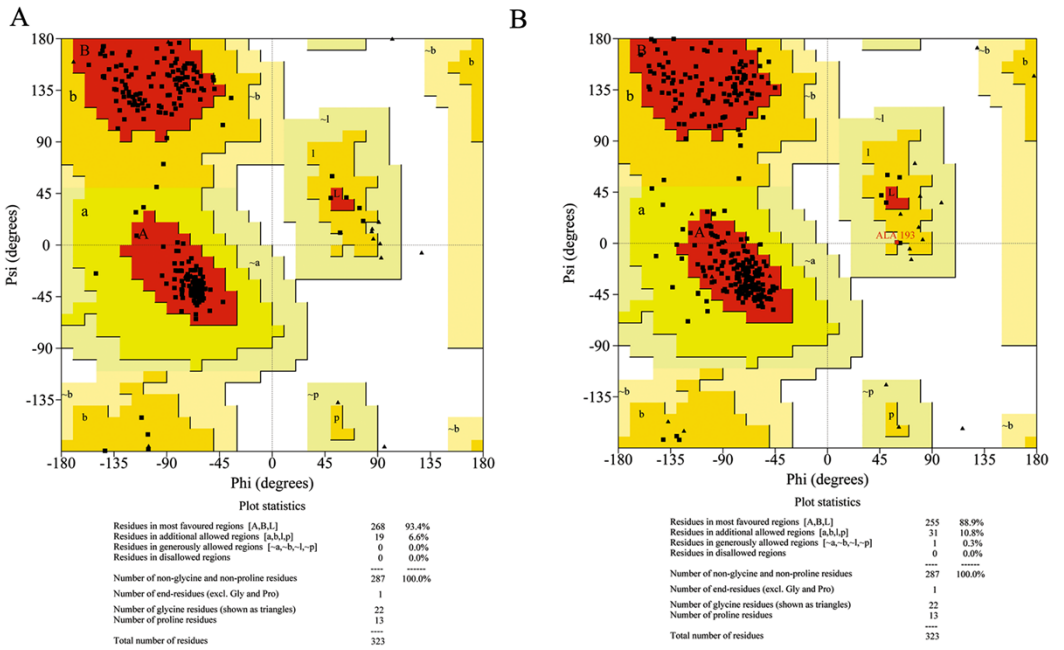
Electronic Supplementary Information

Fig. S1: (A-B). Ramachandran Plot results of predicted and simulated models respectively. (C) Verify 3D Analysis of Predicted and Simulated model of MARK4 Structure.



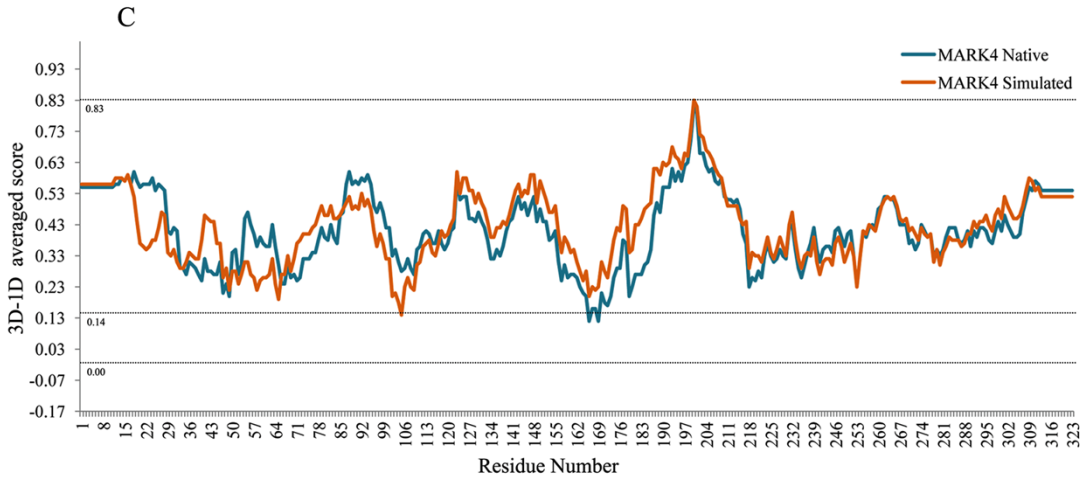
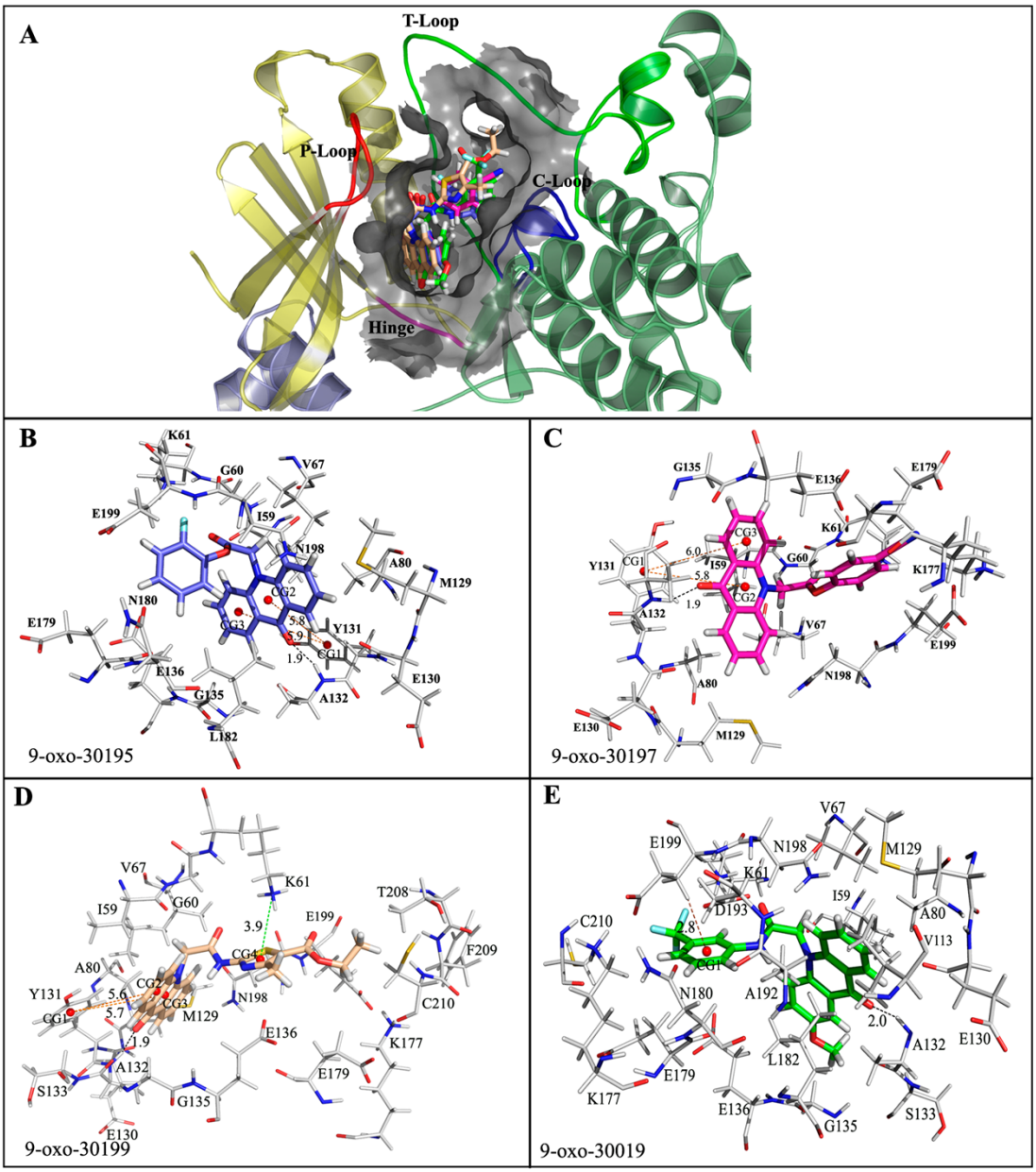


Fig. S2: Binding mode analysis of known MARK2 inhibitors. (A) Known inhibitors (9-Oxo-derivatives) docked into the ATP-binding pocket of MARK2 kinase domain (PDB ID: 2WZJ_A). The protein is represented as cartoon (N-lobe: yellow; P-loop: red; Hinge: Magenta; C-loop: blue; T-loop: green; C-Lobe: light green; UBA domain: Light Blue) and the binding pocket is shown in surface representation (grey). (B-E) shows interactions of 9-oxo-derivatives-30195 (blue), 30197 (magenta), 30199 (sand) and 30019 (green) with MARK2 respectively. Ligands and interacting residues are displayed in stick representation. Hydrogen bonds are denoted as black dotted lines; Pi-Pi (Π-Π) interactions in orange, Pi-Sigma (Π-σ) in brown and Pi-Cation (Π-cat+) in green dotted lines. The centroid of aromatic rings in Pi- interactions are displayed as red spheres. Bond distance in Angstrom (Å) units.



Supplementary Table 1: Relative MM-GBSA ligand binding free energies of the compounds bound to MARK4

S. No.	Compound/ Ligand name	Prime MM-GBSA Complex Energy Kcal/mol	Prime MM-GBSA Binding Energy Kcal/mol
MARK4 with 9-oxo-9H-acridin-10-yl derivatives			
1.	9-oxo-30199	-13776.985	-81.466
2.	9-oxo-30197	-13713.385	-57.549
3.	9-oxo-30195	-13719.804	-62.063
4.	9-oxo-30019	-13741.663	-61.130
MARK4 with identified hits			
5.	411	-13686.420	-67.611
6.	214	-13766.836	-81.283
7.	950	-13751.092	-86.846
8.	389	-13718.303	-61.013
9.	781	-13734.528	-70.569
10.	529	-13750.571	-58.227

Supplementary Table 2: Details the changes observed in interaction during the MD simulation of MARK4 complex with top-scoring hits.

S.No	Time Interval	Hydrogen Bond Interactions		Pi Interactions		
		Donor-Acceptor	Dist. (Å)	Residues	Type	Dist. (Å)
1	**MARK4-411**					
	1 ns	A138:H-UNK:O3 A138:H -UNK:O7	1.69 2.36	F202	Π-Π	4.65
	2 ns	-Nil-				
	3 ns	A138:H-UNK:O3	1.89	-Nil-		
	4 ns	A138:H-UNK:O3 UNK:H7 -E136:O	1.97 2.16	L188:CD2	Π-σ	3.92
	5 ns	A138:H -UNK:O3	1.91	V73:CG1 L188:CD1	Π-σ	3.96 3.60
	6 ns	A138:H -UNK:O3	2.05	L188:CD2	Π-σ	3.72
	7 ns	A138:H - UNK:O3 UNK373:H7-E136:O	1.78 2.44	-Nil-		
	8 ns	K88:HZ2 - UNK:O5 A138:H - UNK:O3 UNK:O4 - M110:O	1.97 2.43 2.56	-Nil-		
	9 ns	A138:H - UNK:O3 UNK:O4 - M110:O	1.86 3.03	-Nil-		
	10 ns	A138:H - UNK:O3	2.09	-Nil-		
2	**MARK4-214**					
	1 ns	-Nil-		Y137	Π-Π	4.31
	2 ns	UNK:H2 - I65:O	2.19	Y137	Π-Π	4.32
	3 ns	-Nil-		Y137	Π-Π	4.62

	4 ns	A138:H - UNK:O1	2.24	-Nil-		
	5 ns	A138:H - UNK:O1	1.95	V119	Π-σ	3.42
	6 ns	A138:H - UNK:O1	2.25	-Nil-		
	7 ns	A138:H - UNK:O1	2.36	-Nil-		
	8 ns	A138:H - UNK:O1		Y137 M135	Π-Π Π-σ	5.80 3.99
	9 ns	A138:H - UNK:O1	1.94	F202	Π-Π	5.50
	10 ns	A138:H - UNK:O1	2.20	-Nil-		
3	**MARK4-950**					
	1 ns	-Nil-				
	2 ns	K88:HZ1 - UNK:O2	1.94	-Nil-		
	3 ns	K88:HZ1 - UNK:O2 A138:H - UNK:N4	2.01 2.33	-Nil-		
	4 ns	K88:HZ1 - UNK:N5	1.99	-Nil-		
	5 ns	K88:HZ3 - UNK:O2	2.04	F202	Π-Π	4.19
	6 ns	-Nil-		F202	Π-Π	4.16
	7 ns	K88:HZ3 - UNK:O2	2.03	-Nil-		
	8 ns	K88:HZ1 - UNK:O2	2.36	F202	Π-Π	4.25
	9 ns	K88:HZ2 - UNK:O2	2.09	-Nil-		
	10 ns	K88:HZ1 - UNK:N5 K88:HZ3 - UNK:O3 A138:H - UNK:N4	2.40 2.25 2.25	-Nil-		
4	**MARK4-389**					
	1 ns	-Nil-		K88:NZ K88:NZ A198:CB	Π-cat+ Π-cat+ Π-σ	4.39 3.12 3.93
	2 ns	A138:H - UNK:N5	2.27	K88:NZ K88:NZ Y137:CA L188:CD1 A198:CB	Π-cat+ Π-cat+ Π-σ Π-σ Π-σ	4.47 3.48 3.85 3.86 3.78
	3 ns	A138:H - UNK:N5	2.35	K88:NZ K88:NZ Y137:CA M110:CG	Π-cat+ Π-cat+ Π-σ Π-σ	4.96 2.96 3.78 3.92
	4 ns	A138:H - UNK:N5	2.01	K88:NZ K88:NZ Y137:CA	Π-cat+ Π-cat+ Π-σ	4.41 2.92 3.85
	5 ns	A138:H - UNK:N5	2.18	K88:NZ Y137 Y137	Π-cat+ Π-Π Π-Π	3.15 4.28 4.78
	6 ns	A138:H - UNK:N5	2.00	K88:NZ K88:NZ	Π-cat+ Π-cat+	5.50 3.69
	7 ns	A138:H - UNK:N5	2.11	K88:NZ K88:NZ Y137:CA	Π-cat+ Π-cat+ Π-σ	4.62 2.96 3.68
	8 ns	A138:H - UNK:N5	2.06	K88:NZ K88:NZ Y137 Y137	Π-cat+ Π-cat+ Π-Π Π-Π	5.22 3.21 5.52 5.64

	9 ns	A138:H - UNK:N5	2.04	K88:NZ K88:NZ Y137 Y137:CA A198:CB	Π-cat+ Π-cat+ Π-Π Π-σ Π-σ	4.16 3.25 4.55 3.99 3.66
	10 ns	A138:H - UNK:N5	2.01	K88:NZ K88:NZ	Π-cat+ Π-cat+	4.46 2.92
5	**MARK4-781**					
	1 ns	K88:HZ3 - UNK:N40 A138:H - UNK:O18 D199:H - UNK:N6	2.10 2.42 2.43	-Nil-		
	2 ns	D199:H - UNK:N6	2.26	F202	Π-Π	4.22
	3 ns	-Nil-				
	4 ns	-Nil-				
	5 ns	A138:H - UNK:O18	1.84	F202	Π-Π	4.13
	6 ns	A138:H - UNK:O18	1.98	-Nil-		
	7 ns	A138:H - UNK:O18 D199:H - UNK:N6	2.12 2.43	-Nil-		
	8 ns	A138:H - UNK:O18	2.35	F202 A198:CA	Π-Π Π-cat+	4.66 3.94
	9 ns	A138:H - UNK:O18	1.88	F202	Π-Π	3.97
		D199:H - UNK:N6	2.21	-Nil-		
	10 ns	A138:H - UNK:O18	2.37	K88:NZ	Π-cat+	5.20
6	**MARK4-529**					
	1 ns	-Nil-		K88:NZ Y137	Π-cat+ Π-Π	4.56 5.39
	2 ns	-Nil-		R63:NH1 Y137 I65:CG1	Π-cat+ Π-Π Π-σ	4.08 4.77 3.41
	3 ns	-Nil-		R63:NH2 R63:NH1 Y137 Y137	Π-cat+ Π-cat+ Π-Π Π-Π	4.20 3.37 4.73 3.79
	4 ns	-Nil-		R63:NH1 K88:NZ Y137	Π-cat+ Π-cat+ Π-Π	4.87 6.07 5.48
	5 ns	-Nil-		R63:NH1 R63:NH2 Y137 L75:CB	Π-cat+ Π-cat+ Π-Π Π-σ	4.22 5.45 6.09 3.91
	6 ns	-Nil-		R63:NH1 R63:NH2 Y137	Π-cat+ Π-cat+ Π-Π	4.50 5.71 5.61
	7 ns	-Nil-		R63:NH2 R63:NH1	Π-cat+ Π-cat+	5.61 4.59
	8 ns	-Nil-				
	9 ns	-Nil-		R63:NH1 R63:NH2	Π-cat+ Π-cat+	5.98 4.87
	10 ns	D199:H - UNK:O14	2.34	R63:NH1	Π-cat+	5.14