

**Supplementary Materials
for Review**

Chemistry and Biological Activity of 11*H*-Indeno[1,2-*b*]quinoxalin-11-ones and Tryptanthrins, Their Oximes, and Related Analogues

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Table S1. Antimicrobial, antiviral, antiparasitic, antitubercular, and antidiabetic effects of tetracyclic ketoximes and related compounds.

Compd.	Pathogen / Model	Key Activity Data and Proposed Mechanism(s)	Ref.
Antimicrobial / Antifungal			
TRP-Ox and 4-aza derivatives	<i>Escherichia coli</i> (growth, viability, mutagenesis)	Viability reduction by factors of 10^{-2} to $<10^{-6}$ at 0.2–40 μM ; 6-oximo derivatives most bactericidal; DNA intercalation; disruption of replication and transcription	[1]
TRP analogues	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i> (Xoo); TMV; citrus canker model	EC_{50} = 1.2 $\mu\text{g/mL}$ vs. Xoo (>25-fold more potent than bismethiazol and thiodiazole copper); ROS accumulation; bacterial apoptosis; biofilm disruption; T2SS/T6SS secretion system inhibition	[2]
TRP derivatives (broad panel)	<i>Phytophthora piricola</i> ; 14 phytopathogenic fungi; TMV	Broad-spectrum fungicidal activity; selectivity to <i>P. piricola</i> surpassing conventional agrochemicals; anti-TMV <i>in vivo</i> ; TMV CP disk decomposition	[3]
Spiro-indenoquinoxaline heterocycles	Gram-positive bacteria (<i>S. aureus</i>)	Enhanced membrane permeation; 50% inhibitory effect; selectivity for Gram-positive pathogens	[4]
Indenoquinoxaline thiocarbohydrazones	<i>S. aureus</i> , <i>C. albicans</i>	Promising antimicrobial activity with concurrent radical-scavenging profiles; molecular modeling (B3LYP/6-31G) supports DNA/protein interaction	[5]
Pd(II)–quinoxaline Schiff base complex	<i>S. aureus</i> , <i>C. albicans</i>	Antimicrobial + antioxidant (ABTS, FRAP assays); square-planar coordination; enhanced bioactivity vs. free ligand	[6]
Antiviral			
TRP	HCoV-NL63 (LLC-MK2 cells)	IC_{50} = 1.5 μM (virus yield); virucidal IC_{50} = 60 nM; blocks early and late replication stages; inhibition of viral RNA genome synthesis; papain-like protease 2 (PLpro2) activity blockade	[7]
TRP derivatives	SARS-CoV-2 (Vero cells); Mpro; PLpro	Fe(III/II) chelation; suppression of viral replication <i>in vitro</i> ; high docking affinity for Mpro and PLpro; iron chelation relevant to COVID-19 pathogenesis	[8]
TRP	IAV: wild-type H1N1, H3N2	Protective effects against both wild-type and resistant IAV strains (CPE reduction assay); multi-target antiviral; network pharmacology identifies TRP as key anti-IAV agent	[9,10]
TRP derivative B1	Potato Virus Y (PVY) VPg protein	K_d = 0.7 μM (MST); 4.0 μM (ITC); suppresses PVY gene expression <i>in vivo</i> ; binds VPg from 3 other Potyviruses	[11]
Antiparasitic / Antiprotozoal			
TRP derivatives	<i>Toxoplasma gondii</i>	Low nanomolar parasite growth inhibition; low host cell cytotoxicity; alcohol analogs most promising; C-6 modification critical for activity; oxime/hydrazone analogs enhance inhibition	[12,13]
TRP	<i>Leishmania infantum</i> ; <i>L. amazonensis</i>	IC_{50} = 8 μM (<i>L. infantum</i>), 11 μM (<i>L. amazonensis</i>) promastigotes; active against amastigotes; mitochondrial membrane depolarization; apoptosis-like death	[14]
Indolo[2,1- <i>b</i>]quinazoline-6,12-diones	<i>L. donovani</i>	Active at concentrations <100 ng/mL; low toxicity to macrophage and neuronal lines; electron transfer to carbonyl/oxime region	[15]

TRP analogs (8-substituted)	<i>Trypanosoma brucei in vitro</i>	EC ₅₀ = 0.4 μ M (most potent; 8-position electron-withdrawing group); electron-withdrawing substituents at C-8 enhance activity	[16]
Imidazoquinolinone C1	<i>Trypanosoma cruzi</i>	IC ₅₀ epi = 1.5 μ M; IC ₅₀ amas = 1.7 μ M; IC ₅₀ try = 34.9 μ M; low host cell toxicity; reduction by intracellular thiol pool $\rightarrow$ oxidative stress $\rightarrow$ parasite apoptosis; antioxidant co-treatment enhances activity 3-fold	[17]
TRP derivatives (NT1, T8)	<i>Plasmodium falciparum</i>	IC ₅₀ = 30 nM (NT1; SI = 156); nanomolar activity (30–100 nM) retained against resistant strains; gametocyte maturation blocked; NT1 reduces exflagellation	[18]
TRP	<i>P. falciparum</i> 3D7 and Dd2	IC ₅₀ = 2.5 μ M (3D7), 3.1 μ M (Dd2); CC ₅₀ > 10 μ M; no hemolysis at 100 μ g/mL; antiplasmodial	[19]
Quinoxaline analogs	<i>Schistosoma mansoni</i>	IC ₅₀ $\leq$ 0.3 μ M (adult <i>S. mansoni</i>); SI $\geq$ 8.9; moderate WBR <i>in vivo</i> (9–46% at 400 mg/kg)	[20]
Antitubercular			
TRP analogs	Mtb (MABA assay; acute murine TB)	Maintained <i>in vitro</i> Mtb activity; improved solubility and oral bioavailability vs. parent; failed to suppress Mtb replication <i>in vivo</i> (up to 400 mg/kg/day $\times$ 4 weeks); illuminates SAR path but highlights PK disconnect; first systematic ADME profiling of TRP class	[21]
2-(Propylthio)-5H-[1,3,4]thiadiazolo[2,3-b]quinazolin-5-one	<i>M. tuberculosis</i>	MIC = 6.5 μ g/mL (100% growth inhibition); very low oral toxicity (GHS category 5); InhA (enoyl-ACP reductase) inhibition; stable binding within InhA active site	[22]
C-6 keto-modified TRP	MDR <i>M. tuberculosis</i> ; InhA	Promising activity against MDR-TB; high InhA affinity; InhA inhibition; favorable predicted PK profiles	[23]
Spiropyrrolidine-tethered indenoquinoxaline	<i>M. tuberculosis</i> H37Rv	MIC = 1.6 μ g/mL; ionic-liquid-accelerated multicomponent 1,3-dipolar cycloaddition	[24]
Antidiabetic / Metabolic			
Hydrazinyl thiazole-linked indenoquinoxaline hybrids	α -Amylase; α -glucosidase	IC ₅₀ = 0.3–77 μ M (α -amylase); IC ₅₀ = 1.1–92 μ M (α -glucosidase); outperform acarbose (IC ₅₀ = 13.5 μ M); DPPH SC ₅₀ = 7.58–125.86 μ M	[25]
Pd(II)–quinoxaline Schiff base complex	α -Amylase (enzyme inhibition + MD simulation)	IC ₅₀ = 326.5 μ g/mL; mixed-mode inhibition kinetics; stable ligand–enzyme interactions (100 ns MD)	[6]

Abbreviations: ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); ADMET, absorption, distribution, metabolism, excretion, and toxicity; ACP, acyl carrier protein; BLG, Banlangen; CP, coat protein; CPE, cytopathic effect; CQ, chloroquine; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC₅₀, half-maximal effective concentration; FRAP, ferric reducing antioxidant power; GHS, Globally Harmonized System; HCoV-NL63, human coronavirus NL63; IAV, influenza A virus; IC₅₀, half-maximal inhibitory concentration; InhA, enoyl-acyl carrier protein reductase; ITC, isothermal titration calorimetry; Kd, dissociation constant; MABA, microplate Alamar blue assay; MD, molecular dynamics; MDR, multidrug resistant; MM/GBSA, molecular mechanics/generalized Born surface area; Mpro, main protease; MST, microscale thermophoresis; NTS, newly transformed schistosomula; PK, pharmacokinetic; PLpro, papain-like protease; PVY, Potato Virus Y; QM, quantum mechanical; ROS, reactive oxygen species; SAR, structure–activity relationship; SC₅₀, half-maximal scavenging concentration; SI, selectivity index; T2SS/T6SS, type II/VI secretion systems; TMV, tobacco mosaic virus; VPg, viral genome-linked protein; WBR, worm burden reduction.

Table S2. Alternative (non-kinase) mechanisms of therapeutic action for tetracyclic ketoximes and related tryptanthrins.

Compd.	Model / System	Key Findings and Molecular Target / Pathway	Ref.
TRP	MCD-induced NASH mice; LPS-induced sepsis mice	Inhibits NLRP3, NLRC4, and AIM2 inflammasomes; ameliorates NASH and sepsis <i>in vivo</i> ; PYD binding; disrupts ASC oligomerization and caspase-1 maturation	[26]
TRP	BV2 microglia (LPS-stimulated); mouse SCI model	M1→M2 microglial polarization; ↓ neuroinflammation; suppressed ER stress-related neuronal apoptosis; ↑ functional recovery cGAS/STING/NF-κB axis inactivation	[27]
TRP	HaCaT keratinocytes; fibroblasts infected with <i>T. benhamiae</i> DSM6916	↑ HBD2 and HBD3 antimicrobial peptide expression; ↓ pro-inflammatory cytokines; prevented dermatophyte-induced cellular damage; immune modulation via AMP upregulation; TLR2 pathway	[28]
TRP	HMC-1 human mast cells; NC/Nga mice; splenocytes	↓ TSLP production and mRNA expression; ↓ IL-4, IFN-γ, TNF; ↓ histidine decarboxylase; ameliorated clinical atopic dermatitis symptoms; ↓ RIP2/caspase-1/NF-κB pathway	[29]
TRP	HMC-1 cells (TSLP-stimulated)	↓ Mast cell proliferation; ↑ p53, PARP, caspase-3; ↓ MDM2, Ki67; ↓ IL-13 and TNF; MDM2/p53 axis modulation; TSLP receptor downregulation	[30]
Pityriazepin and indole metabolites	Recombinant AhR reporter cell lines	Potent AhR agonism; competitive binding; direct stimulation of AhR-dependent DNA binding; species-specific potency	[31]
Indigo naturalis (TRP as key component)	Plaque psoriasis patients	PASI 75 response in 56.3% vs. 0% placebo; gene expression signature returned toward normal; ↓ IL-17 pathway; IL-17 pathway suppression; TRP-mediated IL-17 inhibition in keratinocyte assay	[32]
6-Oximo and 4-aza TRP derivatives	<i>E. coli</i> DNA; computational DFT modeling	Preferential intercalation into GC-rich DNA ($\Delta E \approx 2\text{--}4$ kcal/mol GC vs. TA); disruption of replication and transcription; DNA intercalation; GC-selective π -stacking	[1,37]
TRP sulfonate (TPTS)	Calf thymus DNA (UV spectroscopy)	$K_{\text{bind}} = 1.10 \times 10^4 \text{ M}^{-1}$; moderate hypochromicity; significant viscosity increase; Intercalative DNA binding mode	[38]
Aminoalkylamino indolo[2,1- <i>b</i>]quinazolin-6,12-diones	Synthetic DNA triplex structures	↑ Triplex thermal stability by up to 6 °C; position-8 F or N-CH ₃ substitution enhances stabilization additively; DNA triplex stabilization via side-chain orientation	[39]
Benzo[<i>b</i>]tryptanthrin	HCT15 colon; MCF7/adr breast cancer cells	Non-intercalative ATP-competitive dual topo I/II catalytic inhibitor; reverses adriamycin resistance; ↓ MDR1 expression; topoisomerase I/II catalytic inhibition; MDR1 downregulation	[40,41]
Mostotrin (TRP derivative)	DNA fluorescence quenching assay; tumor cell lines	DNA binding confirmed by fluorescence quenching; 5–10× higher cytotoxicity vs. parent TRP; LD ₅₀ = 375 mg/kg;	[42]

		DNA binding; improved cellular uptake via enhanced aqueous solubility	
TRP	HepG2; Huh7 liver cancer cells; xenograft	Directly binds and inhibits GSTP1; induces ROS accumulation, DDR, NF- κ B-mediated SASP; sensitizes to senolytic ABT263; GSTP1/ROS/DDR/NF- κ B/SASP axis $\rightarrow$ cellular senescence	[43]
Nano-encapsulated CY-1-4 (TRP derivative)	B16-F10 melanoma (<i>in vitro</i> and <i>in vivo</i>)	IDO inhibition + ICD induction as single agent; $\downarrow$ IDO expression in tumor tissue; regulated lymphocyte subsets; $\downarrow$ 58% tumor burden; dual IDO inhibition and immunogenic cell death	[44]
CIQ (8-cyanoindolo[2,1- <i>b</i>]quinazoline-6,12-dione)	MDA-MB-231; MCF-7 breast cancer cells	$\uparrow$ p-ERK, p-JNK, p-p38; caspase-dependent apoptosis; $\downarrow$ invasion; $\downarrow$ MMP-2 and Snail; $\uparrow$ γ -H2AX (DNA damage); pro-apoptotic MAPK (ERK/JNK/p38) activation; ROS generation	[45]
8-Fluorotryptanthrin	K-562/4; HCT-116; HCT-116p53ko	Higher cytotoxicity than parent TRP; cell cycle arrest at G ₁ $\rightarrow$ S transition at nanomolar concentrations; cell cycle blockade at G ₁ /S phase	[46]
TRP	<i>V. splendidus</i> AJ01	$\uparrow$ Biofilm but $\downarrow$ motility, hemolytic activity, and flagellar gene expression; competitive binding to LuxO ₁	[47]
TRP	Toxigenic <i>V. cholerae</i>	$\downarrow$ Biofilm maturation at sub-MIC (2 μ g/mL); synergistic with ciprofloxacin; non-cytotoxic; LuxO quorum-sensing regulator targeting	[48]
Fluorinated/piperazine TRP analogs	<i>X. oryzae</i> pv. <i>oryzae</i> ; citrus canker model	EC ₅₀ = 1.26 μ g/mL (>25 $\times$ more potent than bismethiazol); $\downarrow$ T2SS/T6SS pathways; $\downarrow$ membrane transport; secretion system disruption (T2SS/T6SS; proteomics-confirmed)	[43]
TRP	<i>C. jejuni</i> (<i>in vitro</i> ; chick infection model)	Bactericidal activity; narrow antimicrobial spectrum; low resistance emergence potential; $\downarrow$ cecal colonization in chicks; direct bactericidal mechanism; MIC far lower than other herbal compounds tested	[49]
TRP	<i>C. neoformans</i> ; <i>T. rubrum</i>	MIC = 2 μ g/mL (<i>Cryptococcus</i>); cell cycle arrest at G ₁ /S; synergy with FK506 and CsA; cell cycle regulators (CLN1, MBS1, PCL1, WHI5); Pmc1 calcium transporter; PKA signaling	[50]
Spirooxindole-indenoquinoline	ecTrpRS; <i>S. aureus</i> (MRSA); DLBCL cell lines	IC ₅₀ = 74 nM (ecTrpRS); MIC ₉₀ = 4 μ g/mL (<i>S. aureus</i>); IC ₅₀ = 2.9–4.8 μ M (DLBCL); bacterial autolysis induction; TrpRS inhibition; dual antibacterial/anticancer activity	[51]
5-Substituted TRPs	20S proteasome	Unprecedented inhibition of 20S proteasome activity	[52]
TRP	<i>M. smegmatis</i> (spontaneous resistant mutants)	Resistance via MmpS5-MmpL5 efflux upregulation; MSMEG_1963 (EmrB) high-level resistance; MSMEG_5597 (TetR) low-level resistance; Efflux-mediated resistance (not target-site alteration); MFS transporter involvement	[53]
TRP	BALB-C mice (excisional wound model)	Wound closure rate up to 94% (highest dose); $\uparrow$ VEGF and MMP-9 on days 3 and 7; histopathological improvement; VEGF/MMP-9-mediated tissue repair and angiogenesis	[54]

Abbreviations: AD, atopic dermatitis; AhR, aryl hydrocarbon receptor; AMP, antimicrobial peptide; ASC, apoptosis-associated speck-like protein containing a CARD; BMDMs, bone marrow-derived macrophages; cGAS, cyclic GMP-AMP synthase; CsA, cyclosporine A; DDR, DNA damage response; DLBCL, diffuse large B-cell lymphoma; DSS, dextran sulfate sodium; ecTrpRS, *Escherichia coli* tryptophanyl-tRNA synthetase; ER, endoplasmic reticulum; FICI, fractional inhibitory concentration index; GluR6, glutamate receptor 6; GSTP1, glutathione S-transferase P1; HBD, human β -defensin; ICD, immunogenic cell death; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; MCD, methionine- and choline-deficient diet; MDR1, multidrug resistance protein 1; MFS, major facilitator superfamily; MIC, minimum inhibitory concentration; MLK3, mixed lineage kinase 3; MMP, matrix metalloproteinase; MRSA, methicillin-resistant *Staphylococcus aureus*; NASH, non-alcoholic steatohepatitis; NF- κ B, nuclear factor- κ B; NLRP3, nod-like receptor family pyrin domain containing 3; PARP, poly(ADP-ribose) polymerase; PASI, psoriasis area and severity index; PKA, protein kinase A; PSD-95, postsynaptic density protein 95; PYD, pyrin domain; RCT, randomized controlled trial; RIP2, receptor-interacting protein 2; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCI, spinal cord injury; STING, stimulator of interferon genes; T2SS/T6SS, type II/VI secretion systems; TLR, Toll-like receptor; TNF, tumor necrosis factor- α ; topo, topoisomerase; TrpRS, tryptophanyl-tRNA synthetase; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

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