Bifunctional and Multi-Target Strategies

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“….Not so Long Ago…”

- One Disease……One Target
- One Target……..One Molecule
  - “Magic Bullet”

‘Hybrid Drugs’

“For reasons hard to understand there is a tendency to develop therapeutic compounds with two or even more types of action, which often differ even in their mechanism of action”

E.J. Ariens (1984)

We Now Know….

- Advances in the delineation of biological mechanisms has shown us that diseases are often complex and heterogeneous and involve multiple events.

- A Single MOA is unlikely to treat all disease symptoms or all patient populations.

Current Status

- Lack of Novel Compounds Going into Development.
  - What new and innovative?
- Failures in Clinical Trials;
  - No Drug Exposure!
    - Need new bio-markers or imaging agents upfront
  - More than One Mechanism Involved!
    - Need new approaches to drug discovery
- How Can we address these shortcomings?

Combination drugs

We know, combinations of drugs that impact multiple targets simultaneously are better at controlling complex disease systems, are less prone to drug resistance and are the standard of care in many important therapeutic areas:

Oncology, Hypertension, Anti-Infectives, etc.

How May We Achieve Multi-Target Therapy?

Drug Cocktail:
Two agents given separately

Multi-component Drug:
Two agents given together

Multiple Ligand Drug:
One active agent

Established Marketed API's

Novel Targets or Compounds

Designed Multiple Ligands (DML)

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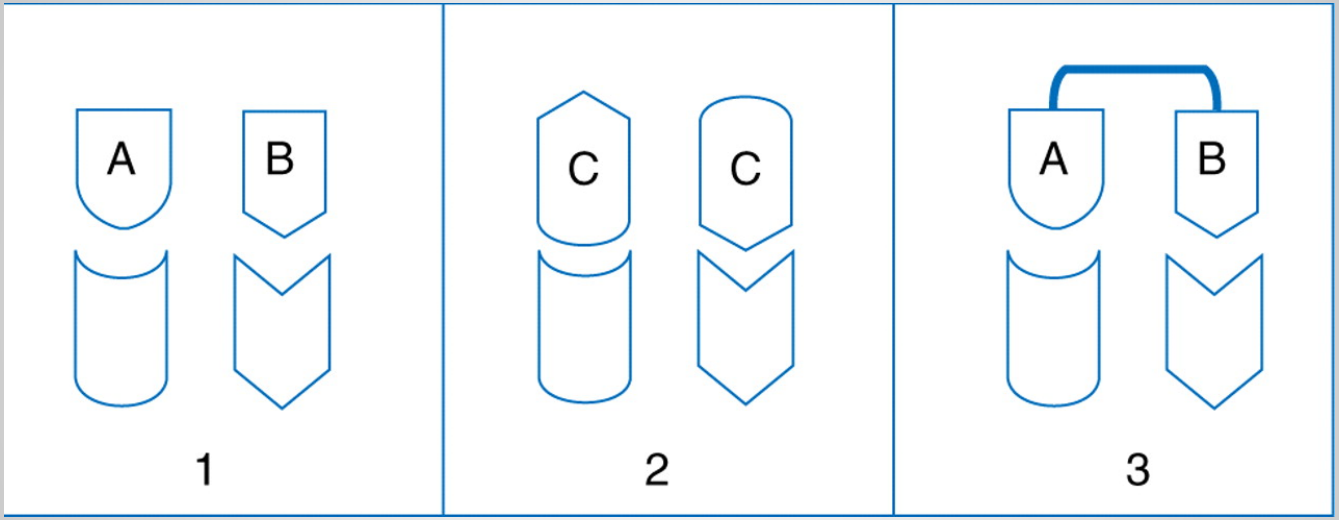
Designed multiple ligands (DML)

A single new chemical entity that will modulate multiple biological targets simultaneously



- *A lower risk of drug-drug interactions*
- Easy formulations
- *Difficult and challenging due to increased complexity in the design and optimization*

Strategy

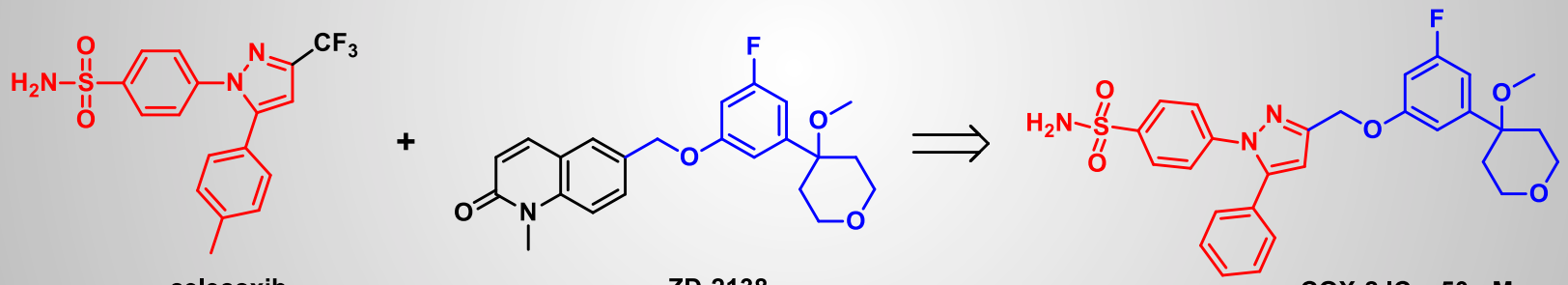
- The most common therapeutic areas for DML projects have been psychiatry, neurodegeneration, oncology, as well as metabolic, cardiovascular and allergic disease.

- One Strategy in multiple ligand design may be to take a target which has been clinically validated for a given disease, and then add one or more additional activities that have been postulated might enhance efficacy or improve safety. --- ***"Design in"***

Merged/Overlapping Pharmacophores

Example: Non-steroidal Anti-Inflammatory Drugs :

Inhibiting COX-1 and COX-2; key enzymes in prostaglandin (PG) biosynthesis from arachidonic acid. COX-1 is involved in synthesis of prostaglandins and thromboxane, but COX-2 is only involved in the synthesis of prostaglandin



celecoxib
COX-2 inhibitor

ZD-2138

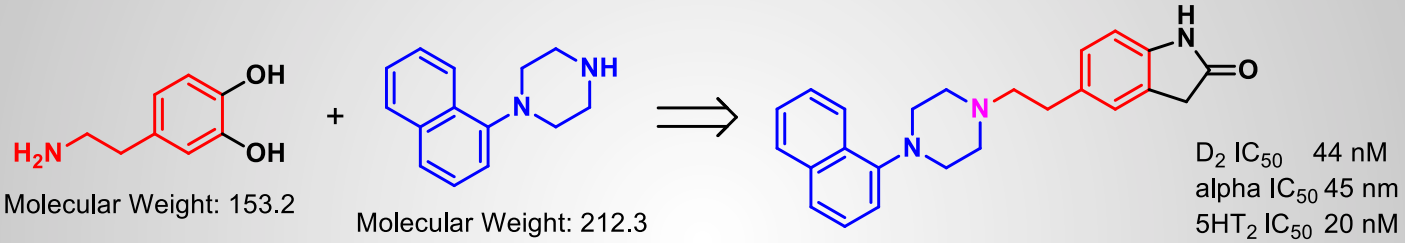
COX-2 IC_{50} 50 nM
5-LOX IC_{50} 3 nM
COX-1 IC_{50} > 10 ?M

- ✓ NSAID-induced gastric toxicity may involve the shunting of arachidonic acid metabolism from the COX to the 5-lipoxygenase (5-LOX) pathway. Combined inhibition of COX-2 and 5-LOX may provide safer and more effective NSAIDs.

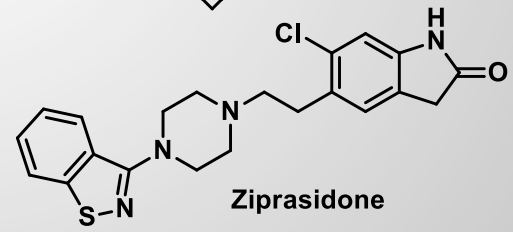
Merged/Overlapping Pharmacophores

Successful application—

Ziprasidone was launched in 2001 for the treatment of schizophrenia



This approach delivered an oral therapy



Molecular Weight: 412.9

D_2 IC_{50} 5 nM
alpha IC_{50} 11 nm
$5HT_2$ IC_{50} 0.42 nM

Merged/Overlapping Pharmacophores

- **A more complex situation**:
- Very different GPCR's
- Different activities required

Required is a Mu opioid Agonist and a CCK Antagonist within a single molecule.

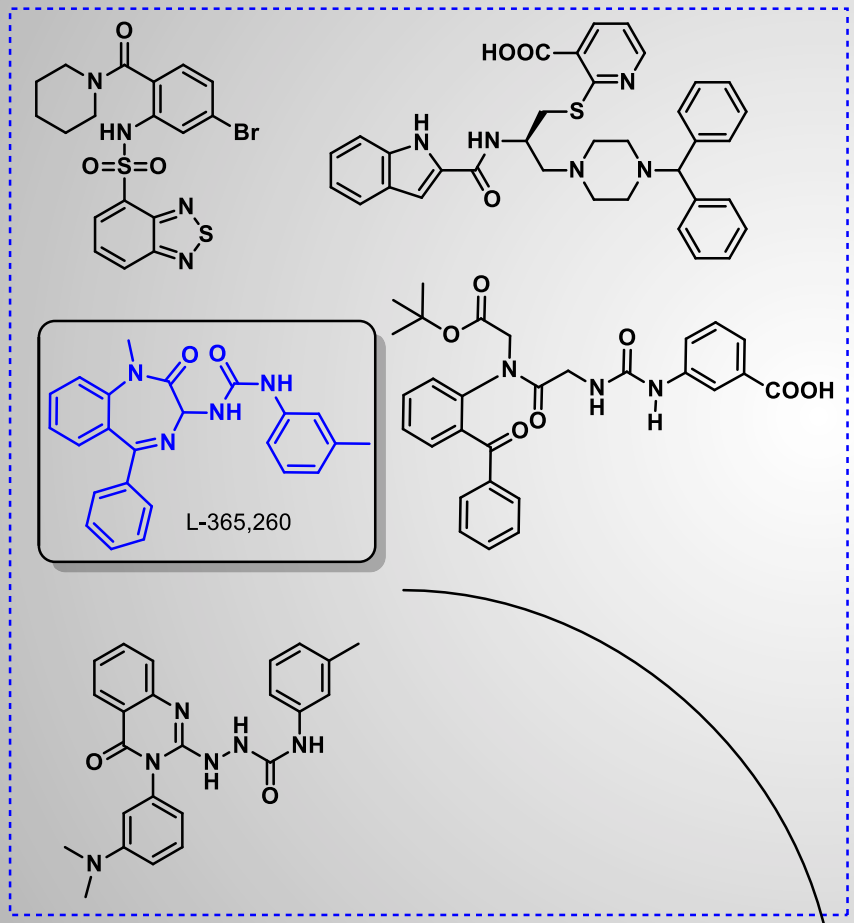
Rationale

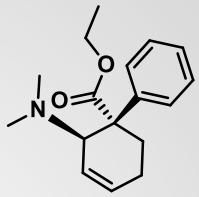
- Chronic Administration of Mu Opiates:
  - Increases release of inflammatory neuropeptides, including Substance P, Cholecystokinin (CCK)

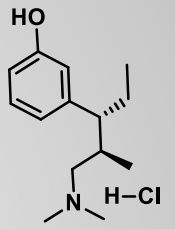
Hypothesis

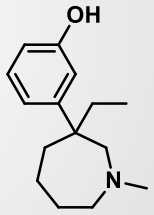
- A mu receptor agonist and an inflammatory neuropeptide (e.g. CCK, NK1) antagonist would be analgesic and also reverse inflammation caused by chronic mu opiate use.
- Pioneering work by Hruby, Porreca et al using peptidic hybrids support this idea.
- Some animal/clinical validation.

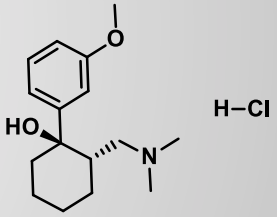
Merged/Overlapping Pharmacophores

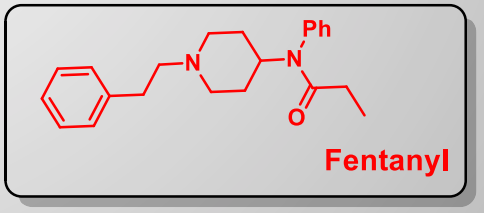



Tilidine


Tapentadol


Meptazinol


Tramadol



CCK antagonist

Mu-opioid agonists

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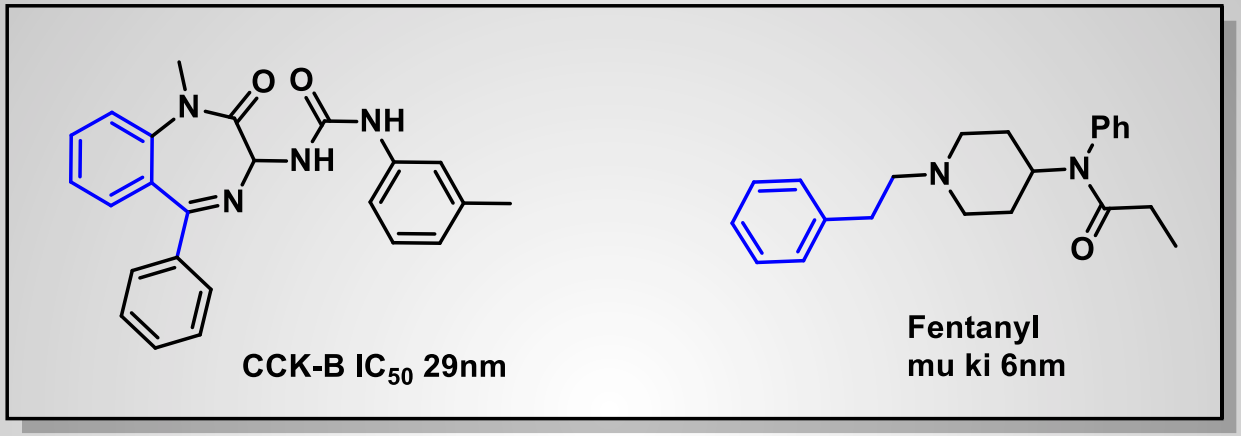
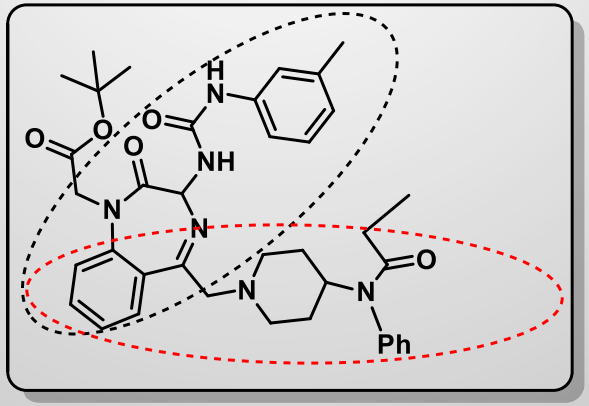
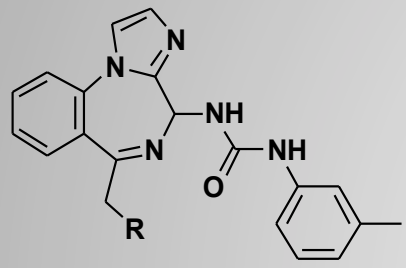
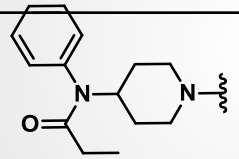
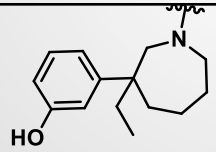
Initial Hits





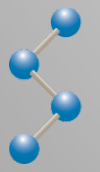
Binding Data of Initial Hits



CYM #	R	MW	rMOR IC50 Ki (nM)	CCK-1 IC50 Ki (nM)	CCK-2 IC50 Ki (nM)
1285	H	345.4	>10,000	32	129
1286		575.7	4	345	512
1287		562.7	70	5	125

Summary Status

- Combining pharmacophores from 2 very different GPCR's yielded "hybrid ligands" that *bind to both protein targets selectively*.
- Initial functional data reveal that these initial hits are full antagonists at the CCK receptor(s), and partial agonists at the Mu opioid receptor.
- Optimization for function, potency and physicochemical parameters are ongoing



Challenges Going Forward

- Physicochemical properties
  - Can we modify enough?
- How can we formulate better?
- How can we use GPCR x-ray structural data?
- Is this a strategy that can be made generic?
- How will this strategy fit with today's requirements for clinical success ?