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*Synthesis of Fluorescent Ion Indicators
Isolation and Structure Identification
of Bioactive Natural Products
Synthesis of Bioactive Compounds*

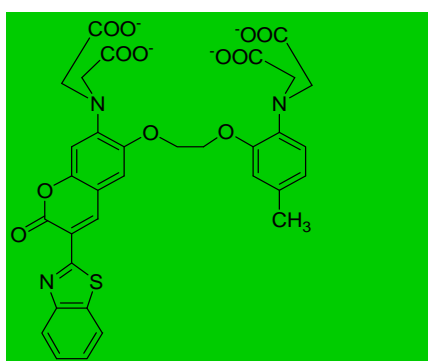
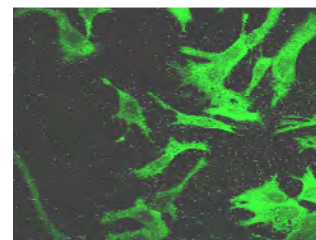
Brief Biography

Harry Katerinopoulos, Professor, Organic Chemistry. Born, Athens, Greece 1954. B.Sc. University of Patras, Greece, (1976); M.Sc. New York University, USA, (1979); Ph.D. New York University, (1984) with Prof. D. I. Schuster; Postdoctoral Fellow, Department of Chemistry, University of Pennsylvania, PA, USA. With Prof. K.C. Nicolaou, (1984-1985); Postdoctoral Fellow, Departments of Medicinal and Organic Chemistry, SmithKline & French Laboratories, PA, USA, with Dr. Robert DeMarinis and Dr. Ivan Lantos, (1985-1988); Faculty, Department of Chemistry University of Crete, Greece, (1988-present); Vice Chairman, Department of Chemistry, University of Crete, (1996-98); Chairman, Department of Chemistry, University of Crete, (1998-2000); Visiting Professor, USC, California with Prof. N.Petasis, (1998); Vice-director of the Graduate Program "Isolation and Synthesis of Natural Products with Biological Activity" (1998-present); Director of the ERASMUS Intensive Summer Course "SYNAPS, Synthesis and Retrosynthesis in the Chemistry of Natural Products" (2007-present). Author or co-author of 40 articles, 3 invited reviews, co-inventor in four international patents.

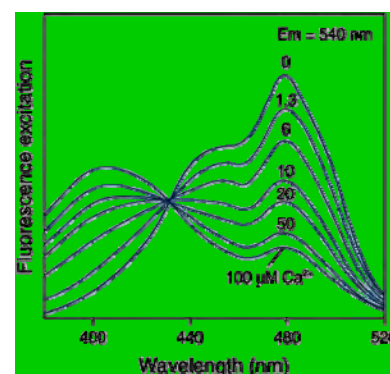
Research Interests

1. Synthesis of Fluorescent Ion Indicators.

Our contribution to this research field includes the synthesis of a number of fluorescent probes of intracellular ions. Initial experiments performed by the author during his post doctoral work at Smith Kline and French Labs (USA), aimed to the synthesis of probes with improved fluorescent properties than those already available in the market such as fura-2. This project ended successfully with the synthesis of a number of intracellular calcium probes such as FuraRed and FuraRed-AM which were patented by SKF Labs and are currently commercially available (Handbook of Fluorescent Probes and Research Chemicals, Molecular Probes, Eugene, OR, USA).

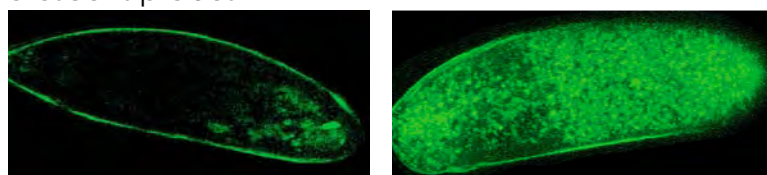


This project was continued in our laboratory resulting in the preparation of seven new calcium probes including BTC and BTC-AM, with improved properties (chemical stability, fluorescence spectra) incorporating the coumarin chromophore. The inventorship on this low affinity calcium indicators has been granted by a joint patent with Molecular Probes-USA).



A number of structural modifications on the above mentioned compounds led to further improved calcium as well as magnesium ion probes such as APTRA-BTC and APTRA BTC-AM). A TREN-type zinc probe was made in collaboration with prof. A. Kay, University of Iowa.

Our work has been extended to near-membrane calcium indicators such as C12-BTIC and C12-ICPBC, as well as selective zinc (ICPBC-Zinc), lead, and mercury-selective fluorescent probes.

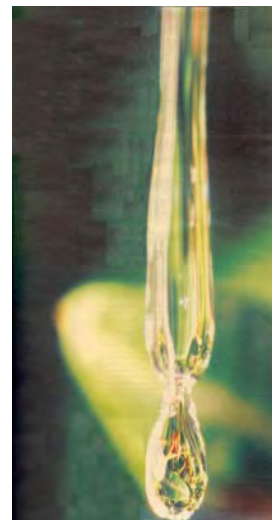


2. Isolation and Structure Determination of Components from Aromatic and Pharmaceutical Plants from the Flora of Crete.

This project, recently initiated and financed from various sources, targets the systematic characterization of the active ingredients from plants with known aromatic and/or pharmaceutical properties and the total synthesis of isolated new natural products.



The shrub of labdanum (*Cistus creticus* L., subspecies creticus), a plant that grows only in a few areas of the Mediterranean and it is known for its pharmaceutical properties, was initially selected as a representative species. The volatiles from the plant (as well as from its resin) have been characterized. The project was extended in a study of the components from a second subspecies of the plant (ssp. *Eriocephalus*) aiming the chemotaxonomic differentiation of the two subspecies, as a part of a project in collaboration with the local Chamber of Commerce. We have been also involved on the component analysis of a number of plants (*Lavandula stoechas* L., *Salvia fruticosa* Miller, *Laura* sp, *Rosmarinus officinalis* L) in collaboration with the local Plant Protection Institute. The total synthesis of *cis*-drima-7,9(11)-diene, a proposed component of *Cistus creticus* L., has been recently completed.



Our latest project was on the activity of components from the plant *Dittrichia viscosa*, as acaricides against *Varroa destructor*, the acari acting as parasite of the European honey bee. Costic acid has been identified as the active component, and the inventorship on these results has been granted by an international patent.

Our group expanded its activities in the study of aromatic and pharmaceutical plants with tasks such as:

- Improvement of the methodology for the isolation of the aromatic resin "Labdanum" from *Cistus Creticus* L. by local companies.
- Use of extracts from rosemary, lavender, sage and laurel as pest control agents in the production of grapes as well as the preservation of raisins.
- Production and quality control of essential oils from sage, dictamo (*O. dictamnus* L.) and the resin of labdanum.
- Securing the certificate of origin of the herb *Origanum dictamnus* L. to the region of Crete (initiative taken by the Co-operative of Embaros, Crete).
- Quality control of local origanum species cultivated under controlled conditions.
- Quality control of herbs available in the local market by using the composition of their essential oils as "fingerprint" of each subspecies.
- Identification of components of aromatic plants with anti-microbial and anti-cancer agents.
- Use of natural colorants from the flora of Crete in textile dyeing.
- Preparation of a recipe for the control of effect of *Varroa destructor* on bees using natural extracts.
- *Pistacia lentiscus* var *chia*: in Vitro and In Vivo Activities of Chios Mastic Gum Extract Constituents against *Helicobacter pylori*.

Synthesis and Structure - Activity Relationship (SAR) Studies of Rigid Dopamine Analogs.

This program, terminated in 1999, included the total synthesis of compounds which incorporate the dopamine moiety in a larger carbon framework. *In vitro* (binding and functional) studies of this analogs provided valuable information on the relation of their activity to structural elements such as O-N distance, dihedral angles and oxygen and nitrogen substitution within the dopamine group. The discovery that a number of these compounds also exhibit adrenergic activity prompted us to extend our studies to α_1 and α_2 adrenergic receptors. A methodology involving "Selected

Disconnections" on known active compounds such as ABBOT-68930 furnished a number of less complex molecules. Results from SAR studies on such compounds provided valuable information on the "active moiety" of the mother molecules, leading to the synthesis of drugs with optimized activity and higher selectivity.

Representative Publications

1. H E. Katerinopoulos
The coumarin Moiety as Chromophore of Fluorescent Ion Indicators in Biological Systems
Curr. Pharm. Design, **2004**, *30*, 3835-3852
2. H. E. Katerinopoulos, G. Pagona, A. Afratis, N. Stratigakis, N. Roidakis
Composition and Insect Attractant Activity of the Essential Oil of Rosmarinus Officinalis L
J. Chem. Ecol. **2005**, *31*, 111-122.
3. K. Hatzellis, G. Pagona, A. Spyros, C. Demetzos H. E. Katerinopoulos
Correction of the Structure of a New Sesquiterpene from Cistus creticus ssp. creticus
J. Nat. Prod. **2004**, *67*, 1996-2001.
4. E. Roussakis, F. Liepouri, T. G. Deligeorgiev, H. E. Katerinopoulos
ICPBC: A new red emitting, low affinity fluorescent Ca^{2+} indicator excited with visible light. Cell Calcium, **2006**, *39*, 3–11.
5. M. Dakanali, E. Roussakis, A. Kay, H. E. Katerinopoulos
Synthesis and Photophysical Properties of a Fluorescent TREN-Type Ligand Incorporating the Coumarin Chromophore, and its Zinc Complex.
Tetrahedron Lett. **2005**, *46*, 4193–4196.
6. D. Hadjipavlou-Litina, C. Kontogiorgis, E. Pontiki, M. Dakanali, A. Akoumianaki, H. E. Katerinopoulos
Anti-Inflammatory and Anti-Oxidant Activity of Coumarins Designed as Potential Fluorescent Zinc Sensors.
J. Enz. Inhib. Med. Chem. **2007**, *22*, 287-292
7. Nifli, A.-P.; Theodoropoulos, P. A.; Munier, S.; Castagnino, C.; Roussakis, E.; Katerinopoulos, H. E.; Vercauteren, J.; Castanas, E.
Quercetin Exhibits a Specific Fluorescence in Cellular Milieu: A Valuable Tool for the Study of Its Intracellular Distribution .
J. Agric. Food Chem., **2007**, *55*, 2873-2878.
8. Roussakis, E., Voutsadaki, S., Pinakoulaki, E., Sideris, D.P., Tokatlidis, K., Katerinopoulos, H.E.
ICPBCZin: A red emitting ratiometric fluorescent indicator with nanomolar affinity for Zn^{2+} ions.

Cell Calcium **2008**, *44*,270-275.

9. Roussakis, E., Pergantis, S.A., Katerinopoulos, H.E.
Coumarin-based ratiometric fluorescent indicators with high specificity for lead ions
Chemical Communications **2008**, *46*, 6221-6223.
10. Dakanali, M., Tsikalas, G.K., Krautscheid, H., Katerinopoulos, H.E.
Formate ester synthesis via reaction of 2-bromoethylamines with dimethylformamide *Tetrahedron Letters* **2008**, *49*, 1648-1651.
11. H. E. Katerinopoulos, D. Isaakidis, K. Sofou, A. Spyros
*Use of costic acid and other components from the plant *Dittrichia viscosa* (Greek: "Aconiza") and related species, as acaricide against *Varroa destructor*, the acari acting as parasite of the European honey bee.*
International Patent, **2009**, PCT Appl. No. 20080100414