

RESEARCH ARTICLE

8-Hydroxyquinolines are bactericidal against *Mycobacterium tuberculosis*

Joshua O. Odingo | Julie V. Early | Jake Smith | James Johnson | Mai A. Bailey | Megan Files | Junitta Guzman | Juliane Ollinger | Aaron Korkegian | Anuradha Kumar | Yulia Ovechkina | Tanya Parish 

TB Discovery Research, Infectious Disease Research Institute, Seattle, Washington

Correspondence

Tanya Parish, TB Discovery Research, Infectious Disease Research Institute, 1616 Eastlake Ave E, Suite 400, Seattle, WA 98102. Email: tanya.parish@idri.org

Funding information

Bill and Melinda Gates Foundation, Grant/Award Number: OPP1024038; Bill and Melinda Gates Foundation, Grant/Award Number: OPP1024038; Eli Lilly and Company, Grant/Award Number: Lilly TB Drug Discovery Initiative

ABSTRACT

There is an urgent need for new treatments effective against *Mycobacterium tuberculosis*, the causative agent of tuberculosis. The 8-hydroxyquinoline series is a privileged scaffold with anti-cancer, antifungal, and antibacterial activities. We conducted a structure–activity relationship study of the series regarding its antitubercular activity using 26 analogs. The 8-hydroxyquinolines showed good activity against *M. tuberculosis*, with minimum inhibitory concentrations (MIC₉₀) of <5 μM for some analogs. Small substitutions at C5 resulted in the most potent activity. Substitutions at C2 generally decreased potency, although a sub-family of 2-styryl-substituted analogs retained activity. Representative compounds demonstrated bactericidal activity against replicating *M. tuberculosis* with >4 log kill at 10× MIC over 14 days. The majority of the compounds demonstrated cytotoxicity (IC₅₀ of <100 μM). Further development of this series as antitubercular agents should address the cytotoxicity liability. However, the 8-hydroxyquinoline series represents a useful tool for chemical genomics to identify novel targets in *M. tuberculosis*.

KEYWORDS

Mycobacterium tuberculosis, antibacterial, hydroxyquinoline, structure–activity relationship, tuberculosis

1 | INTRODUCTION

Tuberculosis is the leading killer among infectious diseases with 1.3 million deaths and >10 million new cases in 2017 (World Health Organization, 2018). The shortest treatment for tuberculosis is a 6-month regimen containing four antibiotics (World Health Organization, 2018). More than half a million multidrug resistant (MDR) cases emerge each year, with treatment of those cases requiring up to 2 years of treatment with second and third line drugs (World Health Organization, 2018). Affordable and innovative treatments with shorter treatment times and unique mechanisms of action are urgently needed.

8-hydroxyquinoline (HQ) is a well-studied, privileged structure, with activity against a wide range of cell types (Prachayasittikul, Prachayasittikul, Ruchirawat, & Prachayasittikul, 2013; Song, Xu, Chen, Zhan, & Liu, 2015), including anticancer activity (Barilli et al., 2014;

Bhat, Shim, Zhang, Chong, & Liu, 2012; Chang, Chen, Wang, Tzeng, & Chen, 2010; Feng et al., 2015; Li et al., 2016; Moret et al., 2009; Mrozek-Wilczkiewicz et al., 2015; Sosić et al., 2013; Spaczyńska, Tabak, Malarz, & Musiol, 2014), antifungal activity (Cieslik et al., 2012; Musiol et al., 2006), and antibacterial activity (Warner, Musto, Turesky, & Soloway, 1975). The HQ are active against several bacterial species including *Staphylococcus aureus* and *Staphylococcus epidermidis* (Abouelhasan et al., 2014, 2015; Basak et al., 2016; Garrison et al., 2017; Lam et al., 2014), *Enterococcus faecium* (Basak et al., 2016; Garrison et al., 2017), *Burkholderia pseudomallei* (Wangtrakuldee et al., 2013), *Neisseria gonorrhoeae*, (Lawung et al., 2018), *Listeria monocytogenes* (Chertrakulkiat et al., 2016), and *Mycobacterium avium* (Hongmanee, Rukseree, Buabut, Somsri, & Palittapongarnpim, 2007; Kos et al., 2015). In addition, activity of the HQ compounds against replicating and nonreplicating *Mycobacterium tuberculosis* has been demonstrated

in medium containing copper and in infected guinea pigs (Ananthan et al., 2009; Darby & Nathan, 2010; Hongmanee et al., 2007; Shah et al., 2016; Tison, 1952; Urbanski, Slopek, & Venulet, 1951). Despite these studies, the structure–activity relationship (SAR) of HQs for antitubercular activity has not been thoroughly explored. To establish a more complete understanding of the SAR of HQ regarding antitubercular activity, we conducted an in vitro study, focusing on growth inhibition of *M. tuberculosis* in standard culture medium using a set of 26 commercially available compounds containing HQ functionality.

2 | METHODS

2.1 | Chemicals

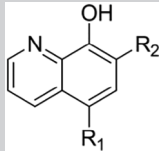












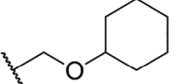

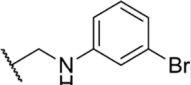

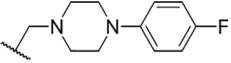

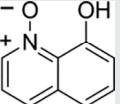
Chemicals were purchased from Chembridge Corp. (San Diego, CA), Sigma-Aldrich Co. (St. Louis, MO), or ChemDiv Inc. (San Diego, CA). Compound purity was verified via LCMS on an Agilent 1100 series instrument (Phenomenex Luna C18, 4.8 mm × 150 mm, 1.0 mL/min, UV 254 nm, electrospray ionization) with MeCN/H₂O (0.05% HCO₂H or NH₄OAc buffer) gradient elution.

2.2 | Cytotoxicity

HepG2 human liver cells (ATCC) were seeded in 384-well plates at 1,800 cells per well and incubated in a humidified atmosphere of 37°C, 5% CO₂ in DMEM (Invitrogen), 10% FBS, 1 mM sodium pyruvate, 2 mM GlutaGro (Corning), 25 mM glucose, 100 I.U./mL penicillin, and 100 µg/mL streptomycin. Compounds were added 24 hr post cell seeding to 1% DMSO final concentration. After a 72 hr incubation period, CellTiter-Glo[®] Reagent was added to the 384-well plates. Relative luminescent units (RLUs) were measured using a Biotek Synergy 4 plate reader. Raw data were normalized by the average RLU value from 1% DMSO treated wells and expressed as percent growth. Growth inhibition curves were fitted using the Levenberg–Marquardt algorithm. The IC₅₀ was defined as the compound concentration that produced 50% of the growth inhibitory response.

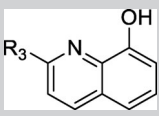









Vero cells (CCL81) were cultured in high-glucose Dulbecco's modified Eagle medium with GlutaMax (Invitrogen), 10% v/v fetal bovine serum, 50 units/mL penicillin, and 50 µg/mL streptomycin. Cells were exposed to compounds for 2 days and viability was determined using CellTiter-Glo (Promega). The % viability was plotted and the concentration that resulted in 50% reduction in cell viability was determined using the Levenberg–Marquardt least-squares method.

TABLE 1 Activity of 5-substituted compounds

Cpd	ID	R ₁	R ₂	MIC (µM)	HepG2 IC ₅₀ (µM)
					
1	IDR-0261683			3.6 ± 0.20 (2)	7.6 ± 0.68 (4)
2	IDR-0257179			3.1 ± 1.1 (4)	6.5 ± 1.7 (2)
3	IDR-0010414			2.9 ± 0.40 (2)	6.9 ± 0.59 (4)
4	IDR-0261686			3.0 ± 1.0 (4)	7.6 ± 1.5 (2)
5	IDR-0105904			8.4 ± 4.5 (6)	7.6 ± 1.2 (4)
6	IDR-0261687			4.8 ± 3.3 (3)	7.7 ± 1.8 (2)
7	IDR-0271627			3.2 ± 0.85 (4)	4.9 ± 1.9 (2)
8	IDR-0257187			>20 (2)	12 ± 0.50 (2)
9	IDR-0257186			>20 (2)	9.8 ± 2.2 (2)
10	IDR-0261684			>20 (2)	<88 ± 17 (2)

Compounds were tested for activity against *M. tuberculosis* (MIC) and HepG2 cells (IC₅₀). Data are the mean ± SD. The number of replicates is in parentheses.

TABLE 2 Activity of 2-substituted compounds

				
Cpd	ID	R ₃	MIC (μM)	HepG2 IC ₅₀ (μM)
11	IDR-0261685		>20 (4)	28 ± 9.0 (2)
12	IDR-0257175		4.6 ± 1.7 (3)	12 ± 0.50 (2)
13	IDR-0257176		6.4 ± 0.35 (2)	22 ± 2.8 (2)
14	IDR-0195922		>20 (2)	>100 (2)
15	IDR-0143082		>20 (2)	>100 (2)
16	IDR-0126687		>20 (2)	3.8 ± 0.45 (2)
17	IDR-0126637		>20 (3)	9.0 ± 1.0 (2)
18	IDR-0257178		>20 (2)	>100 (2)
19	IDR-0257177		>20 (3)	12 ± 0.50 (2)

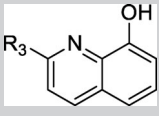
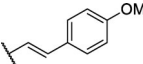
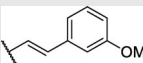
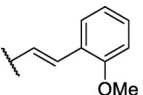
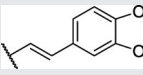
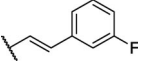
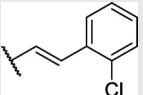
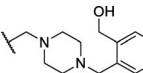
Compounds were tested for activity against *M. tuberculosis* (MIC) and HepG2 cells (IC₅₀). Data are the mean ± SD. The number of replicates is in parentheses.

2.3 | Determination of minimum inhibitory concentration

M. tuberculosis strains were grown in Middlebrook 7H9 supplemented with 10% v/v oleic acid, albumin, dextrose, and catalase (OADC)

(Becton Dickinson) and 0.05% w/v Tween 80 or on Middlebrook 7H10 agar supplemented with 10% v/v OADC. MICs were determined as previously described (Ollinger et al., 2013). In brief, compounds were tested for activity at varying concentrations against a

TABLE 3 Activity of vinylogously 2-substituted compounds

				
Cpd	ID	R ₃	MIC (μM)	HepG2 IC ₅₀ (μM)
20	IDR-0257190		23 ± 7.0 (2)	12 ± 4.0 (2)
21	IDR-0257183		8.7 ± 0.2 (2)	10 ± 1.0 (2)
22	IDR-0257182		13 ± 9.1 (2)	12 ± 2.0 (2)
23	IDR-0257180		15 ± 5.0 (3)	9.1 ± 3.0 (2)
24	IDR-0010378		13 ± 6.3 (4)	8.0 ± 0.60 (2)
25	IDR-0257181		5.8 ± 2.2 (2)	12 ± 1.0 (2)
26	IDR-0257188		>20 (2)	14 ± 0.50 (2)

Compounds were tested for activity against *M. tuberculosis* (MIC) and HepG2 cells (IC₅₀). Data are the mean ± SD. The number of replicates is in parentheses.

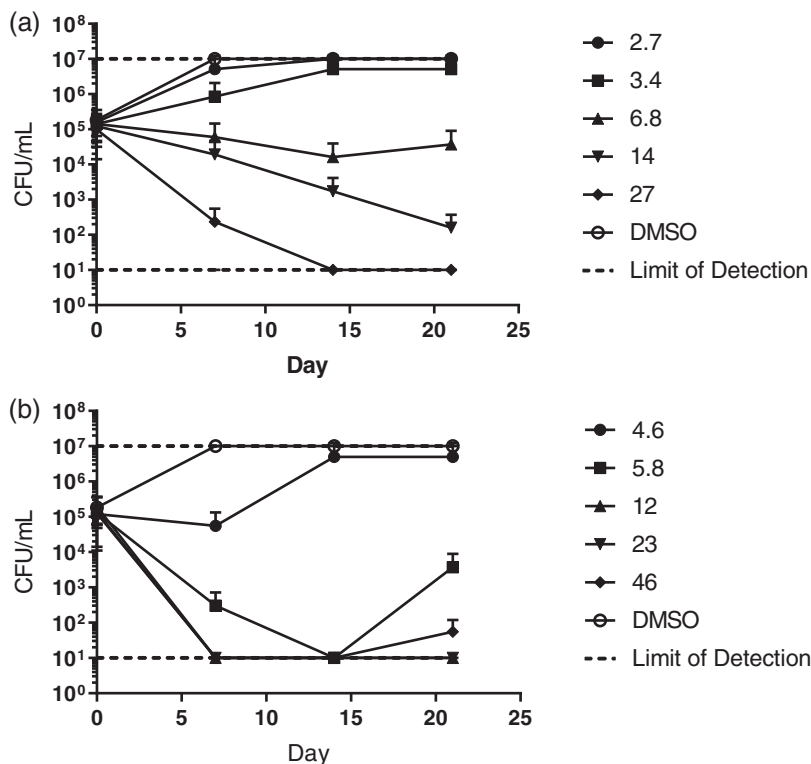


FIGURE 1 Bactericidal activity of compounds against replicating *M. tuberculosis*. Compounds (24) (top) and (4) (bottom) were tested for their ability to kill *M. tuberculosis* under replicating conditions. *M. tuberculosis* was cultured in 7H9-OADC-Tw medium in the presence of compounds from $1\times$ MIC to $10\times$ MIC (concentrations given in μM). Viable bacteria were counted by measuring CFUs. Data are the mean \pm SD from two independent experiments

fluorescent strain of *M. tuberculosis* H37Rv constitutively expressing a red fluorescent protein (mCherry or DsRed) (Carroll et al., 2010; Carroll, Muwanguzi-Karugaba, & Parish, 2018), typically starting at $20\ \mu\text{M}$. Plates were incubated for 5 days and bacterial growth was measured using optical density and fluorescence. Growth was plotted, and the concentration required to inhibit growth by 90% was determined using the Levenberg–Marquardt least-squares method (Lambert & Pearson, 2000).

2.4 | Kill kinetics

Compounds **24** and **4** were tested for their ability to kill *M. tuberculosis* in replicating conditions (Early & Alling, 2015). Compounds were added to *M. tuberculosis* cultures in liquid medium and viability monitored over 3 weeks standing at 37°C by plating for colony-forming units (CFU). Plates were incubated at 37°C for 4 weeks before colonies were counted.

3 | RESULTS AND DISCUSSION

3.1 | SAR studies

The HQ series has good activity against *M. tuberculosis* in vitro. We, and others, identified these compounds in phenotypic screening as hits (Ananthan et al., 2009; Ollinger et al., 2018). We wanted to explore the SAR for this series to determine the scope for further development. We designed a set of compounds representing three

general chemotypes built around the HQ scaffold: (a) substituted at the 5-position (Table 1), (b) substituted at the 2-position (Table 2), and (c) styryl substituents at the 2-position (Table 3). For each compound, we determined activity against *M. tuberculosis* by measuring the minimum inhibitory concentration (MIC_{90}), defined as the concentration required to inhibit growth by 90%. We also determined cytotoxicity against the HepG2 cell line by measuring the IC_{50} , defined as the concentration required to reduce cell viability by 50%. The seed compound, unsubstituted 8-hydroxyquinoline (**1**), had an MIC of $3.6\ \mu\text{M}$ and HepG2 IC_{50} of $7.6\ \mu\text{M}$.

Our exploration began with the introduction of substituents at the 5-position (Table 1). Compounds with methyl (**2**), bromide (**3**), chloride (**4**), and nitro (**6**) substituents had comparable potency and cytotoxicity to the parent (**1**). Addition of a second chloride at the 2-position (**5**) resulted in slightly decreased potency ($8.4\ \mu\text{M}$). The larger (cyclohexyloxy)methyl group (**7**) retained both potency and cytotoxicity. However, introduction of aniline-containing groups (**8** and **9**) abrogated the anti-tubercular activity with only a minor reduction in cytotoxicity. Oxidation to the N-oxide (**10**) resulted in loss of activity and a significant reduction of cytotoxicity, suggesting that the quinoline lone pair was necessary for both.

Of the 8-hydroxyquinolines directly substituted at the 2-position (Table 2), only the simplest amine substitutions **12** and **13** retained measurable anti-tubercular activity. The region proved generally intolerant of larger amine substituents, with dimethylamine (**14**), 1-piperidine (**15**), and aniline (**16**) substituents all resulting in loss of activity. Acylation of the exocyclic amine (**17**) and its reverse amide

TABLE 4 Cytotoxicity of HQ compounds

Compound	ID	Cytotoxicity (IC ₅₀)
1	IDR-0261683	1.4
2	IDR-0257179	1.4
3	IDR-0010414	1.8
4	IDR-0261686	2.4
5	IDR-0105904	1.3
6	IDR-0261687	2.9
7	IDR-0271627	6.2
8	IDR-0257187	7.5
9	IDR-0257186	5.8
10	IDR-0261684	>20
11	IDR-0261685	12
12	IDR-0257175	3.3
13	IDR-0257176	8.2
14	IDR-0195922	>50
15	IDR-0143082	>50
16	IDR-0126687	0.94
17	IDR-0126637	4.9
18	IDR-0257178	>50
19	IDR-0257177	19
20	IDR-0257190	1.6
21	IDR-0257183	2.9
22	IDR-0257182	6.2
23	IDR-0257180	6.0
24	IDR-0010378	7.2
25	IDR-0257181	9.0
26	IDR-0257188	11

Compounds were tested for activity against Vero cells (IC₅₀).

analog (**18**) were similarly not tolerated. Methyl substitution (**11**) was not tolerated. Analogs **14**, **15**, and **18** from this chemotype showed significant attenuation of mammalian cytotoxicity; unfortunately, all were inactive against *M. tuberculosis*.

Finally, the scaffold proved broadly tolerant to substitution with styryl groups at the 2-position, albeit with the induction of significant variation between replicates (Table 3). Substitutions on the styryl ring (**20–25**) led to only minor changes in potency. As with the active compounds from the previous two chemotypes, these compounds were consistently cytotoxic. Replacement of the vinyl substructure with a piperazine (**26**) was not tolerated.

3.2 | Kill kinetics

We determined the kill kinetics of two active compounds that were randomly selected against aerobically-grown, actively replicating *M. tuberculosis*. Compounds **24** and **4** were both bactericidal against *M. tuberculosis* under replicating conditions (Figure 1). Compound **24** killed ≥ 2 logs of bacteria at concentrations above 14 μM (5 \times MIC). At 27 μM (10 \times MIC), the compound sterilized the culture (>4 log kill) within 14 days. Compound **4** killed ≥ 3 logs within 14 days at concentrations of 12 μM (2.5 \times MIC) and higher. These data are consistent with previous reports that this series demonstrates rapid kill kinetics in vitro (Darby & Nathan, 2010). For both compounds, a small increase

in viable bacteria was seen at the lowest concentrations after 21 day (for **24** at 6.8 μM and for **4** at 5.8 μM). It is likely that this represents outgrowth of resistant mutants at the later time point. Alternatively, it could reflect compound instability over the extended exposure period, but that has not been tested.

3.3 | Cytotoxicity

The main liability for this series is cytotoxicity. Three analogs (**14**, **15**, **18**) showed no measurable cytotoxicity against HepG2 cells, but none of these were active against *M. tuberculosis*. All 19 of the active compounds were cytotoxic for this cell line. To compare cell lines, all 26 analogs were tested for cytotoxicity against Vero cells; all active analogs were cytotoxic in this cell line as well (Table 4). These cytotoxicity data are in contrast to results from other groups, where cytotoxicity for 8-hydroxyquinoline (**1**) and related compounds was not noted (Ananthan et al., 2009; Darby & Nathan, 2010; Shah et al., 2016). The differences in these data may reflect the status of cells in the cytotoxicity assay, since, similar to our findings, Shen et al. found HQ analogs to be cytotoxic via inhibition of DNA synthesis in HepG2 cells (Shen, Chen, & Roffler, 1999). Since our assay uses replicating HepG2 or Vero cells to measure toxicity, we would expect to see negative effects from the inhibition of DNA synthesis and by extension cell division. We were unable to identify analogs that lacked toxicity against replicating HepG2 or Vero cells. Further work to identify the mechanism of action of the HQ compounds, which may or may not involve metal chelation, might reveal a way forward in designing analogs with specificity for mycobacteria (Prachayasittikul et al., 2013; Shen et al., 1999).

4 | CONCLUSION

In conclusion, we confirmed that the HQ series have good anti-tubercular properties in vitro with rapid bactericidal activity. SAR demonstrated that small substitutions at the 5-position were tolerated, but substitution at the 2-position was not generally tolerated, except for 2-styrenyl-substitutions. Further work to elucidate the bacterial target could pave a way forward in designing analogs without cytotoxicity.

ACKNOWLEDGMENTS

This study was funded in part by Eli Lilly and Company in support of the mission of the Lilly TB Drug Discovery Initiative and with funding from the Bill and Melinda Gates Foundation under grant OPP1024038.

The authors thank the following for technical assistance: James Ahn, Torey Alling, Devon Dennison, Jack Elder, Lindsay Flint, Megha Gupta, Stephanie Florio, Douglas Joerss, Steven Mullen, Catie Shelton, Dean Thompson, and James Vela.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ORCID

Tanya Parish  <https://orcid.org/0000-0001-7507-0423>

REFERENCES

- Abouelhassan, Y., Garrison, A. T., Bai, F., Norwood, V. M., Nguyen, M. T., Jin, S., & Huigens, R. W. (2015). A phytochemical-halogenated quinoline combination therapy strategy for the treatment of pathogenic bacteria. *ChemMedChem*, 10(7), 1157–1162. <https://doi.org/10.1002/cmdc.201500179>
- Abouelhassan, Y., Garrison, A. T., Burch, G. M., Wong, W., Norwood, V. M., & Huigens, R. W. (2014). Discovery of quinoline small molecules with potent dispersal activity against methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms using a scaffold hopping strategy. *Bioorganic & Medicinal Chemistry Letters*, 24(21), 5076–5080. <https://doi.org/10.1016/j.bmcl.2014.09.009>
- Ananthan, S., Faaleolea, E. R., Goldman, R. C., Hobrath, J. V., Kwong, C. D., Laughon, B. E., ... White, E. L. (2009). High-throughput screening for inhibitors of *Mycobacterium tuberculosis* H37Rv. *Tuberculosis (Edinburgh, Scotland)*, 89(5), 334–353. <https://doi.org/10.1016/j.tube.2009.05.008>
- Barilli, A., Atzeri, C., Bassanetti, I., Ingoglia, F., Dall'Asta, V., Bussolati, O., ... Marchiò, L. (2014). Oxidative stress induced by copper and iron complexes with 8-hydroxyquinoline derivatives causes paraptotic death of HeLa cancer cells. *Molecular Pharmacology*, 11(4), 1151–1163. <https://doi.org/10.1021/mp400592n>
- Basak, A., Abouelhassan, Y., Norwood, V. M., Bai, F., Nguyen, M. T., Jin, S., & Huigens, R. W. (2016). Synthetically tuning the 2-position of halogenated quinolines: Optimizing antibacterial and biofilm eradication activities via alkylation and reductive amination pathways. *Chemistry*, 22(27), 9181–9189. <https://doi.org/10.1002/chem.201600926>
- Bhat, S., Shim, J. S., Zhang, F., Chong, C. R., & Liu, J. O. (2012). Substituted oxines inhibit endothelial cell proliferation and angiogenesis. *Organic and Biomolecular Chemistry*, 10(15), 2979–2992. <https://doi.org/10.1039/C2OB06978D>
- Carroll, P., Muwanguzi-Karugaba, J., & Parish, T. (2018). Codon-optimized DsRed fluorescent protein for use in *Mycobacterium tuberculosis*. *BMC Research Notes*, 11(1), 685. <https://doi.org/10.1186/s13104-018-3798-3>
- Carroll, P., Schreuder, L. J., Muwanguzi-Karugaba, J., Wiles, S., Robertson, B. D., Ripoll, J., ... Parish, T. (2010). Sensitive detection of gene expression in mycobacteria under replicating and non-replicating conditions using optimized far-red reporters. *PLoS One*, 5(3), e9823. <https://doi.org/10.1371/journal.pone.0009823>
- Chang, F.-S., Chen, W., Wang, C., Tzeng, C.-C., & Chen, Y.-L. (2010). Synthesis and antiproliferative evaluations of certain 2-phenylvinylquinoline (2-styrylquinoline) and 2-furanylvinylquinoline derivatives. *Bioorganic & Medicinal Chemistry*, 18(1), 124–133. <https://doi.org/10.1016/j.bmc.2009.11.012>
- Cherdtrakulkiat, R., Boonpangrak, S., Sinthupoom, N., Prachayasittikul, S., Ruchirawat, S., & Prachayasittikul, V. (2016). Derivatives (halogen, nitro and amino) of 8-hydroxyquinoline with highly potent antimicrobial and antioxidant activities. *Biochemistry and Biophysics Reports*, 6, 135–141. <https://doi.org/10.1016/j.bbrep.2016.03.014>
- Cieslik, W., Musiol, R., Nycz, J. E., Jampilek, J., Vejsova, M., Wolff, M., ... Polanski, J. (2012). Contribution to investigation of antimicrobial activity of styrylquinolines. *Bioorganic & Medicinal Chemistry*, 20(24), 6960–6968. <https://doi.org/10.1016/j.bmc.2012.10.027>
- Darby, C. M., & Nathan, C. F. (2010). Killing of non-replicating *Mycobacterium tuberculosis* by 8-hydroxyquinoline. *The Journal of Antimicrobial Chemotherapy*, 65(7), 1424–1427. <https://doi.org/10.1093/jac/dkq145>
- Early, J., & Alling, T. (2015). Determination of compound kill kinetics against *Mycobacterium tuberculosis*. *Methods in Molecular Biology*, 1285, 269–279. https://doi.org/10.1007/978-1-4939-2450-9_16
- Feng, T., Li, D., Wang, H., Zhuang, J., Liu, F., Bao, Q., ... Guo, X. (2015). Novel 5-carboxy-8-HQ based histone demethylase JMJD2A inhibitors: Introduction of an additional carboxyl group at the C-2 position of quinoline. *European Journal of Medicinal Chemistry*, 105, 145–155. <https://doi.org/10.1016/j.ejmech.2015.09.013>
- Garrison, A. T., Abouelhassan, Y., Yang, H., Yousaf, H. H., Nguyen, T. J., & Huigens, R. W. (2017). Microwave-enhanced Friedlander synthesis for the rapid assembly of halogenated quinolines with antibacterial and biofilm eradication activities against drug resistant and tolerant bacteria. *MedChemComm*, 8(4), 720–724. <https://doi.org/10.1039/C6MD00381H>
- Hongmanee, P., Rukseree, K., Buabut, B., Somsri, B., & Palittapongarnpim, P. (2007). In vitro activities of cloxyquin (5-chloroquinolin-8-ol) against *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, 51(3), 1105–1106. <https://doi.org/10.1128/AAC.01310-06>
- Kos, J., Zadrzilova, I., Nevin, E., Soral, M., Gonec, T., Kollar, P., ... Jampilek, J. (2015). Ring-substituted 8-hydroxyquinoline-2-carboxanilides as potential antimycobacterial agents. *Bioorganic & Medicinal Chemistry*, 23(15), 4188–4196. <https://doi.org/10.1016/j.bmc.2015.06.047>
- Lam, K.-H., Gambari, R., Lee, K. K.-H., Chen, Y.-X., Kok, S. H.-L., Wong, R. S.-M., ... Chui, C.-H. (2014). Preparation of 8-hydroxyquinoline derivatives as potential antibiotics against *Staphylococcus aureus*. *Bioorganic & Medicinal Chemistry Letters*, 24(1), 367–370. <https://doi.org/10.1016/j.bmcl.2013.10.072>
- Lambert, R. J., & Pearson, J. (2000). Susceptibility testing: Accurate and reproducible minimum inhibitory concentration (MIC) and non-inhibitory concentration (NIC) values. *Journal of Applied Microbiology*, 88(5), 784–790.
- Lawung, R., Cherdtrakulkiat, R., Nabu, S., Prachayasittikul, S., Isarankura-Na-Ayudhya, C., & Prachayasittikul, V. (2018). Repositioning of 8-hydroxyquinoline derivatives as a new promising candidate for combating multidrug resistant *Neisseria gonorrhoeae*. *EXCLI Journal*, 17, 840–846. <https://doi.org/10.17179/excli2018-1602>
- Li, K., Li, Y., Zhou, D., Fan, Y., Guo, H., Ma, T., ... Zhao, L. (2016). Synthesis and biological evaluation of quinoline derivatives as potential anti-prostate cancer agents and Pim-1 kinase inhibitors. *Bioorganic & Medicinal Chemistry*, 24(8), 1889–1897. <https://doi.org/10.1016/j.bmc.2016.03.016>
- Moret, V., Laras, Y., Cresteil, T., Aubert, G., Ping, D. Q., Di, C., ... Kraus, J.-L. (2009). Discovery of a new family of bis-8-hydroxyquinoline substituted benzylamines with pro-apoptotic activity in cancer cells: Synthesis, structure-activity relationship, and action mechanism studies. *European Journal of Medicinal Chemistry*, 44(2), 558–567. <https://doi.org/10.1016/j.ejmech.2008.03.042>
- Mrozek-Wilczkiewicz, A., Spaczynska, E., Malarz, K., Cieslik, W., Rams-Baron, M., Kryštof, V., & Musiol, R. (2015). Design, synthesis and in vitro activity of anticancer styrylquinolines. The P53 independent mechanism of action. *PLoS One*, 10(11), e0142678. <https://doi.org/10.1371/journal.pone.0142678>
- Musiol, R., Jampilek, J., Buchta, V., Silva, L., Niedbala, H., Podeszwa, B., ... Polanski, J. (2006). Antifungal properties of new series of quinoline derivatives. *Bioorganic & Medicinal Chemistry*, 14(10), 3592–3598. <https://doi.org/10.1016/j.bmc.2006.01.016>
- Ollinger, J., Bailey, M. A., Moraski, G. C., Casey, A., Florio, S., Alling, T., ... Parish, T. (2013). A dual read-out assay to evaluate the potency of compounds active against *Mycobacterium tuberculosis*. *PLoS One*, 8(4), e60531. <https://doi.org/10.1371/journal.pone.0060531>
- Ollinger, J., Kumar, A., Roberts, D. M., Bailey, M. A., Casey, A., & Parish, T. (2018). A high-throughput whole cell screen to identify inhibitors of *Mycobacterium tuberculosis*. *bioRxiv*. doi:<https://doi.org/10.1101/429423>
- Prachayasittikul, V., Prachayasittikul, S., Ruchirawat, S., & Prachayasittikul, V. (2013). 8-Hydroxyquinolines: A review of their metal chelating properties and medicinal applications. *Drug Design, Development and Therapy*, 7, 1157–1178. <https://doi.org/10.2147/DDDT.S49763>
- Shah, S., Dalecki, A. G., Malalasekera, A. P., Crawford, C. L., Michalek, S. M., Kutsch, O., ... Wolschendorf, F. (2016). 8-Hydroxyquinolines are boosting agents of copper-related toxicity in *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, 60(10), 5765–5776. <https://doi.org/10.1128/AAC.00325-16>
- Shen, A. Y., Chen, C. P., & Roffler, S. (1999). A chelating agent possessing cytotoxicity and antimicrobial activity: 7-morpholinomethyl-8-hydroxyquinoline. *Life Sciences*, 64(9), 813–825.
- Song, Y. N., Xu, H., Chen, W., Zhan, P., & Liu, X. (2015). 8-Hydroxyquinoline: A privileged structure with a broad-ranging pharmacological potential. *MedChemComm*, 6(1), 61–74. <https://doi.org/10.1039/C4MD00284A>

- Sosič, I., Mirković, B., Arenz, K., Štefane, B., Kos, J., & Gobec, S. (2013). Development of new cathepsin B inhibitors: Combining bioisosteric replacements and structure-based design to explore the structure–activity relationships of nitroxoline derivatives. *Journal of Medicinal Chemistry*, *56*(2), 521–533. <https://doi.org/10.1021/jm301544x>
- Spaczyńska, E., Tabak, D., Malarz, K., & Musiol, R. (2014). Investigation of the spectrum of applicability of quinolineamides. *Der Pharma Chemica*, *6*, 233–240.
- Tison, F. (1952). The remarkable effect of a combination of iodochloroxyquinoline with a subactive dose of streptomycin on experimental tuberculosis in Guinea pigs. *Annales de l'Institut Pasteur*, *83*(2), 275–276.
- Urbanski, T., Slopek, S., & Venulet, J. (1951). Antitubercular activity of some 8-hydroxyquinoline derivatives. *Nature*, *168*(4262), 29.
- Wangtrakuldee, P., Byrd, M. S., Campos, C. G., Henderson, M. W., Zhang, Z., Clare, M., ... Hagen, T. J. (2013). Discovery of inhibitors of *Burkholderia pseudomallei* methionine aminopeptidase with antibacterial activity. *ACS Medicinal Chemistry Letters*, *4*(8), 699–703. <https://doi.org/10.1021/ml400034m>
- Warner, V. D., Musto, J. D., Turesky, S. S., & Soloway, B. (1975). Synthesis and *in vitro* evaluation of 8-hydroxyquinolines as dental plaque inhibitors. *Journal of Pharmaceutical Sciences*, *64*(9), 1563–1566. <https://doi.org/10.1002/jps.2600640934>
- World Health Organization. (2018). Global Tuberculosis Report 2018. WHO/CDS/TB/2018.20

How to cite this article: Odingo JO, Early JV, Smith J, et al. 8-Hydroxyquinolines are bactericidal against *Mycobacterium tuberculosis*. *Drug Dev Res*. 2019;80:566–572. <https://doi.org/10.1002/ddr.21531>