CAS INSIGHTS™

R&D TRENDS: THE COVALENT INHIBITOR REVOLUTION

CAS
A division of the American Chemical Society

Overview

Advances in structural biology and computational tools have greatly facilitated the rational design of covalent inhibitors, with several therapeutics approved or in development. Balancing potency and selectivity will be crucial for the clinical and commercial success of emerging drug candidates.

Background: Covalent inhibitors have been an area of active R&D in the field of drug discovery.

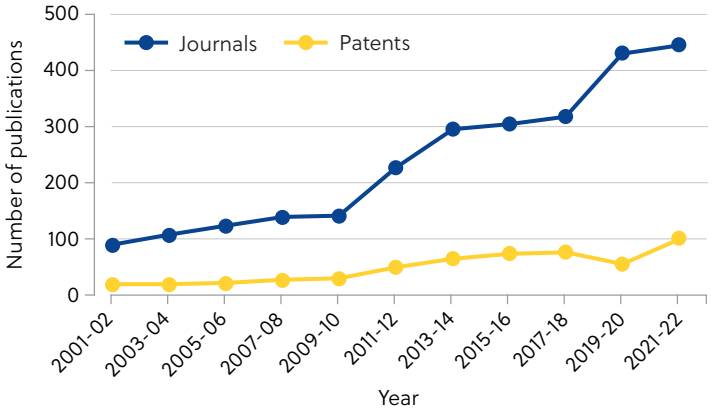
Market potential: There has been a steady growth in journal publications between 2001–2022, particularly in the past decade. The commercial sector has shown considerable interest, owning the majority of patents in the field. While the number of FDA-approved covalent inhibitor therapeutics is modest, the success of BTK inhibitor ibrutinib ($9.8 billion global sales in 2021) is a testament to the potential of these agents as profitable drugs across a diverse range of disease areas.

Key benefits: Enhanced potency and duration of action (vs. more common non-covalent inhibitors), target selectivity, and the ability to inhibit previously "undruggable" targets (e.g., KRAS).

Key challenges: Irreversibility, potential off-target effects, safety concerns, risk of resistance development.

Publication trends

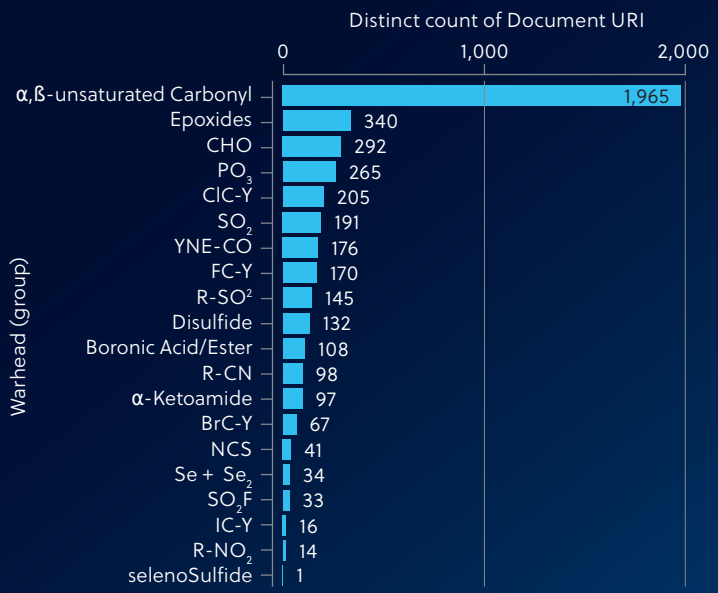
Research into a key subset of covalent inhibitors has undergone intense growth, with a four-fold increase in the number of journal publications in the past decade. In contrast, patent publications have risen steadily year-over-year.



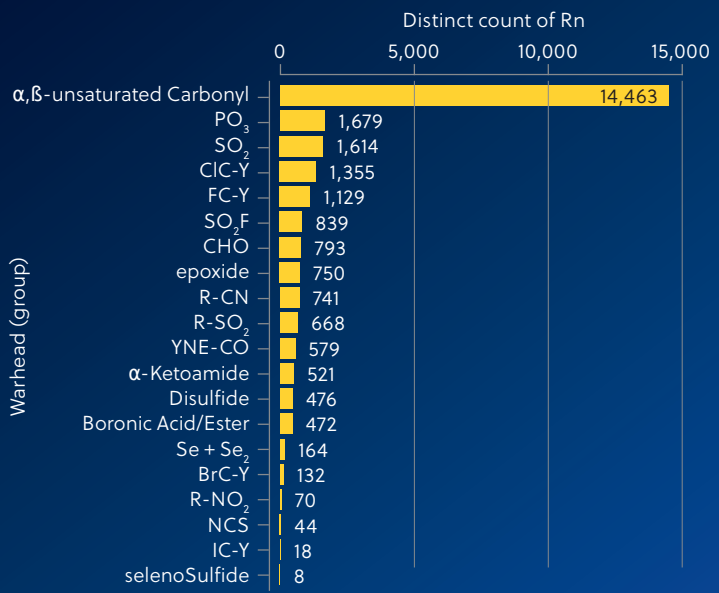
Warhead distribution

The α,β-unsaturated carbonyl 'warheads' (the reactive group of the covalent inhibitor) dominate in publication appearances and registered substances, reflecting their widespread use in many FDA-approved agents, including kinase inhibitors afatinib, osimertinib, and ibrutinib.

Warhead distribution across publications



Warhead distribution of registered substances

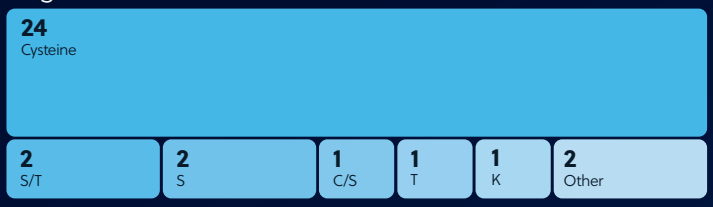


Properties of FDA-approved covalent inhibitor therapeutics

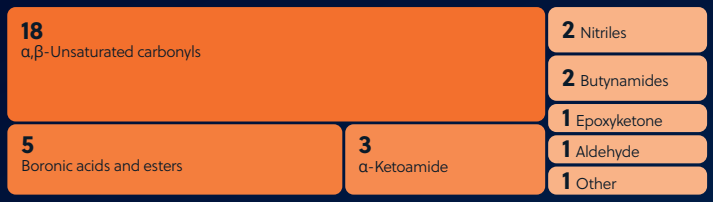
Over 30 covalent inhibitors have been approved in the last 20 years to treat a range of conditions. Covalent inhibitors of EGFR (a key therapeutic target in oncology) dominate, circumventing challenges with acquired resistance observed with reversible tyrosine kinase inhibitors.

(A) Warhead distribution — approved therapies

Target residue distribution



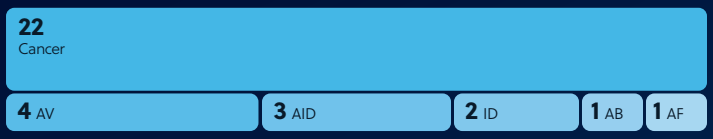
Warhead distribution



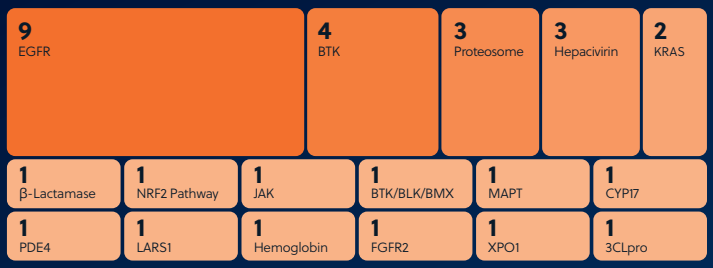
S/T = Serine/Threonine | S = Serine | C/S = Cysteine/Serine
T = Threonine | K = Lysine

(B) Target distribution — approved therapies

Diseases or indication



Target distribution



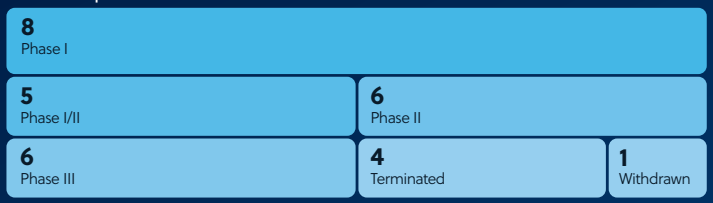
AV = Antiviral | AID = Autoimmune disorders
ID = Inherited disorders | AB = Antibacterial | AF = Antifungal

Covalent inhibitors in clinical development

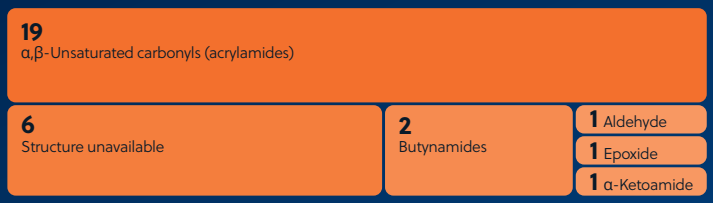
Most covalent inhibitors in development have an acrylamide warhead (a subset of the α,β-unsaturated carbonyls) due to their ease of manufacture and well-defined reactivity profile. Though EGFR and BTK remain crucial targets, there is an urgent need to develop new selective FGFR inhibitors.

(C) Warhead distribution — pipeline agents

Clinical phase distribution

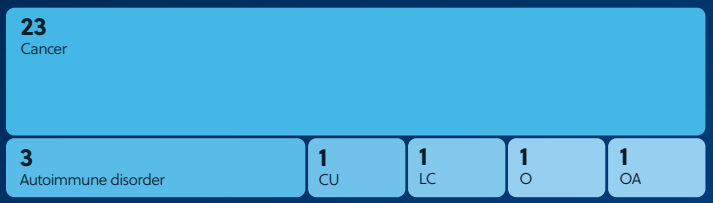


Warheads



(D) Target distribution — pipeline agents

Disease or indication



Targets

CU = Chronic urticaria | LC = Liver cirrhosis | O = Obesity
OA = Osteoarthritis

Looking ahead

The sharp increase in publications indicates a continued boom in covalent inhibitor therapeutics bolstered by innovations in rational drug design. The field has garnered substantial attention from the commercial sector, with this momentum poised to persist as cutting-edge therapies advance through the clinical development pipeline.

Learn more at cas.org/insights

More comprehensive information and references can be found at cas.org/COVALENT

INSGENENGWHP101675231016

CAS
A division of the American Chemical Society