Supplementary Information

Supplementary Table S1. Residue variability of WT HR1 domain of SARS-CoV-2.

Residue	Variability
N914	K, N, A, D, T, Q, S
Y917	N, I, V, Y, T, Q, L, M, S, F
E918	R, Q, D, E, N, K
L922	T, L, Q, E, M, K, I
N925	D, A, K, N, E, Q, T, S
S929	S, E, Q, T, H, R, A, D, K, N
I931	I, V, T, L, P, M, F
G932	Q, M, S, K, A, D, R, H, T, E, L, N, V, Y, G
K933	Q, E, T, F, S, R, D, A, K, N, G, Y, H
D936	T, Q, E, M, S, F, N, K, R, A, D, V, H, G
S939	G, H, R, D, A, N, K, M, S, L, W, E, Q, T
S943	E, L, T, G, V, N, I, M, S, Q, H, D, A, R, K
G946	E, Q, T, S, A, D, R, K, N, G, V, H
D950	G, N, K, D, A, S, T, E, L
Q954	S, E, Q, L, T, G, H, D, A, R, K, N
Q957	T, E, L, N, I, V, Y, G, Q, M, S, K, D, A, H
N960	H, I, N, A, S, T, E, Q,
T961	H, V, Y, N, K, A, D, S, T, Q, E
K964	V, G, N, T, E, P, L, H, K, D, A, R, M, S, Q
S975	A, T, N, Y, H, S
N978	A, D, R, N, K, G, V, E, Q, L, T, S
S982	M, S, Q, H, K, D, A, R, T, E, L, V, Y, G, N
K986	L, E, Q, T, S, M, R, D, A, K, I, N, G, V
V987	L, I, G, V
E988	N, D, A, G, T, E, Q, S

Supplementary Table S2. Sequences selected by CONSURF for conservation analysis of SARS-CoV-2 HR1 domain	
Sequence	**>Input_pdb_SEQRES_A**
1	GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVESG GR----------GGPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY GG
2	>UniRef90_UPI0000518FE8_10_148 GVTQNVLYENQKQIANQF----------NKAISQIQESLTTTSTALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEAE VQ--IDRLITGGRGGSDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY --
3	>UniRef90_UPI0015516385_2_114 AQALNTLVKQLLVPRGSGGSGGSGGLEVLFQGPDVDLGDISGINASVVNIQKEIDRLNEV AK----------NLNESLIDLQELH-- --
4	>UniRef90_A0A6M4NHL5_910_989 GVTQNVLYEXXKLIANQF----------NSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISXVLNDXLSRLDKVEA- ---------- --

5	>UniRef90_A0A7D7XM23_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISXVLNXXXSRLDKVEA- ---------- --
6	>UniRef90_A0A6M8F9N1_745_824 GVTQNVLYENQKLIAXQX----------NSAIXKIQXSLSXTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
7	>UniRef90_A0A7D5SIA1_848_927 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLQDVVNQN AQALNXXXXXXXSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
8	>UniRef90_A0A6N1WNH7_910_989 GVTQXVLYENQKLIANQF----------NSAXXXXXDSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
9	>UniRef90_A0A3Q8AKM0_895_974 GVTQNVLYENQKQIANQF----------NNAISKIQDSLTTTSAALGKLQDVINQN AVALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
10	>UniRef90_E0XIZ3_896_975 GVTQNVLYENQKQIANQF----------NKAISQIQDSLSTTTTALGKLQDVINQN AIALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
11	>UniRef90_A0A7D4CY46_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTXXXXXXXXDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
12	>UniRef90_UPI0003F054F4_2_130 GITQQVLSENQKLIANKF----------NQALGAMQTGFTTTNEAFQKVQDAVNNN AQALSKLASELSNTFGA----------ISASIGDIIQRLDVLEQS GG--RGGSIP--------NFGSLTQINTTLLDLTYEMLSLQQVVKALNESYIDLKELG-- --
13	>UniRef90_A0A7D3YGL0_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASAXXXXXXXXXXX XXALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
14	>UniRef90_A0A6N1WBE0_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQXSXXXXXXXXXXXXXVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
15	>UniRef90_A0A7D4D1T0_910_989 GVTQNVLYEXXXXXXXXX----------XXXXXXXXXSLSSTASALGKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
16	>UniRef90_A0A7D5NRL0_852_931 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLQDVVNQN AQALNXXXXXXXXXGA----------ISXXXXXXXXXDKVEA-

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17	>UniRef90_UPI0003AFF9F2_2_122 AQALSKLASELSNTFGA----------ISASIGDILVPRGSGGSG GSGGLEVLFQ----------GPLTQINTTLLDLTYEMLSLQQVVKALNESYIDLKELL-- --
18	>UniRef90_UPI000BBD49D7_265_361 GVTMNVLSENQKMIASAF----------NNALGAIQDGFDATNSALGKIQSVVNAN AEALNNLLNQLSNRFGA----------ISASLQEILTRLEAVEAK AQ--IDRLIN----------GRLTALNA---------- --
19	>UniRef90_A0A6N0VNQ5_870_949 GVTQNVLYENQKLIANQF----------NSAIGKIXXXXXXXXXXXXXXXXXXNQX XXXXNXXVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
20	>UniRef90_V5N6L2_552_650 GVTMNVLSENQKMIASSF----------NNAIGAIQEGFDATNSALAKIQSVVNAN AEALNNLLNQLSNRFGA----------ISASLQEILSRLDALEAQ AQ--IDRLIN----------GRLTALNAYV---------- --
21	>UniRef90_F1BYL9_934_1013 AAALNTLVTQLGNNFGA----------ISSAINDITQRLDKLEAA ---------- --
22	>UniRef90_A0A088DJY6_954_1033 AQALNNLVAQLTNNFGA----------ISSAINDITQRLDKLEAD ---------- --
23	>UniRef90_A0A2H4MXF2_983_1082 GVTMDVLTQNQKMIANAF----------NNALGAIQDGFDATNSALAKIQSVVNAN AEALNNLLLQLTNRFGA----------ISSSLQEILSRLDSLEAQ VQ--IDRLIN----------GRLTALNAYVA---------- --
24	>UniRef90_A0A2H4MZ26_1011_1109 GVTMDVLSQNQKMIANAF----------NNALGAIQDGFDATNSALAKIQAVVNAN AEALNNLLGQLSNRFGA----------ISSSLQEILSRLDALEAQ VQ--IDRLIN----------GRLTALNAYV---------- --
25	>UniRef90_A0A2H4MXV6_1000_1082 GVTMDVLSENQKMIANAF----------NNALGAIQDGFDATNSALVKIQAVVNAN AEALNNLLQQLSNRFGA----------ISASLQEILSRLDTLEAQ VQ---------- --
26	>UniRef90_A0A096XNG8_988_1070 GVTMDVLSENQKLIANAF----------NNALGAIQNGFDATNSALAKIQNVVNAN AEALNNLLLQLSNRFGA----------ISASLQEILSRLDALEAQ VQ---------- --
27	>UniRef90_A0A6M8F741_910_989 GVTQNVLYENQXXXXXXX----------XXXXXXXXXXXXXXXXXXXKLQDVVNQN AQALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
28	>UniRef90_A0A6G9ZXM6_910_989 GVTQNVLYENQKLIANQF----------NXXXXXXXXXXXXXXXXXXXXXXXNQX XXALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA-

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29	>UniRef90_A0A1B3Q5W5_924_1005 GVTTNVLMENQKLIANAF----------NNALTGIQKGFDATNMALAKMQSVINQH AQQLSTLVDQLGNSFGA----------ISSSINEIFSRLDELEAN A---------- --
30	>UniRef90_A0A096XNH1_1001_1099 GVTMNVLSENQKMIASAF----------NTALGAIQNGFDATNSVLAKIQSVVNEN VDALNNLLQQLSNRFGA----------ISASLQEILSRLDALEAQ AQ--IDRLIN----------GRLTALNAYV---------- --
31	>UniRef90_A0A0A7UZR7_997_1079 GVTMDVLNQNQKMIANAF----------NNALTAIQNGFDATNSALAKIQSVVNAN AEALNNLLQQLSNRFGA----------ISSSLQEILSRLDALEAQ VQ---------- --
32	>UniRef90_Q0ZME7_991_1073 GVTMDVLNKNQKLIANAF----------NKALLSIQNGFTATNSALAKIQSVVNAN AQALNSLLQQLFNKFGA----------ISSSLQEILSRLDNLEAQ VQ---------- --
33	>UniRef90_A0A411D588_459_555 GVTMDVLSQNQKLISNAF----------NNALDAIQEGFDATNSALVKIQSVVNAN AEALNNLLQQLSNRFGA----------ISASLQEILSRLDALEAQ AQ--IDRLIN----------GRLTALNA---------- --
34	>UniRef90_A0A5Q0TVR1_964_1044 GITQNVLMENQKLIANKF----------NQALGAMQTGFTTTNQAFQKVQDAVNAN AQALSKLASELSNTFGA----------ISASIGDILKRLDTLEQE ---------- --
35	>UniRef90_UPI001084956B_29_133 GNSLNHLTSQLRQNFQA----------ISSSIQAIYDRLDTIQSG GRG----------GSLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKELG-- --
36	>UniRef90_Q0Q4F2_981_1077 GITQQVLSENQKLIANKF----------NQALGAMQTGFTTSNLAFSKVQDAVNAN AQALSKLASELSNTFGA----------ISSSISDILARLDTVEQD AQ--IDRLIN----------GRLTSLNA---------- --
37	>UniRef90_A0A6M3YVS3_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLQDXXXXX XXXXXXXXXXXXXXXXX----------XXXXXXDILSRLDKVEA- ---------- --
38	>UniRef90_Q5MQD0_995_1076 GVTMDVLNKNQKLIATAF----------NNALLSIQNGFSATNSALAKIQSVVNSN AQALNSLLQQLFNKFGA----------ISSSLQEILSRLDALEAQ V---------- --
39	>UniRef90_A0A023Y9K3_951_1049 GITQQVLSENQKQIANKF----------NQALGAMQTGFTTTNLAFSKVQDAVNAN AQALSKLASELSNTFGA----------ISSSISDILKRLDAVEQE AQ--IDRLIN----------GRLTSLNAFV---------- --

40	>UniRef90_A3EXD0_981_1079 GITQQVLSENQKIIANKF----------NQALGAMQTGFTTTNLAFNKVQDAVNAN AMALSKLAAELSNTFGA----------ISSSISDILARLDTVEQE AQ--IDRLIN----------GRLTSLNAFV---------- --
41	>UniRef90_K9N5Q8_984_1067 GITQQVLSENQKLIANKF----------NQALGAMQTGFTTTNEAFHKVQDAVNNN AQALSKLASELSNTFGA----------ISASIGDIIQRLDVLEQD AQ--I---------- --
42	>UniRef90_A3EXH4_910_991 GVTTQVLVENQQLIANSF----------NKALVSIQQGFDATNEALSKMQSVINQH AQQLQTLVSQLGNSFGA----------ISSSINEIFSRLDGLEAN A---------- --
43	>UniRef90_F1DAZ1_898_980 GVTTNVLMENQKLIANAF----------NKALVSIQTGFEATNQALNKIQTVVNHN ALQLQALVQQLGNTFGA----------ISSSVNEIFSRLDQLEAN AE---------- --
44	>UniRef90_G5CJB9_1002_1085 GVSMDVLSQNQKLIANAF----------NNALHAIQQGFDATNSALVKIQAVVNAN AEALNNLLQQLSNRFGA----------ISASLQEILSRLDALEAE AQ--I---------- --
45	>UniRef90_E0ZN52_904_985 GVTTQVLVENQKLIANSF----------NNALTNIQKGFDATNEALSKMQLVINQH AQQLQTLVNQLGNSFGA----------ISASINEIFSRLDGLEAD A---------- --
46	>UniRef90_U5LNM4_965_1046 GITQNVLMKNQREIANKF----------NQALGAMQTGFTATNQAFQKVQDVVNAN AQALSKLASELANTFGA----------ISSSIGDILKRLDVLEQE V---------- --
47	>UniRef90_U5NJG5_975_1055 GITQQVLSENQKIIANKF----------NQALGAMQTGFTTTNEAFQKVQDAVNTN AQALAKLASELSNTFGA----------ISSSIGDIIQRLDVLEQE ---------- --
48	>UniRef90_A0A6M3U134_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTAXXXXXXXXXXXXX XXXXXXXXXXXXXXXXA----------ISSVLNDILSRLDKVEA- ---------- --
49	>UniRef90_A3EXG6_907_986 GVTTQVLVENQKLIASSF----------NNALVNIQKGFTETSIALSKMQDVINQH AAQLHTLVVQLGNSFGA----------ISSSINEIFSRLEGLAA- ---------- --
50	>UniRef90_A0A2Z4EVN5_907_988 GVTTNVLMENQQLIANAF----------NKALVSIQEGFTATNQALNKIQTVVNNN ALQLQVLVQQLGNTFGA----------ISASVNEIFSRLDLLEAN A---------- --
51	>UniRef90_A0A6H0C7Y4_910_989 GVTQNVLYXXXXXXXXQF----------NXXXXXXXXXXXXXXXXXXXXXDVVNQN AQALNTLVKQXXSNFGA----------ISSVLNDILSRLDKVEA-

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52	>UniRef90_A0A5B9Y142_909_990 GVTTQVLVQNQQLIANSF----------NNALTNIQKGFDATNLALSQMQSVINQH AQQLQTLVNQLGNSFGA----------ISSSINEIFSRLDGLEAN A---------- --
53	>UniRef90_A0A2R4KP86_985_1083 GITQQVLSENQKQIANKF----------NQAPGAMQTGFTTTNLAFSKVQEAVNAN AKALSKLASELSNTFGA----------ISSSISDILQRLDTVEQE AQ--IDRLIN----------GRLTSLNAFV---------- --
54	>UniRef90_L7UP84_967_1049 GITQQVLLENQKQIANKF----------NKALEAMQAGFDATNSALSKVQTAVNNN AMALNKLTQELSNTFGA----------ISASIADILKRLDTLEQD SQ---------- --
55	>UniRef90_A3EXJ0_907_988 GVTTQVLVDNQKLIASSF----------NNALNQIQKGFDATNSALSKIQAVINQH ATQLQTLVLQLGNTFGA----------ISSSINIIFSRLEGLEAD A---------- --
56	>UniRef90_A0A7D7Q1Q8_910_989 GVTQNVLYENQKLIANQF----------NSAIGKIQDSLSSTASALGKLXXVXXXX XXXXXXXXXXXXXXXXX----------XXXXXXXXLSRLDKVEA- ---------- --
57	>UniRef90_A0A2H4I7G0_776_880 GITQTVLQKNQEQIAKSF----------NRAMTHMQDGFRATSSALREIQDVVNKH SEVINQAMSSLNKNFGA----------ITSVIQDIYNRLDIIEAN AQ--VDRLIS----------GRLSSLSVLAAAKQAE---------- --
58	>UniRef90_A0A6N1WY71_910_989 GVTQNVLYENQKLIAXXX----------XXXXXXXXXXXXXXXXXXXXXXXXXQX XXALNTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
59	>UniRef90_P05135_784_880 GITQSLLFKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQIQDVVNKQ SSILTETMASLNKNFGA----------ISSVLQDIYQQLDSIQAD AQ--VDRIIT----------GRLSSLSV---------- --
60	>UniRef90_A0A7D3XV31_896_975 GVTQNVLYENQKLIANQF----------XXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXTLVKQLSSNFGA----------ISSVLNDILSRLDKVEA- ---------- --
61	>UniRef90_A4ZCS0_788_870 GITQSVLMKNQEKIAASF----------NKAIGHMQEGFKSTSLALQQIQDVVNKQ SAVLSEAMQSLNKNFGA----------ISSVIQDIYQQLDAIQAD AQ---------- --
62	>UniRef90_A0A6M3H873_789_884 GITQSVLLENQEKIAASF----------NKAIGHMQEGFRSTSLALQQIQDVVNKQ SAILTETMAALNKNFGA----------ISSVIQDIYQQLDAIQAD AQ--VDRLIT----------GRLSSLS---------- --

63	>UniRef90_A0A5B8KD01_803_897 GITQTLLLKNQELLANSF----------NNALQYMQQGFEATSQALQQIQDVVNQQ AAVLTEVMSSLNKNFGA----------ISSVIQDIYKQLDELSAN AQ--VDRLIT----------GRLSSL---------- --
64	>UniRef90_A4ZCP1_795_879 GITQTVLQKNQEQIAASF----------NKAMLHMQDGFRATSSALQQIQDVINKQ GSVLQDAMNALNKNFGA----------VSSVIQDIYSRLDTIEAN VQ--VN---------- --
65	>UniRef90_A0A3G6IPR3_787_891 GITQTILLKNQETLANSF----------NKAVRHMQEGFSATSQALVQIQDVINQQ SAILSEVMAALNKNFGA----------ISSVIQDIYKQLDALAAN AQ--VDRLIT----------GRLSALSVLASSKQSE---------- --
66	>UniRef90_D0R1F3_174_278 GITQSLLMKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQIQDVVNKQ SAILTETMNSLNKNFGA----------ITSFIQDIYAQLDAIQAD AQ--VDRLIT----------GRLSSLSVLASAKQSE---------- --
67	>UniRef90_A0A0A1G556_790_889 GITQSLLLKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQVQDVVNKQ SAILTETMAALNKNFGA----------ISSVLQDIYQHLDAIQAD AQ--ADRLIT----------GRLSSLSVLAA---------- --
68	>UniRef90_F4MIQ6_787_894 GITQTILLKNQEKIAASF----------NKAIGHMQEGFKSTSLALQQIQDVVNKQ SAILTETMASLNKNFGA----------ISSVIQEIYQQLDSIQAN AQ--VDRIIT----------GRLSSLSVLASSKQAEYLR---------- --
69	>UniRef90_A0A4D6FWE9_802_907 GITQTLLIDNQKMLAESF----------NNAVKYMQQGFEATSSALQQIQDVVNQQ GAVLQEVLNSLNKNFGA----------VSSVIQDIYKSLDELSAN AQ--MDRLIT----------GRLSALSVLASSKQADQ---------- --
70	>UniRef90_A0A346M347_790_872 GITQSLLMKNQEKIAASF----------NRAIGHMQEGFKSTSLALQQIQDVVNKQ SAILTETMASLNKNFGA----------ISSVLQDIYQQLDAIQAD AQ---------- --
71	>UniRef90_A4ZCU4_790_873 GITQTVLQKNQEQIAASF----------NKAMAHMQNGFRATSSALQQIQDVINKQ GSILQDAMNSLNKNFGA----------VSSIIQDIYSRLDAIEAN VQ--V---------- --
72	>UniRef90_G3FER7_786_891 GITQSLLLKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQVQDVVNKQ SAILTETMNSLNKNFGA----------ISSVIQDIYAQLDVIQAD AQ--VDRLIT----------GRLSSLSVLAFAKQSEY---------- --
73	>UniRef90_F6M7B5_786_869 GITQTVLQKNQEKIAASF----------NKAMAHMQDGFRATSLALQQIQDVLNRQ GSVLQDAMNSLNKNFGA----------ISSVIQDIYSRLDTLEAN TQ--V---------- --
74	>UniRef90_B8YDG3_238_333 GITQSLLMKNQEKIAASF----------NKAMGQMQEGFKSTSLAFQQIQDVVNKQ SAILTETMASLNKNFGA----------ISSVIQDIYQQLDSIQAD

	AQ--VDRLIT----------GRLSSLS---------- --
75	>UniRef90_A0A7D5AAR2_785_887 GITNSLLLKNQEKIAASF----------NKAIGHMQEGFKSTSLALQQIQDVVNKQ SSILTETMQSLNKNFGA----------ISSVIQDIYQQLDAIQAD AQ--VDRLIT----------GRLSSLSVLASAKQ---------- --
76	>UniRef90_Q6R4P5_790_872 GITQAVLLKNQEKIAASF----------NKAIGQMQEGFRSTSLALQQIQDVVNKQ SAILTETMASLNKNFGA----------ISSVIQDIYQQLDVIQAD AQ---------- --
77	>UniRef90_A0A2K8GIS7_784_867 GITQSLLMKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQIQDVVNKQ SAILTETMQSLNKNFGA----------ISSVIQEIYQQLDTIQAN AQ--V---------- --
78	>UniRef90_Q98WQ0_251_353 GITQTVLQKNQEKIAASF----------NKAMKHMQDGFSATSLALQQVQDVVNEQ GAILQQTMHSLNKNFGA----------ISHVIQDIYKQLDALEAN AQ--VDRIIT----------GRLSSLSVLASAKQ---------- --
79	>UniRef90_A0A5B8KH03_798_878 GITQTVILKNQELLANSF----------NNALLHMQEGFKATSNALXQIQDVVNQQ AAVXXEVMXSXNKNFGA----------ISSVIQDIYKQLDXLSAX ---------- --
80	>UniRef90_A0A6M8F2F7_788_884 GITNSLLLKNQEKIAASF----------NKAIGHMQEGFKSTSLALQQVQDVVNKQ SAILTETMAALNKNFGA----------ISSVIQDIYQQLDAIQAN AQ--VDRLIT----------GRLSSLSV---------- --
81	>UniRef90_A0A516UWD6_790_886 GITNSLLLKNQEKIAASF----------NKAIGHMQEGFKSTSLALQQVQDVVNKQ SAILSETMTALNKNFGA----------ISSVIQEIYQQLDAIQAD AQ--VDRIIT----------GRLSSLSV---------- --
82	>UniRef90_A0A1V0G3A1_783_880 GITQSLLLKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQVRDVVNKQ SAILAETMAALNKNFGA----------ITSVIQDIYQQLDAIQAD AQ--VDRLIT----------GRLSSLSVL---------- --
83	>UniRef90_G4RJ69_790_873 GITQSLLLKNQEKIAASF----------NKATGRMQEGFRSTSLALQQIQDVVNKQ SAILIETMASLNKNFGA----------ISSMIQEIYQQLDAIQAN AQ--V---------- --
84	>UniRef90_P11223_783_877 GITQSLLLKNQEKIAASF----------NKAIGHMQEGFRSTSLALQQIQDVVSKQ SAILTETMASLNKNFGA----------ISSVIQEIYQQFDAIQAN AQ--VDRLIT----------GRLSSL---------- --
85	>UniRef90_A0A515L594_780_873 GITQTVLQKNQEKIAASF----------NKAMKNVQEGFSATSLALKQVQDVLNEQ GGILQQTMHSLNKNFGA----------ITHVIQDIYKQLDALEAN AQ--VDRLIT----------GRLSS----------

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86	>UniRef90_Q7T833_790_873 GITQSLLLKNQEKIAASF----------NKAIVHMQEGFRSTSLALQQIQDVVNKQ SAIPAEALVALNKNFGA----------ISSVMQDIYQQLDAIQAD AQ--V---------- --
87	>UniRef90_A0A482K0W7_1001_1086 GEALAQLTKQLSSNFQA----------ISSSIEDIYLRLDKLAAD AQ--VDRLIS----------GRLAGLNAFVTQ---------- --
88	>UniRef90_B6VDY7_764_885 GEALSHLTAQLSNNFQA----------ISTSIQDIYNRLEEVEAN QQ--VDRLIT----------GRLSALNAYVTQLLNQMSQIRQ---------- --
89	>UniRef90_T1SQV2_1076_1185 GEALSQLTSQLQKNFQA----------ISSSIAEIYNRLEKVEAD AQ--VDRLIT----------GRLAALNAYV---------- --
90	>UniRef90_A0A0F6YS09_784_879 SEILNKLMAQLNVNFGA----------ISSSLSDIYSQLDELNAN AQ---------- --
91	>UniRef90_H9MGG6_40_148 GEALSQLTSQLQKNFQA----------ISSSIAEIYNKLEKVEAD AH--VDRLIT----------GRLAALNAY---------- --
92	>UniRef90_A0A6B9KDI7_980_1090 GSALNQLTVQLQNNFQA----------ISSSINDIYSRLDQITAD AQ--VDRLIT----------GRLSALNAFVAQ---------- --
93	>UniRef90_B8YDG2_238_321 GIPQSFLIKNQKKIAAPF----------NKPMGHPQVDYRSTSLALQQIQDVVNKQ SAILTETMPSLNKNLGA----------ISSVIQDIYQQLDAIQAN AQ--V---------- --
94	>UniRef90_A0A482JX42_991_1074 GQALSQLTRQLASNFQA----------ISSSIEDIYNRLDSLAAD AQ--VDRLIT----------GRLGALNAF---------- --
95	>UniRef90_Q09PH3_1074_1185 GEALSQLTSQLQKNFQA----------ISSSIAEIYNRLEKVEAD AH--VDRLIT----------GRLAALNAYVAQ---------- --
96	>UniRef90_F1DB20_970_1079 GQALHQLTKQLSMNFQA----------ISSSIEDIYMRLDALAAD AQ--VDRLIN----------GRLAALNAFV---------- --
97	>UniRef90_A0A1B0YTV9_86_177 GKALSELTKQLAQNFDA----------ISYSIEDIYNRLDKLAAD AQ--VDRLIT----------GRLAALNAFVTQQLTRFTE---------- --
98	>UniRef90_H9MGD2_41_134 GEALSQLTSQLQKNFQA----------ISSSIAEIYNRLERVEAD AQ---------- --

99	>UniRef90_B6VDX8_803_924 GSALNHLTLQLQNNFDA----------ISHSIADIYARLDEVEAN QQ--VDRLIT----------GRLAALNAYVTQVLTQISQLKAQ---------- --
100	>UniRef90_A0A0K2BM62_1088_1199 GNALSQLTQQLQNNFQA----------ISSSIAEIYNRLEKVEAD AQ--VDRLIT----------GRLAALNAYVAQ---------- --
101	>UniRef90_B1PHK2_990_1099 GQALHQLTKQLASNFQA----------ISASIEDIYNRLDGLAAD AN--VDRLIT----------GRLAALNAFVT---------- --
102	>UniRef90_A0A4Y5QS01_798_891 SDILNKLMAQLSVNFGA----------VSSSLNEIYLKLDQLSAD ---------- --
103	>UniRef90_A0A0N6W222_796_891 SDILNKLMVQLSVNFGA----------VSSSLNEIYLKLDQLNAD AQ---------- --
104	>UniRef90_A4ULL1_984_1095 GQALSQLTRQLASNFQA----------ISSSIQDIYNRLNGLEAD AQ--VDRLIT----------GRLAALNAFVTQ---------- --
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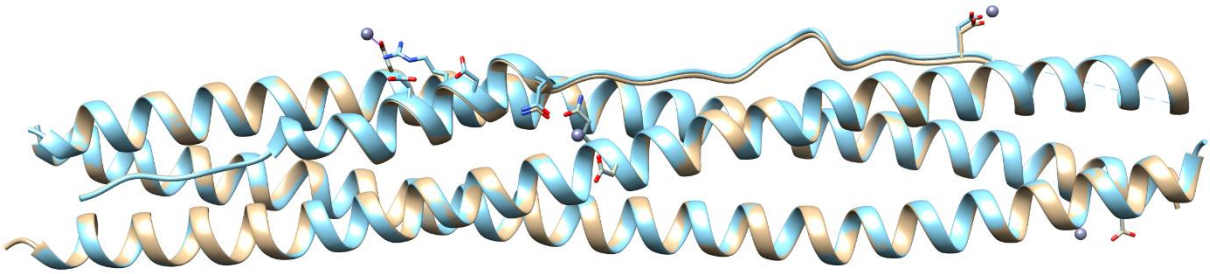
106	>UniRef90_K4JZ69_984_1073 GEALSQLTKQLASNFQA----------ISSSIEDIYNRLDMIAAD AQ--VDRLIT----------GRIGALNAFVTQ---------- --
107	>UniRef90_A0A0C5CJL1_1073_1183 GDALSQLTSQLQNNFQA----------ISSSIAEIYNRLEKVEAD AQ--VDRLIT----------GRLAALNAYVS---------- --
108	>UniRef90_A0A482JZK4_993_1076 GQALSQLTRQLASNFQA----------ISNSIEDIYNRLDGLTAD AQ--VDRLIT----------GRIGALNAFVA---------- --
109	>UniRef90_A0A6B9KDF5_753_833 GVVQNALVDDVSKIANGF----------NQLTASVGKLAATTSSALQAIQAVVNQN AAQVEALVSGISENFGA----------ISTNFRVISQRLDKLEAD ---------- --
110	>UniRef90_A0A1W5YKT3_1031_1114 GMALSQLTKQLASNFQA----------ISSSIEDLYNRLDRVEAD QQ--VDRLIT----------GRLAALNAFVA---------- --
111	>UniRef90_E3W5H9_1074_1183 GESLSQLTSQLQKNFQA----------ISSSIAEIYNRLGKVEAD AQ--VDRLIT----------GRLAALNAYV---------- --
112	>UniRef90_F1DAY3_987_1098 SDALNHLTKQLQHNFQT----------ISNSISDIYGRLNQLEAD AQ--VDRIIV----------GRIAALNAFVSQ---------- --

113	>UniRef90_H9MGD4_58_142 GEALSQLTSQLQKNFQA----------ISSSIAEIYNRLEKVEAD VQ--VDRLIT----------GRLAALNAHVS---------- --
114	>UniRef90_A0A1L2KGB2_982_1089 GQALSHLTKQLQNNFQA----------ISSSIEDIYNRLDSLAAD AQ--VDRLIT----------GRLAALNSF---------- --
115	>UniRef90_A0A0K2SF41_1044_1154 GKALNQLTAQLQNNFQA----------VSSSIADIYYRLDELQAD AQ--VDRLIT----------GRLAALNAFVTQT---------- --
116	>UniRef90_F1DAX6_996_1087 GHALSQLTRQLASNFQA----------ISSSIQDIYNRLEGLEAD AQ--VDRLIT----------GRLAALNAFVTQ---------- --
117	>UniRef90_A0A172AZS6_1067_1151 GKALNHLTAQLQNNFQA----------ISSSIEDIYYKLDEVNAD AQ--VDRLIT----------GRLASLNAFVT---------- --
118	>UniRef90_B2BW33_1066_1154 SQALTKLLGQLNYNFGA----------TTSSIKELYERLAKLEAD VQ---------- --
119	>UniRef90_P10033_1058_1184 GQALSHLTVQLQNNFQA----------ISSSISDIYNRLDELSAD AQ--VDRLIT----------GRLTALNAFVSQTLTRQAEVRAS----------RQLAK- --
120	>UniRef90_A0A1L2KGD0_1014_1098 GAALSQLTRQLASNFQA----------ISASLTDIYNRLDGLAAD AQ--ADRLIN----------GRLAALNAFVT---------- --
121	>UniRef90_F1DB14_1021_1103 GTALSQLTKQLASNFQA----------ISSSIEDLYNRLGAVEAD QQ--VDRLIT----------GRLAALNAFVA---------- --
122	>UniRef90_A0A0U1WHD7_997_1105 GLALSQLTKQLASNFQA----------ISSSIEDLYNRLDRVEAD LQ--VDRLIT----------GRLAALNAFV---------- --
123	>UniRef90_A0A7D5Q9G3_807_934 GQALSSLTSQLSHNFQA----------ISASIADIYNRLNELDAD AQ--VDRLIT----------GRLAALNAFVTQTLSKLAEVRQA----------RQLAK- --
124	>UniRef90_A0A1L7HJ82_772_853 GVMQDALVEDVNKLANGF----------NNLTQYVSDGFKTTSQALSTIQAVVNNN AQQVSQLVQGLSENFGA----------ISNNFALIAERLERIEAA M---------- --
125	>UniRef90_D9J1Z4_1062_1167 GKALNHLTLQLQNNFQA----------ISSSIQDIYYKLDDINAD AQ--VDRLIT----------GRLAALNAFVTQTLTRQAEVRAS----------RQLAK- --
126	>UniRef90_H9BR25_838_922 TTALNQLTQQLANNFQA----------ISSSITDIYNRLGQLEAD AQ--VDRLIT----------GRLAALNAFVS---------- --

127	>UniRef90_A0A286R3Q7_980_1088 GNALNHLTMQLRNNFQA----------ISSSIDDIYGRLDELAAD AQ--VDRLIN----------GRLAALNAFV---------- --
128	>UniRef90_E6YDV6_791_886 SDILNKLMAQLNVNFGA----------ISSSLQDIYAQLGDLSAN AQ---------- --
129	>UniRef90_S5YNL4_1002_1084 GMALNHLTLQLQNNFQA----------ISSSIADIYRRLDQLTAD AQ--VDRLIN----------GRLAALNAFVS---------- --
130	>UniRef90_A0A1L2KGF1_976_1085 GNALNHLTSQLRQNFQA----------ISSSIQAIYDRLDTIQAD QQ--VDRLIT----------GRLAALNAFVA---------- --
131	>UniRef90_A0A6B9KIG7_969_1078 GQALAQLTRQLASNFQA----------ISSSIEDIYNRLDILAAD AQ--VDRLIS----------GRLSALNAFVTQ---------- --
132	>UniRef90_A8JNZ2_762_843 GVVQNALVDDVNKLANGF----------NQLTASVGKLALTTSSALQAIQAVVNQN AAQVESLVSGITENFGA----------ISTNFKVISQRLDKLEAD V---------- --
133	>UniRef90_U4DCU7_800_893 SDILNKLMAXLSVNFGA----------VSSSLNEIYLKLDQLNAD ---------- --
134	>UniRef90_A0A1L2KGD3_986_1095 GLALSHLTKQLKNNFQA----------ISSSIDDIYNRLDELAAN AQ--VDRLIT----------GRLSALNSFVA---------- --
135	>UniRef90_H9BR08_826_938 GHALATLTQQLANNFQA----------ISASISDIYNRLNQLEAD AQ--VDRLIT----------GRLASLNAFVTQTL---------- --
136	>UniRef90_A0A222UC54_1077_1168 GKAINQLTAQLQNNFQA----------ISSSIEDIYYRLDEVNAD AQ--VDRLIT----------GRLAALNAFVTQ---------- --
137	>UniRef90_B1PHI8_987_1096 GTALSQLTKQLASNFQA----------VSSSIEDLYNRLDRLEAD QQ--VDRLIT----------GRLAALNAFVT---------- --
138	>UniRef90_A0A166ZLY7_973_1064 GNALSHLTSQLQNNFQA----------ISASINDIYSRLDQLSAD AQ---------- --
139	>UniRef90_A0A481S1E3_162_242 GVMQDALVNDVNKLANGF----------NNLTQFVADGFKTTSEALSAIQSAVNSN AYQVSQLVQGLSDNFGA----------ISNNFALILERLERIEAA ---------- --
140	>UniRef90_A0A220YLM0_1001_1084 GMALNHLTLQLQHNFQA----------ISSSIADIYRRLDQLTAD AQ--VDRLIN----------GRLAALNAFV---------- --

141	>UniRef90_F6KIE7_60_143 GMALTQLTEQLQNNFQA----------ISSSIQTIYNRLDELSAD AQ--VDRLIT----------GRLASLNAFVAQ---------- --
142	>UniRef90_A0A0M4HA36_990_1105 GAALTQLTVQLQHNFQA----------ISSSIDDIYSRLDILSAD VQ--VDRLIT----------GRLSALNAFVAQILTKY---------- --
143	>UniRef90_A0A5J6DE25_995_1079 GLALSHLTKQLQNNFQA----------ISSSISDIYARLDQLTAD AQ--VDRLIT----------GRLAALNAFV---------- --
144	>UniRef90_A0A1X9JJW0_765_844 GVMQDALVNDVNKLANGF----------NNLTQYVADGFKTTSQALSAIQSVVNNN AQQISQLVQGLSENFGA----------ISNNFLVIAERLERLEA- ---------- --
145	>UniRef90_A0A2U9I6C2_859_939 GMALTQLTNQLSYNFQA----------ISSSISDIYQRLTQLEAD VQ--VDRLIT----------GRLAALNS---------- --
146	>UniRef90_K4KCP3_965_1075 GQAIAHLTQQLTQNFQA----------ISHSIADIYNRLDELAAD AQ--TDRLIT----------GRLSALNAFVTQ---------- --
147	>UniRef90_Q6Q1S2_966_1078 GSALNHLTSQLRHNFQA----------ISNSIQAIYDRLDSIQAD QQ--VDRLIT----------GRLAALNAFVSQVL---------- --
148	>UniRef90_Q0Q4F4_968_1076 GLALSHLTNQLQNNFQA----------ISSSISDIYARLDQLTAD AQ--VDRLIT----------GRLSALNAFVS---------- --
149	>UniRef90_A0A6B9KDC2_1013_1097 GTALSQLTKQLASNFQA----------ISSSIEDLYNRLDTLEAD QQ--VDRLIT----------GRLAALNAFVT---------- --
150	>UniRef90_D3XGI6_1080_1169 GKALNYLTAQLQNNFQA----------ISSSIEDIYHRLDEVNAD VQ--VDRLIT----------GRLAALNAFV---------- --



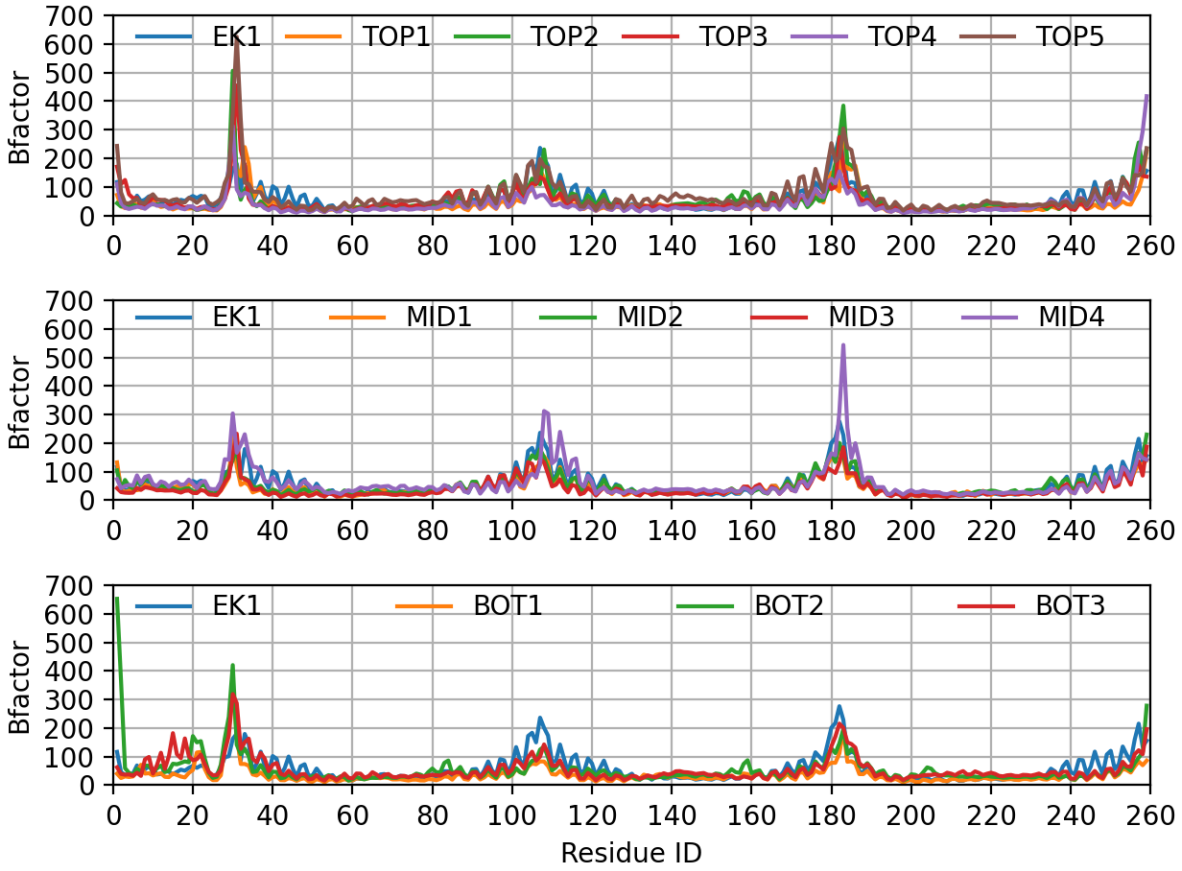
Supplementary Figure S1. Docked HR2 domain to SARS-CoV-2 HR1 domain (tan ribbon) aligned to 6LXT crystal structure of SARS-CoV-2 HR1/HR2 complex (blue ribbon).

Supplementary Table S3. Docking scores and sequences for HR2, EK1, and designed peptide inhibitors.

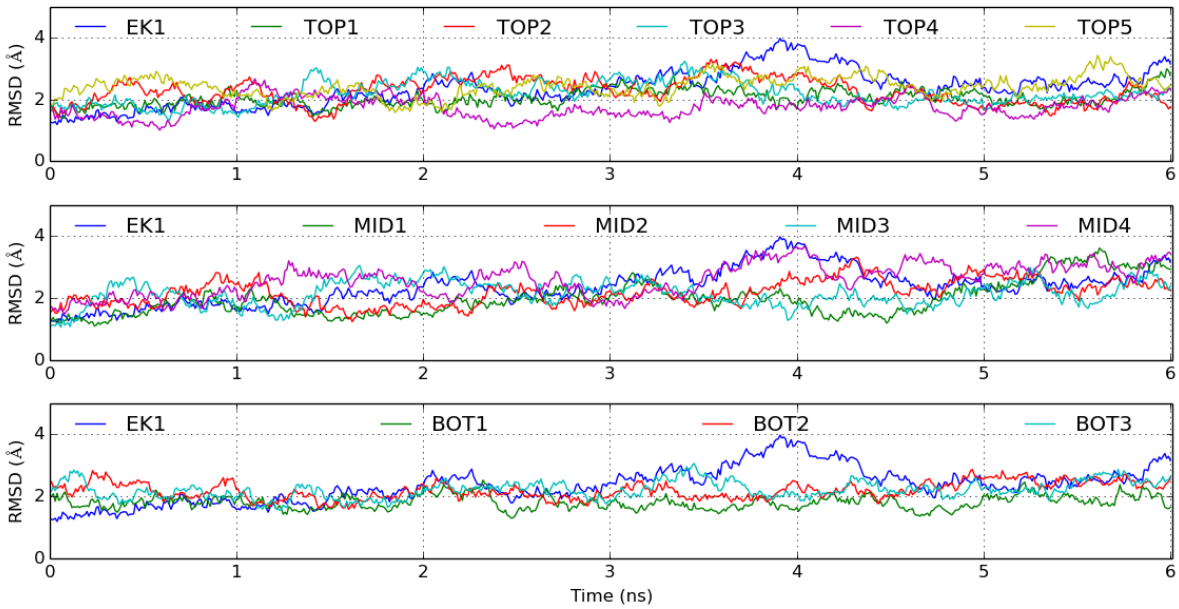
Peptide	HDOCK docking score	Sequence
HR2 peptide	-756.39	DVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE
132D	-702.46	WFLYLWLREMMKKMWRMREGMMETWWWEWE
132C	-698.67	WILYLWLREMMKKMWRMREGMMETWWWEWE
132B	-693.35	WMLYLWLREMMKKMWRMREGMMETWWWEWE
130A_2	-693.34	WVLYLWLREMMKRMWQRREGMMETWWWEWE
130A_4	*-684.38*	*WVLYMWLREMMKRMWQRREGMMETWWWEWE*
130A	-679.61	WVLYVWLREMMKRMWQRREGMMETWWWEWE
132-SDS	-679.54	WRLYWWLREMMWKMWRMREGMMETWWWEWE
130A_3	-678.43	WVLYIWLREMMKRMWQRREGMMETWWWEWE
137B	*-670.31*	*WVLYVWLREMMKKMWRMWKGMWETWWWEWE*
137A	-669.48	WVLYVWLREMMKKMWRMWEGMWETWWWEWE
135B	-668.91	WVLYVWLREMWKKMWRMWKGMMETWWWEWE
135A	-668.8	WVLYVWLREMWKKMWRMWEGMMETWWWEWE
138B	-663.36	WVLYVELREMMKKMWRMRKGM M ETWWWEKE
138A	-662.95	WVLYVELREMMKKMWRMREGMMETWWWEKE
130C	-662.75	WVLYVWLREMMKRMWQVREGMMETWWWEWE
130B	-661.42	WVLYVWLREMMKRMWQAREGMMETWWWEWE
136-SDS	-659.28	WRLYWWLREMMWKMMRMMEGMMETWWWEWE
128A	-653.6	QLYFVWLREMMKRMWQVREGMMETWWWEWE
126A	-637.41	QLYFVWLREMMKRMWQVREGMEETWWMWQE
129A	-635.22	QIYFVELWEMIKRMWQVREGMMETWWWEWE
134A	-629.33	WVLYVWLREMMKKMIRMMEGMGETLWWEWE
134B	-629.23	WVLYVWLREMMKKMIRMMKGMGETLWWEWE
131A	-625.27	WVLYVEVREMMKRMMQVREGMMETWWWEWE
134C	-621.47	WVLYVWLREMMKKMIRMMEGMGVTLWWEWE

125-SDS	-620	QLYFLWLREMKWRMWQRREGMEETWIWFVE
133B	-608.49	WVLYVWLREMMKKKKKRQKGEMETWWWEWE
130A_1	-608.13	WVLYFWLREMMKRMWQRREGMMETWWWEWE
133C	-603.3	WVLYVWLREMMKKKKKRQKGEMETWWWEWE
133A	-600.76	WVLYVWLREMMKKKKKRQEGEMVTWWWEWE
124-SDS	-600.42	QLWFIWLREEKWKMWQKREGLEESYIWFVE
123-redo-SDS	-599.22	QLWWVDLREEKWKMWQKREDLEESYIWFVE
121-SDS	-536.69	QLTWVDLREEKWKMWQAIKDLEESYIWFVE
127-SDS	-535.54	QLYFWWLREMMWRMWQRREGMMETWWMWQE
122-redo-SDS	-520.64	QLTWVDLREEKWKMWQKIEDLEESYIWFVE
120-SDS	-511.86	QLTFLDLREEKKKLEQAIKDLEESYIWFVE
119	-495.23	QLTFLDLEEEKKKLEQAIKDLEESYIWFVE
118	-468.44	QLTFLDLEEEKKKLEQAIKDLEESYIDLKE
SNF-M006	-466.13	NVTFLDLEYEMKKLERAIKKLEESYIDLKE
CLC-M008	-461.36	NVTFLDLEYEMKKLERAIKKLEENYIDLKE
MEM-M019	-461.36	NVTYLDLEYEMKKLKKAIKKLIESYIILKE
SNF-M007	-458.72	NVTFLDLEYEMKKLEEAIKKLEENYIDLKE
KJK-M012	-457.05	NVTYLDLEYIMKKLEEAIKDLRESYIDLKE
MEM-M023	-456.92	NVTFLDLEYEMKKLKKAIKKLIESYIILKE
SVS-W1M2	-456.52	WMTFLDLEYEMKKLEEAIKKLEESYIDLKE
MEM-M016	-454.59	NVTYLDLEYEMKKLEEAIKKLEESYIDLKE
SVS-W1I2	-453.78	WITFLDLEYEMKKLEEAIKKLEESYIDLKE
MEM-M018	-453.26	NVTYLDLEYEMKKLEEAIKDLEESYIDLKE
SGS-M004	-452.92	NVTFLDLEYEMKKLERAIKKLEESYIDLKE
MAM-M001	-452.92	NVTFLDLEYEMKKLERAIKKLEESYIDLKE
MEM-M017	-452.39	NVTYLDLEYEMKKLEEAIKKLHESYIDLKE
MAM-M002	-451.63	NVTFLKLEYEMKKLERAIKKLEESYIDLKE
CLC-M010	-451.62	NVTFLDLKYEMKKLEEAIKKLEESYIDLKE
SVS-W1	-451.00	WVTFLDLEYEMKKLEEAIKKLEESYIDLKE
KJK-M001, SGS-M002	-450.83	NVTFLDLEYEMKKLEEAIKKLRESYIDLKE
KJK-M006	-450.75	NVTFLDLEYMMKKLEEAIKKLEESYIDLKE
MAM-M003	-450.3	NVTFLKLEYEMKKLEEAIKKLEESYIDLKE
MEM-M011, KJK-M003, SGS-M001, LDM-M002	-449.7	NVTFLDLEYEMKKLEEAIKDLEESYIDLKE
EK1	**-449.7**	NVTFLDLEYEMKKLEEAIKKLEESYIDLKE
MEM-M014, KJK-M002	-449.69	NVTFLDLEYEMKKLEEAIKKLHESYIDLKE
MEM-M015	-448.53	NVTFLDLEYEMKKLEEAIKDLHESYIDLKE
SVS-W1-I2L3Y4W6	-444.41	WILYLWLEYEMKKLEEAIKKLEESYIDLKE
SVS-W1I2L3Y4	-443.17	WILYLDLEYEMKKLEEAIKKLEESYIDLKE
LDM-M003	-441.51	NVTFLDLEYEMKKLEEAIKKLEESYIDDKE
MEM-M013	-440.69	NVTFLDLEYEMKKLEEAQKKLEESYIDLKE
SVS-W1I2L3Y4M5	-438.54	WILYMDLEYEMKKLEEAIKKLEESYIDLKE

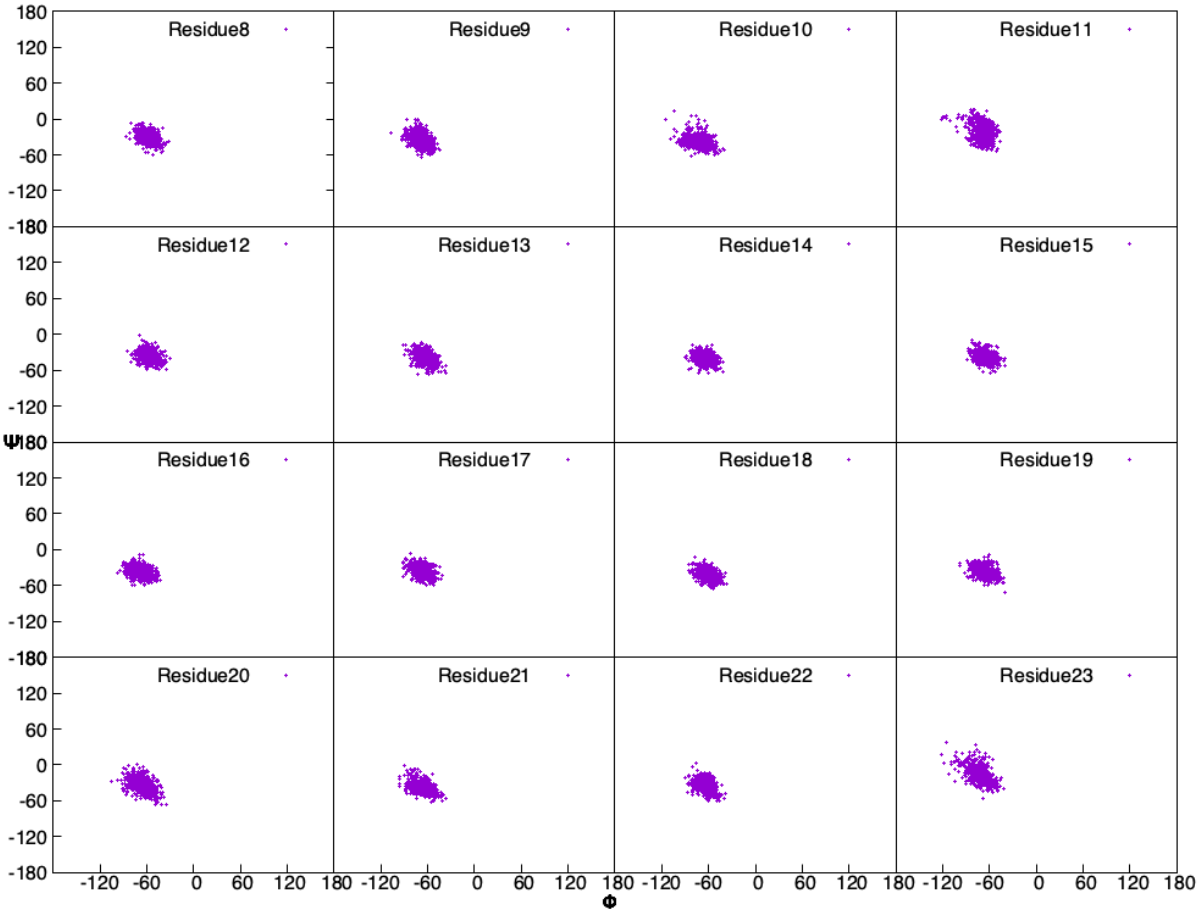
MEM-M009	-438.16	NVTFLDLEYEMKKLEEAIKKLEESYIDLKF
SVS-W1I2L3	-437.84	WILFLDLEYEMKKLEEAIKKLEESYIDLKE
SGS-M003	-431.15	NVTFLDLEYEMKKLEEAIKELEESYIDLKE
LDM-M001	-431.01	NVTFLDLEYEEKKLEEAIKKLEESYIDLKE
KJK-M004	-430.67	NVTFLDLEYEMKKLEEAIKELEESYIDLKE
MEM-M012	-428.52	NVTFLDLEYEMKKLEEAEKKLEESYIDLKE
MEM-M010	-424.73	NVTFLDLEYEMKKLEEAIKKLEESYFDLKE
KJK-M005	-412.24	NVTFLDLEYEMKKKEEAIKKLEESYIDLKE
108	-403.77	NVKFLDLRYEKKRLERKKKKLEESYIDLRE
117	-365.94	NVTFVDIEYELKKIEEALKKVEELYFDLKE
113	-347.78	NVKFVDIRYE**L**KRIERK**K**KKVEELYFDLRE
115	-337.28	NVKFVDIRYE**L**KRIERK**L**KKVEELYFDLRE
114	-327.78	NVKFVDIRYE**K**KRIERK**L**KKVEELYFDLRE
105	-309.75	NETEVD**I**EEELKKIEEALKE**V**EE**D**YFDEKD
104	-294.61	NETEVD**I**EEELKKIEEALKE**V**EE**L**YFDEKD
107	-266.32	NETEVD**I**EEELKKIEEALKE**E**EE**L**YFDEKD
110	-259.59	NETEVD**D**EEELKKIEEALKE**V**EE**D**YFDEKD
106	-255.06	NETEVD**I**EEELKKIEEALKE**E**EE**D**YFDEKD
102	-245.98	NETEVD**D**EEELKKIEEALKE**E**EE**D**YFDEKD
103	-245	NETELDDEEEMKKLEEAIKEEEESYIDEKD
109	-216.34	NETEVD**D**EEELKKIEEALKE**E**EE**L**YFDEKD
101	-196.62	NEKELDDREEKKRLERKKKEEEEDYIDERD



Supplementary Figure S2. MD simulation resulted B-factors for top5, middle 4, and bottom 3 peptide candidates and EK1. Residues 1-30 are from the peptides and 31-259 are from the HR1 domain.



Supplementary Figure S3. RMSD result of the MD simulation.



Supplementary Figure S4. Example Ramachandran plot of the 132B peptide, indicating these residues are all in the helical form.