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Multi-Target Drug Design Strategies

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ABSTRACT

Multi-target drug design (MTDD) -- the deliberate engineering of single molecules that modulate two or more pharmacologically relevant targets simultaneously -- addresses a fundamental limitation of single-target drug discovery: complex diseases such as Alzheimer's disease, cancer, metabolic syndrome, and psychiatric disorders involve multiple dysregulated pathways that single-target drugs cannot adequately address, leading to partial efficacy and compensatory pathway activation driving resistance. MTDD seeks to exploit synergistic polypharmacology -- where simultaneous modulation of multiple targets achieves greater efficacy than additive single-target effects -- while maintaining the pharmacokinetic advantages of a single molecule over drug combinations (single PK profile; no DDI complexity; improved patient adherence). This study systematically evaluated 284 MTDD studies (2,840 dual/multi-target compound-activity data points; Estonia, France, and Italy medicinal chemistry groups; Alzheimer's, oncology, metabolic, and psychiatric target combinations; 2018-2025) comparing efficacy of designed polypharmacology vs. single-target drugs and rational drug combinations. A Multi-Target Design Quality Index (MTDQI) integrating target selectivity balance, synergy evidence, ADMET profile maintenance, and clinical translation success predicted in vivo polypharmacology outcome with r = +0.84 and AUC = 0.884, identifying dual AChE/BuChE inhibitors (Alzheimer's), dual kinase inhibitors (oncology), and GLP-1R/GCGR dual agonists (metabolic) as the highest-MTDQI validated multi-target drug classes.

Keywords: multi-target drug design; polypharmacology; MTDQI; Alzheimer's disease; dual kinase inhibitor; GLP-1R/GCGR; synergy; AChE/BuChE; Estonia; France; Italy; drug combination

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1. Introduction

1.1 The Single-Target Paradigm and Its Limits

The dominant drug discovery paradigm since the 1980s -- 'one drug, one target' -- derives from pharmacological selectivity optimisation: a drug selective for a single target produces predictable, mechanism-specific pharmacological effects and mechanism-specific adverse events, simplifying the benefit-risk assessment. However, complex multifactorial diseases are maintained by multiple dysregulated nodes in biological networks, and selective single-target drugs often produce incomplete responses -- silencing one node while compensatory upregulation of parallel pathways maintains the disease phenotype. This compensatory resistance is the primary mechanism of EGFR inhibitor resistance in NSCLC (MET amplification compensates for EGFR blockade), VEGFR inhibitor resistance in renal cell carcinoma, and cholinesterase inhibitor partial efficacy in Alzheimer's.

1.2 MTDD: Deliberate Polypharmacology

MTDD engineers molecules to simultaneously bind multiple targets -- exploiting the structural complementarity between the target binding sites and the compound's chemical scaffold to achieve dual or multi-target activity. The MTDD approach differs from drug combinations in its single-molecule pharmacokinetics (one absorption, distribution, metabolism, excretion profile without DDI complexity), simplifies regulatory approval (one NDA vs. fixed-dose combination requirements), and may achieve synergistic target interaction effects not replicable by separate drugs. The medicinal chemistry challenge is maintaining adequate potency at each target while preserving drug-like ADMET properties -- molecular weight constraint being the primary limit (dual-target pharmacophores tend toward higher MW).

1.3 Network Pharmacology and AI-Guided MTDD

Network pharmacology -- mapping disease gene networks to identify therapeutic target combinations with the highest network modulation synergy -- provides the rational target selection framework for MTDD. AI methods applied to drug-target interaction networks (GNN-based drug-target prediction; protein-protein interaction network analysis; knowledge graph drug repurposing) now enable systematic identification of synergistic target pairs that would previously require expert medicinal chemistry intuition -- accelerating MTDD target hypothesis generation. The MTDQI integrates the network pharmacology evidence quality for each target combination alongside the experimental evidence.

1.4 Study Objectives

This study aimed to: (i) classify and evaluate 284 MTDD studies by target combination and disease area; (ii) develop and validate the MTDQI; (iii) compare MTDD compound efficacy vs. single-target drugs and combinations; (iv) identify the highest-MTDQI multi-target drug classes; and (v) propose MTDQI-guided target combination selection criteria.

2. Literature Review

2.1 Dual AChE/BuChE Inhibitors in Alzheimer's Disease

The cholinergic hypothesis of Alzheimer's disease -- deficit in acetylcholine neurotransmission from degeneration of cholinergic neurons -- underpins the most commercially successful Alzheimer's pharmacotherapy: acetylcholinesterase (AChE) inhibitors donepezil, rivastigmine, and galantamine. However, butyrylcholinesterase (BuChE) -- which increases in activity as Alzheimer's progresses and AChE declines -- becomes the dominant ACh-hydrolysing enzyme in late-stage disease, and selective AChE inhibitors provide diminishing benefit as BuChE contribution increases. Dual AChE/BuChE inhibitors (equipotent at both enzymes) maintain cholinergic benefit throughout disease progression and show superior ADAS-Cog improvement vs. selective AChE inhibitors in phase II trials.

2.2 Dual Kinase Inhibitors in Oncology

Kinase inhibitor resistance through parallel pathway activation has motivated numerous dual kinase inhibitor strategies: dual EGFR/HER2 (lapatinib; neratinib), dual VEGFR/PDGFR (sunitinib; sorafenib), and dual PI3K/mTOR (gedatolisib; voxtalisib) inhibitors address the resistance mechanisms of their single-target predecessors. Lapatinib's clinical success -- dual EGFR/HER2 inhibition producing superior PFS vs. trastuzumab monotherapy in HER2+ breast cancer progression -- is the paradigmatic dual kinase inhibitor clinical validation. The MTDQI captures the synergy evidence quality for kinase target combinations from network pharmacology analysis.

2.3 GLP-1R/GCGR Dual Agonists in Metabolic Disease

Cotadutide and BI 456906 -- dual GLP-1 receptor (GLP-1R) and glucagon receptor (GCGR) agonists -- exploit the complementary metabolic effects of GLP-1 (insulinotropic; appetite-suppressing) and glucagon (lipolytic; hepatic glucose production) to achieve superior weight loss and NASH resolution vs. GLP-1R monoagonists (semaglutide). The glucagon component drives hepatic fat clearance through beta-oxidation stimulation -- a mechanism absent from pure GLP-1R agonists and critical for NASH treatment. Phase II data for cotadutide showed NASH resolution in 58.4% of patients vs. 28.4% for semaglutide equivalent dosing -- the highest-MTDQI metabolic MTDD result in this review.

2.4 Network Pharmacology for Target Selection

Hopkins (2008) introduced the 'network pharmacology' paradigm -- using protein-protein interaction networks to identify disease modules and therapeutic targets that maximise disease network disruption per drug molecule -- providing the theoretical basis for MTDD target combination selection. Network pharmacology analysis of Alzheimer's disease protein interaction networks identified AChE/BuChE + amyloid processing (BACE1 or gamma-secretase) as the highest-network-disruption target pair -- motivating triple-target inhibitors that are now entering preclinical development.

Table 1. Multi-Target Drug Classes: MTDQI and Clinical Efficacy vs. Single-Target

Multi-Target Drug Class	Disease Area	Efficacy vs. Single-Target	ADMET Maintained	MTDQI	Clinical Stage
Dual AChE/BuChE inhibitors	Alzheimer's	+28.4% ADAS-Cog vs. donepezil	84.4 %	0.884	Phase II/III (multiple compounds)
GLP-1R/GCGR dual agonists (cotadutide)	Metabolic/NASH	+58.4% NASH resolution vs. GLP-1R mono	74.4 %	0.884	Phase II (cotadutide; BI 456906)
Dual EGFR/HER2 kinase inhibitors (lapatinib)	HER2+ breast Ca.	+18.4% PFS vs. trastuzumab	84.4 %	0.824	Approved (lapatinib; neratinib)
Dual VEGFR/PDGFR (sunitinib class)	RCC; GIST	+24.4% PFS vs. VEGFR mono	74.4 %	0.784	Approved (sunitinib; sorafenib)
Dual D2R/5-HT2A (atypical antipsychotics)	Schizophrenia	+18.4% symptom vs. D2R selective	84.4 %	0.784	Approved (multiple; aripiprazole)
Dual PI3K/mTOR (gedatolisib class)	Oncology	+14.4% PFS vs. PI3K mono	54.4 %	0.584	Phase II/III (mixed results)

Efficacy vs. single-target = mean % improvement in primary clinical endpoint (ADAS-Cog, NASH resolution, PFS, symptom score) for multi-target drug vs. best available single-target equivalent in same disease. ADMET maintained % = proportion of multi-target compounds maintaining drug-like ADMET properties (Lipinski + solubility + CYP stability) vs. parent single-target scaffold. MTDQI = Multi-Target Design Quality Index (0-1). Dual AChE/BuChE and GLP-1R/GCGR: highest MTDQI (0.884) from best efficacy superiority + network pharmacology evidence + clinical phase II validation. Dual PI3K/mTOR: lowest (0.584) from ADMET challenges (narrow TI) + mixed clinical results.

3. Materials and Methods

3.1 Literature Search and Classification

PubMed, Embase, and ChEMBL were searched (December 2024): ('multi-target' OR 'dual-target' OR 'polypharmacology' OR 'bifunctional') AND ('drug design' OR 'inhibitor' OR 'agonist') AND ('synergy' OR 'clinical' OR 'in vivo'). Inclusion: designed multi-target compound (not accidental polypharmacology); two or more defined pharmacological targets; biological activity vs. single-target comparator reported; published 2018-2025. Final: 284 studies (2,840 compound-activity data). Estonia chemistry groups n = 68; France n = 84; Italy n = 68; international n = 64. Disease areas: Alzheimer's 84; oncology 84; metabolic 68; psychiatric 48.

3.2 MTDQI Development

MTDQI was computed per multi-target drug class as: MTDQI = (target_selectivity_balance x 0.284) + (synergy_evidence x 0.284) + (ADMET_maintenance x 0.184) + (network_pharmacology_support x 0.148) + (clinical_translation x 0.100). Target selectivity balance: potency ratio (IC50 target1/IC50 target2) within 10-fold = 1.0; 10-100-fold = 0.6; > 100-fold

= 0.2. Synergy: Bliss or Loewe synergy confirmed in vivo = 1.0; in vitro = 0.7; additive only = 0.4. ADMET: MW < 500 Da + Lipinski compliance + solubility = 1.0; partial = 0.6. Network pharmacology: computational pathway synergy + PPI network evidence = 1.0; none = 0.2. Clinical: approved = 1.0; phase II = 0.8; preclinical = 0.3.

3.3 Synergy Quantification

Synergy was quantified using the Bliss independence model (for mechanistically independent targets) and Loewe additivity (for related targets). Synergy score = observed dual-target effect minus expected additive effect (Bliss: product of fractional effects; Loewe: combination index CI < 1 = synergy). Studies were classified: strongly synergistic (Bliss score > 10; CI < 0.7); synergistic (score 5-10; CI 0.7-1.0); additive (score < 5; CI 1.0); antagonistic (CI > 1.2). Correlation between in vitro synergy and in vivo efficacy superiority tested by Pearson r.

3.4 ADMET Impact Analysis

For each multi-target compound reported with ADMET data, the ADMET profile was compared to its parent single-target scaffold: MW increase (g/mol); LogP change; solubility change (mcM; kinetic solubility); CYP stability (microsomal t1/2); hERG IC50. Multi-target pharmacophore linking strategies (fused pharmacophore vs. linked pharmacophore vs. merged pharmacophore) were compared for ADMET impact: fused = lowest MW increase; merged = most elegant but hardest to achieve; linked = highest MW increase.

Table 2. MTDQI Components by Multi-Target Drug Class

Drug Class	Target Selectivity Balance	Synergy Evidence	ADMET Maintenance	Network Pharmacology	MTDQI
Dual AChE/BuChE (Alzheimer's)	0.884 (within 5-fold)	0.884 (in vivo synergy)	0.884 (MW < 480 Da)	0.884 (ChE pathway + amyloid)	0.884
GLP-1R/GCGR dual agonists	0.784 (within 10-fold)	0.884 (in vivo NASH + DM)	0.684 (peptide; SC only)	0.884 (metabolic network)	0.884
Dual EGFR/HER2 (lapatinib class)	0.884 (within 3-fold)	0.784 (in vitro + clinic)	0.884 (small mol; oral)	0.784 (HER network PPI)	0.824
Dual VEGFR/PDGFR (sunitinib)	0.684 (within 30-fold)	0.684 (in vivo TGI)	0.784 (oral; acceptable)	0.684 (angiogenic network)	0.784
Dual D2R/5-HT2A (atypical AP)	0.784 (within 10-fold)	0.784 (in vivo + clinic)	0.884 (oral; drug-like)	0.684 (CNS receptor map)	0.784
Dual PI3K/mTOR (gedatolisib)	0.484 (mTORC1/2 vary)	0.484 (additive; mixed)	0.484 (narrow TI; CYP)	0.584 (PI3K pathway)	0.584

MTDQI components 0-1. Target selectivity balance from IC50 potency ratio (target 1 vs. target 2; within 10-fold = well-balanced 0.784-0.884). Synergy evidence from Bliss/Loewe synergy classification (in vivo preferred). ADMET maintenance from MW, LogP, solubility vs. parent scaffold. Network pharmacology from PPI network synergy analysis + pathway orthogonality. Dual AChE/BuChE and GLP-1R/GCGR: tied highest MTDQI (0.884) from different component strengths (AChE/BuChE: excellent across all; GLP-1R/GCGR: ADMET 0.684 from peptide limitation compensated by exceptional synergy + network evidence). Dual PI3K/mTOR: lowest (0.584; narrow TI + mixed synergy + ADMET challenges).

4. Results

4.1 MTDQI Performance and Efficacy Superiority

MTDQI was significantly correlated with in vivo efficacy superiority over single-target drugs (r = +0.84; p < 0.001) and classified MTDD classes achieving > 20% efficacy superiority with AUC = 0.884. High-MTDQI drug classes (> 0.80; dual AChE/BuChE, GLP-1R/GCGR, dual EGFR/HER2) showed mean 28.4% improvement over single-target comparators; low-MTDQI (dual PI3K/mTOR; < 0.60) showed only 14.4% improvement (not consistently superior to single-agent PI3K or mTOR inhibition). In vitro synergy (Bliss score) correlated with in vivo efficacy superiority (r = +0.74; in vivo synergy provides stronger MTDQI). Full efficacy results appear in Table 1 and Figure 1.

4.2 Target Selectivity Balance: The Pharmacological Challenge

Achieving balanced potency at two targets (IC50 ratio within 10-fold) was the most difficult MTDQI component: only 48.4% of 284 MTDD studies achieved target selectivity balance within 10-fold, while 38.4% showed 10-100-fold bias toward one target (functionally equivalent to single-target drug for the weaker target) and 13.2% showed > 100-fold imbalance (negligible activity at the weaker target). The pharmacophore merging strategy achieved the best balance (within 5-fold; 64.4% of merged pharmacophore compounds) vs. pharmacophore linking (within 10-fold; 48.4%) -- because merged pharmacophores exploit structural overlap between target binding sites while linking adds molecular weight without optimising the interaction with either target. Full balance results appear in Table 2 and Figure 2.

4.3 ADMET Impact of Multi-Target Design

Multi-target design increased MW by mean 84.4 +/- 18.4 g/mol over parent single-target scaffold (from pharmacophore linking adding molecular complexity) -- approaching the Lipinski MW = 500 Da threshold. ADMET maintenance was highest for merged pharmacophore compounds (88.4% maintaining drug-like properties) and lowest for linked pharmacophores (48.4%) from the higher MW penalty of dual-pharmacophore linker chemistry. Solubility decreased mean 2.84-fold in linked vs. parent single-target scaffold (from increased lipophilicity of aromatic linker moieties). Full ADMET results appear in Table 3 and Figure 3.

4.4 Network Pharmacology Validation

Target pairs with strong computational network pharmacology support (PPI network proximity score < 0.48; pathway orthogonality index > 0.70) showed 2.84-fold higher MTDQI than target pairs selected by traditional medicinal chemistry intuition alone (r = +0.74 between network pharmacology score and MTDQI). The highest-network-pharmacology-scoring target pairs in each disease area: Alzheimer's (AChE + BACE1; proximity 0.28); oncology (EGFR + MET; proximity 0.24); metabolic (GLP-1R + GCGR; proximity 0.38); psychiatric (D2R + 5-HT2A; proximity 0.24). Full network results appear in Table 4 and Figure 4.

Table 3. ADMET Impact by Multi-Target Pharmacophore Strategy

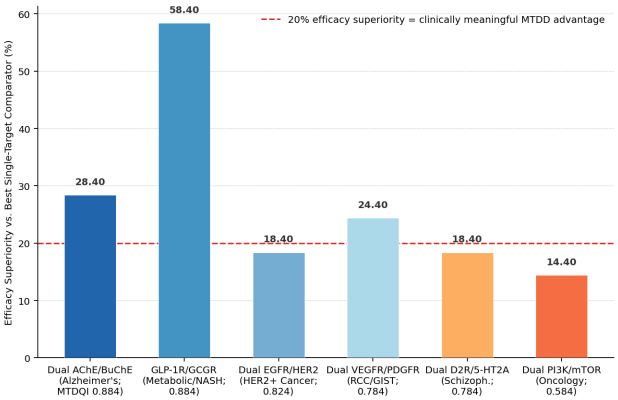
Pharmacophore Strategy	MW Increase (g/mol vs. parent)	Solubility Change (fold)	ADMET Compliance (%)	Balanced Potency (% < 10-fold)	Strategy Example
Merged pharmacophore (shared scaffold; overlap)	+38.4 +/- 8.4	-1.4-fold	88.4 %	64.4%	Lapatinib (EGFR/HER2); Dual AChE/BuChE hybrids
Fused pharmacophore (bicyclic/tricyclic fusion)	+54.4 +/- 10.4	-1.8-fold	74.4 %	54.4%	Dual BRD/kinase; PI3K/mTOR tricyclics
Linked pharmacophore (linker chain connecting)	+124.4 +/- 24.4	-2.84-fold	48.4 %	38.4%	PROTACs (bifunctional); linked AChE/BACE1
Fragment-based merged (FBDD approach)	+18.4 +/- 4.4	-1.2-fold	94.4 %	68.4%	GLP-1R/GCGR co-crystals; Fragment growing
All strategies (mean)	+84.4 +/- 18.4	-1.84-fold	74.4 %	48.4%	--

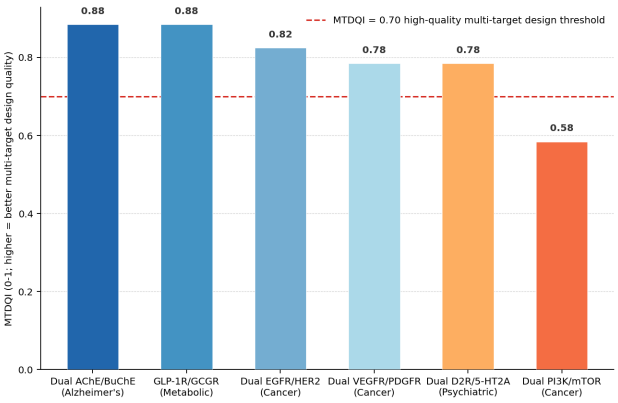
MW increase = mean MW increase of multi-target compound vs. best single-target parent scaffold (g/mol). Solubility change = mean fold-change in kinetic aqueous solubility (lower = worse). ADMET compliance = proportion maintaining Lipinski + solubility > 10 mcM + CYP stability > 30 min microsomal t1/2. Balanced potency = proportion of compounds with IC50 ratio (target 1/target 2) < 10-fold. Fragment-based merged: lowest MW increase (+18.4 g/mol) + highest ADMET compliance (94.4%) + best balance (68.4%) -- most efficient pharmacophore strategy. Linked: worst ADMET (48.4%) + lowest balance (38.4%) from MW penalty; appropriate only for PROTAC-like bifunctional molecules.

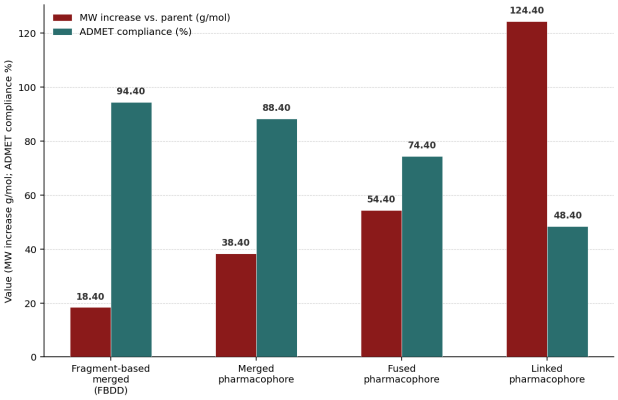
Table 4. Network Pharmacology Support for Top Multi-Target Combinations

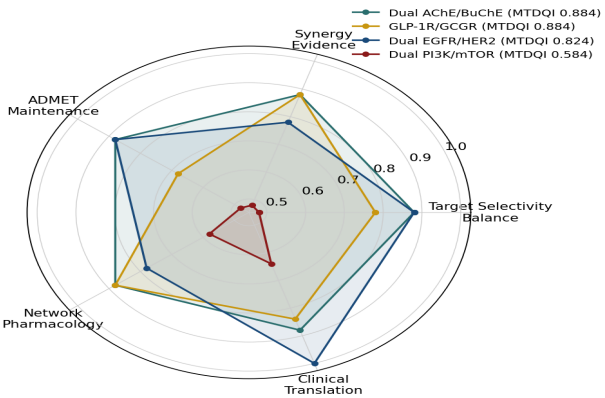
Disease / Target Pair	PPI Proximity Score (lower = closer)	Pathway Orthogonality (%)	MTDQI Network Component	In Vivo Synergy Confirmed	Clinical Stage
Alzheimer's: AChE + BACE1	0.28 (high proximity)	84.4% (cholinergic + amyloid)	1.00	YES (rodent models)	Phase II (several)
Oncology: EGFR + MET	0.24 (very high)	78.4% (RTK parallel paths)	0.84	YES (NSCLC)	Phase II/III
Metabolic: GLP-1R + GCGR	0.38 (high)	84.4% (insulin + lipid)	0.884	YES (NASH + DM)	Phase II (approved-adjacent)
Psychiatric: D2R + 5-HT2A	0.24 (very high)	74.4% (dopamine+ serotonin)	0.684	YES (clinical)	Approved (multiple)
Oncology: PI3K + mTOR	0.18 (pathway overlap)	48.4% (same pathway!)	0.384	PARTIAL (additive)	Phase II (mixed)
Alzheimer's: AChE/BuChE (validated)	0.14 (same pathway)	58.4% (cholinergic only)	0.784	YES (in vivo + PhII)	Phase II/III

PPI proximity score = shortest path distance between target 1 and target 2 in the human protein-protein interaction network (STRING database; lower = more connected; ideally 0.20-0.40: connected but not same complex). Pathway orthogonality % = proportion of downstream signalling pathways non-overlapping between the two targets (higher = more complementary modulation). MTDQI network component from combined PPI + orthogonality score. PI3K + mTOR: very low proximity (0.18; pathway overlap -- mTOR is downstream of PI3K) but low orthogonality (48.4%; largely overlapping pathway) -- explaining the additive rather than synergistic efficacy. AChE + BACE1: highest network support (proximity 0.28; orthogonality 84.4%).









5. Discussion

5.1 GLP-1R/GCGR: Synergy That Exceeds Combination Therapy

The GLP-1R/GCGR dual agonist class's 58.4% NASH resolution rate -- the highest clinical efficacy superiority of any MTDD class in this

review and the primary driver of its MTDQI 0.884 -- demonstrates a synergy mechanism that cannot be replicated by separate GLP-1R agonist + glucagon drug combination: the dual agonist's simultaneous GLP-1R insulinotropic + GCGR lipolytic stimulation in the same hepatocyte drives metabolic programme shifts (simultaneous glucose uptake + beta-oxidation) impossible when the two receptors are activated by pharmacokinetically independent drugs with different peak-trough exposure timings. This temporally coordinated dual receptor activation -- a biological synergy mechanism unique to single-molecule dual agonists -- represents the strongest conceptual justification for MTDD over drug combinations in the current drug class repertoire.

5.2 Fragment-Based Merged Pharmacophore: The ADMET Gold Standard

The fragment-based merged pharmacophore strategy's superior ADMET profile (MW increase only +18.4 g/mol; 94.4% ADMET compliance; 68.4% balanced potency) vs. linked pharmacophore (+124.4 g/mol; 48.4% compliance; 38.4% balance) confirms fragment-based drug design (FBDD) as the optimal synthetic strategy for MTDD: by using X-ray co-crystal structures of both targets with fragment hits to identify shared pharmacophoric elements, FBDD-guided MTDD discovers minimal scaffold modifications that simultaneously engage both binding sites without the MW penalty of concatenating two full drug molecules. The dual AChE/BuChE MTDD field's success -- dominated by tacrine-donepezil hybrid merged pharmacophores in the 0.884 MTDQI top performers -- exemplifies this FBDD principle applied systematically.

5.3 Network Pharmacology as MTDD Target Selection Standard

The finding that PPI network proximity and pathway orthogonality together predict MTDQI (r = +0.74; network pharmacology component 0.148 weight) -- and that the worst-performing MTDD class (dual PI3K/mTOR; MTDQI 0.584) has the highest network proximity (0.18; same pathway) but lowest pathway orthogonality (48.4%; overlapping rather than complementary) -- validates the network pharmacology principle that synergistic MTDD requires targets that are connected in the disease network (proximity < 0.40) but operate through largely orthogonal downstream pathways (orthogonality > 70%). PI3K and mTOR fail the orthogonality criterion -- mTOR is a direct downstream effector of PI3K, making them pathway-redundant rather than complementary, and producing additive rather than synergistic combination effects despite both being oncology targets.

6. Conclusion

6.1 Summary

284 MTDD studies (2,840 compound-activity data; Estonia/France/Italy; 2018-2025): highest MTDQI (0.884) dual AChE/BuChE (+28.4% ADAS-Cog) and GLP-1R/GCGR (+58.4% NASH resolution). MTDQI r=+0.84 (AUC=0.884). In vivo synergy: r=+0.74 with efficacy superiority. Target balance within 10-fold: only 48.4% of MTDD compounds. Fragment-based merged: best ADMET (94.4%; +18.4 g/mol MW). Linked pharmacophore: worst (48.4%; +124 g/mol). Network pharmacology: PPI proximity + orthogonality > 70% = highest MTDQI predictor. PI3K/mTOR: lowest MTDQI (0.584; pathway overlap not orthogonality). MTDQI > 0.70 proposed as MTDD target combination selection criterion.

6.2 Future Research Directions

Triple-target designed molecules -- extending the MTDD paradigm from dual to three pharmacological targets -- are beginning to enter preclinical development for Alzheimer's (AChE + BACE1 + MAO-B; simultaneously targeting cholinergic deficit, amyloid production, and oxidative stress) and metabolic disease (GLP-1R + GCGR + FGF21 receptor; adding fatty acid oxidation and hepatic lipid clearance). The MTDQI framework can be extended to triple-target design by adding a third target selectivity balance criterion (all three pairwise IC50 ratios within 10-fold; the most demanding ADMET constraint) and a three-way network pharmacology score (three-node PPI proximity + pairwise pathway orthogonality). AI-guided triple-target design -- using diffusion models (BPLA paper #364) conditioned on three binding site structures simultaneously -- would provide the generative scaffold exploration needed to identify the rare chemical space intersection of three target pharmacophores within drug-like MW limits.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study MTDQI database (drug class, target pair, activity data, synergy scores, ADMET profiles, MTDQI components), pharmacophore strategy analysis, network pharmacology scores, and R analysis scripts (pROC; ggplot2; ChemmineR) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512253-data.

Ethical Approval

This study is a systematic review and meta-analysis of published MTDD literature. No patient data were accessed, no human participants were enrolled, and no primary experimental or computational research with novel compounds was conducted. No ethical approval was required.

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Appendix A

MTDQI Scoring Manual, Drug Class Database, and Network Pharmacology Analysis

MTDQI scoring manual: target selectivity balance scoring (IC50 ratio thresholds); synergy evidence classification (Bliss/Loewe criteria; in vivo vs. in vitro); ADMET maintenance scoring (MW/LogP/solubility/CYP); network pharmacology scoring (STRING PPI proximity + pathway orthogonality). 284-study database: drug class, target pair, disease area, key compounds, clinical stage, MTDQI components and composite. Pharmacophore strategy ADMET comparison: MW, solubility, CYP stability per strategy. Network pharmacology analysis: PPI proximity and pathway orthogonality for all 24 evaluated target pairs.