

risperidone (Risperdal)

FDA Approval for Schizophrenia: 1993
 FDA Approval for BPD: 2003
 FDA Approval for Autism: 2006

Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson

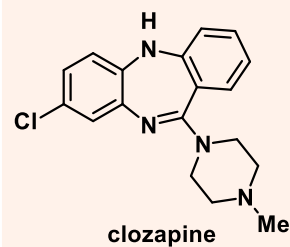
Patent protection expired 2003

- Atypical antipsychotic drug, used for the treatment of Schizophrenia, Bipolar Disorder, and irritability that is associated with Autism Spectrum Disorder.

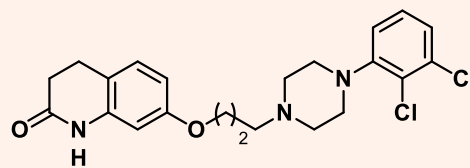
- Now available in generic form for low cost, including in developing countries.

- On WHO List of Essential Medicines

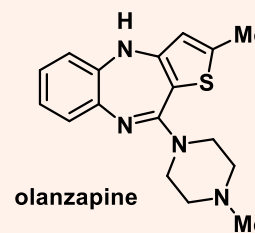
Alternative atypical antipsychotic medications:



clozapine



aripiprazole



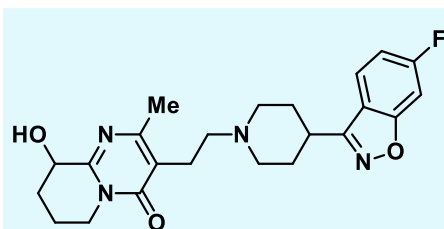
olanzapine

ACS. Chem. Neurosci. 2018, 9, 1520.



available in oral and injectable form

Major metabolite of risperidone: oxidation through CYP enzymes



9-OH-risperidone (paliperidone)
 active, marketed drug (Invega)

This compound is less lipophilic, and crosses the BBB more slowly, but has similar potency to the parent compound, albeit with different selectivity in terms of binding affinity.

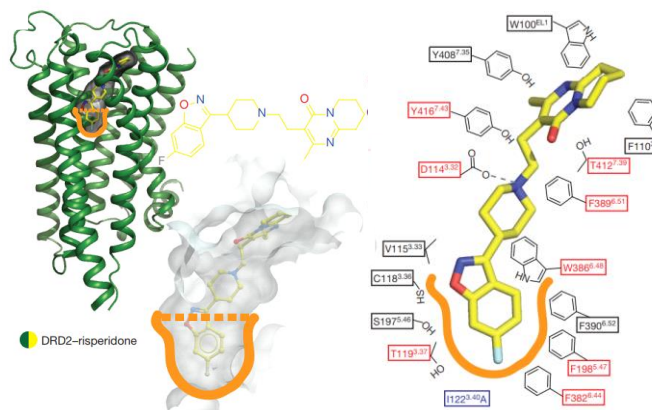


Selected K_i data for risperidone and paliperidone

receptor (action)	risperidone (nM)	paliperidone (nM)
Dopamine (antagonist)		
D ₁	580	554
D ₂	3.2	2.8
D ₃	18	7.5
D ₄	22	38
Serotonin (antagonist)		
5HT _{1A}	282	1030
5HT _{1B}	95	111
5HT _{1D}	16	7.3
Serotonin (inv. agonist)		
5HT _{2A}	0.49	0.83

Drugs R&D 2015, 15, 163.

Crystal structure of Dopamine D₂ receptor and risperidone:



Key interactions include the hydrophobic portion at the lower and upper regions of the binding pocket, in the active site of the protein, and a salt bridge forming between the piperidine nitrogen and Asp₁₁₄.

Risperidone extends further down into the active site than other atypical antipsychotics (orange highlighted portion).

Figures adapted from *Nature* 2018, 555, 269.

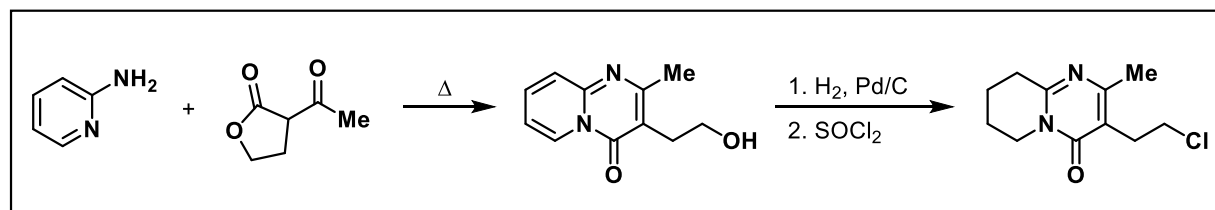
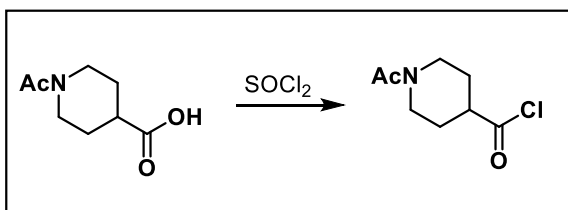
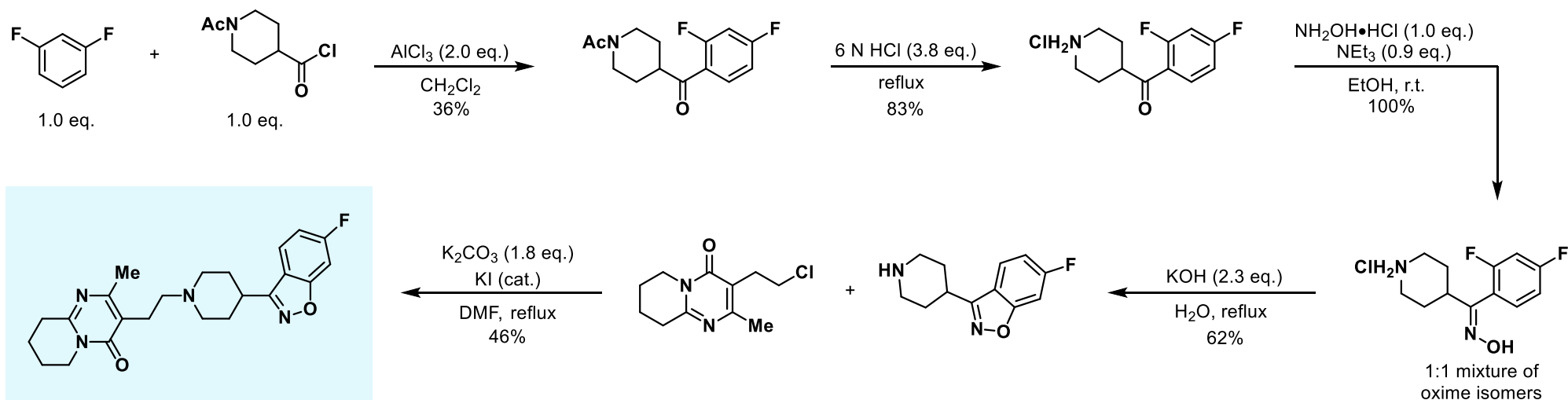
Adverse effects, cost, and controversy:

- Side effects include fatigue, appetite increase, drowsiness, abdominal pain, nausea, dizziness, dry mouth, nasal inflammation
- Cost of oral dosing = 7.66 USD/day
- Has been subject to lawsuits for off-label marketing and downplaying of side effects. see: <https://bloom.bg/2uD1uqc>; <https://bit.ly/2LmaMAv>
- Less EPS side effects (tardive dyskinesia, spasm, tremor) than other similar drugs.

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Drug of the Week: Risperidone

Janssen U.S. Patent Route, 1985 (US4804663A) Modifications: SP 2074966; WO 2004020439



Arch. Pharm. Res. **2005**, 28, 1019.

