

# Representation of Complex Function in the Gene Ontology

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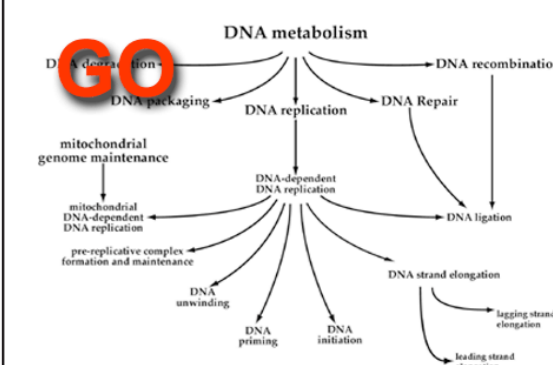
**Abstract**  
There has been a great deal of discussion on the representation of molecular function in the GO. Based on the definition of molecular function, we propose that molecular functions represent the basic molecular activity of a single gene product and they can be resolved into more basic sub-functions. We present a proposal for how to better represent complex molecular functions in the GO.



**GO term:** molecular\_function  
**GO id:** GO:0003674  
**Definition:** Elemental activities, such as catalysis or binding, describing the actions of a gene product at the molecular level. A given gene product may exhibit one or more molecular functions.  
**Number of paths to term:** 1

## What is a molecular function?

We define a function at the level of the gene product!



## Why is representation of the function of G-protein Coupled Receptors Important in the molecular function ontology?

G protein-coupled receptors (GPCRs) constitute the most prominent family of validated drug targets within biomedical research, since approximately 60% of approved drugs elicit their therapeutic effects by selectively addressing members of that target family. (Muller, G. Towards 3D structures of G Protein-Coupled Receptors A multidisciplinary Approach. Current Medicinal Chemistry 7(9):861-888 2000.)

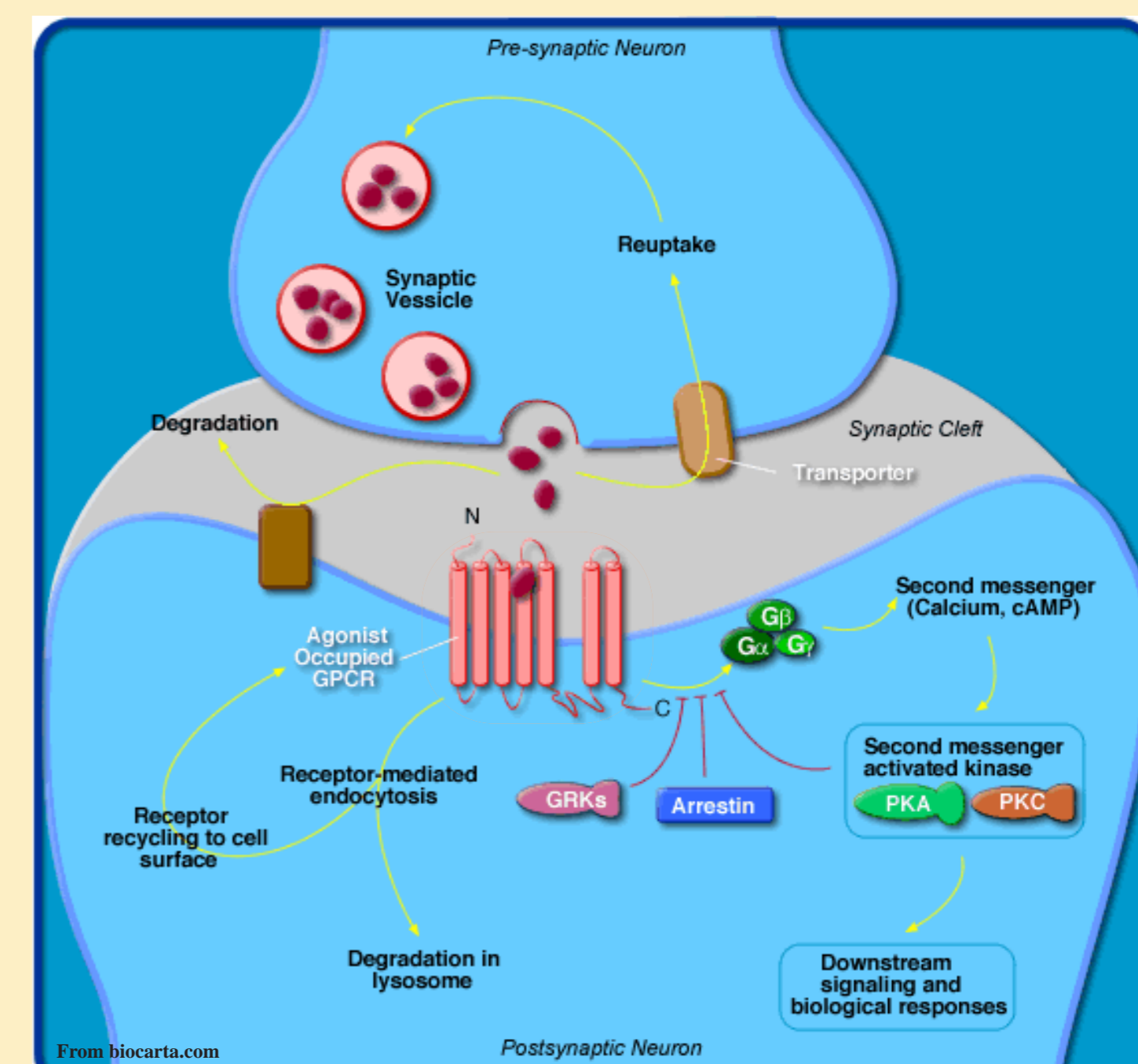
GPCRDB: GPCR entries

Available Swiss-Prot and TrEMBL entries

sorted by ID (or by family or organism)

ID	AC	Gene name	Family	Organism
1. SHT1A_FUGRU	(042395)	Serotonina_type_1	Fugu rubripes (Japanese pufferfish) (Takiyugu rubripes)	
2. SHT1A_HUMAN	(P09098)	5HT1A	Serotonina_type_1	Homo sapiens (Human)
3. SHT1A_MOUSE	(Q64244)	5HT1a	Serotonina_type_1	Mus musculus (Mouse)
4. SHT1A_PANTR	(Q9R298)	5HT1A	Serotonina_type_1	Pan troglodytes (Chimpanzee)
5. SHT1A_PORPY	(Q9K296)	5HT1A	Serotonina_type_1	Pongo pygmaeus (Orangutan)
6. SHT1A_RAT	(P19127)	5HT1a	Serotonina_type_1	Rattus norvegicus (Rat)
7. SHT1A_CANFA	(P79250)	5HT1B	5HT1B	Canis familiaris (Dog)

There are 12,667 GPCRs in UniProt



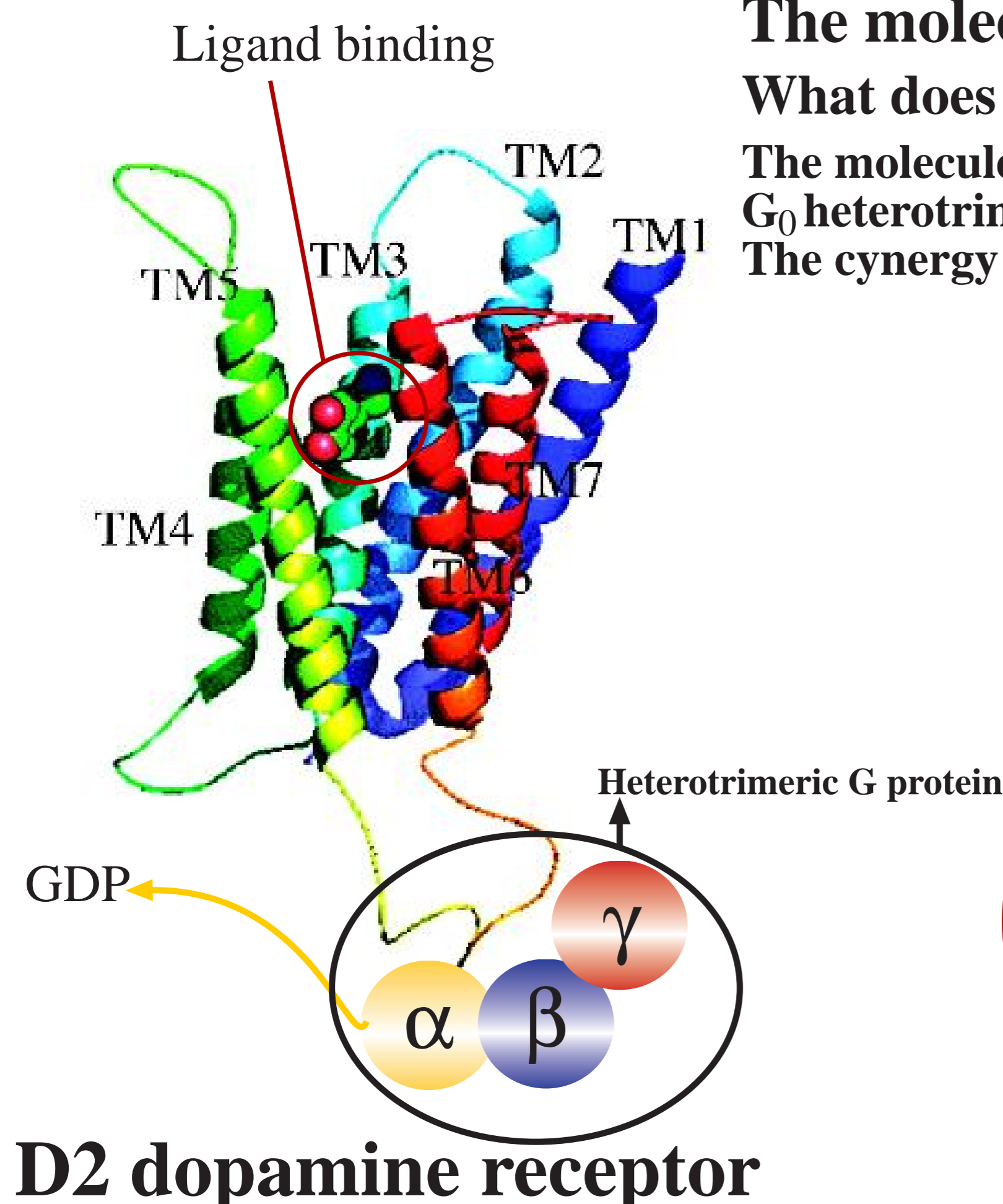
G-protein Coupled Receptors are a key component in a complex signaling pathway

## What GPCRs do as molecules is important!

## The molecular function of the GPCR, DRD2, needs to be described at the level of the whole molecule:

What does it do?

The molecule binds the neurotransmitter dopamine and certain analogs AND it binds either the G<sub>i</sub> or G<sub>o</sub> heterotrimeric G-protein complex AND it releases GDP from the alpha subunit. The synergy of these aspects define the function of this molecule

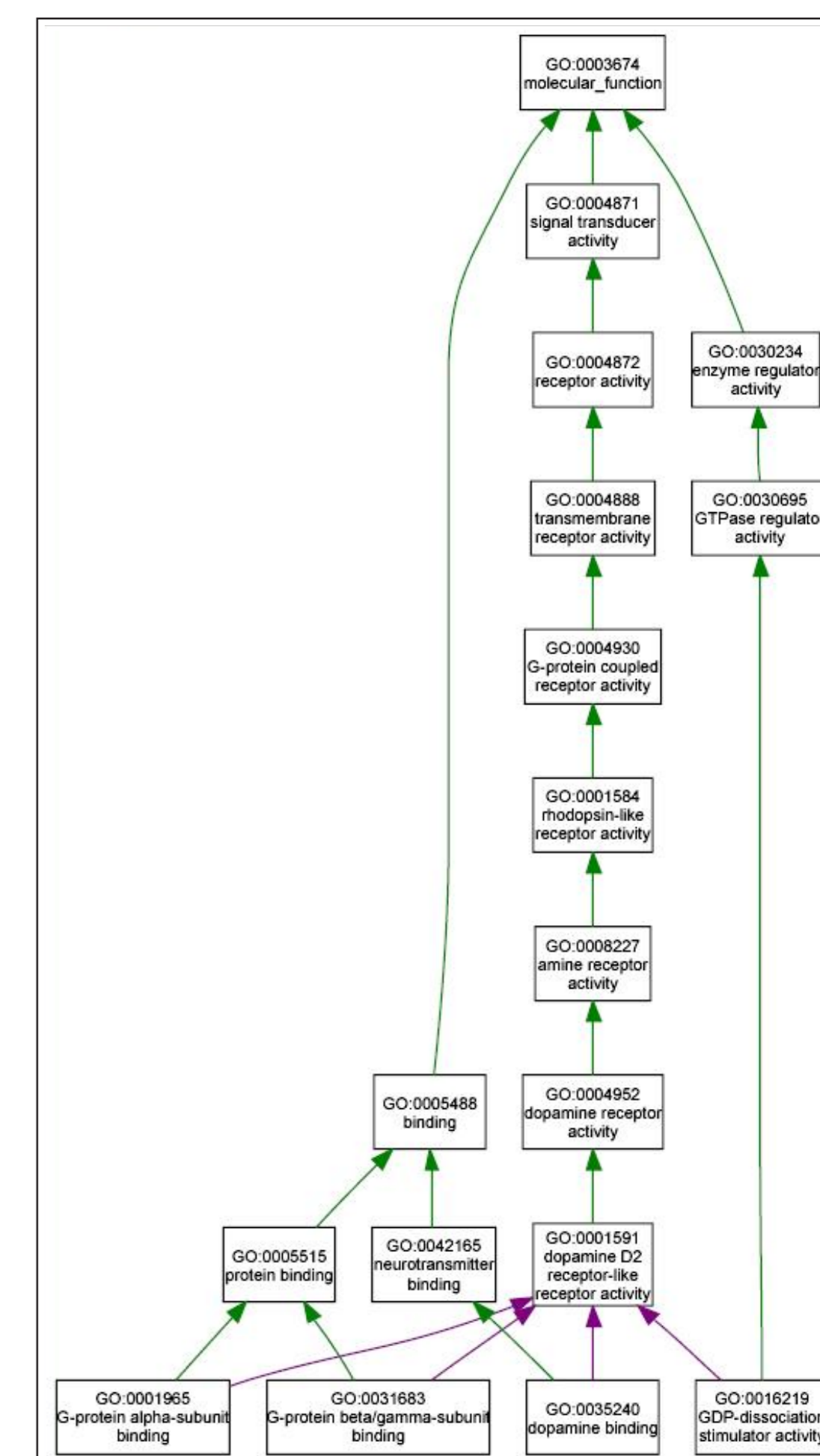


So we could describe the function like this:

- dopamine D2 receptor-like receptor activity ; GO:0001591
- <dopamine binding ; GO:0035240
- <G-protein alpha subunit binding ; GO:0001965
- <G-protein beta/gamma subunit binding ; GO:0031683
- <GDP-dissociation stimulator activity ; GO:0016219

This allows us to express the molecular function of the molecule as the sum of the parts, rather than expressing it as distinct individual activities.

This term structure defines the function of these molecules. Part of means "necessarily has part".

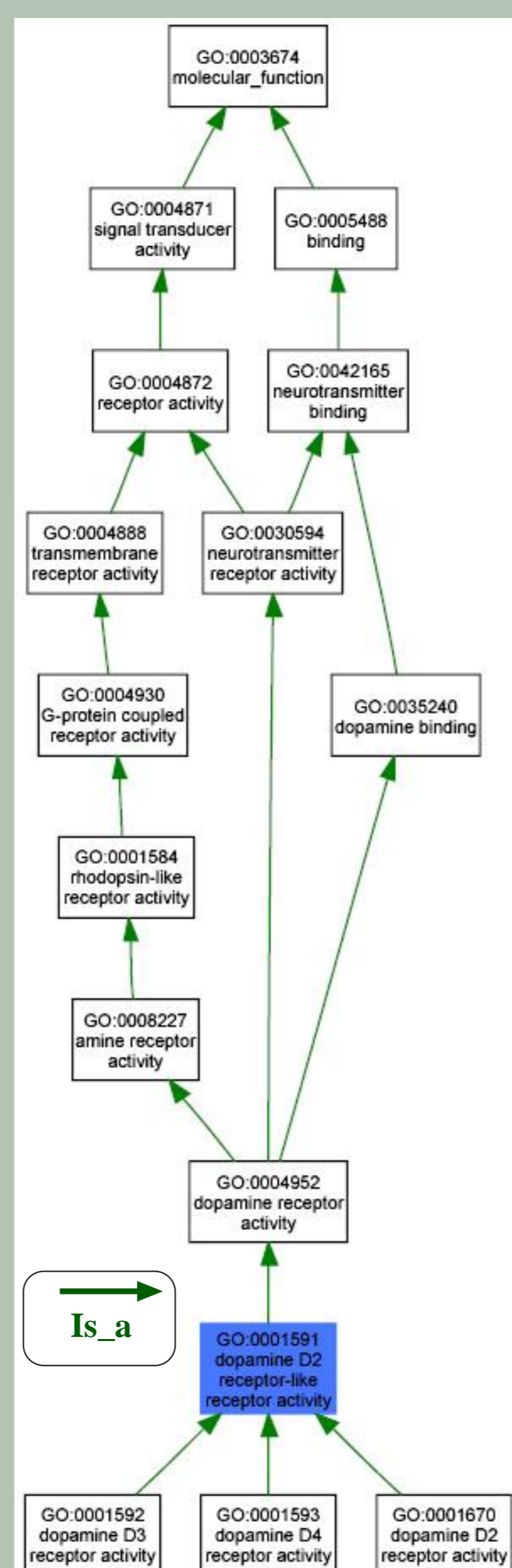


## Current GO representation

**GO term:** G-protein coupled receptor activity  
**GO id:** GO:0004930  
**Definition:** A receptor that binds an extracellular ligand and transmits the signal to a heterotrimeric G-protein complex. These receptors are characteristically seven-transmembrane receptors and are made up of hetero- or homodimers.  
**Number of paths to term:** 1

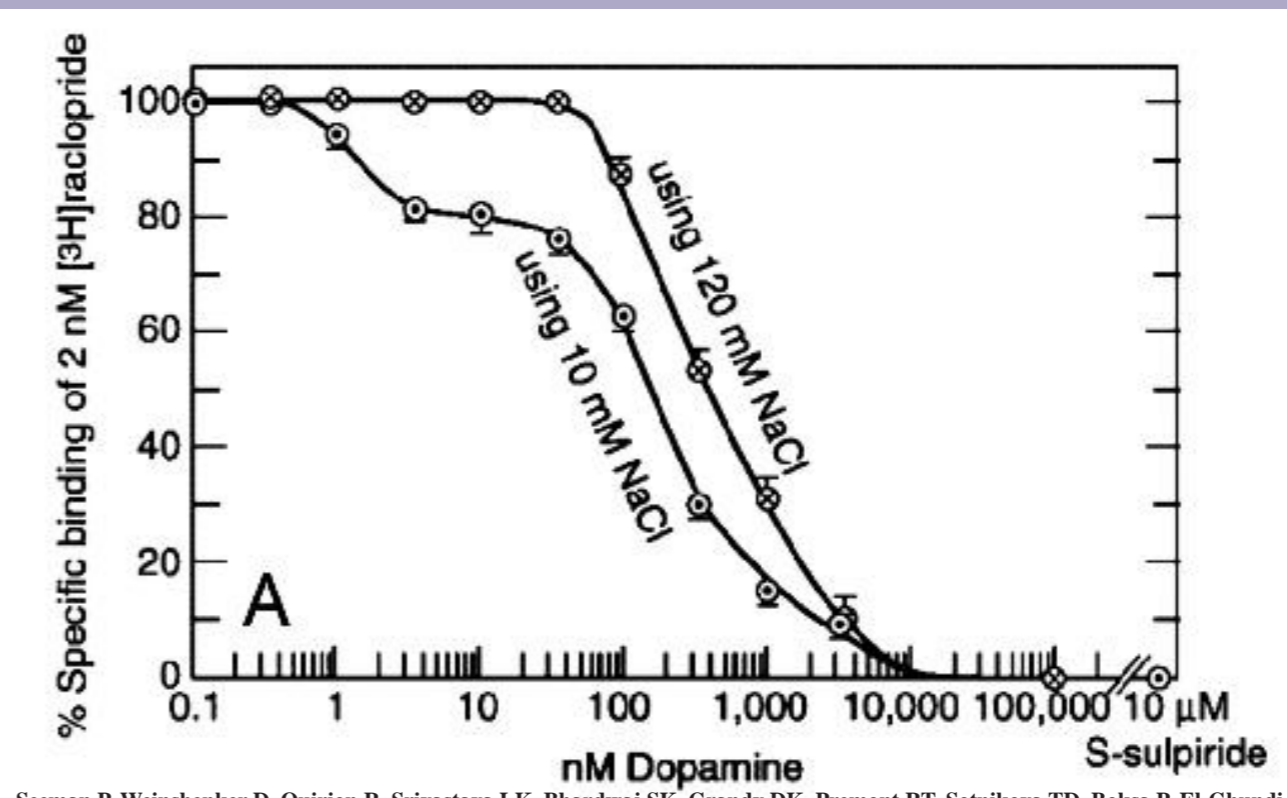


All current relationships are Is\_a



## What does this buy for us in knowledge representation?

If we do experiments to test the parts, then we can make predictions about the function of a molecule based on the assays for its parts.



## Binding experiment

If dopamine binding is only a part of different kinds of dopamine receptor activities and a molecule binds dopamine, then it is a dopamine receptor.

By being exhaustive for parts, we can test the types in the ontology

We can test the ontology because a function should be the sum of its parts. No two complex functions should have exactly the same parts. If they do, then they are the same function. Currently, dopamine D2 receptor-like activity and dopamine D1 receptor-like activity are the same. To distinguish between the two, we would need to describe either the different molecules that can activate them (beyond the scope of GO?) or distinguish between the types of heterotrimeric G-proteins they bind.

Could have:

- dopamine D2 receptor-like receptor activity ; GO:0001591
- <dopamine binding ; GO:0035240
- <G-protein alpha<sub>1/0</sub> subunit binding ; GO:new
- <G-protein beta/gamma<sub>1/0</sub> subunit binding ; GO:new
- <GDP-dissociation stimulator activity ; GO:0016219

- dopamine D1 receptor-like receptor activity ; GO:0001588
- <dopamine binding ; GO:0035240
- <G-protein alpha<sub>s</sub> subunit binding ; GO:new
- <G-protein beta/gamma<sub>s</sub> subunit binding ; GO:new
- <GDP-dissociation stimulator activity ; GO:0016219