Pharmacologically Active Metabolites of Currently Marketed Drugs: Potential Resources for New Drug Discovery and Development

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Biotransformation is the major clearance mechanism of therapeutic agents from the body. Biotransformation is known not only to facilitate the elimination of drugs by changing the molecular structure to more hydrophilic, but also lead to pharmacological inactivation of therapeutic compounds. However, in some cases, the biotransformation of drugs can lead to the generation of pharmacologically active metabolites, responsible for the pharmacological actions. This review provides an update of the kinds of pharmacologically active metabolites and some of their individual pharmacological and pharmacokinetic aspects, and describes their importance as resources for drug discovery and development.

Key words—pharmacologically active metabolite; biotransformation; metabolism; drug discovery

INTRODUCTION

Xenobiotics are chemical substances found in living being but not normally produced or present in body, including pollutants, dietary components and drugs. To defense the body against xenobiotic substances, an array of biotransformation reactions (or metabolic reactions) is undergone. Due to the biotransformation, the molecular structure of a drug is commonly changed to be more hydrophilic and the substances can be readily eliminated from the body.1

Biotransformation reactions are usually divided into two broad categories known as phase I and phase II reactions. In the phase I reaction mediated by enzymes such as cytochrome P450 (CYP), flavin-containing monoxygenase, esterases and amidases, polar functional groups are introduced into the molecules, affording it a suitable substrate for direct excretion. On the other hand, the phase II metabolism, mediated by enzymes such as glucuronosyltransferase, sulfotransferase and N-acetyltransferase, causes conjugation of phase I metabolites or xenobiotics with highly water-soluble endogenous materials such as glucuronic acid, sulfate, amino acids or glutathione.2 After this metabolic process, the drugs are excreted through the bile route.1,3

However, the structural alteration of therapeutic agents exhibited by biotransformation can sometimes lead to the generation of pharmacologically active metabolites, which can responsible for the pharmacological responses.1,4 It has been reported that about 22% of the top 50 drugs prescribed in the USA in 2003 undergo biotransformation into metabolites that play significant roles in the pharmacological actions of the corresponding drugs.6 Active metabolites exerting improved pharmacological, pharmacokinetic behaviors or lower toxicity than its parent drug were already developed as new drugs in some cases.

In this regard, recognizing the pharmacologically active metabolites as significant resources for drug development would be beneficial. This paper provides an update on pharmacological active metabolites with their pharmacological and pharmacokinetic aspects, and further describes their values as resources for drug discovery and development.

FORMATION OF PHARMACOLOGICALLY ACTIVE METABOLITES

Pharmacologically active metabolites are generated through mainly primary and/or secondary, and tertiary metabolism by phase I and phase II reactions. Although metabolites are chemical structurally different from the parent drug, if they have structural similarities to the parent molecules, they might attain biological activities similar to the parent drug in some cases.6 Table 1 lists the active metabolites produced...
from currently marketed drugs. As shown in Table 1, simple reactions mediated via CYP generate active metabolites in many cases such as aromatic or aliphatic hydroxylation, O- or N-dealkylation, and dehydrogenation or in combinations.1,4-6

Many of the pharmacologically active metabolites are generated via hydroxylation or dealkylation reactions. For instance, atorvastatin (Fig. 1 (a)),7 proprafenone,8 alprazolam,9 atomoxetine,10 flutamide,11 nefazodone,12 acetohexamide,13 cyclosporine,14 proptranolol,15 risperidone,16 itraconazole,17 and bupropion (Fig. 1 (b))18 generate their active metabolites via aromatic or aliphatic hydroxylations. Bupropion also forms two other active metabolites, namely threohydrobupropion and erythrohydrobupropion through carbonyl reduction.19 O-Demethylation of venlafaxine (Fig. 1 (c)), ivabradine and artemether gives pharmacologically active O-desmethylvenlafaxine, O-desmethylivabradine and dihydroartemisinin, respectively.19-21 Ivabradine also forms active metabolite by N-demethylation.20 N-Demethylation significantly contributes to produce active metabolites in cases of fluoxetine (Fig. 1 (d)),22,23 sibutramine,24 ferroquine25 and azonafide.26 S-Oxidation of thioridazine and epoxidation of carbamazepine lead to the formation of mesoridazine27 and carbamazepine-10,11-epoxide,28 respectively.

There are also numerous examples of active metabolites that are produced by phase II enzymes. Glucuronidation is normally considered to be detoxifying process, because glucuronides usually possess less intrinsic biological or chemical activity than their parent forms and exhibit higher polarity and excretability.29 However, some glucuronide conjugates are active and may contribute to pharmacological activities. The N, O-glucuronides of hydroxamic acid30 and the acylglucuronides of carboxylic acids form active metabolites.31,32 Particularly, the 6-O-glucuronide of morphine constitutes the most well-known example of a glucuronide possessing pharmacological activity greater than the parent drug.33 And, the sulfation of minoxidil (Fig. 1 (e)), N-acetylation of acetolol or procainamide has also contributed the production of the pharmacologically active metabolites.34-36

**PHARMACOLOGICALLY ACTIVE METABOLITES OF MARKETED DRUGS**

Generally, most of the pharmacologically active metabolites have more hydrophilic property and better *in vivo* metabolic stability compared to their corresponding parent molecules.1,5,6 Although active metabolites have structural similarities to the parent drugs, their protein binding, membrane permeability, tissue distribution, and pharmacological potency might be different from those of the parent compounds.

The degrees of pharmacological activities of metabolites compared to parent drugs are different from each other, but in most cases, metabolites are less potent than parent drugs. For instance, 3-hydroxyquinidine,37 hydroxymetronidazole,30 (R)-norflutamide,35 norverapamil,39 hydroxycyclosporine,14 N-desmethyloanafide,20 hydroxybupropion and threohydrobupropion,18 and many active metabolites have weaker activities than their parents. But, in some cases, metabolites are more potent or have similar biological activities to parent drugs. 2- or 4-Hydroxyatorvastatin,9 2-hydroxyflutamide,17 hydroxynefazodone,40 hydroxycetohexamide,41 5-hydroxypropafenone,39 minoxidil sulfate,34 desmethyloxizolam,42 mesoridazine,27 (S)-norflutamide,22,23 O-desmethylvenlafaxine19 and S-hydroxypoliperidone62 showed comparable activities with parent drugs *in vitro* or *in vivo* experiments.

In this part, pharmacological activities and pharmacokinetic behaviors of active metabolites were illustrated as follows.

**Acetolol** Acetolol is a cardioselective beta-adrenoreceptor blocking agent. The major metabolite, N-acetyl derivative, diazetol is pharmacologically active. This metabolite was reported to be equipotent to acetolol in cats and is more cardio-selective than acetolol.35

**Acetohexamide** Acetohexamide is an oral anti-diabetic drug possessing a moderate duration of action. S-Hydroxycetohexamide and R-hydroxyacetohexamide exhibit similar hypoglycemic effects in rats. Particularly, S-hydroxyacetohexamide demonstrated a more potent hypoglycemic activity than acetohexamide, implying that S-hydroxyacetohexamide plays an important role in overall hypoglycemic effect.13,41 Both acetohexamide and S-hydroxyacetohexamide are rapidly eliminated from the body.43

**Alprazolam** Alprazolam is a benzodiazepine, which is used for the treatment of anxiety, panic disorders, depression and sleeping disorders. It is metabolized to 4-hydroxylprazolam and 4α-hydroxyl-
Table 1. Pharmacologically Active Metabolites of Currently Marketed Drugs

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prazolam which are the main metabolites in plasma. The two metabolites were pharmacologically active accounting for 20 and 60% of the pharmacological activity of alprazolam, respectively.

Amiodarone Amiodarone, an anti-arrhythmic agent, is mainly metabolized to desethylamiodarone. The main metabolite, desethylamiodarone, showed significant electrophysiologic and anti-arrhythmic effects similar to amiodarone itself in animals. The long-term effects of amiodarone therapy were suggested mainly due to desethylamiodarone. The elimination half-life of amiodarone was 15 h after a 100 mg/kg dosage and 105 h after a 200 mg/kg dosage, respectively. Desethylamiodarone was detected over 24 h in relatively low levels in rats after oral administration of amiodarone.

Aripiprazole Dehydroaripiprazole is the main metabolite of aripiprazole and was reported that it...
possesses the anti-psychotic activity equivalent to that of aripiprazole.\textsuperscript{46,49} The elimination half-life of aripiprazole was between 75 h and 94 h after oral administration.\textsuperscript{50}

\textbf{Astemizole} Astemizole has been found to be a useful histamine H\textsubscript{1} receptor antagonist with little or no effect on the central nervous system. The major metabolites identified were desmethylastemizole, 5- and 6-hydroxystemizole and norastemizole.\textsuperscript{51} The metabolites were also effective against allergic reactions.\textsuperscript{51,52} The higher plasma levels and longer half-life of desmethylenastemizole than astemizole appear to contribute to the anti-histamine activity.\textsuperscript{53}

\textbf{Atorvastatin} Atorvastatin is a second-generation potent inhibitor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, clinically approved for lowering plasma cholesterol. Atorvastatin undergoes extensive metabolism to form two active metabolites, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin (Fig. 1(a)). The activity of \textit{in vitro} inhibition of HMG-CoA reductase by 2-hydroxyatorvastatin and 4-hydroxyatorvastatin was known to be equivalent to that of atorvastatin.\textsuperscript{57} 2-Hydroxyatorvastatin also showed the atheroprotective effect in a dose-dependent manner, unlike its parent and other statins (pravastatin, rosvastatin and simvastatin).\textsuperscript{54} Two active metabolites have similar plasma concentration-time profile to that of their parent drug with slightly shorter elimination half-life.\textsuperscript{55}

\textbf{Azathioprine} Azathioprine is a chemotherapy agent, now rarely used for this purpose but popular as an immunosuppressant in organ transplantation and autoimmune disease. Its metabolite 6-mercaptopurine is an important pharmacologic agent used for the therapy of a variety of diseases including autoimmune hepatitis and rheumatoid arthritis.\textsuperscript{56,57} In addition, 6-thioguanine, another metabolite, is frequently used in the treatment of leukemia.\textsuperscript{56,58}

\textbf{Chlordiazepoxide} Chlordiazepoxide was the first benzodiazepine derivative made available for clinical use. The drug is biotransformed to pharmacologically active products such as desmethylichlordiazepoxide, demoxepam, desmethylclomipramine, and oxazepam. The elimination half-life of chlordiazepoxide following a single dose in healthy individuals generally was observed to be from 5 to 30 h.\textsuperscript{60} It is reported that desmethylichlordiazepoxide and demoxepam demonstrated highly significant anti-anxiety property which surpass that of chlordiazepoxide itself.\textsuperscript{61}

\textbf{Citalopram} Citalopram is chemically a bicyclic phthalate and a selective serotonin reuptake inhibitor. Citalopram is metabolized to desmethylcitalopram, which can also inhibit 5-HT reuptake, but its potency was much weaker than that of parent drug. \textit{In vitro} study showed that citalopram is at least 8 times more potent than its metabolite in the inhibition of serotonin reuptake.\textsuperscript{62}

\textbf{Clarithromycin} Clarithromycin is an anti-biotic drug that displays good anti-microbial activity. It is primarily metabolized to its biologically active 14-hydroxyclarithromycin.\textsuperscript{63,64} The compound has demonstrated excellent \textit{in vitro} activity against \textit{Legionella} species than erythromycin. The activity of 14-hydroxyclarithromycin against penicillin-intermediate, penicillin-resistant or erythromycin-resistant \textit{Streptococcus pneumoniae} was approximately a half of that of parent drug. The combination of parent and metabolite was more rapidly bactericidal than clarithromycin alone. Also, 14-hydroxy metabolite significantly increased the activity of fluoroquinolone /clarithromycin combinations.\textsuperscript{45}

\textbf{Clobazam} Clobazam is a 1,5-benzodiazepine with anxiolytic and anti-convulsant properties. \textit{N}-Desmethylobalbazam is the major metabolite possessing pharmacological action similar to the parent drug.\textsuperscript{66} Moreover, \textit{N}-desmethylobalbazam was accumulated during long-term treatment achieving concentration levels up to 8-times greater than clobazam.\textsuperscript{67} Clobazam has a half-life of 18 h, but that of \textit{N}-desmethylobalbazam was found to be about 50 h.\textsuperscript{66}

\textbf{Clomipramine} Clo mipramine, a typical tricyclic anti-depressant, is extensively biotransformed to desmethylclo mipramine and other metabolites, and their glucuronide conjugates. Desmethylclo mipramine, pharmacologically active metabolite, was appeared in plasma in higher concentrations than the parent compound and was a more potent inhibitor of noradrenaline and dopamine uptake than clomipramine.\textsuperscript{45} It was also reported that the metabolite has anti-depressant activity associated with its monoamine uptake inhibitory properties. The elimination half-life of parent compound was 1.6–2.7 h, but that of its active metabolite, desmethylclo mipramine was estimated to be 2.2–3.4 h.\textsuperscript{68}

\textbf{Clozapine} Clozapine is the atypical anti-psychotics and is mainly metabolized to norclozapine and clozapine-N-oxide. Among them, norclozapine was reported to possess the neurobiological activity.\textsuperscript{49}
Additionally, norclozapine was reported to possess the same dopamine D₂ receptor affinity as clozapine and even a higher affinity to the 5-HT receptor.⁶⁷,⁷¹ The plasma concentrations of norclozapine were correlated positively with granulocyte counts in schizophrenic patients.⁷²

**Cyclosporine** Cyclosporine is an immunosuppressive agent. Thirteen metabolites of cyclosporine were isolated from the bile of rabbits receiving intravenous cyclosporine. Of these metabolites, only monohydroxylated metabolites were found to have significant activity being between 5 and 10% of the activity exhibited by the parent drug in an in vitro study.⁷³

**Etretinate** Etretinate is a synthetic aromatic derivative of vitamin A used for the treatment of severe psoriasis. Acitretin is the primary and active metabolite of etretinate and has been effective in the treatment of psoriasis and other skin diseases.⁷⁵ The absolute oral bioavailability of etretinate and acitretin in humans are approximately 40 and 60%, respectively.⁷⁴

**Ferroquine** Ferroquine is an anti-malarial drug and is metabolized mainly via an oxidative pathway into the major metabolite, N-demethylferroquine and then into N,N-didemethylferroquine. The activity of the two main metabolites decreased compared to that of ferroquine; however, the activity of the mono-N-demethyl derivative was significantly higher than that of chloroquine and these results support the potential use against malaria infection of humans.⁷⁶

**Fluoxetine** Fluoxetine is a widely used antidepressant agent, based on inhibition of serotonin reuptake in the central nervous system. S-Norfluoxetine (Fig. 1(d)) is a potent and selective inhibitor of serotonin uptake and has the activity essentially equivalent to R- or S-fluoxetine. R-Norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake.⁷²,⁷³ Also, it was reported that the efficacy of these two compounds in neuronal tissues was equal, either in preventing seizure activity or in blocking the neuronal Ca²⁺ channels. A significant part of the therapeutic activity of fluoxetine is attributable to its most important active metabolite, norfluoxetine.⁷⁵

**Flutamide** Flutamide is an oral anti-androgen drug primarily used to treat prostate cancer. A major metabolite in plasma is biologically active, 2-hydroxyflutamide.⁷¹,⁷⁶ 2-Hydroxyflutamide is a more potent androgen receptor antagonist than parent drug. It was reported that elimination half-life of 2-hydroxyflutamide after oral administration was 2.7 h.⁷⁷,⁷⁸

**Irinotecan** Irinotecan is a synthetic analog of naturally occurring alkaloid, camptothecin and has demonstrated pronounced antitumor activity against a variety of tumors. In humans, irinotecan is rapidly metabolized by an endogenous carboxylesterase present in the intestinal mucosa, plasma and liver into a highly active metabolite, SN-38.⁷⁹ An in vitro preclinical study demonstrated that the cytotoxic activity of SN-38 is 100- to 1000-times greater than that of the parent drug.⁸⁰ Another study also revealed that systemic exposure of SN-38 measured by AUC was deeply related to antitumor activity of irinotecan, despite the fact that SN-38 serum levels were observed to be about 100 times lower than the corresponding irinotecan levels.⁸¹

**Loratadine** Loratadine is a tricyclic anti-histamine agent with selective peripheral histamine H₁-receptor antagonist activity. It is extensively metabolized by N-demethylation in liver. Descarboethoxyloratadine, a main metabolite, showed similar anti-histamine activity to loratadine and other nonsedating anti-histamines.⁸³ The elimination half-life of loratadine was 8–14 h, but that of descarboethoxyloratadine was longer and estimated to be 17–24 h.⁸⁴,⁸⁵

**Losartan** Losartan is an angiotensin II receptor blocker, used mainly to treat hypertension. The angiotensin-II blocking activity of losartan is predominantly caused by carboxylosartan. It has proven to effectively lower elevated arterial blood pressure up to 24 h post-dose and, furthermore, to exert a beneficial effect on the regression of vascular and myocardial hypertrophy associated with hypertension.⁸⁶

**Metronidazole** Metronidazole is widely used for the treatment of protozoal and anaerobic bacterial infections. Metronidazole is metabolized to the two major metabolites being hydroxymetronidazole and 2-methyl-5-nitroimidazole-1-acetic acid. Hydroxyme-
tropanidazole demonstrated an anti-microbial potency approximately 30% of that of metronidazole against certain strains of bacteria.\textsuperscript{38,87} The serum half-life of metronidazole was 7.1 h in the healthy subjects and similar values were observed in the subjects with reduced renal function. The half-life of hydroxymetronidazole was measured to be 18.0 h in the healthy subjects and ranged 9.6–85.5 h in renal impaired patients.\textsuperscript{80}

**Mianserin** Mianserin is a tetracyclic anti-depressant and is administered as a racemate of \(R^\text{(-)}\) and \(S^\text{(+)}\) mianserin. It is metabolized mainly by \(N\text{-}demethylation,\ aromatic hydroxylation, \text{-}N\text{-}oxidation and \text{-}N\text{-}glucuronidation.\textsuperscript{89} \(N\text{-}Desmethylmianserin\) is the major metabolite of mianserin in plasma and contributes substantially to the overall therapeutic effects of mianserin in patients.\textsuperscript{90} \(N\text{-}Desmethylmianserin\) showed the longer elimination half-life than parent drug.\textsuperscript{91}

**Minoxidil** Minoxidil is an anti-hypertensive agent and hair growth promoter that is metabolized by sulfation to the active compound, minoxidil sulfate (Fig. 1(c)). Dose-response studies displayed that minoxidil sulfate was 14 times more potent than minoxidil in stimulating cysteine incorporation in cultured follicles. It was reported that sulfation is a critical step for hair-growth effect of minoxidil and sulfated metabolite directly affects hair follicles.\textsuperscript{34}

**Nefazodone** Nefazodone, an anti-depressant drug, is metabolized to several pharmacologically active as well as non-active metabolites.\textsuperscript{12,40} Among them, hydroxynefazodone showed the equipotent 5-hydroxytryptamine (5-HT) and noradrenalin reuptake inhibition activity. Both parent compound and hydroxynefazodone have short elimination half-lives.\textsuperscript{82}

**Oxybutynin** Oxybutynin is an anti-cholinergic agent acting as a smooth muscle relaxant. Oxybutynin is metabolized in the liver and the gut wall to form an active metabolite, \(N\text{-}desethylxyloxybutynin.\textsuperscript{93} \) Considerably larger values of area under the curve (AUC) of \(N\text{-}desethylxyloxybutynin\) were observed compared to the parent drug after oral administration of oxybutynin.\textsuperscript{84} In vitro experiment revealed that \(N\text{-}desethylxyloxybutynin\) exerted comparable anti-cholinergic effects as its parent compound in human.\textsuperscript{95} It has been suggested that \(N\text{-}desethylxyloxybutynin\) is largely responsible for the anti-cholinergic activity after oral administration of oxybutynin.\textsuperscript{96}

**Propafenone** 5-Hydroxypropafenone is a main metabolite of propafenone and has various pharmacological effects related to anti-arrhythmic action. It has a greater anti-arrhythmic potency in rats and dogs, and a greater negative inotropic effect and Ca\(^{2+}\) antagonistic effect, and a very distinctly weaker beta-adrenoceptor blocking effect than propafenone have been observed.\textsuperscript{8} Moreover 5-hydroxypropafenone accelerates the deactivation and inactivation processes of hERG and blocks the hERG channel to a similar extent to propafenone.\textsuperscript{97} Mean elimination half-life values of \((S)\) and \((R)\) propafenone, and \((S)\) and \((R)\) 5-hydroxypropafenone after oral administration of 300 mg were 2.1, 2.2, 3.3, and 2.9 h, respectively, in healthy Chinese volunteers.\textsuperscript{98}

**Propranolol** Propranolol is a \(\beta\)-adrenoceptor antagonist, widely used in the treatment of arrhythmia, angina pectoris and hypertension. Hydroxypropranolol, the main metabolite, is pharmacologically active with a slightly shorter elimination half-life than parent drug. It has hemodynamic and electrophysiologic effects similar to those of other beta-blocking drugs.\textsuperscript{15} Also, it is 4- to 8-fold more potent than vitamin E and 100-fold more active than propranolol as a anti-oxidant against biomembrane.\textsuperscript{99}

**Risperidone** Risperidone is an atypical antipsychotic drug, acting through selective antagonism of serotonin 5-HT\(_2\) and dopamine D\(_2\) receptors. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity to risperidone.\textsuperscript{16} The plasma concentration of 9-hydroxyrisperidone is in significant correlation with an increase in plasma prolactin, suggesting that the 9-hydroxy metabolite plays a predominant role in risperidone effect on prolactin release. The mean elimination half-life values of risperidone and 9-hydroxyrisperidone are 14.8 and 13.7 \textit{h}, respectively, after oral administration of risperidone in rats.\textsuperscript{100}

**Sertraline** Sertraline is an anti-depressant agent belonging to the selective serotonin reuptake inhibitor. \(N\text{-}Desmethylsertraline\), a main metabolite of sertraline, showed longer half-life than sertraline, thus leading to higher concentrations in plasma at steady-state.\textsuperscript{101} \(N\text{-}Desmethylsertraline\) showed 10 to 20-fold less potency at blocking serotonin (5-HT) reuptake as measured \textit{in vitro} but desmethylsertraline was considered, nonetheless, to inhibit the serotonin transporter after sertraline administration.\textsuperscript{102}
**Sibutramine** Sibutramine is a monoamine-reuptake inhibitor involved in the regulation of food intake in humans. Main metabolites, N-desmethyl-sibutramine and N,N-desmethylsibutramine, showed similar pharmacological profiles to sibutramine *in vivo*, but were up to 100-fold more active than sibutramine as monoamine uptake inhibitors *in vitro*.\(^{103}\) *In vivo* effects of this drug are mainly due to the action of these two metabolites.\(^{20}\) Also, the sibutramine metabolite, N,N-didesmethylsibutramine improved glucose uptake by muscle and reduced hepatic glucose output, thus suggesting that N,N-didesmethylsibutramine could reduce glycaemia.\(^{104}\) And it was known that N,N-didesmethylsibutramine could act directly on human adipose tissue to increase lipolysis via a pathway involving beta-adrenoceptors.\(^{105}\)

**Thiocolchicoside** Thio-colchicoside has been prescribed for several years as a muscle relaxant drug. It is metabolized mainly to 3-O-glucuronidated aglycone (M1) and de-glycosylation of thio-colchicoside (M2). The muscle relaxant activity of M1 was similar to that of thio-colchicoside whereas M2 was devoid of any activity.\(^{106}\)

**Thioridazine** Thioridazine, a piperidine anti-psychotic drug undergoes S-oxidation in the thiazine ring, as well as aromatic hydroxylation, N-demethylation, and N-oxidation.\(^{107,108}\) Mesoridazine and sulforidazine, formed by S-oxidation, were more potent than thioridazine in blocking dopaminergic D\(_2\) and noradrenergic \(\alpha_1\) receptors. Moreover, N-desmethyl-thioridazine still retains the affinity for \(\alpha_1\) receptors.\(^{27,106}\)

**Tibolone** Tibolone is used for the treatment of climacteric symptoms and osteoporosis in menopausal women. 3α- and 3β-Hydroxytibolone are the main metabolites in the circulation with a half life of about 7 h, and are responsible for the effectiveness of tibolone in alleviating climacteric symptoms and prevention of bone loss.\(^{109}\) Tibolone and 7α-methyl-norethisterone have produced similar inhibition of aromatase activity, 58% and 65%, respectively, to those obtained from MCF-7 cell study.\(^{111}\)

**Venlafaxine** Venlafaxine is a phenethylamine bicyclic anti-depressant. O-Desmethylvenlafaxine (Fig. 1(c)), a major metabolite, was reported to have an activity profile similar to that of venlafaxine.\(^{19}\) The elimination half-lives of venlafaxine and O-desmethylvenlafaxine are measured to be about 4–9 and 11–13 h, respectively.\(^{112}\)

### Table 2. Pharmacologically Active Metabolites Developed as New Drugs

<table>
<thead>
<tr>
<th>Parent drugs</th>
<th>Metabolite drugs</th>
<th>Biotransformation</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Oxyipurinol</td>
<td>Oxidation of xanthine</td>
<td>Oxypurin</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Nortriptiline</td>
<td>N-Demethylation</td>
<td>Aventyl</td>
</tr>
<tr>
<td>Bromhexine</td>
<td>Ambroxol</td>
<td>N-Demethylation &amp; Hydroxylation</td>
<td>Mucosovan</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Oxazepam</td>
<td>N-Demethylation &amp; Hydroxylation</td>
<td>Serax</td>
</tr>
<tr>
<td>Eretinate</td>
<td>Acetin</td>
<td>Deesterification</td>
<td>Soriatane</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Cotizine</td>
<td>Carboxylation</td>
<td>Zyrtec</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Desipramine</td>
<td>N-Demethylation</td>
<td>Norpramin</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Desloratadine</td>
<td>Descarboethoxylation</td>
<td>Clarinex</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Amoxapine</td>
<td>N-Demethylation</td>
<td>Asendin</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>Acetaminophen</td>
<td>O-Deethylation</td>
<td>Tylenol</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Fexofenadine</td>
<td>Carboxylation</td>
<td>Allegra</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mesoridazine</td>
<td>S-Oxidation</td>
<td>Serentil</td>
</tr>
</tbody>
</table>
was developed as anti-histamine agent with selective peripheral histamine H₁-receptor antagonist activity. It shows better metabolic stability and lower toxicity than the parent compound. The elimination half-life of fexofenadine was quite long (13.4 h) following oral administration in healthy subjects and mainly eliminated in the feces and urine, in the form of fexofenadine.¹⁴ Eighty percent of the drug administered, and is generally true, in some cases, it generates pharmacologically active metabolites.

Several strategies such as deactivation of aromatic ring with strongly electron-withdrawing groups (e.g., CF₃, SO₂NH₂) and/or introduction of N-butyl group to prevent N-dealkylation have been investigated to enhance in vivo metabolic stability.¹¹⁷,¹¹⁸ Specifically this type of approach was used for example, in the discovery of ezetimibe, a cholesterol absorption inhibitor.¹⁴⁸ In this work, an active metabolite that was already <30-fold more potent than the parent was further modified to generate the final drug candidate (ezetimibe), which was 400-fold more potent than the original drug.

**CONCLUSION**

In this paper, pharmacologically active metabolites were introduced with their individual pharmacological and pharmacokinetic aspects. Although metabolism is a procedure to inactivate and/or eliminate the drug administered, and is generally true, in some cases, it generates pharmacologically active metabolites. Tracking active metabolites is not only important to correctly interpret the pharmacological effects in preclinical studies but may also be used as a promising tool to identify drug candidate for drug discovery and development. A number of active metabolites showed better or equivalent pharmacological potencies compared to their parent compounds. As an alternative approaches in drug discovery, pharmacologically active metabolites can be used as potential drug candidate to obtain better pharmacokinetic and pharmacodynamic profiles by structural modification.

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