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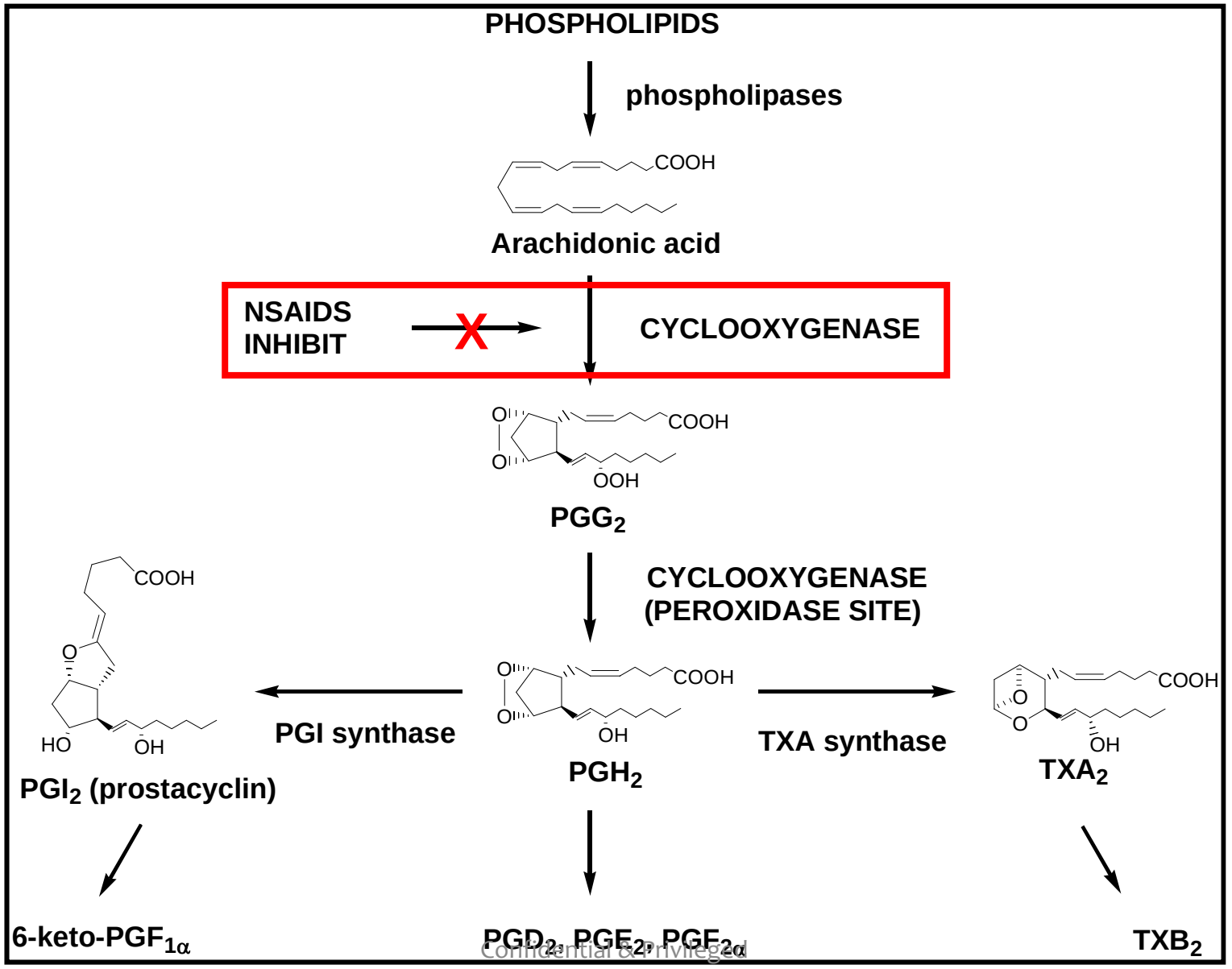
The Discovery of Novel, Potent and Orally Active COX-2 Inhibitors: **‘Hit’ to Candidate**

Site of Action of NSAIDs



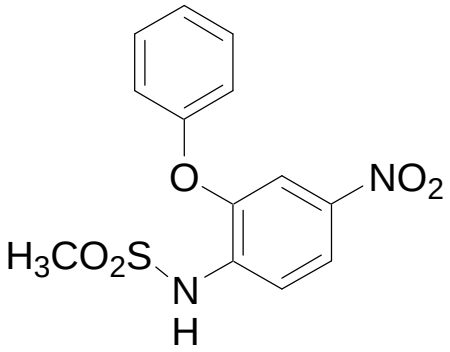
Beneficial and undesired effects attributed to single pharmacological action

- **NSAIDs – diverse chemical structures**

- **Similar therapeutic actions**
  - **Antipyretic**
  - **Anti-inflammatory**
  - **Analgesic**

- **Similar toxic effects**
  - **Ulceration**
  - **Renal toxicity**

Breaking Science



Nimesulide

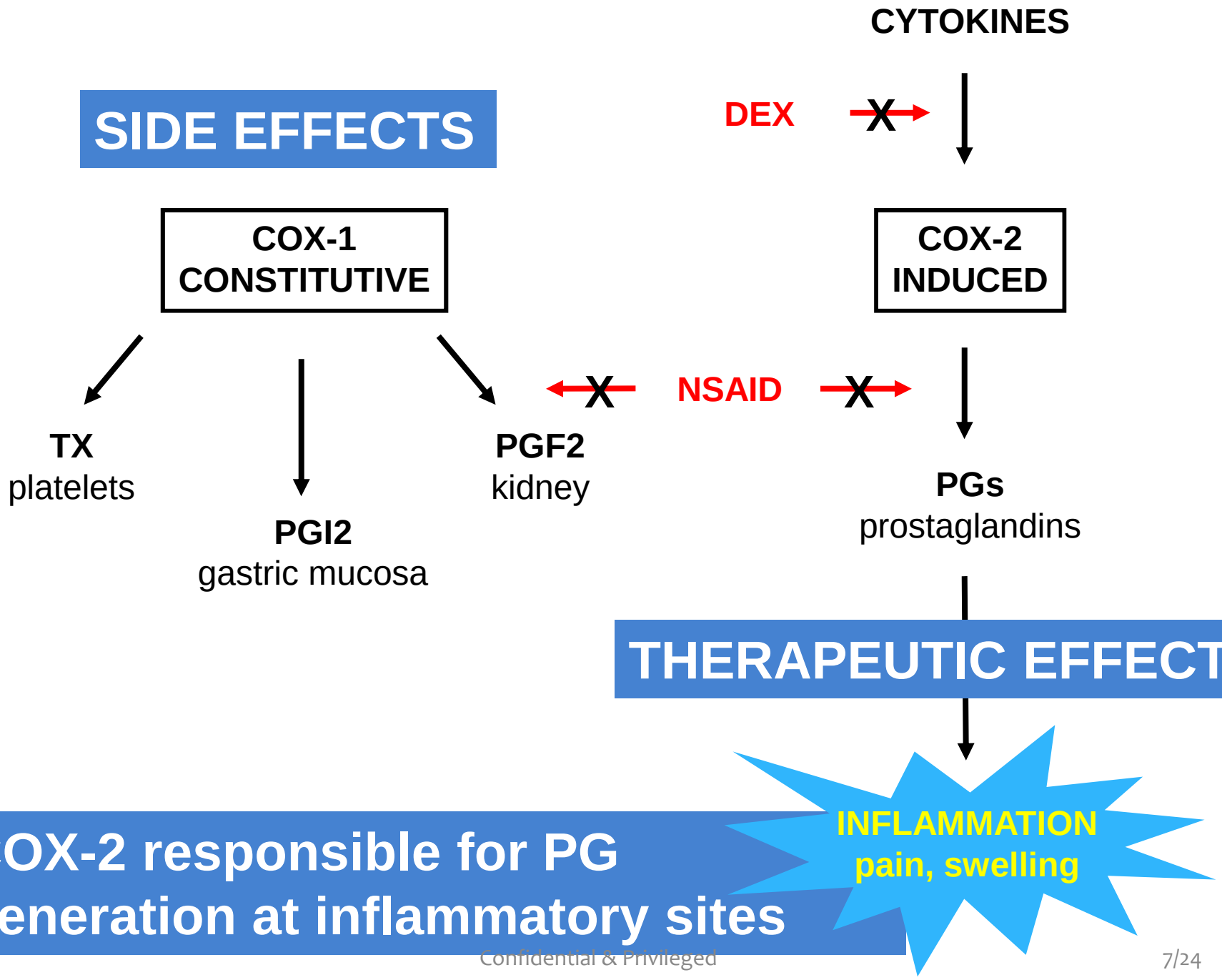
- **Marketed in Italy since 1985**
- **NSAID anti-inflammatory activity but better tolerated**
- **Not COX inhibitor*?***

Breaking Science

Needleman et al

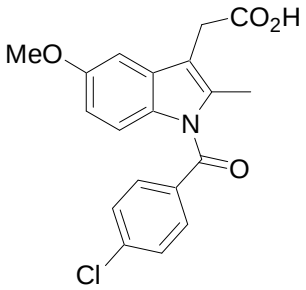
- **In inflammatory conditions there is a marked increase in mass of COX enzyme**
- **Stimulation of inflammatory cells with cytokine (e.g., IL-1) causes increase in PG synthesis capacity and COX enzyme levels**
- **Blocked by dexamethasone, but basal COX not altered**

Hypothesis, two COX enzymes

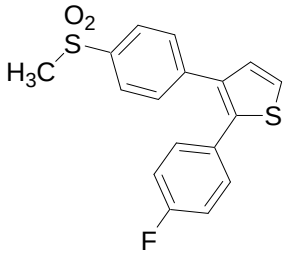


Breaking Science

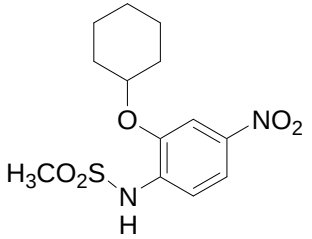
	IC_{50} (μM)			ED_{50} (mg/kg)	
	COX-1	COX-2		Adj Arthritis	GI ulcer
indomethacin	0.2	1.2		0.1	8
DuP 697	0.8	0.01		0.3	>600
NS 398	>10	0.01		4.7	>1000



indomethacin

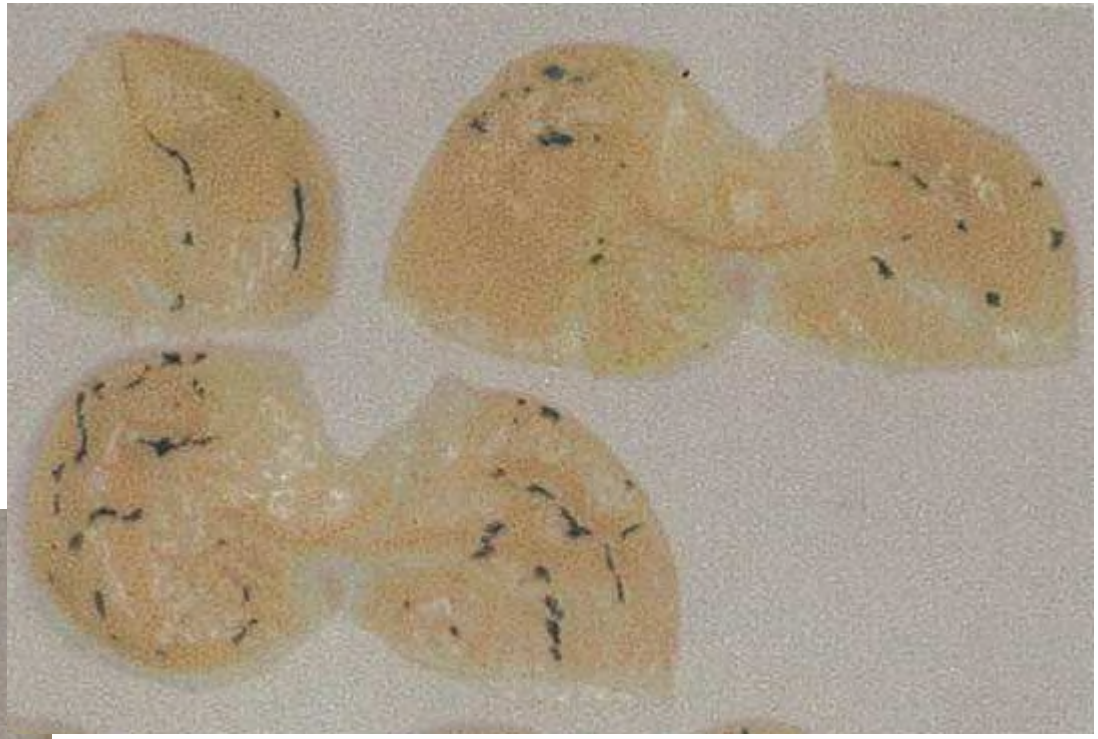


DuP 697



NS 398

Ulceration



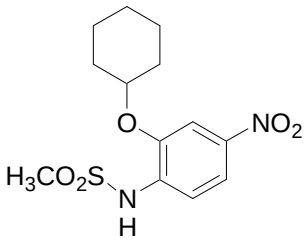
10mg/kg indomethacin

Normal

Competitor Landscape

Sulides

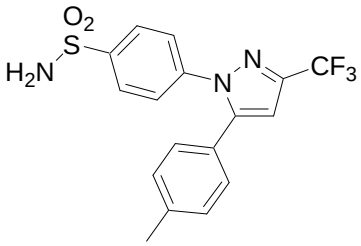
Merck, Ciba Geigy (Novartis), Bayer, Taisho, Fujisawa, Toyama, etc.



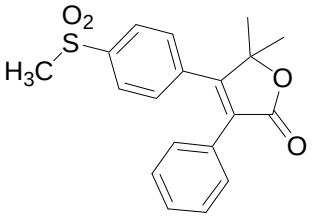
NS 398

Tricyclics

Searle (Pharmacia), Merck, GSK, Roche, JT, Sankyo, Fujisawa, Chugai, etc.



Celebrex

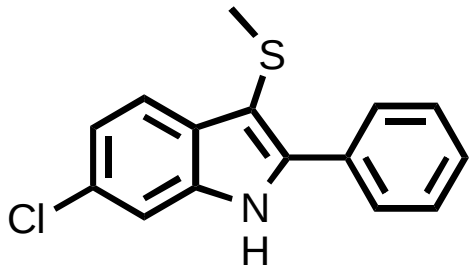


Vioxx

Strategy

- **The Sulide class**
  - preliminary SAR around NS-398 was “tight”
    - limited space
- **Tricyclics**
  - highly competitive, limited patent space, difficult to differentiate
    - limited opportunity (→ License-in)
- **Screen ‘file’ for novel proprietary series**
  - **high risk**
    - initiate HTS

"Hit" Profile



IC_{50} (μM)	
COX-1	COX-2
0.04	0.01

Pharmacology:

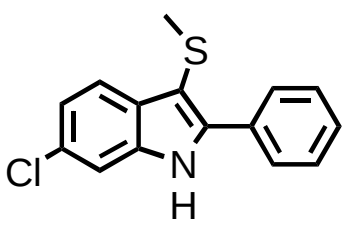
cRFE: 42% inh @ 30 mg/kg, po

Pharmacokinetics:

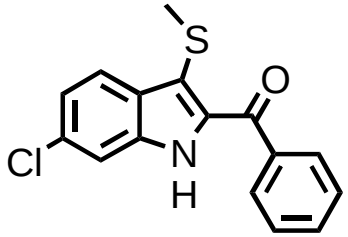
Cmax (rats): 0.15mg/ml @ 10 mg/kg, po

Not well absorbed

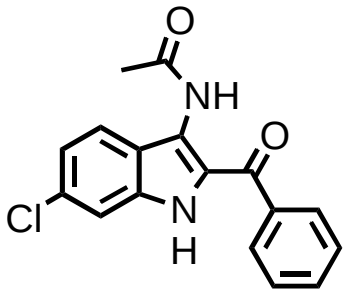
Improvement of Selectivity



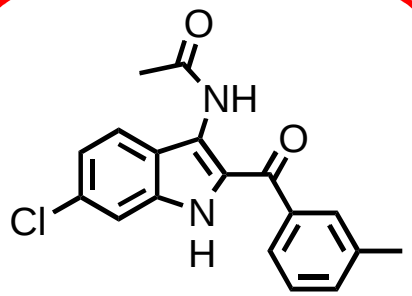
COX-2 (ratio COX-1)
0.01 μM (4)



COX-2 (ratio COX-1)
0.03 μM (10)

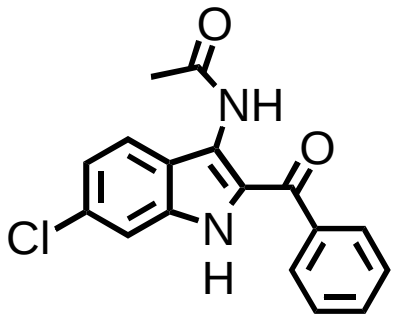


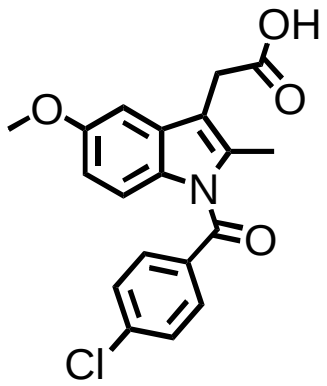
COX-2 (ratio COX-1)
0.12 μM (6)



COX-2 (ratio COX-1)
0.1 μM (35)

“Selectivity was improved, but oral absorption was poor”





INDOMETHACIN

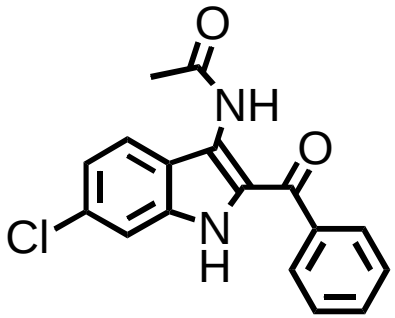
- **H-bond donors: 2**
- **mol. wt: 312.76**
- **cLogP: 4.0 (mLogP: 3.15)**
- **N + O = 4**

- **LogD: 3.6**
- **Solubility in PBS: 7 mg/ml**
- **(Caco-2: high permeability)**

- **H-bond donors: 1**
- **mol. wt: 357.80**
- **cLogP: 4.18 (mLogP: 2.85)**
- **N + O = 5**

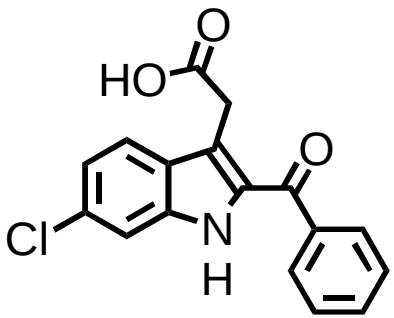
- **logD: 1.5**
- **Solubility in PBS: 208 mg/ml**
- **(Caco-2: high permeability)**

Solubility Significantly Improved



- **H-bond donors: 2**
- **mol. wt: 312.76**
- **cLogP: 4.0 (mLogP: 3.15)**
- **N + O = 4**

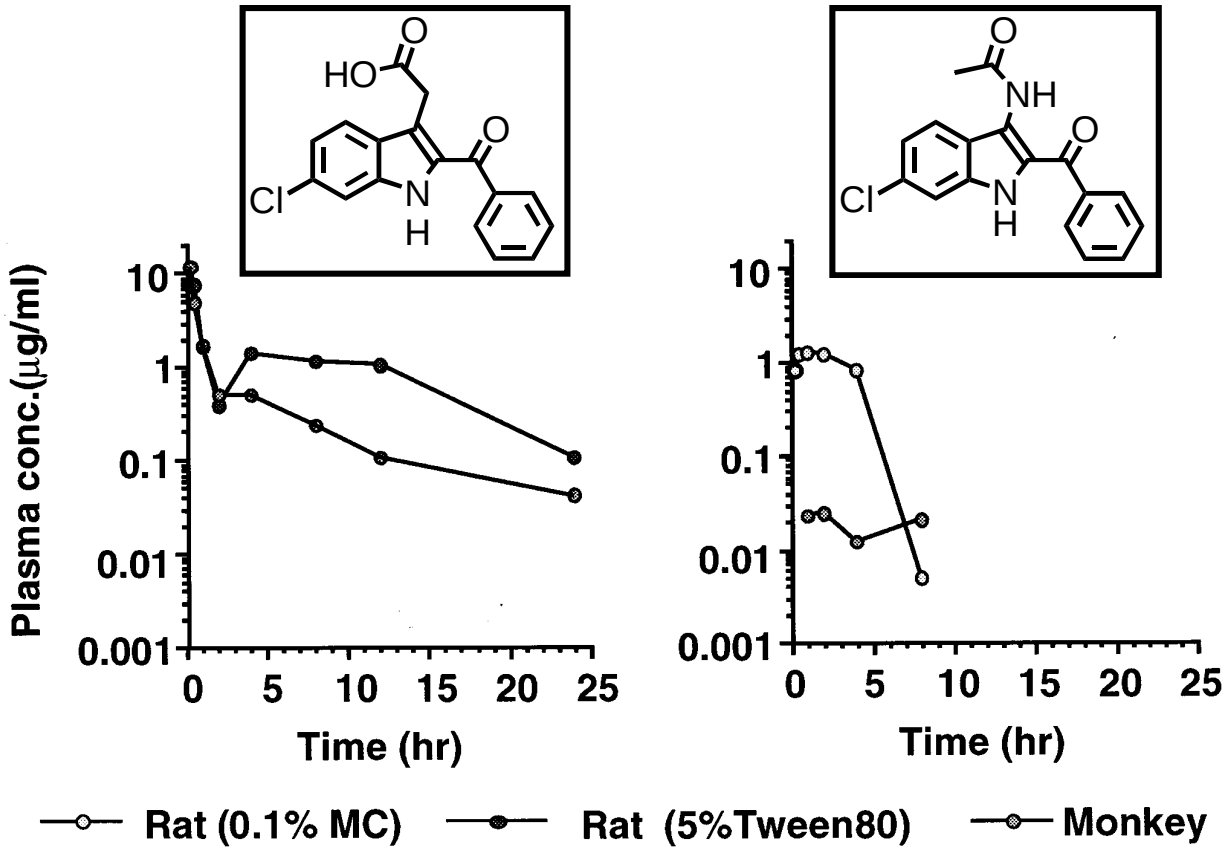
- **LogD: 3.6**
- **Solubility in PBS: 7 mg/ml**
- **(Caco-2: high permeability)**



- **H-bond donors: 2**
- **mol. wt: 357.80**
- **cLogP: 4.18 (mLogP: 2.85)**
- **N + O = 5**

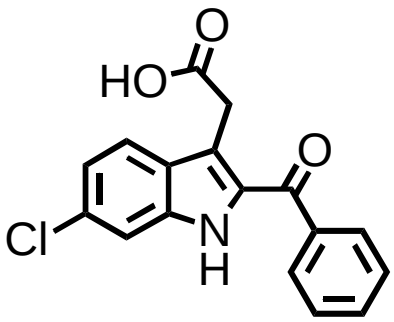
- **logD: 1.7**
- **Solubility in PBS: >1000 mg/ml**

Absorption Improved



PK in rats at 10 mg/kg, po and in monkeys at 5 mg/kg, po

However ---



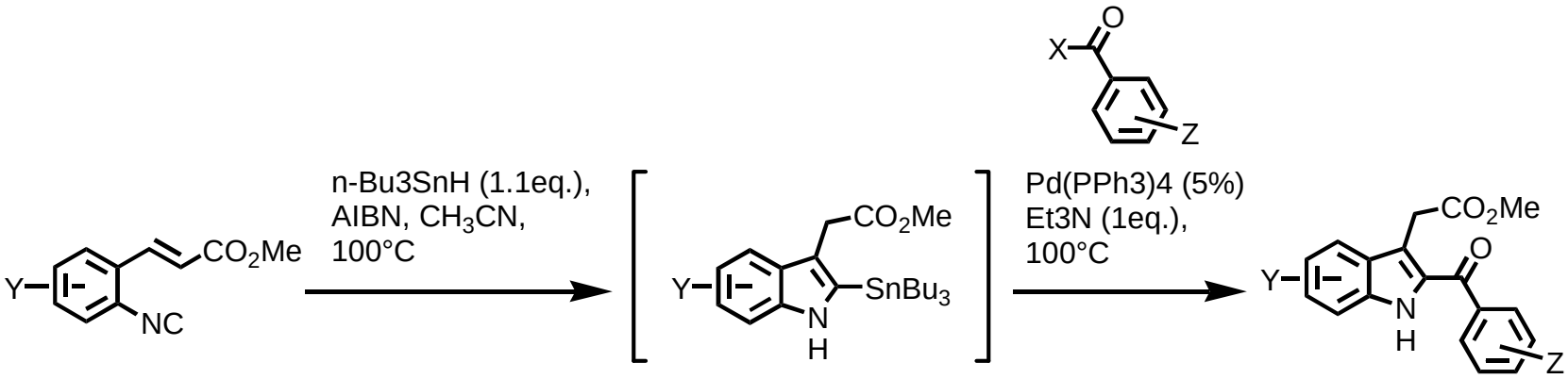
IC_{50} (μM)	
COX-1	COX-2
0.79	0.4

“Need to manifest selectivity for COX-2”

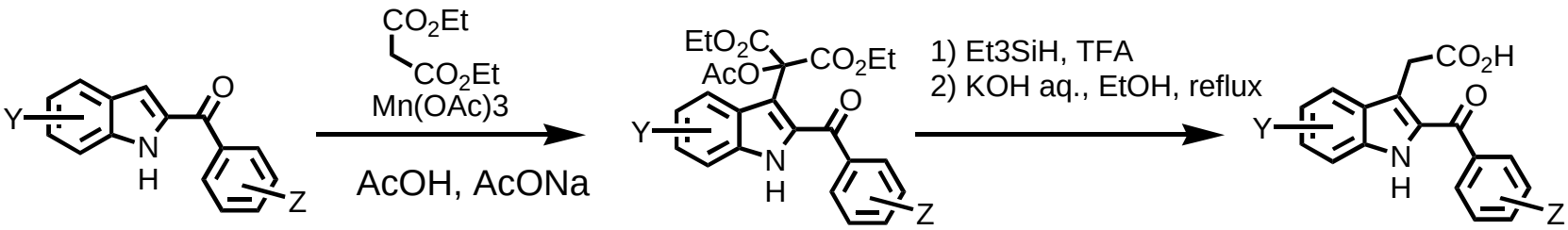
Need to develop synthetic route that,

- **Allows rapid SAR**
  - ✓ **Regio-selective**
  - ✓ **Readily available starting materials**
- **Is scaleable**

Known Synthetic Routes



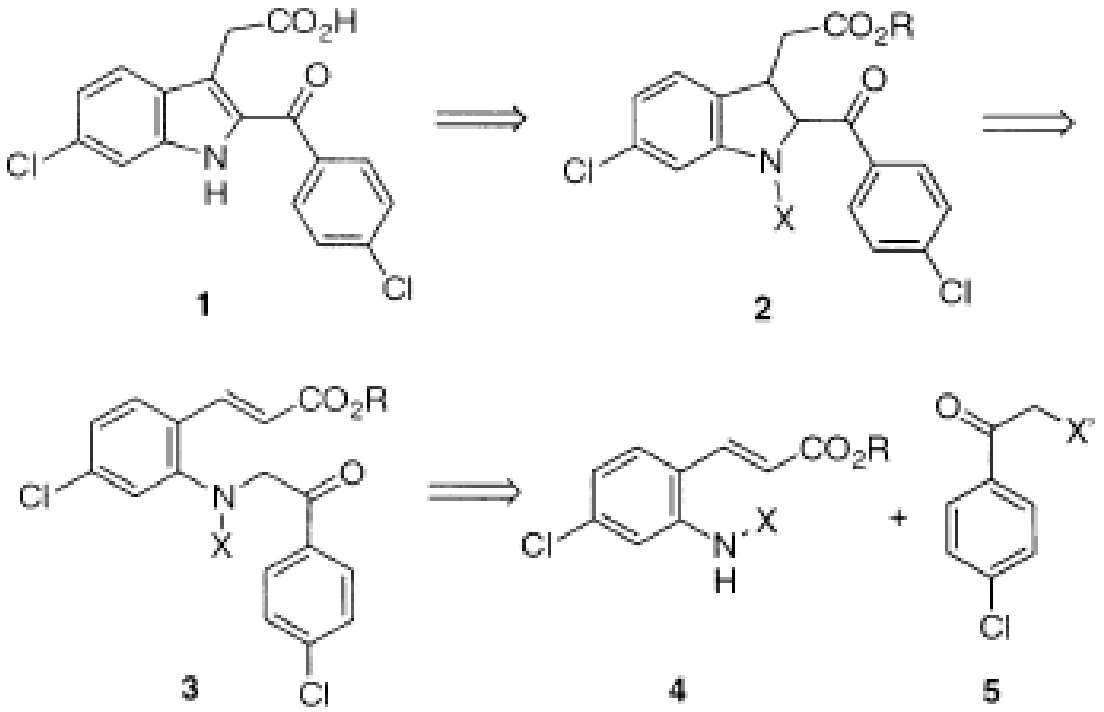
ref. T.Fukuyama et.al, J.Am.Chem.Soc., 116, 3127-3128 (1994)



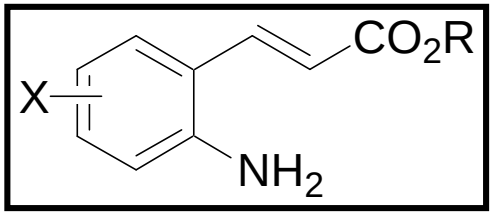
ref. E.Baciocchi et. al, J.Org.Chem., 58, 7610-7612(1993); D.R.Artis et.al, Can.J.Chem., 70, 1838-1842(1992)

Retro-synthesis

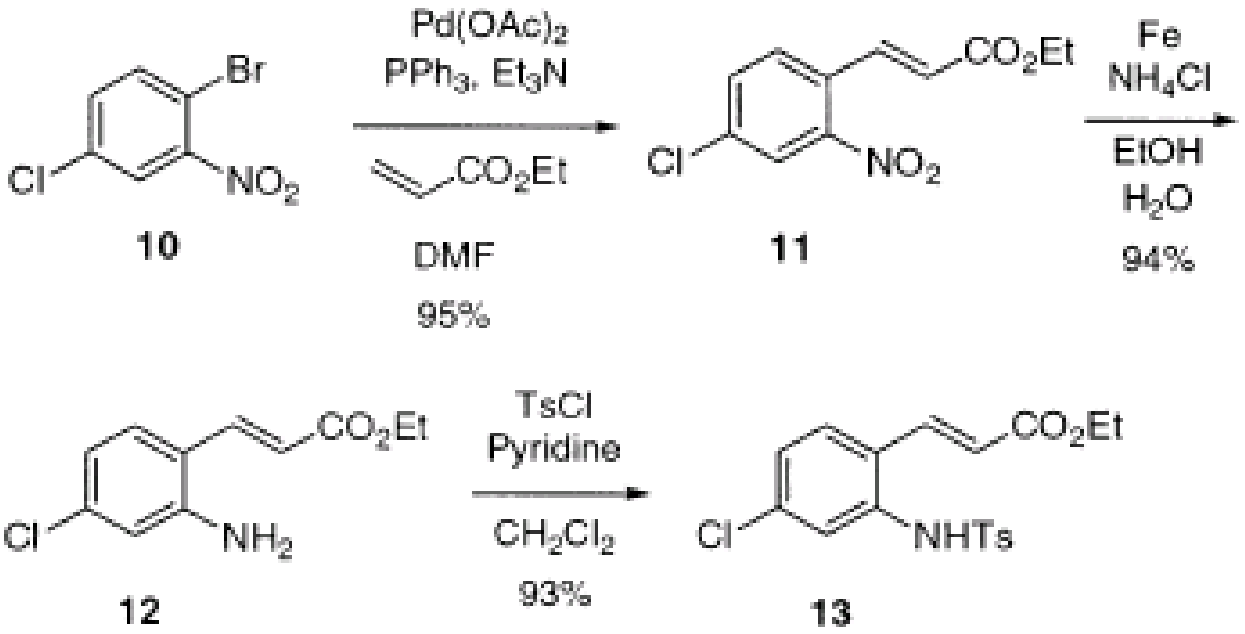
SCHEME 1



Synthesis of Key Intermediate

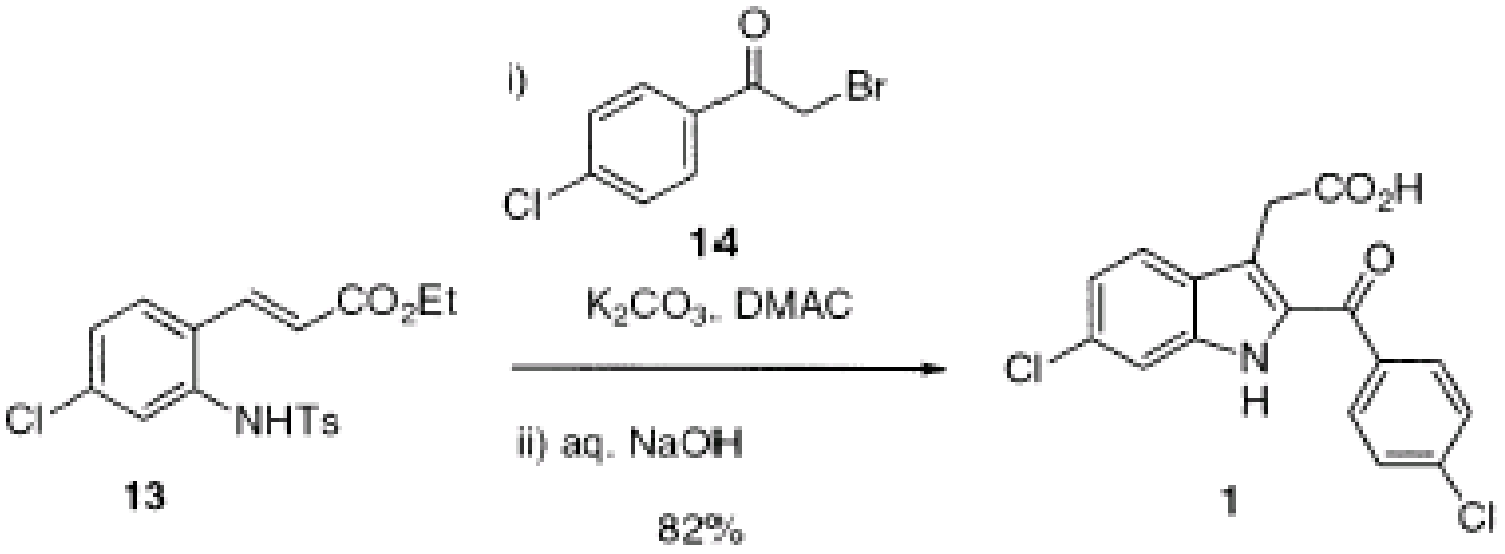


SCHEME 3

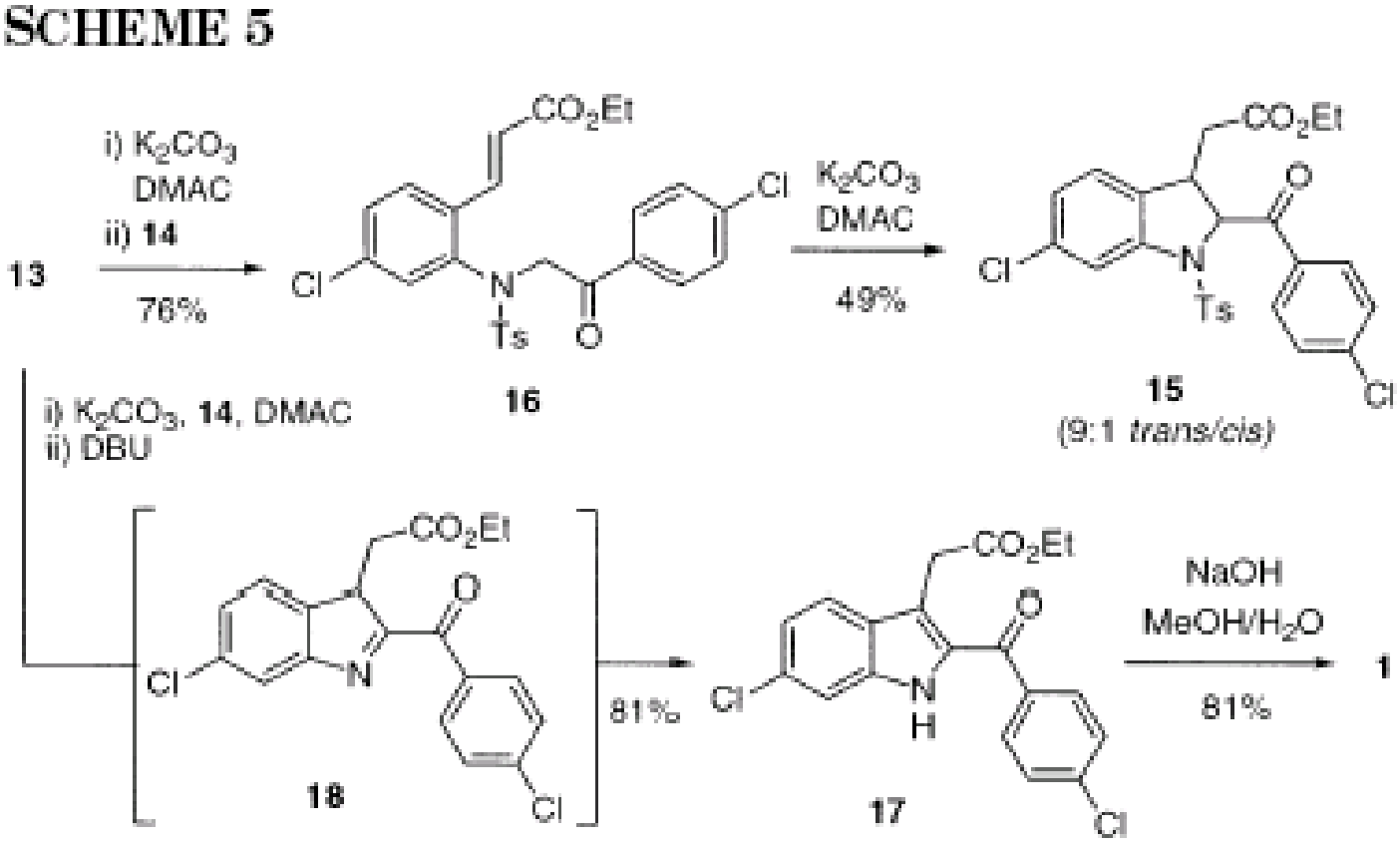


Indole Formation

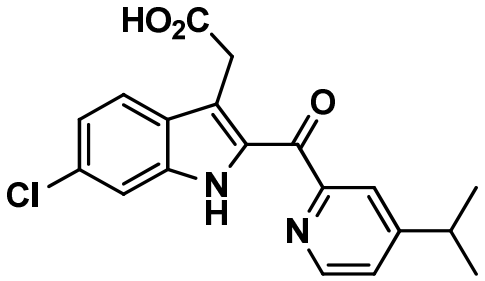
SCHEME 4

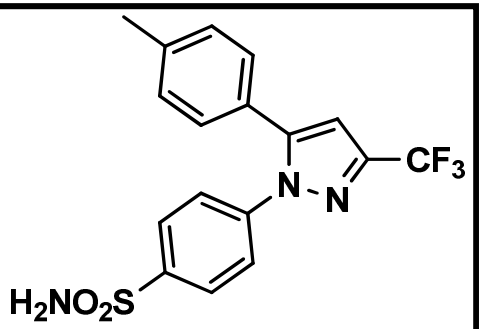


Indole Formation



Candidate vs. celecoxib





		Celebrex
in vitro		
COX-2 (IC50; μM)	0.04	0.045
ratio (to COX-1)	>250	5
in vivo		
cRFE (ED40; mg/kg)	6.9	20-30
car.-Hyperalgesia (ED50; mg/kg)	2.7	1.6
MUD (mg/kg)	>300	>300