

Supporting Information:

Large Language Model Agent for Modular Task Execution in Drug Discovery

Janghoon Ock,[†] Radheesh Sharma Meda,[‡] Srivathsan Badrinarayanan,[†] Neha S Aluru,[¶] Achuth Chandrasekhar,[§] and Amir Barati Farimani^{*,||}

[†]*Department of Chemical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA*

[‡]*Department of Chemical Engineering, Carnegie Mellon University, 5000 Forbes Avenue, Pittsburgh, PA 15213, USA*

[¶]*School of Engineering Medicine, Texas A&M University, Houston, TX, USA*

[§]*Department of Material Science and Engineering, Carnegie Mellon University, Pittsburgh, PA, USA*

^{||}*Department of Mechanical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA*

E-mail: barati@cmu.edu

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S1 Domain-specific Question Answering

We conducted an additional evaluation question that examined AgentD’s ability to extrapolate mechanistic findings to broader therapeutic contexts by asking about the implications of combining ABT-199 and proteasome inhibitors for treating solid tumors compared to hematologic malignancies. This question tests the system’s capacity to synthesize domain-specific knowledge and provide clinically relevant insights beyond the immediate scope of the reference paper. Figure S1 shows the actual responses from both AgentD with RAG and the standard GPT-4o model to illustrate these differences in clinical reasoning and mechanistic understanding.

We evaluated responses using the same Weller et al. study, which primarily focuses on the mechanistic basis of drug synergy through NOXA upregulation and MCL-1 inhibition.^{S1} While this question extends beyond the paper’s direct experimental scope, it remains grounded in the mechanistic principles described in the work. Both AgentD with RAG and the standard GPT-4o model were asked to discuss the therapeutic implications for different cancer types.

The RAG-augmented response demonstrates superior clinical reasoning by directly connecting the paper’s mechanistic findings to therapeutic applications. AgentD correctly identifies that the combination could “significantly impact the treatment of both solid tumors and hematologic malignancies” through the dual mechanism of direct BCL-2 inhibition and indirect MCL-1 inhibition via NOXA activation. Importantly, the response provides specific examples, noting effectiveness in “solid tumors, such as soft tissue sarcoma” and established efficacy in hematologic malignancies including “chronic lymphocytic leukemia and multiple myeloma.”

Domain-specific question:

What are the implications of the findings regarding the combinatorial use of ABT-199 and proteasome inhibitors for treating solid tumors compared to hematologic malignancies?

AgentD (w/ RAG):

The findings indicate that combining ABT-199 (venetoclax) with proteasome inhibitors (PIs) could significantly impact the treatment of both solid tumors and hematologic malignancies. In solid tumors, such as soft tissue sarcoma, this combination synergistically induces apoptosis by activating the pro-apoptotic protein NOXA, which inhibits the anti-apoptotic protein MCL-1, enhancing ABT-199's efficacy. This dual action—direct BCL-2 inhibition and indirect MCL-1 inhibition—suggests effectiveness in solid tumors overexpressing these proteins. In hematologic malignancies, where ABT-199 is already effective, particularly in chronic lymphocytic leukemia and multiple myeloma, combining it with PIs could improve outcomes by overcoming resistance mechanisms involving MCL-1. These findings support further clinical evaluation of this combination in various cancers, potentially expanding therapeutic options for both solid and hematologic malignancies.

Standard GPT4o:

The findings on the combinatorial use of ABT-199 (venetoclax) and proteasome inhibitors have several implications for the treatment of solid tumors compared to hematologic malignancies. Here's a breakdown:

1. Mechanistic Synergy:

Hematologic Malignancies: ABT-199, a BCL-2 inhibitor, is particularly effective because these cancers often rely heavily on the BCL-2 pathway for survival. When combined with proteasome inhibitors, which block protein degradation, the apoptotic pathways are further enhanced, leading to increased cancer cell death.

Solid Tumors: These cancers might not be as dependent on BCL-2 as hematologic malignancies. However, the combination could still disrupt protein homeostasis and induce apoptosis by targeting multiple pathways.

2. Clinical Efficacy:

Hematologic Malignancies: Clinical trials have shown promising results due to the high BCL-2 expression. The combinatorial approach can enhance responses in resistant cases.

Solid Tumors: The efficacy might be more variable due to the diverse nature of these tumors and their reliance on other anti-apoptotic proteins like MCL-1 or BCL-XL.

Resistance Mechanisms:

Hematologic Malignancies: Resistance can develop through mutations or upregulation of alternative survival pathways.

Solid Tumors: The diverse genetic landscape means multiple resistance mechanisms could limit effectiveness.

3. Toxicity and Side Effects:

Combining ABT-199 with proteasome inhibitors can potentially increase toxicity, necessitating careful dose optimization and monitoring in both cancer types.

4. Biomarker Development:

Identifying biomarkers to predict response can help tailor the combination therapy more effectively, particularly in solid tumors where response rates might be heterogeneous.

5. Future Research Directions:

Continued research is needed to understand the specific tumor types and settings where this combination is most beneficial, and to develop strategies to overcome resistance in solid tumors.

Overall, while the combination has shown efficacy in hematologic cancers, its application in solid tumors requires a nuanced understanding of tumor biology and careful clinical evaluation.

Figure S1: AgentD response demonstrating domain-specific question answering capabilities. The question extrapolates beyond the direct scope of the source article.

The RAG response captures the key therapeutic insight that this combination approach could “overcome resistance mechanisms involving MCL-1,” which aligns closely with the ground truth explanation that the strategy “could potentially overcome intrinsic resistance mechanisms in solid tumors that are less dependent on BCL-2 but still rely on MCL-1 for survival.” This mechanistic understanding is crucial for clinical translation, as it identifies the specific molecular rationale for why the combination might succeed where single-agent BCL-2 inhibition fails.

In contrast, the standard GPT-4o response, while comprehensive and well-structured, provides a generic framework that could apply to virtually any combination therapy discussion. The response covers broad categories such as “mechanistic synergy,” “clinical efficacy,” and “resistance mechanisms” but fails to reference the specific NOXA-mediated pathway that makes this particular combination therapeutically promising. Critical omissions include the ISR activation, ATF3/ATF4 transcriptional regulation, and the specific role of MCL-1 inhibition in overcoming resistance.

The standard response does acknowledge that “solid tumors might not be as dependent on BCL-2 as hematologic malignancies” and mentions reliance on “other anti-apoptotic proteins like MCL-1 or BCL-XL,” but it lacks the mechanistic foundation to explain how the combination specifically addresses these dependencies. This represents a missed opportunity to provide actionable clinical insights based on the underlying biology.

Furthermore, while the standard response discusses general considerations such as toxicity management and biomarker development, it does so without the mechanistic context that would guide these clinical decisions. The RAG response, by contrast, grounds its recommendations in the specific findings about NOXA upregulation and MCL-1 inhibition, providing a more targeted foundation for clinical development.

This evaluation demonstrates that even for questions that extend beyond the immediate experimental scope of the reference literature, RAG-augmented responses maintain superior clinical relevance by preserving the mechanistic foundation that underlies therapeutic poten-

tial. The ability to connect specific molecular mechanisms to broader therapeutic applications represents a critical advantage for biomedical question answering systems, particularly in translational research contexts where mechanistic understanding directly informs clinical strategy.

S2 ADMET Properties

Table S1: Complete list of ADMET properties predicted for all compounds in this study.

Category	Property	Description
Absorption	Caco-2 Permeability (log-Paap)	Permeability across Caco-2 cell monolayers
	Human Intestinal Absorption	Fraction absorbed in human intestine
	Human Oral Bioavailability (20%)	Probability of achieving >20% oral bioavailability
	Human Oral Bioavailability (50%)	Probability of achieving >50% oral bioavailability
	MDCK Permeability	Madin-Darby Canine Kidney cell permeability
	P-Glycoprotein Inhibitor	Inhibition of P-glycoprotein efflux pump
	P-Glycoprotein Substrate	Substrate of P-glycoprotein efflux pump
	Skin Permeability	Dermal absorption coefficient
Distribution	Blood-Brain Barrier Penetration	CNS penetration capability
	Blood-Brain Barrier (log-BB)	Blood-brain barrier partition coefficient
	Fraction Unbound (Human)	Unbound fraction in human plasma

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Table S1 – *Continued from previous page*

Category	Property	Description
	Plasma Protein Binding	Extent of protein binding in plasma
	Volume of Distribution	Steady-state volume of distribution
Metabolism	BCRP Substrate	Breast Cancer Resistance Protein substrate
	CYP1A2 Inhibitor	Cytochrome P450 1A2 inhibition
	CYP1A2 Substrate	Cytochrome P450 1A2 substrate
	CYP2C19 Inhibitor	Cytochrome P450 2C19 inhibition
	CYP2C19 Substrate	Cytochrome P450 2C19 substrate
	CYP2C9 Inhibitor	Cytochrome P450 2C9 inhibition
	CYP2C9 Substrate	Cytochrome P450 2C9 substrate
	CYP2D6 Inhibitor	Cytochrome P450 2D6 inhibition
	CYP2D6 Substrate	Cytochrome P450 2D6 substrate
	CYP3A4 Inhibitor	Cytochrome P450 3A4 inhibition
	CYP3A4 Substrate	Cytochrome P450 3A4 substrate
	OATP1B1 Substrate	Organic Anion Transporting Polypeptide 1B1
	OATP1B3 Substrate	Organic Anion Transporting Polypeptide 1B3
Excretion	Clearance	Total body clearance
	Half-Life	Elimination half-life
	OCT2 Substrate	Organic Cation Transporter 2 substrate
Toxicity	AMES Mutagenicity	Bacterial mutagenicity test

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Table S1 – *Continued from previous page*

Category	Property	Description
	Avian Toxicity	Acute toxicity to birds
	Bee Toxicity	Acute toxicity to honeybees
	Bioconcentration Factor	Bioaccumulation potential
	Biodegradation	Environmental biodegradability
	Carcinogenicity	Carcinogenic potential
	Crustacean Toxicity	Acute toxicity to crustaceans
	Daphnia Toxicity	Acute toxicity to <i>Daphnia magna</i>
	Eye Corrosion	Severe eye damage potential
	Eye Irritation	Eye irritation potential
	Fathead Minnow Toxicity	Acute toxicity to <i>Pimephales promelas</i>
	Hepatotoxicity (DILI)	Drug-induced liver injury
	Hepatotoxicity (Alternative)	Alternative liver injury prediction
	Maximum Tolerated Dose	Highest non-toxic dose
	Micronucleus Test	Chromosomal damage potential
	Nuclear Receptor AhR	Aryl hydrocarbon receptor activation
	Nuclear Receptor AR	Androgen receptor binding
	Nuclear Receptor AR-LBD	Androgen receptor ligand binding domain
	Nuclear Receptor Aromatase	Aromatase enzyme inhibition
	Nuclear Receptor ER	Estrogen receptor binding

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Table S1 – Continued from previous page

Category	Property	Description
	Nuclear Receptor ER-LBD	Estrogen receptor ligand binding domain
	Nuclear Receptor GR	Glucocorticoid receptor binding
	Nuclear Receptor PPAR- γ	Peroxisome proliferator-activated receptor γ
	Nuclear Receptor TR	Thyroid receptor binding
	Rat Acute Toxicity	Acute oral toxicity in rats
	Rat Chronic Toxicity	Chronic oral toxicity in rats
	Respiratory Toxicity	Respiratory system toxicity
	Skin Sensitization	Dermal sensitization potential
	Stress Response ARE	Antioxidant response element activation
	Stress Response ATAD5	ATAD5 genotoxicity pathway
	Stress Response HSE	Heat shock response element
	Stress Response MMP	Mitochondrial membrane potential
	Stress Response p53	p53 tumor suppressor pathway
	<i>Tetrahymena pyriformis</i>	Acute toxicity to <i>T. pyriformis</i>
	hERG Inhibition	Human ether-à-go-go-related gene K ⁺ channel
General	Boiling Point	Boiling point temperature
	Hydration Free Energy	Free energy of hydration
	log D (pH 7.4)	Distribution coefficient at physiological pH

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Table S1 – *Continued from previous page*

Category	Property	Description
	log P	Octanol-water partition coefficient
	log S	Aqueous solubility
	log Vapor Pressure	Vapor pressure
	Melting Point	Melting point temperature
	pKa (Acidic)	Acid dissociation constant
	pKa (Basic)	Base dissociation constant
	pKd (Acidic)	Alternative acid dissociation constant

S3 Identified Unfavorable Drug Properties

The molecular optimization process focuses on identifying unfavorable properties and refining SMILES to improve their ADMET profiles. Table S2 summarizes the distribution of properties flagged by AgentD across optimization rounds, grouped by ADMET categories.

An observed limitation is the agent’s frequent selection of $\log P_{\text{app}}$ as a risk factor—despite it being just one among 74 possible properties. This suggests a selection bias, potentially due to the ordering of properties in the input dictionary. Since $\log P_{\text{app}}$ appears near the top of the dictionary entry, the agent may disproportionately attend to it during its reasoning process. Future iterations can address this by randomizing property order or introducing attention calibration techniques.

Table S2: Distribution of weakness properties after 1st and 2nd round of SMILES optimization. The weakness property represents the most critical ADMET deficiency targeted for improvement.

ADMET Category	Cate-	Specific Property	1st Round (%)	2nd Round (%)
Absorption		Caco-2 ($\log P_{\text{app}}$)	59.6	69.5
Toxicity		AMES Mutagenesis	14.1	7.4
		Liver Injury I (DILI)	5.1	4.2
		hERG Blockers	4.0	2.1
		Carcinogenesis	3.0	1.1
General Properties		$\log P$	5.1	3.2
		$\log S$	1.0	–
Other		Absorption/Human Oral Bioavailability (20% and 50%), Invalid SMILES, and other general entries.	6.0	8.4
Total Entries			99	95

S4 Structure Generation Examples

For the examples shown in Figure S2, we applied stricter rule-based filters and slightly more lenient pKd thresholds compared to those used in the main manuscript. Specifically, molecules were selected if they passed more than three rule-based filters, had a QED score above 0.6, and a predicted pKd greater than 5.5. From the set of molecules that underwent two rounds of refinement, three examples were randomly selected for illustration.

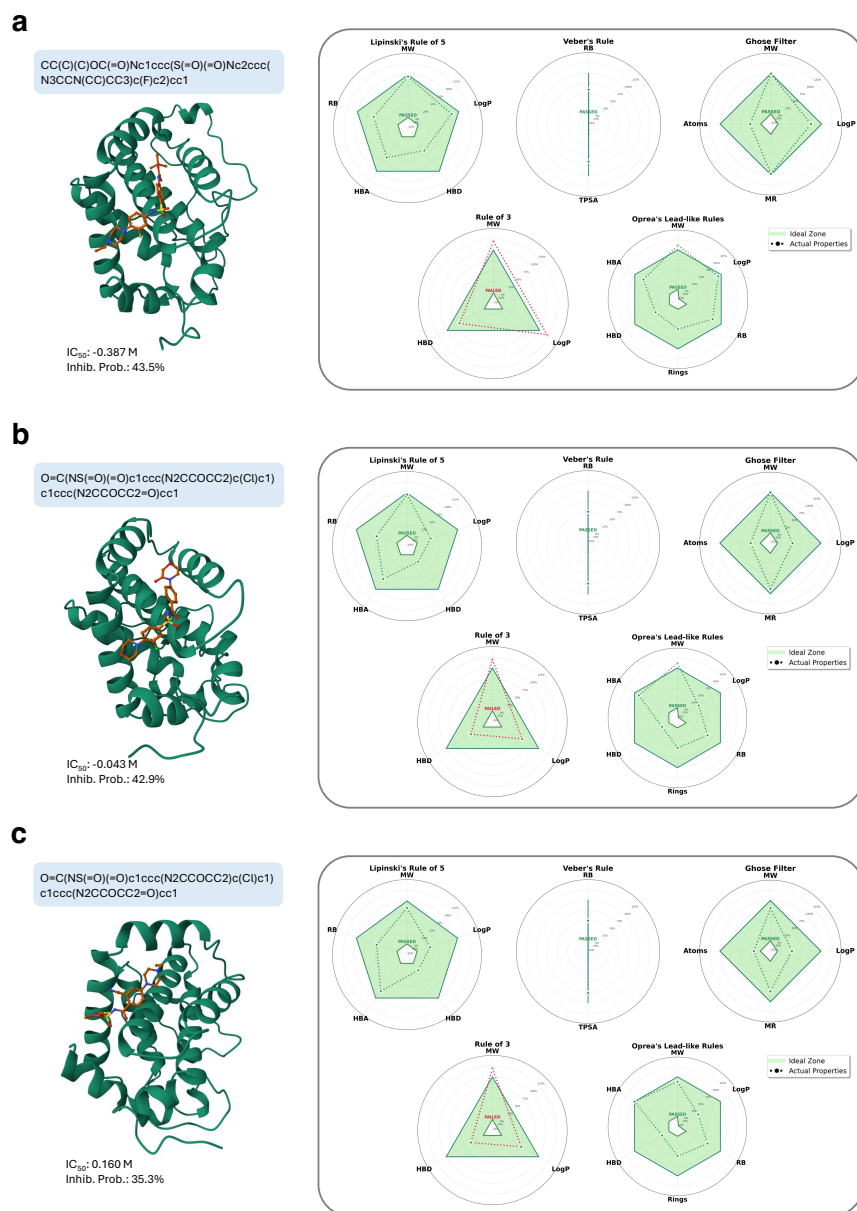


Figure S2: Additional examples of protein–ligand complex generation and evaluation.

S5 Drug-likeness Filters

The listed properties were calculated using RDKit with molecular SMILES as input. Note that these rules serve as illustrative examples and are not the definitive criteria for selecting candidates for 3D structure generation.

Table S3: Summary of rule-based drug-likeness filters and their physicochemical criteria.

Rule	Criterion	Threshold / Range	Pharmacological Rationale
Lipinski’s Rule of Five ^{S2,S3}	Molecular Weight (MW)	≤ 500 Da	High molecular weight is associated with poor intestinal absorption due to size-related transport limitations.
	logP	≤ 5	High lipophilicity ($\log P \leq 5$) correlates with poor aqueous solubility and passive permeability.
	H-bond Donors (HBD)	≤ 5	Excessive H-bond donors increase polarity, reducing membrane permeability.
	H-bond Acceptors (HBA)	≤ 10	Too many acceptors increase polarity, hindering passive diffusion.
	Rotatable Bonds (RB)	≤ 10 rotatable bonds	High flexibility and polar surface area reduce the likelihood of oral activity.
Veber Rule ^{S3}	TPSA	≤ 140 Å ²	High polar surface area decreases oral bioavailability by reducing passive diffusion.
	Rotatable Bonds (RB)	≤ 10	Excess flexibility increases entropy, reducing oral bioavailability and metabolic stability.
Ghose Filter ^{S4}	Molecular Weight (MW)	160–480 Da	Balances molecular size for optimal binding and permeability.
	logP	−0.4 to 5.6	Ensures moderate lipophilicity for both solubility and membrane crossing.
	Molar Refractivity (MR)	40–130	Captures molecular volume and polarizability, influencing receptor binding.
	Atom Count	20–70	Reflects a size range favorable for drug-likeness and synthetic accessibility.
Rule of Three (Ro3) ^{S5}	Molecular Weight (MW)	< 300 Da	Smaller fragments are preferred in fragment-based drug discovery for lead optimization.
	logP	≤ 3	Low lipophilicity promotes solubility in fragment-like compounds.
	H-bond Donors (HBD)	≤ 3	Reduces polarity, supporting fragment permeability and binding.
Oprea Lead-like Filter ^{S6}	Molecular Weight (MW)	200–450 Da	Ideal size range for optimization into drug-like compounds.
	logP	−1 to 4.5	Moderate hydrophobicity for balanced solubility and permeability.
	Rotatable Bonds (RB)	≤ 8	Lower conformational entropy improves binding efficiency.
	Aromatic Rings	≤ 4	Limits excessive aromaticity, which can affect solubility and toxicity.
	H-bond Donors (HBD)	≤ 5	Controls molecular polarity and improves membrane permeability.
	H-bond Acceptors (HBA)	≤ 8	Keeps polarity within bounds for favorable pharmacokinetics.

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