# Peroxisome Proliferator Activated Receptors

***Main mechanism of action***

Nuclear hormone receptors which upon ligand binding, heterodimerize with the retinoic acid receptors (RXR), translocate to nucleus, and bind to specific PPAR-elements (AGGTCA n AGGTCA) present in gene promoters to activate de novo transcription

***Subtypes***

Three major subtypes: α, δ, and γ

***Functions***

| | **"Classic"** | **"Neuro"** |
|---|---|---|
| PPARα | Liver cell proliferation | anti-inflammatory |
| PPARδ | Lipid, cholesterol homeostasis | myelin expression |
| PPARγ | Adipocyte differentiation | anti-inflammatory<br>anti-proliferative<br>enhanced metabolism |

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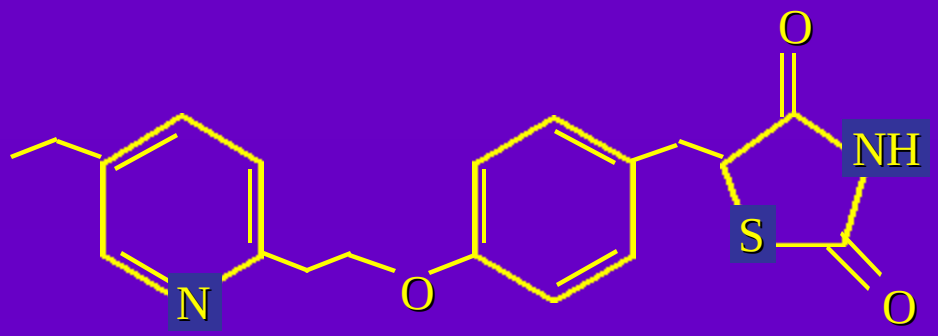
# PPAR Agonists Include

- Fibrates (hypolipidemics)
- Several fatty acids, including naturally occurring 15-deoxy-Δ12,14-PGJ2
  ***but PGJ2 is also a potent inhibitor of IkB kinase
- NSAIDs (indomethacin, ibuprofen, sulindac?) but at high (mM) doses
  *** these also inhibit COX and modulate Aβ processing
- Hi-affinity, selective tyrosine-based drugs (with $EC_{50}$=.001 μM)
- Thiazolidinediones (TZDs), insulin-sensitizing drugs
  *** also exert important receptor-independent metabolic effects
  *** Two (pioglitazone "Actos"; rosiglitazone "Avandia" are currently FDA-approved for treatment of Type 2 diabetes

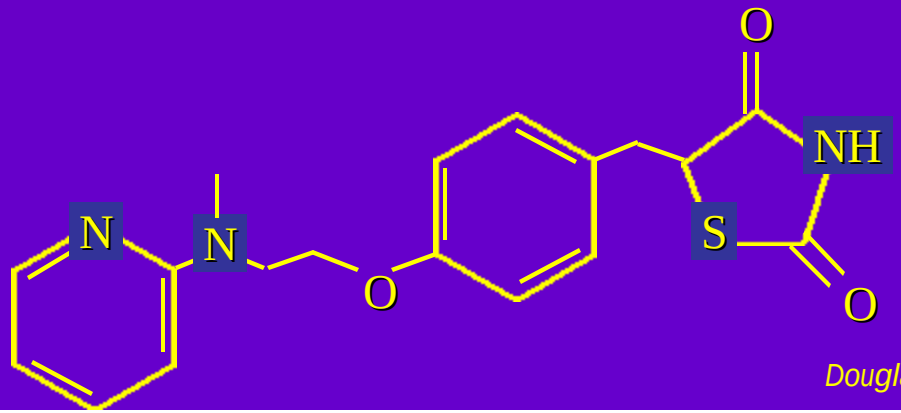
# Structural Comparison of TZDs

Troglitazone (Rezulin)
PPARγ $EC_{50}$ = 0.78 μM


Pioglitazone (Actos)
PPARγ $EC_{50}$ = 0.55 μM




Rosiglitazone (Avandia)
PPARγ $EC_{50}$ = 0.076 μM

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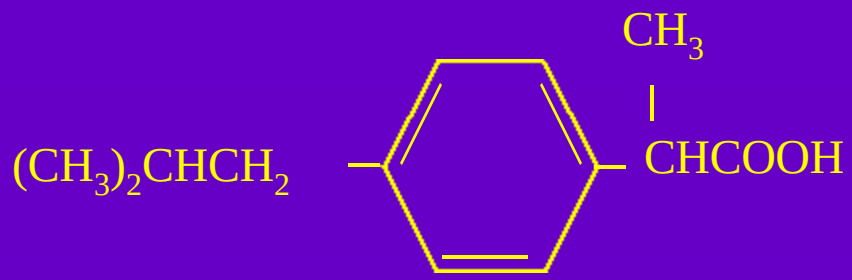
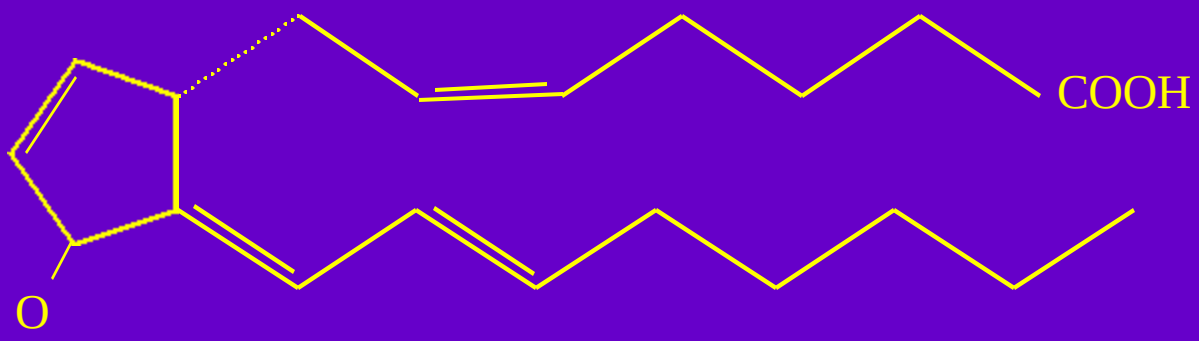
# Structures of Non-TZD PPARγ Agonists




Ibuprofen




15-deoxy-$\Delta^{12,14}$-prostaglandin $J_2$

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# Neurological Indications for PPAR drugs

Alzheimer's disease
Stroke
Parkinson's disease
Multiple Sclerosis
AIDS dementia
Glioma
Sepsis
Remyelination
Complement mediated demyelination

# A Role for PPARg in Alzheimer's Disease?

Epidemiological data show NSAIDs reduce the risk and delay the onset of AD

*Rogers et al. 1993; McGeer 2000*

***However***

Plasma [NSAIDs] are higher than those needed for inhibition of COX2

High [NSAIDs] are PPARγ agonists

In vitro and in vivo, PPARγ agonists prevent neuronal death, while COX2 inhibitors were ineffective or increased death

*Combs et al. 2000; Heneka et al. 1999; Klegeris 1999*

Two COX2 inhibitors (Nimesulide, Celecoxib), as well as other NSAIDs (diclofenac) were ineffective in AD trials

*McGeer 2000*

***Therefore***

*The beneficial effects of NSAIDs in AD may be mediated, in part, by PPARg activation*