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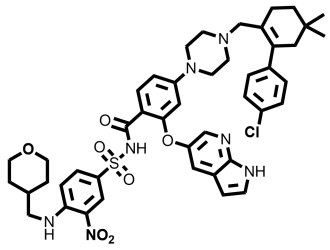
# BCL-2 inhibitor– ABT-199

**Chemical Name:** (4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide)



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|---|---|
| Molecular Weight: | 868.44 |
| Formula: | $C_{45}H_{50}ClN_7O_7S$ |
| Purity: | ≥ 98% |
| CAS#: | 1257044-40-8 |
| Solubility: | DMSO up to 50 mM |
| Storage | Powder: 4°C 1 year<br>DMSO: 4°C 3 month<br>-20°C 1 year |

**Biological Activity:**

ABT-199 is a highly potent, selective, and orally bioavailable BCL-2 inhibitor. ABT-199 has picomolar affinity for BCL-2 (Ki < 0.010 nM) and > 1000 folds selectivity over BCL-$X_L$ (Ki = 48 nM) and BCL-W (Ki = 245 nM). Therefore, ABT-199 is a much improved lead compound over the original ABT-263 (navitoclax) to avoid thrombocytopenia caused by BCL-$X_L$ inhibition. ABT-199's cell-killing effect is selective and mechanism dependent. It can potently kill BCL-2-overexpressing FL5.12 cells ($EC_{50}$ ~ 4 nM) and RS4;11 BCL-2–dependent ALL cells ($EC_{50}$ ~8 nM), but showed much weaker activity against BCL-$X_L$-overexpressing FL5.12 cells ($EC_{50}$ ~261 nM) and H146 ALL cells ($EC_{50}$ ~4,260 nM). ABT-199 inhibits the growth of BCL-2–dependent human hematological tumors in vivo and spares human platelets as a single agent or in combination with rituximab and bendamustine. A single dose of ABT-199 in three patients with refractory chronic lymphocytic leukemia resulted in tumor lysis within 24 h. These data indicates that selective pharmacological inhibition of BCL-2 shows promise for the treatment of BCL-2–dependent hematological cancers.

**How to Use:**

**In vitro:** ABT-199 was used at 0.1-1 μM final concentration in vitro and in cellular assays.

**In vivo:** ABT-199 was orally dosed to mice at 12.5-100 mg/kg once per day in combination with rituximab and Bendamustine, and significantly reduced tumor volume.

**Reference:**

1. Fresquet V, et al. Acquired mutations in BCL2 family proteins conferring resistance to the BH3 mimetic ABT-199 in lymphoma. (2014) Blood. 123(26):4111-9.
2. Souers AJ, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. (2013) Nat Med. 19(2):202-8.
3. Roberts, A.W. et al. Selective inhibition of BCL-2 is active against chronic lymphocytic leukemia (CLL): first clinical experience with the BH3-mimetic ABT-199. Abstract 546 (European Hematology Association 2012, Amsterdam, The Netherlands, June 14–17, 2012).