



GÖTEBORGS UNIVERSITET

Chemical and Dermatological Aspects of UV-absorbing Compounds

Studies of Photoallergens and Synthesis of a Natural UV-filter

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2011

Akademisk avhandling för filosofie doktorsexamen i kemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 14 oktober 2011 kl 10.00 i sal KB, Institutionen för Kemi vid Göteborgs universitet, Kemigården 4, Göteborg. Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent är Professor Fredrik Almqvist, Institutionen för Kemi, Umeå universitet, Sverige

ISBN: 978-91-628-8349-2

ABSTRACT

The sun's UV radiation is necessary for the existence of life on earth. However, too much UV exposure can lead to the development of skin cancer. Therefore, sunscreens are often used by the general population as protection from excessive UV radiation. Unfortunately, many of the chemical UV-filters that are used in sunscreens today have the ability to induce contact and photocontact allergy. In this work two different chemical UV-filters together with the anti-inflammatory drug ketoprofen, all known to induce allergic reactions, have been studied to better understand the reason for these adverse effects. In addition, a synthetic route to the natural UV-filter scytonemin has been developed.

One of the most commonly used UVA-filters today is the well known photoallergen 4-*tert*-butyl-4'-methoxy dibenzoylmethane. We showed that it degrades when irradiated with UV light and that several different photodegradation products are formed. Of particular interest were arylglyoxals and benzils because they were unexplored as potential contact allergens. The benzils were found to be cytotoxic rather than allergenic, whereas the arylglyoxals were found to be strong sensitizers in the murine local lymph node assay (LLNA) used to assess their allergenic potency. Photocontact allergy to dibenzoylmethanes is therefore probably caused by the arylglyoxals that are formed upon photodegradation. Chemical reactivity experiments showed that the arylglyoxals have the ability to form immunogenic complexes via an electrophilic-nucleophilic reaction with the amino acid arginine.

A relatively new UV-filter on the market is octocrylene that has grown in popularity, due to its ability to stabilize other UV-filters such as 4-*tert*-butyl-4'-methoxy dibenzoylmethane. However, recent clinical reports suggest that it is the UV-filter that causes most allergic reactions. Patch and photopatch testing of 172 patients with suspected skin reactions to sunscreens or ketoprofen was performed and 23 of these patients displayed a positive test reaction to octocrylene. Five patients were diagnosed with contact allergy and 18 with photocontact allergy. Notably, many of these patients also displayed a photoinduced reaction to ketoprofen. Without UV radiation, octocrylene was classified as a moderate allergen in the murine LLNA and it was shown to react with amines like lysine via a retro-aldol condensation. In presence of UV radiation, octocrylene also reacted with amines but via acyl substitution resulting in a different product outcome than the reaction in the dark. Both the clinical studies and the chemical reactivity experiments thereby indicate that octocrylene has the ability to induce both contact and photocontact allergy.

The apparent photocross-reactivity between octocrylene and ketoprofen observed in the clinical study could not be explained by the previous reactivity studies of octocrylene. Furthermore, according to other clinical reports, photosensitization to ketoprofen also leads to photocontact allergy to many other compounds. Ketoprofen was therefore irradiated in presence of five amino acid analogs and interestingly a reaction between the tryptophan and lysine analogs was substantially enhanced by ketoprofen. We believe that ketoprofen generates singlet molecular oxygen which activates the tryptophan analog that subsequently reacts with the lysine analog. The formation of an immunogenic complex not containing the allergen itself can explain many of the observed photocross allergies between ketoprofen and other structurally different compounds. In theory all compounds that are able to generate singlet molecular oxygen can promote the formation of the same immunogenic complex.

Finally, the first total synthesis of the dimeric alkaloid scytonemin was developed. This natural occurring UV-filter enables the survival of different species of cyanobacteria in areas of intense solar radiation. The planned structure activity studies of scytonemin and derivatives thereof will hopefully lead to the development of a stable UV-filter that does not cause contact or photocontact allergy.

Keywords: Contact allergy, Dibenzoylmethane, Immunogenic complex, Ketoprofen, Local Lymph Node Assay, Octocrylene, Patch testing, Photoallergen, Photocontact Allergy, Photodegradation, Photopatch testing, Photostability, Scytonemin, UV-filter.