

Chemical Synthesis of Various Limonene Derivatives – A Comprehensive Review

Sadia Kousar¹, Farwa Nadeem^{1*}, Oli Khan² and Aimen Shahzadi¹

¹Department of Chemistry, University of Agriculture, Faisalabad-38040-Pakistan and ²Department of Botany, Bangabasi College, Kolkata, India

Abstract

Limonene (p-mentha-1,8-diene) is the most abundant terpene naturally found in essential oil of many aromatic plants. Present review is planned to compile the scattered available information about structurally related potential derivatives of limonene along with their natural or artificial synthetic pathways, their industrial applications, fruitful market products and their biological activities. The 1,2-limonene oxide, carveols and carvone are the monoterpenes that can be synthesized by using iodosylbenzene as terminal oxidant and known to have anti-yeast and anti-microbial potentials. Similarly, β -amino alcohol based derivatives can be prepared by regioselective aminolysis of limonene that show excellent anti-leishmanial potentials and widely used as catalyst in enantioselective additions and gelatin preparations. Furthermore, aerosols are also formed through ozonolysis of various stereoisomers of limonene and benzaldehyde thio-semicarbazone are prepared by regioselective additions of HSCN that shows anti-leishmanial and anti-tumoral activities thus used for preparation of copper based complexes along with 1,3,4-thiadiazole. The p-cymene is prepared by derivatization of α -limonene in presence of lead impregnated silica via disproportionation reaction that shows anti-bacterial and anti-inflammatory potentials and extends its applications towards food and flavor industry. Synthesis of limonene bisphosphonate is practiced via chemical modification with dialkyl phosphite that is known to have number of applications in tribology as lubricant and in bisphosphonate therapy. Synthesis of p-menthane through catalytic hydrogenation of limonene under high pressure generally yields end products that exhibit physiological effects and found applications as synthetic intermediates.

Key words: Limonene, p-mentha-1,8-diene, 1,2-limonene oxide, carveols, carvone, β -amino alcohol, ozonolysis, regioselective additions, 1,3,4-thiadiazole, p-cymene, p-menthane

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1. Introduction

Essential oils are volatile, aromatic, complex compounds mainly terpenes and terpenoids in nature that are produced as secondary metabolites in aromatic plants [1]. Low molecular weight mixtures of aromatic and aliphatic constituents are used in agronomic, perfume, sanitary, cosmetic, and food industry because of their insecticidal, anti-fungal and anti-bacterial activities [2]. Over 3000 essential oil are being used in these industries for different purposes. Limonene is a naturally occurring cyclic monoterpene, an olefin hydrocarbon (C₁₀H₁₆), found in the essential oils of a number of plants. The (+)-limonene is one of the most important and commonly occurring terpenes in the flavor and fragrance industry. More than 300 plant raw materials ranging from very diverse species of orange and lemon to fir have been used by now for the extraction of essential oils containing limonene. Other than plants, the presence of limonene in headspace of microbes has also been detected in extremely small amounts. Yeast and bacteria are also

being genetically engineered for the production of limonene at commercial scale [3].

A great variety of food products like soft drinks, chewing gums, non-alcoholic beverages and candies contain (+)-limonene as a flavoring compound. Because of its fragrance, it has also been frequently used in perfumes and cleaning products used in household. Relatively high prices of limonene are due to quality requirements that need to be maintained for limonene to be used as a flavor and fragrant ingredient. Hydroxyl radical reaction with limonene produces products such as 4-acetyl-1-methylcyclohexene, keto-aldehyde, formaldehyde, 3-oxobutanal, glyoxal and a C₁₀ dicarbonyl. These products, formic acid and C₈ and C₉ carboxylic acids may also be synthesized as a result of reaction with ozone. Ozonolysis of limonene may also result in production of bis-(hydroxymethyl) peroxide that is a precursor to hydroxymethyl hydro peroxide and hydrogen peroxide hydroxymethyl hydro peroxide. Similarly, bis (hydroxymethyl) peroxide and hydrogen peroxide are also some derivatives of

limonene produced by its ozonolysis. The ozonolysis of d-limonene in the absence of light results in the formation of 4-acetyl-1-methylcyclohexene and formaldehyde. The oxides of nitrogen are known to produce aerosols and also lower molecular weight products like formic acid, acetaldehyde, formaldehyde, peroxyacetyl nitrate and acetone. Carvone another derivative of limonene has antimicrobial and anti-fungal activities and is used as an ingredient of food and pharmaceutical industries. For its importance as a raw material in organic synthesis, limonene usually has high prices in chemical industry [4].

Some monoterpenes along with carvone were found to be able to reduce sprout growth in potatoes without showing any negative effects on potato quality. Secondary organic aerosol formation is also done by ozonolysis of limonene [5]. The aerosol particles are hygroscopic in nature which causes the increase in size of particles under different moisture conditions according to amount of moisture absorbed [6]. Thiosemicarbazone is another derivative of limonene that is prepared by using the method of Sah and Daniel. Anti-fungal properties have also been observed in thiosemicarbazone. Its anti-microbial activity provides the proof of the assumption that it has ability to convert traces of metal into chelates. Thiosemicarbazone has also shown high anti-tumor potentials [7].

The p-cymene is a derivative of limonene that appears to be a worthy intermediate used for their medicinal value in pharmaceutical industries and for the synthesis of pesticides, fungicides and as flavoring agent. Some recent researches or investigations have shown that p-cymene has considerable potential to act as analgesic and anti-inflammatory agent in mice. The p-cymene is also the actual cause of increased anti-bacterial potential of certain plants whose essential oils are rich in this derivative of limonene [8]. Limonene bisphosphonate, a derivative of limonene have potential applications as lubricant additives and as anti-friction agent. The tribological properties of limonene bisphosphonate derivatives were investigated as neat and also as additives in PAO₆ and HOSuO blends [9]. Hydrogenation of limonene at high-pressure in carbon dioxide is an authentic procedure to obtain appreciable yields of important limonene derivatives. The 3-substituted-p-menthanes are used as cold receptor stimulants in the consumer products of this invention may be readily prepared by conventional methods. The monoterpene of the p-menthane family are widespread in nature and are well-known as flavoring ingredients and as valuable synthetic intermediates.

2. Chemical Synthesis of Various Limonene Derivatives

Limonene naturally occurs as a mixture of its two optically active isomers as d-limonene and l-limonene and the racemic mixture Dipentene that is a colourless liquid at room temperature. Its commercial purity is about 90–98%.

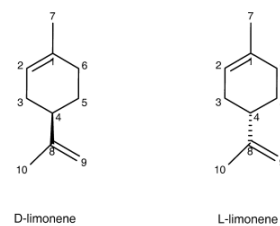


Fig 1 Chemical structure of (a) d-limonene and (b) l-limonene. Being most abundant naturally occurring monoterpene, the enantiomers of limonene are found in a number of plant's essential oil i.e. l-limonene is a constituent of essential oils of trees and herbs like *Mentha* spp., while d-limonene is frequently found in peel oil of oranges and lemons and in the oil of caraway [10]. Recently, biotechnological methods for the production of limonene are gaining importance. Yeast, bacteria and other microbes are being genetically engineered for the synthesis of limonene as it is found that the head space of such microbes are suitable of the generation of required product. Some plants are also experimented by introducing limonene producing genes. A higher yield of limonene can easily be obtained by such genetically engineered plants [11]. Recently, [12] reviewed the biosynthesis and biotechnology of limonene for flavor and fragrance application.

Limonene has a number of different applications based on volume, quality requirements, and price [3]. The (+)-limonene is an important ingredient of citrus-flavored products such as soft drinks and candy and also used as a fragrance imparting compound in perfumes and household cleaning products [13]. As a flavor and fragrance ingredient, better quality assurance causes an increase in price of limonene. The two chiral isomers have different properties as (+)-limonene (also called R-limonene or d-limonene) has a pleasant, orange-like odor whereas the (–)-form (also called S-limonene or l-limonene) has a more harsh turpentine-like odor with lemon note. Other applications of limonene are relatively less highlighted. For example, it is used as insecticide and is being investigated for medical applications due to its anti-microbial and anti-cancer properties [14]. The potential of limonene to be used at large scale is still under investigation. For example, the use of limonene in substantially large volumes as a solvent in place of xylene (BTEX), ethylbenzene, toluene and benzene in oil and gas industry is being tested. The d-limonene is also a functionally active anti-tumor agent whose chemo-preventive activity against spontaneous and chemically-induced rodent mammary, skin, liver, lung and fore stomach cancers as well as rats' oncogene-induced rat mammary cancer. Chemo-preventive effects of limonene in rat mammary carcinogenesis model were prominent for both initiation and promotion. Limonene also has chemotherapeutic activity against rat mammary tumors, causing complete regression of >80% of established DMBA- or NMU-induced mammary carcinomas [15].

The availability of two double bonds and possibility of hydroxylation makes the structure of limonene suitable for its conversion into its derivatives. Such structural transformations play an important role in diversifying the range of applications of

limonene. Some limonene derivatives also occur naturally for example oxidized forms of limonene are known as flavoring ingredient. The (-)-menthol is found in mentha oil and is mint flavoring agent [12]. Furthermore, addition based chemical modifications like hydrogenation of limonene are also important. Limonene after complete hydrogenation, is added to diesel, to control its cloud point and viscosity [16]. Modified forms of limonene attract high price of the product; for example limonene is sold at 9–10 \$/kg, while (-)-menthol makes 15–40 \$/kg. Applications of limonene in chemical industry other than its use as fragrance and flavor ingredient did not gain noticeable importance as evident in scientific literature. However, biomaterials are emerging as a valuable replacement of conventionally used, petrochemical-based materials. A number of biomaterials can be synthesized or derived from limonene.

Polylimonene (piccolyte C₁₁₅) is a polymer derived from limonene and is synthesized from citrus oil. It has a number of applications varying from its use as a resin in adhesives materials to a food packing thermoplastic. The polymer is also used in electro-conductive parts and as a masticatory agent in chewing gum. Chemical composition of terpenes resins is quite appropriate for its usage in medicine industry as drug delivery vehicle. Epoxidation of limonene results in production of limonene monoepoxide or di-epoxide which can be used as monomer units for production of long polymer chains. Metal coatings, varnishes and printing inks are synthesized by limonene epoxide polymers. Fatty-acid based polyesters of limonene are synthesized through polymerization of limonene with two thiols [17]. Synthases are the enzymes which manufacture limonene within the micro-organisms and plants. Synthases that convert GPP to limonene have been identified in twenty seven different plant species from nine plant families. Most limonene synthases are enantio-specific in nature i.e. either one of the isomer is its final product and this can differ even within the family e.g., in the Lamiaceae family, limonene synthase from *Perilla frutescens* makes predominantly (-)-limonene [18]. Similarly, few limonene synthases exclusively synthesize limonene while others produce several products out of which one is limonene.

2.1 Synthesis of Carvone, Carveols and 1,2-Limonene Oxide

Monoterpene are present in most essential oils. In nature, they are of fundamental importance in flavor and fragrance industries. They are used in perfumes and as food and beverage flavors. In addition to that, they also have great importance as raw materials for organic synthesis. Therefore, they usually command high prices in chemicals market. However, R-limonene, which is the main component of the orange essential oil, has a low price and is thus a particularly important substrate for the production of much higher value products such as carvone, carveols and 1,2-limonene oxide.

2.1.1 Chemical Pathway

Reactions were undertaken by using iodobenzene as terminal oxidant between 298 and 303 K. The catalysts were used in sub-stoichiometric amounts having following ratios: catalyst: oxidant: substrate of 0.05:1:1. Experimental results

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obtained in organic solvents are presented in Table 2, 3 and 4 which shows the results of the reaction in super critical carbon dioxide (SCCO₂).

The use of SCCO₂ in the metal (Salen)-catalyzed oxidation of limonene led to atleast comparable selectivities and conversions relative to those obtained in organic (and environmentally more harmful) solvents. The best conversions and selectivities in SCCO₂ were obtained at higher densities (around 0.7 g cm⁻³). Thus it has been demonstrated that SCCO₂, a solvent compatible with green technology, can be used successfully in catalytic oxidations mediated by metal (Salen) complexes. The use of different solvents at room temperature led to differences in conversion and selectivity. These effects were related to the acid-base properties of the solvents and their role in the solvation of intermediates in the catalytic cycle [4].

2.1.2 Activity of Carvone, Carveols and 1,2-Limonene Oxide

The applicants found that carveol is principal anti-yeast and anti-fungal compound that is generated by the oxidation of limonene and is obtained in effective concentrations. Carveols is a monocyclic monoterpene with the following chemical formula:

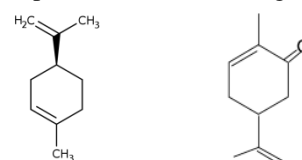


Fig 3 Chemical structure of (a) Carveol and (b) Carvone

The important component of orange essential oil, R-limonene is the main substrate used for the manufacturing of its derivatives such as 1,2-limonene oxide, carvone and carveols which are very costly as compared to it [19]. Carvone is an unsaturated monoterpene ketones and due to the presence of a chiral center, it can be biosynthesized in either its R-(-)-carvone or S-(+)-carvone enantiomer by some plants. Carvone has anti-microbial and anti-fungal properties and is used in the food and pharmaceutical industries [19].

2.1.2.1 Anti-Yeast Activity

Carveols are known for their anti-yeast and anti-fungal activities. Although, the exact way of killing fungi or yeast is not clearly known yet but it is thought that carveols cause the lysis of cell membrane of these organisms which results in death. Carvone is an important constituent of pharmaceutical and food industry because of its anti-microbial and anti-fungal properties. In practice, any surface on which it is desirable to kill or prevent the growth of yeast or fungi, is treated with effective concentrations of carveols to kill yeast, or fungicidal concentrations of carveols to kill fungi by swabbing, wiping, painting, washing, brushing, spraying or any other direct application technique.

2.1.2.2 Anti-Fungal Activity

Carvone has anti-microbial and anti-fungal properties and is used in pharmaceutical and food industries. In contrast, R-(-)-carvone and S-(+)-carvone enantiomers were less potent than the essential oils and exhibited no significant enantioselectivity for both, micro plus larvae and engorged females. The efficiency of carvone against *Aedes aegypti* larvae and females [20] has

been demonstrated. Such differences are probably explained by the evaluation in different species in addition to different mechanisms of action.

2.1.3 Application and Uses

Carveol oil is used as anti-yeast, anti-fungal and anti-bacterial agent and is commercially available. Recent studies have proven the action of carveols as anti-fungal and anti-microbial agent as the viscous liquid would readily cling to the surface to which it is applied such as glass, metal, wood, cloth, rope, book covers, paper, cement, ceramics, paint, plastic, plant surfaces, skin, mucus membranes and teeth leaving an oily film. Because of its hydrophobic nature, it is used in gels, suppositories, paints, sprays, aerosols, tampons, toothpastes, solutions, emulsions, soaps, scrubs, mouth-washes or anti-septics and applied anywhere it is desirable to kill or prevent the growth of yeast or fungi.

2.1.3.1 Sprout Inhibitor

Potatoes are usually used for consumption and for the manufacturing of other processed food products. Potatoes grow sprouts when stored for a certain time period. Sprouting occurs after a specific time period that differs from a minimum of after harvesting to an optimum of a certain storage period [21]. The optimum of this storage depends upon the temperature at which potatoes are stored. If potatoes have to be stored for longer periods of time, then sprouting must be controlled so that the loss of material to the tubers and excessive loss of water can be prevented. Carvone (50-60%) and S-(+)-limonene (35-45%) were found considerably active for prevention of sprouting in potatoes but their usage is tested only at small-scale for short time periods (max. 3 to 4 months) at constant temperature whereas carvone did not show appreciable sprout suppression.

2.2 Synthesis of β -Amino Alcohol Derivatives

Seven different limonene β -amino alcohol derivatives were prepared regioselectively through limonene-oxide aminolysis by N-alkyl and N-aryl amines. Considerably good yields of derivatives were obtained by this method.

2.2.1 Chemical Pathway

For the synthesis of amino alcohols, 1-methyl-2-(allylamino)-4-isopropenyl-cyclohexanol **3a**: R-(+)-limonene oxide **6** (19.7 mmol), water (0.55 mL) and allylamine (56.4 mmol) were stirred for 24 h at 100°C. The obtained amino alcohol product was purified by acid-base extraction and treated with CaCl_2 and drying was done in a rotatory evaporator as a final step. This process of chemical synthesis gave an appreciable percentage yield of 78%.

Synthesis of β -amino alcohols from epoxides through the process of aminolysis gave moderate to low percentage yields of products. R-(+)-limonene oxide **2** was employed, stirred with one equivalent of amine (except for aniline, where it was necessary to use 2 equivalents) and three equivalents of water at reflux for 24 h to prepare the β -amino alcohols **3a-3g** (Fig 4) in moderate to good yield. Moreover, the synthesis of this epoxide from limonene [22] would add an avoidable step to the synthetic pathway.

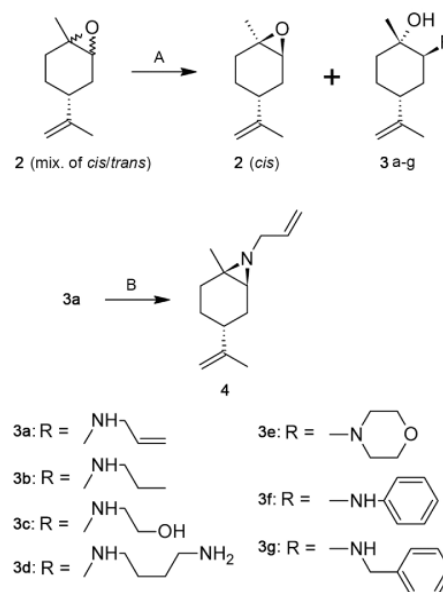


Fig 4 Amine (2 equivalent) and H_2O (3 equivalent) 80°C for 24h

2.2.2 Activity of β -Amino Alcohol

Regioselective synthesis of a series of seven different derivatives of limonene β -amino alcohol gave considerably good yields. Two of these derivatives showed noticeable efficacy against in vitro cultures of the *Leishmania (Viannia) braziliensis* promastigote form in the micro molar range. The activities found for **3b** and **3f** were about 100-fold more potent than the standard drug pentamidine, in the same test, while limonene did not display any activity.

2.2.2.1 Anti-Leishmanial Activity

Parasitic infestations cost a great number of lives all across the world especially in third world countries of Africa, Asia and Latin America. In these regions, economic and social impacts caused by such illnesses are quite high as the disease spreads as epidemics in huge masses of people. The protozoa genera are most effective and is responsible for the principal sicknesses, and leishmaniasis is one of the strictest parasitic diseases caused by multiple species of *Leishmania* [23]. Several β -amino alcohols derivatives were tested for their anti-leishmanial activity, out of which two of them were found more effective than pentamidine ($48.5 \pm 28.7 \mu\text{M}$) which is the standard drug used for this purpose, while the other derivatives were found more active than limonene. Synthesis of biologically compatible and active chemical compounds to be used as effective drug from naturally available biomaterials is an attractive and cost effective way to find new candidates. Currently, research investigations have been made to develop an authenticated mechanism of action for the production of compounds to treat anti-leishmanial activity.

2.2.3 Application and Uses

The β -amino alcohol derivatives have shown potential anti-leishmanial activity thus can be used as potential catalyst and found in various other applications owing to gelatinous nature.

2.2.3.1 Potential Catalyst

Chiral β -amino alcohols are used as promoters in enantioselective addition of dialkyl zinc to aldehydes which is done to introduce asymmetric carbon-carbon bond formation. Peptides constitute one of the most important families of compounds in chemistry and biology. Short peptides have found intriguing biological and synthetic application. Dehydrogenative coupling of β -amino alcohols results in the formation of both cyclic and linear peptides.

2.2.3.2 Gelation Property

Four new organic gelators which were of low molecular weight and chiral in nature, namely bis (amino alcohol) oxalamides (1-4: amino alcohol leucinol, valinol, phenylglycinol and phenylalaninol) have been prepared. Their gelation ability in various mixtures and organic solvents was determined. A comparison of them with related bis (amino acid) oxalamides gelators was also established.

2.3 Aerosol Formation by Ozonolysis

Due to high emission rates from household solvents and from biogenic sources, the doubly unsaturated monoterpene, d-limonene has a significantly high aerosol formation potential. It is through gas-phase reactions with OH, NO₃ and O₃ that the primary removal mechanism of d-limonene from the atmosphere produces non-volatile and semi-volatile compounds that can condense onto particulate matter (PM) and contribute to ambient secondary organic aerosol (SOA) and tropospheric ozone production.

2.3.1 Chemical Pathway

The structure of d-limonene contains two C=C double bonds, an internal and the other external which makes it an optimal substrate for ozonolysis. The two unequivalent double bonds will give two different O₃-limonene adducts which can produce four Criegee intermediates [24]. The reaction pathways of O₃ addition to the internal-ring C₁=C₂ double bonds are analyzed firstly. In the ER (1), adduct intermediate form which is Vander Waals complexes. The second addition channel of limonene with O₃ is the external-ring addition pathways, adding the O₃ molecule to the C₇=C₈ double bonds. Firstly, another Vander Waals complex, IM8 is formed. There are two isomers of adducts.

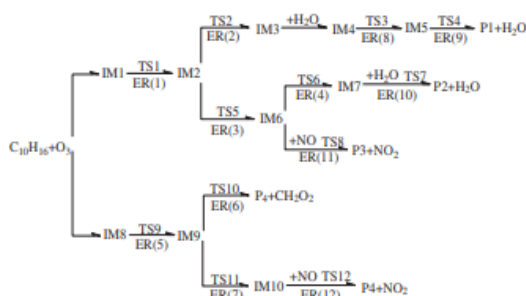


Fig 5 Reaction pathway for the reaction of limonene with O₃

2.4 Synthesis of Benzaldehyde Thiosemicarbazone

The synthesis of benzaldehyde thiosemicarbazone is of extreme commercial importance owing to the wide-ranging applications and excellent biological activities.

2.4.1 Chemical Pathway

The synthesis of thio-semi-carbazone 4-22 was initiated by chemo-selective and regio-selective addition of HSCN to exocyclic double bond of R-(+)-limonene in order to obtain the iso-thio-cyano-terpene with retaining of chiral integrity from original natural monoterpene. Compound 2 was then reacted with hydrazine providing thio-semi-carbazide. R-(+)-limonene thio-semi-carbazone 4-22 were obtained by condensation of equimolar amounts of thio-semi-carbazide 3 with different oxo compounds (aldehydes and ketones) in ethanol, using hydrochloric acid 10% as catalyst. The reaction was conducted until complete consumption of 3 occurred, leading to thio-semi-carbazone 4-22 in good yields (68-95%) after recrystallization from ethanol.

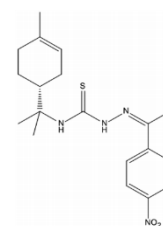


Fig 6 Structure of benzaldehyde thiosemicarbazone derived from limonene

2.4.2 Activity of Benzaldehyde Thiosemicarbazone

Thiosemicarbazone is important limonene derivative which has gained importance in pharmacological industry because of its wide ranging activities. A number of studies have reported the actions of thiosemicarbazone, including anti-viral, anti-bacterial anti-tumor, anti-oxidant, anti-fungal, anti-trypanosomal and anti-malarial effects [25]. Its versatility as a ligand and chemical stability under various reaction conditions has been reported. Benzaldehyde thiosemicarbazone is also an important intermediate during the preparation of several heterocyclic compounds, for example 1,3,4-thiadiazole. Anti-tumor activity of thiosemicarbazone is due to its inhibitive effect on the enzyme ribonucleoside diphosphate reductase (RDR) which is involved in the biosynthesis of deoxyribonucleic acid (DNA). Triapine, 3-aminopyridine-2-carboxaldehyde-thiosemicarbazone is a derivative known for its anti-cancer activity and is found as a promising candidate. Recently, the cytotoxic activity against different type of tumor cells such as lungs, prostate, ovary, pancreas and kidney is being test at laboratory levels. Other thiosemicarbazone derivatives which have structures similar to triapine might also be found biologically active because of the presence of aryl or alkyl groups on the carbon at the imines moiety [7].

2.4.2.1 Anti-Leishmanial Activity

Sicknesses related to leishmaniasis pose serious health problems in about 88 countries including mainly underdeveloped countries. To counteract this health problem, new and effective drug therapy discoveries are required to be made. Pentavalent anti-moniols are being used as first line treatment for cutaneous leishmaniasis but toxicity level of this drug hinders its usage. In spite of that, no better drug than pentavalent anti-moniols has been discovered till date that can excel it in terms of safety, cost effectiveness and most importantly in terms of efficacy [26].

2.4.2.2 Anti-Tumoral Activity

Cancer is one of the most lethal disorders posing highest death rate all over the world. In men, lung, stomach, melanoma and prostate cancers are found to be the most common types of cancer, while women suffer more from breast and uterus cancer. A high potential of anti-tumoral activity have been demonstrated in thiosemicarbazone. The enzyme ribonucleoside diphosphate reductase (RDR) can be inhibited by the action of thiosemicarbazone. This enzyme is involved in the biosynthesis of deoxyribonucleic acid (DNA). Monoterpene moieties, such as citronellal and citral, attached on the imine group of thiosemicarbazone showed appreciable anti-tumor activity against leukemia cells [7].

2.4.3 Application and Uses

Since the discovery by Domagk (I) of the anti-tubercular activity of thiosemicarbazone, several research investigations have been made on the pharmacology of this type of compounds and have been published. Thiosemicarbazone has also shown anti-fungal activities as it can prevent further growth of certain fungi. The microbial activity of thiosemicarbazone is a clue to their chelating ability where metal complexes are active ingredients. There is enough experimental proof that the formation of a toxic metal-organo complex is the actual reason for the fungicidal action shown by thiosemicarbazone.

2.4.3.1 Preparation of Copper Complex

In a recent study, thiosemicarbazone is demonstrated to give copper complexes. Some were colored solid compounds with very low solubility in water and organic solvents. The least soluble were the aliphatic ones.

2.4.3.2 Preparation of 1,3,4-Thiadiazole

Thiosemicarbazone have many applications as intermediates for the synthesis of important heterocyclic compounds and can be used to obtain 1,3,4-thiadiazole. The 1,3,4-thiadiazole is one of the most well-known compounds studied till date. It is widely used in the pharmaceutical, agricultural and chemical industries.

2.5 Synthesis of p-Cymene

The α -limonene is used as a naturally and abundantly available feedstock for commercial scale production of its derivatives such as p-cymene that is prepared in presence of Pd impregnated silica. As terpenes like limonene are produced largely in nature by several plants, it is a renewable source and can be commercially used. The α -limonene is a by-product obtained at large scale from pulp and paper industry as well as lemon and orange juice producing units. Over 50,000 tons of limonene is estimated to be produced every year only in citrus industry. Industrially, p-cymene synthesis is done by Friedel-Crafts alkylation of benzene or toluene. Use of solid heterogeneous catalyst for p-cymene synthesis is being implemented in place of traditionally used homogeneous liquid acid or base catalyst which makes the process of synthesis more toxic and less environment friendly [27].

2.5.1 Chemical Pathway

As a result of its dehydrogenation, α -limonene disproportionates into two of its derivatives such as p-cymene

and p-menthane. This conversion of limonene has been studied in an integral fixed bed reactor. The reaction conditions for the process were $\theta=300^\circ\text{C}$ pure hydrogen as carrier gas with a volumetric flow of 1.5 NL h^{-1} , 7 mL h^{-1} of liquid flow as starting material and a catalyst charge of 2g which was equal to a weight hourly space velocity (WHSV) of 3 h^{-1} and temperature was 200°C and 400°C . Both homogeneous and heterogeneous catalysts have been studied by researchers for the dehydrogenation reaction of limonene. With increasing the amount of catalyst, the selectivity to p-cymene decreases with an increase in the amount of p-menthane by-product. The conversion of α -limonene over silica based Pd catalysts provides p-cymene with yields over 95 wt%. The main by-products are p-menthane, when hydrogen is present in the carrier gas and p-menthadienes and p-menthene, when pure nitrogen is the carrier gas.

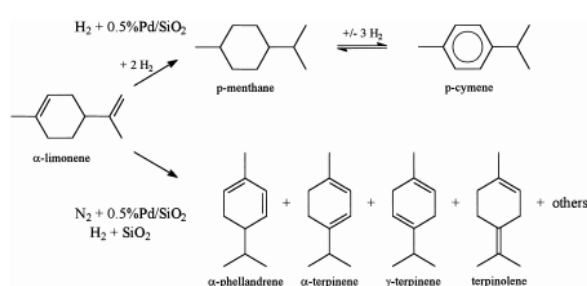


Fig 7 Chemical structure for the conversion of α -limonene to p-cymene

2.5.2 Activity of p-Cymene

The p-cymene (p-isopropyl toluene), a monoterpene related hydrocarbon is a naturally-occurring aromatic organic compound which is found in essential oils of more than 100 plants and in 200 foods (orange juice, oregano, carrots, butter, tangerine, nutmeg, grape fruit and almost every spice). The p-cymene plays important role in pharmaceutical industries as an intermediate. Its anti-fungal and pesticidal activities are also well known. The p-cymene, like limonene, is also used in food industry as a flavoring agent. Some research investigations have also demonstrated its analgesic and anti-inflammatory properties in mice. Due to their biological activities, their usage as drug delivery systems is under experimentation [28].

2.5.2.1 Anti-Bacterial Activity

Anti-bacterial activity of p-cymene is due to its ability to act as a substitutional impurity in the membranes of microorganisms which results in expansion of membrane and affects the membrane potential of intact cells. It does not influence the permeability/movement of substances across the membrane but the temperature and enthalpies of membrane are decreased [29]. The effect of p-cymene on protein synthesis machinery and mechanism and also on motility of cell has also been demonstrated. The proton motive force is affected which results in slower flagella movement. The anti-microbial activity of p-cymene is enhanced to appreciable levels when used along with compounds like carvacrol and polymyxin-B nano-peptide.

2.5.2.2 Anti-Inflammatory Activity

Biological activity of p-cymene or p-cymene/-CD complex as an anti-inflammatory agent was studied in the paw edema model. The p-cymene/-CD complex but not p-cymene, showed capability of suppressing the edema formation induced by carrageenan (1%), an effect observed at 2, 3 and 4 h after its administration. The p-cymene had effectiveness ($p < 0.05$) only in higher dose during the first 1 of evaluation.

2.5.3 Application of p-Cymene

A number of applications of p-cymene have been discussed in literature on the basis of their activities and other properties. It is widely used as an important ingredient of food and flavor industry. It is also known as an intermediate for the chemical synthesis of a number of important derivatives and other products.

2.5.3.1 Production of Thyme Oil

The p-cymene is the main constituent of thyme oil, contributing about 75% of its chemical composition. Thyme oil is known for its anti-bacterial properties which are actually imparted by its active component i.e. p-cymene. Almost all monoterpenes' essential oils are known to have anti-bacterial properties. Some research investigations have proved that the use of essential oils to combat pathogens is very helpful.

2.6 Synthesis of Limonene Bisphosphonate

Limonene bisphosphonates was synthesized in inert atmosphere by chemical modification of limonene with dialkyl phosphites of varying alkyl structures in the presence of free radical initiators. Both double bonds of limonene were made to react completely so that only di-adduct product, limonene bisphosphonate of the reaction can be obtained. Characterization of obtained product was done by GC-MS, FTIR and NMR (^1H , ^{13}C and ^{31}P) spectroscopy. The physical and tribological properties of bisphosphonate were investigated and demonstrated. The density and viscosity of alkyl bisphosphonate were found to be a function of the type of alkyl group (methyl, ethyl and n-butyl) attached. They also displayed improved oxidation stability but lower viscosity index and solubility in polyalphaolefin (PAO₆) and high oleic sunflower oil (HOSuO) base oils.

2.6.1 Chemical Pathway

The reactions involved in the synthesis of limonene bisphosphonate are described as a scheme in figure 8 which were performed in a round-bottom flask with magnetic stirrer. Nitrogen-filled balloon was used to maintain an inert atmosphere. The radical initiator used for the initiation of radical formation, was BPO, which has a half-life of ten hours and temperature was maintained at 125°C using thermocouple and heating mantle. The progress of the reaction was monitored using GC-MS and was stopped when the limonene double bonds had completely reacted.

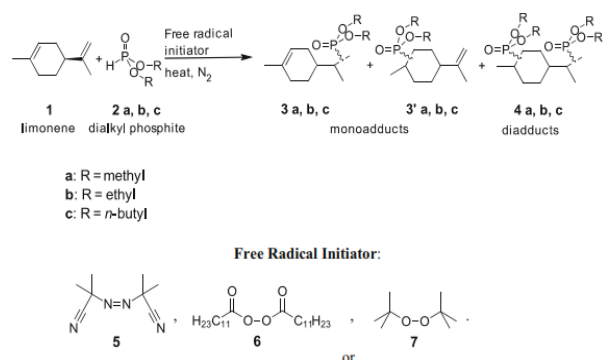


Fig 8 Chemical structure for the synthesis of limonene bisphosphonate

Excess phosphite is distilled first for the isolation of desired limonene bisphosphonate from reaction mixture. The remaining product mixture is then dissolved in hexanes and acidic residues are removed by extraction with saturated aqueous NaHCO_3 and dried over anhydrous Na_2SO_4 . The purified phosphonate product mixture is then isolated by removing the hexanes by distillation. The GC-MS, FTIR and NMR results confirmed the presence of both mono-phosphonate and bis-phosphonate in the reaction mixture.

2.6.2 Property of Limonene Bisphosphonate

Limonene bisphosphonate has a number of properties which makes it to play an important role in pharmaceutical industry. It has been used in therapy of osseous malignancies such as multiple myeloma and osteoblastic and osteolytic metastases and metabolic bone diseases [30].

2.6.2.1 Tribological Property

All three di-adducts produced in the reaction mixture showed improved extreme pressure weld point when tribological characterization of the neat modified oils on a four-ball tribometer were made. Only butyl di-adduct has shown significant values for anti-wear coefficient of friction (COF) and wear scar diameter (WSD). When added into base oils like PAO₆ and HOSuO at low concentrations, the limonene bisphosphonate also displayed improved COF and WSD values. An increase in polarity, insertion of heavy atoms (from PO_3) into the limonene structure and complete absence of unsaturation in limonene after its chemical modification into a new compound is the actual cause of change in physical and tribological properties.

2.6.3 Application of Limonene Bisphosphonate

Due to its unique chemical nature, limonene bisphosphonate has been recognized to use as lubricant additive in bisphosphonate therapy as described in detail below.

2.6.3.1 Lubricant Additive

Lubricants that are commonly available in the market are derived from fossil fuels and are petroleum based. A renewable category of lubricants called "biobased lubricants" are now gaining importance as these are synthesized by natural plant material. Biobased lubricants are being preferred because of their renewability, environmental friendly nature and ability to provide sustainable economic development to rural communities. Limonene bisphosphonate have potential applications as lubricant additives with AW, anti-friction and EP properties. Considerable solubility as well as compatibility with base oils

are essential parameters for a particular compound to be used in lubricant formulations. Thus, the room-temperature solubility of limonene and its bisphosphonate derivatives in PAO₆ and HOSuO were investigated [9].

2.6.3.2 Bisphosphonate Therapy

Bisphosphonate (BPs) are important therapeutic agents used to prevent bone resorption. Limonene-bisphosphonates are known for the treatment of a number of bone related disorders and diseases such as osteoporosis, Paget's disease, multiple myeloma and cancer metastases to the bone. Bisphosphonate-associated osteonecrosis of the jaws (BP-ONJ) is a major side effect seen in patients treated with intravenous nitrogen-containing BPs (N-BPs) such as zoledronate [31].

2.7 Synthesis of p-Menthane

Limonene is converted into its important derivatives such as p-menthane through catalytic (Pt and Pd) hydrogenation under high CO₂ pressure. The amount of catalyst used decides the ratio of product obtained because of its regioselective nature. Equimolar ratios of the two stereoisomers of p-menthane are preferably produced when platinum is used as catalyst palladium produces 2:1 ratio of trans-p-menthane and cis-p-menthane. Platinum is a more active catalyst than palladium, but higher activity results in lower chemical stability of the catalyst. The composition of products obtained at the end of process is significantly affected by rate of flow of reaction mixture through stationary catalyst bed. Low flow rate of reaction mixture over stationary catalyst bed results into partial hydrogenation of limonene while higher flow rate ensures the complete hydrogenation of limonene into its desired derivatives.

Hydrogenation of terpenes is commonly done at industrial scale [32]. In the hydrogenation reaction, extent of solubility of hydrogen can be increased by using high-pressure carbon dioxide so that the mass-transfer limitation can be avoided. Carbon dioxide is used either as supercritical solvent or as a "liquid expander". In general, supercritical CO₂ is highly soluble in most terpenes at pressure values near its critical pressure. Even upto 80 mol% of carbon dioxide may be present in liquid phase in a biphasic mixture. The CO₂ in fact can act as a "liquid expander" as it can itself dissolve in large amounts of liquid phases.

2.7.1 Chemical Pathway

Hydrogenation of limonene at high-pressure in carbon dioxide proceeds with good yields of very distinct relative concentrations of reactants either under biphasic or in supercritical conditions. Fig 9 presents the pathways of the reactions analysed in this work. Precious metals like platinum were used as catalyst for the hydrogenation of terpenes. For efficient usage of catalyst, it is exploited till it loses its ability to further hydrogenate any limonene. The hydrogenation of limonene was carried out at a constant pressure of hydrogen (4 MPa), with a range of different pressures of carbon dioxide: 8.5 or 7 MPa for two phases and 12.0 MPa for monophase.

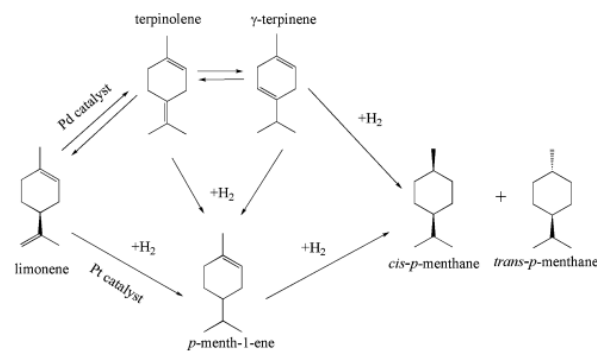


Fig. 9 Chemical conversion of limonene to p-menthane platinum-catalyzed hydrogenation of limonene yields p-menth-1-ene and trans-p-menthane/cis-p-menthane [33].

2.7.2 Effect of p-Menthane

The 3-substituted-p-menthanes used as cold receptor stimulants. It may also be synthesized by using some acid chloride (obtained by reacting p-menthane-3-carboxylic acid with thionyl chloride) with the appropriate mono or di-substituted amine. The reaction will usually be carried out in solution in the presence of a hydrogen chloride receptor e.g. sodium hydroxide. The reaction proceeds smoothly at room temperature.

2.7.2.1 Physiological Effect

In accordance with this invention, there are number of provided consumer products for consumption by the human body comprising a consumer product base and a means for stimulating the cold receptors of the nervous system of human body wherein said means comprise an effective amount of one or more 3-substituted-p-menthanes of the formula hereinbefore set forth. By consumer product, we mean a manufactured product applied to or consumed by the human person for toilet, cosmetic, hygienic, nutritive, curative, prophylactic or other purposes and constituting a vehicle by means of which the said 3-substituted-p-menthane may be brought into contact with the skin, mucous membranes or other surface tissues of the body, whether external tissues or internal, for example tissues of nose, throat, mouth and gastrointestinal tract and includes liquid and solid phase preparations of an essentially formless nature e.g. solutions, emulsions, pastes, ointments and powders etc., where solid phase preparations of semi-permanent form, e.g. shaped toilet and cosmetic preparations and shaped edible preparations, whose shaped form is only temporary and which lose that form on use, and articles of permanent form but which are of an essentially disposable nature e.g. cleansing tissues and toothpicks [34].

By use of this invention, number of different products like chewing gum, confectioneries, cachous, alcoholic and non-alcoholic beverages, ice-creams and jellies can be used as vehicles for the applications of 3-substituted-p-menthane compounds to human beings. Toiletries including creams and foams, deodorants, after-shave lotions, shaving soaps, toilet water and anti-perspirants along with solid colognes of toilet may also be used for this purpose. Soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouth

washes, hair tonics and eye drops. Medicaments including anti-septic ointments, pile ointments, liniments, lotions, decongestants, counter irritants, cough mixtures, throat lozenges, ant acid, indigestion preparations and oral analgesics. Miscellaneous compositions like water soluble adhesive compositions for envelopes, postage stamps and adhesive labels etc.

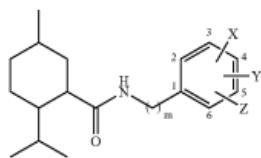


Fig 10 Chemical structure of cooling compound

2.7.3 Application of p-Menthane

The preparation of flavors and fragrances by isolating them from natural resources began in ancient times. Concurrently, the production of fermented foods (beer, wine and others) allowed the generation of new aromas and formed the roots of modern biotechnology. For many centuries, these were the only methods for obtaining this type of compound, albeit in complex mixtures.

2.7.3.1 Synthetic Intermediate

The monoterpene of the p-menthane family are widespread in nature and are well-known as flavoring ingredients and as valuable synthetic intermediates. Many industrial processes depend on this class of compounds because of the high commercial requirement for (K)-menthol. In addition, some new findings on peculiar organoleptic properties of different p-menthane alcohols, lactones and ethers have prompted studies on their synthesis [35].

Table 1 Physiochemical Properties of Limonene

Specifications	d-Limonene	l-Limonene	Dipentene
CAS No.	5989-27-5	5989-54-8	138-86-3
Chemical Name	(R)-1-Methyl-4-(1-methylethenyl) Cyclohexane	(S)-1-methyl-4-(1-methylethenyl) Cyclohexane	1-methyl-4-(1-mwthylethenyl) Cyclohexane
Empirical Formula	C ₁₀ H ₁₆	C ₁₀ H ₁₆	C ₁₀ H ₁₆
Molecular Weight	136.23	136.23	136.23
Melting Point (°C)	174.35	174.35	195.9
Boiling Point (°C)	175.5-176.0	175.5-176.0	175.5-176.0
Density (g/cm ³ at 20°C)	0.8411	0.8422	0.8402
Vapour Pressure (Pa at 20°C)	190	190	190
Water Solubility (mg/liter at 25°C)	13.8°	-	-
Henry Law Constant (kPa m ³ /mol at 25°C)	34.8°	-	-
Log k	4.23 ^d	-	4.83 (limonene)

Table 2 Results with M (Salen) complex under room condition-reaction time 24 h

Metal	Solvent	Conversion (%)	Selectivity (%)		
			Epoxide	Carveol	Carvone
Mn	CH ₂ C ₁₂	9.8	37.2	3.1	1.3
Mn	CH ₃ COCH ₃	4.7	5.6	0.0	0.0
Mn	CH ₃ CN	5.7	4.5	5.0	0.0
Mn	ACOET	14.6	46.0	4.1	9.3
Ni	CH ₂ C ₁₂	5.8	15.0	24.5	9.8
Ni	CH ₃ COCH ₃	5.0	21.5	17.8	4.3
Ni	CH ₃ CN	12.0	19.6	11.7	2.0
Ni	ACOET	13.2	25.9	19.6	8.0

Table 3 Results with M (Salen) complex super critical condition-reaction time 4 h

Metal	P (g.cm ⁻³)	Conversion (%)	Selectivity (%)		
			Epoxide	Carveol	Carvone
Mn	0.6986	6.5	6.3	26.3	0.0
Mn	0.4890	6.9	26.8	15.3	0.0
Ni	0.6986	4.7	13.6	24.4	2.6
Ni	0.5059	4.6	13.4	23.6	2.7

Table 4 Results with M (Salen) complex super critical condition-reaction time 2 h

Metal	P(g.cm ⁻³)	Conversion (%)	Selectivity (%)		
			Epoxide	Carveol	Carvone

Mn	0.6986	15.7	39.4	11.9	0.0
Mn	0.5059	7.5	23.5	17.5	0.0
Ni	0.6986	9.1	19.1	13,4	0.0
Ni	0.5059	6.7	16.6	21.0	1.6

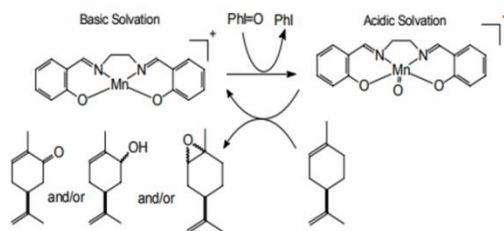


Fig 2 Mechanism of cationic specie

3. Future Suggestions

Limonene, as one of the most abundant monoterpene in nature, could be as high as 16% of essential oil components that is commonly used in flavor and fragrance industry. The potential of limonene for its medicinal benefits in humans and animals must also be explored to a maximum level. Anti-oxidant and anti-cancer activities of limonene have been recognized and therefore, it must be exploited as a food ingredient for the prevention of cancer. Derivatization or chemical conversion of limonene for the synthesis of various compounds is of great importance to get highly valuable and cost effective marketable products that are not available naturally. A number of novel ways of synthesis can be adopted to improve the yield and quality of chemical compounds.

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