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Commercial Incense: Compound Analysis and Its Molecular Docking Studies as Anxiolytic Agents

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Abstract

In the context of Indonesian culture, incense has been traditionally utilized in various rituals. Incense possesses a calming impact and has the potential to reduce anxiety. This physiological response stems from the interplay of chemical components within incense and receptors associated with relaxation, specifically $GABA_A$. This research aims to explore the interaction between substances found in commercially incenses with the $GABA_A$ receptors. The compounds of incense were identified through Gas Chromatography-Mass Spectrometry (GCMS) analysis. And there were 54 compounds identified from the 5 incense samples. Next, the ligands employed for docking studies were compounds predicted to traverse the blood-brain barrier (BBB). There were 31 compounds potential of crossing the blood-brain barrier (BBB). Docking results indicated that the majority of tested compounds exhibited notably lower S-scores during receptor interaction, suggesting their potential as anxiety-relieving agents. Furthermore, molecular docking outcomes highlighted that 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester showed the lowest S-score (-6.573). These findings imply that odorant and other volatile organic compounds (VOCs) present in incenses possess the ability to function as anxiety-reducing (anxiolytic) agents, potentially assisting in anxiety treatment.

Keywords: Anxiety; aroma; fragrances; *in silico*; VOCs.

Abbreviations: BBB: blood-brain barrier; VOCs: volatil organic compounds; $GABA_A$: Gamma-aminobutyric acid A; GCMS: Gas Chromatography-Mass Spectrometry; RMSD: Root-Mean-Square Deviation.

INTRODUCTION

According to the Great Dictionary of the Indonesian Language/Kamus Besar Bahasa Indonesia [KBBI], incense is a substance such as frankincense or twigs that emits a pleasant-smelling smoke when ignited (KBBI 2023). Incense is widely utilized in religious rituals across various faiths, including Buddhism, Daoism, Confucianism (Habkirk et al. 2017), Christianity, Hinduism (Yadav et al. 2020), Roman Catholicism (Hartley et al. 2022), Judaism, Islam (Yadav et al. 2020; Faizal 2017; Karyadi 2022; Ergin 2014), as well as in the tribal and customary practices of certain nations like those in Africa (Wepener 2015; Sagrove et al. 2020), the Middle East & the Arabian Gulf region (Elsayed et al. 2016), China (Habkirk et al. 2017; Cheung 2020), Japan (Cheung 2020; Uriu et al. 2018), and India (Yadav et al. 2020). Particularly in Javanese (Indonesian) culture, incense has long been used in traditional rituals. These include engaging in traditional arts like dance, Gamelan, Kuda Lumping, Reog, and ceremony events like weddings and funerals. It can also be used in prayer and meditation practices, visits to graves and pilgrimage sites, cleaning heirlooms during *jamasan* ceremonies, and other purifying customs (Jamhari 2001; Nasir 2019; Perkasa et al. 2020; Yuningtyas et al. 2020; Putri 2022). Incense, frankincense, and other aromatic materials provide spiritual, psychological, and physical benefits. Incense is a proactive means of safeguarding noble ideals, customs, and ancestral wisdom, which are rich in philosophical meaning and profundity, and it is a calming and centering perfume. The rising billowing smoke symbolizes that the Almighty will hear the prayed-over or wished-for request (Wepener 2015). From a physiological standpoint, the anxiolytic qualities of some volatile substances combine to produce an environment

that is favorable for reflection and calm. These are conducive to the traditional practice of attaining a state of calmness.

The aromatic ingredients utilized in incense production are commonly derived from plants and may encompass a range of resins, barks, seeds, roots, flowers, and mixtures of these (Coppen 1995; Yagi and Yagi 2021; Alqethami 2017; Djordjevic 2017; González-Minero et al. 2023). When breathed, the aromatic molecules bind to specific receptors, triggering a cascade of brain processes that alleviate anxiety and encourage tranquillity (Borges e Soares, 2022). This interaction is not limited to the senses; it also affects the neurotransmitter system (Sowndhararajan and Kim 2016; Masuo et al. 2021). Numerous receptors are involved in the mechanism of this anxiolytic effect, namely serotonin receptor ((5-hydroxytryptamine 1A (5-HT_{1A}) (Heisler et al. 1998; Olivier et al. 2000) & 5-hydroxytryptamine 3 (5-HT_3) (Olivier et al. 2000)), Gamma-aminobutyric acid (GABA) receptor (Nuss 2015; Islam et al. 2022), Corticosteroid receptor (GR) (Barkus et al. 2010), N-methyl-D-aspartate (NMDA) receptor (Hauger et al. 2009), corticotropin-releasing factor (CRF) receptor, cannabinoid receptor (CB1R), neurokinin-1 (NK1) receptor, melatonin (MT_2) receptors, muscarinic (M_1) receptors (Kaur and Singh, 2017), and nicotinic acetylcholine receptors (nAChRs), dopamine (D_2/D_3) receptor, orexin receptor (OX1R, OX2R) (Chellappa and Aeschbach 2022), and adenosine (A_{2A} & A_1) receptor (van Calker et al. 2019). The primary fast-inhibitory neurotransmitter receptors in the human brain are called $GABA_A$ receptors, and these receptors are the target of numerous clinically significant medications that are frequently used to treat anxiety disorders (Vashchinkina et al. 2014).

Numerous studies have reported that support the efficacy of scents and their components in reducing symptoms or behaviors associated with anxiety (Hartley and McLachlan 2022). The mechanism underlying the anxiolytic effect is still unknown, mainly how the compounds interact with the receptor. An *in silico* method such as docking studies can be used to predict the interactions between compounds and their target receptors. Compounds contained in commercial incense will act as ligands. In this research, the incense employed consists of commercially accessible products distributed within the Yogyakarta Special Region. Therefore, this study aims to investigate how substances found in commercial incense interact with $GABA_A$ receptors. Additionally, this study is anticipated to scientifically elucidate the potential of utilizing incense and other aromatic fragrances to aid in anxiolytic therapy.

MATERIALS AND METHODS

Materials

The materials were five incenses with different brands purchased around the Special Region of Yogyakarta, ethanol pro analysis (p.a) (Merck), analytical balance (Shimadzu ATX224), ultrasonic bath (Labocon LUC-101), microcentrifuge (Thermo Scientific™ Fresco™ 21), microtube (Biologix), screw cap vials, and other glassware. The compound analysis required a set of Gas Chromatography Mass Spectrometry (GCMS) (Thermo Scientific TRACETM 1310 Gas Chromatography (GC) & Thermo Scientific ISQTM LT Single Quadropole Mass Spectrometer (MS)), HP-5MS UI 30M, 0.25Mm 0, 25um column (Agilent Technologies Inc, US). For *in silico* studies, the docking simulation was performed in Molecular Operating Environment (MOE) software (Montreal, Canada) (licensed by the Faculty of Pharmacy, Universitas Gadjah Mada) which is installed at a computer with specifications as follows Windows 10, Intel Core i7 CPU 11800H, and RAM 16 GB.

Extraction of Compounds from Commercial Incense

Compounds extracted from commercial incense were recovered by modifying and combining well-established research methods (Bagherian et al. 2011; West et al. 2014; Nadilah et al. 2019; Rahmanto et al. 2018). Using a mortar and stamper, incense was ground into powder. 96% ethanol (p.a.) was then used for the extraction, and the sample-to-solvent ratio was 1:100 (w/v). The extract was obtained by employing intermittent ultrasonication, involving cycles of emission for 5 minutes followed by a pause for 5 minutes, and this process was repeated until reaching a total duration of 30 minutes. After the ultrasonication procedure, maceration was carried out for 24 hours at room temperature. The extract was centrifuged at 10,000 rpm for 5 minutes to obtain clearer and entirely particle residue-free results. The supernatant was then collected in 5 mL screw-on vials. After that, the ethanolic extract was kept refrigerated (± 4 °C) for the following procedure.

Identification of Compounds in Commercial Incense using GCMS

GSMS analyzed the chemical constituents of incense. Ethanolic incense extract was injected into GCMS. The GC utilized a column of HP-5MS UI (Ultra Inert) 30 m, 0.25 mm, 0.25 µm (Agilent Technologies Inc, US). The chromatography system was programmed at 60 °C for 2 min, then ramped at 105 °C/min to 280 °C, and held for 8 min, with a retention time (Rt) total of 32 min. The mobile phase used was Helium UHP (He), and the flow rate was 1,0 mL/min. The injector and transfer line temperatures were 230 °C, with a split ratio of 50:1.

Blood-Brain Barrier Permeability Prediction

The compounds identified in the samples underwent evaluation for permeability across the blood-brain barrier (BBB) using the SwissADME server (http://www.swissadme.ch/) (Daina et al. 2017 and Rashid et al. 2022).

Molecular Docking

Ligand Preparation

The ligands used for docking studies were compounds identified in the samples and could penetrate the BBB. The 3D Ligand structures were generated using the builder feature in the MOE software by entering the SMILES code of the compounds obtained from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Kim et al. 2023). The energy minimization was applied to the compounds using the MOPAC system, employing PM3 as the potential energy function to assign charge to the compound. Subsequently, the optimized structures werearchived in a database in *.mdb format.

Homology Modelling

The $GABA_A$ receptor alpha-2 subunit ($GABA_A$ α2) is known to play a role in anxiolytic activity. Identification of template proteins from $GABA_A$ subunit alpha-2 in Homo sapiens (human) organisms was carried out using the SWISS-MODEL server (Waterhouse et al. 2018). The receptor sequence was obtained from the UniProt database (https://www.uniprot.org/) (The UniProt Consortium 2023) with protein code P47869. The model chosen was a model that has the highest seq value, which was Model 1 (99.78%) with the Q5RCC5 template.

The $GABA_A$ α2 has been known to play a role in anxiolytic activity. Since its 3D structure is not available yet in database thus the human $GABA_A$ α2 (*Homo sapiens*) need to be modelled. Identification of template proteins for homology modelling the $GABA_A$ subunit alpha-2 was carried out using the SWISS-MODEL server (Waterhouse et al. 2018). The receptor sequence was obtained from the UniProt database (https://www.uniprot.org/) (The UniProt Consortium 2023) with protein code P47869. The chosen model was Model 1 which has the highest sequence value (99.78%) with the Q5RCC5 template.

Protein preparations

The model protein sequence was aligned with the reference protein (PDB:8BHK), which includes the native ligand (Diazepam), using MOE's protein align/superpose function. The native ligand from the reference protein was incorporated into the model protein. Subsequently, active sites were identified using MOE's site finder tool. The $GABA_A$ subunit alpha-2 protein complex derived from SWISS-MODEL was prepared using MOE's Quickprep program for structure preparation, including atomic modifications and protonation. The forcefield parameter AMBER was then used to minimize energy and assign a charge to the protein. Finally, the prepared protein was stored in PDB format (.pdb).

The sequence of $GABA_A$ subunit alpha-2 protein model was aligned with the reference protein (PDB:8BHK), which includes Diazepam as the native ligand using MOE's protein align/superpose function. The native ligand from the reference protein was incorporated into the model protein. The homology model derived from SWISS-MODEL was prepared using MOE's Quickprep program for structure preparation, including atomic modifications and protonation. The forcefield parameter AMBER was then used to minimize energy and assign the charge to the protein. Finally, the prepared protein was stored in PDB format (.pdb).

Pose Validation

Pose validation can be done by redocking the native ligand (Diazepam) bound in the protein. Docking tool was employed with the atomic ligand designated as the active site, and set triangle matcher, induced fit, and London Dg as the parameters for placement, refinement, and scoring, respectively. RMSD (Root-Mean-Square of Deviation) is a parameter used to determines the validity of the redocking method. This parameter will evaluate the redocking process's reliability. A RMSD value of $\leq$ 2.0 Å indicates good or valid docking protocol (Su et al. 2018).

Molecular Docking

The docking method that has been validated was used to dock the test compounds in incense. The analysis of docking results involves the best pose and the best score evaluation and the interaction of those compounds amino acid residues within the protein's active site.

RESULTS AND DISCUSSION

This research has four primary data, i.e., 1) List of compound results from GCMS analysis, 2) Prediction of BBB Permeant, 3) Docking score, and 4) Visualization of ligand interactions with receptors.

Identification of Compounds in Commercial Incense using GCMS

The ethanolic extract of incense can be seen in Figure 1. The results of identification from the five incense samples are displayed in Table 1. In total, 54 compounds were identified across the five samples. Notably, incense sample B exhibited the highest number of compounds, precisely 31 compounds. Visually, incense B displayed the deepest black hue (Figure 1) and had the most pungent aroma compared to the other samples.

Conversely, incense A boasted the lowest number of compound, totalling 19, among the five samples. Incense A, derived from authentic agarwood without any synthetic additives, exudes a comparatively milder aroma than incenses B, C, D, and E. Physically, the extract of incense A showcases a brownish hue (Figure 1) and has a subtle woody scent. On the other hand, Incenses C, D, and E present a golden yellow appearance in their extracts (Figure 1), with a mild floral aroma, including a mixture of flower fragrances, jasmine, and lotus, respectively.

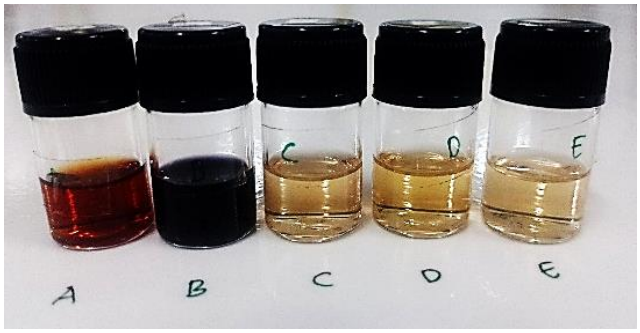

Figure 1. Ethanolic extract of incense.

The constituents within incense consist of fragrance compounds, volatile organic compounds (VOCs), and additional ingredients utilized in incense manufacturing, such as solvents. For instance, fragrance compounds encompass dihydromyrcenol; linalol; a-terpineol; dodecanoic acid; 3-hydroxy-, (R)-lavandulyl acetate; linalyl acetate; 4-tert-butylcyclohexyl acetate; geranyl vinyl ether; 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate ; 2,5,5,8a-tetramethyl-3,5,6,7,8,8a-hexahydro-2H-naphthalen-1-one; lilial, among others. The confirmation of fragrance compounds can be verified through databases such as the Good Scents Company's database (http://www.thegoodscentscompany.com/misc/about.html), which serves as an information resource for the flavor, food, and fragrance industry, and Aroma DB (https://aroma.irap.omp.eu/) (Sabbah et al. 2017). Diethyl Phthalate is also detected in incense containing synthetic fragrances (samples B, C, D, E), typically serving as solvents or diluents for fragrance agents (Api 2001).

Prediction of BBB Permeant

The outcomes of predictive analyses conducted through the SwissADME server are presented in Table 1. These predictions are formulated utilizing the BOILED-Egg methodology, which entails a visual assessment of human intestinal absorption relative to the molecular characteristics of small compounds plotted on the WLOGP versus TPSA graphs. The white segment within the BOILED-Egg model signifies a heightened likelihood of passive absorption within the gastrointestinal tract, while the yellow region (yolk) indicates a propensity for brain permeation (note that the yolk and white areas are not mutually exclusive) (Pavlović et al. 2023). Subsequently, compounds demonstrating positive BBB permeability are identified as ligands and subjected to docking studies with the $GABA_A$ receptor.

Molecular Docking and Ligand-Receptors Interaction

The homology modeling results reveal that Model 1 corresponds to a template protein derived from the Q5RCC5 protein with a sequence value of 99.78%. Pose validation yielded an RMSD value of 0.4423, indicating the docking methodology's suitability (including placement, refinement, and scoring parameters). Subsequently, a superimposed was made between the native ligand crystal and the re-docking results on the receptor (Figure 2). The docking score (S) of Diazepam was calculated as -4.3911. The docking procedure involving the test ligands and $GABA_A$ was conducted using the designated method, with 31 compounds employed as the test ligands (see Table 1). Visualization of the interaction between the best-scoring ligand and the receptor is depicted in Figure 3.

Figure 2. The alignment of the native ligand crystal (purple) with the re-docking native ligand (blue).

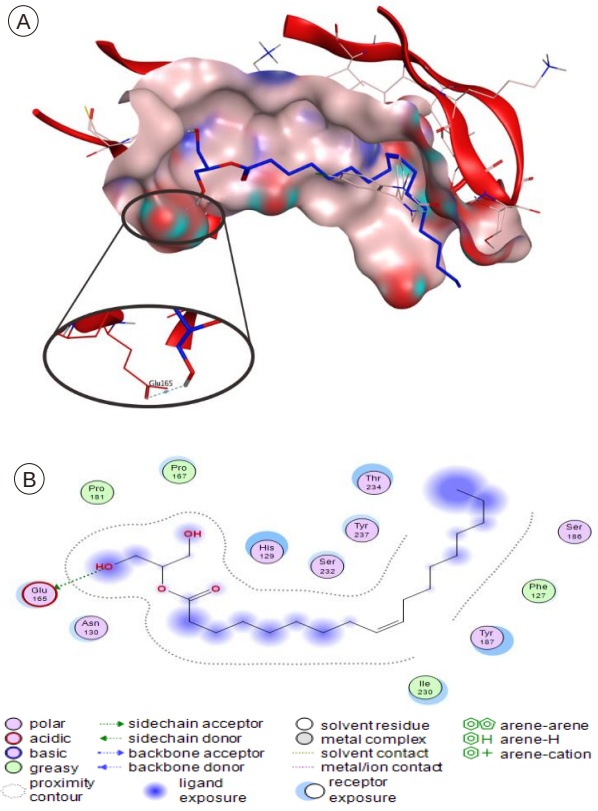

Figure 3. Visualization of 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester with receptor (**A**). Interactions within the active site (3D visualization) (**B**). 2D interaction with amino acid residues on the receptor.

Discussion

Based on the predictions from ADMET, it was identified that 31 compounds could potentially penetrate the BBB,

and these were utilized as ligands for docking studies. The S-score serves as a crucial metric for assessing docking outcomes in MOE docking, indicating the affinity between receptor and ligand across various conformations (Attique et al. 2019). A lower S-score was favored, as it suggested stronger receptor interactions (Konyar et al. 2022). Evaluation of docking outcomes revealed that nearly all tested compounds exhibited lower S-scores compared to the native ligand, except for Patchouli alcohol. It can be seen in table 1, the VOCs compound 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester showed the lowest S-score, indicating strongest affinity for the $GABA_A$ receptor. Compounds with lower S-scores than the native ligand were presumed to possess better anxiolytic activity. Generally, VOCs are associated with either pleasant or off odors (Dudley et al. 2010). While specific aroma data for 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester is unavailable, its ability to evaporate and accumulate in the air. Other ligands with distinctive aromas had lower S-scores compared to native ligands (Diazepam) include Dihydromyrcenol (citrusy, floral, sweet), Linalool (floral, spicy wood), α-Terpineol (sweet lilac floral, pine-woody), (R)-lavandulyl acetate (floral, lavender-like), Linalyl acetate (floral, sweet, citric), 4-tert-Butylcyclohexyl acetate (fruity with woody undertones), Geranyl vinyl ether (floral), 4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate (floral green herbal), etc (Table 1). The interaction of 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester with $GABA_A$ (Figure 3b) encompasses numerous interactions, predominantly with polar amino acid residues, specifically Asn130, His129, Ser232, Tyr237, Thr234, Ser186, Tyr187, and Glu165. One hydrogen bonding was observed between hydroxyl group with Glu165. Additionally, there are hydrophobic interactions occurring with amino acid residues Pro181, Pro167, Phe127, and Ile230.

These findings suggest that aromatherapy, incense, or other fragrances containing these compound types could aid in anxiety therapy. When incense is burned, these compounds transform into their oxidized forms. While this study didn't conduct GCMS analysis of the incense smoke due to limited resources, however research conducted supports the idea that aromas and other VOCs can act as anxiolytic agents.

CONCLUSIONS

The molecular docking outcomes indicated that the compound 9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester exhibited the lowest S-score (-6.573) when interacting with the $GABA_A$ receptor, suggesting its promise as an anxiety-relieving agent. Furthermore, nearly all aroma compounds exhibit a lower S-score compared to Diazepam. These findings suggest that the aroma compounds present in incense possess the capability to function as anxiolytic agents and could serve as adjuncts in anxiety treatment. These results still have the potential to be proven through *in vivo* research approaches.

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Competing Interests: The authors declare that there are no competing interests.

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Table 1. List of compounds in incense, BBB permeant prediction, and docking score.

No	Compounds	Chemical Formula	Molecular Weight	Similarity Index (SI)	BBB permeant	Pubchem ID	SMILES	Aroma	Score (S-score)	Samples				
										A	B	C	D	E
1	2,6-dimethyloct-7-en-2-ol (Dihydromyrcenol)	$C_{10}H_{20}O$	156	891	Yes	29096	CC(CCCC(C)(C)O)C=C	fresh citrus, floral, bergamot, lime	-4.809	-	-	✓	-	✓
2	3,7-dimethylocta-1,6-dien-3-ol (Linalool)	$C_{10}H_{18}O$	154	913	Yes	6549	CC(=CCCC(C)(C=C)O)C	floral, spicy wood, somewhat resembling French lavender plants, bergamot oil or lily of the valley	-4.825	-	✓	-	✓	✓
3	Methyl N-(N-benzyloxycarbonyl-beta-l-aspartyl)-beta-d-glucosaminide	$C_{19}H_{26}N_2O_{10}$	442	703	No	562266	COC1C(C(C(C(O1)CO)O)O)NC(=O)CC(C(=O)O)NC(=O)OCC2=CC=CC=C2	Unknown	-	-	-	-	✓	-
4	2-(4-methylcyclohex-3-en-1-yl)propan-2-ol (α-Terpineol)	$C_{10}H_{18}O$	154	775	Yes	17100	CC1=CCC(CC1)C(C)(C)O	slightly harsh sweet lilac, floral, pine-woody clean delicate fresh, pine, lavender pineneedle	-4.820	-	✓	-	-	-
5	Dodecanoic acid, 3-hydroxy-	$C_{12}H_{24}O_3$	216	720	Yes	94216	CCCCCCCCCC(CC(=O)O)O	Unknown	-5.394	-	-	✓	-	-
6	Cholestan-3-ol, 2-methylene-, (3ß,5a)-	$C_{28}H_{48}O$	400	719	No	22213932	C[C@H](CCCC(C)C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC[C@@H]4[C@@]3(CC(=C)[C@@H](C4)O)C)C	Unknown	-	-	✓	-	-	-
7	(5-methyl-2-prop-1-en-2-ylhex-4-enyl) acetate *or* (R)-lavandulyl acetate	$C_{12}H_{20}O_2$	196	802	Yes	30247	CC(=CCC(COC(=O)C)C(=C)C)C	floral, lavender-like odor	-5.337	-	✓	-	-	-
8	3,7-dimethylocta-1,6-dien-3-yl acetate *or* Linalyl acetate	$C_{12}H_{20}O_2$	196	809	Yes	8294	CC(=CCCC(C)(C=C)OC(=O)C)C	floral, sweet and citric, and additionally as minty and slightly caraway-like	-5.316	-	-	-	✓	✓
9	4-tert-Butylcyclohexyl acetate	$C_{12}H_{22}O_2$	198	848	Yes	36081	CC(=O)OC1CCC(CC1)C(C)(C)C	Fruity scent, balanced with woody undertones	-4.767	-	-	✓	-	-
10	4-(2,2-Dimethyl-6-methylenecyclohexyl)butanal	$C_{13}H_{22}O$	194	728	Yes	549482	CC1(CCCC(=C)C1CCCC=O)C	Unknown	-4.888	-	✓	-	-	-

No	Compounds	Chemical Formula	Molecular Weight	Similarity Index (SI)	BBB permeant	Pubchem ID	SMILES	Aroma	Score (S-score)	Samples				
11	Z,Z-2,5-Pentadecadien-1-ol	$C_{15}H_{28}O$	224	721	No Data	5364952	CCCCCCCCC/C=C\C/C=C\CO	Unknown	-	-	-	-	-	✓
12	(2E)-1-ethenoxy-3,7-dimethylocta-2,6-diene *or* Geranyl vinyl ether	$C_{12}H_{20}O$	180	739	Yes	5365842	CC(=CCC/C(=C/COC=C)/C)C	Fruity or floral	-5.140	-	✓	-	-	-
13	4,7-methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate	$C_{12}H_{16}O_2$	192	851	Yes	98478	CC(=O)OC1CC2CC1C3C2CC=C3	Floral green herbal	-5.000	-	-	-	-	✓
14	1-(4-tert-Butylphenyl)propan-2-one	$C_{13}H_{18}O$	190	724	Yes	6423283	CC(=O)CC1=CC=C(C=C1)C(C)(C)C	Unknown	-4.568	-	-	-	✓	-
15	2,5,5,8a-Tetramethyl-3,5,6,7,8,8a-hexahydro-2H-naphthalen-1-one	$C_{14}H_{22}O$	206	719	Yes	585286	CC1CC=C2C(CCCC2(C1=O)C)(C)C	Powdery-ionone type odours	-4.850	-	✓	-	-	-
16	3-(4-tert-butylphenyl)-2-methylpropanal *or* Lilial	$C_{14}H_{20}O$	204	724	Yes	228987	CC(CC1=CC=C(C=C1)C(C)(C)C)C=O	Floral neroli muguet	-4.745	-	-	✓	✓	-
17	Naphthalene, 2-ethoxy-	$C_{12}H_{12}O$	172	722	Yes	7129	CCOC1=CC2=CC=CC=C2C=C1	Powdery, floral, naphthyl and citrus	-4.481	-	-	-	✓	-
18	Diethyl Phthalate	$C_{12}H_{14}O_4$	222	957	Yes	6781	CCOC(=O)C1=CC=CC=C1C(=O)OCC	Solvents/deluents	-4.962	-	✓	✓	✓	✓
19	9-Octadecenoic acid, (2-phenyl-1,3-dioxolan-4-yl)methyl ester, trans-	$C_{28}H_{44}O_4$	444	750	No	5366356	CCCCCCCC/C=C/CCCCCCCC(=O)OCC1COC(O1)C2=CC=CC=C2	Unknown	-	✓	✓	✓	-	-
20	Methyl 5,7-hexadecadiynoate	$C_{17}H_{26}O_2$	262	743	Yes	14957560	CCCCCCCCC#CC#CCCCC(=O)OC	Unknown	-6.211	-	-	-	-	✓
21	2,5-Octadecadiynoic acid, methyl ester	$C_{19}H_{30}O_2$	290	761	Yes	42151	CCCCCCCCCCCCC#CCC#CC(=O)OC	Unknown	-6.079	-	✓	-	-	-
22	Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester	$C_{13}H_{22}O_3$	226	777	Yes	102861	CCCCCC1C(CCC1=O)CC(=O)OC	Floral and jasmine-like odor	-5.645	-	-	-	✓	✓
23	(1R,3R,6S,7S,8S)-2,2,6,8-tetramethyltricyclo[5.3.1.03,8]undecan-3-ol *or* Patchouli alcohol	$C_{15}H_{26}O$	222	768	Yes	10955174	C[C@H]1CC[C@@]2([C@@]3([C@H]1C[C@H](C2(C)C)CC3)C)O	Woody, patchouli, earthy	-4.121	-	✓	-	-	-
24	(7a-Isopropenyl-4,5-dimethyloctahydroinden-4-yl)methanol	$C_{15}H_{26}O$	222	776	Yes	605599	CC1CCC2(CCCC2C1(C)CO)C(=C)C	Unknown	-4.614	-	-	-	-	✓
25	4-(3,3-Dimethyl-but-1-ynyl)-4-hydroxy-2,6,6-	$C_{15}H_{22}O_2$	234	741	Yes	535329	CC1=CC(CC(C1=O)(C)C)(C#CC(C)(C)C)O	Unknown	-5.027	-	-	-	-	✓

No	Compounds	Chemical Formula	Molecular Weight	Similarity Index (SI)	BBB permeant	Pubchem ID	SMILES	Aroma	Score (S-score)	Samples				
	trimethylcyclohex-2-enone						CC1=CC(O)(CC(C)(C)C1=O)C#CC(C)(C)C							
26	Benzene, 1,1'-(2-butene-1,4-diyl)bis-	$C_{16}H_{16}$	208	716	Yes	5370638	C1=CC=C(C=C1)C/C=C/CC2=CC=CC=C2	Unknown	-4.917	✓	✓	✓	✓	✓
27	12,15-Octadecadiynoic acid, methyl ester	$C_{19}H_{30}O_2$	290	745	Yes	538453	CCC#CCC#CCCCCCCCCCCC(=O)OC	Unknown	-6.229	✓	✓	-	-	✓
28	N,N'-Bis(Carbobenzyloxy)-lysine methyl(ester)	$C_{23}H_{28}N_2O_6$	428	749	No	75487878	COC(=O)[C@H](CCCCNC(=O)OCC1=CC=CC=C1)NC(=O)OCC2=CC=CC=C2	Unknown	-	-	-	✓	✓	✓
29	Acetamide, N-methyl-N-[4-[2-acetoxymethyl-1-pyrrolidyl]-2-butynyl]-	$C_{14}H_{22}N_2O_3$	266	742	No	580233	CC(=O)N(C)CC#CCN1CCCC1COC(=O)C	Unknown	-	✓	✓	-	-	-
30	Octanal, 2-(phenylmethylene)-	$C_{15}H_{20}O$	216	847	Yes	1715135	CCCCCC/C(=C/C1=CC=CC=C1)/C=O	Jasmine-like odor	-5.073	-	-	✓	✓	✓
31	Cyclodeca[b]furan-2,9(3H,4H)-dione, 4-(acetyloxy)-3a,7,8,10,11,11a-hexahydro-6-methyl-3,10-bis(methylene)-, [3ar-(3ar*,4R*,5E,11as*)]-	$C_{17}H_{20}O_5$	304	709	Yes	5363090	C/C/1=C\C(C2C(CC(=C)C(=O)CC1)OC(=O)C2=C)OC(=O)C	Unknown	-5.165	-	-	-	-	✓
32	Ethanone, 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-	$C_{17}H_{26}O$	246	849	Yes	16220111	C[C@@H]1CC[C@@H]2[C@@]13C[C@H](C2(C)C)C(=C(C3)C(=O)C)C	Warm woody amber musk	-4.938	-	-	-	-	✓
33	"Ethanol, 2-(9-octadecenyloxy)-, (Z)- *or* Emulphor	$C_{20}H_{40}O_2$	312	801	No	5364713	CCCCCCCC/C=C\CCCCCCCCOCCO	As emulsifiers, surfactants	-	✓	✓	✓	✓	-
34	10-Heptadecen-8-ynoic acid, methyl ester, (E)-	$C_{18}H_{30}O_2$	278	723	Yes	5367407	CCCCCC/C=C/C#CCCCCCCC(=O)OC	Unknown	-6.242	-	✓	-	-	-
35	Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-(Galaxolide)	$C_{18}H_{26}O$	258	754	Yes	91497	CC1COCC2=CC3=C(C=C12)C(C(C3(C)C)C)(C)C	Clean sweet musky floral woody odor	-4.932	-	-	-	✓	✓
36	Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- *or*	$C_{12}H_{15}N_3O_6$	297	781	No	62329	CC1=C(C(=C(C(=C1[N+](=O)[O-])C(C)(C)C)[N+](=O)[O-])C)[N+](=O)[O-]	Musk, animalistic, earthy and woody	-	-	✓	-	-	-

No	Compounds	Chemical Formula	Molecular Weight	Similarity Index (SI)	BBB permeant	Pubchem ID	SMILES	Aroma	Score (S-score)	Samples				
	Musk xylene													
37	"[1,1'-Bicyclopropyl]-2-octanoic acid, 2'-hexyl-, methyl ester Methyl 8-[2-(2-hexylcyclopropyl) cyclopropyl]octanoate"	$C_{21}H_{38}O_2$	322	785	No	552098	CCCCCCC1CC1C2CC2CCCCCCCC(=O)OC	Unknown	-	✓	✓	✓	✓	✓
38	Phenethylamine, 3-benzyloxy-2-fluoro-ß-hydroxy-	$C_{15}H_{16}FNO_2$	261	756	No	-	CCCCCCC1CC1C2CC2CCCCCCCC(=O)OC	Unknown	-	-	✓	✓	-	-
39	Hexadecane, 1,1-bis(dodecyloxy)-	$C_{40}H_{82}O_2$	594	721	No	41920	CCCCCCCCCCCCCCCC(OCCCCCCCCCCC)OCCCCCCCCCCCC	Unknown	-	✓	✓	✓	-	✓
40	2-Myristynoyl pantetheine	$C_{25}H_{44}N_2O_5S$	484	756	No	535560	CCCCCCCCCCCC#CC(=O)SCCNC(=O)CCNC(=O)C(C(C)(C)CO)O	Unknown	-	-	-	-	✓	-
41	Cyclopropanebutanoic acid, 2-[[2-[[2-[(2-pentylcyclopropyl)methyl]cyclopropyl]methyl]cyclopropyl]methyl]-, methyl ester	$C_{25}H_{42}O_2$	374	793	No	554084	CCCCCC1CC1CC2CC2CC3CC3CC4CC4CCCC(=O)OC	Unknown	-	✓	✓	✓	-	-
42	Musk ketone	$C_{14}H_{18}N_2O_5$	294	795	No	6669	CC1=C(C(=C(C(=C1[N+](=O)[O-])C(C)(C)C)[N+](=O)[O-])C)C(=O)C	Floral, sweet, powdery	-	-	✓	-	-	-
43	Z-(13,14-Epoxy)tetradec-11-en-1-ol acetate	$C_{16}H_{28}O_3$	268	806	Yes	5363633	CC(=O)OCCCCCCCCCC/C=C\C1CO1	Unknown	-5.804	✓	✓	✓	✓	✓
44	9-Hexadecenoic acid	$C_{16}H_{30}O_2$	254	827	Yes	5282745	CCCCCC/C=C/CCCCCCCC(=O)O	Unknown	-5.669	✓	✓	✓	✓	✓
45	11-Octadecenoic acid, methyl ester *or* Methyl vaccenate	$C_{19}H_{36}O_2$	296	854	No	5364432	CCCCCC/C=C/CCCCCCCCCC(=O)OC	Unknown	-	✓	✓	✓	✓	✓
46	10-Octadecenoic acid, methyl ester *or* methyl (E)-octadec-10-enoate	$C_{19}H_{36}O_2$	296	816	No	5364425	CCCCCCC/C=C/CCCCCCCCC(=O)OC	Unknown	-	-	-	-	✓	✓
47	trans-13-Octadecenoic acid	$C_{18}H_{34}O_2$	282	846	No	6161490	CCCC/C=C/CCCCCCCCCCCC(=O)O	Unknown	-	✓	✓	✓	-	-
48	1-Heptatriacotanol	$C_{37}H_{76}O$	536	820	No	537071	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCO	Unknown	-	✓	✓	✓	✓	✓

No	Compounds	Chemical Formula	Molecular Weight	Similarity Index (SI)	BBB permeant	Pubchem ID	SMILES	Aroma	Score (S-score)	Samples				
49	Ethyl iso-allocholate	$C_{26}H_{44}O_5$	436	827	No	6452096	CCOC(=O)CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1([C@H](C[C@H]3[C@H]2[C@@H](C[C@H]4[C@@]3(CC[C@H](C4)O)C)O)O)C	Unknown	-	✓	✓	✓	✓	✓
50	9-Octadecenoic acid, 1,2,3-propanetriyl ester, (E,E,E)- *or* Trielaidin	$C_{57}H_{104}O_6$	884	788	No	537-39-3	CCCCCCCC/C=C/CCCCCCCC(=O)OCC(OC(=O)CCCCCCC/C=C/CCCCCCCC)COC(=O)CCCCCCC/C=C/CCCCCCCC	Unknown	-	✓	-	-	-	-
51	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	$C_{21}H_{40}O_4$	356	781	Yes	5319879	CCCCCCCC/C=C\CCCCCCCC(=O)OC(CO)CO	Unknown	-6.573	✓	✓	-	✓	-
52	Tricyclo[20.8.0.0(7,16)]triacontane, 1(22),7(16)-diepoxy-	$C_{30}H_{52}O_2$	444	766	No	543764	C1CCCCC23CCCCCC45CCCCCCCCC4(O5)CCCCCC2(O3)CCC1	Unknown	-	✓	✓	-	-	-
53	Z-5-Methyl-6-heneicosen-11-one	$C_{22}H_{42}O$	322	761	No	5363254	CCCCCCCCCCC(=O)CCC/C=C\C(C)CCCC	Unknown	-	✓	✓	-	-	-
54	2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde	$C_{23}H_{32}O$	324	795	No	5363101	CC1=C(C(CCC1)(C)C)/C=C/C(=C/C=C/C2=C(CCCC2)C=O)/C	Unknown	-	✓	-	-	-	✓