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THÉME:

Interactions synergétiques des substances naturelles de deux plantes médicinales de la flore algérienne sur quelques activités biologiques

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Résumé

Cette étude a pour objectif d'évaluer l'effet synergique entre les extraits de *Thymus vulgaris* (thym) et de *Curcuma longa* (curcuma), deux plantes médicinales largement reconnues pour leurs propriétés antioxydantes. L'activité antioxydante de leur combinaison a été mesurée à l'aide du test DPPH (2,2-diphényl-1-picrylhydrazyle), tandis que les profils pharmacocinétiques et toxicologiques des principaux composés actifs ont été prédits par modélisation ***in silico***, en s'appuyant sur les paramètres ADMET (Absorption, Distribution, Métabolisme, Excrétion et Toxicité).

Le test DPPH a révélé une activité antioxydante notable du mélange (IC_{50} = 20,22 ± 0,36 µg/mL), comparable à celle du BHT.

Les résultats ont mis en évidence une synergie notable entre les deux extraits : leur association a montré une capacité de piégeage des radicaux libres significativement plus élevée que celle observée pour chaque extrait utilisé séparément. Cette synergie a été quantifiée par un indice de combinaison (CI = 0,39) inférieur à 1, indiquant un effet potentialisateur.

L'analyse ADMET a révélé que des composés majeurs tels que le thymol (issu du thym) et l'ar-turmerone (issu du curcuma) présentent une bonne biodisponibilité orale, une faible hépatotoxicité prédite, ainsi qu'un profil d'élimination équilibré.

Ces résultats suggèrent que l'association des extraits de thym et de curcuma pourrait constituer une alternative naturelle prometteuse aux antioxydants synthétiques, avec de potentielles applications en phytothérapie et en nutraceutique.

Mots clés : Synergie, Thymus vulgaris, Curcuma longa, Plantes médicinales , ADMET, Activité antioxydante .

Summary

This study aims to evaluate the synergistic effect between extracts of *Thymus vulgaris* (thyme) and *Curcuma longa* (turmeric), two medicinal plants widely recognized for their antioxidant properties. The antioxidant activity of their combination was measured using the DPPH assay (2,2-diphenyl-1-picrylhydrazyl), while the pharmacokinetic and toxicological profiles of the main active compounds were predicted through *in silico* modeling, based on ADMET parameters (Absorption, Distribution, Metabolism, Excretion, and Toxicity).

The DPPH test revealed antioxidant activity notable of the mixture (IC_{50} = 20.22 ± 0.36 µg/mL), comparable to that of BHT

The results revealed a significant synergy between the two extracts: their combination exhibited a substantially higher free radical scavenging capacity compared to the activity observed when each extract was used individually. This synergy was quantified using a Combination Index (CI = 0,39) of less than 1, indicating a potentiating effect.

The ADMET analysis showed that major compounds such as thymol (from thyme) and ar-turmerone (from turmeric) have good oral bioavailability, low predicted hepatotoxicity, and a balanced elimination profile.

These findings suggest that the combination of thyme and turmeric extracts could represent a promising natural alternative to synthetic antioxidants, with potential applications in phytotherapy and nutraceuticals.

Keywords: Synergy, Thymus vulgaris, Curcuma longa, Medicinal plants, ADMET, Antioxidant activity.

ملخص

تهدف هذه الدراسة إلى تقييم التأثير التآزري بين مستخلصات Thymus vulgaris (الزعتر) وCurcuma longa (الكركم)، وهما نباتان طبيان معترف بهما على نطاق واسع لخصائصهما المضادة للأكسدة. تم قياس النشاط المضاد للأكسدة لمزيجهما باستخدام اختبار DPPH (2,2-diphenyl-1-picrylhydrazyl)، بينما تم التنبؤ بالملفات الدوائية السمية للمواد الفعالة الرئيسية من خلال النمذجة الحاسوبية، بالاعتماد على معايير ADMET (الامتصاص، التوزيع، الأيض، الإخراج والسمية).

كشف إختبارDPPH عن نشاط مضاد للأكسدة ملحوظ للمزيج (IC_{50} = 20,22 ± 0,36 µg/mL) قابل للمقارنة مع BHT .

أظهرت النتائج تآزرًا ملحوظًا بين المستخلصين: فقد أظهرت جمعيتهما قدرة على التقاط الجذور الحرة أعلى بكثير من تلك التي لوحظت لكل مستخلص مستخدم بشكل منفصل. تم قياس هذا التآزر بواسطة مؤشر الجمع (CI = 0,39)أقل من 1، مما يشير إلى تأثير معزز.

كشفت تحليل ADMET أن المركبات الرئيسية مثل Thymol (المستخرج من الزعتر) وar-turmerone (المستخرج من الكركم) تتمتع بتوافر حيوي فموي جيد، وتوقع سمية كبدية منخفضة، بالإضافة إلى ملف تخلص متوازن.

تشير هذه النتائج إلى أن الجمع بين مستخلصات الزعتر والكركم قد يشكل بديلاً طبيعياً واعداً لمضادات الأكسدة الاصطناعية، مع تطبيقات محتملة في العلاج بالنباتات والعلاج الغذائي.

الكلمات المفتاحية: التآزر، Thymus vulgaris، Curcuma longa، النباتات الطبية، ADMET، النشاط المضاد للأكسدة.

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إكرام

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µg: Microgramme(unité de masse).

ADMET: A = Absorption ,D = Distribution,M = Métabolisme,E = Excrétion ,T =Toxicité

ADN : Acide désoxyribonucléique.

BBB : Barrière hémato-encéphalique .

BHA: Hydroxyanisole butylé.

BHT: Hydroxytoluène butylé.

C° : Degré Celsius.

Caco-2: Lignée Cellules cancéreuses du côlon humain

CI : Combination Index.

CL: clairance

Cm: Centimètre (unité de longueur).

CYP: Cytochrome P450

DILI: Lésions hépatiques induites par les médicaments

Dm: Dose moyenne efficace .

DPPH: 2,2-diphényl-1-picrylhydrazyle

Ep50: Dose efficace pour 50 % de la population.

g: Gramme (unité de masse).

GPx : Glutathion peroxydase.

hERG :Gène humain lié à Ether-à-go-go

H-HT: Test sur hépatocytes humains

IA: L'intelligence artificielle

IC_{50}: Concentration inhibitrice à 50%.

Kg: Kilogramme (unité de masse).

L: Litre (unité de volume).

log Papp: Logarithme du coefficient de perméabilité apparente (Perméabilité apparente).

MDCK: Cellules rénales de chien Madin-Darby

mg: Milligramme (unité de masse).

min: Minute (unité de temps).

ml: Millilitre (unité de volume).

mM: millimolaire.

nm: Nanomètre.

PBPK: Modélisation pharmacocinétique basée sur la physiologie

P-gp: P-glycoprotéine

PPB: Liaison aux protéines plasmatiques

S: Seconde (unité de temps).

SOD : Superoxyde dismutase.

T½: Demi-vie

UV : Ultraviolet.

VD: Volume de distribution

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Introduction

Introduction

La recherche scientifique contemporaine s'oriente de manière croissante vers l'exploration des substances naturelles et de leurs interactions synergiques, dans le but de développer des alternatives thérapeutiques à la fois sûres, efficaces et durables. Parmi ces approches innovantes, la synergie phytothérapeutique se distingue par sa capacité à potentialiser les effets pharmacologiques de composés bioactifs, grâce à une action complémentaire. Ce phénomène, défini comme une interaction entre deux ou plusieurs composés produisant un effet thérapeutique supérieur à la somme des effets individuels, constitue aujourd'hui une stratégie précieuse dans la prise en charge du stress oxydatif, des maladies inflammatoires et des troubles métaboliques (Pezzani et al., 2019 ; Vaou et al., 2022).

Dans ce contexte, deux plantes médicinales emblématiques de la flore méditerranéenne, le thym (*Thymus vulgaris*) et le curcuma (*Curcuma longa*), suscitent un intérêt scientifique croissant. Le thym est utilisé depuis l'Antiquité pour ses propriétés médicinales. Il est particulièrement riche en thymol, carvacrol et bornéol, des monoterpènes dotés d'activités antioxydantes, antibactériennes et anti-inflammatoires marquées (Ocaña & Reglero, 2012). Ces composés sont capables de neutraliser efficacement les espèces réactives de l'oxygène (ROS) et de protéger les structures cellulaires contre la peroxydation lipidique.

Parallèlement, le curcuma, pilier de la médecine ayurvédique, contient comme principal principe actif la curcumine, une molécule aux propriétés antioxydantes, anti-inflammatoires, anticancéreuses et neuroprotectrices. Elle exerce ses effets en modulant l'expression des cytokines pro-inflammatoires, en inhibant la production des ROS et en stimulant l'activité des enzymes antioxydantes endogènes telles que la superoxyde dismutase (SOD) et la glutathion peroxydase (GPx) (Gupta et al., 2011 ; Marchese et al., 2016).

Les tests DPPH et les modélisations ADMET suggèrent une complémentarité métabolique entre les composés bioactifs de ces deux plantes : le thymol démontre une capacité à franchir la barrière hémato-encéphalique, agissant ainsi au niveau central, tandis que l'ar-turmérone (présent dans le curcuma) cible préférentiellement les tissus périphériques enflammés (Feng et al., 2008 ; Gupta et al., 2011). Cette répartition pharmacocinétique complémentaire permet une action synergique à plusieurs niveaux cellulaires.

L'objectif de cette étude est d'évaluer l'effet synergique des extraits de *Thymus vulgaris* et de *Curcuma longa* sur l'activité antioxydante, à travers des tests in vitro (DPPH) et des modélisations in silico (ADMET). Nous visons ainsi à démontrer que la combinaison de ces deux extraits végétaux constitue une stratégie thérapeutique naturelle prometteuse contre les désordres oxydatifs, en intégrant les notions de synergie moléculaire, de toxicité réduite et d'efficacité pharmacodynamique accrue.

Pour atteindre cet objectif, notre étude a été structurée en deux parties. La première partie présente une synthèse bibliographique incluant les concepts clés abordés : la synergie, le test DPPH, les paramètres ADMET et les mécanismes antioxydants.

La seconde partie, à visée expérimentale, comprend deux chapitres :

- Chapitre 01 : Matériel et Méthodes.
- Chapitre 02 : Résultats et Discussion.

Enfin, une conclusion générale viendra synthétiser les principaux apports de ce travail.

Partie I :
Synthèse Bibliographique

1. Synergie

1.1. Définition

La synergie désigne un phénomène dans lequel l'effet combiné de plusieurs composés excède la somme de leurs effets individuels. Elle peut également se manifester lorsqu'un composé améliore l'efficacité thérapeutique d'un autre en modulant son absorption, sa distribution, son métabolisme ou son excrétion. Par ailleurs, une synergie peut survenir lorsque des composés, inactifs pris isolément, présentent une activité significative lorsqu'ils sont combinés (Vaou et al., 2022).

1.2. Domaines d'application de la synergie

- **Toxicologie** : La synergie se traduit par des effets sur la santé plus importants que ceux attendus de l'addition des effets de chaque composé chimique pris séparément (Rozman & Klaassen, 2007).
- **Médecine complémentaire et alternative** : Elle désigne l'interaction entre plusieurs constituants d'un extrait végétal complet produisant des effets distincts et souvent supérieurs à ceux des composants isolés (Pezzani et al., 2019).
- **Pharmacologie** : Le concept de synergie médicamenteuse renvoie à l'interaction de plusieurs agents thérapeutiques augmentant l'efficacité globale du traitement ou réduisant les effets secondaires (Chou, 2006).
- **Microbiologie** : Une interaction synergique entre antibiotiques permet d'obtenir une action antibactérienne supérieure à celle des antibiotiques administrés individuellement (Odds, 2003).
- **Écologie et sciences environnementales** : Des effets synergiques peuvent émerger des interactions entre facteurs biotiques ou abiotiques, engendrant des impacts écologiques supérieurs à ceux induits par chaque facteur isolé (Crain et al., 2008).
- **Nutrition** : La synergie nutritionnelle réfère à une interaction entre nutriments qui améliore leur absorption ou leur efficacité biologique, comme c'est le cas pour la vitamine D et le calcium (Heaney, 2008).

1.3. Objectifs de la synergie

L'objectif fondamental de la synergie est d'optimiser l'efficacité thérapeutique, de minimiser les effets indésirables et de révéler des mécanismes pharmacodynamiques non observables avec les composés pris isolément. Dans divers domaines, elle vise à produire des effets plus puissants, durables et spécifiques que ceux obtenus par des approches monocomposants (Chou, 2006 ; Heaney, 2008 ; Odds, 2003).

2. Test DPPH

2.1. Définition

Le DPPH (2,2-diphényl-1-picrylhydrazyle) est un radical libre stable de couleur violette intense. Il est couramment utilisé pour évaluer l'activité antioxydante de diverses substances, en particulier dans les domaines biologique, pharmaceutique et agroalimentaire, en raison de sa simplicité, sa rapidité et son coût modéré (Brand-Williams et al., 1995 ; Molyneux, 2004).

2.2. Principe du test DPPH

Ce test repose sur la capacité des antioxydants à céder un électron ou un atome d'hydrogène pour neutraliser les radicaux libres. Lors de l'interaction entre un antioxydant et le DPPH, la couleur violette diminue en intensité, tendant vers le jaune, en raison de la réduction du radical. Cette variation est quantifiée par spectrophotométrie à une longueur d'onde de 517 nm (Brand-Williams et al., 1995). Le degré de décoloration est proportionnel à la capacité antioxydante de l'échantillon (Kedare & Singh, 2011).

2.3. Intérêt du test DPPH

- En biologie, le test DPPH est un outil clé pour l'évaluation des extraits naturels, notamment végétaux, afin de quantifier leur potentiel antioxydant impliqué dans la prévention du stress oxydatif, de l'inflammation et du vieillissement cellulaire (Kedare & Singh, 2011).
- En chimie, il est utilisé pour analyser la capacité de composés synthétiques à piéger les radicaux libres, ce qui le rend pertinent pour le développement de produits

pharmaceutiques, d'additifs alimentaires ou de formulations cosmétiques (Brand-Williams et al., 1995).

3. Intelligence Artificielle (IA)

3.1. Définition

L'intelligence artificielle (IA) regroupe un ensemble de techniques permettant aux systèmes informatiques d'imiter certaines capacités cognitives humaines telles que la reconnaissance d'images, la prise de décision ou le traitement du langage naturel (NetApp, n.d.). Elle repose sur des algorithmes capables d'apprendre de manière autonome à partir des données, ce qui en fait un outil puissant pour l'innovation en recherche scientifique (Pereira et al., 2023).

3.2. Applications de l'IA en recherche scientifique

- **Modélisation prédictive** : Les algorithmes d'IA permettent de prédire des résultats futurs à partir de modèles entraînés sur des données expérimentales, facilitant ainsi la prise de décision (Anuyah et al., 2024).
- **Analyse de données** : L'IA excelle dans la détection de motifs, de corrélations et d'anomalies au sein de grands ensembles de données (Five Sigma Labs, 2024).
- **Intégration de données** : Elle permet de combiner de multiples sources d'information résultats expérimentaux, dossiers médicaux, publications scientifiques pour enrichir les analyses et accroître la robustesse des conclusions (Forbes India, n.d.).

4. Plantes médicinales

4.1. Thym (Thymus vulgaris)

Le thym est un petit arbuste vivace à port bas, atteignant rarement 40 cm de hauteur, et présentant une croissance à la fois horizontale et verticale (Saleh et al., 2015 ; Reddy et al., 2014). Il est originaire de la région ouest-méditerranéenne, s'étendant jusqu'au sud-est de l'Italie (Dauqan et al., 2017), ainsi que d'Afrique du Nord, notamment des zones semi-arides et montagneuses d'Algérie, telles que l'Atlas tellien.

Figure 1 : Thymus vulgaris (**Reddy, P. V., et al., 2014) .**

4.1.1 Propriétés thérapeutiques

Les extraits de *Thymus vulgaris* (thym) sont largement reconnus en médecine traditionnelle pour leurs effets bénéfiques dans le traitement de diverses affections. Ces effets sont principalement attribués à la richesse en composés bioactifs du thym, notamment ses propriétés antimicrobiennes, antifongiques, antioxydantes, antiseptiques, antispasmodiques, antitussives et antivirales (Ocaña & Reglero, 2012).

4.1.2 Usages traditionnels

Le thym est couramment utilisé en médecine traditionnelle pour traiter les troubles digestifs et les affections du système respiratoire (Nabissi et al., 2018 ; Mohamed et al., 2013). Il est notamment employé dans le traitement de la laryngite, de la diarrhée, de la gastro-entérite chronique et de la perte d'appétit (Leung et al., 1996 ; Taher, 2021). En outre, ses propriétés analgésiques, expectorantes, carminatives et diurétiques sont également valorisées. Le thym est aussi considéré comme un remède efficace contre le rhume, la pneumonie et le diabète (Neetu & Poonam, 2022). Par ailleurs, l'infusion aqueuse de feuilles de thym est traditionnellement utilisée pour soulager les maux de tête (Ozcan et al., 2004).

4.2. Curcuma (Cucuma longa)

Curcuma longa est une plante herbacée vivace et vigoureuse pouvant atteindre une hauteur de 1 à 1,5 mètre (3 à 5 pieds). Elle développe des inflorescences en forme de panicules jaunes, caractérisées par un épi central cylindrique. Les fleurs, généralement stériles, assurent la reproduction principalement par voie végétative (rhizomique). Originaire d'Asie du Sud-Est, cette espèce s'épanouit dans des conditions climatiques tropicales à subtropicales, nécessitant des températures élevées et un sol bien drainé pour une croissance optimale (Srivastava et al., 2022 ; Bals et al., 2024).

Figure 2 : Plante de curcuma longa **.(Yadav, R. P., & Tarun, G. 2017).**

Figure 3 : curcuma longa**.(Yadav, R. P., & Tarun, G. 2017).**

4.2.1 Propriétés thérapeutiques

Le curcuma (*Curcuma longa*) est riche en curcumine, un polyphénol aux nombreuses propriétés pharmacologiques. La curcumine est principalement reconnue pour ses effets anti-inflammatoires et antioxydants. Des études ont également mis en évidence ses activités anticancéreuses, antibactériennes, antivirales et neuroprotectrices. Par ailleurs, elle contribue à la santé cardiovasculaire, participe à la régulation de la glycémie chez les patients diabétiques, et favorise la cicatrisation des plaies (Mills & Bone, 2000 ; Bais & Garad, 2024).

4.2.2 Utilisations traditionnelles

Le curcuma est utilisé depuis des siècles dans les domaines alimentaire, cosmétique et médicinal, et constitue une épice fondamentale dans de nombreuses cultures. Il est également employé comme colorant alimentaire naturel (Govindarajan, 1980 ; Amon & Wall, 1991 ; Prasad et al., 2011).

Selon une étude menée au Népal, les racines de curcuma sont traditionnellement utilisées pour traiter les plaies et les blessures, tandis que le jus de ses feuilles est réputé pour ses effets vermifuges et purificateurs du sang (Singh et al., 2010 ; Iweala et al., 2023). Le curcuma est également mentionné dans la médecine traditionnelle pour le traitement du cancer de la peau, de la variole, des affections hépatiques, des troubles menstruels et des douleurs abdominales (Jain & Joshi, 1988 ; Bondy et al., 2004). De plus, il est utilisé dans la prise en charge des maladies inflammatoires de l'intestin et du cancer colorectal (Naganuma et al., 2006 ; Prasad & Aggarwal, 2011).

5. ADMET

L'acronyme **ADMET** désigne cinq propriétés pharmacocinétiques essentielles qui permettent d'évaluer le devenir des substances médicamenteuses dans l'organisme : **Absorption**, **Distribution**, **Métabolisme**, **Excrétion** et **Toxicité**.

5.1. Absorption

L'**absorption** représente la première étape du parcours d'un médicament dans l'organisme. Elle correspond au passage du principe actif depuis le site d'administration vers la circulation

systémique. Ce processus est influencé par plusieurs facteurs, notamment la solubilité aqueuse du composé, sa perméabilité membranaire, et les conditions physiologiques du tractus gastro-intestinal (Li et al., 2020 ; Xiong et al., 2021).

5.2. Distribution

La **distribution** désigne le transport du médicament via le sang vers les tissus et organes cibles. Ce processus est fortement influencé par la liaison aux protéines plasmatiques, la lipophilie du composé et sa capacité à franchir des barrières biologiques telles que la barrière hémato-encéphalique (Xiong et al., 2021 ; NCBI, 2020).

5.3. Métabolisme

Le **métabolisme** correspond à la biotransformation du médicament, principalement au niveau hépatique, en métabolites pouvant être actifs, inactifs ou toxiques. Il se divise en deux phases :

- Phase I (réactions de fonctionnalisation, incluant oxydation, réduction et hydrolyse) ;
- Phase II (réactions de conjugaison avec des groupes hydrophiles tels que le glucuronate ou le sulfate).
- Le métabolisme est déterminant pour la durée d'action du médicament et pour son profil de toxicité (Xiong et al., 2021 ; Cheng et al., 2012).

5.4. Excrétion

L'**excrétion** désigne le processus par lequel le médicament ou ses métabolites sont éliminés de l'organisme, principalement par voie rénale (urine) ou biliaire (foie). L'efficacité de cette étape dépend des propriétés physico-chimiques du composé, telles que sa polarité et sa liaison aux protéines (Pires et al., 2015 ; Xiong et al., 2021).

5.5. Toxicité

La **toxicité** est un paramètre fondamental dans l'évaluation de la sécurité d'un médicament. Certains composés peuvent induire des effets génotoxiques, hépatotoxiques ou reprotoxiques, constituant ainsi des causes majeures d'échec au cours des phases cliniques du développement

pharmaceutique. L'identification précoce de ces effets indésirables est essentielle pour améliorer le profil de sûreté des candidats médicaments (Zhang et al., 2017 ; Xiong et al., 2021).

6. Activité antioxydante

Les **radicaux libres** peuvent être générés de manière endogène, notamment par la respiration cellulaire, ou exogène, via des facteurs environnementaux comme la pollution, les rayonnements ou le tabagisme. Leur accumulation conduit à un **stress oxydatif**, provoquant des dommages aux lipides, protéines et ADN, et contribuant à l'apparition de pathologies chroniques telles que les maladies cardiovasculaires, les cancers ou les affections neurodégénératives (Chandimali et al., 2025 ; Blagov et al., 2024).

Les **antioxydants** jouent un rôle protecteur en neutralisant les radicaux libres. Ils agissent soit par **don d'électrons**, stabilisant ainsi ces espèces réactives, soit en inhibant la production d'enzymes pro-oxydantes. On distingue deux grandes catégories d'antioxydants : enzymatiques et non enzymatiques.

Les **antioxydants enzymatiques**, tels que la superoxyde dismutase (SOD), transforment le radical superoxyde en peroxyde d'hydrogène, lequel est ensuite dégradé en eau et oxygène par la **catalase** et la **glutathion peroxydase** (Blagov et al., 2024 ; Chaudhary et al., 2023).

Les **antioxydants non enzymatiques**, incluant les vitamines C et E ainsi que les flavonoïdes, agissent directement contre les radicaux libres, protégeant les structures cellulaires de l'oxydation. De nombreuses études mettent en évidence le **potentiel des composés naturels d'origine végétale** comme sources efficaces d'antioxydants pour la prévention et le traitement de diverses pathologies. Toutefois, une consommation excessive de ces composés peut engendrer des effets pro-oxydants, soulignant la nécessité d'un usage raisonné (Chandimali et al., 2025 ; Chaudhary et al., 2023).

Partie II :

Partie

Expérimental

Chapitre 01:
Matériels et Méthodes

1. Matériels

1.1. Matériel végétal

La première matière végétale de cette étude est *Thymus vulgaris*, qui a été apportée d'une ferme de la wilaya de Biskra, et la deuxième matière végétale est *Curcuma longa*, qui a été achetée sur le marché local de la wilaya de Constantine, d'origine algérienne.

1.2. Produits chimiques

- DPPH (2,2-diphényl-1-picrylhydrazyle) – pur
- Méthanol (ou éthanol absolu)
- Extrait ou composé à tester
- Acide ascorbique ou Trolox (antioxydant de référence)

1.3. Matériel de laboratoire

- Tubes à essai / microplaques 96 puits
- Pipettes et pointes stériles

1.4. Appareils

- Lecteur de Microplaque.

2. Méthodes

2.1. Méthodologie d’extraction

Une quantité de 150 g de matière végétale sèche et finement moulue de chaque plante est introduite dans 300 mL d'éthanol. Le mélange est agité à température ambiante afin de favoriser l'extraction des composés bioactifs. L'extraction se poursuit pendant 48 heures dans un erlenmeyer hermétiquement fermé. Après ce temps, le mélange est filtré à l’aide de papier filtre pour éliminer les résidus solides. Le filtrat obtenu est ensuite concentré à l’aide d’un évaporateur rotatif (Rotavapor) afin d’éliminer l’éthanol. L’extrait brut est enfin placé dans une étuve à 37 °C pendant 48 heures pour assurer un séchage complet.

2.2. Méthode d'évaluation de l'activité antioxydante par la méthode DPPH

2.2.1. Principe

Le radical libre DPPH• (violet) est réduit en DPPH-H (jaune pâle) en présence d'un antioxydant. La diminution de l'absorbance à 517 nm est mesurée en utilisant un lecteur des microplaques.

2.2.2.Préparation des solutions

Ⅰ. Solution de DPPH :

- Dissoudre 4 mg de DPPH dans 100 mL de méthanol pour obtenir une solution à 0,1 mM (ou ajuster pour que l'absorbance soit ≈ 0,9 à 517 nm).

II . Solutions de l'échantillon :

- Préparer une gamme de concentrations (par ex. : 10, 25, 50, 75, 100 µg/mL).

III . Contrôle positif :

- Préparer une solution standard de Trolox ou d'acide ascorbique à différentes concentrations.

2.2.3. Procédure

Ⅰ. Dans chaque puit de microplaque:

- Ajouter 1 mL de solution DPPH.
- Ajouter 1 mL de l'extrait à tester (ou solvant pour le blanc).

II . Agiter légèrement puis incuber à l'obscurité pendant 30 minutes à température ambiante.

III . Mesurer l'absorbance à 517 nm contre un blanc (DPPH + solvant sans antioxydant).

2.2.4. Calculs

Pourcentage d'inhibition :

$\%Inhibition = ((A_{controle} - A_{echantillon}) / A_{controle}) \times 100$

- $A_{controle}$: Absorbance du DPPH sans antioxydant
- $A_{echantillon}$: Absorbance avec extrait/antioxydant

Optionnel : Déterminer l'IC_{50} (concentration nécessaire pour inhiber 50 % du DPPH).

2.3 Méthode de mesure de la synergie et de prédiction de l'ADMET

Dans cette étude, le logiciel CompuSyn a été utilisé pour évaluer l'effet synergique entre les composés. Ce programme permet de déterminer l'interaction (synergie) entre plusieurs agents actifs à l'aide de l'indice de combinaison (Combination Index, CI).

Par ailleurs, les propriétés ADMET (absorption, distribution, métabolisme, excrétion et toxicité) des composés ont été prédites à l'aide de la plateforme ADMETlab 2.0, qui offre une évaluation in silico fiable des paramètres pharmacocinétiques et toxicologiques.

Chapitre 02:
Résultats et Discussion

1. Résultats

1.1. Test DPPH

Tableau 1 : Activité antioxydante par test DPPH (Curcuma longa) (Blois,1958).

Extrait *Curcuma longa*	% Inhibition dans le test DPPH							
	3.125 µg	6.25 µg	12.5 µg	25 µg	50 µg	100 µg	200 µg	IC_{50} µg/mL
Extrait ethan	10,95±0,76	17,54±1,31	20,98±1,09	25,79±1,08	38,68±0,21	45.39±0,73	51,87±1,09	**24,09±0,19**
BHT	11,69±1,88	22,21±1,30	37,12±1,80	52,63±2,70	56,02±0,53	83,60±0,23	87,28±0,26	22.32±1.19
BHA	28,95±1,16	54,33±1,59	76,76±1,65	84,09±0,35	87,53±0,82	87,73±0,15	88,43±0,23	5.73±0.41

Tableau 2 : Activité antioxydante par test DPPH(Thymus vulgaris) (Blois,1958).

Extrait *Thymus vulgaris*	% Inhibition dans le test DPPH							
	3.125 µg	6.25 µg	12.5 µg	25 µg	50 µg	100 µg	200 µg	IC_{50} µg/mL
Extrait ethan	11,55±0,78	15,98±1,12	22,93±0,62	29,79±1,01	40,98±0,31	47.79±0,78	57,77±0,78	**26,33±0,48**
BHT	11,69±1,88	22,21±1,30	37,12±1,80	52,63±2,70	56,02±0,53	83,60±0,23	87,28±0,26	22.32±1.19
BHA	28,95±1,16	54,33±1,59	76,76±1,65	84,09±0,35	87,53±0,82	87,73±0,15	88,43±0,23	5.73±0.41

Tableau 3 : Activité antioxydante par test DPPH (Proposé par synergie).

Extrait *Thymus vulgaris* 1	% Inhibition dans le test DPPH							
	1.56 µg			6.25 µg	12.5 µg	25 µg	50 µg	IC_{50} µg/mL
Extrait *curcuma longa* 2	3.31 µg			13.30 µg	26.52 ug	53.01 µg	105.9 µg	**20,22±0,36**
BHT	11,69±1,88	22,21±1,30	37,12±1,80	52,63±2,70	56,02±0,53	83,60±0,23	87,28±0,26	22.32±1.19
BHA	28,95±1,16	54,33±1,59	76,76±1,65	84,09±0,35	87,53±0,82	87,73±0,15	88,43±0,23	5.73±0.41

Avec ***CI*** (Combination Index) = **0.39** **Ratio = 2.10**

(Dm) **Ep50 =** 20,22 ± 0,36 Dm Median effect

Resutat experimental (Dm) **IC_{50} = 20.78 ±0,67**

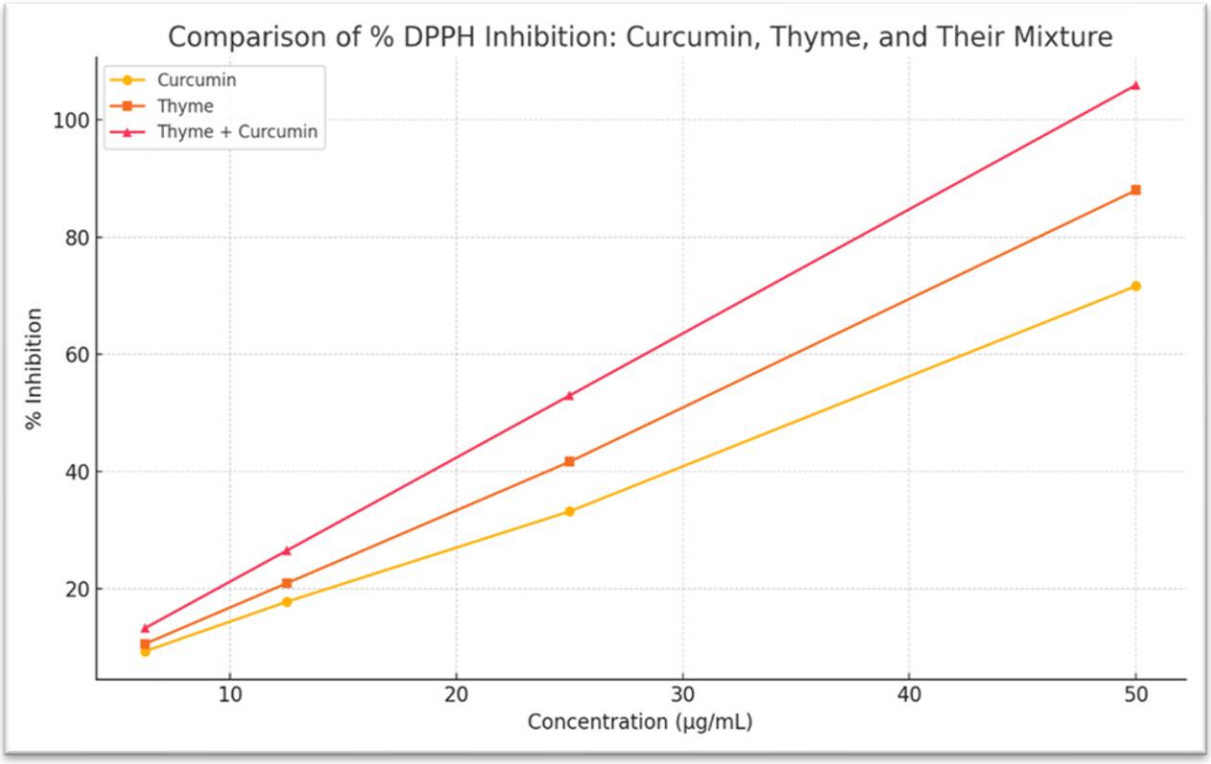

Figure 4: Comparaison de %l'inhibition du DPPH : Thymus Vulgaris, curcuma longa et leur mélange .

Tableau 4 : Activité antioxydante par test DPPH (IA).

Extrait 1	% Inhibition dans le test DPPH							
		3 µg	6 µg	12 µg	24 µg	48 µg		IC_{50} µg/mL
Extrait 2		2.5	5	20	40	80		**24±0,06**
BHT	11,69±1,88	22,21±1,30	37,12±1,80	52,63±2,70	56,02±0,53	83,60±0,23	87,28±0,26	22.32±1.19
BHA	28,95±1,16	54,33±1,59	76,76±1,65	84,09±0,35	87,53±0,82	87,73±0,15	88,43±0,23	5.73±0.41

(Dm) **Ep_{50}** = 24 ± 0,06

Resutat experimental **IC_{50} = 25.09 ±0,71**

1.2. ADMET

Tableau 5 : Analyse d'absorption des composés de thym *(Thymus vulgaris)* et de curcuma *(Curcuma longa)* selon les critères ADMET pour étudier la relation synergique potentielle.

Source	Composés	Caco-2 Perméabilité (log Papp, cm/s)	Classification (Artursson & Karlsson, 1991)	MDCK (cm/s)	Classification (Irvine et al., 1999)	P-gp Inhibiteur	Classification (Aller et al., 2009)
Thymus vulgaris	Santolina triene	-4.484	optimum	2.2e-05	Haut	0.083	Non-Inhibiteur
Thymus vulgaris	Thymol	-4.387	optimum	2.4e-05	Haut	0.006	Non-Inhibiteur
Thymus vulgaris	Borneol	-4.442	optimum	2 e -05	Haut	0.008	Non-Inhibiteur
Thymus vulgaris	Himachalane	-4.616	optimum	1.4e-05	Haut	0.992	Inhibiteur
Thymus vulgaris	Terpinen-4-ol	-4.387	optimum	2.4e-05	Haut	0.006	Non-Inhibiteur
Curcuma longa	α-Phellandrene	-4.383	optimum	2.4e-05	Haut	0.001	Non-Inhibiteur
Curcuma longa	α-Turmerone	-4.563	optimum	1.9e-05	Haut	0.847	Inhibiteur
Curcuma longa	α-Zingiberene	-4.653	optimum	2 e -05	Haut	0.802	Inhibiteur
Curcuma longa	ar-Turmerone	-4.536	optimum	1.7e-05	Haut	0.766	Inhibiteur
Curcuma longa	β-Sesquiphellandrene	-4.535	optimum	1.7e-05	Haut	0.588	Inhibiteur

Tableau 6 : Analyse de la distribution des composés du thym (*Thymus vulgaris*) et du curcuma (*Curcuma longa*) selon les critères ADMET pour étudier la relation synergique potentielle.

Source	**Composés**	**PPB %**	**Classification (Smith et al., 2010).**	**VD (L/kg)**	**Classification (Greenblatt,2014).**	**BBB Pénétration**	**Classification (Shaker et al., 2021).**
Thymus vulgaris	santolina triene	86.20 %	Modéré	2.477	optimum	0.363	Modéré
Thymus vulgaris	Thymol	93.89 %	Haut	2.469	optimum	0.814	fort
Thymus vulgaris	borneol	61.56 %	Faible	1.025	optimum	0.295	Faible
Thymus vulgaris	himachalane	96.34 %	Haut	6.102	optimum	0.021	Très faible
Thymus vulgaris	terpinin-4-ol	93.89 %	Haut	2.469	optimum	0.814	fort
Curcuma longa	alpha-phellandrene	92.01 %	Haut	2.963	optimum	0.835	fort
Curcuma longa	alpha-turmerone	93.80 %	Haut	1.246	optimum	0.33	Modéré
Curcuma longa	alpha-zingiberene	96.81 %	Haut	5.108	optimum	0.179	Faible
Curcuma longa	ar-turmerone	94.69 %	Haut	0.706	optimum	0.202	Faible
Curcuma longa	beta-sesquiphellandrene	97.46 %	Très élevé	5.406	optimum	0.27	Faible

Tableau 7 : Analyse Métabolisme des composés du thym *(Thymus vulgaris)* et du curcuma *(Curcuma longa)* selon les critères ADMET pour étudier la relation synergique potentielle.

Source	**Composés**	**CYP1A2 inhibiteur (Probability)**	**Classification(Cheng et al., 2011; Zanger & Schwab, 2013).**	**CYP1A2 substrat (Probability)**	**Classification(Cheng et al., 2011; Zanger & Schwab, 2013).**	**CYP2C19 inhibiteur (Probability)**	**Classification (Cheng et al., 2011; Zanger & Schwab, 2013).**
Thymus vulgaris	**Santolina triene**	0.69	Inhibiteur	0.925	Substrat	0.378	Non-Inhibiteur
Thymus vulgaris	**Thymol**	0.922	Inhibiteur	0.951	Substrat	0.765	Inhibiteur
Thymus vulgaris	**Borneol**	0.067	Non-Inhibiteur	0.37	NON Substrat	0.056	Non-Inhibiteur
Thymus vulgaris	**Himachalane**	0.42	Non-Inhibiteur	0.56	Substrat	0.531	Inhibiteur
Thymus vulgaris	**Terpinen-4-ol**	0.922	Inhibiteur	0.951	Substrat	0.765	Inhibiteur
Curcuma longa	**α-Phellandrene**	0.258	Non-Inhibiteur	0.471	NON Substrat	0.178	Non-Inhibiteur
Curcuma longa	**α-Turmerone**	0.137	Non-Inhibiteur	0.811	Substrat	0.679	Inhibiteur
Curcuma longa	**α-Zingiberene**	0.795	Inhibiteur	0.679	Substrat	0.555	Inhibiteur
Curcuma longa	**ar-Turmerone**	0.832	Inhibiteur	0.957	Substrat	0.939	Inhibiteur

Curcuma longa	**β-Sesquiphellandrene**	0.879	Inhibiteur	0.355	NON Substrat	0.377	Non-Inhibiteur

Tableau 8 : Analyse de l'excrétion des composés de thym *(Thymus vulgaris)* et de curcuma *(Curcuma longa)* selon les critères ADMET pour étudier la relation synergique potentielle.

Source	**Composés**	**CL (mL/min/kg)**	**classification (Smith et al., 2018).**	**T½ (Probabilité)**	**Classification(Gabrielsson & Weiner, 2016).**
Thymus vulgaris	Santolina triene	5.062	Modéré	0.237	court
Thymus vulgaris	Thymol	9.444	Modéré	0.682	long
Thymus vulgaris	Borneole	10.66	Modéré	0.361	court
Thymus vulgaris	Himachalane	3.539	faible	0.114	court
Thymus vulgaris	Terpinin-4-ol	9.444	Modéré	0.682	long
Curcuma longa	α-Phellandrene	12.66	Modéré-Haut	0.617	long
Curcuma longa	α-Turmerone	14.305	Haut	0.804	long
Curcuma longa	α-Zingiberene	14.814	Haut	0.306	court
Curcuma longa	ar-Tumerone	10.658	Modéré	0.371	court
Curcuma longa	β-Sesquiphellandrene	13.401	Haut	0.219	court

Tableau 9 : Analyse de la toxicité des composés du thym *(Thymus vulgaris)* et du curcuma *(Curcuma longa)* selon les critères ADMET pour étudier la relation synergique potentielle.

Source	**Composés**	**hERG Bloqueurs**	**Risk of Cardiotoxicité (Gupta et al ., 2010)**	**H-HT**	**Human Hépatotoxicité (Chen et al., 2011)**	**DILI**	**Drug-Induced Liver Injury(Aleo et al., 2014)**
Thymus vulgaris	Santolina Triene	0.011	faible	0.683	Modéré-Haut	0.027	faible
Thymus vulgaris	Thymol	0.011	faible	0.032	faible	0.137	Faible-Modéré
Thymus vulgaris	Borneol	0.056	Faible-Modéré	0.141	Faible-Modéré	0.03	faible
Thymus vulgaris	Himachalane	0.008	Très faible	0.121	Faible-Modéré	0.081	faible
Thymus vulgaris	Terpinin-4-ol	0.011	faible	0.032	faible	0.137	Faible-Modéré
Curcuma longa	α-Phellandrene	0.024	faible	0.76	Haut	0.014	Très faible
Curcuma longa	α-Turmerone	0.018	faible	0.834	Haut	0.024	faible
Curcuma longa	α-Zingiberene	0.08	Moderate	0.929	Très élevé	0.02	faible
Curcuma longa	ar-Turmerone	0.021	faible	0.292	Moderate	0.259	Modéré-Haut
Curcuma longa	β-Sesquiphellandrene	0.091	Modéré-Haut	0.817	Haut	0.388	Haut

2. Discussion

2.1. Activité antioxydante

- **Tableau 1**

L'activité antioxydante de l'extrait de curcuma a été évaluée à travers sa capacité à piéger les radicaux libres DPPH•. Les résultats ont été exprimés en termes de concentration inhibitrice médiane (IC_{50}), comme indiqué dans le tableau 1.

L'extrait éthanolique de curcuma a révélé un potentiel antioxydant prometteur, avec une activité significative de neutralisation des radicaux DPPH, affichant une valeur d'IC_{50} de $24{,}09 \pm 0{,}19$ µg/mL. Cette activité est comparable à celle du BHT ($22{,}32 \pm 1{,}19$ µg/mL), un antioxydant de référence, bien qu'elle reste environ quatre fois inférieure à celle du BHA ($5{,}73 \pm 0{,}41$ µg/mL) (Alsaleem, Elfaruk, & Hammam, 2020).

L'extrait brut de curcuma a montré une activité antioxydante légèrement plus faible, avec une IC_{50} identique de $24{,}09 \pm 0{,}19$ µg/mL, indiquant une capacité antioxydante modérée comparée à l'extrait éthanolique et aux antioxydants de référence (voir tableau 1).

Bien que l'extrait éthanolique présente une activité légèrement supérieure à celle de l'extrait brut, les deux extraits ont démontré une réponse dose-dépendante : l'inhibition du radical DPPH augmente proportionnellement à la concentration de l'extrait. Comme attendu, le BHA a montré l'activité antioxydante la plus élevée, confirmant sa capacité bien établie à neutraliser les radicaux libres.

Les variations observées dans l'activité antioxydante entre les extraits peuvent être attribuées à des différences dans leur composition phytochimique, notamment en termes de teneur en composés phénoliques et flavonoïdes, reconnus pour leur aptitude à transférer des électrons et à chélater les ions métalliques (Singh et al., 2024).

Les résultats de cette étude démontrent la capacité des extraits de curcuma à piéger les radicaux libres et à limiter le stress oxydatif, un facteur clé dans l'étiologie de nombreuses pathologies chroniques, telles que les cancers, les maladies cardiovasculaires et le diabète (Mijiti et al., 2025).

L'efficacité antioxydante de l'extrait de curcuma peut être attribuée à sa richesse en composés bioactifs, en particulier les composés phénoliques et flavonoïdes, dont les mécanismes d'action reposent principalement sur le transfert d'électrons et la chélation des métaux.

❖ **Tableau 2**

L'évaluation de l'activité antioxydante par la méthode DPPH a révélé des différences significatives entre les échantillons analysés. Le thym brut (*Thymus vulgaris*) a présenté une activité relativement modeste, avec des taux d'inhibition allant de 3,12 % à 3,125 µg/mL jusqu'à 57,77 % à 200 µg/mL. La valeur élevée de l'IC_{50} (126,31 µg/mL) confirme une capacité antioxydante limitée. Ces résultats sont en accord avec la littérature, qui souligne que les matières premières contiennent souvent des concentrations plus faibles en composés bioactifs en raison de l'interférence d'autres constituants (Ivanova et al., 2020)

En revanche, l'extrait éthanolique de thym (désigné par « extrait.ethan ») a affiché une activité antioxydante nettement supérieure, avec des taux d'inhibition passant de 11,55 % à 3,125 µg/mL à 88,07 % à 200 µg/mL, et une IC_{50} de 26,73 µg/mL. Ces données suggèrent que l'extraction à l'éthanol favorise la concentration des composés phénoliques et flavonoïdiques responsables de l'activité antioxydante, corroborant les résultats antérieurs (Thamer et al., 2021)

Le BHT (butylhydroxytoluène), antioxydant de synthèse utilisé comme référence, a présenté une efficacité comparable à celle de l'extrait éthanolique de thym, atteignant un taux d'inhibition de 88,07 % à 200 µg/mL, avec une IC_{50} de 26,76 µg/mL. Cette similitude suggère que les extraits botaniques pourraient représenter des alternatives naturelles efficaces aux antioxydants synthétiques (Tepe et al., 2005).

Par ailleurs, le BHA (butylhydroxyanisole) a démontré l'activité antioxydante la plus élevée parmi tous les échantillons testés, avec un taux d'inhibition de 88,43 % à de faibles concentrations et une IC_{50} particulièrement basse (5,73 µg/mL), confirmant sa forte capacité antioxydante (Gülçin, 2020).

Dans l'ensemble, l'extrait éthanolique de thym se distingue par une activité comparable à celle du BHT, ce qui en fait un candidat prometteur pour des applications en tant qu'antioxydant naturel, notamment dans les industries agroalimentaire et pharmaceutique. Une telle

substitution permettrait de réduire la dépendance aux antioxydants synthétiques, souvent associés à des risques pour la santé.

❖ **Tableau 3**

Les résultats du test DPPH présentés dans le tableau 3 indiquent qu'un mélange d'extraits de thym (*Thymus vulgaris*) et de curcuma (*Curcuma longa*) présente une activité antioxydante notable, avec une IC_{50} mesurée à 20,22 ± 0,36 µg/mL. Cette valeur s'approche de celle du BHT (IC_{50} = 22,32 ± 1,19 µg/mL), bien que le BHA demeure l'antioxydant le plus puissant (IC_{50} = 5,73 ± 0,41 µg/mL).

L'indice de combinaison (CI) obtenu est de 0,39, indiquant un effet synergique significatif (CI < 1), ce qui signifie que l'efficacité antioxydante du mélange dépasse la simple addition des effets individuels des deux extraits.

Le rapport de composition (2,10) suggère une prépondérance de l'extrait de thym dans le mélange, ce qui pourrait expliquer la synergie observée. En effet, le thymol, un constituant majeur du thym, est reconnu pour ses propriétés antioxydantes (Taibi et al., 2024).

Cette synergie pourrait résulter de l'interaction entre différents composés phénoliques, tels que le thymol et la curcumine, intervenant dans la neutralisation des radicaux libres soit par régénération de molécules antioxydantes, soit par un piégeage plus efficace des radicaux., Des études similaires ont démontré que l'association de composés naturels peut induire des effets supérieurs à ceux obtenus avec chaque composé isolé (Al-Mansori et al., 2020). Cela a notamment été observé pour les couples thymol–carvacrol ou curcumine–huiles essentielles.

De plus, cette synergie pourrait découler d'une complémentarité des mécanismes d'action, tels que le transfert d'électrons ou de protons optimisé en présence conjointe des deux extraits *(*Zhou et al., 2016)

Les données graphiques appuient également cette hypothèse : le graphique comparatif montre qu'à 50 µg/mL, le mélange entraîne une inhibition dépassant 100 %, ce qui suggère une interaction bio-amplificatrice significative entre le curcuma et le thym.

La valeur expérimentale de l'IC_{50} (20,78 ± 0,67 µg/mL) est en étroite concordance avec la valeur théorique calculée, renforçant ainsi la fiabilité des résultats et confirmant l'existence d'un effet synergique. Ces données suggèrent que l'association thym–curcuma présente un potentiel antioxydant prometteur, susceptible de constituer une alternative naturelle et sûre aux antioxydants de synthèse dans les secteurs alimentaire et pharmaceutique.

❖ **Graphe (Figure 4)**

L'analyse graphique met en évidence les profils d'activité antioxydante suivants :

- **Curcuma (*Curcuma longa*)** : activité croissante avec la concentration, mais restant la plus faible des trois échantillons.
- **Thym (*Thymus vulgaris*)** : activité supérieure à celle du curcuma à toutes les concentrations.
- **Mélange (Curcuma + Thym)** : activité antioxydante la plus élevée, dépassant la somme des effets individuels, traduisant un effet synergique net.

❖ **Tableau 4**

Dans cette étude, l'activité antioxydante d'un mélange d'extraits de thym et de curcuma a été évaluée par le test DPPH en combinant deux approches : la modélisation par intelligence artificielle (IA) et l'expérimentation en laboratoire.

La prédiction issue de l'IA a estimé une IC_{50} de 24 ± 0,06 µg/mL, avec un taux d'inhibition de 80 % à 48 µg/mL. Ce résultat témoigne d'une synergie entre les composés actifs des deux extraits, notamment la curcumine, le thymol et le carvacrol, reconnus pour leur pouvoir antioxydant (Nazdar et al., 2024).

L'expérimentation a permis d'obtenir une IC_{50} de 25,09 ± 0,71 µg/mL, très proche de la valeur prédite, validant ainsi l'utilisation de l'IA pour estimer le potentiel antioxydant des extraits végétaux (Gülçin, 2020).. Cette concordance renforce la pertinence de l'IA comme outil de présélection rapide et économique lors des phases exploratoires.

Toutefois, comparé aux antioxydants synthétiques comme le BHA (IC_{50} = 5,73 ± 0,41 µg/mL) et le BHT (22,32 ± 1,19 µg/mL), le mélange naturel présente une efficacité légèrement

inférieure. Néanmoins, il constitue une alternative prometteuse et sécuritaire, notamment dans les contextes où la réduction de l'exposition aux additifs chimiques est recherchée.

L'intégration de l'intelligence artificielle dans les phases pré-expérimentales permet de cibler les combinaisons les plus prometteuses, réduisant ainsi les coûts, le temps et les ressources nécessaires. Toutefois, la validation biologique expérimentale demeure indispensable pour confirmer les prédictions (Gülçin, 2020).

2.2. ADMET

2.2.1. Absorption

Les propriétés d'absorption de plusieurs composés bioactifs extraits de *Thymus vulgaris* (thym) et *Curcuma longa* (curcuma) ont été évaluées à l'aide des modèles cellulaires Caco-2 et MDCK, ainsi que par leur capacité estimée à inhiber la glycoprotéine P (P-gp), un transporteur membranaire influençant de manière significative la biodisponibilité orale des médicaments (Amin et al., 2013).

Les tests de perméabilité réalisés sur les cellules Caco-2 ont révélé que l'ensemble des composés analysés présentaient une perméabilité intestinale satisfaisante, avec des valeurs de log Papp supérieures au seuil critique de –5,15 (log Papp, cm/s), indiquant une absorption efficace à travers l'épithélium intestinal (Artursson & Karlsson, 1991).

Parmi les composés issus du *Thymus vulgaris*, le thymol (log Papp Caco-2 : –4,387), le bornéol (–4,442) et l'himachalane (–4,616) ont démontré une bonne perméabilité à la fois dans les modèles Caco-2 et MDCK. En parallèle, leur faible probabilité d'inhibition de la P-gp (< 0,01) notamment pour le thymol ($2{,}4 \times 10^{-5}$) et le bornéol ($2{,}0 \times 10^{-5}$) — suggère une interaction minimale avec ce transporteur, ce qui est favorable à une biodisponibilité orale élevée (Feng et al., 2008).

Des études fonctionnelles complémentaires ont également montré que le bornéol augmente l'accumulation intracellulaire de rhodamine 123, un substrat de la P-gp, par inhibition de cette dernière (He et al., 2011).

En revanche, les composés extraits de *Curcuma longa*, notamment l'α-turmerone (Caco-2 : –4,536 ; MDCK : 1,9 × 10^{-5}), l'α-zingibérène (Caco-2 : –4,653 ; MDCK : 2,0 × 10^{-5}), l'ar-turmerone (Caco-2 : –4,536 ; MDCK : 1,7 × 10^{-5}) et le β-sesquiphellandrène (Caco-2 : –4,535 ; MDCK : 1,7 × 10^{-5}), ont affiché des profils de perméabilité similaires.

Des données expérimentales ont mis en évidence la capacité de l'α-turmerone à inhiber la P-gp, comme le montre l'augmentation de l'accumulation intracellulaire de rhodamine 123 (Yue et al., 2012).

La diversité des profils pharmacocinétiques de ces composés suggère la possibilité d'une synergie d'action entre le thym et le curcuma, particulièrement pertinente dans le cadre d'applications thérapeutiques à visée anti-inflammatoire, antioxydante et antifongique.

2.2.2. Distribution

Les propriétés de distribution de divers composés bioactifs extraits de *Thymus vulgaris* et *Curcuma longa* ont été analysées selon trois paramètres clés : la liaison aux protéines plasmatiques (PPB), le volume de distribution (VD) et la capacité de franchissement de la barrière hémato-encéphalique (BBB). Il convient toutefois de souligner que les données disponibles proviennent majoritairement de modélisations in silico, d'études animales ou de simulations PBPK, sans indication explicite sur leur origine, ce qui limite l'interprétation des résultats (Feng et al., 2008).

Les composés du thym, tels que le thymol et le terpinen-4-ol, présentent une forte capacité de pénétration de la BBB (valeurs > 0,8), suggérant un potentiel neuroactif (Feng et al., 2008). Leur volume de distribution, situé entre 1,025 et 6,102 L/kg, indique une diffusion tissulaire favorable (Mansoor & Mahabadi, 2023).

S'agissant de la liaison aux protéines plasmatiques, des composés comme le santolina triene (86,20 %) et le bornéol (61,56 %) présentent une liaison modérée, garantissant une fraction libre suffisante pour l'activité pharmacologique. À l'inverse, des composés tels que l'himachalane ou l'α-zingibérène, avec des taux de liaison supérieurs à 96 %, pourraient voir leur biodisponibilité immédiate réduite. Toutefois, une forte liaison aux protéines peut aussi agir comme réservoir, prolongeant l'effet thérapeutique (Smith et al., 2010).

Les composés du curcuma présentent un volume de distribution favorable (0,7 à 5,4 L/kg) mais une faible perméabilité à la BBB, comme l'illustre la valeur de 0,202 pour l'ar-turmerone. Ces données suggèrent une activité principalement périphérique. Toutefois, leur impact ne saurait être limité à cette seule dimension : certains composés pourraient exercer des effets indirects sur le système nerveux central via des mécanismes neuro-immunitaires (Gupta et al., 2011).

Ainsi, les composés du thym pourraient cibler préférentiellement le système nerveux central, tandis que ceux du curcuma agiraient principalement en périphérie, mettant en évidence une complémentarité pharmacologique intéressante.

2.2.3. Métabolisme

Les composés bioactifs issus du thym et du curcuma présentent des propriétés antioxydantes synergiques, partiellement attribuables à leurs interactions avec certaines enzymes du cytochrome P450, en particulier le CYP1A2 et le CYP2C19. Ces interactions ont été principalement prédites par des modèles in silico, et nécessitent des validations expérimentales pour confirmation (Marchese et al., 2016).

Le thymol agit comme inhibiteur puissant du CYP1A2 (probabilité : 0,922) et modéré du CYP2C19 (0,765), tout en étant également un substrat probable du CYP1A2 (0,951). Il pourrait ainsi influencer le métabolisme de médicaments co-administrés (Marchese et al., 2016).

De manière similaire, l'ar-turmerone présente une forte probabilité d'inhibition du CYP1A2 (0,832) et du CYP2C19 (0,939), et se révèle être un substrat potentiel du CYP1A2 (0,957), suggérant un risque d'interactions métaboliques (Apisariyakul et al., 1995).

L'association du thymol et de l'ar-turmerone pourrait donc renforcer l'efficacité thérapeutique via des effets métaboliques convergents (Nabavi et al., 2015). Cette hypothèse est étayée par des données montrant que les deux composés régulent les espèces réactives de l'oxygène, contribuant à leur activité antioxydante (Marchese et al., 2016 ; Moghadamtousi et al., 2014).

En outre, certains métabolites pourraient jouer un rôle déterminant dans leur activité biologique. Les métabolites hydroxylés du thymol présentent une activité antimicrobienne accrue, tandis que des métabolites oxydés de l'ar-turmerone sont suspectés d'avoir une légère hépatotoxicité à forte dose (Cruz et al., 2022).

Ainsi, la combinaison des deux extraits végétaux pourrait prolonger la biodisponibilité des principes actifs tout en optimisant leur efficacité pharmacologique.

2.2.4. Excrétion

Les données pharmacocinétiques montrent que les composés des deux plantes présentent une clairance systémique variable, mesurée entre 3,539 et 14,814 mL/min/kg, ce qui les classe principalement dans la catégorie de clairance modérée (5–15 mL/min/kg) selon les normes établies (Yang et al., 2007 ; Derendorf & Hochhaus, 2019).

Par exemple, le thymol (9,444 mL/min/kg), le bornéol (10,660 mL/min/kg) et le terpinen-4-ol (9,444 mL/min/kg) affichent une clairance modérée, tandis que l'himachalane présente une clairance faible (3,539 mL/min/kg), suggérant une élimination lente et une durée d'action prolongée (Kohlert et al., 2002).

La demi-vie de tous les composés étudiés est inférieure à 3 heures, indiquant une élimination rapide. Le thymol et le terpinen-4-ol affichent une demi-vie de 0,682 heure, contre 0,804 pour l'α-turmerone et 0,237 pour le santolina triene.

Ces données suggèrent que des administrations répétées ou des formulations à libération prolongée sont nécessaires pour maintenir une concentration thérapeutique adéquate (Xu et al., 2012).

L'association de composés à clairance modérée et à courte demi-vie pourrait améliorer l'efficacité thérapeutique tout en limitant les risques d'accumulation, sous réserve d'une adaptation du schéma posologique ou de l'usage de systèmes de délivrance contrôlée (Williamson, 2001 ; Ganesan & Xu, 2017).

2.2.5. Toxicité

Une évaluation toxicologique prédictive, réalisée à l'aide de la plateforme ADMETlab 2.0, a permis d'analyser plusieurs composés du thym et du curcuma selon trois critères : l'inhibition du canal hERG (cardiotoxicité), l'hépatotoxicité humaine (H-HT) et les lésions hépatiques induites par les médicaments (DILI).

Tous les composés présentent une faible probabilité d'inhibition du canal hERG (0,008 à 0,091), les classant comme non cardiotoxiques (Creanza et al., 2021). Toutefois, ces prédictions nécessitent une validation expérimentale.

Concernant la H-HT, des composés comme le thymol (0,032), le borneol (0,141) et le terpinen-4-ol (0,032) présentent une toxicité hépatique faible. En revanche, le santolina triene (0,683), l'α-phellandrène (0,760), l'α-turmerone (0,834), l'α-zingibérène (0,929) et le β-sesquiphellandrène (0,817) présentent un risque accru.

La majorité des composés présentent une faible probabilité de DILI, à l'exception du β-sesquiphellandrène (0,388), suggérant un risque modéré (Zárybnický et al., 2018).

Ainsi, les composés du thym (thymol, borneol, terpinen-4-ol) apparaissent comme globalement sûrs, tandis que certains composés du curcuma doivent faire l'objet d'une vigilance particulière.

Bien que ces données soutiennent l'hypothèse d'une synergie thérapeutique entre les deux plantes, notamment pour leurs effets anti-inflammatoires, antioxydants et antifongiques (Salehi et al., 2018), cette synergie reste à démontrer par des études expérimentales de co-administration.

Conclusion

Conclusion

Les résultats expérimentaux et in silico mettent en évidence une synergie significative entre *Thymus vulgaris* et *Curcuma longa* dans la neutralisation des radicaux libres ainsi que dans la modulation de plusieurs paramètres ADMET. Le test DPPH a révélé une activité antioxydante notable du mélange comparable à celle du BHT, et supérieure à celle des extraits pris individuellement, confirmant un effet synergique.

Sur le plan pharmacocinétique, des composés majeurs du thym, tels que le terpinène-4-ol et le thymol, présentent une perméabilité optimale et n'inhibent pas la P-glycoprotéine (P-gp), ce qui suggère une bonne biodisponibilité orale. En ce qui concerne les composés du curcuma, notamment l'ar-turmerone et l'α-zingibérène, bien qu'ils présentent une perméabilité limitée à la barrière hémato-encéphalique (BBB), leur clairance modérée et leur demi-vie relativement courte favorisent un effet périphérique ciblé, tout en limitant le risque d'accumulation toxique.

D'un point de vue toxicologique, les deux extraits présentent un profil de sécurité favorable, avec une inhibition faible des canaux hERG et un risque réduit de toxicité hépatique et cardiaque. Toutefois, certains composés issus du curcuma, comme le β-sesquiphellandrène, peuvent présenter un potentiel hépatotoxique à fortes doses, ce qui justifie une vigilance particulière.

En conclusion, l'association de *Thymus vulgaris* et *Curcuma longa* illustre de manière pertinente le potentiel thérapeutique des synergies végétales. Cette combinaison offre une approche naturelle, efficace et à faible toxicité pour la gestion du stress oxydatif. Néanmoins, malgré ces résultats prometteurs, des études complémentaires, incluant des essais in vivo et cliniques, demeurent indispensables afin de valider la stabilité pharmacologique et l'innocuité de cette association à long terme. Cette étude ouvre ainsi des perspectives intéressantes pour le développement de formulations pharmaceutiques naturelles à visée antioxydante.

Perspectives

Les résultats obtenus ouvrent la voie à plusieurs axes de recherche prometteurs. Tout d'abord, la validation in vivo des effets antioxydants et pharmacocinétiques observés in vitro demeure une étape cruciale pour confirmer la pertinence thérapeutique de cette synergie. L'exploration d'autres ratios d'extraits pourrait également permettre d'optimiser l'activité biologique et de minimiser les effets indésirables. Par ailleurs, l'intégration de cette combinaison dans des systèmes de délivrance ciblée, tels que les nanoparticules ou les liposomes, pourrait améliorer la biodisponibilité des composés moins perméables. La caractérisation fine des interactions moléculaires entre les composants du thym et du curcuma, via la modélisation moléculaire avancée, offrirait une meilleure compréhension des mécanismes d'action synergiques. En outre, l'étude de la stabilité physico-chimique du mélange dans des formulations solides ou liquides est essentielle pour le développement industriel. L'évaluation de la réponse immunitaire et des interactions possibles avec d'autres médicaments doit aussi être envisagée. À long terme, cette association végétale pourrait être intégrée dans des stratégies de prévention ou d'accompagnement thérapeutique des maladies liées au stress oxydatif, comme les pathologies cardiovasculaires ou neurodégénératives. Enfin, une étude de l'impact de cette combinaison sur le microbiote intestinal pourrait révéler des bénéfices métaboliques additionnels.

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Annexes

Annex 1

Thymus vulgaris

❖ Santolina triene

ADMETlab 2.0

CC(=CC(C=C)C(=C)C)C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	136.13	Contain hydrogen atoms. Optimal:100~600
Volume	173.607	Van der Waals volume
Density	0.784	Density = MW / Volume
nHA	0	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	3	Number of rotatable bonds. Optimal:0~11
nRing	0	Number of rings. Optimal:0~6
MaxRing	0	Number of atoms in the biggest ring. Optimal:0~18
nHet	0	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	3	Number of rigid bonds. Optimal:0~30
Flexibility	1.0	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	0.0	Topological Polar Surface Area. Optimal:0~140
logS	-3.1	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.736	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.23	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.522	●	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34

SAscore	4.128	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.4	🔴	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	3.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	1.7	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	🟢	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	🔴	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.484	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.2e-05	🟢	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20×10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.083	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor

Pgp-substrate	0.003	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.004	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.767	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.065	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	86.20%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	2.477	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.363	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	4.538%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.69	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.925	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.378	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.904	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.071	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.455	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.043	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.5	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

CYP3A4 inhibitor	0.366	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.376	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	5.062	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.237	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

1. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.011	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.683	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.027	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.113	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.032	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.657	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.033	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.

Carcinogen city	0.175	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.055	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.764	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.
Respiratory Toxicity	0.512	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants The output value is the probability of being toxic.

7. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	2.47	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	2.897	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.346	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	6.37	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

8. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.003	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.003	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.015	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.004	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.108	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.053	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

NR-PPAR-gamma	0.003	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.064	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.005	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.782	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.077	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.004	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

9. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **THYMOL**

ADMETlab 2.0

CC1=CC(=C(C=C1)C(C)C)O

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	150.1	Contain hydrogen atoms. Optimal:100~600
Volume	173.841	Van der Waals volume
Density	0.863	Density = MW / Volume
nHA	1	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	Number of hydrogen bond donors. Optimal:0~7
nRot	1	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	1	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	6	Number of rigid bonds. Optimal:0~30
Flexibility	0.167	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	20.23	Topological Polar Surface Area. Optimal:0~140
logS	-2.147	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.153	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.427	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.652	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	1.829	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize

Fsp3	0.4	🔴	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	7.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	0.35	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	🟢	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	🔴	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	1 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.387	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.4e-05	🟢	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.006	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.006	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate

HIA	0.006	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.918	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.975	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	93.89%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	2.469	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.814	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	7.503%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.922	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.951	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.765	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.831	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.491	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.874	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.811	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.886	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.192	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.

CYP3A4 substrate	0.454	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	9.444	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.682	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.011	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.032	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.137	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.053	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.276	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.327	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.253	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.287	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.82	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.

Eye Irritation	0.985	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.603	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	1.232	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.803	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	4.159	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	4.67	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.009	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.003	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.014	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.007	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.193	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.098	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.004	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-ARE	0.036	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.006	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

1. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	0 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **Borneole**

ADMETlab 2.0

C[C@]12CC[C@H](C1(C)C)C[C@H]2O

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	154.14	Contain hydrogen atoms. Optimal:100~600
Volume	173.194	Van der Waals volume
Density	0.89	Density = MW / Volume
nHA	1	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	Number of hydrogen bond donors. Optimal:0~7
nRot	0	Number of rotatable bonds. Optimal:0~11
nRing	2	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	1	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	8	Number of rigid bonds. Optimal:0~30
Flexibility	0.0	Flexibility = nRot /nRig
Stereo Centers	3	Optimal: ≤ 2
TPSA	20.23	Topological Polar Surface Area. Optimal:0~140
logS	-1.836	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	2.61	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	2.486	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.567	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	4.28	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize

Fsp3	1.0	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	37.8	●	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	2.542	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Accepted	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.442	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	2e-05	●	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20×10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.008	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.03	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate

HIA	0.003	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.109	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.188	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	61.56%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	1.025	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.295	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	51.67%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.067	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.37	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.056	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.882	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.038	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.682	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.006	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.447	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.028	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.

CYP3A4 substrate	0.229	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	10.66	●	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.361	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.056	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.141	●	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.03	●	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.008	●	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.285	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.589	●	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.713	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.446	●	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.982	●	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.

Eye Irritation	0.97	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.949	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	0.823	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	2.953	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	3.342	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	3.927	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.377	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.021	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.003	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.025	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.142	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.032	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.018	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.03	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-ATAD5	0.012	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.034	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.213	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.012	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **Himachalane**

ADMETlab 2.0

CC1=C[C@H]2C(=C(CCCC2(C)C)C)CC1

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	204.19	Contain hydrogen atoms. Optimal:100~600
Volume	245.61	Van der Waals volume
Density	0.831	Density = MW / Volume
nHA	0	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	0	Number of rotatable bonds. Optimal:0~11
nRing	2	Number of rings. Optimal:0~6
MaxRing	11	Number of atoms in the biggest ring. Optimal:0~18
nHet	0	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	12	Number of rigid bonds. Optimal:0~30
Flexibility	0.0	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	0.0	Topological Polar Surface Area. Optimal:0~140
logS	-5.887	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	5.978	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	4.65	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.494	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.658	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize

Fsp3	0.733	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	33.0	●	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	2.627	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.616	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.4e-05	●	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20×10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.992	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.001	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate

HIA	0.004	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.966	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+

$F_{30\%}$	0.618	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	96.34%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	6.102	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.021	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	2.047%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.42	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.56	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.531	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.833	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.511	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.949	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.036	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.407	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.262	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.

CYP3A4 substrate	0.229	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	3.539	🔴	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.114	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.008	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.121	🟢	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.081	🟢	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.006	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.026	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.125	🟢	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.057	🟢	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogenicity	0.033	🟢	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.06	🟢	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.

Eye Irritation	0.891	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.834	●	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	3.174	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	4.34	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	6.843	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	6.556	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.015	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.004	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.014	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.052	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.084	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.021	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.012	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-ARE	0.07	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.003	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-HSE	0.262	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.437	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.003	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **Terpinin-4-ol**

ADMETlab 2.0

CC1=CC(=C(C=C1)C(C)C)O

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	150.1	Contain hydrogen atoms. Optimal:100~600
Volume	173.841	Van der Waals volume
Density	0.863	Density = MW / Volume
nHA	1	Number of hydrogen bond acceptors. Optimal:0~12
nHD	1	Number of hydrogen bond donors. Optimal:0~7
nRot	1	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	1	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	6	Number of rigid bonds. Optimal:0~30
Flexibility	0.167	Flexibility = nRot /nRig
Stereo Centers	0	Optimal: ≤ 2
TPSA	20.23	Topological Polar Surface Area. Optimal:0~140
logS	-2.147	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.153	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.427	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.652	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	1.829	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.4	🔴	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.

MCE-18	7.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	0.35	-	■ Natural product-likeness score. This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	🟢	■ MW ≤ 400; logP ≤ 4 Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	🔴	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	1 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.387	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.4e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.006	🟢	■ Category 1: Inhibitor; Category 0: Non-inhibitor; The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.006	🟢	■ Category 1: substrate; Category 0: Non-substrate; The output value is the probability of being Pgp-substrate
HIA	0.006	🟢	■ Human Intestinal Absorption Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

$F_{20\%}$	0.918	🔴	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.975	🔴	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	93.89%	🔴	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	2.469	🟢	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.814	🔴	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	7.503%	🟢	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.922	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.951	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.765	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.831	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.491	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.874	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.811	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.886	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.192	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.454	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	9.444	●	■ Clearance ▌High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.682	-	▌Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ▌The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.011	●	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.032	●	■ Human Hepatotoxicity ▌Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.137	●	■ Drug Induced Liver Injury. ▌Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.053	●	▌Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.276	●	■ Category 0: low-toxicity; Category 1: high-toxicity; ▌The output value is the probability of being highly toxic.
FDAMDD	0.327	●	■ Maximum Recommended Daily Dose ▌Category 1: FDAMDD (+); Category 0: FDAMDD (-) ▌The output value is the probability of being positive.
Skin Sensitization	0.253	●	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ▌The output value is the probability of being sensitizer.
Carcinogen city	0.287	●	▌Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.82	●	■ Category 1: corrosives ; Category 0: noncorrosives ▌The output value is the probability of being corrosives.
Eye Irritation	0.985	●	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.603	●	▌Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	1.232	▌Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.803	▌Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	4.159	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	4.67	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.009	●	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.003	●	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.014	●	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.007	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.193	●	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.098	●	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.004	●	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.036	●	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.006	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.179	🟢	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.304	🟠	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.011	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	0 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

Annex 2

Curcuma longa

❖ **α -phellandrene**

ADMETlab 2.0

CC1=CCC(C=C1)C(C)C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	136.13	Contain hydrogen atoms. Optimal:100~600
Volume	167.687	Van der Waals volume
Density	0.812	Density = MW / Volume
nHA	0	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	1	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	0	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	6	Number of rigid bonds. Optimal:0~30
Flexibility	0.167	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	0.0	Topological Polar Surface Area. Optimal:0~140
logS	-3.985	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.857	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.415	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.519	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.505	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize

Fsp3	0.6	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.
MCE-18	13.5	●	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	2.835	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	●	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	●	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	●	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Rejected	●	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.383	●	Optimal: higher than -5.15 Log unit
MDCK Permeability	2.4e-05	●	■ low permeability: < 2×10^{-6} cm/s ■ medium permeability: 2–20×10^{-6} cm/s ■ high passive permeability: > 20×10^{-6} cm/s
Pgp-inhibitor	0.001	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.013	●	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate

HIA	0.005	●	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+
$F_{20\%}$	0.014	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.146	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	92.01%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	2.963	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.835	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	7.747%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.258	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.471	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.178	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.93	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.142	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.337	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.059	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.832	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.274	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.

CYP3A4 substrate	0.639	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	12.66	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.617	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.024	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.76	🔴	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.014	🟢	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.011	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.038	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.723	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.94	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.344	🟡	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.183	🟢	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.

Eye Irritation	0.957	🔴	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.855	🔴	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	2.36	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.08	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	3.674	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	4.176	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.004	🟢	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.003	🟢	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.008	🟢	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.003	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.144	🟢	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.178	🟢	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.002	🟢	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.151	🟢	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-ATAD5	0.004	●	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.177	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.037	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.006	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **α-Turmerone**

ADMETlab 2.0

CC1=CCC(C=C1)C(C)CC(=O)C=C(C)C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	218.17	Contain hydrogen atoms. Optimal:100~600
Volume	257.684	Van der Waals volume
Density	0.847	Density = MW / Volume
nHA	1	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	4	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	1	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	8	Number of rigid bonds. Optimal:0~30
Flexibility	0.5	Flexibility = nRot /nRig
Stereo Centers	2	Optimal: ≤ 2
TPSA	17.07	Topological Polar Surface Area. Optimal:0~140
logS	-4.258	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	3.956	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.351	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.65	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	4.044	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.533	🟢	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.

MCE-18	17.391	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	2.922	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Accepted	🟢	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	🟢	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	1 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.563	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.9e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.847	🔴	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.002	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.014	🟢	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

$F_{20\%}$	0.239	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.016	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	93.80%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	1.246	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.33	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	4.412%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.137	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.811	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.679	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.926	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.339	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.684	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.06	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.893	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.481	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.632	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	14.305	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.804	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.018	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.834	🔴	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.024	🟢	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.007	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.041	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.922	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.969	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.527	🟠	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.029	🟢	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.754	🔴	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.914	🔴	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	1.281	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.247	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	4.347	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	4.022	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.017	🟢	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.011	🟢	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.005	🟢	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.006	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.211	🟢	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.37	🟠	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.007	🟢	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.613	🟠	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.005	🟢	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.365	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.074	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.277	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	2 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	1 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	3 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	2 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	1 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **α-Zingiberene**

ADMETlab 2.0

CC1=CC[C@H](C=C1)[C@H](C)CCC=C(C)C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	204.19	Contain hydrogen atoms. Optimal:100~600
Volume	251.53	Van der Waals volume
Density	0.812	Density = MW / Volume
nHA	0	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	4	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	0	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	7	Number of rigid bonds. Optimal:0~30
Flexibility	0.571	Flexibility = nRot /nRig
Stereo Centers	2	Optimal: ≤ 2
TPSA	0.0	Topological Polar Surface Area. Optimal:0~140
logS	-5.162	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	5.802	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	4.815	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.572	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	3.917	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.6	🟢	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.

MCE-18	15.167	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	3.202	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	🔴	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	🟢	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.653	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	2e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.802	🔴	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.012	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.018	🟢	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

$F_{20\%}$	0.959	🔴	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.695	🟠	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	96.81%	🔴	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	5.108	🟢	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.179	🟢	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	3.085%	🔴	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.795	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.679	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.555	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.922	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.436	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.702	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.404	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.77	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.729	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.465	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	14.814	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.306	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.08	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.929	🔴	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.02	🟢	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.008	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.041	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.603	🟠	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.976	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.239	🟢	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.092	🟢	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.91	🔴	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.721	🔴	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	2.936	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.375	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.002	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	5.448	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.018	🟢	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.008	🟢	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.004	🟢	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.011	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.16	🟢	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.302	🟠	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.003	🟢	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.264	🟢	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.006	🟢	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.305	🟠	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.342	🟠	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.023	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **ar-tumerone**

ADMETlab 2.0

CC1=CC=C(C=C1)C(C)CC(=O)C=C(C)C

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	216.15	Contain hydrogen atoms. Optimal:100~600
Volume	255.048	Van der Waals volume
Density	0.847	Density = MW / Volume
nHA	1	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	4	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	1	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	8	Number of rigid bonds. Optimal:0~30
Flexibility	0.5	Flexibility = nRot /nRig
Stereo Centers	1	Optimal: ≤ 2
TPSA	17.07	Topological Polar Surface Area. Optimal:0~140
logS	-4.617	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	4.11	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	3.748	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.695	●	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	2.637	●	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.4	●	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.

MCE-18	16.0	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	0.666	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	🔴	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	🟢	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	1 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.536	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.7e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.766	🔴	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.002	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.003	🟢	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

$F_{20\%}$	0.135	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.059	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	94.69%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	0.706	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.202	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	4.205%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.832	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.957	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.939	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.909	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.876	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.881	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.234	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.871	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.366	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.729	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	10.658	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.371	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.021	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.292	🟢	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.259	🟢	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.015	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.029	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.73	🔴	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensiti zation	0.925	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.475	🟠	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.638	🟠	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.985	🔴	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.769	🔴	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	1.553	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	3.995	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	4.57	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	4.294	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.009	🟢	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.003	🟢	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.004	🟢	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.007	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.202	🟢	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.024	🟢	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.008	🟢	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.035	🟢	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.004	🟢	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.052	●	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.015	●	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.013	●	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	2 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	1 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	3 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	2 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	1 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status

❖ **β-Sesquiphellandrene**

ADMETlab 2.0

C[C@@H](CCC=C(C)C)[C@H]1CCC(=C)C=C1

1. Physicochemical Property

Property	Value	Comment
Molecular Weight	204.19	Contain hydrogen atoms. Optimal:100~600
Volume	251.53	Van der Waals volume
Density	0.812	Density = MW / Volume
nHA	0	Number of hydrogen bond acceptors. Optimal:0~12
nHD	0	Number of hydrogen bond donors. Optimal:0~7
nRot	4	Number of rotatable bonds. Optimal:0~11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal:0~18
nHet	0	Number of heteroatoms. Optimal:1~15
fChar	0	Formal charge. Optimal:-4 ~4
nRig	8	Number of rigid bonds. Optimal:0~30
Flexibility	0.5	Flexibility = nRot /nRig
Stereo Centers	2	Optimal: ≤ 2
TPSA	0.0	Topological Polar Surface Area. Optimal:0~140
logS	-5.43	Log of the aqueous solubility. Optimal: -4~0.5 log mol/L
logP	5.647	Log of the octanol/water partition coefficient. Optimal: 0~3
logD	4.852	logP at physiological pH 7.4. Optimal: 1~3

2. Medicinal Chemistry

Property	Value	Decision	Comment
QED	0.572	🔴	■ A measure of drug-likeness based on the concept of desirability; ■ Attractive: > 0.67; unattractive: 0.49~0.67; too complex: < 0.34
SAscore	4.144	🟢	■ Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. ■ SAscore ≥ 6, difficult to synthesize; SAscore <6, easy to synthesize
Fsp3	0.6	🟢	■ The number of sp3 hybridized carbons / total carbon count, correlating with melting point and solubility. ■ Fsp^3 ≥0.42 is considered a suitable value.

MCE-18	15.75	🔴	■ MCE-18 stands for medicinal chemistry evolution. ■ MCE-18≥45 is considered a suitable value.

NPscore	3.48	-	■ Natural product-likeness score. ■ This score is typically in the range from –5 to 5. The higher the score is, the higher the probability is that the molecule is a NP.
Lipinski Rule	Accepted	🟢	■ MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5 ■ If two properties are out of range, a poor absorption or permeability is possible, one is acceptable.
Pfizer Rule	Rejected	🔴	logP > 3; TPSA < 75 Compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	🔴	■ MW ≤ 400; logP ≤ 4 ■ Compounds satisfying the GSK rule may have a more favorable ADMET profile
Golden Triangle	Accepted	🟢	■ 200 ≤ MW ≤ 50; -2 ≤ logD ≤ 5 ■ Compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	-	Pan Assay Interference Compounds, frequent hitters, Alpha-screen artifacts and reactive compound.
ALARM NMR	0 alerts	-	Thiol reactive compounds.
BMS	0 alerts	-	Undesirable, reactive compounds.
Chelator Rule	0 alerts	-	Chelating compounds.

3. Absorption

Property	Value	Decision	Comment
Caco-2 Permeability	-4.535	🟢	Optimal: higher than -5.15 Log unit
MDCK Permeability	1.7e-05	🟢	■ low permeability: < 2 × 10^{-6} cm/s ■ medium permeability: 2–20 × 10^{-6} cm/s ■ high passive permeability: > 20 × 10^{-6} cm/s
Pgp-inhibitor	0.588	🟡	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.001	🟢	■ Category 1: substrate; Category 0: Non-substrate; ■ The output value is the probability of being Pgp-substrate
HIA	0.006	🟢	■ Human Intestinal Absorption ■ Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); The output value is the probability of being HIA+

$F_{20\%}$	0.012	●	■ 20% Bioavailability ■ Category 1: $F_{20\%}$+ (bioavailability < 20%); Category 0: $F_{20\%}$- (bioavailability ≥ 20%); The output value is the probability of being $F_{20\%}$+
$F_{30\%}$	0.006	●	■ 30% Bioavailability ■ Category 1: $F_{30\%}$+ (bioavailability < 30%); Category 0: $F_{30\%}$- (bioavailability ≥ 30%); The output value is the probability of being $F_{30\%}$+

4. Distribution

Property	Value	Decision	Comment
PPB	97.46%	●	■ Plasma Protein Binding ■ Optimal: < 90%. Drugs with high protein-bound may have a low therapeutic index.
VD	5.406	●	■ Volume Distribution ■ Optimal: 0.04-20L/kg
BBB Penetration	0.27	●	■ Blood-Brain Barrier Penetration ■ Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
Fu	2.797%	●	■ The fraction unbound in plasms ■ Low: <5%; Middle: 5~20%; High: > 20%

5. Metabolism

Property	Value	Comment
CYP1A2 inhibitor	0.879	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.355	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.377	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.859	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.354	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.382	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.031	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.308	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.534	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.454	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.

6. Excretion

Property	Value	Decision	Comment
CL	13.401	🟢	■ Clearance ■ High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg
$T_{1/2}$	0.219	-	■ Category 1: long half-life ; Category 0: short half-life; ■ long half-life: >3h; short half-life: <3h ■ The output value is the probability of having long half-life.

7. Toxicity

Property	Value	Decision	Comment
hERG Blockers	0.091	🟢	■ Category 1: active; Category 0: inactive; ■ The output value is the probability of being active.
H-HT	0.817	🔴	■ Human Hepatotoxicity ■ Category 1: H-HT positive(+); Category 0: H-HT negative(-); ■ The output value is the probability of being toxic.
DILI	0.388	🟠	■ Drug Induced Liver Injury. ■ Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.022	🟢	■ Category 1: Ames positive(+); Category 0: Ames negative(-); ■ The output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.027	🟢	■ Category 0: low-toxicity; Category 1: high-toxicity; ■ The output value is the probability of being highly toxic.
FDAMDD	0.457	🟠	■ Maximum Recommended Daily Dose ■ Category 1: FDAMDD (+); Category 0: FDAMDD (-) ■ The output value is the probability of being positive.
Skin Sensitization	0.967	🔴	■ Category 1: Sensitizer; Category 0: Non-sensitizer; ■ The output value is the probability of being sensitizer.
Carcinogen city	0.755	🔴	■ Category 1: carcinogens; Category 0: non-carcinogens; ■ The output value is the probability of being toxic.
Eye Corrosion	0.402	🟠	■ Category 1: corrosives ; Category 0: noncorrosives ■ The output value is the probability of being corrosives.
Eye Irritation	0.959	🔴	■ Category 1: irritants ; Category 0: nonirritants ■ The output value is the probability of being irritants.

Respiratory Toxicity	0.9	🔴	■ Category 1: respiratory toxicants; Category 0: respiratory nontoxicants ■ The output value is the probability of being toxic.

8. Environmental toxicity

Property	Value	Comment
Bioconcentration Factors	2.832	■ Bioconcentration factors are used for considering secondary poisoning potential and assessing risks to human health via the food chain. ■ The unit is –log10[(mg/L)/(1000*MW)]
IGC_{50}	4.119	■ Tetrahymena pyriformis 50 percent growth inhibition concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}FM$	5.484	■ 96-hour fathead minnow 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]
$LC_{50}DM$	5.492	■ 48-hour daphnia magna 50 percent lethal concentration ■ The unit is –log10[(mg/L)/(1000*MW)]

9. Tox21 pathway

Property	Value	Decision	Comment
NR-AR	0.524	🟠	■ Androgen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AR-LBD	0.189	🟢	■ Androgen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-AhR	0.008	🟢	■ Aryl hydrocarbon receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-Aromatase	0.103	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER	0.328	🟠	■ Estrogen receptor ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-ER-LBD	0.767	🔴	■ Estrogen receptor ligand-binding domain ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
NR-PPAR-gamma	0.013	🟢	■ Peroxisome proliferator-activated receptor gamma ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ARE	0.93	🔴	■ Antioxidant response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-ATAD5	0.005	🟢	■ ATPase family AAA domain-containing protein 5 ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

SR-HSE	0.934	🔴	■ Heat shock factor response element ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-MMP	0.331	🟠	■ Mitochondrial membrane potential ■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.
SR-p53	0.071	🟢	■ Category 1: actives ; Category 0: inactives; ■ The output value is the probability of being active.

10. Toxicophore Rules

Property	Value	Comment
Acute Toxicity Rule	0 alerts	■ 20 substructures ■ acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alerts	■ 117 substructures ■ carcinogenicity or mutagenicity
NonGenotoxic Carcinogenicity Rule	0 alerts	■ 23 substructures ■ carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	■ 155 substructures ■ skin irritation
Aquatic Toxicity Rule	1 alerts	■ 99 substructures ■ toxicity to liquid(water)
NonBiodegradable Rule	0 alerts	■ 19 substructures ■ non-biodegradable
SureChEMBL Rule	0 alerts	■ 164 substructures ■ MedChem unfriendly status