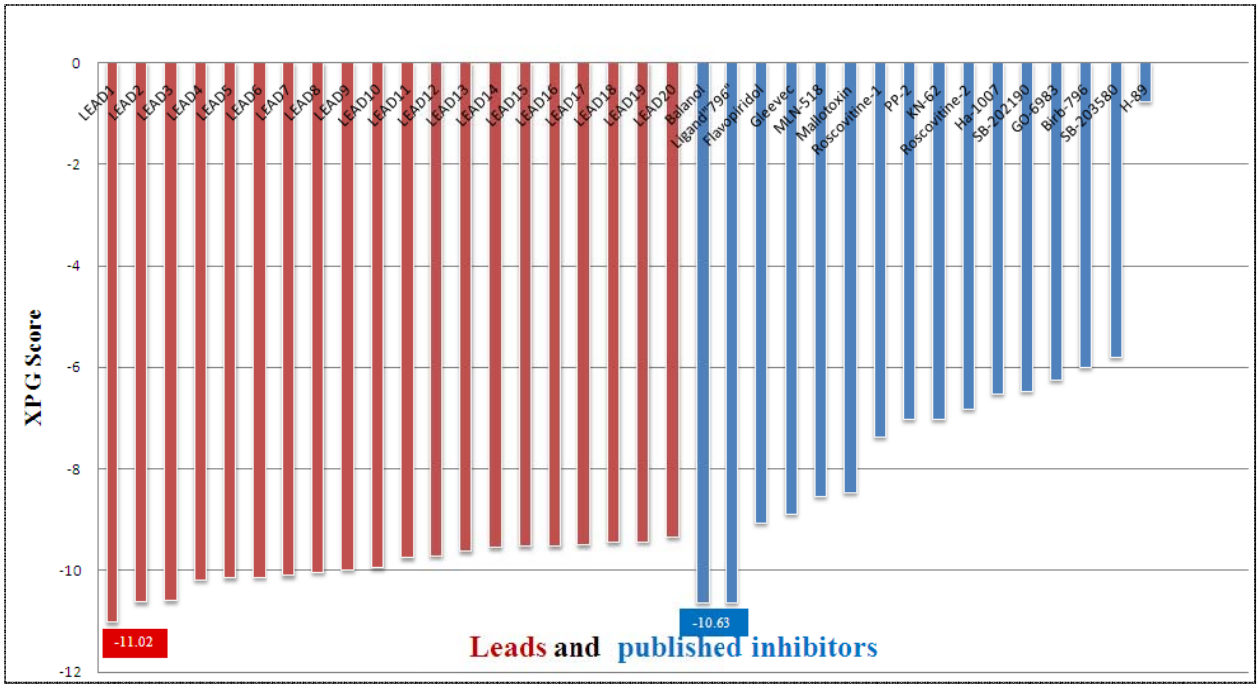
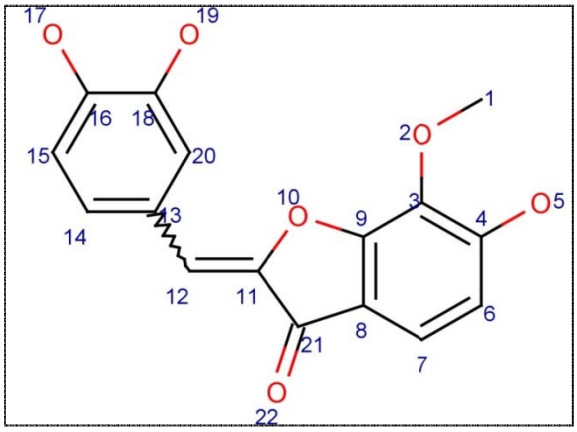
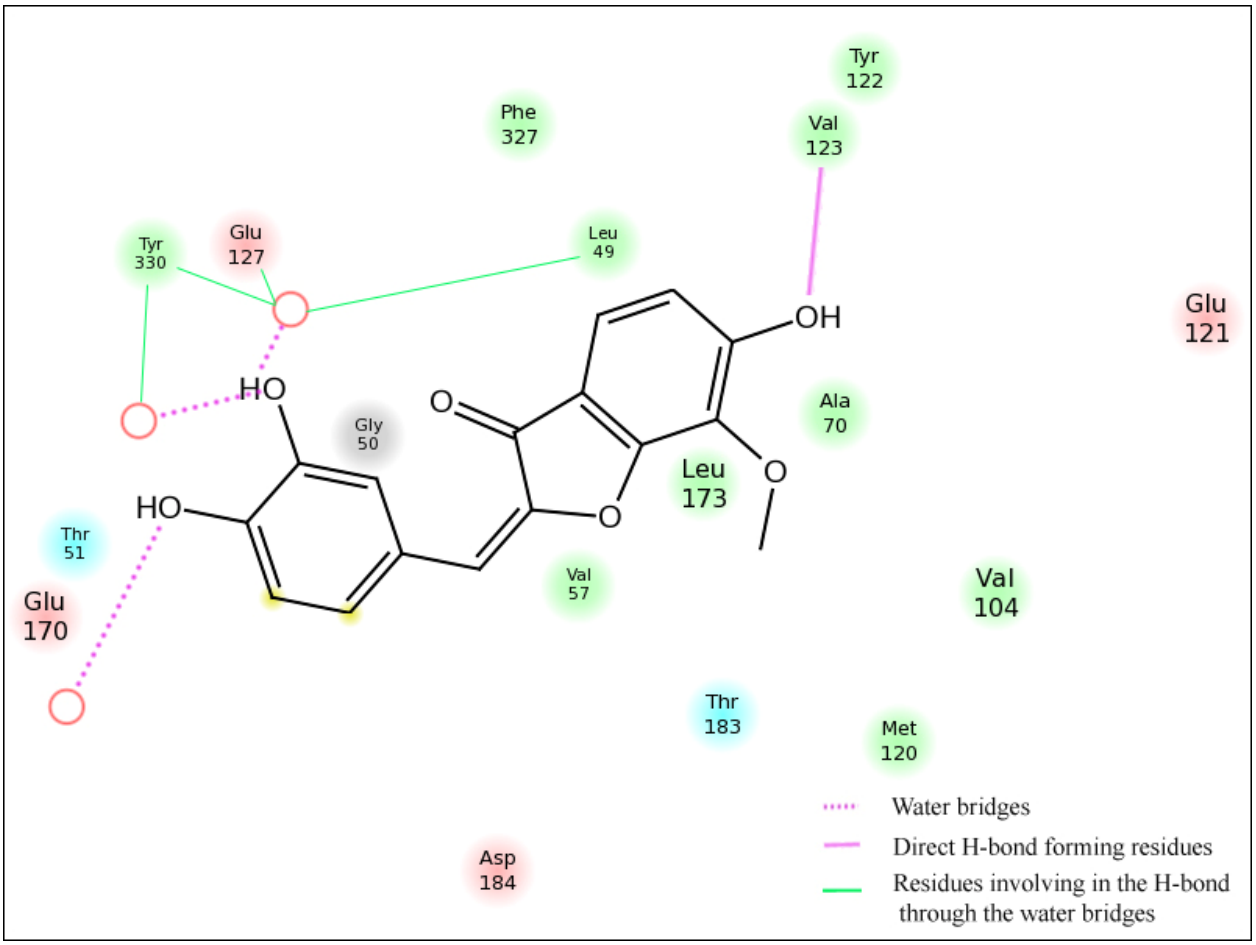


Supplementary Fig. 1. XP Gscore of 20 leads and 15 published inhibitors of PRKACA.



Supplementary Fig. 2. 2D representation of lead1 (leptosidin).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Phe
327
Val
123
Tyr
330
Glu
127
Leu
49
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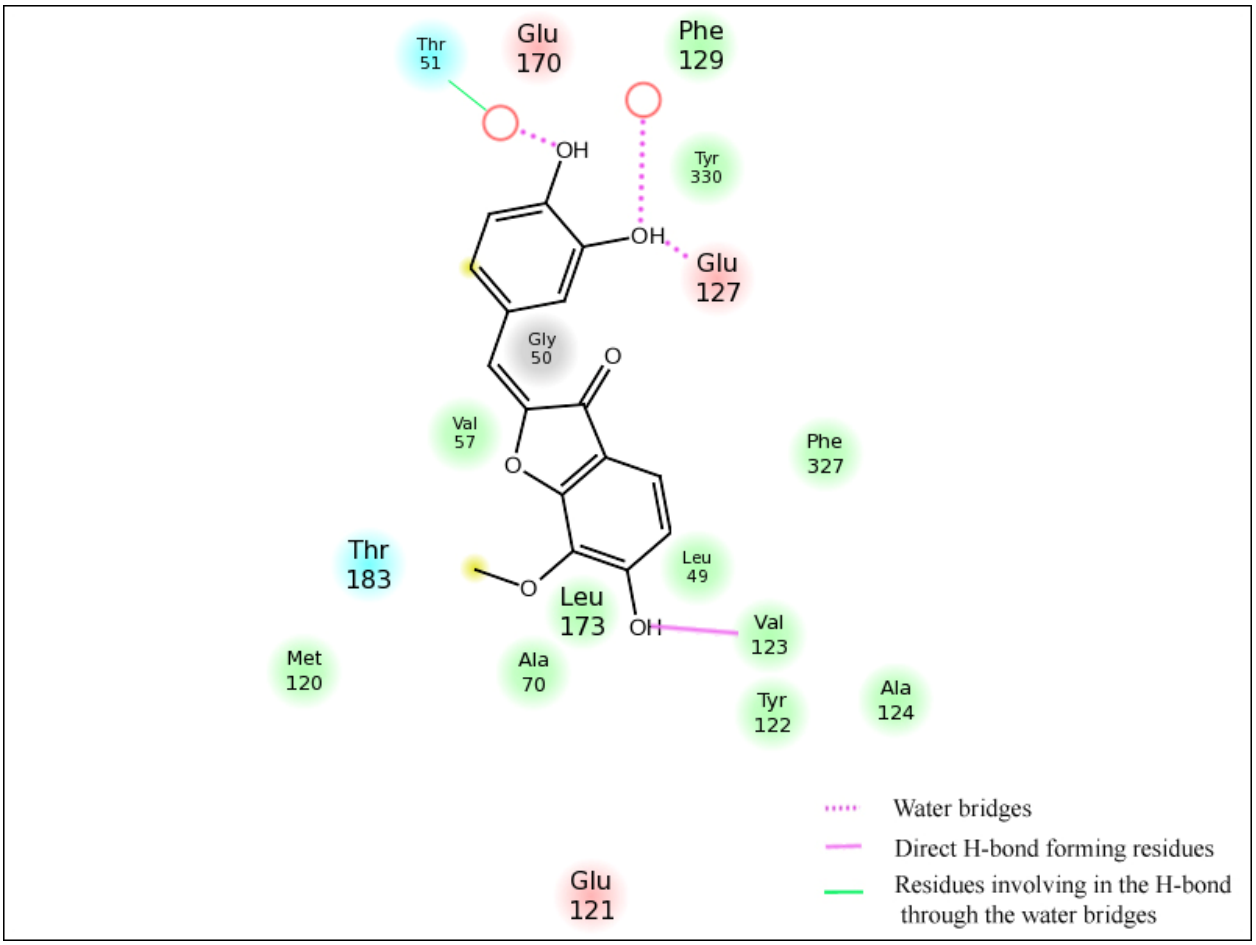
121
OH
HO
O
Ala
70
Gly
50
Leu
173
O
HO
O
Thr
51
Val
57
Val
104
Glu
170
Thr
183
Met
120
Water bridges
Direct H-bond forming residues
Residues involving in the H-bond
through the water bridges
Asp
184

A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Thr
183
O
Leu
49
Leu
173
OH
Val
123
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Ala
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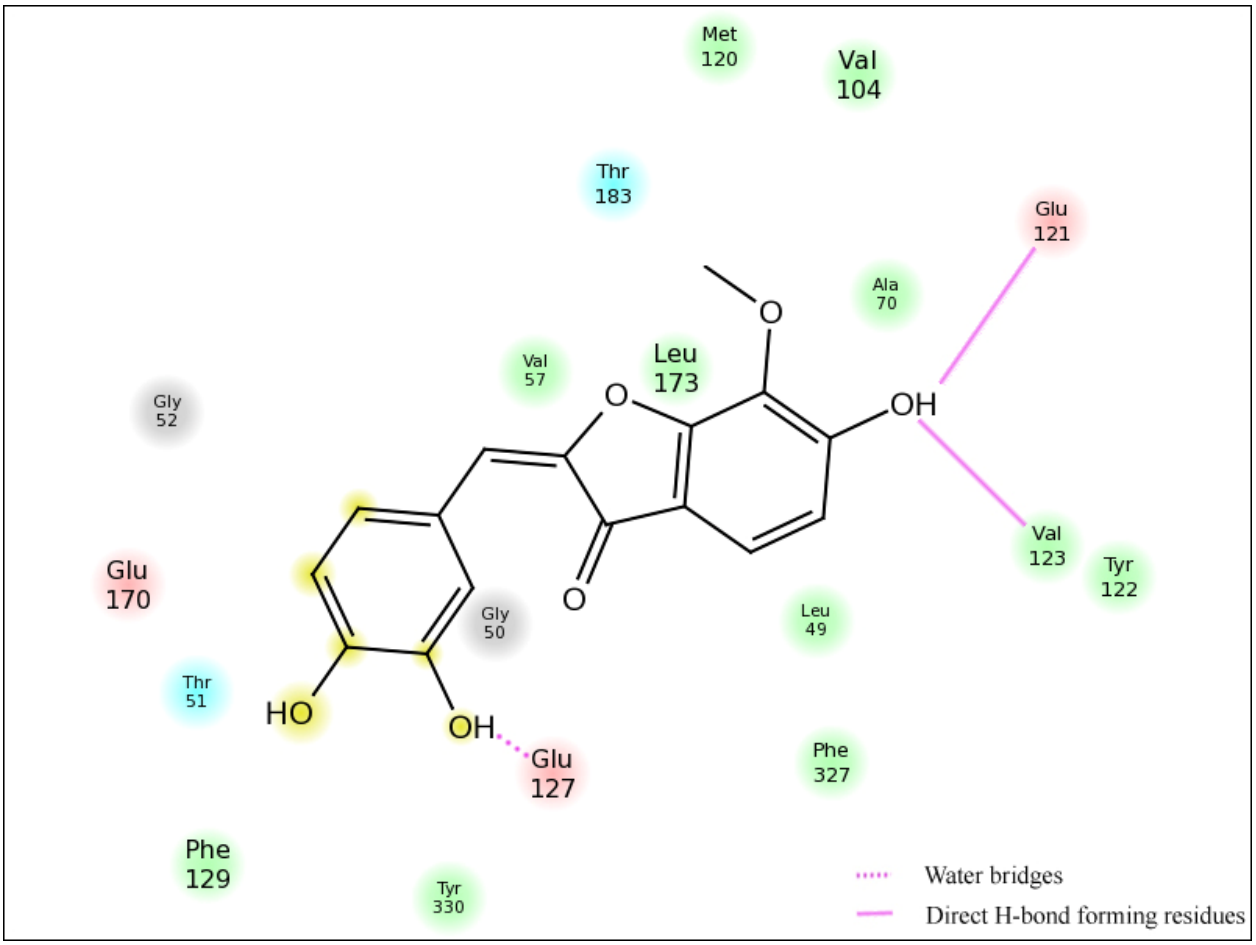
Water bridges
Direct H-bond forming residues
Residues involving in the H-bond
through the water bridges
Glu
121

B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Glu
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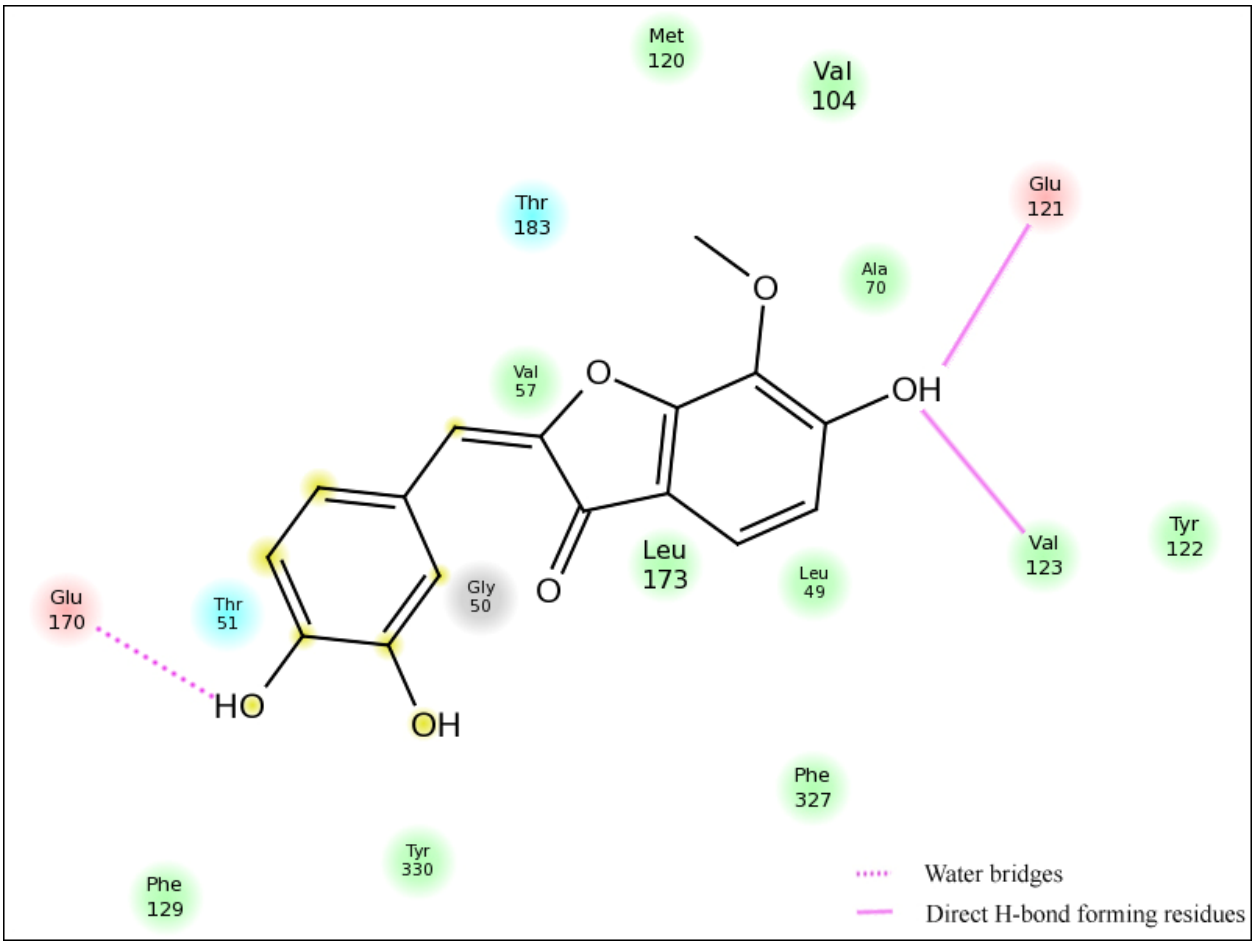
Phe
129
Tyr
330
Water bridges
Direct H-bond forming residues

C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Leu
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Gly
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HO
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Phe
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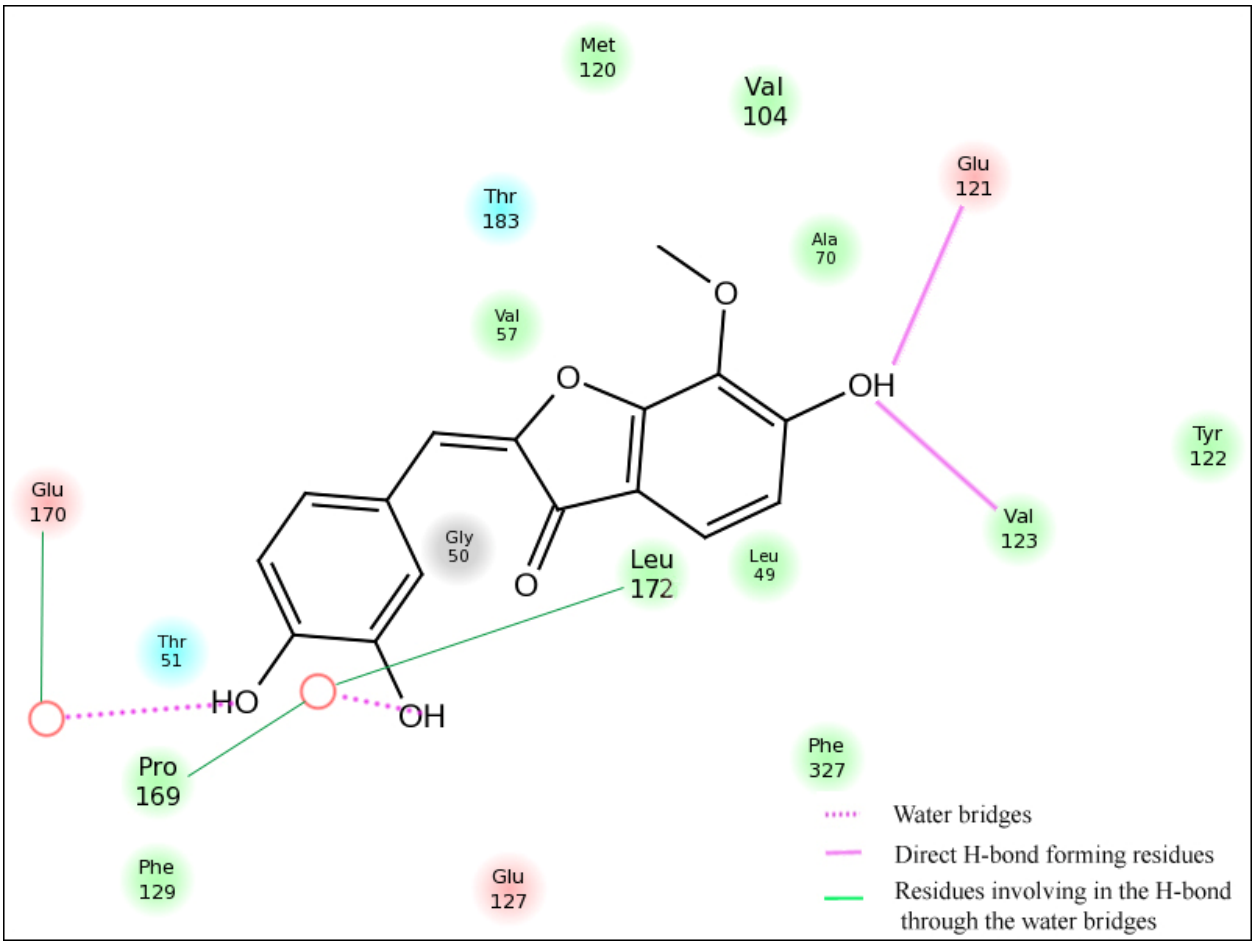
Tyr
330
Phe
129
Water bridges
Direct H-bond forming residues

D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Leu
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Val
123
O
Thr
51
HO
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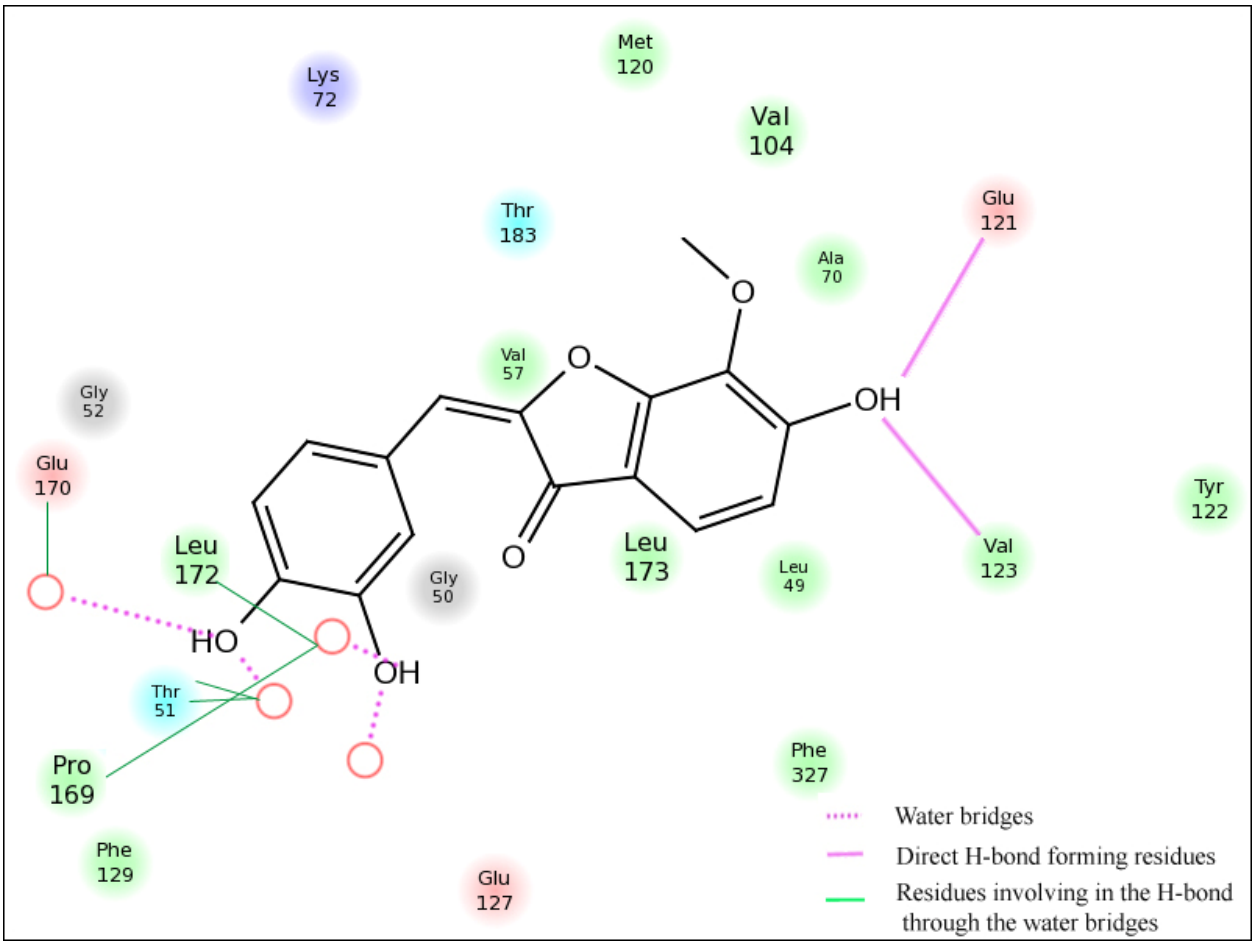
Phe
327
Water bridges
Direct H-bond forming residues
Residues involving in the H-bond through the water bridges
Phe
129
Glu
127

E



F

Supplementary Fig.3. Trajectories of PRKACA-leptosidin Docking Complex During Molecular Dynamics Simulations. 3A. 0th trajectory **3B.** 1-20th trajectories. **3C.** 21-200th trajectories. **3D.** 201-220th trajectories. **3E.** 221-540th trajectories. **3F.** 541-2084th trajectories.