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REVIEW ARTICLE

BIOLOGICALLY ACTIVE ALCOHOLS: CYCLIC ALCOHOLS

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Summary

The subjects of this article are cyclic alcohols with hydroxyl group bound directly to one carbon of the three- up to six-membered ring. They are thus predominantly secondary alcohols. These are substances frequently used as synthons in organic synthesis and many of them are important raw materials of chemical industry, such as cyclohexanol. Some cyclic alcohols were also found in nature, the bulk of them belong to the category of monoterpene substances. Many of them have biological activity, which is also discussed in this article.

Key words: cyclic alcohols, coprine; monoterpene; menthol; pestalothiopsin; biological activity

INTRODUCTION

Alcohols are one of the most important functional groups in organic chemistry. Alcohols are polar, since they have oxygen-hydrogen bonds, which allow alcohol molecules to attract each other through hydrogen bonds. Since oxygen atoms are much more electronegative than hydrogen atoms, the oxygen-hydrogen bond is especially polar. Alcohols are a good source of reagents for synthestic reactions (Sethupathy et al., 2012) and often display biological activity (Patočka and Kuča, 2012).

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Cyclic alcohols are essentially twofold. Among some of them, the hydroxyl group is bound directly to one carbon of the cyclic hydrocarbon, such as cyclohexanol. These are secondary alcohol, and are the leading interest of our article. The second group consists of alcohols, in which the -OH group is linked to a cyclic structure via one or more atoms, such as cyclohexyl-methanol. Both families of cyclic alcohols are also quite widespread in nature and constitute an important group of natural substances, which include cyclic terpenes, sugar alcohols, or a substance such as cholesterol. But they are outside the interest of our article.

Cyclic secondary alcohols are oxidized to ketones, which cannot be oxidized any further. Cyclic secondary alcohols are also oxidized in the body via liver alcohol dehydrogenase, and their metabolites can be more toxic than the parent compounds (Merrit and Tonkins, 1959; Cheng et al., 2002). Some important derivatives of cyclic secondary alcohols,

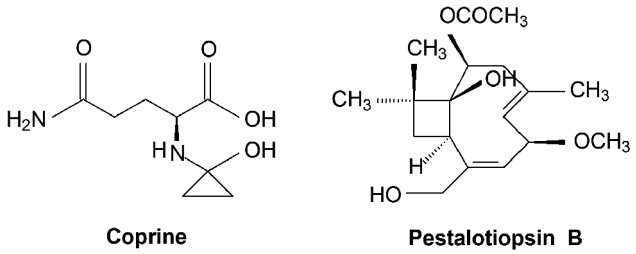
from cyclopropanol up to cyclohexanol, are discussed in this article. In several cases there are tertiary alcohols or glycols.

CYCLOPROPANOLS

Cyclopropanol substances are used as synthons in organic synthetic chemistry, with no significant acute toxicity or serious risk to human health.

Cyclopropanol, (CAS Numer 16545-68-9) is a volatile liquid highly unstable (density 0.917 g/mL, boiling point 101–102 °C) due to the three-membered ring, and is susceptible to reactions that open the ring (Roberts and Chembers, 1951). Cyclopropanol can be used as a synthon for the homoenolate of propanal. The chemical is also useful as a reagent to introduce a cyclopropyl group into ester, sulfate, and amine linkages. The synthetic cyclopropyl-containing compounds have been used for example in investigations of potential antiviral drugs (Cottel et al., 2009). Biological properties of cyclopropanol are not well known. According to Dijkstra et al. (1984), quinoprotein alcohol dehydrogenases can be inactivated by cyclopropanol.

Coprine (1-cyclopropanol-1-N5-L-glutamine, CAS Number 58919-61-2) is a natural derivative of cyclopropanol (Fig. 1) produced by edible mushrooms of the genus *Coprinopsis* (e.g. *C. atramentaria*, the death cap, the ink cap) that cause a marked ethanol sensitivity on ingestion. Coprine is responsible for poisoning when ingested with alcohol (Michelot, 1992). The mechanism appears to be inhibition of the low K_m form of liver acetyldehyde dehydrogenase by the active metabolite 1-amino-cyclopropanol.



Coprine **Pestalotiopsin B**

Figure 1. Biologically active naturally observed derivatives of cyclic alcohols. Coprine, natural derivative of cyclopropanol produced by edible muschrroms of the genus *Coprinopsis* and pestalotiopsin B, caryophyllene-type sesquiterpenoid, from the endophytic fungus *Pestalotiopsis* sp.

CYCLOBUTANOLS

Substituted cyclobutanols are very often used as synthons in organic synthetic chemistry. Natural products with cyclobutane moiety in molecule exist, but practically none of these substances is among the alcohols with -OH group in cyclobutane core.

Cyclobutanol (CAS Number 2919-23-5) is flammable liquid with boiling point 124 °C and log P (octanol-water) = 0.660. Safety Data Sheet for cyclobutanol (MSDS, 1997) shows that this substance may cause chemical conjunctivitis and corneal lesion may cause skin irritation and in ingestion it may cause gastrointestinal irritation with nausea, vomiting and diarrhoea. Ingestion of large amounts may cause CNS depression. Aspiration may lead to pulmonary edema. Vapors may cause dizziness, suffocation or burning sensation in the chest. No information about chronic toxicity, reproductive toxicity, teratogenicity and DD_{50}/LC_{50} was available.

2-ethylcyclobutanol (CAS Number 35301-43-0) was found as one of the volatile components of vanilla fragrance (Toth et al., 2011). No toxicological information was available.

2,2,4,4-Tetramethyl-1,3-cyclobutanediol (TMCD, CAS Number 3010-96-6) is a cyclic diol. This diol is produced as a mixture of *cis*- and *trans*-isomers, depending on the relative stereochemistry of the hydroxyl groups. It is used as a monomer for the synthesis of polymeric materials. TMCD is currently being researched as an alternative to bisphenol A (BPA). BPA is a precursor used in the production of a wide range of polymers including polycarbonates, polyesters, polysulfones,

and polyester ketones. Like BPA, CBDO is a diol with a structure suitable for making polyesters. It is very stable thermally and mechanically. Polyesters prepared from TMCD are rigid materials, but the combination of TMCD with flexible diols results in materials with high impact resistance, low color, thermal stability, good photooxidative stability and transparency (Hoppens et al., 2004). Recent data indicate that TMCD do not pose an androgenic or estrogenic risk to humans (Osimitz et al., 2012).

Pestalotiopsin B is one from pestalotiopsins, caryophyllene-type sesquiterpenoids (Fig. 1), which were isolated by Sugawara and co-workers (Pulici et al., 1996) from the endophytic fungus *Pestalotiopsis* sp., associated with the bark and leaves of *Taxus brevifolia*. The structure of pestalotipsin B is the hitherto unknown skeleton that is composed of a cyclobutane ring fused with a cyclononadiene ring. From the biological perspective, pestalotiopsins (A and B) show immunosuppressive activity in the mixed lymphocyte reaction and cytotoxicity, but the details have not been reported (Takao et al., 2008, 2009).

CYCLOPENTANOLS

Cyclopentanol and its derivatives are mainly used as synthons in organic synthetic chemistry. Natural products with cyclopentane moiety in molecule exist, but practically none of these substances is among the alcohols with -OH group in cyclopentane core.

Cyclopentanol (CAS Number 96-41-3) alone is a colorless viscous liquid with a pleasant odor, slightly less dense than water. Melting point is -19 °C, boiling point 140.4 °C and flash point 51 °C. Vapors are heavier than air. It is used to make perfumes and pharmaceuticals. Cyclopentanol may cause toxic effects if inhaled or absorbed through skin. Inhalation or contact with material may irritate or burn skin and eyes. Burning of cyclopentanol will produce irritating, corrosive and/or toxic gases. Vapors may cause dizziness or suffocation. Runoff from fire control or dilution water may cause pollution. In general, cyclopentanol is anestetics and CNS depressant with a relative low order of acute toxicity. Cumulative toxicity from repeated exposure to low atmospheric concentration is improbable (Patty, 1963).

Some cyclopentanol derivatives are accessible synthetically and are used as synthons in organic chemistry, but their toxicological properties are not described and their toxicity to humans is not very significant. There are, for example 1-methylcyclopentan-1-ol (CAS Number 1462-03-9), 2-methylcyclopentan-1-ol (CAS Number 25144-04-1), 3-methylcyclopentan-1-ol (CAS Number 18729-48-1) and others.

CYCLOHEXANOLS

Cyclohexanol (CAS Number 108-93-0) is a colorless to light-yellow flammable viscous liquid that reacts strongly with strong oxidants and that

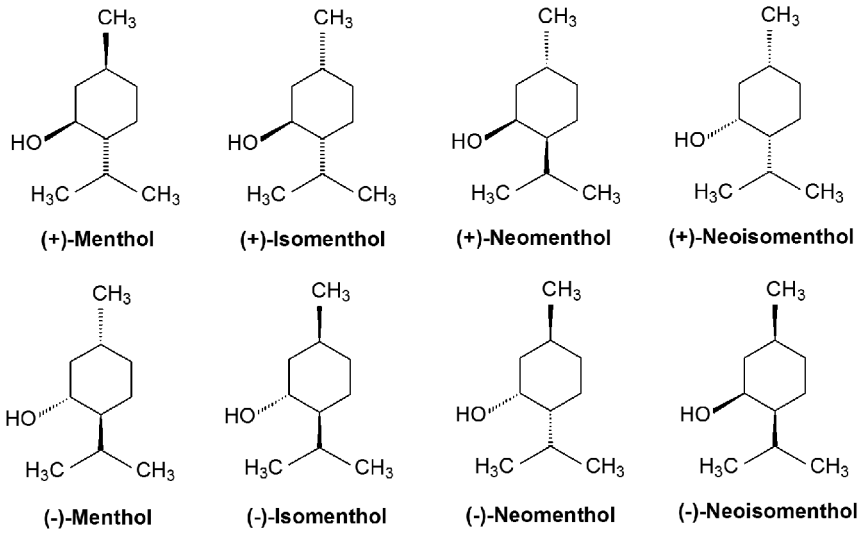


Figure 2. Biologically active naturally observed derivatives of cyclic alcohols. Stereoisomers of menthol.

attacks plastics. This is a high volume chemical with production exceeding 1 million pounds annually only in the U.S.A. Cyclohexanol is used in the production of nylon, lacquers, paints, varnishes, degreasers, plastics, soaps, detergents, and insecticides. It may be used also in the production of a highly deadly chemical warfare agent cyclosarin (Proctor et al., 2006).

There is very little research available on cyclohexanol's acute toxicity to humans. It is an eye and skin irritant (Gilbert, 2012). No data is available on its reproductive or developmental toxicity. Synthetically prepared cyclohexanol derivatives are used as synthons in organic chemistry, but their toxicological properties are not described and their toxicity to humans is not very significant.

A large group of substances derived from cyclohexanol is represented by monoterpenic alcohols (Fig. 2). These compounds are present in esential oils, natural products with many different applications, especially in medical and cosmetic areas. The toxicity of monoterpene alcohols to humans is not significant, but many of them are found to exhibit varied biological properties, such as spasmolytic (Lis-Balchin and Hart, 1999) and anticonvulsant (Almeida et al., 2003) activities.

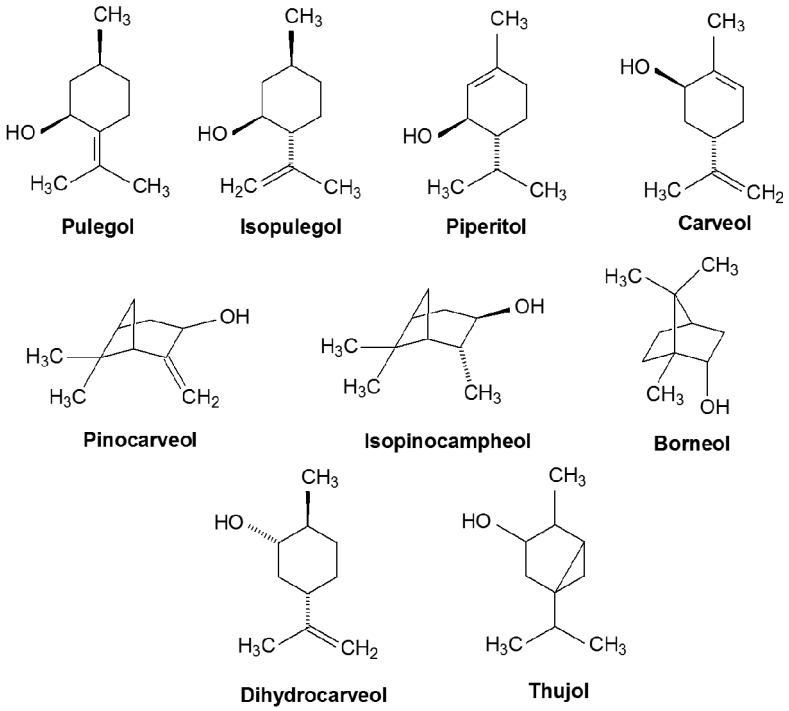


Figure 3. Biologically active naturally observed derivatives of cyclic alcohols. Monoterpenic alcohols from different esential oils: menthol, neomenthol, pulegol, isopulegol, piperitol, carveol, pinocarveol, dihydroacarveol, thujol, borneol, isoborneol, and isopinocampheol.

Most available information exists about menthol. It is a substance used in many areas of life: food, cosmetics, medicine etc. Nevertheless, menthol exists in other seven stereoisomers (Fig. 3).

Menthol (2-isopropyl-5-methylcyclohexan-1-ol) is a naturally occurring cyclic terpene alcohol of plant origin, obtained from cornmint, peppermint or other mintoils. Menthol has been used since antiquity for medicinal purposes (Patel et al., 2007). Its use in dermatology is ubiquitous, where it is frequently part of topical antipruritic, antiseptic, analgesic, and cooling formulations. It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above. The menthols category is comprised of the isomers L-menthol (CAS Number 2216-51-5), D-menthol (CAS Number 15356-60-2) and the racemate D/L-menthol (CAS Number 89-78-1). The menthols can be considered as a category because of their

similarity in physico-chemical, toxicological, ecotoxicological and environmental fate properties. The main form of menthol occurring in nature is L-menthol, which is assigned the (1R,2S,5R) configuration. Because menthol is used in many applications where it is in contact with humans, the pharmacology and toxicology of this compound received considerable attention (Ahijevych and Garrett, 2004).

Menthol has local anesthetic (Leffler et al., 2011) and counterirritant qualities (Huffman et al., 2010), and it is widely used to relieve minor throat irritation (Willis et al., 2011). Menthol also acts as a weak kappa opioid receptor agonist (Galeotti et al., 2002). Menthol's ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin is responsible for the well-known cooling sensation it provokes when inhaled, eaten, or applied to the skin (Eccles, 1994; Keh et al., 2011).

All menthol isomers are of very low acute oral toxicity with LD_{50} values normally greater than 2000 mg/kg (Jenner et al., 1064). It can be estimated from unreferenced citations in pharmaceutical texts, such as Gleason et al. (1969), that the lethal human dose of menthol is 50-500 mg/kg. Clinical signs of intoxication are unspecific, and included apathy and reduced activity. Based on old and limited studies for the racemate and the unspecified isomer, it can be assumed that the acute dermal toxicity of the mentol isomers is low (Morton et al., 1995). All studied isomers of menthol are moderately irritating to the skin and slightly irritating to the eye. The skin sensitization potency of menthol isomers in animals and humans is low.

The NOEL (no-observable-effect level) in 13-week studies of toxicity with D/L-menthol in the diet was 560 mg/kg bw per day in mice and 750 mg/kg bw per day in rats on the basis of slightly increased incidences of interstitial nephritis at the next highest dose (US National Cancer Institute, 1979). Even the highest dose of D/L-menthol tested in the long-term studies in mice and rats had no specific toxic effect. As the survival of mice was reduced at the high dose of 600 mg/kg per day, the Committee allocated an ADI in the range of 0 - 4 mg/kg (IPCS, 1999).

Neomenthol, (+)-neomenthol (CAS Numer 3623-51-6), stereoisomer of menthol, is volatile oil component of *Mentha* species (Kjonaas et al., 1982). It is liquid not mixing with water and strong sensory irritant. Skin contact is not thought to have harmful health effects, however the material may still produce health damage following entry through wounds, lesions or abrasions. Neomenthol can cause respiratory irritation in some persons. The body's response to such irritation can cause further lung damage. Long-term exposure to respiratory irritants may result in disease of the airways involving difficult breathing and related systemic problems (MSDS, 2010).

Pulegol (CAS Number 529-02-2), 5-methyl-2-(1-methylethylidene)-cyclohexanol), is monoterpene from essentials oil of *Menta Pulegium* L. Pulegol is also one of matabolites hepatotoxic pulegone in mammals (Madyastha and Raj, 1993).

Isopulegol (CAS Number 89-79-2) is a mono-terpene alcohol (melting point 78 °C) intermediate in the preparation of (-)-menthol and it is present in the essential oils of various plants. Isopulegol is CNS active compound (Bhatia et al., 2008). Silva et al. (2007) showed that, similar to diazepam (1 mg/kg), isopulegol significantly modified all the observed parameters in the elevated plus maze (EPM) test, without altering the general motor activity in the open field test. Similarly to diazepam, isopulegol significantly prolonged the latency for convulsions and mortality of mice (Silva et al., 2009a). Isopulegol also increased the number of head dips in the hole-board test. Forced swimming and tail suspension tests showed that isopulegol (25 and 50 mg/kg) was able to induce a significant increase in the immobility time, in opposite to imipramine, a recognized antidepressant drug. Different from diazepam (2 mg/kg), isopulegol (25 and 50 mg/kg) had no effect on the motor coordination of animals in the rota rod test. These results showed that isopulegol presented depressant- and anxiolytic-like effects (Silva et al., 2007). This psychoactive monoterpene has the profile of a sedative drug (de Sousa et al., 2007). The results of Silva et al. (2009b), suggested that isopulegol presents significant gastroprotective effects in both ethanol- and indomethacin-induced ulcer models, which appear to be mediated, at least in part, by endogenous prostaglandins, K+(ATP) channel opening, and antioxidant properties.

Piperitol (CAS Numer 491-04-3) is mono-terpenic alcohol isolated from *Paulownia tomentosa* (Ina et al., 1987) and together with other stereoisomers (cis-piperitol and trans-pipertotol) is present in the essential oils of *Mentha* species plants.

Carveol (CAS Number 99-48-9) is mono-terpenic alcohol present in the essential oils of some *Mentha* species plants (Bhatia et al., 2008b). Cerveol has not been classified as harmful, nevertheless may still be damaging to the health of the individual, following ingestion, especially where preexisting organ (e.g. liver, kidney) damage is evident. Carveol can cause eye irritation and cause inflammation of the skin on contact in some person (Bhatia et al., 2008c).

Pinocarveol (CAS Number 5947-36-4, 6,6-dimethyl-4-methylidenebicyclo[3.1.1]heptan-3-ol) is a volatile component of essential oils occurring in many plants. Two stereoisomers, cis-pinocarveol (CAS Number 19889-99-7) and trans-pinocarveol (CAS Number 547-61-5), exist. Cis-pinocarveol is present, for example, in the essential oil from aerial parts of *Artemisia annua* (Juteau et al., 2002) and trans-pinocarveol in essentials oil of *Haplopappus greenei* A. Gray (Demirci et al., 2006) or in essential oil from a *Cistus ladanifer* L. (Verdeguer et al., 2012). Both stereoisomers exhibit antibacterial activity.

Dihydrocarveol (CAS Number 38049-26-2, 2-methyl-5-(1-methylethenyl)cyclohexanol) is liqiud (boiling point 224.5 °C) present, for example, in essentials oil from *Cunila spicata* (Manns, 1993) or in seed essentials oil of *Momordica charantia* (Braca et al., 2008). Dihydrocarveol is a strong sensory irritant. Skin contact is not thought to have harmful health effects, however the material may still produce health damage following entry through wounds, lesions or abrasions (Bhatia rt al., 2008). Acute dihydrocarveol toxicity is low, LD_{50} in rabbit at skin administration and in rat at oral administration is 5.000 mg/kg (Anonymous, 1979).

Thujol (CAS Number, 21653-20-3, 3-thujol, (1S,3S,4R,5R)-4-methyl-1-(1-methylethyl)-bicyclo (3.1.0)hexan-3-ol) is one of the components of the volatile fraction of *Salvia* species (Rzepa et al., 2009). Thujol is one of α-thujone metabolites (Höld et al., 2000), toxic monoterpene, which is responsible for the pharmacological and toxicological properties of absinthe (Patocka and Plucar, 2003). Toxicological information about thujol is not available.

Borneol (CAS Number 507-70-0) and **Isoborneol** (CAS Number 124-76-5; 24393-70-2), are two stereoisomers of bicyclic monoterpene alcohol, exo-1,7,7 trimethylbicyclo[2.2.1]heptan-2-ol. Borneol exists as two enantiomers. Naturally occurring d-(+)-borneol can be found in essentials oils of several species of *Artemisia*, *Dipterocarpaceae*, in *Blumea balsamifera* and *Kaempferia galanga* (Ong and Lim, 2006). Borneol is used in traditional Chinese medicine (Stockman, 1888).

Research over the last years showed that there is an interesting substance in borneol usable in medicine.

For example, Borneol protects primary rat hepatocytes against exogenous oxidative DNA damage (Horváthová et al., 2012), protects cortical neurons against oxygen-glucose deprivation/reperfusion (Liu et al., 2010). Borneol protected SH-SY5Y cells against Aβ-induced toxicity, exerted an antioxidative effect and suppressed apoptosis. It increases our knowledge about neuroprotective mechanism of borneol, and it is hopeful to be a candidate compound for developing a therapeutic drug for the prevention and treatment of Alzheimer disease and other Aβ-related neurodegenerative diseases (Hur et al., 2012). Park et al. (2003) previously suggesedt that borneol specifically inhibits the nicotinic acetylcholine receptor in a noncompetitive way.

As regards isoborneol, this compound showed dual viricidal activity against herpes simplex virus 1 (HSV-1) (Armaka et al., 1999). Isoborneol also protected against 6-OHDA-induced increases in caspase-3 activity and cytochrome C translocation into the cytosol from mitochondria. Results of Tian et al. (2007) indicate that the protective function of isoborneol is dependent upon its antioxidant potential and strongly suggest that isoborneol may be an effective treatment for neurodegenerative diseases associated with oxidative stress. Historically isobornol was used in flucculatin test for diagnosis of syphylis (Hamelin, 1950; Saint-Prix and Mutermilch, 1950).

Acute toxicities of borneol and isobnorneol are low. The LD_{50} of borneol in mouse is 1059 mg/kg (Horikava and Okada, 1975) and in rabbit (Beier, 1990), both at oral administration, is 5800 mg/kg. The LD_{50} in rabbit at skin administration and in rat at oral administration is 5 000 mg/kg (Anonymous, 1979). The acute toxicity of isoborneol was estimated in mouse (i.v. administration, LD_{50} = 56 mg/kg) (NIOSH), rabbit (percutaneous administration, LD_{50} > 5 000 mg/kg) and rat (oral administration, LD_{50} = 5 200 mg/kg) (Anonymous, 1979).

Isopinocampheol (CAS Number 24041-60-9), bicyclic monoterpene alcohol, is one of the components

of the volatile fraction of *Dracocephalum nutans* (Misra et al., 1988). The results of de Sousa et al. (2007) show that isopinocampheol is psychoactive monoterpene and has the profile of a sedative drug.

Inositol (CAS Number 87-89-8, cyclohexane-1,2,3,4,5,6-hexol) is a sixfold alcohol (polyol) of cyclohexane. It exists in nine possible stereoisomers, of which the most prominent form, widely occurring in nature, is cis-1,2,3,5-*trans*-4,6-cyclohexanehexol, or *myo*-inositol (Fig. 4). *myo*-Inositol plays an important role as the structural basis for a number of secondary messengers in eukaryotic cells, the various inositol phosphates (Strunecká and Patočka, 2007). In addition, inositol serves as an important component of the structural lipids phosphatidylinositol (PI) and its various phosphates, the phosphatidylinositol phosphate (PIP) lipids (Endo-Streeter et al., 2012). All inositol isomers are of very low acute toxicity with LD_{50} greater than 3.000 mg/kg at oral application and greater than 1.750 mg/kg at intravenous application in rat for myo-inositol (Japanese Kokai Tokyo Koho Patents. Vol. #92-9328).

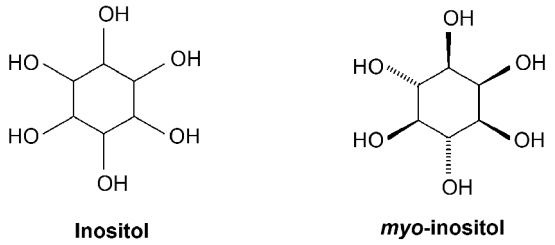


Figure 4. Biologically active naturally observed derivatives of cyclic alcohols. Sixfold alcohol inositol and *myo*-inositol, one from nine possible stereoisomers of cyclohexane-1,2,3,4,5,6-hexol.

CONCLUSION

Cyclic alcohols are frequently used as synthons in organic synthesis and many of them are important raw materials of chemical industry. Some of them were also found in nature, the bulk of them belong to the category of monoterpene substances. Some cyclic alcohols have biological activity.

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