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ORIGINAL PAPER

A computational investigation of sulfur-containing heterocyclic components from the anal sac secretions of *Mustela* species

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Abstract A computational investigation of the sulfur-containing heterocyclic components (substituted thietanes and 1,2-dithiolanes) of *Mustela* anal sac secretions has been carried out. A cluster analysis of the chemical compositions of *Mustela* anal sac volatiles reveals little similarity with established phylogenetic relationships between members of the genus. *Ab initio* calculations [MP2/6–311++G(2*df*,2*p*)// B3LYP/6–311++G**] show the lowest-energy $C_5H_{10}S$ isomeric thietane to be 2,2-dimethylthietane, which is also the most abundant of the *Mustela* thietanes. Similarly, 3,3-dimethyl-1,2-dithiolane is the lowest-energy $C_5H_{10}S_2$ compound. 2-*n*-Propylthietane is the highest-energy $C_6H_{12}S$ compound, but the most abundant *Mustela* $C_6H_{12}S$ compound produced, whereas *cis*-2-ethyl-4-methylthietane, the lowest-energy $C_6H_{12}S$ thietane, has never been observed in *Mustela* anal sac secretions. A molecular docking analysis of the *Mustela* sulfur-containing heterocycles into both porcine and bovine odorant binding proteins reveals the interactions of the docked ligands with the proteins to be largely hydrophobic, and have binding energies generally lower than typical odorant molecules such as linalool or eugenol.

Keywords *Ab initio* molecular orbital theory · Cluster analysis · Density functional theory · Dithiolanes · Molecular docking · *Mustela* · Odorant binding protein · Thietanes

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Introduction

Members of the genus *Mustela* (family Mustelidae) are characterized by their production of anal gland secretions that are rich in malodorous sulfur-containing heterocycles, principally substituted thietanes and 1,2-dithiolanes (Fig. 1). Volatile components of *Mustela* anal gland secretions have been analyzed for the American mink, *M. vison* [1–3], the ermine, *M. erminea* [4, 5], the domestic ferret, *M. furo* [5–7], the mountain weasel, *M. nivalis* [3], the Siberian weasel, *M. sibirica* [8, 9], the European polecat, *M. putorius* [3], and the steppe polecat, *M. eversmanni* [8, 9]. The sulfur-containing heterocyclic compounds that have been implicated in *Mustela* anal sac secretions include 2,2-dimethylthietane (**1**), 2-ethylthietane (**2**), *cis*-2,3-dimethylthietane (**3**), *trans*-2,3-dimethylthietane (**4**), *cis*-2,4-dimethylthietane (**5**), *trans*-2,4-dimethylthietane (**6**), 2-isopropylthietane (**7**), 2-*n*-propylthietane (**8**), *cis*-2-ethyl-3-methylthietane (**9**), *trans*-2-ethyl-3-methylthietane (**10**), 2-*n*-pentylthietane (**11**), 3,3-dimethyl-1,2-dithiolane (**12**), 3-ethyl-1,2-dithiolane (**13**), *cis*-3,4-dimethyl-1,2-dithiolane (**14**), *trans*-3,4-dimethyl-1,2-dithiolane (**15**), 3-*n*-propyl-1,2-dithiolane (**16**), and 4-*n*-propyl-1,2-dithiolane (**17**).

This report presents a computational investigation of the substituted thietanes and 1,2-dithiolanes, including a cluster analysis of the compositions from the different species of *Mustela*, an *ab initio* analysis of the compounds using both density functional theory (B3LYP/6–311++G**) and post-Hartree-Fock [MP2/6–311++G(2*df*,2*p*)] methods, and a molecular docking analysis of the compounds into odorant binding proteins. To my knowledge, no such computational investigations have been previously carried out with mustelid sulfur-containing heterocyclic compounds.

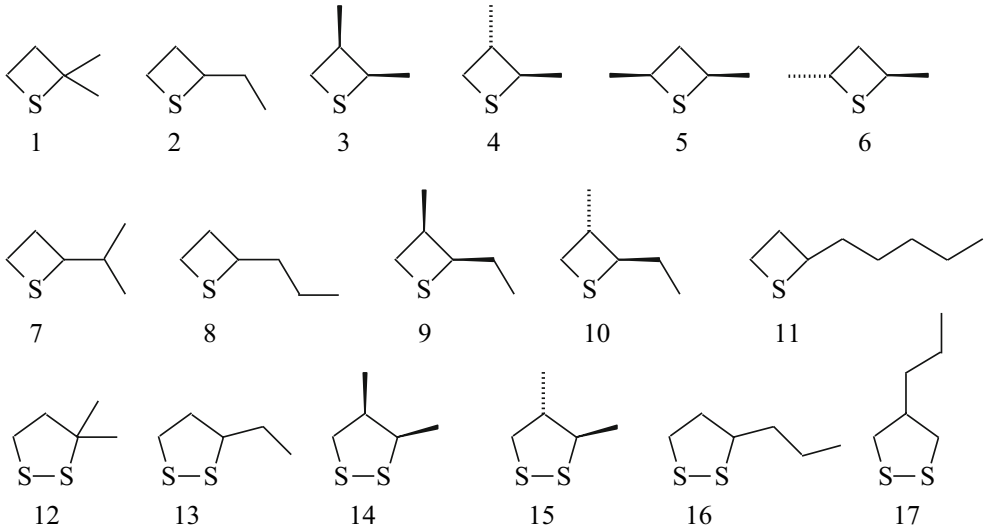

Fig. 1 Sulfur-containing heterocyclic compounds from the anal sac secretions of *Mustela* species

Computational studies

Numerical cluster analysis Twelve *Mustela* samples were treated as operational taxonomic units (OTUs). The percentage composition of the sulfur-containing heterocyclic components was used to determine the chemical relationship between the different *Mustela* anal sac sections by cluster analysis using the NTSYSpc software, version 2.2 [10]. Correlation was selected as a measure of similarity, and the unweighted pair-group method with arithmetic average (UPGMA) was used for cluster definition.

Quantum chemical analysis All calculations were carried out using SPARTAN'06 for Windows [11]. The hybrid B3LYP functional [12, 13] and the 6–311++G** basis set [14] were used for the optimization of all stationary points in the gas phase. Single-point Hartree-Fock *ab initio* energies were calculated using the DFT geometries (above), followed by a correlation energy calculation using the second-order Møller-Plesset model (MP2) [14] at the 6–311++G(2df,2p) [14] level. Frequency calculations were used to characterize stationary points as minima or first-order saddle points. All enthalpies reported are zero-point (ZPE) corrected with unscaled frequencies, but with no thermal corrections; they are, therefore, $H_{(0K)}$. Entropies were calculated using the linear harmonic oscillator approximation.

Molecular docking analysis Protein-ligand docking studies were carried out based on the crystal structures of porcine odorant binding protein (three different structures, PDB: 1dzj, 1dzk, and 1e00) [15] and bovine odorant binding protein (three structures, PDB: 1pbo, 1hn2, and 1g85) [16, 17]. All solvent molecules and the co-crystallized ligands were removed from the structures. Molecular docking calculations for all compounds with each of the odorant binding proteins were undertaken using Molegro Virtual Docker 2.3 [18, 19], with a sphere of radius 13 Å centered on each of the two binding sites of each protein structure in order to allow each ligand to search. Different orientations of the ligands and energy minimizations (force-field conformational analyses) were searched and ranked based on their energy scores. As a check of docking accuracy, a comparison was carried out using ArgusLab 4.0.1 [20]. A box of 17×17×17 Å was centered on each binding site.

Results and discussion

A simplified dendrogram (Fig. 2), created using the unweighted pair-group method with arithmetic averages

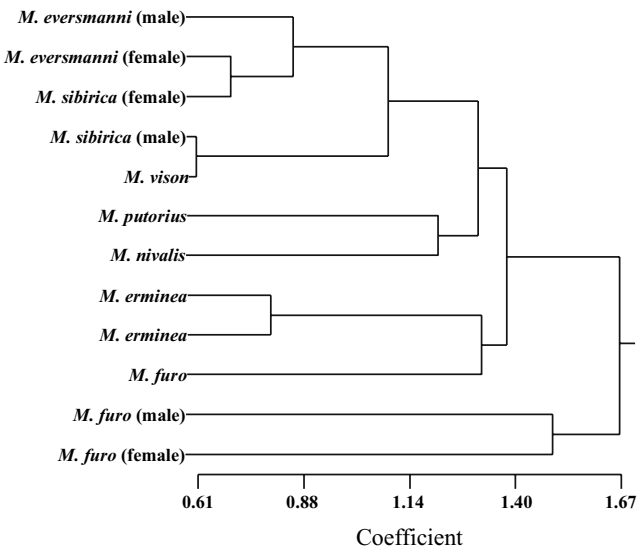

Fig. 2 Dendrogram obtained by cluster analysis of the percentage composition of *Mustela* anal sac volatiles, based on correlation and using the unweighted pair-group method with arithmetic average (UPGMA)

Table 1 *Ab initio* calculated thermodynamic properties (kcal/mol) of *Mustela* anal sac thietane and 1,2-dithiolane volatile compounds

Compound	B3LYP/6–311++G**				MP2/6–311++G(2*df*,2*p*)	
	$H_{(0K)}$	H_{rel}	G^o	G_{rel}	$H_{(0K)}$	H_{rel}
2,2-dimethylthietane (**1**)	−373163.04	1.43	−373182.32	1.71	−372507.23	0.00
2-ethylthietane (**2**)	−373160.98	3.50	−373180.71	3.32	−372502.99	4.24
cis-2,3-dimethylthietane (**3a**)	−373161.48	3.00	−373180.85	3.18	−372504.73	2.50
cis-2,3-dimethylthietane (**3b**)	−373161.29	3.19	−373180.70	3.33	−372504.66	2.57
trans-2,3-dimethylthietane (**4**)	−373163.51	0.96	−373182.96	1.07	−372506.22	1.02
cis-2,4-dimethylthietane (**5**)	−373164.47	0.00	−373184.03	0.00	−372506.88	0.35
trans-2,4-dimethylthietane (**6**)	−373163.66	0.81	−373183.20	0.83	−372506.13	1.10
2-isopropylthietane (**7**)	−397820.60	2.23	−397841.37	2.35	−397096.74	1.06
2-*n*-propylthietane (**8**)	−397819.63	3.20	−397840.98	2.74	−397093.53	4.28
cis-2-ethyl-3-methylthietane (**9a**)	−397820.19	2.64	−397840.85	2.87	−397096.21	1.59
cis-2-ethyl-3-methylthietane (**9b**)	−397819.21	3.61	−397839.78	3.94	−397095.52	2.28
trans-2-ethyl-3-methylthietane (**10**)	−397822.28	0.55	−397843.19	0.53	−397097.59	0.22
cis-2-ethyl-4-methylthietane	−397822.83	0.00	−397843.72	0.00	−397097.80	0.00
2-*n*-pentylthietane (**11**)	−447136.97	—	−447161.55	–	−446274.58	—
3,3-dimethyl-1,2-dithiolane (**12**)	−623057.82	0.25	−623078.33	1.22	−622091.71	0.00
3-ethyl-1,2-dithiolane (**13**)	−623057.50	0.56	−623078.64	0.91	−622088.39	3.32
cis-3,4-dimethyl-1,2-dithiolane (**14a**)	−623056.58	1.48	−623077.60	1.96	−622088.94	2.77
cis-3,4-dimethyl-1,2-dithiolane (**14b**)	−623056.81	1.26	−623077.53	2.03	−622089.16	2.55
trans-3,4-dimethyl-1,2-dithiolane (**15a**)	−623058.06	0.00	−623079.32	0.23	−622090.06	1.65
trans-3,4-dimethyl-1,2-dithiolane (**15b**)	−623057.79	0.28	−623079.55	0.00	−622089.74	1.97
3-*n*-propyl-1,2-dithiolane (**16**)	−647716.16	0.00	−647738.61	0.00	−646679.14	0.00
4-*n*-propyl-1,2-dithiolane (**17**)	−647714.64	1.52	−647737.53	1.08	−646677.21	1.93

(UPGMA) measures the chemical similarities or dissimilarities between *Mustela* anal gland compositions. This cluster analysis shows two clusters: a 2,2-dimethylthietane-rich cluster (*M. eversmanni*, *M. sibirica*, and *M. vison*), and a 2,2-dimethylthietane-poor cluster. Phylogenetic analyses indicate a close relationship between *M. putorius*, *M. furo*, *M. eversmanni*, and *M. sibirica*, with *M. nivalis*, *M. erminea*, and *M. vison*, as outliers. [21–25]. The domestic ferret (*M. furo*) has been suggested to have derived from either the European polecat (*M. putorius*) or the steppe polecat (*M. eversmanni*) [22], but the cluster analysis based on anal sac chemical composition belies this phylogenetic similarity. The chemical cluster analysis also shows similarity between *M. sibirica* and *M. vison*, again in marked contrast to phylogenetic relationships.

The *ab initio* calculated thermodynamic properties for the mustelid sulfur-containing heterocycles are compiled in Table 1. For the $C_5H_{10}S$ isomers, the B3LYP lowest-energy compound is *cis*-2,4-dimethylthietane (**5**), whereas the MP2 calculations indicate 2,2-dimethylthietane (**1**) to be lowest in energy. Overall, the most abundant $C_5H_{10}S$ compounds produced by *Mustela* species are 2,2-dimethylthietane (**1**) and *cis*-2,4-dimethylthietane (**5**), along with *trans*-2,3-dimethylthietane (**4**), only about 1 kcal/mol higher in energy. Interestingly, 2-*n*-propylthietane (**8**) is the highest-energy $C_6H_{12}S$ isomer, but is also the most abundant *Mustela* $C_6H_{12}S$ compound produced. In addition, *cis*-2-ethyl-4-methylthietane, never observed in *Mustela* anal sac volatiles, is the lowest-energy $C_6H_{12}S$ thietane isomer. 3,3-Dimethyl-1,2-dithiolane (**12**) is the lowest-energy $C_5H_{10}S_2$ compound according to the MP2 results, whereas B3LYP calculations show *trans*-3,4-dimethyl-1,2-dithiolane (**15**) to

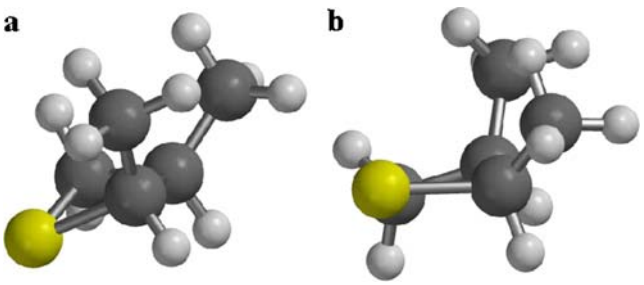

Fig. 3 Low-energy conformations of *cis*-2,3-dimethylthietane, **3**

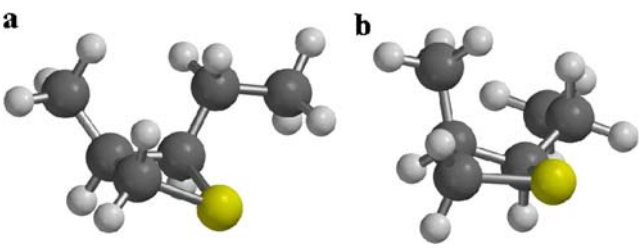

Fig. 4 Low-energy conformations of *cis*-2-ethyl-3-methylthietane, **9**

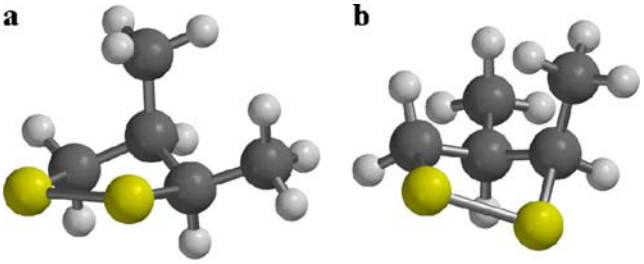

Fig. 5 Low-energy conformations of *cis*-3,4-dimethyl-1,2-dithiolane, **14**

be lowest. The different relative energies in the B3LYP compared to the MP2 methods are likely due to medium-range electron correlations that are not appropriately included in the B3LYP implementation [26, 27].

There are two low-energy conformations for *cis*-2,3-dimethylthietane (Fig. 3), and these are very close in energy with **3a** slightly lower in energy than **3b**. Similarly, *cis*-2-ethyl-3-methylthietane, conformation **9a** is slightly lower in energy than **9b** (Fig. 4). There are two alternative envelope conformations for *cis*-3,4-dimethyl-1,2-dithiolane (Fig. 5). The conformation with the eclipsed C-S-S-C dihedral angle (**14a**) is slightly higher in energy than conformation with the gauche C-S-S-C (**14b**), consistent with what is generally observed in disulfides [28].

Scent communication in mammals is important not only for intraspecific interactions (e.g., territorial, individual, or sex recognition) [29, 30], but can also be important in interspecific interactions [31, 32]. The thietanes and 1,2-dithiolanes of mustelid anal gland secretions are important scent marking chemicals used by these solitary animals as a major form of communication [33, 34]. It would be interesting to examine the docking of thietanes and dithiolanes with olfactory receptors from various species. However, no crystal structures any olfactory receptors are currently known. There are, however, X-ray crystal structures of several odorant binding proteins available. It is generally understood that in order for airborne odorants to reach the membrane bound olfactory receptors, they are conveyed through the aqueous nasal mucosa by way of odorant binding proteins [35, 36]. These proteins reversibly bind odorant molecules, which are typically hydrophobic, using a β-barrel motif that defines a hydrophobic cavity [37].

It has been found that the best odorant ligands for porcine and bovine odorant binding proteins are heterocyclics such as alkyl substituted pyrazines and thiazoles and monoterpenoids such as menthol and thymol [37], while linalool and eugenol were excellent ligands for rat odorant binding protein [38]. Sequence diversity of odorant binding proteins along with the identification of different subclasses has led to the suggestion that different subtypes of odorant binding proteins may be specialized to bind preferentially to different classes of odorant molecules [39]. A molecular dynamics study of binding and unbinding of porcine odorant binding protein has suggested that Tyr 82, Ala 83, Pro 34, and Phe 66 are involved in odorant binding protein door opening and closing to allow capture and release of the odorant molecule [40].

This present study addresses the questions: (a) What is the nature of binding of mustelid sulfur-containing heterocycles to odorant binding proteins? (b) How strong is the binding of these compounds compared to previously studied odorant ligands and essential oil components? (c) Are there differences in binding affinities of the mustelid odorants between different odorant binding proteins? In order to address these questions, a molecular docking analysis was carried out using both Molegro Virtual Docker

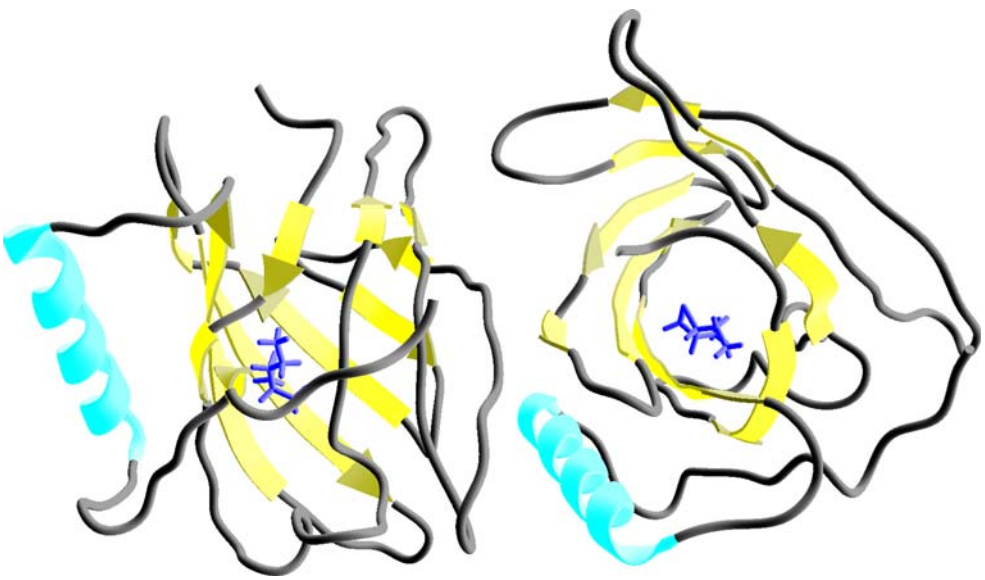

Fig. 6 Porcine odorant binding protein (PDB: 1dzk) with docked ligand (*cis*-2-ethyl-3-methylthietane) in the two binding sites

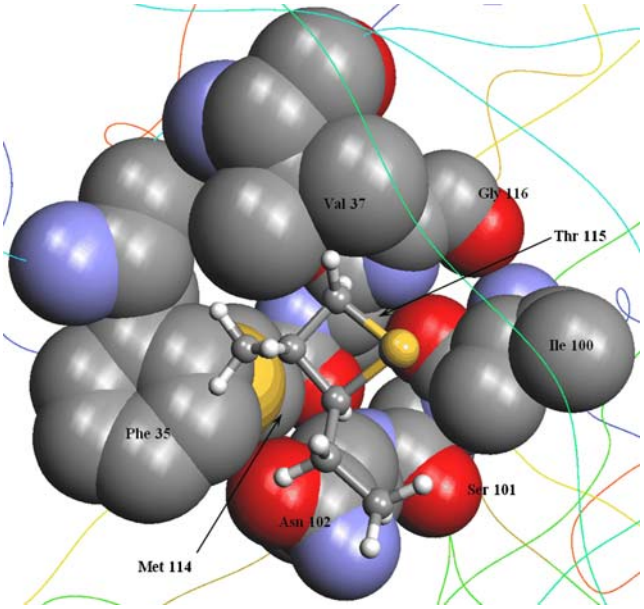

Fig. 7 *trans*-2-Ethyl-3-methylthietane in binding pocket "A" of porcine odorant binding protein (PDB: 1dzk)

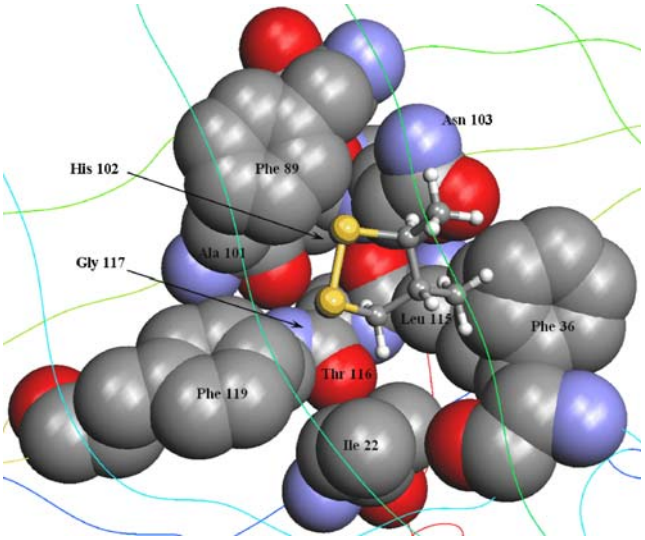

Fig. 9 *trans*-3,4-Dimethyl-1,2-dithiolane in binding pocket "B" of bovine odorant binding protein (PDB: 1hn2)

2.3 and ArgusLab 4.0.1 on X-ray crystal structures of porcine odorant binding proteins (PDB: 1dzj, 1dzk, and 1e00) and bovine odorant binding proteins (PDB: 1pbo, 1hn2, and 1g85).

All of the mustelid heterocycles bind to porcine odorant binding protein sites A and B in hydrophobic pockets that the co-crystallized ligands from the X-ray crystal structures (1dzj, 1dzk, and 1e00; see Fig. 6) had occupied. Important amino acid contacts are Asn 102, Gly 116, Ile 21, Ile 100, Met 114, Phe 35, Ser 101, Thr 115, and Val 37 (Fig. 7). There does not seem to be any consistent orientation of the heterocycles in this binding pocket; the locations of the sulfur atoms, for example, are random. This is consistent with what has been found experimentally by X-ray crystallographic analysis of bound odorant molecules [15, 37]. Similarly, in the bovine odorant binding protein, the sites occupied by the co-crystallized ligands are also preferentially docked by the thietanes and dithiolanes (Fig. 8). The binding site environments are somewhat different between the two binding proteins. This is not surprising, however, as there is generally little sequence homology between different odorant binding proteins [37]. The important amino acid contacts in the bovine structures (1pbo, 1hn2, and 1g85) are Ala 101, Asn 103, Gly 117, His 102, Ile 22, Leu 115, Phe 36, Phe 89, Phe 119, and Thr 116 (Fig. 9). This site is consistent with experimentally (X-ray crystal structures) bound ligands [17, 41].

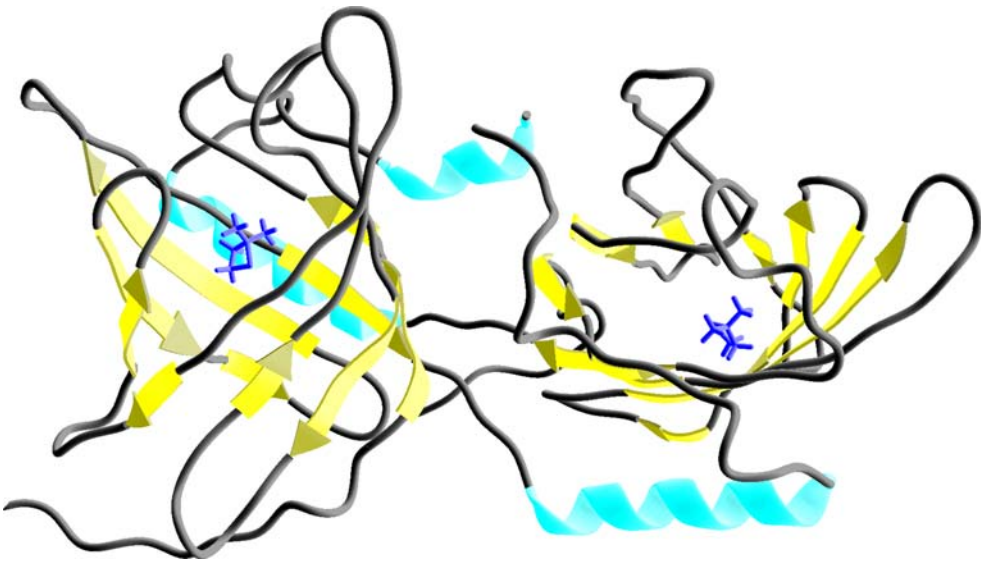

Fig. 8 Bovine odorant binding protein (PDB: 1hn2) with docked ligand (2,2-dimethylthietane) in the two binding sites

Table 2 Docking results for *Mustela* thietanes, 1,2-dithiolanes, and other odorant molecules to porcine and bovine odorant binding proteins

Ligands	Average binding energies (kcal/mol)			
	Molegro		ArgusDock	
	Porcine	Bovine	Porcine	Bovine
2,2-dimethylthietane (**1**)	−9.4	−10.5	−8.5	−9.1
2-ethylthietane (**2**)	−9.6	−10.6	−8.7	−9.2
cis-2,3-dimethylthietane (**3**)	−9.4	−10.3	−8.5	−9.2
trans-2,3-dimethylthietane (**4**)	−9.5	−10.2	−8.7	−9.3
cis-2,4-dimethylthietane (**5**)	−9.8	−11.0	−8.7	−9.2
trans-2,4-dimethylthietane (**6**)	−9.6	−10.8	−9.4	−9.9
2-isopropylthietane (**7**)	−10.7	−11.6	−9.4	−9.9
2-*n*-propylthietane (**8**)	−10.7	−11.7	−9.2	−9.9
cis-2-ethyl-3-methylthietane (**9**)	−10.8	−11.3	−9.1	−9.9
trans-2-ethyl-3-methylthietane (**10**)	−10.8	−11.4	**−10.5**	**−11.0**
2-*n*-pentylthietane (**11**)	**−12.9**	**−14.0**	−9.1	−9.7
3,3-dimethyl-1,2-dithiolane (**12**)	−10.9	−11.3	−8.8	−9.2
3-ethyl-1,2-dithiolane (**13**)	−10.8	−11.6	−9.4	−10.0
cis-3,4-dimethyl-1,2-dithiolane (**14**)	−10.5	−10.9	−9.1	−9.9
trans-3,4-dimethyl-1,2-dithiolane (**15**)	−10.9	−10.8	−9.2	−10.0
3-*n*-propyl-1,2-dithiolane (**16**)	−11.6	−12.9	−9.8	−10.7
4-*n*-propyl-1,2-dithiolane (**17**)	−11.6	−12.6	−9.7	−10.4
cis-2-ethyl-4-methylthietane	−10.7	−12.0	−9.3	−9.7
artemisia ketone	−13.4	−14.4	−10.1	−11.0
benzaldehyde	−10.3	−9.9	−9.0	−9.5
camphor	−13.0	−13.7	−10.1	−10.6
d-carvone	−12.7	−13.4	−10.2	−11.1
l-carvone	−13.0	−13.5	−10.3	−10.9
1,8-cineole	−11.6	−11.4	−9.5	−10.2
eugenol	−13.9	**−16.4**	−9.7	−10.4
isoamyl acetate	−12.6	−13.6	−7.6	−8.3
d-limonene	−11.5	−12.8	**−10.8**	**−12.0**
linalool	**−14.7**	−15.9	−10.2	−10.9
menthol	−10.9	−13.7	−10.2	−10.8
2-phenethanol	−12.9	−13.2	−9.2	−9.9
skatole	−13.4	−14.1	−9.3	−10.1
thymol	−12.2	−13.0	−10.4	−11.0

The calculated binding energies (averages for the best poses in binding sites "A" and "B" for three different crystal structures for both porcine and bovine odorant binding proteins) are summarized in Table 2. The mustelid sulfur heterocycles generally bind to odorant binding proteins less well than other odorant compounds. Additionally, the compounds generally bind to the bovine odorant binding protein better than they bind to the porcine. Because the binding of odorant compounds is largely due to hydrophobic interactions, the hydrophobic surface of the molecule is important. Poor binding ligands such as 2,2-dimethylthietane (**1**) are relatively small (surface area = 138 Å^2) whereas the better binding thietanes **10** and **11** are larger (159 and 200 Å^2, respectively). The monoterpenoids linalool and limonene are also relatively large (227 and 197 Å^2, respectively). The generally tighter binding in the bovine odorant binding protein can be rationalized in terms of hydrophobic interactions. The bovine binding pocket is smaller than the porcine (average Molegro calculated cavity sizes are 95.8 and 107.2 Å^3, respectively). In addition, there are more hydrophobic residues in contact with the docked ligands in the bovine odorant binding protein compared to that of the porcine (see Figs. 7 and 9). Interestingly, the Molegro docking indicated linalool to be the best binding ligand (of those studied) in the porcine odorant binding protein, while eugenol was the best binder in the bovine protein. These two ligands were experimentally found to be excellent ligands for rat odorant binding protein [38].

Summary

The cluster analysis, based on volatile anal sac components, does not mirror phylogenetic relationships between *Mustela*

species, and therefore, cannot be a reliable chemotaxonomic tool for this genus. Consistent with what has been observed in alkanes, the more highly branched thietanes and 1,2-dithiolanes are lower in energy than the *n*-alkyl-substituted heterocycles. These relatively small, hydrophobic compounds favorably dock to odorant binding proteins, but generally have smaller (less negative) interaction energies than "typical" odorant molecules such as linalool or eugenol.

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