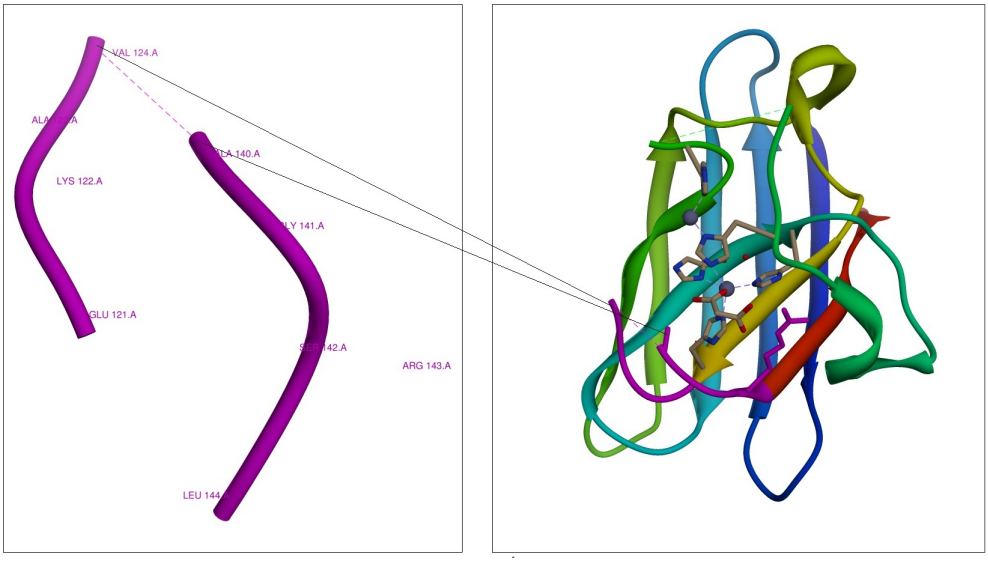
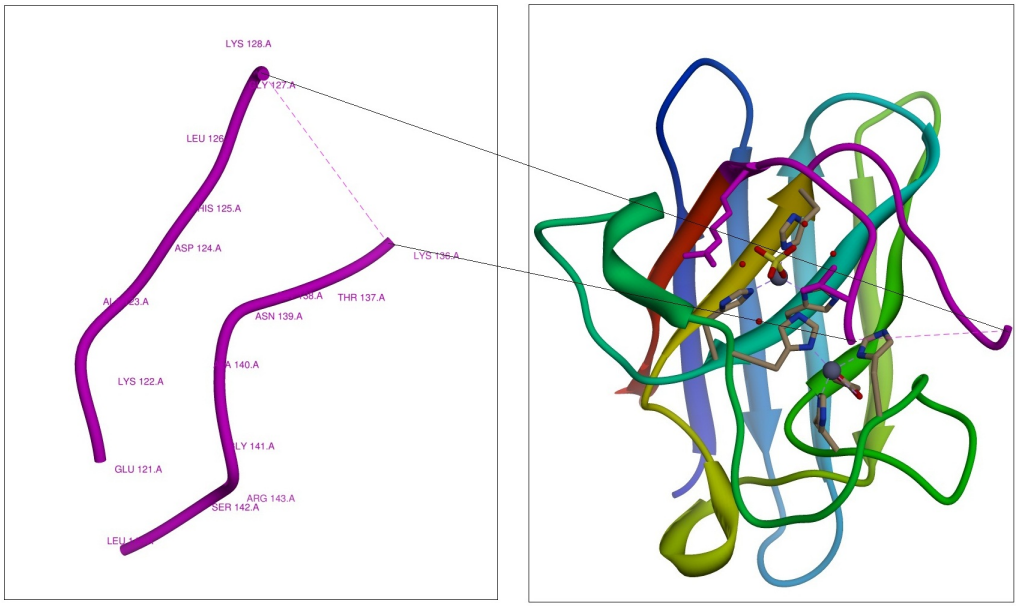
Electronic Supplementary Material (ESI) for RSC Advances.

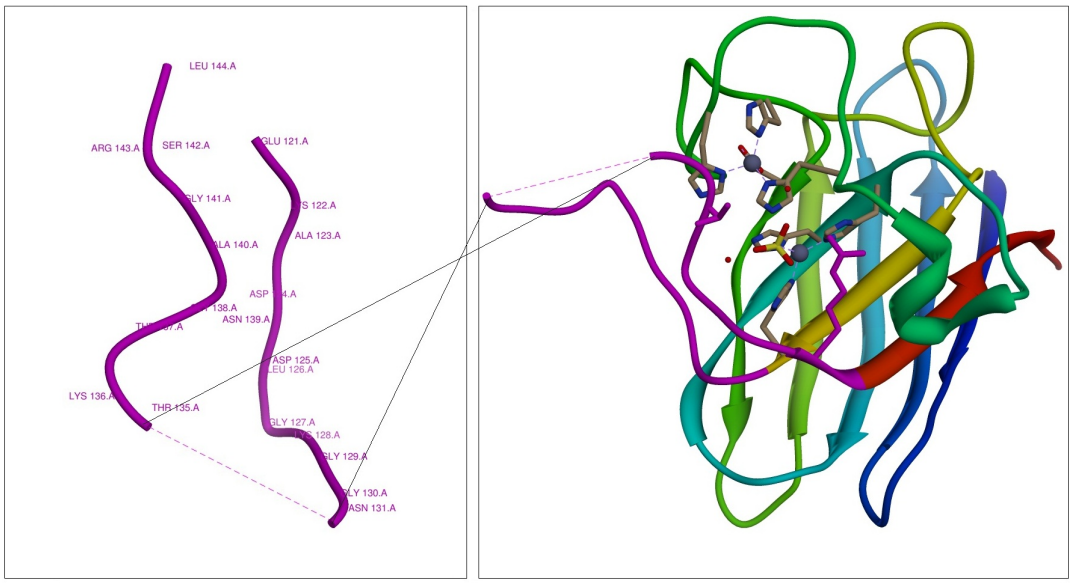
SUPPORTING INFORMATION



a) D124V (3H2P)

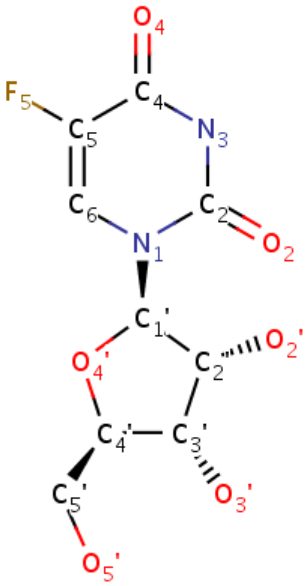


b) D125H (1P1V)

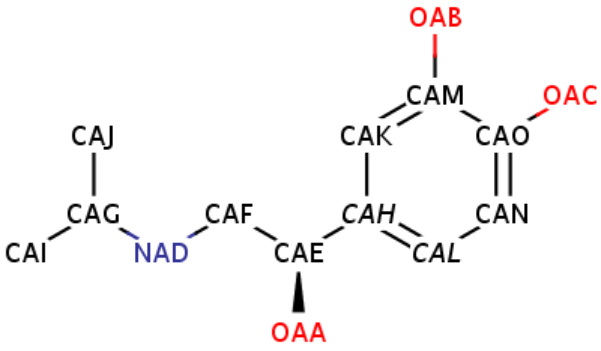


c) S134N (1OZU)

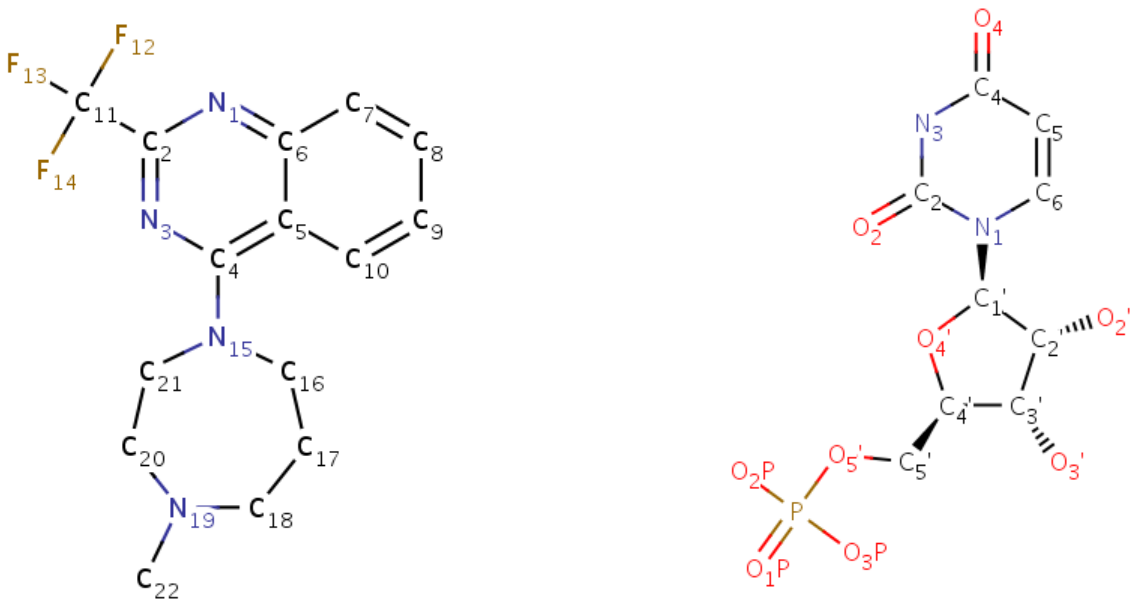
Fig. S1 Representing the D124V, D125H and S134N mutated E-loops in whole protein structure. The individual E-loop for the respective mutations is shown in left side labelled with residue names and numbers a) D124V (PDB CODE: 3H2P) b) D125H (PDB CODE: 1P1V) and c) S134N (PDB CODE: 1OZU)



a) 5-Fluorouridine



b) Isoproteranol

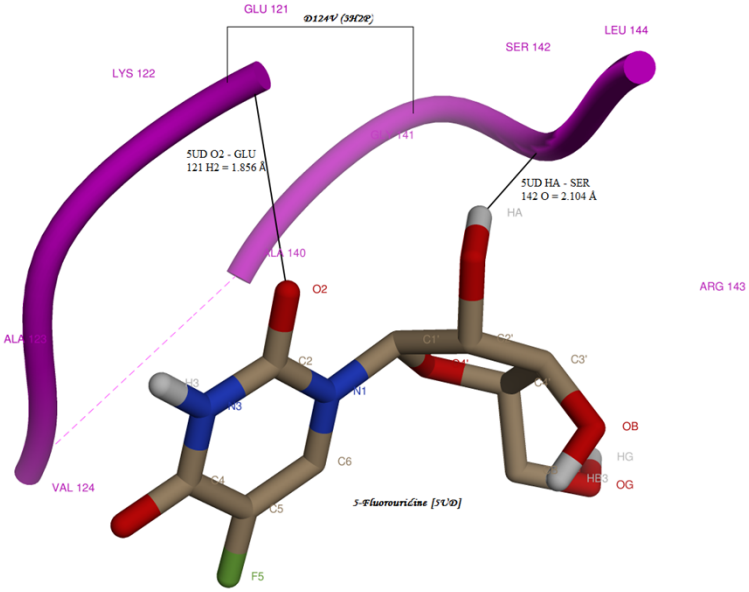


c) (4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline)

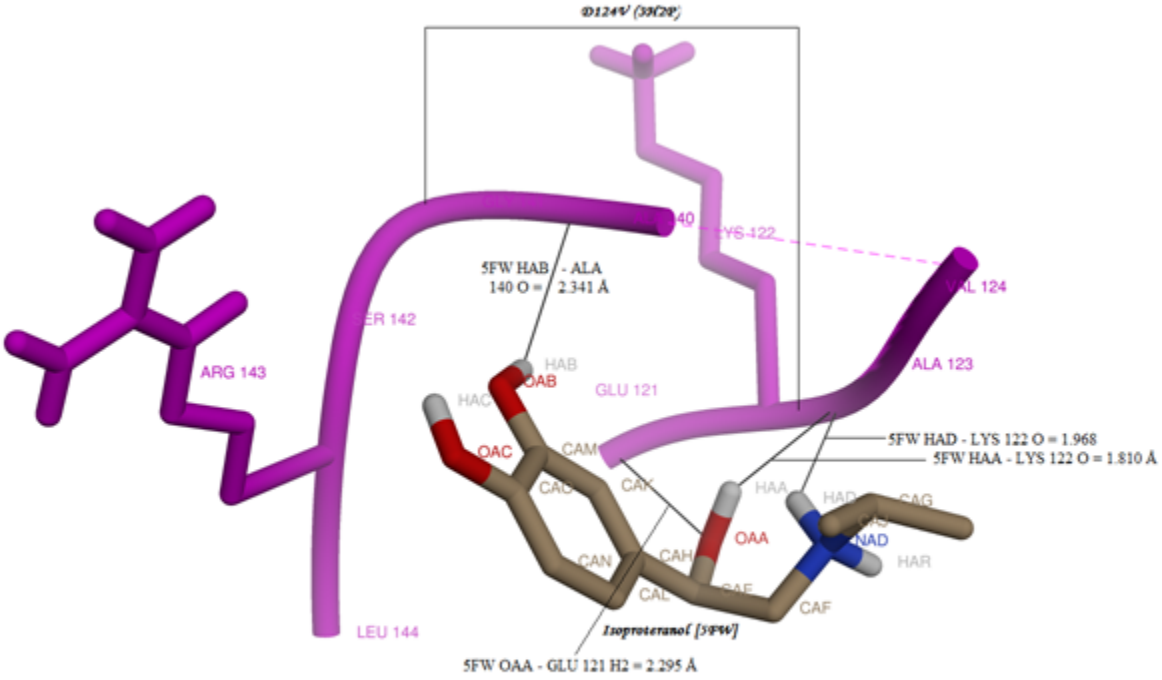
d) Uridine-5'-Monophosphate

Fig. S2 Representing the structure of various chemical compounds a) 5-Fluorouridine, b) Isoproteranol, c) (4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline), d) Uridine-5'-Monophosphate.

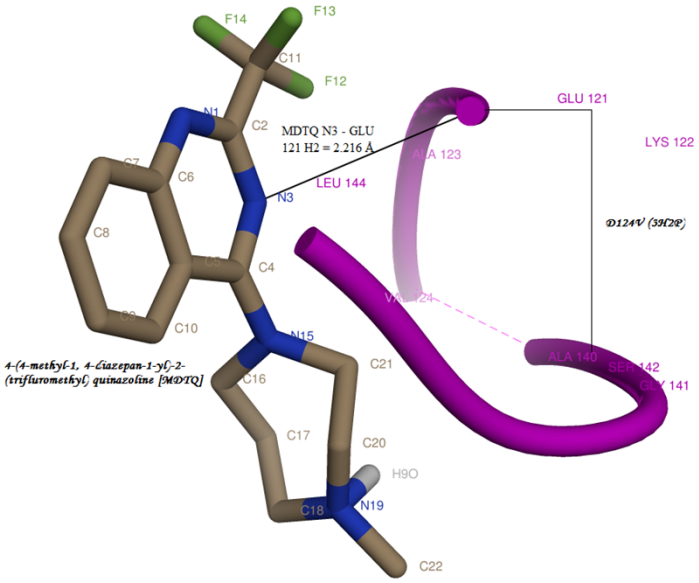
a)



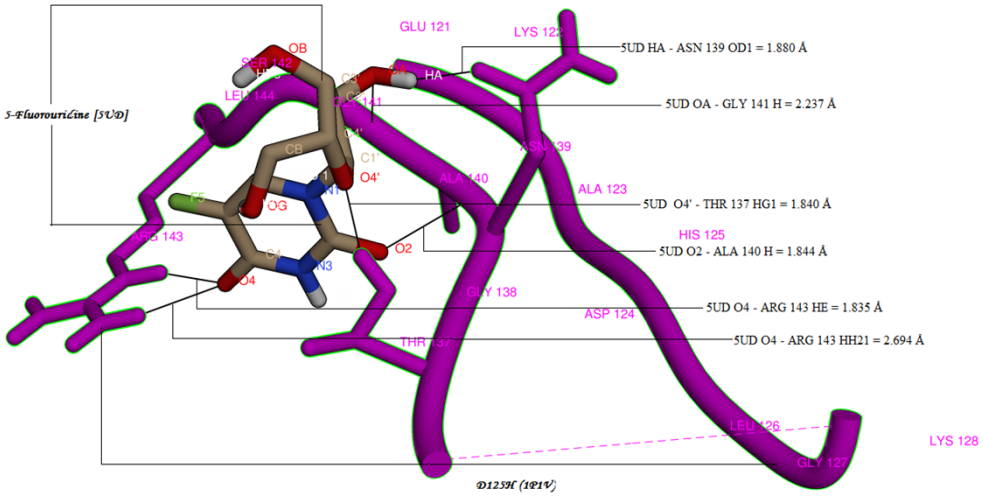
b)


D124V (3H2P)
5FW HAB - ALA
140 O = 2.341 Å
ARG 143
ER 142
LEU 144
HAB
OAB
GLU 121
HAC
OAC
CAM
CAC
CAY
HAA
OAA
CAN
CAH
CAL
CAF
NAD
HAR
ALA 123
5FW HAD - LYS 122 O = 1.968
5FW HAA - LYS 122 O = 1.810 Å
Isoproterenol [5FW]
5FW OAA - GLU 121 H2 = 2.295 Å

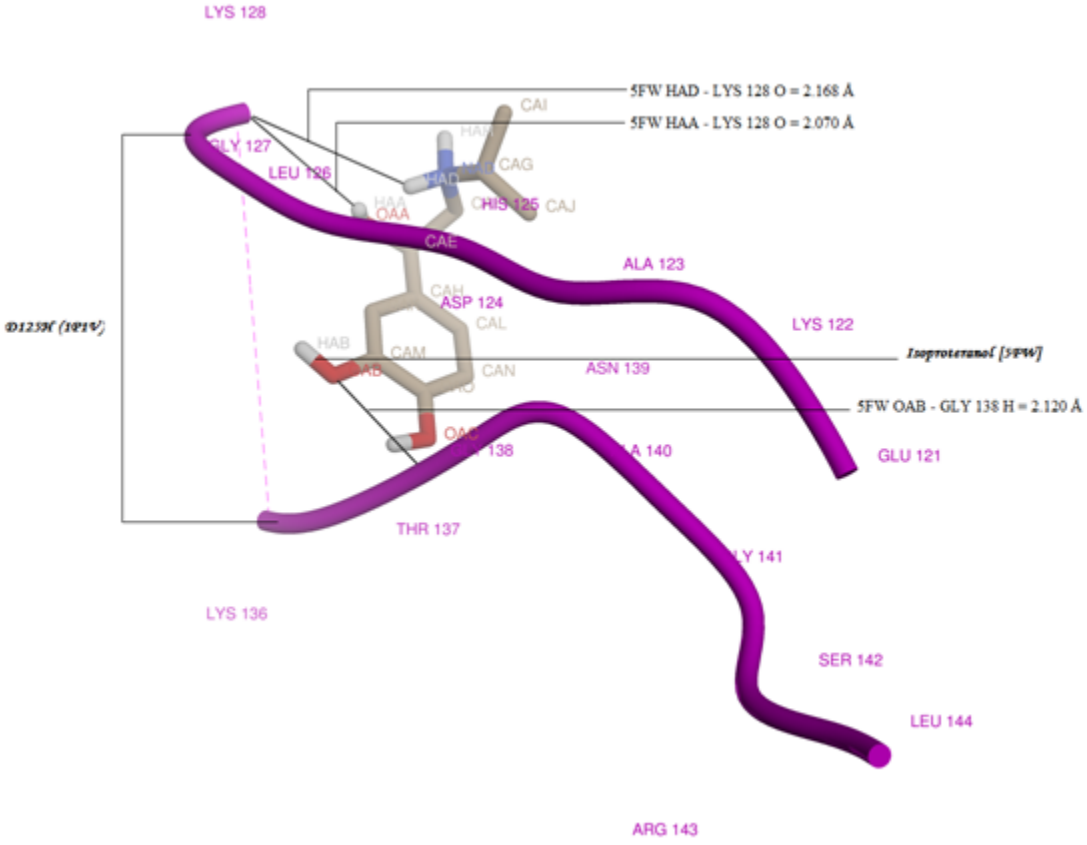
c)


F14
F13
C11
F12
N1
C2
C7
C6
N3
C8
C4
C10
N15
C21
C16
C17
C20
H9O
C18
N19
C22
MDTQ N3 - GLU
121 H2 = 2.216 Å
LEU 144
4-(4-methyl-1, 4-diazepan-1-yl)-2-
(trifluoromethyl) quinazoline [MDTQ]
GLU 121
LYS 122
ALA 123
D124V (3H2P)
ALA 140
SER 142
GLY 141

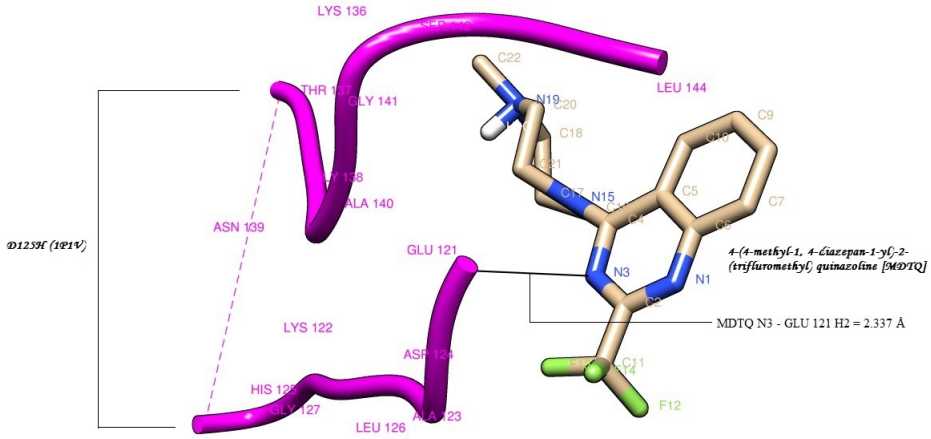
d)


5-Fluorouridine [5UD]
GLU 121
LYS 122
5UD HA - ASN 139 OD1 = 1.880 Å
5UD OA - GLY 141 H = 2.237 Å
ASN 139
ALA 140
ALA 123
5UD O4' - THR 137 HG1 = 1.840 Å
HIS 125
5UD O2 - ALA 140 H = 1.844 Å
ARG 143
GLY 138
ASP 124
5UD O4 - ARG 143 HE = 1.835 Å
THR 137
5UD O4 - ARG 143 HH21 = 2.694 Å
LEU 126
LYS 128
GLY 127
D123H (1P1V)

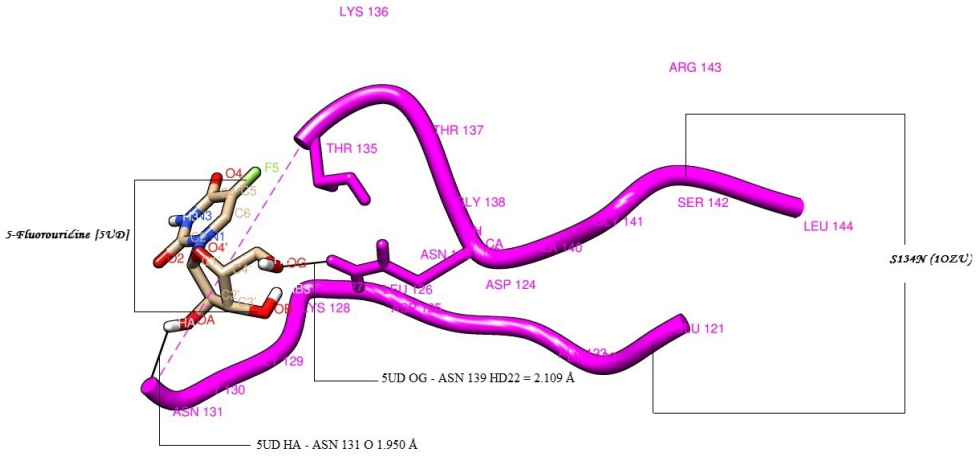
e)


LYS 128
5FW HAD - LYS 128 O = 2.168 Å
5FW HAA - LYS 128 O = 2.070 Å
GLY 127
LEU 126
HIS 125
ALA 123
ASP 124
LYS 122
D123H (1P1V)
Isoproterenol [5FW]
ASN 139
5FW OAB - GLY 138 H = 2.120 Å
GLU 121
THR 137
LYS 136
SER 142
LEU 144
ARG 143

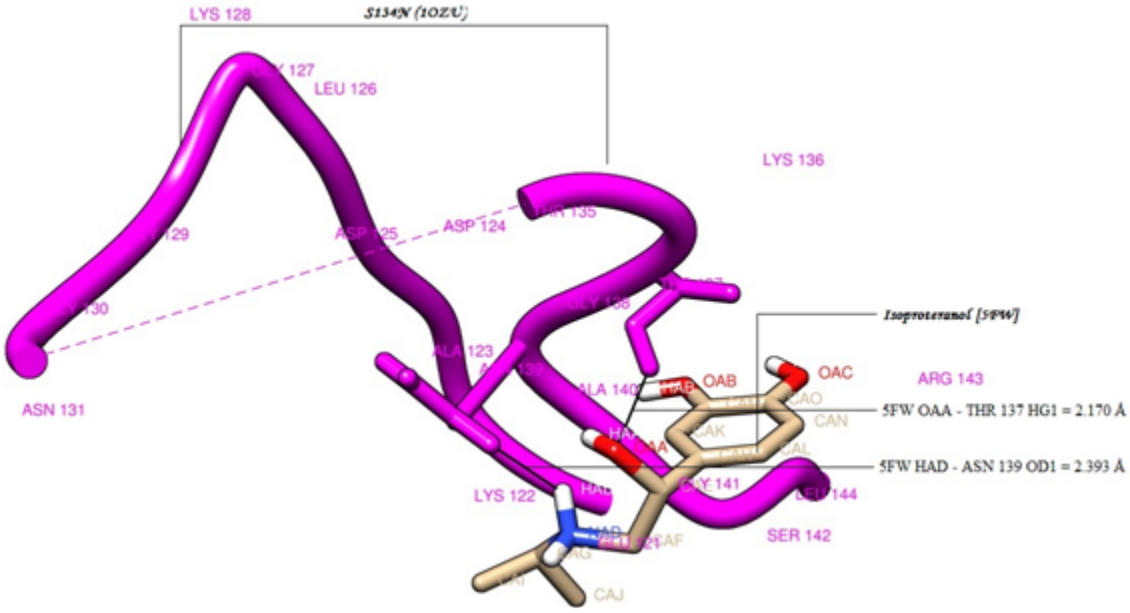
f)


LYS 136
C22
LEU 144
THR 137
GLY 141
N19
C20
C18
C9
C21
C5
C7
N15
ALA 140
ASN 139
D1259H (1Q1V)
GLU 121
4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline [MDTQ]
N3
N1
MDTQ N3 - GLU 121 H2 = 2.337 Å
LYS 122
ASP 123
C11
F4
HIS 125
GLY 127
F12
LEU 126

g)


LYS 136
ARG 143
THR 137
THR 135
O4
F5
C5
C6
GLY 138
SER 142
LEU 144
5-Fluorouricine [5UD]
N3
N1
O4'
ASN
ASP 124
S134N (1OZU)
HA
OA
LYS 128
GLU 121
129
5UD OG - ASN 139 HD22 = 2.109 Å
130
ASN 131
5UD HA - ASN 131 O 1.950 Å

h)



i)

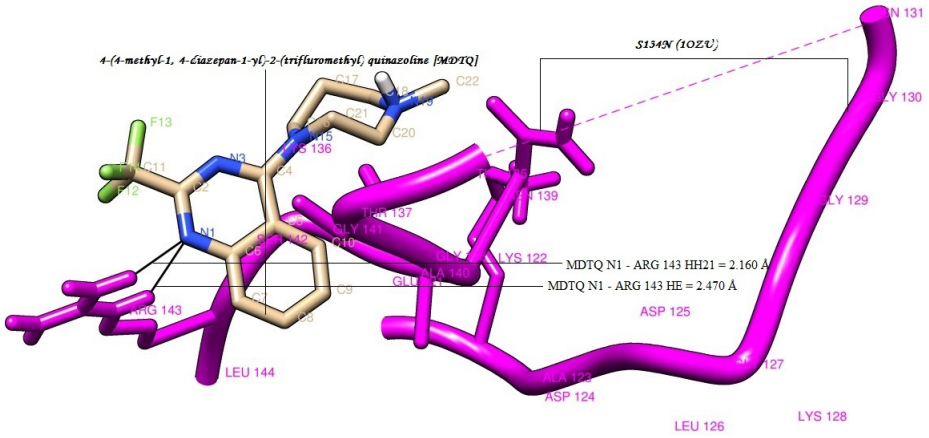
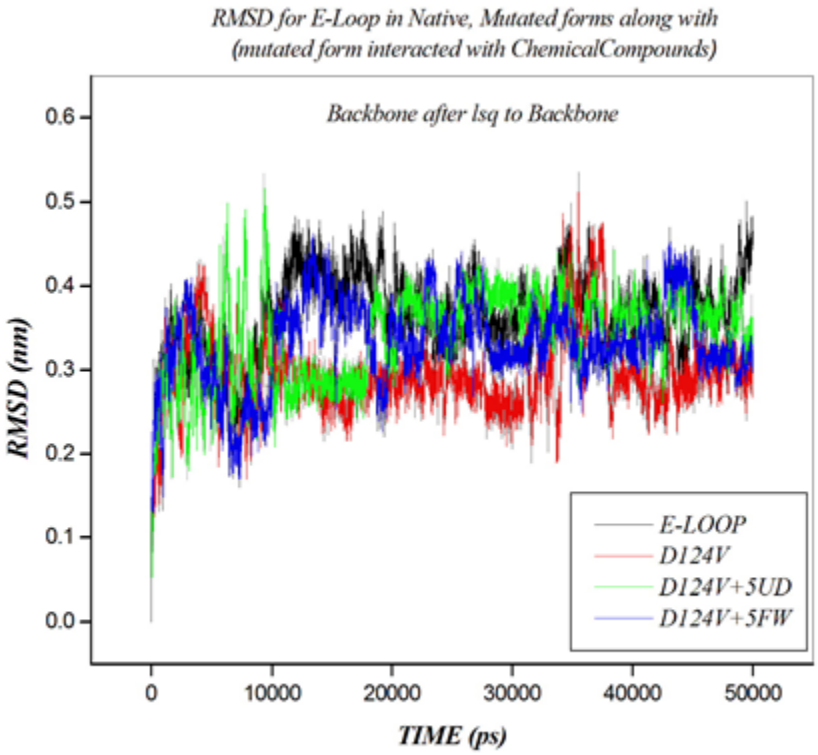
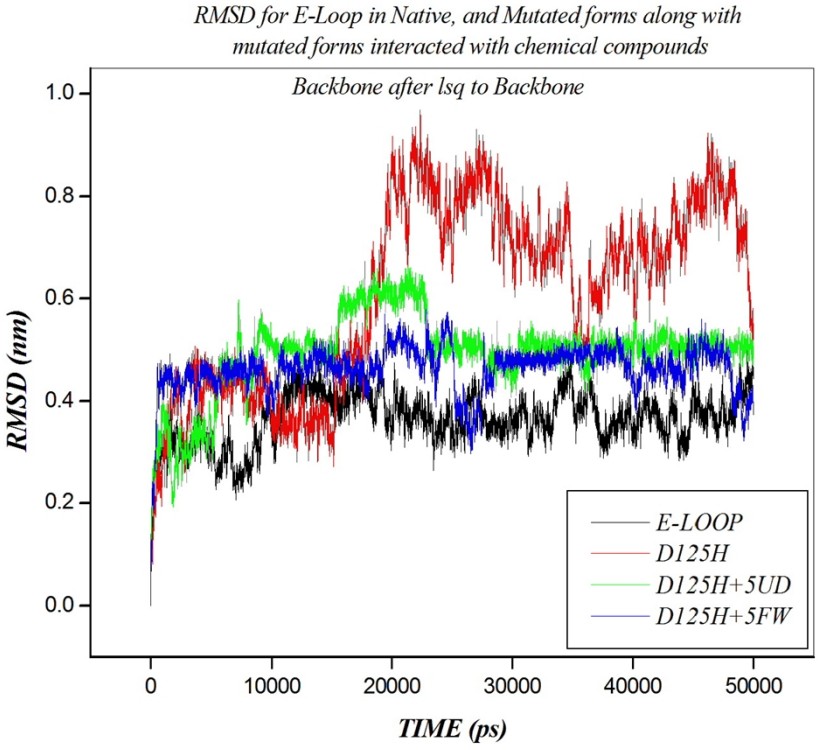


Fig. S3 Representing the best docked structure of three mutated E-loops subjected to docking with 5-Fluorouridine [5UD], Isoproteranol [5FW] and 4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline [MDTQ]. a) D124V + 5UD, b) D124V +5FW, c) D124V + MDTQ, d) D125H + 5UD, e) D125H + 5FW, f) D125H + MDTQ, g) S134N + 5UD, h) S134N + 5FW, i) S134N + MDTQ.

a)


RMSD for E-Loop in Native, Mutated forms along with
(mutated form interacted with ChemicalCompounds)
Backbone after lsq to Backbone
RMSD (nm)
TIME (ps)
E-LOOP
D124V
D124V+5UD
D124V+5FW

b)


RMSD for E-Loop in Native, and Mutated forms along with
mutated forms interacted with chemical compounds
Backbone after lsq to Backbone
RMSD (nm)
TIME (ps)
E-LOOP
D125H
D125H+5UD
D125H+5FW

c)

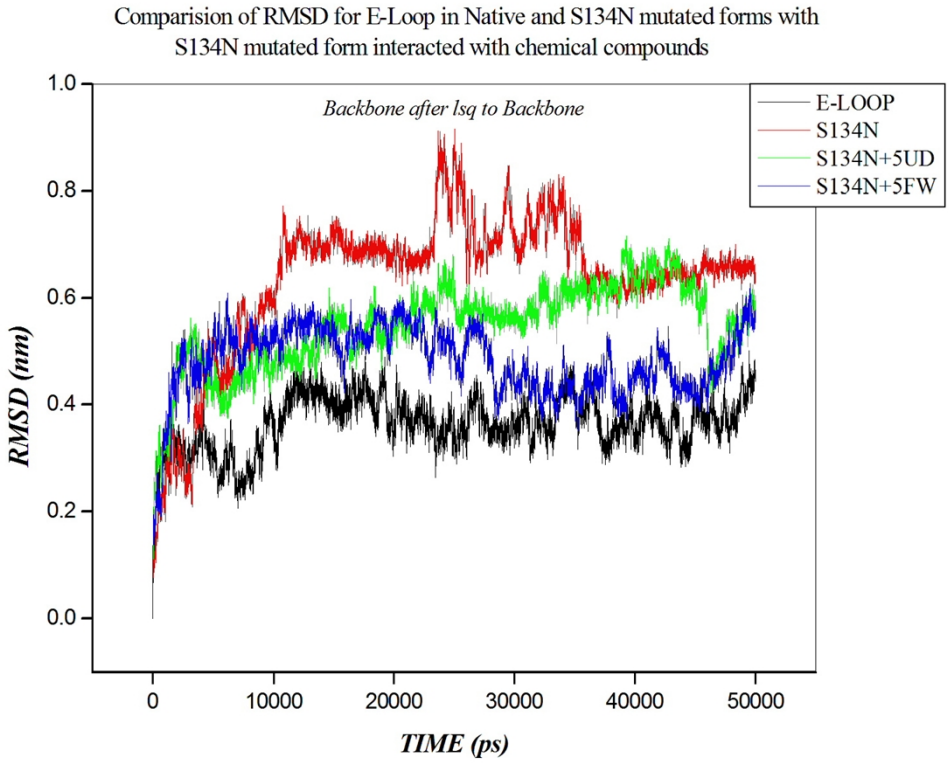
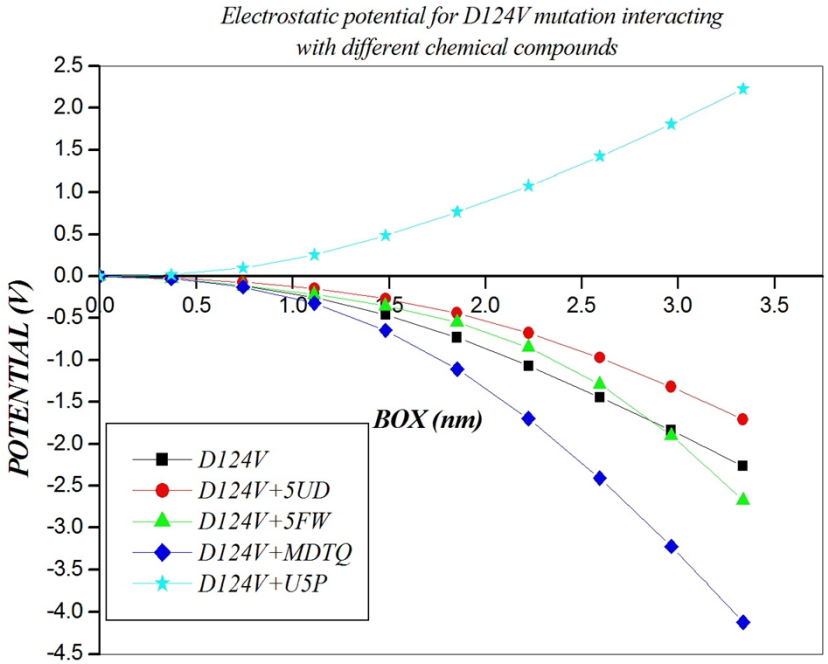
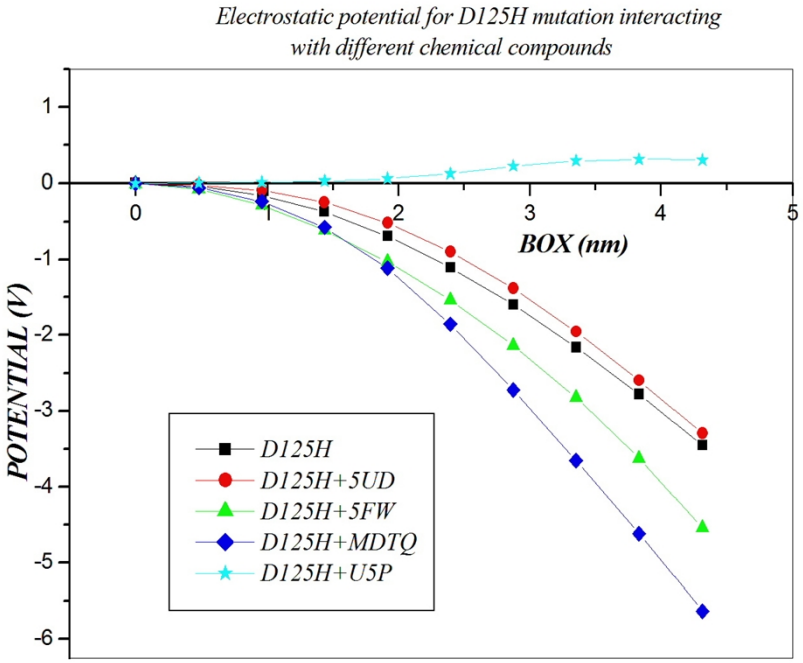


Fig. S4 Representing the RMSD for different mutated E-loops interacting with 5-Fluorouridine [5UD] and Isoproteranol [5FW] along with native state E-loop. a) D124V mutated E-loop interacting with 5UD and 5FW, b) D125H mutated E-loop interacting with 5UD and 5FW, c) S134N mutated E-loop interacting with 5UD and 5FW.

a)


Electrostatic potential for D124V mutation interacting
with different chemical compounds
POTENTIAL (V)
BOX (nm)
D124V
D124V+5UD
D124V+5FW
D124V+MDTQ
D124V+U5P

b)


Electrostatic potential for D125H mutation interacting
with different chemical compounds
POTENTIAL (V)
BOX (nm)
D125H
D125H+5UD
D125H+5FW
D125H+MDTQ
D125H+U5P

c)

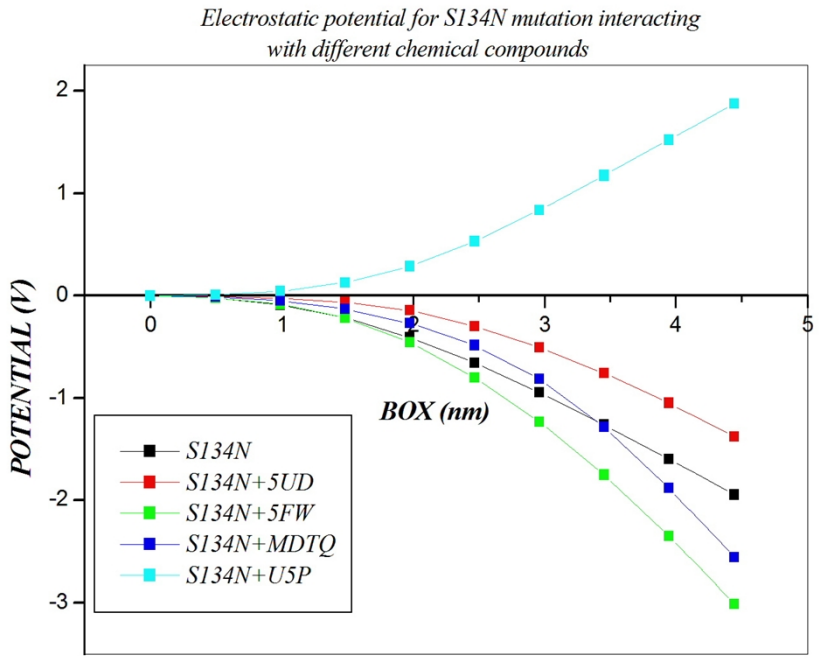
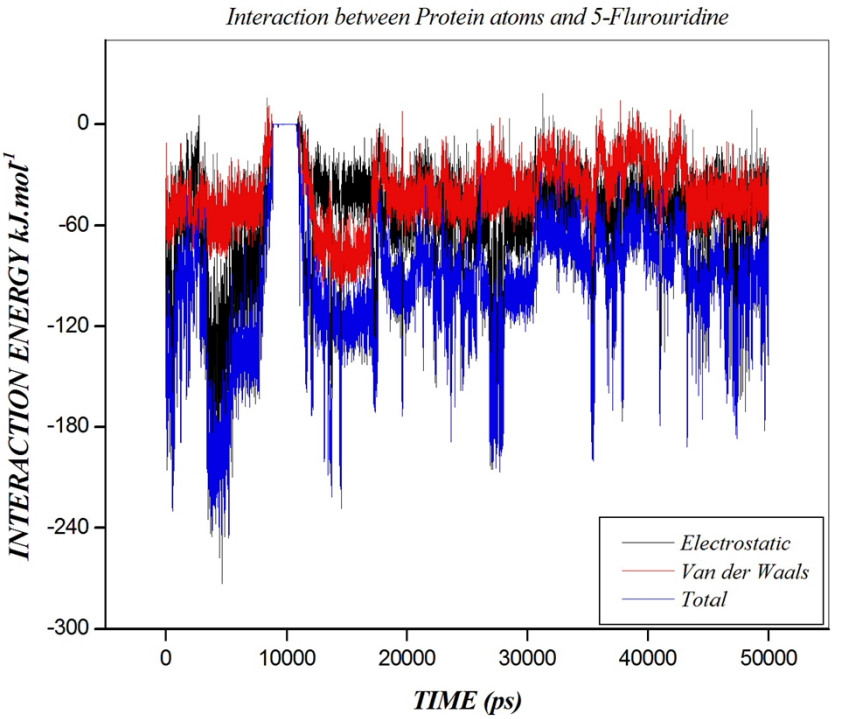
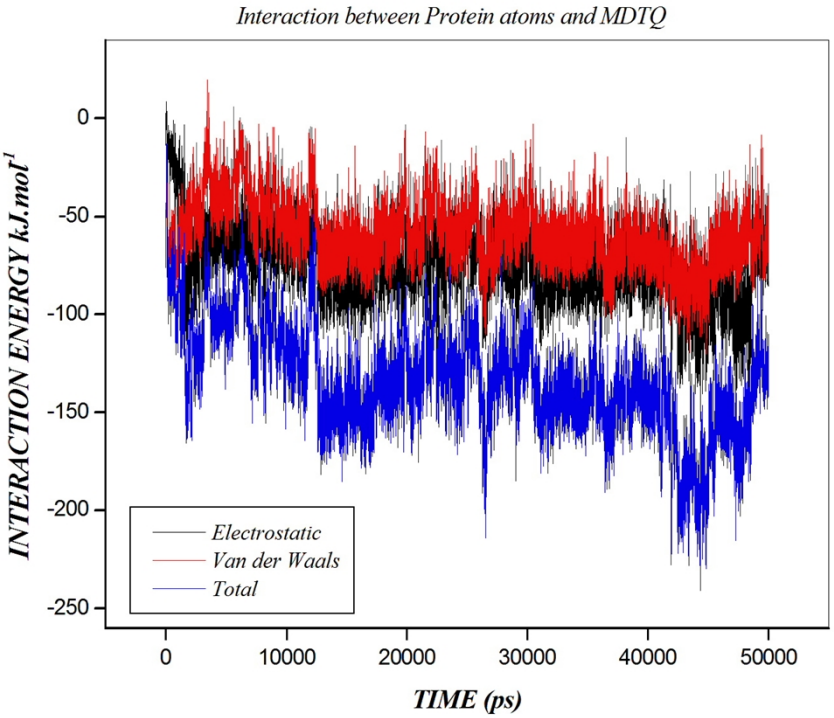


Fig. S5 Representing the spatial distribution of Electrostatic potential across the box. a) D124V mutated E-loop interacting with different chemical compounds, b) D125H mutated E-loop interacting with different chemical compounds, c) S134N mutated E-loop interacting with different chemical compounds.

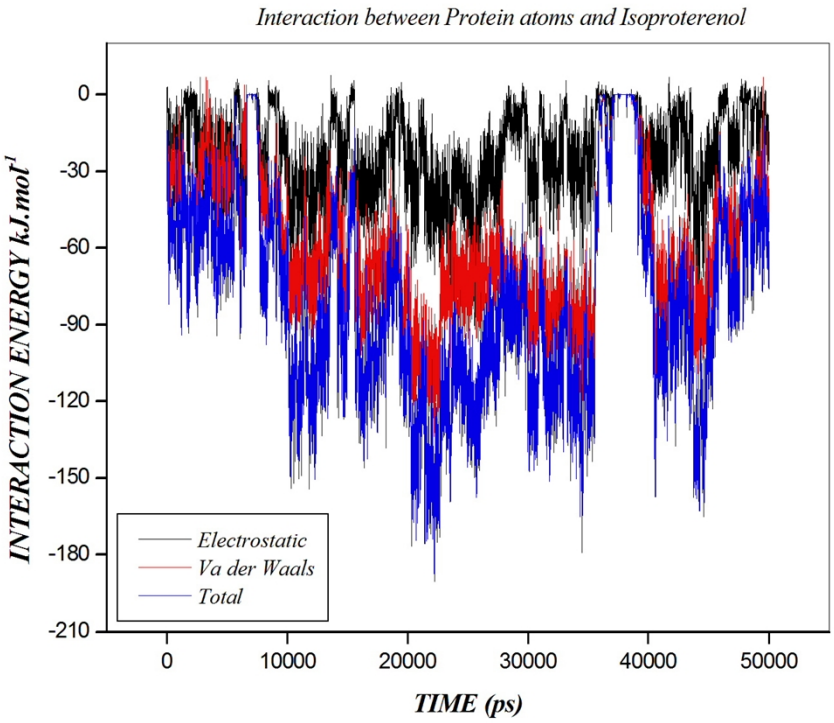
a)



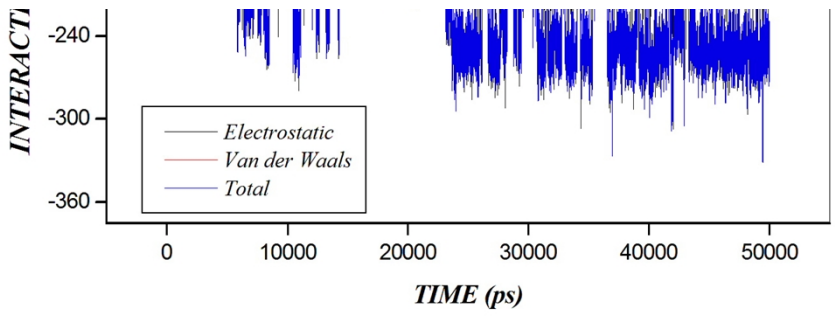
b)


Interaction between Protein atoms and MDTQ
INTERACTION ENERGY kJ.mol-1
0
-50
-100
-150
-200
-250
0
10000
20000
30000
40000
50000
TIME (ps)
Electrostatic
Van der Waals
Total

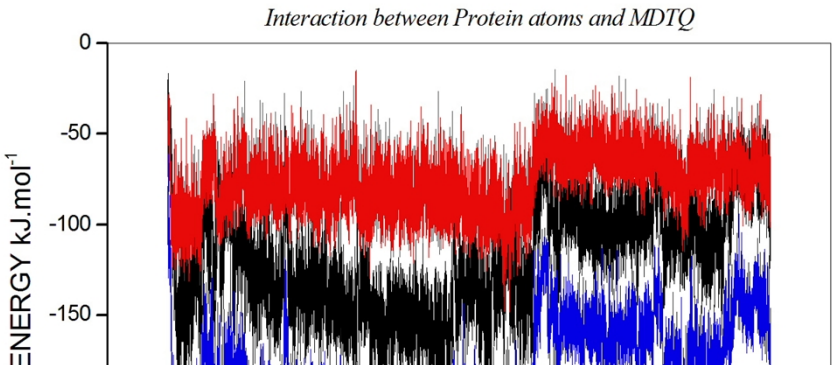
c)


Interaction between Protein atoms and Isoproterenol
INTERACTION ENERGY kJ.mol-1
0
-30
-60
-90
-120
-150
-180
-210
0
10000
20000
30000
40000
50000
TIME (ps)
Electrostatic
Va der Waals
Total

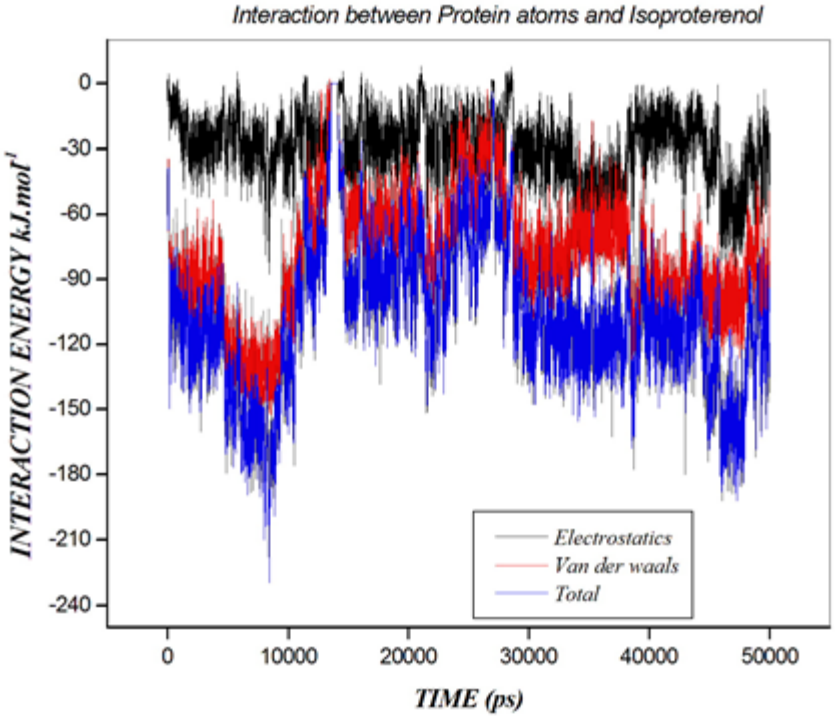
d)


INTERACTI
-240
-300
-360
0
10000
20000
30000
40000
50000
TIME (ps)
Electrostatic
Van der Waals
Total

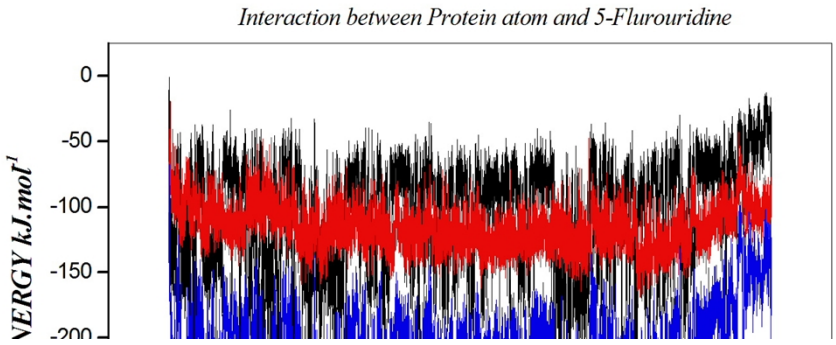
e)


Interaction between Protein atoms and MDTQ
0
-50
-100
-150
ENERGY kJ.mol-1

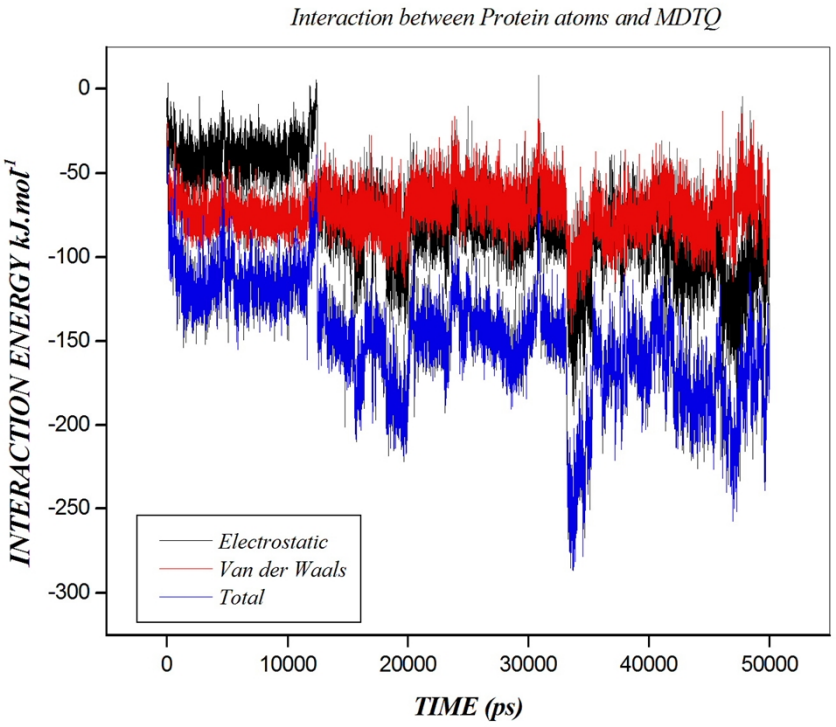
f)


Interaction between Protein atoms and Isoproterenol
INTERACTION ENERGY kJ.mol-1
0
-30
-60
-90
-120
-150
-180
-210
-240
Electrostatics
Van der waals
Total
0
10000
20000
30000
40000
50000
TIME (ps)

g)


Interaction between Protein atom and 5-Flurouridine
0
-50
-100
-150
-200
ENERGY kJ.mol-1

h)


Interaction between Protein atoms and MDTQ
INTERACTION ENERGY kJ.mol-1
0
-50
-100
-150
-200
-250
-300
Electrostatic
Van der Waals
Total
0
10000
20000
30000
40000
50000
TIME (ps)

i)

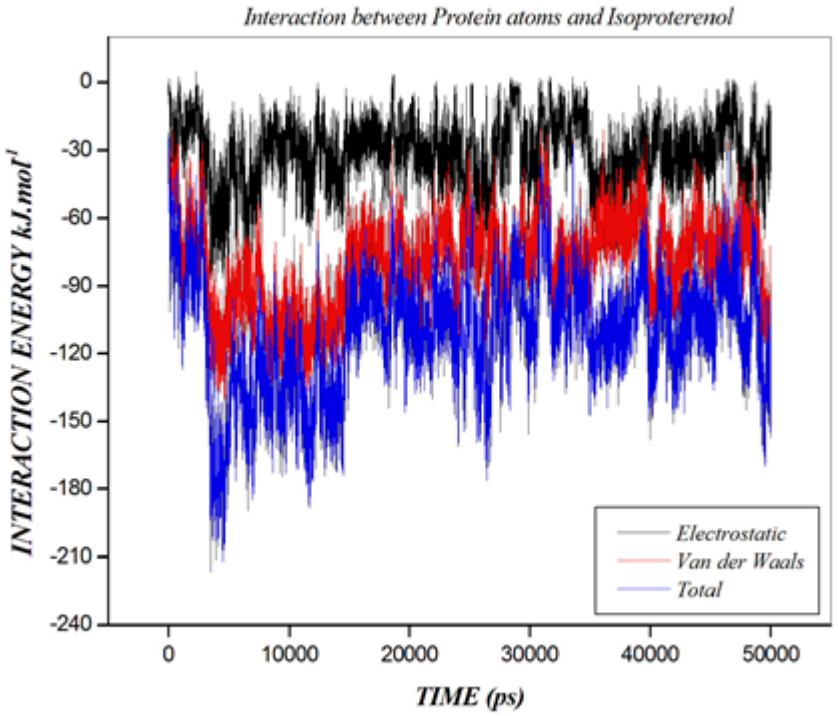
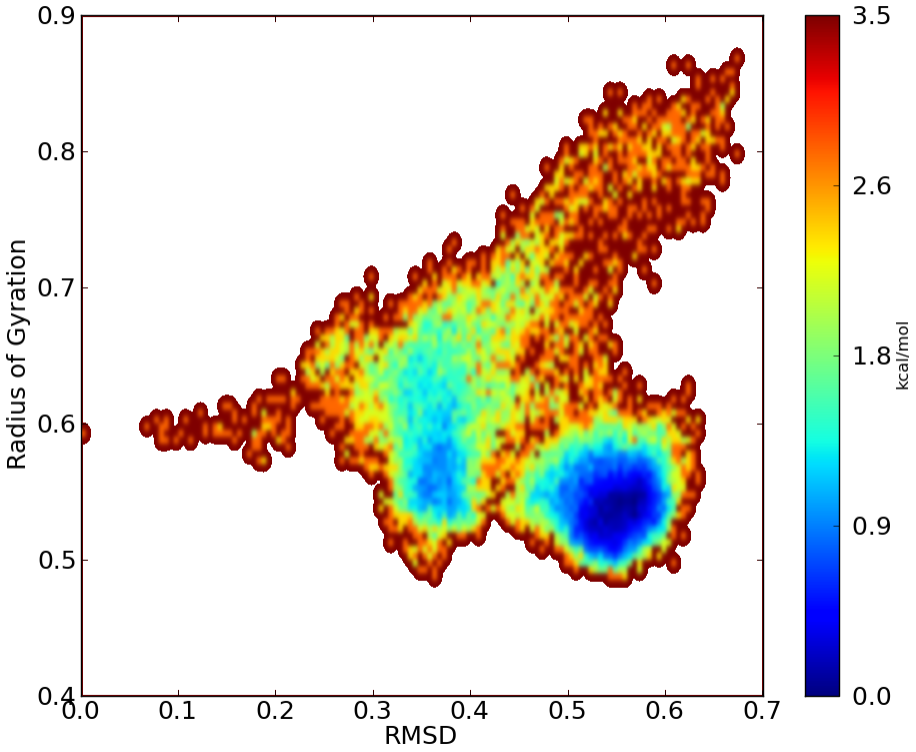
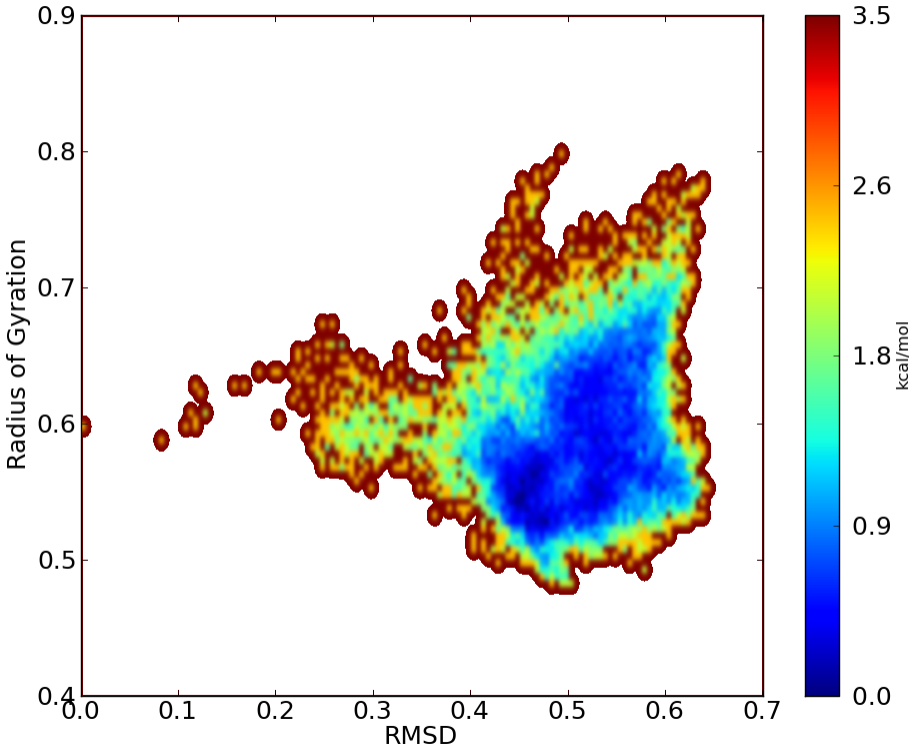

Interaction between Protein atoms and Isoproterenol
INTERACTION ENERGY kJ.mol-1
0
-30
-60
-90
-120
-150
-180
-210
-240
0
10000
20000
30000
40000
50000
TIME (ps)
Electrostatic
Van der Waals
Total

Fig. S6 Representing Interaction energy for mutated E-loops with 5-Fluorouridine [5UD], 4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline [MDTQ] and Isoproteranol [5FW]. a) D124V+5UD, b) D124V+MDTQ, c) D124V+5FW, d) D125H+5UD, e) D125H+MDTQ, f) D125H+5FW, g) S134N+5UD, h) S134N+MDTQ, i) S134N+5FW.

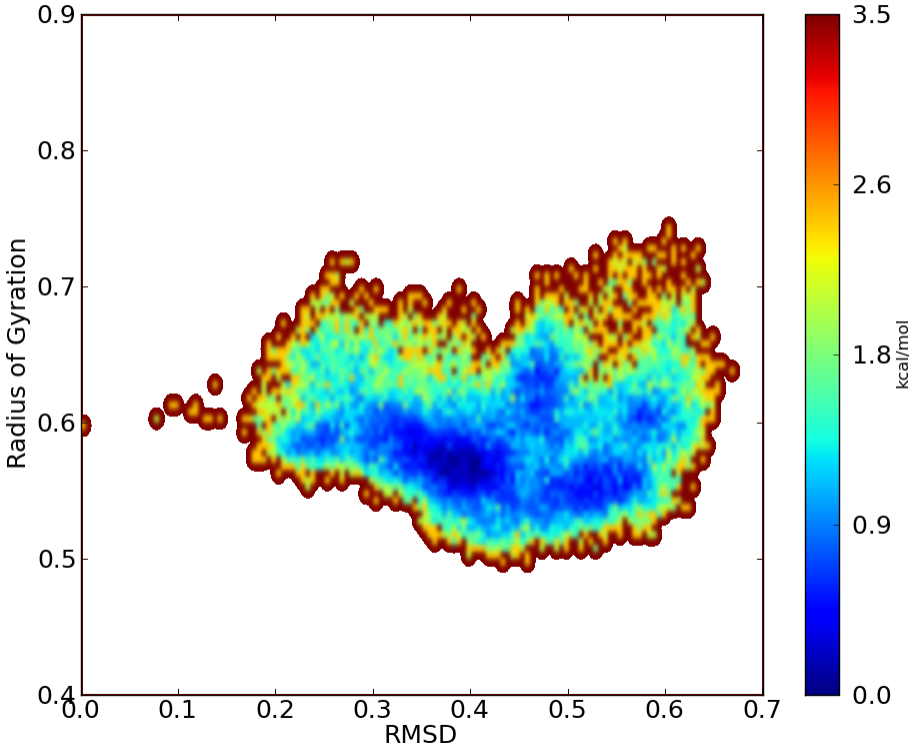
a)



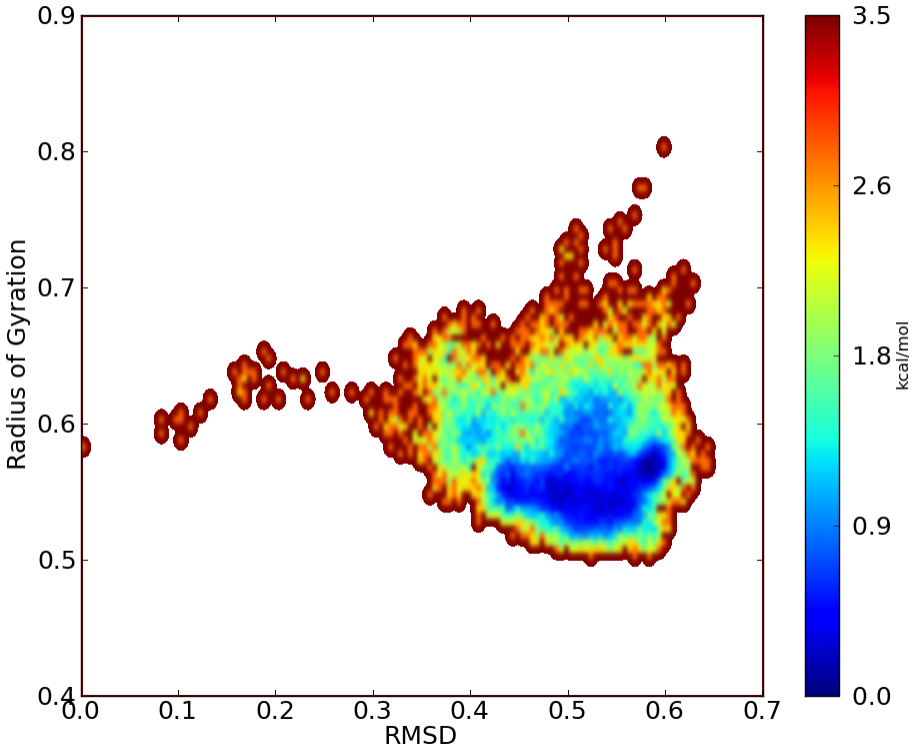
b)


0.9
0.8
0.7
0.6
0.5
0.4
Radius of Gyration
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

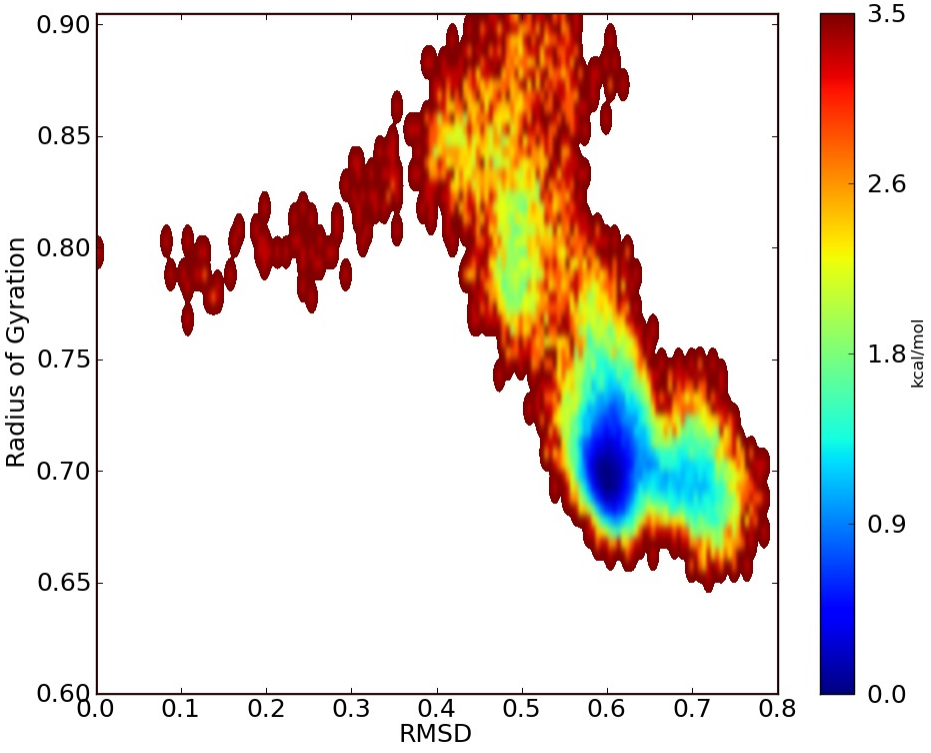
c)


0.9
0.8
0.7
0.6
0.5
0.4
Radius of Gyration
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

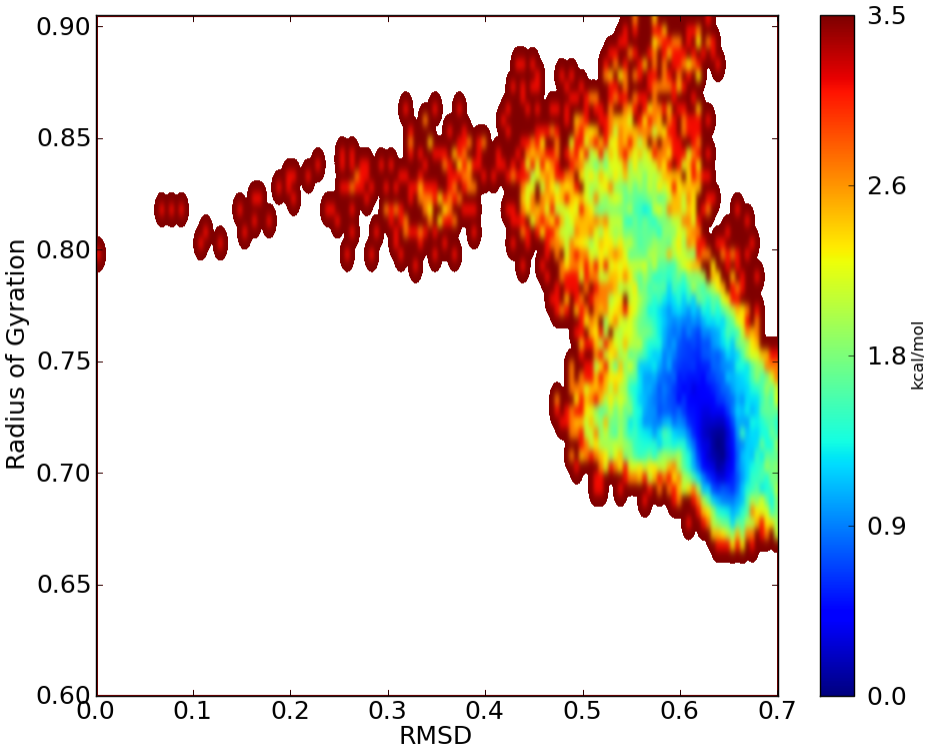
d)


Radius of Gyration
RMSD
kcal/mol
0.9
0.8
0.7
0.6
0.5
0.4
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3.5
2.6
1.8
0.9
0.0

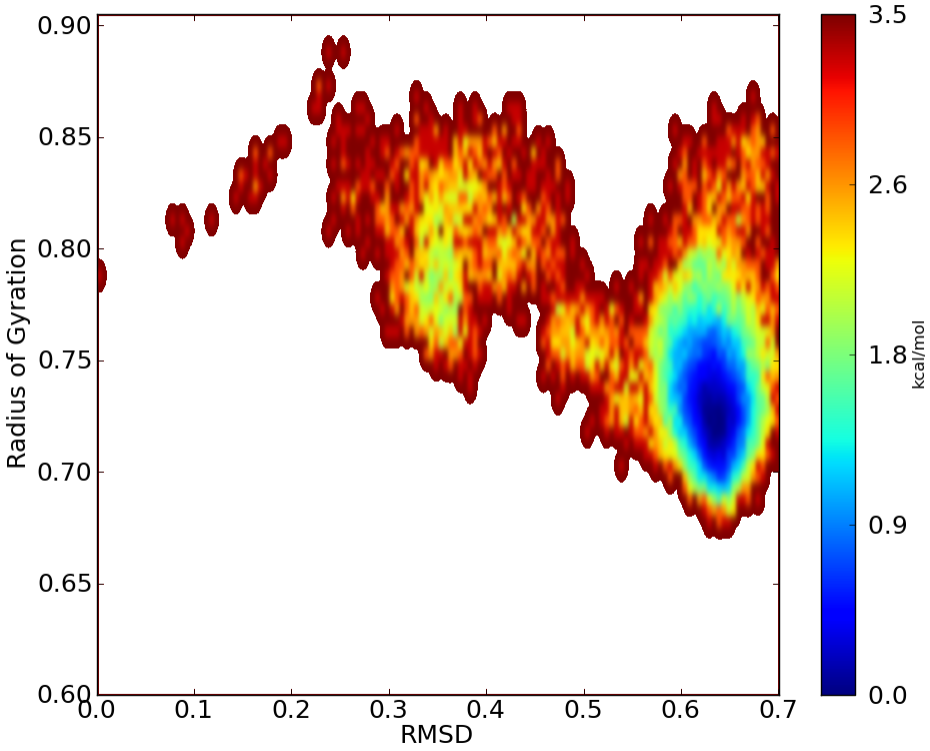
e)


Radius of Gyration
RMSD
kcal/mol
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
3.5
2.6
1.8
0.9
0.0

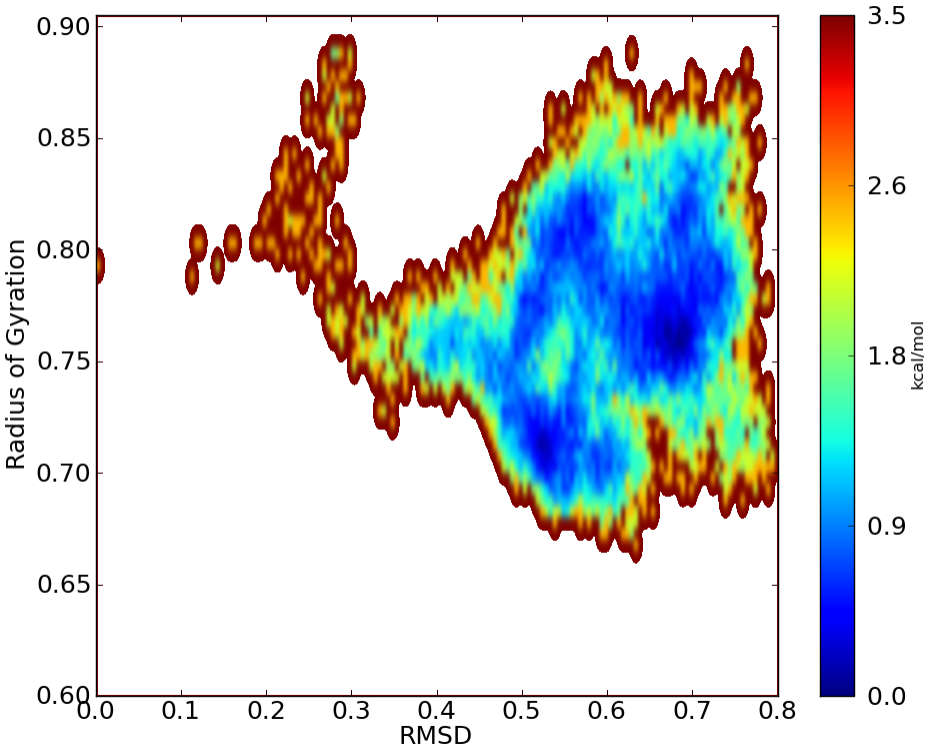
f)


Radius of Gyration
RMSD
kcal/mol
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3.5
2.6
1.8
0.9
0.0

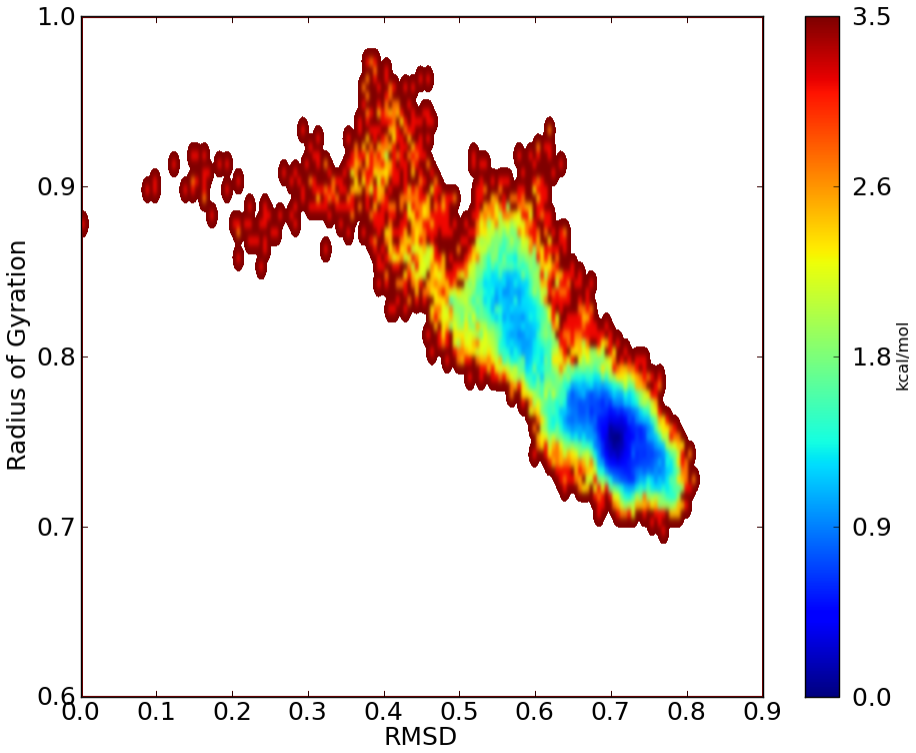
g)


Radius of Gyration
RMSD
kcal/mol
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3.5
2.6
1.8
0.9
0.0

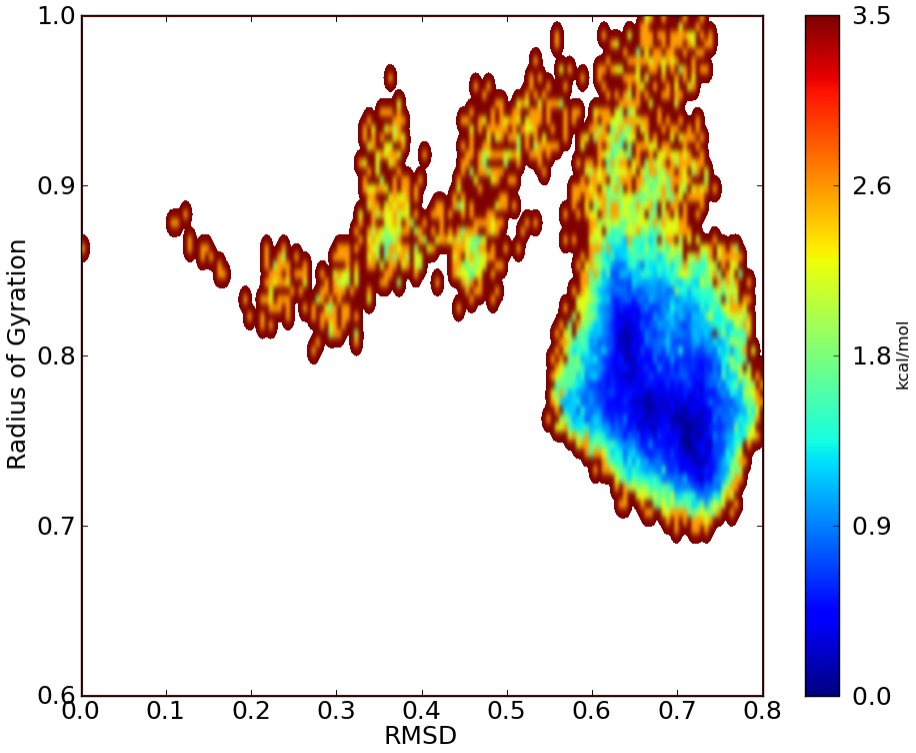
h)


0.90
0.85
0.80
0.75
0.70
0.65
0.60
Radius of Gyration
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

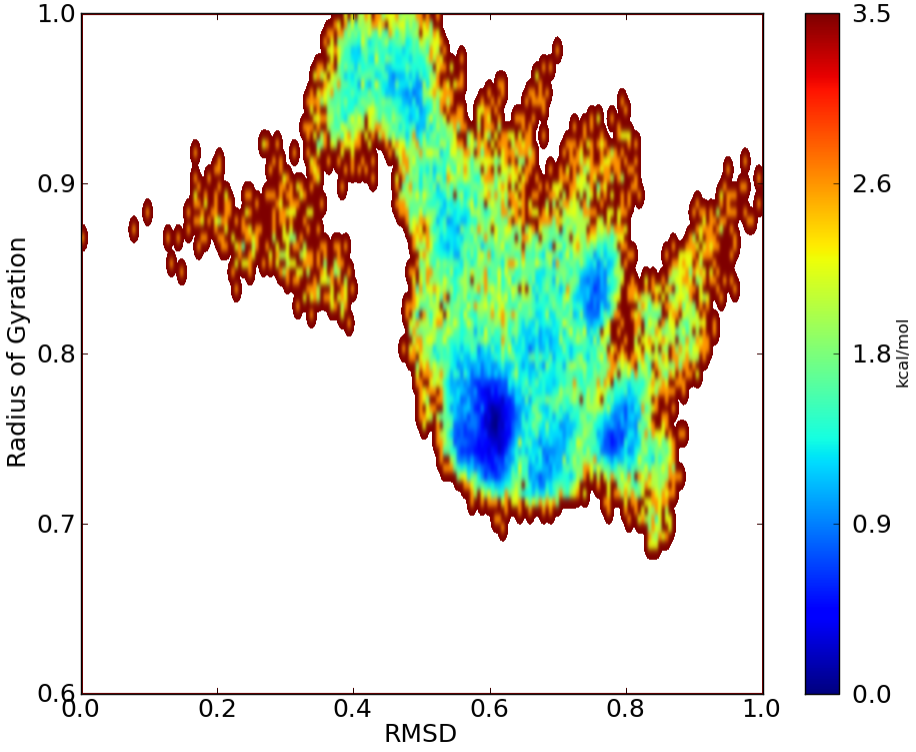
i)


1.0
0.9
0.8
0.7
0.6
Radius of Gyration
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

j)


1.0
0.9
0.8
0.7
0.6
Radius of Gyration
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

k)


1.0
0.9
0.8
0.7
0.6
Radius of Gyration
0.0
0.2
0.4
0.6
0.8
1.0
RMSD
3.5
2.6
1.8
0.9
0.0
kcal/mol

l)

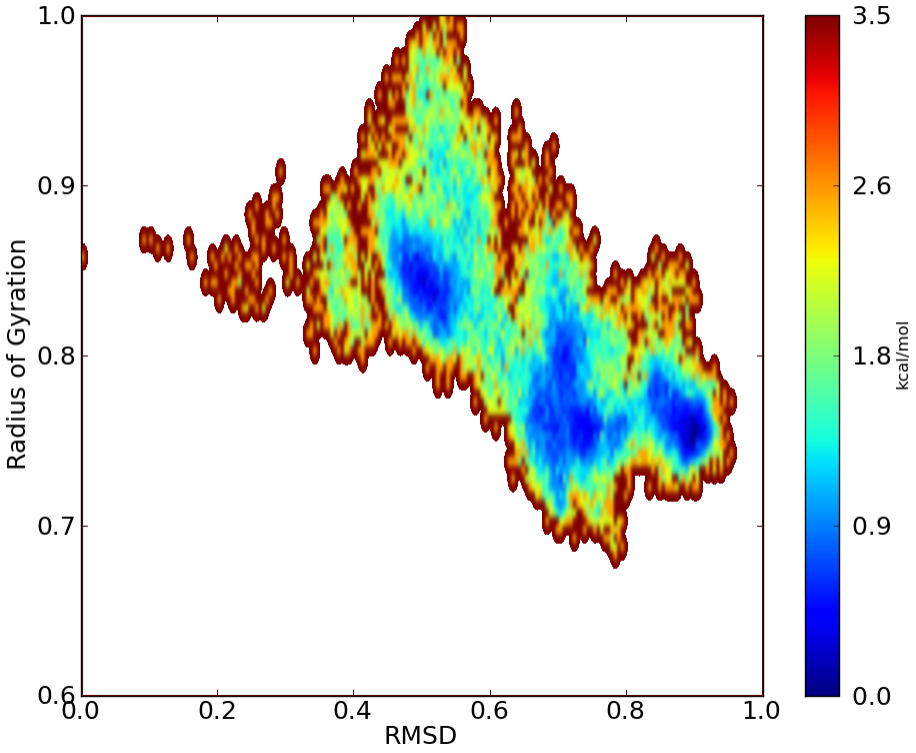


Fig. S7 Representing the Free energy landscape of three mutated E-loops interacting with 5-Fluorouridine [5UD], Isoproteranol [5FW], 4-(4-methyl-1, 4-diazepan-1-yl)-2-(trifluromethyl) quinazoline [MDTQ] and Uridine-5'-Monophosphate [U5P] involving RMSD and Rg for the trajectory of 50ns for. a) D124V+5UD, b) D124V+5FW, c) D124V+U5P, d) D124V+MDTQ, e) D125H+5UD, f) D125H+5FW, g) D125H+U5P, h) D125H+MDTQ, i) S134N+5UD, j) S134N+5FW, k) S134N+U5P, l) S134N+MDTQ.