# Agonists in the Extended Conformation Stabilize the Active State of β-Adrenoceptors

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> Received March 21, 2022 Revised June 21, 2022 Accepted June 21, 2022

Abstract—In this study, we conducted a comparative analysis of the structure of agonists and antagonists of transmembrane (TM)  $\beta$ -adrenoceptors ( $\beta$ -ARs) and their interactions with the  $\beta$ -ARs and proposed the mechanism of receptor activation. A characteristic feature of agonist and antagonist molecules is the presence of a hydrophobic head (most often, one or two aromatic rings) and a tail with a positively charged amino group. All  $\beta$ -adrenergic agonists have two carbon atoms between the aromatic ring of the head and the nitrogen atom of the amino group. In antagonist molecules, this fragment can be either reduced or increased to four atoms due to the additional carbon and oxygen atoms. The agonist head, as a rule, has two H-bond donors or acceptors in the *para*- and *meta*-positions of the aromatic rings, while in the antagonist heads, these do-nors/acceptors are absent or located in other positions. Analysis of known three-dimensional structures of  $\beta$ -AR complexes with agonists showed that the agonist head forms two H-bonds with the TM5 helix, and the tail forms an ionic bond with the D3.32 residue of the TM3 helix and one or two H-bonds with the TM7 helix. The tail of the antagonist can form similar bonds, but the interaction between the head and the TM5 helix is much weaker. As a result of these interactions, the agonist molecule acquires an extended "strained string" of the agonist interacts with the TM6 helix (primarily with the W6.48 residue) and turns it, which leads to the opening of the G protein-binding site on the intracellular side of the receptor, while flexible and larger antagonist molecules do not have the same effect on the receptor.

DOI: 10.1134/S0006297922070057

Keywords: β-adrenoceptor, GPCR, agonist, antagonist, activation mechanism

### INTRODUCTION

G protein-coupled receptors (GPCRs) constitute the largest family of cell membrane receptors that includes over 800 human proteins targeted by at least 30% of current medicines (see reviews [1, 2]). This might be the main reason why GPCRs have been extensively studied in several recent decades, resulting in the elucidation of many aspects of their biology, biochemistry, and pharma-

cology. Originally, the behavior of GPCRs was described in terms of a simple two-state model; however, there is growing body of evidence that GPCRs are not molecular switches, but rather molecular relays, i.e., dynamic proteins with multiple states between active and inactive conformations [4-8].

Recent crystallography data have provided the snapshots of both active and inactive functional states of GP-CRs [9, 10]. GPCR structures solved so far share the same overall fold – a bundle of seven transmembrane (TM)  $\alpha$ -helices with three extra- and three intracellular

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loops. The extracellular interface is responsible for the ligand binding, while the intracellular portion interacts with G proteins,  $\beta$ -arrestins, and other downstream effectors. Analysis of known GPCR structures indicates that receptor activation is associated with subtle changes in the extracellular portion of the protein and extensive rearrangement of the TM helices on the cytoplasmic side [11, 12]. Agonist binding at the GPCR extracellular interface results in the opening of the intracellular part for the G protein binding, which promotes G protein activation (GDP release) and initiates the signaling cascade.

The progress in membrane protein crystallography and related techniques in the past decade [7, 13] has allowed to elucidate many aspects of GPCR structure, activation, and physiology; however, some details of ligand recognition and receptor activation remain poorly understood. One of the main aims of this study was comparative analysis of the structures of  $\beta$ -adrenoceptor ( $\beta$ -AR) ligands. Based on the results of this analysis, we proposed that agonist molecules adopt an extended ("strained string") conformation and stabilize the active state of  $\beta$ -AR, in contrast to antagonist molecules, which have longer and flexible tail and fail to produce the same effect on the receptors.

#### MATERIALS AND METHODS

As the main research approaches in this study, we used stereochemical analysis of the known three-dimensional structures of  $\beta$ -AR complexes with the corresponding ligands and comparative analysis of the chemical structure of agonists and antagonists and their conformations in the complexes. For this, we created a database of such complexes that included 64 structures determined by crystallography so far and a database of β-AR sequences from the Swiss-Prot UniProt [14]. The atomic coordinates of the complexes were taken from the Protein Data Bank (PDB, URL: https://www.rcsb.org) [15]. The three-dimensional structures of the receptors and their ligands were analyzed using RasMol [16] and PyMOL Molecular Graphics System Version 1.4.1 Schrödinger, LLC. β-AR subtypes designated using the nomenclature recommended by the NC-IUPHAR Subcommittee on Adrenergic Receptors. Amino acid residues in  $\beta$ -ARs were designated according to the Ballesteros and Weinstein nomenclature [17]. Multiple sequence alignment was performed with the Clustal Omega program (1.2.4) included in the UniProt resource [14]. Images of ligand molecules were taken from the Drug Informational Portal, ChEBI, and ChemSpider.

## **RESULTS AND DISCUSSION**

Comparative analysis of chemical structures of  $\beta$ -AR ligands. In terms of receptor activation (intrinsic effica-

cy), GPCR ligands can be categorized into four groups: (i and ii) full and partial agonists that produce the maximal or sub-maximal functional response, respectively; (iii) inverse agonists that decrease the basal receptor activity (activity in the absence of ligand); and (iv) neutral antagonists, that compete with other ligands for the orthosteric binding site, but their interaction with the receptor does not result in the G protein binding.

Table 1 shows chemical structures of  $\beta$ -AR agonists that have been co-crystallized with the receptor. A characteristic feature of these molecules is the presence of an aromatic head and a tail with a positively charged amine. The tail consists of ethanolamine core and various substitutes connected to the amine group. Hydroxyl groups in the *para*- and *meta*-positions of the catechol moieties and in the *para*-position in aromatic rings of non-catechol agonists can form hydrogen bonds with the receptor helices.

Aromatic heterocyclic heads of non-catechol agonists can have other donors and acceptors of hydrogen bonds that might be involved in the binding with the receptor. Hence, GPCR agonists have two centers of polar interactions with the receptor (donors/acceptors of H-bonds of the head and donors/acceptors and positively charged amine of the tail). One may ask if the distance between these centers has any influence on the specificity of receptor-ligand interactions. As seen in Table 1, the length of the tail fragment between the N-atom and the aromatic ring is the same in all agonists and comprises three covalent bonds. In other words, the N-atom is separated by 2 carbons from the substituted benzene or other aromatic ring. Moreover, in all agonists with six-membered aromatic rings, the O-atoms of hydroxyls located in the para- and meta-positions and the N-atoms of the tail are separated by seven and six covalent bonds, respectively.

tFor comparison, Table 2 shows partial agonists, antagonists, and inverse agonists (referred to as β-blockers after Emtage et al. [28]. These compounds also have aromatic heads and tails with positively charged amine groups. However, compared to agonists, these ligands have either longer (Table 2) or shorter (e.g., doxepin and bretylium tosylate not shown here) tail fragments between the amine N-atom and the aromatic ring. In most cases, the N-atom of the amine group is separated from the aromatic ring by 4 atoms (often one of them is O). Moreover, antagonists and inverse agonists presented in Table 2 do not contain donors or acceptors of H-bonds in the para-position of the aromatic head or even lack them at all. Note that the NH-groups of cyanopindolol and carazolol are located in the meta-position relative to the tail. Another feature of  $\beta$ -blockers is that they typically have larger heads consisting of two and three rings as compared to the agonists.

Two centers of polar interactions between  $\beta$ -ARs and their agonists. The orthosteric binding pocket of  $\beta$ -ARs is located within the TM region and is primarily composed of the extracellular fragments of the TM helices 3, 5, 6,

Table 1.	β-AR	agonists that	have been co	o-crystallized	with the receptor

β-AR agonist	Structure	β-AR, organism	PDB ID	Resolution, Å	References
Carmoterol		$\beta_1$ -AR, turkey	2Y02	2.60	[18]
Dobutamine	Но от станование от станов	6 - AR turkey	2Y00	2.50	[18]
Dooutainine	HO CH <sub>3</sub>		6H7L	2.70	[19]
Eninophrina	ОН НО ОН Н К СН	$\beta_1$ -AR, human	4LDO	3.20	[20]
	но	$\beta_2$ -AR, human	7BTS	3.13	[21]
	OH NH	$\beta_1$ -AR, turkey	6IBL 6TKO	2.70 3.30	[22]
Formoteror	HOWW CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	$\beta_2$ -AR, human	7BZ2	3.82	[23]
Hydroxybenzyl-isoproterenol	HN HO HO OH	β <sub>2</sub> -AR, human	4LDL	3.10	[20]
	HO HO HO HO CH <sub>3</sub>	Q AD tool	2Y03	2.85	[18]
Isoprenaline			6H7J	2.80	[19]
		$\beta_2$ -AR, human	7DHR	3.80	[24]

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β-AR agonist	Structure	β-AR, organism	PDB ID	Resolution, Å	References
Noradrenaline	HO HO HO	$\beta_1$ -AR, human	7BU6	2.70	[21]
	он он I I н	6 AD turkov	6H7M	2.76	[19]
Salbutamol		p <sub>1</sub> -AK, turkey	2Y04	3.05	[18]
	Но	$\beta_2$ -AR, human	7DHI	3.26	[24]
Salmeterol	OH OH H HO O	$\beta_2$ -AR, human	6MXT	2.96	[25]
		$\beta_1$ -AR, human	7BU7	2.60	[21]
B11(7107(0074(4000)		$\beta_2$ -AR, human	4LDE	2.79	[20]
B110/10/(Q2/404220)			3P0G 3SN6	3.50 3.20	[26]
			6N48	3.20	[27]



β-AR blocker	Structure	β-AR, organism	PDB ID	Resolution, Å	References
	CH <sub>2</sub> CH <sub>3</sub>		3NYA	3.16	[29]
Alprenolol		$\beta_2$ -AR, human	6PS2 6PRZ	2.40 2.80	[30]
	ОН		60BA	3.10	[31]

Table 2 (Cont.)

β-AR blocker	Structure	β-AR, organism	PDB ID	Resolution, Å	References
Bucindolol	CH <sub>3</sub> HN HO N	β <sub>1</sub> -AR, turkey	4AMI	3.20	[32]
		$\beta_1$ -AR, human	7BVQ	2.50	[21]
		$\beta_1$ -AR, turkey	2YCW	3.00	[33]
			2R4R 2R4S	3.40	[34]
			2RH1	2.40	[35]
Carazolol			4GBR	3.99	[36]
		$\beta_2$ -AR, human	5D5A 5D5B	2.48 3.80	[37]
			5JQH	3.20	[38]
			6PS0	3.40	[30]
Comudilal		$\beta_1$ -AR, turkey	4AMJ	2.30	[32]
Carveanoi		$\beta_2$ -AR, human	6PS3	2.50	[30]
	$\checkmark$		2VT4	2.70	[39]
			2YCX 2YCY	3.25 3.15	[33]
Cyanopindolol	ļ	$\beta_1$ -AR, turkey	4BVN	2.10	[40]
			5F8U	3.35	[41]
			6H7O	2.80	[19]

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	1	1	(	Tab	le 2 (Cont.)
β-AR blocker	Structure	β-AR, organism	PDB ID	Resolution, Å	References
Iodocyanopindolol		$\beta_1$ -AR, turkey	2YCZ	3.65	[33]
7-Methylcyanopindolol		$\beta_1$ -AR, turkey	5A8E	2.40	[42]
Propranolol		$\beta_2$ -AR, human	6PS5	2.90	[30]
Timolol	HO HN CH <sub>3</sub> CH <sub>3</sub>		3D4S	2.80	[43]
11110101		$p_2$ -AK, numan	6PS1 6PS6	3.20 2.70	[30]

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 $\beta_1$ -AR, turkey

6H7N

2.50

Xamoterol

Table 2 (Cont.)

β-AR blocker	Structure	β-AR, organism	PDB ID	Resolution, Å	References
101 119 551	H <sub>3</sub> C H <sub>3</sub> CH <sub>3</sub> OH		3NY8	2.84	[29]
ICI-118,551	CH <sub>3</sub>	p <sub>2</sub> -AK, numan	6PS4	2.60	[30]
Q27460040	HOW HN	β <sub>2</sub> -AR, human	3PDS	3.50	[44]
Q27461782		β <sub>2</sub> -AR, human	3NY9	2.84	[29]

and 7 (Fig. 1). Multiple biochemical and mutagenesis studies, as well as analysis of crystal structures of aminergic GPCRs, have allowed to locate critical amino acid residues in the TM helices [45]. It was demonstrated that the charged amine of the ligand interacts with Asp residue D3.32. GPCRs with D3.32 also have a Tyr residue at position Y7.43 and contain Asn at position N7.39, which suggests that their side chains are involved in the interactions with the positively charged moieties in the ligands. Therefore, these key amino acids form the center for the binding of amino groups and other polar groups of the ligand tail.

In the second center of polar interactions, all catecholamine receptors have Ser residues at positions S5.42 and S5.46; most of them also have Ser at position S5.43, so that these residues can form H-bonds with the donors and/or acceptors of the aromatic head. Recent data [10] indicate that Thr at position T3.37 also can interact with polar groups of the ligand head. Figure 2 shows the alignment of amino acid sequences of TM helices 3, 5, 6, and 7 in  $\beta$ -AR subtypes  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  from different animal species. All key amino acid residues mentioned above are highly conserved in all  $\beta$ -ARs.

Comparison of conformations of agonists, antagonists, and inverse agonists bound to  $\beta$ -ARs. Figure 3 shows crystal structures of the agonist isoprenaline (panel a) and neutral antagonist cyanopindolol (panel b) bound in the



Fig. 1. Typical structure of the agonist complex with TM helices 3, 5 6, and 7 forming the binding site in  $\beta$ -ARs. The key amino acid residues interacting with the ligand are shown as circles.

main binding pocket of  $\beta_1$ -Ars [18, 33]. The figure shows the side chains of the amino acid residues forming the two centers of polar interactions as well as ligand conformations. As seen in Fig. 3b, the O-C-C-C group of atoms in cyanopindolol tail acquires a *gauche*-conformation (i.e., forms a kink in the tail), while the C-C-C-N group of atoms in the isoprenaline tail has a *trans*-conformation (Fig. 3a).

Figure 4 shows the superimposed structures from Fig. 3. It is clearly seen that the O-C-C-C group of atoms forms a kink in the cyanopindolol tail, and the isoprenaline tail has an extended conformation. Analysis shows that the same picture is observed in other complexes of agonists and antagonists with the receptors (Tables 1 and 2).

The amine groups of both ligands are located in the amine-binding center (D3.32, N7.39, Y7.43), while catechol hydroxyls of isoprenaline and NH- and cyanogroups of cyanopindolol are situated in the other center of polar interactions (S5.42, S5.43, S5.46). However, the overall geometries of the agonist and antagonist molecules are different. In isoprenaline, the tail has an extended (*trans-*) conformation, and the molecule resembles a "strained string" that stabilizes the active state of the receptor. The tail of cyanopindolol is bent between the amine N-atom and the aromatic ring, resulting in the zigzag-like conformation (Figs. 3 and 4). Under other conditions (for example, in a native membrane, and not in a crystal), the tail of the antagonist can be transformed into an extended conformation and back, i.e., TM helices in the receptor complexes with antagonists can have a greater dynamic mobility than in the complexes with agonists (see Nygaard et al. (2013) [6]).

$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$		TM3			TM5		TM6			TM7			
SP1P058081088L INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 223-240 GKALKTIGTURAVYTLAWLED 550-300   SP1P05801 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 223-240 GKALKTIGTURAVYTLAWLED 550-300   SP10259591 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 223-240 GKALKTIGTURAVYTLAWLED 539 90217991 339 90217991 343-365   SP10259591 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 223-240 GKALKTIGTURAVYTLAWLED 350-375 90217991 343-365   SP1037051 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 233-240 GKALKTIGTURAVYLKAR 36-345 PDRIFYFENLUGANSARNETLY 352-377   SP1P037061 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 233-240 GKALKTIGTURAVYLKAR 36-345 PDRIFYFENLUGANSARNETLY 351-347   SP1P037061 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELDURAVYLKYP 233-240 GKALKTIGTURAVYLKAR 363-35 PDRIFYFENLUGANSARNETLY 351-345   SP1P03761 INTENDUCURASIETLUVIL 133-154 ATALASSYNSPYVELUNAVYLKYP		D3.32	T3.37		S5.42 S5.43 S5.46 S5.46			W6.48 P6.50 F6.51 F6.52		N7.39	Y7.43	N7.49	
SP  47599  ADREL  MACHO LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 33-352 PDRLFVERNLGXANSARNEIIY 345-366 SP  025959  ADREL  FIG LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 310-339 PDRLFVERNLGXANSARNEIIY 345-366 SP  025951  ADREL  FIGL LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 310-339 PDRLFVERNLGXANSARNEIIY 352-375 SP  05751  ADREL  FIGL LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 317-346 PDRLFVERNLGXANSARNEIIY 352-375 SP  05750  ADREL  FIGL LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 317-346 PDRLFVERNLGXANSARNEIIY 321-345 SP  04554  ADREL   FAGL LATINGVILUVASIETLUVIL 133-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 309-338 PDRLFVERNLGXANSARNEIIY 344-366 SP  945971  ADREL   MOUSE LATINGVILUVASIETLUVIL 113-154 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 309-338 PDRLFVERNLGXANSARNEIIY 344-366 SP  94574   ADREL   MOUSE LATINGVILUVASIETLUVIL 110-131 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 309-338 PDRLFVERNLGXANSARNEIIY 344-366 SP  945750   ADREL   MUAN FWISTNULUVASIETLUVIL 10-131 AVALASSVVSFVELUMARVILVE 223-240 GKALKILGILMSVFTLUKUFELANVKAF 309-338 PDRLFVERNLGXANSARNEIIY 344-366 SP  905750   ADREL   MUAN FWISTNULUVASIETLUVIL 10-129 GVALASSIVSFVELUMINEVYS 197-220 LGILMSTFILMSFERINKINK 200-235 PDRLFVERNLGXANSARNEIIY 344-366 SP  905751   ADREL   MUAN FWISTNULUVASIETLUVIN 107-129 GVALASSIVSFVELUMINEVYS 197-220 LGILMSTFILMSFERINKINK 200-235 PDRLFVERNLGXANSARNEIIY 200	SP P08588 ADRB1 HUMAN	LWISVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	320-349	PDRLEVEENW	LGYANS	AFNPIIY	355-377
SP   047796   ADRBL   INTSVUYLOTASIETLUVIAL 133-154   AYAITSSVVSYYVELCIMAFYLIKY 223-240   OKALKTLGIIMOYFLICKLEPFLIANVVKAF   310-335   PDELVYEFNIGVANSAFRPIIY     SP   025996   ADRBL   INTSVUYLOTASIETLUVIAL 133-154   AYAITSSVVSYYVELCIMAFYLIKY 223-240   OKALKTLGIIMOYFLICKLEPFLIANVVKAF   310-335   PDELVYEFNIGVANSAFRPIIY     SP   75146   ADRBL   INTSVUYLOTASIETLUVIAL 133-154   AYAITSSVVSYYVELCIMAFYLIKY 223-240   OKALKTLGIIMOYFLICKLEPFLIANVVKAF   310-345   PDELVYEFNIGVANSAFRPIIY     SP   950750   ADRBL   INTSVUYLOTASIETLUVIAL 133-154   AYAIASSVVSYYVELCIMAFYLIKY 223-240   OKALKTLGIIMOYFLICKLEPFLIANVVKAF   310-345   PDELVYEFNIGVANSAFRPIIY     SP   950750   ADRBL   INTSVUSUTASIETLUVIAL 133-154   AYAIASSVVSYYVELCIMAFYLIKY 223-240   CKALKTLGIIMOYFLICKLEPFLINNVKAF   309-335   PDELVYEFNIGVANSAFRPIIY     SP   950550   ADRBL   INTSVUSUTASIETLUVIAL 107-120   OXAIASSIVSYYVELUMAFYLIKY   223-240   CKALKTLGIIMOYFLICKLEPFLINNVKAF   309-335   PDELVYEFNIGVANSAFRPIIY   303-325     SP   025050   ADRBL   INTSVUSUTASIETLUVIAL 107-129   OXAIASSIVSYYVELUMAFYLIKY   232-240   CKALKTLGIIMOYFLICKLEPFLINNVKY   275-296   VYILLINNGVNSSFRIVELY   303-325     SP   025050   ADRBL   INTSVESTVEPULINHYVIKY <td< td=""><td>SP P47899 ADRB1_MACMU</td><td>LWTSVDVI</td><td>LCVTASIETLCVIAL</td><td>133-154</td><td>AYAIASSVVSFYVPLCIMAFVYLRVF</td><td>223-248</td><td>QKALK</td><td>TLGIIMGVFTLCWLPFFLANVVKAF</td><td>323-352</td><td>PDRLEVEENW</td><td>LGYANS</td><td>AFNPIIY</td><td>358-380</td></td<>	SP P47899 ADRB1_MACMU	LWTSVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	323-352	PDRLEVEENW	LGYANS	AFNPIIY	358-380
$ \begin{split} \text{SP}[23999] \text{ADBB} = \text{IG}  \text{LMTSUDUCURASIETLUVIA} \\ 133-154  \text{AVALASSVYSTYPECTMAPYULAVE} \\ 222-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 107-350  \text{DREFFERMIC/ABSIETLUVIA} \\ 133-154  \text{AVALASSVYSTYPECTMAPYULAVE} \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 107-36  \text{DREFFERMIC/ABSIETLUVIA} \\ 1133-154  \text{AVALASSVYSTYPECTMAPYULAVE} \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 107-36  \text{DREFFERMIC/ABSIETLUVIA} \\ 1133-154  \text{AVALASSVYSTYPECTMAPYULAVE} \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 107-36  \text{DREFFERMIC/ABSIETLUVIA} \\ 116-137  \text{AVALASSVYSTYPECTMAPYULAVE } \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 107-36  \text{DREFFERMIC/ABSIETLUVIA} \\ 116-137  \text{AVALASSVYSTYPECTMAPYULAVE } \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 206-35  \text{DREFFERMIC/ABSIETLUVIA} \\ 1133-154  \text{AVALASSVYSTYPECTMAPYULAVE } \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 206-35  \text{DREFFERMIC/ABSIETLUVIA} \\ 133-154  \text{AVALASSVYSTYPECTMAPYULAVE } \\ 223-240  \text{CKALTLGIIMOVETUCULEPPELANVVKAF} \\ 206-35  \text{DREFFERMIC/ABSIETLUVIA } \\ 107-120  \text{CMTASSTETUCUVASSTETUCUVASSAFFFII } \\ 344-366  \text{SP}[94597] \text{ADBB} \\ \text{ANDE METSTDUCUVASSIETLUVIA } \\ 107-120  \text{CMTASSTETUCUVASSTETUCUVASSAFFFII } \\ 345-367  \text{SP}[9750] \text{ADBB} \\ \text{ANDE METSTDUCUVASSIETLUVIA } \\ 107-120  \text{CMTASSTETUCUVASSAFFFII } \\ 345-367  \text{SP}[9750] \text{ADBB} \\ \text{ANDE METSTDUCUVASSIETLUVIA } \\ 107-120  \text{CMTASSTETUCUVASSAFFFII } \\ 345-367  \text{SP}[9750] \text{ADBB} \\ \text{ANDE METSTDUCUVASSIETLUVIA } \\ 107-120  \text{CMTASSTETUCUVASSAFFFII } \\ 345-367  \text{SP}[9750] \text{ADBB} \\ \text{ANDE METSTDUCUVASSAFFFII } \\ 107-120  \text{CMTASSTETUCUVASSAFFFII } \\ 345-367  CMT$	SP Q9TT96 ADRB1 BOVIN	LWTSVDVI	LCVTASIETLCVIAL	133-154	GYAITSSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	307-336	PDRLEVEENW	LGYANS	AFNPIIY	342-364
SP [02927] ADBB_SHEEP LMTSTOULCURASIETLUVIA 1133-154 GYAITSSVVSTYPECIMAPYURVE 223-240 GKALTIGUINOVETUGLEPELANVKAF 317-36 PDRIFYERNLGKANSARPEIT 332-264   SP [07916] ADBB_HELGA LMTSTOULCURASIETLUVIA 1133-154 AVALASSVSTYPECIMAPYURVE 223-240 GKALTIGUINOVETUGLEPELANVKAF 317-366 PDRIFYERNLGKANSARPEIT 332-361   SP [07070] ADBB_HELGA LMTSTOULCURASIETLUVIA 1133-154 AVALASSVSTYPECIMAPYURVE 223-240 GKALTIGUINOVETUGLEPELANVKAF 309-338 PDRIFYERNLGKANSARPEIT 334-366   SP [04090] ADBB_HKAT LMTSTOULCURASIETLUVIA 1133-154 AVALASSVSTYPECIMAPYURVE 223-240 GKALTIGUINOVETUGLEPELANVKAF 309-338 PDRIFYERNLGKANSARPEIT 344-366   SP [042574] ADBB_HKAR EMTSTOULCURASIETLUVIA 1107-129 QVALAISSVSTYPECIMAPYURVE 223-240 GKALTIGUINOVETUGLEPELANVKAF 309-338 PDRIFYERNLGKANSARPEIT 343-366   SP [023504] ADBB_HKAR EMTSTOULCURASIETLUVIA 107-129 QVALAISSVSTYPELVIMPYVS 197-220 GEIMMETFICLEPERINIVHUT 175-286 EVYILLINGVANSARPEITCRS 306-325   SP [026399] ADBB2 EMTSTOULCURASIETLUVIA 107-129 QVALAISSVSTYPELVIMPYVS 197-220 GEIMMETFICLEPERINIVHUT 175-286 EVYILLINGVANSARPEITCRS 306-325 SP [04031] ADBB2 EVYILLINGVANSARPEITCRS 306-325 SP [04031] ADBB2 EVYILLINGVANSARPEITCRS 306-325 SP [04041] ADBB2 EVYILLINGVANSARPEITCRS 306-325	SP Q28998 ADRB1_PIG	LWTSVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	222-247	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	310-339	PDRLFVFFNW	LGYANS	AFNPIIY	345-367
SP [979146]ADRB_TELC. LHTSTÖVLCUTASIEILCUIA 133-154 AYALASSVVSTVPLCUTAFYLERV 223-240 (XALKTLGIIMOVTLGULPPELANVVKAF 31-345 PORLFYFFNNLGXANSARPIIY 321-357 SP [970700]ADRB_TRAI. LHTSTÖVLCUTASIEILCUIA 1133-154 AYALASSVJSTVPLCUTAFYLERV 223-240 (XALKTLGIIMOVTLGULPPELANVVKAF 316-351 PORLFYFFNLGXANSARPIIY 321-357 SP [970700]ADRB_TRAI. HTSTÖVLCUTASIEILCUIA 1133-154 AYALASSVJSTVPLCUTAFYLERV 223-240 (XALKTLGIIMOVTLGULPPELANVVKAF 309-335 PORLFYFFNLGXANSARPIIY 344-366 SP [934971]ADRB1_KDLA. KYTSTÖVLCUTASIEILCUIA 1133-154 AYALASSVJSTVPLCUTAFYLERV 223-240 (XALKTLGIIMGVTLGULPPELANVVKAF 309-335 PORLFYFFNLGXANSARPIIY 344-366 SP [93501]ADRB2_HMAN EFWISTÖVLCUTASIEILCUIA 107-129 (AYALASSVJSTVPLUTMFYVIR 121-220-241 (XALKTLGIIMGVTLGULPPELANVVKAF 309-335 PORLFYFFNLGXANSARPIIY 344-366 SP [9028061]ADRB2_HMAN EFWISTÖVLCUTASIEILCUIA 107-129 (AYALASSIVSTVPLUTMFYVIR 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNIGVINSGERPLIYCES 306-325 SP [038044]ADRB2_BOVIN EFWISTÖVLCUTASIEILCUIA 107-129 (AYALASSIVSTVLEUVMFYVS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNIGVINSGERPLIYCES 306-325 SP [038044]ADRB2_DOVIN EFWISTÖVLCUTASIEILCUIA 107-129 (AYALASSIVSTVLEUVMFYVS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVVINSGERPLIYCES 306-325 SP [03807]ADRB2_DCA 107-129 (AYALASSIVSTVLEUVMFYVS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVVINSARPLIYCES 306-325 SP [04842]ADRB2_CANDF KYTSIDVLCUTASIEILCUIA 107-129 (AYALASSIVSTVLEUVMFYVS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVVINSARPLIYCES 306-325 SP [0474]ADRB2_KARD (ANDFO KYTSIDVLCUTASIEILCUIA 107-129 (AYALASSIVSTVLEUVMFYVS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVINSARPLIYCES 306-325 SP [0474]ADRB2_KARD (ANDFO KYTSIDVLCUTASIEILCUIA 107-129 (AYALASSIVSTVLEUVMFYYS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVINSARPLIYCES 306-325 SP [0474]ADRB2_KARD (ANDFO KYTSIDVLCUTASIEILCUIA 107-129 (AYALASSIVSTVPLUVMFYYS 197-220 LGIIMGTTLGULPPETINIYUT 275-298 EVVILLINNGVINSARPLIYCES 306-325 SP [0474]ADRB2_KARD (KNFO KYTSIDVLCUTASIEILCUIA 107-129 (AYALASSIVSTVPLUVMFYYS 197-220 LGIIMGTTLGULPP	SP Q28927 ADRB1_SHEEP	LWTSVDVI	LCVTASIETLCVIAL	133-154	GYAITSSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVETLCWLPFFLANVVKAF	307-336	PDRLEVEENW	LGYANS	AFNPIIY	342-364
SP 075T6 ADR81_FELCA LATSYDVLCYRASIETLCVIAL 133-154 AYALASSTVEFYVPLCUMAFYVL223-248 CKALKTLGIMGYTLCKLPFLANVVKAF 306-315 PDRLVFFMLCKANSARNPITY   SP 075T6 ADR81_MELGA CATSLDVLCYRASIETLCVIAL 133-154 AYALASSTVEFYVPLCUMAFYVL223-248 CKALKTLGIMGYTLCKLPFLANVVKAF 309-338 PDRLVFFMLCKANSARNPITY   SP 043574 ADR81_MCUS LMTSVDVLCYRASIETLCVIAL 133-154 AYALASSTVEFYVPLCUMAFYVL223-248 CKALKTLGIMGYTLCKLPFLANVVKAF 309-338 PDRLVFFMLCKANSARNPITY   SP 043574 ADR81_KUNL FMTSUDVLCYRASIETLCVIAV 107-129 CAYLIASSTVEFVVPLVIMFYVE 213-246   SP 028509 ADR82_HACMU FMTSUDVLCYRASIETLCVIAV 107-129 CAYLIASSTVEFVVPLVIMFYVE 197-220 LGIMGTFLCKLPFFINILWIT 275-298 EVYILLMNGGYNSGENPLIYCES 306-325   SP 028509 ADR82_HACMU EFMTSIDVLCYRASIETLCVIAV 107-129 QYALASSTVEFVPLVIMVFYVS 197-220 LGIMGTFLCKLPFFINILWIT 275-298 EVYILLMNGGYNSGENPLIYCES 306-325   SP 028509 ADR82_CAMCH EFMTSIDVLCYRASIETLCVIAV 107-129 QYALASSTVEFVPLVMMYFYS 197-220 LGIMGTFLCKLPFFINILWI 275-298 EVYILLMNGGYNSARNPLIYCES 306-325   SP 04574 ADR82_MELGA EFMTSIDVLCYRASIETLCVIAV 107-129 QYALASSTVEFVPLVMMYFYS 197-220 LGIMGTFLCKLPFFINILWIT 275-298 EVYILLMNGGYNS	SP P79148 ADRB1_CANLF	LWTSVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	317-346	PDRLEVFENW	LGYANS	AFNPIIY	352-374
SP P07700 ADRE1_MELG CMTSIDULCUTASIETLCUIAI 118-137 AYALASSIEFYFELILMIFYTRWI 206-231 HEALKTLGIHMSFTLGULPFLLWUVFLCWES15 309-335 PDRIFFYFRWLGKANSARPHITY 344-366   SP P4370 ADRE1_RAT HTNSTUDUCUTASIETLCUIAI 133-154 AYALASSUSFYVELUNAFYTRYE 223-246 OKALKTLGIHMSFTLGULPFELNWUVKF 309-335 PDRIFFYFRWLGKANSARPHITY 344-366   SP P0350 ADRE2_HUAN EFWISIDUCUTASIETLCUIAI 107-129 QAYALASSUSFYVELUNMFYVE 197-220 LGIHMSFTLGULPFELNWUVKF 260-237 EVYILLMUCGWANSARPHITYRS 306-325   SP 02804 ADRE2_HUAN EFWISIDUCUTASIETLCUIAV 107-129 QAYALASSUSFYVELUNMFYVS 197-220 LGIHMSFTLGULPFELNWUNFV 275-298 EVYILLMWUGWNSARPHITYRS 306-325   SP 02804 ADRE2_CAULF EFWISIDUCUTASIETLCUIAV 107-129 QAYALASSUSFYVELUNMFYVS 197-220 LGIHMSFTLGULPFELWUNHVI 275-298 EVYILLMWUGWNSARPHITYRS 306-325   SP 02804 ADRE2_CAULF EFWISIDUCUTASIETLCUIAV 107-129 QAYALASSUSFYVELUNMFYVS 197-220 LGIHMSFTLGULPFELWUNHVI 275-298 EVYILLMWUGWNSARPHITYRS 306-325   SP 02804 ADRE2_CAULF EFWISIDUCUTASIETLCUIAV 107-129 QAYALASSUSFYVELUNMFYVS 197-220 LGIHMSFTLGULPFELWUNHVI 275-298 EVYILLMWUGWNSARPHITYRS 306-325   SP 04274 ADRE3_CAULF EFWISIDUCUTASIETLCUIAV 107-129 QAYALASSUSFYVELUNMFYYS 197-220 LGIHMSFTLGULPFELWUNHVY 175-288 EVYILLMUGWNSARPHITYRS 306-325   SP 04274 A	SP Q9TST6 ADRB1_FELCA	LWISVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	316-345	PDRLEVFENW	LGYANS	AFNPIIY	351-373
SP   210301 ADREL FAT LNTSVD/LUVTASTETLC/IAL 133-154 AYALASSVDSFYVE/LUNAFYIRVE 223-240 OKALKTIGING/FTLC/LPFELANVVKF 309-335 PDRIFYFYRMLG/ANSARPHITY 344-366   SP   24571 ADREL MOREL LNTSVD/LUVTASTETLC/IAL 133-154 AYALASSVDSFYVE/LUNAFYIRVE 223-246 OKALKTIGING/FTLC/LPFELANVVKF 309-335 PDRIFYFYRMLG/ANSARPHITY 334-326   SP   025501 ADREL MARKI FUNCTASTETLC/IAV 107-129 OXALASSVDSFYVE/LUNAFYYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPLI/CRS 306-325   SP   028041 ADREL / LUAN FEWISID/LUVTASTETLC/IAV 107-129 OPYILASSVDSFYVE/LUVAFYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPLI/CRS 306-325   SP   028047   ADREL / ENTSID/LUVTASTETLC/IAV 107-129 OPYILASSVSFYVE/LUVAFYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPLI/CRS 306-325   SP   04574   ADREL / ENTSID/LUVTASTETLC/IAV 107-129 OAYALASSVSFYVE/LUVAFYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPLI/CRS 306-325   SP   04574   ADREL / ENTSID/LUVTASTETLC/IAV 107-129 OAYALASSVSFYVE/LUVAFYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPLI/CRS 306-325   SP   04574   ADREL / ENTSID/LUVTASTETLC/IAV 107-129 OAYALASSVSFYVE/LUVAFYS 197-220 LGINGFTLC/LPFE/NUNUYI 275-296 EVYILLMWG/WNSGRPNLI/CRS 306-325   SP   04574   ADREL / ENTSID/LUVTA	SP P07700 ADRB1_MELGA	CWISLDVI	LCVTASIETLCVIAI	116-137	AYAIASSIISFYIPLLIMIFVYLRVY	206-231	HKALK	TLGIIMGVFTLCWLPFFLVNIVNVF	286-315	PDWLFVFFNW	LGYANS	AFNPIIY	321-343
SPP39193971AVALASSVVSTVPLELVARVIEVT2P23-248CKALKTLGIIMOYTLCMULPFELANVKAF 309-338PDELEFUFFNLUGANSAFNPIIT344-366SPP0025501AVALASSUSSTVPLINIFYTRYP220CGIIMOTTLCMULPFELANVKAF 309-338PDELEFUFFNLUGANSAFNPIIT304-366SPP0025501AVALASSUSSTVPLINIFYTRY197-220CGIIMOTTLCMULPFETINIVEVTPDELEFUFFNLUGANSAFNPIIT306-325SPP002501AVALASSUSSTVPLINIFYTS197-220LGIIMOTTLCMULPFETINIVEVT275-298EVTILINUGANSAFNPIITCS306-325SPP0280971AVALASSUSSTVPLINIFYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPIITCS306-325SPP0280971ADADZCANIASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPIITCS306-325SPP0287551ADADZCANIASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPIITCS306-325SPP0287551ADADZAVALASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPIITCS306-325SPP028751ADADZAVALASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPIITCS306-325SPP028751ADADZAVALASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPLITCS306-325SPP028751ADADZAVALASSIVSTVPLUMMEYTS197-220LGIIMOTTLCMULPFETINIVENI275-298EVTILINUGANSAFNPLITCS306-325SP <td< td=""><td>SP P18090 ADRB1_RAT</td><td>LWISVDVI</td><td>LCVTASIETLCVIAL</td><td>133-154</td><td>AYAIASSVVSFYVPLCIMAFVYLRVF</td><td>223-248</td><td>QKALK</td><td>TLGIIMGVFTLCWLPFFLANVVKAF</td><td>309-338</td><td>PDRLEVEENW</td><td>LGYANS</td><td>AFNPIIY</td><td>344-366</td></td<>	SP P18090 ADRB1_RAT	LWISVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	309-338	PDRLEVEENW	LGYANS	AFNPIIY	344-366
SP 042574 ADRB1_KENLA FWISTØVLCUTASIETLCVIST 110-131 AVALASSIISSYPLLIMFYYIS 20.3-226 GKALKIGIHMOFFILANUMPY 26.2-37 PDKLIFLENNLGYANSAFNEITY 30.3-225   SP 025059 ADRB2_MACMU EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYVELUMPYYS 197-220 LGIHMOFFILGUPEFVINIVAVI 275-298 EVVILLNVUGVISGRPLIYCRS 306-325   SP 022641/ADRB2_DIG EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYLEULWAFYYS 197-220 LGIHMOFFILGUPEFVINIVAVI 275-298 EVVILLNVUGVISGRPLIYCRS 306-325   SP 0226931 ADRB2_FIG EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYLEULWAFYYS 197-220 LGIHMOFFILGUPEFVINIVENI 275-298 EVVILLNVUGVISGRPLIYCRS 306-325   SP 03755 ADRB2_FELCA EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYLEUWMYFYS 197-220 LGIHMOFFILGUPFFVINIVUT 275-298 EVVILLNVUGVUSAFNELIYCRS 306-325   SP 04741 ADR2_MESAL EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYLEUWMYFYS 197-220 LGIHMOFFILGUPFFVINIVUT 275-298 EVVILLNVUGVUSAFNELIYCRS 306-325   SP 04741 ADR2_MESAL EFWISTØVLCUTASIETLCVIAV 107-129 QAVALASSIVSSYLEUWMYFYS 197-220 LGIHMOFFILGUPFFVINIVUT 275-298 EVVILLNVUGVUSAFNELIYCRS 306-325 SVILLNVUGVUSAFNELIYCRS	SP P34971 ADRB1_MOUSE	LWTSVDVI	LCVTASIETLCVIAL	133-154	AYAIASSVVSFYVPLCIMAFVYLRVF	223-248	QKALK	TLGIIMGVFTLCWLPFFLANVVKAF	309-338	PDRLEVFFNW	LGYANS	AFNPIIY	344-366
SPDOTSON LARB2_HUMAN EFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYUPLIMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMUGVMSSGNELIYCRS 306-325SPQ28044 LARB2_BOVIN EFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYUPLIMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMUGVMSSGNELIYCRS 306-325SPQ28044 LARB2_CANLF EFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMVGVMSSGNELIYCRS 306-325SPQ59125520CANLF EFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMVGVMSAFNPLIYCRS 306-325SPQ59125521DARE2_CANLF EFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMVGVMSAFNPLIYCRS 306-325SPQ5042741 LARB2_CAVP FWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMVGVMSAFNPLIYCRS 306-325SPP1020081 DARB2_AMESAEFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMUGVMSAFNPLIYCRS 306-325SPP1020081 DARB2_AMESAEFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMUGVMSAFNPLIYCRS 306-325SPP104214 LARB2_CAVPAEFWISIDVLCVTASIETLCVIAV 107-129QAYALASSIVSFYLPLVMVFYS197-220LGIIMGTETLCMLPFFIVNIVAVI 275-298EVVILLMUGVMSAFNPLIYCRS 306-325SPP104214 LARB2_CAVPAEFWISIDVLCVTASIETLCVIAVI 107-129QAYALASSIVSFYLPLVMVFYS197-220LGII	SP 042574 ADRB1_XENLA	FWISVDVI	LCVTASIETLCVISI	110-131	AYAIASSIISFYFPLIIMIFVYIRVF	201-226	QKALK	TLGIIMGTFTLCWLPFFLANVVNVF	268-297	PDKLFLFLNW	LGYANS	AFNPIIY	303-325
SPC285091ADR82_MACMU EFWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMVFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVYILLNWVGVMSGRNPLIVCRS 306-325SPC280971ADR82_FIGEFWISIDVLCVTASIETLCVIAV 107-129OPVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVYILLNWVGVMSGRNPLIVCRS 306-325SPC9289971ADR82_FIGEFWISIDVLCVTASIETLCVIAV 107-129OPVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVYILLNWVGVMSGRNPLIVCRS 306-325SPSPOSTSTSIADR82_CANDFWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVYILLNWVGVMSGRNPLIVCRS 306-325SPPG42741ADR82_CANDFWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVYILLNWUGVMSGRNPLIVCRS 306-325SPPG42741ADR82_MEGAUEHWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVVILLNWUGVMSGRNPLIVCRS 306-325SPPG42741ADR82_MEGAUEHWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVVILLNWUGVMSGRNPLIVCRS 306-325SPPG4311ADR82_MEGAUEHWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVVILLNWUGVMSGRNPLIVCRS 306-325SPPG45214ADR83LORBE_CANCHEHWISIDVLCVTASIETLCVIAV 107-129OAVAIASSIVSTVELUMMFYYS197-220LGIIMGTFLICMLPFFVNIVMVI 275-296EVVILLNULGVMSGRNPLIVCRS 306-325SPPG45214ADR83LORBE_CANCHEHWISIDVLCVTASIETLCVIAV 107-129OAV	SP P07550 ADRB2_HUMAN	EFWISIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYVPLVIMVFVYS	197-220		LGIIMGIFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	IGYVNS	GFNPLIYCRS	306-329
SP (202044) ADRB2_BOVIN EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-296 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (202097) ADRB2_FLG EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-296 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (204751) ADRB2_FLG EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-296 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (204751) ADRB2_FLG EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-295 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (20474) ADRB2_CAVPO FWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-295 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (20474) ADRB2_MESA EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-295 EVYILLMAUGVINSAFNELIYCRS 306-325   SP (204051) ADRB2_ART EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHVI 275-296 EVYILLMUGVNSAFNELIYCRS 306-325   SP (204051) ADRB2_TISCT EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHI 201-226 EVYILLMUGVNSAFNELIYCRS 306-325   SP (20474) ADRB2_ONCHY EFWISIDVLCVTASIETLCVIAV 107-129 OPXALASSIVSFYLEUWAVFYYS 197-220 LGIIMGTFTLCMLPFFIVNLVHI 275-296 EVYILLMUGVNSAFNELIYCRS 306-325 <td< td=""><td>SP Q28509 ADRB2_MACMU</td><td>EFWTSIDVI</td><td>LCVTASIETLCVIAV</td><td>107-129</td><td>QAYAIASSIVSFYVPLVIMVFVYS</td><td>197-220</td><td></td><td>LGIIMGTFTLCWLPFFIVNIVHVI</td><td>275-298</td><td>EVYILLNW</td><td>VGYVNS</td><td>GFNPLIYCRS</td><td>306-329</td></td<>	SP Q28509 ADRB2_MACMU	EFWTSIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYVPLVIMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	VGYVNS	GFNPLIYCRS	306-329
SP (28997) ADR82_PIG EFWISIDVLCVTASIEILCVIAV 107-129 OPYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRGI 275-298 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (96433) ADR82_CALLS EFWISIDVLCVTASIEILCVIAV 107-129 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-298 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (964274) ADR82_FELCA EFWISIDVLCVTASIEILCVIAV 107-129 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-298 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (964274) ADR82_MESAU EFWISIDVLCVTASIEILCVIAV 107-129 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-298 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (964274) ADR82_MESAU EFWISIDVLCVTASIEILCVIAV 107-129 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-298 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (964274) ADR82_MESAU EFWISIDVLCVTASIEILCVIAV 107-129 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-296 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (96452) ADR82_MESAU EFWISIDVLCVTASIEILCVIAV 33-55 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-296 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (96451) ADR82_MESAU EFWISIDVLCVTASIEILCVIAV 33-55 OAYALASSIVSFYLEUVMVFYS 197-220 LGIIMGTEILCWLPFFIVNIVRUI 275-296 EVYILLNWUGYUSASPRELIYCRS 306-325   SP (	SP Q28044 ADRB2_BOVIN	EFWTSIDVI	LCVTASIETLCVIAV	107-129	QPYAIASSIVSFYLPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EIYILLNW	LGYINS	AFNPLIYCRS	306-329
SPP54033ADRB2CALLE FEWTSIDVLCUTASIETLCVIAV107-129QAYALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVI275-296EVVILLNVGVDISASRPELIYCRS306-325SPQ64241ADRB2CANDOFWTSIDVLCUTASIETLCVIAV101-129QAYALASSIVSFYLEUVMVFVY197-220LGIIMSTFTLCMLPFFVNIVIV275-295EVVILLNVGVDISASRPELIYCRS306-325SPP404241ADRB2MESAUEHVTSIDVLCUTASIETLCVIAV107-129QAYALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNVGVDISASRPELIYCRS306-325SPP104001ADRB2REATEHVTSIDVLCUTASIETLCVIAV107-129QAYALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNVLGVDISAFRELIYCRS306-325SPP104021ADRB2RATEHVTSIDVLCUTASIETLCVIAV107-129QAYALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNVLGVDISAFRELIYCRS306-325SPP104021ADRB2REVTSIDVLCUTASIETLCVIAV107-129QAYALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNVLGVDISAFRELIYCRS306-325SPP04051ADRB2TSCAVALASSIVSFYLEUVMVFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNULGVUSAFRELIYCRS306-325SPP04052IADRB2REVTSIDVLCUTASIETLCALAV107-129QAYALASSIVSFYLEUVMFVYS197-220LGIIMSTFTLCMLPFFVNIVIVIVI275-296EVVILLNULGVUSAFRELIYCRS306-325SPP040510ADRB2REVTSIDVLCUTASIETLCA	SP Q28997 ADRB2_PIG	EFWISIDVI	LCVTASIETLCVIAV	107-129	QPYAIASSIVSFYLPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHGI	275-298	EVYILLNW	VGYVNS	AFNPLIYCRS	306-329
SP   05755   ADRB2_FELCA EFWISIDVLCUTASIETLCVIAV 107-1290AVAIASSIVSFUELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNWUGVUSASPRELIVCE 307-327SP   064274   ADRB2_MESAU EFWISIDVLCUTASIETLCVIAV 107-1290AVAIASSIVSFVLELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 307-327SP   064274   ADRB2_MESAU EFWISIDVLCUTASIETLCVIAV 107-1290AVAIASSIVSFVVELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   10600   DARDE_PATEFWISIDVLCUTASIETLCVIAV 107-1290AVAIASSIVSFVVELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   047043   ADRB2_MESUEFWISIDVLCUTASIETLCVIAV 33-550AVAIASSIVSFVPELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   047043   ADRB2_MERUEFWISIDVLCUTASIETLCVIAV 33-550AVAIASSIVSFVPELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   047043   ADRB2_MERUEFWISIDVLCUTASIETLCULAV 107-1290AVAIASSIVSFVPELUWMEYVS197-220LGIIMOTFILCULPFETVNIVWI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   047043   ADRB2_MERUADRB2_MERUCAVAIASSIVSFVPELUWMEYVS197-220LGIIMOTFILCULPFETVNIVVI 275-296EVVILLNUGVUSASPRELIVCE 306-325SP   04704   ADRB2_MERUADRB2_MERUCAVAIASSIVSFVPELUWMEYVS197-220LGIIMOTFILCULPFETVNIVVIVI 275-296EVVILLNUGVUSASPRELIVCE 307-307SP   04254   ADRB3   ADRB4LMTSVDVLCUTASIETLCALAV 112-133YULSSSVSFVELUWHEYYA200-225LGIIMOTFILCULPFETVNIVVIVI 233-314AFLAINUGVASASPRELIVCE 373-307SP   04554	SP P54833 ADRB2_CANLF	EFWISIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYLPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	VGYVNS	AFNPLIYCRS	306-329
SP [048424] ADRB2_CAVPO FWTSIBVLCUTASIBITLOVIA 108-128 AVAIASSIVSFYLPLUWMFYYS 199-218 LGIIMGTETLCMLPFFTINIV 278-255 VILLNAWGYMSASHPLIYCE 307-327   SP [04274] ADRB2_CAVPO FWTSIBVLCUTASIBITLOVIAV 107-129 GAVAIASSIVSFYLPLUWMFYYS 197-220 LGIIMGTETLCMLPFFTINIVUWIT 275-250 EVVILLNUGYMSASHPLIYCE 306-325   SP [04761] ADRB2_MESA EFWTSIBVLCUTASIBITLOVIAV 107-129 GAVAIASSIVSFYLPLUWMFYYS 197-220 LGIIMGTETLCMLPFFTINIVUWIT 275-250 EVVILLNUGYMSASHPLIYCE 306-325   SP [04761] ADRB2_MERN EFWTSIBVLCUTASIBITLOVIAV 107-129 GAVAIASSIVSFYLPLUWMFYYS 197-220 LGIIMGTETLCMLPFFTINIVUWIT 275-250 EVVILLNUGYMSASHPLIYCE 306-325   SP [04761] ADRB2_MERN EFWTSIBVLCUTASIBITLOVIAV 33-55 GAVAIASSIVSFYLPLUWMFYS 197-220 LGIIMGTETLCMLPFFTUNIVKIT 275-250 EVVILLNUGYMSASHPLIYCE 306-325   SP [04561] ADRB3_MERD EFWTSIBVLCUTASIBITLOVIAVIST 910-4571 LGIIMGTETLCMLPFFTUNIVKIT 275-240 EVVILLNUGYMSASHPLIYCE 306-325   SP [04561] ADRB3_MERD EFWTSIBVLCUTASIBITLOVIAVIST 310-337 LGIIMGTETLCMLPFFUNIVKIT 275-347 EVVILLNUGYMSASHPLIYCE 307-375   SP [045524	SP Q9TST5 ADRB2_FELCA	EFWTSIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYLPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	VGYVNS	AFNPLIYCRS	306-329
SP PO4274 ADRE2_MESAU EFWISIDVLCVTASIETLCVIAV 107-129 QAYALASSIVSFYVPLVMVFYS 197-220 LGIIMGTETLCMLPFFVNIVIVI 275-296 EVVILLINLGVNSASPRELIYCRS 306-325   SP PL01009 LORDE_BAT EFWTSIDVLCVTASIETLCVIAV 107-129 QAYALASSIVSFYVPLVMVFYS 197-220 LGIIMGTETLCMLPFFVNIVIVI 275-296 EVVILLINLGVNSASPRELIYCRS 306-325   SP PL01009 LORDE_BAT EFWTSIDVLCVTASIETLCVIAV 107-129 QAYALASSIVSFYVPLVMVFYS 197-220 LGIIMGTETLCMLPFFVNIVHVI 275-296 EVVILLINLGVNSASPRELIYCRS 306-325   SP QAVALASSIVSFYVPLVMVFYS 123-216 LGIIMGTETLCMLPFFVNIVHI 275-296 EVVILLINLGVNSASPRELIYCRS 306-325   SP QAVALASSIVSFVPLVMVFYS 197-220 LGIIMGTETLCMLPFFVNIVHI 203-306 INNIGVASASPRELIYCRS 306-325   SP QAVALASSIVSFVPLVMVFYS 197-220 LGIIMGTETLCMLPFFVNIVHI 203-306 INNIGVASASPRELIYCRS 306-325   SP QAVALASSIVSFVPLLVMLFYG 200-223 LGIIMGTETLCMLPFFVNIVHI 233-304 INNIGVASASPRELIYCR 306-325   SP PL045616 JORBE JAVADSVCVTASIETLCALAV 112-133 YVLLSSVSYUPULVMEFY 200-225 LGIIMGTETLCMLPFFVNIVVI 233-314 AFLAINLGVASASPRELIYCR 307-347   SP PL045616 JORBE JAVADSVCVTASIETLCALAV 112-133 YALLSSVSYSTUPLLVMEFYA 204-225 TLGLIMGTETLCMLPFFVNIVV	SP Q8K4Z4 ADRB2_CAVPO	FWTSIDVI	LCVTASIETLCVIA	108-128	AYAIASSIVSFYLPLVVMVFV	198-218		LGIIMGTFTLCWLPFFIVNIV	275-295	VYILLNW	VGYVNS	AFNPLIYC	307-327
SP  P10600 ADRB2_RAT EFWTSIDVLCUTASIEITLCVIAV 107-129 QAYALASSIVSTYDEUWMYFYS 197-220 LGIIMGTFILCMLPFFIVNIVMYI 275-290 EVVILLINLGYNASAFNELIYCRS 306-325 SP  070431 ADRB2_MERUN EFWTSIDVLCUTASIEITLCVIAV 33-55 QAYALASSIVSTYDEUWMYFYS 197-220 LGIIMGTFILCMLPFFIVNIVMYI 275-290 EVVILLINLGYNASAFNELIYCRS 306-325 SP  070431 ADRB2_MERUN EFWTSIDVLCUTASIEITLCVIAV 33-55 QAYALASSIVSTYDEUWMYFYS 197-220 LGIIMGTFILCMLPFFIVNIVMAI 201-224 EVVILLINLGYNASAFNELIYCRS 306-325 SP  070431 ADRB2_MERUN EFWTSIDVLCUTASIEITLCVIAV 132-93 QAYALASSIVSTYDEUWMYFYS 197-220 LGIIMGTFILCMLPFFIVNIVMI 275-296 EVVILLINLGYNASAFNELIYCRS 306-325 SP  070431 ADRB2_NCMU FFFIANUCUTASIEITLCVIAV 110-132 QAYALASSIVSTYDEUWMFYYS 197-220 LGIIMGTFILCMLPFFIVNIVMI 275-296 EVVILLINLGYNASAFNELIYCRS 306-325 SP  070431 ADRB2_NCMU FFFIANUCUTASIEITLCVIAV 110-132 QAYALASSIVSTYDEUWMFYYS 197-220 LGIIMGTFILCMLPFFINNUV 275-296 EVVILLINLGYNASAFNELIYCRS 306-325 SP  030421 ADRB3_MERUN LMTSVDVLCUTASIEITLCALAV 112-133 VXLLSSVSYETUELUMIFYX 204-225 ILGLIMGTFILCMLPFFVANVVI 293-314 AFIAINNLGYANSAFNELIYC 327-347 SP  045251 ADRB3_BOVIN LMTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVNNVV 293-314 AFIAINNLGYANSAFNELIYC 327-347 SP  045251 ADRB3_SHEEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVNNVV 293-314 AFIAINNLGYANSAFNELIYC 327-347 SP  045541 ADRB3_SHEEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVNNVV 293-314 AFIAINNLGYANSAFNELIYC 327-347 SP  045541 ADRB3_CANEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVNNVV 293-314 AFIAINNLGYANSAFNELIYC 327-347 SP  045541 ADRB3_CANEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVNNVV 293-314 TFIAINNLGYANSAFNELIYC 327-347 SP  045541 ADRB3_CANEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVANVV 293-314 TFIAINNLGYANSAFNELIYC 327-347 SP  045541 ADRB3_CANEP LWTSVDVLCUTASIEITLCALAV 112-133 VALLSSVSFYLELUMIFYXA 204-225 ILGLIMGTFILCMLPFFVANVV 293-314 TFIAINNLGYANSAF	SP P04274 ADRB2_MESAU	EFWISIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYVPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	LGYVNS	AFNPLIYCRS	306-329
SP P13762 ADR82_MOUSE FEWTSIDVLCUTASIETLCVIAV 107-129 QAYAIASSU'SSYUPLUWMEYYS 197-220 LGIIMGTETLCMLPFFUNUVMUT 275-298 EVVILLNALGYMSAENELIYCRS 236-325   SP Q70431 ADR82_MENDETYCS LGIIMGTETLCMLPFFUNUVMUT 201-226 EVVILLNALGYMSAENELIYCRS 236-325 EVVILLNALGYMSAENELIYCRS 236-325   SP Q4WL2 ADR82_TSCTR EFWTSIDVLCUTASIETLCVIAV 107-129 QAYAIASSU'SSYUPLUWMEYYS 197-220 LGIIMGTETLCMLPFFUNUVHUT 207-208 EVVILLNALGYMSAENELIYCRS 236-325   SP Q4WL2 ADR82_TSCTR EFWTSIDVLCUTASIETLCVIAV 107-129 QAYAIASSU'SSYUPLUWMEYG 200-223 LGIIMGTETLCMLPFFUNUVHUT 293-314 AFLAINULGYMSAENELIYCRS 319-337   SP Q43524 ADR83_HUMAN LMTSVDVLCUTASIETLCALAV 112-133 YVLLSSSVSFYLPLLWMEFYA 204-225 TLGLIMGTETLCMLPFFLANVL 293-314 AFLAINULGYMSAENELIYCR 327-347   SP Q45252 ADR83_HGCMU LMTSVDVLCUTASIETLCALAV 112-133 YALLSSSVSFYLPLLWMEFYA 204-225 TLGLIMGTETLCMLPFFVANVV 293-314 AFLAINULGYMSAENELIYC 327-347   SP Q5252 ADR83_FIG LMTSVDVLCUTASIETLCALAV 112-133 YALLSSSVSFYLPLLWMEFYA 204-225 TLGLIMGTETLCMLPFFVANVV 293-314 AFLAINULGYMSAENELIYC 327-347 327-347   SP Q5252 ADR83_FIG LMTSVDVLCUTASIETLCALAV 112-133 YALLSSSVSFYLPLLWMEFYA 204-225 TLGLIMGTETLCMLPFFVANVV 293-314 AFLAINULGYMSAENELIYC <	SP P10608 ADRB2_RAT	EFWTSIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYVPLVVMVFVYS	197-220		LGIIMGTETLCWLPPPIVNIVHVI	275-298	EVYILLNW	LGYVNS	AFNPLIYCRS	306-329
SP  OTWOIS    ADDRE_TESTED REWON DEWISIDVLOUTASIETLOLIAN 33-55 OKALARSENSETVEDUWERYNS 123-146 LGIIMETFILOMLDEFINDUDEFINNUNAL 201-224 EVYILLANLOGWASAFNELLYCRS 366-325 SP   OGWUSE  ADDRE_TESTED REWISIDVLOUTASIETLOLIAN 112-133 VALLSSUSSYLELUMERYNS 197-220 LGIIMETFILOMLPFFINNUN VINT 233-306 LNHIGGANSAFNELLYCRS 366-325 SP   OGWUSE  ADDRES_TOKUT ENTITADVLOUTASIETLOLIAN 112-133 VALLSSUSSYLELUMERYNS 200-223 LGIIMETFILOMLPFFINNUN 233-314 AFLAINHUGANSAFNELLYCRS 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LGIIMETFILOMLPFFINNUN 293-314 AFLAINHUGANSAFNELLYCR 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LGIIMETFILOMLPFFINNUN 293-314 AFLAINHUGANSAFNELLYCR 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LGIIMETFILOMLPFFINNUN 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LGIIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LGIIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLELUMERYNS 201-225 LIGLIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLETULAN 112-133 VALLSSUSSYLEUMERYNS 201-225 LIGLIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLETULAL 112-133 VALLSSUSSYLEUMERYNS 201-225 LIGLIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLETULAL 112-133 VALLSSUSSYLEUMERYNS 201-225 LIGLIMETFILOMLPFFUNNUV 293-314 AFLAINHUGANSAFNELLYC 327-347 SP   OZSAFLANDUS VALLSSUSSYLEUMERYNS 201-225 LIGLIMETFILOMPFFUNNUVAL 294-317 AFLANDUSANSAFNELLYC 325-345 SP   OZGAFLANDUS VALLSSUSSYLEUM	SP P18762 ADRB2_MOUSE	EFWTSIDVI	LCVTASIETLCVIAV	107-129	QAYAIASSIVSFYVPLVVMVFVYS	197-220		LGIIMGTFTLCWLPFFIVNIVHVI	275-298	EVYILLNW	LGYVNS	AFNPLIYCRS	306-329
SP QHWL2 ADRE_ISCIR EWISIDVLCUTASIEILCUIAL 110-132 AATAASSI'SSYUSTYELDWIFYYS 200-223 LGIIMGTEICULPFYLIVNUVH'I 23-364 AFALAINLGVANSAFNELIUG'S 319-373 SP P13945 ADREB_UNAN LWISTDVLCUTASIEILCUIAL 110-132 AATAASSU'SSYUSTYELDWIFYY 200-223 LGIIMGTEICULPFYLANVL 293-314 AFILAINLGVANSAFNELIUG'S 319-373 SP P13945 ADREB_MUNAN LWISTDVLCUTASIEILCUIAL 112-133 YULLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYLANVL 293-314 AFILAINLGVANSAFNELIUG'S 327-347 SP P46626 ADRB3_BOVIN LWISTDVLCUTASIEILCUIAL 112-133 YULLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 AFILAINLGVANSAFNELIUG'S 327-347 SP P46626 ADRB3_BOVIN LWISTDVLCUTASIEILCUIAL 112-133 YULLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 AFILAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_BOVIN LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 TFILAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHI LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 TFILAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHI LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 TFILAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHI LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFYNNVV 293-314 TFILAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHI LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFFYNNV 293-314 ALLAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHO LWISTDVLCUTASIEILCUIAL 112-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFFYNNV 293-314 ALLAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHO LWISTDVLCUTASIEILCUIAL 110-133 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFFYNNV 293-314 ALLAINLGVANSAFNELIUG'S 327-347 SP QSXIS7 ADRB3_CAPHO LWISTDVLCUTASIEILCUIAL 100-130 YALLSSVSFYLELUMIFYY 200-225 ILGLIMGTEICULPFFYNNV 293-314 YLLINGVANSAFNELIUG'S 325-345 SP QG043 ADRB3_CAPHO LWISTDVLCUTASIEILCUIAL 109-130 YALLSSVSFYLELUMIFYY 200-222 ILGLIMGTEICULPFYLANVL 290-311 YLLINGVANSAFNELIUG'S 325-345 SP QS0453 ADRB3_CAPHO LWISTDVLCUTASIEILCUIAL 109-130 YA	SP 070431 ADRB2_MERUN	EFWISIDVI	LEVIASIETLEVIAV	33-55	QAYAIASSIVSEYVPLVVMVEVYS	123-146		LGIIMGTETLCWLPFFIVNVVHAI	201-224	EVYILLNW	LGYVNS	AFNPLI	232-251
SP [00016] ALREAD LORDED FILLOWING LOW ARDITLOCHAR 110-132 ALRAVARSAVUSETIFLELWERFUG 200-223 LGIINGTETLOWIPPTLANVL 233-314 AFLAINUGANASAMPLICCE 327-347 SP [023524] ADRED ALMAR LWTSDVLCUTASIETLOLIAV 112-133 YVLLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTLANVL 233-314 AFLAINUGANASAMPLICC 327-347 SP [023524] ADRED FILLOWIPPTLANVL 233-314 AFLAINUGANASAMPLICC 327-347 SP [035252] ADRED FILS THE SVECUCTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTLANVL 233-314 AFLAINUGANASAMPLICC 327-347 SP [035252] ADRED FILS THE SVECUCTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 AFLAINUGANASAMPLICC 327-347 SP [035252] ADRED FILS THE SVECUCTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 AFLAINUGANASAMPLICC 327-347 SP [035252] ADRED CALLE LWTSDVLCUTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 TELAINUGANASAMPLICC 327-347 SP [035757] ADRED CALLE LWTSDVLCUTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 TELAINUGANASAMPLICC 327-347 SP [035757] ADRED CALLE LWTSDVLCUTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 ALLAINUGANASAMPLICC 327-347 SP [03574] ADRED CALLE LWTSDVLCUTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 ALLAINUGANASAMPLICC 327-347 SP [03574] ADRED CALLE LWTSDVLCUTASIETLOLIAV 112-133 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 ALLAINUGANASAMPLICC 327-347 SP [03574] ADRED CALLE LWTSDVLCUTASIETLOLIAV 110-130 YALLSSSVSFTLELWERFUG 200-225 TLGLIMGTETLOWIPPTVNVV 233-314 ALLAINUGANASAMPLICC 327-347 SP [03574] ADRED CALLE LWTSDVLCUTASIETLOLIAV 110-130 YALLSSSVSFTLELWERFUG 200-225 TLGLIMERFUNU 230-317 AV SP [04043] ADRED CALLE LWTSDVLCUTASIETLOLIAV 109-130 YALLSSSVSFTLELWERFUG 201-222 TLGLIMERFUNU 240-317 VELIANUGANASAMPLICC 325-345 SP [040453] ADRED CALLE LWTSDVLCUTASIETLOLIAV 109-130 YALLSSSVSFTLELWERFUG 201-222 TLGLIMERFUNU 240-317 VELIAMUGANASAMPLICC 325-345 SP [040453] ADRED CALLE LWTSDVLCUTASIETLOLIAV	SP Q4KWL2 ADRB2_ISCIR	EFWISIDVI	LEVTASIETLEVIAV	107-129	QAYALASSIVSEYVPLVVMVEVYS	197-220		LGIIMGIFILCWLPFFIVNIVHVI	275-298	EVILLINW	LGIVNS	AFNPLIYCRS	306-329
SP 23534 ADB3_HOARA LWISVULUUTASIEILULALAV 112-133 VULUSSUSSIEILUMIEVIA 204-225 ILGIMOTFILUMIEVIA 293-314 AFIALMULUGANSAFNELIUC 327-347 SP 24626 ADB3B_BOVIN LWISVULUUTASIEILULALAV 112-133 VULUSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUL 233-314 AFIALMULUGANSAFNELIUC 327-347 SP 29525 ADB3B_DVIN LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 AFIALMULUGANSAFNELIUC 327-347 SP 205252 ADB3B_PIG LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 TFIALMULUGANSAFNELIUC 327-347 SP 205751 ADB3B_CAPHI LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 TFIALMULUGANSAFNELIUC 327-347 SP 205751 ADB3B_CAPHI LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 TFIALMULUGANSAFNELIUC 327-347 SP 205751 ADB3B_CAPHI LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 ALLANUUGANSAFNELIUC 327-347 SP 205751 ADB3B_CAPHI LWISVULUUTASIEILULALAV 112-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 ALLANUUGANSAFNELIUC 327-347 SP 205754 ADB3B_CAPHO LWISVULUUTASIEILULALAV 110-133 VALLSSUSSIVETUELUMIEVIA 204-225 ILGIMOTFILUMIEPTIANUU 293-314 ALLANUUGANSAFNELIUC 327-347 SP 205754 ADB3B_CAPHO LWISVULUUTASIEILULALV 110-133 VALLSSUSSIVETUELUMIEVIA 202-225 LGIMOTFILUMIEPTIANUU 294-317 PAFIALMUUGANSAFNELIUC 327-347 SP 205754 ADB3B_CAPHO LWISVULUUTASIEILULALV 110-133 VALLSSUSSIVETUELUMIEVIA 202-225 LGIMOTFILUMIEPTIANUU 294-317 PAFIALMUUGANSAFNELIUC 325-345 SP 205754 ADB3B_CAPHO LWISVULUUTASIEILULALV 110-130 VALLSSUSSIVETUELUMIEVIA 201-222 ILGIMOTFILANUU 294-317 VILLENANUUGANSAFNELIUC 325-345 SP 220554 ADB3B_CAVPO LWISVULUUTASIEILULALV 109-130 VALLSSUSSIVETUELUMIEVIA 201-222 ILGIMOTFILANUU 290-311 VITAINUUGANSAFNELIUC 325-345 SP 22554 ADB3B_CAUPE LWISVULUUTASIEILULALV 109-130 VALLSSUSSIVETUELUMIEVIA 201-222 ILGIMOTFILANUU 290-311 VITAINUUGANSAFNELIUC 325-345	SP Q800Y8 ADRB2_ONCMY	EFWTAADVI	LCVTASIETLCVIAL	110-132	AAYAVASSVVSFYIPLAVMAFVYG	200-223		LGIIMGTFTLCWLPPPVLNVVVTI	283-306	LNW	IGYANS	AFNPLIYCRS	319-337
SP  045241 ADRB3_BARABO UNISYUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOULPEPUNIVV 293-314 AFLAINAUSYANSAENELIUC 327-347 SP  045261 ADRB3_BOUIN LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOULPEPUNIVV 293-314 AFLAINAUSYANSAENELIUC 327-347 SP  052521 ADRB3_BIG LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOULPEPUNIVV 293-314 FILAINAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHI LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOULPEPUNIVV 293-314 FILAINAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHI LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEPUNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHI LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEPUNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHI LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEVNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHO LMTSUVLOUTASIEILDALAV 112-133 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEVNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHO LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEVNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHO LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEVNIVV 293-314 ALLANAUSYANSAENELIUC 327-347 SP  05X151 ADRB3_CAPHO LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 204-225 ILGLIMSIFILOUPPEVANVV 293-314 VILLINAUSYANSAENELIUC 325-345 SP  0540431 ADRB3_CAPHO LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 201-222 ILGLIMSIFILOUPPEVANVU 290-311 VILLINAUSYANSAENELIUC 325-345 SP  052552 ADRB3_MOUSE LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 201-222 ILGLIMSIFILOUPPEVANVU 290-311 VILLINAUSYANSAENELIUC 325-345 SP  252552 ADRB3_MOUSE LMTSUVLOUTASIEILDALAV 109-130 VALLSSVSYLPLUMIEVYA 201-222 ILGLIMSIFILOUPPEVANVU 290-311 VILLINAUSYANSAENELIUC 325-345	SP P13945 ADRB3_HOMAN	LWISVDVI	LCVTASIEILCALAV	112-133	IVELSSOVSFILPELVMLEVIA	204-225		ILGLIMGIFILCWLPFFLANVL	293-314	AFLALNW	LGIANS	AFNPLIIC	327-347
SP 97522 ADRB3_BOIN LWISUVLOTASIELLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWWV 293-314 AFLAINULGANSAFNELIC 327-347 SP 05XT58 ADRB3_ENEEP LWISUVLOTASIELLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWWV 293-314 AFLAINULGANSAFNELIC 327-347 SP 05XT58 ADRB3_ENEEP LWISUVLOTASIELLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWWV 293-314 TFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIELLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWWV 293-314 TFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIETLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWNV 293-314 AFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIETLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWNV 293-314 AFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIETLCALAV 112-133 YALLSSVSFYLELUMETYA 204-225 TLGLINEFTLOWLPFYWNVAR 293-314 AFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIETLCALAV 110-130 YALLSSVSFYLELUMETYA 204-225 TLGLINETTLOWLPFYNANYA 293-314 AFLAINULGANSAFNELIC 327-347 SP 002662 ADRB3_CANLF LWISUVLOTASIETLCALAV 109-130 YALLSSVSFYLELUMETYA 204-225 TLGLINETTLOWLPFYNANYA 294-312 VLLENNULGANSAFNELICG 326-346 SP 002642 ADRB3_CANLF LWISUVLOTASIETLCALAV 109-130 YALLSSVSFYLELUMETYA 201-222 TLGLINETELANULFFIANVL 290-311 VFLAINULGANSAFNELICG 326-346 SP 02554 ADRB3_MOUSE LWISUVLOTASIETLCALAV 109-130 YALLSSVSFYLELUMETYA 201-222 TLGLINEFTLANVL 290-311 VFLAINULGANSAFNELICG 326-346 SP 02554 ADRB3_MOUSE LWISUVLOTASIETLCALAV 109-130 YALLSSVSFYLELUMETYA 201-222 TLGLINEFTLANVL 290-311 VFLAINULGANSAFNELICG 326-346	SPIQ28524 ADRB3 MACHU	LWISVDVJ	LCVTASIEILCALAV	112-133	IVLLSSSVSFILPLLVMLFVIA	204-225		ILGLIMGIFILCWLPFFLANVL	293-314	AF LALINW	LGIANS	AFNPLIYC	327-347
SP (95352) ADRB3_FIG LWISVDVLOVTASIEILDALAV 112-133 YALLSSVSSTUELUMIEVYA 204-225 ILGLIMSIFILOULPEFVNNVV 293-314 TELAINLOYANSAFNELIC 327-347 SP (95352) ADRB3_SHEE LWISVDVLOVTASIEILDALAV 112-133 YALLSSVSSTUELUMIEVYA 204-225 ILGLIMSIFILOUPEFVNNVV 293-314 TELAINLOYANSAFNELIC 327-347 SP (95352) ADRB3_CAPHI LWISVDVLOVTASIEILDALAV 112-133 YALLSSVSSTUELUMIEVYA 204-225 ILGLIMSIFILOUPEFVNNVV 293-314 TELAINLOYANSAFNELIC 327-347 SP (95452) ADRB3_CAPHI LWISVDVLOVTASIEILDALAV 112-133 YALLSSVSSTUELUMIEVYA 204-225 ILGLIMSIFILOUPEFVNNVV 293-314 ALLAINLOYANSAFNELIC 327-347 SP (95452) ADRB3_FELCA ELWISVDVLOVTASIEILDALAV 109-130 YALLSSVSSTUELUMIEVYA 202-225 ILGLIMSIFILOUPEFVNNVVAL 294-317 PAFLAINUGYANSAFNELIVC 325-345 SP (266463) ADRB3_CAPFO LWISVDVLOVTASIEILDALAV 109-130 YALLSSVSSTUELUMIEVYA 201-222 ILGLIMSIFILOUPEFLANVL 294-317 VALLENUGYANSAFNELIVC 325-345 SP (266463) ADRB3_CAPFO LWISVDVLOVTASIEILDALAV 109-130 YALLSSVSSTUELUMIEVYA 201-222 ILGLIMSIFILOUPEFLANVL 290-311 VILLIPUNLGYANSAFNELIVC 325-345 SP (26542) ADRB3_CAVFO LWISVDVLOVTASIEILDALAV 109-130 YALLSSVSSTUELUMIEVYA 201-222 ILGLIMSIFILOUPEFLANVL 290-311 VILLIPUNLGYANSAFNELIVC 325-345 SP (26552) ADRB3_MOUSE LWISVDVLOVTASIEILDALAV 109-130 YALLSSVSSTUELUMIEVYA 201-222 ILGLIMSIFILOUPEFLANVL 290-311 VILLIPUNLGYANSAFNELIVC 324-344	SP P40626 ADRB3_BOVIN	LWISVDVI	LUVIASIEILUALAV	112-133	IALLSSSVSFILPLLVMLFVIA	204-225		ILGLIMGIFILCWLPFFVVNVV	293-314	I E LALINW	LGIANS	AFNPLIIC	327-347
SP QXX150 ACMD5_SHEED KUSUUCUTASIBILICALAV 112-133 YALLSSVSFYLELUMIEYYA 204-225 ILGLIMSIFILCULPEFYNWV 293-314 TFLAINALGAMISAFNELIC 327-347 SP Q0X157 ADRB5_CANLE LWTSVDVLCTASIBILICALAV 112-133 YALLSSVSFYLELUMIEYYA 204-225 ILGLIMSIFILCULPEFYNWV 293-314 TFLAINALGAMISAFNELIC 327-347 SP Q02662 ADRB5_CANLE LWTSVDVLCTASIBILICALAV 112-133 YALLSSVSFYLELUMIEYYA 204-225 ILGLIMSIFILCULPEFYNWV 293-314 ALLAINALGAMISAFNELIC 327-347 SP Q04053 ADRB5_CANLE LWTSVDVLCTASIBILICALAV 112-133 IYALLSSVSFYLELUMIEYYA 204-225 ILGLIMSIFILCULPEFYNNVA 294-314 ALLAINALGAMISAFNELIC 327-347 SP Q04053 ADRB5_CANLE LWTSVDVLCTASIBILICALAV 110-130 IYALLSSVSFYLELUMIEYYA 204-225 ILGLIMSIFILCULPEFYNNVA 294-314 ALLAINALGAMISAFNELIYC 325-345 SP Q04053 ADRB5_CANLE LWTSVDVLCTASIBILICALAV 109-130 YALLSSVSFYLELUMIEYYA 201-222 ILGLIMSIFILCULPEFYLANVL 294-314 VILLENNLGAMISAFNELIYC 325-345 SP P225542 ADRB5_MOUSE LWTSVDVLCTASIBILICALAV 109-130 YALLSSVSFYLELUMIEYYA 201-222 ILGLIMSIFILCULPEFTLANVL 290-311 VFLANNLGAMISAFNELIYC 324-344	SPIQ95252 ADRB3 PIG	LWISVDVI	CUTASIEILCALAV	112-133	VALLSSSVSFILPLLVMLFVIA	204-225		TIGLINGIFILOWLPFFVVNVV	293-314	AFLALNW	LGIANS	AFNPLIIC	327-347
SP 02662 ADRB3_CAPPI LWISVUVLOVIASIEIILALAV 112-133 YALLSSVSFIDELUMLEYVA 204-225 ILGLINGIFILGULEPFVANVV 293-314 ALLAINAUSAANSAFNELIYC 327-347 SP 02662 ADRB3_CAPPO LWISVUVLOVIASIEIILCALAV 112-133 YALLSSVSFIDELUMLEYVA 204-225 ILGLINGIFILGULEPFVANVVRAL 294-317 PAFLAINAUSAANSAFNELIYC 326-345 SP 0260483 ADRB3_CAPPO LWISVUVLOVIASIEIILCALAV 109-130 YALLSSVSFIDELUMLEYVA 201-222 ILGLINGIFILGULEPFTAAVVL 291-312 VILPINUGVVASAFNELIYC 325-345 SP 22625 ADRB3_RAI LWISVUVLOVIASIEIILCALAV 109-130 YALLSSVSFIDELUMLEYVA 201-222 ILGLINGIFISLGWLPFFLANVL 290-311 VIIAINUSYANSAFNELIYC 324-344 SP P25962 ADRB3_MOUSE LWISVUVLOVIASIEIILCALAV 109-130 YALLSSVSFIDELUMLEYVA 201-222 ILGLINGIFISLGWLPFFLANVL 290-311 VIIAINUSYANSAFNELIYC 324-344	SPICONTS INDEDS SHEEP	LWISVDVI	LCVIASIEILCALAV	112-133	TALLSSSVSF ILFLLVMLF VIA	204-225		TIGLINGIFILCWLPFFVVNVV	293-314	TELALINW	LGIAND	AFNELIIC	327-347
SP QOTST4 ADRB3_EELCA ELWTSVDVLCVTASIETLCLALV 111-133 IPXALSSVSFVLELUMIEVYA 202-225 LGLIMGTESLCMLPFFVANVRAL 294-317 PAFLAINALGYANSAFNELIYCRS 326-345 SP QO483 ADRB3_CAVPO LWTSVDVLCVTASIETLCALAV 109-130 YALLSSVSFVLELUMIEVYA 201-222 TLGLIMGTESLCMLPFFLANVL 294-317 PAFLAINALGYANSAFNELIYCRS 326-345 SP P225542 ADRB3_MOUSE LWTSVDVLCVTASIETLCALAV 109-130 YALLSSVSFVLELUMIEVYA 201-222 TLGLIMGTESLCMLPFFLANVL 290-311 VFIAINALGYANSAFNELIYCR 324-344	SPIQUATS/ ADRBS CAPHI	LWISVDVI	LCV MASIEILCALAV	112-133	VALLESSVEPTI DI LIMI TUVA	204-225		TIGLINGIFILCWLPFFVVNVV	293-314	DI LALINW	LGIANS	AFNPLIIC	327-347
SP[091314]AURB_RELCAL LWISTONGUTASIETICALAV 109-13 FALLSSSSSFTUPLIVMEFYA 201-222 TIGLINGFFLANUL 291-312 VILPINAUGANSAFNPLIVCS 325-345 SP[204043]AURB3_CAVDPFLANUL 291-312 VILPINAUGANSAFNPLIVCS 325-345 SP[202053]AURB3_RAT LWISTOVICUTASIETICALAV 109-130 YALLSSSVSFYLPLIVMEFYA 201-222 TIGLINGFFLANUL 290-311 VFIALNULGYANSAFNPLIVC 324-344 SP[225562]ADRB3_MOUSE LWISTOVICUTASIETICALAV 109-130 YALLSSSVSFYLPLIVMEFYA 201-222 TIGLINGFFLANUL 290-311 VFIALNULGYANSAFNPLIVC 324-344	SPICOZECZIADRES CANLE	ELUTOUDU	CUMPACIETICALAV	111 122	TRALISSOVEF ILFELVILEVIA	204-225		I CLINCTERI CHI DEFUNNUUNI	293-314	DAFLALNW	LGIANS	AFNPLIIC	32/-34/
SP   201525   ADDRD _ MATSUDUCUTASISTICLAAV 109-130 YALLSSVSTYLELUVIEFYA 201-222 TLGINGIFSLCWPFFLAWL 290-311 VFIALMULGYANSAFWELIYC 324-344 SP   22555   ADDRD _ AND _ STATUS _	SPIQ91314 ADRB3 FELCA	LUTSUDVI	LCVIADICILCALAV	100 120	VALLESSOVEFUL DI LING FUVA	202-223		TI CLIVCTENI CHI DEPI ANUI	294-317	VILL DI NU	LGIAND	AFNPLIICKS	326-345
SP[F20235]ADKD5]KAI LWS90VLOVIASIELELEARV 105-130 IRLD5355FIEFLDVILEVIR 201-222 ILGLIMSIFSUCMEPFERRVL 290-311 VIIALNHLOIRASAEMFLIIC 324-344 SP[P25962]ADRB3_MOUSE LWTS9DVLCVTASIETLCALAV 109-130 YALLSSSVSFIEFLDVILEVIR 201-222 ILGLIMSIFSUCMEPFERRVL 290-311 VIIALNHLOIRASAEMFLIIC 324-344	SPIQEONOSIADRBS_CAVPO	LWISVDVI	CURRENTICALAV	109-130	VALLOODVOFILPLLVMLFVIA	201-222		TLOLINGIFALONLPFFLANVL	291-312	VELPENW	LGIVNS	AFNPLIIC	224-244
SETEZSTOLIKUSE RODE DATSTOLICURSTELECHER USSTOL HALBONGETBELDENERVIK ZUISZZZ ILGELIKUSTESENUL ZUSSTOLI VERKARGARKEVIC ZZIST	CDID256221ADRD3 KAI	TELECODA	CUMPACIETICALAV	109-120	VALLEGOVERVLET LIMITEUVA	201-222		TIGI THOTESI CHI DEPI ANUI	290-211	VETALNW	LOVANG	AFMPUTYC	224-244
	SETERSON ADRES_HOUSE	* * • ***	*********** ···	100-100	* • ** •*** ** •* *** **	201-222	* *	****** ***********	200-011	** 1ALAW	·** **	*****	521-511

Fig. 2. Multiple sequence alignment of TM3, TM5, TM6, and TM7 domains of  $\beta$ -ARs for different animal species. Domain information and protein sequences were taken from Swiss-Prot UniProt Knowledgebase (35 proteins) [14]. Key amino acids in the sequences are shown with a gray background.

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Fig. 3. The main binding pocket of the  $\beta_1$ -AR with (a) agonist (isoprenaline; PDB ID, 2Y03) and (b) antagonist (cyanopindolol; PDB ID, 2YCY). Images are generated using PyMOL Molecular Graphics System.



Fig. 4. Comparison of structures of the agonist (isoprenaline, orange) and antagonist (cyanopindolol, dark cyan) complexes with  $\beta_1$ -AR (PDB ID, 2Y03, yellow, and 2YCY, blue). a) View from the receptor extracellular side; important residues are labeled according to Ballesteros–Weinstein notation [17]; b) overview of bound ligand conformation. The images are generated using PyMOL Molecular Graphics System.

We have examined other agonists bound to the corresponding aminergic GPCRs and, indeed, the tail fragment between the amine N-atom and the aromatic ring in these complexes also has an extended conformation (PDB ID: 2Y00, 2Y02, 2Y04, 3P0G, 3PDS, 3SN6, and other structures presented in Table 1). On the other hand, antagonist molecules are bent in the tail fragments between the amine N-atom and the aromatic ring (PDB ID: 2VT4, 2YCW, 2RH1, 3D4S, 3NY8, 3NY9, 3NYA, 3PBL, 3RZE, and other structures presented in Table 2). These data suggest that the extended conformation of the agonist tail is of particular importance in the active state stabilization in  $\beta$ -ARs and other aminergic GPCRs. We can also speculate that the distance between the two centers of polar interactions with the agonists should be equal (or close) to the distance between the corresponding centers in the activated GPCR.

The role of the agonist "strained string" conformation in the  $\beta$ -AR activation. Simple geometry considerations outlined above suggest that the agonist molecule can act as a "strained string" that stabilizes the arrangement of TM helices 3, 5, 6, and 7 corresponding to the receptor active state (Fig. 1). It appears that the interaction with the agonist bring the TM5 helix closer to the TM3 and TM7 helices. In particular, this "strained string" interacts with Trp at position W6.48 and Phe residues at positions F6.51

and F6.52. These interactions are likely to be responsible for the rearrangement of TM6, i.e., for its rotation and/or vertical see-saw movement around a pivot in the middle of the membrane, which results in the opening of the intracellular portion for the G protein binding [46-48]. The interactions with W6.48 result in a subtle rotation of TM6 in the extracellular portion, which is amplified towards the cytoplasmic side by the characteristic kink in the helix introduced by Pro residue P6.50 [11]. Unlike an agonist, an antagonist or an inverse agonist has a longer tail fragments with a loose conformation, a kink in the middle of the tail, and weak polar interactions of the head with the TM5 helix. Therefore, they cannot act as a "strained string", but instead occupy the active site of the receptor due to the polar and hydrophobic interactions.

Based on these findings, we propose several predictions on how minor differences in the ligand structure can influence its functional characteristics:

1. Elongation of the agonist tail between the amine N-atom and the aromatic ring could result in the agonist conversion into antagonist.

2. Shortening of the tail fragment in the antagonist or inverse agonist with polar moieties in the corresponding positions of their heads may result in their transformation into agonists or partial agonists.

3. Removal of catechol hydroxyls or the corresponding polar substitutes in other aromatic heads could reduce the agonist activity. Modifications of these polar substitutes with aromatic or aliphatic groups substitutes, especially bulky ones, are likely to have a similar effect.

4. Modification of amine groups of ligands (both agonists and antagonists) with bulky substitutes reduce or even prevent ligand binding to GPCRs.

5. The *trans*-conformation (extended conformation) of the agonist tail can be transformed into a *gauche*- or *cis*-conformation by chemical modification, which can result in the reduction of agonist activity or even transform it into an antagonist.

**Funding.** This work was supported by the Russian Foundation for Basic Research (project no. 20-04-00453).

**Ethics declarations.** The authors declare no conflicts of interest. This article does not contain descriptions of studies involving humans or animals as study subjects.

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