 1998; Falls et al. 1997; Furnes and Schlenk 2004; Gao et al. 2018; Grothusen et al. 1996; Itagaki et al. 1996; Kim and Ziegler 2000; Koukouritaki et al. 2007; Krueger et al. 2002a; Krueger and Williams 2005; Overby et al. 1997; Yamazaki et al. 2014)
N-Methylamphetamine, methamphetamine	**FMO1,** FMO3	*N*-	Stereoselective for (*S*-)-*N*-methylamphetamine, hydroxylamine formation, P450 2D6 catalyze aromatic hydroxylation and N-demethylation, activation to toxic product(s)	33928430, 15352021, 10027866	(Cashman et al. 1999b; Hong et al. 2021; Szöko et al. 2004)
N-Methylamphetamine, (*R*)-	FMO1	*N*-	Hydroxylamine formation, activation to toxic metabolite(s)	15352021	(Szöko et al. 2004)
N-Methylamphetamine, (*S*)-	**FMO1,** FMO3	*N*-	Hydroxylamine formation, activation to toxic product(s)	15352021	(Szöko et al. 2004)
S-Methyl-*N*,*N*-diethyldithiocarbamate	FMO1	*S*-	Sulfine formation, intermediate K_m (15 μM)	11159801, 10443982	(Pike et al. 1999, 2001)
S-Methyl-esonarimod	**FMO1,** FMO3, FMO5	*S*-	Low K_m, intermediate activity	14742144	(Ohmi et al. 2003)
Moclobemide	FMO3	*N*-	Low to intermediate contribution to microsomal metabolism	11531003, 28784689	(Hoskins et al. 2001; Jones et al. 2017)
NSC 366140	FMO3	*N*-	High K_m, also P450 substrate	14977851	(Reid et al. 2004)
Olanzapine	FMO1, FMO3	*N*-	*N*-Oxidation also catalyzed by P450 1A2 and 2D6 (minor), P450 catalyzed *N*-demethylation and C2- and C7-hydroxylations	8632334, 23147717	(Ring et al. 1996; Söderberg et al. 2013)
Olopatadine	FMO1, FMO3	*N*-	Minor reaction in overall metabolism	12433826	(Kajita et al. 2002)

Table 3 (continued)

Drug	Enzyme*	Atom affected	Comments	PMID numbers	References
Pargyline	FMO1, FMO3	*N*-	FMO1 forms only the (+)-enantiomer, FMO3 predominantly forms the (-)-enantiomer of the *N*-oxide	7720101	(Phillips et al. 1995)
Pentoxifylline	FMO5	Carbon–carbon cleavage by Baeyer–Villiger oxidation	Acetate ester formation	28783300	(Fiorentini et al. 2017)
Phospho-sulindac	FMO1, FMO3, FMO5	*S*-	Sulfone formation	22489789	(Xie et al. 2012)
Quazepam	FMO1	*S*-	Desulfuration (2-oxo-formation), intermediate K_m and activity, minor reaction	15801544	(Miura and Ohkubo 2004)
Ranitidine	FMO1, FMO2, **FMO3,** FMO5	*N*- and *S*-	High activity, major reaction	11128045, 9305407, 11773868, 10739174, 11465082, 15363661	(Cashman 2000; Chung et al. 2000a, b; Kang et al. 2000; Overby et al. 1997; Park et al. 2002; Ryu et al. 2004)
S 16020	FMO3	*N*-	Major metabolite	14709624	(Pichard-Garcia et al. 2004)
Selegiline, L-deprenyl	**FMO1**, FMO3	*N*-	Selective inhibitor et low concentrations, high K_m for FMO3, stereoselective for enantiomers, FMO1 and FMO3 have opposite preference in the formation of chiral center, also MAO inhibitor	15352021, 28137602	(Catucci et al. 2017; Szöko et al. 2004)
SNI-2011	FMO1	*N*-	*N*-Oxide formation, intermediate to low activity	11725960	(Washio et al. 2001)
Sulfamethoxazole	FMO1, FMO3	*N*-	Hydroxylamine formation, activation to toxic product(s)	16857727	(Vyas et al. 2006)
Sulindac (sulfoxide, prodrug)	FMO1, FMO3, FMO5	*S*-	Low activity, sulfone formation	22489789, 24821112	(Xie et al. 2012; Yamazaki et al. 2014)
Sulindac sulfide	FMO3	*S*-	High stereoselectivity for (*R*)-sulindac sulfoxide formation	10807940	(Hamman et al. 2000)
Tamoxifen	FMO1, **FMO3**	*N*-	Intermediate K_m	15987777, 10630426, 16684653, 23161341, 28137602	(Catucci et al. 2017; Hodgson et al. 2000; Krueger et al. 2006; Parte and Kupfer 2005; Yeniceli et al. 2013)
Tazarotenic acid	FMO1, FMO3	*S*-	Sulfoxide formation, also catalyzed by P450 2C8	12642475	(Attar et al. 2003)
TG100435	FMO1, **FMO3,** FMO5	*N*-	*N*-Oxide formation, P450 3A4-catalyzed retro reduction	17881660	(Kousba et al. 2007)

Table 3 (continued)

Drug	Enzyme*	Atom affected	Comments	PMID numbers	References
Thioacetazone	FMO1, FMO2, FMO3	*S*-	Sulfinic acid and carbodiimide formation from sulfenic acid, activation to toxic product(s)	16544950, 18948378	(Francois et al. 2009; Qian and Ortiz de Montellano 2006)
Tozasertib	FMO1, FMO3	*N*-	Intermediate K_m and catalytic efficiency	28137602, 24821112, 25760532, 28784689, 33290197, 32197603, 23358255	(Catucci et al. 2020, 2013, 2017; Jones et al. 2017; Shimizu et al. 2015; Taniguchi-Takizawa et al. 2015; Yamazaki et al. 2014)
Trifluoperazine	FMO3	*N*-	High K_m	8117918	(Lomri et al. 1993)
Vandetanib	**FMO1,** FMO3	*N*-	Minor metabolite in humans	31837525, 31295928	(Indra et al. 2019, 2020)
Voriconazole	FMO1, **FMO3**	*N*-	Intermediate K_m, also catalyzed by P450 3A4	18362161, 31239195, 32998136, 19841059	(Wang et al. 2021; Yamada et al. 2019; Yanni et al. 2008, 2010)
Xanomeline	FMO1, **FMO3**	*N*-	Intermediate K_m	10497134	(Ring et al. 1999)

*Major enzyme is in bold font

(aromatic and aliphatic), thiols, and mercaptopurines (Table 2). Some intermediates formed in *S*-oxidations (e.g., sulfenes, sulfines) are reactive and potentially toxic because they can react with proteins and lipids in cells (Table 7). The final products (*S*-oxides) of the *S*-oxygenation reactions may also exert toxic effects (Furnes and Schlenk 2004; Shimizu et al. 2007; Siddens et al. 2014).

Mechanism of oxygenation of heteroatoms (*N*- and *S*-oxygenation)

Compounds possessing a soft nucleophilic heteroatom are substrates of FMO enzymes. Structure–activity studies suggest that in addition to nucleophilicity, the size and charge of potential substrates are important parameters limiting access to the enzyme-bound hydroxylating intermediate form of the enzyme (4a-hydroperoxide) (Ziegler 2002).

The mechanism of oxygenation of nucleophilic groups catalyzed by FMO enzymes is presented in the context of the following three steps (Phillips and Shephard 2019; Siddens et al. 2014; Ziegler 1988) (Fig. 4): (1) NADPH binds to the enzyme and reduces FAD to $FADH_2$ (a rapid reaction). The result is the formation of a ternary complex (Enzyme-$FADH_2$-$NADP^+$). (2) $FADH_2$ binds molecular oxygen, as a co-substrate, and produces a relatively stable C4a-hydroperoxyflavin (also a rapid reaction). The cofactor $NADP^+$ remains attached to the enzyme during the reaction, stabilizing the complex. (3) The C4a-hydroperoxyflavin is a strong electrophile and can oxygenate a nucleophilic group, with an attack of activated oxygen (electrophile) atom from the C4a-hydroperoxyflavin molecule on the nucleophilic atom (nitrogen, sulfur, phosphorus) in the substrate molecule, without prior binding of the substrate to the enzyme. The transfer of the oxygen atom to a substrate (reaction of monooxygenation of the substrate) results in the formation of 4a-hydroxyflavin. (3a) If there is no substrate that can be oxygenated near the enzyme, the C4a-hydroperoxyflavin releases H_2O_2, the oxidized form of the enzyme, and $NADP^+$. (4) Removal of the water molecule (dehydration) (and release of $NADP^+$ from the complex) regenerates the oxidized form of the enzyme (slow reaction).

Access to the active form of oxygen on the prosthetic group (flavin) is observed for non-ionizable lipophilic amines and amines that are found in the form of mono-cations at physiological pH (step 3). Amines that possess two cationic groups at physiological pH (and amines with one or more anionic groups) cannot approach the active site and are not preferred substrates for FMO enzymes. These structural requirements prevent many endogenous substances from being substrates of the enzymes.

The catalytic cycle and mechanism of monooxygenation catalyzed by FMO enzymes differ significantly from the mechanism that P450s generally use in catalysis. The latter

Table 4 Examples of general chemicals as substrates in reactions catalyzed by human FMO enzymes

Chemical	Subcategory	Enzyme*	Reaction	Comments	PMID numbers	References
Aldicarb	Insecticide, carbamate	**FMO1,** FMO3	*S*-	Sulfoxide and sulfone formation, also catalyzed by P450s, activation to toxic products(s)	https://doi.org/10.1016/S0048-3575(02)00013-5	(Schlenk et al. 2002)
Aryl-1,3-dithiolane derivatives	Aryl-1,3-dithiolane	FMO3	*S*-	Preference for the *trans*-*S*-oxide formation	8117918, 9844806	(Cashman 1998; Lomri et al. 1993)
Se-Benzyl-L-selenocysteine	Selenium compound	FMO1, **FMO3**	*Se*-	High K_m, selenoxide formation	11170516	(Rooseboom et al. 2001)
(4-Bromophenyl)-1,3-oxathiolane	Aryl-1,3-oxathiolane	FMO3	*S*-	High K_m, *cis*- and *trans*-(+)-(4-bromophenyl)-1,3-oxathiolane *S*-oxide formation, stereoselectivity for (1*R*,2*R*)-*trans*-*S*-oxide diastereomer	9844806, 8117918	(Cashman 1998; Lomri et al. 1993)
n-Butyl-*p*-tolyl sulfide	Aryl sulfide	FMO3	*S*-	Stereoselective for (*R*)-isomer formation	9280409	(Brunelle et al. 1997)
Demeton-O	Insecticide, phosphorothioate	**FMO1,** FMO3	*S*-	Intermediate K_m	15547051	(Furnes and Schlenk 2005)
S-(1,2-Dichlorovinyl)-L-cysteine	Neurotoxic cysteine conjugate	FMO3	*S*-	Selenoxide formation	9884308	(Ripp et al. 1999b)
10-*N*,*N*-Dimethylaminopentyl)-2-(trifluoromethyl)phenothiazine (5-DPT)	Phenothiazine derivative	**FMO1**, FMO3, FMO4	*N*-	High activity	https://doi.org/10.1016/S0048-3575(02)00013-5	(Schlenk et al. 2002)
N,*N*-Dimethylaniline	Aromatic amine; Arylamine	FMO1 FMO2 FMO3	*N*-	*N*-Demethylation catalyzed by P450 enzymes	9010587, 2882987	(Grothusen et al. 1996; McManus et al. 1987)
Disulfoton	Insecticide, organophosphate, phosphonodithioate	FMO1	*S*-	Intermediate K_m; also catalyzed by multiple P450s and FMO enzymes	14977868	(Usmani et al. 2004)
Ethiofencarb	Insecticide, carbamate	**FMO1,** FMO3	*S*-	High K_m	15547051	(Furnes and Schlenk 2005)
N-Ethyl-*N*-methylaniline, benzenamine	Arylamine	FMO1, FMO3	*N*-	Stereoselective for (-)-(*S*)-*N*-oxide	7720101	(Phillips et al. 1995)
Ethyl *p*-tolyl sulfide	Aryl sulfide	FMO3	*S*-	Intermediate to high K_m, high activity, low stereoselectivity for (*R*)-isomer formation	9224773	(Haining et al. 1997)
Fenthion	Insecticide, organothiophosphate	**FMO1,** FMO3, FMO5	*S*-	High K_m, stereoselective for (*R*)-(+)- sulfoxide formation, also substrate for multiple P450 enzymes at lower concentrations	14976351, 15547051, 18845175	(Furnes and Schlenk 2004, 2005; Leoni et al. 2008)
Fonofos	Insecticide, organothiophosphate	**FMO1**, FMO3	*S*-	Limited catalytic activities	15547051	(Furnes and Schlenk 2005)

Table 4 (continued)

Chemical	Subcategory	Enzyme*	Reaction	Comments	PMID numbers	References
N′-4-Imidazoleethylthiourea derivatives	Thiourea derivative	FMO1	*S*-	Sulfinic acid formation via sulfenic acid, activation to toxic product(s)	16864509	(Onderwater et al. 2006)
Indoline	Aromatic heterocyclic	FMO3	*N*-	Hydroxylation and dehydrogenation	17502430	(Sun et al. 2007)
Methiocarb	Insecticide, carbamate, acetylcholinesterase inhibitor	**FMO1,** FMO3	*S*-	Sulfoxide and sulfone formation, stereoselective for FMO1, also catalyzed by multiple P450s, activation to toxic products(s)	14977868, 15547051, 30117405	(Furnes and Schlenk 2005; Giri et al. 2018; Usmani et al. 2004)
Se-L-Methionine	Selenium compound	FMO1, FMO3	*Se*-	High K_m, selenoxide formation	17173378, 22216454	(Hai et al. 2010; Krause et al. 2006)
2-Methyl-1,3-benzodithiole	Aryl-1,3-dithiolane	FMO3	*S*-	Stereoselectivity for the formation of 2-methyl-1,3-benzodithiole *cis*-sulfoxide	8117918, 9844806	(Cashman 1998; Lomri et al. 1993)
Methyl-*p*-tolyl sulfide	Aryl sulfide, FMO probe substrate	FMO1, FMO3	*S*-	High K_m, high activity, stereoselective for (*R*)- formation (FMO1), intermediate to high K_m, high activity, low stereoselectivity for (*R*)-formation (FMO3)	10950857, 14976351, 12695352, 17142560, 19571433, 9224773, 17531949, 15922018	(Dalmadi et al. 2003; Furnes and Schlenk 2004; Haining et al. 1997; Krueger and Williams 2005; Nagashima et al. 2009; Shimizu et al. 2007; Yeung et al. 2007, 2000)
n-Octylamine	Aliphatic amine	FMO5	*N*-	Intermediate activity	7872795	(Overby et al. 1995)
N-(*n*-Octylamino-phenethylamine), C8 and C10	Phenethylamine derivative	FMO3	*N*-	*trans*-Oxime formation via hydroxylamine	8902275	(Lin et al. 1996)
Phenothiazine derivatives	Phenothiazine derivative	FMO3	*N*-	*cis*-Oxime formation	8902275, 8117918	(Lin et al. 1996; Lomri et al. 1993)
Phenylthiourea	Thiocarbamide	FMO1, FMO2	*S*-	Sulfenic acid formation, activation to toxic product(s)	10901713, 15144220, 24727368	(Henderson et al. 2004b, 2014; Kim and Ziegler 2000)
Phorate	Insecticide, organophosphate, phosphorothioate	FMO1, FMO2	*S*-	Intermediate K_m, (-)-sulfoxide formation, also catalyzed by multiple P450 enzymes	14977868, 3354230, 15294458	(Henderson et al. 2004a; Levi and Hodgson 1988; Usmani et al. 2004)
n-Propyl-*p*-tolyl sulfide	Aryl sulfide	FMO3	*S*-	Stereoselective for (*R*)-isomer formation	9280409	(Brunelle et al. 1997)
Sulprofos	Insecticide, organothiophosphate	FMO1	*S*-	Intermediate K_m, also catalyzed by multiple P450 enzymes	14977868	(Usmani et al. 2004)
Thiobenzamide and derivatives	Thioamide	FMO3	*S*-	Intermediate to high K_m, also catalyzed by P450s, activation to toxic products(s)	11773868, 8117918, 2882987	(Lomri et al. 1993; McManus et al. 1987; Park et al. 2002)

Table 4 (continued)

Chemical	Subcategory	Enzyme*	Reaction	Comments	PMID numbers	References
Thiourea and derivatives	Thiocarbamide	FMO1, **FMO2**, FMO3	*S*-	Intermediate K_m, high activity, sulfinic and sulfenic acid formation, activation to toxic products(s)	14976351, 12093470, 10901713, 11744609, 15144220, 24727368, 12214664, 17050781	(Furnes and Schlenk 2004; Henderson et al. 2004b, 2014; Kim and Ziegler 2000; Koukouritaki et al. 2007; Krueger et al. 2002a, 2002b; Smith and Crespi 2002)

*Suggested major enzyme is in bold font

mechanism takes place via an intermediate reactive form of oxygen (FeO^{3+}) that involves radical species (Ziegler 2002). An interesting kinetic feature of the FMO mechanism is that (in general, with a given FMO) the k_{cat} does not vary much and the K_m varies among substrates, and the K_m is not a measure of inherent affinity for the enzyme (K_d).

Oxidations of ketones by FMOs in Baeyer–Villiger oxidations

FMOs, like other flavin-based monooxygenases in general, utilize flavin 4a-hydroperoxides in their mechanisms (Walsh 1979), with the hydroperoxide acting as an electrophile to oxygenate nitrogen or sulfur (Fig. 4). Flavin 4a-hydroperoxides can also act as nucleophiles, when deprotonated, catalyzing Baeyer–Villiger reactions with carbonyls (Fig. 5) (Walsh and Chen 1988). This is an important reaction in some bacteria, allowing the breaking of a (ketone) ring structure to generate acidic products that can be degraded (e.g., by fatty acid oxidation enzymes) for use as a carbon source. An example of a mammalian enzyme that does this is human FMO5 (Fiorentini et al. 2016; Walsh 1979).

FMO5 appears to be adapted for the nucleophilic Baeyer–Villiger chemistry. Examples of reactions attributed to FMO5 are presented in Fig. 5, including four drugs (Fiorentini et al. 2016, 2017; Lai et al. 2011; Meng et al. 2015). This is an interesting reaction, in that the lactones can be readily cleaved to open-chain products by the action of esterases or by non-enzymatic base-catalyzed hydrolysis (Fig. 6).

Thus, a C–C oxygen insertion reaction can be utilized to cleave a C–C bond (Guengerich and Yoshimoto 2018). Recently an alternate flavin mechanism involved in some oxygenations has been shown to involve a flavin N^5-oxide (Teufel et al. 2015), but it is unknown whether this intermediate could also be involved in Baeyer–Villiger oxidations.

Substrates and reactions catalyzed by human FMO enzymes

Substrates contain nucleophilic heteroatoms nitrogen, sulfur, phosphorus, or selenium. As already pointed out, the best substrates are cyclic and acyclic amines that are not ionized at physiological pH (Kim and Ziegler 2000; Rettie et al. 1994; Rooseboom et al. 2001; Ziegler 1988). Many drugs possessing nucleophilic heteroatoms in their structure are substrates of these enzymes (Phillips and Shephard 2017; Sawada and Yokosawa 1991; Yamazaki et al. 2014; Cashman, 2000) (Table 3), as well as general chemicals (Table 4) and natural products and physiological compounds (Table 5). Additional substrates are iodides and boron-containing compounds (Jones and Ballou 1986). Drug oxidations are the most studied group of reactions with human FMOs (Tables 3, 4, 5), followed by general chemicals and

Table 5 Examples of natural products and physiological compounds as substrates for human FMO enzymes

Substrate	Category	Enzyme*	Group/atom oxygenated	Comments	PMID numbers	References
S-Allyl-L-cysteine	Natural compound, sulfur-containing amino acid fresh garlic constituent	**FMO3,** FMO4	*S*-	K_m 3 mM, stereoselective with FMO3, no stereoselectivity with FMO4	10395751, 9884308	(Ripp et al. 1999a, b)
Arecoline	Natural product, alkaloid	**FMO1,** FMO3	*N*-	Intermediate K_m, *N*-oxide mutagenic in mammalian test system and cultured fibroblasts, activation to toxic product(s)	17123469, 21370913, 33270010	(Das and Giri 2020; Giri et al. 2007; Lin et al. 2011)
Cysteamine	Physiological compound, coenzyme A degradation product	FMO2	*S*-	Disulfide formation	15922018	(Krueger and Williams 2005)
Hypotaurine	Physiological compound, aminosulfinic acid	FMO1	*S*-	Taurine biosynthesis	32156684	(Phillips and Shephard 2019)
Lipoamide	Physiological compound, functional form of lipoic acid	FMO	*S*-	*S*-Oxygenation	15922018	(Krueger and Williams 2005; Phillips and Shephard 2019)
Lipoic acid	Physiological compound and natural product, organosulfur compound	FMO2	*S*-	*S*-Oxygenation	15922018	(Krueger and Williams 2005; Phillips and Shephard 2019)
Methionine, L-	Physiological compound, sulfur-containing amino acid	FMO1, FMO2, **FMO3,** FMO4	*S*-	High K_m, stereoselectivity for L-isomer (FMO4) and D-isomer (FMO3), sulfoxide formation	15680226, 10395751, 9884308, 15922018	(Elfarra and Krause 2005; Krueger and Williams 2005; Ripp et al. 1999a, 1999b)
Methionine-containing peptides (free N-terminal)	Physiological compound	FMO1, FMO3	*S*-	FMOs oxidize peptides containing a free *N*-terminal methionine	15680226	(Elfarra and Krause 2005)
Nicotine	Natural compound, alkaloid, adenosine receptor ligand	FMO1, FMO2, **FMO3,** FMO4, FMO5	$N^{1'}$-	Stereoselective, *trans*-(*S*)-(−)-*N*-1′-oxide formation	8117928, 7720103, 11465082, 30381441, 23211429, 28290528	(Bloom et al. 2013; Cashman 2000; Cashman et al. 1995; Park et al. 1993; Perez-Paramo et al. 2019; Teitelbaum et al. 2018)
Phenethylamine, β-phenethylamine	Natural product and physiological compound, monoamine alkaloid, and trace amine	FMO3	*N*-	*trans*-Oxime via hydroxylamine	9316835	(Lin and Cashman 1997b)
Trimethylamine (TMAO)	Natural product and physiological compound	FMO1**, FMO3,** FMO4	*N*-	Used as a test substrate for the measurement of FMO3 activity in humans	9776311, 12678693, 11461189, 17050781, 17142560, 17531949, 22819296, 30351217	(Cashman et al. 2003; Koukouritaki et al. 2007; Lambert et al. 2001; Lang et al. 1998; Shimizu et al. 2012, 2007, 2019; Yeung et al. 2007)

Table 5 (continued)

Substrate	Category	Enzyme*	Group/atom oxygenated	Comments	PMID numbers	References
Tyramine, *p*-	Natural product and physiological compound, trace amine	FMO3	*N*-	*trans*-Oxime formation through hydroxylamine that terminates the pharmacological activity of tyramine, also substrate for MAO enzymes, P450 2D6 (dopamine formation) and alcohol dehydrogenase (aldehyde reduction), activation to toxic product(s)	9282832, 21679153, 15922018	(Krueger and Williams 2005; Lin and Cashman 1997a; Niwa et al. 2011)

*Suggested major enzyme is in bold font

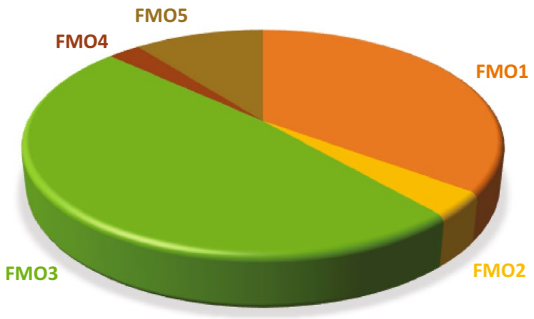


Fig. 1 Human FMO enzymes participating in the metabolism of drugs (data calculated for major and minor enzymes from Table 3; a total of 114 drugs used in calculations)

physiological compounds. In addition, FMO-catalyzed reactions are predominately detoxication reactions, with some examples of contributions of the reactions to bioactivation and formation of toxic products or intermediates (Table 7) (Cashman 2002a).

In many of the cases, the results presented were obtained using purified and recombinant human enzymes expressed in different systems. Although information obtained by studies in such systems is of great value for further research, the results obtained may not be representative of the most important processes occurring in cells or tissues. In addition, some FMO-catalyzed reactions can also be catalyzed by other enzymes in cells, e.g., P450 (Tables 3, 4, 5) and AOX enzymes (Table 3). The participation of P450 enzymes in the metabolism of the FMO substrates by *N*-oxidation may be a minor contribution to overall metabolic reactions of the compound in some cases (e.g., *N*-oxygenations of cediranib, C-1311, benzydamine, selegiline, dapsone (Table 3)) or might predominate in the overall metabolic pathway of a compound, e.g., disulfoton, methiocarb, phorate, sulprofos (Table 4), M-04579 (Table 3). Dapsone *N*-oxygenation is, for instance, catalyzed by several P450 enzymes (P450s 1A2, 2C, 2D6, 2E1, 3A4) with high or intermediate K_m values, contributing to its activation to toxic *N*-hydroxylamine formation (Li et al. 2003; Winter et al. 2000). Dapsone was, in addition, reported to be a substrate-dependent activator of P450 2C9 enzyme activity and thus activating its own oxidation (Hummel et al. 2004). However, P450-catalyzed *N*-oxidation of dapsone appears to be of minor importance to its overall metabolism (Rendić and Guengerich 2021). In addition to being substrates of P450 enzymes, FMO substrates can also be either strong P450 inhibitors with the potential for drug–drug interactions (e.g., cimetidine Rendić et al. 1983, 1979) (Fig. 9), or weak inhibitors of P450 enzymes with minor potential for inducing drug–drug interactions (e.g., ranitidine) (Fig. 10) (Rendić et al. 1982, 1983).

An additional characteristic of the reactions catalyzed by FMO enzymes is stereoselectivity which, depending on

Table 6 Examples of natural products and physiological compounds as inhibitors of human FMO enzymes

Inhibitor	Category	Enzyme	Comments	PMID numbers	References
Brussels sprouts	Gemmifera group of cabbages	FMO3	Competitive inhibition	10509757	(Cashman et al. 1999a)
Indole-3-carbinol	Natural product, diindolylmethane; Brussels sprouts constituent	FMO3	Competitive inhibition	10509757	(Cashman et al. 1999a)
Indole-3-carbinol acid condensation products	Physiologically derived compound from indole-3-carbinol	FMO3	Competitive inhibition	10509757	(Cashman et al. 1999a)
Nitric oxide	Physiological compound	FMO3	Decreased expression and activity	15363661	(Ryu et al. 2004)

the substrate, can occur with high or low selectivity for a substrate or product formed. Stereoselectivity can occur regarding both *N*- and *S*-oxygenations (Tables 3, 4, 5). For instance, no selectivity is observed for product formation by *N*-oxygenation of two geometric isomers of clomiphene, but high regioselectivity in the conversion of only one of the two isomers of GSK5182 has been reported (the *Z*-isomer) (Table 3). For sulindac sulfide (a sulindac metabolite), a high degree of stereoselectivity towards the *R*-isomer was observed (Table 3), and stereoselectivity for *N*-oxidation is reported for deprenyl (Table 3) and *trans*-(*S*)-(-)-*N*-1′-nicotine oxide (Table 5). Stereoselectivity was also reported for *S*-oxidation of the L-isomer (FMO4) and the D-isomer of methionine (FMO3) (Table 5), *N*-oxygenation of (*S*)-*N*-methylamphetamine, and *S*-oxygenation of (*R*)-sulindac sulfide (Table 3).

In addition to their interaction with FMO and/or P450 enzymes, the drugs/chemicals that interact with FMOs can also induce or inhibit the activity of drug transporters. Clozapine, for instance, is a substrate for FMO3-catalyzed *N*-oxygenation (Table 3) and also a substrate and/or inhibitor of P450 enzymes (Rendić 2002). The drug is a substrate in P450 1A2, 2D6, and 3A4 catalyzed *N*-demethylations, and P450 1A2 and 3A4 catalyzed *N*-oxygenation (Fig. 7) (Buur-Rasmussen and Brøsen 1999; Murray et al. 2018; Tugnait et al. 1999). Furthermore, clozapine *N*-oxide is reported to be an inhibitor of P450 2B6 and 2C19 enzymes (Giri et al. 2017). In addition, clozapine was reported to be an inhibitor of the drug transporter P-glycoprotein, with the potential to affect the pharmacokinetic properties of co-administered drugs (Liu et al. 2021b; Wang et al. 2006). This example illustrates the complexity of predicting possible drug–drug interactions when a drug is a substrate and/or inhibitor of multiple drug-metabolizing enzymes and/or drug transporters, the properties which are also affected by the properties of the co-administered drug(s).

In the reactions of drug substrates of FMO enzymes, the oxygenated products produced are usually more polar (Table 3) and may be more rapidly eliminated from the body or maybe substrates in conjugation reactions. As shown in Table 3, drugs belonging to several important therapeutical categories are substrates of FMO enzymes, e.g., anticancer (cediranib), antiulcer (cimetidine, ranitidine), antidepressants, CNS stimulants (amphetamine and derivatives), and antibacterial drugs (sulfamethoxazole). In some cases, substrates of the FMO enzymes are metabolites produced by the catalytic activity of other enzymes, e.g., *S*-methyl esonarimod, sulindac sulfide, 3-hydroxynabumetone, tazarotenic acid, and *S*-methyl-*N*,*N*-diethyldithiocarbamate (a disulfiram metabolite). The data also show that in humans FMO3 and FMO1 are the most frequently represented among the FMO enzymes catalyzing the metabolism of drugs (Fig. 1), as well as with the general chemicals (possessing a tertiary amine group, thiols, thiolates, sulfides, thiourea derivatives, and organothiophosphate insecticides) (Table 4), and natural products (e.g., (*S*)-nicotine, phenethylamine, cysteamine, and methionine-containing compounds) (Table 5). In the case of natural compounds as substrates the enzymes often exert stereoselectivity for a particular isomer (e.g., L-methionine as substrate) or for the formation of a particular isomer (e.g., formation of *trans*-(*S*)-(-)-*N*-1′-nicotine oxide). Also, the products of the reactions are, in some cases, more toxic than the parent compounds (Table 7). Prominent among the reactions producing reactive metabolites are those involving thiourea and derivatives (e.g., thiourea, thioacetazone, ethionamide) as substrates. The metabolite(s) of the compounds are potentially carcinogenic compounds formed by the oxygenation of a sulfur atom. Exposure to thiourea, for instance, can damage bone marrow, causing reductions in the number of red blood cells, white blood cells, and/or blood platelets. Thiourea and derivatives are oxidized by FMO1, FMO2, and FMO3 enzymes with the formation of sulfinic and sulfenic acids (Tables 4, 7); however, the toxicity of thiourea and its derivatives was assigned to the activity of the FMO3 enzyme (Smith and Crespi 2002). In some cases, the same activation reaction (i.e., *S*-oxidation) might also be catalyzed by P450 enzymes (e.g., activation of the insecticides methiocarb and aldicarb) (Costa et al. 2003; Fujino et al. 2016) (Tables 4, 7).

Table 7 Examples of **c**ompounds activated to toxic products by human FMO enzymes**

Compound	Category	Enzyme*	Group/ atom oxidized	Comments	PMID numbers	References
Aldicarb	Insecticide, carbamate	**FMO1,** FMO3	*S*-	Sulfoxide and sulfone formation, also catalyzed by P450s	https://doi.org/10.1016/S0048-3575(02)00013-5	(Schlenk et al. 2002)
Amphetamine	Central nervous system (CNS) stimulant, drug of abuse	FMO3	*N*-	Hydroxylamine and *trans*:*cis* oxime 5:1 formation	10027866, 15352021	(Cashman et al. 1999b; Szöko et al. 2004)
Arecoline	Natural product, alkaloid	**FMO1**, FMO3	*N*-	Intermediate K_m, *N*-oxide mutagen in mammalian test system and cultured fibroblasts	17123469, 21370913, 33270010	(Das and Giri 2020; Giri et al. 2007; Lin et al. 2011)
Dapsone	Antibiotic, sulfone	FMO1, FMO3	*N*-	Arylhydroxylamine formation	16857727	(Vyas et al. 2006)
Ethionamide	Antituberculotic, thiourea, prodrug	FMO1, FMO2 FMO3	S-	High K_m, sulfinic acid formation via sulfenic acid product	16544950, 18930751	(Henderson et al. 2008; Qian and Ortiz de Montellano 2006)
N′-4-Imidazoleethylthiourea derivatives	Thiourea derivative	FMO1	*S*-	Sulfinic acid formation via sulfenic acid	16864509	(Onderwater et al. 2006)
Ketoconazole, *N*-deacetyl	Imidazole, ketoconazole metabolite	FMO1 FMO3	*N*-	Hepatotoxic product(s)	10950853, 27422753	(Fukami et al. 2016; Rodriguez and Miranda 2000)
Methiocarb	Insecticide, carbamate, acetylcholinesterase inhibitor	**FMO1,** FMO3	*S*-	Intermediate K_m, sulfoxide and sulfone formation, stereoselective for FMO1, also catalyzed by multiple P450s	14977868, 15547051, 30117405	(Furnes and Schlenk 2005; Giri et al. 2018; Usmani et al. 2004)
N-Methylamphetamine, methylamphetamine	Central nervous system stimulant, drug of abuse	**FMO1** FMO3	*N*-	Hydroxylamine formation	33928430, 15352021, 10027866	(Cashman et al. 1999b; Hong et al. 2021; Szöko et al. 2004)
Phenylthiourea	Thiocarbamide	FMO1, FMO2	*S*-	Sulfenic acid formation	10901713, 15144220, 24727368	(Henderson et al. 2004b, 2014; Kim and Ziegler 2000)
Sulfamethoxazole	Antibacterial, sulfonamide	FMO1, FMO3	*N*-	Hydroxylamine formation	16857727	(Vyas et al. 2006)
Thioacetazone	Antituberculotic, thiourea, prodrug	FMO1, FMO2.1 FMO3	*S*-	Sulfinic acid and carbodiimide formation via sulfenic acid product	16544950, 18948378	(Francois et al. 2009; Qian and Ortiz de Montellano 2006)
Thiobenzamide and derivatives	Thioamide	FMO3	*S*-	Intermediate to high K_m, also catalyzed by P450s	11773868, 8117918, 2882987	(Lomri et al. 1993; McManus et al. 1987; Park et al. 2002)

Table 7 (continued)

Compound	Category	Enzyme*	Group/ atom oxidized	Comments	PMID numbers	References
Thiourea and derivatives	Thiocarbamide	FMO1, **FMO2**, FMO3	S-	Sulfinic and sulfenic acid formation, intermediate K_m, high activity	14976351, 12093470, 10901713, 11744609, 15144220, 24727368, 12214664, 17050781	(Furnes and Schlenk 2004; Henderson et al. 2004b, 2014; Kim and Ziegler 2000; Koukouritaki et al. 2007; Krueger et al. 2002a, 2002b; Smith and Crespi 2002)
Tyramine, *p*-	Natural compound and physiological compound, trace amine	FMO3	*N*-	*trans*-Oxime formation through hydroxylamine that terminates the pharmacological activity of tyramine, also substrate for MAO enzymes, P450 2D6 (dopamine formation) and ADH (aldehyde reduction)	9282832, 21679153, 15922018	(Krueger and Williams 2005; Lin and Cashman 1997a; Niwa et al. 2011)

*Major enzyme is in bold font

**Data extracted from Tables 3, 4, 5

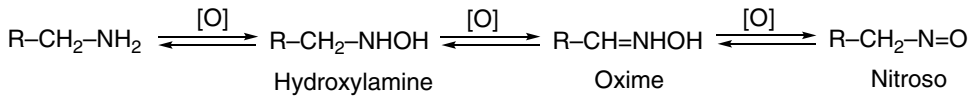


Fig. 2 General reaction of *N*-oxygenation of primary amines by FMO

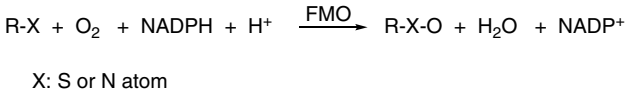


Fig. 3 Typical oxygenation reaction catalyzed by FMO enzymes, where R denotes part of the molecule and X is a heteroatom, usually N or S

Examples of substrates and reactions resulting in the formation of non-toxic metabolites

Nicotine (stimulant, agonist at nicotinic acetylcholine receptors)

Nicotine *N*′-oxygenation is one of the direct detoxication pathways for nicotine, accounting for 4–7% of total urinary nicotine metabolites (Fig. 8). Several FMO enzymes catalyze the reaction, and the role of this reaction increases in subjects with deficient P450 2A6 activity. While all of the

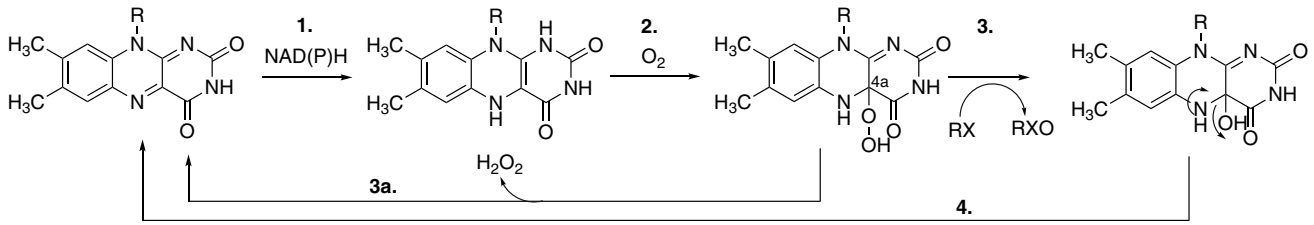


Fig. 4 Oxygenation of substrates with FMO enzymes

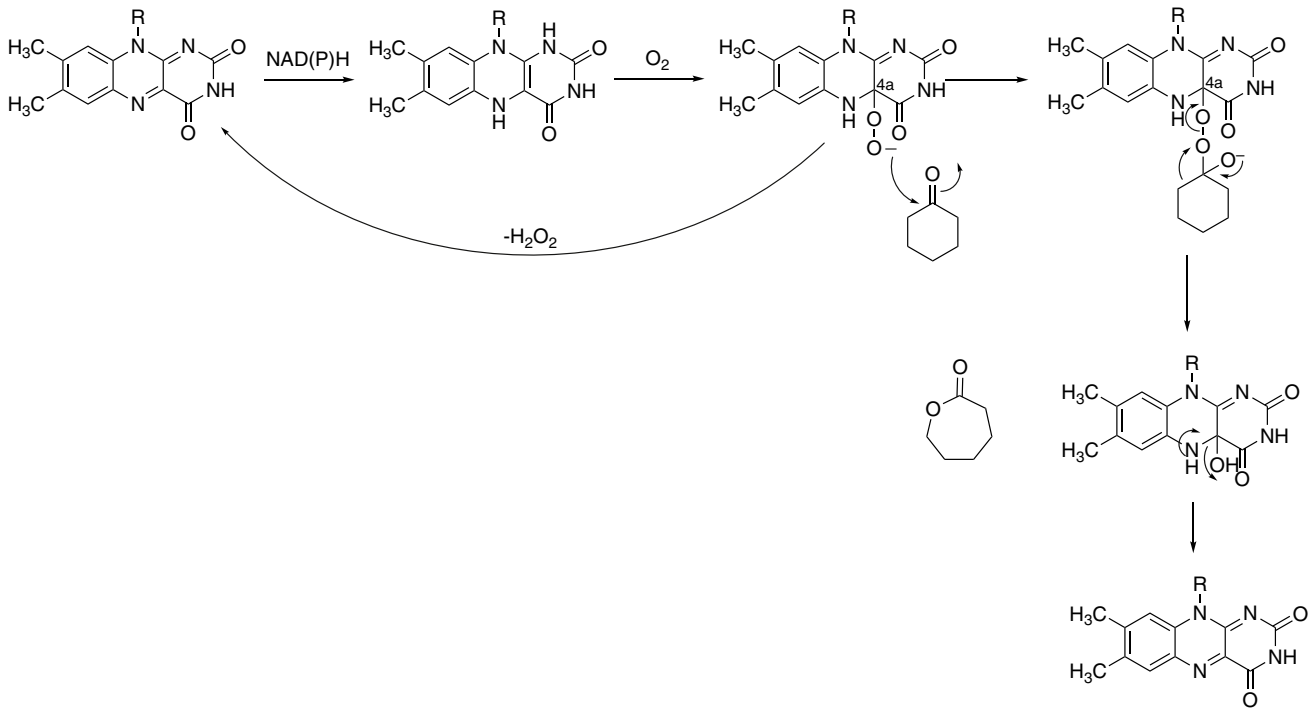


Fig. 5 Baeyer–Villiger oxidation of cyclohexanone by the flavoprotein monooxygenase FMO5 (Guengerich and Yoshimoto 2018). Some uncoupling also occurs to generate H_2O_2 (Fiorentini et al. 2016; Walsh 1979)

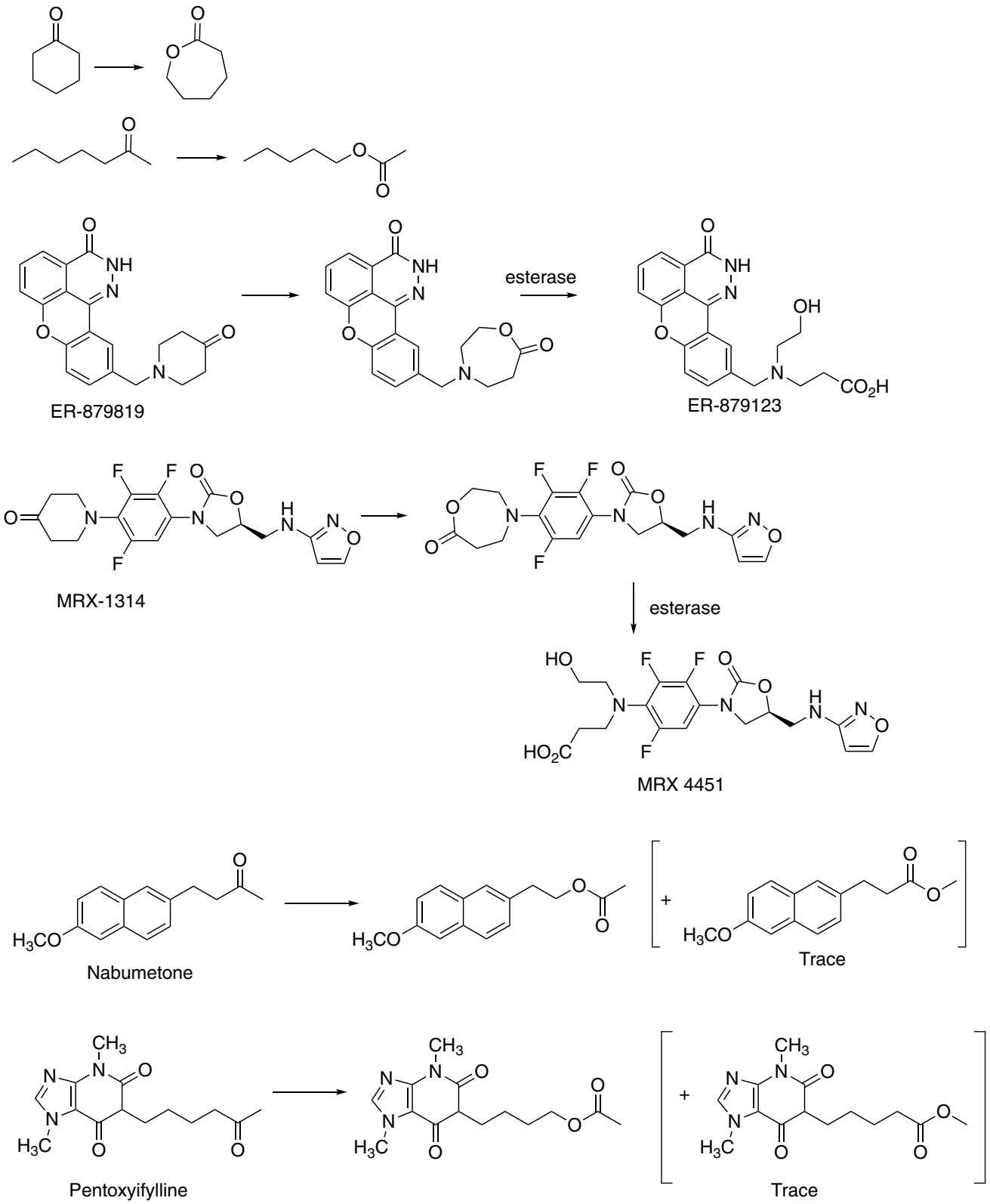


Fig. 6 Some Baeyer–Villiger C–C oxidations of drugs catalyzed by FMO (Guengerich and Yoshimoto 2018)

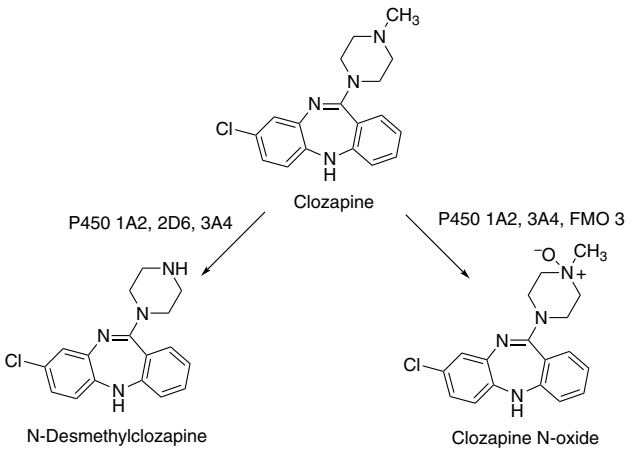


Fig. 7 Clozapine metabolism by human FMO and P450 enzymes (Fang et al. 1998; Tugnait et al. 1999, 1997)

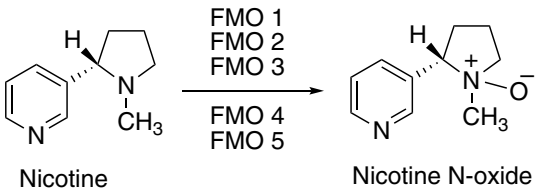


Fig. 8 Oxygenation of nicotine by FMO enzymes

recombinant FMO enzymes can mediate nicotine *N*-oxide formation, FMO1, FMO2, and FMO3 exhibit the highest activity. It was reported that oxidation of nicotine in humans occurs with a certain degree of stereoselectivity, and the formation of *trans*-nicotine *N*-1′-oxide catalyzed by FMO3 has been reported as a highly stereoselective probe of human FMO3 (Cashman et al. 1995) (Table 5). In other animal species (rat, swine, rabbit) the oxidation is catalyzed by FMO1, and approximately the same amounts of nicotine isomers are formed (Cashman 2000; Cashman et al. 1992; Park et al. 1993; Perez-Paramo et al. 2019) (Fig. 8).

Cimetidine (histamine H2 receptor antagonist)

Cimetidine *S*-oxygenation has been suggested as a stereoselective functional probe of human FMO3 activity (Cashman 2000; Cashman et al. 1995; Lu et al. 1998). FMO1 produces more of the *S*-oxide-(−)-enantiomer and FMO3 generates mainly the *S*-oxide-(+)-enantiomer (with no activity for FMO5) (Hai et al. 2009) (Table 3) (Fig. 9).

Ranitidine (histamine H2 receptor antagonist)

The FMO enzymes in human liver microsomes formed the *S*- (13–18%) and *N*-oxides (66–76%) as products. Recombinant

Fig. 9 Oxygenation of cimetidine by FMO enzymes

human FMO1, FMO2, FMO3, and FMO5 all formed the *N*-oxide, with FMO3 as the major enzyme. *S*-Oxide formation catalyzed by FMO3 was reported to be very low, as well as *N*-oxide formation by FMO5. Based on these results, it has been suggested that ranitidine *N*-oxide formation can be used as an in vivo probe to determine hepatic FMO3 activity (Cashman 2000; Chung et al. 2000a, b; Overby et al. 1997) (Table 3, Fig. 10).

Chlorpromazine (antipsychotic, phenothiazine)

The *N*-oxide derivative of chlorpromazine is a stable and pharmacologically active chlorpromazine metabolite. Chlorpromazine is a substrate for both FMO and P450 enzymes (Table 3, Fig. 11). In humans, it is metabolized to 7-hydroxy-*N*-desmethylchlorpromazine in reactions catalyzed by multiple P450 enzymes (Rendić 2002). Chlorpromazine *N*-oxide, formed by FMO1 as a major enzyme, is oxidized to a sulfoxide by P450 enzymes (chlorpromazine *N*,*S*-dioxide formation) and generates additional metabolites (7-hydroxy, *N*-desmethyl, 7-hydroxy-*N*-desmethyl, and *N*-desmethyl sulfoxide derivatives). The in vivo metabolites are formed in the order: chlorpromazine *N*-oxide > chlorpromazine sulfoxide > 7-hydroxychlorpromazine > norchlorpromazine sulfoxide > norchlorpromazine. Chlorazepine *N*-oxide was also reduced back to chlorpromazine (Beckett et al. 1988; Cashman et al. 1993b; Chetty et al. 1994; Jaworski et al. 1990; Ohmiya and Mehendale 1984). This example illustrates the complexity of drug metabolism and activity when metabolic reactions are components of multiple metabolic pathways and effects (Adali et al. 1998, 1999).

Dimethylamphetamine (CNS stimulant and anorectic)

N,*N*-Dimethylamphetamine is an *N*-methylamphetamine analog with weaker central nervous system stimulant activity. One of the metabolites of dimethylamphetamine in humans is the stable *N*-oxide (Fig. 12), possessing much lower neurotoxic potential compared to amphetamine and *N*-methylamphetamine (Lee et al. 2009a, b; Ricaurte et al. 1989). The reaction is catalyzed by FMO1 (as the major enzyme) and FMO3. The reaction catalyzed by FMO1 was reported to be enantioselective for L-*N*-oxide formation (Table 3).

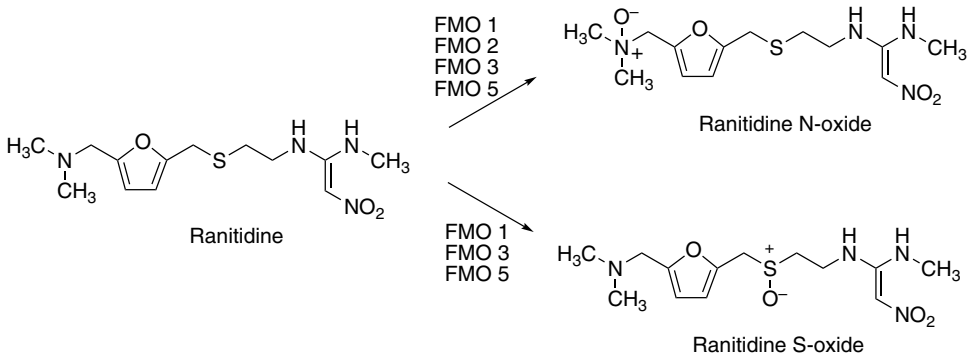


Fig. 10 Oxygenation of ranitidine by FMO enzymes

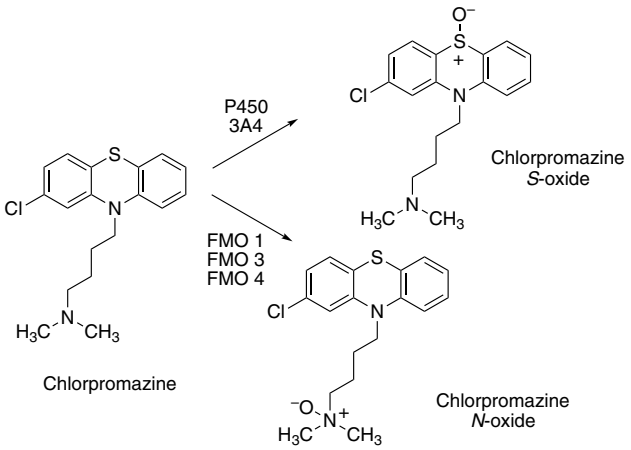


Fig. 11 Chlorpromazine oxygenations by FMO and P450 enzymes

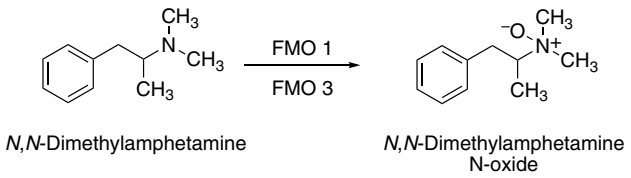


Fig. 12 *N*-Oxygenation of dimethylamphetamine

Sulfides

Sulfide drugs and general chemicals, or their metabolites, are oxidized to *S*-oxides by human FMO enzymes (Tables 3, 4). The reaction of sulfide oxidation showed differential structurally dependent stereoselectivity. For instance, sulfoxidation of methyl and ethyl *p*-tolyl sulfides by recombinant human FMO3 proceeds with little stereochemical preference, whereas sulfoxidation of the n-propyl and n-butyl homologs demonstrated increasing selectivity for formation of the (*R*)-sulfoxide. In addition, *S*-oxidation of methyl-*p*-tolyl sulfide by FMO1 was stereoselective for (*R*)-sulfoxide formation (Table 4).

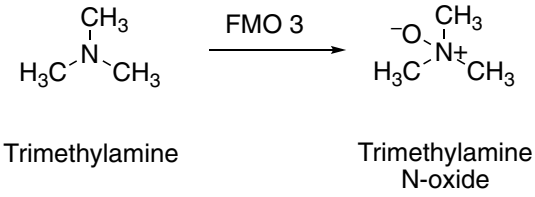


Fig. 13 *N*-Oxygenation of trimethylamine by FMO3

Examples of reactions resulting in the formation of toxic metabolites

N-oxygenations

Trimethylamine (an agonist of human TAAR5 (trace amine associated receptor 5))

In humans, FMO3 is polymorphic and can be associated with clinically relevant drug–drug or drug–chemical interactions. FMO3 enzyme polymorphism in humans is related to a rare hereditary disorder of the inability to metabolize trimethylamine. This leads to the accumulation of trimethylamine and to a disorder called trimethylaminuria, which results in a so-called "fish odor" syndrome (Al-Waiz et al. 1987; Dolphin et al. 1997; Phillips et al. 1995).

In humans, trimethylamine is formed mainly from the metabolism of phosphatidylcholine/choline, carnitine, betaine, dimethylglycine, and ergothioneine from food by intestinal microflora in the colon. It is absorbed into the bloodstream and transformed into trimethylamine *N*-oxide (TMAO) (Fig. 13) by hepatic FMO1 and FMO3 but can be also converted to (mono)methylamine, dimethylamine, and ammonia within the colon. Although the oxidation of trimethylamine to its *N*-oxide had been known for years, the detrimental effects of TMAO were discovered only recently. Elevated TMAO plasma levels have been correlated with an elevated risk for cardiovascular disease (atherosclerosis and thrombosis) and were implicated in reverse cholesterol

transport and glucose and lipid homeostasis. High plasma TMAO levels were also positively associated with the incidence of gallstone disease in humans (Gatarek and Kaluzna-Czaplinska 2021; Papandreou et al. 2020; Schneider et al. 2018; Steel et al. 1988; Zhu et al. 2018). The major enzyme involved in trimethylamine *N*-oxygenation is FMO3 (Table 5). In some individuals, due to the genetic polymorphism of FMO3, decreased trimethylamine oxidation occurs (Fig. 13) with an accumulation of trimethylamine resulting in "fish odor." Trimethylamine *N*-oxide accounts for almost 98% of the administered dose of the parent compound trimethylamine. However, in individuals deficient in the FMO3 the formation of toxic trimethylamine *N*-oxide is reduced to 80%, with the remainder (i.e., 20%) being present as trimethylamine. This polymorphism in amine metabolism, due to attenuated catalytic activity of FMO3, is heritable (Cashman et al. 2003; Phillips and Shephard 2020; Shimizu et al. 2014).

The ratio of trimethylamine to TMAO in urine is used as an index of FMO3 activity, FMO3 polymorphism, and the occurrence of trimethylaminuria.

Amphetamine (CNS stimulant, anorexic)

Multiple mechanisms are involved and interact to promote neurotoxicity from amphetamine and derivatives, which are widely abused psychostimulant drugs (Carvalho et al. 2012; Yamamoto et al. 2010). Oxygenation of the amino group of amphetamine occurs less in humans because deamination and aromatic hydroxylation predominate, catalyzed by P450 enzymes (Bach et al. 1999; Miranda et al. 2007). *N*-Oxygenation of amphetamine is catalyzed by FMO3, and reactive and toxic metabolites are formed that can contribute to the toxic effects of amphetamine by participating in the autooxidation of dopamine, norepinephrine, and serotonin (Tables 3, 7).

Potential toxic effects are ascribed to amphetamine hydroxylamine. A proposed mechanism of amphetamine activation is *N*-oxygenation to a hydroxylamine in the first step, which is then re-oxygenated with FMO3 to form an unstable intermediate that, after spontaneous dehydration, is transformed into a *trans*-oxime (Cashman et al. 1999b; Szöko et al. 2004) (Fig. 14).

N-Methylamphetamine (CNS psychostimulant)

N-Methylamphetamine (methamphetamine) is an illicit, highly addictive psychostimulant amphetamine derivative that is widely abused. Large doses of the drug are associated with serious neuropsychiatric consequences including agitation, anxiety, hallucinations, paranoia, and psychosis (Jayanthi et al. 2021). *N*-Methylamphetamine can severely damage the central nervous system and is toxic to the cardiovascular system (Halpin et al. 2014; Tan et al. 2021; Zhao et al. 2021). Metabolism of *N*-methylamphetamine proceeds with the initial formation of *N*-methylamphetamine hydroxylamine, and the final product is phenyl propanone (Tables 3, 7) (Fig. 15). The formation of phenyl propanone oxime and the nitrone are proposed as part of an overall detoxication process, with the potentially toxic effects ascribed to *N*-methylamphetamine hydroxylamine (Cashman et al. 1999b; Szöko et al. 2004).

Arecoline (tetrahydropyridine alkaloid)

The alkaloid arecoline, a major constituent of areca nuts, has been classified as a Class I carcinogen by the International Agency for Research on Cancer (IARC) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans,

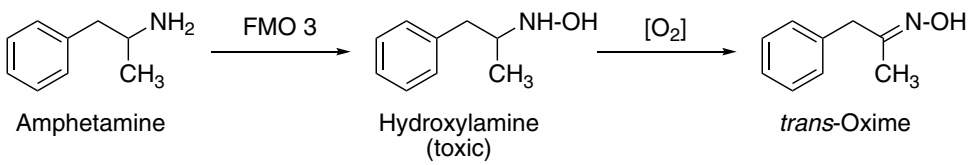


Fig. 14 *N*-Oxygenation of amphetamine

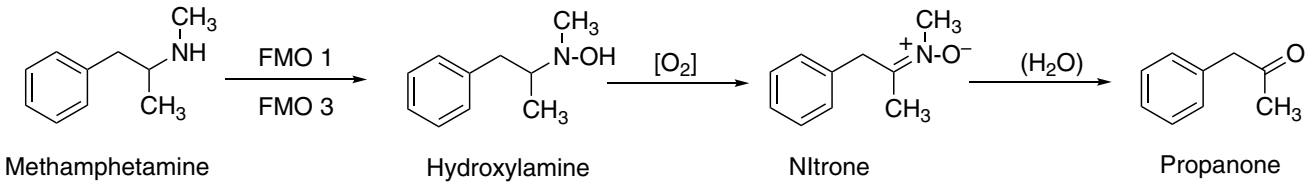


Fig. 15 *N*-Oxygenation of *N*-methylamphetamine

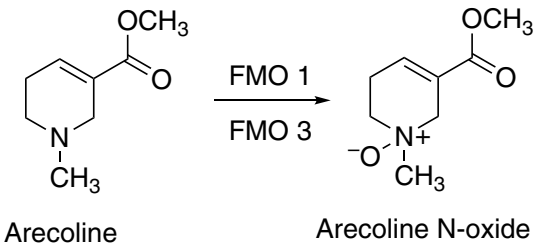


Fig. 16 *N*-Oxygenation of arecoline by FMO enzymes

2004). Arecoline is converted to the metabolite arecoline *N*-oxide by human FMO1 and FMO3, with FMO1 as the major enzyme (Tables 5, 7) (Fig. 16). Arecoline *N*-oxide was shown to be mutagenic in bacterial tester strains and to induce DNA damage in mammalian test systems, including cultured fibroblasts. The metabolite arecoline *N*-oxide is further converted to mercapturic acid derivatives in vivo (Das and Giri 2020; Giri et al. 2007; Lin et al. 2011; Oliveira et al. 2021).

S-Oxygenations

Substances with a sulfur atom can be oxygenated with FMO enzymes to form electrophilic intermediates (e.g., thiols, thioamide, 2-mercaptoimidazole, thiocarbamate, thiocarbamide metabolites). Such electrophilic metabolites can bind to cellular proteins and inactivate enzymes in the endoplasmic reticulum, e.g., P450s (Başaran and Can Eke 2017; Jones and Ballou 1986).

Thiourea and derivatives (organosulfur compounds)

Thiourea (also called thiocarbamide) is a pro-carcinogenic, moderate to a highly toxic substance that is oxidized to carcinogenic products by FMO enzymes. The thiourea moiety is part of chemicals with different applications, including rodenticides, bactericides, components used in the manufacture of rubber, and therapeutic agents. Some derivatives of thiourea are known toxins (e.g., phenylthiourea) (Henderson et al. 2014; Smith and Crespi 2002).

Thiourea is oxygenated via a sulfenic acid to a sulfinic acid by human FMO1, FMO2, and FMO3, with FMO2 as a major enzyme (Tables 4, 7) (Fig. 17). The sulfinic acid formed can be detoxicated in the cells by reaction with glutathione. Similarly, *N*-substituted derivatives of thiourea (e.g., *N*′-(4-imidazole-ethyl)thiourea derivatives) exerted cytotoxicity and are activated by oxygenation of the sulfur atom to sulfenic acids (Furnes and Schlenk 2004; Kim and Ziegler 2000; Onderwater et al. 2006; Smith and Crespi 2002).

Fenthion (organophosphate, insecticide)

Fenthion, an inhibitor of human acetylcholinesterase, is a substrate in the reaction of *S*-oxygenation catalyzed by FMO1, FMO3, and FMO5, with FMO1 being the major enzyme. The reaction is characterized by high K_m values and by the stereoselective formation of (*R*)-(+)- sulfoxide (Table 4) (Fig. 18). At lower concentrations, fenthion is predominately metabolized by multiple P450 enzymes, with P450 1A2 as the major one (Furnes and Schlenk 2004, 2005; Gadepalli et al. 2007; Leoni et al. 2008) (Fig. 18).

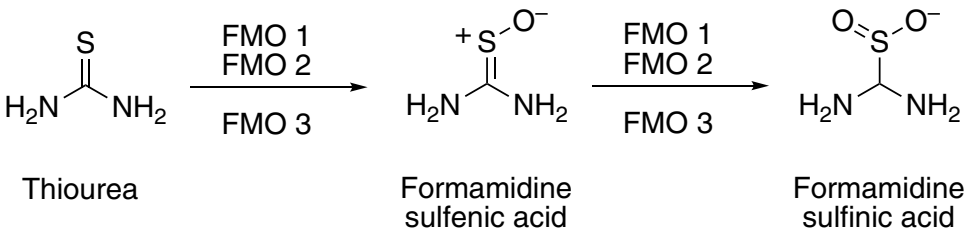


Fig. 17 Oxygenation of thiourea by FMO enzymes

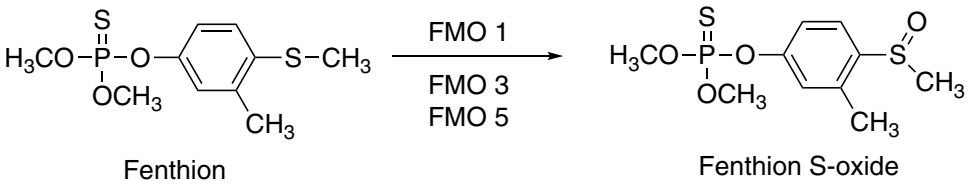


Fig. 18 Oxygenation of fenthion by FMO enzymes

Table 8 Examples of drugs as substrates in oxidation reactions catalyzed by human MAO enzymes

Drug	Category	Enzyme*	Comments	PMID numbers	References
2C-series	Psychedelic drugs of phenethylamine of the 2C family	**MAO A**, MAO B	Deamination, aldehyde formation, intermediate K_m (MAO A) and high K_m (MAO B), intermediate activity, also catalyzed by P450 2D6	17067556	(Theobald and Maurer 2007)
Almotriptan	Antimigraine, 5-HT1B,1D receptor agonist, Triptan	MAO A	Deamination, aldehyde, and indole acetic acid formation, high K_m, major reaction, also, substrate for P450s (*N*-demethylation) and FMO3 (*N*-oxidation)	15762767; 27582896	(Capi et al. 2016; McEnroe and Fleishaker 2005)
Bicifadine	Analgesic, norepinephrine, and serotonin uptake inhibitor	MAO A, **MAO B**	Lactam formation, also substrate for P450s by methyl hydroxylation	17881661	(Erickson et al. 2007)
Citalopram, *N*-desmethyl and *N*-didesmethyl	Citalopram metabolites	MAO A, MAO B,	Deamination, citalopram propionic acid formation, stereoselective for *S*-enantiomer formation	9698084; 11226815; 11840311	(Kosel et al. 2001, 2002; Rochat et al. 1998)
Citalopram, racemate, (*R*)-, (*S*)-, escitalopram	Antidepressant, selective serotonin reuptake inhibitor, SSRI	MAO A, MAO B	Deamination, aldehyde, and propionic acid formation, selective for (+)-(*S*)-formation, high K_m, also substrate for multiple P450s by *N*-demethylation	7577348; 9698084; 11840311; 11226815	(Kosel et al. 2001, 2002; Rochat et al. 1995, 1998)
Milacemide	Anticonvulsant, glycine prodrug	MAO A, **MAO B**	Deamination to glycinamide	3346666; 14697904	(Janssens de Varebeke et al. 1988; Matsukawa et al. 2004)
Naratriptan	Antimigraine, HT1B/1 receptor agonist, triptan	MAO A	Deamination, predominately P450 substrate	27582896	(Capi et al. 2016)
Nomifensine	Antidepressant, tetrahydroisoquinoline, withdrawn from the market	MAO A	Dehydrogenation, dihydroisoquinolinium ion formation, also formed by other enzymes, risk of anemia and hepatotoxicity, activation to toxic product(s)	16679384	(Obach and Dalvie 2006)
Ozanimod	Immunomodulator, sphingosine 1-phosphate receptor modulator	MAO B	Deamination, pharmacologically active product formation	33025342; 33674268	(Surapaneni et al. 2021; Tran et al. 2020)
Phenelzine	Antidepressant	MAO A, MAO B	Oxidation, β-phenylethylamine, phenylacetic acid, and β-phenylethylidenehydrazine formation	23934742; 30857888; 33839994; 10319194	(Baker et al. 2019, 1999; Matveychuk et al. 2021; Shulman et al. 2013)

Table 8 (continued)

Drug	Category	Enzyme*	Comments	PMID numbers	References
Phenylephrine	Decongestant; a-1 adrenergic agonist	**MAO A,** MAO B	Deamination, metabolic clearance of MAO substrate drugs in MAO expression systems	28361200	(Masuo et al. 2017)
Primaquine, racemic and (*R*)-enantiomer	Antimalarial, 8-aminoquinoline	MAO A	Deamination, carboxyprimaquine formation, the major metabolite, also multiple P450s	2045714; 6721990; 33922294	(Chaurasiya et al. 2021; Frischer et al. 1991; Mihaly et al. 1984)
Rizatriptan	Antimigraine, $HT_{1B/1D}$ receptors receptor agonist, triptan	MAO A	Deamination, indole 3-acetic acid derivative formation, also, a substrate for P450 1A2	11453892; 14651728; 28361200; 27582896; 10417495	(Capi et al. 2016; Goldberg et al. 2001; Iwasa et al. 2003; Masuo et al. 2017; Van Haarst et al. 1999)
Rizatriptan *N*-desmethyl metabolite	Antimigraine, $HT_{1B/1D}$ receptors receptor agonist, triptan	MAO A	Deamination, indole 3-acetic acid derivative formation	10417495	(Van Haarst et al. 1999)
Sumatriptan	Antimigraine, HT1B/1D receptors receptor agonist, triptan	MAO A	Deamination, indole 3-acetic acid derivative formation	8161354; 19925626; 28361200; 27582896	(Masuo et al. 2017; Capi et al. 2016; Dixon et al.1994; Fox 2010)
Ticlopidine	Inhibitor of platelet aggregation, thienopyridine, prodrug	MAO	Oxidation, minor participation in overall metabolic reactions	14709620	(Dalvie and O'Connell 2004)
Zolmitriptan	Antimigraine, HT1B/1D receptors receptor agonist, triptan	MAO A	Deamination, indole ethyl alcohol derivative formation from *N*-desmethyl metabolite formed by P450 1A2	10553725; 17125411; 27582896	Capi et al. 2016; Sternieri et al. 2006; Wild et al. 1999)

*Suggested major enzyme is in bold font

Table 9 Examples of natural products and physiological compounds as substrates in oxidation reactions catalyzed by human MAO enzymes

Substrate	Category	Enzyme*	Remarks	PMID numbers	References
Dopamine	Physiological compound, catecholamine, neurotransmitter	MAO A, **MAO B**	3,4-Dihydroxyphenylacetaldehyde formation, activation to toxic product(s)	6408492, 22906103, 29417334, 31807952, 10202537	(Goldstein 2020; Goldstein et al. 2012; O'Carroll et al. 1983; Shih et al. 1999; Szökő et al. 2018)
Epinephrine (adrenaline)	Physiological compound, neurotransmitter, hormone	MAO A	Aldehyde formation, activation to toxic product(s)	21971001	(Bortolato and Shih 2011)
3-Iodothyronamine	Physiological compound, iodinated thyronamine	MAO B	3-Iodothryoacetic acid formation	24627446	(Ghelardoni et al. 2014)
Kynuramine	Physiological compound, biogenic amine, alkylphenyl ketone	MAO A, MAO B	Deamination, propionaldehyde, and 4-hydroxyquinoline formation, activation to toxic product(s)	28185143, 28302559, 30809547, 3081342325455893	(Chaurasiya et al. 2019; Santillo 2014; Shaik et al. 2017; Wagmann et al. 2017; Zhang et al. 2019b)
Melatonin	Physiological compound, hormone	MAO A	Oxidation, also metabolized by P450 1A2	3008207	(Murphy et al. 1986)
5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT)	Natural product and physiological compound, psychedelic, tryptamine	MAO A	5-Methoxyindoleacetic acid formation	20206139, 20942780	(Shen et al. 2010a, b)
Norepinephrine, noradrenaline	Physiological compound, catecholamine, neurotransmitter	MAO A	3,4-Dihydroxyphenylglycolaldehyde formation, activation to toxic product(s)	21971001, 23934742	(Bortolato and Shih 2011; Shulman et al. 2013)
Octopamine	Natural product and physiological compound; trace amine, sympathomimetic	MAO B	Hydroxymandelic acid formation	21971001, 2509446	(Bortolato and Shih 2011; Szutowicz et al. 1989)
β- Phenylethylamine	Natural product and physiological compound, trace amine, CNS stimulant	MAO A, **MAO B**	Deamination, phenylacetaldehyde, and β-phenylacetic acid formation	6788990, 7205271, 20227955, 21971001, 11134050, 26091526, 3244400	(Bortolato and Shih 2011; Geha et al. 2001; Lewinsohn et al. 1980; Oguchi et al. 1981; Reid et al. 1988; Suzuki et al. 1981; Zapata-Torres et al. 2015)
Serotonin (5-hydroxytryptamine)	Physiological compound, indolamine, neurotransmitter	MAO A	5-Hydroxyindolaldehyde formation, activation to toxic product(s)	3008207, 10202537, 31344280, 21971001, 11134050, 23934742	(Bortolato and Shih 2011; Geha et al. 2001; Kyritsi et al. 2020; Murphy et al. 1986; Shih et al. 1999; Shulman et al. 2013)
Tryptamine	Physiological compound, indolamine, trace amine	MAO A	Indole-3-acetaldehyde formation	12538805	(Yu et al. 2003)
Tyramine	Natural product and physiological compound, trace amine	**MAO A,** MAO B	4-Hydroxyacetaldehyde formation, also substrate for FMO3, P450 2D6 (dopamine formation) and alcohol dehydrogenase (aldehyde reduction), activation to toxic products(s)	14697899, 6788990, 21679153, 23934742, 7272178, 7272177	(Martini et al. 1981a, b; Niwa et al. 2011; Oguchi et al. 1981; Shulman et al. 2013; Youdim and Weinstock 2004)

*Suggested major enzyme is in bold font

Table 10 Examples of general chemicals as substrates in oxidation reactions catalyzed by human MAO enzymes

Chemical	Subcategory	Enzyme*	Remarks	PMID numbers	References
Benzylamine	Phenylmethylamine	MAO B	Deamination, benzaldehyde formation, activation to toxic product(s)	3244400, 2509446, 20227955	(Lewinsohn et al. 1980; Reid et al. 1988; Szutowicz et al. 1989)
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Tetrahydropyridine	MAO A, **MAO B**	$MPDP^+$ and pyridine MPP^+ formation, reactive metabolite formation (mechanism-based inactivation), neurotoxic, activation to toxic product(s)	3083305, 3874094, 3287698 3295117 21992679, 21554916	(Fritz et al. 1985; Glover et al. 1986; Herraiz 2012; Herraiz and Guillén 2011; Trevor et al. 1987a, 1988)

*Suggested major enzyme is in bold font

Monoamine oxidase (MAO)

We previously reported that human MAOs participate in ~ 1% of the metabolism of xenobiotic and physiological compounds, including natural products. In the metabolism of general chemicals, MAO enzymes participate in ~ 2%, drugs ~ 1%, and natural and physiological chemicals ~ 1% (Rendić and Guengerich 2015). The previous analysis indicated more extensive participation of MAO enzymes in the metabolism of general chemicals when compared to the metabolism of drugs and natural products and physiological compounds, but this pattern may reflect more basic studies and efforts at drug discovery (Rendić and Guengerich 2012, 2015).

Enzymes

Two MAO enzymes are known (MAO A and MAO B), which are encoded by the *MAOA* and *MAOB* genes. The enzymes are primarily involved in the catalytic oxidative deamination of endogenous monoamines (Bach et al. 1988; Benedetti 2001; Bortolato et al. 2008; Bortolato and Shih 2011; Edmondson and Binda 2018; Grimsby et al. 1990; Ramsay 2012; Shih et al. 1990; Strolin Benedetti et al. 2007) The MAOs are mitochondrial, membrane-bound enzymes, and are located in many tissues, of which the most significant may be the brain. The enzymes are present also in the liver, where they catalyze the oxidative deamination of some xenobiotics.

MAO A is present in the brain, small intestine, heart, placenta, liver, portal system, and peripheral adrenergic neurons, and it is selective for the metabolism of norepinephrine and serotonin. MAO B is found in blood platelets, cerebral glial cells, and hepatic cells and is relatively selective for the metabolism of benzylamine and phenylethylamine. Physiological substrates are amines that are oxidized to aldehydes, which may be reduced by aldehyde reductase to alcohols. In vivo inhibition of MAO with either irreversible or nonselective compounds permits the up-take of high concentrations of tyramine and other sympathomimetic molecules into the blood circulation, where they gain access to peripheral adrenergic neurons, trigger catecholamine release, and cause a marked and rapid increase in blood pressure (Lavian et al. 1993).

Substrates

The substrates are nitrogen-containing compounds, including primary, secondary, and tertiary amines (Kalgutkar et al. 2001; Strolin Benedetti et al. 2007) (Tables 8, 9, 10). Substrates have also been synthesized as prodrugs (e.g., dopamine prodrugs synthetized as esters, amides, dimeric amides, carrier-mediated, peptide transport-mediated, cyclic, chemical delivery systems) to enhance their bioavailability in the treatment of Parkinson's disease (Haddad et al. 2017; Sozio et al. 2012). Endogenous substrates include biogenic and dietary amines, monoamine hormones, and neurotransmitters such as serotonin, dopamine, norepinephrine, and epinephrine, as well as tyramine, tryptamine, 2-phenylethylamine, 5-hydroxytryptamine, monoacetyl putrescine (a precursor to γ-aminobutyric acid (GABA), adrenaline, and metanephrine) (Bortolato and Shih 2011). Similar to FMO enzymes, the substrates of MAO enzymes are often substrates for other drug-metabolizing enzymes as well (e.g., P450 and/or FMO enzymes).

Inhibitors

The inhibitors of MAO enzymes are developed and tested either as selective or nonselective reversible or irreversible inhibitors. Many compounds (drugs, natural products, as well as general chemicals) have been shown to inhibit MAO enzymes. In the clinic, drugs are used either as selective or nonselective MAO inhibitors in the therapy of several

Table 11 Drugs as inhibitors of human MAO enzymes

Compound	Subcategory	Enzyme*	Remarks	PMID numbers	References
Amitriptyline	Antidepressant, tricyclic	MAO B	Atypical biphasic response in human platelet and brain preparations, inhibition in vivo	3244400, 6932067, 835743	(Giller et al. 1980; Reid et al. 1988; Sullivan et al. 1977)
Amphetamine	Central nervous system (CNS) stimulant, drug of abuse	**MAO A,** MAO B	Intermediate inhibitor (MAO A), weak inhibitor (MAO B)	25455893, 15035814	(Ramsay and Hunter 2003; Santillo 2014)
Befloxatone	Oxazolidinone	**MAO A,** MAO B	Selective, reversible inhibitor	8613928, 18652859, 10.4236/ojd.2017.62004	(Bortolato et al. 2008; Curet et al. 1996; Entzeroth and Ratty 2017)
Brofaromine	Antidepressant, piperidyl benzofuran	**MAO A,** MAO B	Selective, reversible inhibitor	10063483, 18652859, 7905288, 10.4236/ojd.2017.62004	(Bortolato et al. 2008; Entzeroth and Ratty 2017; Lotufo-Neto et al. 1999; Nair et al. 1993)
Caroxazone	Antidepressant	MAO A, MAO B	Non-selective, short-acting reversible inhibitor	7272177, 7272178, 7272163, 10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017; Martini et al. 1981a, b; Moretti et al. 1981)
Cimoxatone	Oxazolidinone	**MAO A**, MAO B	Selective, reversible inhibitor	18652859, 10.4236/ojd.2017.62004	(Bortolato et al. 2008; Entzeroth and Ratty 2017)
Clomipramine	Antidepressant, tricyclic amine	MAO	Atypical biphasic response in human platelet and brain preparations	3244400	(Reid et al. 1988)
Clorgyline	Antidepressant	**MAO A**, MAO B	Selective, highly strong, irreversible inhibitor	9564606, 3008207, 14651728, 30734773, 20642018, 18652859, 21992679, 29496172, 111275, 6304562, 10.4236/ojd.2017.62004, 27575476, 28188065, 29395970, 33922294	(Baek et al. 2018a; Bortolato et al. 2008; Chaurasiya et al. 2021; Entzeroth and Ratty 2017; Finberg and Youdim 1983; Herraiz 2012; Iwasa et al. 2003; Larit et al. 2018; Lee et al. 2016; Lee et al. 2017c; Leung 2004; 1998 351; Murphy et al. 1979; Murphy et al. 1986; Yang et al. 2019a, b)
Desipramine	Antidepressant, Tricyclic amine	MAO	Inhibition in human brain cortex and platelets	3244400	(Reid et al. 1988)
Desmethylclomipramine	Clomipramine metabolite	MAO	Inhibition in human brain cortex and platelets	3244400	(Reid et al. 1988)
Eprobemide	Antidepressant	**MAO A,** MAO B	Selective, non-competitive, reversible inhibitor	10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017)
Esuprone	Antidepressant	**MAO A,** MAO B	Selective, reversible inhibitor	10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017)
Fluoxetine	Antidepressant, bicyclic	MAO	Inhibition in human brain cortex and platelets	3244400	(Reid et al. 1988)
Haloperidol and metabolites	Antipsychotic	**MAO B**	Selective, reversible, or irreversible, uncompetitive inhibitors	6733172, 7617809	(Fang et al. 1995; Giller et al. 1984)
Imipramine	Antidepressant, tricyclic amine	MAO	Atypical biphasic response in human platelet and brain preparations, inhibition in vivo	3244400, 835743	(Reid et al. 1988; Sullivan et al. 1977)

Table 11 (continued)

Compound	Subcategory	Enzyme*	Remarks	PMID numbers	References
Iproclozide	Antidepressant, hydrazine	MAO A, MAO B	Nonselective, irreversible inhibitor	18652859	(Bortolato et al. 2008)
Iproniazid	Antituberculotic, antidepressant, hydrazine	MAO A, MAO B	Nonselective, irreversible inhibitor	24856304, 10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017; He et al. 2014)
Isocarboxazid	Antidepressant	MAO A, MAO B	Nonselective, irreversible inhibitor	18652859, 23934742, 10.4236/ojd.2017.62004	(Bortolato et al. 2008; Entzeroth and Ratty 2017; Shulman et al. 2013)
Ketoconazole	Antifungal	MAO A, **MAO B**	Non-competitive inhibitor	28185143	(Shaik et al. 2017)
Ladostigil	Neuroprotective, acetylcholine-butyrylcholinesterase and brain selective monoamine oxidase inhibitor, investigated for the treatment of neurodegenerative disorders, rasagiline derivative	MAO A, MAO B	Non-selective, irreversible inhibitor	17017566, 22280345, 34207264, 14697899	(Behl et al. 2021; Weinreb et al. 2012; Weinstock et al. 2006; Youdim and Weinstock 2004)
Lazabemide	Pyridine carboxamide	**MAO B**	Selective, strong, reversible, inhibitor	29186917, 30143367, 28188065, 29395970, 30396116	(Baek et al. 2018a, 2019b; Hoon et al. 2017; Lee et al. 2017c; Zhou et al. 2018)
Linezolid	Antibacterial, oxazolidinone	MAO A, MAO B	Nonselective, reversible, weak inhibitor	18652859, 23612197	(Bortolato et al. 2008; Flanagan et al. 2013)
Metaxalone	Muscle; relaxant, oxazolidin-2-one	MAO A	Inhibitor at high, toxic concentrations	31373522	(Cherrington et al. 2020)
Methylamphetamine	Central nervous system stimulant; Drug of abuse	**MAO A,** MAO B	Intermediate inhibitor of MAO A, a weak inhibitor of MAO B	25455893	(Santillo 2014)
Metralindole	Antidepressant	**MAO A,** MAO B	Selective, reversible inhibitor	10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017)
Minaprine	Antidepressant, amino-phenylpyridazine	**MAO A,** MAO B	Selective, reversible, inhibitor	10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017)
Moclobemide	Antihyperlipidemic, antidepressant, benzamide	**MAO A**	Short-acting, selective, time-dependent, reversible inhibitor	2193111, 14651728, 23934742, 18652859, 7905288	(Bortolato et al. 2008; Da Prada et al. 1990; Iwasa et al. 2003; Nair et al. 1993; Shulman et al. 2013)
Mofegiline	Allylamine	**MAO B**	Selective, irreversible inhibitor	7955818, 19053775	(Huebert et al. 1994; Milczek et al. 2008)
Nialamide	Antidepressant, hydrazine, withdrawn from the market	MAO A, MAO B	Nonselective irreversible inhibitor, hepatotoxic	18652859	(Bortolato et al. 2008)
Pargyline	Antihypertensive, antidepressant, withdrawn from the market	MAO A, **MAO B**	Partially selective, strong, and irreversible inhibitor, CNS toxicity, generation of H_2O_2, toxic metabolite(s) formation	9564606, 111275, 6304562, 29395970	(Baek et al. 2018a; Finberg and Youdim 1983; Murphy et al. 1998, 1979)
PF9601N	Propargylamine	MAO B	Inhibitor at a high drug concentration	18331475, 21971010	(Sanz et al. 2008; Unzeta and Sanz 2011)

Table 11 (continued)

Compound	Subcategory	Enzyme*	Remarks	PMID numbers	References
Phenelzine	Antidepressant	MAO A, MAO B	Nonselective, irreversible inhibitor	23934742, 30857888, 33839994, 10319194	(Baker et al. 2019, 1999; Matveychuk et al. 2021; Shulman et al. 2013)
Phentermine	Central nervous system (CNS) stimulant, anorectic	MAO A, MAO B	Very weak, competitive inhibitor	11911838, 25455893	(Nandigama et al. 2002; Santillo 2014)
Phenylpropanolamine	Sympathomimetic, anorectic, and decongestant	MAO A, MAO B	Competitive and reversible inhibitor, weak inhibitor	3961266	(Yu 1986)
Pirlindole	Antidepressant, tetracyclic	**MAO A,** MAO B	Selective, reversible inhibitor	10.4236/ojd.2017.62004	(Entzeroth and Ratty 2017)
Primaquine, (*R*)-(-)-	Antimalarial, 8-aminoquinoline	MAO A, MAO B	Nonselective, weak, competitive, inhibitor	33922294, 3569526	(Brossi et al. 1987; Chaurasiya et al. 2021)
Primaquine, (*S*)-(+)-	Antimalarial, 8-aminoquinoline	**MAO A,** MAO B	Marginally selective, competitive, very weak inhibitor	33922294, 3569526	(Brossi et al. 1987; Chaurasiya et al. 2021)
Primaquine, racemic	Antimalarial, 8-aminoquinoline	MAO A, MAO B	Competitive, weak inhibitor	33922294	(Chaurasiya et al. 2021)
Rasagiline	Anti-Parkinsonian, propargylamines	MAO A, **MAO B**	Selective, irreversible inhibitor	15850677, 17296539, 29417334, 17545750, 18035186, 18652859	(Bortolato et al. 2008; Chen et al. 2007; Fernandez and Chen 2007; Guay 2006; Mandel et al. 2005; Szökő et al. 2018)
Safinamide and derivatives	Treatment of Parkinson's disease	MAO A, **MAO B**	Selective, strong, reversible inhibitor	10.4236/ojd.2017.62004, 26821152, 17915852, 33922294	(Binda et al. 2007; Chaurasiya et al. 2021; Entzeroth and Ratty 2017; Gidaro et al. 2016)
Selegiline, L-deprenyl	Antiparkinsonian, propargylamine	MAO A, **MAO B**	Selective (at lower concentrations/doses), strong, irreversible inhibitor, also FMO inhibitor	3083305, 8959982, 3008207, 29417334, 23934742, 17545750, 18652859, 14697898, 34207264, 30813423, 21992679, 29496172, 6304562, 33922294	(Behl et al. 2021; Bortolato et al. 2008; Fernandez and Chen 2007; Finberg and Youdim 1983; Murphy et al. 1986; Shulman et al. 2013; Szökő et al. 2018; Herraiz 2012;Chaurasiya et al. 2019; Gerlach et al. 1996; Glover et al. 1986; Magyar and Szende 2004; Chaurasiya et al. 2021)
Sembragiline	Alzheimer's disease drug, pyrrolidin-3-yl-acetamide derivative	MAO A, **MAO B**	Selective, irreversible, strong, long-lasting inhibitor	28642233, 10.4236/ojd.2017.62004	(Borroni et al. 2017; Entzeroth and Ratty 2017)
Tedizolid	Antibiotic, oxazolidinone	MAO A, MAO B	Non-selective, reversible, weak inhibitor	23612197	(Flanagan et al. 2013)
Toloxatone	Antidepressant, oxazolidinone	**MAO A,** MAO B	Selective, strong, reversible inhibitor	18652859, 10.4236/ojd.2017.62004, 28188065, 29395970, 29925480	(Baek et al. 2018a, b; Bortolato et al. 2008; Entzeroth and Ratty 2017)
Tranylcypromine	Antidepressant, amphetamine derivative	MAO A, MAO B	Nonselective, irreversible inhibitor	18652859, 23934742	(Bortolato et al. 2008; Shulman et al. 2013)
(±)-5-(*m*- Trifluoromethylphenoxy)primaquine	Antimalarial, primaquine derivative	MAO A, MAO B	Non-competitive (MAO A) and non-competitive (MAO B) strong inhibitor	3569526	(Brossi et al. 1987)

* Major enzyme is in bold font

Table 12 Examples of natural products as inhibitors of human MAO enzymes (Kong et al. 2004; Lee et al. 2008)

Inhibitor	Category	Enzyme*	Comments	PMID numbers	References
Acacetin	Natural compound, flavone	MAO A, MAO B	Strong, reversible, competitive inhibitor	27754693, 28634060, 30813423	(Chaurasiya et al. 2016, 2019; Lee et al. 2017a)
Acacetin 7-methyl ether	Natural product, flavone	**MAO B**	Strong, highly selective, reversible, and time-dependent inhibitor	30813423	(Chaurasiya et al. 2019)
Acacetin 7-*O*-(6-*O*-malonylglucoside)	Natural product, flavonoid glycoside	MAO A, MAO B	Reversible, competitive inhibitor	28634060	(Lee et al. 2017a)
Afromosin	Natural product, isoflavone	MAO A, MAO B	Nonselective, intermediate inhibitor	32087226	(Oh et al. 2020)
Alizarin	Natural product, Anthraquinone	**MAO A,** MAO B	Selective, intermediate inhibitor	28188065	(Lee et al. 2017c)
Angelicin, isopsoralen	Natural product, furocoumarin	MAO A, MAO B	Nonselective, intermediate to strong inhibitor	30686752	(Baek et al. 2019a)
Apigenin	Natural product, flavonoid	**MAO A**, MAO B	Strong, reversible, and selective inhibitor	25412041	(Chaurasiya et al. 2014)
Baicalein	Natural product, flavonoid, 5,6,7-Trihydroxyflavone	MAO A	Intermediate, selective inhibitor	28109809	(Lee et al. 2017b)
Bakuchicin	Natural product, furanocoumarin	MAO A, MAO B	Nonselective, intermediate to strong inhibitor	30686752	(Baek et al. 2019a)
Bavachinin	Natural product, flavanone	MAO A, **MAO B**	Selective and competitive MAO B inhibitor	26557867	(Zarmouh et al. 2015)
Bellidifolin	Natural product, xanthone	**MAO A,** MAO B	Strong inhibitor	18336006	(Urbain et al. 2008)
Bellidin	Natural product from *Gentianella amarella spp. Acuta*, xanthone	**MAO A**, MAO B	Strong inhibitor	18336006	(Urbain et al. 2008)
Biochanin A 7-*O*-β-D-gentibioside	Natural product, isoflavone	MAO A, **MAO B**	Selective, intermediate inhibitor	32087226	(Oh et al. 2020)
Biochanin-A	Natural product, benzopyrone	MAO A, **MAO B**	Strong, reversible, and selective MAO B inhibitor	28069007	(Zarmouh et al. 2017)
Caffeine	Natural product, methylxanthine	**MAO A,** MAO B	Weak, competitive, reversible, inhibitor	23850513, 33540300	(Grzelczyk et al. 2021; Petzer et al. 2013)
Calycosin	Natural product, isoflavone	MAO A, **MAO B**	Selective, strong, competitive, reversible inhibitor	32087226	(Oh et al. 2020)
Chelerythrine	Natural product, isoquinoline	**MAO A,** MAO B	Selective, reversible, and competitive strong inhibitor	29925480	(Baek et al. 2018b)
Chrysin	Natural product, flavonoid	**MAO A,** MAO B	Strong MAO A and intermediate MAO B inhibitor	33540300, 29496172, 34286787	(El-Hawary et al. 2021; Grzelczyk et al. 2021; Larit et al. 2018)
Cigarette smoke	Natural product, mainstream smoke from commercial cigarettes	MAO A, MAO B	Partly reversible, competitive inhibition of MAO A and mixed-type inhibition for MAO B	15582589, 21992679	(Herraiz 2012; Herraiz and Chaparro 2005)

Table 12 (continued)

Inhibitor	Category	Enzyme*	Comments	PMID numbers	References
Cinnamaldehyde	Natural product, component of bark of *Cinnamomum* species	MAO B	Weak inhibitor	33249607	(Chowdhury and Kumar 2021)
Cinnamyl alcohol	Natural product, aromatic alcohol	MAO A, **MAO B**	Weak inhibitor	19168123	(van Diermen et al. 2009)
cis-Cassigarol E	Natural product, dimeric stilbene	MAO A, MAO B	Nonselective, intermediate inhibitor	32087226	(Oh et al. 2020)
Coffee brews	Natural product	MAO A, MAO B	Reversible, competitive inhibition	16139309	(Herraiz and Chaparro 2006)
Coffee extracts	Natural product	MAO A	Selective, intermediate to strong inhibitor	33540300	(Petzer et al. 2013)
Corydaline	Natural product, isoquinoline	MAO A, **MAO B**	Selective, intermediate inhibitor	29925480	(Baek et al. 2018b)
Coumarin	Natural product, benzopyran	MAO A, MAO B	Nonselective, intermediate inhibitor	23517722	(Patil et al. 2013)
Curcumin	Natural product, diarylheptanoid	MAO A, **MAO B**	Intermediate inhibitor	31539917, 30809547	(Prinsloo et al. 2019; Zhang et al. 2019b)
Daidzein	Natural product, isoflavone	MAO A, MAO B	Nonselective, intermediate inhibitor	32087226	(Oh et al. 2020)
Decursin	Natural product, pyranocoumarin	MAO A	Strong selective inhibitor	28109809	(Lee et al. 2017b)
Decursinol angelate	Natural product, pyranocoumarin	MAO A	Intermediate inhibitor	28109809	(Lee et al. 2017b)
Dehydrocorydaline	Natural product, alkaloid	MAO A	Weak inhibitor	30712820	(Zhang et al. 2019a)
Dieckol	Natural product, phlorotannin	MAO A, MAO B	Mixed-type inhibition	28251489	(Jung et al. 2017)
Eckol	Natural product, phlorotannin	MAO A, MAO B	Mixed-type inhibition (MAO A); non-competitive inhibitor of MAO B	28251489	(Jung et al. 2017)
Epigallocatechin gallate	Natural product	MAO A, MAO B	Weak inhibitor	24218136	(Carradori et al. 2014)
Epigallocatechin gallate (EGCG) dimer	Natural product	MAO A, MAO B	Weak inhibitor	19168123	(van Diermen et al. 2009)
Eugenol	Natural product, allylbenzene	**MAO A**, MAO B	Competitive, intermediate MAO A inhibitor, weak MAO B inhibitor	33249607, 15936201	(Chowdhury and Kumar 2021; Tao et al. 2005)
Ferulic acid	Natural product, antioxidant	**MAO A,** MAO B	Selective MAO A Inhibitor	33540300, 34286787	(El-Hawary et al. 2021; Grzelczyk et al. 2021)
Fisetin hydrate	Natural product, flavonoid, flavanol	**MAO A**,	Strong and selective inhibitor	25412041	(Chaurasiya et al. 2014)
Formononetin	Natural product, pterocarpan	**MAO A**, MAO B	Nonselective or selective intermediate inhibitor	27575476, 32087226	(Lee et al. 2016; Oh et al. 2020)
Galangin	Natural product, flavonoid, polyphenol	**MAO A**, MAO B	Strong, reversible, and selective inhibitor	25412041	(Chaurasiya et al. 2014)

Table 12 (continued)

Inhibitor	Category	Enzyme*	Comments	PMID numbers	References
Genistein	Natural product, flavonoid	MAO A, MAO B	Nonselective intermediate to strong inhibitor	29496172, 28109809, 27575476, 32087226	(Larit et al. 2018; Lee et al. 2017b, 2016; Oh et al. 2020)
Genkwanin	Natural product, monomethoxyflavone	MAO A, MAO B	Nonselective strong inhibitor	30396116	(Baek et al. 2019b)
Green Robusta coffee extract	Natural product	MAO A	Weak, reversible, inhibitor	33540300	(Grzelczyk et al. 2021)
Guaiacol	Natural product, monomethoxybenzene	MAO A, MAO B	Weak inhibitor	30809547	(Zhang et al. 2019b)
Harmaline	Natural product, harmala alkaloid	MAO A	Competitive, reversible inhibitor	28302559, 23393220	(Herraiz and Guillén 2011; Wagmann et al. 2017)
Harman	Natural product, pyridoindole	**MAO A**	Strong, reversible, competitive inhibitor	15582589, 16139309, 21992679, 21554916, 24218136	(Carradori et al. 2014; Herraiz 2012; Herraiz and Chaparro 2005)
Harmine	Natural product, alkaloid	**MAO A,** MAO B	Selective, very strong, reversible inhibitor	28302559, 24218136, 2682115, 33922294	(Carradori et al. 2014; Chaurasiya et al. 2021; Herraiz and Guillén 2011; Wagmann et al. 2017)
Hispidol	Natural product, hydroxyaurone	**MAO A,** MAO B	Selective, competitive, strong inhibitor	29395970	(Baek et al. 2018a)
(-)-4-Hydroxy-3-methoxy-8,9-methylenedioxypterocarpan	Natural product, pterocarpan	MAO A, MAO B	Nonselective, intermediate inhibitor	27575476	(Lee et al. 2016)
Isoeugenol	Natural product, phenylpropene	**MAO A**, MAO B	Selective inhibitor	30809547	(Zhang et al. 2019b)
Isolupalbigenin	Natural product, isoflavone	MAO A, **MAO B**	Selective, intermediate inhibitor	32087226	(Oh et al. 2020)
Jatrorrhizine	Natural product, alkaloid, protoberberine	MAO A	Weak inhibitor	30712820	(Zhang et al. 2019a)
Kaempferol	Natural product, flavonoid	**MAO A,** MAO B	Selective, reversible, strong inhibitor	30396116, 26821152	(Baek et al. 2019b; Gidaro et al. 2016)
Kavain and kavalactones	Natural products, kavalactones	MAO A,**MAO B**	Reversible, intermediate, competitive inhibitor	31539917	(Prinsloo et al. 2019)
Kava-kava	Natural product, plant extract	MAO B	Reversible, intermediate inhibitor	9832350	(Uebelhack et al. 1998)
Kushenol F	Natural product, pterocarpan	**MAO A,** MAO B	Intermediate inhibitor of MAO A, weak inhibitor of MAO B	27575476	(Lee et al. 2016)
Liquiritigenin	Natural product, flavanone	MAO A, MAO B	Nonselective, intermediate inhibitor	32087226	(Oh et al. 2020)
(-)-Maackiain	Natural product, pterocarpan	MAO A, **MAO B**	Selective, strong inhibitor	27575476	(Lee et al. 2016)
(-)-Medicarpin	Natural product, pterocarpan	MAO A, **MAO B**	Strong, selective inhibitor	32087226	(Oh et al. 2020)
9-Methylnorharman, 9-Methyl-β-carboline	Natural product, pyridoindole	**MAO A**, MAO B	Intermediate inhibitor	21554916, 21651332, 32285253	(Herraiz and Guillén 2011; Keller et al. 2020; Polanski et al. 2011)
8-*O*-Methylretusin	Natural product, isoflavone	MAO A, **MAO B**	Selective, strong, competitive, reversible inhibitor	32087226	(Oh et al. 2020)

Table 12 (continued)

Inhibitor	Category	Enzyme*	Comments	PMID numbers	References
Norharman	Natural product, pyridoindole, β-carboline alkaloid	MAO A, MAO B	Nonselective, intermediate, reversible, competitive inhibitor	15582589, 16139309, 21992679, 21554916, 24218136	(Carradori et al. 2014; Herraiz 2012; Herraiz and Chaparro 2005, 2006; Herraiz and Guillén 2011)
Ononin	Natural product, isoflavone	MAO A, **MAO B**	Selective, intermediate inhibitor	32087226	(Oh et al. 2020)
Osthenol	Natural product, prenylated coumarin	**MAO A,** MAO B	Selective, strong inhibitor	30686752	(Baek et al. 2019a)
Palmatine	Natural product, isoquinoline alkaloid	MAO A	Weak inhibitor	30712820	(Zhang et al. 2019a)
Piperine	Natural product, piperidine alkaloid	MAO B	Weak inhibitor	33249607	(Chowdhury and Kumar 2021)
Propolis extract	Natural product	MAO A, MAO B	Strong and selective inhibitor	25412041	(Chaurasiya et al. 2014)
Psoralea corylifolia L. ethanolic extract	Natural product	MAO A, **MAO B**	Weaker inhibitor	26557867, 28069007	(Zarmouh et al. 2017, 2015)
Pterostilbene	Natural product, stilbenoid, polyphenol	**MAO B,** MAO A	Selective MAO B, competitive inhibitor	30809547	(Zhang et al. 2019b)
Purpurin	Natural product, anthraquinone	**MAO A,** MAO B	Selective, strong, reversible, and competitive inhibitor	28188065	(Lee et al. 2017c)
(-)-PwTX-I	Natural product, indolyl alkaloid	MAO A, **MAO B**	Intermediate inhibitor, non-competitive inhibitor	19501115	(Saidemberg et al. 2009)
(+)-PwTX-I	Natural product, indolyl alkaloid	MAO A, **MAO B**	Intermediate inhibitor, non-competitive inhibitor	19501115	(Saidemberg et al. 2009)
Retusin	Natural product, isoflavone	MAO A, **MAO B**	Selective intermediate inhibitor	32087226	(Oh et al. 2020)
Rhamnocitrin	Natural product, monomethoxy-flavone	**MAO A,** MAO B	Selective, strong, and reversible inhibitor	30396116	(Baek et al. 2019b)
Rhodiocyanoside A	Natural product, cyanogenic glycoside	MAO A, **MAO B**	Weak inhibitor	19168123	(van Diermen et al. 2009)
Rhodiola rosea L	Natural product, root extracts	MAO A, MAO B	Intermediate to strong inhibitors	24218136	(Carradori et al. 2014)
Rhodioloside B and C isomers, mixture	Natural product, monoterpene glycosides	MAO A, **MAO B**	Intermediate inhibitor	24218136, 19168123	(Carradori et al. 2014; van Diermen et al. 2009)
Rosavin	Natural product, cinnamyl alcohol glycoside	MAO A, MAO B	Weak inhibitor	24218136	(Carradori et al. 2014)
Rosin	Natural product; solid form of resin from pine trees	MAO A, MAO B	Weak inhibitor	24218136	(Carradori et al. 2014)
Rosiridin	Natural product, monoterpene	MAO A, **MAO B**	Intermediate inhibitor	24218136, 19168123	(Carradori et al. 2014; van Diermen et al. 2009)
Rubrofurasin	Natural product, naphtho-γ-pyrone	MAO A	Competitive, intermediate inhibitor	31460269	(Paudel et al. 2019)
Rutamarin	Natural product, coumarin	MAO A, **MAO B**	Selective, strong MAO B inhibitor	32527030	(Kozioł et al. 2020)

Table 12 (continued)

Inhibitor	Category	Enzyme*	Comments	PMID numbers	References
Salidroside	Natural product, tyrosol glucoside	MAO A, **MAO B**	Weak inhibitor	24218136	(Carradori et al. 2014)
Sigmoidin E	Natural product, flavanone	MAO A, **MAO B**	Selective, intermediate inhibitor	32087226	(Oh et al. 2020)
Sophoraflavanone B	Natural product, from roots of *Sophora flavescens*, pterocarpan	**MAO A,** MAO B	Selective, intermediate inhibitor	27575476	(Lee et al. 2016)
Sulfuretin	Natural product, aurone derivative	**MAO A,** MAO B	Selective, intermediate inhibition	29395970	(Baek et al. 2018a)
Swertianolin	Natural product, xanthone	MAO A, **MAO B**	Strong inhibitor	18336006	(Urbain et al. 2008)
Taxifolin, dihydroquercetin	Natural product, flavonoid, flavanonol	MAO A, MAO B	Intermediate inhibitor	25412041	(Chaurasiya et al. 2014)
Tectorigenin	Natural product, isoflavone	MAO A, MAO B	Nonselective, intermediate inhibitor	32087226	(Oh et al. 2020)
Tetrahydrocolumbamine	Natural product, alkaloid	MAO A	Weak inhibitor	30712820	(Zhang et al. 2019a)
Tetrahydropalmatine	Natural product, isoquinoline alkaloid	MAO A	Weak inhibitor	30712820	(Zhang et al. 2019a)
Theobromine	Natural product, methylxanthine	MAO	Weak, reversible, inhibitor	32252407	(Haj Ahmed et al. 2020)
Triandrin	Natural product, phenylpropanoid	MAO A, **MAO B**	Weak inhibitor	19168123	(van Diermen et al. 2009)
3,5,7-Trihydroxy-8-methoxy flavanone	Natural product, 8-*O*-methylated flavonoid	**MAO A**	Selective, intermediate inhibitor	30396116	(Baek et al. 2019b)
Tyrosol	Natural product, antioxidant, phenethyl alcohol derivative	MAO A, **MAO B**	Weak inhibitor	19168123	(van Diermen et al. 2009)
Ursolic acid	Natural product, iridoid glycoside, phytoconstituent compound	MAO B	Selective inhibitor	28034283	(Singla et al. 2017)
Vanillin	Natural product, aldehyde	MAO	Intermediate to strong inhibitor	31536738	(Truman et al. 2019)
Venom fraction from *Parawixia bistriata* (spider)	Natural product, crude extract from *P. bistriata*	MAO A, MAO B	Non-competitive inhibitor	19501115	(Saidemberg et al. 2009)
Wogonin	Natural product, *O*-methylated flavone	MAO A, MAO B	Intermediate inhibitor	28109809	(Lee et al. 2017b)
Yohimbine	Natural compound; Indole alkaloid	MAO A	Irreversible inhibitor	28302559	(Wagmann et al. 2017)

*Suggested major enzyme is in bold font

Table 13 Examples of general chemicals as inhibitors of human MAO enzymes

Inhibitor	Enzyme*	Comments	PMID numbers	References
1-Aminobenzotriazole	MAO A, MAO B	Non-selective and non-competitive inhibitor	28185143	(Shaik et al. 2017)
Benzimidazole arylhydrazones	MAO B	Strong to intermediate inhibitors, neuroprotective	33818516	(Anastassova et al. 2021)
Benzylamine-sulfonamide derivatives	MAO B	Strong inhibitors	32602377	(Sağlık et al. 2020)
5-Bromoindazole	MAO B	Competitive inhibitor	21554916	(Herraiz and Guillén 2011)
Carboxamide derivatives	MAO B	Selective, reversible inhibitor	2089085, 3794699, 2314388, 3126263	(Cesura et al. 1990a, 1987, 1988, 1990b)
Chalcone derivatives	MAO B	Strong, selective inhibitors	33571810	(Mellado et al. 2021)
2*H*-Chromene-3-carboxamides and *S*-2*H*-chromene-3-carbothioates	MAO B	Strong, selective inhibitors	24856304	(He et al. 2014)
Chromone derivatives	MAO B	Strong, selective, reversible inhibitors	28245770, 22850212, 22309913	(Legoabe et al. 2012a, 2012b; Mathew et al. 2017)
Coumarin derivatives	MAO A, MAO B	Strong, selective MAO A, or MAO B inhibitors	22137786, 33640631, 23231397, 21316817, 21872365, 23517722, 21923181, 24393810, 34723016, 17915852, 19267475, 34723016, 20659799, 21684743	(Binda et al. 2007; Chimenti et al. 2009; Delogu et al. 2011; Liu et al. 2021a; Matos et al. 2011a, 2011b, 2010, 2012; Mattsson et al. 2014; Patil et al. 2013; Rehuman et al. 2021; Secci et al. 2011; Serra et al. 2012)
N-Cyclopropyltetrahydropyridine analogs	**MAO B**	Time- and concentration-dependent inhibitors	8870990	(Nimkar et al. 1996)
N, α-Diethylphenethylamine	MAO A, MAO B	Very weak inhibitor	25455893	(Santillo 2014)
α-Ethylphenethylamine	**MAO A**, MAO B	Selective, competitive, intermediate inhibitor	25455893	(Santillo 2014)
Ethyl vanillin	MAO	Intermediate to strong inhibitor	31536738	(Truman et al. 2019)
Harmine derivatives	**MAO A**	Strong inhibitors	24218136	(Carradori et al. 2014)
1-Indanone and indane derivatives	MAO A, MAO B	Strong MAO B inhibitors (indanones)	25820651	(Mostert et al. 2015)
Indole and benzofuran derivatives	**MAO B**	Strong and selective inhibitors	20674099	(Prins et al. 2010)
Methylene blue	MAO A, MAO B	Strong, mixed-type, predominantly uncompetitive inhibitor	21554916	(Herraiz and Guillén 2011)
6-Methyl-3-phenylcoumarin derivatives	MAO B	Strong, selective inhibitors	19628387	(Matos et al. 2009)
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	MAO A, MAO B	Competitive, time-dependent, irreversible inhibitor	3489461, 3872126, 3295117	(Singer et al. 1986, 1985; Trevor et al. 1987b)
1-Methyl-4-phenylpyridinium (MPP^+)	MAO A, MAO B	Competitive inhibitor	3489461, 3494215, 3295117	(Singer et al. 1986; Takamidoh et al. 1987; Trevor et al. 1987b)
5-Nitroindazole	MAO B	Competitive inhibitor	21554916	(Herraiz and Guillén 2011)
NPC1161 racemic, 8-Aminoquinoline	MAO A, MAO B	Intermediate inhibitor	33922294	(Chaurasiya et al. 2021)
NPC1161A, (*S*)-(+)-, 8-Aminoquinoline	MAO A, **MAO B**	Strong selective, mixed type irreversible inhibitor	33922294	(Chaurasiya et al. 2021)
NPC1161B, (*R*)-(−)-, 8-Aminoquinoline	MAO A, MAO B	Intermediate, mixed type reversible inhibitor	33922294	(Chaurasiya et al. 2021)

Table 13 (continued)

Inhibitor	Enzyme*	Comments	PMID numbers	References
Phentermine	MAO A, MAO B	Very weak, competitive inhibitor	11911838, 25455893	(Nandigama et al. 2002; Santillo 2014)
Phenylcyclopropylamine derivatives, fluorinated	MAO A	Strong, selective irreversible inhibitors	15755651	(Ye et al. 2005)
Phenylisopropylamine derivatives	**MAO A**, MAO B	Strong, selective competitive inhibitors	17521909	(Fierro et al. 2007)
Pyrazoline derivatives	MAO A, MAO B	Selective, reversible inhibitors	24533911	(Mathew et al. 2013)
Ro 16-6491	MAO B	Reversible or irreversible inhibitor (condition-dependent)	3126263, 14651728	(Cesura et al. 1988; Iwasa et al. 2003)
Ro 19-6327	MAO B	Time-dependent, selective, reversible inhibitor	2744079, 3126263	(Cesura et al. 1989, 1988)
Ro 41-1049	MAO A	Selective inhibitor	14651728	(Iwasa et al. 2003)
Tryptamine α-methylated analogs	MAO A, MAO B	Weak to strong inhibitors (MAO A) or weak to intermediate inhibitors (MAO B)	28302559	(Wagmann et al. 2017)

*Suggested major enzyme is in bold font

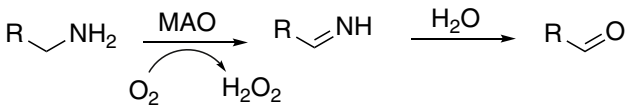


Fig. 19 Typical reaction catalyzed by MAO enzymes, where R denotes part of the molecule

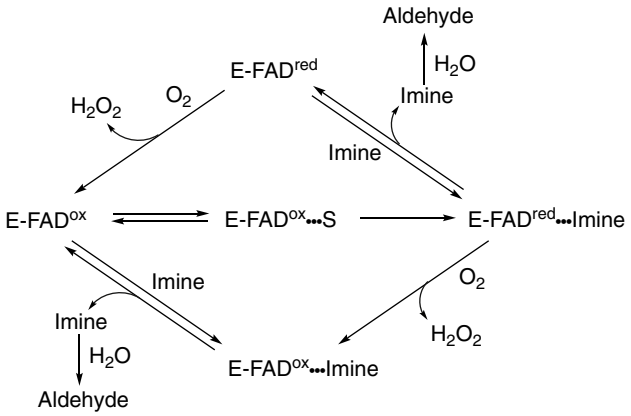


Fig. 20 Substrate oxidation by MAO enzymes (Edmondson et al. 2007)

neuropsychiatric disorders (mood disorders, Parkinson's disease, Alzheimer's disease) (Table 11). Tested natural products have shown a variety of activities and some of them were selective and strong as either MAO B (e.g., (−)-maackiain and (−)-medicarpin) or MAO A (e.g., apigenin) inhibitors (Table 12). In addition, extensive work has been done to synthesize derivatives of natural products as MAO inhibitors to be used as CNS drugs (Gulcan and Orhan 2020; Lu et al. 2013; Mathew and Kim 2020) (Table 13).

Activators and inducers

Valproic acid, which has been widely used in clinics for the treatment of multiple neuropsychiatric disorders such as epilepsy and bipolar disorder, exerts its activity by regulating the brain levels of serotonin. The compound was reported to increase MAO A catalytic activity, mRNA levels, and promoter activity (Wu and Shih 2011).

Bavachin, a *Psoralea corylifolia* L. seed compound, has been also reported to be an activator of the activity (Zarmouh et al. 2015), along with clomipramine (Reid et al. 1988).

Reactions

The general reaction catalyzed by MAO enzymes (Ramsay and Albreht 2018) is shown in Fig. 19.

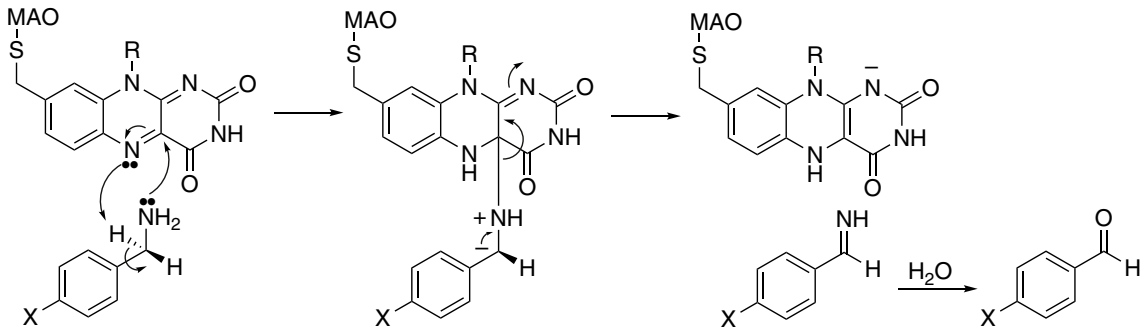


Fig. 21 Deamination of benzylamines by MAO enzymes

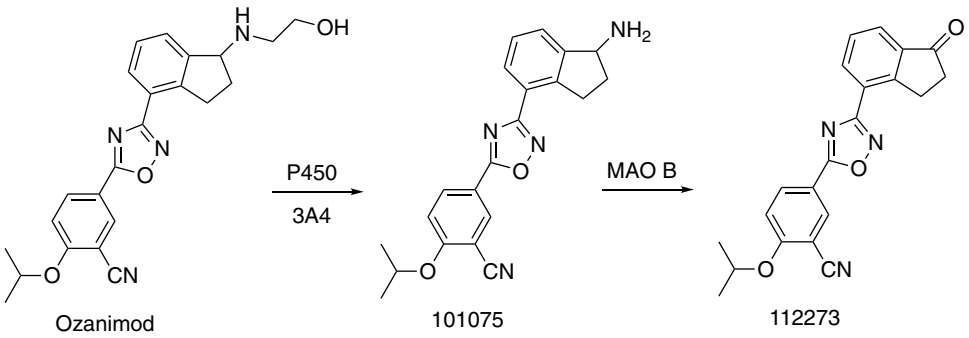


Fig. 22 Ozanimod metabolism by P450 and MAO enzymes

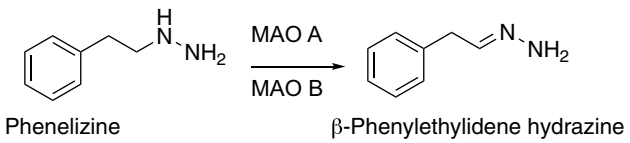


Fig. 23 Phenelzine oxidation to β-phenylethylidenehydrazine

MAO enzymes catalyze oxidative deamination reactions, including cleavage of C–N bonds with the formation of several chemical species with neurotoxic potential, e.g., hydrogen peroxide, ammonia, and aldehydes. As a consequence, prolonged excessive activity of these enzymes can lead to mitochondrial damage and neurodegenerative disorders.

Oxidative deamination reactions are also catalyzed by P450 enzymes. However, the mechanism catalyzed by MAO enzymes differs from the reaction catalyzed by P450s in that one of the products of the overall reaction is hydrogen peroxide (Fig. 19), while in the reactions catalyzed by cytochromes P450 the product is a water molecule, i.e. fully reduced oxygen (Guengerich 2022).

Substrate oxidation by MAO enzymes

The MAO enzymes share similar overall structures, with nearly identical FAD-binding domains, but contain varied substrate binding sites. It should be noted that, in contrast to the FMOs, AOX, XOR, and NADPH-P450 reductase, the MAO enzymes have the flavin covalently attached to the protein via a histidine residue. As flavoprotein oxidases, they catalyze substrate oxidation via two half-reactions. In the reductive half-reaction two hydrogen atoms are transferred to the MAO FAD complex when it accepts a hydride equivalent from the substrate, while in the oxidative step the MAO $FADH_2$ complex is oxidized to form MAO FAD by molecular oxygen (generating H_2O_2) (Figs. 20, 21). Due to the ability of the flavin prosthetic group to accept either one or two electrons (i.e., as a biological "transformer" (Walsh 1979)), several mechanisms have been proposed for the transfer of electrons from the substrate to the prosthetic group (Behl et al. 2021; Edmondson et al. 2007; Fitzpatrick 2010; Gaweska and Fitzpatrick 2011; Ramsay and Albreht 2018; Scrutton 2004).

Drugs as substrates of MAO enzymes

Numerous drugs possessing a nucleophilic heteroatom are substrates of MAO enzymes (Table 8). Knowledge of the involvement of either MAO A, MAO B, or both enzymes in the metabolism of a drug allows for the prediction of drug–drug interactions with selective or non-selective MAO inhibitors. It should be emphasized that these are mitochondrial enzymes and that in vitro studies with microsomes will not include these enzymes or evaluate

Table 14 Examples of compounds activated to toxic products by human MAO enzymes**

Compound	Category	Enzyme*	Comments	PMID numbers	References
Benzylamine	Phenylmethylamine	MAO B	Deamination, benzaldehyde formation	3244400, 2509446, 20227955	(Lewinsohn et al. 1980; Reid et al. 1988; Szutowicz et al. 1989)
Dopamine	Physiological compound, catecholamine, neurotransmitter	MAO A, **MAO B**	Deamination, 3,4-dihydroxyphenylacetaldehyde formation	6408492, 22906103, 29417334, 31807952, 10202537	(Goldstein 2020; Goldstein et al. 2012; O'Carroll et al. 1983; Shih et al. 1999; Szökő et al. 2018)
Epinephrine, adrenaline	Physiological compound, neurotransmitter, hormone	MAO A	Deamination, aldehyde formation	21971001	(Bortolato and Shih 2011)
Kynuramine	Physiological compound, biogenic amine, alkyl-phenyl ketone	MAO A, MAO B	Deamination, propionaldehyde and 4-hydroxyquinoline formation	28185143, 28302559, 30809547, 30813423, 25455893	(Chaurasiya et al. 2019; Santillo 2014; Shaik et al. 2017; Wagmann et al. 2017; Zhang et al. 2019b)
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Tetrahydropyridine	MAO A, **MAO B**	$MPDP^+$ and pyridine MPP^+ formation, mechanism-based inactivation, 1,4-dihydropyridine adducts formation, neurotoxic	3083305, 3874094, 3287698, 3295117, 21992679, 21554916	(Fritz et al. 1985; Glover et al. 1986; Herraiz 2012; Herraiz and Guillén 2011; Trevor et al. 1987a, 1988)
Nomifensine	Antidepressant, tetrahydroisoquinoline, withdrawn from the market	MAO A	Dihydroisoquinolinium ion formation (also formed by other enzymes), risk of anemia, and hepatotoxicity	16679384	(Obach and Dalvie 2006)
Norepinephrine, Noradrenaline	Physiological compound, catecholamine, neurotransmitter	MAO A	3,4-Dihydroxyphenylglycolaldehyde formation,	21971001, 23934742	(Bortolato and Shih 2011; Shulman et al. 2013)
Pargyline	Antihypertensive, antidepressant, withdrawn from the market	MAO A, **MAO B**	Partially selective, strong, and irreversible inhibitor, CNS toxicity, generation of H_2O_2	9564606, 111275, 6304562, 29395970	(Baek et al. 2018a; Finberg and Youdim 1983; Murphy et al. 1998, 1979)
Serotonin, 5-hydroxytryptamine	Physiological compound, indolamine, neurotransmitter	MAO A	5-Hydroxyindolaldehyde formation,	3008207, 861051, 10202537, 31344280, 21971001, 11134050, 23934742	(Bortolato and Shih 2011; Donnelly and Murphy 1977; Geha et al. 2001; Kyritsi et al. 2020; Murphy et al. 1986; Shih et al. 1999; Shulman et al. 2013; Zhang et al. 2019b)
Tyramine	Natural product and physiological compound, trace amine	**MAO A,** MAO B	4-Hydroxyacetaldehyde formation, also substrate for FMO3, P450 2D6 (dopamine formation), and alcohol dehydrogenase (aldehyde reduction)	14697899, 6788990, 21679153, 23934742, 7272178, 7272177	(Martini et al. 1981a, 1981b; Niwa et al. 2011; Oguchi et al. 1981; Shulman et al. 2013; Youdim and Weinstock 2004)

*Suggested major enzyme is in bold font

**Data extracted from Tables 8, 9, 10

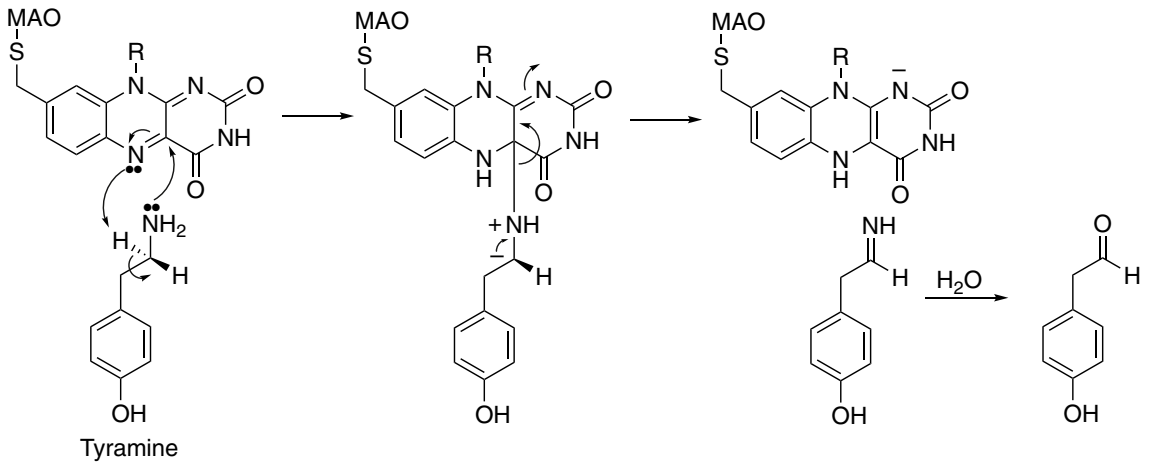


Fig. 24 Deamination of tyramine by MAO enzymes

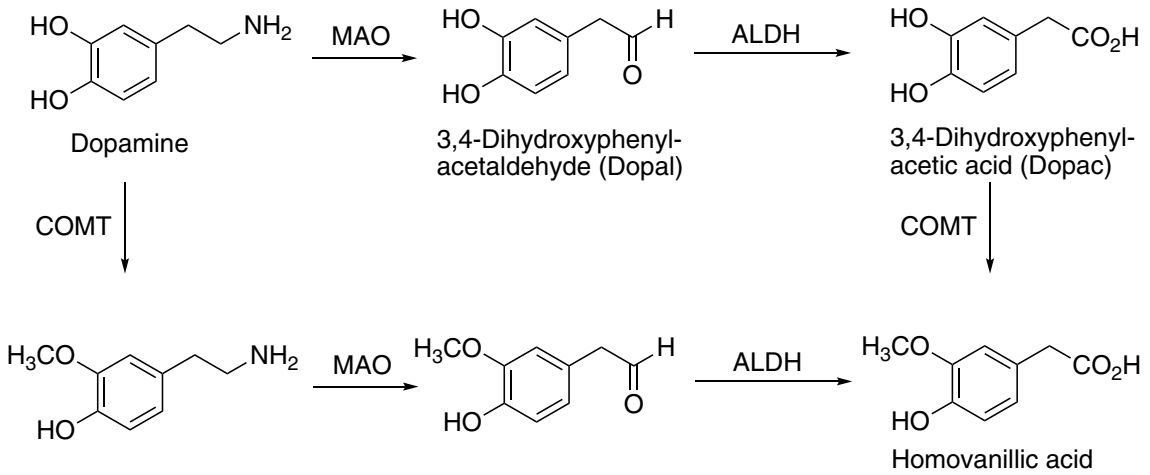


Fig. 25 Activation and deactivation of dopamine

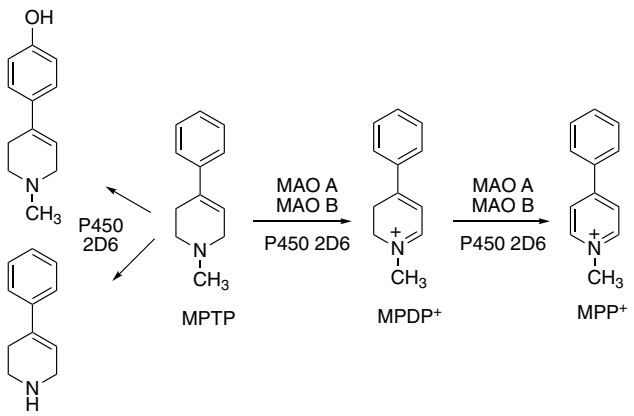


Fig. 26 Bioactivation and detoxication of MPTP by MAO and P450 enzymes

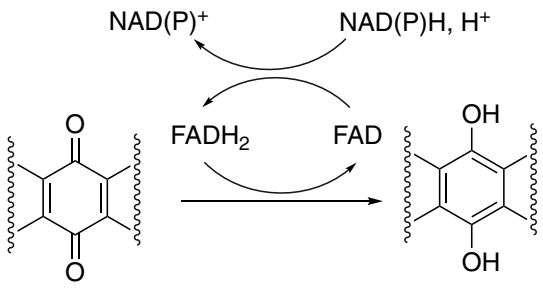


Fig. 27 Typical reaction catalyzed by NQO enzymes

their metabolic potential. The metabolism of a drug that is deaminated by both forms of MAO is not necessarily inhibited in vivo by selective MAO A or MAO B inhibitors. If a drug is metabolized by MAOs, competitive interactions

Table 15 Examples of drug substrates in reactions catalyzed by human AOX1

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
A-77-01	Strong inhibitor of the TGF-β1 receptor	Oxidation	Quinoline portion proposed in reaction	29615437	(Dick 2018)
ABT-418	Selective agonist of nicotinic acetylcholine receptors with cognitive enhancing and anxiolytic activities	Oxidation	Lactam metabolite formation, also formed by P450 enzymes	8654204, 7530622	(Rodrigues et al. 1994, 1995)
Allopurinol	Xanthine oxidase inhibitor used for gout	Oxidation	Oxypurinol formation	10481935, 16702728	(Kitamura et al. 2006; Shibutani et al. 1999)
AMG900	Strong and highly selective pan-aurora kinase inhibitor	Oxidation	Aminopyrimide-pyridine ring oxidation	29615437	(Dick 2018)
(*S*)-4-(2-Amino-8-((1-hydroxypropan-2-yl)amino)quinazolin-6- yl)-5-ethyl-2-fluorophenol	Janus kinase inhibitor, compound 46e	Oxidation	Quinazolinone formation	34928601	(Wellaway et al. 2022)
(*S*)-4-(2-Amino-8-((1-methylpiperidin-3-yl)amino)quinazolin-6- yl)-5-ethyl-2-fluorophenol	Janus kinase inhibitor, compound 51e	Oxidation	Quinazolinone formation	34928601	(Wellaway et al. 2022)
4-(2-Amino-8-((1-methylpiperidin-4-yl)amino)quinazolin-6-yl)- 5-ethyl-2-fluorophenol	Janus kinase inhibitor, compound 51b	Oxidation	Quinazolinone formation	34928601	(Wellaway et al. 2022)
Azathioprine	Immunosuppressant, thiopurine, prodrug	Oxidation	8-Hydroxyazathiopurine formation	32282298, 22495427, 5795466, 3905317	(Chalmers et al. 1969; Kurzawski et al. 2012; Mahasneh et al. 2020; Van Scoik et al. 1985)
Azelnidipine	Calcium channel antagonist, Dihydropyridine	Reduction	Nitro reduction, weak reduction	30367827	(Ogiso et al. 2018)
Bafetinib	Anticancer, tyrosine kinase inhibitor	Oxidation	Terminal pyrimidine proposed	29615437	(Dick 2018)
O^6-Benzylguanine	Antineoplastic; guanine derivative	Oxidation	8-Oxidation, used as a biomarker	30337443, 22522748, 29615437, 28884164, 7503788, 9586894 20444863 28281401 30787100	(Abbasi et al. 2019; Crouch et al. 2018; Dick 2018; Dolan et al. 1998; Paragas et al. 2017b; Roy et al. 1995; Strelevitz et al. 2012; Xie et al. 2019; Zientek et al. 2010)
BILR 402	BIL 355, HIV-1 reverse transcriptase inhibitor, gut flora metabolite	Oxidation	BILR 516 formation, oxidation of azaheterocycle	22393121, 22393120	(Li et al. 2012a, 2012b)
Brimonidine	α -2 Adrenergic agonist, ocular hypertension treatment in glaucoma	Oxidation	2-Oxobrimonidine, 3-oxobrimonidine, and 2,3-dioxobrimonidine formation	8905918	(Acheampong et al. 1996)
BRL 55792	Anti-viral, guanine derivative, prodrug	Oxidation	C6-Oxidation, the major enzyme	8013273	(Harrell et al. 1994))

Table 15 (continued)

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
Capmatinib (INCB28060)	Antineoplastic, mesenchymal-epithelial transition (MET) tyrosine kinase inhibitor	Oxidation	Lactam formation, imidazotriazinone formation, most abundant in vivo metabolite	32665418, 29615437	(Dick 2018; Glaenzel et al. 2020)
Carbazeran	Phosphodiesterase inhibitor	Oxidation	4-Oxo formation, used as a catalytic marker, high metabolic clearance	3130251, 4024658, 22031625, 32357972, 30337443, 32393528, 31289113, 29615437, 25249692, 28474310, 20444863 22190693	(Beedham et al. 1987; Chen et al. 2019; Dick 2018; Hutzler et al. 2012; Kaye et al. 1985; Manevski et al. 2014; Sharma et al. 2012; Tan et al. 2020; Uehara et al. 2020; Wilkinson et al. 2017; Xie et al. 2019; Zientek et al. 2010)
Citalopram aldehyde	MAO and P450 citalopram metabolite, selective serotonin reuptake inhibitor	Oxidation	Citalopram propionic acid derivative formation	9698084, 22335465, 31128989	(Dalvie and Di 2019; Garattini and Terao 2012; Rochat et al. 1998)
CL-387785	Irreversible inhibitor of epidermal growth factor receptor	Oxidation	Unsubstituted carbon of the quinazoline between the two nitrogens	29615437	(Dick 2018)
Clonazepam	Benzodiazepine	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
CP-544439	Selective inhibitor of matrix metalloproteinase-13	Reduction	Hydroxamate reduction to an amide metabolite	18566038, 14709625	(Dalvie et al. 2008; Obach 2004)
DACA	Anticancer, DNA intercalating dual topoisomerase I/II poison, 4-methyl acridine derivative	Oxidation	Acridone metabolite formation, used as probe substrate	22335465, 22996261, 24006961, 22522748, 10810450, 20444863, 28884164, 30023718 30787100 11569919	(Abbasi et al. 2019; Al-Salmy 2001; Barr and Jones 2013; Barr et al. 2013; Garattini and Terao 2012; Montefiori et al. 2017; Paragas et al. 2017b; Schofield et al. 2000; Strelevitz et al. 2012; Zientek et al. 2010)
Dantrolene	Skeletal muscle relaxant	Reduction	Nitro reduction, aminodantrolene formation, hydroxylamine formation, activation to a toxic product	29522712, 30367827, 33020066	(Abbasi et al. 2020; Amano et al. 2018; Ogiso et al. 2018)
6-Deoxypenciclovir	Famciclovir metabolite	Oxidation	Penciclovir and 8-oxo-6-deoxypenciclovir formation, activation to active metabolite, also XOR substrate	9224775, 28474310, 20444863	(Rashidi et al. 1997; Wilkinson et al. 2017; Zientek et al. 2010)
DS-1971a	Selective Na V 1.7 inhibitor	Oxidation	Pyrimidine ring oxidation	34330191	(Asano et al. 2021)
Duvelisib	Antineoplastic, phosphatidylinositol 3-kinase inhibitor	Oxidation	Aminopurine moiety	29615437	(Dick 2018)

Table 15 (continued)

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
4-(8-((*endo*-8-Azabicyclo[3.2.1]octan-3-yl)amino)-2-aminoquinazolin-6-yl)-5-ethyl-2-fluorophenol	Janus kinase inhibitor, compound 51f	Oxidation	Quinazolinone formation	34928601	(Wellaway et al. 2022)
Falnidamol (BIBX 1382)	Selective EGFR tyrosine kinase inhibitor	Oxidation	Oxidation of pyrimido-pyrimidine core, high metabolic clearance	22031625, 28939686, 28281401, 25035284, 30787100	(Abbasi et al. 2019; Crouch et al. 2017; Crouch et al. 2018; Dick 2018; Hutzler et al. 2014; Hutzler et al. 2012)
Famciclovir	Antiviral, prodrug of penciclovir, 2-aminopurine derivative	Oxidation	Dideacetylation and 6-oxidation to penciclovir, activation to the active metabolite	7736920, 9224775	(Clarke et al. 1995; Rashidi et al. 1997)
Fasudil	Strong Rho-kinase inhibitor and vasodilator	Oxidation	2-Hydroxyfasudil	28166443	(Mao et al. 2018)
Favipiravir	Antiviral, anti-influenza drug, purine nucleic acid analog, prodrug	Oxidation	Inactive metabolite formation	33754379, 32536670	(Hanioka et al. 2021; Mishima et al. 2020)
FK3453	Adenosine A1/2 dual inhibitor	Oxidation	Aminopyrimidine moiety, high metabolic clearance	21984595, 21385103	(Akabane et al. 2011; Sanoh et al. 2012)
Flunitrazepam	Central nervous system depressant, benzodiazepine	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
5-Fluoro-2-pyrimidinone	Anti-cancer, prodrug	Oxidation	5-Fuorouracil formation, activation to a reactive metabolite	16702728, 12003195	(Kitamura et al. 2006; LoRusso et al. 2002)
Flutamide	Antineoplastic, antiandrogen	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
GDC-0834	Bruton's tyrosine kinase inhibitor	Hydrolysis	Unique amide hydrolysis, also hydrolyzed by carboxylesterase	25845827, 21742900	(Liu et al. 2011; Sodhi et al. 2015)
Idelalisib	Antineoplastic, phosphatidylinositol 3-kinase inhibitor	Oxidation	Formation of inactive GS-563117	25821156, 26242379	(Jin et al. 2015; Ramanathan et al. 2016)
Imatinib	Antineoplastic, Bcr-Abl tyrosine kinase inhibitor	Oxidation	Imatinib AO-M1 formation	29615437	(Dick 2018)
Imrecoxib	Selective cyclooxygenase-2 inhibitor	Oxidation	Oxidation following hydroxylation by P450 enzymes	29980580	(Hou et al. 2018)
5-Iodo-2-pyrimidinone-2′-deoxyribose	Anti-cancer, radiosensitizer, prodrug of 5-iodo-2′-deoxyuridine	Oxidation	5-Iodo-2′-deoxyuridine formation: activation to the active metabolite	1599512, 10778979, 15001663	(Chang et al. 1992; Kinsella et al. 2000; Rooseboom et al. 2004)
JNJ-38877605	Anticancer, Selective c-Met tyrosine kinase Inhibitor	Oxidation	Oxidation of an azaheterocycle, insoluble metabolite formation, activation to the toxic metabolite	25745036	(Lolkema et al. 2015)

Table 15 (continued)

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
KW-2449	Multikinase inhibitor	Oxidation	Oxidation following MAO B oxidation to iminium intermediate	28751116	(Hosogi et al. 2017)
Lapatinib	Antineoplastic, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor	Oxidation	Quinazoline oxidation	29615437, 31492693	(Bissada et al. 2019; Dick 2018)
Lapatinib metabolite M1	Debenzylated metabolite	Oxidation	Quinazoline oxidation	29615437, 31492693	(Bissada et al. 2019; Dick 2018)
Lenvatinib	Antineoplastic, vascular endothelial growth factor (VEGF), multityrosine kinase inhibitor	Oxidation	Quinolinone formation	24914245	(Inoue et al. 2014)
LDN-193189	Strong and selective ALK2 and ALK3 inhibitor	Oxidation	Quinoline part of the molecule	29615437	(Dick 2018)
LU AF09535	High-affinity negative allosteric modulator at the human metabotropic glutamate 5 receptor	Oxidation	Hydroxy metabolite formation, high metabolic clearance	27737930	(Jensen et al. 2017)
6-Mercaptopurine	Anticancer drug and treatment of autoimmune diseases, purine antagonists	Oxidation	Oxidation to 6-thioxanthine (6TX) by AO, XOR, and XDH, further oxidation to 6-thiouric acid by XOR and XDH, metabolic inactivation	22335465, 24824603	(Choughule et al. 2014; Garattini and Terao 2012)
Methotrexate	Antineoplastic, Antifolate, Antirheumatic	Oxidation	7-Hydroxymethotrexate formation, activation to insoluble toxic metabolite	10385213, 26032640, 32393528, 20444863	(Choughule et al. 2015; Jordan et al. 1999; Tan et al. 2020; Zientek et al. 2010)
ML-347	Strong and selective ALK2 and ALK1 inhibitor	Oxidation	Quinoline hydroxylation	29615437	(Dick 2018)
Momelotinib	Anticancer, an inhibitor of Janus kinase (JAK)1/2 and of activin A receptor type 1 (ACVR1)	Oxidation	Azaheterocycle oxidation, P450 oxidation of morpholine to carbinolamine intermediate followed by AO oxidation to morpholino lactam, the active metabolite	29311136	(Zheng et al. 2018)
Nifedipine	Calcium-channel blocker	Reduction	Nitro reduction, weak reduction	30367827	(Ogiso et al. 2018)
Nilutamide	Antineoplastic, nonsteroidal antiandrogen	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimesulide	Non-selective non-steroidal anti-inflammatory (NSAID)	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimetazepam	Hypnotic and sedative, Benzodiazepine	Reduction	Nitro reduction, hydroxylamine formation, Activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimodipine	Calcium channel blocker	Reduction	Nitro reduction, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)

Table 15 (continued)

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
Nitrazepam	Hypnotic, Benzodiazepine	Reduction	Nitro reduction, 7-aminonitrazepam formation, activation to toxic metabolite after *N*-acetylation	28606603, 30367827	(Konishi et al. 2017; Ogiso et al. 2018)
Oxycodone *N*-oxide	Oxycodone metabolite	Reduction	*N*-Oxide reduction to oxycodone, reduction also catalyzed by quinone reductase and hemoglobin	31727673	(Cashman et al. 2020)
PF-945863	Macrolide antibiotic	Oxidation	Naphthyridine oxidation	20444863	(Zientek et al. 2010)
PF-4217903	Anticancer, selective inhibitor of c-Met kinases	Oxidation	Quinoline oxidation	20444863	(Zientek et al. 2010)
PF-5190457	Ghrelin receptor inverse agonist	Oxidation	2-Pyrimidone formation	31182423	(Adusumalli et al. 2019)
Pyrazinamide	Antitubercular agent	Oxidation	5-Hydroxypyrazinamide and pyrazinone formation	10481935, 16702728	(Kitamura et al. 2006; Shibutani et al. 1999)
Quinidine	Antiarrhythmic and antimalarial	Oxidation	2′-Quinidine formation	3130251	(Beedham et al. 1987)
Quinine	Antimalarial	Oxidation	2′-Quinine formation, weak substrate	3130251	(Beedham et al. 1987)
Quinoline triazolopyridine analogs	c-Met inhibitors, various N-substituents at the 3-position	Oxidation	Quinolinone formation	30209037	(Zhang et al. 2018)
Ripasudil, K-115	Selective and Strong Rho-associated coiled coil-containing protein kinase (ROCK) inhibitor, ophthalmic agent	Oxidation	Hydroxyquinoline metabolite formation, also oxidized by P450 3A4/5 to iminium ion intermediate followed by AO mediated lactam formation	26678038	(Isobe et al. 2016)
RO-1	Anticancer, p38 Kinase inhibitor	Oxidation	C4-Hydroxylation, high metabolic clearance	20177421	(Zhang et al. 2011)
RS-8359	Antidepressant activity, selective MAO A inhibitor	Oxidation	(*S*)-2-Oxo formation, stereospecific oxidation of (*S*)-enantiomer	16192108, 20444863	(Itoh et al. 2005; Zientek et al. 2010)
SB-525334	Selective inhibitor of transforming growth factor-β receptor	Oxidation	Quinozaline oxidation	29615437	(Dick 2018)
SGX523	Anticancer, inhibitor of MET receptor tyrosine kinase	Oxidation	2-Quinolinone formation, insoluble metabolite formation, species-specific renal toxicity	20421447, 22547164, 28281401	(Crouch et al. 2018; Diamond et al. 2010; Infante et al. 2013)
Sulindac	NSAID	Reduction	Sulfoxide reduction, sulindac sulfide formation	31993760	(Sung et al. 2020)
6-Thioguanine	Anticancer, leukemia treatment	Oxidation	8-Hydroxythioguanine formation	10525111	(Kitchen et al. 1999)
Tolbutamide benzaldehyde metabolite	P450 2C9/aldehyde dehydrogenase tolbutamide metabolite	Oxidation	4-Carboxytolbutamide formation, P450 2C9 metabolism to 4-hydroxytolbutamide followed by aldehyde dehydrogenase catalyzed conversion to benzaldehyde intermediate	33455497, 20853847, 31128989	(Dalvie and Di 2019; Pryde et al. 2010; Uehara et al. 2021)

Table 15 (continued)

Drug	Category	Reaction	Comments/site of metabolism	PMID numbers	References
VU0424238 (Auglurant)	Negative allosteric modulator of metabotropic glutamate receptor subtype 5 (mGlu5 NAM)	Oxidation	6-Oxopyrimidine formation, secondary oxidation to 2,6-dioxopyrimidine via AOX or XO (species-dependent)	28939686	(Crouch et al. 2017)
VU0409106	Negative allosteric modulator of metabotropic glutamate receptor subtype 5	Oxidation	6-Oxopyrimidine formation, XO oxidation to 2,6-dioxopyrimidine	22711749, 26936972	(Crouch et al. 2016; Morrison et al. 2012)
VX-509 (Decernotinib)	Strong and selective Janus kinase 3 inhibitor	Oxidation	Oxidation of azaheterocycle to form hydroxydecernotinib, metabolite is time-dependent inhibitor of P450 3A4	29615437, 27298338	(Dick 2018; Zetterberg et al. 2016)
XK-469	Anticancer agents; selective topoisomerase II β inhibitor	Oxidation	Pyrazine oxidation	22335465, 29615437, 24300566, 22031625, 20444863, 15895233, 30135244	(Anderson et al. 2005; Burton et al. 2018; Dick 2018; Garattini and Terao 2012; Hutzler et al. 2012; Ramírez et al. 2014; Zientek et al. 2010)
Zaleplon	Sedative, hypnotic agent	Oxidation	5-Oxo-zaleplon formation, also substrate of P450 enzymes	12419014, 28029084, 22031625, 32393528, 22522748, 28884164, 28474310, 20444863, 30787100, 28281401, 12419015	(Abbasi et al. 2019; Crouch et al. 2018; Hutzler et al. 2012; Lake et al. 2002; Paragas et al. 2017b; Renwick et al. 2002; Strelevitz et al. 2012; Tan et al. 2020; Tanoue et al. 2017; Wilkinson et al. 2017; Zientek et al. 2010)
Zebularine	Anticancer, nucleoside analog of cytidine, inhibitor of cytidine deaminase	Oxidation	Azauridine formation	22335465, 16143537	(Garattini and Terao 2012; Klecker et al. 2006)
Ziprasidone	Second-generation antipsychotic	Reduction	Reduction of benzisothiazole ring to dihydroziprasidone; also, substrate of oxidative metabolism catalyzed by P450 enzymes	16282848, 22559212, 15821046, 9224781	(Miao et al. 2005; Obach et al. 2012; Obach and Walsky 2005; Prakash et al. 1997)
Zoniporide	Strong and selective human NHE-1 inhibitor	Oxidation	2-Oxozoniporide formation, active metabolite formation	22522748, 23046389, 20040581, 29615437, 25249692, 28884164, 20444863, 30787100, 28281401, 22190693	(Abbasi et al. 2019; Crouch et al. 2018; Dalvie et al. 2013, 2010; Dick 2018; Manevski et al. 2014; Paragas et al. 2017b; Sharma et al. 2012; Strelevitz et al. 2012; Zientek et al. 2010)
Zoniporide analogs	Zoniporide analogs with modifications of the acylguanidine moiety, the cyclopropyl group on the pyrazole ring and the quinoline ring	Oxidation	Quinolinone formation	22587988	(Dalvie et al. 2012)

Table 16 Drug inhibitors of human AOX1

Compound	Category	Comments	PMID numbers	References
Acolbifene	Antiestrogen, selective estrogen receptor modulator	Weak inhibition	31289113	(Chen et al. 2019)
Amitriptyline	Antidepressant, tricyclic	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Amlodipine	Calcium channel blocker	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Amodiaquine	Antimalarial and anti-inflammatory, 4- aminoquinoline	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Amsacrine	Antineoplastic	Intermediate inhibition	20853847, 10810450	(Pryde et al. 2010; Schofield et al. 2000)
Antimycin A	Antibiotic, inhibitor of oxidative phosphorylation	Intermediate inhibition	4226961	(Johns 1967)
Bazedoxifene	Antiestrogen, selective estrogen receptor modulator	Competitive inhibitor	31289113	(Chen et al. 2019)
5-Benzyl acyclouridine	Acyclouridine derivative, strong inhibitor of uridine phosphorylase, antitumor activity, reduction of 5-FU toxicity	Intermediate inhibition	16143537	(Klecker et al. 2006)
Chlorpromazine	Antipsychotic, phenothiazine	Intermediate to strong inhibition, predominately competitive inhibition, does not inhibit reduction reaction	12419014, 21940905, 14681337, 22996261, 4226961, 24156774, 16282848	(Barr and Jones 2011, 2013; Johns 1967; Lake et al. 2002; Nirogi et al. 2014; Obach et al. 2004; Obach and Walsky 2005)
Cimetidine	Histamine H2-receptor antagonist	Weak competitive inhibitor, also inhibitor of P450 enzymes	12419014, 12419015, 14681337, 20853847	(Lake et al. 2002; Obach et al. 2004; Pryde et al. 2010; Renwick et al. 2002)
Clomiphene	Non-steroidal fertility drug	Intermediate inhibition	14709625	(Obach 2004)
Clomipramine	Tricyclic antidepressant	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Clozapine	First-generation antipsychotic	Intermediate inhibition, does not inhibit reduction reaction	21940905, 14681337, 22996261, 16282848	(Barr and Jones 2011, 2013; Obach et al. 2004; Obach and Walsky 2005)
Cyclobenzaprine	Centrally acting muscle relaxant	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Desmethylerlotinib	Erlotinib metabolite	Strong competitive inhibitor	32393528	(Tan et al. 2020)
Desmorpholinopropylgefitinib	Gefinitib metabolite	Partial competitive inhibition	32393528	(Tan et al. 2020)
Diethylstilbestrol	Synthetic estrogen	Strong to intermediate inhibition	4226961, 20853847, 14709625	(Barr and Jones 2011, 2013; Obach 2004)
Domperidone	Antiemetic; Dopamide D2 receptor antagonist	Intermediate, predominantly competitive inhibition, does not inhibit reduction reaction	21940905, 14681337, 22996261, 16282848	(Barr and Jones 2011, 2013; Obach et al. 2004; Obach and Walsky 2005)

Table 16 (continued)

Compound	Category	Comments	PMID numbers	References
Droloxifene	Anticancer, antiestrogen	Strong inhibition	14709625	(Obach 2004)
Erolitinib	Anticancerepidermal growth factor receptor tyrosine kinase inhibitor	Strong, partially competitive inhibition	32393528	(Tan et al. 2020)
Erythromycin	Macrolide antibiotic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
17 α -Ethynylestradiol	Estrogen, oral contraceptive	Strong inhibition, weakly inhibits reduction reaction	21940905, 14681337, 33455497, 24156774, 22996261, 16282848	(Barr and Jones 2011, 2013; Nirogi et al. 2014; Obach et al. 2004; Obach and Walsky 2005; Uehara et al. 2021)
Felodipine	Calcium channel blocker	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Fulvestrant	Anticancer, estrogen receptor antagonist	Strong inhibition	14709625	(Obach 2004)
GDC-0834	Bruton's tyrosine kinase inhibitor	Strong reversible inhibition	25845827	(Sodhi et al. 2015)
Gefitinib	Anticancer, epidermal growth factor receptor-tyrosine kinase inhibitor	Intermediate competitive inhibition	32393528	(Tan et al. 2020)
GW5638	Tamoxifen analog	Weak inhibition	14709625	(Obach 2004)
Hydralazine	Direct vasodilator, antihypertensive	Strong selective time-dependent inactivation, also time-dependent inhibitor of P450 1A2, used to determine fraction metabolized by AO	22522748, 12419014, 30448524, 22031625, 24156774, 29615437, 28281401, 25297949, 22996261	(Barr and Jones 2013; Crouch et al. 2018; Dick 2018; Hutzler et al. 2012; Lake et al. 2002; Nirogi et al. 2014; Strelevitz et al. 2012; Yang et al. 2019a, b; Zientek and Youdim 2015)
7-Hydroxy-DACA	DACA metabolite	Strong inhibition	10810450	(Schofield et al. 2000)
4- Hydroxytamoxifen	Tamoxifen metabolite	Strong inhibition	14709625	(Obach 2004)
Ketoconazole	Antifungal	Intermediate inhibition, also inhibits reductive reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
KW-2449 iminium ion	MAO B catalyzed iminium ion metabolite	Time-dependent irreversible inhibition, MAO B conversion of KW-2449 to iminium ion intermediate which covalently binds and inactivates AOX	29451686	(Hosogi et al. 2018)
Lasofoxifene	Antiestrogen, selective estrogen receptor modulator	Competitive inhibition	31289113	(Chen et al. 2019)
Levormeloxifene	Selective estrogen receptor modulator	Strong inhibition	14709625	(Obach 2004)
Loperamide	Anti-diarrheal	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Loratadine	Antihistamine, second generation H1 receptor antagonist	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Loxapine	First-generation antipsychotic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)

Table 16 (continued)

Compound	Category	Comments	PMID numbers	References
Maprotiline	Antidepressant, tetracyclic	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Metoclopramide	Antiemetic, D2 receptor antagonist	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Nafoxidine	Antineoplastic, nonsteroidal selective estrogen receptor modulator	Strong inhibition	14709625	(Obach 2004)
Norclomipramine	Antidepressant, a metabolite of clomipramine	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Nortriptyline	Tricyclic antidepressant, a metabolite of amitriptyline	Strong inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Olanzapine	Antipsyhotic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Ondansetron	Serotonin 5-HT3 receptor antagonist, prevention of nausea and vomiting	Intermediate inhibition, also inhibits reductive reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Oligomycin	Inhibitor of ATP synthase	Weak inhibition	4226961	(Johns 1967)
Perphenazine	Antipsychotic, piperazinyl phenothiazine	Strong inhibition, does not inhibit reduction reaction	14681337, 20853847, 16282848	(Obach et al. 2004; Obach and Walsky 2005; Pryde et al. 2010)
Promazine	Tranquilizer, phenothiazine derivative	Intermediate to strong inhibition, does not inhibit reduction reaction	4226961, 14681337, 16282848	(Johns 1967; Obach et al. 2004; Obach and Walsky 2005)
Promethazine	Antihistamine and antipsychotic	Strong non-competitive inhibitor, does not inhibit reduction reaction	4226961, 12419014, 14681337, 16282848	(Johns 1967; Lake et al. 2002; Obach et al. 2004; Obach and Walsky 2005)
Propafenone	Antiarrhythmic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Quetiapine	Atypical antipsychotic	Strong inhibition, does not inhibit reduction reaction	14681337, 24156774, 16282848	(Nirogi et al. 2014; Obach et al. 2004; Obach and Walsky 2005)
Quinacrine	Antimalarial and antibiotic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 4226961, 16282848	(Johns 1967; Obach et al. 2004; Obach and Walsky 2005)
Raloxifene	Antiestrogen, selective estrogen receptor modulator	Very strong uncompetitive inhibition, substrate-dependent competitive vs uncompetitive mode of inhibition, does not inhibit reduction reaction	14709625, 24406683, 14681337, 31289113, 22996261, 33455497, 16143537, 24156774, 16282848, 25297949, 34415167	(Barr and Jones 2013; Chen et al. 2019; Klecker et al. 2006; Mota et al. 2021; Nirogi et al. 2014; Obach 2004; Obach et al. 2004; Obach and Walsky 2005; Uehara et al. 2021; Weidert et al. 2014; Zientek and Youdim 2015)
Ripasudil, K-115	Selective Rho-associated coiled coil-containing protein kinase (ROCK) inhibitor, ophthalmic agent	Intermediate inhibition	26678038	(Isobe et al. 2016)
Salmeterol	Long-acting β2 adrenergic receptor agonist, anti-asthmatic	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)

Table 16 (continued)

Compound	Category	Comments	PMID numbers	References
Tacrine	Centrally acting acetylcholinesterase inhibitor and indirect cholinergic agonist	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)
Tamoxifen	Antiestrogen, selective estrogen receptor modulator	Intermediate competitive inhibition, weakly inhibits reduction reaction	14681337, 16282848, 31289113, 14709625	(Chen et al. 2019; Obach 2004; Obach et al. 2004; Obach and Walsky 2005)
Thioridazine	Trifluoro-methyl phenothiazine derivative, management of schizophrenia and other psychotic disorders	Strong non-competitive inhibition, allosteric inhibitor, does not inhibit reduction reaction	14681337, 16282848, 34415167, 26322824	(Coelho et al. 2015; Mota et al. 2021; Obach et al. 2004; Obach and Walsky 2005)
Trifluoperazine	Antipsychotic, phenothiazine derivative	Strong inhibition	4226961, 14681337, 16282848	(Johns 1967; Obach et al. 2004; Obach and Walsky 2005)
Trimeprazine	Antihistamine	Intermediate inhibition	4226961	(Johns 1967)
Verapamil	Calcium channel blocker	Intermediate inhibition, does not inhibit reduction reaction	14681337, 16282848	(Obach et al. 2004; Obach and Walsky 2005)

can occur with other drugs that are MAO substrates, e.g., with β-adrenoceptor agonists and antagonists, prodrugs of dopamine, and serotonin 5-HT1-receptor agonists, as well as with primaquine, flurazepam, and citalopram (Benedetti 2001; Masuo et al. 2017).

Drugs or drug metabolites that are substrates for human MAOs include β-blockers (i.e., amines formed by dealkylations of β-blockers), primaquine, β-phenylethylamine, phenelzine (also an irreversible inhibitor), almotriptan, bicifadine, citalopram, and its active metabolite desmethylcitalopram, rizatriptan, and zolmitriptan (Table 8).

The drug ozanimod is oxidatively deaminated to a pharmacologically active metabolite by MAO B, yielding the major circulating active compound. The reaction follows a prior *N*-dealkylation reaction catalyzed by P450 3A4 (Fig. 22) (Table 8). Also involved in the overall metabolism of ozanimod are P450s 1A1 and 2C8, aldehyde dehydrogenase, and alcohol dehydrogenase, plus reductive metabolism by gut microflora (Surapaneni et al. 2021; Tran et al. 2020).

Drugs as MAO inhibitors

In addition to being substrates of MAO enzymes, many nitrogen-containing drugs are also MAO inhibitors (Table 11) and were among the first agents shown to be efficacious in the treatment of clinical depression (Fernandez and Chen 2007; Kalgutkar et al. 2001; Suchting et al. 2021). For instance, the therapeutic effects of some antidepressants, hydrazine derivatives (e.g., iproniazid), and tranylcypromine are based on irreversible inhibition of the MAO enzyme and result in the accumulation of sympathetic amines in adrenergic neurons.

As already mentioned, the drugs used in clinical practice are either nonselective and irreversible MAO enzymes inhibitors or selective inhibitors for either MAO A or MAO B enzymes. Some irreversible inhibitors include rasagiline (MAO A and B, selective MAO B inhibitor), tranylcypromine (MAO A and B, nonselective), iproniazid (MAO A and B, nonselective), phenelzine (MAO A and B, nonselective inhibitor), selegiline (MAO A and B, selective MAO B inhibitor at lower concentrations/doses), pargyline (MAO A and MAO B, partially MAO B selective inhibitor), iproniazid (MAO A and B, nonselective inhibitor), clorgyline (MAO A, MAO B, selective MAO A inhibitor), ladostigil (MAO A and B, non-selective inhibitor), and isocarboxazid (MAO A and B, non-selective inhibitor). Some selective reversible MAO enzyme inhibitors are lazabemide (MAO B selective inhibitor), befloxatone (MAO A and B, selective MAO A inhibitor), toloxatone (MAO A and B, selective MAO A inhibitor), brofaromine (MAO A and B, selective MAO A inhibitor), and moclobemide (MAO A selective inhibitor) (Table 11).

Table 17 Natural products and physiological compounds as substrates in reactions catalyzed by human AOX1

Substrate	Category	Reaction	Comments	PMID numbers	References
N^1-Methylnicotinamide	Physiological compound	Oxidation	*N*-1-Methyl-2-pyridone-5-carboxamide and *N*-1-methyl-4-pyridone-3-carboxamideformation, serves as electron donor in AO catalyzed reduction reactions,	18332084, 22453079, 4226961, 9161710, 8043023, 17375106, 29522712, 28606603	(Amano et al. 2018; Johns 1967; Kitamura et al. 2008; Konishi et al. 2017; Rodrigues 1994; Sugihara et al. 1997; Tayama et al. 2007, 2012)
Nicotinamide riboside	Physiological compound, nicotinamide metabolite	Oxidation	*N*-1-Methyl-4-pyridone-3-carboxamideformation, endothelial toxicity, activation to the toxic metabolite	26321286	(Pelikant-Malecka et al. 2015)
Nicotine-Δ^1(5')-iminium ion	P450 metabolite of nicotine	Oxidation	Cotinine formation	14709625, 22335465	(Garattini and Terao 2012; Obach 2004)
Nitrite	Physiological compound	Reduction	Nitric oxide radical formation	30196191, 25537183	(Maia and Moura 2018; Maia et al. 2015)
Pyridoxal	Vitamin B6 compound, aldehyde	Oxidation	4-Pyridoxic acid formation	22335465, 4226961	(Garattini and Terao 2012; Johns 1967)
Retinal (all-*trans*-retinaldehyde)	Physiological compound, vitamin A aldehyde	Oxidation	All *trans*-retinoic acid formation	22335465, 20853847, 10559215, 33355213	(Ambroziak et al. 1999; Garattini and Terao 2012; Pryde et al. 2010; Zhong et al. 2021)
Vanillin, vanillic aldehyde	Natural product, flavor component of vanilla	Oxidation	Vanillic acid formation	14709625, 24533630, 19356090, 34169906	(Behera et al. 2014; Obach 2004; Sahi et al. 2008; Subash et al. 2021)

Table 18 Natural products and physiological compounds as inhibitors of human AOX1

Inhibitor	Category	Comments	PMID numbers	References
Apigenin	Flavone, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Coumestrol	Natural product, phytoestrogen	Strong inhibition	14709625	(Obach 2004)
Epicatechin (EC)	Catechin, natural product, component of green tea, antioxidants (electron acceptor)	Competitive inhibition	25326286, 21084768	(Barr et al. 2015; Tayama et al. 2011)
Epicatechin gallate (ECG)	Catechin, natural product, component of green tea, antioxidants (electron acceptor)	Mixed inhibition	25326286, 21084768	(Barr et al. 2015; Tayama et al. 2011)
Epigallocatechin (EGC)	Catechin, natural product, component of green tea, antioxidants (electron acceptor)	Weak inhibition	25326286, 21084768	(Barr et al. 2015; Tayama et al. 2011)
Epigallocatechin gallate (EGCG)	Catechin, natural product, component of green tea, antioxidants (electron acceptor)	Competitive inhibition	25326286, 21084768	(Barr et al. 2015; Tayama et al. 2011)
β-Estradiol	Physiological compound, estrogen steroid hormone	Strong inhibition, weakly inhibits reduction reaction	21940905, 14681337, 22996261, 4226961, 16282848 14709625	(Barr and Jones 2011, 2013; Johns 1967; Obach 2004; Obach et al. 2004; Obach and Walsky 2005)
Estrone	Physiological compound, steroid hormone	Strong inhibition	14709625	(Obach 2004)
Genistein	Natural product, isoflavone, phytoestrogen	Strong inhibition	14709625	(Obach 2004)
Hydrogen peroxide	Byproduct of AO catalysis	Time-dependent inactivation	34183377	(Garrido and Leimkühler 2021)
Isosilybin A	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Isosilybin	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Isosilychristin	Flavanonol, diet-derived constituent	Competitive inhibition	25326286	(Barr et al. 2015)
Kaempferol	Flavonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Menadione	Natural product, 1,4-naphthoquinone, vitamin K	Strong, predominantly uncompetitive inhibition	7736920, 12419014, 21940905, 14681337, 22996261, 4226961, 10810450, 14709625, 28474310	(Barr and Jones 2011, 2013; Clarke et al. 1995; Johns 1967; Lake et al. 2002; Obach 2004; Obach et al. 2004; Schofield et al. 2000; Wilkinson et al. 2017)
4-Methylumbelliferone	Coumarin, diet-derived constituent	Mixed inhibition mode	25326286	(Barr et al. 2015)
Naringenin	Flavanone, diet-derived constituent	Mixed inhibition mode	25326286	(Barr et al. 2015)
Progesterone	Physiological compound, progestogenic hormone	Strong inhibition	4226961	(Johns 1967)
Quercetin	Flavanol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Resveratrol	Stilbenoid, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Silybin A	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Silybin B	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)

Table 18 (continued)

Inhibitor	Category	Comments	PMID numbers	References
Silychristin	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Silydianin	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Superoxide	Byproduct of AO catalysis	Time-dependent inactivation, greater effect on L438V variant vs wild-type enzyme	34183377	(Garrido and Leimkühler 2021)
Taxifolin	Flavanonol, diet-derived constituent	Mixed inhibition	25326286	(Barr et al. 2015)
Testosterone	Male hormone	Intermediate inhibition	4226961	(Johns 1967)

Due to the observed toxic effects, irreversible inhibitors of MAO enzymes have been largely replaced in therapy with selective reversible inhibitors.

Antidepressant drugs, besides inhibiting the active uptake of amines into presynaptic cells (Stahl 1998), also exert inhibitory activity on MAO enzymes with potencies dependent on the model and experimental conditions used. For instance, when testing mitochondrial MAO activity in mouse, rat, dog, and monkey brains with antidepressant drugs (zimeldine, imipramine, maprotiline, and nomifensine) (which inhibit MAO A and MAO B at high concentrations), inhibition was dependent on the species used and experimental conditions applied. Imipramine, for instance, inhibited MAO B more strongly than MAO A activity in mouse and rat brains. When dog and monkey brains were investigated, MAO A activity was inhibited with greater potency than MAO B activity at high concentrations of imipramine; at low concentrations, however, MAO B activity was more strongly inhibited. Also, maprotiline and nomifensine inhibited mouse and rat brain MAO B activity more strongly than MAO A activity, while the inverse was found for dog and monkey brain models (Egashira et al. 1999).

As an example, the non-selective MAO A and MAO B irreversible inhibitor phenelzine (Table 11, Fig. 23) elevates brain levels of the monoamine neurotransmitters 5-hydroxytryptamine (serotonin), noradrenaline, and dopamine. Phenelzine is also a substrate for MAO enzymes, and different metabolites are formed including β-phenylethylamine, phenylacetic acid, *p*-hydroxyphenyl acetic acid, β-phenylethylidenehydrazine, and phenylethyldiazenephenylethylidenehydrazine. Of these metabolites, neuroprotective/neuro-rescue activity has been suggested for the metabolite β-phenylethylidenehydrazine and irreversible inactivation of MAO enzymes has been ascribed to the formation of phenethyl free radicals (Ortiz de Montellano et al. 1983; Rumyantseva et al. 1991). Thus, besides its MAO inhibiting activity, phenelzine also elevates brain levels of γ-aminobutyric acid (GABA) which may also contribute to its anxiolytic effects, and the effects ascribed to the phenelzine intermediate metabolite β-phenylethylidenehydrazine, a weak MAO inhibitor (Baker et al. 2019; Parent et al. 2002). Phenelzine may also ameliorate the effects of oxidative stress by reducing the formation of reactive metabolites (aldehydes, hydrogen peroxide, ammonia/ammonia derivatives) produced by the interaction of MAO with biogenic amines, as well as by inhibiting primary amine oxidase (Baker et al. 2019; Matveychuk et al. 2021). This example illustrates the complex interactions of the parent drug and its metabolite(s) on the final effects.

The first generation of non-selective (iproniazid, tranylcypromine, phenelzine) and irreversible MAO A inhibitors was shown to produce associations with the "cheese reaction," whereas MAO B inhibitors (used at the recommended

Table 19 General chemicals as substrates in reactions catalyzed by human AOX1

Chemical	Category	Reaction	Comments /site of metabolism	PMID numbers	References
3-Aminoquinoline	Quinoline	Oxidation	2-Oxo-3-aminoquinoline formation	28884164	(Paragas et al. 2017b)
Acetaldehyde	Aliphatic aldehyde, ethanol metabolite	Oxidation	Acid formation, poor substrate	4226961	(Johns 1967)
Anilides	Thiophene and non-thiophene-containing structural derivatives	Hydrolysis	Strongly toxic amine formation, structure-dependent	28373537	(Lepri et al. 2017)
Aza-heterocycles	Structural derivatives	Oxidation	*ortho* C-H is often oxidized, substituent dependent	28373537	(Lepri et al. 2017)
Benzaldehyde	Aromatic aldehyde	Oxidation	Benzoate formation	4226961, 22279051, 9161710, 11569919, 8043023	(Al-Salmy 2001; Hartmann et al. 2012; Johns 1967; Rodrigues 1994; Sugihara et al. 1997)
Benzothiazole derivatives	Substituted benzothiazoles	Oxidation	Oxidation of thiazole	34818997	(Teffera et al. 2021)
o-Chlorobenzaldehyde	Aromatic aldehyde	Oxidation	Acid formation	4226961	(Johns 1967)
Chloroquinazolinone	Quinazolinone derivative	Oxidation	Site of metabolism not reported	22279051	(Hartmann et al. 2012)
6-Chloro-4-quinazolinone	Quinazolinone derivative	Oxidation	C2-oxidation	19741035	(Alfaro et al. 2009)
Clothianidin	Insecticide, neonicotinoid	Reduction	Reduction of nitro to nitroso group	19391582	(Shi et al. 2009)
4-Dimethylaminocinnamaldehyde	Aromatic aldehyde	Oxidation	Acid formation	29329804, 19801639	(Apenova et al. 2018; Li et al. 2009)
Formaldehyde	Aldehyde	Oxidation	Poor substrate	4226961	(Johns 1967)
2-Hydroxy-5-fluoropyrimidine	General chemical	Oxidation	5-Fluorouracil formation	4226961	(Johns 1967)
Isoquinolines	Structural derivatives	Oxidation	C1/C3-oxidation, good substrates	28373537	(Lepri et al. 2017)
6-Methylpurine	Toxic adenine analog	Oxidation	Site of oxidation not reported	8043023	(Rodrigues 1994)
6-methyl-4-quinazolinone	Quinazolinone derivative	Oxidation	C2-oxidation	19741035	(Alfaro et al. 2009)
6-methoxy-4-quinazolinone	Quinazolinone derivative	Oxidation	C2-oxidation	19741035	(Alfaro et al. 2009)
o-Nitrobenzaldehyde	Aromatic aldehyde	Oxidation	Poor substrate	4226961	(Johns 1967)
5-Nitroquinoline	Quinoline	Oxidation	2-Oxo-5-nitroquinoline formation	28888950	(Paragas et al. 2017a)
5-Nitroquinoline	Quinoline	Reduction	5-Aminoquinoline formation	28888950, 30787100	(Abbasi et al. 2019; Paragas et al. 2017a)
Phenanthridine	Nitrogen heterocyclic compound, DNA-binding fluorescent dyes	Oxidation	Phenanthridinone formation	26842593, 12419014, 30023718, 22279051	(Foti et al. 2016; Hartmann et al. 2012; Lake et al. 2002; Montefiori et al. 2017)
Phenazine methosulfate	Phenazine derivative	Oxidation	3-Hydroxylation	4226961	(Johns 1967)
N-Phenylquinolinium chloride	Quinoline	Oxidation	4-Quinolone formation	3130251	(Beedham et al. 1987)
Phthalazine	Heterocyclic organic compound	Oxidation	1-Phthalazinone formation, used as a probe substrate	3130251, 7786031, 12419014, 21940905, 22996261, 26842736, 30787100, 22279051, 22190693	(Abbasi et al. 2019; Barr and Jones 2011; Barr and Jones 2013; Beedham et al. 1987; Beedham et al. 1995; Hartmann et al. 2012; Lake et al. 2002; Pryde et al. 2010; Sharma et al. 2012)

Table 19 (continued)

Chemical	Category	Reaction	Comments /site of metabolism	PMID numbers	References
Phthalazine derivatives	Phthalazines	Oxidation	Formation of phthalazinone derivatives	7786031	(Beedham et al. 1995)
Propionaldehyde	Aliphatic aldehyde	Oxidation	Acid formation	4226961	(Johns 1967)
Quinazoline	Heterobicyclic compound	Oxidation	2,4-Oxidation	7786031, 30023718, 28373537	(Beedham et al. 1995; Lepri et al. 2017; Montefiori et al. 2017)
Quinazoline derivatives	Heterobicyclic compounds	Oxidation	2,4-Oxidation	7786031, 30023718	(Beedham et al. 1995; Montefiori et al. 2017)
Quinazolinone	Heterobicyclic compound	Oxidation	C2-Oxidation	19741035	(Alfaro et al. 2009)
Quinoline	Heterocyclic aromatic organic compound	Oxidation	2,4-Quinolone formation	16702728, 30023718, 22190693, 28373537	(Kitamura et al. 2006; Lepri et al. 2017; Montefiori et al. 2017; Sharma et al. 2012)
Quinolines	Structural derivatives	Oxidation	C2-Oxidation, good substrates, *N*-methylation increases reactivity	28373537	(Lepri et al. 2017)
Quinoxaline	Heterobicyclic compound	Oxidation	Quinoxalinone formation	22190693, 28373537	(Lepri et al. 2017; Sharma et al. 2012)
Quinoxaline derivatives	Structural derivatives	Oxidation	Good substrates	28373537	(Lepri et al. 2017)

selective dosage) did not produce the effect. The cheese reaction occurs because of potentiation of the sympathomimetic activity of ingested tyramine present in cheese and other fermented food. This cheese reaction provoked by inhibition of MAO A may consequently produce a hypertensive crisis due to the increased release of norepinephrine. In contrast to irreversible MAO A inhibitors, reversible MAO A inhibitors (e.g., the antidepressants moclobemide and brofaromine) exert limited tyramine potentiation activity (McCabe 1986; Youdim and Weinstock 2004). In addition, some of the early MAO inhibitors have been withdrawn from the market due to hepatotoxic reactions (e.g., nialamide, pargyline). Because of the observed toxic effects, nonselective irreversible inhibitors of MAO enzymes have been replaced with selective reversible inhibitors in clinical therapy. At present, drugs that are inhibitors of MAO A are used and investigated for the treatment of depression, while selective MAO B inhibitors (e.g., rasagiline, selegiline), are used in the treatment of Parkinson's disease, avoiding severe side effects. It has been suggested that MAO B inhibitor drugs might be effective in the treatment of Alzheimer's disease (Finberg 2014; Özdemir et al. 2021; Shulman et al. 2013; Szökő et al. 2018; Yamada and Yasuhara 2004; Youdim 1975; Youdim and Bakhle 2006).

Natural products and physiological compounds, derivatives, preparations, and MAO enzymes

The physiological substrates of MAO enzymes are brain neurotransmitters (e.g., serotonin, dopamine, norepinephrine, and epinephrine), as well as trace amines (e.g., tyramine, tryptamine, 2-phenylethylamine, octopamine, 3-iodothyronamine (Table 9). The products of oxidative deamination are aldehydes and H_2O_2, both of which have some potential toxicity in cells (Tables 9, 14). The formation of potentially toxic metabolites has been associated with neurodegenerative disorders of the central nervous system such as Parkinson's disease and dementia. Thus, the reactions of physiological compounds catalyzed by MAO enzymes are examples of the bioactivation of non-toxic amines to potentially toxic metabolites. However, in the cells, the aldehydes that are formed are either oxidized to polar carboxylic acids by the activity of aldehyde dehydrogenases (ALDH) or reduced to alcohols or glycols by aldehyde reductases (AKR enzymes). These polar products can often be excreted through kidneys and/or participate in conjugation reactions. Dopamine and norepinephrine can alternatively participate as substrates in methylation reactions catalyzed by catechol *O*-methyltransferase (COMT) to form 3-methoxytyramine and epinephrine, respectively, or participate in conjugation reactions such as

Table 20 General chemicals as inhibitors of human AOX1

Inhibitor	Category	Comments	PMID numbers	References
Acetonitrile	Organic solvent	Strong inhibition	24533630, 24156774	(Behera et al. 2014; Nirogi et al. 2014)
Benzamidine	Competitive inhibitor of trypsin	Mixed inhibition mode	34415167	(Mota et al. 2021)
6-Chloroquinazolinone	Quinazoline derivative	Intermediate competitive inhibition	21940905	(Barr and Jones 2011)
2,6-Dichlorophenolindophenol	Quinone imine	Intermediate uncompetitive inhibition	21940905	(Barr and Jones 2011)
Dimethylsulfoxide	Organic solvent	Strong inhibition	24156774, 24533630	(Behera et al. 2014; Nirogi et al. 2014)
α,α-Dipyridyl	Iron-chelating agent	Intermediate inhibition	4226961	(Johns 1967)
Ethanol	Ethyl alcohol	Strong inhibition	24533630	(Behera et al. 2014)
4-Hydrazinoquinazoline	Quinazoline derivative	Intermediate, competitive inhibition	7786031	(Beedham et al. 1995)
p-Hydroxymercuribenzoate	Thiol-protein modifier	Strong inhibition	4226961	(Johns 1967)
Isovanillin	Phenolic Aldehyde	Intermediate, inhibition	7736920, 20853847	(Clarke et al. 1995; Pryde et al. 2010)
Methanol	Methyl alcohol	Strong inhibition	4226961, 24156774, 24533630	(Behera et al. 2014; Johns 1967; Nirogi et al. 2014)
Phthalazine	Heterocyclic organic compound	Weak inhibition	7786031, 30023718	(Beedham et al. 1995; Montefiori et al. 2017)
Phthalazine derivatives	Phthalazines	Weak competitive inhibition	7786031	(Beedham et al. 1995)
Potassium cyanide	Cyanide salt	Intermediate inhibition	4226961	(Johns 1967)
Quinazoline derivatives	Quinazolines	Weak competitive inhibition	7786031	(Beedham et al. 1995)
Triton X-100	Non-ionic surfactant and emulsifier	Strong inhibition	4226961	(Johns 1967)

sulfoconjugation (Behl et al. 2021; Buu 1985; Danielczyk et al. 1988; Ji et al. 2005; Rivett et al. 1982).

Some natural products are substrates of MAO enzymes, but there is also a growing interest in testing natural products and compounds as inhibitors of MAO enzymes (Table 12) for possible use in the treatment of Parkinson's disease (Zarmouh et al. 2016) or to explain possible side effects or their toxicity when ingested.

When using natural products, care should be taken because the same preparation may contain a compound that inhibits the enzymes, as well as compounds that act as enzyme activators. For example, ethanolic extracts of the seeds of *Psoralea corylifolia* L. contain flavanone bavachinin, which showed competitive MAO A and MAO B inhibition. *P. corylifolia* L. extracts also contain its analog bavachin, which has stimulatory properties (Zarmouh et al. 2015).

General chemicals and synthetic derivatives of natural products as MAO enzyme inhibitors

In the group of general chemicals as substrates of MAO enzymes, special attention has been focused on the tetrahydropyridine compound MPTP, which is oxidized to the neurotoxic products $MPDP^+$ and MPP^+ by MAO B as the major enzyme. During the reaction the enzyme is inactivated (Tables 10, 13, 14, Fig. 26).

Some of the synthetic MAO enzyme inhibitors are compounds with structures based on scaffolds of natural compounds known to be MAO inhibitors, e.g., caffeine, coumarin, piperazine, and chalcone (a structural isomer of coumarin) (Tables 12, 13). Caffeine, an adenosine receptor antagonist (A2A), is a weak and reversible MAO A and MAO B inhibitor, both in vivo and in vitro (Grzelczyk et al. 2021; Haj Ahmed et al. 2020). Its structure has been used to design compounds having both A2A receptor antagonist and MAO A and MAO B inhibition activity. The compounds have been developed with the potential for treating Parkinson's disease. Although structural modifications of caffeine

Table 21 Compounds activated to pharmacologically active metabolites by human AOX1

Compound	Subcategory	Reaction	Comments/site of metabolism	PMID numbers	References
6-Deoxypenciclovir	Famciclovir Metabolite, intermediate metabolite in conversion of famciclovir to active penciclovir	Oxidation	6-Oxidation to active metabolite penciclovir, also XOR substrate	9224775, 28474310, 20444863	(Rashidi et al. 1997; Wilkinson et al. 2017; Zientek et al. 2010)
Famciclovir	Antiviral, prodrug of penciclovir, 2-aminopurine derivative	Oxidation	Famciclovir di-deacetylation to 6-deoxypenciclovir followed by oxidation to active metabolite penciclovir	7736920, 9224775, 30023718	(Clarke et al. 1995; Montefiori et al. 2017; Rashidi et al. 1997)
Fasudil	Strong Rho-kinase inhibitor and vasodilator	Oxidation	Formation of 2-hydroxyfasudil, the active metabolite	28166443	(Mao et al. 2018)
5-Fluoro-2-pyrimidinone	Anti-cancer, prodrug	Oxidation	Formation of 5-fuorouraci, the active metabolite	16702728, 12003195	(Kitamura et al. 2006; LoRusso et al. 2002)
5-Iodo-2-pyrimidinone-2′-deoxyribose	Anti-cancer, radiosensitizer, prodrug	Oxidation	5-Iodo-2′-deoxyuridine formation: active metabolite	1599512, 10778979, 15001663	(Chang et al. 1992; Kinsella et al. 2000; Rooseboom et al. 2004)
Momelotinib	Anticancer, inhibitor of Janus kinase (JAK)1/2 and of activin A receptor type 1 (ACVR1)	Oxidation	Azaheterocycle oxidation, P450 oxidation of morpholine to carbinolamine intermediate followed by AO oxidation to morpholino lactam, active metabolite,	29311136	(Zheng et al. 2018)

led to strong MAO inhibitors, the MAO inhibitory activity of caffeine itself is not likely to be of pharmacological relevance in typical coffee consumption (Petzer et al. 2013; Petzer and Petzer 2015).

The β-carboline alkaloids, which are also components of coffee (and also present in cigarette smoke), were reported to be reversible, competitive, and strong inhibitors of MAO enzymes and linked to a reported lower incidence of Parkinson's disease in coffee drinkers and cigarette smokers (Herraiz and Chaparro 2005, 2006). However, the MAO inhibitory activity of natural products may be dependent on and affected by the type of product used (e.g., type of coffee), as well as by the method of preparation of the sample for testing (e.g., light or dark roasted coffee beans) (Grzelczyk et al. 2021) (Table 12).

Coumarin, for instance, exhibited nonselective intermediary MAO A and MAO B inhibitory activity, but some of its natural derivatives exhibited selective strong MAO A (osthenol) or MAO B inhibitory activity (rutamarin) (Table 12). Furthermore, some synthetic coumarin derivatives exerted strong, selective inhibition of either MAO A or MAO B activity. Many other derivatives of various natural compound-based structures (e.g., indoles, chromones, chalcones, carboxamides, benzylamine, sulfonamide, benzofuran, pyrazole, pyrrole, quinazolinone, and others) were synthesized and reported to exhibit strong, selective inhibition of either MAO A or MAO B activity (Table 13) (Patil et al. 2013).

Stereoselective inhibition of MAO enzymes was reported for enantiomers of the 8-aminoquinoline derivative NPC1161. Racemic NPC1161 exerted both MAO A and MAO B inhibitory activity with 3.7-fold selectivity of MAO A compared to MAO B, while the (*S*)-(+)- enantiomer was shown to be an intermediate (MAO A) and strong (MAO B) mixed-type irreversible inhibitor with about tenfold selectivity for inhibition of MAO B over MAO A. The (*R*)-(−)-enantiomer was shown to be a mixed-type nonselective intermediate reversible inhibitor (Table 13). Stereoselective MAO inhibition was also observed in the interaction of enantiomers of antimalarial drug primaquine. Racemic primaquine and (*R*)-(−)-primaquine were weak and very weak inhibitors, respectively, both being nonselective inhibitors. (*S*)-(+)-Primaquine was also a weak inhibitor but showed 1.5-fold selectivity for inhibition of MAO A over MAO B (Chaurasiya et al. 2021) (Table 11).

Examples of compounds bioactivated to toxic products by MAO enzymes

Examples of compounds that are bioactivated to toxic products by MAO enzymes include physiological compounds (e.g., neurotransmitters dopamine, serotonin, noradrenaline, the biogenic amine kynuramine) that are metabolized

Table 22 Compounds activated to toxic metabolites by human AOX1

Compound	Subcategory	Reaction	Comments/site of metabolism	PubMed numbers	References
Clonazepam	Benzodiazepine	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Dantrolene	Skeletal muscle relaxant	Reduction	Nitro-reduction, amino dantrolene formation, hydroxylamine formation, activation to the toxic metabolite	29522712, 30367827, 33020066	(Abbasi et al. 2020; Amano et al. 2018)
Flunitrazepam	Central nervous system (CNS) depressant	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Flutamide	Antineoplastic, antiandrogen	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
JNJ-38877605	Anticancer, selective c-Met tyrosine kinase Inhibitor	Oxidation	Oxidation of azaheterocycle, insoluble metabolite formation, activation to toxic metabolite (renal toxicity)	25745036	(Lolkema et al. 2015)
Methotrexate	Antineoplastic, antifolate, antirheumatic	Oxidation	7-Hydroxymethotrexate formation, insoluble metabolite formation, activation to toxic metabolite (renal toxicity)	10385213, 26032640, 32393528, 20444863	(Choughule et al. 2015; Jordan et al. 1999; Tan et al. 2020; Zientek et al. 2010)
Nicotinamide riboside	Physiological compound, nicotinamide metabolite	Oxidation	*N*-1-Methyl-4-pyridone-3-carboxamideformation, endothelial toxicity, activation to the toxic metabolite	26321286	(Pelikant-Malecka et al. 2015)
Nilutamide	Antineoplastic, nonsteroidal antiandrogen	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimesulide	Non-selective non-steroidal anti-inflammatory, NSAID	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimetazepam	Hypnotic and sedative, benzodiazepine	Reduction	Nitro reduction, hydroxylamine formation, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nimodipine	Calcium channel blocker	Reduction	Nitro reduction, activation to the toxic metabolite	30367827	(Ogiso et al. 2018)
Nitrazepam	Hypnotic, benzodiazepine	Reduction	Nitro reduction, 7-aminonitrazepam formation, activation to toxic metabolite after *N*-acetylation	28606603	(Konishi et al. 2017)
SGX523	Anticancer, Inhibitor of MET receptor tyrosine kinase	Oxidation	2-Quinolinone formation, insoluble metabolite formation, activation to toxic metabolite (renal toxicity)	20421447, 22547164	(Diamond et al. 2010; Infante et al. 2013)

Table 23 Examples of drugs as substrates in reactions catalyzed by human XOR

Drug	Category	Reaction	Comments	PubMed numbers	References
Allopurinol	Anti-gout, xanthine oxidase inhibitor; Prodrug	Oxidation	Oxypurinol formation, production of superoxide radicals, toxic effects, oxypurinol formation probably mediated primarily by AOX	16702728, 16507884, 2323062, 3010873	(Kitamura et al. 2006; Krenitsky et al. 1986; Pacher et al. 2006)
O^6-Benzylguanine	Antineoplastic; guanine derivative	Oxidation	Minimal XO metabolism, predominantly AOX substrate	7503788	(Roy et al. 1995)
BRL 55,792	Anti-viral; Guanine derivative; Prodrug	Oxidation	C6-Oxidation, minor enzyme	8013273	(Harrell et al. 1994)
Capmatinib	Antineoplastic, mesenchymal-epithelial transition (MET) tyrosine kinase inhibitor	Oxidation	Imidazo-triazinone formation, most abundant in vivo metabolite	32665418	(Glaenzel et al. 2020)
6-Deoxyacyclovir	Antiherpetic agent; Prodrug; Acyclic guanine nucleoside analogue	Oxidation	Acyclovir formation, active drug formation	3010873, 3793661	(Krenitsky et al. 1986; Rees et al. 1986)
Favipiravir	Antiviral; anti-influenza drug; Purine nucleic acid analog; Prodrug	Hydroxylation	Inactive metabolite formation	32536670	(Mishima et al. 2020)
Formycin B	Antileishmanial agent	Oxidation	Oxidation site not specified	3010873	(Krenitsky et al. 1986)
Inosine	Component of combination antiviral agent inosine pranobex	Oxidation	Oxidation site not specified	3010873	(Krenitsky et al. 1986)
6-Mercaptopurine	Anticancer and treatment of autoimmune diseases; Purine antagonists; active metabolite of azathioprine	Oxidation	Oxidation to thioxanthine intermediate followed by second oxidation to 6-thiouric acid formation	3470165, 1451710, 24824603, 5226511, 6580097, 32282298, 22495427	(Balis et al. 1987; Choughule et al. 2014; Kurzawski et al. 2012; Lennard 1992; Mahasneh et al. 2020; Rundles 1966; Zimm et al. 1983)
Methotrexate	Anti-rheumatic; Immunosuppressant	Oxidation	7-Hydroxymethotrexate formation, primarily AOX-mediated	9728483	(Chládek et al. 1997)
PF-5190457	Ghrelin receptor inverse agonist	Oxidation	2-Pyrimidone formation	31182423	(Adusumalli et al. 2019)
Pyrazinamide	Antituberculotic; prodrug	C5-hydroxylation	5- Hydroxypyrazinamide formation, activation to toxic species 5-hydroxypyrazionic acid via amidase-mediated conversion of amide to carboxylic acid	3663245, 23357778, 3620591, 2737233	(Lacroix et al. 1989; Shih et al. 2013; Whitehouse et al. 1987; Yamamoto et al. 1987)
Pyrazinoic acid	Antituberculotic	C5-hydroxylation	5- Hydroxypyrazinoic acid formation, activation to a toxic product	3663245, 23357778	(Shih et al. 2013; Yamamoto et al. 1987)
6-Thioxanthine	6-mercaptopurine metabolite; also 6-thioguanine metabolite	Oxidation	6-Thiouric acid formation	24824603, 10525111	(Choughule et al. 2014; Kitchen et al. 1999)
VU0409106	Negative allosteric modulator of metabotropic glutamate receptor subtype 5	Oxidation	2,6-Dioxopyrimidine formation	28939686	(Morrison et al. 2012)

Table 24 Drugs that inhibit human XOR

Compound	Subcategory	Comments	PubMed numbers	References
Acyclovir	Antiherpetic agent	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
Allopurinol	Antigout; Oxypurinol prodrug	Mechanism based inhibitor, used for XO reaction phenotyping	6580097, 7736920, 16507884, 32789757, 28672082, 20878424, 27021957, 29071435, 33040063, 29415653, 25297949, 5843095, 17301077	(Bove et al. 2017; Bredemeier et al. 2018; Cicero et al. 2021; Clarke et al. 1995; Ferreira Antunes et al. 2016; Kumar et al. 2018; Pacher et al. 2006; Peglow et al. 2011; Vickneson and George 2021; Watts et al. 1965; Yamaguchi et al. 2007; Zientek and Youdim 2015; Zimm et al. 1983)
Allopurinol ribonucleoside	Ribonucleoside derivative of allopurinol	Non-competitive inhibitor	3010873	(Krenitsky et al. 1986)
Azathioprine	Immunosuppressant; thiopurine	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
Febuxostat	Thiazolecarboxylic acid derivative	Selective inhibitor	32789757, 24406683, 29071435, 20109996, 33040063, 29415653	(Bove et al. 2017; Bredemeier et al. 2018; Cicero et al. 2021; Ernst and Fravel 2009; Vickneson and George 2021; Weidert et al. 2014)
Guanine arabinoside	Nelarabine metabolite; antineoplastic	Phosphorylated to the active metabolite, a weak inhibitor	3010873	(Krenitsky et al. 1986)
Methotrexate	Anti-rheumatic; Immunosuppressant	Strong inhibitor	3470165, 8599862	(Balis et al. 1987; Innocenti et al. 1996)
2′-Nor-2′-deoxyguanosine	Antiviral agent; guanine nucleoside	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
Oxypurinol	Antigout; Xanthine, Allopurinol metabolite	Strong inhibitor	3190993, 15139781, 16507884, 9231821, 32789757, 29071435, 3755906, 3010873, 17301077	(Bove et al. 2017; Cardillo et al. 1997; Day et al. 1988; Krenitsky et al. 1986; Pacher et al. 2006; Spector et al. 1986; Vickneson and George 2021; Yamaguchi et al. 2007)
Raloxifene	Selective estrogen receptor modulator	Inhibition of XO-catalyzed NO_2 reduction to ·NO	24406683	(Weidert et al. 2014)
Theophylline	Nonselective phosphodiesterase inhibitor	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
Topiroxostat	Anti-gout; xanthine oxidase (XO) inhibitor	Hybrid competitive and covalent inhibitor	32789757, 33040063, 29415653	(Bredemeier et al. 2018; Cicero et al. 2021; Vickneson and George 2021)

Table 25 Natural products and physiological compounds as substrates in oxidation reactions catalyzed by human XOR

Substrate	Category	Reaction	Comments	PMID numbers	References
Adenine	Purine nucleobase	Oxidation	Oxidation site not specified	3010873	(Krenitsky et al. 1986)
Caffeine	Natural compound; CNS stimulant; methylxanthine	Oxidation	Oxo derivative formation, 1-methylxanthine and 1-methylurate formation	8738764, 1934864, 10027663, 19519341, 10741629, 1458773	(Chung et al. 2000a, b; Fuchs et al. 1999; Hakooz 2009; Kalow and Tang 1991; Rasmussen and Brøsen 1996; Relling et al. 1992)
Hypoxanthine	Physiological compound: Inosine metabolite	Oxidation	Xanthine formation	16507884, 29733945, 27816314, 176879, 17301077	(Balis 1976; Battelli et al. 2018; Murase et al. 2016a; Pacher et al. 2006; Yamaguchi et al. 2007)
N-Methylnicotinamide	Physiological compound	Oxidation	Pyridone formation	3010873	(Krenitsky et al. 1986)
1-Methylxanthine	Natural compound; Caffeine metabolite	Oxidation	1-Methyluric acid formation	3190993, 8919637	(Day et al. 1988; Miners and Birkett 1996)
7-Methylxanthine	Theobromine metabolite	Oxidation	7-Methyluric acid formation	6130921	(Miners et al. 1982)
Nitrite	Physiological and natural compound	Reduction	Nitric oxide radical formation under hypoxia	30196191, 25537183	(Maia and Moura 2018; Maia et al. 2015)
Pterin	Natural compound, Pigment	Oxidation	Isoxanthopterin formation	8811453	(Yamamoto et al. 1996)
Xanthine	Physiological compound: Hypoxanthine metabolite	Oxidation	Uric acid formation	12535843, 16507884, 29733945, 27006202, 31085741, 27021957, 176879, 3010873, 3755906, 17301077	(Balis 1976; Battelli et al. 2018; Ferreira Antunes et al. 2016; Krenitsky et al. 1986; Kurajoh et al. 2020; Liu et al. 2003; Murase et al. 2016a; Pacher et al. 2006; Spector et al. 1986; Yamaguchi et al. 2007)

Table 26 Examples of natural and physiological compounds as inhibitors of human XOR enzymes

Inhibitor	Category	Comments	PMID numbers	References
Folic acid	B vitamin	Strong inhibitor	1611054	(Kozhemiakin et al. 1992)
Guanine	Purine nucleobase	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
Hypoxanthine	Physiological compound: inosine metabolite	Competitive inhibitor (substrate)	3010873	(Krenitsky et al. 1986)
Menadione	Natural compound; vitamin K3	Inhibition of XO-catalyzed NO_2^- reduction to NO·	27006202	(Murase et al. 2016b)
Uric acid	Physiological compound; purine derivative; Xanthine metabolite	Uncompetitive inhibitor	24406683	(Weidert et al. 2014)
Xanthine	Physiological compound: hypoxanthine metabolite	Competitive inhibitor (substrate)	3010873, 27006202, 8134172	(Krenitsky et al. 1986; Murase et al. 2016b; Tan et al. 1993)

Table 27 Examples of general chemical as substrates in reactions catalyzed by human XOR enzymes

Chemical	Subcategory	Reaction	Comments	PMID numbers	References
Benzaldehyde	Aromatic aldehyde	Oxidation	Benzoate formation	17301077, 3010873	(Krenitsky et al. 1986; Yamaguchi et al. 2007)
p-(Dimethylamino) cinnamaldehyde	Aromatic aldehyde	Oxidation	Acid formation	17301077	(Yamaguchi et al. 2007)
6-Nitroquinazolinone	Substituted quinazoline	Oxidation	6-Nitroquinazolinedione formation	24430612	(Barr et al. 2014)
Purine derivatives	Substituted purines	Oxidation		3010873	(Krenitsky et al. 1986)
Purine nucleosides	Ribonucleoside and deoxy-ribonucleoside purine derivatives	Oxidation		3010873	(Krenitsky et al. 1986)
Quinazoline	Aromatic heterocycle	Oxidation	4-Quinazolinone formation	27021957	(Ferreira Antunes et al. 2016)

Table 28 Examples of general chemicals as inhibitors of human XOR enzymes

Inhibitor	Category	Comments	PMID numbers	References
1-Deazahypoxathine	Hypoxanthine derivative	Non-competitive inhibitor	3010873	(Krenitsky et al. 1986)
3-Deazahypoxanthine	Hypoxanthine derivative	Non-competitive inhibitor	3010873	(Krenitsky et al. 1986)
4-Hydroxy-6-mercaptopyrazolo[3,4-*d*] pyrimidine	Allopurinol derivative	Greater potency than oxypurinol	2557043	(Spector et al. 1989)
6-Methylthio-3-deazapurine	Deazapurine	Competitive inhibitor	3010873	(Krenitsky et al. 1986)
9-Methylxanthine	Xanthine derivative	Non-competitive inhibitor	3010873	(Krenitsky et al. 1986)

to toxic aldehydes, the antidepressant drug nomifensine (by forming dihydroisoquinolinium ions exerting risks of anemia and hepatotoxicity), and the general chemical MPTP, which was shown to be mechanism-based inhibitor inactivating the enzyme and forming 1,4-dihydropyridine adducts. Benzylamine, widely used as a model substrate for MAO B, is converted to toxic benzaldehyde, which is consequently reduced and deactivated to an alcohol by aldehyde dehydrogenase (Table 14).

Examples of metabolic reactions of MAO substrates

Tyramine

The aromatic amine tyramine, which is both a natural product and physiological compound, is oxidatively deaminated preferentially by MAO A. The product of its metabolism is the toxic 4-hydroxyacetaldehyde, which is converted to

Table 29 Compounds activated to toxic/pharmacologically active metabolites by human XOR

Compound	Subcategory	Reaction	Comments	PubMed numbers	References
Allopurinol	Antigout, xanthine oxidase inhibitor, prodrug	Oxidation	Oxypurinol formation, active metabolite formation	9231821, 16702728, 16507884	(Cardillo et al. 1997; Kitamura et al. 2006; Pacher et al. 2006)
6-Deoxyacyclovir	Antiherpetic agent; prodrug, acyclic guanine nucleoside analogue	Oxidation	Acyclovir formation, active metabolite formation	6587347	(Krenitsky et al. 1984)
Pyrazinamide	Antituberculotic, prodrug	C5-hydroxylation	5-Hydroxypyrazinamide formation, activation to toxic species	3663245, 23357778	(Shih et al. 2013; Yamamoto et al. 1987)
Pyrazinoic acid	Antituberculotic	C5-hydroxylation	5-Hydroxypyrazinoic acid formation, activation to toxic species	3663245, 23357778	(Shih et al. 2013; Yamamoto et al. 1987)

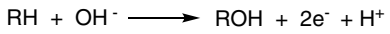


Fig. 28 General reaction catalyzed by molybdenum hydroxylases

nontoxic 4-hydroxyphenyl acetic acid by aldehyde dehydrogenase (ALDH) (Tables 9, 14) (Fig. 24). Alternatively, tyramine can be hydroxylated to dopamine by P450 2D6 in a reaction considered as the main elimination/detoxication pathway for tyramine (Niwa et al. 2004). In a minor reaction, tyramine is converted to tyrosol by alcohol dehydrogenase (ADH) and, in human liver microsomes, to a *trans*-oxime by FMO3 through a hydroxylamine intermediate (Lin and Cashman 1997a; Niwa et al. 2011; Phillips and Shephard 2019). The oxidative deamination reaction can potentially be inhibited by MAO A inhibitors, resulting in an enhanced concentration of other sympathomimetics in peripheral adrenergic neurons and causing a rapid increase in blood pressure and the onset of the cheese reaction (McCabe 1986).

Dopamine and other neurotransmitters

MAO plays a central role in the metabolism of the neurotransmitter dopamine, as well as norepinephrine and serotonin (Table 9). Dopamine metabolism is complex (Meiser et al. 2013) and, in addition to MAO enzymes, dopamine is also a substrate for catechol *O*-methyl transferase (COMT). 3,4-Dihydroxyphenylacetaldehyde (DOPAL), a product of the MAO-catalyzed deamination reaction, is toxic and is converted to 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH), which rapidly exits the neurons and is also a substrate for COMT, producing homovanillic acid (Fig. 25). In addition to DOPAL, the oxidative deamination produces H_2O_2, which (in the presence of divalent metal atoms) may form hydroxyl radicals (OH·). The formation of toxic species from dopamine (and also from other neurotransmitter substrates of MAO enzymes) has been suggested to contribute to catecholaminergic

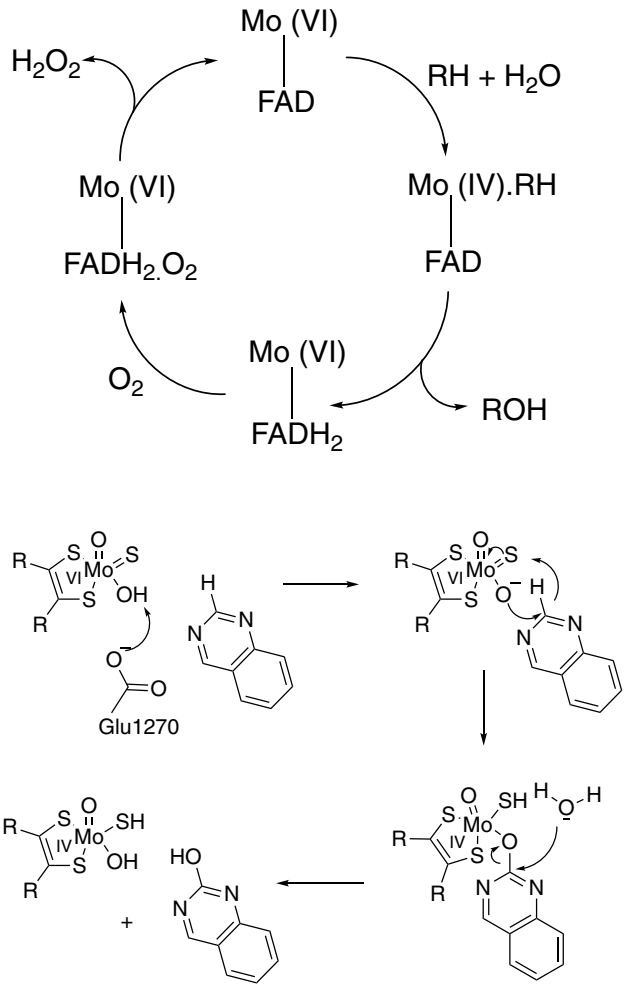


Fig. 29 Catalytic cycle and proposed mechanism for the oxidation of aromatic heterocycles and aldehydes by the molybdenum hydroxylases using quinazoline as an example (glutamate numbering represents human AOX) (Alfaro and Jones 2008)

denervation in Parkinson's disease. Cytoplasmic dopamine levels are maintained at low, non-toxic levels by the

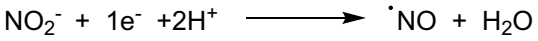


Fig. 30 General reaction of nitrite reduction catalyzed by molybdenum hydroxylases

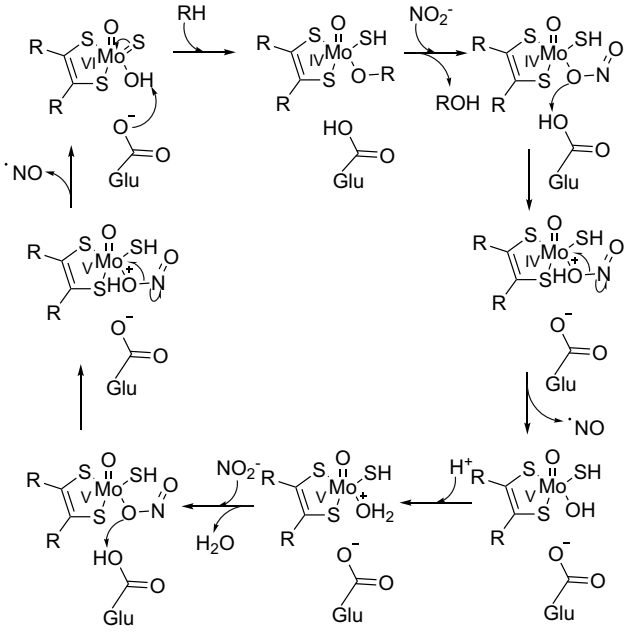


Fig. 31 Proposed mechanism for reduction of nitrite to nitric oxide in the presence of a reducing substrate by the molybdenum hydroxylases (Maia and Moura 2018)

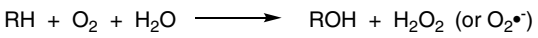


Fig. 32 Typical reaction catalyzed by AOX and XO enzymes

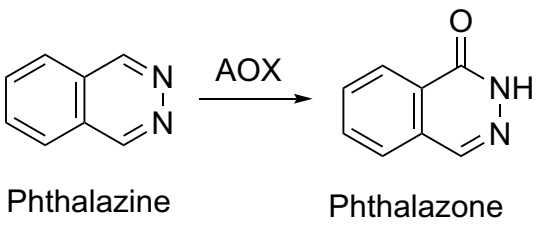


Fig. 33 Oxidation of phthalazine by AOX

combined activity of the vesicular monoamine transporter (VMAT) and MAO and ALDH enzymes (Goldstein 2020; Goldstein et al. 2012).

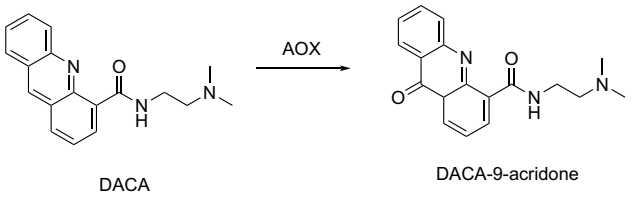


Fig. 34 Oxidation of DACA by AOX

MPTP

MPTP, a selective nigrostriatal neurotoxin, is bioactivated by MAO B (and less effectively by MAO A) to 2,3-MPDP$^+$, and this intermediate undergoes further oxidation to MPP$^+$ by MAOs (Fig. 26). MPTP and its two primary metabolites are competitive and mechanism-based inactivators of MAO A and MAO B enzymes (Trevor et al. 1988, 1987b). To express the selective nigrostriatal neurotoxicity of MPTP, bioactivation by MAO B is required, leading to the formation of the potentially reactive products MPDP$^+$ and (the 4-electron oxidation product) MPP$^+$. The latter product accumulates in brain striatal tissue, is a substrate for dopaminergic active uptake systems, and is an inhibitor of mitochondrial NADH dehydrogenase, a respiratory chain enzyme located in the inner mitochondrial membrane (Peterson et al. 1985; Singer et al. 1988; Trevor et al. 1987a). Both reactions, MPTP activation to MPP$^+$ and its deactivation by *N*-demethylation, are catalyzed by MAO B and P450s (Fig. 26) (Bajpai et al. 2013; Hanna et al. 2001; Herraiz et al. 2006; Nakamura et al. 2020; Trevor et al. 1987a; Uehara et al. 2015).

NAD(P)H-quinone oxidoreductase (NQO) enzymes

NAD(P)H quinone oxidoreductase 1 (NQO1) and NAD(P)H quinone oxidoreductase 2 (NQO2), are homodimeric flavoproteins containing one molecule of non-covalently bound FAD per monomer. These enzymes are members of a larger mammalian quinone oxidoreductase family and catalyze the reduction of quinones and similar molecules possessing quinone-like structures, e.g. quinone imines, benzotriazine oxides, tocopherols (Fig. 27). Nitro groups are also reduced by NQO enzymes. These enzymes use both NADH and NADPH and were termed "DT diaphoras" in the early literature because they use both DPNH (NADH) and TPNH (NADPH) (former names used for these pyridine nucleotides) (Ernster et al. 1962).

These enzymes are generally considered to be detoxicating enzymes that protect cells by catalyzing the 2-electron reduction of quinones and thus participate in the protection of cells against toxicity. NQO enzymes are constitutively expressed in a variety of tissues and also in many solid tumors. The latter property has been considered in

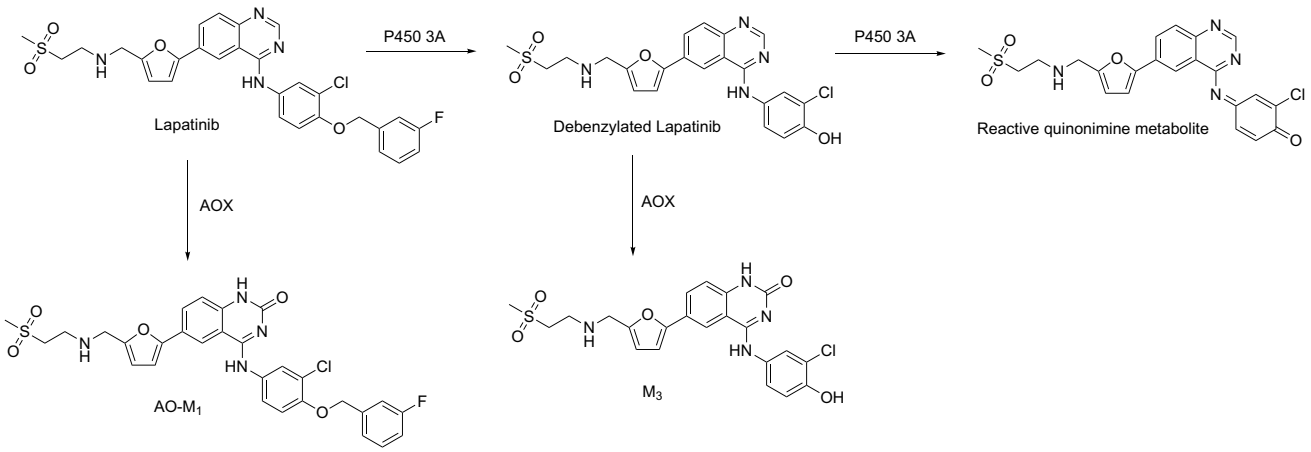


Fig. 35 Bioactivation of lapatinib by P450 3A enzymes and oxidation by AOX

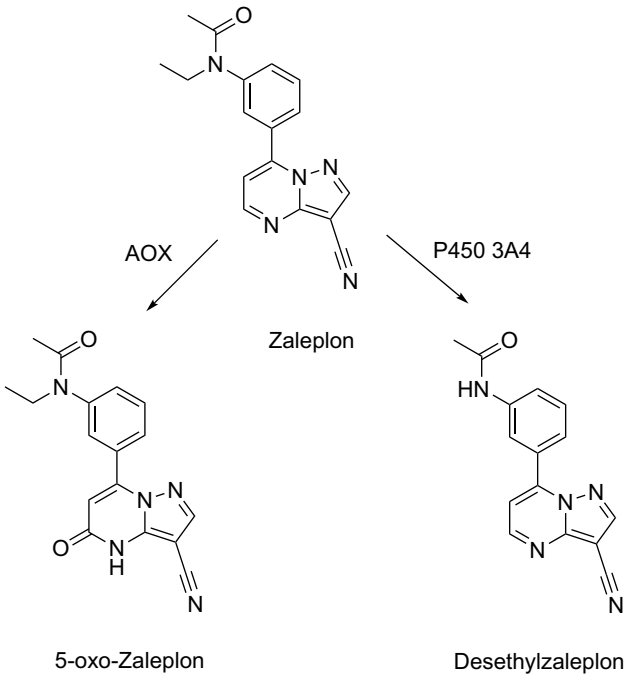
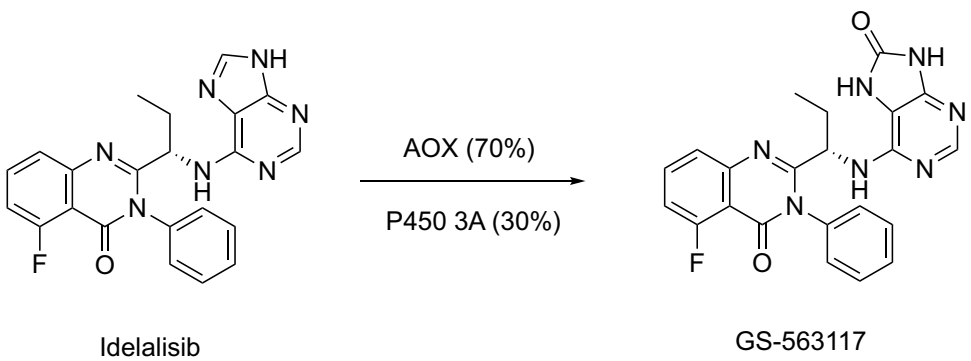


Fig. 36 Oxidation and N-deethylation of zaleplon by AOX and P450 3A enzymes

the context of potential targets for the activation of certain bioreductive anticancer agents (e.g., activation of the anticancer drug mitomycin C in tumor cells) (Siegel et al. 2004; Workman 1994). In our previous reports, human quinone reductase enzymes were classified in the group of "other oxidoreductases" (Rendić and Guengerich 2012, 2015). These enzymes participate in < 1% of the metabolism of xenobiotics and natural products, including drugs. The enzymes were also classified in the group of enzymes participating to the extent of < 4% of the activation of chemical carcinogens.

Changes in the activity of NQO1 are associated with different pathologies (including cancer and cardiovascular and neurodegenerative diseases), and these properties have been considered in the context of potential targets for the treatment of the diseases. Induction or depletion (knockout) of NQO1 was shown to be associated with decreased or increased susceptibilities to oxidative stress, respectively. Human NQO1 is often over-expressed in cancer cells, and the enzyme has been considered as a possible drug target. Two common polymorphic forms of human NQO1, pR139W and pP187S, were found to be associated with an increased risk of several forms of cancer. Dicumarol and some structurally related compounds act as competitive inhibitors of both variants. In addition, NQO1 was reported

Fig. 37 Oxidation of idelalisib by AOX and P450 3A enzymes



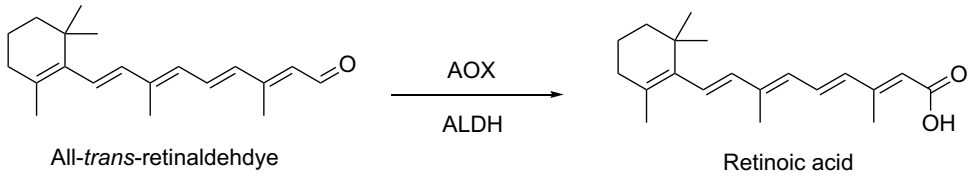


Fig. 38 Oxidation of retinaldehyde to retinoic acid by AOX

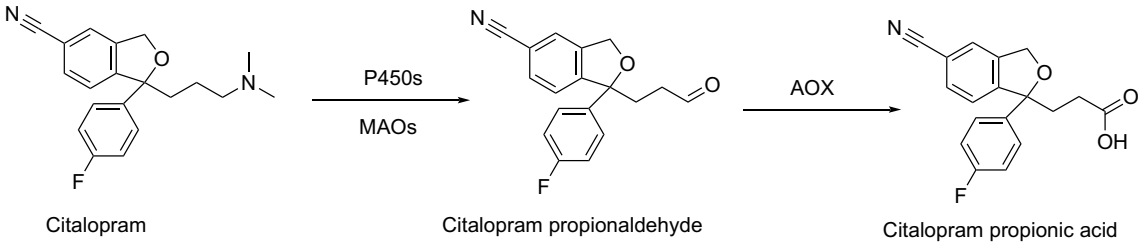


Fig. 39 Oxidation of citalopram by P450, MAO, and AOX enzymes to citalopram propionic acid

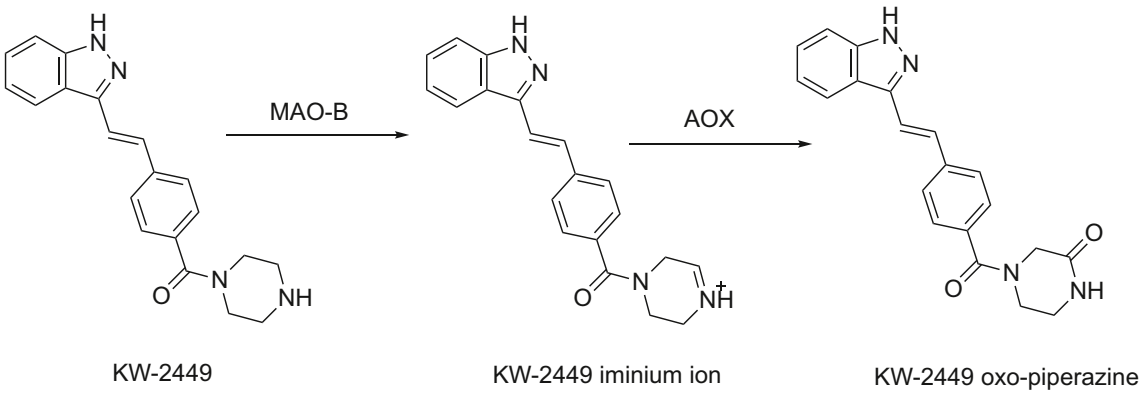


Fig. 40 Oxidation of KW-2449 to an oxo-piperazine metabolite by MAO B and AOX

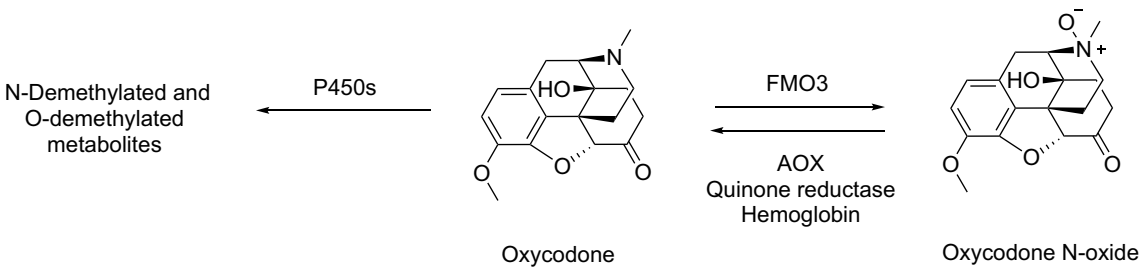


Fig. 41 *N*-Oxidation of oxycodone by FMO and retro-reduction by AOX and other enzymes

to be inhibited by nicotinamide, and resveratrol inhibited both NQO1 and NQO2 (Megarity and Timson 2019; Nolan et al. 2012; Pey et al. 2019). On the other hand, quercetin was shown to increase NQO1 transcription in human MCF-7 human breast cells (Valerio et al. 2001), and resveratrol increased NQO1 protein levels in K562 cells (Hsieh et al. 2006).

A review of the literature and examples of drugs, physiological, and environmental compounds that interact with NQO1 and NQO2 enzymes is provided in a recently published article (Rashid et al. 2021). The compounds are presented as being either activated (e.g., mitomycin C, doxorubicin, porfiromycin) or inactivated (e.g., acetaminophen, menadione, amrubicin) by NQO enzymes. One

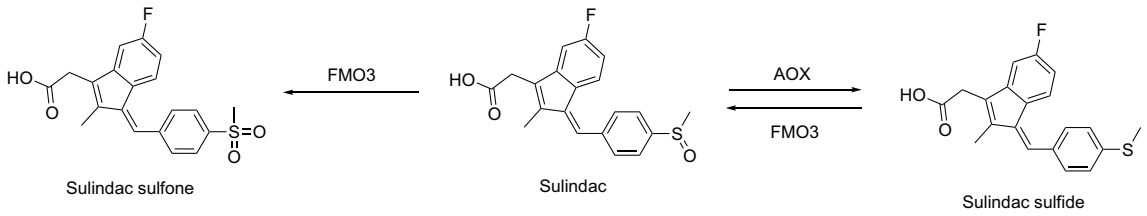


Fig. 42 *S*-Oxidation of sulindac by FMO and sulfoxide reduction by AOX

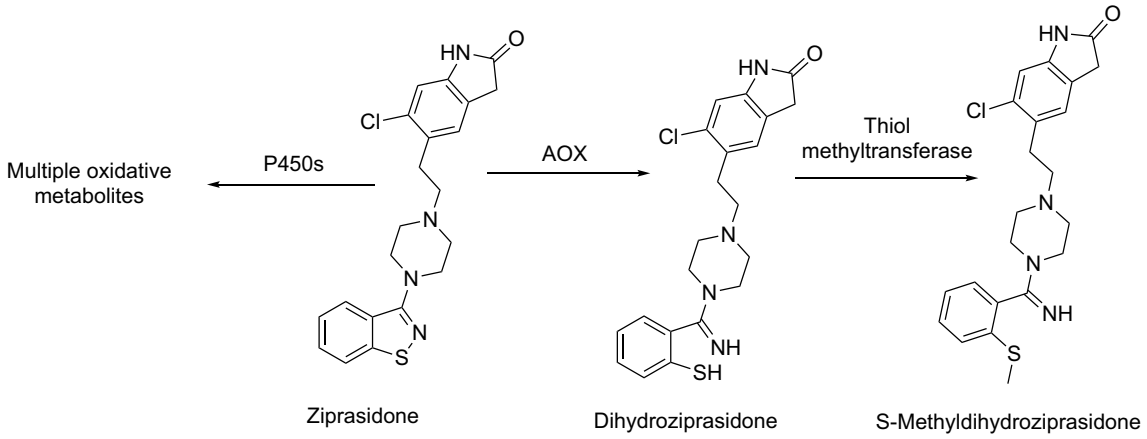


Fig. 43 Benzisothiazole reduction and thiol methylation of ziprasidone by AOX and thiol methyltransferase

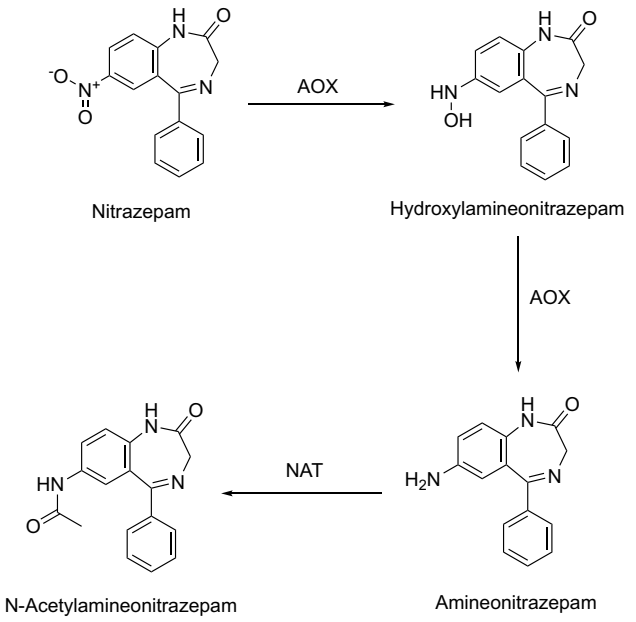


Fig. 44 Nitro reduction and *N*-acetylation of nitrazepam by AOX and NAT

of the physiological substrates of the NQO1 enzyme is the highly unstable DOPA quinone, formed by auto-oxidation of dopamine catechol. DOPA-quinone may induce neuronal damage resulting from the formation of reactive oxygen species, e.g. superoxide radicals and hydrogen peroxide. In a mouse model, that quinone formed up-regulates astroglial NQO, which might reduce the potentially toxic dopamine quinone to more stable hydroquinone, a detoxication reaction catalyzed by NQO enzymes (Drukarch et al. 2001; van Muiswinkel et al. 2000).

Molybdenum-containing hydroxylases

Molybdenum hydroxylases are cytosolic molybdoflavoproteins with a molecular mass of approximately 300 kDa (Hille 2005). Human molybdenum-containing hydroxylase enzymes were classified in the group of "other oxidoreductases" in our previous work (Rendić and Guengerich 2012); (Rendić and Guengerich 2015). According to this classification, as mentioned before, the enzymes from this group participate in < 1% of the metabolism of xenobiotics and natural products, including drugs. The enzymes were also classified in the group of enzymes participating to the extent of < 4% of the activation of chemical carcinogens (Rendić and Guengerich 2012); (Rendić and Guengerich 2015).

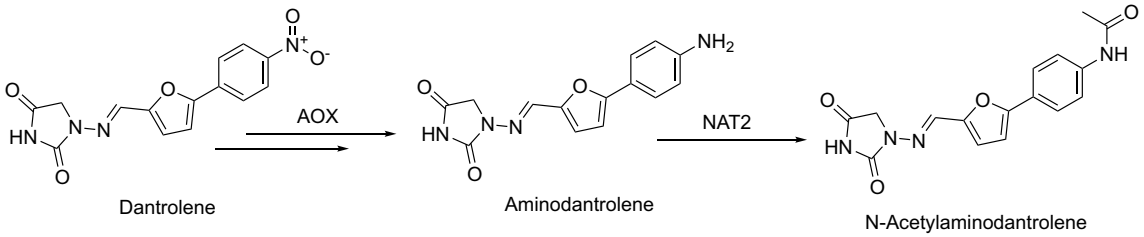


Fig. 45 Nitro reduction and *N*-acetylation of dantrolene by AOX and NAT

Fig. 46 Oxidation of SGX-523 to a poorly soluble lactam metabolite by AOX

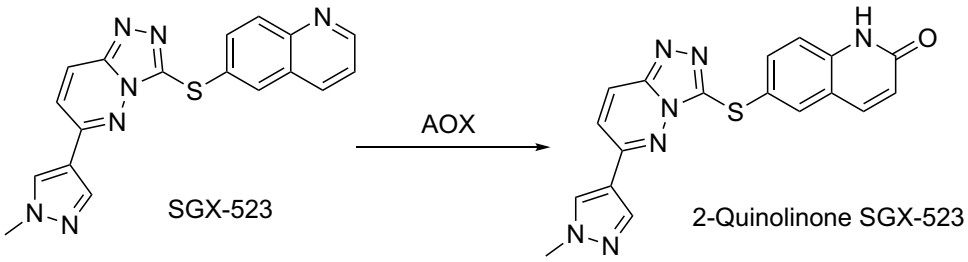
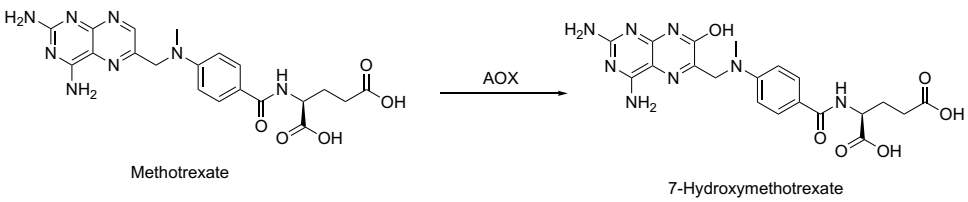


Fig. 47 Oxidation of methotrexate to a poorly soluble lactam metabolite by AOX



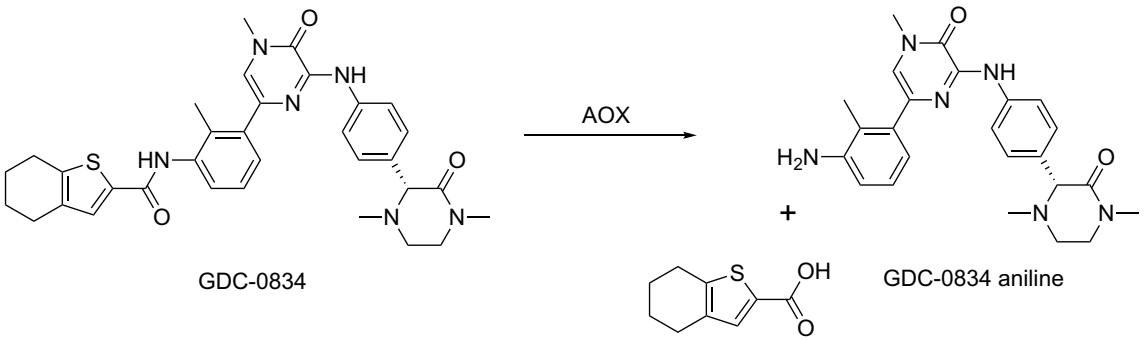


Fig. 48 Hydrolysis of GDC-0834 to an aniline metabolite by AOX

Enzymes

The molybdoflavoenzyme family in humans is composed of aldehyde oxidase (AOX), xanthine oxidoreductase (XOR), sulfite oxidase, and an enzyme known as mitochondrial amidoxime-reducing component (Terao et al. 2020) (Tables 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29). This review focuses on AOX and XOR, which are known to play roles in the metabolism of drugs and other xenobiotics (Tables 15, 19, 23). AOX and XOR enzymes also catalyze the metabolism of physiological compounds (Tables 17, 25) and are involved in both detoxications and activation of substrates to toxic/pharmacologically active intermediates or products (Tables 21, 22, 29).

The functional XOR and AOX enzymes are homodimers composed of two identical subunits of approximately 150 kDa, each possessing three cofactor-binding domains connected by flexible linker regions (Terao et al. 2020). The N-terminal domain contains two distinct iron–sulfur (2Fe–2S) redox centers, the central domain binds FAD,

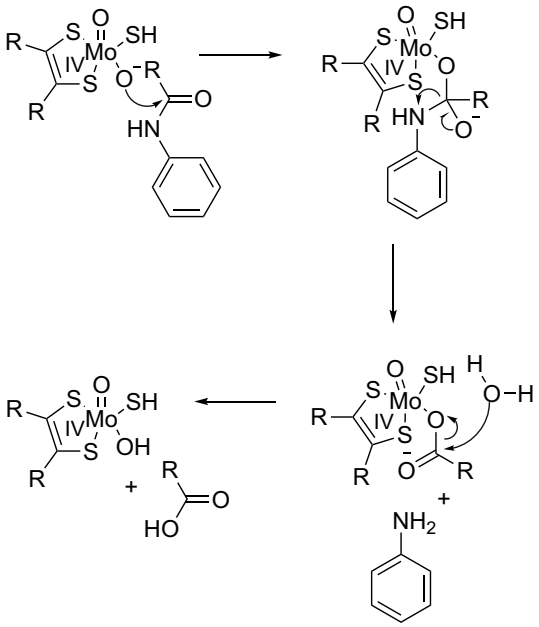


Fig. 49 Proposed mechanism of hydrolysis of GDC-0834 by AOX

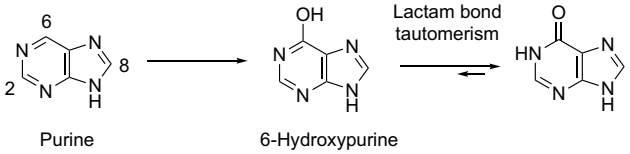


Fig. 50 Oxygenation of purine compounds by XOR enzymes

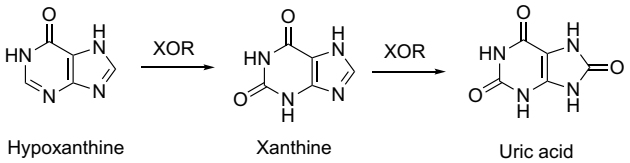


Fig. 51 Oxidation of hypoxanthine to xanthine and uric acid by XOR

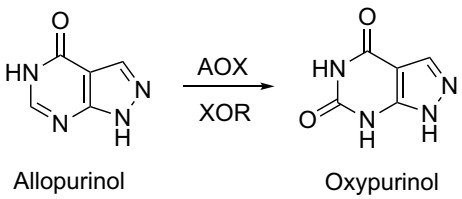


Fig. 52 Oxidation of allopurinol to oxypurinol by AOX and XOR enzymes

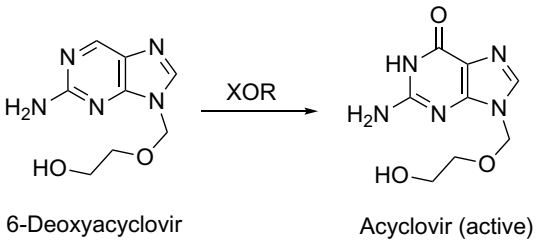


Fig. 53 Oxidation of 6-deoxyacyclovir to the active metabolite acyclovir by XOR

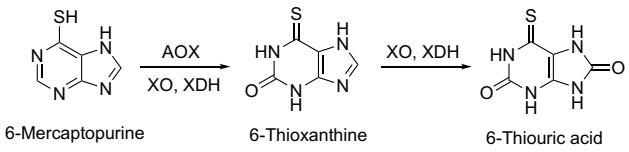


Fig. 54 Oxidation of 6-mercaptopurine to 6-thiouric acid by AOX, XO, and XDH

and the C-terminal domain houses a molybdenum cofactor (Moco) within the active site. The molybdenum atom of the Moco is coordinated with a sulfido ligand that is essential for catalytic activity. Whereas AOX exists only in a single form, mammalian XOR can interconvert between a dehydrogenase (XDH) and an oxidase (XO) (Battelli et al. 1973; Corte and Stirpe 1972; Della Corte and Stirpe 1968; Stirpe and Della Corte 1969). Accordingly, AOX and the XO utilize molecular oxygen as a final electron acceptor, whereas only XDH can transfer electrons to NAD^+. With amino acid sequence identities of approximately 50%, AOX and XOR enzymes possess similarities in substrate specificity (e.g., aromatic azaheterocycles); however, the larger, more anionic active site of AOX is able to accommodate a wider range of substrates relative to XOR (Mahro et al. 2013).

The tissue distribution of both AOX and XOR is species-dependent. AOX expression in humans is distributed across many different tissues, including liver (major), kidneys, lungs, gastrointestinal tract, skin, male reproductive tissues, and endocrine tissues, most notably the adrenal glands (Moriwaki et al. 2001; Terao et al. 2016). Constitutive expression of XOR in human tissues is low, and consequently, XOR activity is primarily present in the liver and gastrointestinal tract, as well as in lactating breast and kidney (Battelli et al. 2016a; Bortolotti et al. 2021). Notably, XOR is located in the vascular endothelium and can also be released into the systemic circulation, e.g., as a consequence of hepatic or intestinal damage (Kumar et al. 2018; Pritsos 2000).

The exact physiological roles of AOX and XOR are not well-defined, particularly with regard to AOX. Of the four human molybdenum hydroxylases, only sulfite oxidase is an

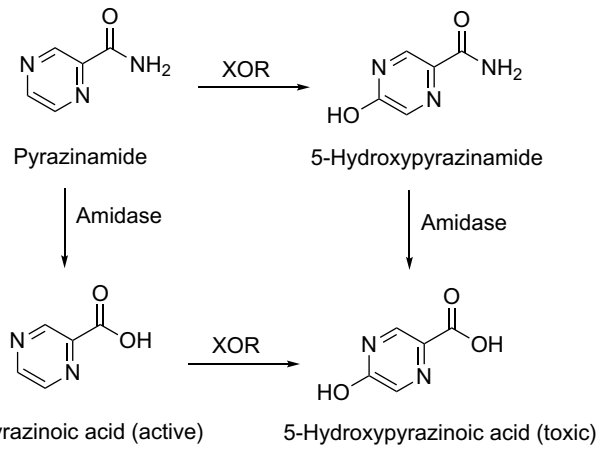


Fig. 55 Metabolism of pyrazinamide to active and toxic metabolites via amidase and XOR catalyzed reactions

essential enzyme (Duran et al. 1978; Shih et al. 1977; Terao et al. 2020; Veldman et al. 2010). XOR is responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid (Balis 1976; Krenitsky et al. 1986). Consequently, XOR deficiency leads to the accumulation of xanthine, a condition referred to as xanthinurea (Kumar et al. 2018). Xanthinurea is an autosomal recessive disorder and is categorized as either Type I (Nakamura et al. 2012), which is associated with a deficiency in XOR alone, or Type II, which is associated with a deficiency of both XOR and AOX (Reiter et al. 1990). In addition, XOR is capable of reducing nitrates to nitrites and both AOX and XOR have been shown to reduce nitrites to nitric oxide (Maia and Moura 2018; Maia et al. 2015). Because AOX and XO utilize molecular oxygen as an electron acceptor, both enzymes produce reactive oxygen species (hydrogen peroxide and/or superoxide) as by products in catalyzing the oxidation of substrates. Oxidative damage has been linked to the development of cancer (Oberley 2002), and both AOX and XOR have been implicated in tumor growth and development (Kusano et al. 2019; Qiao et al. 2020; Takeuchi et al. 2018).

Reactions

Molybdenum hydroxylases catalyze the transfer of an oxygen atom, ultimately derived from water, to a substrate in a two-electron redox reaction (Fig. 28) (Kisker et al. 1997). The enzymes oxidize carbon atoms of a number of different aldehyde and heteroaromatic rings. In general, aromatic azaheterocyclic compounds are better substrates of molybdenum-hydroxylases than aldehydes.

The catalytic mechanism of molybdenum hydroxylases used to oxidize aromatic azaheterocycles and aldehydes involves the oxidation of an electrophilic carbon, typically located adjacent to a nitrogen in heterocyclic substrates (Alfaro and Jones 2008). The process begins with deprotonation of a hydroxyl group on the Moco by a conserved glutamate residue, followed by a nucleophilic attack on the electron deficient carbon atom of the heteroaromatic substrate. Hydride transfer from the electrophilic carbon of the substrate to the sulfur of the Moco then follows, resulting in a reduction of the molybdenum from Mo(VI) to Mo(IV). While the reaction could proceed via a tetrahedral intermediate in a step-wise mechanism, it is believed to proceed via a concerted mechanism (Fig. 29). The reaction intermediate is hydrolyzed, releasing the oxidized product, and a water molecule replaces the lost hydroxyl ligand on the molybdenum. The reducing equivalents are shuttled from the Moco to FAD via the iron-sulfur clusters. $FADH_2$ is then reoxidized by molecular oxygen via a one or two-electron transfer, generating superoxide ion or H_2O_2, respectively. The oxidized products are structurally similar to those generated by P450 enzymes. However, the oxygen molecule used to oxidize substrates of molybdenum hydroxylases is derived from water (Garattini and Terao 2012), unlike P450s which use molecular oxygen as the source of the oxygen in the product (Guengerich 2001). Accordingly, the inclusion of $H_2{}^{18}O$ in incubations with molybdenum hydroxylases is utilized as a reaction phenotyping strategy for these enzymes.

In addition to oxidation reactions, AOX and XOR are capable of catalyzing reduction reactions. Both AOX and XOR have been demonstrated to reduce nitrite to nitric oxide (Fig. 30), an important signaling molecule involved in numerous physiological functions, including vasodilation, platelet aggregation, and immune response (Godber et al. 2000; Li et al. 2009; Maia et al. 2015). AOX is also known to reduce a variety of other functional groups, including *N*- and *S*-oxides, heterocycles, and nitro groups (Amano et al. 2018; Cashman et al. 2020; Dalvie and Di 2019; Ogiso et al. 2018; Pryde et al. 2010; Sung et al. 2020).

While reductive reactions and mechanisms have received less attention relative to oxidation reactions catalyzed by molybdenum hydroxylases, Maia and Moura have described the mechanism of nitrite reduction to nitric oxide (Fig. 31), which takes place at the Moco center (Maia and Moura 2018). A reducing substrate, such as an aldehyde or aromatic heterocycle, is required to reduce the Moco from Mo(VI) to Mo(IV) as previously described in Fig. 29. The nitrite reduction then proceeds via sequential one electron transfer to two molecules of nitrite, reoxidizing the Moco from Mo(IV) to Mo(V) and then back to Mo(VI). Maia and Moura also demonstrated that the reaction is independent of the FAD center with experiments using an FAD inhibitor or enzyme lacking FAD.

Aldehyde oxidase 1 (AOX1)

Mammalian aldehyde oxidases (AOXs) are cytosolic molybdoflavoenzymes involved in the metabolism of drugs, natural and physiological compounds, and general chemicals (Tables 15, 17, 19). The enzymes participate not only in the detoxication of toxic metabolites endogenously formed by other enzymes such as P450s (e.g., aldehyde intermediates) but also in the production of toxic and therapeutically active metabolites (Tables 21, 22), and the generation of reactive oxygen species (ROS) as a byproduct of their enzymatic activity.

Enzymes

Different animal species are characterized by a different complement of aldehyde oxidase genes clustering at a short distance on the same chromosome (chromosome 2 in humans) (Terao et al. 2016). Humans contain a single active gene, *AOX1*, and two pseudogenes, while rodents are characterized by four active genes. Both AOX1 and AOX3 are major enzymes present in rodent liver (with the exception of guinea pigs, which only express AOX1 in the liver). The mouse Aox1 enzyme bears 85% sequence identity with human AOX1, whereas mouse Aox3 is only 65% identical to human AOX1 (Garattini et al. 2008). Primates, like humans, have only a single functional AOX enzyme (AOX1) in the liver, which bears 96% sequence identity with the human enzyme (Hoshino et al. 2007). Accordingly, marked species differences in AOX-mediated metabolism are common, and these differences present in a substrate-dependent manner (Beedham et al. 1987; Choughule et al. 2015; Crouch et al. 2018; Dalvie et al. 2013; Diamond et al. 2010; Hutzler et al. 2014; Sahi et al. 2008). However, AOX catalytic activity generally tends to be highest in monkeys and humans and lowest in mice and rats, whereas rabbits and guinea pigs tend to fall somewhere in between. Dog liver is completely devoid of an active AOX enzyme (Terao et al. 2016).

The human AOX1 protein has been reported in many tissues, including liver, pancreas, kidney, adrenal gland, thyroid gland, prostate, bladder, gastrointestinal tract, testis, bronchi, uterus, and skin (Moriwaki et al. 2001). The liver contains the highest concentration of AOX1 protein, though substantial quantities are also present in the adrenal glands. *AOX1* mRNA expression has been found in many human tissues as well (Terao et al. 2016).

Humans have functionally inactive AOX1 allelic variants as well as variants encoding enzymes with different catalytic activities (i.e., slow and rapid metabolizers) (Foti et al. 2016; Hartmann et al. 2016; Mota et al. 2019). In addition, single nucleotide polymorphisms affecting the FAD binding site have been demonstrated to increase the rate of superoxide production (Foti et al. 2017). The clinical relevance of these variants has yet to be established. Garrido and Leimkühler demonstrated that the L438V variant, which produces a higher ratio of superoxide/H_2O_2 relative to the wild-type enzyme, is more extensively inactivated over time (i.e. inactivated by ROS production) relative to the wild type enzyme (Garrido and Leimkühler 2021). The L438V variant, which bears a single nucleotide polymorphism affecting the FAD binding site, produces superoxide at a rate of 75% compared to the amount of H_2O_2 produced, whereas the wild-type enzyme produces only 10% superoxide in comparison to H_2O_2.

As the name suggests, AOX catalyzes not only the aldehydes but can also catalyze the oxidation of aromatic azaheterocycles, as well as reductive reactions. AOX is best understood for its role in xenobiotic metabolism, but the enzyme may have additional physiological functions. Species differences in the expression and activity of AOX present a challenge in defining the physiological role(s) of human AOX. The list of endogenous substrates of AOX includes *N*-methylnicotinamide, pyridoxal, and all-*trans*-retinaldehyde (Table 17) (Johns 1967; Zhong et al. 2021). AOX has also been shown to be capable of reducing nitrites to nitric oxide and has been proposed to be involved in adipogenesis (Heid et al. 2020; Maia et al. 2015; Weigert et al. 2008). Due to its function in producing ROS, AOX may also contribute to pathological conditions resulting from oxidative stress (e.g., cancer). However, the exact physiological/pathological roles of AOX remain poorly understood.

Substrates

AOX is characterized by broad substrate specificity, in contrast to XOR, which has a specificity more limited to purine-like compounds. AOX has been most frequently reported to oxidize aromatic azaheterocycles, e.g. substituted pyrroles, pyridines, pyrimidines, purines, pteridines, and quinolines, among others (Dalvie and Di 2019; Garattini and Terao 2012; Kitamura et al. 2006; Manevski et al. 2019; Pryde et al. 2010). In addition, compounds containing iminium ions (often intermediate metabolites generated by P450s or MAOs) are relatively common AOX substrates. Aliphatic and aromatic aldehydes (which also often arise as intermediate metabolites) are oxidized by AOX as well. However, compounds containing aldehydes tend to be more efficiently oxidized by ALDH. AOX substrates for reduction include nitro-containing compounds, sulfoxides, *N*-oxides, and nitrites, as well as heterocycles such as isoxazoles and isothiazoles. More recently, AOX has also been demonstrated to be capable of hydrolyzing amides (Sodhi et al. 2015). While AOX and P450s have somewhat opposing substrate preferences due to different catalytic mechanisms (e.g. P450s prefer to oxidize electron-rich carbon atoms, whereas AOXs prefer electron deficient carbon atoms), they can sometimes

share heterocyclic substrates and produce the same hydroxylated products (e.g., idelalisib) (Jin et al. 2015).

Inhibitors

A number of drugs, natural compounds, and general chemicals have been reported to inhibit human AOX (Tables 16, 18, 20). The strongest known inhibitor of AOX is the selective estrogen receptor modulator, raloxifene (IC_{50} 2.9 nM), while several other drugs have also been also reported to strongly inhibit the enzyme, particularly phenothiazines (e.g. perphenazine, IC_{50} 33 nM) (Obach et al. 2004). 17 β-Estradiol and 17α-ethinylestradiol are also strong inhibitors. In addition to a number of general chemical compounds (e.g., phenothiazines, dibenzazepines, flavonoids, purines, and pyrimidines) (Table 20), a number of diet-derived natural products have been found to inhibit AOX activity, including various catechins, flavones, flavonoids, flavonols, and flavanonols (Table 18). The compounds most commonly used to phenotype AOX reactions are raloxifene, menadione, and the time-dependent inhibitor hydralazine. Each of these three compounds is selective for AOX over XOR, but they exhibit varying degrees of inhibition toward various microsomal enzymes (Zientek and Youdim 2015). As the inhibition kinetics of AOX is complex (and substrate-dependent), the use of multiple probe substrates is recommended when results are used to assess the potential for drug–drug and/or drug–chemical interactions (Barr and Jones 2013). Clinically significant drug–drug interactions involving AOX inhibition have not been reported, with the exception of zaleplon and cimetidine. Zaleplon inhibits not only the AOX-mediated metabolism (of zaleplon) but also the CYP3A-mediated pathway, which represent approximately 70% and 30% of the fractional metabolism of zaleplon, respectively (Renwick et al. 2002).

Inducers

Limited reports are available on the regulation of AOX expression, particularly regarding the human enzyme. Maeda et al. demonstrated regulation of the human AOX gene involving the Nrf2 pathway (Maeda et al. 2012). In addition, Zhou et al. reported increased AOX-mediated metabolism of methotrexate, increased AOX protein levels, and a minimal increase in AOX mRNA following treatment of human hepatocytes with the nonsteroidal anti-inflammatory drug nimesulide (Zhou et al. 2020). Others have demonstrated induction of AOX activity, mRNA, and/or protein in animals by various compounds (e.g. phthalazine, dioxin) (Johnson et al. 1984; Rivera et al. 2005). Notably, androgens have been reported to increase AOX expression in rodents, while estrogens reduced expression, which is consistent with sex-dependent AOX activity observed in rodents (Al-Salmy 2001; Beedham 1985; Garattini and Terao 2012). Humans, however, appear to exhibit no sex-dependent differences in AOX activity, although estrogens are known to inhibit human AOX in vitro (Obach 2004).

Reactions

AOX catalyzes the oxidation of aromatic and aliphatic aldehydes into the corresponding carboxylic acids, hydroxylation of electrophilic carbon atoms on heteroaromatic rings, oxidation of iminium ion intermediates to the corresponding lactams, and hydrolysis of amides. AOX is also reported to catalyze the reductive metabolism of nitro groups, *N*-oxides, sulfoxides, isoxazoles, isothiazoles, benzisoxazoles, nitrite, and hydroxamic acids. Certain reductive transformations (e.g., nitro-reduction) have the potential to cause toxicity due to the formation of reactive metabolites. Reductive reactions may be accelerated in the presence of a reducing substrate, as was demonstrated for the reduction of dantrolene in the presence of *N*-methylnicotinamide (Amano et al. 2018).

AOX catalyzes the oxidation of heteroaromatic rings, iminium ions, and aldehydes. During the oxidation of the substrate, the enzyme is reduced and reoxidized with molecular oxygen, therefore behaving as an oxidase (Fig. 32). For both AOX and the XO form of XOR, the reduction of molecular oxygen produces the reactive oxygen species (ROS), hydrogen peroxide and superoxide anion, with AOX favoring the production of hydrogen peroxide (Foti et al. 2017). However, it has been suggested that AOX may produce more than 20-fold higher amounts of superoxide versus XOR, based on the enzymatic activities of the two enzymes in the human liver (Krenitsky et al. 1972; Kundu et al. 2007). Although NAD^+ is the preferred electron acceptor for the XDH form of the XOR enzyme, it is capable of transferring electrons to O_2 and thus producing ROS by acting as an NADH oxidase (Sanders et al. 1997).

Garrido and Leimkühler recently reported that AOX is inactivated in a substrate-dependent manner by ROS production, with a high turnover substrate inactivating the enzyme more rapidly than a low turnover substrate (Garrido and Leimkühler 2021). Alternatively, because the enzyme inactivation was not prevented by ROS scavengers (catalase and superoxide dismutase) in their studies, Abbasi et al. reported that the enzyme inactivation results, not from ROS production, but rather from the rate-limiting transfer of electrons to O_2, which is required to reoxidize the enzyme (Abbasi et al. 2019). Similar to the results obtained by Garrido and Leimkühler with AOX, Lynch and Fridovich previously reported that XO is autoinactivated by ROS production (Lynch and Fridovich 1979). Differences in incubation conditions were cited as a possible explanation for the discrepancy between the findings in the two AOX studies.

Other compounds can also serve as electron acceptors for AOX as well. While some accept electrons at the FAD site (e.g. 5-nitroquinoline) (Abbasi et al. 2019), where O_2 accepts electrons, others may directly receive electrons from the Moco site (e.g. 2,6-dichlorophenolindophenol) (Foti et al. 2017; Garrido and Leimkühler 2021).

Examples of substrates and reactions resulting in the formation of nontoxic metabolites

Oxidation of aromatic heterocycles

Phthalazine (general chemical)

Phthalazine is a bicyclic heteroaromatic compound that is rapidly oxidized by AOX to phthalazone (Beedham et al. 1987, 1995) (Fig. 33). Phthalazine is commonly used as an AOX probe substrate (Table 19). The time-dependent AOX inhibitor hydralazine is a derivative of phthalazine. Because phthalazine and phthalazone are metabolites of hydralazine, it is not a suitable inhibitor to evaluate the AOX-mediated metabolism of phthalazine.

DACA (antineoplastic, DNA intercalating dual topoisomerase I/II poison)

While most heterocyclic substrates of AOX are oxidized on an electrophilic carbon atom adjacent to a nitrogen atom, in some cases the oxidation may occur para to the nitrogen, as is the case for the antineoplastic agent DACA (Fig. 34). DACA is oxidized to an acridone product by AOX on the carbon atom opposite the nitrogen in the acridine moiety (Schofield et al. 2000) (Table 15).

Lapatinib (antineoplastic, EGFR inhibitor)

Lapatinib, an anticancer agent known to be associated with hepatotoxicity, is debenzylated by P450 3A enzymes to a metabolite that subsequently undergoes metabolic activation via P450 3A enzymes (Castellino et al. 2012) (Fig. 35). Lapatinib and its debenzylated metabolite are also oxidized by AOX to AO-M1 and M3, respectively (Dick 2018), which may serve as a detoxication pathway in opposition to the bioactivation pathway (Table 15).

Zaleplon (nonbenzodiazepine sedative hypnotic)

Zaleplon is a dual AOX and P450 substrate, undergoing oxidation by AOX to 5-oxo-zaleplon (Table 15, Fig. 36) and *N*-dealkylation by P450 3A4 to desethyl-zaleplon. Species differences are noted in the fractional metabolism by AOX and P450, with 5-oxo-zaleplon representing the major metabolite in humans and monkeys (approximate $f_{m,AO}$ (fraction of metabolism due to AOX)) = 0.7 in humans) and desethyl-zaleplon representing the major metabolite in rodents (Crouch et al. 2018; Kawashima et al. 1999; Strelevitz et al. 2012). In addition, an interaction between cimetidine and zaleplon is one of the only known clinically relevant drug–drug interactions associated with AOX metabolism (Renwick et al. 2002). However, cimetidine inhibits not only the AOX metabolism pathway but also the P450 3A4 pathway as well.

Idelalisib (antineoplastic, phosphatidylinositol 3-kinase inhibitor)

Despite differences in catalytic mechanism and general substrate preference, some metabolites may be produced by both AOX and P450 enzymes, as is the case for idelalisib. Both AOX and P450 3A4 catalyze the oxidation of idelalisib to the inactive metabolite GS-563117, which is a mechanism-based inactivator of P450 3A (Jin et al. 2015; Ramanathan et al. 2016) (Table 15) (Fig. 37).

Oxidation of aldehydes

All-trans-retinaldehyde (vitamin A derivative)

Retinal is the most well-studied endogenous substrate of AOX (Ambroziak et al. 1999; Zhong et al. 2021). The aldehyde undergoes oxidation to produce the active metabolite retinoic acid, a reaction that is catalyzed by both AOX and ALDH (Table 17) (Fig. 38). Zhong and coworkers recently reported that ALDH1A1 serves as the low K_m, low k_{cat} enzyme contributing to the biosynthesis of retinoic acid in the human liver, while AOX serves as the high K_m, high k_{cat} enzyme (Zhong et al. 2021).

Citalopram aldehyde (metabolite of SSRI citalopram)

Aldehydes are relatively uncommon in parent drug molecules. However, they are often generated by enzymes such as P450s. Citalopram is demethylated and converted to an aldehyde metabolite by a combination of P450 and MAO enzymes (Rochat et al. 1998) (Table 8) (Fig. 39). The aldehyde metabolite undergoes subsequent oxidation by AOX to the carboxylic acid (Table 15).

Oxidation of iminium ions

Like aldehyde intermediates, AOX has been found to oxidize iminium ion intermediates generated by P450s or MAOs. As iminium ions have the potential to produce toxic effects,

AOX-mediated oxidation of iminium ion intermediates may serve as a detoxication pathway.

KW-2449 (multikinase inhibitor)

KW-2449 is a multikinase inhibitor that was previously under investigation for the treatment of leukemia. The drug, which has been discontinued from further development, displayed unexpected rapid metabolism to an oxo-piperazine metabolite in clinical trials (Hosogi et al. 2018). The pharmacologically active metabolite was determined to be generated via sequential metabolism by MAO B to an iminium ion intermediate, followed by AOX-mediated oxidation to the oxo-piperazine metabolite (Table 15, Fig. 40). In addition, the iminium ion intermediate was found to be a time-dependent inhibitor of AO, reducing exposure of the active metabolite following repeat dosing (Table 16). Interspecies differences in both MAO B and AOX likely contributed to the failure to recognize this metabolic pathway prior to clinical trials.

Reduction of *N*-oxides

Oxycodone *N*-oxide (metabolite of the opioid analgesic oxycodone)

Oxycodone is extensively metabolized by P450 enzymes, but it is also converted to oxycodone *N*-oxide by FMO3 (Cashman et al. 2020). The *N*-oxide metabolite was found to be retro-reduced back to oxycodone by AOX, quinone reductase, and hemoglobin (Table 15) (Fig. 41). Consequently, interindividual variability in AOX activity could potentially influence the duration of action and toxicity of oxycodone across patients.

Reduction of *S*-oxides

Sulindac (NSAID)

Fewer examples of AOX-mediated *S*-oxidation are available in the literature relative to *N*-oxidation. The reduction of the nonsteroidal anti-inflammatory drug sulindac to its pharmacologically active sulfide metabolite represents one example of this reaction (Sung et al. 2020) (Table 15). Alternatively, the sulfide can be oxidized back to sulindac by FMO enzymes, which also oxidize sulindac to an inactive sulfone metabolite (Table 3, Fig. 42).

Reduction of heterocycles

Ziprasidone (second generation antipsychotic)

Ziprasidone represents an example of a drug containing a heterocycle that is reduced by AOX (Miao et al. 2005; Prakash et al. 1997). The drug is extensively metabolized to multiple metabolites, including several oxidative P450 metabolites. However, the major circulating metabolite results from AOX-mediated reductive cleavage of the benzisothiazole ring, followed by methylation of the thiol (Table 15, Fig. 43).

Toxic effects of drugs as substrates of AO catalyzed reactions

Several examples of therapeutically successful candidate drugs tested in animal models have been removed from further testing due to differences in the formation of a toxic metabolite in preclinical species relative to humans (e.g., SGX523) (Hutzler et al. 2013; Manevski et al. 2019). Some examples of drugs converted into toxic metabolites by AOX are listed in Table 22. Alternatively, examples of drugs that are converted to active metabolites by AOX are listed in Table 21, which includes metabolites possessing desirable cytotoxic properties (e.g., anti-cancer agents).

Reduction of nitro-groups

Drugs containing nitro groups have been associated with mutagenicity and genotoxicity. AOX is capable of reducing nitro-groups to their corresponding amines, producing a hydroxylamine intermediate in the process. As hydroxylamines are reactive species that have the potential to produce toxic effects, the toxicities (e.g., hepatotoxicity) associated with nitro-aromatic containing drugs such as nimesulide, nitrazepam, dantrolene, and others (Table 22) may result, at least in part, from AOX-mediated nitro-reduction of these drugs.

Nitrazepam (benzodiazepine)

Koneshi et al. demonstrated that AOX participates in the reduction of nitrazepam to hydroxylaminonitrazepam and aminonitrazepam (Konishi et al. 2017). The aminonitrazepam metabolite is further metabolized by *N*-acetyltransferases (NATs) to *N*-acetylaminonitrazepam (Table 15, Fig. 44).

Dantrolene (skeletal muscle relaxant)

Dantrolene, like nitrazepam, contains a nitro-group that is reduced to a hydroxylamine, followed by a second reduction

to aminodantrolene (Amano et al. 2018; Ogiso et al. 2018) (Table 22). Aminodantrolene is also *N*-acetylated by NAT2 (Fig. 45). Dantrolene carries a black box warning for severe hepatotoxicity, which is attributed to the formation of the hydroxylamine intermediate.

Oxidation of heterocycles to poorly soluble lactam metabolites

SGX523 (antineoplastic, c-MET inhibitor)

SGX-523 is an anticancer agent that was discontinued in clinical trials due to renal toxicity that went undetected in toxicity studies conducted in rats and dogs (Infante et al. 2013). Diamond et al. determined that the toxicity likely resulted from precipitation of an AOX metabolite in the renal tubules, which was not observed in animals studies due to species differences in AO activity (Diamond et al. 2010) (Tables 15, 22). The 2-quinolinone (Fig. 46) metabolite was undetected in dog liver post-mitochondrial supernatant fraction (S9) and only trace amounts were produced in rat S9, unlike human and monkey S9, in which the 2-quinolinone was a major metabolite. Following administration of SGX-523 to cynomologus monkeys, the 2-quinolinone metabolite was present in urine at concentrations 70-fold higher than the parent drug and its solubility was only 3% of the parent solubility. A structural analog of SGX-523, JNJ-38877605, was also discontinued during clinical trials due to renal toxicity, which was presumed to occur via the same AOX-mediated mechanism (Lolkema et al. 2015). JNJ-38877605 has a difluoro-substituted ether linkage rather than a thioether linkage and is otherwise structurally identical to SGX-523.

Methotrexate (antineoplastic, antirheumatic, antifolate)

Methotrexate is also known to cause renal toxicity, particularly when administered in high doses (Jordan et al. 1999). As with SGX-523 and JNJ-38877605, renal toxicity is believed to be associated with AOX-mediated oxidation to 7-hydroxymethotrexate, a poorly soluble metabolite (Table 22, Fig. 47).

Hydrolysis of anilides

GDC-0834 (antirheumatic, Bruton's tyrosine kinase inhibitor)

GDC-0834 was previously under investigation for the treatment of rheumatoid arthritis but was discontinued from further development due to rapid hydrolysis of the anilide moiety, producing an aniline metabolite (Liu et al. 2011; Sodhi et al. 2015) (Fig. 48). While neither preclinical nor clinical toxicity was reported as a concern or reason for discontinuation of GDC-0834, anilines are known to have the potential to produce toxic effects, if for no reason than guilt by association. Lepri et al. evaluated a series of anilide-containing compounds for their susceptibility to AOX-mediated amide hydrolysis and found several of the compounds to be AOX substrates, thus highlighting this reaction as a potential source of toxicity for anilide-containing drugs (Lepri et al. 2017) (Table 15).

Sodhi et al. have proposed a mechanism for the hydrolysis of GDC-0834, on the basis of in silico modeling, that involves a nucleophilic reaction between a hydroxyl group of the Moco and the carbonyl group of the anilide (Sodhi et al. 2015). The authors speculated that this reaction would be more likely to take place with the Moco in the reduced state (Fig. 49) due to the higher electron density, which would require the presence of a reducing substrate. Once the enzyme has initially been reduced, the proposed hydrolysis mechanism does not require any transfer of electrons in order to complete the catalytic cycle, meaning that the entire process would take place at the Moco center without the involvement of the FAD and 2Fe-2S centers.

Xanthine oxidoreductase (XOR)

Xanthine oxidoreductase (XOR), perhaps the better-known molybdenum hydroxylase, plays an important role in the catabolism of endogenous purines and pyrimidines in humans, as well as drugs such as thiopurines and methylxanthine compounds (Tables 23, 25, 27). XOR is less promiscuous than AOX, preferring substrates that are more purine-like, although some compounds are substrates for both enzymes.

Enzymes

Unlike AOX, XOR can exist in two interconvertible forms, as a dehydrogenase (XDH), which prefers NAD^+ as an electron acceptor, or an oxidase (XO), which can only transfer electrons to O_2. Based upon studies with rat liver and bovine milk XOR, the XDH form can be postranslationally modified to the XO form either irreversibly through limited proteolysis, or reversibly through the formation of two disulfide bonds involving four cysteine residues (Battelli et al. 1973; Corte and Stirpe 1972; Della Corte and Stirpe 1968; Stirpe and Della Corte 1969). In both cases, either reversible or irreversible conversion from XDH to XO, the modification takes place within a peptide that links the Moco- and FAD-containing domains.

Tissue distribution of XOR is species-dependent, with lower constitutive expression in humans relative to other mammals, presumably due to promotor suppression (Xu et al. 2000). Human XOR enzymes have been found in the lactating mammary gland, intestine, liver, lungs, kidneys,

and vascular endothelium, with the highest specific activity in the liver and intestine (Linder et al. 1999; Moriwaki et al. 1996). In addition, relative levels of an inactive enzyme (for example, de-molybdo and/or de-sulfo forms of the enzyme) may contribute to species differences in the tissue distribution of XOR activity (Battelli et al. 2014). For example, in human milk, active XOR was found to account for < 2% of the total enzyme content, and the xanthine oxidizing activity in human milk was found to be 2–3 orders of magnitude lower than bovine milk, despite similar total XOR enzyme content (Abadeh et al. 1992).

XOR has been detected in the vascular endothelial cells of various human tissues (Kooij et al. 1992; Linder et al. 1999; Moriwaki et al. 1993). While XOR is a cytosolic enzyme like AOX, it has also been detected on the outer surface of bovine and porcine endothelial cells (Vickers et al. 1998). XOR is also present (in the XO form) in circulating plasma, although the constitutive presence in plasma is species-dependent (Al-Khalidi and Chaglassian 1965). For example, studies evaluating the plasma stability of a quinoxaline-containing compound within a series of cyanopyridine derivatives revealed a species-specific oxidation of the quinaoxaline mediated by plasma XOR (Sharma et al. 2011). The quinoxaline-containing compound was rapidly degraded in rat, mouse, and guinea pig plasma but not in dog, monkey, or human plasma. The lactam metabolite was also detected in human liver cytosol; however, a further evaluation to distinguish whether the metabolite was produced by human hepatic XOR vs AOX was not reported. Though plasma levels of XOR in healthy humans is low, increased levels of circulating plasma XOR have been associated with various pathological conditions, primarily related to hepatic injury, including viral hepatitis, toxic agents, transplantation, hypoxia, and ischemia/reperfusion (Battelli et al. 2014). Other conditions that have been associated with elevated circulating XOR include pneumonia, type 2 diabetes, postsurgical procedures, and sickle cell disease, among others (Battelli et al. 2014).

Products of XOR catalyzed reactions have been associated with both beneficial and toxic effects and elevated XOR activity has been connected to different pathological conditions causing tissue damage and cell necrosis (Battelli et al. 2016b; Bortolotti et al. 2021; Harrison 2002). Uric acid, the product of xanthine oxidation, and NO, the product of nitrite reduction, play a role in blood pressure regulation and vascular tone. In addition, uric acid has anti-oxidant activity, contributes to the inflammatory response, and promotes gluconeogenesis and fat accumulation. Consequently, XOR may play a role in the pathogenesis of metabolic syndrome and insulin resistance. While ROS produced by XOR can contribute to pathological conditions associated with oxidative stress such as cancer, uric acid plays a role in preventing these pathological conditions. Beneficial effects are also derived from ROS production, for example, via their bactericidal action.

Substrates

Similar to AOX, XOR utilizes a variety of heterocycles and some aldehydes as substrates. However, XOR has a narrower specificity than AOX, generally preferring substrates that are more purine-like (Tables 23, 25, 27). Oxidation of purines occurs at C-atoms in positions C2-, C6-, and C8- (Okamoto et al. 2013) (Fig. 50). The affinity of C-atoms for oxidation increases with the number of adjacent N-atoms.

The substrate specificity for AOX and XOR does sometimes overlap. For example, 6-mercaptopurine is oxidized by both AOX and XOR to 6-thioxanthine, whereas oxidation of 6-thioxanthine to 6-thiouric acid is catalyzed by XOR alone (Choughule et al. 2014). In some cases, a compound may be a dual substrate for XOR and AOX, but the site of metabolism may differ. Examples of this observation in the literature, however, have been determined using non-human sources of XOR and/or AOX. For example, 6-deoxyacyclovir was reported to be oxidized to the active metabolite acyclovir by bovine milk XOR and to the inactive metabolite 8-hydroxy-6-deoxyacyclovir by rabbit liver AOX (Krenitsky et al. 1984). In fact, many compounds not reported in this review are substrates for mammalian XOR or AOX but have not been confirmed to be substrates of the human enzymes. XOR studies in particular have been frequently carried out using a non-human enzyme source, most often bovine milk XOR owing to its wide availability and low cost. Due to species differences in AOX/XOR substrate specificities, it cannot be assumed that a substrate for a non-human enzyme is also a substrate for the human enzyme. For example, using enzyme-selective inhibitors in multiple species of S9 preparations, the 6-oxopyrimidine metabolite of VU424238, for example, was found to be oxidized to a 2,6-oxopyrimidine metabolite by either AOX or XOR in a species-dependent manner (Crouch et al. 2017).

Inhibitors

As previously mentioned, XOR is responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid, the accumulation of which is associated with the pathophysiology of gout. Consequently, inhibition of XOR is a therapeutic strategy in the treatment of gout, and multiple drugs that inhibit XOR are on the market (allopurinol, febuxostat, and topiroxostat). Allopurinol has been in use since the 1960s, whereas febuxostat only received FDA approval in 2009. Topiroxostat is not available in the United States but was approved for use in Japan in 2013. Allopurinol is a substrate of both XOR and AOX and is converted to the active metabolite oxypurinol, which forms a covalent bond with

Mo(IV) and strongly inhibits XOR (Okamoto et al. 2008). Febuxostat is characterized as a structure-based inhibitor and can bind to the enzyme regardless of the Moco oxidation state (Okamoto et al. 2003). Topiroxostat initially displays competitive inhibition, followed by a covalent type of inhibition, based on studies with bovine milk XOR (Matsumoto et al. 2011). Several additional purine and nonpurine-like compounds have been found to inhibit XOR but are not utilized as clinical XOR inhibitors (Tables 24, 26, 28).

Inducers

Constitutive activity of XOR in human tissues is relatively low in comparison with other mammals (Harrison 2002). Increased activity and/or expression of XOR in various tissues has been associated with several compounds, including interferon, 3-methylcholanthrene, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), prolactin, and cortisol in mice (Ghezzi et al. 1984; McManaman et al. 2000; Sugihara et al. 2001), and sodium metabisulfite and phenytoin in rats (Ercan et al. 2015; Ekaidem et al. 2014). TCDD and 3-methylcholanthrene also increase AOX activity in mouse liver, and these effects were diminished in aryl hydrocarbon receptor-null mice (Sugihara et al. 2001). Cytokines have also been shown to increase XOR activity on a transcriptional and/or post-translational level in rodent, bovine and human cultured cells of various tissues (Dupont et al. 1992; Page et al. 1998; Pfeffer et al. 1994). Menadione, an inhibitor of AOX, stimulates human XOR activity, presumably by functioning as an electron acceptor to reoxidize the enzyme following substrate oxidation (Ferreira Antunes et al. 2016).

Examples of substrates and reactions resulting in the formation of nontoxic metabolites

Hypoxanthine and xanthine (endogenous purines)

XOR catalyzes the oxidation of hypoxanthine into xanthine and further oxidizes xanthine into uric acid (Fig. 51) (Table 22) (Okamoto et al. 2013). In the purine metabolism, hydroxylation of hypoxanthine (6-hydroxypurine) initially takes place at the 2-position, yielding xanthine (2,6-dihydroxypurine). The next hydroxylation occurs at the 8-position, affording uric acid (2,6,8-trihydroxypurine). Studies using bovine milk XOR indicated that xanthine accumulates prior to conversion into uric acid, suggesting that oxidation of the 2-position influences oxidation of the 8-position (Okamoto et al. 2013). In addition, 6,8-dihydroxypurine was not detected. Dimethylated (theophylline, theobromine) and trimethylated xanthine derivatives (caffeine) are better substrates of cytochrome P450 enzymes than XOR.

Allopurinol and oxypurinol (antigout, XOR inhibitor)

Allopurinol is a substrate and specific XOR inhibitor. An analog of hypoxanthine, allopurinol has a nitrogen atom in 8-position with a carbon atom in the 7-position. Both AOX and XOR can metabolize allopurinol to the active metabolite oxypurinol (Fig. 52) (Tables 15, 23), although this reaction is probably mediated primarily by AOX. Allopurinol is both a competitive (at lower concentrations), and uncompetitive inhibitor (at higher concentrations) of hypoxanthine and xanthine oxidations, catalyzed by XOR (Table 24). Oxypurinol is an uncompetitive inhibitor and covalently binds to the reduced form of XOR (Okamoto et al. 2008; Spector 1988; Spector et al. 1986) (Table 24). Allopurinol/oxypurinol inhibit the conversion of hypoxanthine and xanthine to uric acid, thus regulating blood urate levels and is used to treat gout and hyperuricemia. In addition, it was suggested that allopurinol, by suppression of XOR activity, ameliorates myocardial inefficiency and poor vascular flow, and accordingly, may present an innovative contribution to the future treatment of ischemia and reperfusion (I/R) injury in heart failure patients (Harzand et al. 2012; Lee et al. 2009a, b). Allopurinol is also associated with potentially life-threatening severe cutaneous adverse reactions (Table 29) for which the HLA-B*5801 allele has been identified as a genetic risk factor (Hung et al. 2005).

When human liver tissue is harvested, it is commonly perfused with a solution containing allopurinol to prevent XOR-related oxidative damage. Barr et al. reported the presence of both allopurinol and oxypurinol at micromolar concentrations in cytosolic human liver fractions obtained from livers perfused with an allopurinol-containing solution, with a corresponding lack of XOR activity in these samples (Barr et al. 2014). Importantly, the authors noted that commercial liver fractions are likely to contain residual allopurinol and/or oxypurinol and should be screened prior to use in metabolism studies.

Acyclovir (prodrug, antiviral, antiherpetic)

6-Deoxyacyclovir is an example of a prodrug that is activated by the catalytic activity of XOR (Fig. 53). 6-Deoxyacyclovir is converted into the active drug acyclovir via 6-oxidation (Krenitsky et al. 1986; Rees et al. 1986) (Table 29). Rabbit liver AOX was found to oxidize both 6-deoxyacyclovir and acyclovir at the 8-position to inactive metabolites (Krenitsky et al. 1984), but whether or not this deactivating reaction is catalyzed by human AOX has not been reported.

6-Mercaptopurine (antineoplastic)

6-Mercaptopurine, a thiopurine drug, can be oxidized to 6-thioxanthine (6TX) and 6-thiouric acid (6TUA) through

6TX as an intermediate (Fig. 54). Both AOX and XOR are found to be involved in the formation of the 6TX intermediate, whereas only XOR was responsible for the conversion of 6TX to 6TUA (Choughule et al. 2014) (Tables 15, 23). In addition, both the xanthine dehydrogenase (XDH) and xanthine oxidase (XO) forms of XOR were evaluated and found to contribute to the formation of 6TX and 6TUA in studies with human liver cytosol in the presence and absence of NAD^+, the preferential electron acceptor for XDH.

Toxic effects of drugs as substrates of XOR catalyzed reactions

Pyrazinamide (antituburculosis prodrug)

Pyrazinamide is a prodrug used to treat tuberculosis, but it is associated with dose-related hepatotoxicity. Pyrazinamide is converted into the active metabolite pyrazioic acid by amidases, and it can also be oxidized by XOR to 5-hydroxypyrazinamide (5-OH-PZN) (Fig. 55) (Lacroix et al. 1989; Yamamoto et al. 1987) (Table 23). Both metabolites can undergo further conversion to 5-hydroxypyrazinoic acid (5-OH-PA) via the action of XOR on pyrazinoic acid or amidases on 5-hydroxypyrazinamide. The 5-OH-PA metabolite is proposed to be primarily responsible for the hepatotoxicity associated with pyrazinamide, as inhibition of amidase activity decreased pyrazinamide-induced hepatotoxicity, but did not prevent pyrazinoic acid-induced hepatotoxicity in rats (Shih et al. 2013). These data were also supported by in vitro studies demonstrating increased toxicity of pyrazinoic acid and 5-OH-PA relative to pyrazinamide in HepG2 cells. In addition, greater hepatotoxicity was observed in tuberculosis patients receiving pyrazinamide who had higher urine ratios of pyrazinoic acid/pyrazinamide and 5-OH-PA/pyrazinamide.

Concluding remarks

We have presented an overview of the metabolic reactions of drugs, natural products, physiological compounds, and other (general) chemicals catalyzed by the major non-P450 human oxidoreductase enzymes, i.e., FMOs, MAOs, NQOs, and molybdenum hydroxylases (AOX and XOR). All of these enzymes, in addition to their roles of facilitating excretion of exogenous and endogenous compounds, also catalyze reactions producing toxic products from both physiological compounds (e.g., bioactivation of neurotransmitters by MAO enzymes activity), as well as from xenobiotic compounds under specific conditions (e.g., supra-physiological substrate concentrations, anaerobic vs aerobic conditions, presence of specific inhibitors, presence/absence of cofactors, enzyme polymorphism). The participation of non-P450 oxidoreductases in the activation reactions forming toxic products is relatively low, compared to P450 enzymes (Rendić and Guengerich 2012, 2015). However, important therapeutic agents (including antibiotics, antibacterial, antitubercular, and CNS stimulants) (Table 7) are substrates in some bioactivation reactions catalyzed by FMO enzymes. An important role of MAO inhibitors is as drugs that are used in the clinic to treat depression (Table 11), and potential roles exist for natural products and their derivatives (Tables 12, 13). In addition, potential roles for toxic/reactive metabolites in the MAO-catalyzed metabolic reactions have to be considered with neurotransmitters as substrates (i.e., formation of aldehydes and H_2O_2) (Table 14). The toxic products can be eliminated by detoxication reactions catalyzed by aldehyde dehydrogenases and aldehyde reductases. Another example of detoxication is illustrated by the deactivation of highly reactive DOPA quinone, which might be formed by oxidation of dopamine or 3,4-L-DOPA by the catalytic activity of tyrosine oxidase (Asanuma et al. 2003; Ito et al. 2020). DOPA quinone might be deactivated by NQO enzymes or by conjugation with glutathione. These examples illustrate the multiple factors that can affect bioactivation/detoxication reactions and the outcome of the metabolic reactions with a particular compound as substrate. The literature also indicates that a number of compounds that are substrates of non-P450 oxidoreductases are also substrates of one or more P450 or other enzymes, and they might also interact with drug transporters in addition. Thus, multiple metabolic properties of a compound/drug have to be considered when drug–drug metabolic interactions or toxicity caused by a compound is evaluated.

Acknowledgements We thank K. Trisler for assistance in the preparation of the manuscript.

Author contributions All authors participated in the writing of this manuscript.

Funding F.P.G. acknowledges current support from the United States National Institutes of Health Grant R01 GM118122. This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Availability of data and materials All the data are available in the text and tables of the review.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest, financial or otherwise.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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