
Compounds containing lactol functionality are widely distributed in many natural product and biologically active compounds such as callipeltoside A isolated from the lithistid sponge *Callipelta sp*.; ginkgolides present in Ginkgobiloba; dysidiolide, a novel sesterterpenoid isolated from the caribbean sponge *Dysidea etheria de Laubenfels*, an antitumor agent active at the micro molar level; cladocorans A and B, isolated from the mediterranean coral *Cladocora cespitosa*.; acuminolide, a cytotoxic labdane diterpene, isolated from the stem bark of *Neouvaria acuminatissima*; spongianolide A, a cytotoxic sesterterpene isolated from marine sponge; manoalide and cacospongionolide B2, sesterterpenes isolated from soft sponges; peniolactol isolated from the wood attacked by the fungus *Peniophora sanguinea Bres*.

Lactol is also important precursor for many biologically active compounds such as in the synthesis of illudalic acid, a potential LAR inhibitor, synthesis of small molecule inhibitors of the orphan nuclear receptor steroidogenic factor-1 (NR5A1) based on isoquinolinone scaffolds, synthesis of benzopyran-1-ones, caronaldehyde, synthesis of mevalonate and mevaldate.

Construction of lactol unit has been reported earlier in several steps by different research groups, the earliest being from Schöpf and Kühne in four steps; its crystal structure was subsequently reported by Valente et al. The synthetic utility of tungstic acid–hydrogen peroxide in 2-methyl-2-propanol to furnish the corresponding *trans*-dial of (Z,Z)-cycloocta-1,5-diene in 65 % yield has been demonstrated by our group earlier. Further investigation of this reagent combination revealed that its treatment with *endo*-dicyclopentadiene unexpectedly resulted in the formation of polycyclic oxetanes. Our continued interest in the dihydroxylation using tungstic acid-hydrogen peroxide prompted us to explore the hydroxylation of indene in order to prepare indan-*trans*-1,2-diol which is an important intermediate for Indinavir, an HIV protease inhibitor.

It was interesting to observe that the treatment of tungstic acid–hydrogen peroxide with indene resulted in the formation of not only *racemic* indan-*trans*-1,2-
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diol but also *racemic* 3,4-dihydro-3-hydroxyisochromen-1-one (also known as lactol or pseudoacid).

![Scheme 1. Reaction of indene with hydrogen peroxide-tungstic acid](image)

Various lactol derivatives show wide variety of biological activities such as dysidiolide acts as the inhibitor of phosphatase cdc25A and inhibits the growth of A-549 human lung carcinoma; Cladocorans A and B, are also used as a inhibitor of protein phosphatase cdc25A; illudalic acid is a potential LAR inhibitor; manoalide is a potent, irreversible inhibitor of phospholipase A2 (PLA2); cacospionolide B has shown a comparable activity on recombinant human synovial PLA2 *in vitro*; (+)- acuminolide display cytotoxic activity in human cancer cell lines and cultured P388 cells; (-)- spongianolide A inhibits proliferation of the mammary tumor cell line MCF-7 and protein kinase; The acetals of nepetatic acid exhibits prominent mosquito repellency. These interesting biological properties prompted us to prepare the acetal derivatives of lactol.

![Scheme 2. Synthesis of acetal derivatives of 3,4-dihydro-3-hydroxyisochroman-1-one](image)

The first chapter of the thesis provides synthesis of *racemic* indan-trans-1,2-diol 2 and *racemic* lactol 3 from indene 1 (Scheme 1). Several experiments were carried out to discuss probable mechanism of formation of the products from indene.
One-pot synthesis of 3,4-dihydro-3-hydroxyisochroman-1-one 3 from indene 1 under such mild conditions (Scheme 1) is hitherto unknown in the literature. Further work involves reaction of lactol 3 with various alcohols in the presence of acid furnished different acetal derivatives of lactol 4(a-h) (Scheme 2).

A long standing problem in agricultural field is menace of various pests damaging the useful crops. The use of insecticides in agriculture is continuously increasing with simultaneous addition of new types of insecticides. The development of effective insecticides has obviously been a major activity in the past decades for controlling the ruinous attack by the pests. A wide range of insecticides including organophosphorus, carbamates, pyrethroids and other class of pesticides have been used on crops to control insects.

There are many factors which affect the insecticidal activity when exposed to external environment like microbial decomposition, hydrolysis, volatilization and photolysis. Photodegradation due to sunlight is one of the major pathways which lessen insecticidal activity after their application in the field. On exposure to sunlight, the insecticide molecules undergo a variety of primary processes often leading to their degradation. To overcome these problem chemical modifications were attempted which seriously affected the insecticidal activity and also caused ecological problems. Alternatively, the UV absorbing molecules, also known as photostabilizers were used in the formulations to extend the environmental life of the insecticides.

Chlorpyrifos 5, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate (C₉H₁₁Cl₃NO₃PS), is most widely used insecticide all over the world for the protection against variety of pests. It is used both for agriculture and household purposes. US alone uses almost 30 million pounds per year while in Europe, more than 50,000 kg/year are used. It is used for various crops such as corn, alfalfa, cotton, soyabean, cereals, tobacco, peaches, vegetables and citrus fruits to control a wide spectrum of chewing, sucking and boring insects like aphids, caterpillars, Helicoverpa spp, mites, moths, jassids, budworm, stem borer and locusts.
Chlorpyrifos is also subject to degradation on exposure to sunlight resulting in formation of various photoproducts which are more stable to UV radiation than chlorpyrifos itself. Chlorpyrifos-oxon 6 is one such photoproduct which is more persistent and about 3000 times more toxic to humans than chlorpyrifos (Scheme 3). On exposure to UV light, sulfotep 7 is also formed from chlorpyrifos (Scheme 3) which is highly toxic and often exists as an impurity in chlorpyrifos.

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\begin{align*}
\text{Chlorpyrifos 5} & \xrightarrow{\text{hv}} \text{Chlorpyrifos-oxon 6} + \text{Sulfotep 7}
\end{align*}
\]

Scheme 3. Photodegradation of chlorpyrifos to chlorpyrifos-oxon and sulfotep

In order to extend environmental life of chlorpyrifos and consequently to minimize the formation of toxic, UV stable photoproducts, use of effective and efficient photostabilizers is indispensable. The photostabilizers absorb UV radiation and dissipate the absorbed energy harmlessly and also persist in the matrix for the expected lifetime. Photostabilization of the insecticide can take place either by preferential absorption of light by photostabilizer, thereby preventing photo-excitation of the insecticide molecules or transfer of excess energy from the excited insecticide molecules to the photostabilizers through various energy transfer mechanisms such as excited-state intramolecular proton transfer (ESIPT) or keto-enol tautomerism. Intramolecularly H-bonded photostabilizers such as hydroxyphenyl-benzotriazoles, hydroxyphenyl-s-triazines, oxanilides and 2-hydroxybenzophenones are widely used for the protection of various products against photodegradation.

Earlier our group has studied the effect of photostabilization of azadirachtin-A on exposure to UV light in the presence of four structurally different photostabilizers, namely 4-aminobenzoic acid, 2,4-dihydroxybenzophenone, 4,4’-dihydroxybenzophenone and phenyl salicylate. In continuation with our research directed towards design and synthesis of novel photostabilizers, we conceived benzils...
having structures of the type 10 (Scheme 4) with two such hydroxy and keto pairs assembled into a single structure. It was envisioned that these benzils would possess enhanced efficiency and usefulness as photostabilizers due to the inherent structural features.

**Scheme 4.** Synthesis of novel benzil derivatives

The second chapter includes design and synthesis of novel benzil compounds from resorcinol and their study of photostabilization property. Photostabilization study of chlorpyrifos insecticide was carried out using these novel benzils under irradiation with HPMV-lamp for 10 h and percentage recovery of these insecticides in methanol was analyzed by HPLC.⁹

It is estimated that every year at least 500 million people in the world suffer from one or the other tropical diseases that include malaria, chikungunya, lymphatic filariasis, schistosomiasis, dengue, trypanosomiasis and leishmaniasis. One to two million deaths is reported annually due to malaria worldwide. Lymphatic filariasis affects at least 120 million people in 73 countries in Africa, India, Southeast Asia, and Pacific Islands. These diseases not only cause high levels of mortality, but also inflict great economic loss and social disruption on developing countries such as India, China, etc. India alone contributes around 40% of global filariasis burden and the estimated annual economic loss is about Rs. 720 crore.

Mosquitoes are the most important single group of insects well-known for their public health importance, since they act as vector for many tropical and subtropical diseases such as dengue fever, yellow fever, malaria, filariasis and encephalitis of different types including, Japanese encephalitis. *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus* are the major urban vectors of malaria,
dengue and lymphatic filariasis, respectively. The approach to combat these diseases largely relied on interruption of the disease transmission cycle by either targeting the mosquito larvae through spraying of stagnant water breeding sites or by killing the adult mosquitoes using insecticides. Generally, two types of vector control methods, namely indoor residual spraying (IRS) and long-lasting insecticide-treated nets (LNs) are used for controlling malaria transmission.

The part A of the third chapter is focused on exploring mosquitocidal activity of lactol and its acetal derivatives. Anopheles species of mosquito, responsible for malaria was reared into the entomology laboratory at National Institute of Malaria Research (NIMR), Nadiad, Gujarat, India and used for studying mosquitocidal activity. The study includes various testing methods such as tunnel test, and adult susceptibility test for the above activities.

Human body is closely influenced by the activities of microorganisms. Microorganisms are a part of our lives in many ways. They are employed in the manufacture of dairy products, certain foods, processing of certain medicines and therapeutic agents, in manufacture of certain chemicals and in numerous other ways. Despite of the established useful functions and potentially valuable activities of microorganism, they are also harmful to mankind in many ways. Different microorganisms are responsible for many diseases such as Acquired Immune Deficiency Syndrome [AIDS], herpes, legionnaire’s disease, influenza, jaundice, tuberculosis, typhoid, dermatomycoses, dysentery, malaria etc. Microorganisms can cause diseases either when they come in contact and invade the tissues or if they find suitable condition for their growth. Therefore control of microbial population is necessary to prevent transmission of disease and infection. Protection against such diseases can be achieved by inhibition of microbial growth or by killing them.

The work incorporated in part B of the third chapter is the study of antimicrobial activity of benzils, lactol and acetics of lactol prepared in first and third chapters of the thesis. The compounds were tested on a variety of microorganisms such as gram positive and gram negative bacteria and on fungi. For the testing of antibacterial activity two species of gram positive bacteria i.e. Staphylococcus
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*aureus* and *Streptococcus pyogenes* and two species of gram negative bacteria i.e. *Escherichia coli* and *Pseudomonas aeruginosa* have been used. For antifungal activity two fungi i.e. *Candida albicans* and *Aspergillus niger* have been employed.

Among biologically active heterocyclic compounds, derivatives of oxindole [3,3-bis(1H-indol-3-yl) indolin-2-one, 3a in Scheme 1) attract much attention as anti-inflammatory, anti-HIV and antitumor agents, among other things. Oxindole is also an integral component of many natural products including convolutamydines, arundaphine, donaxaridine, paratunamide and maremycins.

There are many reactions known for the synthesis of oxindole derivatives by condensation of isatins and indoles in the presence of various catalysts. Although these methods work well, many of them involve harsh reaction conditions, long reaction time, or the use of corrosive acids. Most of the Lewis acid catalysts, being moisture sensitive, require usually more than stoichiometric amounts, the use of inert atmosphere, and easily undergo decomposition.

We have been involved in the study of the catalytic activity of tungstic acid in organic reactions. Many tungstic acid-catalyzed organic transformations are known. Tungstic acid, a low-cost and readily available heterogeneous catalyst, exhibits high catalytic efficiency. We found that tungstic acid efficiently catalyzes condensation of indoles with isatins to form corresponding oxindole derivatives in high yields. The
present method involves relatively mild conditions and easy work-up procedure (Scheme 5).

The fourth chapter describes thorough characterization of tungstic acid, a heterogeneous catalyst and its application for the synthesis of various oxindole derivatives.11

References


List of Publication

**Patents**


**Research Papers**


2. Gautam M. Patel, Pradeep T. Deota “Serendipitous one-pot synthesis of 3,4-dihydro-3-hydroxyisochroman-1-one from indene” *(Manuscript under preparation)*


5. Gautam M. Patel, Hemant Parmar, Pradeep T. Deota “Novel water soluble photostabilizers for disulfoton” *(Manuscript under preparation)*
Paper presented in conferences

1. **Oral** presentation in **National Conference** on **Green Chemistry** 6-8 February 2009 at Veer Narmad South Gujarat University, Surat, Gujarat, India.

2. **Poster** presentation in **Regional Science Congress** on “**Science for Shaping the Future of India**” 15-16 September 2012 at The M. S. University of Baroda, Vadodara, Gujarat, India.

3. **Poster** presentation in **44th world chemistry congress (IUPAC)** 11-16 August 2013 at Istanbul, Turkey.