Supporting Information

Design and Synthesis of Orally Bioavailable Piperazine Substituted 4(1*H*)-Quinolones with Potent Antimalarial Activity: Structure-Activity and Structure-Property Relationship Studies

Raghupathi Neelarapu,[#,§] Jordany R. Maignan,[#,§] Cynthia L. Lichorowic,[†] Andrii Monastyrskyi,[§] Alexis N. LaCrue,[¥] Tina S. Mutka,[¥] Lynn D. Blake,[¥] Debora Casandra,[¥] Sherman Mashkouri,[¥] Jeremy N. Burrows,[€] Paul A. Willis,[€] Dennis E. Kyle,[¥] and Roman Manetsch.[*,†,⊥]

[§]Department of Chemistry, University of South Florida, CHE 205, 4202 E. Fowler Ave, Tampa, Florida 33620, United States

[†]Department of Chemistry and Chemical Biology, Northeastern University, 102 Hurtig Hall, 360 Huntington Avenue, Boston, MA 02115, United States

[¥]Department of Global Health, College of Public Health, University of South Florida, 3720 Spectrum Blvd, Suite 304, Tampa, Florida 33612, United States

[€]Medicines for Malaria Venture, 20, Route de Pré-Bois, P.O. Box 1826, 1215 Geneva 15, Switzerland

[⊥]Department of Pharmaceutical Sciences, Northeastern University, 102 Hurtig Hall, 360 Huntington Avenue, Boston, MA 02115, United States

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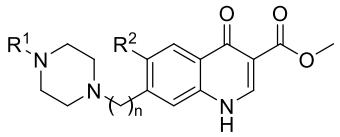
Table S1: Solubility and LogD of Piperazinyl-Substituted 4(1*H*)-Quinolones



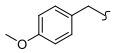
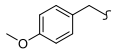
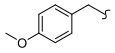
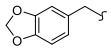
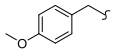
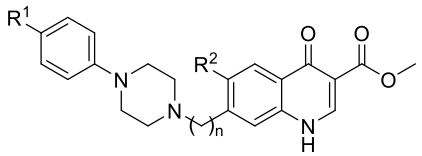
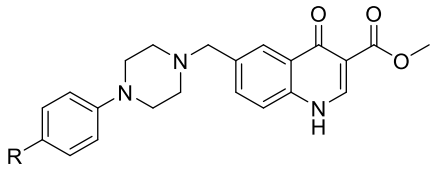
Compound	R^1	R^2	n	Solubility pH 2.0 (µM)	Solubility pH 6.5 (µM)	LogD pH 7.4
8ac		-H	2	≥ 80	≥ 80	5.11
8ad		-H	2	≥ 80	≥ 80	1.72
8ae		-H	2	≥ 80	≥ 80	1.68
8a		-H	0	1-19.9	1-19.9	2.58
8b		-H	0	60-79.9	60-79.9	2.21
8i		-H	0	≥ 80	40-59.9	2.08
8j		-H	1	≥ 80	≥ 80	0.86
8k		-H	1	≥ 80	≥ 80	2.06
8l		-H	1	≥ 80	≥ 80	1.66
8m		-H	1	≥ 80	≥ 80	0.87
8q		$-CH_3$	1	≥ 80	60-79.9	2.81
8r		$-CH_3$	1	≥ 80	≥ 80	1.94
8s		$-CH_3$	1	≥ 80	≥ 80	2.03
8w		$-OCH_3$	1	≥ 80	≥ 80	1.32
8x		$-OCH_3$	1	≥ 80	60-79.9	1.28
8c		$-CH_3$	0	≥ 80	40-59.9	2.31
8g		$-CH_3$	0	≥ 80	≥ 80	2.37
8d		$-OCH_3$	0	≥ 80	1-19.9	2.64
8h		$-OCH_3$	0	60-79.9	40-59.9	2.03

Table S2: Solubility and LogD of Piperazinyl-Substituted 4(1*H*)-Quinolones



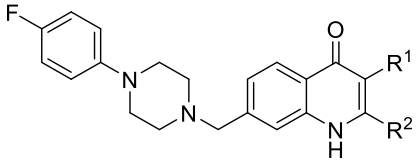
Compound	R^1	R^2	n	Solubility pH 2.0 (µM)	Solubility pH 6.5 (µM)	LogD pH 7.4
8o	-F	-H	1	≥ 80	≥ 80	2.38
8u	-F	$-CH_3$	1	≥ 80	40-59.9	2.90
8aa	-F	$-OCH_3$	1	60-79.9	≥ 80	1.31
8e	$-OCH_3$	-H	0	40-59.9	20-39.9	2.44
8f	$-OCH_3$	$-OCH_3$	0	60-79.9	20-39.9	2.48
8n	$-OCH_3$	-H	1	≥ 80	40-59.9	2.11
8t	$-OCH_3$	$-CH_3$	1	≥ 80	20-39.9	2.61
8z	$-OCH_3$	$-OCH_3$	1	≥ 80	≥ 80	2.19
8p	$-CF_3$	-H	1	≥ 80	1-19.9	3.23
8v	$-CF_3$	$-CH_3$	1	≥ 80	1-19.9	3.73
8ab	$-CF_3$	$-OCH_3$	1	1-19.9	1-19.9	1.29

Table S3: Solubility and LogD of Piperazinyl-Substituted 4(1*H*)-Quinolones



Compound	R	Solubility pH 2.0 (µM)	Solubility pH 6.5 (µM)	LogD pH 7.4
8af	-H	≥ 80	20-39.9	2.03
8ag	-OCH_3	≥ 80	20-39.9	1.91
8ah	-F	≥ 80	≥ 80	2.17
8ai	-CF_3	≥ 80	1-19.9	3.01

Table S4: Solubility and LogD of Piperazinyl-Substituted 4(1*H*)-Quinolones



Compound	R	R^2	Solubility pH 2.0 (µM)	Solubility pH 6.5 (µM)	LogD pH 7.4
8ak	-Br	-H	≥ 80	20-39.9	2.91
8al	-Cl	-H	≥ 80	40-59.9	2.57
8am	-H	$-CH_3$	≥ 80	≥ 80	2.44
8an	-Br	$-CH_3$	≥ 80	1-19.9	2.83
8ao	-Cl	$-CH_3$	≥ 80	1-19.9	2.73