Supplementary materials

Antitubercular, Cytotoxicity, and Computational Target Validation of Dihydroquinazolinone Derivatives

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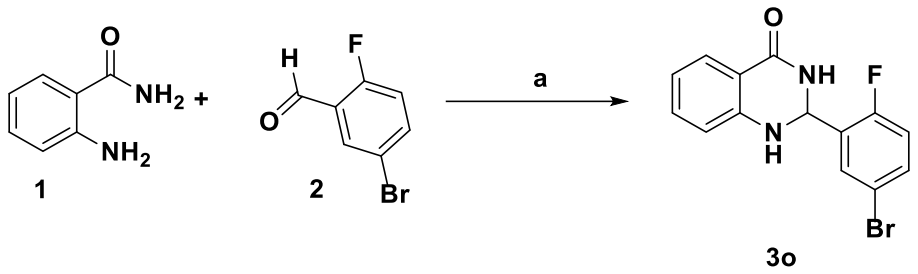
Table of contents



Scheme S1. Synthetic scheme for the preparation of 2-(5-bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**3l**). Reagents and conditions: (**a**) graphene oxide (2.5%), water, stirred at room temperature; yield 82%–95%.

Synthetic procedure for 2-(5-bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3l)

A mixture of 5-bromo-2-fluorobenzaldehyde (1.5 mmoL) and 2-aminobenzamide (1 mmoL) in 10 mL of water was stirred in a round-bottom flask with graphene oxide (2.5%) at room temperature, as depicted in Scheme S1. The progress of the reaction was monitored with TLC. After completion of the reaction, the insoluble precipitate obtained was separated and filtrated, and the crude product was washed with 50% cold ethanol. The crude product was recrystallized from 75% ethyl alcohol to obtain 65% of the title compound 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one at 98% purity.

FT-IR (KBr, cm^{-1}) 3303, 3232, 3195, 3076, 2920, 1650, 1612, 1512, 1477, 1396, 1251, 1157, 821, 750. ^{1}H-NMR (400 MHz,, DMSO-d_6) δ = 8.45 (1H, s), 7.83-7.81 (1H, m), 7.66-7.59 (2H, m), 7.30-7.13 (3H, m), 6.84-6.71 (2H, m), 6.05 (1H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ= 164.56, 158.36, 157.78, 147.37, 134.55, 133.55, 133.23, 131.05, 130.58, 126.44, 118.72, 118.13, 116.00, 115.48, 114.46. Anal. calculated for $C_{14}H_{10}BrFN_2O$: C, 52.36; H, 3.14; N, 8.72; found C, 52.27, H, 3.19; N, 8.68.

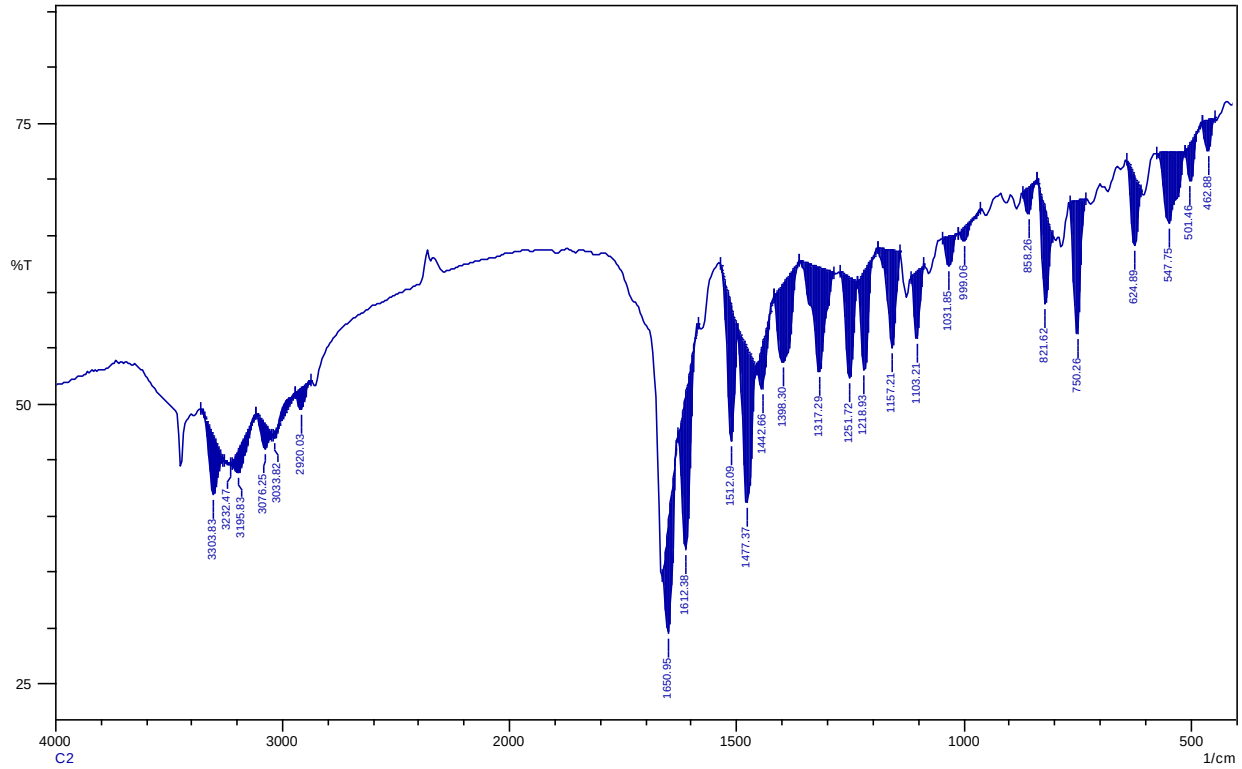


Figure S1: FTIR of 2-(5-Bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**3l**)

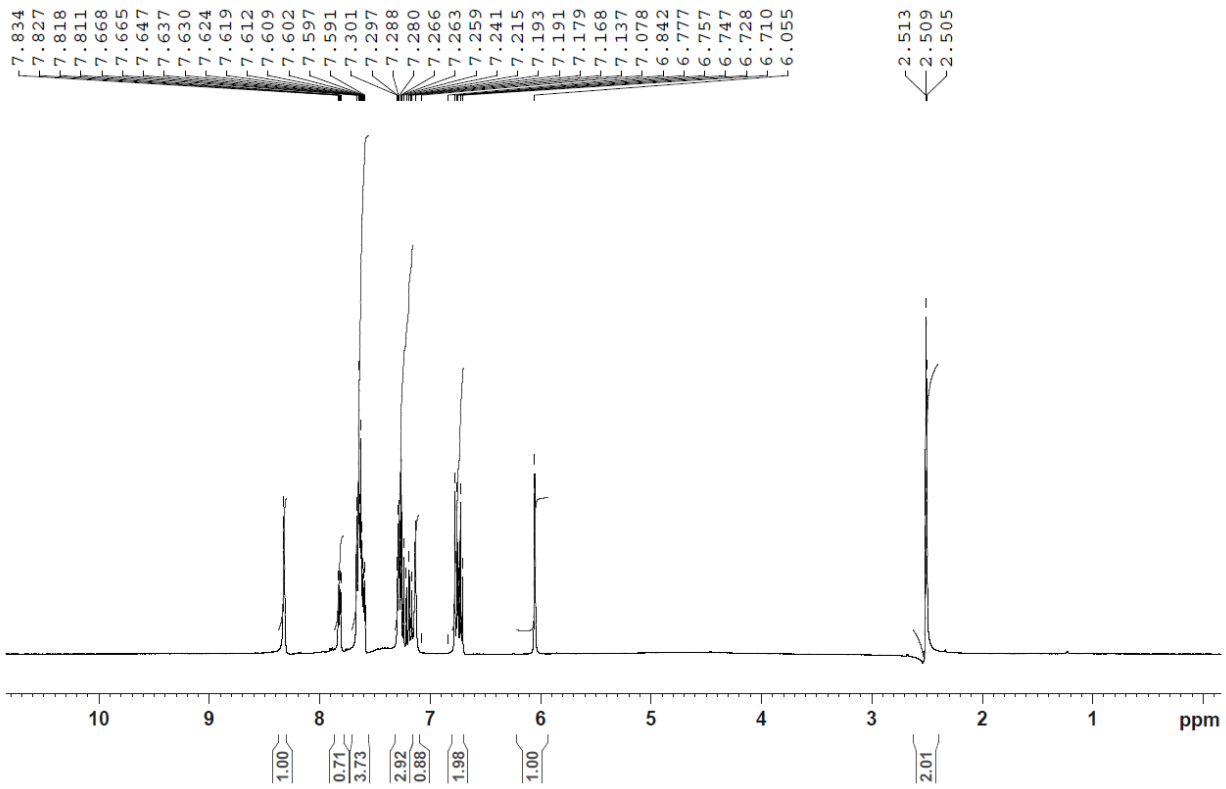


Figure S2: [1]H-NMR of 2-(5-bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**3l**)

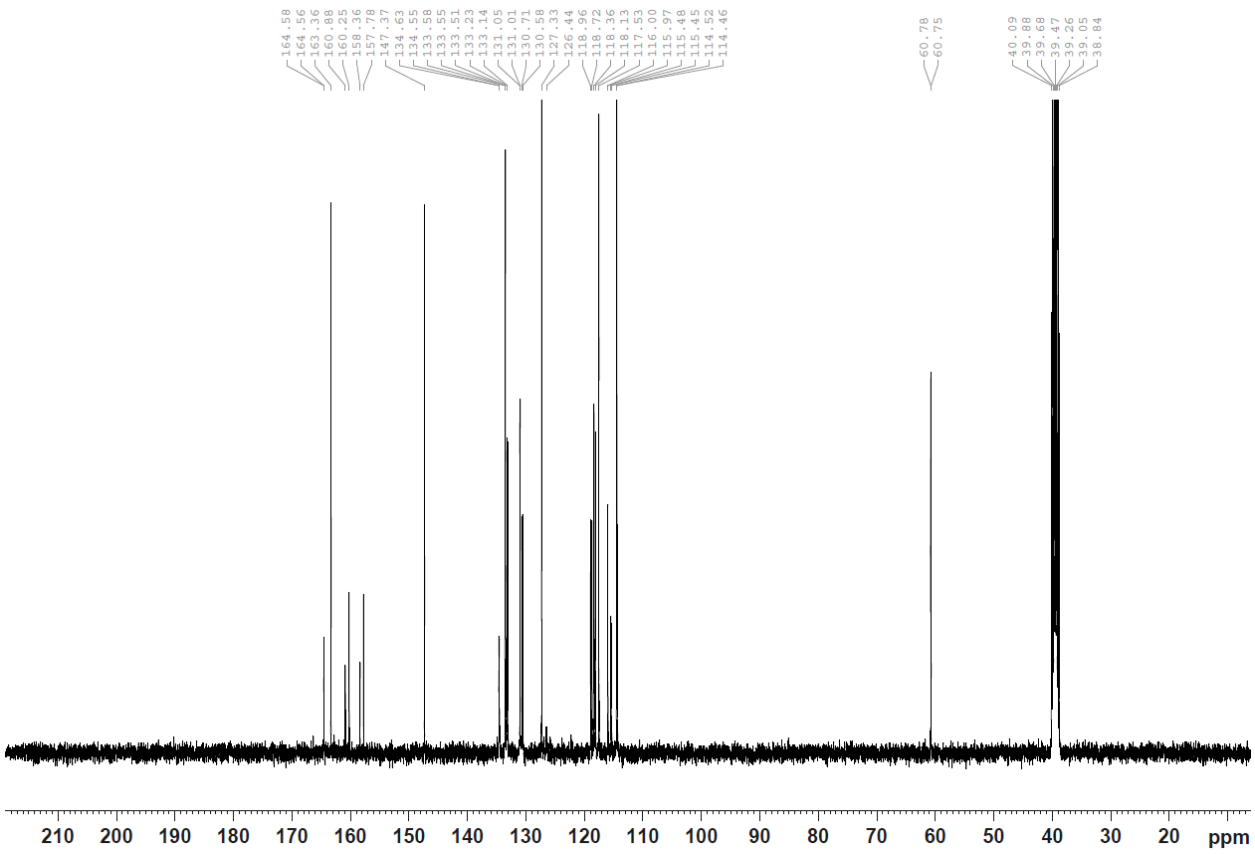


Figure S3: ^{13}C-NMR of 2-(5-bromo-2-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**3l**)

Table S1: Reported essential and potential mycobacterial drug targets.

Index	MTB Protein Target	Targeted pathway	Availability of 3D structure	References
1	Decaprenylphosphoryl-β-d-ribofuranose oxidoreductase (DprE1)	Cell wall synthesis: arabinogalactan biosynthesis	Yes	[1-3]
2	Enyol-ACP-reductase, (InhA)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[4]
3	Mycolic acid cyclopropane synthase (CmaA2)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[5]
4	Alanine racemase (alr)	Cell wall biosynthesis: peptidoglycan biosynthesis	Yes	[6]
5	3-oxoacyl-[acyl-carrier-protein] synthase 3 (FabH)	Fatty acid biosynthesis	Yes	[7]
6	β-ketoacyl-ACP reductase (MabA)	Fatty Acid Biosynthesis	Yes	[8]
7	Aspartyl-tRNA Synthetase (AspS)	Protein synthesis	Yes	[9]
8	leucyl-tRNA synthase (LeuRS)	Protein synthesis	Yes	[10]
9	Bifunctional enzyme (GlmU)	Cell wall biosynthesis	Yes	[11]
10	Pantothenate kinase (PanK, type 1)	Cofactor biosynthesis: Coenzyme A biosynthesis	Yes	[12]
11	Protein kinase B (PknB)	Signal transduction	Yes	[13]
12	Protein kinase A (PknA)	Signal transduction	Yes	[14]
13	β-ketoacyl acyl carrier protein synthase I (KasA)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[7]
14	Polyketide synthase (Pks13)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[15, 16]
15	5′-pyridoxal phosphate (PLP)-dependent aminotransferase (BioA)	Cofactor biosynthesis: biotin biosynthesis	Yes	[17]
16	Aspartate aminotransferase (aspAT)	Asp biosynthesis, and Asp-dependent nitrogen metabolism	Yes	[18]
17	Enoyl-CoA hydratase 6 (EchA6)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[19]
18	Transcriptional repressor of EthA monooxygenase (EthR)	Cell wall synthesis: mycolic acid biosynthesis (indirect)	Yes	[20]
19	MurE (Mur Ligase family)	Cell wall biosynthesis: peptidoglycan biosynthesis	Yes	[21]
20	2-methylcitrate synthase (PrpC) or (GltA3)	Fatty Acid Biosynthesis	Yes	[22]
21	Transmembrane transport protein large (MmpL3)	Cell wall synthesis: mycolic acid biosynthesis	Yes	[2]
22	CTP synthetase (PyrG)	DNA synthesis	Yes	[23]
23	3-oxoacyl-(Acyl-carrier-protein) reductase FabG4 (FabG-1)	Fatty Acid Biosynthesis	Yes	[24]
24	Triosephosphate isomerase (TpiA)	Gluconeogenetic pathways	Yes	[25]
25	Serine hydroxymethyltransferase 1 (GlyA1)	Tetrahydrofolate interconversion	Yes	[26]
26	Glycine cleavage system H protein (gcvH)	Degradation of glycine	Yes	[24]
27	6-phosphogluconolactonase (pgl) or (devB)	Carbohydrate degradation	Yes	[24]
28	O-succinylhomoserine sulfhydrylase (metZ)	Amino-acid biosynthesis	Yes	[24]

29	S-adenosylmethionine synthetase (metK)	Amino-acid biosynthesis	Yes	[24]
30	Thymidylate synthase (ThyX)	Pyrimidine metabolism	Yes	[27]
31	steroid-degrading 9lavin monooxygenase (HsaA) and (HsaB)	Cholesterol metabolism	Yes	[22]
32	phosphatidyl-myoinositol mannosyltransferase (PimA)	Cell wall synthesis	No, M. seg.	[28]
33	DNA topoisomerases and DNA gyrase	DNA replication	Yes	[29]
34	Malate synthase (GlcB)	Fatty acid metabolism: The glyoxylate shunt	Yes	[30]
35	D-alanine:D-alanine Ligase	Cell wall biosynthesis: peptidoglycan biosynthesis	Yes	[31]
36	Arabinosyltransferase C, A, and B (embC); (embA); (embB)	Cell wall synthesis: arabinogalactan biosynthesis	Yes	[32, 33]
37	Phospho-N-acetylmuramoyl-pentapeptide-transferase (mraY)	Cell wall biosynthesis: peptidoglycan biosynthesis	No	[32]
38	ESX-3 secretion system ATPase (EccB3)	ESX-3 specialized secretion system	No, M. seg.	[15]
39	1,4-dihydroxy-2-naphthoate octaprenyltransferase (MenA)	Energy metabolism	No	[7]
40	Demethylmenaquinone methyltransferase (MenG)	Energy metabolism	No	[7]
41	MoeW	Cofactor biosynthesis: molybdenum biosynthetic	No	[1]
43	Cytochrome b subunit of the cytochrome bc1 complex (QcrB)	Energy metabolism and ATP synthesis	No	[2]
44	Acid resistance periplasmic serine protease (MarP)	Intracellular pH homeostasis	No	[10]
45	Decaprenyl-phosphate N-acetylglucosaminephosphotransferase (wecA)	Cell wall synthesis: arabinogalactan biosynthesis	No	[34]
46	50S ribosomal protein L3 (rplC)	Protein synthesis	No	[32]
47	ATP synthase (atpE)	Energy metabolism	Yes, rotor ring	[2]
48	Dihydrofolate reductase (dfrA)	DNA precursor synthesis	Yes	[10, 35]

Table S2: The selected 20 essential mycobacterial drug targets that we used for molecular modeling studies.

Index	MTB Protein Target	Targeted pathway	PDB ID	References
1	Decaprenylphosphoryl-β-d-ribofuranose oxidoreductase (DprE1)	Cell wall biosynthesis: arabinogalactan biosynthesis	4P8C	[1-3]
2	Enyol-ACP-reductase, (InhA)	Cell wall biosynthesis: mycolic acid biosynthesis	6R9W	[4]
3	Mycolic acid cyclopropane synthase (CmaA2)	Cell wall biosynthesis: mycolic acid biosynthesis	1KPI	[5]
4	β-ketoacyl acyl carrier protein synthase I (KasA)	Cell wall biosynthesis: mycolic acid biosynthesis	6P9L	[7]
5	Polyketide synthase (Pks13)	Cell wall biosynthesis: mycolic acid biosynthesis	5V3Y	[15, 16]
6	Enoyl-CoA hydratase 6 (EchA6)	Cell wall biosynthesis: mycolic acid biosynthesis	5DUF	[19]
7	Transcriptional repressor of EthA monooxygenase (EthR)	Cell wall biosynthesis: mycolic acid biosynthesis (indirect)	5EYR	[20]
8	Alanine racemase (alr)	Cell wall biosynthesis: peptidoglycan biosynthesis	1XFC	[6]
9	MurE (Mur Ligase family)	Cell wall biosynthesis: peptidoglycan biosynthesis	2WTZ	[21]
10	Bifunctional enzyme (GlmU)	Cell wall biosynthesis	2QKX	[11]
11	2-methylcitrate synthase (PrpC) or (GltA3)	Fatty Acid Biosynthesis	3HWK	[22]
12	3-oxoacyl-[acyl-carrier-protein] synthase 3 (FabH)	Fatty acid biosynthesis	1HZP	[7]
13	β-ketoacyl-ACP reductase (MabA)	Fatty Acid Biosynthesis	1UZN	[8]
14	Aspartyl-tRNA Synthetase (AspS)	Protein synthesis	5W25	[9]
15	leucyl-tRNA synthase (LeuRS)	Protein synthesis	5AGS	[10]
16	Protein kinase B (PknB)	Signal transduction	5U94	[13]
17	Protein kinase A (PknA)	Signal transduction	6B2Q	[14]

18	Pantothenate kinase (PanK, type 1)	Cofactor biosynthesis: Coenzyme A biosynthesis	4BFZ	[12]
19	5′-pyridoxal phosphate (PLP)-dependent aminotransferase (BioA)	Cofactor biosynthesis: biotin biosynthesis	4XJO	[17]
20	Aspartate aminotransferase (aspAT)	Asp biosynthesis, and Asp-dependent nitrogen metabolism	6U7A	[18]
21	Transmembrane transport protein large (MmpL3)	Cell wall synthesis: mycolic acid biosynthesis	6AJJ	[2]

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