

# **Química Medicinal**

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# Planejamento baseado em fragmento (FBDD)

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- Espaço químico estimado para compostos orgânicos:  $10^{60}$
- Coleção de pequenas moléculas estimada em  $10^{8-9}$
- Análise combinatória de composto com 11 átomos (C, N, O, F)  $> 10^8$
- Triagem por HTS de qualquer destas coleções é inviável
- Um número menor de fragmentos pode levar a cobertura de uma grande diversidade química

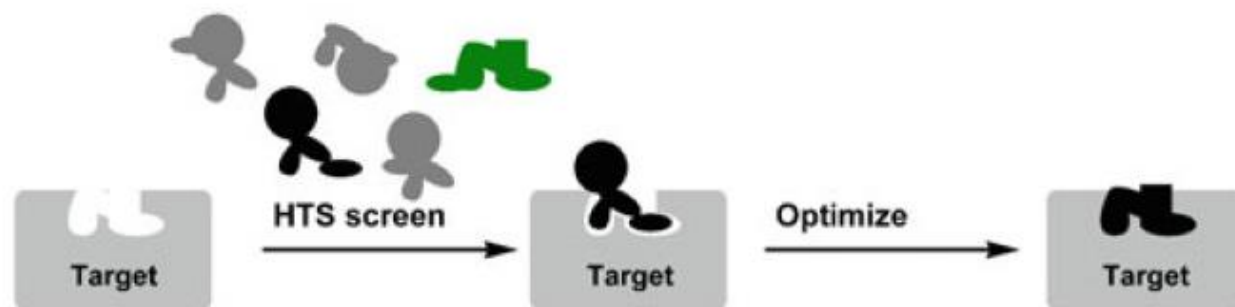
# Planejamento baseado em fragmento (FBDD)

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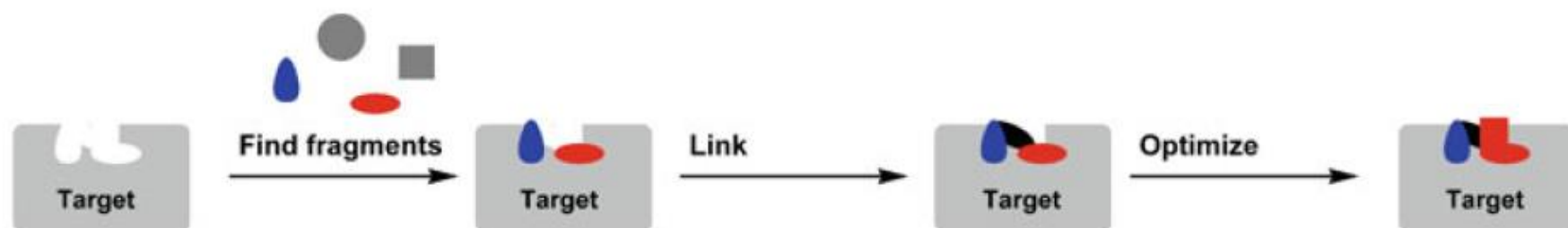
- Primeira proposta de FBDD por William Jencks da Brandeis University:

“It can be useful to describe the Gibbs free energy changes for the binding to a protein of a molecule, A–B, and of its component parts, A and B, in terms of the “intrinsic binding energies” of A and B,  $\Delta G_A^i$  and  $\Delta G_B^i$ , and a “connection Gibbs energy,”  $\Delta G_c$  that is derived largely from changes in translational and rotational entropy.”

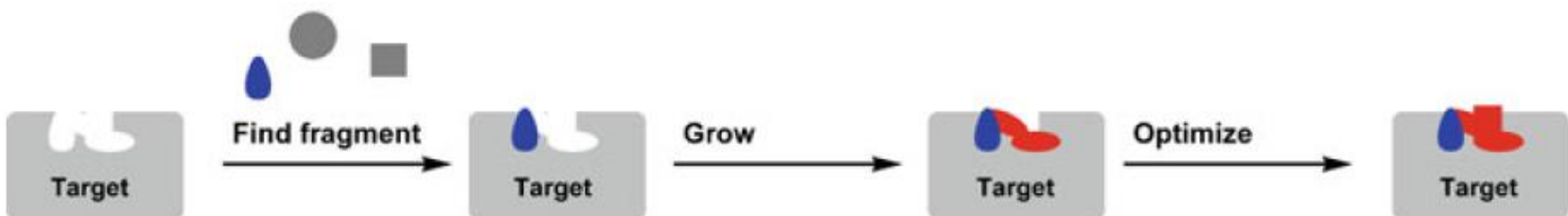
### Traditional HTS



### Fragment-based drug discovery, linking fragments



### Fragment-based drug discovery, growing fragments



**Fig. 1** Comparison of high-throughput screening (HTS, *top*) with fragment linking (*middle*) and fragment growing (*bottom*)

# O que é considerado um fragmento?

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- Fragmentos são compostos que apresentam as seguintes propriedades delimitadas pela regra dos 3:
  - Molecular weight  $< 300$  Da
  - Number of hydrogen bond donors  $\leq 3$
  - Number of hydrogen bond acceptors  $\leq 3$
  - ClogP (computed partition coefficient of a compound)  $\leq 3$

Additionally, they proposed that:

- Number of rotatable bonds  $\leq 3$
- Polar surface area (PSA)  $\leq 60 \text{ \AA}^2$

# Exemplos de sucesso

➤ Inibidor de CDK2 com atividade antineoplásica:

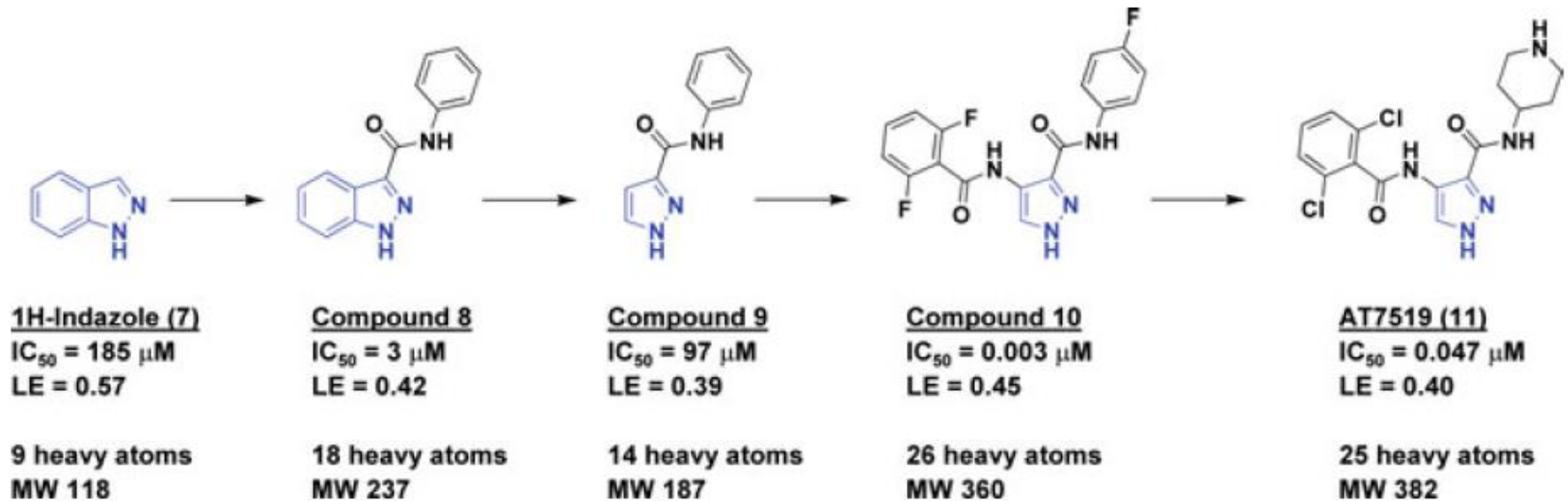


Fig. 4 Fragment growing to discover AT7519

# Exemplos de sucesso

➤ Inibidor de aurora quinase com atividade antineoplásica:

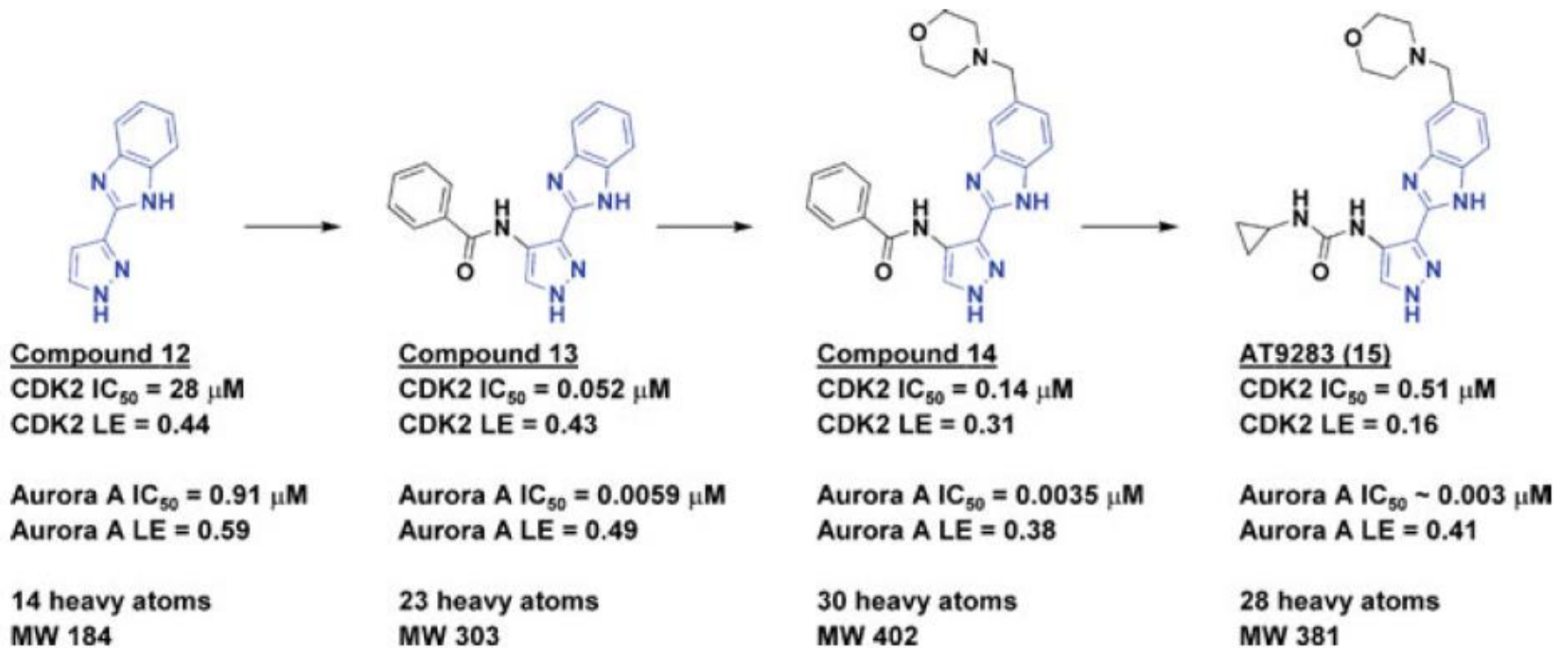
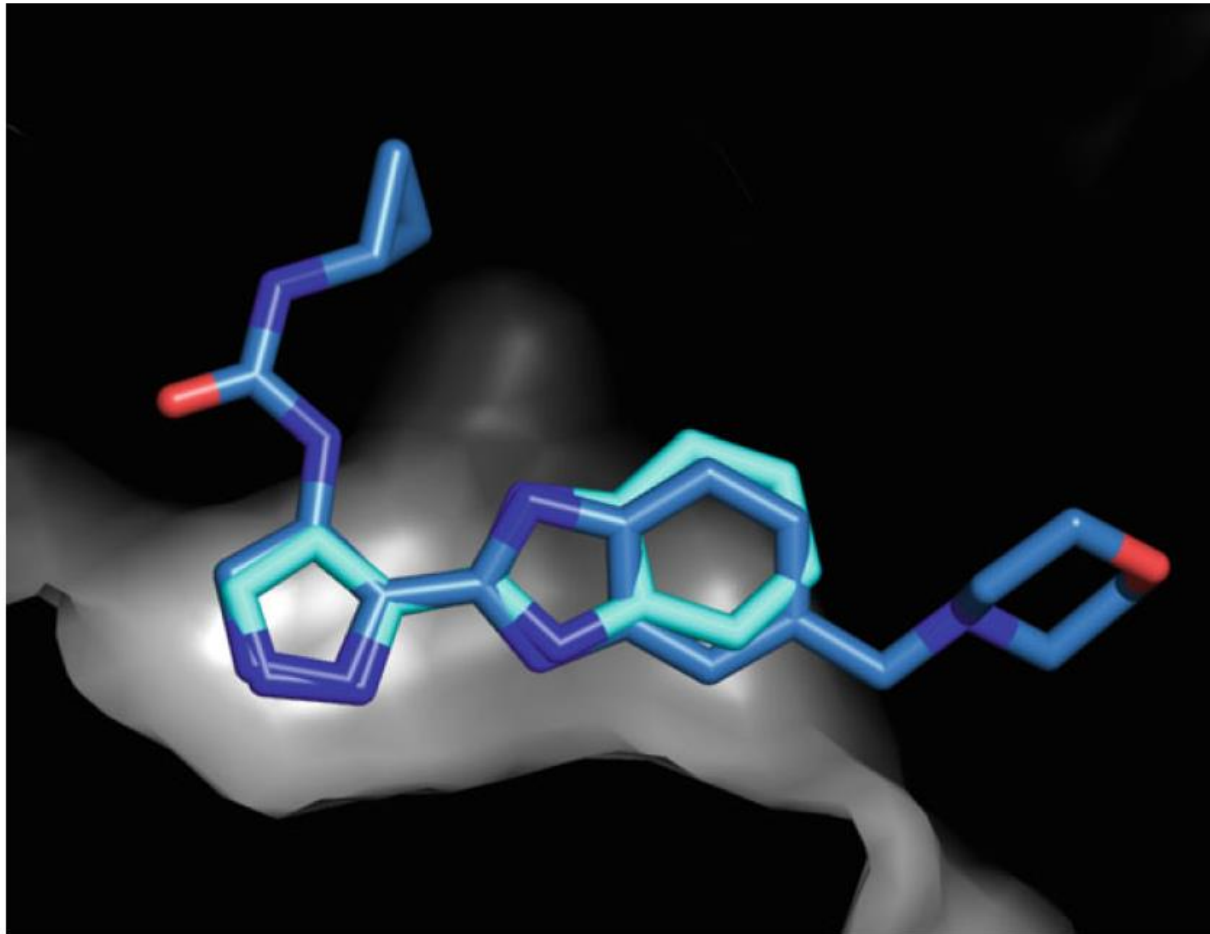


Fig. 5 Fragment growing to discover AT9283

# Exemplos de sucesso

- Inibidor de aurora quinase com atividade antineoplásica:



**Fig. 6** Superposition of initial fragment (compound **12**, *light blue*) and final compound AT9283 (*dark blue*) bound to Aurora A