

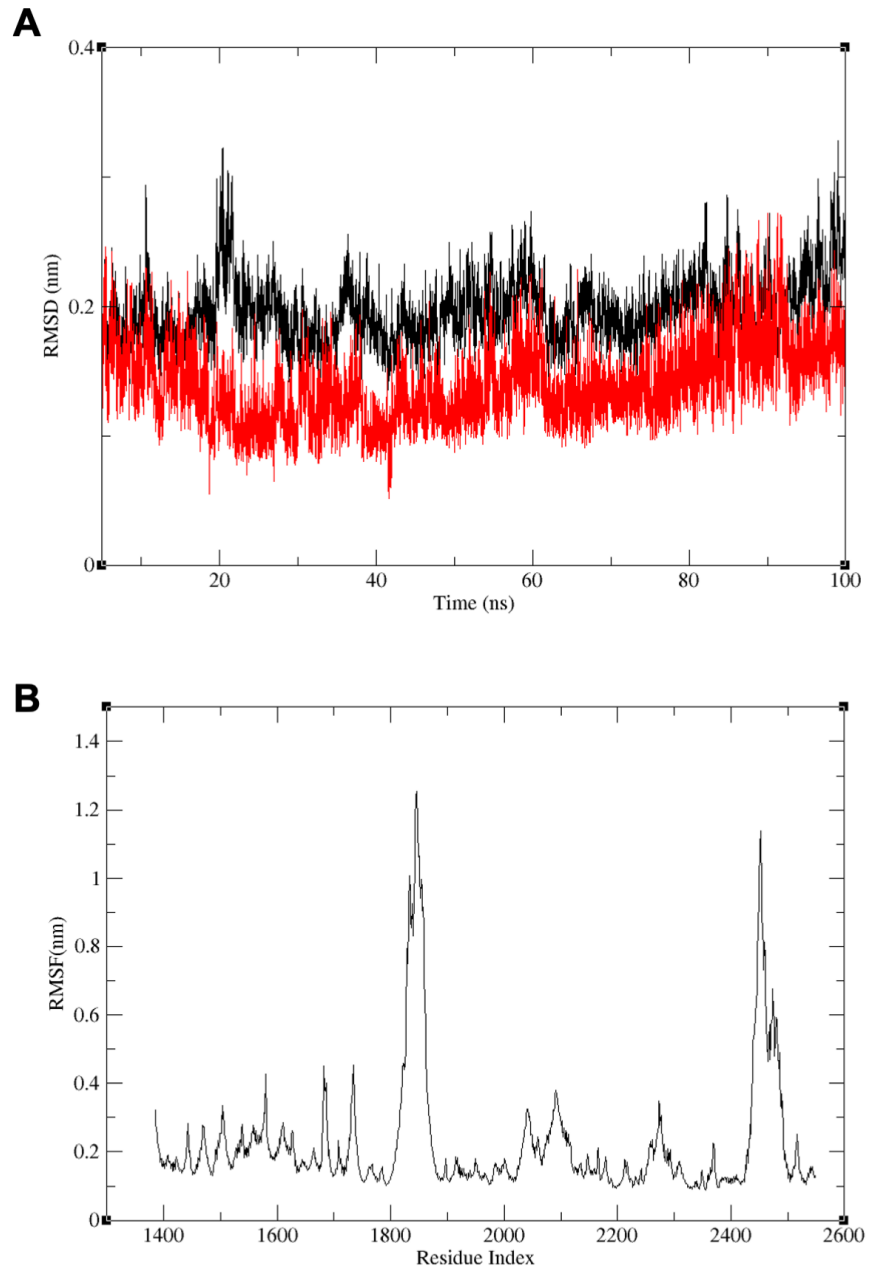
Supplementary Figures S1-S3

AI-predicted mTOR inhibitor reduces cancer cell proliferation and extends the lifespan of *C. elegans*

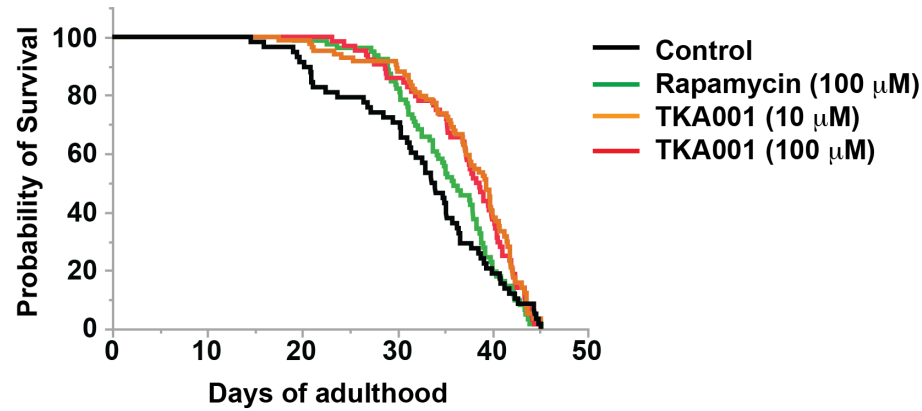
Tinka Vidovic, Alexander Dakhovnik, Oleksii Hrabovskyi, Michael R. MacArthur, Collin Y. Ewald

Medicinal Chemistry		Absorption		Metabolism		Tox21 Pathway		Physicochemical Property	
QED	0.859	Caco-2 Permeability	-5.408	CYP1A2 inhibitor	++	NR-AR	---	MW	369.18
SAScore	2.509	MDCK Permeability	1.70E-05	CYP1A2 substrate	+	NR-AR-LBD	---	Volume	365.854
Fsp3	0.421	Pgp-inhibitor	+	CYP2C19 inhibitor	--	NR-AhR	++	Density	1.009
MCE-18	48.889	Pgp-substrate	+++	CYP2C19 substrate	--	NR-Aromatase	---	nHA	8
NPscore	-1.856	HIA	---	CYP2C9 inhibitor	---	NR-ER	-	nHD	2
Lipinski Rule	Accepted	F20%	---	CYP2C9 substrate	--	NR-ER-LBD	---	nRot	6
Pfizer Rule	Accepted	F30%	---	CYP2D6 inhibitor	--	NR-PPAR-gamma	---	nRing	4
GSK Rule	Accepted			CYP2D6 substrate	++	SR-ARE	+	MaxRing	9
Golden Triangle	Accepted			CYP3A4 inhibitor	-	SR-ATAD5	---	nHet	8
PAINS	0 alert(s)			CYP3A4 substrate	-	SR-HSE	---	fChar	0
ALARM NMR Rule	0 alert(s)	Plasma Protein Binding	93.08%			SR-MMP	-	nRig	23
BMS Rule	0 alert(s)	Volume Distribution	0.702			SR-p53	+	Flexibility	0.261
Chelator Rule	0 alert(s)	BBB Penetration	--					Stereo Centers	0
		Fu (fraction unbound in plasmas)	6.46%	Excretion				TPSA	88.61
				CL	5.107			logS	-4.606
				T1/2	0.546			logP	1.817
								logD	2.583

Supplementary Figure S1. ADMET of TKA001. The SMILES string of TKA001 was used to obtain the prediction of ADMET properties using the ADMETlab 2.0 tool. QED is a measure of drug-likeness based on the concept of desirability (attractive: > 0.67; unattractive: 0.49~67; too complex: < 0.34). SAscore is the synthetic accessibility score and is designed to estimate the ease of synthesis of drug-like molecules (SAscore > 6, difficult to synthesize. SAscore < 6, easy to synthesize). Fsp3 is the number of sp3 hybridized carbons / total carbon count, and it correlates with melting point and solubility (Fsp3 > 0.42 is considered a suitable value). MCE-18 stands for medicinal chemistry evolution (MCE-18 > 45 is considered a suitable value). NP is a Natural product-likeness score. This score is typically in the range from -5 to 5; the higher the score, the higher the probability that the molecule is an NP. Lipinski rule: MW < 500; logP < 5; Hacc < 10. Hdon < 5, if two properties are out of range, poor absorption or permeability is possible, and one is acceptable. Pfizer rule: logP > 3. TPSA < 75. Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic. GSK rule: MW < 400. logP < 4. Compounds satisfying the GSK rule may have a more favorable ADMET profile. PAINS - Pan Assay Interference Compounds, frequent hitters, alpha-screen artifacts, and reactive compounds. ALARM NMR - Thiol reactive compounds. BMS - Undesirable, reactive compounds. Chelator rule: chelating compounds. Caco-2 permeability - Optimal: higher than -5.15 Log unit. MDCK permeability - low permeability: < 2 × 10⁻⁶ cm/s; medium permeability: 2–20 × 10⁻⁶ cm/s; high passive permeability > 20 × 10⁻⁶ cm/s. Pgp-inhibitor - the output value is the probability of being a Pgp-inhibitor. Pgp-substrate - The output value is the probability of being Pgp-substrate. HIA - Human Intestinal Absorption; Category 1: HIA+ (HIA < 30%). Category 0: HIA- (HIA > 30%). The output value is the probability of being HIA+. F20% - 20% Bioavailability. Category 1: F20%+ (bioavailability < 20%). Category 0: F20%- (bioavailability > 20%). The output value is the probability of being F20%+. F30% - 30% Bioavailability. Category 1: F30%+ (bioavailability < 30%). Category 0: F30%- (bioavailability > 30%). The output value is the probability of being F30%+. PPB - Plasma Protein Binding (Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index). VD - Volume Distribution. Optimal: 0.04-20L/kg. BBB - Blood-Brain Barrier Penetration. Category 1: BBB+. Category 0: BBB-. The output value is the probability of being BBB+. Fu - The fraction unbound in plasmas. Low: < 5%. Middle: 5~20%. High: > 20%. CL - Clearance. High: >15 mL/min/kg. Moderate: 5-15 mL/min/kg. Low: <5 mL/min/kg. T1/2 - Category 1: long half-life; Category 0: short half-life; long half-life: >3h; short half-life: <3h. The output value is the probability of having a long half-life. The prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).



Supplementary Figure S2. Molecular Dynamics of TKA001 with mTOR kinase. A) Root-Mean-Square Deviation (RMSD) values extracted from 100 ns molecular dynamics simulation. RMSD of protein backbone (in black line) and RMSD of TKA001 ligands heavy atoms (in red line). B) Root mean square fluctuations (RMSF) values extracted from protein C α atoms during 100 ns molecular dynamics simulation.



Supplementary Figure S3. Automated lifespan analysis of mTOR inhibitor TKA001. Adult wild-type (N2) *C. elegans* were supplemented with 10, 100 μ M TKA001, and 100 μ M rapamycin (as a positive control for mTOR inhibition), which increased the mean lifespan of *C. elegans* compared to 0.2% DMSO-treated control. The survival was scored by the automated lifespan machine. Raw data and statistics are presented in Supplementary Table S2.