

TASTE:

**ANALOGUES OF THE NEUROTRANSMITTERS
ACETYLCHOLINE SEROTONIN AND ADRENALINE
INCREASE OR CHANGE THE PERCEPTION OF
FLAVOR.**

Draft study project

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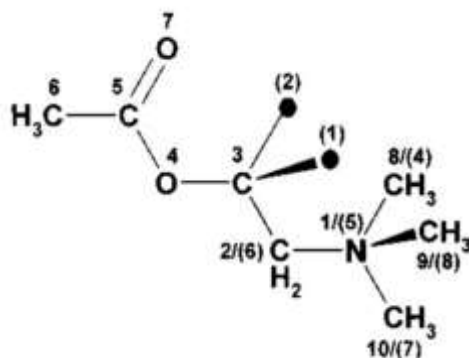


Fig 1 acetylcholine

ABSTRACT

In this study, a ligand-based computational comparison is performed between the compounds that characterize the flavor of certain foods and neurotransmitters in particular acetylcholine.

According to some studies, acetylcholine improves the perception of flavors

(Ref. 1) similarly serotonin and norepinephrine (Ref. 2).

Volatile compounds in beer, volatile compounds in hops (*Humulus lupulus*) and cocoa (*Theobroma cacao*) are taken into account.

In this study project there is an almost linear trend between the analogy with the acetylcholine of the volatile substances contained in beer and the respective olfactory threshold.

THE homology between acetylcholine and compounds that characterize the aroma of foods is evaluated

The compounds contained in cocoa are also compared with the neurotransmitters acetylcholine serotonin and norepinephrine.

INTRODUCTION

I grow aromatic and official plants for passion and for work and I have noticed that the species of which I perceive the characteristic aroma the most, relieve me more than other symptoms of pathologies, here I need to understand the link between aromas and biological activities of the compounds in foods and plant matrices

Mechanisms of taste perception: according to some studies (references 1 and 2) neurotransmitters such as acetylcholine, glutamate, serotonin and norepinephrine improve taste perception

Acetylcholine stimulates M3 muscarinic receptors on the cells of the taste buds of the receptor (type II)

Ach is synthesized and released by receptor taste button cells (Type II) during gustatory stimulation.

This autocrine muscarinic feedback amplifies Ca^{++} signals evoked by taste and improves the release of Afferent neurotransmitters (ATP) from receptor cells (type II).

Taste receptor cells in mice lacking M3 muscarinic receptors show depressed sensitivity to gustatory stimulation (Reference 1)

When a bite is ingested, a real screening is made on the biological activity of the food, the acetylcholine agonists present in the food partially depolarize the type 1 glial cells by opening the calcium or potassium ion channels, a neurotransmitter is emitted that affects the type 2 and 3 cells (lowering the threshold of signal activation) (references 1 and 2) increasing the perception of flavor, while other agonists (e.g. nicotine) discourage the intake of the food that contains them by increasing the perception of the bitterness of the sour and decreasing the sensitivity to the sweet taste (reference 5)

The computational comparisons ligand-based are performed with Forge (Cresset): the analogy is calculated by evaluating the electromagnetic fields generated by the molecules and other parameters such as the excluded volume of the receptor protein

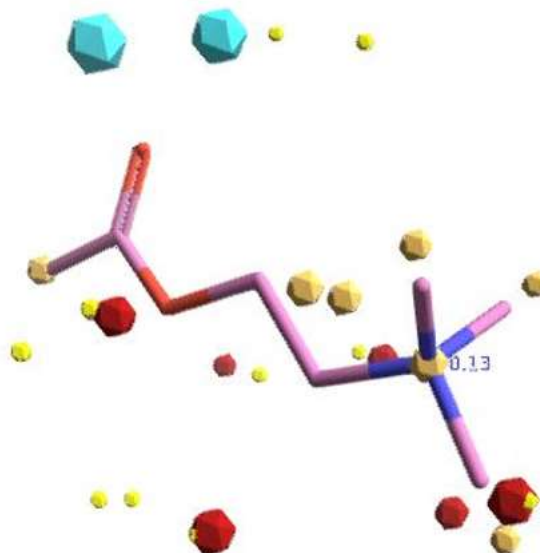


Fig 2: three-dimensional representation of acetylcholine (sticks) atoms in carbon pink, nitrogen in blue, oxygen red, the prisms represent with their position the maximum point of the fields (positive-red, negative-blue, yellow-VanDerVals, golden-lipophilia) while the size represents the intensity of the field.

Alignment of acetylcholine and volatile hop compounds

The volatile compounds of hops are aligned (table 2) (reference 3) obtaining a coefficient of similarity (between zero and 1) methyl hexanoate, nonanone and linalool appear to have the greatest analogy for acetylcholine among the volatile compounds of hops, while isoamyl-acetate, produced during alcoholic fermentation is the most similar.

In Figure 3 alignment of acetylcholine and isoamyl acetate

	ACEYLCHOLIN E	ACEYLCHOLIN E	ACEYLCHOLIN E	ACEYLCHOLIN E	ACEYLCHOLIN E	ACEYLCHOLIN E
ACEYLCHOLINE	1					
ISOAMYL-ACETATE		0,855				
METHYL-HEXANOATE			0,755			
2 NONANONE				0,735		
LINALOOL					0,721	
ISOBUTYL-ISOBUTYRATE						0,692

Fig 3: table of alignment results: the color of the values indicates how correct they are: favorable green, unfavorable red.

Alignment of volatile compounds present in beer and acetylcholine

Acetylcholine is aligned with the volatile compounds present in beer indicated in Table 1 with Forge Cresset obtaining similarity values that have a relatively linear trend with respect to the olfactory threshold. (figure 4)

Table 1 Different taste compounds in beer and organoleptic threshold

Compound	Taste in beer	Organoleptic threshold (ppm)	Reference
<i>Higher alcohols</i>			
n-propanol	Alcohol	800.00	Kobayashi et al., 2008
Isobutyl alcohol	Alcohol	200.00	Kobayashi et al., 2008
Amyl alcohol	Alcohol, banana, medicinal, solvent, fruity	65.00	Kobayashi et al., 2008
Isoamyl alcohol	Alcohol, banana, sweetish, aromatic	70.00	Kobayashi et al., 2008
2-phenyl etanol	Roses, sweetish, perfumed	125.00	Kobayashi et al., 2008
<i>Esters</i>			
Ethyl acetate	Solvent, fruity, sweetish	21.00	Piddocke, 2009
Isoamyl acetate	Banana, apple, solvent, estery, pear	1.40	Piddocke, 2009
2-phenylethyl acetate	Roses, honey, Apple, sweetish	3.80	Kobayashi et al., 2008
Ethyl caproate	Sour apple, anniseed	0.17	Willaert and Nedovic, 2006
Ethyl caprylate	Sour Apple	0.30	Willaert and Nedovic, 2006
<i>Vicinal diketones</i>			
Diacetyl	Butter	0.15	Kobayashi et al., 2008
2,3-pentanedione	Honey, toffee-like	1.00	Willaert and Nedovic, 2006
<i>Organic and fatty acids</i>			
Caprylic	Goaty, fatty acid	14.00	Verbelen and Devaux, 2009
Caproic	Goaty, fatty acid	8.00	Verbelen and Devaux, 2009
Capric	Waxy, rancid	10.00	Verbelen and Devaux, 2009
<i>Aldehydes</i>			
Acetaldehyde	Grassy, green leaves, fruity	25.00	Kobayashi et al., 2008

Table 1 (reference 4)

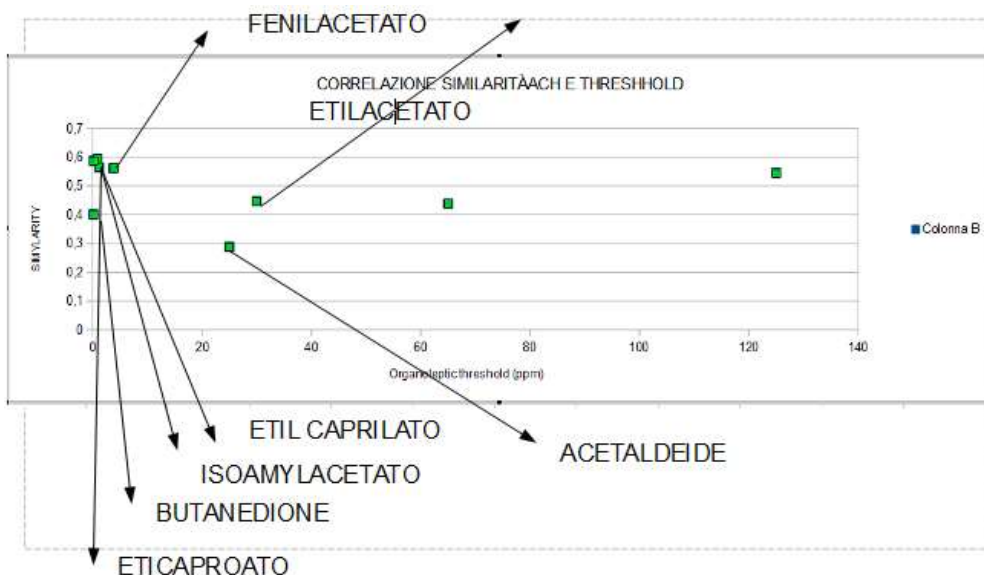


Fig 4 graph indicating the trend, almost linear, between the coefficient of similarity with acetylcholine and the threshold of perception of volatile hop compounds

Alignment of compounds that characterize the flavor of foods and acetylcholine:

A ligand-based screening is performed between acetylcholine and compounds that characterize foods (list in Table 3) with Forge Cresset

FOOD/COMPOUND	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE
ACETYLCHOLINE	1								
GORGONZOLA/2-EPTANONE		0,798							
MINT/(-) CARVONE			0,767						
COCONUT/GAMMA NONALACTONE				0,695					
APPLE/METIL-2 BUTANOATE					0,679				
LAVANDER/LINALIL ACETATE						0,669			
PEACH/ GAMMA UNDECALATTONE							0,64		
LEMON/LIMONENE								0,598	

Figure 5: Similarity scores of the flavoring compounds of gorgonzola(2 heptanone), mint (-carvone) and coconut have the greatest analogy with acetylcholine (screenshot 2)

Alignment of acetylcholine and cocoa and acetylcholine compounds

Alignment with Forge between cocoa compounds (Table 4) and acetylcholine is performed, histamine was found with the greatest analogy shown by the following figure, tetrahydrobetacarboline and phenylethylamine are analogous

COCOA COMPOUNDS									
	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE	ACETYLCHOLINE
ACETYLCHOLINE	1								
HISTAMINE		0,733							
TETRAIDROBETACARBOLINE			0,653						
PHENIL ETIL AMINE				0,644					
TRIPTAMINE					0,642				
SAFFROLE						0,599			
VANILLIC ACID							0,585		
TEOFILLINE								0,548	

Figure 6: Similarity scores of cocoa compounds, screenshot 4

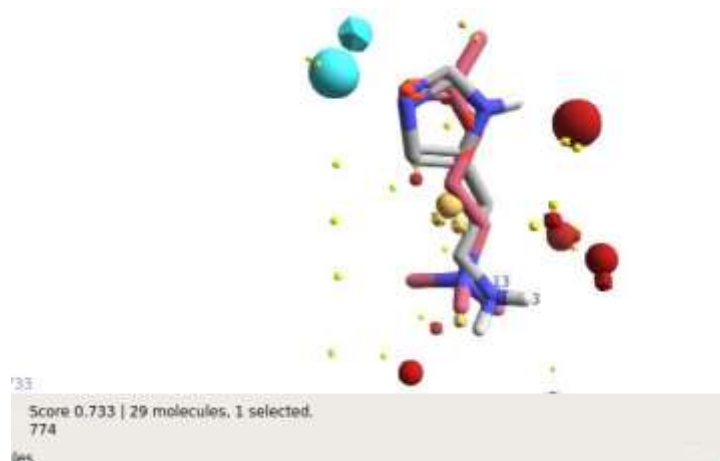


Figure 7: Histamine acetylcholine alignment.

ALL ACETYLCHOLINE ALIGNMENTS USE THE PROTEIN PRESENT IN PROTEIN DATABANK WITH PDB ID 2PGZ AS THE EXCLUDED VOLUME.

ALIGNMENT OF COCOA AND SEROTONIN COMPOUNDS

Alignment is performed between serotonin (bound mouse serotonin receptor 5-HT₃, F conformation, Protein data bank ID 6HIN) and cocoa compounds (table 4).

COMPOUND	SEROTONIN	SEROTONIN	SEROTONIN	SEROTONIN	SEROTONIN	SEROTONIN	SEROTONIN
SEROTONIN	1						
TRIPTAMINE	0,878						
TETRAIDROBETACARBOLINE		0,816					
SAFROLE			0,766				
PHENILRTIAMINE				0,738			
HISTAMINE					0,703		
CAFFEIC ACID							0,699

Fig 8: Scores of cocoa compounds related to serotonin.

Tryptamine, tetrahydrobetacarboline, saffrol and phenylethylamine have a remarkable analogy with serotonin, the 5HT₃ receptor is considered a target for antidepressant drugs, antagonists on this protein that has the function of ion channel (allow the passage of sodium and potassium)(reference 7), analogy scores do not give indications however, whether the molecules are agonists or antagonists.

ALIGNMENT OF NOREPINEPHRINE AND COCOA COMPOUNDS

Ligand-based screening referred to norepinephrine bound to Anopheles gambiae D7R4 (PDB DOI: 10.2210/pdb2QEO/pdb) on cocoa compounds (Table 4)

COMPOUND	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN	NORADRENALIN
NORADRENALIN	1									
CAFFEIC ACID		0,772								
TRYPTAMINE			0,762							
PHENILETIAMINE				0,759						
TYRAMINE					0,753					
SAFROLE						0,688				
TETRAIDROCARBOLINE							0,683			
VANILLIC ACID								0,679		
HISTAMINE										0,636

Fig. 9: Comparison of norepinephrine-cocoa compounds

Caffeic acid has the greatest analogy to norepinephrine, tryptamine and phenylethylamine, and tyramine (usually present in abundance in aged cheeses) denote a high similarity score.

A note for nicotine, analogue of acetylcholine, modifies the taste perception by increasing the sensitivity to bitter and harsh substances and decreases the sensitivity to sweetness (reference 5)

CONCLUSIONS

A computational comparison was performed between the volatile compounds present in beer, hops and cocoa and the substances that characterize some foods and the neurotransmitters acetylcholine, serotonin and norepinephrine that according to Dando et al and Heath et al increase the perception of flavors and illustrate their cellular mechanisms.

An analogy of acetylcholine with histamine (present in cocoa) with isoamyl acetate (banana flavor aroma) and 2 heptane (gorgonzola) and carvone (mint) emerged.

Serotonin has very high analogy scores with tryptamine, tetrahydrobetacarboline and saffrol.

Norepinephrine has the highest coefficient of similarity for caffeic acid also present in polyphenolic structures such as rosmarinic acid

An almost linear trend between the coefficient of similarity and the threshold limit of sensitivity emerged from the ligand-based screening of compounds belonging to the aromas that characterize the taste of foods (figure 4)

It would be interesting to perform an organoleptic examination with a panel of tasters to verify how much the addition of these compounds influences the perception of the taste of food.

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Neuroscience and biobehavioral reviews

Volume 64 , May 2016 , pages 311-325

TABLES

TABLE 2: VOLATILE HOP COMPOUNDS (*Humulus lupulus*)















 2-nonanone	 Isoamyl-acetato
 beta myrcene	 Isobutylisobutyrate
 beta pinene	 limonene
 caryophyllene oxide	 linalool
 -caryophyllene	 Methylheptanoate
 Damascenone	 methylhexanoate
 humulene	 pinene alpha

Table 3: Compounds characterising food flavour
(<https://it.wikipedia.org/wiki/Aroma>)

α -pinene (conifers, turpentine, turpentine essence, some balsamic candies containing α -pinene)

cinnamic acid and cinnamic aldehyde (cinnamon)

Benzaldehyde or benzoic aldehyde (almond and black cherry)

anethole (anise)

limonene (orange, mandarin, clementine, lemon, cedar, grapefruit and other citrus fruits)

citric acid (lemon)

γ -nonalactone (coconut)

eugenol (cloves)

eugenol, estragole, linalool, cineol, methyl eugenols (basil)

geraniol (geranium)

menthol (mint)

eucalyptol (eucalyptus)

thymol (thyme)

cyanide (bitter almonds)

diacetyl and butyric acid C4 (butter)

L-carvone (peppermint)

vanillin or ethylvanillin (vanilla)

bismethylthiomethane (truffle)

Ethyl 2-methylbutyrate (apple)

ethyl butanoate or ethyl acetate (kiwi)

amyl acetate (banana)

fencone (fennel)

apiol (parsley)

2-ylmetantioI, or α -furfurylmercaptan (coffee)

β -damascenone, or 2,3,5,6-tetramethylpyrazine (tea)

phenylacetic acid, ethyl phenylacetate (honey)

γ -undecalactone (peach)

allyl capronate (pineapple)

frambinone or "raspberry ketone" (raspberry)

ethyl cinnamate (cherry)

Ethyl 2-methylbutanoate (red fruits)

3-Methyl-thio-propanol (boiled potatoes)

diallyl disulfide (garlic)

allylpropyl disulfide (onion)

2-Methoxy-5-methylpyrazine (pepper)

2-Heptanol, 1-Oct-3-OI (mushrooms)

valerianic acid, isobutyric acid (cheese)

2-Heptanone, 2-methylthiobutyrate (gorgonzola)

trimethylamine (fish)

methyl-2-peridylketone (popcorn)

Ethyl 3-hydroxybutanoate (meringue)

linalyl acetate (lavender)

phenylethanol (pink)

β -ionone (purple)

pyroligneous acid (smoked)

hexanal (freshly cut grass)

3-methylbutanoic acid (sweat)

ethyl butyrate (strawberry)

2-Methoxy-3-methylpyrazine (toasted hazelnut)

ethyl methylphenyl glycide (strawberry)

Table 4. Compounds contained in cocoa (ref 6)



























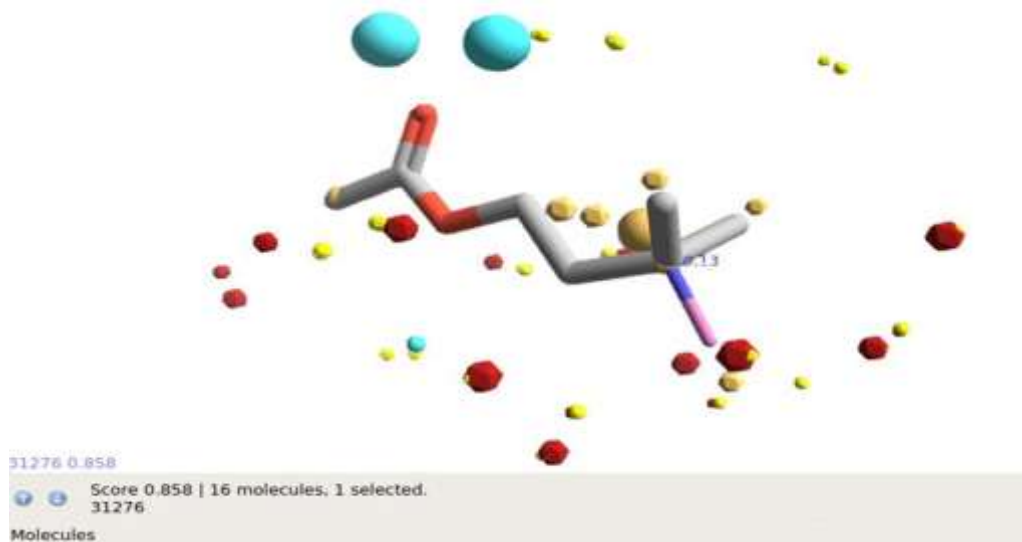
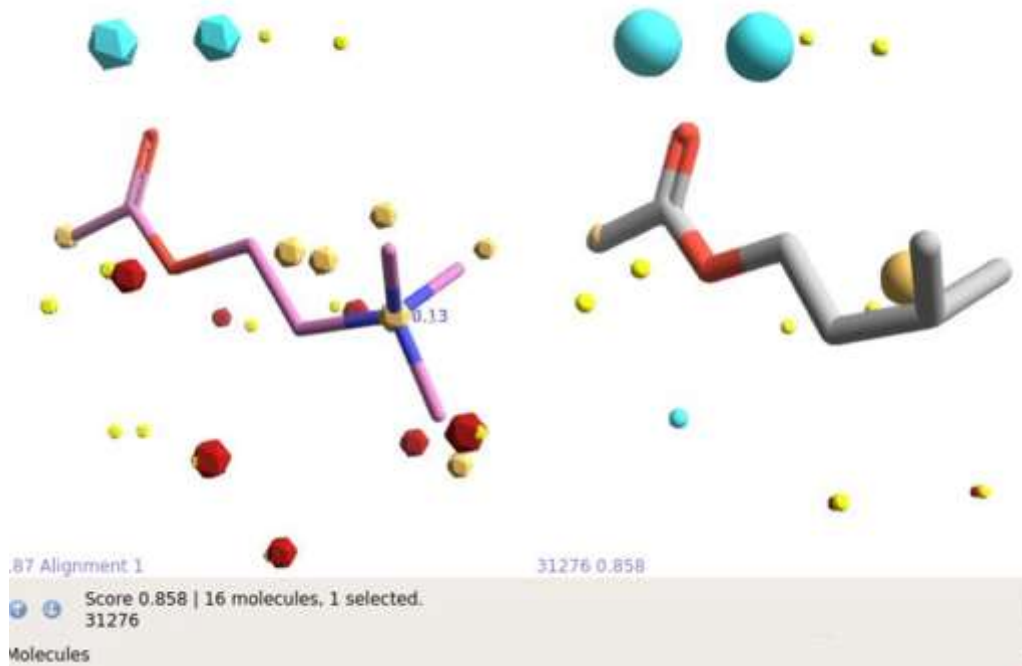
 (-)-Epicatechin	 Epicatechin gallate	 Tyramine_
 (-)-Epigallocatechin gallate	 Epigallocatechin	 Vanillic acid
 + catechin	 Gallocatechin	
 1-Phenylethylamine_	 histamine_	
 amandamideStructure2D	 luteolin	
 apigenina	 Naringenin_	
 Caffeic acid	 Oxalic acid	
 caffeina	 safrolo	
 -Catechin gallate_	 teofilina	
 chinina	 tetraidrobeta-carbolina	
 Chlorogenic acid	 Theobromine	
 clovamide	 tryptamine	

Fig 3: alignment acetylcholine (pink) isoamyl acetate (gray), separated and overlapped, the spheres represent the electrostatic fields of isoamylacetate, the prisms of acetilcholine

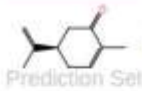



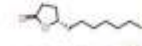


SCREENSHOT:

SCREENSHOT 1: Alignment with Acetylcholine Forge Volatile Hop Compounds



SCREENSHOT 2: Alignment with Forge between acetylcholine and food compounds

	Fav Structure	Title	Radial Plot	Sim	Tags	Confs	Alns	MW	#Atoms	2D Sim	SlogP	TPSA	Flexibility	RofS	Filename
1		8051	0.685	0.798		31	10	114.2	8	0.281	0	17	4	0	gorgonzo...
9	 Prediction Set	439570	0.646	0.767		10	10	150.2	11	0.136	0	17	1	0	menta(-)-Carvone...
4	 Prediction Set	7710	0.606	0.695		100	10	156.2	11	0.136	0	26	4	0	cocco-gamma-Nonalact...
2	 Prediction Set	76153	0.608	0.622		2	10	124.1	9	0.052	0	33	0	0	Zpeperro...
6	 Prediction Set	8294	0.574	0.609		200	10	196.3	14	0.172	0	26	5	0	Lavandylinalyl acetate.sdf
3	 Prediction Set	7363	0.500	0.625		6	10	114.2	7	0.031	0	13	2	0	cfa-Furfuryl mercaptan.sdf
13	 Prediction Set	3000322	0.500	0.595		100	10	304.4	22	0.042	0	62	5	0	isoscinoscopofa...
7	 Prediction Set	311	0.500	0.598		100	10	189.1	13	0.017	0	20	6	0	limonene...
8	 Prediction Set	24020	0.586	0.679		37	10	130.2	9	0.157	0	26	3	0	meta-Ethyl 2-methylbu...
9	 Prediction Set	439570	0.646	0.767		10	10	150.2	11	0.136	0	17	1	0	menta(-)-Carvone...
10	 Prediction Set	17898	0.608	0.549		2	10	124.1	9	0.025	0	33	0	0	nocciolatosata-2-Methoxy-3-methylpy...
11	 Prediction Set	7714	0.550	0.64		100	10	184.3	13	0.108	0	26	6	0	pescogamma-Undecalact...

Computational calculations and depictions of molecules are performed with Forge, thanks to Cresset for the academic license.

The study project is self-funded, there are no conflicts of interest

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