A comprehensive review on importance and quantitation of atypical antipsychotic drugs and their active metabolites in commercial dosage forms

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Abstract

Antipsychotic drugs are frequently prescribed for the schizophrenia patients and cure psychotic depression and bipolar disorder. These drugs controlled the function of receptors present in the dopamine pathway and help to work with receptors present in the serotonin and are classified as typical and atypical antipsychotics. Clozapine is the first clinically approved atypical antipsychotic drug introduced to the market in 1989. This article presents a comprehensive review on history, classification and importance of the antipsychotic drugs. In addition to this, it also schematically explains the cytochrome P450 related biotransformation in humans of twelve atypical antipsychotic drugs. A detailed literature was also presented on application of analytical techniques especially spectrophotometric and chromatographic techniques for the determination of four atypical drugs (clozapine, olanzapine, aripiprazole and quetiapine) and their active metabolites in bulk, pharmaceutical formulations and biological fluids.

Keywords

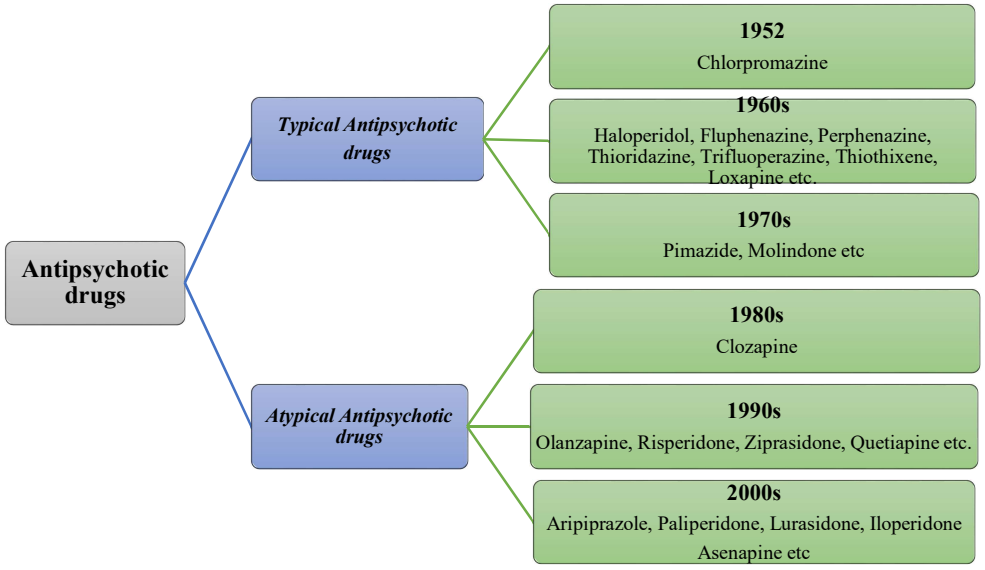
Antipsychotic drugs; typical and atypical; chromatographic and spectroscopic techniques; pharmaceutical formulations; biological fluids

1. Introduction

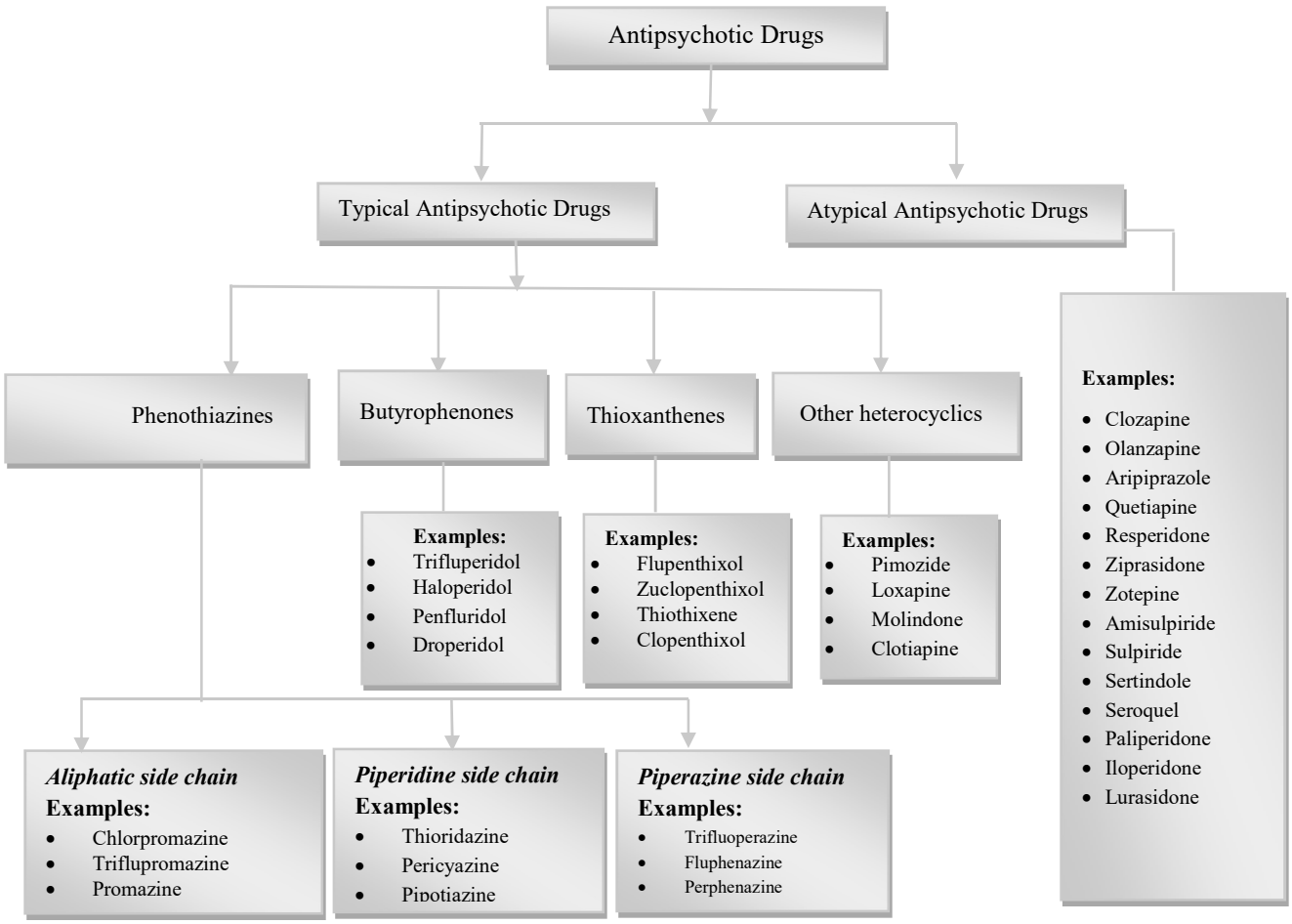
Psychosis is a type of mental disorder that can be characterized by the disturbance of reality and perception. It is related to the abnormality of a human mind in which the patient loses contact with the present situation and declines the cognitive function. People who are facing this problem change their way of thinking, perceiving, believing and behaving. To overcome this situation, antipsychotic medications are believed to be most effective in the treatment of psychosis. The standard antipsychotic drugs like chlorpromazine, perphenazine, and haloperidol etc. have been used for the treatment of psychotic diseases for a long time. The patient's social and occupational desires are challenged and interfere significantly after introducing these drugs into the body (Breier et al., 1991) and cause adverse effects that may be life threating, disabling, disfiguring including dyskinesia, neuro malignant syndrome and parkinsonian symptoms (Baldessarini, 1988; Levenson, 1985; Sovner et al., 1978). Globally, about forty antipsychotics were introduced between 1954 and 1975. Thereafter, there was a break in the development of antipsychotic drugs until the introduction of clozapine which opened a new era called "atypical" antipsychotic drugs. Clozapine was first introduced in

Europe for the treatment of endogenous depression as an atypical antipsychotic drug (Nahunek et al., 1973). Later on, it was shown that it can cause agranulocytosis, leads to decrease the number of white cells in the blood (neutropenia) and cause the death of patients, force to the manufacturer to withdraw clozapine in 1975. In 1989, researcher investigation proved that clozapine is useful for schizophrenia (Kane et al., 1988). Finally, the drug was approved for maintaining the white cell and neutrophil in the blood by United States Food and Drug Admiinsitration (USFDA) (Shuman et al., 2012) and reported that atypical antipsychotics are essential for the treatment of dipolar depression (Wu, 2015; Gentile et al., 2007). It also worked as an adjunctive and combined in unipolar depression profiles which helped more antipsychotics to get official approval, in terms of efficacy (Nelson, 2009; Chen et al., 2011). It was reported that extrapyramidal symptoms are the major limitation due to which atypical antopsychotics were prefreed over typical antippshchotics (Christine et al., 2012).

Antipsychotic drugs are classified as first-generation antipsychotics (FGA) known as "typical" and second-generation antipsychotics (SGA) known as "atypical" antipsychotics (Petty, 1999; Gruen et al., 1978). History of antipsychotics development as typical and atypical drugs is shown in **Scheme 1** (Sumiyoshi, 2013; Chaitra, 2009; Shen et al., 1999) and a broader chemical classification of antipsychotics as conventional/typical which include phenothiazines, butyrophenones and thioxanthine, and newer/atypical antipshychotics which include dibenzodiazepines, thiobenzodiazepines, dibenzothiazepines and substituted benzamide schematically shown in **Scheme 2**.



Scheme 1. History of antipsychotic drugs development



Scheme 2. Classification of Antipsychotic drugs

1.1. Atypical antipsychotic drugs

The atypical antipsychotic drugs are used in animals as well as human beings. It does not affect the catalepsy in animals, extrapyramidal symptoms or tardive dyskinesia in humans but it has a minor or sometimes no effect on plasma prolactin levels. These drugs found suitable for negative symptoms, non–responders and classical neuroleptics (Nordstrom et al., 1998). The extrapyramidal symptoms are induced by the drug itself as side effects are less or absence for atypical rather than the typical drugs although, the clinical efficacy of both types of drugs seem to be similar (Borison et al., 1997). Atypical drugs have less influence on D2 receptors than the typical drugs because it primarily blockades the dopamine D2 receptor in mesolimbic pathways. The most complex psychiatric disorder is schizophrenia and almost 1.5% of the populations are

affected by this lifelong disease worldwide. These drugs are used for schizophrenia symptoms such as hallucination and delusion. It only minimizes the intensity and permits the person to make supportive environment. But the medication doesn't have the ability to eliminate and cure the illness. The atypical drug clozapine was approved by the USFDA in 1989 and clinically available for the treatment of schizophrenia in 1990. The main action of clozapine was that it has low impact to cause extrapyramidal symptoms along with an ability to increase the prolactin levels in serum. After that many atypical drugs have been brought in the market and these drugs showed capabilities to improve the function of disorder patients. According to short – term efficacy of schizophrenia and dementia, few differences were seen between all the atypical drugs. The studies suggested that the clozapine associated with a major adverse effect which may cause seizures, weight gain, sedation and agranulocytosis (Young, 1998; John et al., 2010). The other atypical drugs like olanzapine, risperidone, ziprasidone, quetiapine are more useful because these drugs did not introduce any major side effect like agranulocytosis (Farah, 2005; Lee et al., 2006). The adverse effect can be speculated from the pharmacological profile of each drug. The most significant side effect from the drug was hyperglycemia and the common effects were weight gain, sedation, constipation, dizziness, akathisia, nausea or vomiting. The studies suggested that the clozapine associated with a major adverse effect as shown in Figure **1** (Alp, 2008; Rasimas, 2012; Raymond et al., 2013).

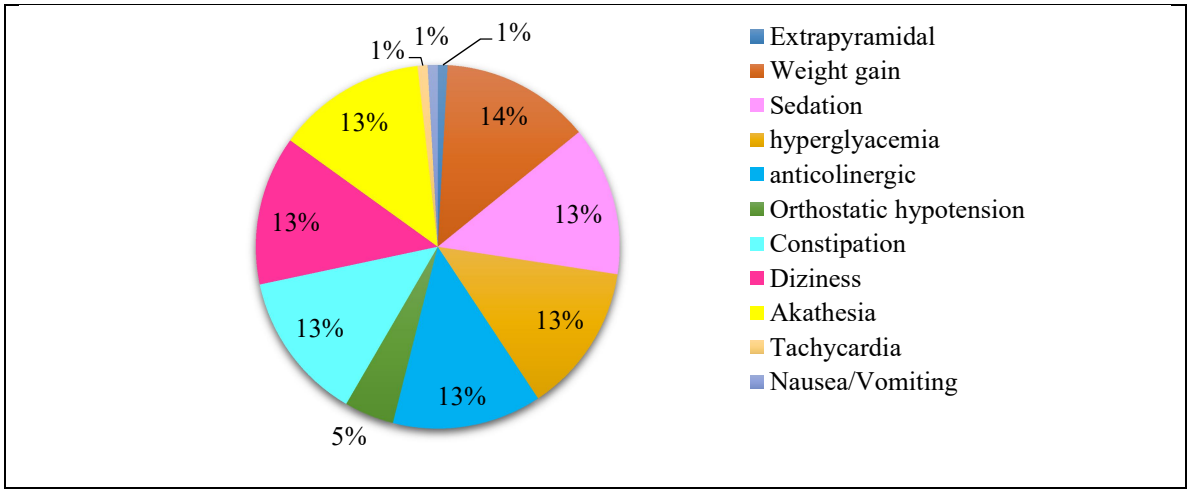


Figure 1. Adverse effects of clozapine

The advantage of clozapine for schizophrenia patient is to reduce the suicide and suicidal behaviour, however other drugs were found more favourable than clozapine due to its adverse effects on humans. However, there is no comparative study of atypical drugs used for the major dipressive disorder and disruptive bheviour in adults and children. It was observed that regular use of olanzapine has the influence to gain weight (6 to 13 pounds or more) and risk of new onset diabetes as a side effect. It was reported and diagnosed that the probability of developing schizophrenia in children and siblings are 13 and 9%, respectively. The possibility of a child to get the disorder from the parent is 6% and risks are increases up to 48% for identical twins (Walker, 2008; Gottesman et al., 1991). Life time risks of developing schizophrenia tothe realtives of schizophrenia sufferers are shown in Figure **2** (Pirjo, 2005; Matthew et al., 2016). The previous studies reported (Kessler, 2003; Naqvi, 2005; Whiteford et al., 2013) that schizophrenia, the most complex mental disorder disease was occurred before the age of 13 years and increases with age as shown in Figure **3**. However, severity can be reducing by timely interventions and counselling. In recent years, a number of atypical drugs such as clozapine, olanzapine, aripiprazole, quetiapine, asenapine, zotepine, risperidone, ziprasidone, sulpiride, paliperidone, lurasidone, iloperidone and sertindole are developed by various pharmaceutical companies for the above purposes.

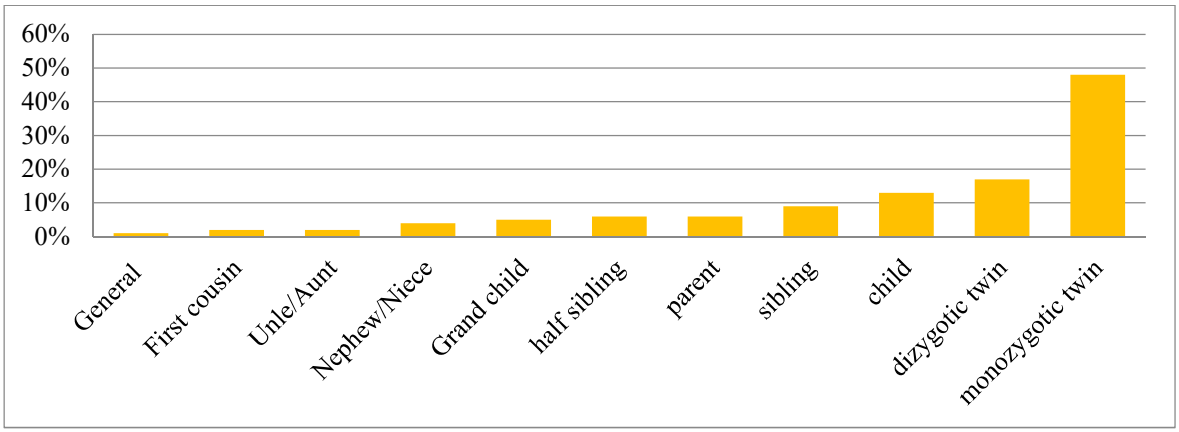


Figure 2. Lifetime risk of developing schizophrenia

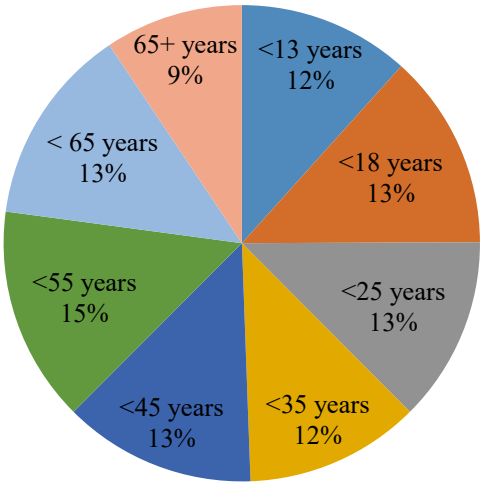


Figure 3. Schizophrenia with age and % patients.

The present review provides a brief history of atypical antipshychotic drug development which includes its clinical importance, adverse effects, the lifetime risk and patient age ratio for schizophrenia. Cytochrome P450 catalysed metabolic pathways and metabolites formed during biotransformation of tweleve important atypical antipsychotic drugs were introduced from the 1980s. Additinlay, it also provides comprehensive analytical applications of commonly used analytical methods especially chromatographic and spectrophotometric methods for the analysis of selected atypical drugs (clozapine, olanzapine, aripiprazole and quetiapine) and its metabolites in pure, matrices, blood, tissues, urine and pharmaceutical formulations.

1.2. Common Atypical Drugs

The atypical drugs are quiet popular for the last two decades among patients and clinicians due to its ability to lowering the extrapyramidal side effects than the antipsychotics from first generation. These drugs are widely used for the treatment of psychotic disorders because it was considering high efficacy and safety than the typical drugs. The structure of common antipsychotic drugs is shown in Figure **4**.

1.2.1. Clozapine

Clozapine is an atypical antipshychotic drug of the dibenzodiazepine class. It shows to be effective in reduction both the positive and negative symptoms of schizophrenia and to be associated with an extremely low incidence of extrapyramidal side effects. It is chemically known as 8-chloro-11-(4-methyl- 1-piperazinyl)-5H-dibenzo [b,e][1,4] diazepine (Cody et al., 2013) and have molar mass of 326.8 g/mole. It is yellow crystalline powder and freely soluble in chloroform, soluble in acetone and slightly soluble in water.

1.2.2. Olanzapine

It is an FDA approved atypical antipsychotic blocks and has strong serotonin recepator (5HT2) than dopamine (D2). Olanzapine is thienobenzodiazepine derivative, an important antipsychotic drug effective in treatemnet against the positive and negative symptoms of schizophrenia and has lower extrapyramidal effect than other antipsychotic drugs. It is approved by USFDA in the year 1996 used and may also used in combination with other medication to treat dipression (Fuller, 1992; Bhana et al., 2001). The structure of olanzapine is similar to clozapine. It is chemically known as 2-Methyl-4-(4-methyl-1-piperazinyl)- 10*H*-thieno[2,3-b][1,5] benzodiazepine, have molecular formula $C_{17}H_{20}N_4S$ and molar mass of 312.4. It is yellow colored powder, soluble in organic solvents such as ethanol, dimethyl sulphoxide and dimethyl formamide and sparingly soluble in aqueous buffers.

1.2.3. Aripiprazole

Aripiprazole is a second generation atypical antipsychotic drug popular in the market due to its ability to cure the disease with depression and avaialable in tablets, solutions and injections. It showed similar efficacy to olanzapine for long- term treatment of acutely psychotic and chronic, stable schizophrenia patients, lower liability for weight gain or increased lipid levels (Komossa et al., 2009). It is chemically known as 7-4-[4-(2,3-dichlorophenyl)-1 piprazenyl]butoxy]-3,4-dihydro-(1H)-quinolinone ($C_{23}H_{27}Cl_2N_3O_2$) have molecular weight 448.38.

1.2.4. Quetiapine

This drug has a unique receptor-binding profile, prescribed for the treatment of schizophrenia and manic episodes associated with bipolar disorder. Quetiapine is a dibenzothiazepine derivative, is one of the most recent antipsychotic drug commonly used for the

treatment of schizophrenia, bipolar disorder and major dipressive order. It is chemically known as 2-(2-(4-dibenzo [1, 4] thiazepine-11-yl-1-piperazinyl) ethoxy-ethanol (Molecular formula; $C_{21}H_{25}N_3O_2S$, Molar mass: 383.51). It is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5HT2) and dopamine type 2 (D2) receptors (Riedel et al., 2007).

1.2.5. Zotepine

Zotepine is a substituted dibenzothiepine tricyclic atypical drug developed in 1982. It is chemically similar to clozapine, quetaipine and active against positive symptoms of schizophrenia. It is a second generation antipsychotic drug indicated for acute and chronic schizophrenia and chemically known as 2-(3-chlorobenzo[b][1]benzothiepin-5-yl)oxy-N,N-dimethylethanamine (Molecular formula; C_{18} $H_{18}ClNOS$, Molar mass: 331.8) and structurally related to clozapine but with some distinguishing pharmacologic and clinical properties (Green et al., 2009).

1.2.6. Iloperidone

It is a second generation antipsychotic agent and mood stabilizer and a recently approved at ypical drug for the acute tretaement of Schizophernia in adults especially for patients who cannot tolerate with antipshychotics. It is well absorbed orally, with a bioavailability of 96% (Citrome, 2 010; Arif el al., 2011). It is benzisoxazole phenylethanone and chemicaly named as 1-[4-[3-[4-(6 -fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyphenyl]ethanone have the M. Fo rmula $C_{24}H_{27}FN_2O_4$ with molecular weight 426.48.

1.2.7. Asenapine

Asenapine is a dibenzoxepinopyrolidine derivative atypical antipsychotic drug used for the acute treatment of schizophrenia and manic or mixed episodes of bipolar I disorder. It is mainly works by controlling the psychotic symptoms with or without psychotic features in adults. Asenapine belongs to the class dibenzo-oxepino pyrroles used for the treatment of schizophrenia and bipolar mania/mixed episodes and chemically known as (3aRS, 12bRS)-5-Chloro-2-methyl2, 3, 3a, 12b-tetrahydro-1H dibenzo [2, 3:6, 7] oxepino [4,5c] pyrrole (2Z)-2-butenedioate. It is approved drug for schizophrenia in the USA, Japan and other countries, but

not in the EU. It has molecular formula is $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ and its molecular weight is 401.84. The exact mechanism of action of asepanine is unknown but it is believed to involve a combination of antagonist activity at D2 and 5-HT2A receptors. Somnolence, dizziness, extrapyramidal symptoms, weight gain and oral hypoesthesia are the most common adverse effects associated with asenapine. However, the studies shows the incidence of these events, particularly weight gain, is generally lower than with olanzapine and to improve health-related quality of life (Plosker et al., 2016).

1.2.8. Risperidone

It is a selective blocker of dopamine D2 receptors and serotonin 5-HT2 receptors and effective drug for the treatment for positive and negative symptoms of schizophrenia and mania symptoms of bipolar disorder in children and adolscenct. It binds 10-20 times greater affinity to 5-HT2A receptors compares to D2 receptors. Paliperidone, the main metabolite of risperidone, is also used as an antipsychotic but quantitatively different from risperidone from the perspective of pharmacodynamics as well as pharmacokinetics (Moller et al., 2005). It is chemically known as 3-{2-[4[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-6,7,8-tetrahydro-4H-pyrido[1,2 a]pyrimidin-4-one (Mol Formula: $C_{23}H_{27}FN_4O_2$, Mol. weight of 410.5), is a white to off-white powder, freely soluble in methylene chloride, sparingly soluble in alcohol and practically insoluble in water. However, it dissolves in dilute acid solutions.

1.2.9. Lurasidone

It is one the recent FDA approved benzisothiazolone derivative antipsychotic medication used for the teeatment of schizophrenia and depression associated with bipolar disorder. It is chemically known (3aR,4S,7R,7aS)-2-[((1R,2R)-2-{[4-(1,2- benzisothiazol-Michele 3-yl)-piperazin-1–yl]methyl}cyclohexyl}hexahydro-1H-4,7-methanisoindol-1,3-dione and have molecular formula $C_{28}H_{36}N_4O_2S$ and molar mass 492.68 (Michele et al., 2017).

1.2.10. Ziprasidone

Ziprasidone is a recently approved benzylisothiazolylpiprazine antipsychotic drug approved for the treatment of schizophrenia, acute, mixed mania and adjunctive for the treatment

of bipolar disorder. Ziprasidone is a novel benzylisothiazolylpiperazine antipsychotic and has highly selective antagonistic activity on the D2 and 5HT2A receptors. It is a novel benzylisothiazolylpiperazine antipsychotic drug which effectvlely stablises mood in schizophrenia and bipolar disorder (Elbe et al., 2008). It is chemically known as 5-[2-[4- (1,2-benzisothiazol-3- yl)-1-piperazin-1yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride (($C_{21}H_{21}ClN_4OS$). It is white to slightly pink powder freely soluble in organic solvents such as primary alocohols and chloroform and sparingly soluble in acetonitrile and octanol.

1.2.11. Sulpiride

Sulpiride is an atypical drug and widely prescribed neuroleptic agent, used as a behaviour regulator in the psychopathology of senescence for the treatment of depression and schizophrenia. It is a substituted benzamide derivative class and a slecetive dopamine D2 receptors used in the treatment of psychosis associated with schizophrenia and major depressive disorder. It may be used in low dosage to treat anxiety and mild depression and marked as a low incidence of adverse effects (Soares et al., 2000). It is chemically and clinically similar to amisulpride and chemically known as 5-(aminosulfonyl)-N-((1-ethyl-2-pyrrolidinyl) methyl)-2-methoxybenzamide (mol formula: $C_{15}H_{23}N_3O_4S$ and molar mass 341.43).

1.2.12. Sertindole

It is an important arylpiperidylindole antipsychotic medication used for the treatment of neuroleptic-resistant schizophrenia and effcteive in improving negative symptoms. It has affinity for 5-HT2c, 5-HT2a, D2, α1, and α2 receptors (Murdoch et al., 2006). Its IUPAC name is 1-(2-{4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone(Chemical Formula:$C_{24}H_{26}ClFN_4O$ and Mol. Wt. 440.94).

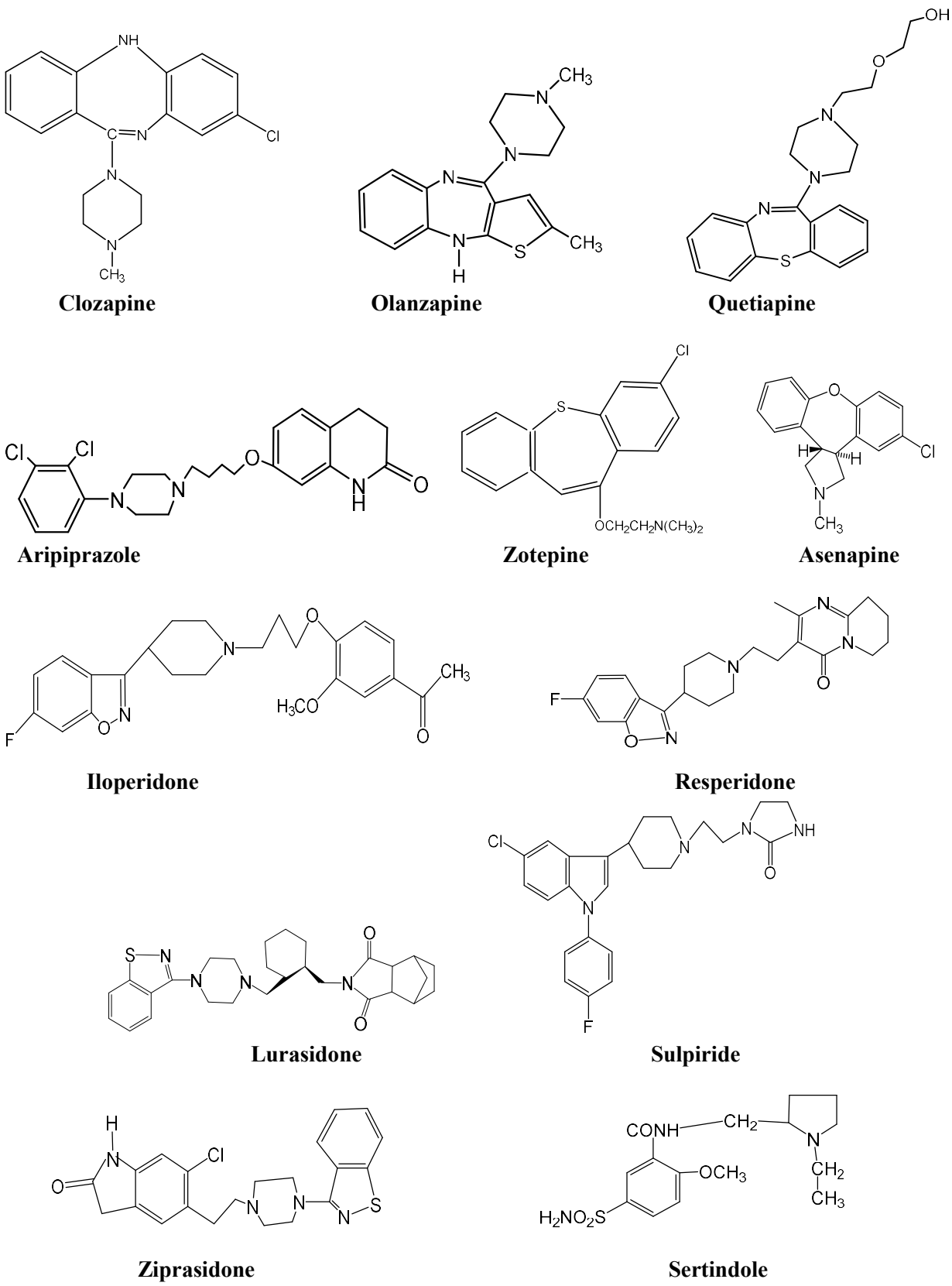


Figure 4. Chemical structures of atypical antipshychotic drugs.

2. Biotransformation

To cure diseases in living organism, medicines (drugs) are required, but at the same time, drugs are considered as foreign objects to the body, which can be excreted and finally gets eliminated after showing their action. The human body has a natural mechanism to eliminate these drugs which is mainly facilitated by the process known as drug metabolism. Metabolism can be defined as a biochemical modification of one chemical form to another, which occurs usually through specialized enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body (Coleman et al., 2010). However, in some cases, the same metabolic process can also lead to the generation of reactive metabolites, which are toxic to the human body (Attia et al., 2010). This is termed as bioactivation of drugs, which depends specifically on important structural features present in these drug molecules (Kalgutkar et al., 2009). The metabolism of a drug in a body is an example of a biotransformation and metabolites can be defined as the products of biotransformation. Biotransformation produces chemically stable metabolites that are neither pharmacologically nor toxicologically active (Kebamo, 2015; Mauri et al., 2014). The metabolites which are chemically stable and pharmacologically active are known as active metabolites. Thermodynamic and pharmacokinetic properties of active metabolites may similar or different from the original drug compound. Active metabolites may involve on drug's therapeutic effect completely or partially. A number of metabolites are formed through major biotransformation pathways such as hydroxylation, N-dealkylation, deamination, desulfuration, dehydrogenation, oxidation, reduction and conjugation (Shen et al., 1999). Most pharmacokinetic interactions with atypical antipsychotics occur at the metabolic level usually changes in the activity of the major drug-metabolizing enzymes involved in their

biotransformation such as cytochrome P450 (CYP) monooxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT). The most important isoenzyme system cytochrome P-450 (CYP450) catalyzes the drugs through oxidation (Urichuk et al., 2008). The enzymes involved in metabolism are present in many tissues but in general, liver is the principal site of drug metabolism. The cytochromes P-450 constitutes the major enzyme family capable of catalyzing the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore of particular relevance for clinical pharmacology (Halpert, 1994; Zanger et al., 2008). The highest expressed forms in liver are CYPs 3A4/A5, 2C9, 2C8, 2E1, and 1A2., while 2A6, 2D6, 2B6, 2C19 and 3A5 are less abundant and CYPs 2J2, 1A1, and 1B1 are mainly expressed extrahepatically. Figure **5** shows the involvement and contribution of CYPs in major metabolism of drugs. UGT enzymes catalyse the glucuronidation of a large number of drugs located in the endoplasmic reticulum, mainly in the liver, but also in the kidney, intestine, skin, lung, prostate and brain. Drugs that inhibit or induce the CYP or UGT isoenzymes involved in metabolism of the various antipsychotics may alter their plasma concentrations with subsequent risk of adverse effects or decreased efficacy. A list of atypical drugs with their active as well as inactive metabolites are given in Table **1** and major biotransformation are shown in Fig. **6a, b, c, d, e, f, g, h, i, j, k, l** (Dragovic, 2013; Kirschbaum, 2009; Kassahun, 1997; Bakken, 2009; Bakken, 2009; Shiraga, 1999; Mutlib, 1998; Van de, 2011; Spina, 2007; Caccia, 2012; Prakash, 1997; Sugnaux, 1978; Sakamoto et al., 1995).

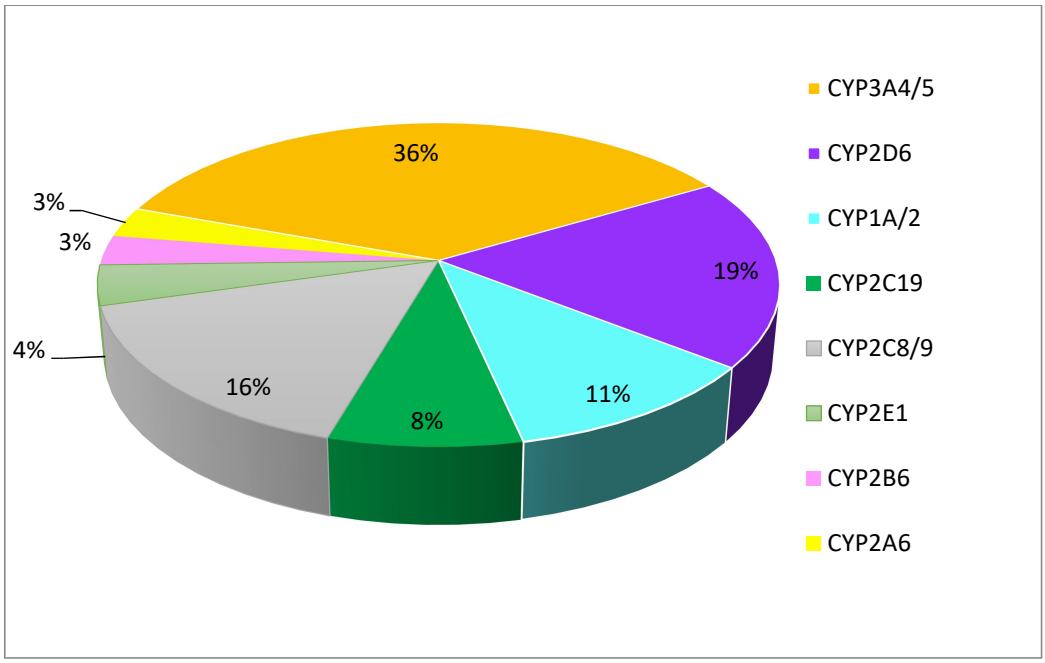


Figure 5. Contribution of cytochrome P450 (CYPs) enzymes in drug metabolism.

3. Metabolites

Clozapine forms polar metabolites during the metabolism in liver by cytochrome P450 and eliminate through urine and feces (Sheehan et al., 2010). Two major metabolites (clozapine N-oxide and norclozapine are formed by hepatic cytochrome P450s through N-oxidation and demethylation. Norclozapine (N-desmethylclozapine) was reported as most pharmacologically active metabolite. The cytochrome P450 (CYP1A2) enzyme was catalyzed in the liver, intestine, kidney, lung and brain through oxidation. The CYP1A2 pathway is mainly responsible for the metabolism and other pathways like CYPs (2C, 2D6, 2E1, 3A and 3A4) are also helpful (Zanger, 2013; Prior et al., 1999). Cytochrome P450s were also able to bioactivate clozapine to a glutathione-reactive nitrenium ion. The studies reported that dose optimization, prevention to toxicity, metabolism and compliance with efficacy are the main parameters to use clozapine, norclozapine and proved by monitoring plasma levels in humans (Mitchell, 2000). Aripiprazole is mainly metabolized via CYP3A4 and 2D6 through dehydrogenation and forms dehydroaripiprazole as an active metabolite. Other metabolites of aripiprazole were also formed through hydroxylation and N-dealkylation catalyzed by CYP3A4 (Molden et al., 2006). Olanzapine undergo hepatic metabolism by direct glucuronidation and CYP1A2 mediated

oxidation forming 10-,4'-N-glucuronides and 4'-N-desmethylolanzapine, respectively. Minor metabolic pathways are catalyzed by Flavin-containing monooxygenase produce olanzapine N-oxide and 2-hydroxymethylolanzapine also produces via CYP2D6 (Iwahashi et al., 2004) and mainly excreted in urine and feces.

Quetiapine is extensively metabolized by liver following oral administration via CYP3A4 with a minor influence of CYP3A5. The quetiapine metabolism involves sulfoxidation, N and O-dealkylation and to some extent hydroxylation of the dibenzothiazepine ring. *N*-desalkylquetiapine (norquetiapine) is the most important active metabolite whereas quetiapine sulfoxide is considered as the most important pharmacological inactive metabolite. In addition, CYP3A metabolizes norquetiapine into 7-hydroxyquetiapine, which is pharmacologically active. The elimination of quetiapine and its metabolites is mainly by urine (73%) and feces (21%) (Bakken et al., 2009). Zotepine blocks 5HT receptors more potently than DA rececptors. N-demethylation is the major metabolic pathway by cytochrome P450 (CYP) to form norzotepine. N-demethylation and S-oxidation are mediated mainly by CYP3A4 produce norzotepine and zotepine S-oxide, whereas in 2 and 3-hydroxylation are mediated by CYP1A2/2D6 produce 3-hydroxyzotepine and 2-hydroxyzotepine (Shobo et al., 2010), Iloperidone undergoes hepatic metablosim involving CYP540 isozymes (CYP 3A4 and CYP2D6) mediates through O-dealkylation (CYP3A4), hydroxylation (CYP2D6), and decarboxylation/reduction processes and excreted in bile and feces. It was observred that iloperidone has high binding affinity for D2, D3 and 5-HT_{2A} receptors which results in improving negatie symtopms, anxiety and substance abuse and has less extra pyrimadial side effect compare to risperidone (Arif, 2011; Citrome et al., 2010). Asenapine undergoes hepatic metabolism via direct glucurinodation by UGT1A4 and oxidative metabolim via CYP1A2. In general, gulucuronidation is considered a detoxification pathway which transforms the lipophilic drung molecules to hydrophilic metabolite. Asenapine-N^+- gulucuronide is the principal metobilte formed by this pathway (Van de, 2011; Gandhimathi et al., 2012). Risperidone is primarly metabolized by CYP2D6 and produce an active metabolite called 9-hydroxy risperidone (paliperidone) through hydroxylation. Many articles demonstrated that risperidone and its active metabolite have neither the same pharmacological nor the same toxicological activity. Therefore, most patients who has taken this drug orally would exhibit 5–10 times plasma levels higher than risperidone, hence the the active metabolite, paliperidone play an effective role in antipsychotic's antidepressant effect (Fang, 1999; Mannens et al., 1993).

Lurasidone is eliminated by heaptic metabolism primarily by CYP3A4. Oxidative N-dealkylation, hydroxylation of cyclohexane ring or norbornane ring, and S-oxidation are the the major biotransformation pathways. It shows better results than the quetiapine and has almost no effect on weight, prolactin, glucose, lipids and QT. The excretion of lurasidone was recovered in urine (9%) and feces (80%) (Martin et al., 2011). Ziprasidone undergoes extensive metabolism after oral administration in humans with very small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. It was observed that CYP3A4 contribute as major isozyme in oxidative metabolism of ziprasidone and S-methyl-dihydroziprasidone. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyldihydroziprasidone (Beedham, 2003; Prakash et al., 1997). The metaboilites of sulpiride were determined in urine and plasma of rats, dogs and humans. The chemical structure of the six isolated metabolites as well as unchanged product obtained by biological pathways was confirmed that none of these metabolites was found in human urine. Hence, the pharmacological properties of sulpiride could therefore be attributed to the unchanged product (Sugnaux et al., 1978). Sertindole is an oral arylpiperidylindole antipsychotic improves negative symptoms and effective in the treatment of neuroleptic-responsive schizophrenia. It was metabolized through hydroxylation at the 4- and 5-positions of the imidazolidinone ring, *N*-dealkylation, and 1, 2-hydride shift at the fluorophenyl group via CYP2D6 and CYP3A4. Dehydration, oxidation, hydroxylation, glucuronidation and sulphation were also observed in metabolism. 5-hydroxy-sertindole and 4-hydroxy-sertindole were reported as major metabolites where as nor-sertindole and dehydro-sertindole were minor ones in liver microsomal metabolic patterns in rat, monkey and man. It was reported that the metabolism of sertindole in man, rat and monkey resembles each other but different in the dog. Oxidation at the imidazolidinone ring and *N*-dealkylation are the main metabolic reactions in the rat (Sakamoto et al., 1995).

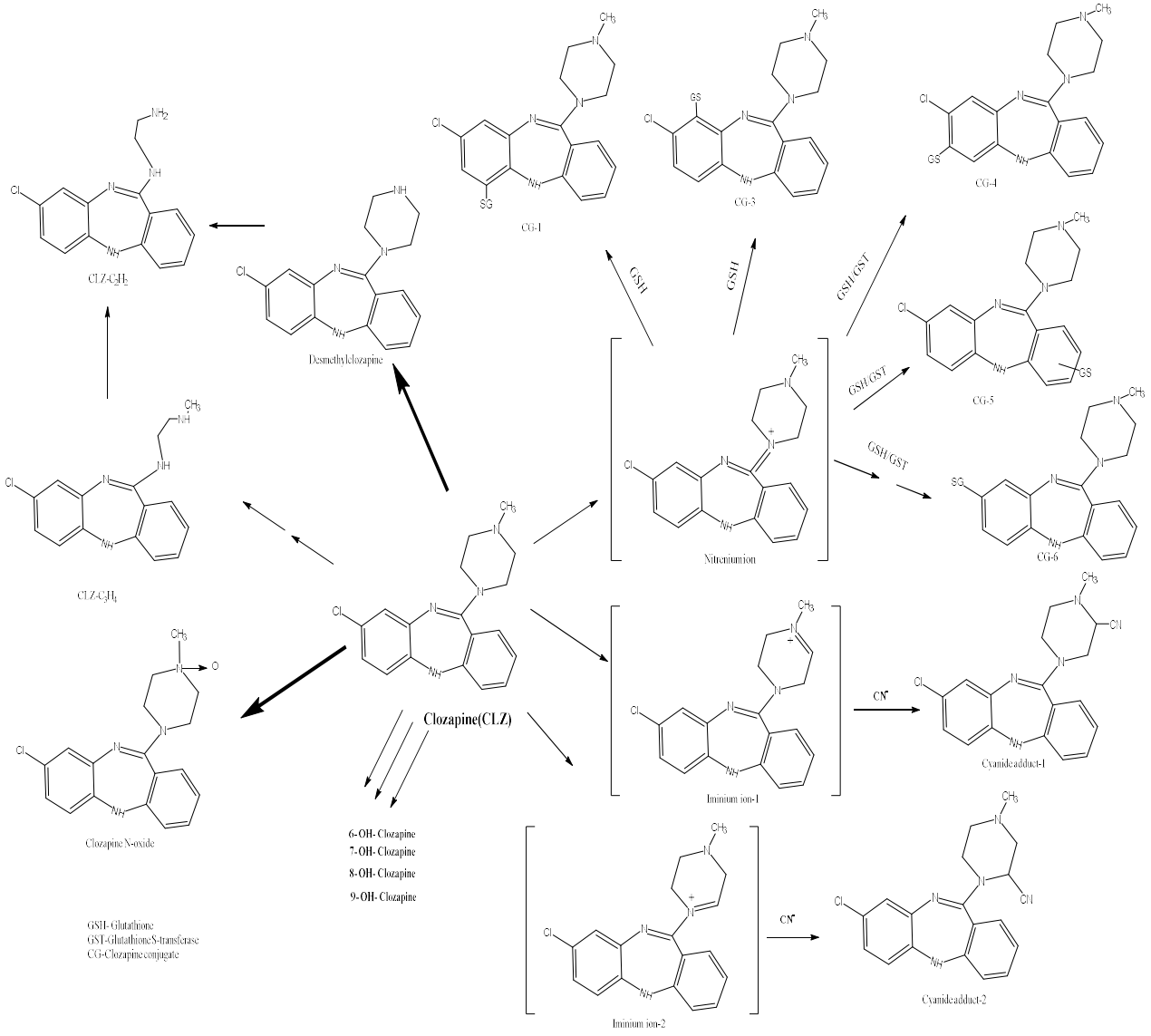

CLZ-C2H2
Desmethylclozapine
CG-1
CG-3
CG-4
GSH
GSH/GST
CG-5
CG-6
Nitrenium ion
CLZ-C3H4
Clozapine(CLZ)
Clozapine N-oxide
Iminium ion-1
Cyanide adduct-1
CN-
6-OH- Clozapine
7-OH- Clozapine
8-OH- Clozapine
9-OH- Clozapine
Iminium ion-2
Cyanide adduct-2
GSH- Glutathione
GST-Glutathione S-transferase
CG-Clozapine conjugate

Fig. (6a).

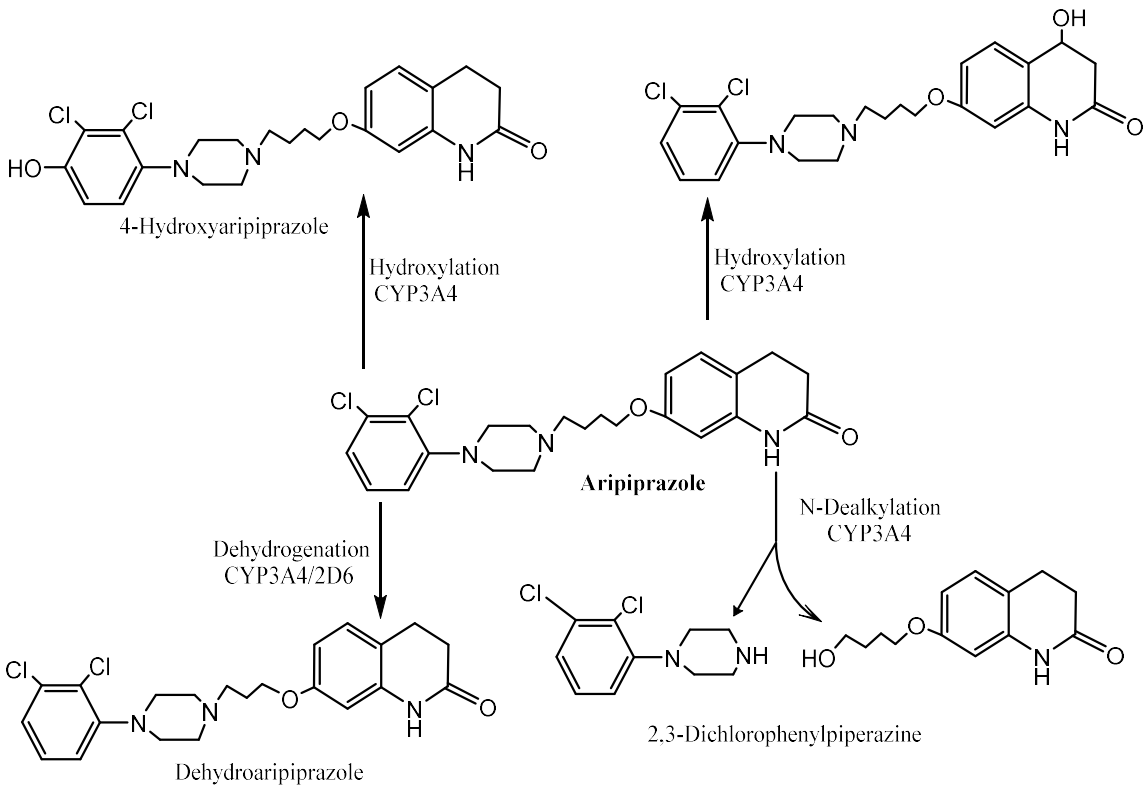

4-Hydroxyaripiprazole
Hydroxylation
CYP3A4
Hydroxylation
CYP3A4
Aripiprazole
Dehydrogenation
CYP3A4/2D6
N-Dealkylation
CYP3A4
Dehydroaripiprazole
2,3-Dichlorophenylpiperazine

Fig. (6b).

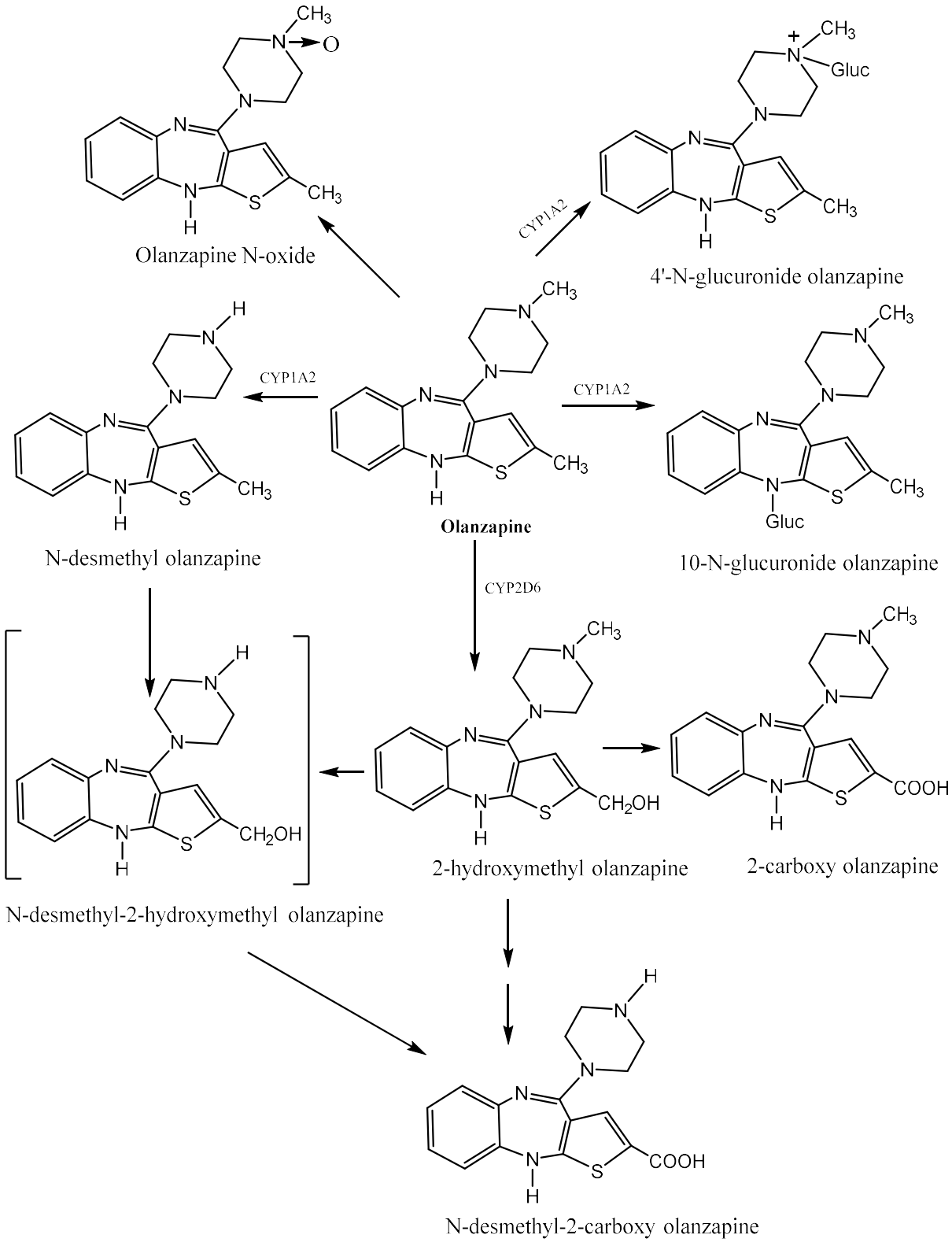

Olanzapine N-oxide
4'-N-glucuronide olanzapine
CYP1A2
CYP1A2
CYP1A2
N-desmethyl olanzapine
Olanzapine
10-N-glucuronide olanzapine
CYP2D6
N-desmethyl-2-hydroxymethyl olanzapine
2-hydroxymethyl olanzapine
2-carboxy olanzapine
N-desmethyl-2-carboxy olanzapine

Fig. (6c).

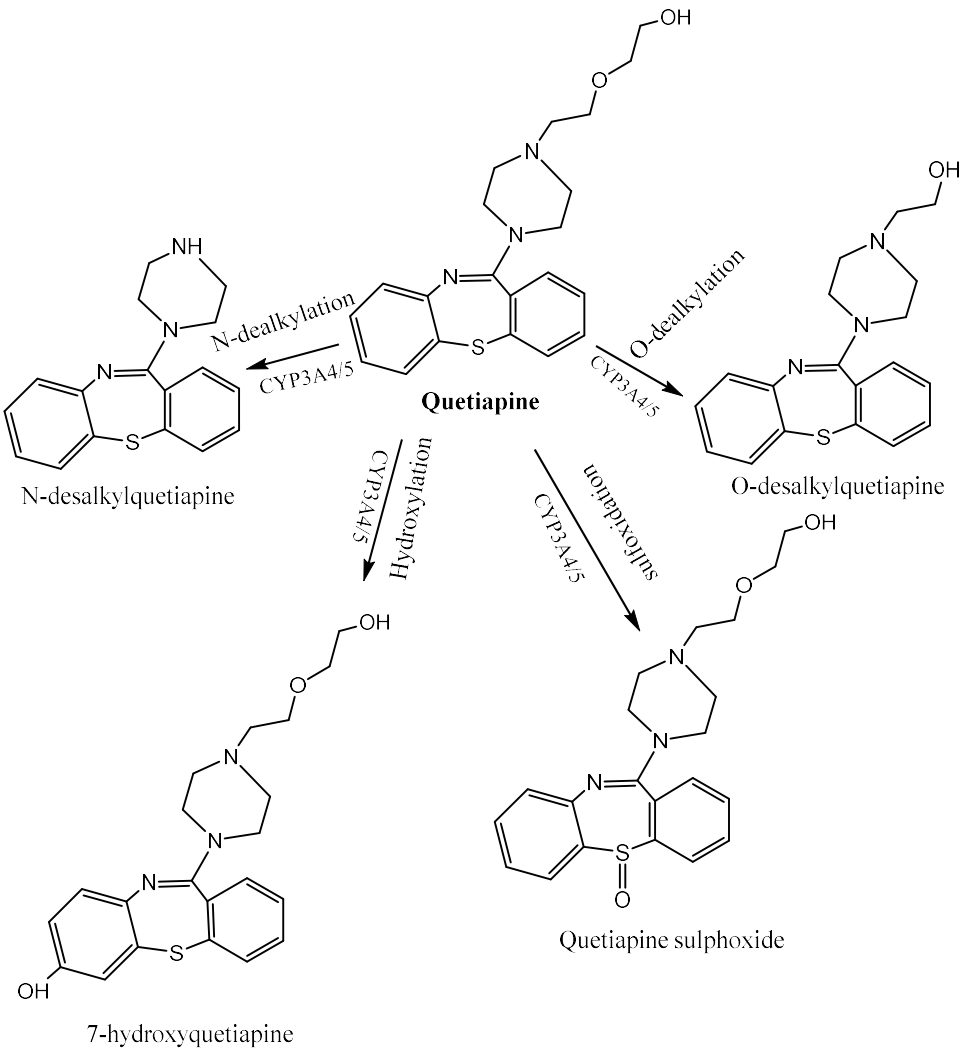

Quetiapine
N-dealkylation
CYP3A4/5
O-dealkylation
CYP3A4/5
CYP3A4/5
Hydroxylation
sulfoxidation
CYP3A4/5
N-desalkylquetiapine
O-desalkylquetiapine
7-hydroxyquetiapine
Quetiapine sulphoxide

Fig. (6d).

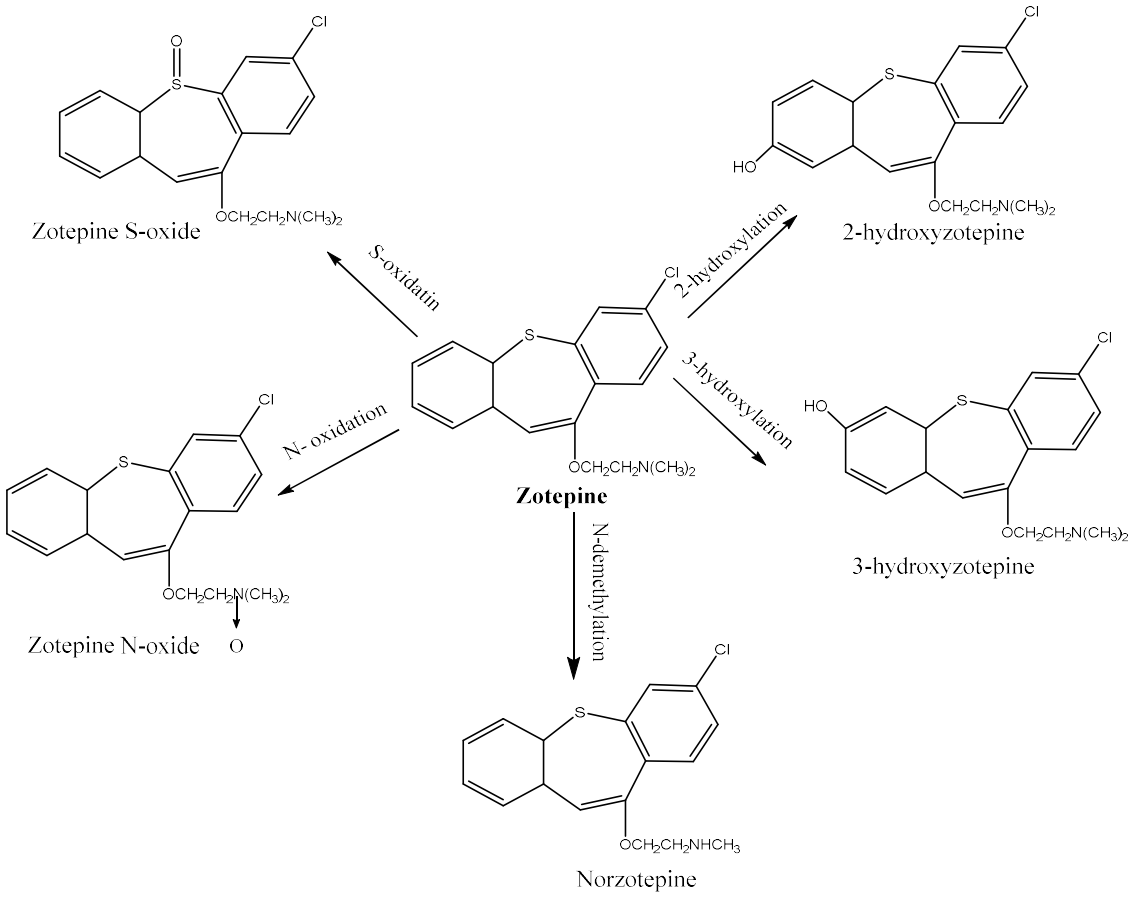

Zotepine S-oxide
S-oxidatin
2-hydroxylation
2-hydroxyzotepine
N- oxidation
Zotepine
3-hydroxylation
3-hydroxyzotepine
Zotepine N-oxide
N-demethylation
Norzotepine

Fig. (6e).

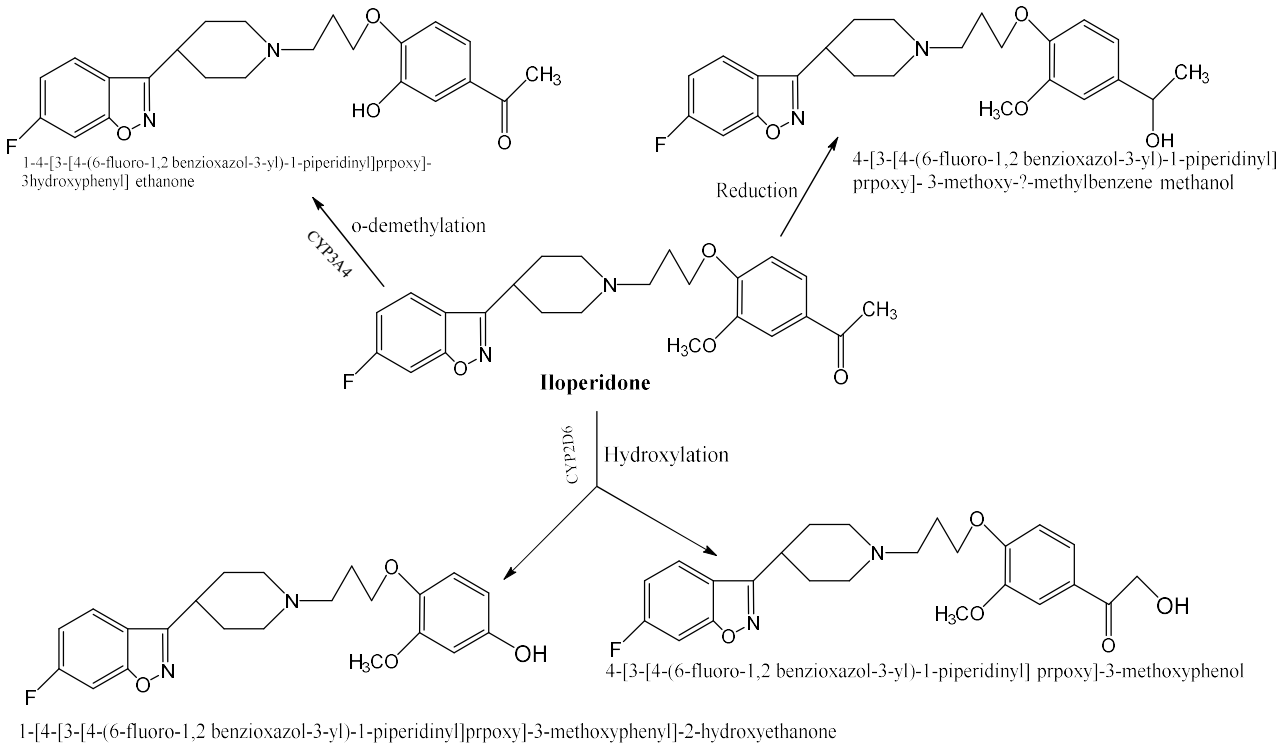

1-4-[3-[4-(6-fluoro-1,2 benzioxazol-3-yl)-1-piperidinyl]prpoxy]-3hydroxyphenyl] ethanone
4-[3-[4-(6-fluoro-1,2 benzioxazol-3-yl)-1-piperidinyl] prpoxy]- 3-methoxy-?-methylbenzene methanol
Reduction
o-demethylation
CYP3A4
Iloperidone
CYP2D6
Hydroxylation
4-[3-[4-(6-fluoro-1,2 benzioxazol-3-yl)-1-piperidinyl] prpoxy]-3-methoxyphenol
1-[4-[3-[4-(6-fluoro-1,2 benzioxazol-3-yl)-1-piperidinyl]prpoxy]-3-methoxyphenyl]-2-hydroxyethanone

Fig. (6f).

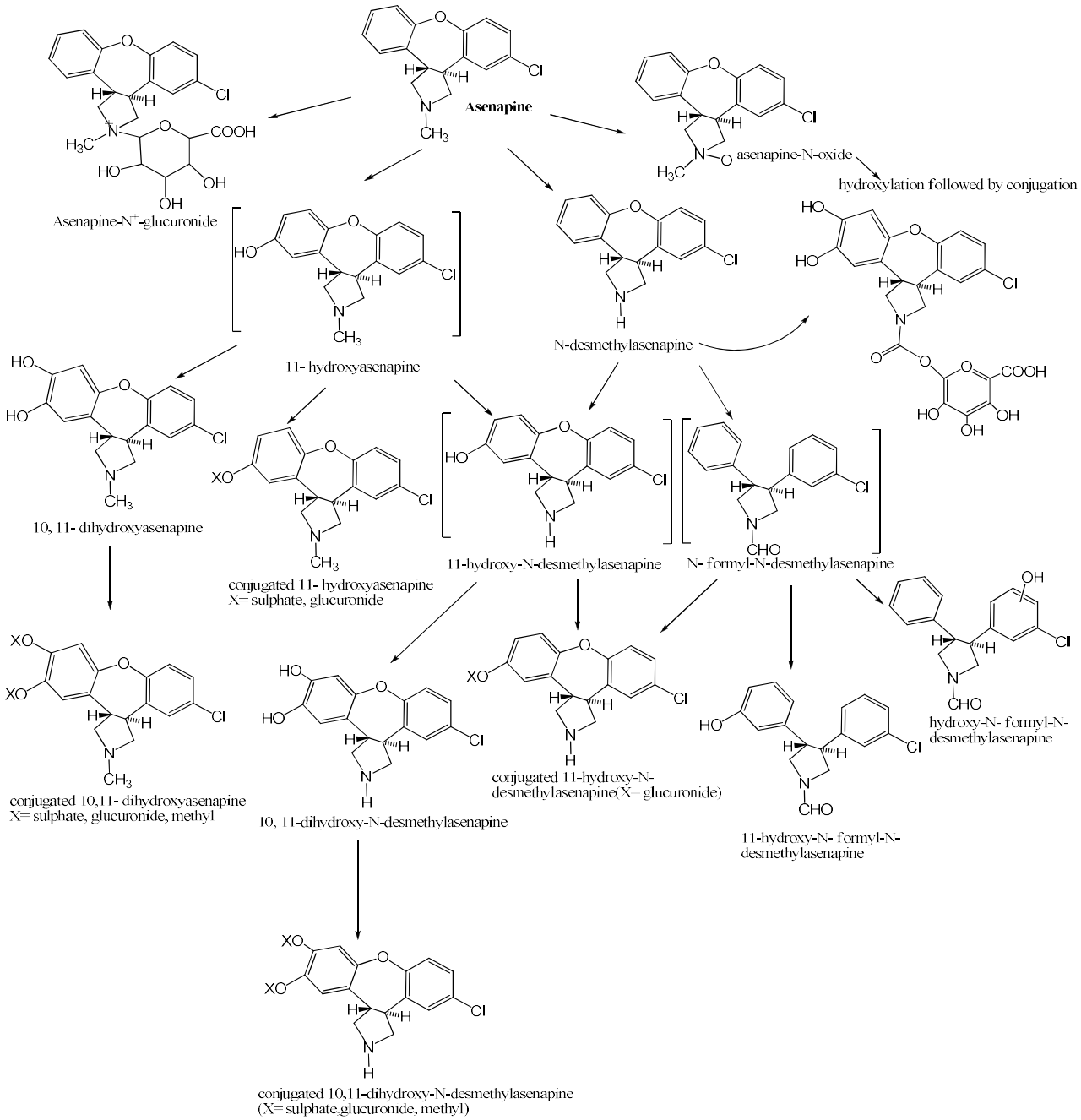

Asenapine
Asenapine-N+-glucuronide
asenapine-N-oxide
hydroxylation followed by conjugation
11- hydroxyasenapine
N-desmethylasenapine
10, 11- dihydroxyasenapine
conjugated 11- hydroxyasenapine
X= sulphate, glucuronide
11-hydroxy-N-desmethylasenapine
N- formyl-N-desmethylasenapine
hydroxy-N- formyl-N-
desmethylasenapine
conjugated 10,11- dihydroxyasenapine
X= sulphate, glucuronide, methyl
10, 11-dihydroxy-N-desmethylasenapine
conjugated 11-hydroxy-N-
desmethylasenapine(X= glucuronide)
11-hydroxy-N- formyl-N-
desmethylasenapine
conjugated 10,11-dihydroxy-N-desmethylasenapine
(X= sulphate,glucuronide, methyl)

Fig. (6g).

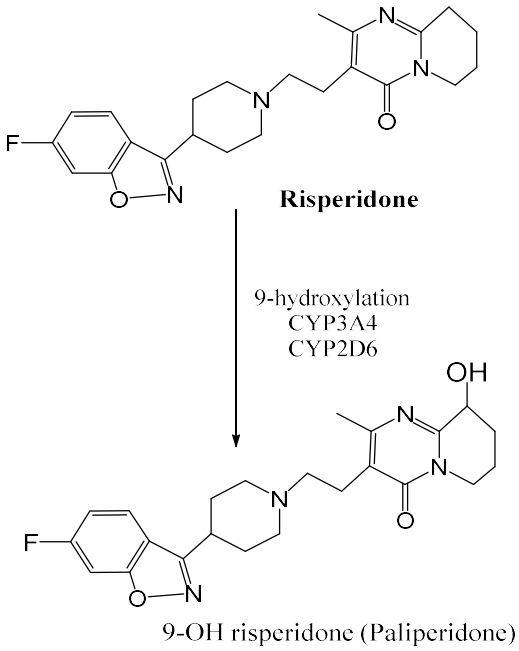

Risperidone
9-hydroxylation
CYP3A4
CYP2D6
9-OH risperidone (Paliperidone)

Fig. (6h).

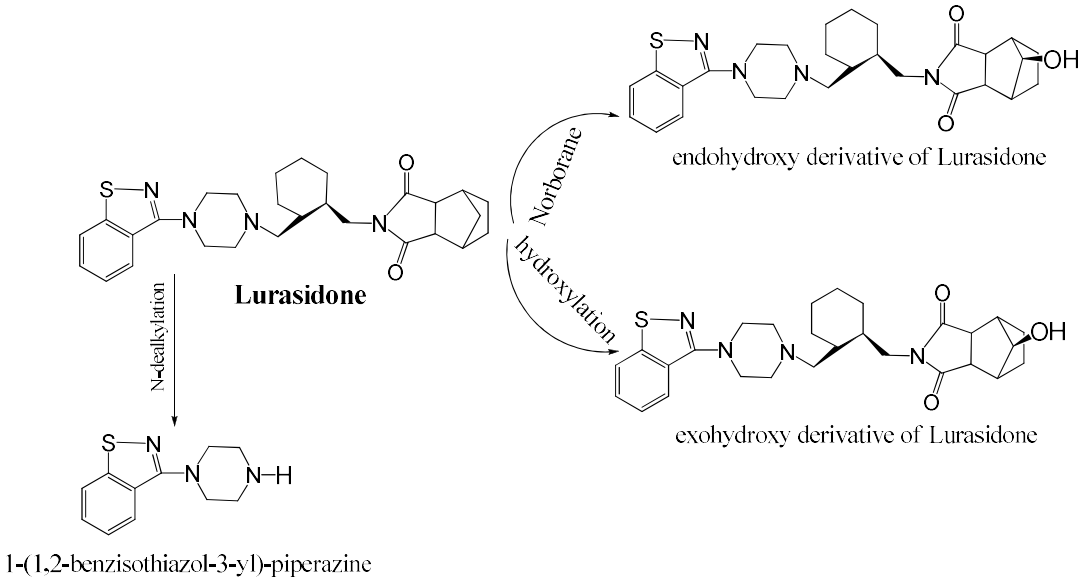

Lurasidone
N-dealkylation
1-(1,2-benzisothiazol-3-yl)-piperazine
Norborane
hydroxylation
endohydroxy derivative of Lurasidone
exohydroxy derivative of Lurasidone

Fig. (6i).

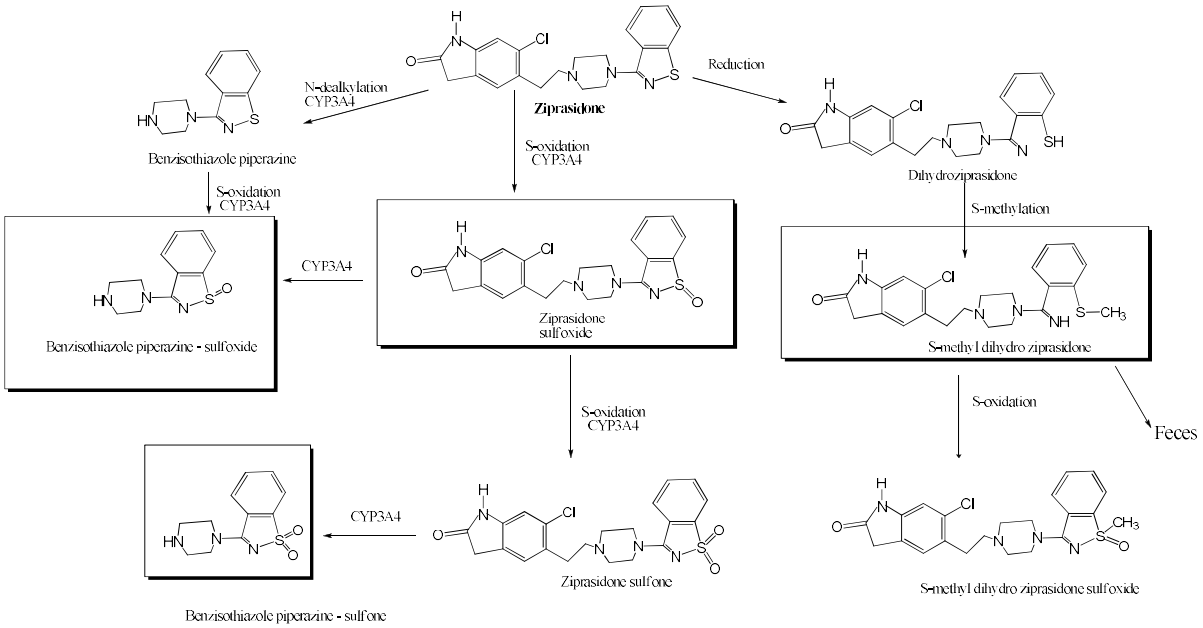

Ziprasidone
N-dealkylation
CYP3A4
Benzisothiazole piperazine
Reduction
Dihydroziprasidone
S-oxidation
CYP3A4
S-methylation
Benzisothiazole piperazine - sulfoxide
CYP3A4
Ziprasidone sulfoxide
S-methyl dihydro ziprasidone
S-oxidation
CYP3A4
Feces
CYP3A4
Ziprasidone sulfone
S-methyl dihydro ziprasidone sulfoxide
Benzisothiazole piperazine - sulfone

Fig. (6j).

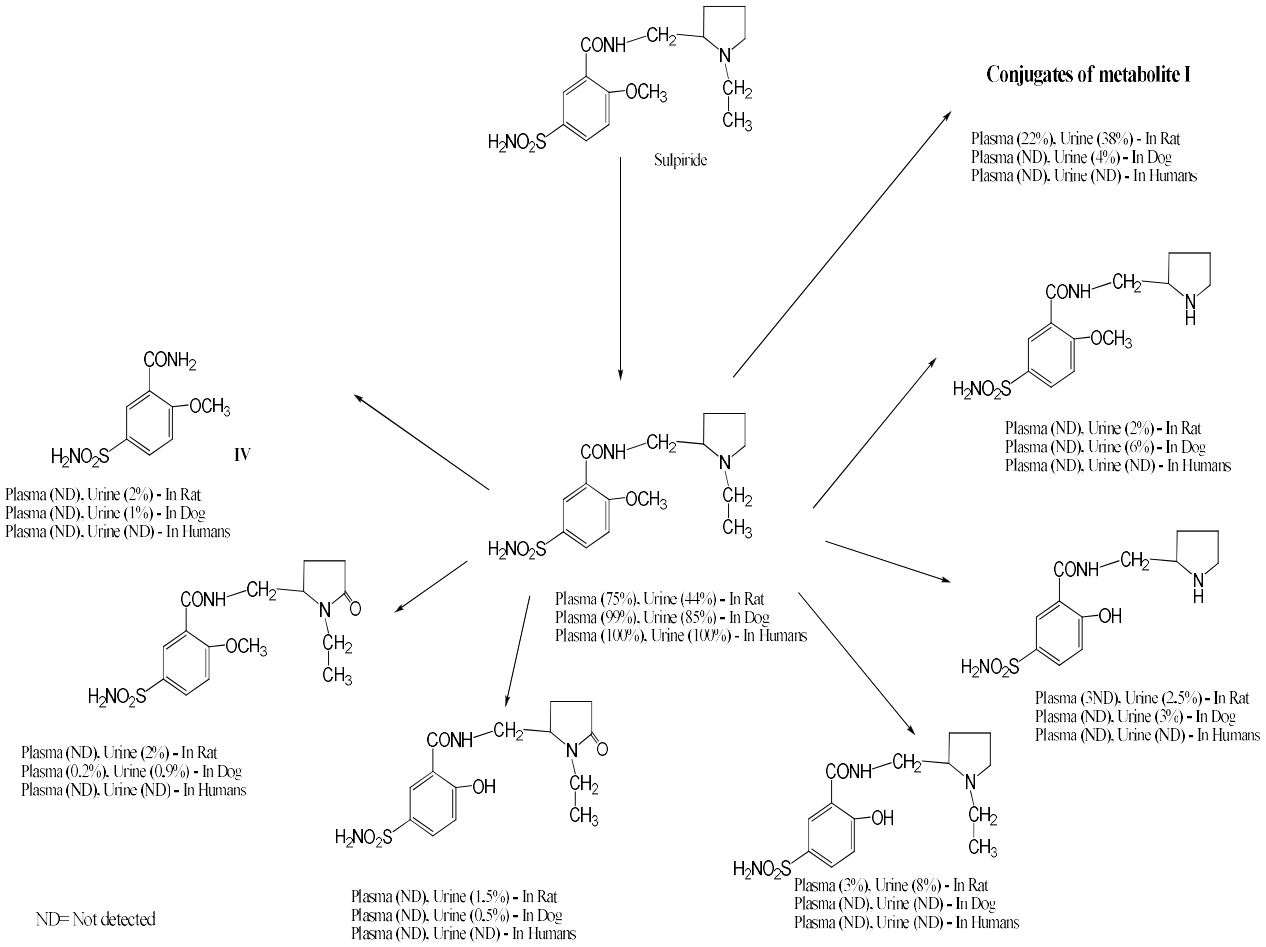

Sulpiride
Conjugates of metabolite I
Plasma (22%), Urine (38%) - In Rat
Plasma (ND), Urine (4%) - In Dog
Plasma (ND), Urine (ND) - In Humans
Plasma (ND), Urine (2%) - In Rat
Plasma (ND), Urine (6%) - In Dog
Plasma (ND), Urine (ND) - In Humans
IV
Plasma (ND), Urine (2%) - In Rat
Plasma (ND), Urine (1%) - In Dog
Plasma (ND), Urine (ND) - In Humans
Plasma (75%), Urine (44%) - In Rat
Plasma (99%), Urine (85%) - In Dog
Plasma (100%), Urine (100%) - In Humans
Plasma (3ND), Urine (2.5%) - In Rat
Plasma (ND), Urine (3%) - In Dog
Plasma (ND), Urine (ND) - In Humans
Plasma (ND), Urine (2%) - In Rat
Plasma (0.2%), Urine (0.9%) - In Dog
Plasma (ND), Urine (ND) - In Humans
Plasma (ND), Urine (1.5%) - In Rat
Plasma (ND), Urine (0.5%) - In Dog
Plasma (ND), Urine (ND) - In Humans
Plasma (2%), Urine (8%) - In Rat
Plasma (ND), Urine (ND) - In Dog
Plasma (ND), Urine (ND) - In Humans
ND= Not detected

Fig. (6k).

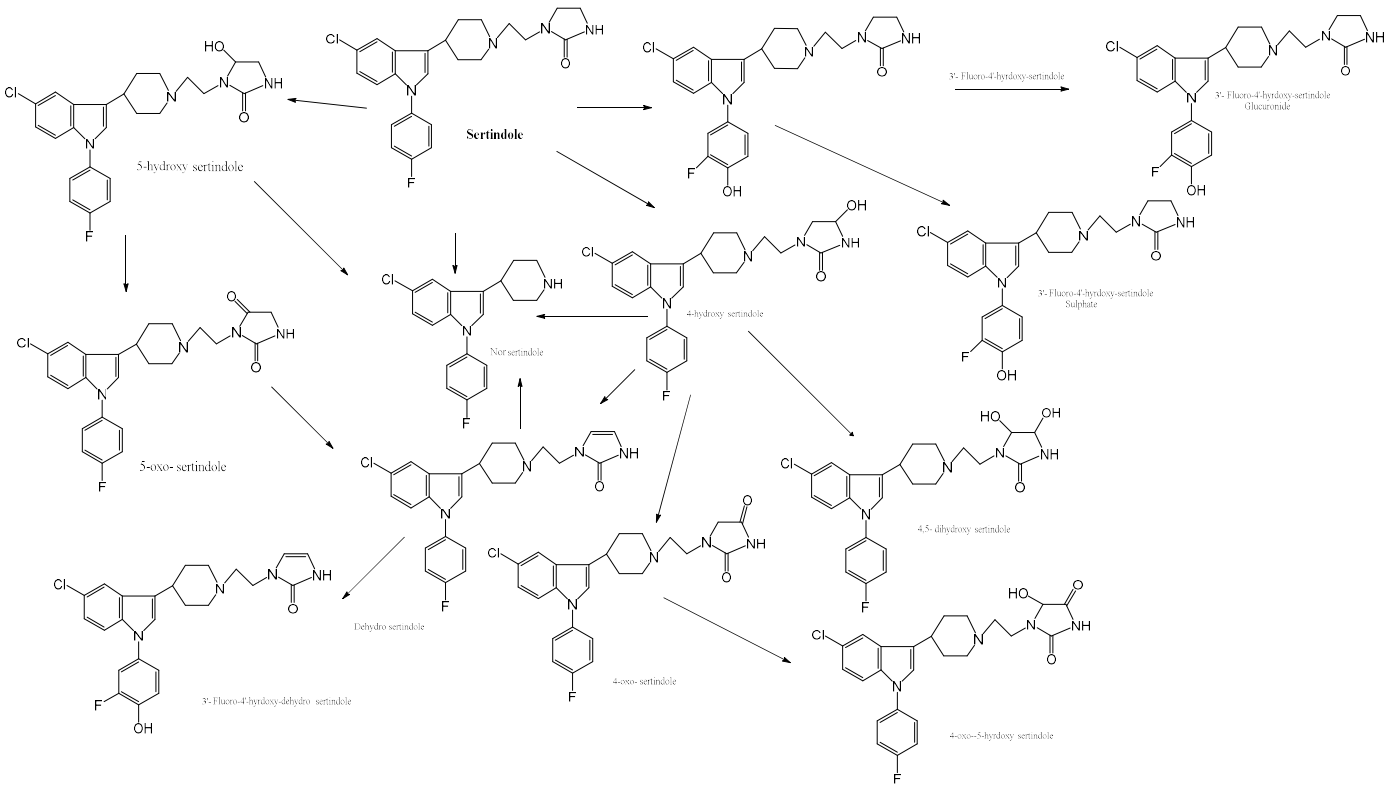

Sertindole
5-hydroxy sertindole
3'- Fluoro-4'-hydroxy-sertindole
3'- Fluoro-4'-hydroxy-sertindole Glucuronide
3'- Fluoro-4'-hydroxy-sertindole Sulphate
4-hydroxy sertindole
Nor sertindole
5-oxo- sertindole
4,5- dihydroxy sertindole
Dehydro sertindole
4-oxo- sertindole
3'- Fluoro-4'-hydroxy-dehydro sertindole
4-oxo--5-hydroxy sertindole

Fig. (6l).

Table 1. List of atypical antipsychotic drugs and their metabolites.

Atypical antipsychotic drug	Active metabolites	Other metabolites	References
Clozapine	N-desmethylclozapine (norclozapine);Clozapine N-oxide	-	Gauch, 1971; Schaber et al., 1998
Olanzapine	*N*-desmethylolanzapine	10-*N*-glucuronide; 4-N-oxide-olanzapine; 2 hydroxymethylolanzapine; 4-*N*-glucuronide	Kassahun, 1997; Ring, 1996; Linnet et al., 2002
Aripiprazole	Dehydroaripiprazole	*2-3* dichlorophenylpiperazine; *m*- Chlorophenylpiperazine	Wood, 2006; Martignoni et al., 2006
Risperidone	9-OH-risperidone (Paliperidone)	-	Alamo, 2013; Spina et al., 2007
Quetiapine	N–desalkylquetiapine (norquetiapine); 7–Hydroxyquetiapine	O – desalkylquetiapine; Quetiapine sulfoxide	Bakken, 2009; Grimm, 2006; Grimm et al., 1997
Asenapine	N-Desmethylasenapine; Asenapine 11 –O–sulfate Asenapine N^+-Glucuronide; N–desmethylasenapine N– carbamoylglucuronide	Asenapine N–oxide; N–Formylasenapine; 11–Hydroxyasenapine; 11–Hydroxy–N–desmethylasenapine; 7–Hydroxyasenapine; 11–Hydroxy–N–formylasenapine; 11–Methoxyasenapine; 11–Hydroxyasenapine N–oxide	Von dem, 1990; Van de et al., 2011
Zotepine	Norzotepine; Zotepine S-oxide; 2-Hydroxyzotepine; 3-Hydroxyzotepine	Zotepine N-oxide	Noda, 1979; Ono,1996; Shiraga et al., 1999

Iloperidone	1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone; 4-[3-[4-(6-fluoro-1,2-benzisoxazol- 3-yl)-1-piperidinyl]propoxy]-3-methoxy-a-methylbenzene methanol; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2-hydroxyethanone; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol- 3-yl)-1-piperidinyl]propoxy-3-ethoxyphenyl]ethanone		Andersson, 1993; Chang, 1994; Halpert, 1994; Inaba, 1985; Miners, 1995; Miners, 1988; Murray, 1990; Tassaneeyakul,1993a; Tassaneeyakul, 1993b; Thummel, 1993; Veronese, 1991; Wrighton, 1993; Mutlib et al., 1998
Lurasidone	Endohydroxy derivative of Lurasidone (ID-14326); Endohydroxy derivative of Lurasidone (ID – 14283)	1-(1,2-benzisothiazol-3-yl)-piperazine (ID – 11614)	Caccia, 2012; Katteboina et al., 2016
Ziprasidone	S-methyldihydroziprasidone sulfoxide S-methyldihydroziprasidone	Ziprasidone sulfone Ziprasidne sulfoxide	Prakash et al., 1997
Sulpiride	Not detetected in humans		Sugnaux et al., 1978
Sertindole	5-hydroxy-serindole; 4-hydroxy-serindole;	Nor-sertindole; dehydro-sertindole	Sakamoto et al., 1995

4. Determination of important atypical antipsychotic drugs

Several techniques/methods include traditional to very advanced techniques using sophisticated instrumentation were used for the determination of drugs in bulk and pharmaceutical dosage forms, urine, tissues and plasma. Impurities were also determined to evaluate the toxicity profiles of the impurities to distinguish from that of the active pharmaceutical ingredients (API). This review presents the analytical methods used in qualitative and quantitative analysis of atypical drugs, their metabolites and biological samples in pharmaceutical laboratories and industries such as chromatographic and spectroscopic and other methods includes voltammetry, electrophoresis, flow injection and sequential injection analysis and hyphenated techniques.

4.1. Spectrophotometry

In recent years, this technqiue has increased rapid application for the analysis of pharmaceutical dosage forms due to low time and labor consumption with excellent precision. It provides quantitative measurement based on natural UV absorption and chemical reactions known as spectrophotometry.

4.1.1. Clozapine

It was determined in the presence of its degradation product by UV-Visible spectrophotometry (Hasan et al., 2002). It was also determining by formation of colored complex with eriochrome black T (EBT) and potassium bromate in human urine, serum and pharmaceutical formulations (El-Didamony, 2015a; Mohamed, 2004). Extraction based spectrophotometric method was also developed for clozapine in tablets and biological fluids. An ion pair complex formed after reaction with clozapine and bromothymol blue, bromophenol blue and methyl orange measured at 406, 408 nm and 428 nm, respectively (El-Didamony, 2015b; El-Didamony et al., 2014).

4.1.2. Olanzapine

An ion pair complex formed after reaction with olanzapine and methyl orange measured at 428 nm (El-Didamony et al., 2014). The oxidation of olanzapine with Ce(IV), Iodate, chloramine–T and *p*- dimethylaminobenzaldehyde (Basavaiah, 2009a; Basavaiah, 2009b; Upadhyay, 2013; Adegoke et al., 2014) were studied. The idea of derivatization with drugs and reagents were established in the early 1950s which find a very useful technique for drug analysis. The

olanzapine was used to form derivatives with 1, 2- naphhaquinone-4-sulphonate (Elbashir et al., 2012), iodate (Basavaiah, 2009c; Revanasiddappa, 2008; Rajendraprasad et al., 2009a), potassium permanganate (Rajendraprasad et al., 2009b) and sulphonaphthalein acid dyes (Basavaiah et al., 2011). The secondary amine of the diazepine ring of the olanzapine molecule undergoes a condensation reaction with p-dimethylaminobenzaldehyde, the carbinolamine form a stable C=C double bond of enamine. However, no stable condensation product was obtained with primary amines. The vierordt's method was employed to develop an analytical procedure using ICH guidelines which confirm that there is no interference of excipients with the main ingredients although the analysis was done without separating all the excipients. Olanzapine and its commercial tablets were kinetically studied by utilizing the increase in abosorbance with potassium iodate (Mohamed et al., 2008), N- bromosuccinimide (Krebs et al., 2006) and N-bromosuccinimide with two dyes (Basavaiah et al., 2010). The first and second order UV derivative techniques utilized for estimation of olanzapine and the results in terms of average and relative standard deviations were accurate and reproducible (Vivek et al., 2010). The ultraviolet (UV) spectrophotometry was developed to quantify the olanzapine in pharmaceutical formulations in methanolic medium (Firdous et al., 2005) which absorbs maximally at 226 nm. The results suggested that there is no interference of excipients present in the dosage forms. In another method, the olanzapine and fluoxetine was silmultaneously determined by UV spectrophotometry at 258 nm (Kumar et al., 2011). A coloured complex was developed with potassium hexacyanoferrate (III) in acidic medium, potassium cerium (IV) sulphate or potassium hexacyanoferrate (III) and studied at 425 and 540 nm using batch and flow injection spectrophotomteric approach and successfully appllied for the quantification of olanzapine in pharmaceutical formulations (Jasinska et al., 2004). In recent years, charge transfer complesex and couping products were produced with olanzapine and successfully applied in analysis of pharmaceutical formulations (Sahar, 2016; Olajire et al., 2016).

4.1.3. Aripiprazole

The aripiprazole was determined by developing a simple ultraviolet spectrophotometric method in pharmaceutical formulations. The absorbances were measured at 256 and 219 nm using ethanol and methanol as a blank, respectively and quantified in the range of 5–30 and 2–10 mg/l, respectively with good accuracy and precision (Dey, 2011; Kalaichelvi et al., 2009). The analysis

of aripiprazole tablets was performed by dissolving and dilutiting with a thermaly stable mixture of acetonitrile and 0.05 M phosphoric acid (60:40) and quantified at 218 nm. Finaly the method was validated and evaluated the percentage of aripiprazole present in tablets which shows excellent recovery and no interference observed from the excipients present in the tablets (Nagamallika et al., 2011). Multivariate calibration technique was also utilized to study and determine the aripiprazole in dosage forms (Sandeep et al., 2013). An economical method was proposed for the analsysi of aripiprazole in pharmaceutical formulations, prepared in acidic mediun which was mixed with buffer and bromocresol green to form yellowish orange ionic complex absorbs maximally at 414 nm (Jain et al., 2011). Another spectrophotometric analysis of aripiprazole was performed by taking the bulk powder and dissolved with sodium hydroxide and refluxed in methanolic hydrochloric acid for one hour. After refluxing, the remaining part was diluted to prepare standard solution followed by addition of 3-methyl-2-benzothiazolinone-hydrazone and Fe (III) (Subbayamma et al., 2008) which formed a colored complxes after 5 minutes and quantified at 480 nm. Other coloured products of aripiprazole were also formed by charge transfer complexation reaction with iodine, 2, 3-dichloro-5, 6-dicyano-p-benzoquinone, chloranilic acid More ion pair complexes were produced by reaction with acidic dyes and successfully developed a visible spectrophotometric method for pharmaceutical formulations (Helmy, 2012; Sri Ramya et al., 2015).

4.1.4. Quetiapine

Spectrophotometry has been utilized quantitatively by measuring the 2D-values at 254.76nm where 0.1N HCl was used as background solvent (Bagade et al., 2009). Methanol: water (50:50) was used for simple UV determination of quetiapine (Valarmathi et al., 2013). In another attempt to quantify quetiapine, ion pair complexation reaction was used where target drug was analyses using dye tropaeolin ooo (Vinay et al., 2012).

Table 2. Use of spectrophotometric methods in the analysis of Clozapine, Olanzapine, Aripiprazole and Quetiapine.

Name of drug	Method/ Reagents used	λ_{max} (nm)	Linear range (µg/ml)	LOD (µg/ml)	Applications	References
Clozapine	UV	315 305 295 325	3-10 3-10 4-10 10-25	1.21 1.35 1.59 3.85	Bulk powder and pharmaceutical formulations	Hasan et al., 2002
	Eriochrome black T	514	2–18	0.530	Tablets and biological fluids	El-Didamony et al., 2015a
	$KBrO_3$	308	0-12	0.1	Dosage forms	Mohamed et al., 2004
	Bromophenol blue Bromothymol blue	408 406	1–11 1–7	0.123 0.081	Tablets and biological fluids	El-Didamony et al., 2015b
	Methyl Orange	428	2-14	0.0734	Dosage forms and biological fluids	El-Didamony et al., 2014
Olanzapine	Methyl Orange	428	2-14	0.0765	Dosage forms and biological fluids	El-Didamony et al., 2014
	Ce(IV) + N-phenyl-anthranilic acid or sulphanilic acid	440 545	0.3-1.8 5.0-75.0	0.03 0.61	Tablets	Basavaiah et al., 2009a
	Bromocresol purple Bromothymol blue	405 410	1-10 1-8	0.15 0.32	Pharmaceutical formulations	Basavaiah et al., 2009b
	KIO_3 + leuco crystal violet	598	0.05-2	0.038	Pharmaceuticals	Upadhyay et al., 2013
	chloramine-T + rhodamine B	550	0.1-1.6	0.064	Pharmaceuticals	Upadhyay et al., 2013
	p-dimethylaminobenzald	410	5-160	6	Pharmaceuticals	Adegoke et al., 2014

	ehyde					
	1,2-naphthoquinone -4-sulphonate	454	0.4-4	0.09	Dosage forms	Ali et al., 2012
	Iodine + Nile blue	400	15-120	3.93	bulk drug and tablet	Basavaiah et al., 2009c
	ICl and thymol blue Ce(IV) + leuco crystal violet	536 580	0.2-1.6 0.1-1.4	0.0218 0.0149	Pure and dosage forms.	Revanasiddappa et al., 2008
	Ce (IV)+ iron(II)+ thiocyanate, tiron or ferrocyanide	480 640 or 700	0.2-2.0 1.0-9.0 0.3-3.0	0.02, 0.11 0.03	bulk drug and in tablets	Rajendraprasad et al., 2009a
	$KMnO_4$ in either acid or alkaline medium	550 610	2.0- 20 1.0- 10	0.37 0.16	Tablets	Rajendraprasad et al., 2009b
	N-bromosuccinimide (NBS) with quinoline yellow and metanil yellow	410 530	0.1-1.2 0.1-1.5	0.07 0.05	Tablets	Basavaiah et al., 2011
	*KIO_3 *Kinetis (initial rate and maximum absorbance methods)	537	4-7	0.1 and 0.15	Dosage forms and spiked serum	Mohamed et al., 2008
	N-Bromosuccinimide Cerium(IV)sulfate Clestine Blue	532 538 538	10 – 120 0.5 – 6.0 0.6 – 3.0	6.99 0.3 0.37	Pure and pharmaceutical formulations	Krebs et al., 2006
	N-bromosuccinimide with amaranth and janus green B	520 620	0.1-0.9 0.1-1.2	0.05 0.09	Dosage forms	Basavaiah et al., 2010
	UV	222 230	2–12 2–12	500 ng/ml 499 ng/ml	Bulk and Pharmaceutical dosage form	Vivek et al., 2010
	UV	226	0.1-50	0.1	Pure and dosage forms	Firdous et al., 2005

	UV	258	1-100	1-10	Bulk Drug and formulations	Kumar et al., 2011
	Potassium hexacyanoferrate (III)	425	2.5-40	2.17	Pharmaceutical formulations	Jasinska et al., 2004
	Diazotized p-Nitroaniline	405	0.5-45	0.3148	Tablets	Sahar et al., 2016
	p-chloranilic acid	520	2–40	1.57	Tablets	Olajire et al., 2016
Aripiprazole	UV	256	5-30	-----	Soild dosage forms	Dey et al., 2011
	UV	219	2-10	-----	Pharmaceutical preparations	Kalaichelvi et al., 2009
	UV	218	2.5-20	0.01	Pure form and Tablets	Nagamallika et al., 2011
	UV	255	5-30	0.3	pharmaceutical formulations	Sandeep et al., 2013
	Bromocresol green	414	10-60	-----	Tablets	Jain et al., 2011
	3-methyl-2-benzothiazolinone-hydrazone (MBTH) + Fe (III)	480	2-12	0.5835	Pharmaceutical formulations	Subbayamma et al., 2008
	2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) Iodine (I_2) Bromocresol green Bromocresol purple	457 364 413 400	10-120 2-28 2-24 2-20	2.44 0.39 0.50 0.30	Tablets	Helmy et al., 2012
	p–chloranillic acid	543	80-400	5.17	Bulk and pharmaceutical formulations	Ramya et al., 2015
	Methyl Orange	428	2-14	0.0716	Dosage forms and biological fluids.	El-Didamony et al., 2014

Quetiapne	Derivative UV	254.76	10-30	------	Tablet	Bagade et al., 2009
	UV	290	15.99-24.09	------	Bulk and tablets	Valarmathi et al., 2013
	Tropaeolin ooo	480	2-20	0.43	bulk drug, tablets and human urine	Vinay et al., 2012

4.2. Fluorimetry

Fluorimetry is the luminescent phenomenon that involved with electromagnetic radiation and measures the enhanced fluorescent signal. The clozapine was oxidized by strong oxidant such as Ce (IV) in acidic medium and determined fluorrmetrically (Darwish et al., 2005). 4-chloro-7-nitrobenzofurazane (NBD-Cl) in Mcllvaine buffer was used for fluorimetric determination of quetiapine. Authors reported that nuclear substitution reaction resulted in the formation of the fluorescent product (Mostafa et al., 2018) oxidation reaction using Cerium (IV) was exploited for quantitative analysis of quetiapine along with flupentixol dihydrochloride spectrofluorimetrically (El-Enany et al., 2009).

4.3. Chromatographic methods

Chromatography and their related techniques stimulated the development of new methods in pharmaceutical laboratories and provide more accurate procedure for the analysis of various drugs in bulk and dosage forms. These chromatographic techniques also enable studies to assess the stability of drugs, test for impurities and degradation products as well as in pharmacokinetic studies. Atpical drugs and their metabolites were determined using HPLC/HPTLC/UPLC/TLC in bulk, pharmaceutical dosage forms.

4.3.1. HPLC

HPLC provides information about the main ingredient and its metabolites in biological fluids during metabolism and clinical studies. It is mainly applied for raw materials, finished products, dosage forms and quality control samples. During organic synthesis and degradation monitoring, several impurities were obtained which can also be identified by HPLC.

The clozapine was extracted (liquid –liquid extraction) from biological matrix using methyl terbutyl ether and determined by HPLC (Rosland et al., 2007). Two major metabolites norclozapine, clozapine N- oxides were identified and quantified by HPLC in humans and dog plasma (Liu, 2001; Mosier et al., 2003). The clozapine was quantified in the presence of degraded product and pharmaceutical preparation. The clozapine and degraded peak were eluted isocratically at 30.9 and 14.4 min (Rohnert et al., 2003). HPLC with UV detector were used to quantify clozapine and its metabolites in tablets and human plasma (Mercolini, 2007; Shen,

2002; Kaewvichit, 2010; Dural, 2015; Kaur, 2013; Tyagi, 2012; Patil, 2009; Laura et al., 2007). Olanzapine and its major metabolites were quantified using HPLC with ultraviolet and diode array detector in bulk, tablets, rat brain, human breast milk and plasma (Basavaiah, 2014; Concetta, 2006; Saracino, 2007; Saracino, 2006; Raggi, 2001a; Kasper, 1999; Reddy, 2007; Shah, 2007; Pathak, 2009, Mahmoud et al., 2013). Aripiprazole was estimated using RP-HPLC bulk and in pharmaceutical dosage froms (Nandini, 2010; Soponar, 2014; Filijovic, 2014; Shimokawa, 2005; Vijaya, 2005; Koduri, 2008; Lancelin, 2008; Akamine, 2010; Bhanotu, 2012; Sastry, 2009; Mondal, 2013; Kalaichelvi, 2010; Dedania, 2011; Pai, 2012; Ravindra, 2014; Kumari, 2016; Prashanthi, 2016; El-Maraghy, 2017; Nagasarapu et al., 2017).

HPLC has always been a good choice for the pharmaceutical scientists, majority of the literature dealing in the quetiapine determination involve the chromatographic analysis. Quetiapine was analysed in human plasma, where pH 1.9-phosphate buffer was used as a mobile phase along with methanol and acetonitrile as organic modifiers and solid phase extraction process was used for the sample preparation. The detection limit was found to be 4 ng/ml (Mandrioli et al., 2002). Acetonitrile and phosphate buffer was further used determination of quetiapine in presence of two of its degradation products, quetiapine N-oxide and quetiapine lactam (Belal et al., 2008). Quetiapine along with other psychotropic drugs was determined using DAD and MS detector (Petruczynik et al., 2015). These drugs were analyzed on XSELECT CSH phenyl-hexyl column with methanol acetate buffer and diethylamine. Magnetic ODS-PAN thin film was prepared by Li and his co-worker for the microextraction of quetiapine and clozapine, which were further detected in plasma and urine samples (Li et al., 2016), linear range of 0.070–9.000 μg/ml were reported for both the drugs in plasma and 0.012–9.000 μg/ml for urine. The results further show that LOD for quetiapine using the method was found to be 0.013 μg/ml in plasma and 0.003 μg/ml in urine.

4.3.2. High performance thin layer chromatography (HPTLC)/UPLC

It offers a wide range of separation and short analysis time with outstanding clarity of visual evaluation of sample and its components. The sample preparation is simple because it consists of single stationary phase and the multiple evaluations are possible by stroring fraction of all samples in the plate. The technique is very fast and reproducible. Identification of compounds by HPTLC is highly demanding because of independent sample application, chromatogram development, easy detection and identification compare to thin layer chromatography (TLC). It

can be used for the qualitative and quantitative analysis, however, it is not suitable for lipid sample analyses.

HPTLC were used to study the stability of clozapine in pharmaceutical formulations in the presence of acids, bases and hydrogen peroxide under the influence of heat and light. The degraded products were well separated and validated according to the guidelines (Zaheer et al., 2009). Olanzapine, aripiprazole and quetiapine were also studied in bulk, tablets, human plasma, rat brain, plasma and raw materials using TLC, HPTLC (Younes, 2014; Shah, 2007; Dhaneshwar et al; 2009) and UPLC (Punugoti, 2013; Khandelwal, 2015; Thakkar et al., 2011) in phamceutical formulations. The complete details about the pahses used and detectors were summarized in Table **3** for the analysis of four slected atypical antipsychotic drugs.

4.3.3. Hyphenated techniques

Hyphenated techniques actually refer to the online combination/ coupling of the different analytical techniques that is mainly consist of chromatographic with spectroscopic detetction techniques. The hypehnation provides a remarkable improvement that significantly broadened their applications in the analysis of various types of drugs in bulk and dosage forms. With the advancement of the instrumentation hyphenated technique finds a great application in the analysis of pharmettaceuticals. Various hyphenated techniques such as HPLC-MS, UPLC-MS-MS, GC-MS and LC-MS were used to determine many important atypical antipsychotic drugs and their active metabolites in pharmaceutical dosage forms, urine, serum and plasma.

4.3.3.1. HPLC- Electrospray ionization mass spectrometry (HPLC- MS/ESI)

Electrospray ionization mass spectrometry (ESI-MS) is an accurate and reliable tool for studying nonvolatile and thermally liable analytes. HPLC coupled with MS/ESI is a dynamic technique for the analysis of small and large molecules with different polarities. Plasma sample of schizophrenia patient was collected and investigated by HPLC-MS/ESI (Aravagiri et al., 2001). The compounds were extracted from plasma and eluted isocratically with electrospray

mass spectrophotometer. The results of ion transitions confirmed the presence of clozapine and its metabolites (Zhou et al., 2004).

The clozapine alongwith five other antipsychotics were quantified by employing liquid chromatography combined with tandem mass spectrometry and electrospray ionization in rat plasma (Zhang et al., 2007). The method required liquid-liquid extraction and midazolam was used as an internal standard. The extraction was followed by separation on Waters Atlantis column with gradient elution and detected on multiple reactions monitor.

Olanzapine and its active metabolite were also determined using LC-MS in human urine, serum and cerebrospinal fluids (Urdigere, 2012; Josefsson et al., 2010). Aripiprazole was determined in the presence of other forty-seven antidepressants in human serum using methanol and 5 mM acetate buffer of pH 3.9 as a mobile phase with monolithic column C_{18} (50×4.6 mm) combined with multiple reactions monitoring detector ESI-MS/MS (Kirchherr et al., 2006). The investigation was continued for aripiprazole in serum and plasma because the technique needs small volume of sample for the determination (Wang, 2013; Caloro, 2012; Ravinder et al., 2012).

4.3.3.2. Liquid Chromatogrpahy mass spectrometry (LC-MS/MS)

A LC-MS/MS was developed for plasma sample based on solid phase extraction with electrospray ionization detector in which quetiapine used as an internal standard (Patel et al., 2012). The triple quadrupole tandem mass spectrophotometer combined with electrosparay ionization detector worked as ionization source and mobile phase (ammonium acetate buffer, methanol) found suitable for the separation of olanzapine in plasma (Bonde et al., 2014). The method used olanzapine–d3 as internal standard and pharmacokinetic studies was discussed for the healthy patients.

The dehydroaripiprazole can be determined in basic medium with gradient mode in human plasma using solid phase extraction followed by MS combined with LC (Choong et al., 2009). Papaverine was used as internal standard for quantification of metabolite in human plasma (Song et al., 2009). Sodium hydrogen carbonate was added in plasma sample to make slightly basic and metabolite extracted in the presence of internal standard OPC-14714. The reverse phase C_{18} column with flow rate 0.2 ml/min and less than 7.5 minutes needed for the analysis (Masanori et al., 2005). Barette et al. used HPLC-MS/MS technique for quetiapine determination in human

plasma. Solid phase extraction process was used for sample extraction while the extracted sample was found to be linear over the concentration range of 1.0–382.2 ng/ml subjected to analyses by HPLC-MS/MS (Barrett et al., 2007). In another attempt LC-MS/MS was used for photogradation study of quetiapine. The study observed five degradation products whose formulae and masses were stablished (Skibinski et al., 2012).

4.3.3.3. Ultra-pressure liquid chromatography-tandem mass spectrometry (UPLC-MS-MS)

Presently, the ultra-pressure liquid chromatography–tandem mass spectrometry technique has high demand in pharmaceutical and food industries. The polar contaminants from biological, environmental samples can be investigated and quantified. The technique needed efficient extraction and cleanup procedure of the sample before analysis of sample. It has shorter run time compare to other techniques.

Clozapine and its major metabolites were identified in human serum using UPLC-MS-MS with triple quadrupole detection system (Ming et al., 2009). The metabolites determined by SPE-LC-MS in serum (Niederlander et al., 2006), were more favourable because it concern about sample handling and throughput in therapeutic drug monitoring. The sensitive liquid chromatography–tandem mass spectrophotometry was used to quantify clozapine, norclozapine in serum, plasma, brain tissues of rat, human and discussed their pharmacokinetic studies (Demacker, 2009; Rao, 2009; Hass, 2012; Zhang et al., 2007). All metabolites of clozapine can be determined in serum and urine by extraction with ethyl acetate in alkaline medium followed by LC-MS/MS (Wohlfarth et al, 2011).

It was reported that main drug transporters, p-glycoprotein control the drugs to the central nervous system. However, there is no clear justification that the aripiprazole penetrates through blood brain barrier or it interacts with its metabolites on drug transporters. Fast and high speed UPLC-MS/MS technique was developed to give answers of the questions. The analysis was carried out with acquity UPLC BEH C_{18} (100×2.1 mm, 1.7 µm). 30 mM ammonium acetate and acetonitrile with ratio 38:62 (v/v) used as mobile phase and required 3 minutes for the separation (Li et al., 2007). The ESI mode was helpful for determination of aripiprazole and it metabolites in biological fluids. Sensitive and validated method applied in human plasma to determine aripiprazole. The main advantages of the technique involved are solid phase extraction,

aripiprazole d_8 as internal standard, multiple reactions monitoring in the positive ionization mode and isocratic elution (Patel et al., 2013).

4.3.3.4. Gas Chromatography (GC) and Gas Chromatography-Mass spectrometry (GC-MS)

The gas chromatography is a powerful technique for separation and identification of volatile compounds. High molecular and thermally unstable samples can be determined. Clozapine was determined usind capillary GC (Richter et al., 1988). The gas chromatography coupled with mass spectrophotometry combined with micro extraction is well known advanced technique to determine the concentration of clozapine and its metabolites in human plasma (Vardaku, 2010; Da Fonseca et al., 2013). GC-MS method was studied with plasma samples collected from seven schizo affective disorder patients receiving 10-20 mg aripiprazole per day. This technique introduced solid phase extraction with N-methyl-N-trimethylsilylfluoro acetamide for aripiprazole and dehydroaripiprazole in blood samples (Liang et al., 2012).

4.4.Other techniques involved in atypical drug analysis

4.4.1. Capillary Zone Electrophoresis

Capillary zone electrophoresis (CZE) is a powerful separation technique for small and large molecules. However, the disadvantage of this method is that it required extraction step for the analysis. It was used for the determination of clozapine utilizing end column amperometric detection with carbon fiber array micro disk electrode (Jin et al., 2000). The CZE method is combining with factorial design that can be helpful for the separation of atypical antipsychotics. It was useful to determine the effect of concentration and pH during separation of four atypical drugs (Hillaert et al., 2004). The studies revealed that the pH 3.5 (80 mM sodium phosphate buffer) is the best for the separation. This method is well established and employed to quantify the clozapine in serum and plasma (Zhou and lee, 2000). This technique was applied for the determination of clozapine in human plasma using fused silica capillary combined with background electrolyte at low pH and separate analyte as well as metabolite within three minutes (Raggi et al., 2001b).

The CZE analysis of olanzapine was carried out using phosphate buffer and uncoated fused silica capillary in pharmaceutical tablets. The studies revealed, high pH of background electrolyte would cause the loss of analyte as well as distortion in the peak shape. Hence, the analysis was performed at pH 3 to reduce the electroosmotic flow and increase the separation efficiency in pharmaceutical formulations (Raggi et al., 2000). The CZE is performed to separate and quantify olanzapine simultaneously with other antipsychotic drugs chlorpromazine hydrochloride, fluphenazine hydrochloride, perphenazine, pipotiazine (Qin et al., 2001). The separation was carried out with fused silica capillary column and measured at 254 nm with applied voltage of 18 kV. The reproducibility of the method was efficient for the determination of olanzapine. The analysis of aripiprazole was also carried out in human plasma using fused silica tube and capillary. It was able to detect aripiprazole in human plasma. 50 mM phosphate buffer of pH 2.5 worked as a background electrolyte with +20 kV and loxapine was used as internal standard. The sample was initially pretreated on cyano cartridge for solid phase extraction (Musenga et al., 2008).

4.4.2. Voltammetry

The clozapine was determined by utilizing glassy carbon electrode and thin film carbon nanotubes by doping with polypyrrole and sodium dodecyl sulphate (SDS) (Shahrokhian, 2013; Manjunatha et al., 2011). The investigation was continued with TiO_2 nanoparticles modified carbon paste electrode (Mashhadizadeh et al., 2013). The adsorption and electrochemical properties of clozapine were studied in pharmaceutical preparations (Farhadi et al., 2007). This method can be applied for quantification of the drug in spiked urine samples. The carbon ionic electrode with SDS used for blood serum and plasma samples (Arvand et al., 2012). The adsorptive cyclic voltammetry with mercury electrode combined with supportive electrolyte is helpful to determine the clozapine in pharmaceutical products (Hammam et al., 2004). The drug is reducing in the mercury electrode followed by reduction of azomethine group in the heterocyclic ring. This method can be utilized to determine clozapine in human serum. The main advantages of this technique are that it does not require any pretreatment process and short analysis time.

Voltammetric technique has been successfully used for determination of two antipsychotic quetiapine and olanzapine. The behavior of these drugs was monitored on a glassy carbon electrode, where the oxidation peak was obtained using Britton-Robinson (BR) buffer (pH 2.0). This voltametric procedure was reported to be fast and the analyses time was less than 5 minutes (Manal et al., 2013). Ławrywianiec and co-worker voltammetrically quantified Quetiapine on a carbon black nanoparticle modified glassy carbon electrode. This method was able to detect quetiapine in a concentration as low as 7×10^{-9} mol L^{-1} with a recovery of 99 % - 107 %. (Lawrywianiec et al., 2018).

5. Conclusion

Antipsychotic medications are one of the fastest growing products in the pharmaceutical industry and atypical antipsychotic drugs are currently among the most frequently prescribed drugs all over the world for psychotic disorder. Over the past several decades, the number of psychiatric patients has gradually declined.

Three structurally related atypical antipsychotics, clozapine, olanzapine and aripiprazole are used in the treatment of schizophrenia and other psychotic syndromes. It was reported that they are effective in the treatment of both positive and negative symptoms of schizophrenia and are less likely to produce extra pyramidal side effects when compared with classical antipsychotics. The advantages of the therapeutic profile of these three drugs have lead to increasing use of them in treatment of schizophrenic patients.

However, high dose of these atypical antipsychotics are suspected to pose an increased risk factor. From the above studies we could know the therir metabolic pathways and their product during metabolism and the various analytical techniques developed for atypical drugs and commonly used in the acute and long term treatment of schizophrenia as well as in all stages, i.e. in first episode and chronic patients. Antipsychotic drug analysis is not only important in psychiatry, but also in sports. According to predictions, consumption of atypical drugs will be increasing, especially in high income countries. Moreover, treatment of mental diseases usually demands chronic, often combined therapy. High consumption of psychiatric pharmaceuticals leads also to their accumulation in the environment. Many analytical methods were used for determination of atypical drugs, however chromatographic, spectroscopic and spectrometric methods were the most often applied. This review summarizes analytical applications of potentiometry, high performance liquid chromatography, liquid chromatography, gas chromatography, ultra performance liquid chromatography, mass spectrometry, capillary electrophoresis, voltammetry, spectrophotometry, hyphenated techniques such as LC-MS, LC-MS/MS and GC/MS of selected antipsychotics such as clozapine, olanzapine, aripiprazole, quetiapine and its metabolites. The application of these methods for determination of these drugs in biological, environmental and pharmaceutical samples has also been discussed.

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