

Research Article

Comparative Cytochrome P450 *In Vitro* Inhibition by Atypical Antipsychotic Drugs

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The goal of this study was to assess in human liver microsomes the inhibitory capacity of commonly used antipsychotics on the most prominent CYP450 drug metabolizing enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A). Chlorpromazine was the only antipsychotic that inhibited CYP1A2 activity ($IC_{50} = 9.5 \mu M$), whilst levomepromazine, chlorpromazine, and thioridazine significantly decreased CYP2D6-mediated formation of 1'-hydroxybufuralol (IC_{50} range, 3.5–25.5 μM). Olanzapine inhibited CYP3A-catalyzed production of 1', and 4'-hydroxymidazolam ($IC_{50} = 14.65$ and 42.20 μM , resp.). In contrast, risperidone ($IC_{50} = 20.7 \mu M$) and levomepromazine ($IC_{50} = 30 \mu M$) showed selectivity towards the inhibition of midazolam 1'-hydroxylation reaction, and haloperidol did so towards 4'-hydroxylation (IC_{50} of 2.76 μM). Thioridazine displayed a K_i of 1.75 μM and an inhibitory potency of 1.57 on CYP2D6, suggesting a potential to induce *in vivo* interactions. However, with this exception, and given the observed K_i values, the potential of the assayed antipsychotics to produce clinically significant inhibitions of CYP450 isoforms *in vivo* seems limited.

1. Introduction

In contrast to conventional neuroleptics, atypical antipsychotics have been shown to be effective against both positive and negative symptoms of schizophrenia while showing a reduced propensity to induce extrapyramidal effects [1]. The cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A enzymes are responsible for the metabolism of many of these and other psychoactive compounds [2–8]. Traditionally, studies on pharmacological interactions involving antipsychotics have examined the inhibition of these isoforms by drugs that are concomitantly administered, especially serotonin reuptake inhibitors [9–13]. However, there is still limited information on the capacity of antipsychotics to inhibit the metabolism of other coadministered drugs and the potentially clinically significant interactions that could arise [14].

In this paper we have assessed the potential for nine of the most commonly used atypical antipsychotics (clozapine, olanzapine, iloperidone, quetiapine, haloperidol, chlorpromazine, levomepromazine, thioridazine, and

risperidone) and abaperidone (7-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one; FI-8602), an underdevelopment compound with a potentially atypical antipsychotic profile [15, 16], to cause significant drug-drug interactions by using *in vitro* inhibition techniques in human liver microsomes.

2. Methods

2.1. Reference Substances. Abaperidone and iloperidone were gifts from Centro de Investigación Farmacéutica, Grupo Ferrer (Barcelona, Spain). Chlorpromazine, levomepromazine, thioridazine, haloperidol, risperidone, clozapine, quinidine, sulphaphenazole, ketoconazole, diclofenac, furafylline, phenacetine, and acetaminophen were purchased from Sigma Chemical Co. (Madrid, Spain). Midazolam, 1'-hydroxy-midazolam, and 4-hydroxymidazolam were supplied by Hoffman-La-Roche (Basel, Switzerland). Bufuralol and 1'-hydroxybufuralol were obtained from Ultrafine Chemicals (Manchester, England), 4-hydroxydiclofenac

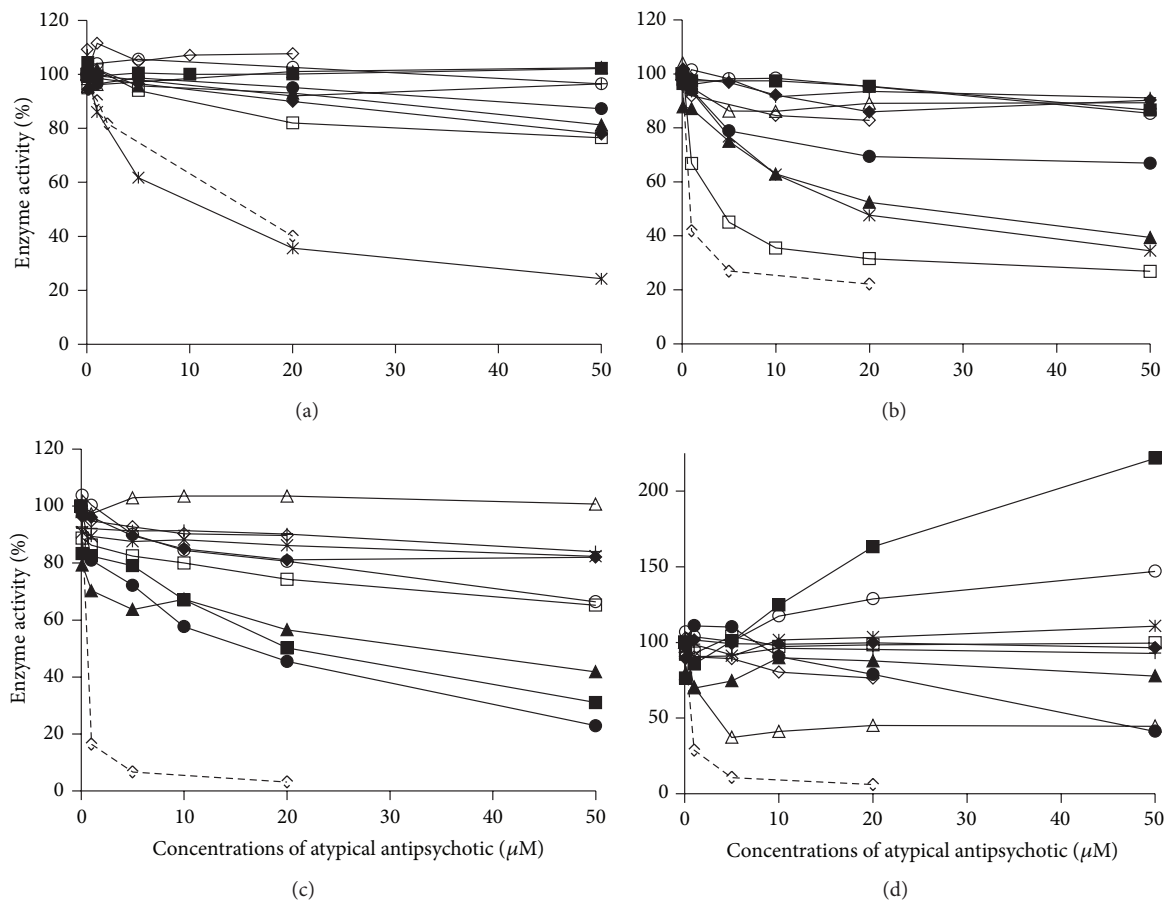


FIGURE 1: Inhibition of CYP1A2-mediated phenacetin O-deethylation (a), CYP2D6-mediated bufuralol 1-hydroxylation (b), and CYP3A-mediated midazolam 1'- (c) and 4'-hydroxylation (d) by atypical antipsychotics. Drugs depicted are clozapine (\blacklozenge), olanzapine (\bullet), iloperidone (+), quetiapine (\circ), haloperidol (\triangle), chlorpromazine (x), levomepromazine (\blacktriangle), thioridazine (\square), risperidone (\blacksquare), and abaperidone (\diamond). Dotted line denotes the corresponding prototypic inhibitor.

from Gentest Corp (Woburn, MA), -quetiapine from Astra Zeneca (Macclesfield, Cheshire, UK), and olanzapine from Lilly Laboratories (Indianapolis, IN).

2.2. Chemicals. Methanol and acetonitrile were of HPLC grade (Merck, Barcelona, Spain). Acetic and formic acids were of analytical grade and supplied by Merck (Barcelona, Spain). Glucose-6-phosphatedehydrogenase, glucose-6-phosphate, and NADPH were purchased from Roche Diagnostics SL (Barcelona, Spain). All other chemicals and reagents used were of the highest commercially available quality. Water was filtered by a Milli Q water system from Millipore Ibérica, S.A. (Madrid, Spain).

2.3. Chromatography. Chromatographic separation was performed with a system consisting of a Hewlett-Packard (HP) 1100 series (Agilent Technologies Spain S.L., Madrid, Spain) that had a degasser (model G1322A), quaternary pump (model G1311A), autosampler (model G1313A), column oven compartment (model G1316A), ultraviolet/visible detector (model G1315A), and fluorescence detector (model G and

a mass spectrometer engine (model G1946A). A computer-assisted HP G2710AA LC/MS ChemStation (Agilent Technologies Spain S.L., Madrid, Spain) was used to operate modules and facilitate data management.

Phenacetin and its metabolite paracetamol were separated on a Hypersil BDS C18, 3 μm particle size, 100 cm \times 3.0 mm reversed-phase column (Agilent Technologies Spain S.L., Madrid, Spain). The composition of the mobile phase was 18% acetonitrile: 82% acetic acid (0.1%) (vol/vol). The flow rate through the column at 30 $^{\circ}\text{C}$ was 0.3 mL/minute and phenacetin and its oxidized metabolite paracetamol were monitored by ultraviolet absorbance at 247 nm.

Bufuralol and its metabolite 1'-hydroxybufuralol were separated on an Ultrasphere ODS, 3 μm particle size, 7.5 cm \times 4.6 mm reversed-phase column (Beckman Instruments, Madrid, Spain). The composition of the mobile phase was 40% acetonitrile: 60% acetic acid (0.1%) (vol/vol). The flow rate through the column at 30 $^{\circ}\text{C}$ was 1 mL/minute. Bufuralol and its oxidized metabolite 1'-hydroxybufuralol were monitored by fluorescence detection (excitation at 252 nm; emission at 302 nm).

TABLE 1: Inhibitory effect of atypical antipsychotics on human liver microsomal CYP450 activity.

Antipsychotic	I_{\max} (%)	$^a K_i$ (μM)	b Therapeutic range (μM)	c Inhibitory potency
CYP1A2				
Chlorpromazine	75.7	4.75	0.1–1	0.1158
CYP2D6				
Levomepromazine	60.6	12.75	0.05–0.2	0.0098
Chlorpromazine	65.5	10.0	0.1–1	0.0550
Thioridazine	73.2	1.75	0.5–5	1.5714
CYP3A (1-hydroxylation)				
Olanzapine	77.1	7.30	0.06–0.25	0.0212
Risperidone	70.0	10.35	0.04–0.15	0.0092
Levomepromazine	58.2	15.0	0.05–0.2	0.0083
CYP3A (4'-hydroxylation)				
Olanzapine	58.8	21.1	0.06–0.25	0.0073
Haloperidol	55.4	1.38	0.01–0.04	0.0181

I_{\max} , maximum inhibition.

$^a K_i$ estimates were obtained as described previously [17].

b Retrieved from Kirchherr and Kühn-Velten [18].

c Intrinsic inhibitory potency ($[\text{inhibitor}]/K_i$), a measure of the potency of an inhibitor [19], was calculated relative to the mean of reported therapeutic concentrations [18].

Diclofenac and its metabolite 4'-hydroxydiclofenac were separated on a Hypersil BDS C18, 3 μm particle size, 100 cm \times 3.0 mm reversed-phase column (Agilent Technologies Spain S.L., Madrid, Spain). The composition of the mobile phase was 50% acetonitrile:50% acetic acid (0.1%) (vol/vol). The flow rate through the column at 30°C was 0.4 mL/minute, and diclofenac and its oxidized metabolite 4'-hydroxydiclofenac were monitored by ultraviolet absorbance at 220 nm. Midazolam, 4-hydroxymidazolam and 1'-hydroxymidazolam were separated on an Ultrasphere ODS, 3 μm particle size, 7.5 cm \times 4.6 mm reversed-phase column (Beckman Instruments, Madrid, Spain). The composition of the mobile phase was 39% acetonitrile:61% formic acid (0.1%) (vol/vol). The flow rate through the column at 30°C was 0.5 mL/minute and midazolam, 4-hydroxymidazolam, and 1'-hydroxymidazolam were monitored by means of an HPLC/electrospray ionization-mass spectrometry (LC/ESI-MS) method with isocratic elution.

The mass spectrometer was run in the positive ion mode. Nitrogen as the drying gas was supplied at a flow of 10 L/minutes and at a temperature of 350°C. The capillary voltage was adjusted to 4100 V. To quantitate midazolam, 4-hydroxymidazolam, and 1'-hydroxymidazolam, the mass spectrometer was operated in the selected ion-monitoring mode (SIM) with a dwell time of 229 msec. The eluant from HPLC was introduced into the source via the electrospray interface, generating the positively charged pseudomolecular ions (MH⁺) at m/z 326 and 342.

2.4. Inhibition Studies. Inhibition studies on four different CYP isoform-specific substrates were carried out in human liver microsomes (Gentest Corporation, Woburn, MA). Assessed reactions were phenacetin O-deethylation for CYP1A2, (+/-)-bufuralol 1'-hydroxylation for CYP2D6, diclofenac 4'-hydroxylation for CYP2C9, and midazolam

1'- and 4'-hydroxylation for CYP3A. The different antipsychotics were dissolved in methanol and serially diluted with 100 mM tris buffer (pH = 7.5) to obtain final concentrations ranging from 0.05 to 50 μM . Abaperidone was an exception and was dissolved in hot water up to a maximum concentration of 20 μM .

The conditions of the incubation reactions as well as the concentration of the substrate reaction probes utilized were established based on previous CYP450 inhibition studies by our group in human liver microsomes [20–24]. In brief, a 0.25 mL reaction mixture consisting of 0.8 mg/mL microsomal protein, a NADPH regenerating system, and the specific reaction substrate at a concentration equivalent to its K_m value (100 μM phenacetin, 50 μM bufuralol, 15 μM diclofenac, or 10 μM midazolam) was incubated in the absence or presence of increasing concentrations of the tested antipsychotics. Reactions were started by adding microsomal protein and the mix was then vortexed and incubated at 37°C for 30 min. The process was stopped by the addition of acetonitrile and incubation on ice during 10 minutes. Samples were then centrifuged at 10,000 g for 3 minutes, and the supernatant was taken for subsequent HPLC analysis. Control inhibition studies were carried out with prototypic inhibitors in increasing concentrations up to 20 μM , namely, furafylline (CYP1A2), quinidine (CYP2D6), sulphaphenazole (CYP2C9), and ketoconazole (CYP3A).

The effect of antipsychotics on the rate of CYP-catalyzed probe substrates was expressed as a percentage of the control activity with no antipsychotic present. The concentration of inhibitor causing 50% reduction of activity relative to the appropriate control value (IC_{50}) was calculated by interpolation of a regression line of the log concentration versus percent inhibition plot over at least three concentrations of inhibitor. K_i estimates were obtained as described previously [17].

3. Results and Discussion

The chromatographic conditions efficiently separated the compounds of interest in all the assays. Calibration curves were linear (coefficients of correlation >0.99) within the range of concentrations established (0.5 to $100\ \mu\text{M}$ for phenacetin and bufuralol assays, 1 – $25\ \mu\text{M}$ for diclofenac, and 0.2 to $20\ \mu\text{M}$ for midazolam). The retention times (given in minutes) for the analyzed substances were as follows: paracetamol: 2.3; phenacetin: 11.2; 1'-hydroxybufuralol: 4.6; bufuralol: 27; 4'-hydroxydiclofenac: 2.5; diclofenac: 5.4; 4'-hydroxymidazolam: 4.9; 1'-hydroxymidazolam: 5.8; midazolam: 8.7.

The incubation of $100\ \mu\text{M}$ phenacetin with multiple antipsychotic concentrations showed that only chlorpromazine was an inhibitor of CYP1A2 activity ($\text{IC}_{50} = 9.5\ \mu\text{M}$; Figure 1(a)). In line with this, a recent study have suggested that pharmacokinetic interactions involving chlorpromazine and CYP1A2 substrates are likely to occur, as chlorpromazine biotransformation exhibits a stricter CYP1A2 preference compared to other phenothiazines [25].

Levomepromazine, chlorpromazine, and thioridazine were significant inhibitors of CYP2D6, showing IC_{50} values of 25.5 , 20 , and $3.5\ \mu\text{M}$, respectively (Figure 1(b)). In this regard, Shin et al. have previously shown that chlorpromazine and thioridazine were able to significantly inhibit CYP2D6 [26], albeit the authors also reported an inhibitory effect of risperidone, clozapine, and haloperidol, which we did not observe under our experimental conditions.

We could not identify any inhibitors of the CYP2C9 activity under our experimental conditions.

The observed CYP3A inhibition rates were different depending on the measured metabolite. Thus, olanzapine ($\text{IC}_{50} = 14.65\ \mu\text{M}$), risperidone ($\text{IC}_{50} = 20.7\ \mu\text{M}$), and levomepromazine ($\text{IC}_{50} = 30\ \mu\text{M}$) inhibited midazolam 1'-hydroxylation (Figure 1(c)). Eap et al. have previously argued against risperidone being an inhibitor of CYP450 [27], but it should be noted that the authors did not assess CYP3A activity. The other CYP3A-mediated reaction, midazolam 4'-hydroxylation, was inhibited by both olanzapine ($\text{IC}_{50} = 42.20\ \mu\text{M}$) and haloperidol ($\text{IC}_{50} = 2.76\ \mu\text{M}$) (Figure 1(d)).

Given the K_i estimates presented in Table 1, the most likely antipsychotic to produce an *in vivo* inhibition of a CYP enzyme would be thioridazine on CYP2D6. Indeed, our group has previously reported that subjects taking thioridazine were more prone to display a CYP2D6 poor metabolizer phenotype [28]. K_i values obtained for the other antipsychotics do not allow for anticipating a significant effect *in vivo* (Table 1). However, there are a number of reports of *in vivo* interactions caused by these agents; for example, risperidone and olanzapine have been shown to modify the pharmacokinetics of aripiprazole, another antipsychotic metabolized by CYP450 isoforms [29]. A possible explanation for this fact would be the existence of drug concentrations in the liver far superior to those in blood [30, 31] or inhibitions due to drug metabolites [32].

Interestingly, abaperidone did not cause a significant inhibition of any of the CYP enzymes assayed. This is a pharmacologically active substance underdevelopment, which

therefore appears to be a remarkably safe agent with regard to CYP-mediated drug interactions, the main mechanism underlying interactions involving atypical antipsychotics [33, 34]. It should be noted, however, that certain antipsychotics may also interact with other drugs via P-glycoprotein inhibition [35], and further studies are warranted to evaluate the effect of this drug on this and other ABC transporters.

In summary, the results show that several commonly used atypical antipsychotics exerted a significant *in vitro* inhibitory capacity of CYP450 enzymes. However, and with the exception of thioridazine, the potential to cause significant *in vivo* interactions appears to be limited.

Conflict of Interests

The authors state that the present work was funded in part by Ferrer International (Barcelona, Spain), which is developing one of the tested compounds, abaperidone (7-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one; FI-8602), as an atypical antipsychotic for the treatment of schizophrenia.

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References

- [1] J. A. Lowe, T. F. Seeger, and F. J. Vinick, "Atypical antipsychotics—recent findings and new perspectives," *Medicinal Research Reviews*, vol. 8, no. 4, pp. 475–497, 1988.
- [2] L. P. Pan, P. Wijnant, C. De Vriendt, M. T. Rosseel, and F. M. Belpaire, "Characterization of the cytochrome P450 isoenzymes involved in the *in vitro* N-dealkylation of haloperidol," *British Journal of Clinical Pharmacology*, vol. 44, no. 6, pp. 557–564, 1997.
- [3] J. A. Carrillo, A. G. Herráiz, S. I. Ramos, G. Gervasini, S. Vizcaíno, and J. Benítez, "Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine," *Journal of Clinical Psychopharmacology*, vol. 23, no. 2, pp. 119–127, 2003.
- [4] L. Bertilsson, J. A. Carrillo, M. L. Dahl et al., "Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test," *British Journal of Clinical Pharmacology*, vol. 38, no. 5, pp. 471–473, 1994.
- [5] J. A. Carrillo, A. G. Herraiz, S. I. Ramos, and J. Benítez, "Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients," *Journal of Clinical Psychopharmacology*, vol. 18, no. 4, pp. 311–316, 1998.
- [6] J. Benítez, M. L. Dahl, E. Spina, and J. A. Carrillo, "Genetic an environmental factors causing variability in psychotropic drug response," in *Interindividual Variability in Human Drug Metabolism*, G. M. Pacifici and O. Pelkonen, Eds., pp. 85–128, Taylor & Francis, London, UK, 2001.

- [7] E. L. Michalets, "Update: clinically significant cytochrome P-450 drug interactions," *Pharmacotherapy*, vol. 18, no. 1, pp. 84–112, 1998.
- [8] J. O. Miners and D. J. Birkett, "Cytochrome P4502C9: an enzyme of major importance in human drug metabolism," *British Journal of Clinical Pharmacology*, vol. 45, no. 6, pp. 525–538, 1998.
- [9] J. Wójcikowski and W. A. Daniel, "Influence of antidepressant drugs on chlorpromazine metabolism in human liver—an *in vitro* study," *Pharmacological Reports*, vol. 62, no. 6, pp. 1062–1069, 2010.
- [10] J. Wójcikowski and W. A. Daniel, "Thioridazine-fluoxetine interaction at the level of the distribution process *in vivo*," *Pharmacological Reports*, vol. 54, no. 6, pp. 647–654, 2002.
- [11] J. A. Carrillo, S. I. Ramos, A. G. Herraiz et al., "Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients," *Journal of Clinical Psychopharmacology*, vol. 19, no. 6, pp. 494–499, 1999.
- [12] O. V. Olesen and K. Linnet, "Fluvoxamine-clozapine drug interaction: inhibition *in vitro* of five cytochrome P450 isoforms involved in clozapine metabolism," *Journal of Clinical Psychopharmacology*, vol. 20, no. 1, pp. 35–42, 2000.
- [13] E. Spina, A. Avenoso, M. G. Scordo et al., "Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction," *Journal of Clinical Psychopharmacology*, vol. 22, no. 4, pp. 419–423, 2002.
- [14] T. Nakagami, N. Yasui-Furukori, M. Saito et al., "Thioridazine inhibits risperidone metabolism: a clinically relevant drug interaction," *Journal of Clinical Psychopharmacology*, vol. 25, no. 1, pp. 89–91, 2005.
- [15] J. Bolós, S. Gubert, L. Anglada et al., "7-[3-(1-piperidinyl)propoxy]chromenones as potential atypical antipsychotics," *Journal of Medicinal Chemistry*, vol. 39, no. 15, pp. 2962–2970, 1996.
- [16] J. Bolós, L. Anglada, S. Gubert et al., "7-[3-(1-piperidinyl)propoxy]chromenones as potential atypical antipsychotics. 2. Pharmacological profile of 7-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)chromen-4-one (abaperidone, FI-8602)," *Journal of Medicinal Chemistry*, vol. 41, no. 27, pp. 5402–5409, 1998.
- [17] R. Z. Cer, U. Mudunuri, R. Stephens, and F. J. Lebeda, "IC50-to-Ki: a web-based tool for converting IC50 to Ki values for inhibitors of enzyme activity and ligand binding," *Nucleic Acids Research*, vol. 37, no. 2, pp. W441–W445, 2009.
- [18] H. Kirchherr and W. N. Kühn-Velten, "Quantitative determination of forty-eight antidepressants and antipsychotics in human serum by HPLC tandem mass spectrometry: a multi-level, single-sample approach," *Journal of Chromatography B*, vol. 843, no. 1, pp. 100–113, 2006.
- [19] A. R. Boobis, "Prediction of inhibitory drug-drug interactions by studies *in vitro*," in *Advances in Drug Metabolism in Man*, G. Pacifici and G. Fracchia, Eds., pp. 513–539, The European Commission, Luxembourg, 1995.
- [20] J. A. Agúndez, L. Gallardo, C. Martínez, G. Gervasini, and J. Benítez, "Modulation of CYP1A2 enzyme activity by indoleamines: inhibition by serotonin and tryptamine," *Pharmacogenetics*, vol. 8, no. 3, pp. 251–258, 1998.
- [21] G. Gervasini, C. Martínez, J. A. G. Agúndez, F. J. García-Gamito, and J. Benítez, "Inhibition of cytochrome P450 2C9 activity *in vitro* by 5-hydroxytryptamine and adrenaline," *Pharmacogenetics*, vol. 11, no. 1, pp. 29–37, 2001.
- [22] G. Gervasini, C. Martínez, J. Benítez, and J. A. Agúndez, "Effect of neurotransmitters on NADPH-cytochrome P450 reductase *in vitro* activity," *Drug Metabolism Letters*, vol. 1, no. 3, pp. 172–175, 2007.
- [23] C. Martínez, J. A. G. Agúndez, G. Gervasini, R. Martín, and J. Benítez, "Tryptamine: a possible endogenous substrate for CYP2D6," *Pharmacogenetics*, vol. 7, no. 2, pp. 85–93, 1997.
- [24] C. Martínez, G. Gervasini, J. A. G. Agúndez et al., "Modulation of midazolam 1-hydroxylation activity *in vitro* by neurotransmitters and precursors," *European Journal of Clinical Pharmacology*, vol. 56, no. 2, pp. 145–151, 2000.
- [25] J. Wójcikowski, J. Boksa, and W. A. Daniel, "Main contribution of the cytochrome P450 isoenzyme 1A2 (CYP1A2) to *N*-demethylation and 5-sulfoxidation of the phenothiazine neuroleptic chlorpromazine in human liver—a comparison with other phenothiazines," *Biochemical Pharmacology*, vol. 80, no. 8, pp. 1252–1259, 2010.
- [26] J. G. Shin, N. Soukhova, and D. A. Flockhart, "Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms *in vitro*: preferential inhibition of CYP2D6," *Drug Metabolism and Disposition*, vol. 27, no. 9, pp. 1078–1084, 1999.
- [27] C. B. Eap, G. Bondolfi, D. Zullino et al., "Pharmacokinetic drug interaction potential of risperidone with cytochrome P450 isozymes as assessed by the dextromethorphan, the caffeine, and the mephenytoin test," *Therapeutic Drug Monitoring*, vol. 23, no. 3, pp. 228–231, 2001.
- [28] E. Spina, C. Martines, A. P. Caputi et al., "Debrisoquine oxidation phenotype during neuroleptic monotherapy," *European Journal of Clinical Pharmacology*, vol. 41, no. 5, pp. 467–470, 1991.
- [29] R. B. Waade, H. Christensen, I. Rudberg, H. Refsum, and M. Hermann, "Influence of comedication on serum concentrations of aripiprazole and dehydroaripiprazole," *Therapeutic Drug Monitoring*, vol. 31, no. 2, pp. 233–238, 2009.
- [30] E. C. Dinovo, R. O. Bost, I. Sunshine, and L. A. Gottschalk, "Distribution of thioridazine and its metabolites in human tissues and fluids obtained postmortem," *Clinical Chemistry*, vol. 24, no. 10, pp. 1828–1830, 1978.
- [31] A. Forsman, M. Larsson, H. Lundborg, and P. Renstrom, "On the distribution and elimination of haloperidol in cholecystectomized patients," *European Journal of Drug Metabolism and Pharmacokinetics*, vol. 6, no. 4, pp. 249–253, 1981.
- [32] J. I. Javaid, "Clinical pharmacokinetics of antipsychotics," *Journal of Clinical Pharmacology*, vol. 34, no. 4, pp. 286–295, 1994.
- [33] C. L. DeVane and J. S. Markowitz, "Antipsychotics," in *Metabolic Drug Interactions*, R. Levy, K. Thummel, W. Trager, P. Hansten, and M. Eichelbaum, Eds., pp. 245–257, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2000.
- [34] K. Thummel, K. Kunze, and D. Shen, "Metabolically-based drug-drug interactions: principles and mechanisms," in *Metabolic Drug Interactions*, R. Levy, K. Thummel, W. Trager, P. Hansten, and M. Eichelbaum, Eds., pp. 3–19, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2000.
- [35] U. Schmitt, K. Krischbaum, B. Poller et al., "In vitro P-glycoprotein efflux inhibition by atypical antipsychotics is *in vivo* nicely reflected by pharmacodynamic but less by pharmacokinetic changes," *Pharmacology Biochemistry and Behavior*, vol. 102, no. 2, pp. 312–320, 2012.