Gefitinib

(Brand names: Iressa®)

For curing lung cancers

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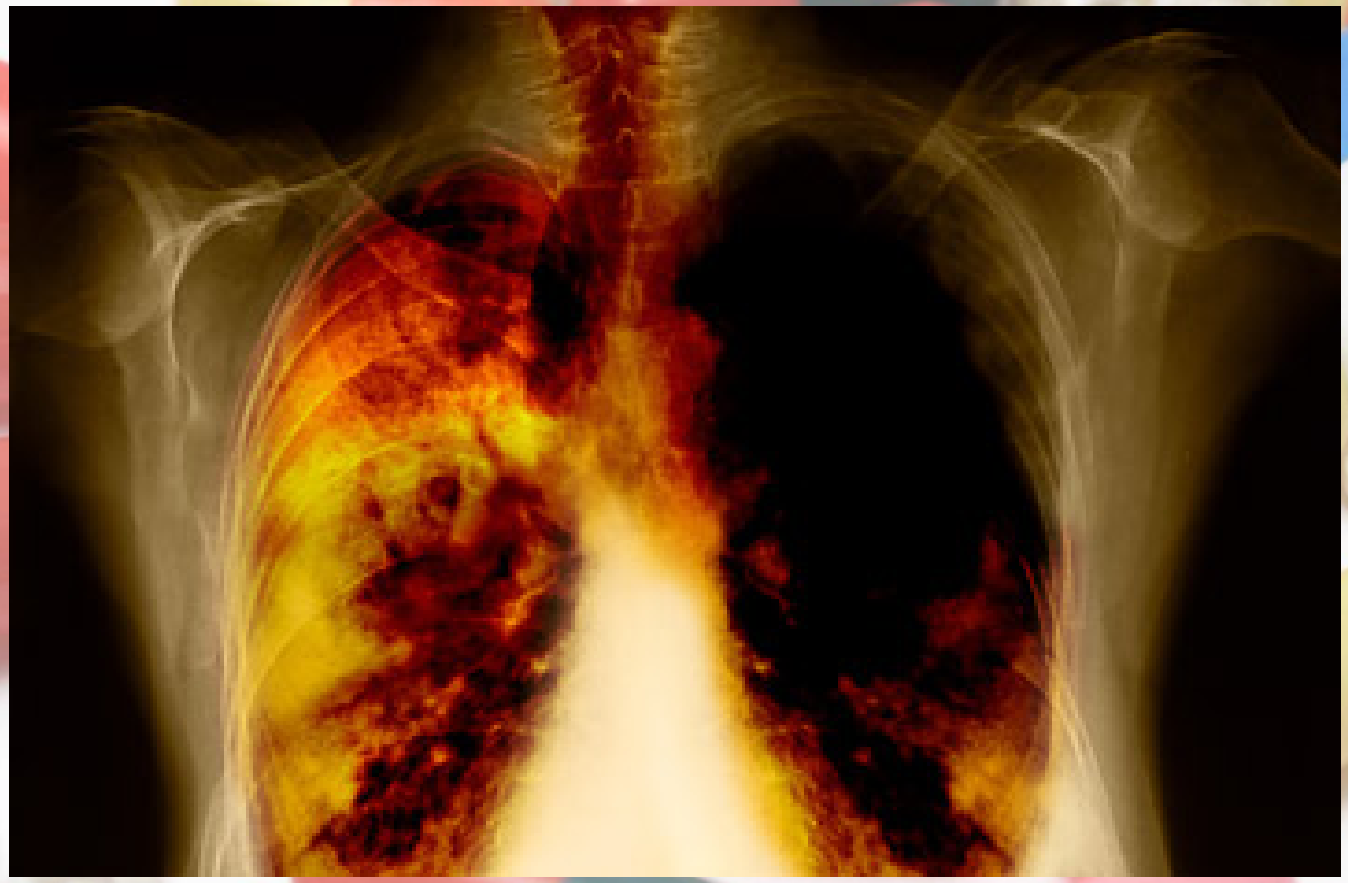
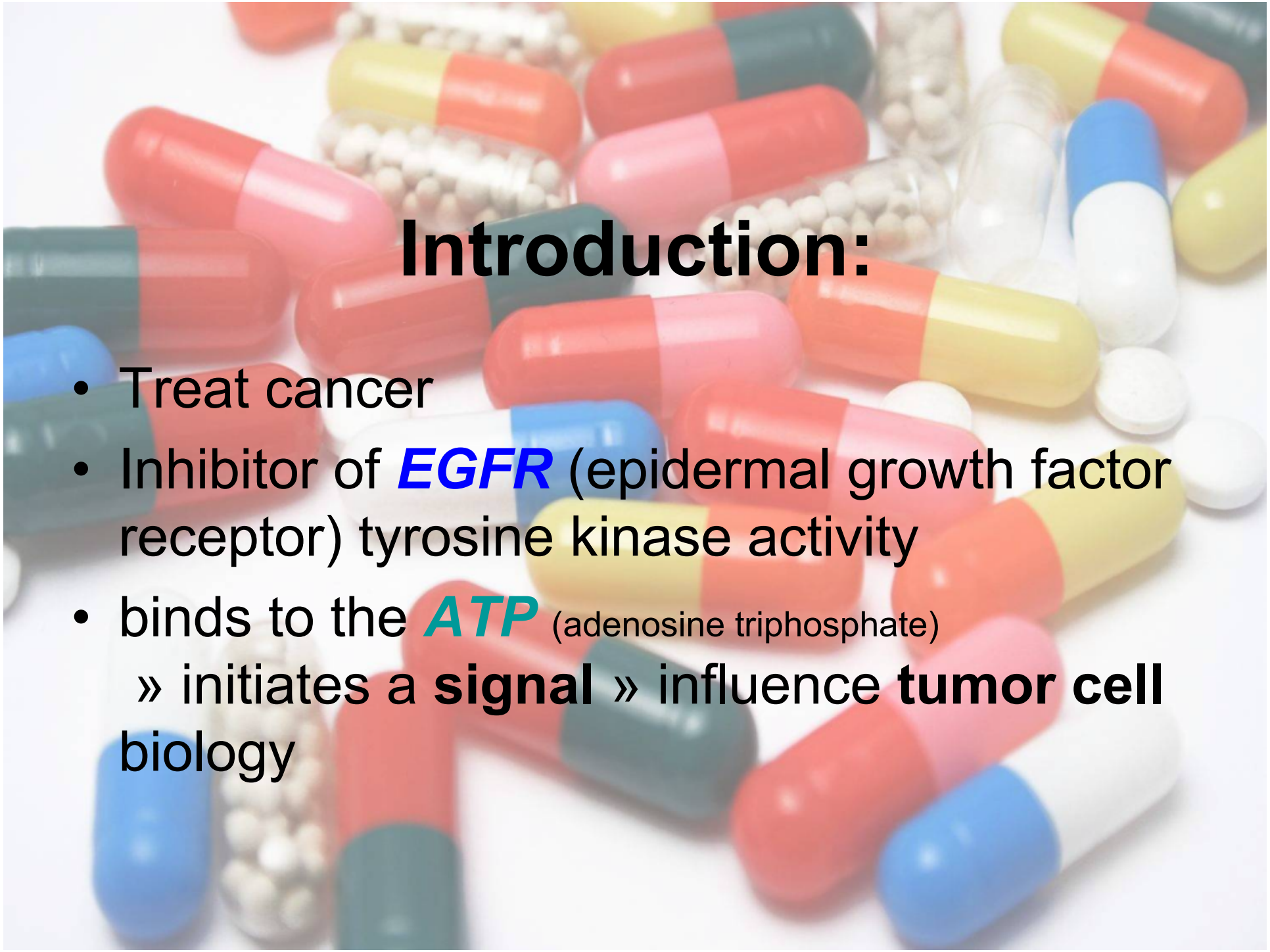


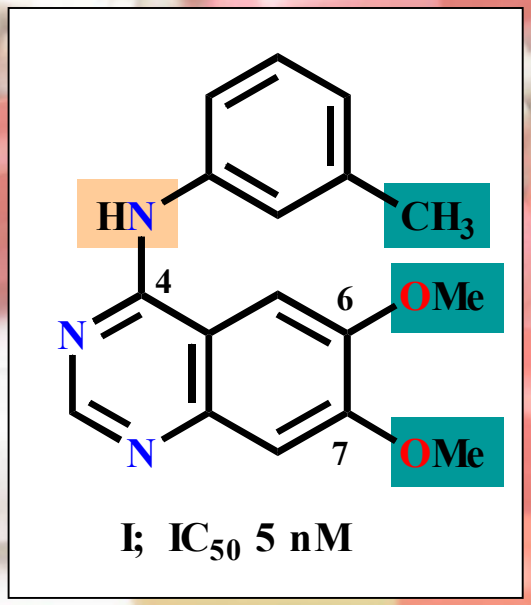
1.18 million people
die of Lung cancer each year



Introduction:

- Treat cancer
- Inhibitor of ***EGFR*** (epidermal growth factor receptor) tyrosine kinase activity
- binds to the ***ATP*** (adenosine triphosphate)
  » initiates a **signal** » influence **tumor cell** biology

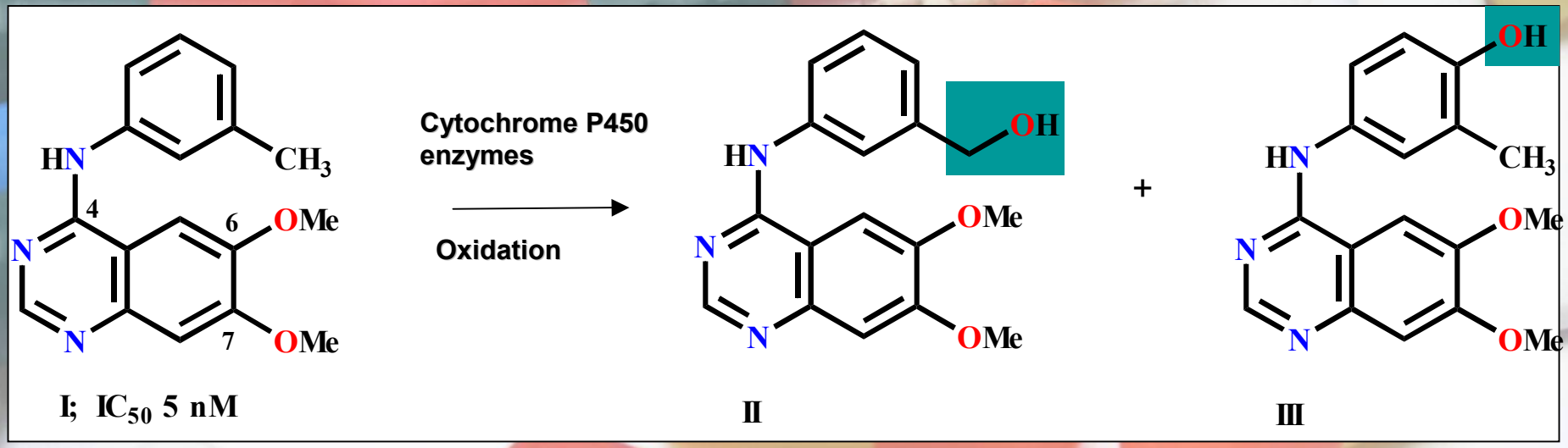
Lead compound discovery



I; IC_{50} 5 nM

The **secondary amine**, electron-donating substituents and small lipophilic group are all important for activity. Useful *in vitro* activity, lower *in vivo* activity due to rapid metabolism. It is metabolised by cytochrome P450 enzymes.

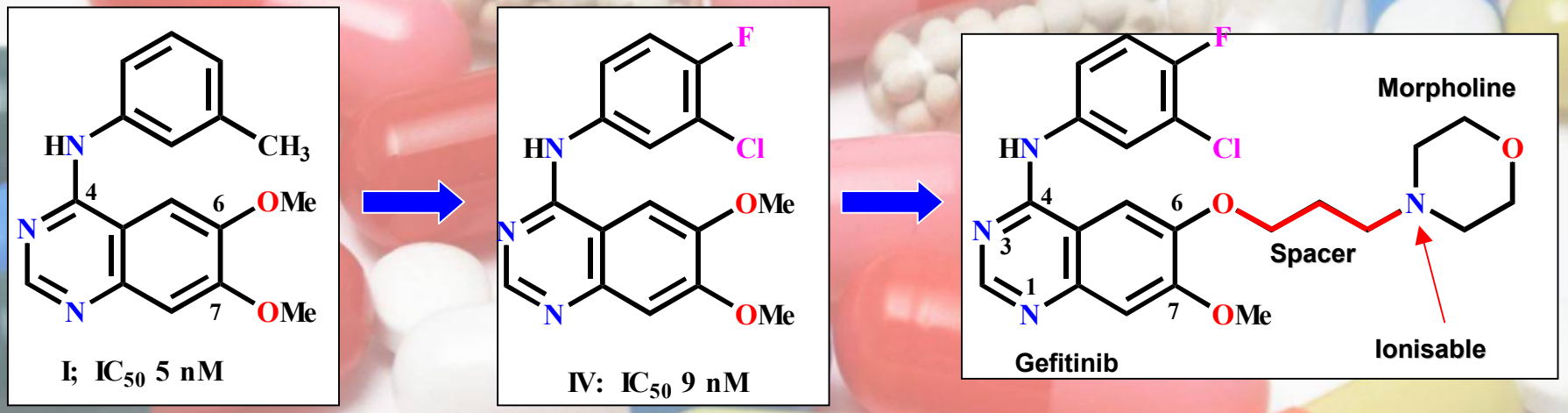
Metabolism of the lead compound



- **Methyl group** and ***para*-position** of aromatic ring are susceptible positions.
- **Blocking** metabolism should improve the half life of the drug.

Molecular modification

- **Drug design**

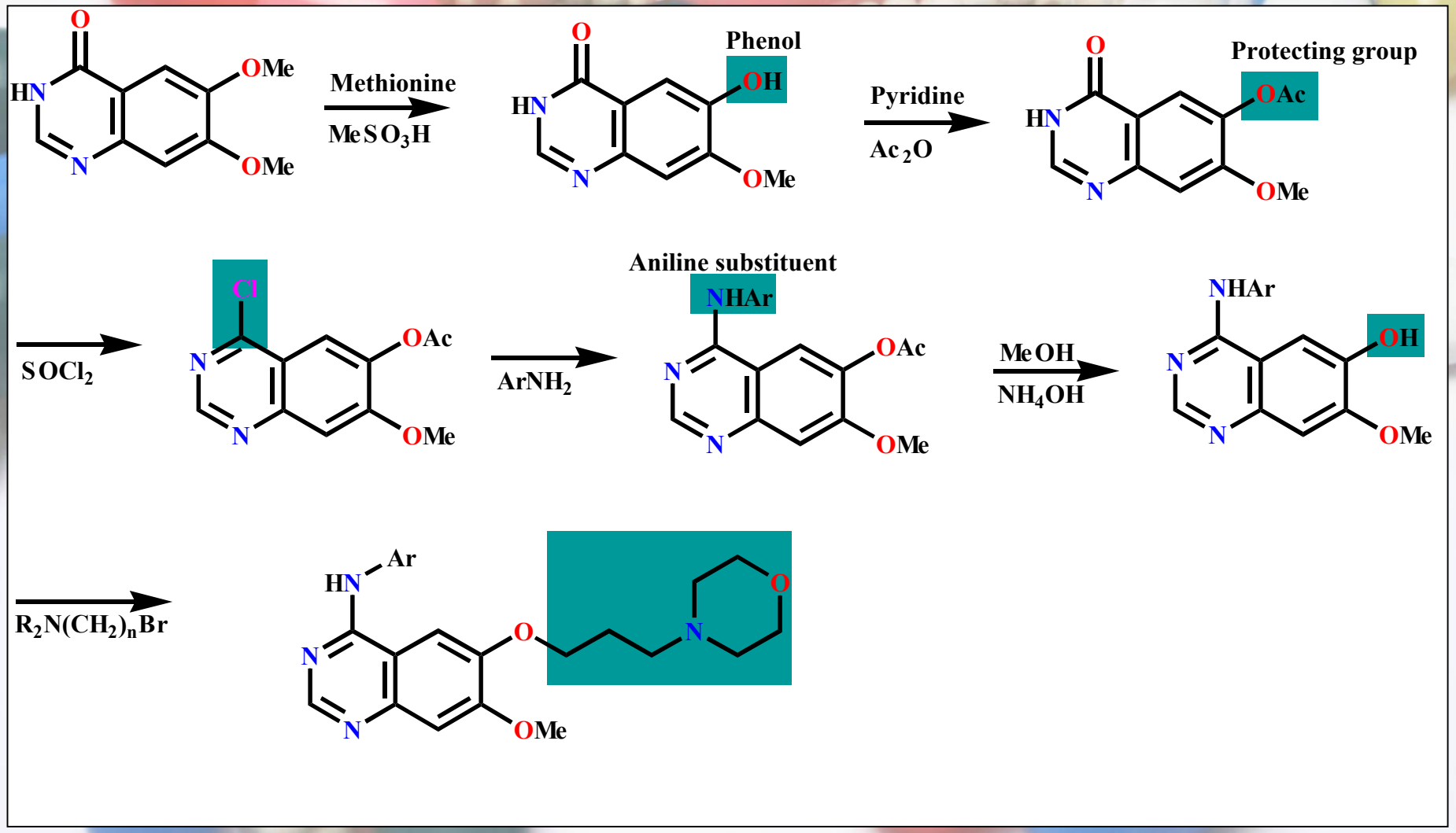


- Fluoro-substituent blocks *para*-hydroxylation
- Fluorine similar in size to hydrogen
  - no steric effect
- Methyl group replaced by chloro substituent -
  - similar sizes and lipophilicities
  - Chlorine acts as a **bio-isotere**
  - Chlorine is resistant to oxidation
- Compound is less active *in vitro*, but more active *in vivo*

(* **bioisosteres** are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.)

- Morpholine嗎啉ring increases water solubility
- Morpholine nitrogen allows generation of water soluble amine salts
- Spacer allows morpholine to protrude out使突出of the active site

Synthesis of gefitinib and analogues



Formualtion development

- **Dosage Form:**
  - oral tablets
  - each tablet : **250mg**
- - absorbed slowly
  - mean bioavailability : **60%**
  - elimination : by **metabolism** and **excretion** in faeces
  - elimination half-life : **48 hours**
  - daily oral administration : **2-fold** accumulation
- Steady state plasma concentrations are achieved within **10 days**.

Safety tests and human trials:

- **Asia** in patients with locally advanced or metastatic
- **Ex-light smokers** or **never smokers**.
- **1217 patients** from **87** centres in **China**, **Hong Kong**, **Indonesia**, **Japan**, **Malaysia**,**Philippines**, Singapore, **Taiwan**, and **Thailand** were studied
- Progression-free survival (PFS)
- Overall survival (OS)
- Objective tumour response rate(ORR)
- Quality of life (QoL)
- Symptom improvement
- Has not been studied in patients with severely **reduced kidney function**

Approval for marketing:

- **"Product Monograph"** published
- IRESSA was approved for sale in **Canada**
- Prescribed by a health care professional
- Should not be used in patients with **EGFR mutation negative tumours**
- Not recommended for use in patients under **16**

Side Effects:

- Diarrhea, nausea, vomiting, stomatitis (red and sore mouth)
- Loss of appetite
- **Skin reactions** (rash, itching dry skin and redness)
- Nosebleed or blood in the urine
- **Protein** in **urine**
- Nail problems
- **Loss of hair**
- **Eye problems** (dry, red, itchy eye or red and sore eyelid)
- **Fever**
- Bleeding from the lungs