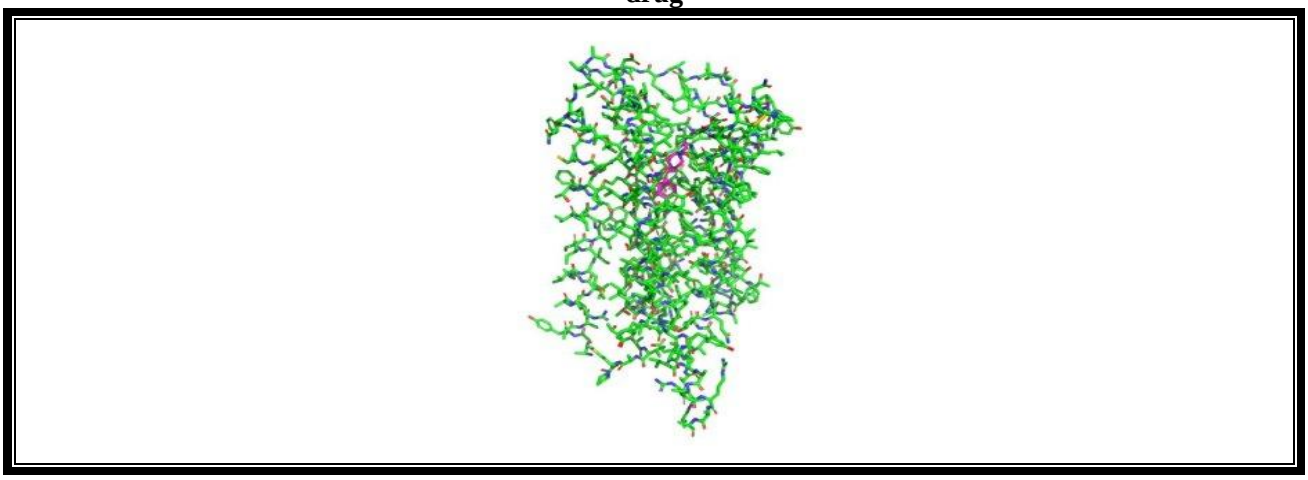
BREAKTHROUGH COULD LEAD TO BETTER ANTIPSYCHOTIC DRUGS

Research reveals the first-ever crystal structure of the dopamine 2 receptor bound to an antipsychotic drug



Full chemical structure of the dopamine 2 receptor bound to the antipsychotic drug risperidone

Although antipsychotic drugs are among the most widely prescribed medications, individuals with schizophrenia, bipolar disorder and autism-spectrum disorders often experience severe side effects because the drugs interact with dozens of other brain receptors. Now, scientists at the UNC School of Medicine and UC San Francisco (UCSF) have solved the first high-resolution crystal structure of the dopamine 2 receptor (DRD2) bound to the antipsychotic drug risperidone, yielding a long-awaited tool for drug developers, psychiatrists, and neuroscientists.

The research, published in *Nature*, will allow researchers to selectively activate DRD2 thus potentially limiting a host of serious antipsychotic drug side effects such as weight gain, anxiety, dizziness, severe digestive problems, agitation, and many others.

"If we want to create better medications, the first step is to see what the D2 receptor looks like in high-resolution detail when it's bound tightly to a drug," said senior author Bryan L. Roth, MD, PhD, the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics at the UNC School of Medicine. "We now have the structure, and we're exploring it to find new compounds we hope can help the millions of people in need of better treatments."

About 30 percent of medications on the market activate G-protein coupled receptors on cell surfaces and trigger chemical signals inside cells to yield their therapeutic effects. For antipsychotic medications, one effect is alleviating psychotic symptoms associated with schizophrenia, bipolar disorder and many other psychiatric diseases. Unfortunately, because scientists haven't understood the structural differences between the many different kinds of receptors in the brain, most drugs cannot be designed to target only one type of receptor; they interact with not only DRD2, but a myriad of other dopamine, serotonin, histamine, and alpha adrenergic receptors, leading to serious side effects.