Química Medicinal

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Planejamento baseado em fragmento (FBDD)

- 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

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Introduction to Fragment-Based Drug Discovery

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Planejamento baseado em fragmento (FBDD)

- 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, ΔG_A^i and ΔG_B^i, and a "connection Gibbs energy," ΔG_s that is derived largely from changes in translational and rotational entropy."

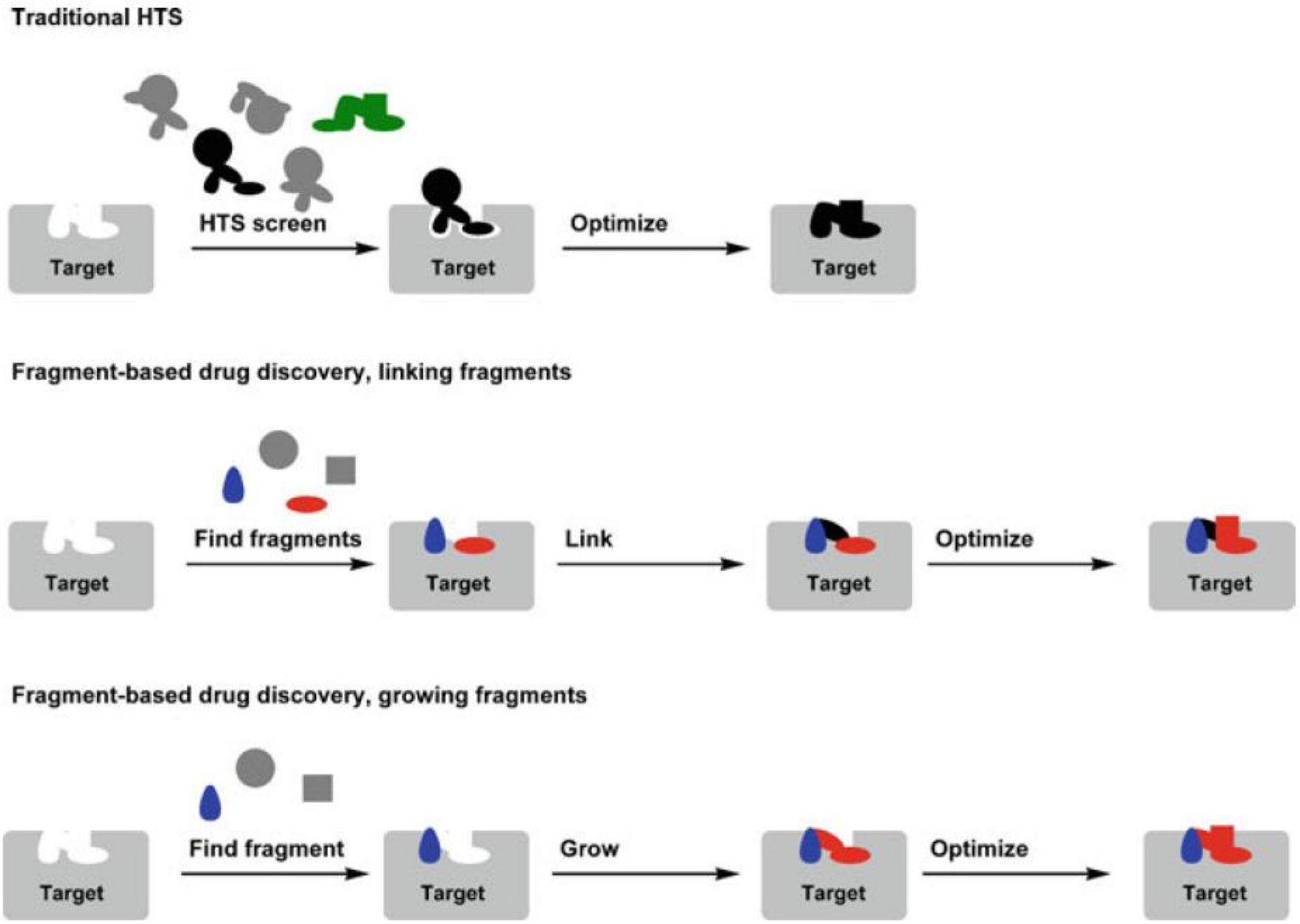


Fig. 1 Comparison of high-throughput screening (HTS, *top*) with fragment linking (*middle*) and fragment growing (*bottom*)

O que é considerado um fragmento?

- Fragmentos são compostos que apresentam as seguintes propriedades delimitadas pela regra dos 3:

- Molecular weight < 300 Da
- Number of hydrogen bond donors ≤ 3
- Number of hydrogen bond acceptors ≤ 3
- ClogP (computed partition coefficient of a compound) ≤ 3

Additionally, they proposed that:

- Number of rotatable bonds ≤ 3
- Polar surface area (PSA) ≤ 60 Å^2

Exemplos de sucesso

- Inibidor de CDK2 com atividade antineoplásica:

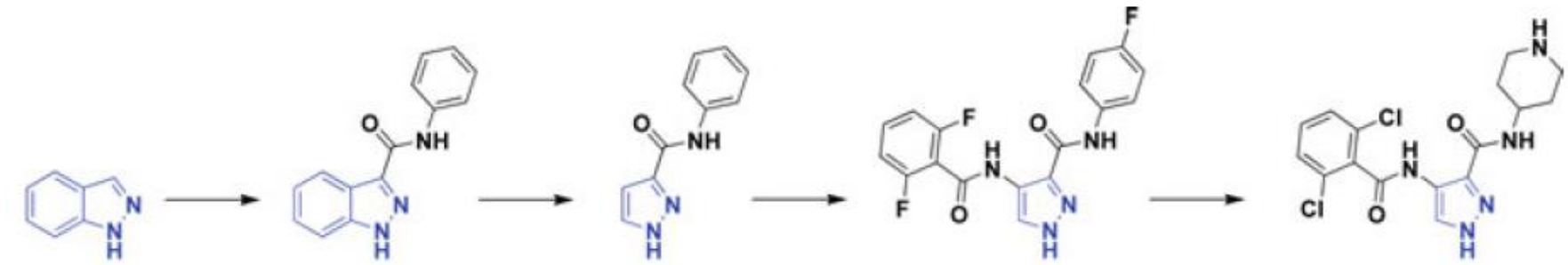
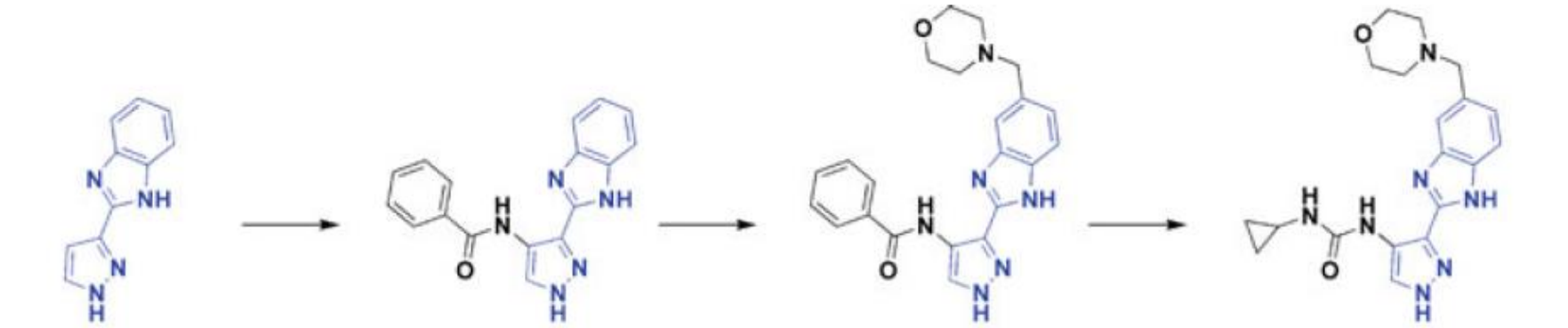


Fig. 4 Fragment growing to discover AT7519

Exemplos de sucesso

- Inibidor de aurora quinase com atividade antineoplásica:



Compound 12	Compound 13	Compound 14	AT9283 (15)
CDK2 IC_{50} = 28 μM	CDK2 IC_{50} = 0.052 μM	CDK2 IC_{50} = 0.14 μM	CDK2 IC_{50} = 0.51 μM
CDK2 LE = 0.44	CDK2 LE = 0.43	CDK2 LE = 0.31	CDK2 LE = 0.16
Aurora A IC_{50} = 0.91 μM	Aurora A IC_{50} = 0.0059 μM	Aurora A IC_{50} = 0.0035 μM	Aurora A IC_{50} ~ 0.003 μM
Aurora A LE = 0.59	Aurora A LE = 0.49	Aurora A LE = 0.38	Aurora A LE = 0.41
14 heavy atoms	23 heavy atoms	30 heavy atoms	28 heavy atoms
MW 184	MW 303	MW 402	MW 381

Fig. 5 Fragment growing to discover AT9283

Exemplos de sucesso

- Inibidor de aurora quinase com atividade antineoplásica:

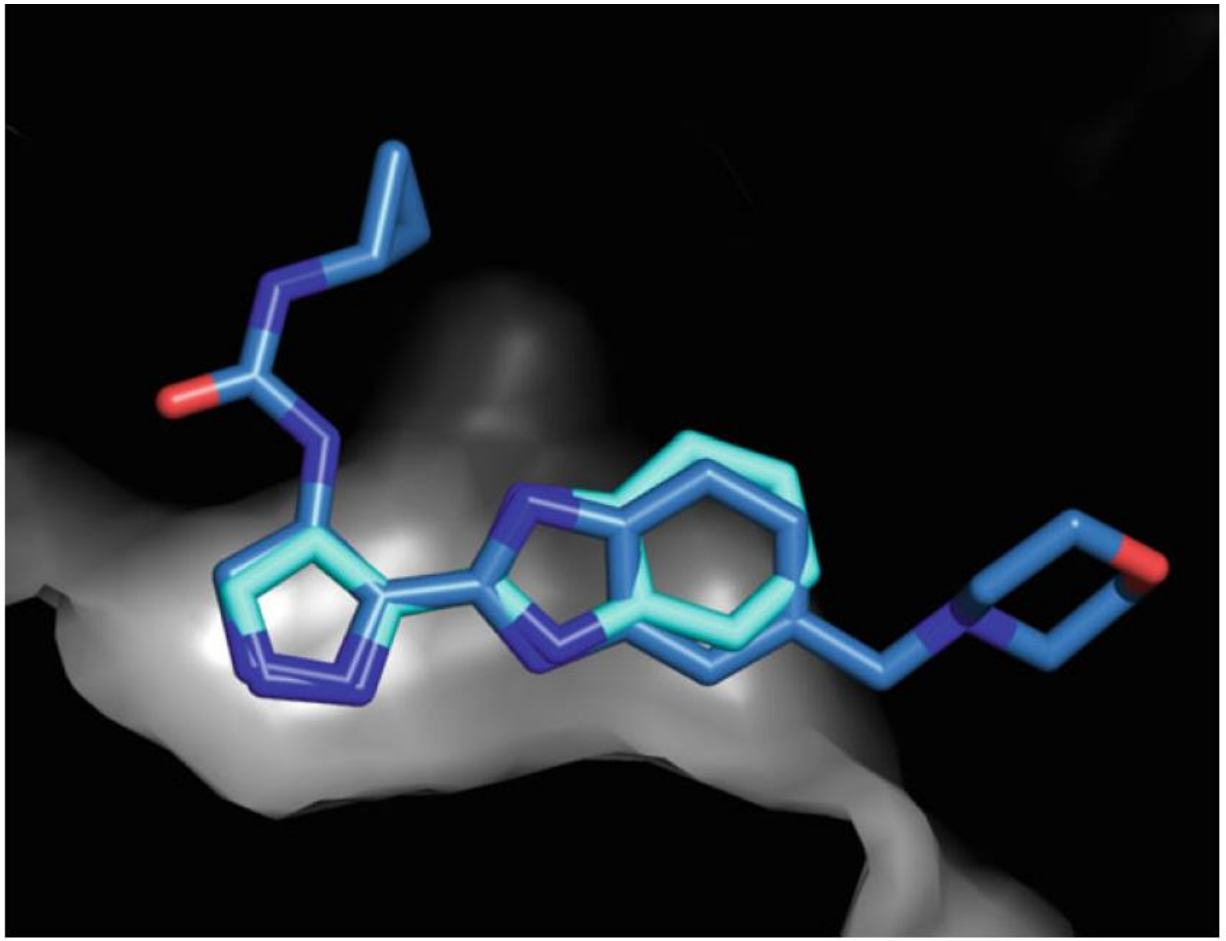


Fig. 6 Superposition of initial fragment (compound **12**, *light blue*) and final compound AT9283 (*dark blue*) bound to Aurora A