SUPPORTING INFORMATION: Sequence alignment of class B1 GPCRs, binding sites of CRF1 antagonists in stereo representation and table showing correlation between protein-ligand interaction energies and the experimental binding affinities of three chemical series of CRF1 antagonists.

Secretin family receptors alignment

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ADCYAP1R1       -WSEPFP-------HYFDACG-FDEYESETGDQ----------DYYYLSVKALYTVGYST
VIPR2           -WSETFP-------DFVDACG-YSDPEDESKIT----------FYILVKAIYTLGYSV
VIPR1           -WTHLEPG------PYPIACG-LDDKAASLDEQQT---------MFYGSVKTGYTIGYGL
GHRHR           -WSEPFP-------PYPVACP--VPLELLAEEES----------YFSTVKIIYTVGHSI
SCTR            -WSETFP-------RPNLACG--VNVNDSSNEKRHS---------YLLKLKVMYTVGYSS
GIPR            -QWGLW--------RDHTQCENPEKNEAFLDQR----------LILERLQVMYTVGYSL
GLP1R           -LWLQKDNS-SLPWRDLSECEESKRGERSSPEE----------QLLFLYIIYTVGYAL
GLP2R           -TWQTIENA-TDIWQDDSECSENHSFKQNVDRYA----------LLSTLQLMYTVGYSF
PTHR1           -SWELVPGH-NRTWANYSECVKFLTNETRERE-----------VFDRLGMIYTVGYSV
PTHR2           -TWDFMHSL-NKTWANYSDCLRFLQPDISIGKQE----------FFERLYVMYTVGYSI
CALCR           VWFKHPEN--NRTWSNYTMCNAFTPEKLKNAY----------------VLYYLAIVGHSL
CALCRL          NWFRHPAS--NRTWTNYTQCNVNTHEKVKTALN----------------LFYLTIIGHGL
CRHR1           SWAAR---------VNYSECQEILNE-EKKSKV-----------HYHVAVIINYLGHCI
CRHR2           TWASK---------INYSQCEPILDDKQRKYDL-----------HYRIALVVNYLGHCV
                                      *                                :*:
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TM1

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ADCYAP1R1       SLVTLTTAMVILCRFRKLHCTR------NFIHMNLFVSFMLRAISVFIKDWILYAE----
VIPR2           SLMSLATGSIILCLFRKLHCTR------NYIHLNLFLSFILRAISVLVKDDVLYSS----
VIPR1           SLATLLVATAILSLFRKLHCTR------NYIHMHLFISFILRAAAVFIKDLALFDS----
GHRHR           SIVALFVAITILVALRRLHCPR------NYVHTQLFTTFILKAGRVFLKDAALFHS----
SCTR            SLVMLLVALGILCAFRRLHCTR------NYIHMHLFVSFILRALSNFIKDAVLFSS----
GIPR            SLATLLLALLILSLFRRLHCTR------NYIHINLFTSFMLRAAAILSRDRLLPRPG---
GLP1R           SFSALVIASAILLGFRHLHCTR------NYIHLNLFASFILRALSVFIKDAALKWMY---
GLP2R           SLISLFLALTLLLFLRKLHCTR------NYIHMNLFASFILRTLAVLVKDVVFYNSY---
PTHR1           SLASLTVAVLILAYFRRLHCTR------NYIHMHLFLSFMLRAVSIFVKDAVLYSGATLD
PTHR2           SFGSLAVAILIIGYFRRLHCTR------NYIHMHLFVSFMLRATSIFVKDRVVHAHIGVK
CALCR           SIFTLVISLGIFVFFRSLGCQR------VTLHKNMFLTYILNSMIIIIHLVEVVPNGELV
CALCRL          SIASLLISLGIFFYFKSLSCQR------ITLHKNLFFSFVCNSVVTIIHLTAVANNQALV
CRHR1           SLVALLVAFVLFLRLRSIRCLR------NIIHWNLISAFILR--NATWFVVQLTMSPEVH
CRHR2           SVAALVAAFLLFLALRSIRCLR------NVIHWNLITTFILR--NVMWFLLQL-VDHEVH
                *.  *  .  ::  :: : * *       :* ::: ::: .         .
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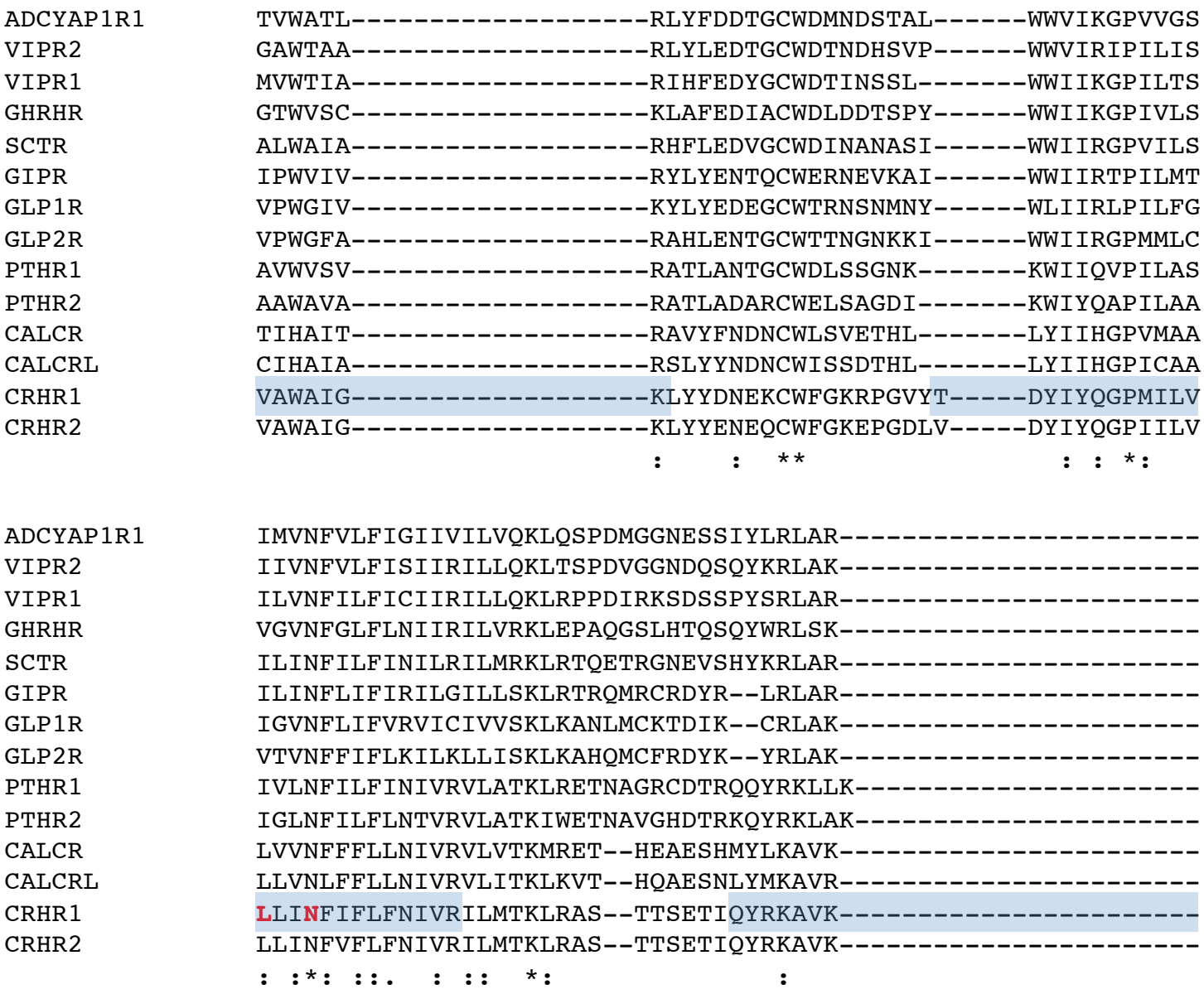
TM2

Secretin family receptors alignment

Secretin family receptors alignment



Residues in red are conserved residues which contact NBI 27914

Secretin family receptors alignment

```
ADCYAP1R1       --------------------STLLLIPLFGIHYTVFAFSPENVSK---------RERLVF
VIPR2           --------------------STLLLIPLFGVHYMVFAVFPISISS---------KYQILF
VIPR1           --------------------STLLLIPLFGVHYIMFAFFPDNFKP---------EVKMVF
GHRHR           --------------------STLFLIPLFGIHYIIFNFLPDNAGL---------GIRLPL
SCTR            --------------------STLLLIPLFGIHYIVFAFSPEDAM----------EIQLFF
GIPR            --------------------STLTLVPLLGVHEVVFAPVTEEQARGALR-----FAKLGF
GLP1R           --------------------STLTLIPLLGTHEVIFAFVMDEHARGTLR-----FIKLFT
GLP2R           --------------------STLVLIPLLGVHEILFSFITDDQVEGFAK-----LIRLFI
PTHR1           --------------------STLVLMPLFGVHYIVFMATPYTEVSGTLW-----QVQMHY
PTHR2           --------------------STLVLVLVFGVHYIVFVCLP-HSFTGLGW-----EIRMHC
CALCR           --------------------ATMILVPLLGIQFVVFPWRPSNKMLG--------KIYDYV
CALCRL          --------------------ATLILVPLLGIEFVLIPWRPEGKIAE--------EVYDYI
CRHR1           --------------------ATLVLLPLLGITYMLFFVNPGEDEVSR-------VVFIYF
CRHR2           --------------------ATLVLLPLLGITYMLFFVNPGEDDLSQ-------IMFIYF
                                    :*: *: ::*    ::
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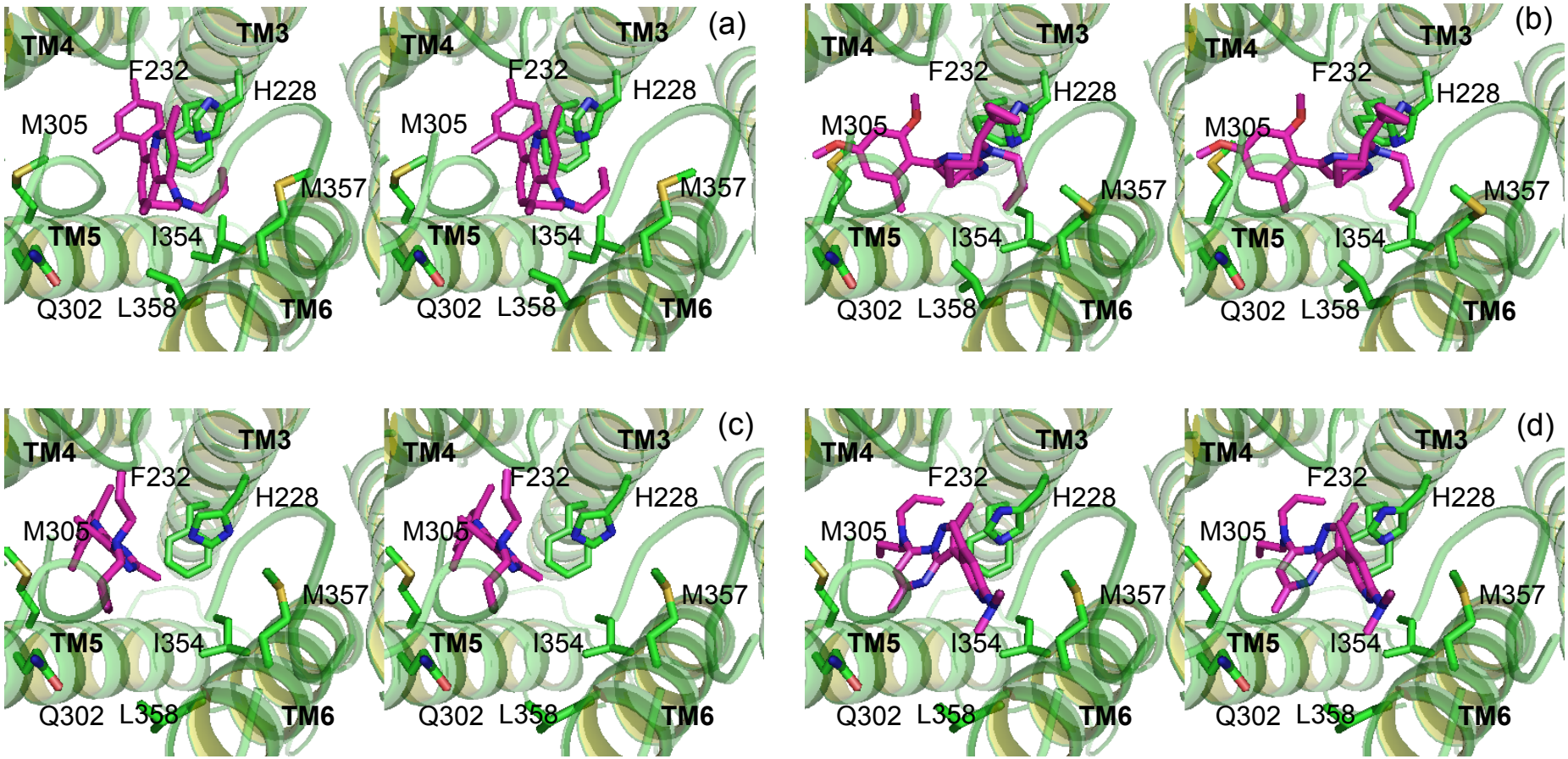
TM7

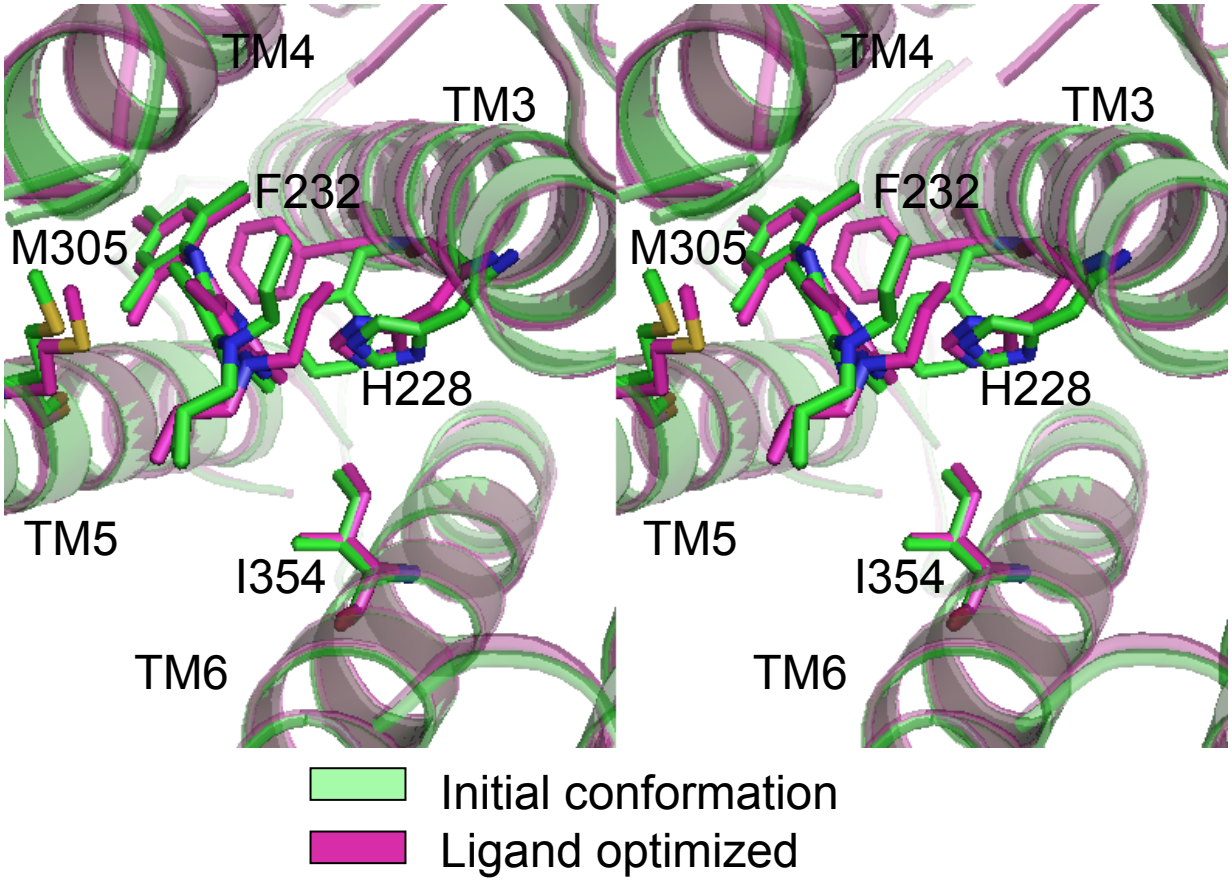
```
ADCYAP1R1       ELGLGSFQGFVVAVLYCFLNGEVQAEIKR--KWRSWKVNRYFAVDFKHRHPSLASSGVNG
VIPR2           ELCLGSFQGLVVAVLYCFLNSEVQCELKR--KWRSRCPTPSASRDYRVCGSSFSRNGSEG
VIPR1           ELVVGSFQGFVVAILYCFLNGEVQAELRR--KWRRWHLQGVLGWNPKYRHPSGGSNGATC
GHRHR           ELGLGSFQGFIVAILYCFLNQEVRTEISR--KWHGHDPELLPAWRTRAKWTTPSRSAAKV
SCTR            ELALGSFQGLVVAVLYCFLNGEVQLEVQK--KWQQWHLREFPLHPVASFSNSTKASHLEQ
GIPR            EIFLSSFQGFLVSVLYCFINKEVQSEIRR--GWHHCRLRRSLGEEQRQLPERAFRALPSG
GLP1R           ELSFTSFQGLMVAILYCFVNNEVQLEFRK--SWERWRL-EHLHI-QRD---SSMKPLKCP
GLP2R           QLTLSSFHGFLVALQYGFANGEVKAELRK--YWVRFLLARHSGCRACVLG-KDFRFLGKC
PTHR1           EMLFNSFQGFFVAIIYCFCNGEVQAEIKK--SWSRWTLALDFKRKARSGSSSYSYGPMVS
PTHR2           ELFFNSFQGFFVSIIYCYCNGEVQAEVKK--MWSRWNLSVDWKRTPPCGSRRCGS-VLTT
CALCR           MHSLIHFQGFFVATIYCFCNNEVQTTVKR--QWAQFKIQWNQRWGRRPSNRSARAAAAAA
CALCRL          MHILMHFQGLLVSTIFCFFNGEVQAILRR--NWNQYKIQFGNSFSNSEALRSASYTVSTI
CRHR1           NSFLESFQGFFVSVFYCFLNSEVRSAIRK--RWHRWQDKHSIRARVARAMSIPTSPTRVS
CRHR2           NSFLQSFQGFFVSVFYCFFNGEVRSAVRK--RWHRWQDHHSLRVPMARAMSIPTSPTRIS
                   .  *:*:.*:  : : * **:  . :   *
```

Fig. S1



Predicted binding sites of selected compounds in *h*CRF$_1$-R. Residues within 5Å of the ligand are shown in each figure in stereo representation. (a) binding site for compound **1**; (b) compound **4**; (c) NBI-27914; (d) NBI-30775.

Fig. S2



Comparison of the apo receptor structure of *h*CRF$_1$-R to the NBI-27914 stabilized *h*CRF$_1$-R structure from LITiCon shown in stereo representation.

Table S1.

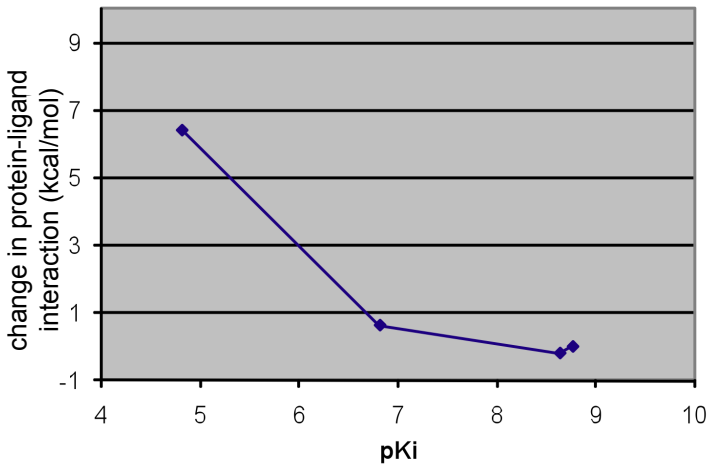
4 series

compound	Change in protein-ligand interaction (Kcal/mol)	Experimental binding affinity (pKi)
1	0	9.05
2	1.47	7.49
3	4.37	6.38

7 series

compound	Change in protein-ligand interaction (Kcal/mol)	Experimental binding affinity (pKi)
4	0	7.96
5	1.47	6.07
6	6.69	inactive

compound	Change in protein-ligand interaction (Kcal/mol)	Experimental binding affinity pKi
NBI27914	0	8.77
66221	-0.2	8.64
66225	0.6	6.82
66226	6.4	4.82



Comparison of the protein-ligand interaction energies and the experimental binding affinities of three chemical series of CRF1 antagonists. The best binder in each series is marked in pink and the weakest binder is marked in blue. Also the change in binding energy vs experimental binding affinity for the NBI-27914 series is shown graphically.