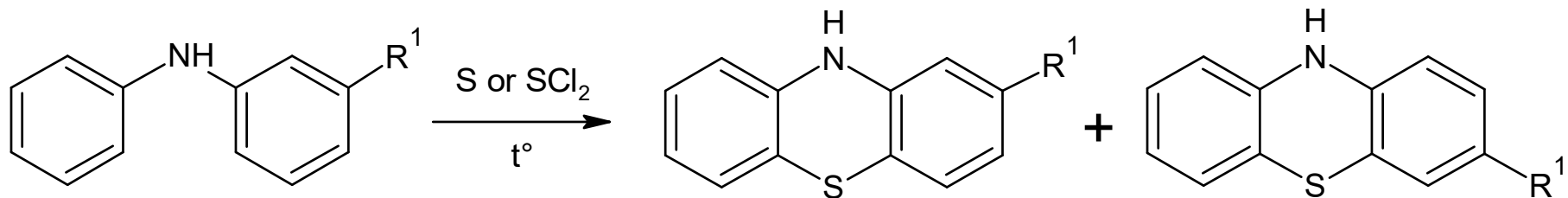


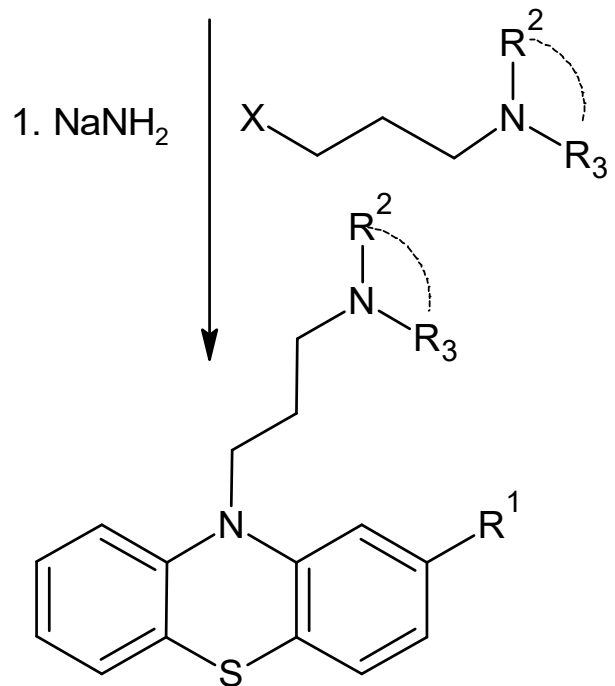
Syntheses and metabolism of selected antipsychotics

General synthesis of phenothiazine neuroleptics

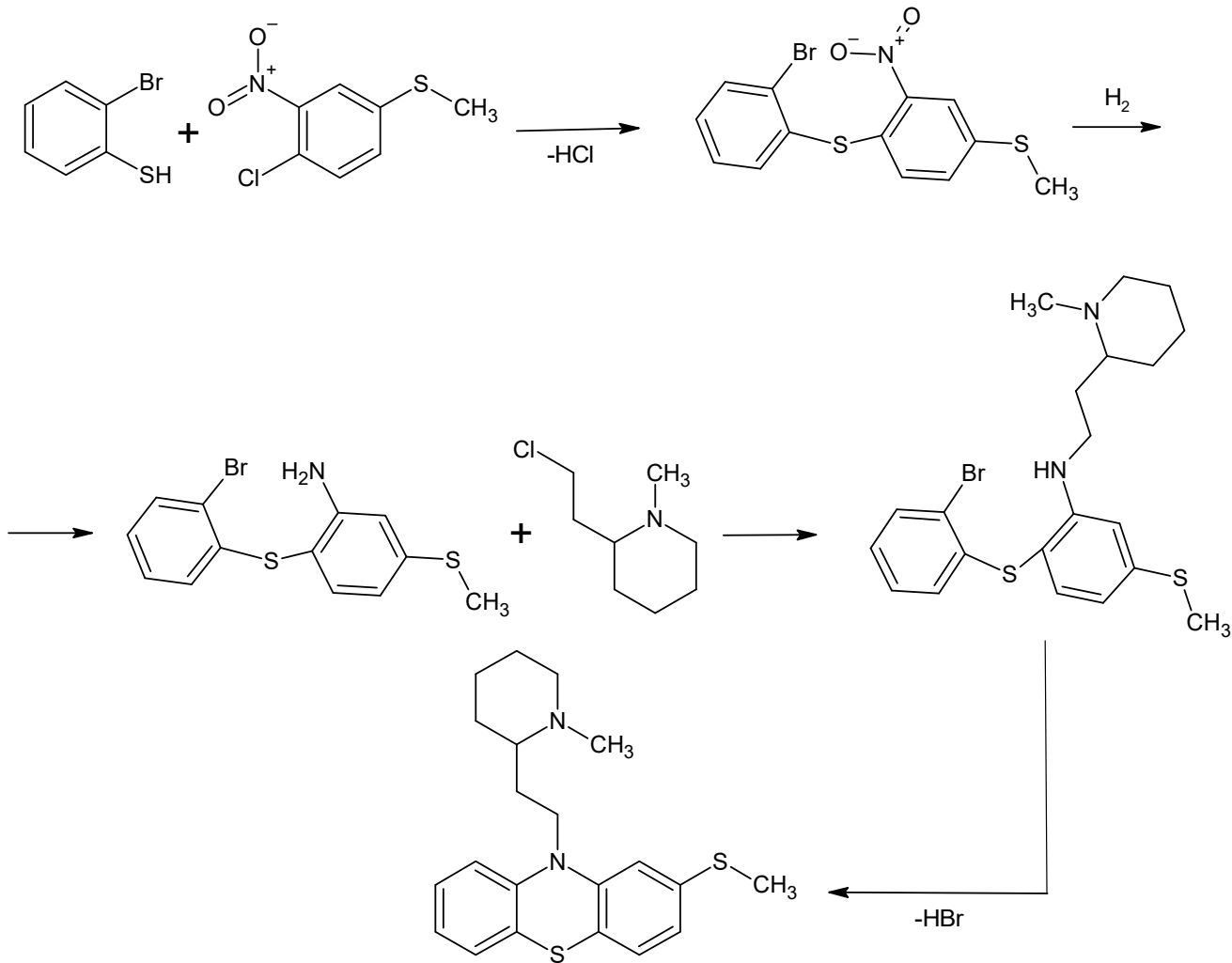


R¹: -Cl, -OCH₃, -CN, -CF₃

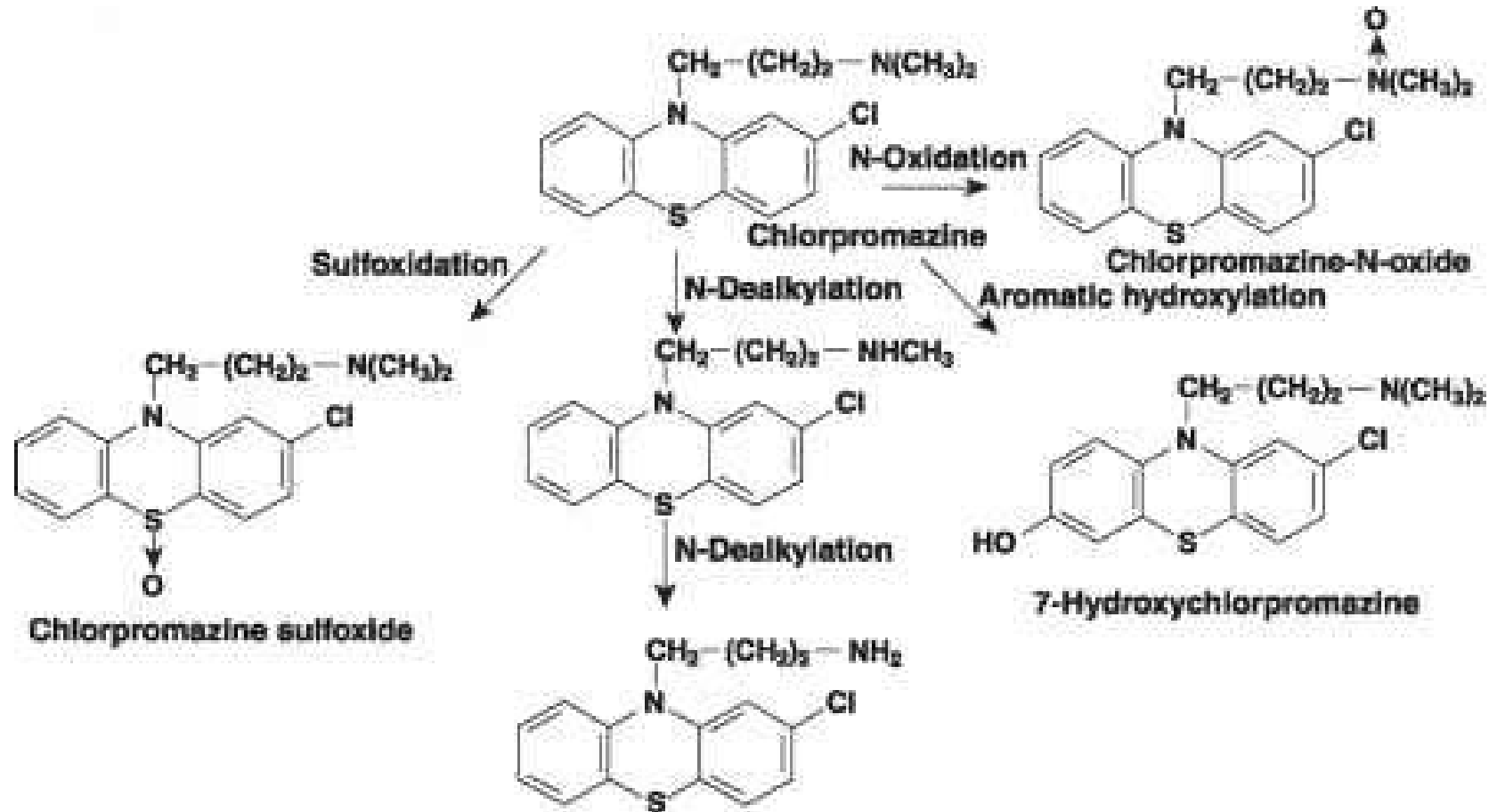
R², R³: -CH₃, or R²+R³=piperidine, piperazine



Other approach to phenothiazine skeleton: synthesis of thioridazine

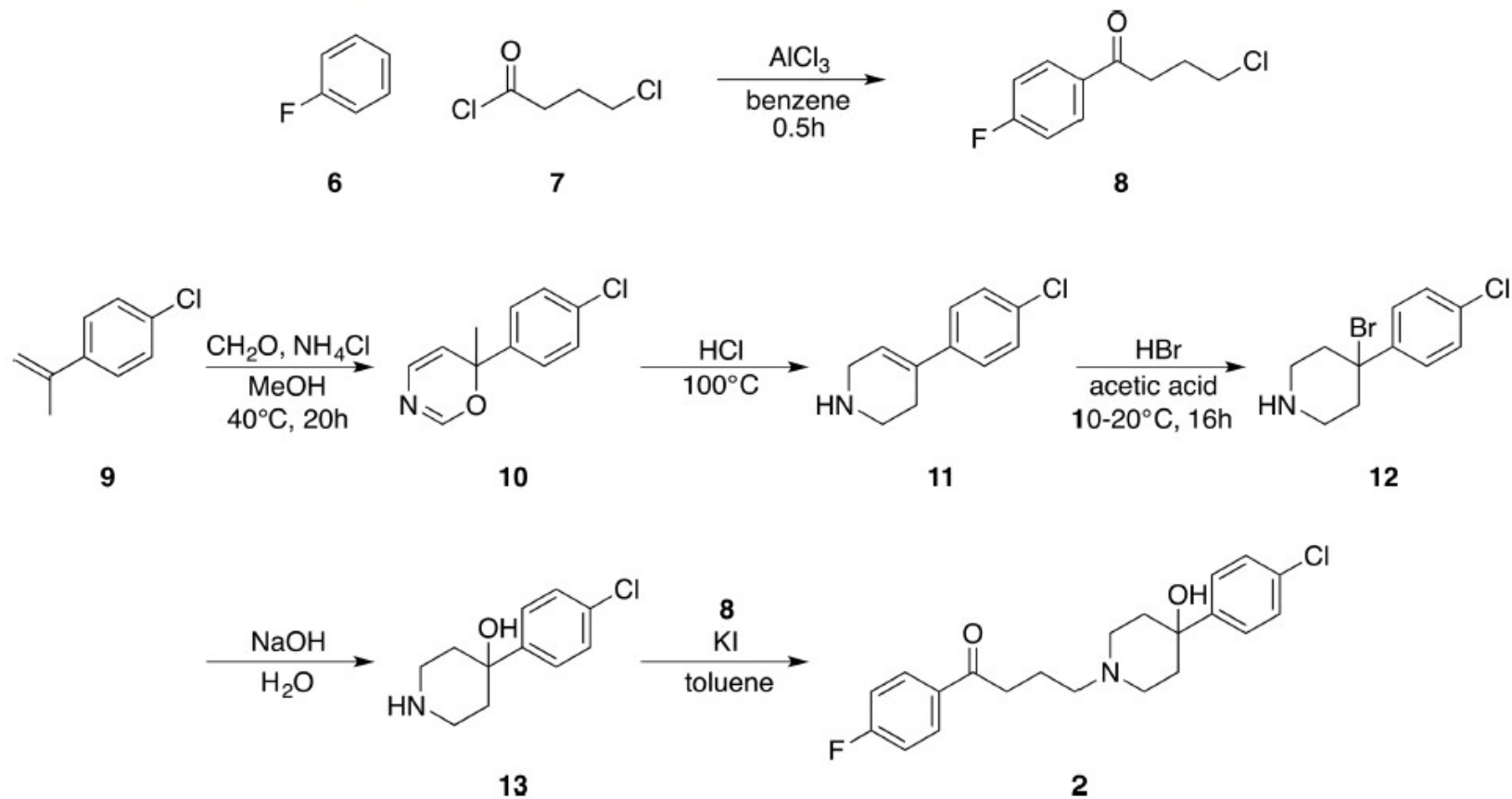


Metabolism of chlorpromazine



Original synthesis of haloperidol

Scheme 1. Original Synthesis of Haloperidol by Janssen Pharmaceutica in 1958



Metabolism of haloperidol

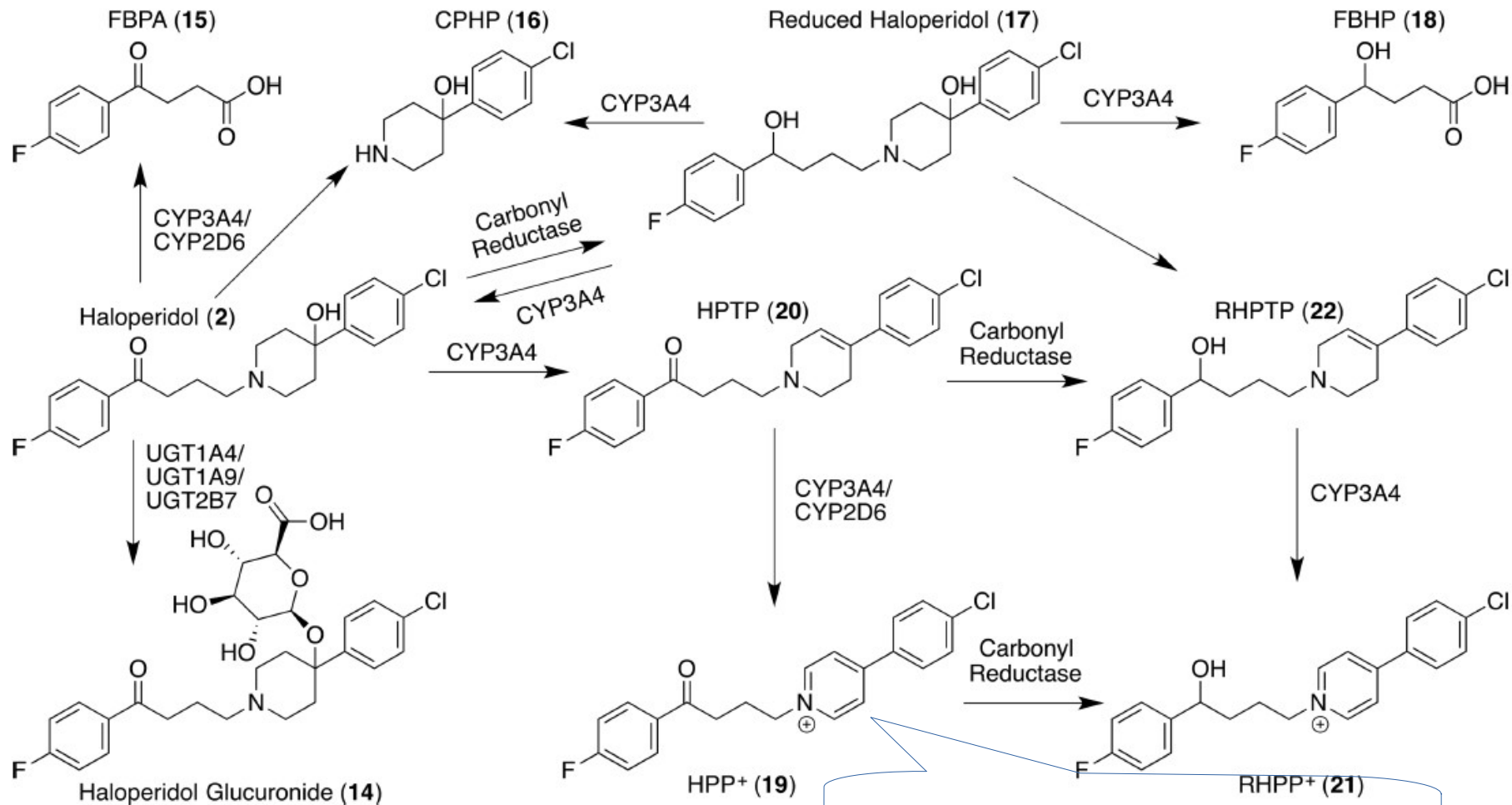
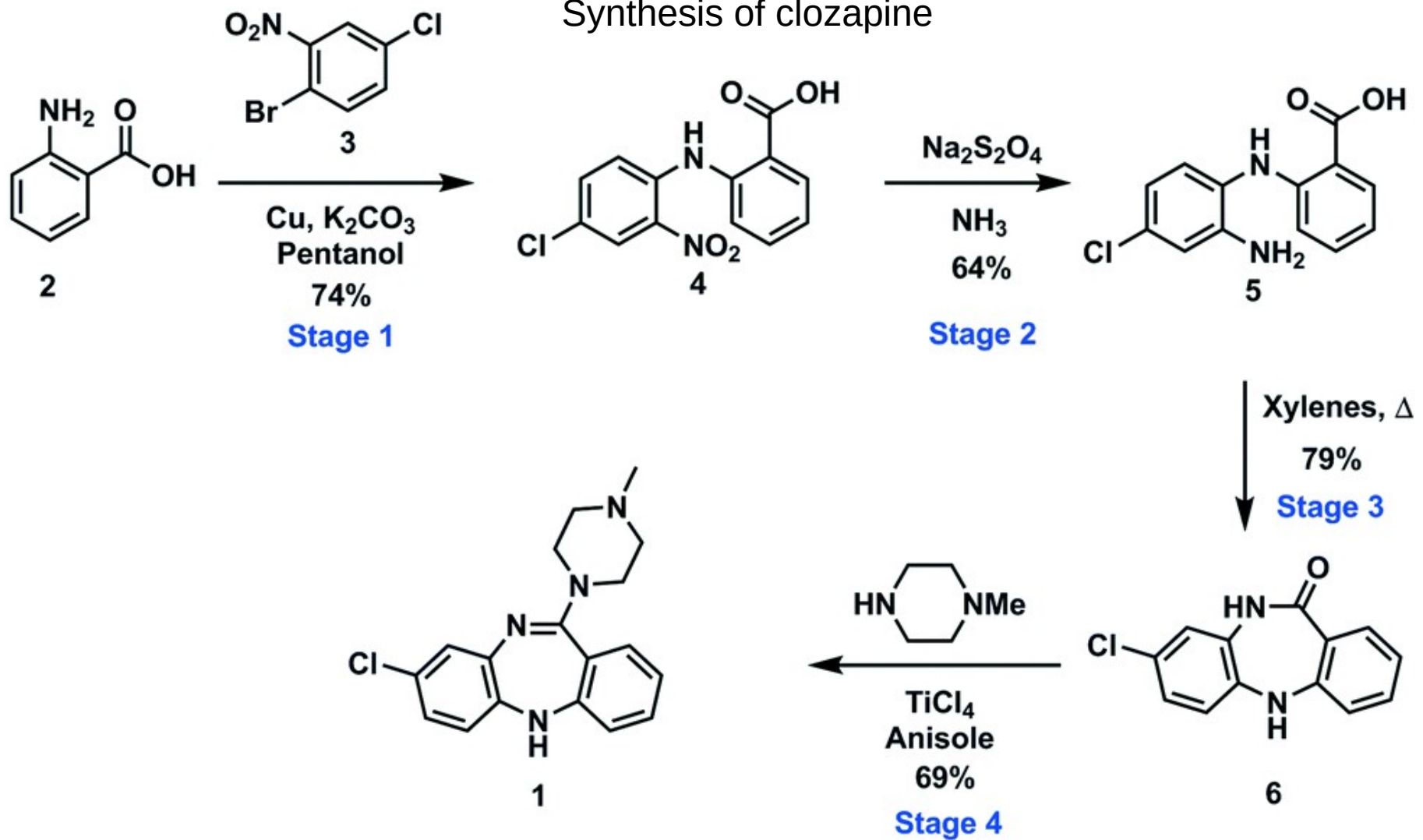
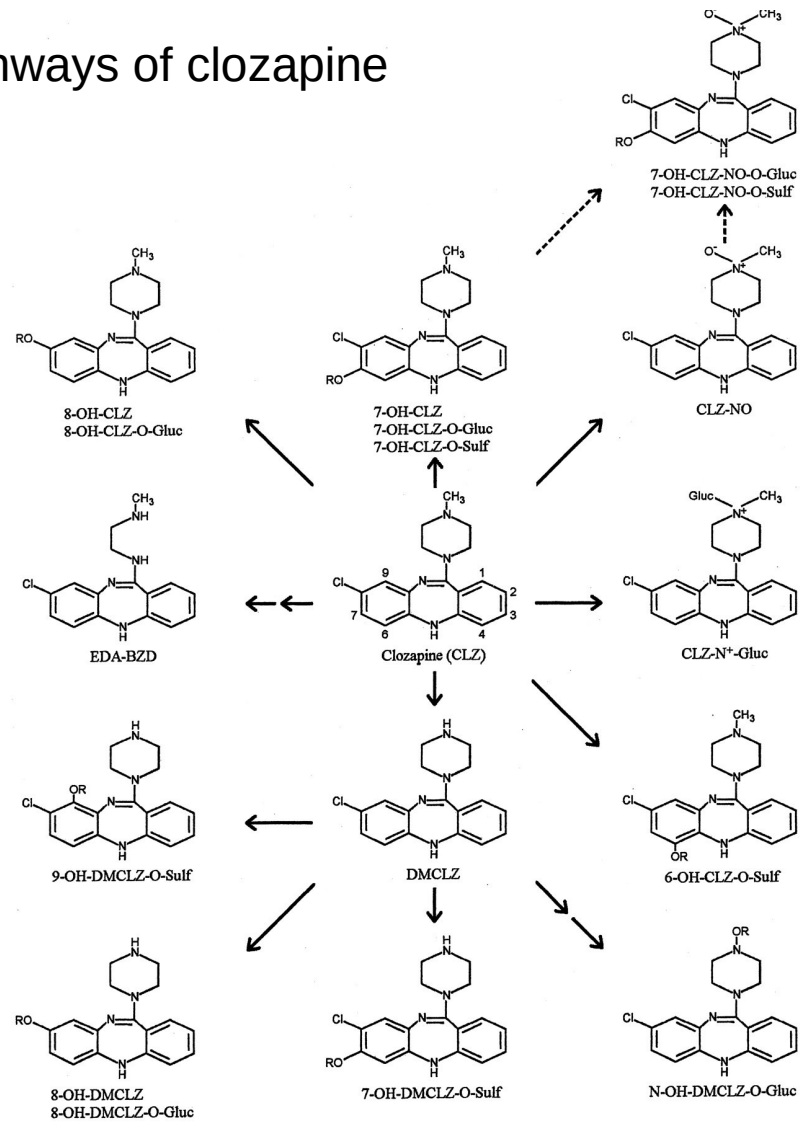


Figure 3. Structures of metabolites of haloperidol (2).

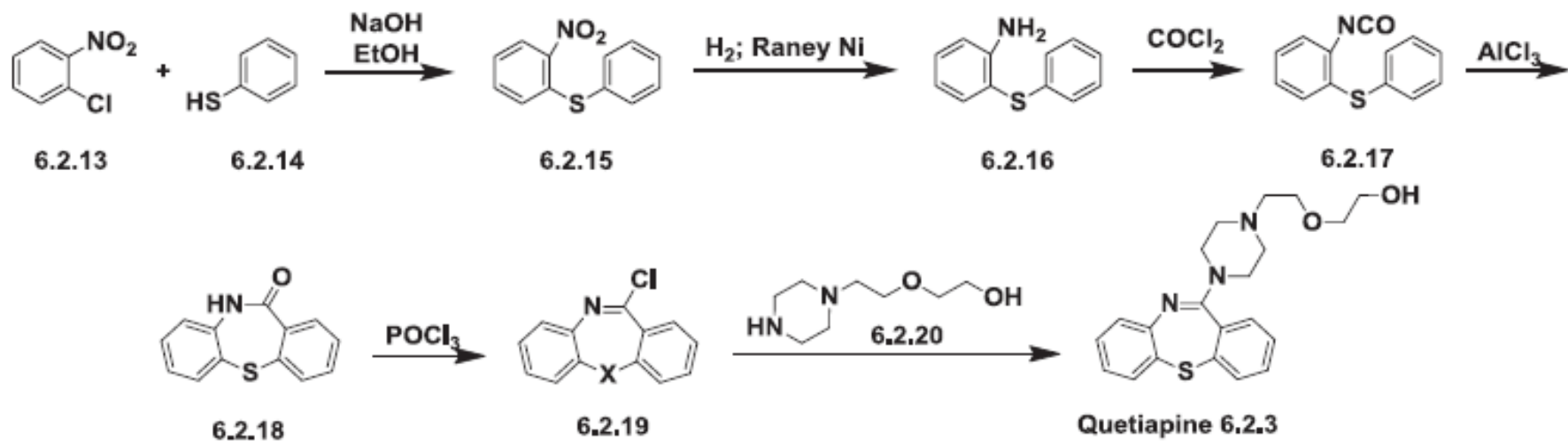
Synthesis of clozapine



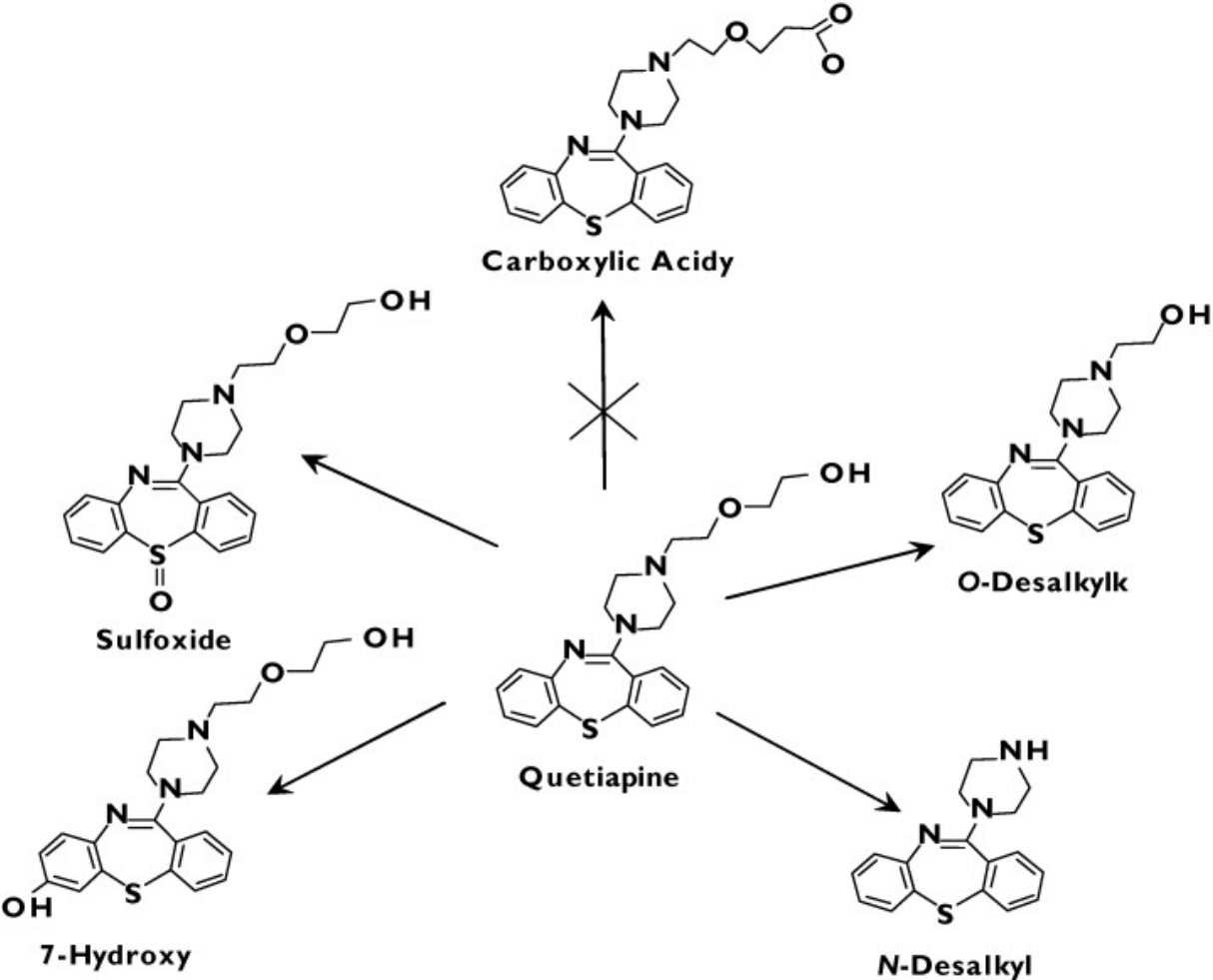
Main metabolic pathways of clozapine



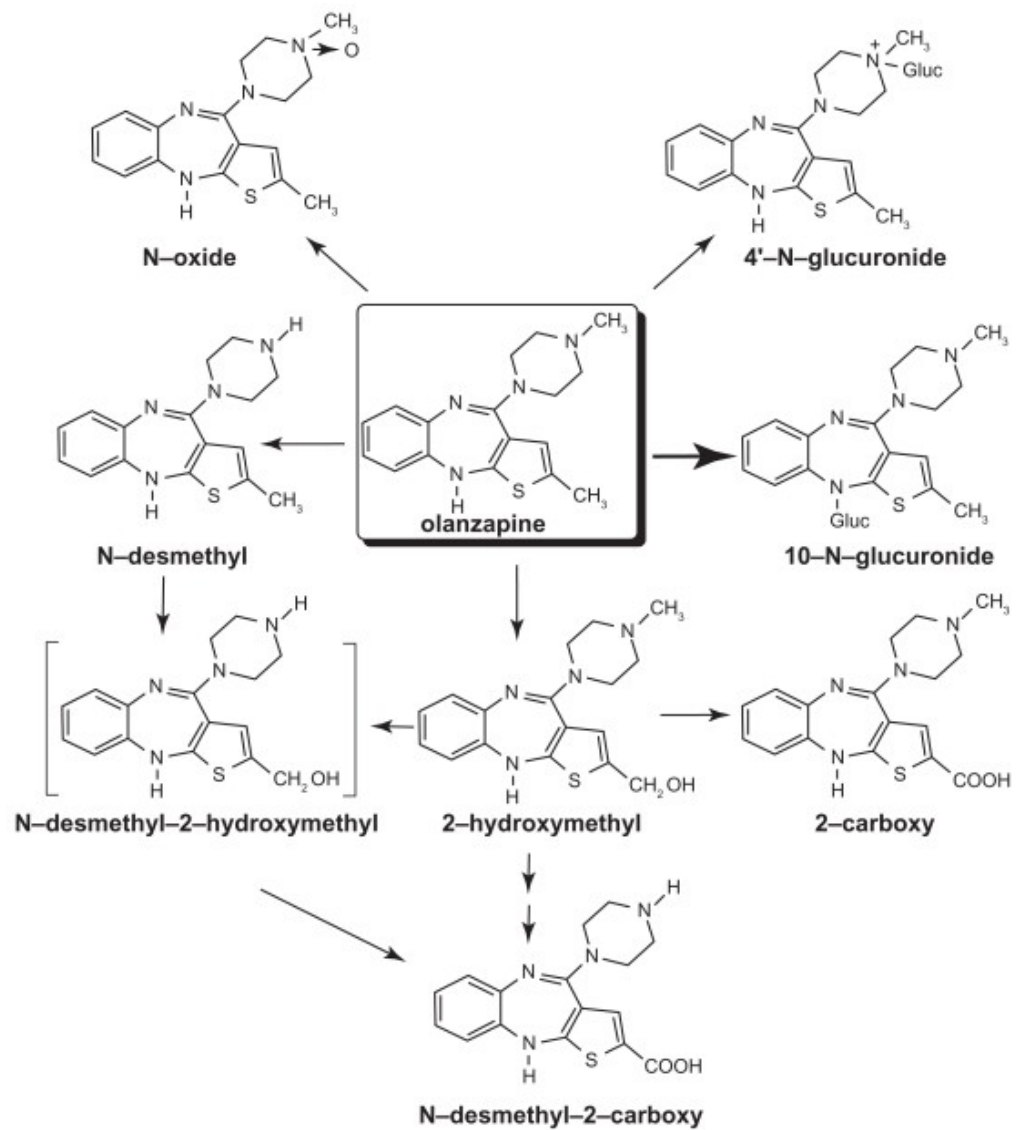
Synthesis of quetiapine



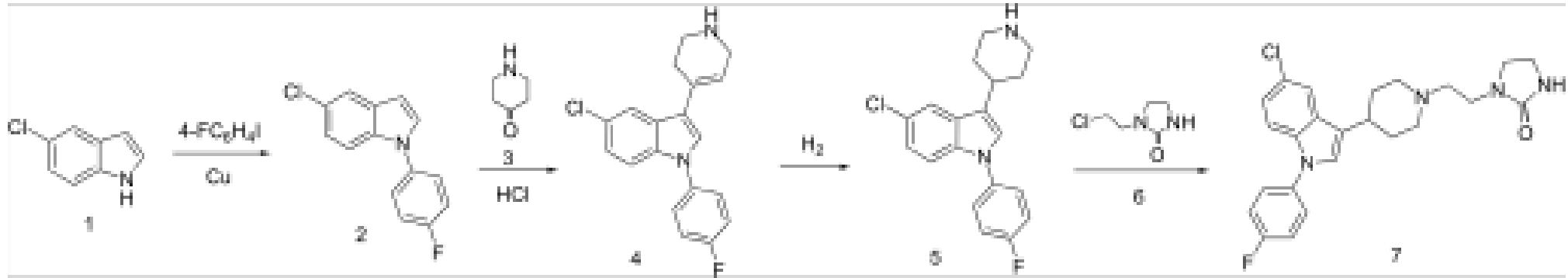
Quetiapine metabolism



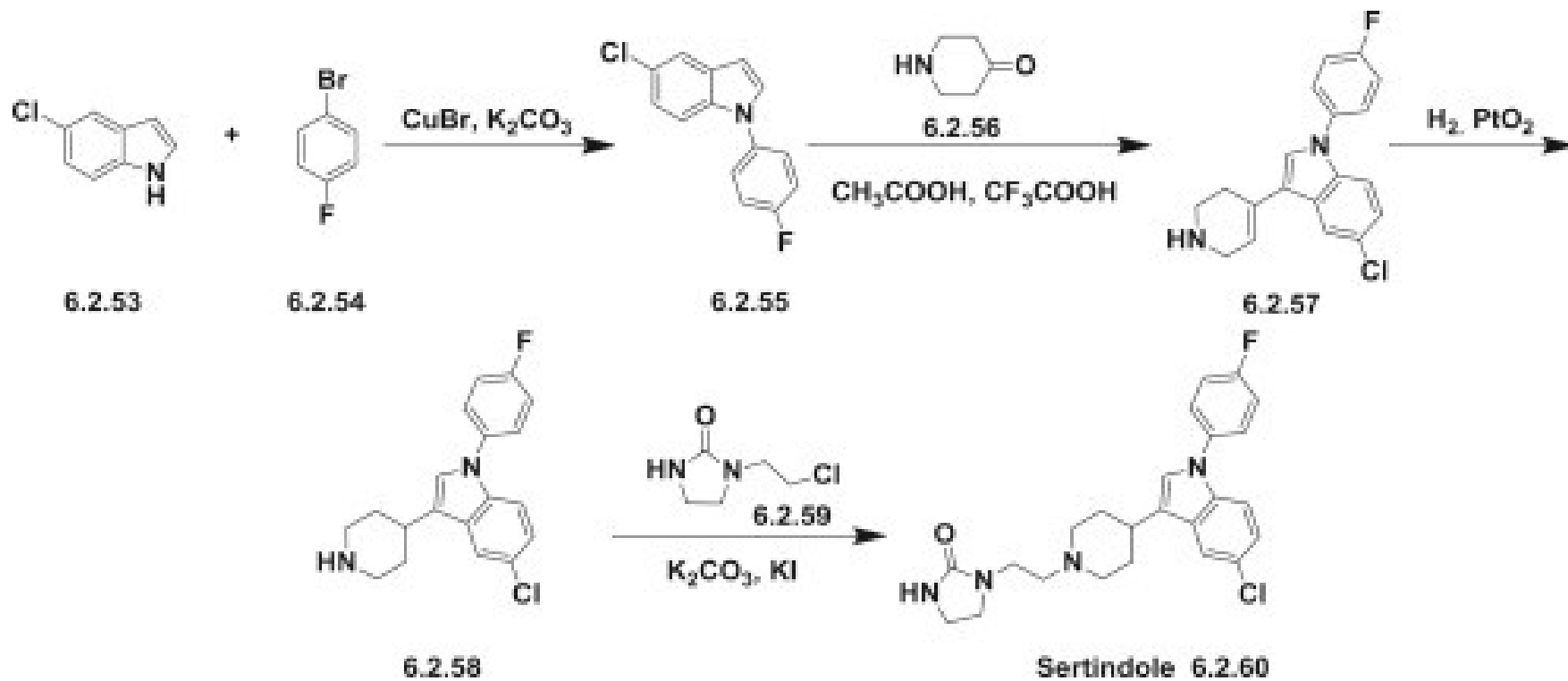
Olanzapine metabolism



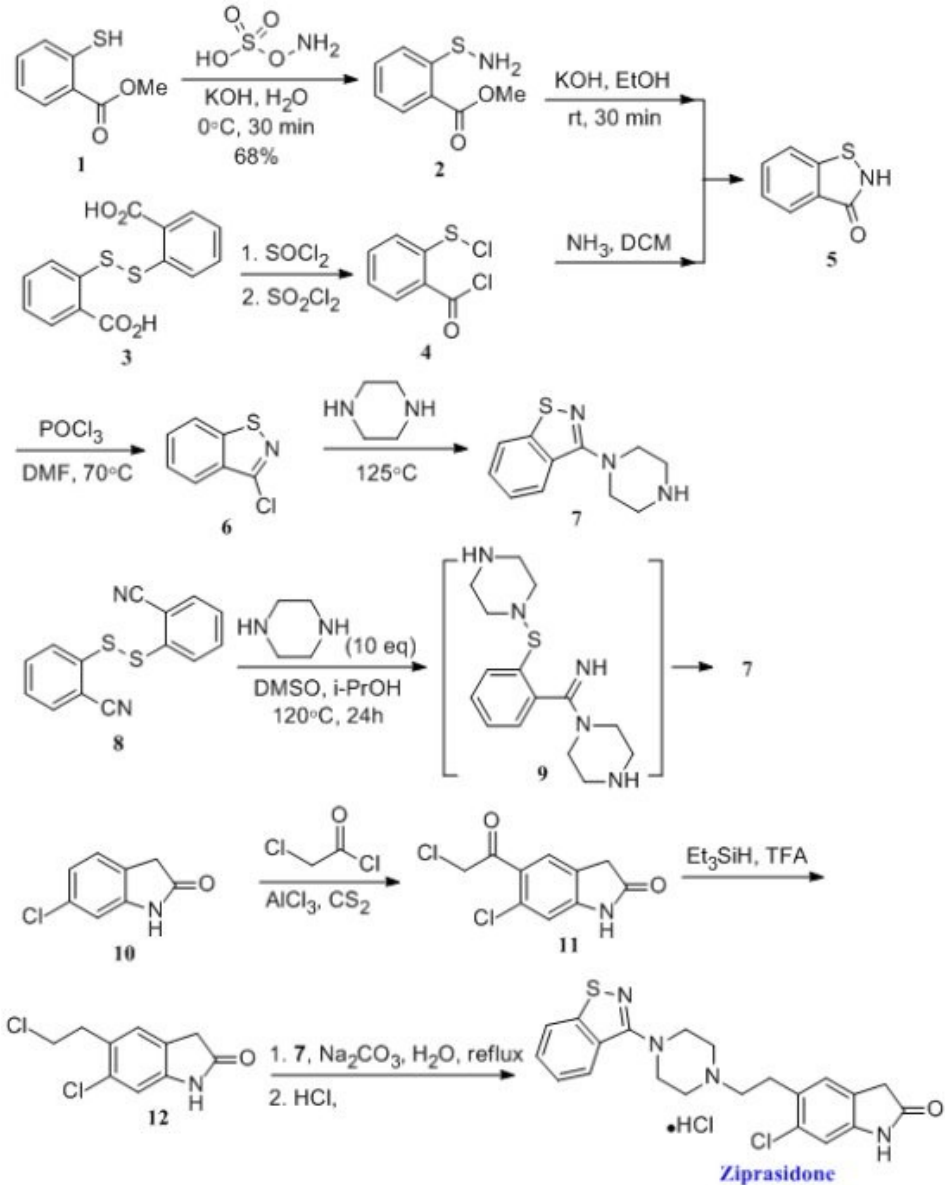
Sertindole synthesis



Other modification of sertindole synthesis



Synthesis of ziprasidone



Main metabolites of ziprasidone

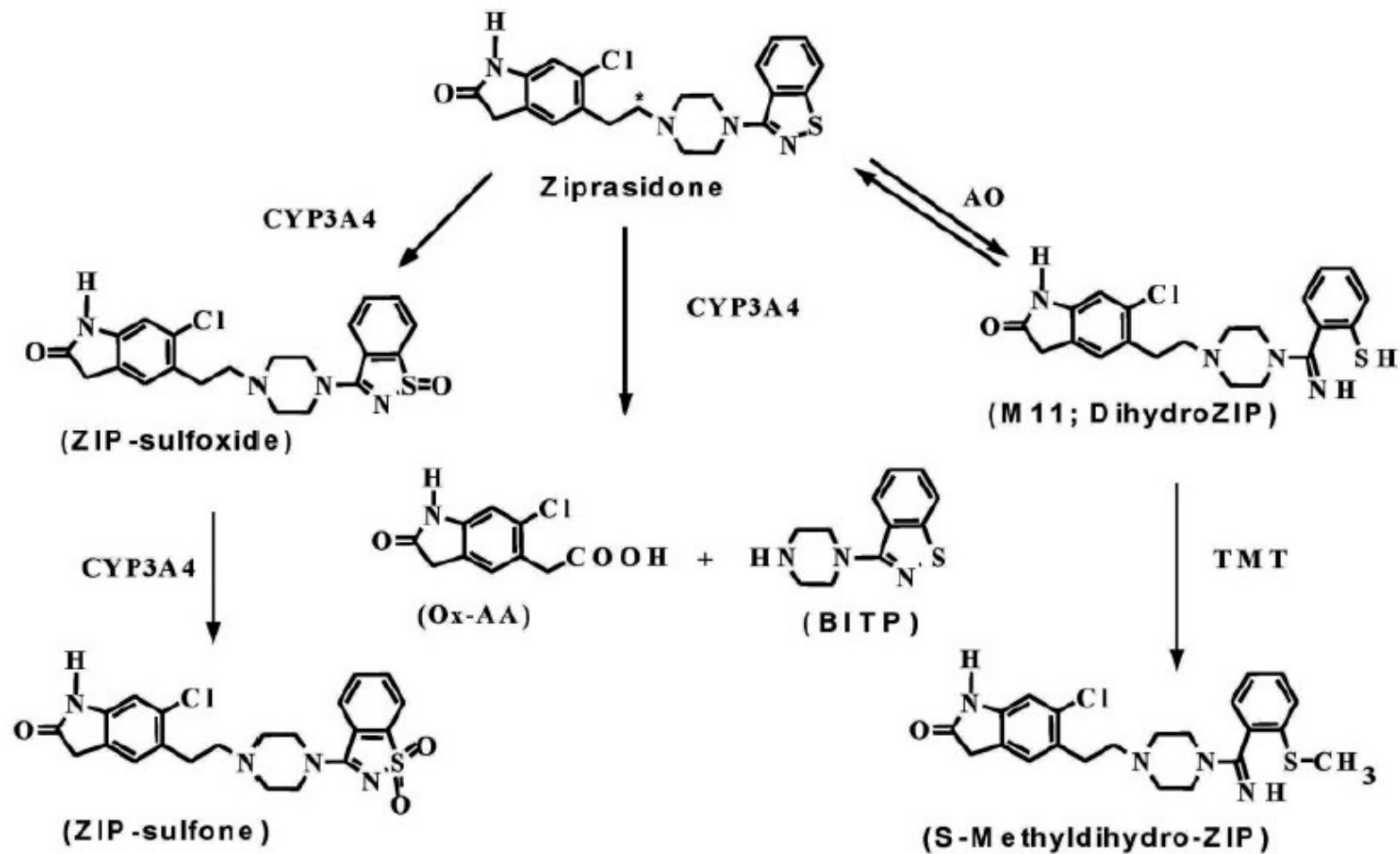
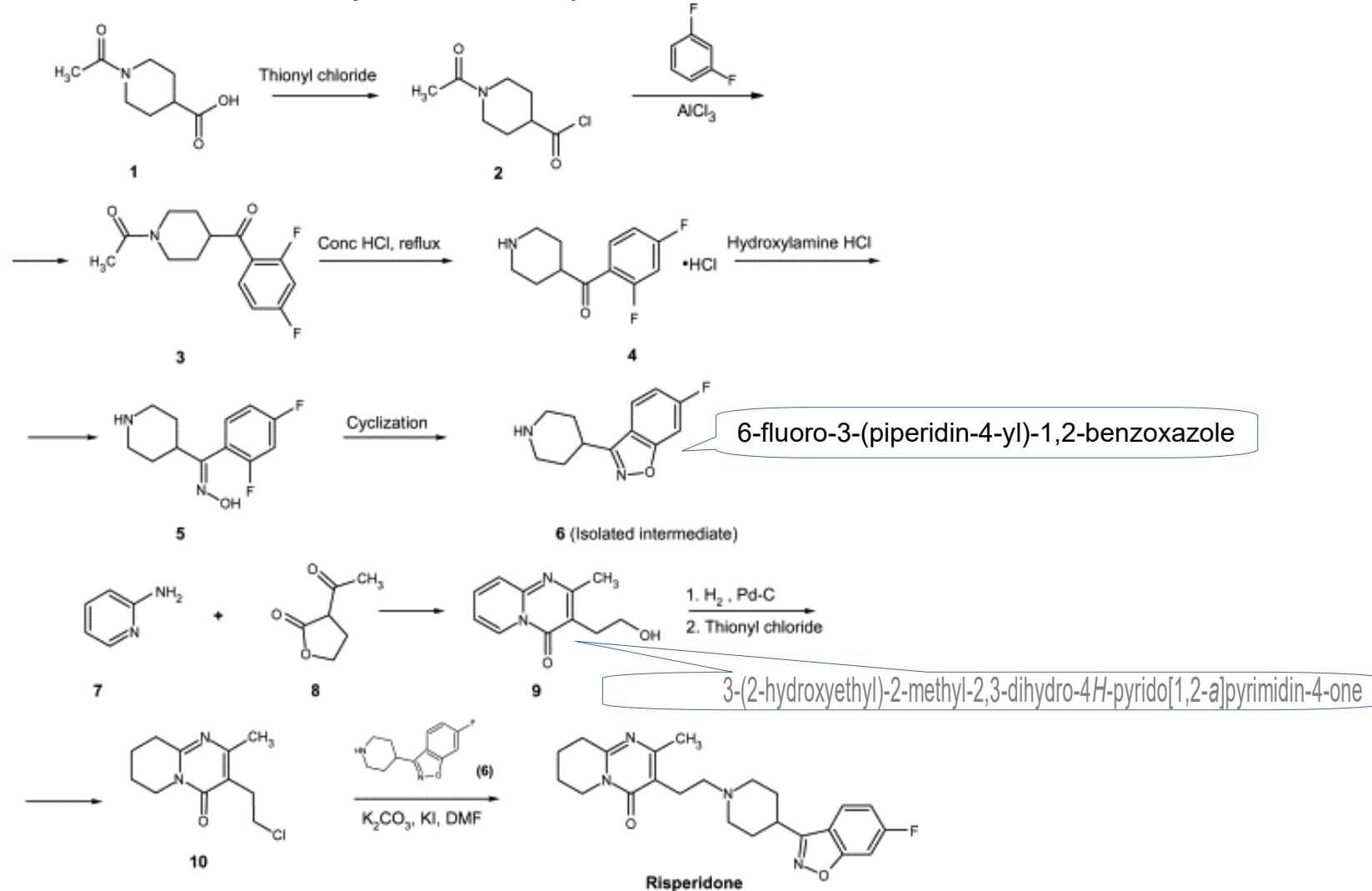
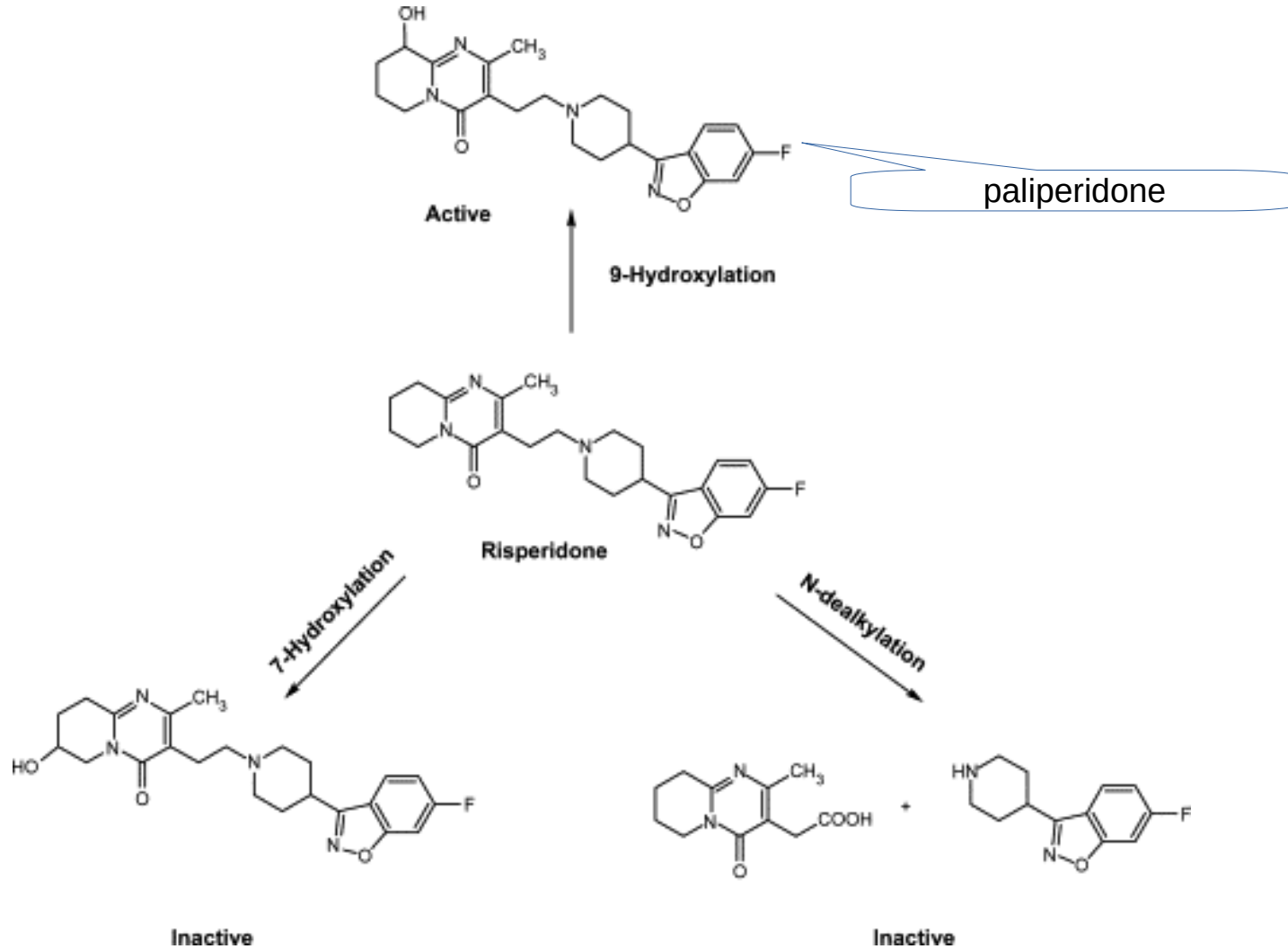


FIG. 1. Structures of ziprasidone and its major metabolites. TMT, thiol methyltransferase.

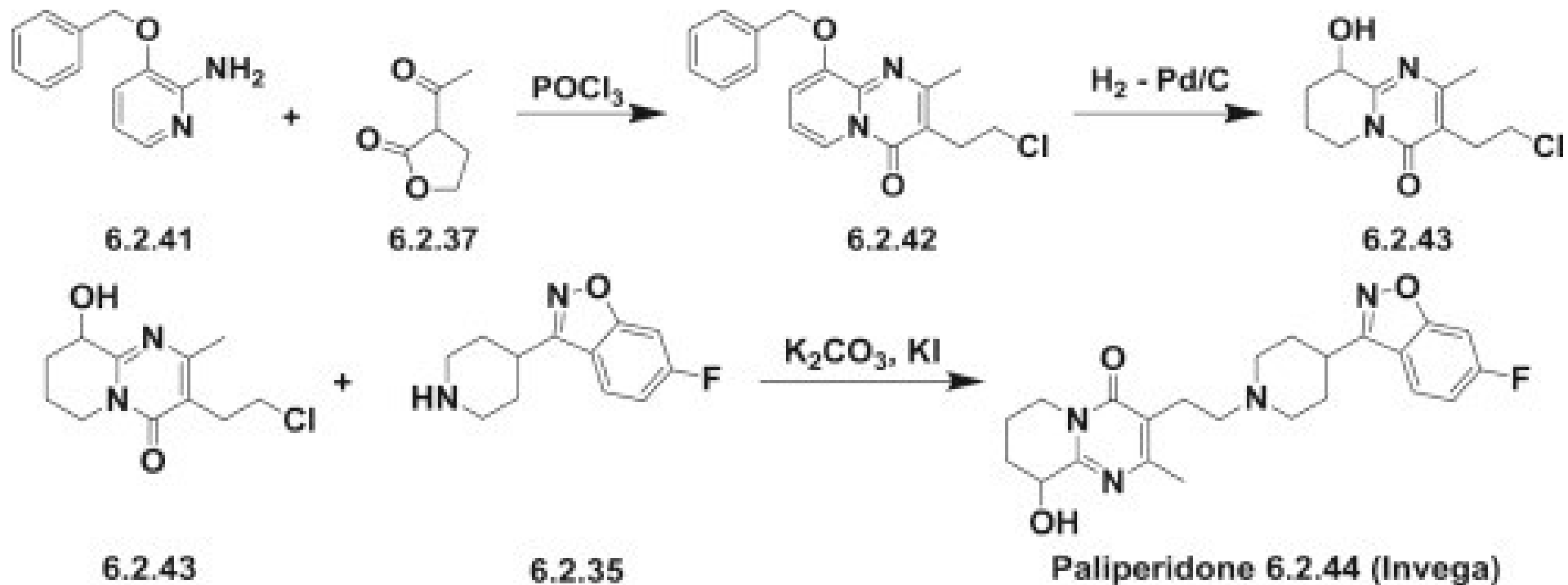
Synthesis of risperidone



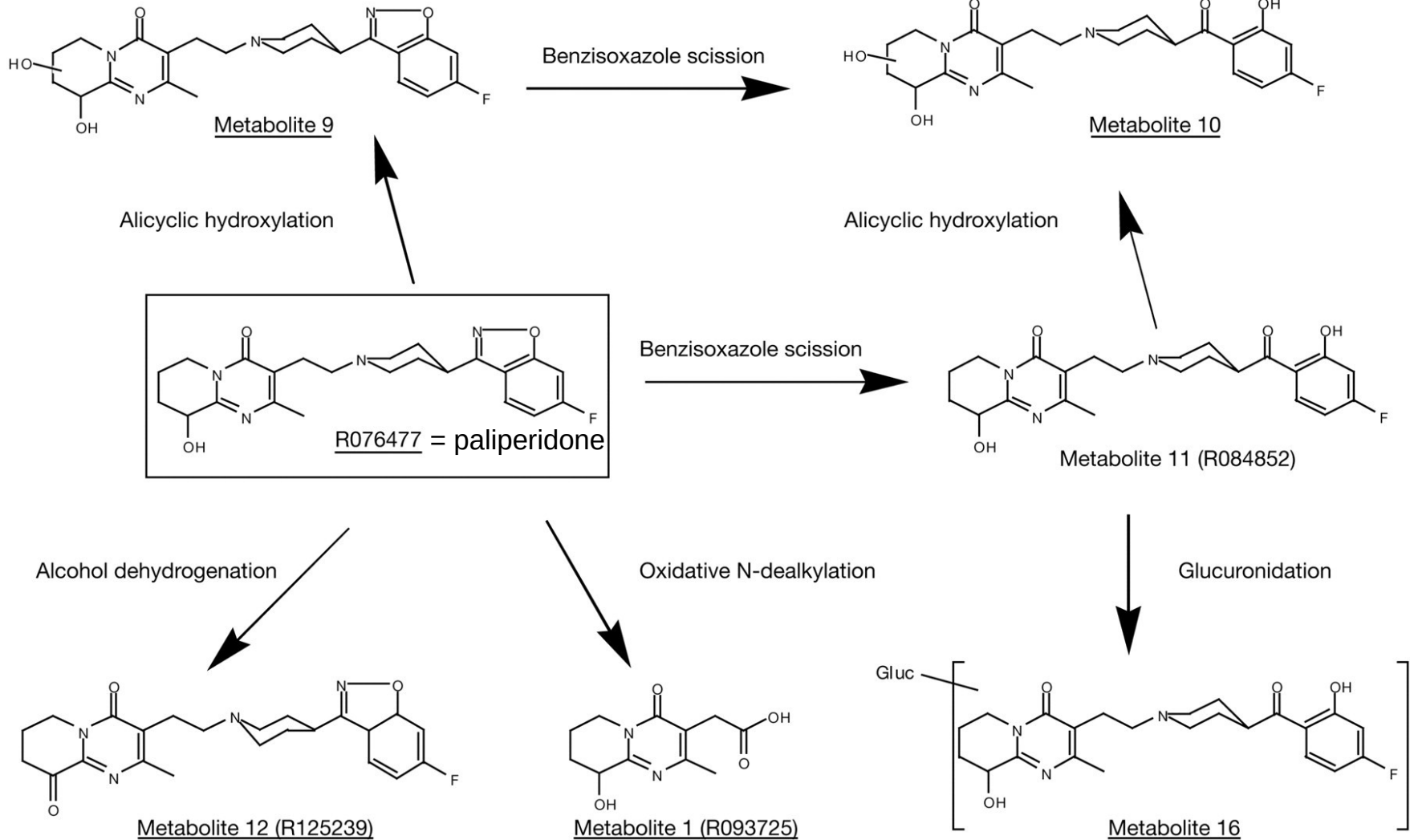
Main metabolic pathways of risperidone



Synthesis of paliperidone



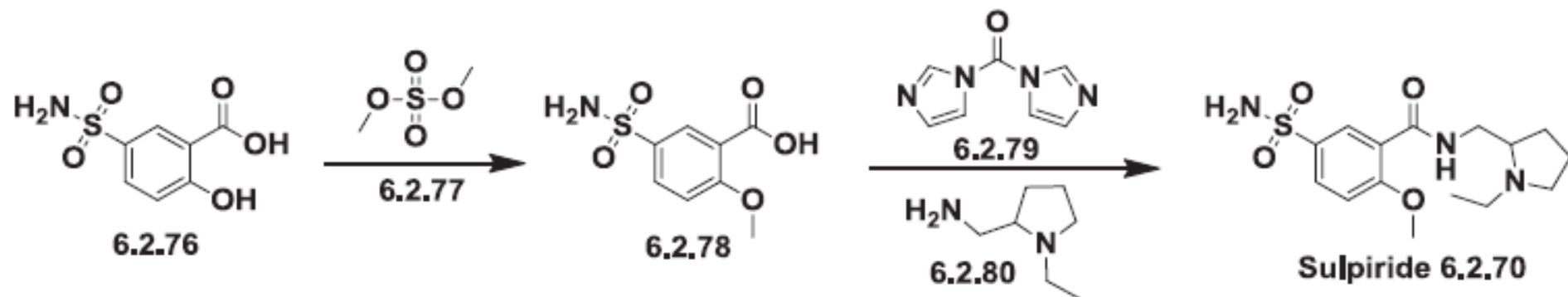
Main metabolites of paliperidone



Lurasidone and its main metabolites

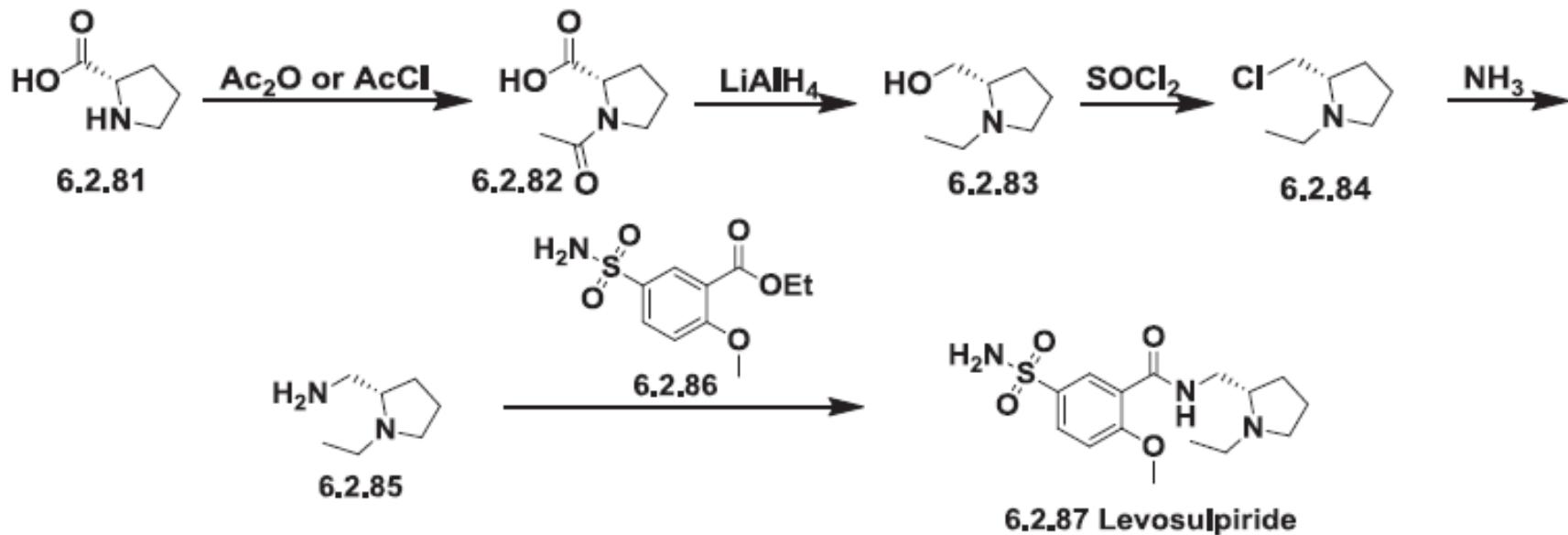
Table 1: Structure of lurasidone and select metabolites	
<p>(i) (ii)</p> <p>Lurasidone (C₂₈H₃₆N₄O₂S), m/z = 493</p>	
<p>M10, ID-14324 (C₂₈H₃₆N₄O₃S), m/z = 509 <i>Lurasidone sulfoxide</i></p>	<p>M5, ID 20220 (C₁₇H₂₃NO₅), m/z = 322</p>
<p>M11, ID-20219 (C₁₇H₂₃NO₄), m/z = 306</p>	<p>M7, M11 Glucuronide (C₂₃H₃₁NO₁₀), m/z = 482</p>
<p>M8, ID-14283 (exo-OH), (C₂₈H₃₅N₄O₃), m/z = 509 <i>Hydroxylurasidone</i></p>	<p>M9, ID-14326 (endo-OH), (C₂₈H₃₅N₄O₃), m/z = 509 <i>Hydroxylurasidone</i></p>
<p>ID-20221 (exo-OH) (C₂₈H₃₅N₄O₄S), m/z = 525</p>	<p>ID-20222 (exo-OH) (C₂₈H₃₅N₄O₅S), m/z = 541</p>
<p>M22 (C₂₉H₄₀N₄O₃S), m/z = 525 <i>S-Methyl hydroxylurasidone</i></p>	<p>M21 (C₂₉H₄₀N₄O₂S), m/z = 509 <i>S-Methyl lurasidone</i></p>

Synthesis of sulpiride



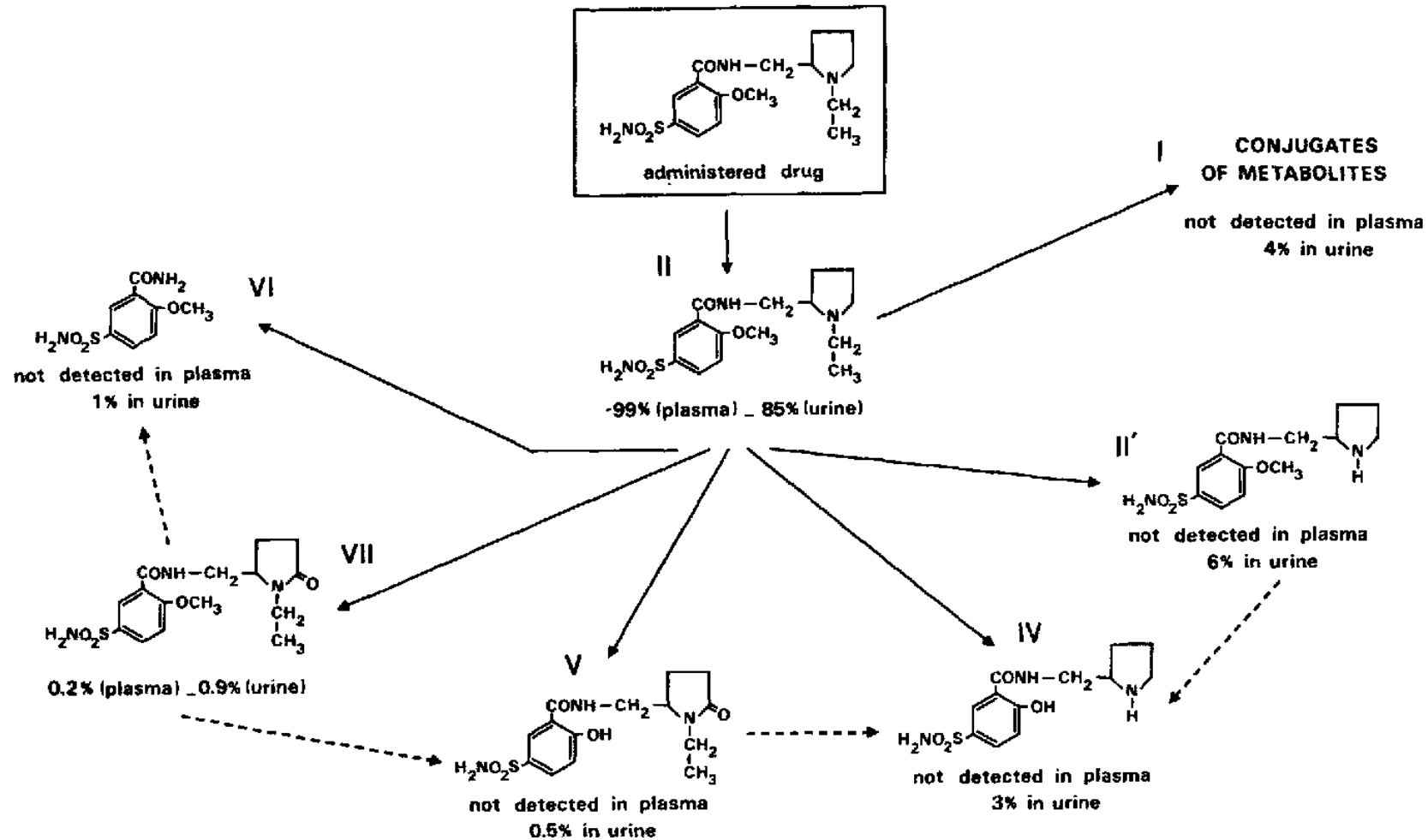
SCHEME 6.14 Synthesis of sulpiride.

Synthesis of levosulpiride

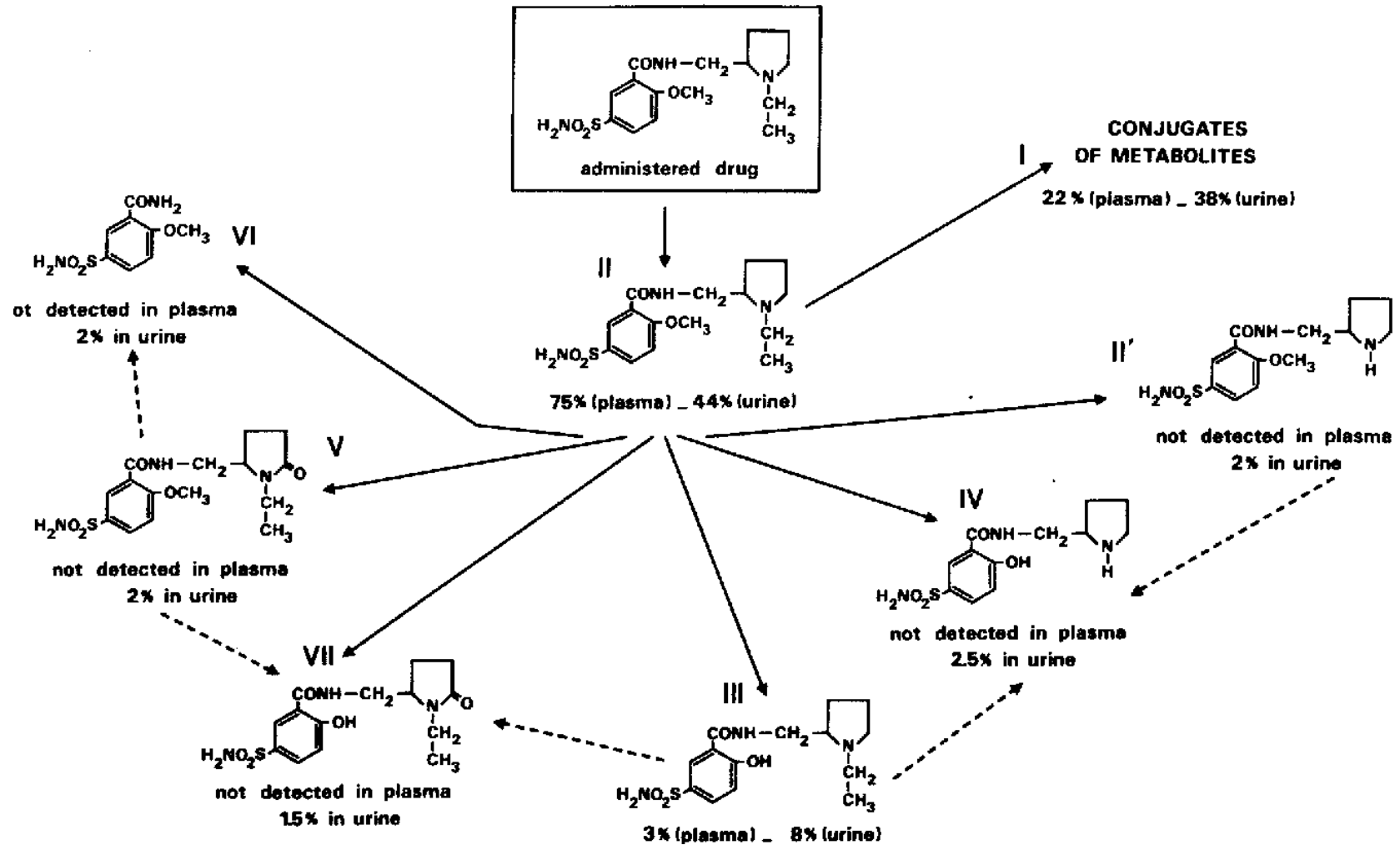


SCHEME 6.15 Synthesis of levosulpiride.

METABOLIC PATHWAY OF SULPIRIDE IN DOG



METABOLIC PATHWAY OF SULPIRIDE IN RAT



Synthesis of amisulpride

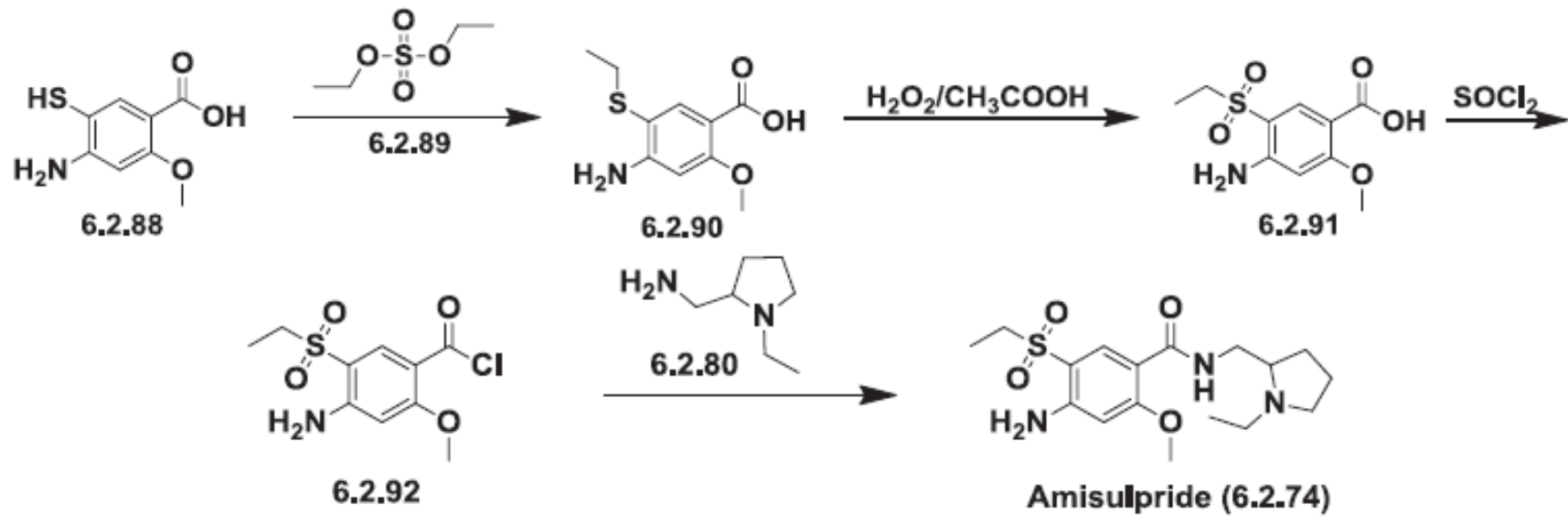
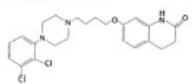
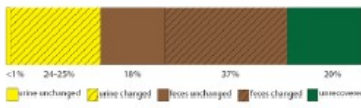
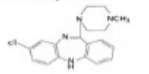
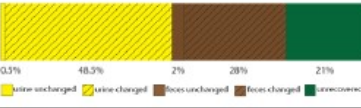
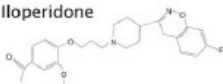
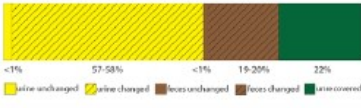

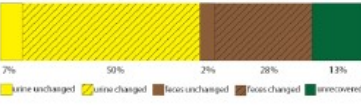
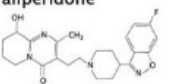

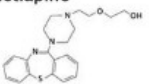
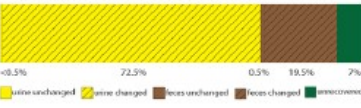
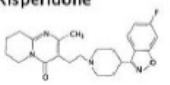
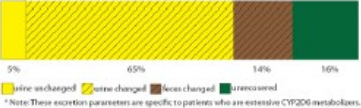
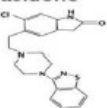
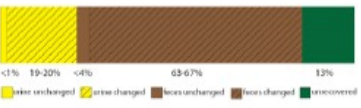


Table 1. Summary of the Chemical Structures and Excretion Profiles of the Atypical Antipsychotics

Chemical Structure	Excretion
<p>Aripiprazole</p> 	 <p><math><1\%</math> 24-25% 18% 37% 20%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>
<p>Clozapine</p> 	 <p>0.3% 48.3% 2% 28% 21%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>
<p>Iloperidone</p> 	 <p><math><1\%</math> 57-58% <math><1\%</math> 19-20% 22%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>
<p>Olanzapine</p> 	 <p>7% 50% 2% 28% 13%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>
<p>Paliperidone</p> 	 <p>60% 20% 11% 9%</p> <p>urine unchanged urine changed feces changed unrecovered</p>
<p>Quetiapine</p> 	 <p><math>>0.5\%</math> 72.5% 0.5% 19.5% 7%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>
<p>Risperidone</p> 	 <p>5% 65% 14% 16%</p> <p>urine unchanged urine changed feces changed unrecovered</p>
<p>Ziprasidone</p> 	 <p><math><1\%</math> 19-20% <math><1\%</math> 63-67% 13%</p> <p>urine unchanged urine changed feces unchanged feces changed unrecovered</p>

The chemical structures of each of the 8 reviewed atypical antipsychotic agents are presented with a bar chart depicting the relationship between the excretory (i.e., urine or feces, changed or unchanged) profiles. These data highlight the magnitude of differences in the excretory profiles among the atypical antipsychotic agents.