

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 defend 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 monooxygenase, 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 a-

gents exhibited by biotransformation can sometimes lead to the generation of pharmacologically active metabolites, which can be responsible for the pharmacological responses.^{1,4-6)} 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 pharmacologically 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 chemically 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

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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⁾ propranolol,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.¹⁸⁾ *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 excreatability.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 acebutol 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,³⁸⁾ (R)-norfluoxetine,^{22,23)} norverapamil,³⁹⁾ hydroxycyclosporine,¹⁴⁾ *N*-desmethylazonafide,²⁶⁾ 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,⁷⁾ 2-hydroxyflutamide,¹¹⁾ hydroxynefazodone,⁴⁰⁾ hydroxyacetohexamide,⁴¹⁾ 5-hydroxypropafenone,⁸⁾ minoxidil sulfate,³⁴⁾ desmethylclomipramine,⁴²⁾ mesoridazine,²⁷⁾ (S)-norfluoxetine,^{22,23)} *O*-desmethylvenlafaxine¹⁹⁾ and *S*-hydroxyrisperidone¹⁶⁾ showed comparable activities with parent drugs *in vitro* or *vivo* experiments.

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

Acebutolol Acebutolol is a cardioselective beta-adrenoreceptor blocking agent. The major metabolite, *N*-acetyl derivative, diacetolol is pharmacologically active. This metabolite was reported to be equipotent to acebutolol in cats and is more cardioselective than acebutolol.³⁵⁾

Acetohexamide Acetohexamide is an oral anti-diabetic drug possessing a moderate duration of action. *S*-Hydroxyacetohexamide 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-hydroxyalprazolam and 4 α -hydroxyal-

Table 1. Pharmacologically Active Metabolites of Currently Marketed Drugs

Drug	Active metabolites	Biotransformation	Therapeutic actions
Atomoxetine ¹⁰⁾	4-Hydroxyatomoxetine		Treatment of attention-deficit hyperactivity disorder
Atorvastatin ⁷⁾	2- or 4-Hydroxyatorvastatin		Anti-hypercholesterolemia
Chlorpromazine ¹¹⁹⁾	7-Hydroxychlorpromazine		Anti-depressive
Clomiphene ¹²⁰⁾	4-Hydroxyclophene	Aromatic hydroxylation	Anti-uterotrophic
Granisetron ¹²¹⁾	7-Hydroxygranisetron		Anti-nausea
Indapamide ¹²²⁾	5-Hydroxyindapamide		Anti-hypertensive
Levamisole ⁸²⁾	4-Hydroxylevamisole		Anthelmintic
Propafenone ⁸⁾	5-Hydroxypropafenone		Anti-arrhythmic
Propranolol ¹⁵⁾	4-Hydroxypropranolol		Anti-arrhythmic
Alprazolam ⁹⁾	4-Hydroxyalprazolam		Anti-depressant
Bupropion ¹⁸⁾	Hydroxybupropion		Anti-mental depression
Clarithromycin ⁶⁵⁾	14-Hydroxycarithromycin		Anti-biotic
Cyclosporin A ¹⁴⁾	Hydroxycyclosporin A		Immunosuppressive
Ibuprofen ¹²³⁾	Hydroxyibuprofen		Anti-inflammatory
Itraconazole ¹⁷⁾	Hydroxyitraconazole		Anti-mycotic
Metronidazole ³⁸⁾	Hydroxymetronidazole	Aliphatic hydroxylation	Anti-biotic
Midazolam ¹²⁴⁾	1'-Hydroxymidazolam		Anxiolytic effect
Nebivolol ¹²⁵⁾	4- or 4'-Hydroxyneбиволol		Vasodilation
Nefazodone ¹²⁾	Hydroxynefazodone		Anti-depressant
Praziquantel ¹²⁶⁾	4-Hydroxypraziquantel		Anti-neurocysticercosis
Quinidine ³⁷⁾	3-Hydroxyquinidine		Anti-arrhythmic
Risperidone ¹⁶⁾	9-Hydroxyrisperidone		Anti-psychotic
Simvastatin ^{127,128)}	Simvastatin hydroxylic acid		Anti-hypercholesterolemia
Amiodarone ⁴⁵⁾	Desethylamiodarone		Anti-arrhythmic
Azonafide ²⁶⁾	<i>N</i> -Desmethylazonafide		Anti-tumoral
Chlordiazepoxide ⁶¹⁾	Desmethylchlordiazepoxide		Anxiolytic
Citalopram ⁶²⁾	Desmethylcitalopram		Anti-depressant
Clobazam ⁶⁶⁾	<i>N</i> -Desmethylclobazam		Anti-epileptic
Clomipramine ⁴²⁾	<i>N</i> -Desmethylclomipramine		Anti-depressant
Clozapine ⁶⁹⁾	Norclozapine		Anti-psychotic
Ferroquine ²⁵⁾	<i>N</i> -Demethylferroquine <i>N,N</i> -Didemethylferroquine		Anti-malarial
Fluoxetine ²²⁾	Norfluoxetine		Anti-depressant
Ivabradine ²⁰⁾	<i>N</i> -Desmethylivabradine	<i>N</i> -Dealkylation	Bradycardia
Lumefantrine ¹²⁹⁾	Desbutylumefantrine		Anti-malarial
Mianserin ⁹⁰⁾	<i>N</i> -Desmethylmianserin		Anti-depressant
Verapamil ¹³⁰⁾	Norverapamil		Anti-arrhythmic
Oxybutynin ⁹⁵⁾	<i>N</i> -Desethyloxybutynin		Smooth muscle relaxant
Rosuvastatin ¹³¹⁾	<i>N</i> -Desmethylrosuvastatin		Anti-hypercholesterolemia
Sertraline ¹⁰²⁾	<i>N</i> -Desmethylsertraline		Anti-depressant
Sibutramine ²⁴⁾	<i>N</i> -Desmethylsibutramine <i>N,N</i> -Didesmethylsibutramine		Treatment of obesity
Zolmitriptan ¹³²⁾	<i>N</i> -Demethylzolmitriptan		Treatment of migraine
Zopiclone ¹³³⁾	(<i>S</i>)-Desmethylzopiclone		Treatment of insomnia
Artemether ²¹⁾	Dihydroartemisinin		Anti-malarial
Ivabradine ²⁰⁾	<i>O</i> -Demethylivabradine	<i>O</i> -Dealkylation	Bradycardia
Tramadol ¹³⁴⁾	<i>O</i> -Demethyltramadol		Centrally acting analgesic
Venlafaxine ¹⁹⁾	<i>O</i> -Desmethylvenlafaxine		Anti-depressant
Acebutol ³⁵⁾	Diacetolol	<i>N</i> -Acetylation	Anti-hypertensive
Albendazole ¹³⁵⁾	Albendazole sulfoxide	Sulfoxidation	Anti-parasitic
Aripiprazole ⁴⁸⁾	Dehydroaripiprazole	Dehydrogenation	Anti-psychotic
Bupropion ¹⁸⁾	Threo/erythro-hydrobupropion	Carbonyl reduction	Anti-depressant
Carbamazepine ²⁸⁾	Carbamazepine-10,11 epoxide	Epoxidation	Anti-epilepsy
Diacerein ¹³⁶⁾	Rhein	Deacetylation	Treatment of osteoarthritis
Isosorbide dinitrate ¹³⁷⁾	5- or 2-Isosorbide mononitrate	Denitration	Treatment of angina pectoris
Losartan ⁸³⁾	Carboxylosartan	Carboxylation	Anti-hypertensive
Minoxidil ³⁴⁾	Minoxidil sulfate	Sulfation	Stimulating hair growth
Oxcarbazepine ¹³⁸⁾	10-Hydroxy-10,11-dihydrocarbamazepine	Hydroxylation & Dehydrogenation	Anti-epileptic
Procainamide ³⁶⁾	<i>N</i> -Acetyl procainamide	<i>N</i> -Acetylation	Anti-arrhythmic
Rifampicin ¹³⁹⁾	25-Desacetyl rifampicin	Deacetylation	Treatment of tuberculosis
Thiocolchicoside ¹⁰⁶⁾	3- <i>O</i> -Glucuronidated-Thiocolchicoside	Glucuronidation	Muscle relaxant
Tramadol ¹³⁴⁾	<i>O</i> -Demethyl- <i>N</i> -demethyltramadol	<i>N,O</i> -Dealkylation	Centrally acting analgesic
Triamterene ¹⁴⁰⁾	Hydroxytriamterene sulfate	Sulfation	Diuretic

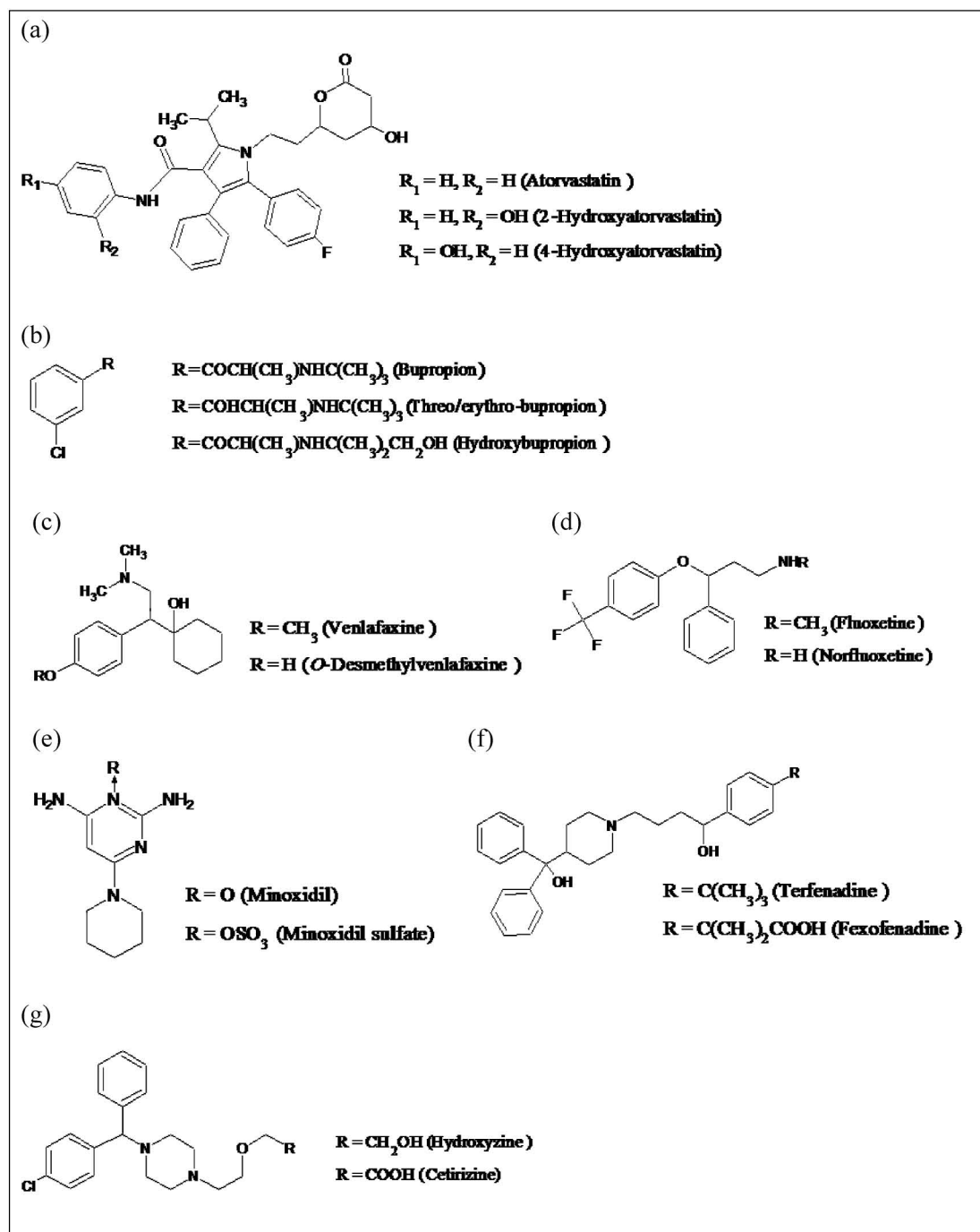


Fig. 1. Examples of Structural Changes of Parent Drugs to Pharmacologically Active Metabolites

prazolam which are the main metabolites in plasma.⁴⁴⁾ The two metabolites were pharmacologically active accounting for 20 and 60% of the pharmacological activity of alprazolam, respectively.⁹⁾

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.^{45,46)} 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.⁴⁷⁾

Aripiprazole Dehydroaripiprazole is the main metabolite of aripiprazole and was reported that it

possesses the anti-psychotic activity equivalent to that of aripiprazole.^{48,49)} The elimination half-life of aripiprazole was between 75 h and 94 h after oral administration.⁵⁰⁾

Astemizole Astemizole has been found to be a useful histamine H₁ receptor antagonist with little or no effect on the central nervous system. The major metabolites identified were desmethylastemizole, 5- and 6-hydroxyastemizole and norastemizole.⁵¹⁾ The metabolites were also effective against allergic reactions.^{51,52)} The higher plasma levels and longer half-life of desmethylastemizole than astemizole appear to contribute to the anti-histamine activity.⁵³⁾

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 *in vitro* inhibition of HMG-CoA reductase by 2-hydroxyatorvastatin and 4-hydroxyatorvastatin was known to be equivalent to that of atorvastatin.⁷⁾ 2-Hydroxyatorvastatin also showed the atheroprotective effect in a dose-dependent manner, unlike its parent and other statins (pravastatin, rosuvastatin and simvastatin).⁵⁴⁾ Two active metabolites have similar plasma concentration-time profile to that of their parent drug with slightly shorter elimination half-life.⁵⁵⁾

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.^{56,57)} In addition, 6-thioguanine, another metabolite, is frequently used in the treatment of leukemia.^{58,59)}

Chlordiazepoxide Chlordiazepoxide was the first benzodiazepine derivative made available for clinical use. The drug is biotransformed to pharmacologically active products such as desmethylchlordiazepoxide, demoxepam, desmethyldiazepam, 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.⁶⁰⁾ It is reported that desmethylchlordiazepoxide and demoxepam demonstrated highly significant anti-anxiety property which surpass that of chlordiazepoxide itself.⁶¹⁾

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. *In vitro* study showed that citalopram is at least 8 times more potent than its metabolite in the inhibition of serotonin reuptake.⁶²⁾

Clarithromycin Clarithromycin is an anti-biotic drug that displays good anti-microbial activity. It is primarily metabolized to its biologically active 14-hydroxyclearithromycin.^{63,64)} The compound has demonstrated excellent *in vitro* activity against *Legionella* species than erythromycin. The activity of 14-hydroxyclearithromycin against penicillin-intermediate, penicillin-resistant or erythromycin-resistant *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.⁶⁵⁾

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

Clomipramine Clomipramine, a typical tricyclic anti-depressant, is extensively biotransformed to desmethylclomipramine and other metabolites, and their glucuronide conjugates. Desmethylclomipramine, 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.⁴²⁾ 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, desmethylclomipramine was estimated to be 2.2–3.4 h.⁶⁸⁾

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.⁶⁹⁾

Additionally, norclozapine was reported to possess the same dopamine D₂ receptor affinity as clozapine and even a higher affinity to the 5-HT receptor.^{70,71)} 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.¹⁴⁾

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.⁷³⁾ The absolute oral bioavailabilities 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.²⁵⁾

Fluoxetine Fluoxetine is a widely used anti-depressant 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.^{22,23)} 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.^{11,76)} 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⁾

Levamisole Levamisole is an anti-biotic medication which has been tested in combination with fluorouracil to treat colon cancer. The metabolite identified in humans is *p*-hydroxylevamisole and its glucuronide conjugate. The *p*-hydroxy metabolite has been assessed as being equivalent to the parent drug in terms of potency in modulating the anti-proliferative activity of 5-fluorouracil.⁸²⁾

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 non-sedating 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-

trionidazole demonstrated an anti-microbial potency approximately 30% of that of metronidazole against certain strains of bacteria.^{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.⁸⁸⁾

Mianserin Mianserin is a tetracyclic antidepressant and is administered as a racemate of *R* (–) and *S* (+) mianserin. It is metabolized mainly by *N*-demethylation, aromatic hydroxylation, *N*-oxidation and *N*-glucuronidation.⁸⁹⁾ *N*-Desmethylmianserin is the major metabolite of mianserin in plasma and contributes substantially to the overall therapeutic effects of mianserin in patients.⁹⁰⁾ *N*-Desmethylmianserin showed the longer elimination half-life than parent drug.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(e)). 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.³⁴⁾

Nefazodone Nefazodone, an anti-depressant drug, is metabolized to several pharmacologically active as well as non-active metabolites.^{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.⁹²⁾

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*-desethyloxybutynin.⁹³⁾ Considerably larger values of area under the curve (AUC) of *N*-desethyloxybutynin were observed compared to the parent drug after oral administration of oxybutynin.⁹⁴⁾ *In vitro* experiment revealed that *N*-desethyloxybutynin exerted comparable anti-cholinergic effects as its parent compound in human.⁹⁵⁾ It has been suggested that *N*-desethyloxybutynin is largely responsible for the anti-cholinergic activity after oral administration of oxybutynin.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 Ca²⁺ antagonistic effect, and a very distinctly weaker beta-adrenoceptor blocking effect than propafenone have been observed.⁸⁾ Moreover 5-hydroxypropafenone accelerates the deactivation and inactivation processes of *hERG* and blocks the *hERG* channel to a similar extent to propafenone.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.⁹⁸⁾

Propranolol Propranolol is a β -adrenoceptor antagonist, widely used in the treatment of arrhythmia, angina pectoris and hypertension. 4-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.¹⁵⁾ Also, it is 4- to 8-fold more potent than vitamin E and 100-fold more active than propranolol as an anti-peroxidant against biomembrane.⁹⁹⁾

Risperidone Risperidone is an atypical antipsychotic drug, acting through selective antagonism of serotonin 5-HT₂ and dopamine D₂ receptors. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity to risperidone.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 h, respectively, after oral administration of risperidone in rats.¹⁰⁰⁾

Sertraline Sertraline is an anti-depressant agent belonging to the selective serotonin reuptake inhibitor. *N*-Desmethylsertraline, a main metabolite of sertraline, showed longer half-life than sertraline, thus leading to higher concentrations in plasma at steady-state.¹⁰¹⁾ *N*-Desmethylsertraline showed 10 to 20-fold less potency at blocking serotonin (5-HT) reuptake as measured *in vitro* but desmethylsertraline was considered, nonetheless, to inhibit the serotonin transporter after sertraline administration.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*-didesmethylsibutramine, 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.²⁴ 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 Thiocolchicoside 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 thiocolchicoside (M2). The muscle relaxant activity of M1 was similar to that of thiocolchicoside 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 D₂ and noradrenergic α_1 receptors. Moreover, *N*-desmethylthioridazine still retains the affinity for α_1 receptors.^{27,109}

Tibolone Tibolone is used for the treatment of climacteric symptoms and osteoporosis in meno-

pausal women. 3 α - and 3 β -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.¹¹⁰ Tibolone and 7 α -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

ACTIVE METABOLITES AS RESOURCES FOR DRUG DISCOVERY AND DEVELOPMENT

With the recent advances in molecular biology, genomics and chemical synthetic techniques, a number of new drug candidates have tremendously been discovered. However their possibility to be developed to the market product is extremely low because of poor pharmacological activity, unfavorable pharmacokinetic and pharmacodynamic behaviors or high toxicity.¹¹³

As an alternative approach in new drug development, pharmacologically active metabolites might be used as potential resources for drug discovery and development.⁶ Actually, active metabolites having improved pharmacological activity or lower toxicity than those parent compounds were already marketed as new drugs (Table 2). For example, fexofenadine (Fig. 1(f)), the primary metabolite of terfenadine,

Table 2. Pharmacologically Active Metabolites Developed as New Drugs

Parent drugs	Metabolite drugs	Biotransformation	Brand name
Allopurinol ¹⁴¹	Oxypurinol	Oxidation of xanthine	Oxyprim
Amitriptyline ¹⁴²	Nortriptyline	<i>N</i> -Demethylation	Aventyl
Bromhexine ¹⁴³	Ambroxol	<i>N</i> -Demethylation & Hydroxylation	Mucosovan
Diazepam ¹⁴⁴	Oxazepam	<i>N</i> -Demethylation & Hydroxylation	Serax
Etretinate ⁷³	Acitretin	Deesterification	Soriatane
Hydroxyzine ¹¹⁴	Cetirizine	Carboxylation	Zyrtec
Imipramine ¹⁴⁵	Desimipramine	<i>N</i> -Demethylation	Norpramin
Loratadine ⁸³	Desloratadine	Descarboethoxylation	Clarinox
Loxapine ¹⁴⁶	Amoxapine	<i>N</i> -Demethylation	Asendin
Phenacetin ¹⁴⁷	Acetaminophen	<i>O</i> -Deethylation	Tylenol
Terfenadine ¹¹⁴	Fexofenadine	Carboxylation	Allegra
Thioridazine ²⁷	Mesoridazine	<i>S</i> -Oxidation	Serentil

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.^{114,115} Also cetirizine (Fig. 1(g)), a primary metabolite of hydroxyzine, was developed as new drug. It has equivalent anti-histamine activity to parent drug with lower side effects.¹¹⁴

Furthermore pharmacologically active metabolites can be used as candidates during optimization phase of drug discovery. Through some structural modification, the enhancement of metabolic stability and receptor binding affinity can successfully be achieved.¹¹⁶ In particular, improvement of the half-life in plasma and the metabolic stability of drugs has been widely investigated with 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 phar-

macokinetic and pharmacodynamic profiles by structure modification.

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