

A structural chemogenomics analysis of aminergic GPCRs: lessons for histamine receptor ligand design

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Running title: Structural chemogenomics analysis of aminergic GPCRs

Supporting Information

Table S1. Binding affinities from site directed mutagenesis studies on histamine receptors and crystallized aminergic GPCRs (see separate excel file). The 2D structures of all the compounds are depicted in Figures 3 and S7. The single-letter amino acid codes indicated in the grey rows are the human wild-type residues. ^aSDM study on guinea pig H₁R. ^bOnly functional SDM data available for histamine (**8**) in H₂R. ^cSDM study on rat M₃R.

Table S2. Aminergic GPCR crystal structures available in the PDB

	Resolution	Release date	PubMed ID
M₂R			
3UON	3.0	2012-02-01	22278061
M₃R			
4DAJ	3.4	2012-02-22	22358844
β₁AR			
2VT4	2.7	2008-06-24	18594507
2Y00	2.5	2011-01-12	21228877
2Y01	2.6	2011-03-30	21228877
2Y02	2.6	2011-01-12	21228877
2Y03	2.9	2011-01-12	21228877
2Y04	3.1	2011-01-12	21228877
2YCW	3.0	2011-06-01	21540331
2YCX	3.3	2011-06-01	21540331
2YCY	3.2	2011-06-08	21540331
2YCZ	3.7	2011-06-01	21540331
4AMI	3.2	2012-05-23	22579251
4AMJ	2.3	2012-05-23	22579251
4GPO	3.5	2013-02-27	23435379
β₂AR			
2R4R	3.4	2007-11-06	17952055
2R4S	3.4	2007-11-06	17952055
2RH1	2.4	2007-10-30	17962520
3D4S	2.8	2008-06-17	18547522
3KJ6	3.4	2010-02-16	20054398
3NY8	2.8	2010-08-11	20669948
3NY9	2.8	2010-08-11	20669948
3NYA	3.2	2010-08-11	20669948
3P0G	3.5	2011-01-19	21228869
3PDS	3.5	2011-01-12	21228876
3SN6	3.2	2011-07-20	21772288
D₃R			
3PBL	2.9	2010-11-03	21097933
H₁R			
3RZE	3.1	2011-06-15	21697825

Table S3. The number of ligands for which the activity for both receptors is known (as annotated in the ChEMBL)

	hH ₁ R	hH ₂ R	hH ₃ R	hH ₄ R	hM ₂ R	hM ₃ R	hβ ₁ AR	hβ ₂ AR	hD ₃ R
hH ₁ R	-	246	107	57	100	91	80	78	172
hH ₂ R	246	-	92	45	77	74	66	66	113
hH ₃ R	107	92	-	280	10	8	4	3	18
hH ₄ R	57	45	280	-	5	5	5	4	6
hM ₂ R	100	77	10	5	-	789	83	83	121
hM ₃ R	91	74	8	5	789	-	84	94	111
hβ ₁ AR	80	66	4	5	83	84	-	628	122
hβ ₂ AR	78	66	3	4	83	94	628	-	116
hD ₃ R	172	113	18	6	121	111	122	116	-

Table S4. The percentage (%) of the pairwise sequence identity between the TM domains of the histamine receptors as well as the aminergic receptors with a crystal structure available. The gradient from blue to white to red indicates a low to high sequence similarity.

	hH ₁ R	hH ₂ R	hH ₃ R	hH ₄ R	hM ₂ R	hM ₃ R	rM ₃ R	hβ ₁ AR	mβ ₁ AR	hβ ₂ AR	hD ₃ R
hH ₁ R	-	34	31	29	36	36	37	33	35	33	32
hH ₂ R	35	-	30	26	31	31	32	43	42	36	38
hH ₃ R	31	30	-	50	32	34	34	34	33	27	32
hH ₄ R	29	25	50	-	29	32	32	28	28	27	31
hM ₂ R	37	31	32	29	-	68	67	29	30	29	33
hM ₃ R	37	31	34	32	68	-	96	31	32	33	32
rM ₃ R	37	32	34	32	67	96	-	32	33	34	31
hβ ₁ AR	33	43	34	28	29	31	31	-	84	66	39
mβ ₁ AR	35	41	33	28	30	32	33	84	-	66	39
hβ ₂ AR	33	36	27	27	29	33	34	66	66	-	36
hD ₃ R	33	38	32	31	33	31	31	39	39	36	-

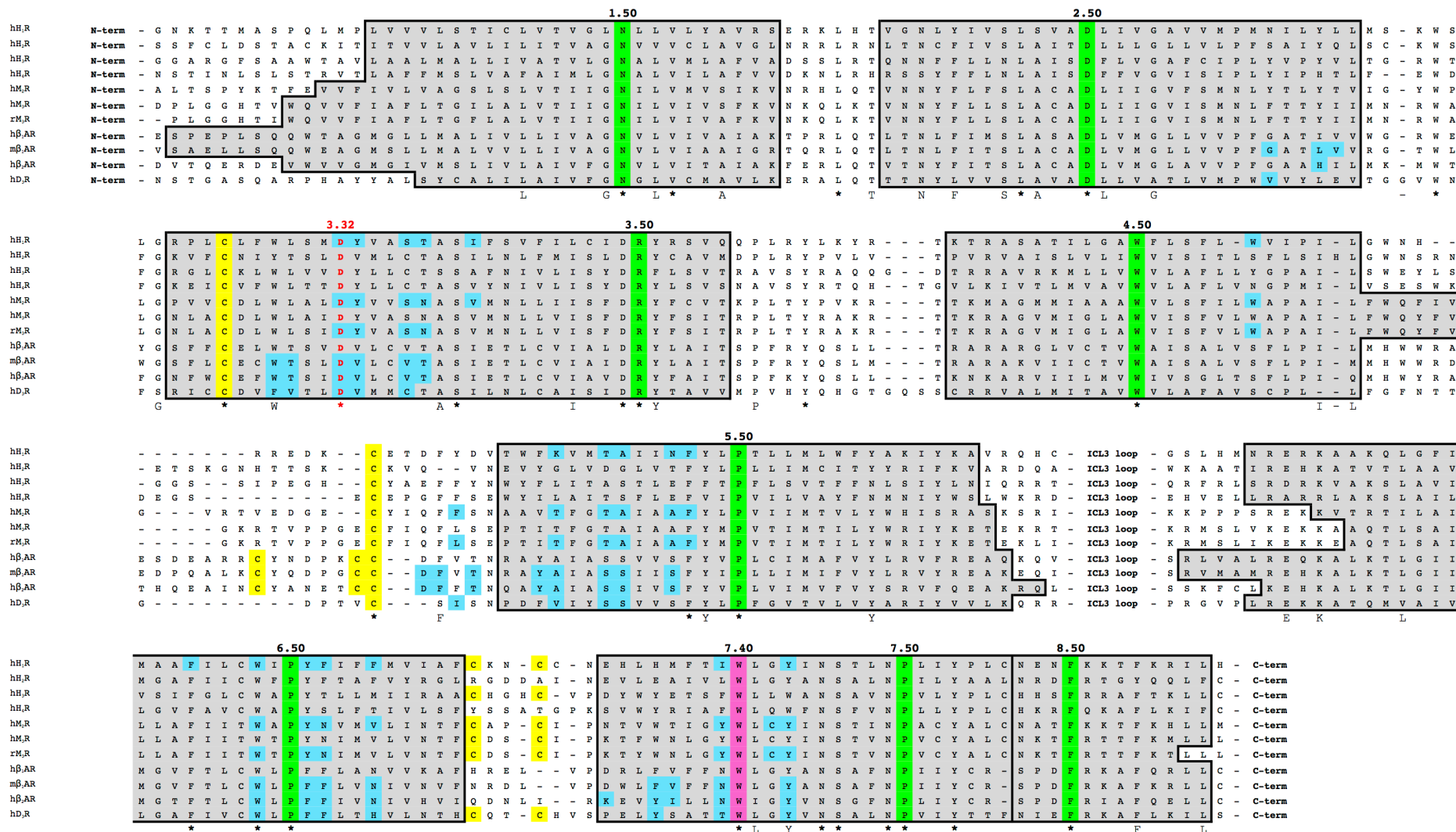


Figure S1. Full sequence alignment of the histamine and all crystallized aminergic GPCR receptors.

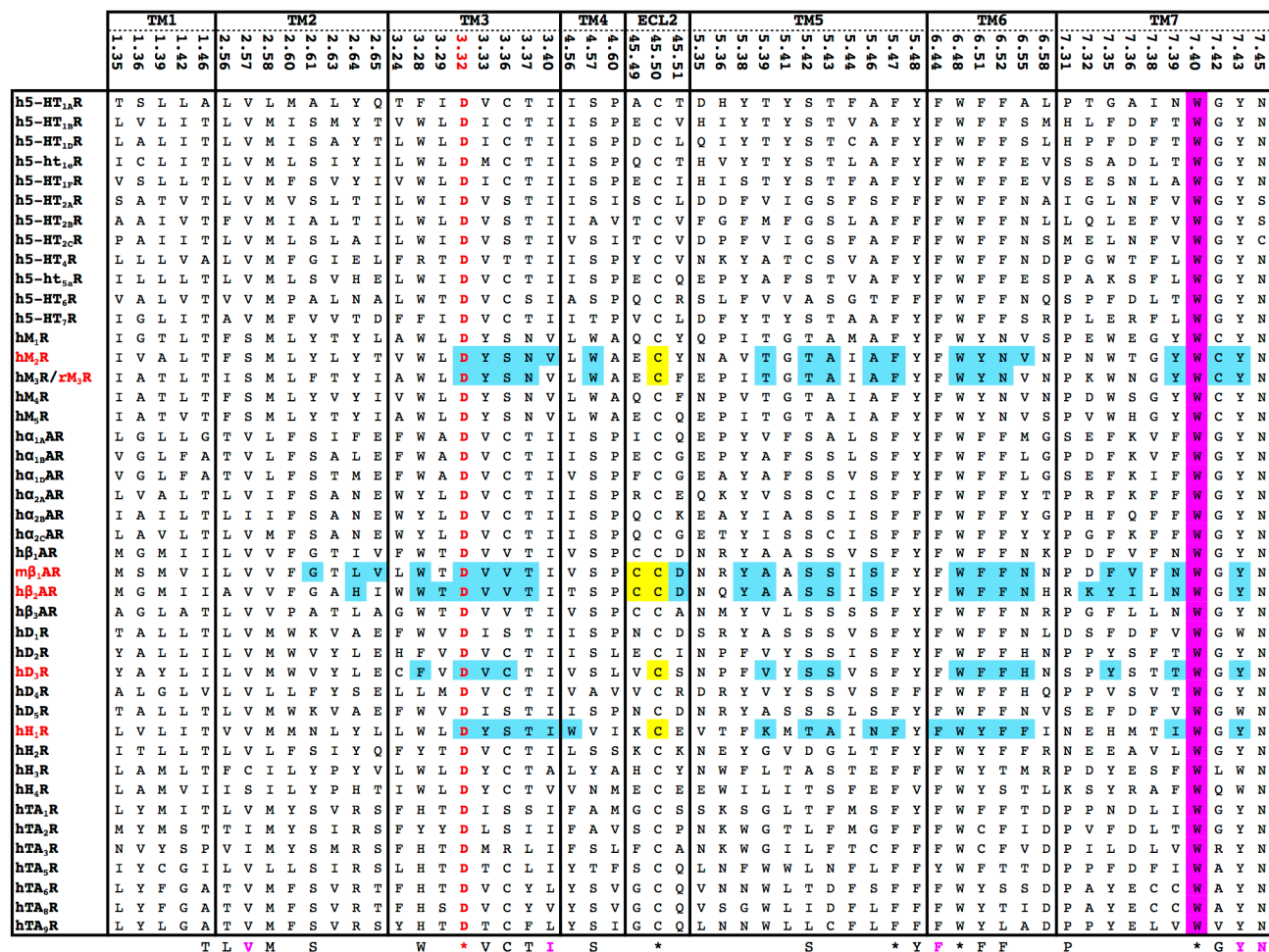


Figure S2. Sequence alignment of the selected pocket residues for all aminergic GPCR receptors.

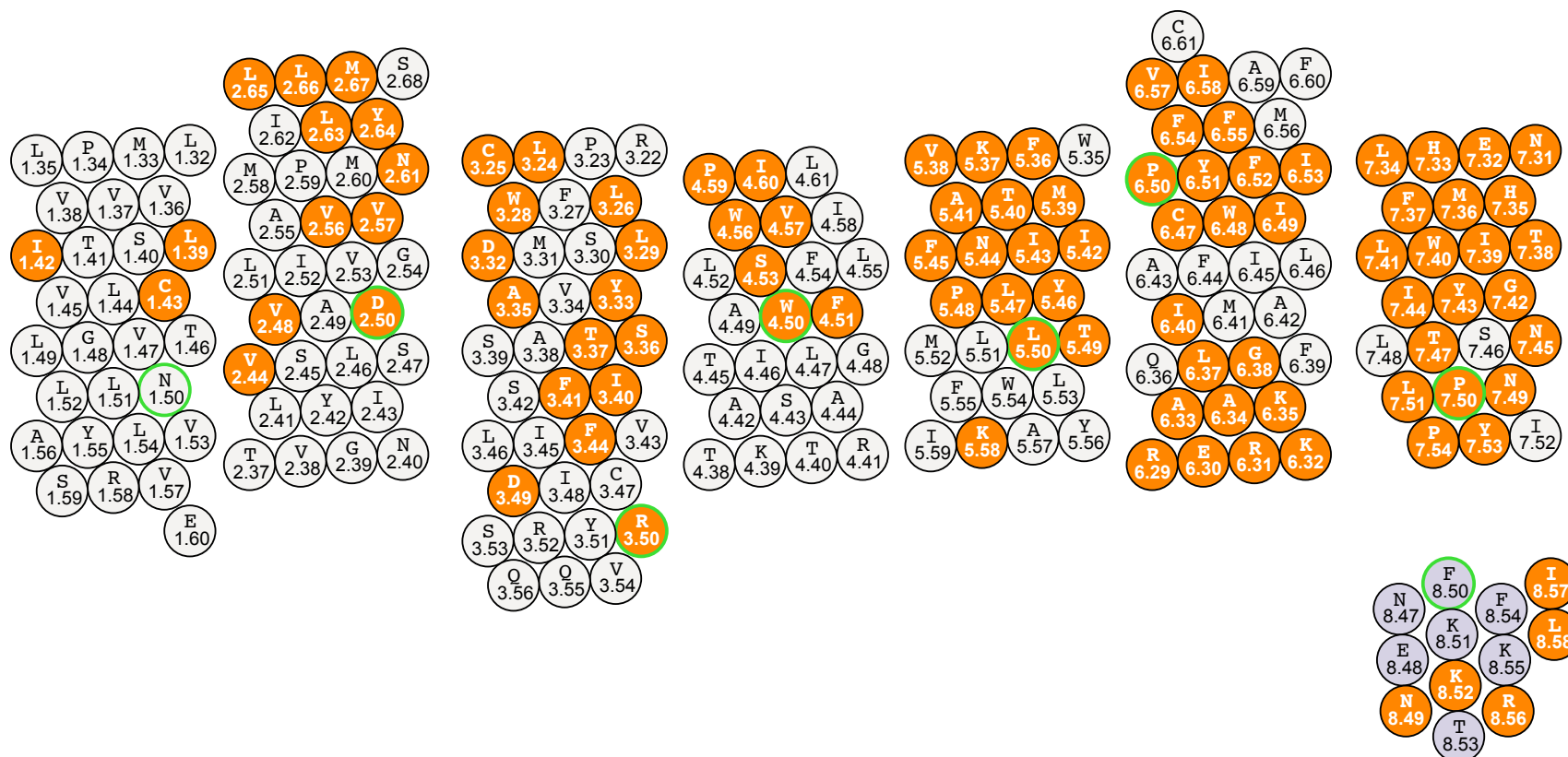


Figure S3. Snakeplot (http://www.ssfa-7tmr.de/ssfe/snakes/snakes_designer.php) showing the helices of H₁R. All B&W numbers are given within the circles as well as the amino acids in H₁R, all B&W positions within the TM helices that were mutated during single-point SDM studies for the aminergic GPCRs from SI Table 1 are shown in orange. The most conserved residues (i.e. the numbers as indicated by <TM>.50 in the Ballesteros-Weinstein numbering scheme) are circled in green.

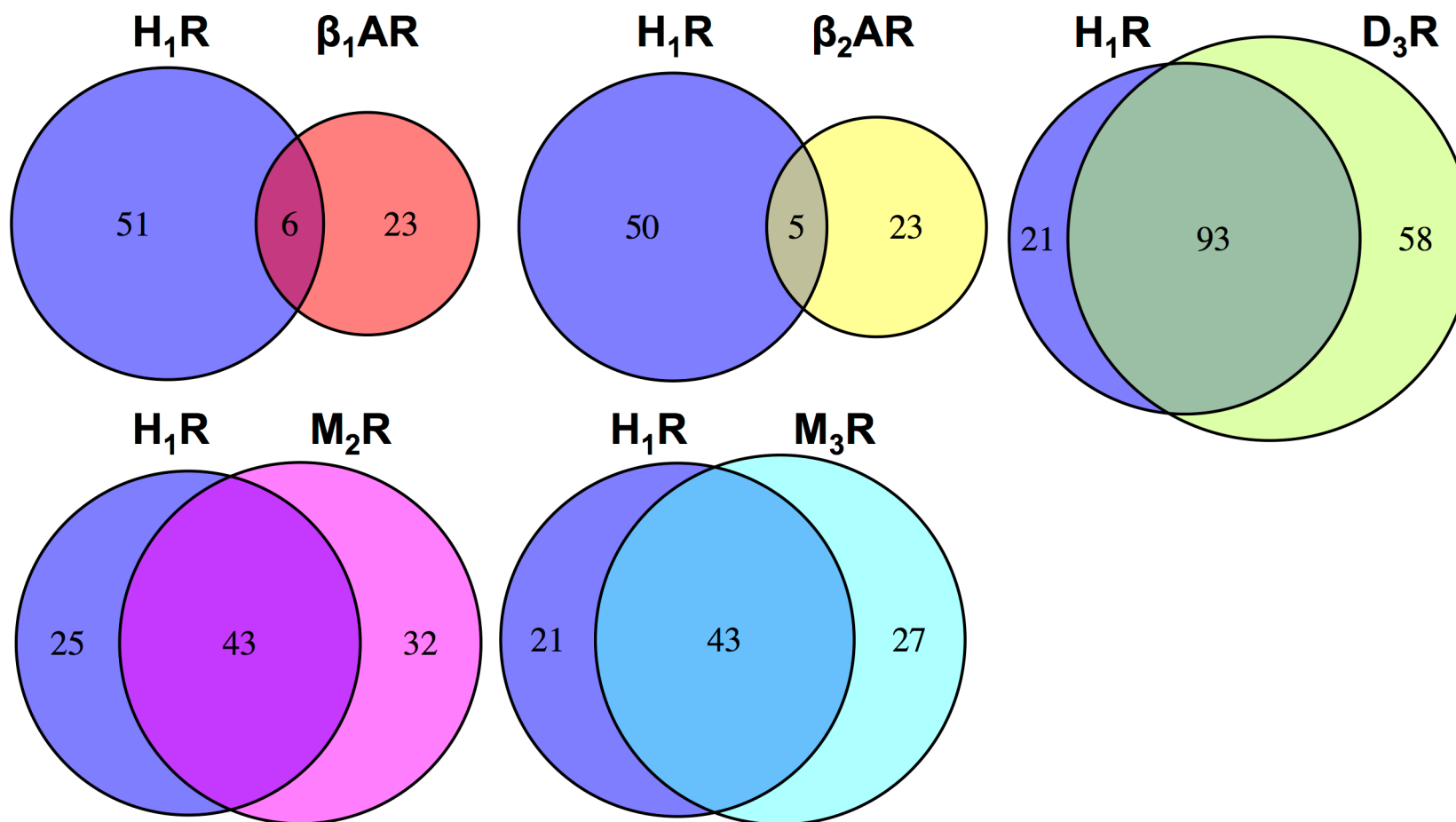


Figure S4. Venn diagram visualizing the overlap between the ligands of H₁R and all crystallized GPCR receptors according to ligand binding data obtained from the ChEMBL.

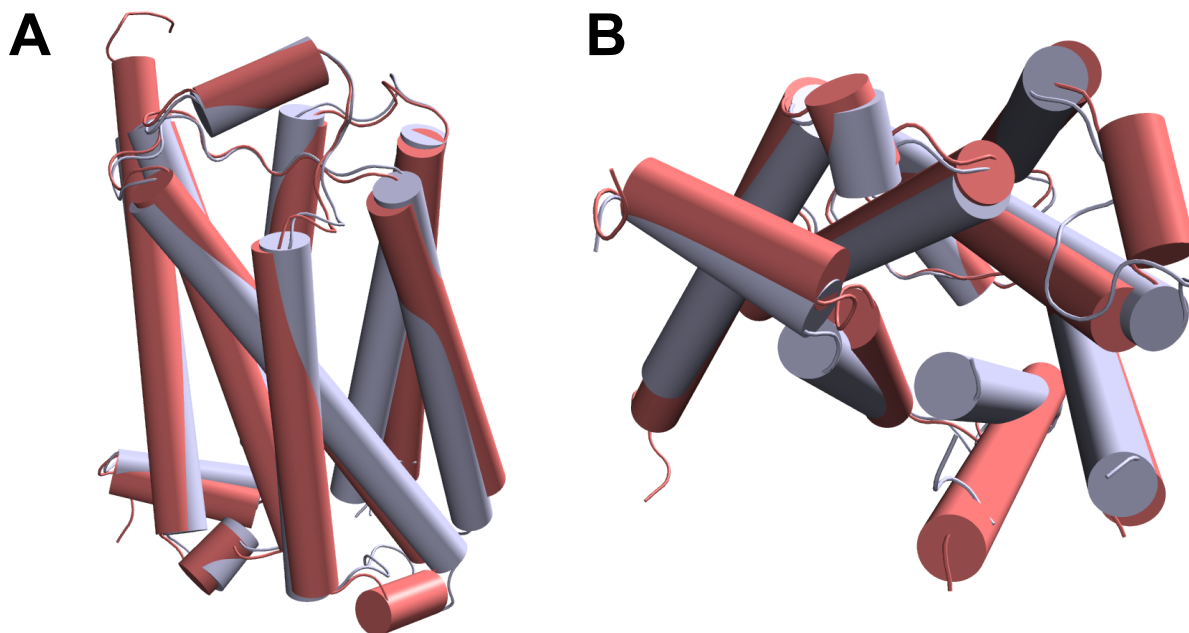


Figure S5. A) front and B) bottom view displaying the changes in the orientation of the TM helices of β_2 AR upon activation. The structure of the inactive (PDB-code 2RH1) and active and (PDB-code 3P0G) β_2 AR structure are shown in red and light blue respectively.

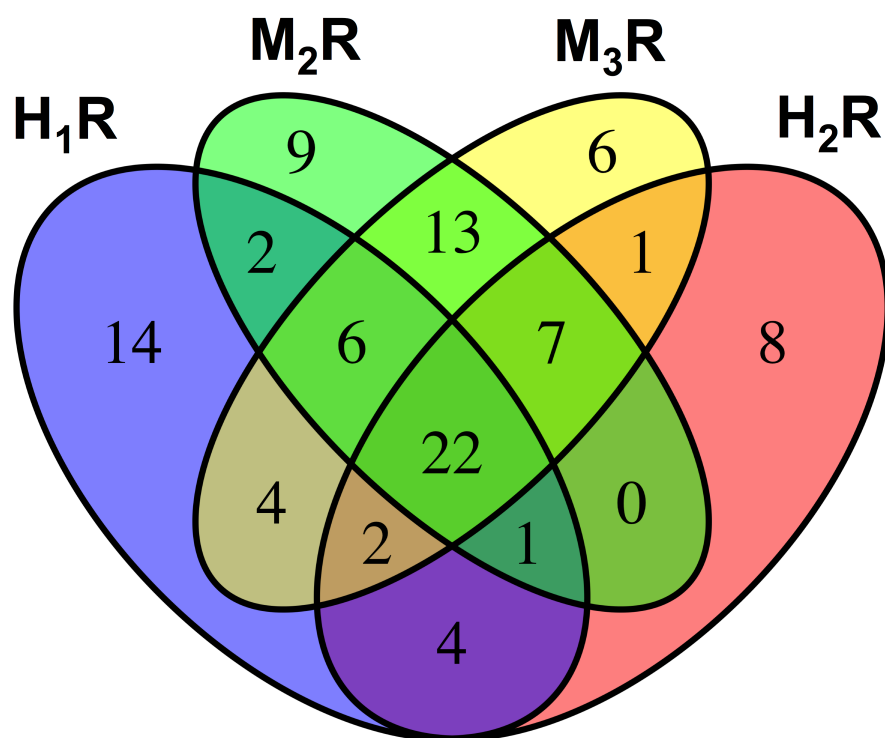
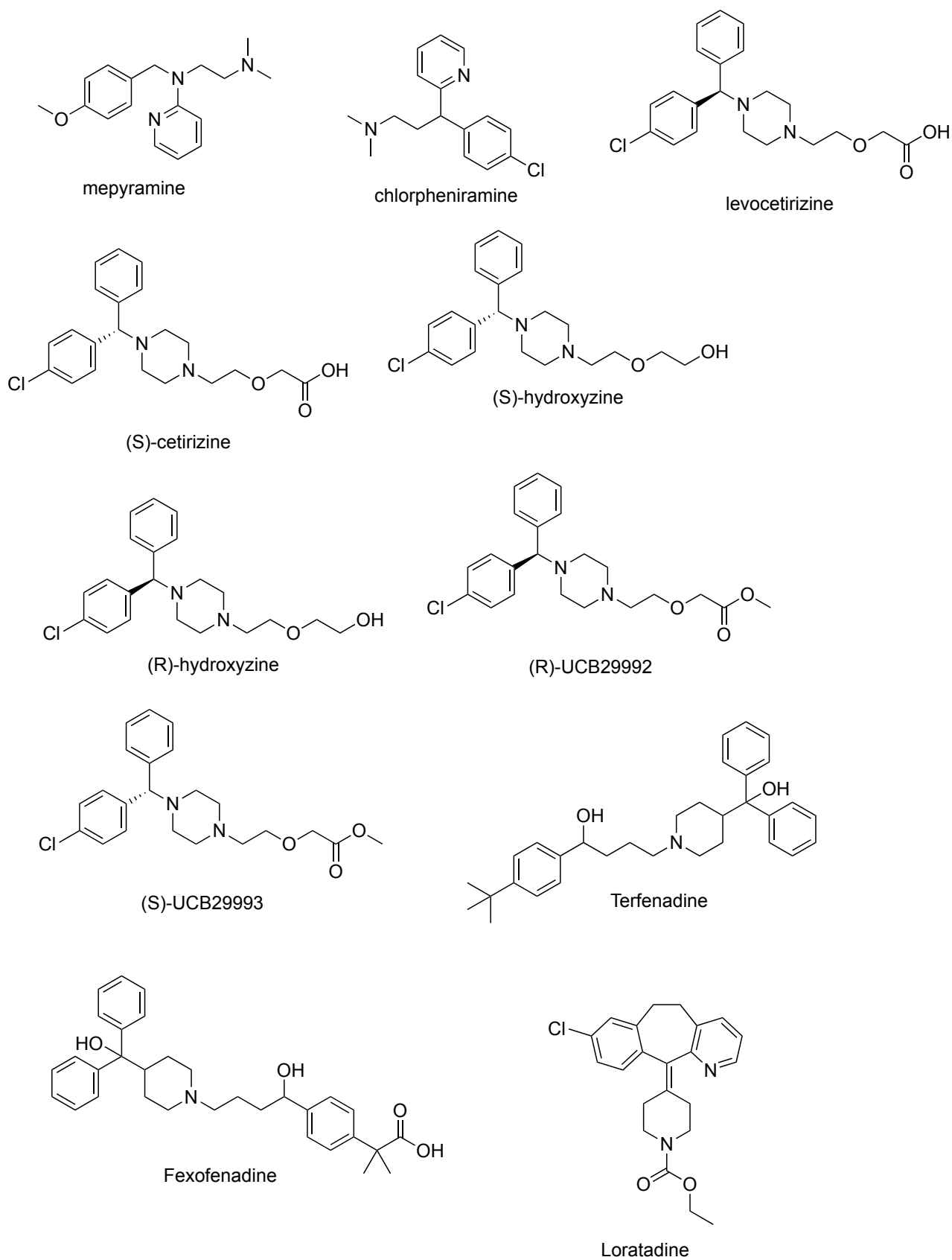
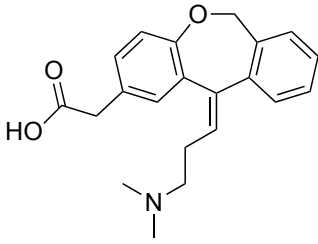


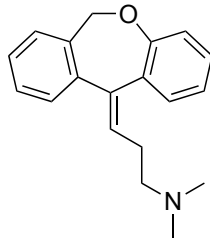
Figure S6. Venn diagram visualizing the overlap between the ligands of H₁R, H₂R, M₂R and M₃R.

Figure S7. 2D structures for most of the ligands for which SDM data is annotated in Table S1. The structures omitted here are depicted in Figure 3.

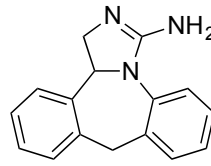




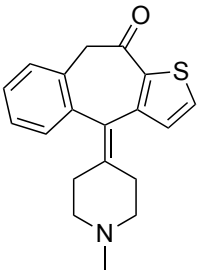
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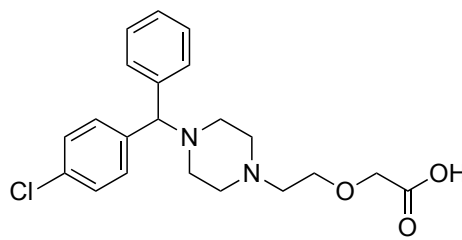
Doxepin



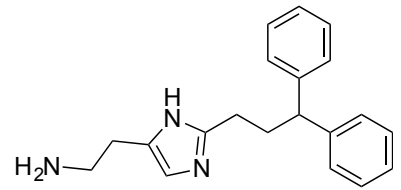
Epinastine



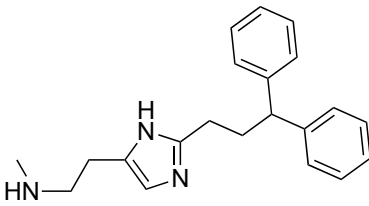
Ketotifen



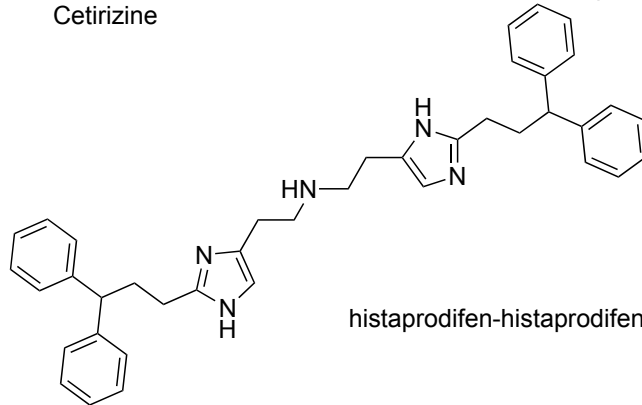
Cetirizine



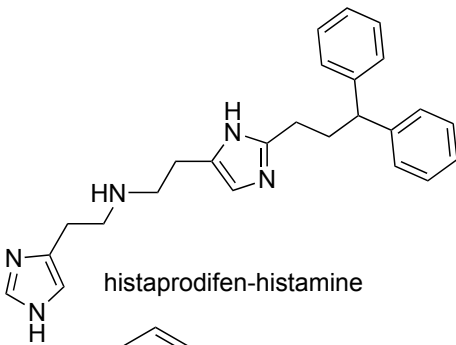
Histaprodifen



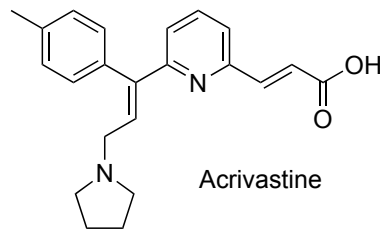
methylhistaprodifen



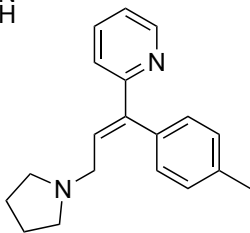
histaprodifen-histaprodifen



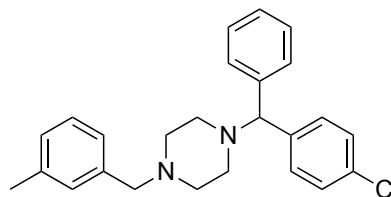
histaprodifen-histamine



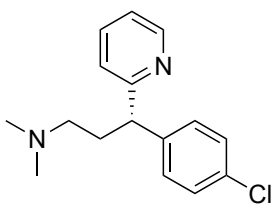
Acrivastine



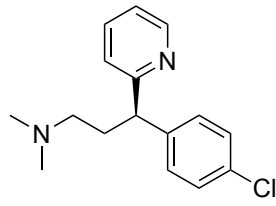
Triprolidine



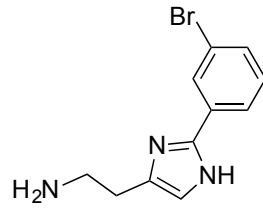
Meclozine



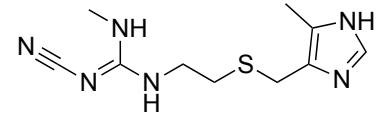
(S)-chlorpheniramine (D)



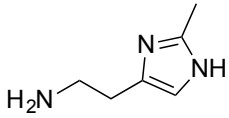
(R)-chlorpheniramine (L)



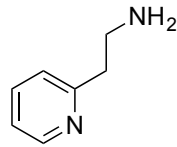
2-(3-bromophenyl)histamine



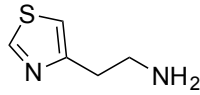
Cimetidine



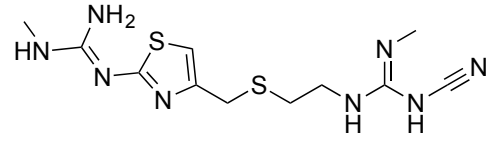
2-methylhistamine



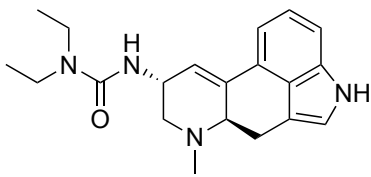
2-pyridylethylamine



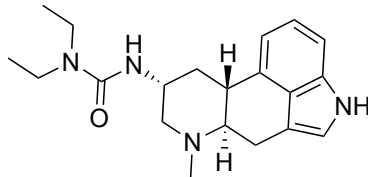
2-thiazolylthethylamine



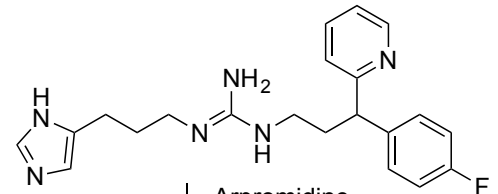
methyltiotidine



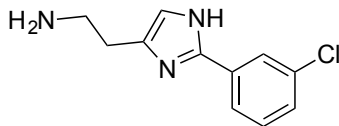
8R-Lisuride



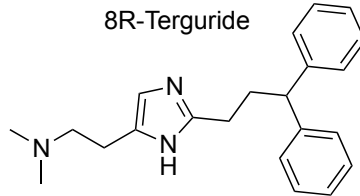
8R-Terguride



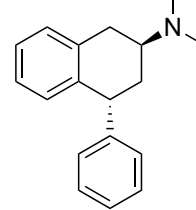
Arpmidine



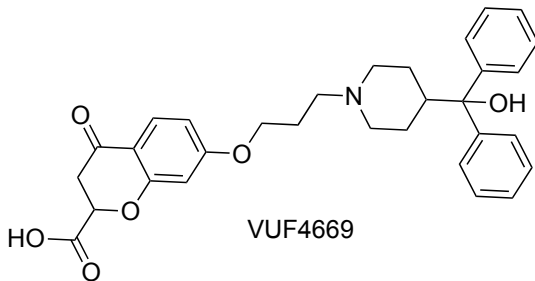
2-(3-chlorophenyl)histamine



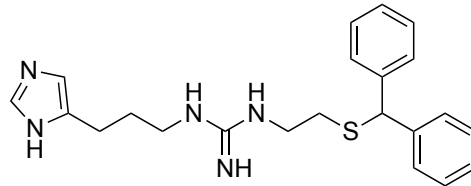
dimethylhistaprodifen



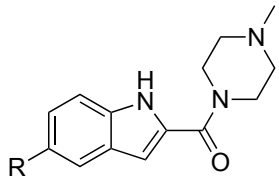
(2S,4R)-PAT



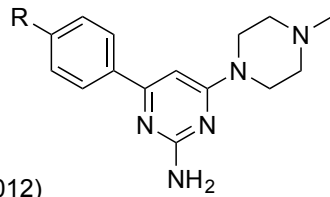
VUF4669



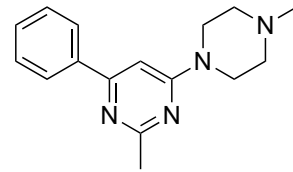
VUF8401



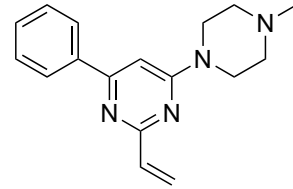
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R = Cl (JNJ7777120)



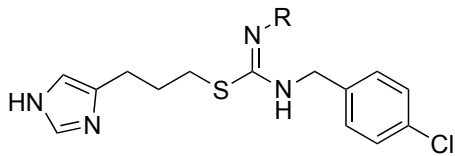
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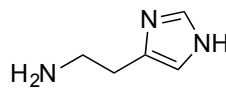
VUF14481



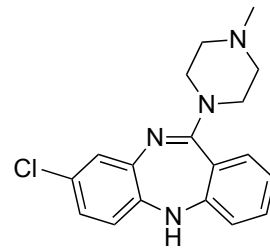
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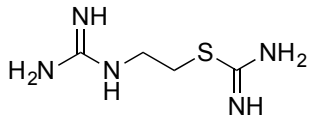
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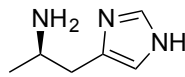
histamine



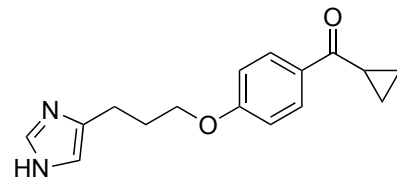
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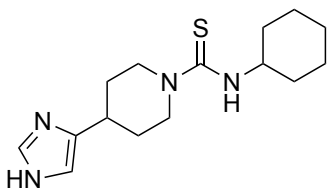
VUF8430



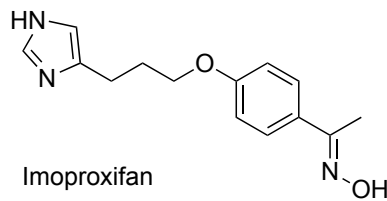
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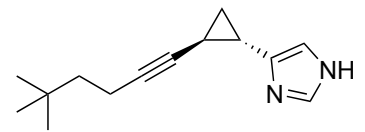
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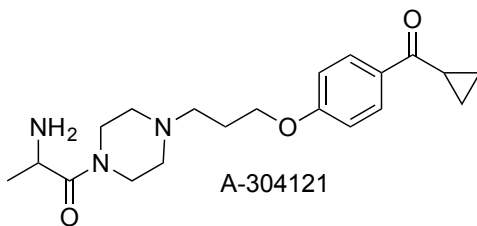
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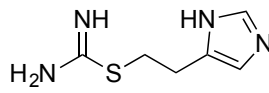
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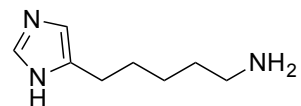
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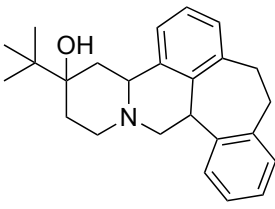
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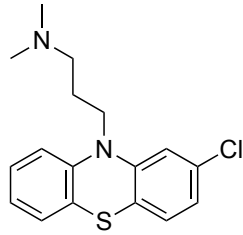
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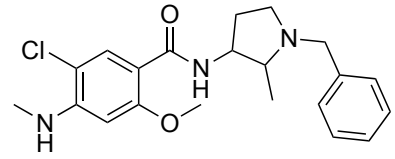
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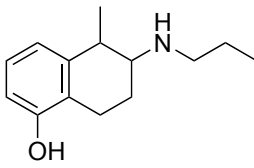
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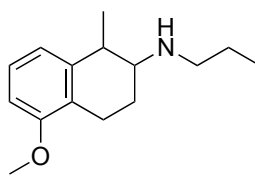
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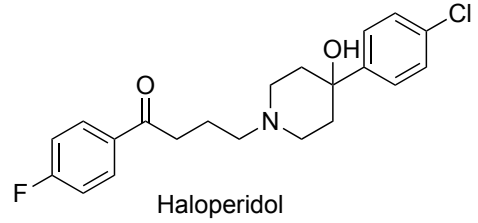
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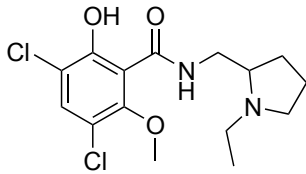
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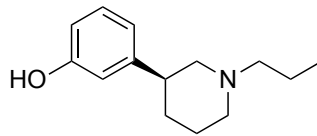
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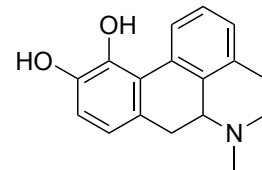
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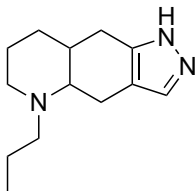
Raclopride



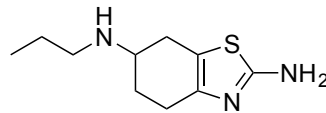
(-)-3-PPP



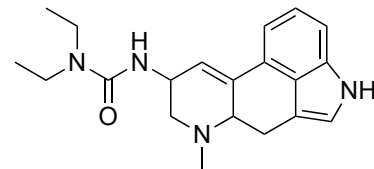
Apomorphine



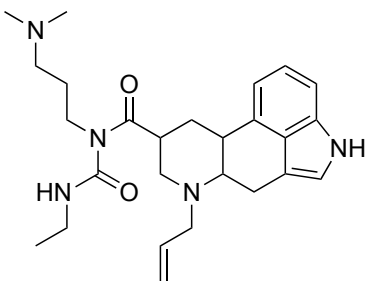
Quinpirole



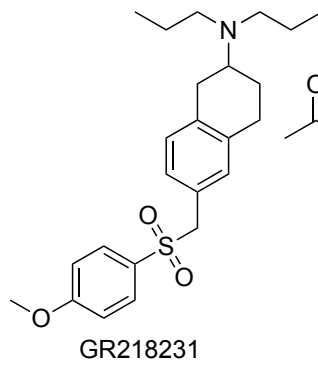
Pramipexole



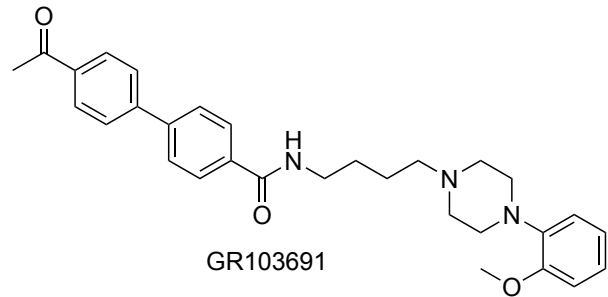
Lisuride



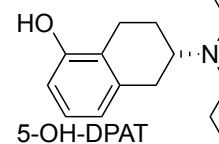
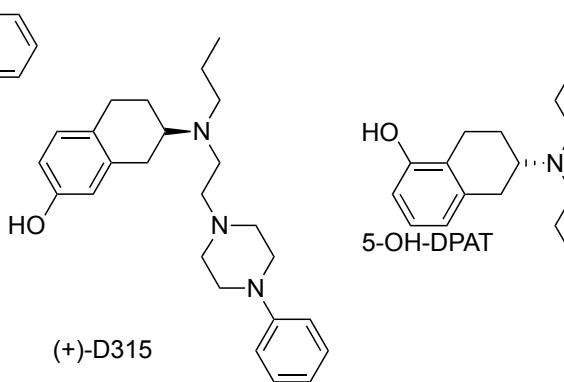
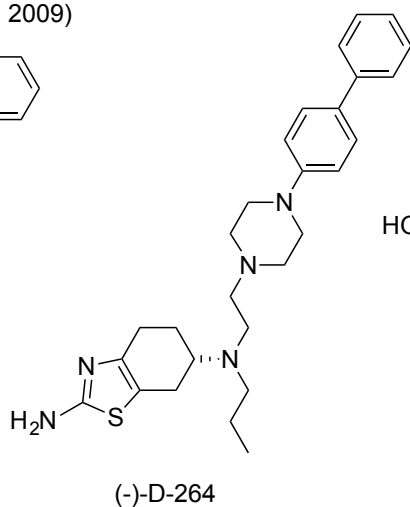
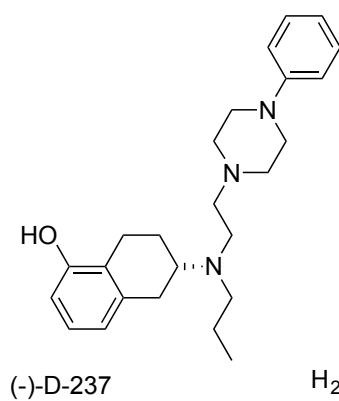
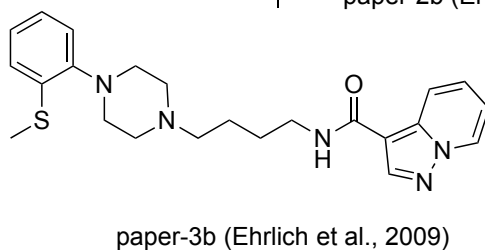
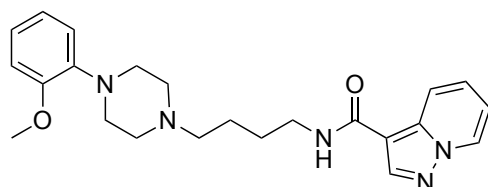
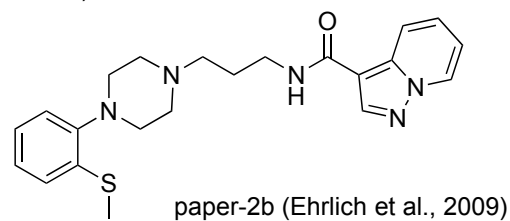
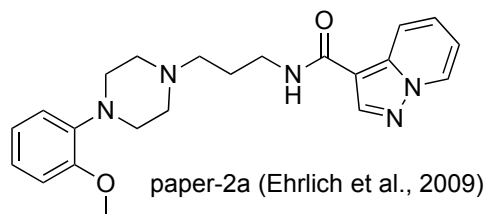
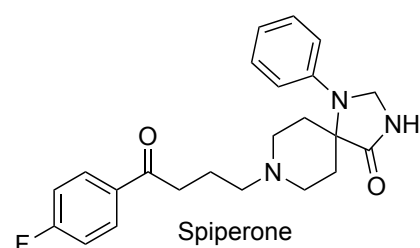
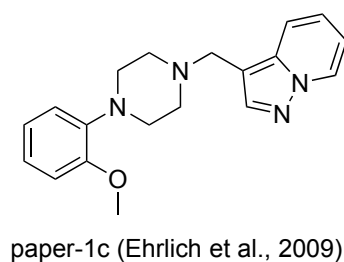
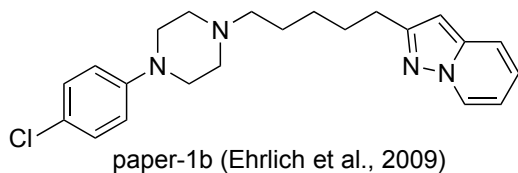
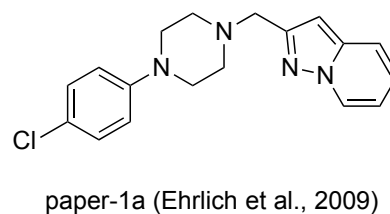
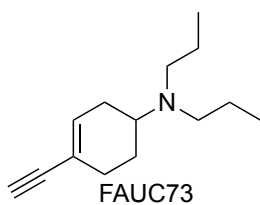
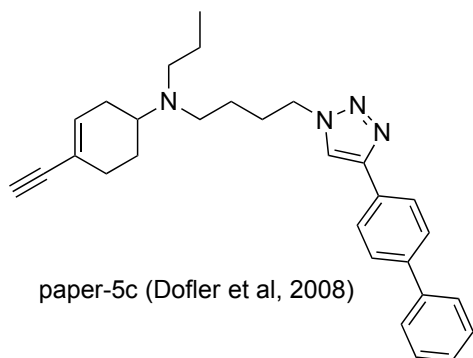
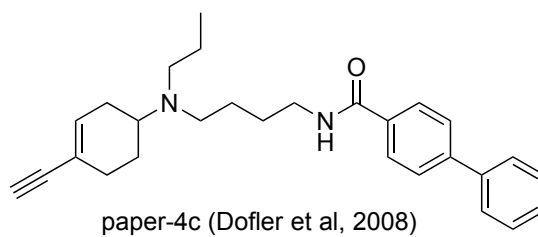
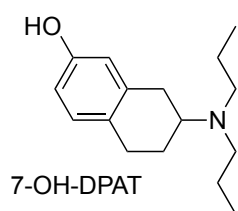
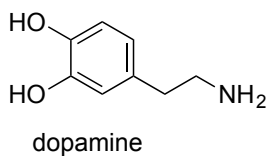
Cabergoline

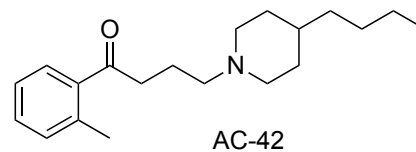
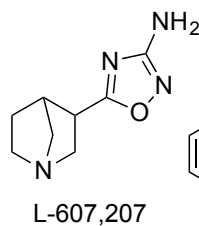
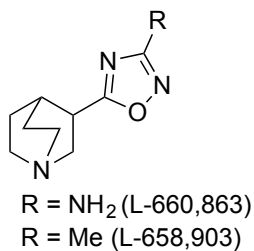
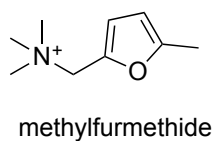
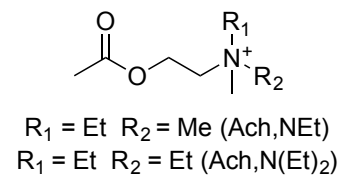
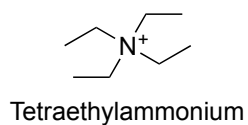
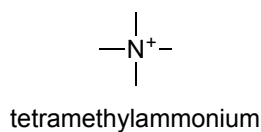
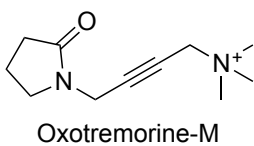
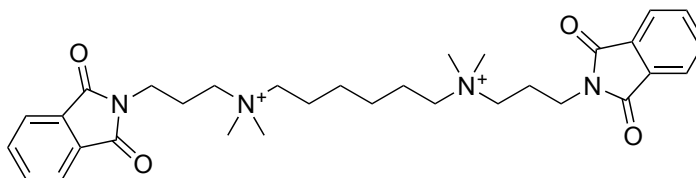
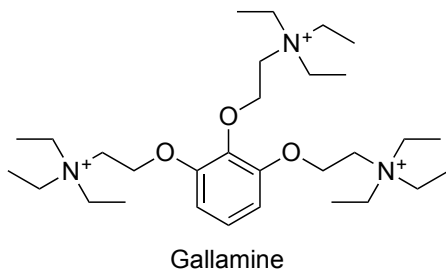
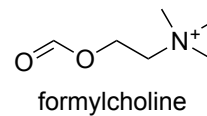
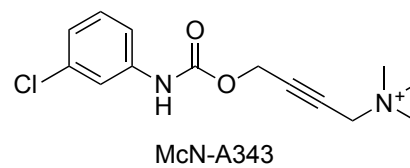
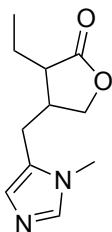
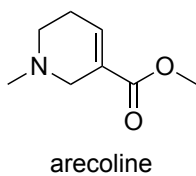
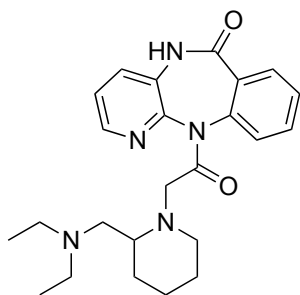
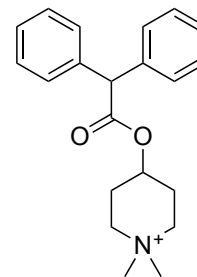
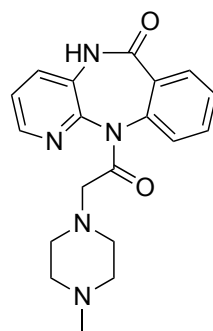
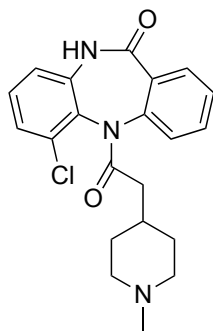
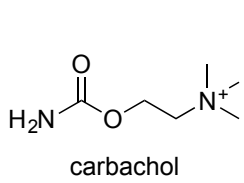


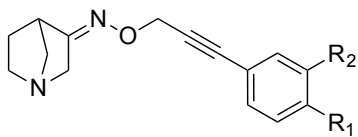
GR218231



GR103691





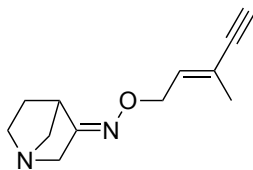


$R_1 = H$ $R_2 = H$ (Arylacetylene oxime-1)

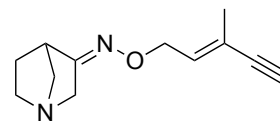
$R_1 = MeO$ $R_2 = H$ (Arylacetylene oxime-2)

$R_1 = H$ $R_2 = MeO$ (Arylacetylene oxime-3)

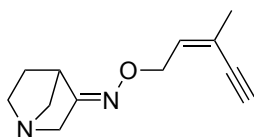
$R_1 = MeO$ $R_2 = MeO$ (Arylacetylene oxime-4)



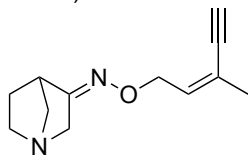
Aryl-ene-yne oxime-5



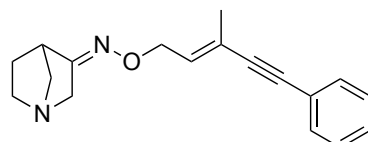
Aryl-ene-yne oxime-6



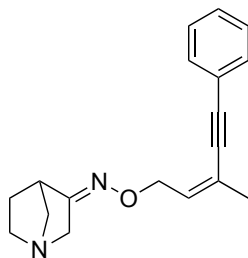
Aryl-ene-yne oxime-7



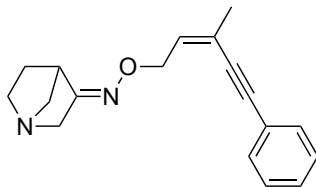
Aryl-ene-yne oxime-8



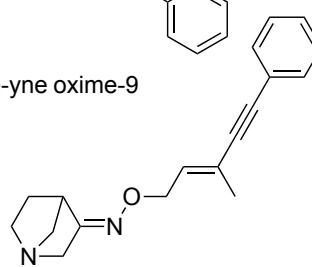
Aryl-ene-yne oxime-9



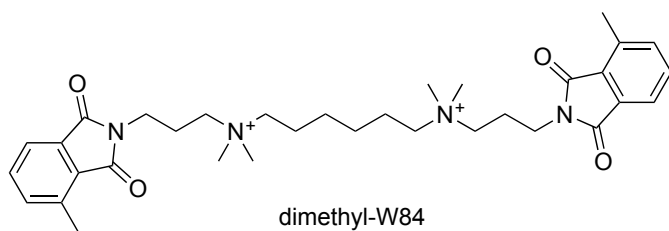
Aryl-ene-yne oxime-10



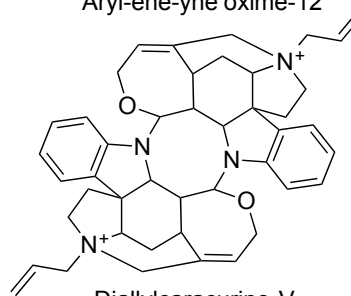
Aryl-ene-yne oxime-11



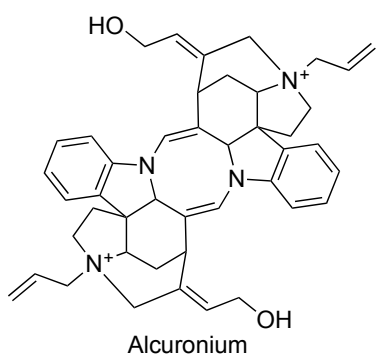
Aryl-ene-yne oxime-12



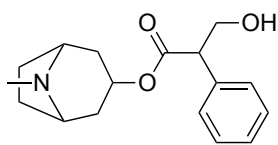
dimethyl-W84



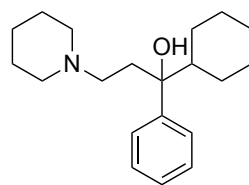
Diallylcaracurine V



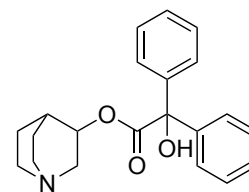
Alcuronium



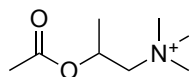
Atropine



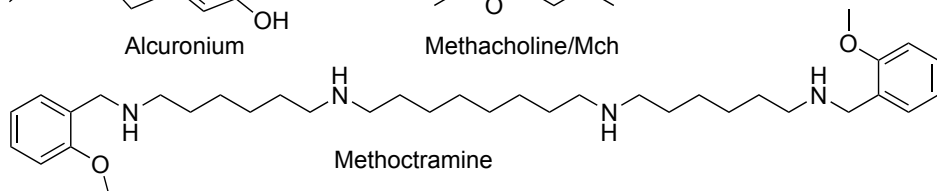
Trihexyphenidyl



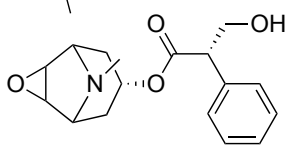
QNB/Quinuclidinyl benzylate



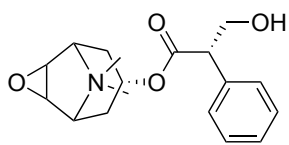
Methacholine/Mch



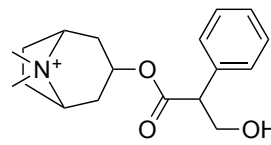
Methoctramine



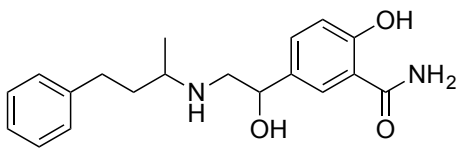
scopolamine



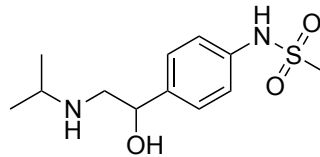
N-methylscopolamine/NMS



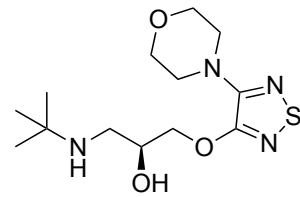
N-methylatropine



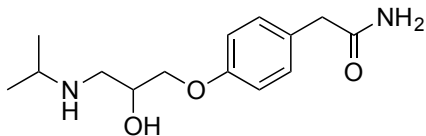
Labetalol



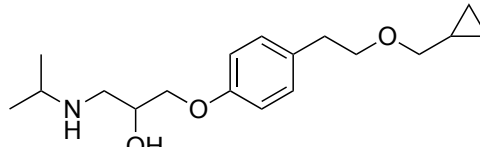
Sotalol



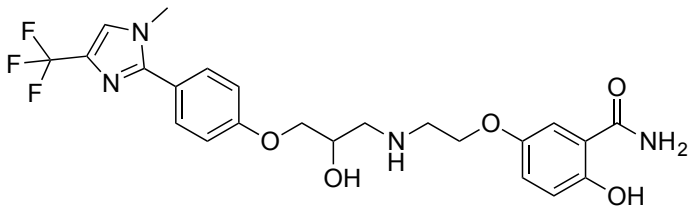
Timolol



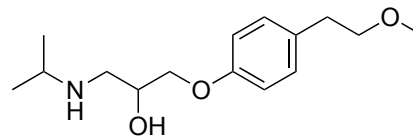
Atenolol



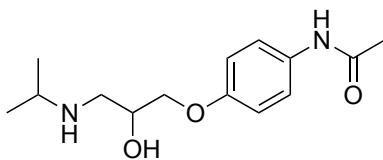
Betaxolol



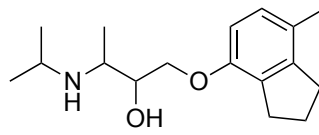
CGP20712(A)



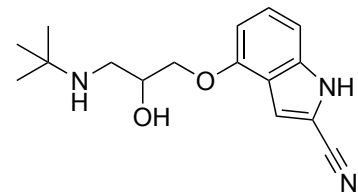
Metoprolol



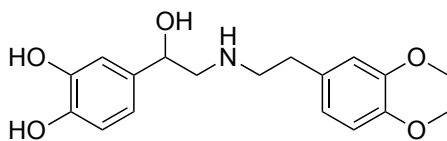
Practolol



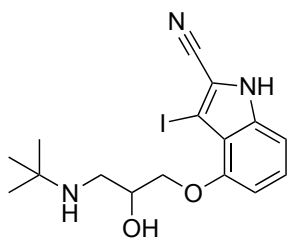
ICI118,551



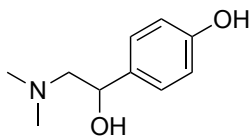
Cyanopindolol



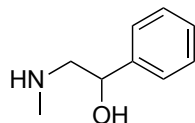
(-)-RO363



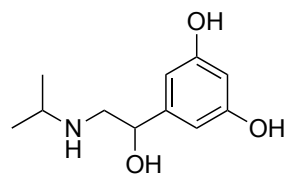
iodocyanopindolol



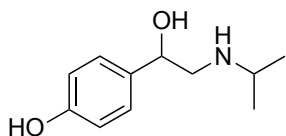
isopropyl-norsynephrine



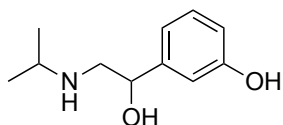
MAPE



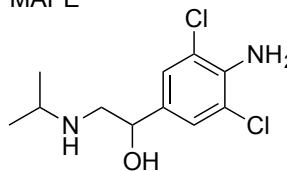
Metaproterenol



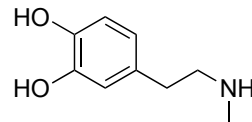
Para-hydroxyl isoprenaline



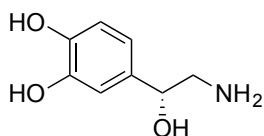
Meta-hydroxyl isoprenaline



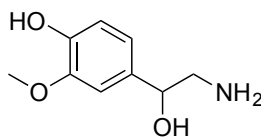
NAB 277



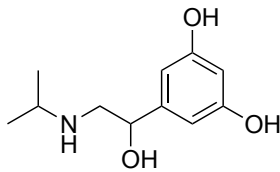
N-Methyl-Dopamine



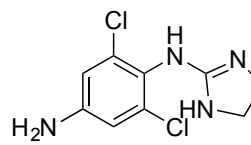
Norepinephrine



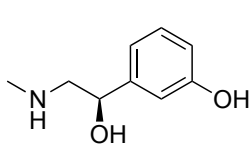
Normetanephrine



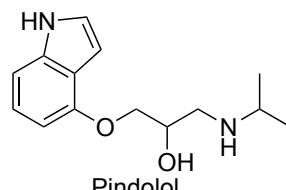
Orciprenaline



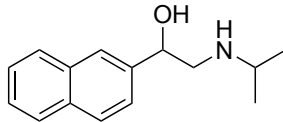
P-aminoclonidine



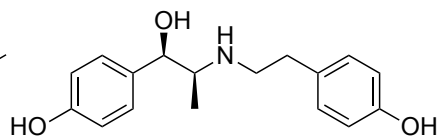
Phenylephrine



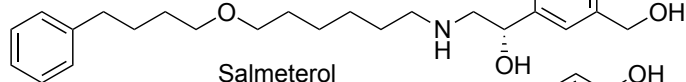
Pindolol



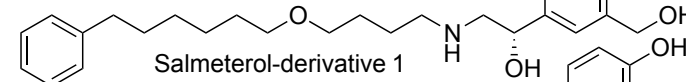
Pronethalol



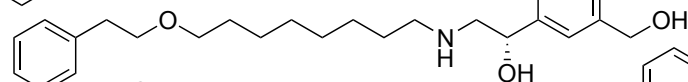
Ritodrine



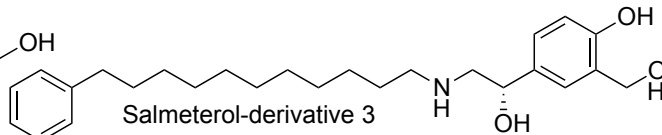
Salmeterol



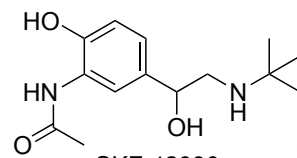
Salmeterol-derivative 1



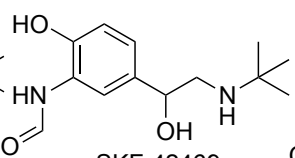
Salmeterol-derivative 2



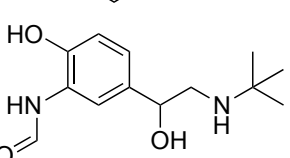
Salmeterol-derivative 3



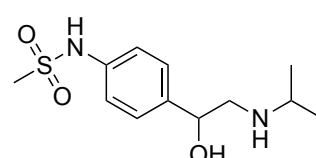
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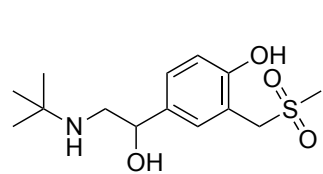
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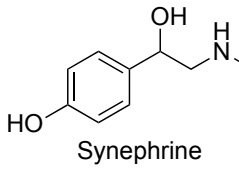
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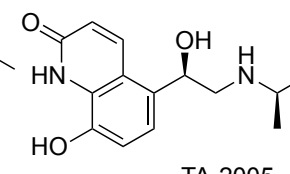
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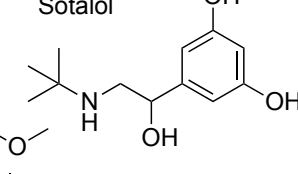
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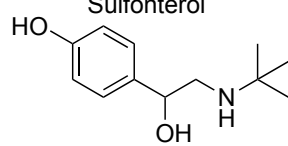
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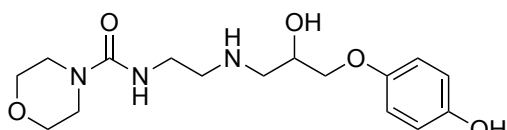
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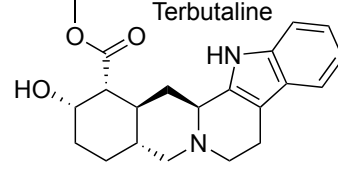
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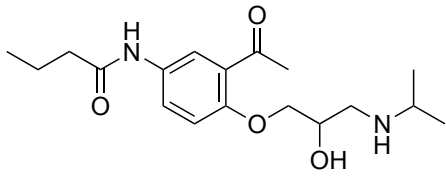
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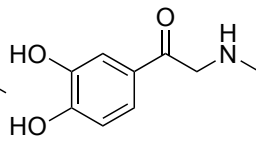
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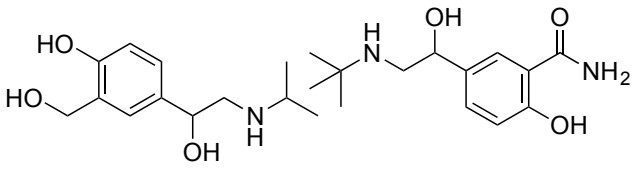
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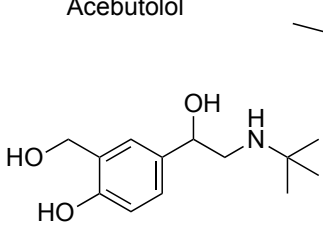


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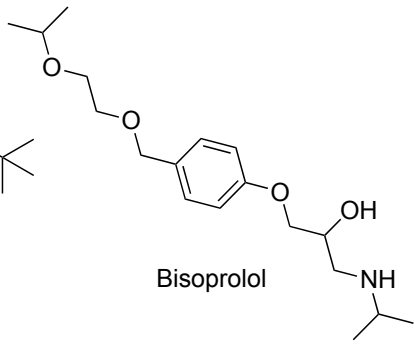


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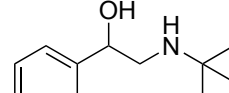
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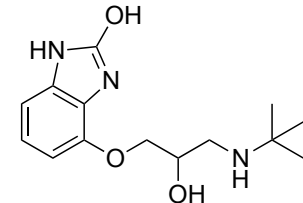
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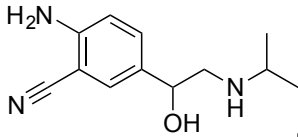
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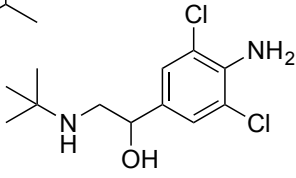
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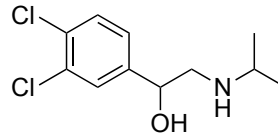
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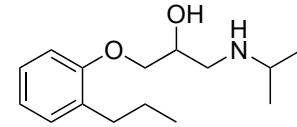
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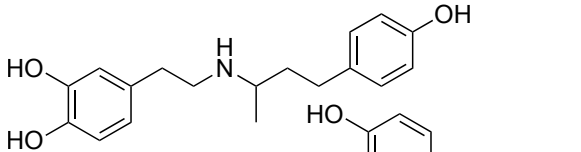
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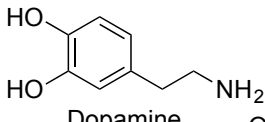
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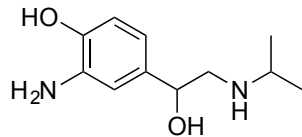
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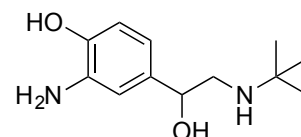
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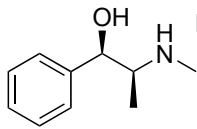
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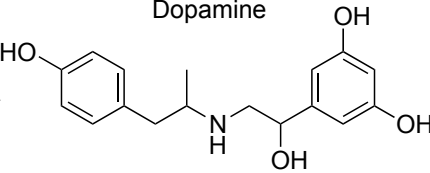
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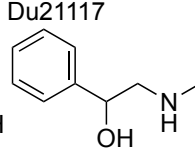
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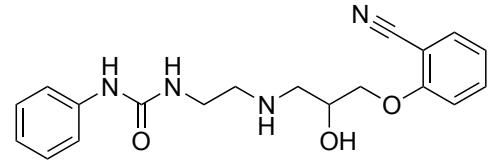
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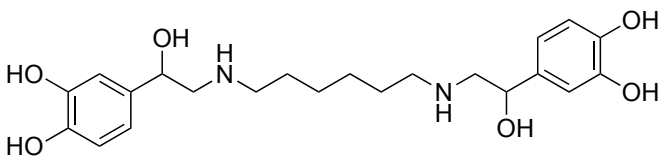
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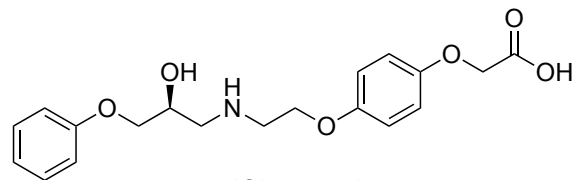
Halostachine



ICI-89406



Hexoprenaline



ICI-215,001

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