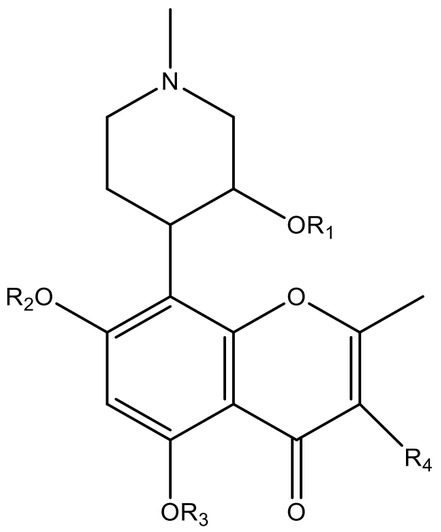
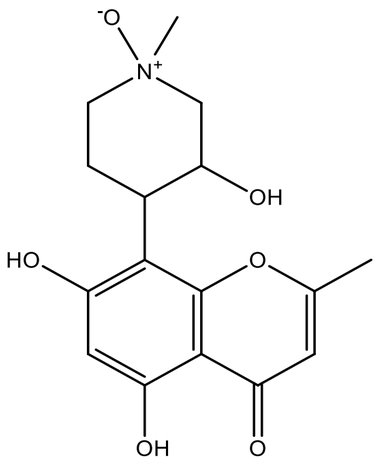
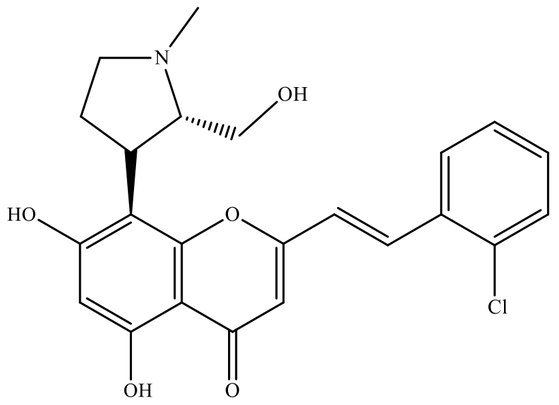


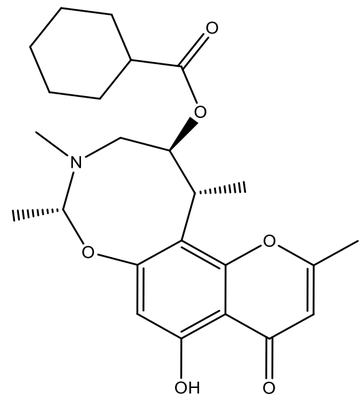
$R_{1,}R_2,R_3,R_4$=H : Rhitukine (**1**)
R_1,R_2,R_3=H; R_4= -Ome : Methoxylated rohitukine (**3**)
R_2,R_{33},R_4=H; R_1= -C=Ome : rohitukine acetate (**4**)
R_3,R_4=H; R_1,R_2 = -C=Ome : Rohitukine diacetate (**5**)
R_1,R_2,R_3= -C=OMe; R_4= H : Rohitukine triacetate (**6**)
R_2,R_3,R_4=H; R_1= -Glu : Rohitukine glycolated (**7**)
R_3,R_4=H; R_1,R_2 = -C=OPh(3-Br) : Rohitukine 3,7-di-p-bromobenzoate (**8**)
R_1,R_2,R_3,R_4=H; R_5=Ph(Cl) : flavopiridol (**9**)
R_1,R_2,R_3,R_4=H; R_5=-C=C-Ph(di-Cl) : IIM-290 (**10**)
R1= -COC(Me)=CH-Me : Chrotacumine B (**13**)
R1= -COPh(3,4,5-tri-OMe) : Chrotacumine C (**14**)
R1= -COPh(3,4-di-OMe) : Chrotacumine D (**15**)
R1= -CO-CH=CH-Ph : Chrotacumine F (**17**)
R1= -CO-CH=CH-Ph (3,4,5-tri-OMe) : Chrotacumin G (**18**)



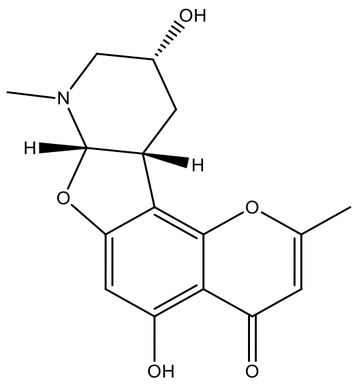
Rohitukine NO (**2**)



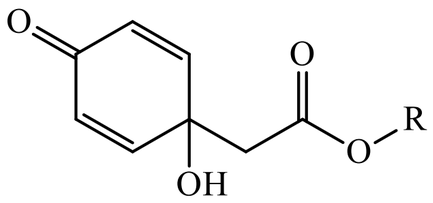
Riversiclib (P276) (**11**)



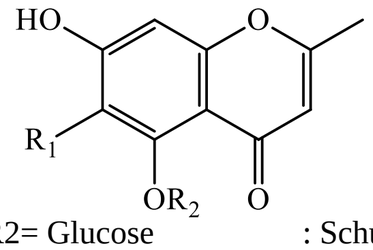
Chrotacumine A **(12**)



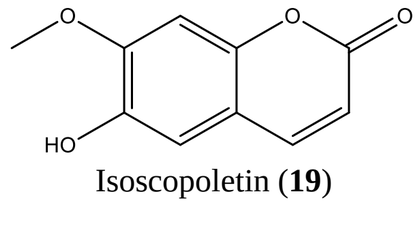
Chrotacumin E (**16**)



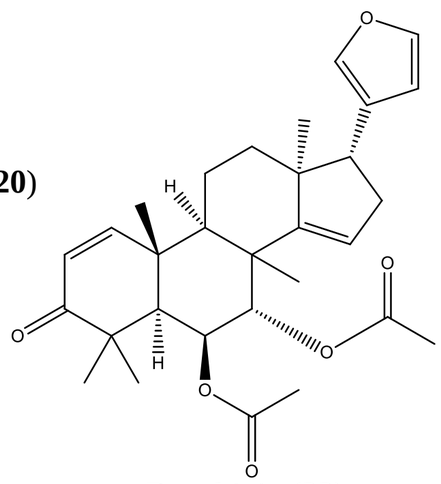
R=CMe : α-[4-4-Hydroxy-Cyclohexad-2,5-Diene-1-One (**20**)
R= Me : Jacaranone (**21**)



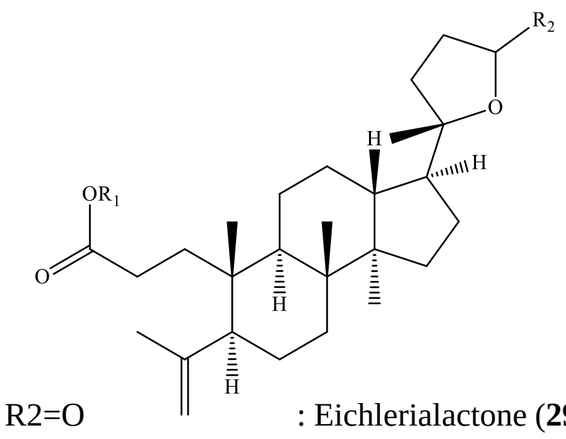
R1= H; R2= Glucose : Schumaniofioside A (**22**)
R1 = OC1CN(C)CCC1; R2=H : Dysoline (**24**)



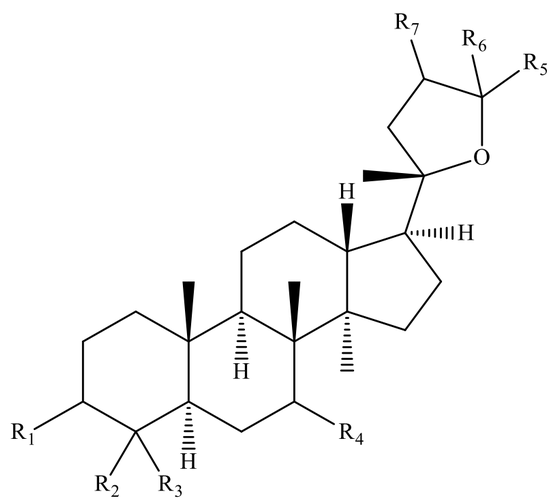
Isoscopoletin (**19**)



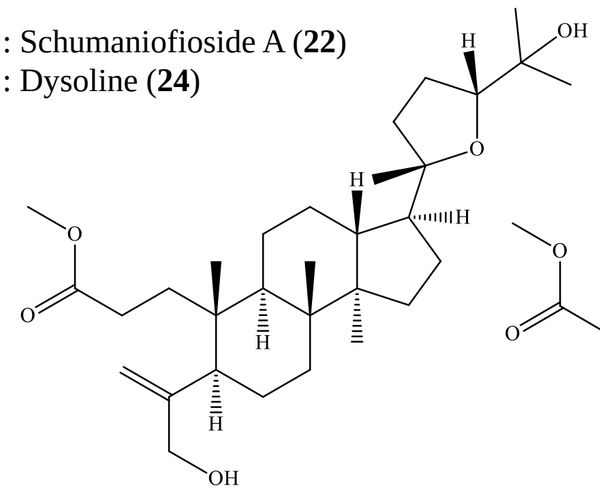
Dysobinin (**23**)



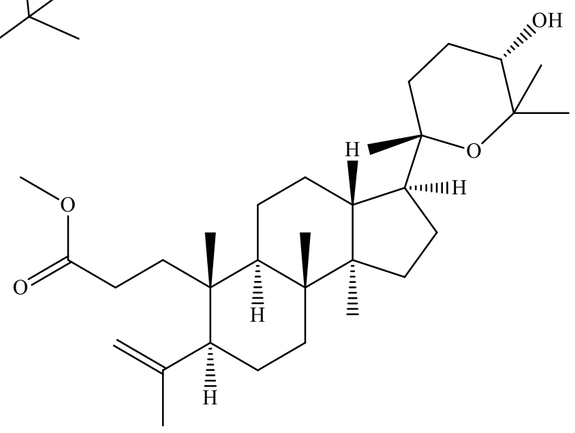
R1=H; R2=O : Eichlerialactone (**29**)
R1= -Me R2=O : Methyl Eichlerialactone (**30**)
R1= -CMe R2=O : Ethyl Eichlerialactone (**31**)
R1= -Me R2=C(OH)2Me : Methyl Eichlerianate (**32**)
R1=-CMe R2= -C(OH)2Me : Ethyl Shoreate (**33**)



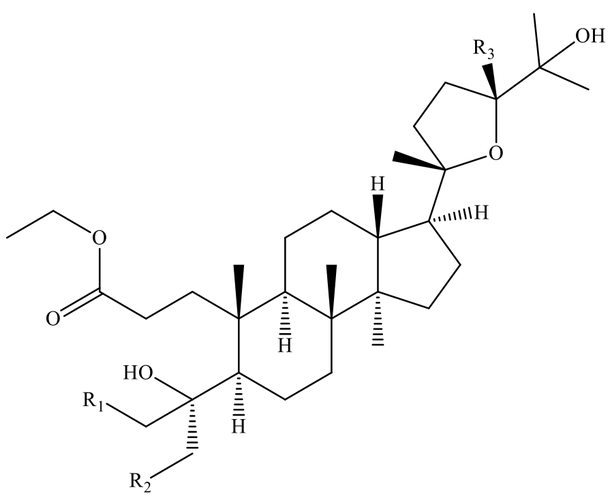
R_1,R_5= O; R_2,R_3=-Me; R_4=H; R_6,R_7=H : Cabralelactone (**25**)



methyl (20S,24S)-epoxy-25,29-dihydroxy-3,4-secodammar-4(28)-en-3-oate (**43)**



methyl (20S,25)-epoxy-24α-hydroxy-3,4-secodammar-4(28)-en-3-oate (**44)**



R_1= -OH; R_2,R_3=-Me; R_4=H; R_5=C(OH)2Me; R_6,R_7=H : Cabraleadiol (**26**)
R_1= -OH; R_2,R_3=-Me; R_4=H; R_5= O; R_6,R_7=H : Cabraleahydroxylactone (**27**)
R_1= -OH; R_2,R_3 =-Me; R_4=H; R_5=C(OH)2Me; R_6,R_7=H : 3-Epiocotillol (**28**)
R_1= αOH; R_2= -CH; R_3= -COH; R_5=C(OH)2Me; R_4,R_6,R_7=H : (20S,24S)-epoxydammarane-3α,25,28-triol (**35**)
R_1= O; R_2= -CMe; R_3=-COH; R_5=C(OH)2Me; R_4,R_6,R_7=H : (20S,24R)-epoxydammarane-3α,25,28-triol (**36**)
R_1= O; R_2= -COH; R_3 =-CMe; R_5=C(OH)2Me; R_4,R_6,R_7=H : (20S,24R)-Epoxy-25,28-Dihydroxydammar-3-One (**37**)
R_1= O; R_2,R_3= -CMe; R_4=*β*-OH; R_5=C(OH)2Me; R_6,R_7=H : (20S,24S)-Epoxy-25,28-Dihydroxydammar-3-One (**38**)
R_1= αOH; R_2=-Me; R_3 =-COH; R_5=C(OH)2Me; R_4,R_6,R_7=H : (20S,24S)-epoxy-25,29-dihydroxydammar-3-one (**39**)
R_1= O; R_2=-Me; R_3 =-COH; R_5=C(OH)2Me; R_4,R_6,R_7=H : (20S,24S)-epoxy-7β,25-dihydroxydammar-3-one (**40**)
R_1= αOH; R_2,R_3=-Me; R_5=O; R_4,R_7=H : 3α-Hydroxy-25,26,27-Trinordammar-22(23)-En-24,20Alpha-Olide (**41**)
R_1,R_5= O; R_2,R_3=-Me; R_4=H; R_7=OH : 23α-Hydroxy-3-Oxo-25,26,27-Trinordammar-24,20-α-Olide (**42**)

R_1= H; R_2= -OH; R_3= wedge H : ethyl (4R,20S,24R)-epoxy-4,25,28-trihydroxy-3,4-secodammar-3-oate (**45**)
R_1= H; R_2= -OH; R_3= dash H : ethyl (4R,20S,24S)-epoxy-4,25,28-trihydroxy-3,4-secodammar-3-oate (**46**)
R_1= -OH; R_2= H; R_3= wedge H : ethyl (4S,20S,24S)-epoxy-4,25,29-trihydroxy-3,4-secodammar-3-oate (**47**)
R_1= -OH; R_2= H; R_3= dash H : ethyl (4S,20S,24R)-epoxy-4,25,29-trihydroxy-3,4-secodammar-3-oate (**48**)

Fig. 1. Metabolites of *D. binectariferum*

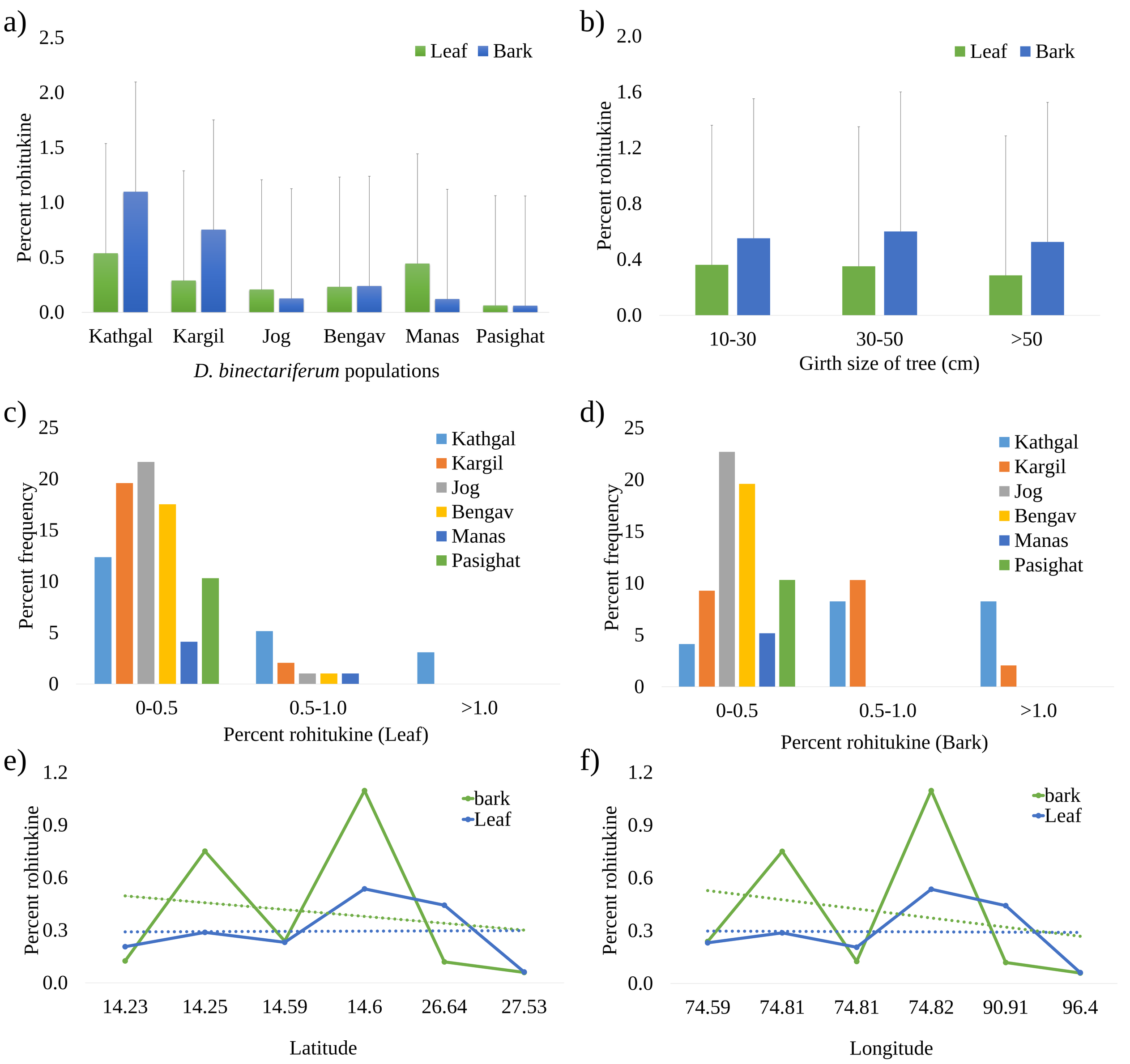
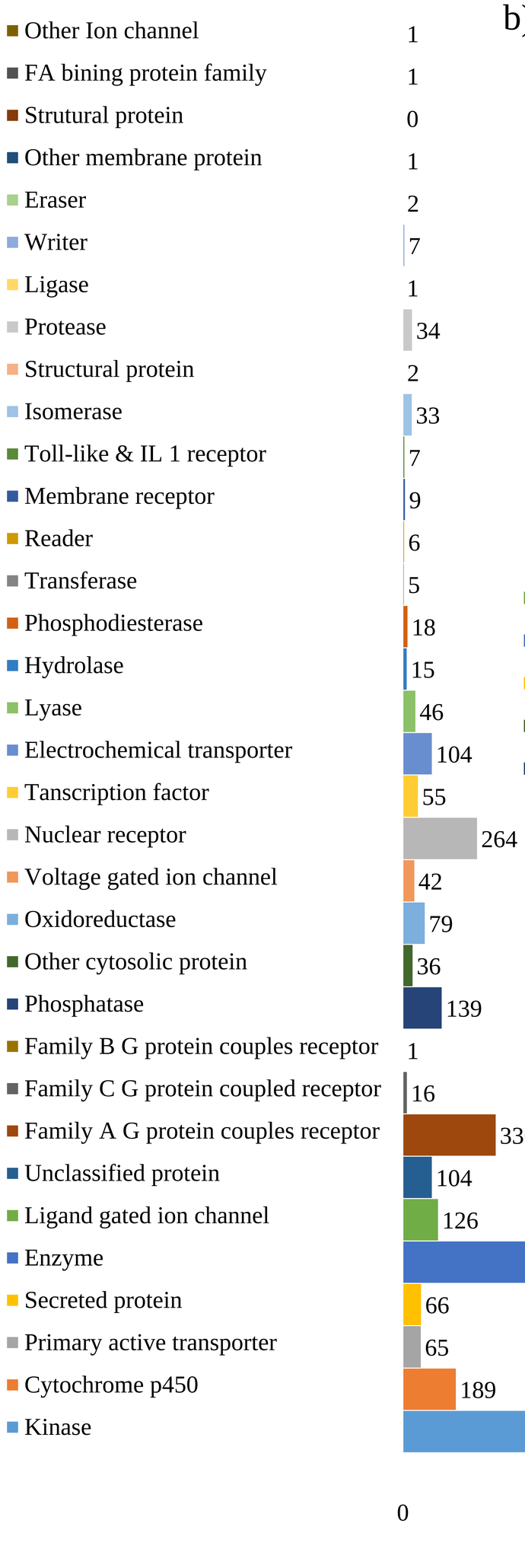
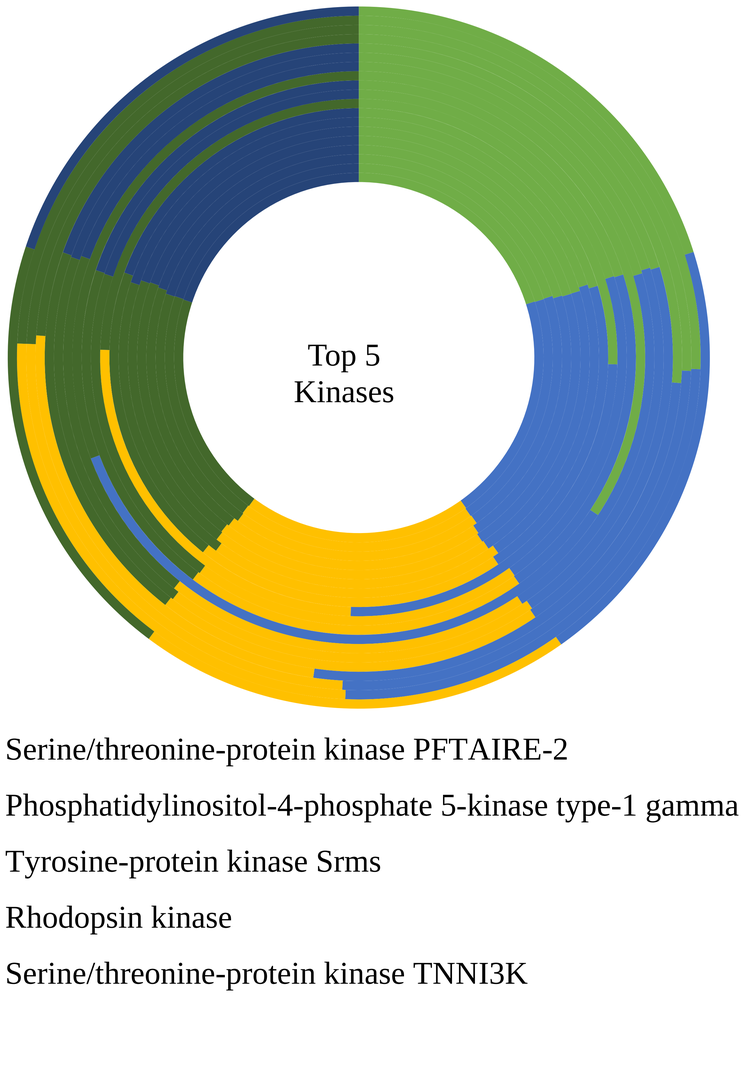


Fig. 2. Distribution of rohitukine in leaf and bark of *D. binectariferum* populations. a) Average rohitukine content, b) Average rohitukine content in different girth size, c) Percent frequency of rohitukine in leaf, d) Percent frequency of rohitukine in bark, e) Rohitukine distribution across Latitude, f) Rohitukine distribution across Longitude

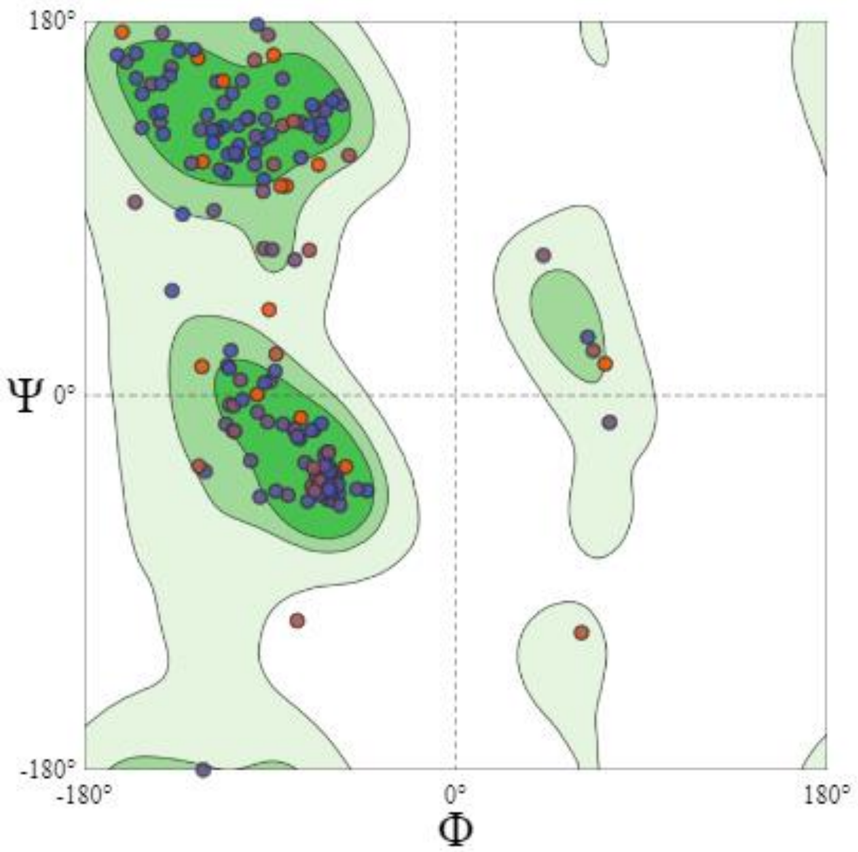
a)



b)



c)



Plot statistics (Q96Q40-6)

MolProbity Score	:	1.81
Clash Score	:	4.23
Ramachandran Favored	:	95.15%
Ramachandran Outliers	:	1.46%
Rotamer Outliers	:	2.23%
C-Beta Deviations	:	4
Bad Bonds	:	0 / 1690
Bad Angles	:	18 / 2296

d)

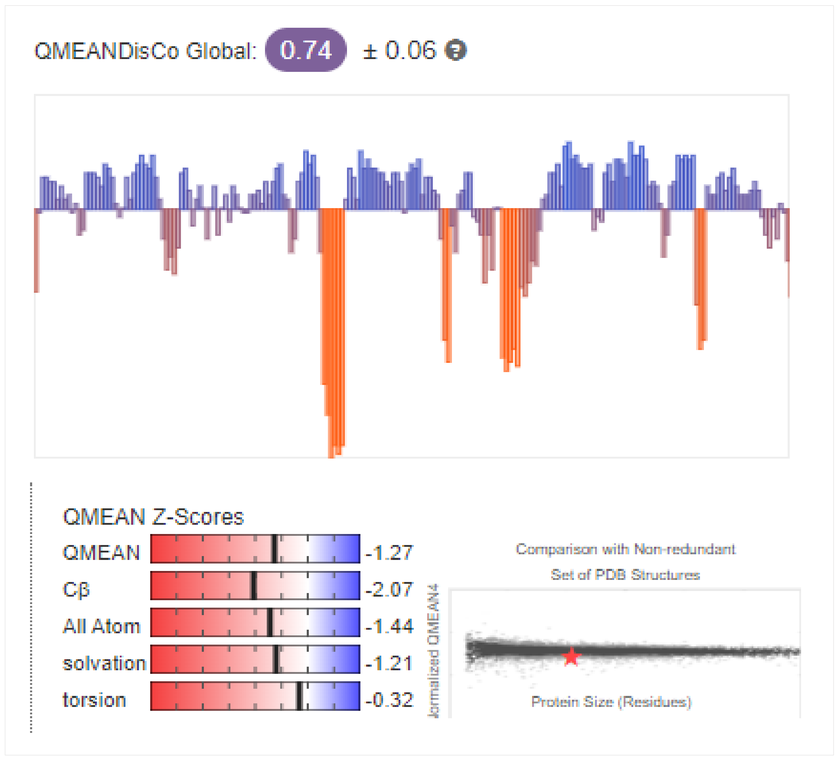


Fig. 3. a) Protein target prediction for *D. binectariferum* compounds, b) Top 5 kinases with high confidence level, c) Ramachandran plot of CDK15 homology model, and d) Quality estimate of the model

a)

comp26
comp28
comp35
comp36
comp40
comp39
comp37
comp38
comp48
comp47
comp45
comp46
comp44
comp43
comp32
comp33
comp34
comp27
comp41
comp25
comp42
comp29
comp30
comp31
comp23

Terpenoids

comp20
comp21
comp19
comp7
comp22
comp14
comp15
comp18
comp8

Chromone alkaloids

comp17
comp11
comp9
comp10

Control

comp1
comp2
comp3
comp24
comp16
comp12
comp4
comp13
comp5
comp6

Chromone alkaloids

b)

CDK1

CDK2

CDK4

CDK6

CDK9

CDK15

c)

-7.90	-7.2	-7.4	-7.1	-7.2	-8.3	48
-8.10	-8	-7.8	-8.2	-6.8	-8.9	47
-8.20	-7.7	-7.3	-8.3	-6.8	-8.6	46
-6.90	-7.3	-7.7	-8	-7.2	-8.8	45
-7.70	-7.2	-7.2	-7	-6.6	-8.8	44
-7.50	-7.4	-7.3	-8.2	-7	-9	43
-8.10	-9.4	-11.1	-8.8	-7.9	-10	42
-8.60	-8.5	-8.3	-10	-7.7	-10	41
-7.60	-8.5	-7.8	-8.8	-8.8	-10.2	40
-7.60	-8.8	-8.7	-8.2	-8.5	-10	39
-8.20	-9	-8.6	-8.2	-8.5	-9.7	38
-7.90	-7.9	-7.7	-8.9	-8.4	-9.8	37
-7.50	-8.5	-8.3	-8.3	-8	-10	36
-7.50	-8.5	-8.3	-8.3	-8	-10	35
-7.50	-8.2	-7.8	-8.1	-7.4	-9.1	34
-6.90	-7.6	-7.7	-8.1	-7.2	-8.9	33
-7.30	-7.4	-7.1	-8.2	-7.3	-9.1	32
-7.80	-7.6	-7.6	-8.8	-6.6	-9.3	31
-7.80	-8	-7.5	-8.8	-7.1	-9	30
-8.20	-9.5	-10	-8.6	-7.5	-9.3	29
-8.00	-8.6	-9	-8.7	-7.7	-10.5	28
-8.30	-8.3	-8.4	-8.5	-6.8	-9.8	27
-7.90	-8.2	-8.3	-8.7	-7.9	-10	26
-8.70	-8.7	-8.2	-9.6	-8.4	-9.8	25
-6.40	-6.8	-6.7	-7.6	-7.3	-7.9	24
-6.90	-7.7	-8	-8.7	-6.8	-8.9	23
-7.70	-8.6	-7.9	-6	-7	-8	22
-6.30	-6.3	-5.9	-5.6	-5.4	-5.4	21
-6.50	-6.5	-5.7	-5.8	-5.5	-5.5	20
-6.80	-7.3	-6.4	-6.6	-6.6	-6.8	19
-6.10	-7.4	-7.1	-8.6	-6.8	-8.6	18
-10.60	-7.5	-9.6	-8.3	-9	-8.7	17
-6.70	-7.8	-7.3	-7.9	-9	-8.9	16
-7.50	-8.7	-7.1	-8	-7.4	-8.4	15
-6.70	-8.4	-9.6	-7.8	-8.6	-8.4	14
-5.80	-7.8	-9.2	-7.2	-6.8	-8.2	13
-9.10	-8.4	-8.8	-9.2	-7.6	-10.3	12
-9.10	-7.5	-7.9	-8.6	-8	-8.2	11
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-8.40	-8.3	-7.6	-8.3	-6.8	-9.8	8
-5.80	-7.8	-7.8	-7.1	-7.6	-8	7
-5.40	-6.7	-6.5	-7.5	-6.3	-7.2	6
-6.6	-7.3	-6.5	-6.6	-7.2	-7.80	5
-7.40	-6.4	-7	-7.6	-6.1	-7.7	4
-7.60	-8.3	-7.4	-7.4	-6.2	-7.4	3
-3.10	-8.3	-7	-7.4	-8.4	-7.6	2
-7.30	-7.3	-7.8	-7.8	-8	-7.5	1

-60 -50 -40 -30 -20 -10 0

Kcal/mol

CDK1 CDK2 CDK4
CDK6 CDK9 CDK15

Fig. 4. Molecular docking of *D. binectariferum* compounds with CDKs. a) Structural similarity of *D. binectariferum* compounds, b) Surface structure of CDK proteins (CDK1, 2, 4, 6, 9 and 15), c) Binding energy (Kcal/mol) of *D. binectariferum* compounds docked with CDKs

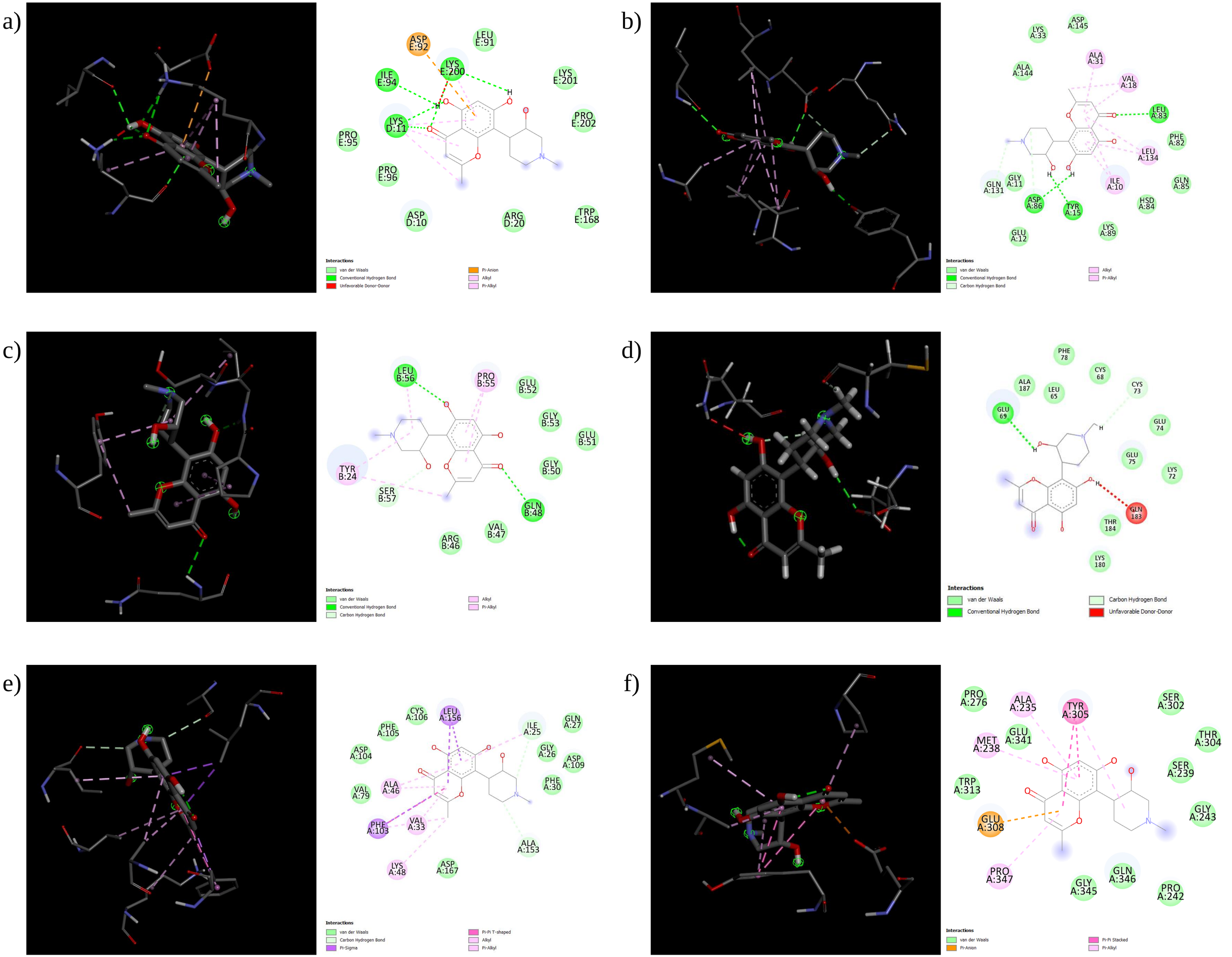


Fig. 5. 2D and 3D interactions of rohitukine docked with CDKs

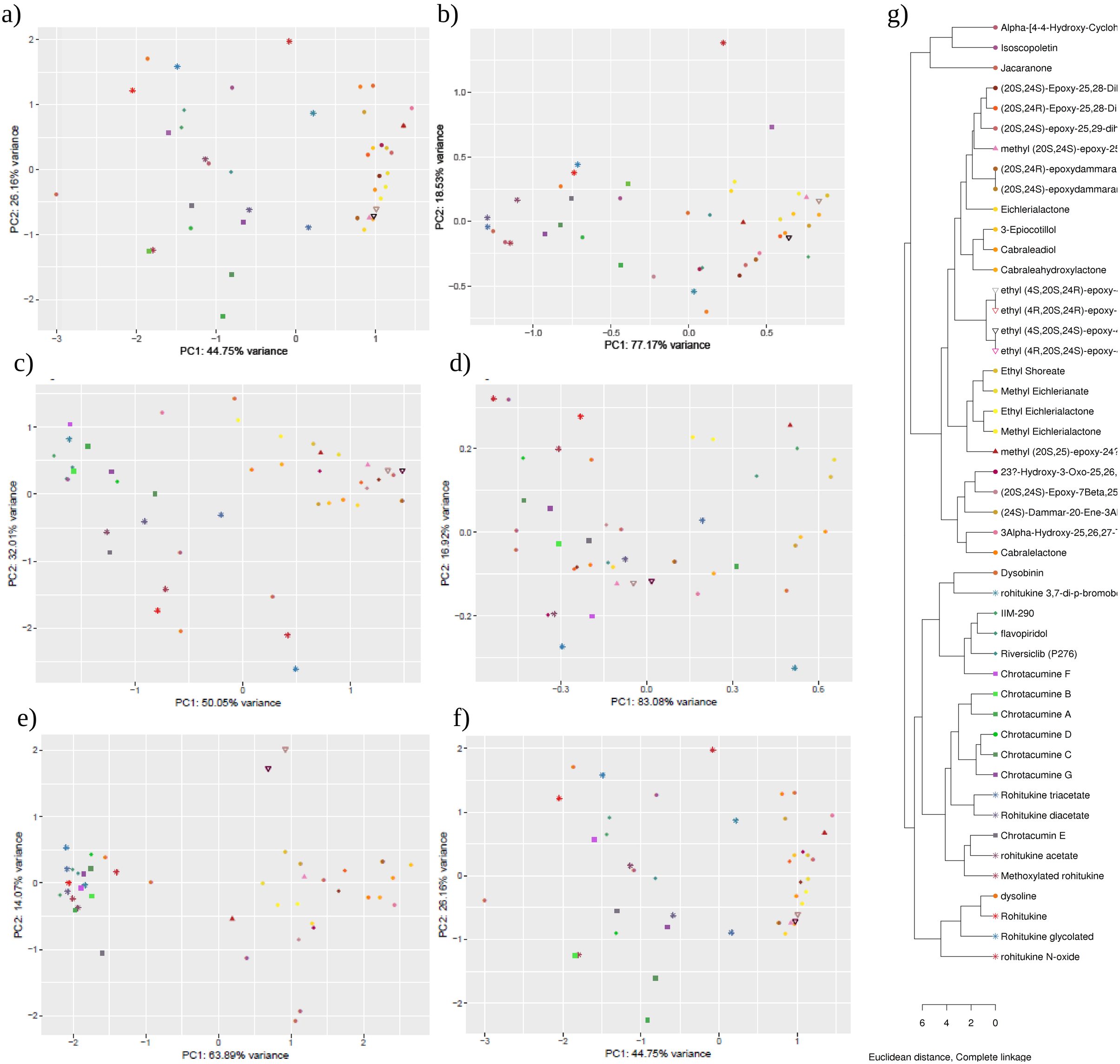
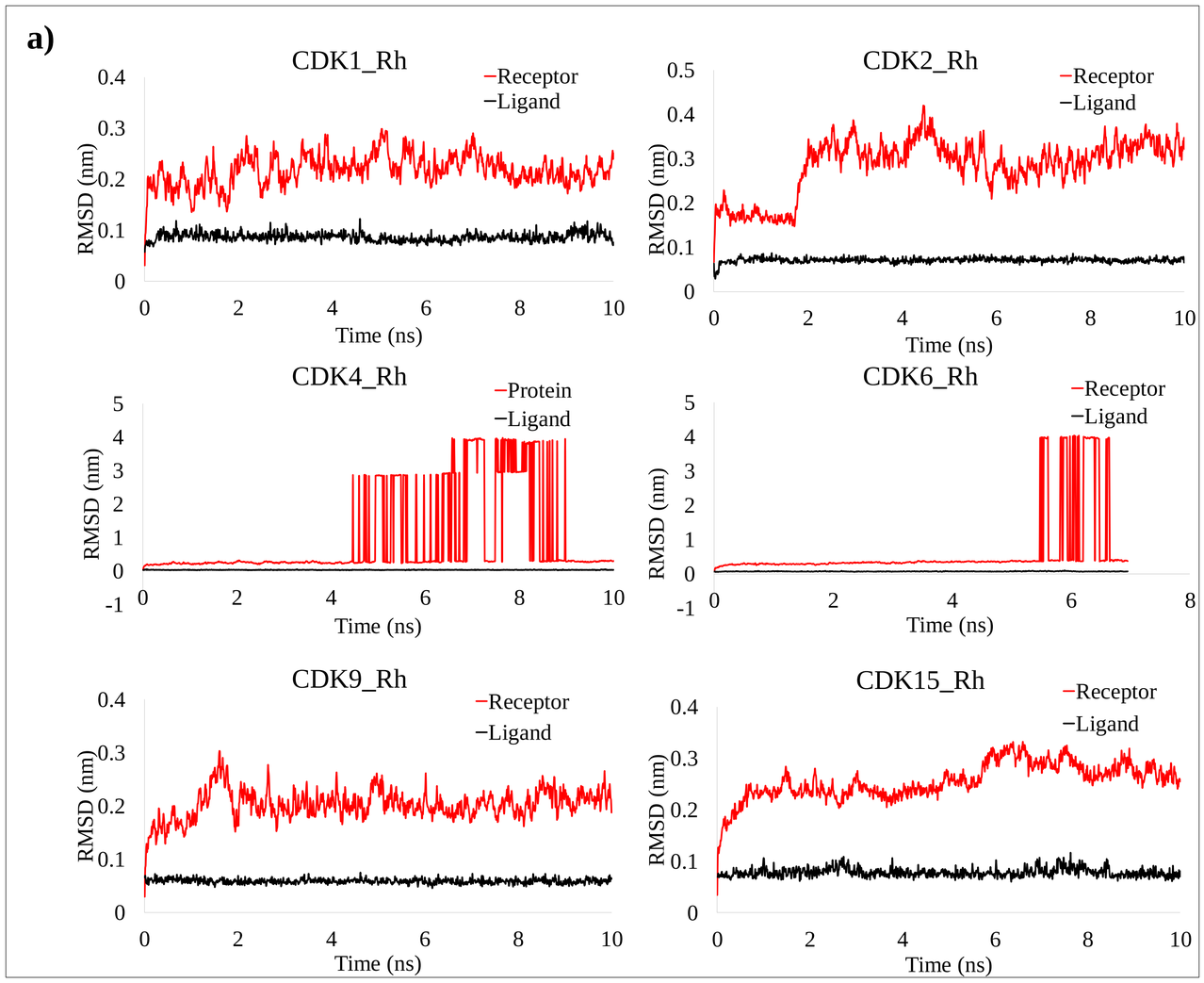
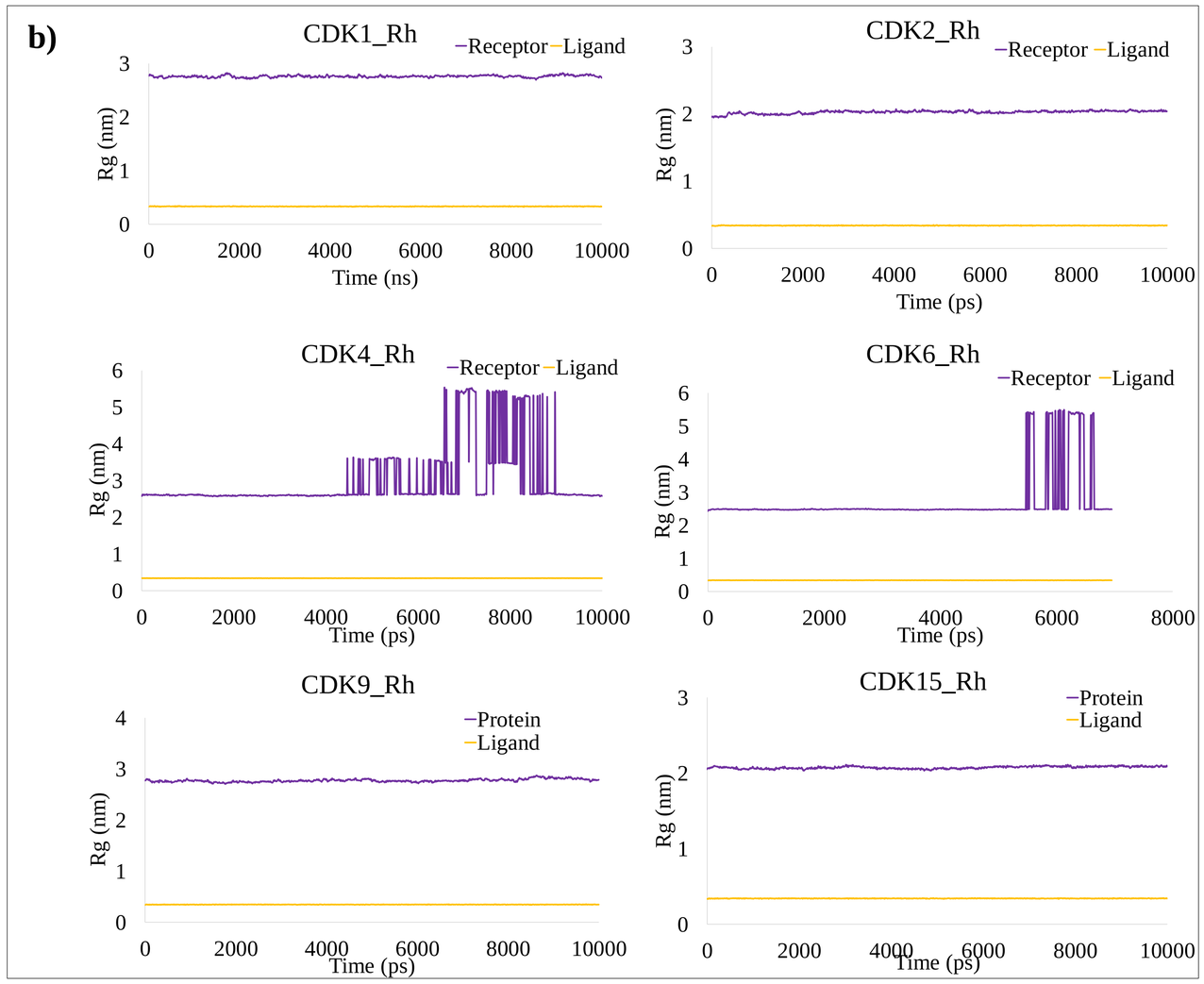
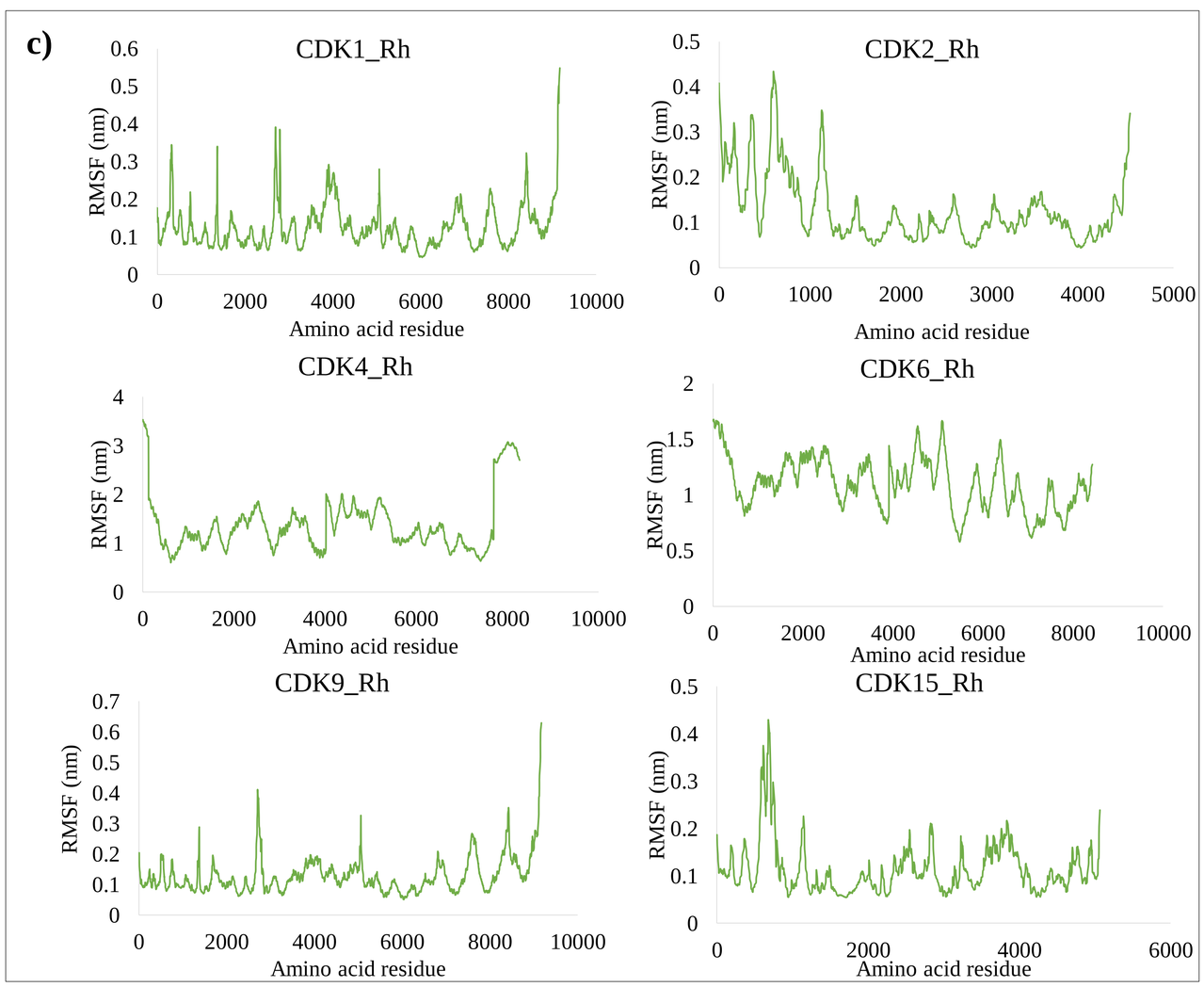


Fig. 6. *Insilico* ADMET analysis a) Absorption b) Distribution c) Metabolism d) Excretion e) Toxicity f) ADMET and g) Cluster (ADMET)







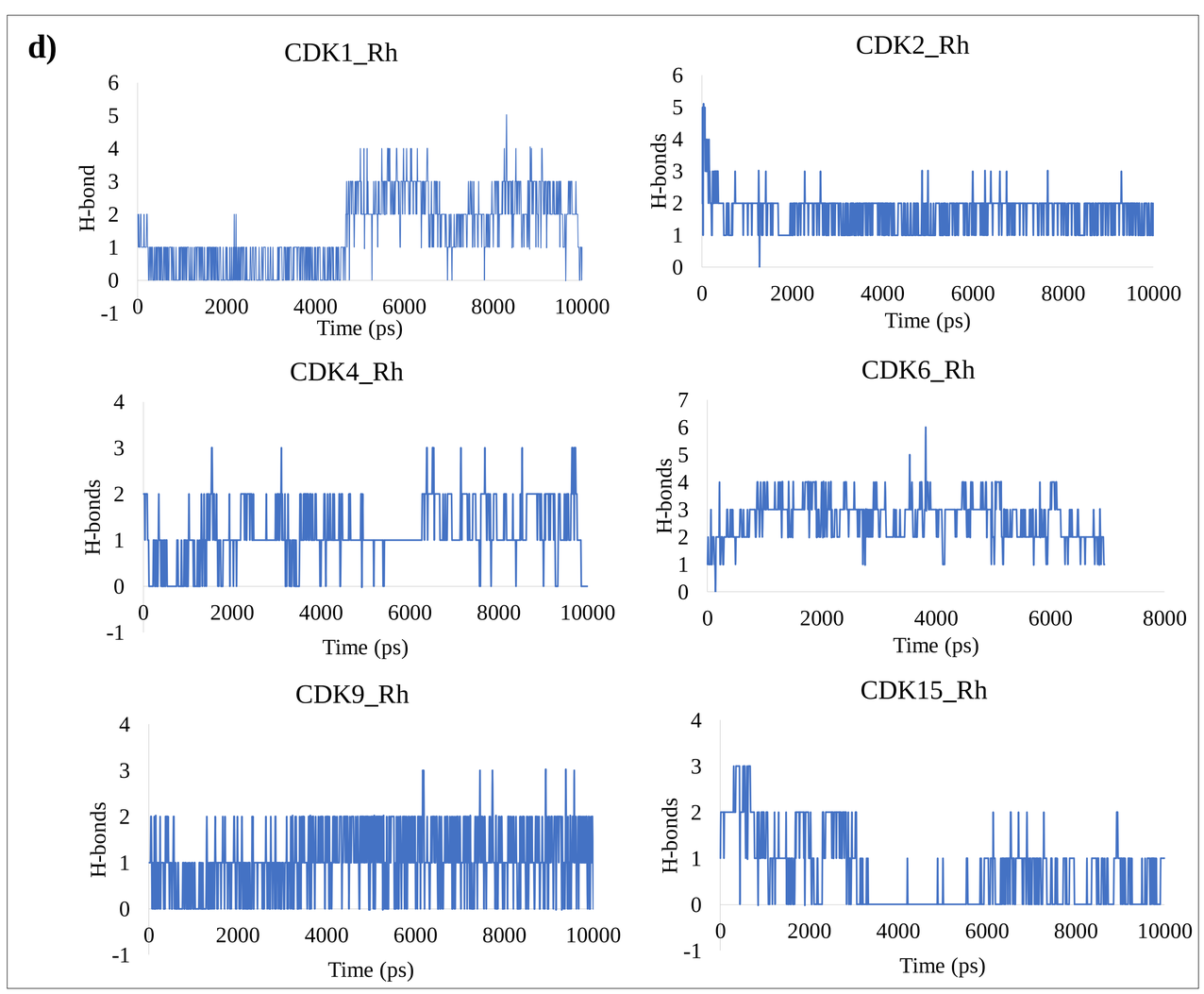


Fig. 7. MD simulation of rohitukine docked with CDKs a) RMSD, b) Radius of gyration (Rg), c) RMSF, and d) H-bonds interactions