

Fighting antibiotic resistance: New pyrimidine-clubbed benzimidazole derivatives as potential DHFR inhibitors

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Table S1. The molecular interactions of designed derivatives with DHFR

Figure S1. Mass Spectrum of Synthesized Compound 27

Figure S2. Mass Spectrum of Synthesized Compound 29

Figure S3. Mass Spectrum of Synthesized Compound 30

Figure S4. Mass Spectrum of Synthesized Compound 33

Figure S5. Mass Spectrum of Synthesized Compound 37

Figure S6. Mass Spectrum of Synthesized Compound 38

Figure S7. Mass Spectrum of Synthesized Compound 41

Table S1. The molecular interactions of designed derivatives with DHFR

Active amino acid	Bond length	Bond type	Bond Category	Binding energy	Docking score
Native ligand					
ASP27	1.88237	Hydrogen bond	Conventional hydrogen bond	209.71	-8.5
ASP27	2.19462				
ALA6	3.00495				
ILE5	1.91594				
ARG57	1.96549				
ARG57	2.17225				
ILE94	3.19208	Hydrophobic	Carbon hydrogen bond		
ILE50	3.71343		Pi-Sigma		
PHE31	5.0747		Pi-Pi T-shaped		
PHE31	4.82737				
ILE94	4.98884		Alkyl		
ILE5	5.06209		Pi-Alkyl		
ALA7	4.05078				
25					
GLY15	3.55047	Hydrogen Bond	Carbon Hydrogen Bond	470.6	-7.2
ALA7	3.53102				
GLY15	3.56798				
GLY95	3.56301				
GLY96	3.62775				
LEU28	3.69758	Hydrophobic	Pi-Sigma		
ILE50	5.308		Alkyl		
LEU28	4.67657				
MET20	4.73921		Pi-Alkyl		
LEU28	5.28802				
MET20	5.1395				
26					
ALA7	3.49842	Hydrogen Bond	Carbon Hydrogen Bond	587.12	-8.5
LEU28	3.93756	Hydrophobic	Pi-Sigma		
LEU28	3.78875				
PHE31	4.56793		Pi-Pi T-shaped		
ILE50	5.31688		Alkyl		
LEU28	4.80815				
MET20	4.84878		Pi-Alkyl		
LEU28	5.18977				
MET20	5.32265				

ILE5	5.29874				
ALA7	4.42874				
27					
LEU28	3.96052	Hydrophobic	Pi-Sigma	588.4	-8.6
LYS32	3.58775		Alkyl		
LEU28	4.33004		Pi-Alkyl		
ALA7	4.25134				
PHE31	4.87554				
28					
GLY15	3.73566	Hydrogen Bond	Carbon Hydrogen Bond	588.98	-8.4
ASP27	3.17092	Halogen	Halogen (Fluorine)		
ASP27	3.60693				
ASP27	3.87889	Electrostatic	Pi-Anion		
LEU28	3.76687	Hydrophobic	Pi-Sigma		
LEU28	3.97034				
LYS32	3.61835		Alkyl		
ALA7	4.24717		Pi-Alkyl		
PHE31	4.82023				
29					
ALA7	3.46744	Hydrogen Bond	Carbon Hydrogen Bond	589.31	-9.3
LEU28	3.93237	Hydrophobic	Pi-Sigma		
LEU28	3.75872				
PHE31	4.58907		Pi-Pi T-shaped		
ILE50	5.22086		Alkyl		
LEU28	4.7552				
ILE5	4.57366				
ALA7	4.25461				
MET20	4.94999		Pi-Alkyl		
LEU28	5.15219				
MET20	5.31113				
ILE5	5.26508				
ALA7	4.46628				
TRP30	5.07411				
30					
ALA7	3.54199	Hydrogen Bond	Carbon Hydrogen Bond	589.91	-9.6
LEU28	3.97283	Hydrophobic	Pi-Sigma		
LEU28	3.8096				
PHE31	4.51892		Pi-Pi T-shaped		
ILE50	5.22229		Alkyl		

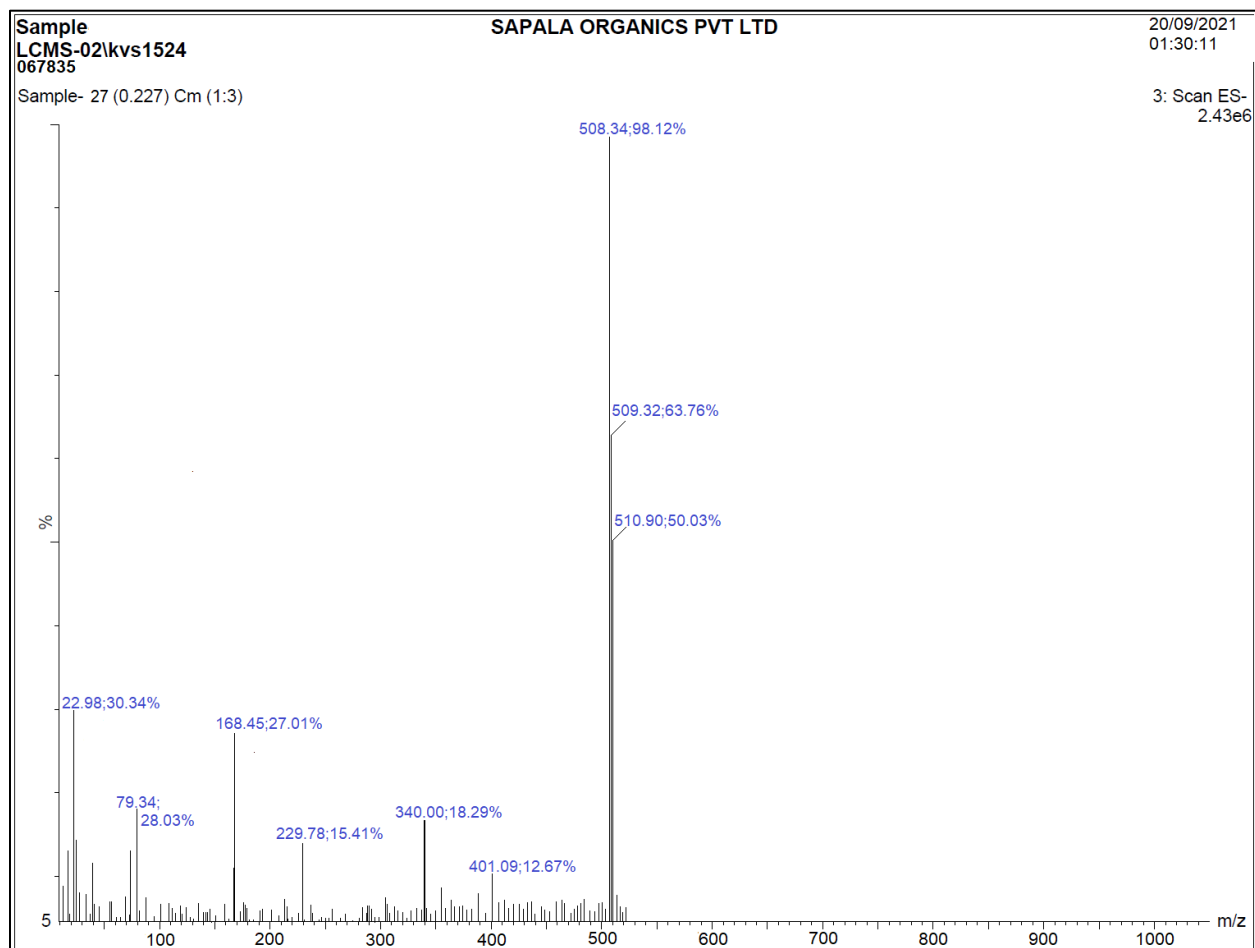
LEU28	4.75714				
ILE5	4.54982				
ALA7	4.2748				
MET20	4.92106		Pi-Alkyl		
LEU28	5.19863				
MET20	5.29169				
ILE5	5.24046				
ALA7	4.50596				
TRP30	5.21682				
31					
PRO21	3.05404	Hydrogen Bond	Conventional Hydrogen Bond	520.64	-8.2
TRP22	2.07363				
ASN23	2.52579				
GLU17	2.67449				
GLU17	2.78723				
GLY15	3.65443		Carbon Hydrogen Bond		
MET20	5.37113	Hydrophobic	Alkyl		
ILE5	4.2758				
ALA7	4.27882				
ALA7	4.89267		Pi-Alkyl		
PHE31	4.98391				
32					
ASP27	2.57625	Hydrogen Bond	Conventional Hydrogen Bond	588.87	-8.3
ASP27	3.95287	Electrostatic	Pi-Anion		
LEU28	3.98413	Hydrophobic	Pi-Sigma		
LYS32	3.6357		Alkyl		
LEU28	4.3027		Pi-Alkyl		
ALA7	4.30063				
PHE31	4.80426				
33					
MET20	3.0518	Hydrogen Bond	Conventional Hydrogen Bond	826.79	-9
ILE94	2.68072				
ASP27	3.72887		Carbon Hydrogen Bond		
MET20	3.78307	Hydrophobic	Pi-Sigma		
PHE31	5.67997		Pi-Pi T-shaped		
PHE31	5.73244				
ILE50	4.96304		Alkyl		
LYS32	3.95492				
LEU54	4.99074				

LEU28	5.28126	Pi-Alkyl				
ILE50	4.93483					
LEU28	4.63308					
ILE14	5.34255					
PHE31	4.91521					
34						
ILE94	2.86179	Hydrogen Bond	Conventional Hydrogen Bond	518.55	-8	
TRP22	1.9705					
TRP22	2.35691					
MET20	4.3483	Other	Pi-Sulfur			
PHE31	4.86059	Hydrophobic	Pi-Pi T-shaped			
ALA6:ALA7	4.36561		Amide-Pi Stacked			
MET20	5.22922		Alkyl			
ILE5	4.79331					
ALA7	3.97847					
ALA7	5.28805		Pi-Alkyl			
MET20	5.45896					
ILE5	5.34592					
ALA7	4.54534					
35						
GLU17	5.23367	Electrostatic	Attractive Charge	650.26	-8.2	
ILE94	2.49803	Hydrogen Bond	Conventional Hydrogen Bond			
ALA7	3.05679					
LEU28	3.83897	Hydrophobic	Pi-Sigma			
LEU28	3.72044		Alkyl			
PRO25	4.0166					
ILE5	4.55375					
ALA7	4.09288		Pi-Alkyl			
PHE31	4.97521					
36						
ASP27	3.64005	Hydrogen Bond	Carbon Hydrogen Bond	544.97	-7.9	
ALA7	3.48216					
GLY15	3.50798					
GLU17	4.88488	Electrostatic	Pi-Anion			
LEU28	3.7657	Hydrophobic	Pi-Sigma			
MET20	5.71901	Other	Pi-Sulfur			
MET20	5.75583					
PHE31	4.72955	Hydrophobic	Pi-Pi T-shaped			
LEU28	5.34773		Alkyl			
ILE50	5.22702					
LEU28	5.4916		Pi-Alkyl			

ILE5	5.16431					
ALA7	4.16746					
37						
ALA7	2.56058	Hydrogen Bond	Conventional Hydrogen Bond	605.87	-8.7	
ASP27	3.62684		Carbon Hydrogen Bond			
TYR100	5.20995	Hydrophobic	Pi-Pi T-shaped			
ILE50	5.0427		Alkyl			
MET20	4.83558		Pi-Alkyl			
MET20	4.53183					
LEU28	5.48553					
ILE14	4.73176					
38						
GLU17	4.78972	Electrostatic	Attractive Charge	705.74	-9	
ILE94	2.50758	Hydrogen Bond	Conventional Hydrogen Bond			
LEU28	3.94835	Hydrophobic	Pi-Sigma			
MET20	5.89342	Other	Pi-Sulfur			
PHE31	5.00102	Hydrophobic	Pi-Pi T-shaped			
ALA6:ALA7	4.55365		Amide-Pi Stacked			
ILE5	4.83846		Alkyl			
ALA7	3.94521					
MET20	5.46796		Pi-Alkyl			
ALA7	4.74961					
LEU28	5.15282					
MET20	4.85642					
PHE31	5.29782					
39						
ARG57	2.58638	Hydrogen Bond	Conventional Hydrogen Bond	937.76	-8.3	
ARG57	2.18282					
PHE31	4.7992	Hydrophobic	Pi-Pi T-shaped			
MET20	5.18068		Alkyl			
ILE5	4.84697					
ALA7	4.48924					
MET20	5.37667		Pi-Alkyl			
ILE5	5.45489					
ALA7	4.556					
LEU28	5.02873					
LEU54	5.45716					
TRP30	5.46865					
PHE31	5.01022					

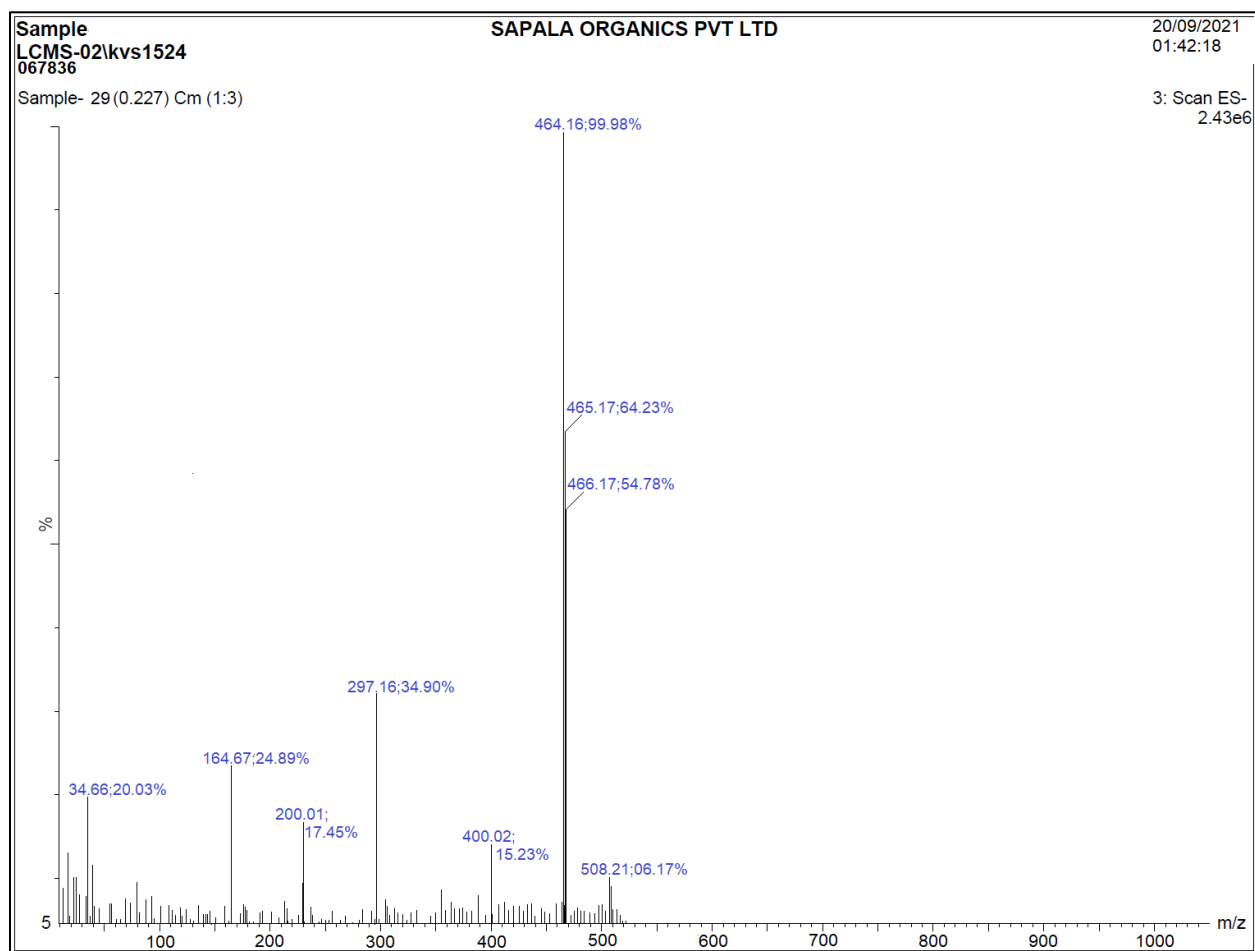
40					
GLU17	5.19129	Electrostatic	Attractive Charge	622.83	-7.1
SER49	3.54558	Hydrogen Bond	Carbon Hydrogen Bond		
	4.54671	Hydrophobic	Pi-Pi Stacked		
PHE31	5.46322				
	3.75304				
PHE31	4.10963				
LEU28	5.15441		Pi-Alkyl		
ILE50	5.32509				
ILE50	5.13593				
MET20	5.13796				
41					
THR113	2.73475	Hydrogen Bond;Halogen	Conventional Hydrogen Bond;Halogen (Fluorine)	596.44	-9
TRP30	3.57593	Hydrogen Bond	Carbon Hydrogen Bond		
ILE5	3.54683	Halogen	Halogen (Fluorine)		
ALA6	3.42515				
ALA6	3.17175				
ASP27	3.59013				
ASP27	2.97815				
ASP27	3.08315				
ASP27	3.22541				
LEU28:	3.98408	Hydrophobic	Pi-Sigma		
LYS32	3.49227		Alkyl		
ILE5	4.58651				
ALA7	4.22775				
LEU28	4.3502		Pi-Alkyl		
ALA7	4.17323				
PHE31	4.91107				
PHE31	5.25311				

Figure S1. Mass Spectrum of Synthesized Compound 27



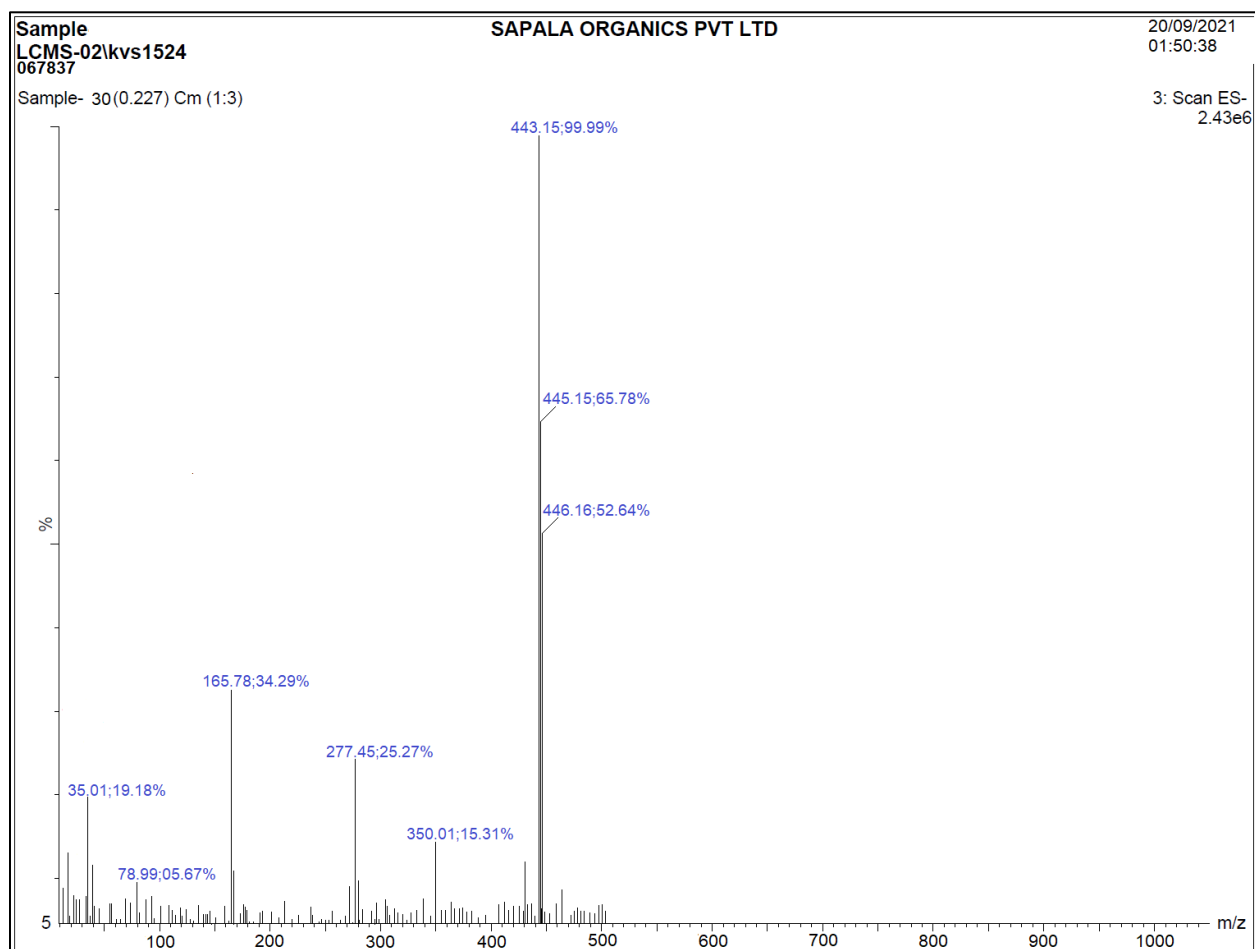
Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate (**27**)

Figure S2. Mass Spectrum of Synthesized Compound 29



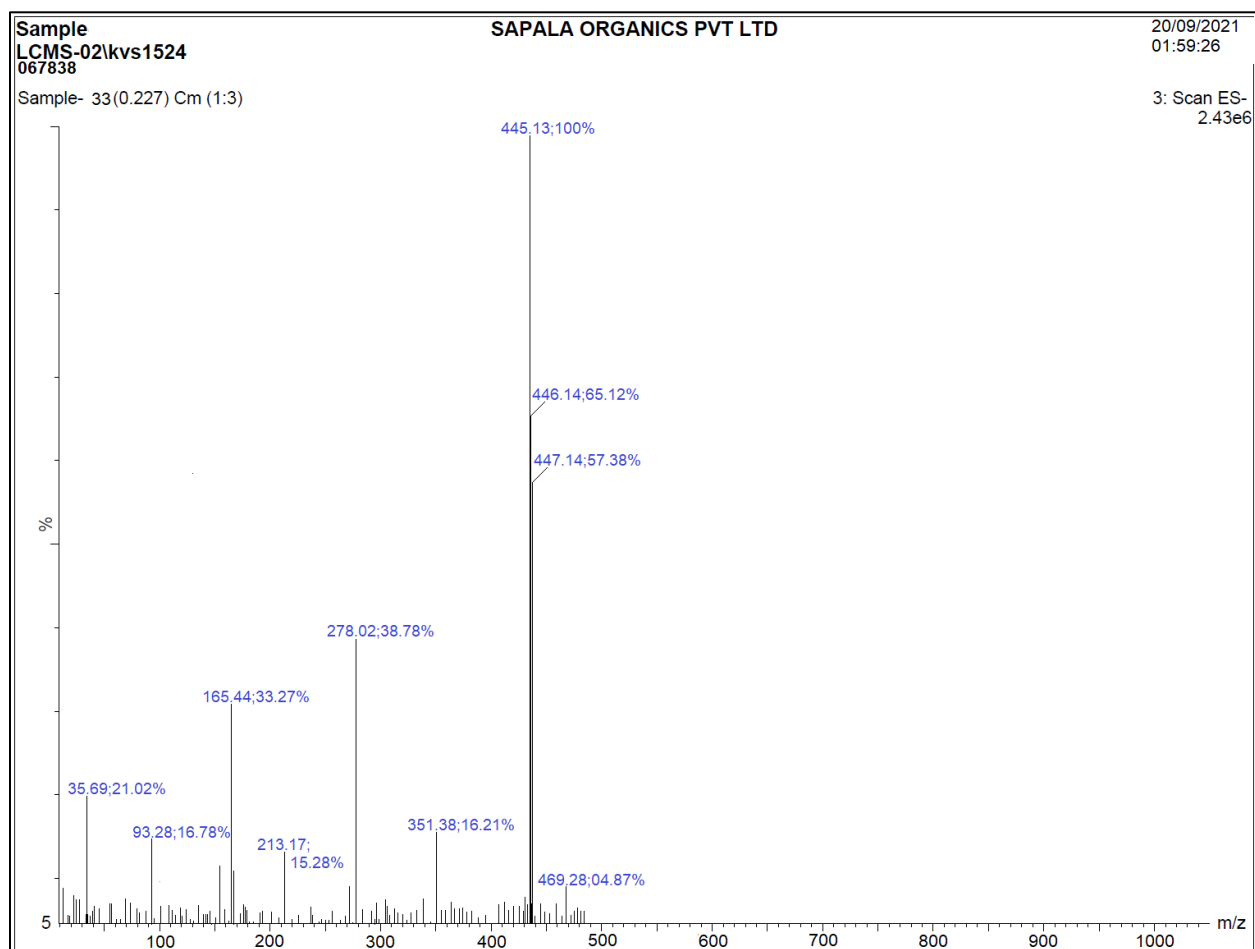
Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl) methylthio)-4-(4-chlorophenyl)-1, 2, 3, 4-tetrahydro-6-methylpyrimidine-5-carboxylate (29)

Figure S3. Mass Spectrum of Synthesized Compound 30



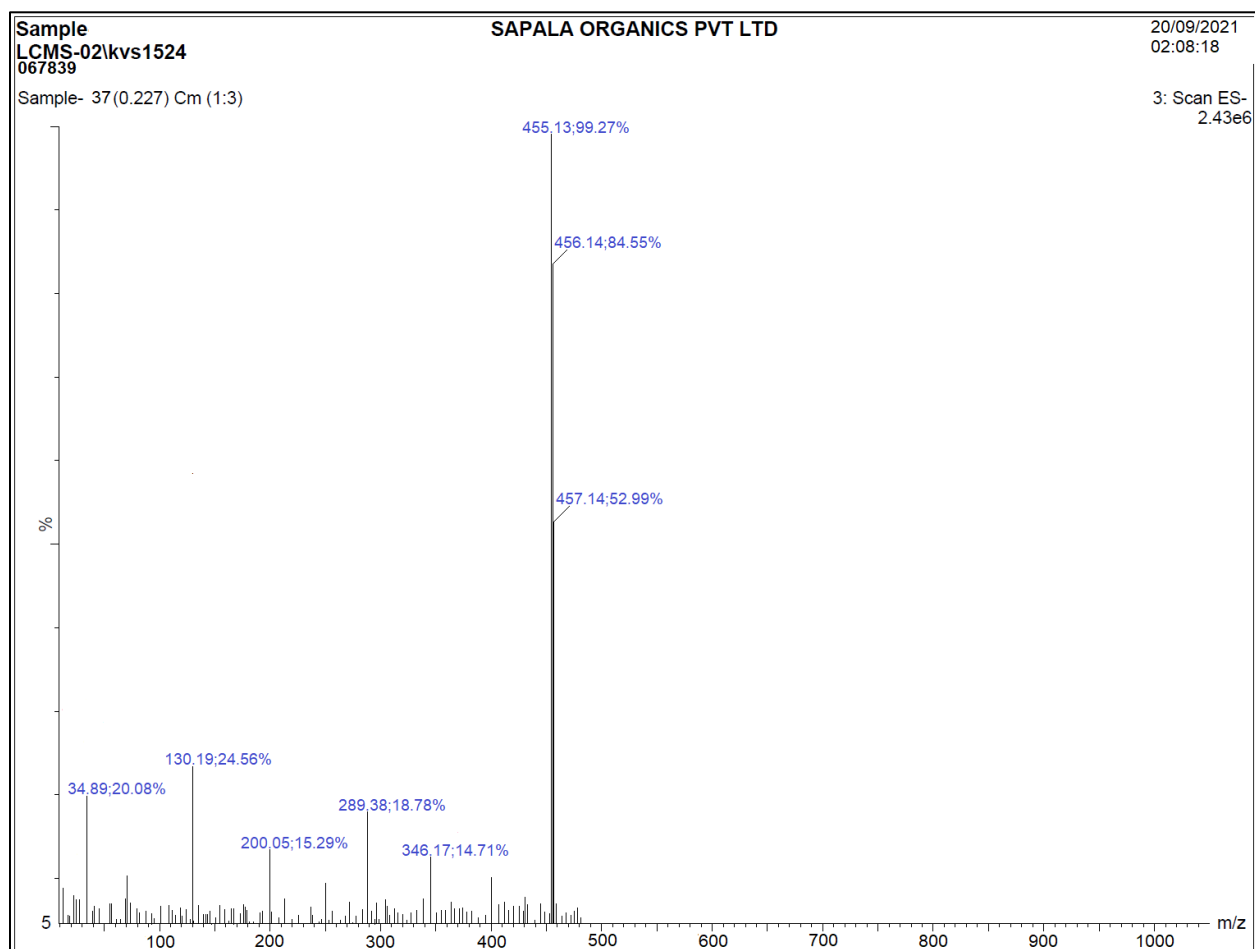
Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-1,2,3,4-tetrahydro-6-methyl-4-p-tolylpyrimidine-5-carboxylate (30)

Figure S4. Mass Spectrum of Synthesized Compound 33



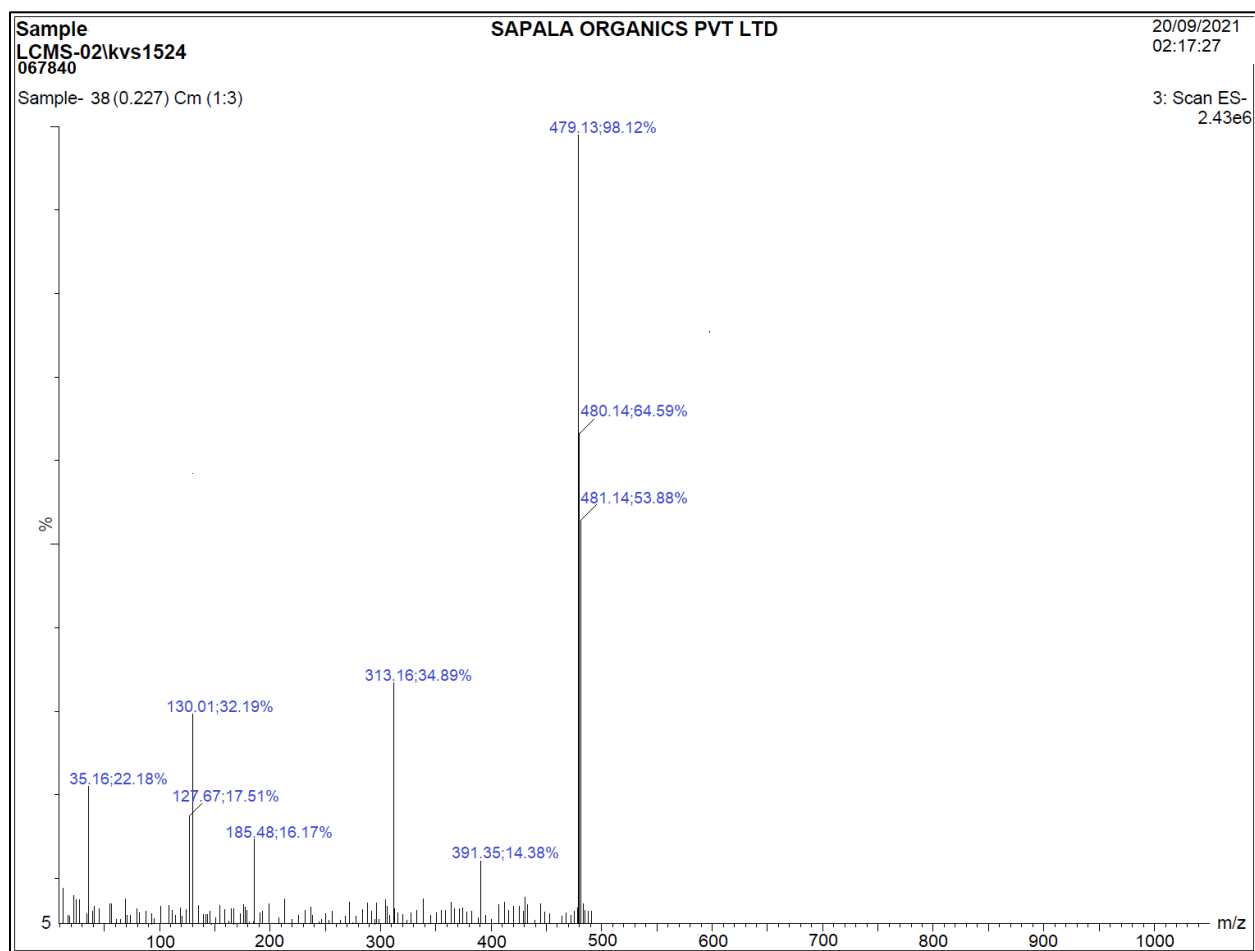
Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-1,2,3,4-tetrahydro-4-(3-hydroxyphenyl)-6-methylpyrimidine-5-carboxylate (33)

Figure S5. Mass Spectrum of Synthesized Compound 37



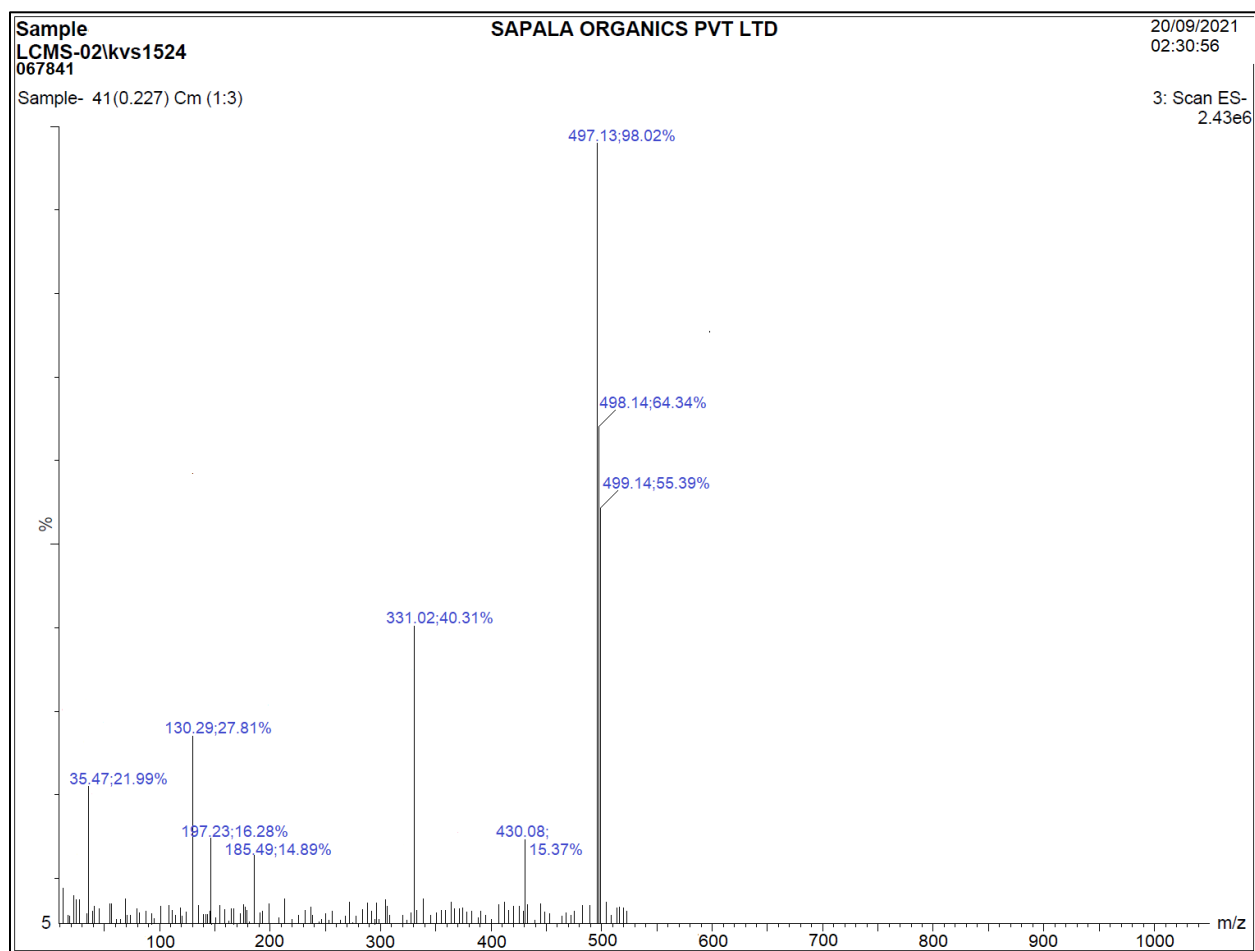
Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-1,2,3,4-tetrahydro-6-methyl-4-styrylpyrimidine-5-carboxylate (**37**)

Figure S6. Mass Spectrum of Synthesized Compound 38



Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-1,2,3,4-tetrahydro-6-methyl-4-(naphthalen-1-yl)pyrimidine-5-carboxylate (38)

Figure S7. Mass Spectrum of Synthesized Compound 41



Methyl 2-((6-chloro-1H-benzo[d]imidazol-2-yl)methylthio)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate (41)