

RESEARCH MONOGRAPH . COMPOUND PROFILE

Navitoclax (ABT-263)

A BH3 mimetic BCL-2/BCL-XL/BCL-W inhibitor; the prototype clinical senolytic.

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ABSTRACT

Navitoclax (ABT-263; CAS 923564-51-6; molecular formula $C_{47}H_{55}ClF_3N_5O_6S_3$; molecular weight 974.61) is a BH3-mimetic BCL-2 family inhibitor developed at Abbott (now AbbVie) for hematologic malignancies. The compound binds the BH3-binding groove of BCL-2, BCL-XL, and BCL-W, releasing pro-apoptotic BAX and BAK from sequestration and triggering mitochondrial apoptosis in cells that depend on these survival proteins. Senescent cells upregulate BCL-XL as part of the senescence-associated apoptosis-resistance program, making them selectively vulnerable to BCL-XL inhibition; navitoclax was demonstrated to selectively eliminate senescent cells in mouse models (Chang et al. Nat Med 2016). Clinical development for cancer was complicated by thrombocytopenia (BCL-XL inhibition kills platelets, which depend on BCL-XL for survival), motivating the development of platelet-sparing analogs (BCL-XL-targeted PROTACs, BCL-2-selective venetoclax). The compound remains the canonical research senolytic. Plasma half-life is approximately 18 to 20 hours.

1. Compound Identification

Navitoclax (ABT-263) is described as bcl-2 family inhibitor / senolytic. A BH3 mimetic BCL-2/BCL-XL/BCL-W inhibitor; the prototype clinical senolytic.

1.1 Class summary

BCL-2 family inhibitor / senolytic

1.2 Subtitle

A BH3 mimetic BCL-2/BCL-XL/BCL-W inhibitor; the prototype clinical senolytic.

2. Abstract

Navitoclax (ABT-263; CAS 923564-51-6; molecular formula $C_{47}H_{55}ClF_3N_5O_6S_3$; molecular weight 974.61) is a BH3-mimetic BCL-2 family inhibitor developed at Abbott (now AbbVie) for hematologic malignancies. The compound binds the BH3-binding groove of BCL-2, BCL-XL, and BCL-W, releasing pro-apoptotic BAX and BAK from sequestration and triggering mitochondrial apoptosis in cells that depend on these survival proteins. Senescent cells upregulate BCL-XL as part of the senescence-associated apoptosis-resistance program, making them selectively vulnerable to BCL-XL inhibition; navitoclax was demonstrated to selectively eliminate senescent cells in mouse models (Chang et al. Nat Med 2016). Clinical development for cancer was complicated by thrombocytopenia (BCL-XL inhibition kills platelets, which depend on BCL-XL for survival), motivating the development of platelet-sparing analogs (BCL-XL-targeted PROTACs, BCL-2-selective venetoclax). The compound remains the canonical research senolytic. Plasma half-life is approximately 18 to 20 hours.

3. Mechanism of Action

BH3-mimetic BCL-2/BCL-XL/BCL-W inhibitor; releases BAX/BAK from sequestration to trigger mitochondrial apoptosis. Senolytic activity via BCL-XL dependence in senescent cells. Thrombocytopenia is dose-limiting.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Cancer trial doses 200 to 400 mg per oral administration daily. Senolytic mouse studies 50 mg/kg/day intermittent.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Chang J, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med 2016.
2. Zhu Y, et al. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. Aging Cell 2016.
3. Tse C, et al. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res 2008.

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