Heterocycles in the Service of Humankind

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Abstract
Alleviating the scourge of biting insects; Bioconjugates for new directions in pharmaceutical research; Sharing the benefits of research

Keywords: Malaria, insect repellents, bioconjugates, chemistry publishing

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Contents

1. Overcoming the Problems of Biting Insects (Research with the participation of U. Bernier, D. Dobchev, G. Clark, C. D. Hall, K. Linthicum, S. Slavov, M. Tsikolia, Z. Wang)

Mosquito-borne diseases such as malaria, arboviral encephalitis, dengue fever, Rift Valley fever, and yellow fever, still result in significant morbidity and mortality in humans. Insect repellents often serve as a first line of personal protection. Disadvantages of current repellents include limited duration of protection from insect bites due to evaporative loss, absorption into the skin, removal by dissolution in water, skin irritation and a stinging sensation when in contact with eyelids or lips. Some repellents are only efficient when used in large quantities on the skin or clothing. The repellent most often used is DEET but a major drawback is that DEET can lead to adverse side effects in some individuals, especially from its systemic uptake via dermal absorption.

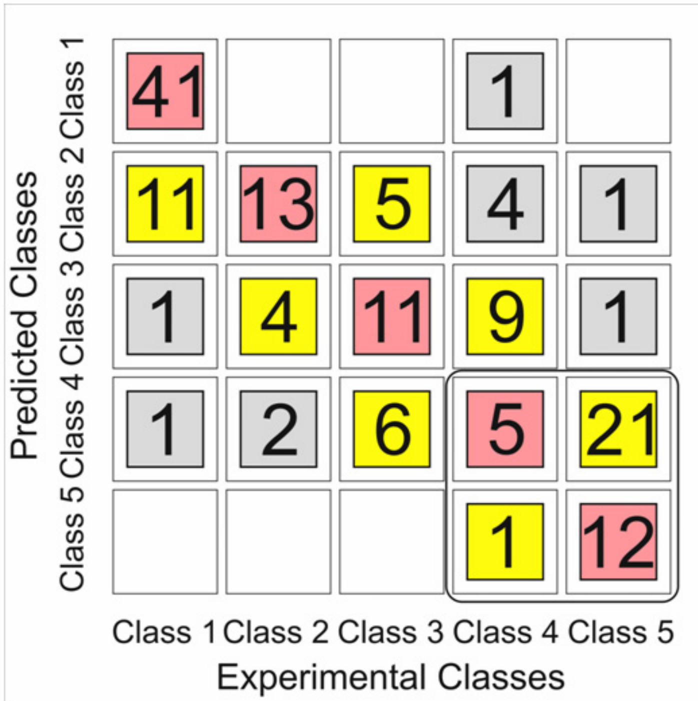
New, improved long lasting repellents that are safe and efficacious against a wide range of insects are needed. Thus, there is a long-standing interest in the design of compounds that will be effective repellents against mosquitoes, sand flies, stable flies, black flies, tsetse flies, biting gnats and tabanids, all of which spread human and animal diseases.

Although the design of new insect repellents by computer-aided molecular modeling was discussed in a recent book, there have been few previous attempts to correlate the repellency of compounds towards mosquitoes with their chemical structure.[2] Suryanarayana *et al.*[1] used a small set of 31 repellants to propose the model (eqn 1) with the rather low R^2 of 0.304: where PT = Protection Time; *log P* = lipophilicity; *V*p = Vapor pressure; *ML* = Molecular Length.

$$\mathrm{PT} = \mathbf{a}\ \log P + \mathbf{b}\ \log V\mathrm{p} + \mathbf{c}\ \log ML + d \qquad (1)$$

With the same data-set, and using descriptors derived solely from the chemical structures of the repellants we found an improved model with an R^2 of 0.79. This encouraged us to go further. Over the last few years we have been collaborating with the U.S. Department of Agriculture at the University of Florida, which over the past 60 years have recorded tests covering a wide range of insect species and some 30,000 different compounds. Properties such as protection time, effective dose and lethal dose towards a large numbers of insects including various species of mosquitoes, houseflies and other pests were amassed. We were given access to these records and in agreement with the Department of Agriculture embarked on a program to try and extract from them some information that would allow us to understand the relationship between the biological activity of compounds and their chemical structures. This lecture concerns the work that we have carried out with *N*-acylpiperidines, and which is described in detail in *Proc. Nat. Acad. Sci. USA,* 2008.

The USDA records included more than 150 different *N*-acylpiperidines which had been tested for their effectiveness as mosquito repellants. These compounds were classified according to their effectiveness into five classes, 1 being the least active and class 5 being the most active. The most active compounds retained effectiveness for 21 days. By building a neural network model, we were able to correlate protection times from the old USDA data with the chemical structures as is shown in Figure 1.



Class	Prediction
-3	2
-2	5
-1	35
on spot	82
+1	22
+2	3
+3	1

Figure 1. Correlation of protection times (old USDA data) with chemical structures by ANN.

We re-synthesized 11 of the *N*-acylpiperidines that were previously tested in order to anchor the envisaged biological testing into the existing data. Piperidines were synthesized utilizing acylbenzotriazoles prepared from carboxylic acids by treatment with thionyl chloride and benzotriazole. In addition to the 11 previously tested *N*-acylpiperidines, we synthesized 23 novel *N*-acylpiperidines as potential repellants. These 23 compounds were selected by first using our neural network model to predict the likely activity of many hundreds of compounds. Most of the 23 compounds selected were expected to be highly active but a few were also chosen that were predicted to have lower activity.

Biological testing was carried out for all 23+11=34 compounds synthesized, together with DEET. Bioassays were conducted by covering the hand of a volunteer with a soft-embossed long cuff poly glove and powder-free latex glove. To cover the arm a stocking is pulled over. A sleeve with an opening (3 cm x 8 cm) was fastened around the arm. Each cloth patch assembly was affixed over the open window with masking tape to hold it in place on the sleeve. The arm is then inserted into the cage of mosquitoes and held stationary for 1 minute. The number of feeding mosquitoes was counted prior to removal with a quick, brisk shake of the arm. Feeding mosquitoes that remained in the window were considered to have been biting.

The failure threshold for repellency for these experiments was set at 1% biting (5 bites) confirmed by achievement of two consecutive days of 5 or more bites. The results are shown in Table 1 and graphically in Figure 2. Gratifyingly, several of the compounds prepared showed considerably improved protection times compared to DEET.

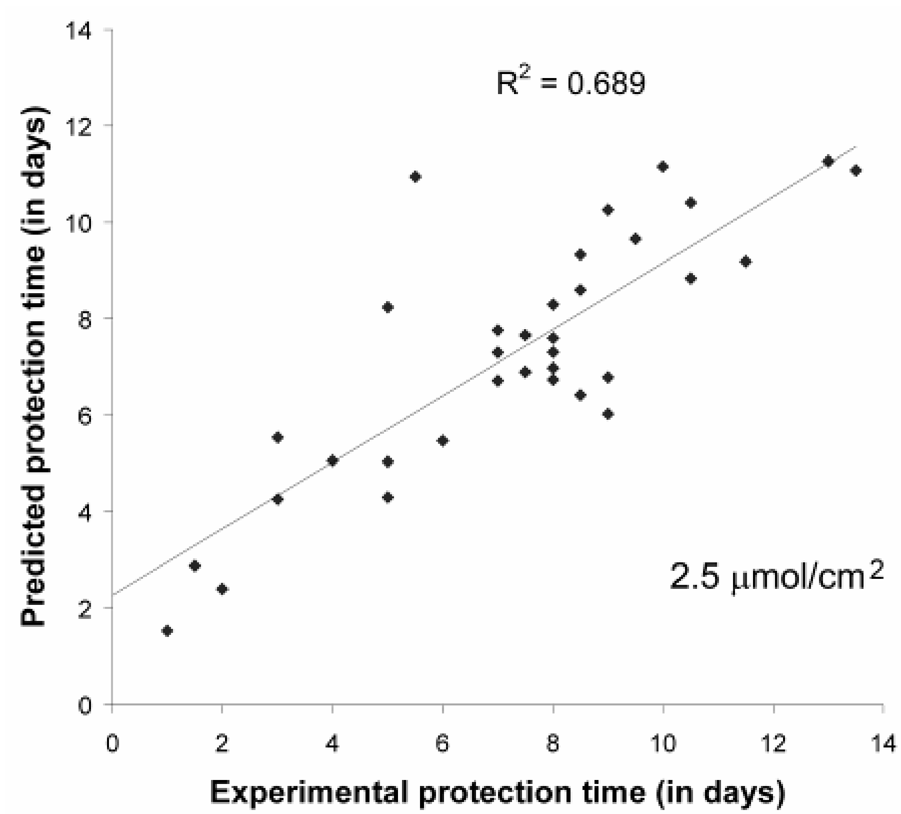


Figure 2. Correlation of protection time with chemical structure for the newly synthesized N-acylpiperidines.

The structures of the most effective compounds and their protection times are compared with DEET in Figure 3. These compounds are now being subjected to toxicity and other tests to see if they can be applied. We have particularly not asked for any patent protection for any of this work in order to make the results available to the whole world as quickly as possible.

Table 1. Average protection time in days

Compound			Average PT		Compound			Average PT	
ID #	R	R'	25 µmol/cm²	2.5 µmol/cm²	ID #	R	R'	25 µmol/cm²	2.5 µmol/cm²
DEET			17.5	2.5					
4a	Me	2-Me	2	2	**4a'***	1-*c*-C_6H_9	H	17	5
4b	Et	H	5	4	**4b'***	*c*-C_6H_{11}	H	14	8
4c	Et	2-Et	5	3	**4c'***	*c*-C_6H_{11}	3-Me	17	6
4d	*n*-C_6H_{13}	2-Me	17	5	**4d'***	*c*-C_6H_{11}	4-Me	24.5	8.5
4e	*n*-C_6H_{13}	3-Me	15.5	7.5	**4e'***	*c*-$C_5H_9(CH_2)_2$	H	35	9
4f	*n*-C_7H_{15}	4-Me	48	8	**4f'***	1-Me-*c*-C_6H_{10}	3-Me	12	7
4g	*n*-C_7H_{15}	4-Bn	13	7	**4g'**	4-Me-*c*-C_6H_{10}	2-Me	33	8.5
4h	*n*-C_8H_{17}	2-Et	43	9.5	**4h'***	*c*-C_6H_{11}	2-Et	21.5	7
4i	*n*-C_9H_{19}	2-Me	49.5	8	**4i'***	*c*-$C_6H_{11}CH_2$	2-Me	29.5	7.5
4j	*n*-C_9H_{19}	4-Me	41	11.5	**4j'***	*c*-$C_6H_{11}(CH_2)_2$	2-Me	47.5	10
4k*	CH_2=CH(CH_2)	H	50	13.5	**4k'***	*c*-$C_6H_{11}(CH_2)_2$	3-Me	35	9
4l	CH_2=CH(CH_2)	2-Et	53	9	**4l'**	*c*-$C_6H_{11}(CH_2)_2$	4-Me	45.5	8
4m	CH_2=CH(CH_2)	4-Bn	8.5	8	**4m'**	*c*-$C_6H_{11}(CH_2)_3$	4-Me	33	3
4n	CH_2=CH(CH_2)	4-Me	73	10.5	**4n'**	*c*-$C_5H_9(CH_2)_2$	2-Et	40.5	8.5
4o	*n*-$C_{10}H_{21}$	H	39.5	13	**4o'**	*c*-$C_6H_{11}(CH_2)_2$	2-Et	42	10.5
4p	*n*-$C_{11}H_{23}$	2-Me	14.5	5	**4p'**	*c*-$C_6H_{11}CH_2$	4-Bn	3	1.5
4q	*n*-$C_{11}H_{23}$	3-Me	19.5	5.5	**4q'**	*c*-$C_6H_{11}(CH_2)_2$	4-Bn	12	1

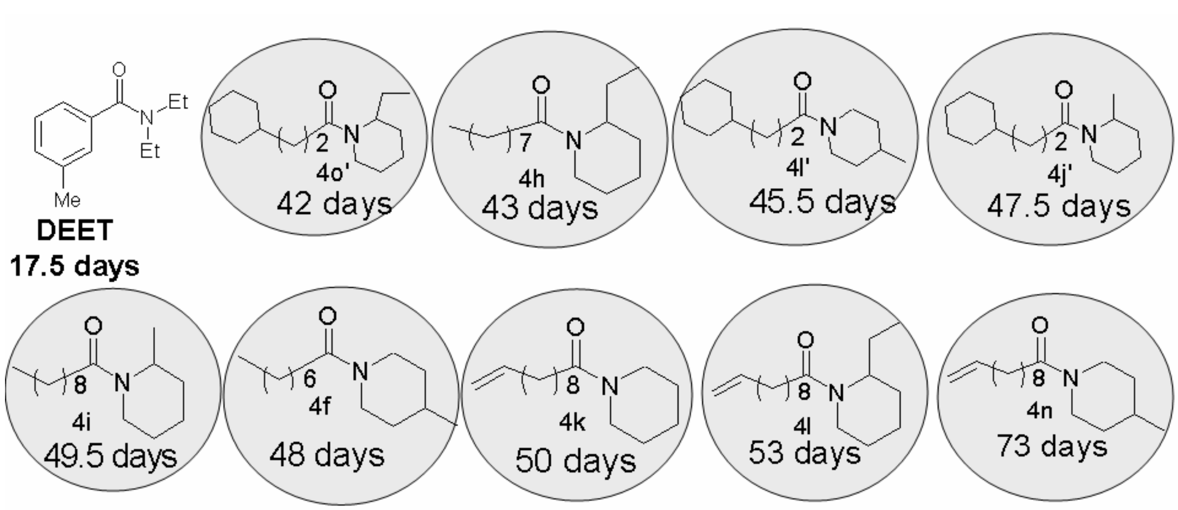


Figure 3. Protection time (25 µmol/cm^2) and structures.

2. Bioconjugates for New Directions in Pharma Research: Applications of Acylbenzotriazoles. (Research with the participation of P. Angrish, B. E.-D. M. El-Gendy, D. Haase, L. Khelashvili, T. Narindoshvili, S. Tala)

The pharmaceutical industry is in crisis. It is becoming increasingly difficult to find new major drugs. Many of the time-honored strategies for drug research seem to be failing. One direction that is opening up is that of bioconjugates. Bioconjugates can be defined as compounds in which at least two fundamentally different types of organic structure are linked together. Table 2 shows the possibilities considering two out of six compound classes to be linked to each other or to another class. Some of the different types of bioconjugates displayed in Table 2 are very well known, but others have hardly been studied.

Table 2. Bioconjugates for new directions in pharma research

	Amino Acids	Mono Saccharides	Lipids	Steroids Terpenes	Porphyrins	Biomarkers
Amino Acids	Proteins	Glycoproteins Glycopeptides	Lipoprotein Lipoamino acids Lipopeptides	Peptidyl steroids	Porphyrin-amino acid derivatives	Biomarked amino acids
Mono Saccharides	Glycoproteins Glycopeptides	Sugars Starches	Glycolipids Lipopolysacch aride	Steroidal glycosides	Glycoporphyrins	Biomarked carbohydrates
Lipids	Lipoprotein Lipoamino acids Lipopeptides	Glycolipids Lipopolysaccharide	Fats	Lipoproteins	Lipoporphyrins	Biomarked lipids
Steroids Terpenes	Peptidyl steroids	Steroidal glycosides	Lipoproteins	Higher Terpenoids	——	Biomarked steroids
Porphyrins	Porphyrin-amino acid derivatives	Glycoporphyrins	Lipoporphryins	——	Polyporphyrins	Biomarked porphyrins
Biomarkers	Amino acid biomarkers	Carbohydrate biomarkers	Lipid biomarkers	Steroid biomarkers	Porphyrin biomarkers	——

An easy and often convenient way of linking two structural units together in organic chemistry is acylation. The classical way to affect acylation uses acid chlorides, but there are disadvantages. Recently[3] we introduced *N*-acylbenzotriazoles as substitutes for acid chlorides. Several advantages are associated with these reagents:

1. Preparation: rapid one-pot procedures with mild reaction conditions (THF; 20 ^{o}C; 2 hr)
   BtH + $SOCl_2$ $\rightarrow$ [BtSOBt] + RCO_2H $\rightarrow$ RCOBt; RCO_2Na + BtTs $\rightarrow$ RCOBt +TsONa.
2. Isolation: easily in crystalline form; high yields and purity without chromatography.
3. Stability: can be weighed out and handled in air, and stored at 20°C for many weeks.

4. Insensitive to water and thus can be used in partly aqueous solution: this allows peptide-coupling using amino acids with free carboxyl groups.
5. Protection not usually required for aliphatic or aromatic -OH, heterocyclic -NH, -SH, or -CONH$_2$.
6. They are more reactive and more crystalline than acyl imidazoles.
7. The Bt group is readily replaced by N-, S-, O-, and C- nucleophiles.

Acylbenzotriazoles can be applied to classical problems such as the synthesis of "difficult" peptide sequences, one of which is shown in Figure 4.[4]

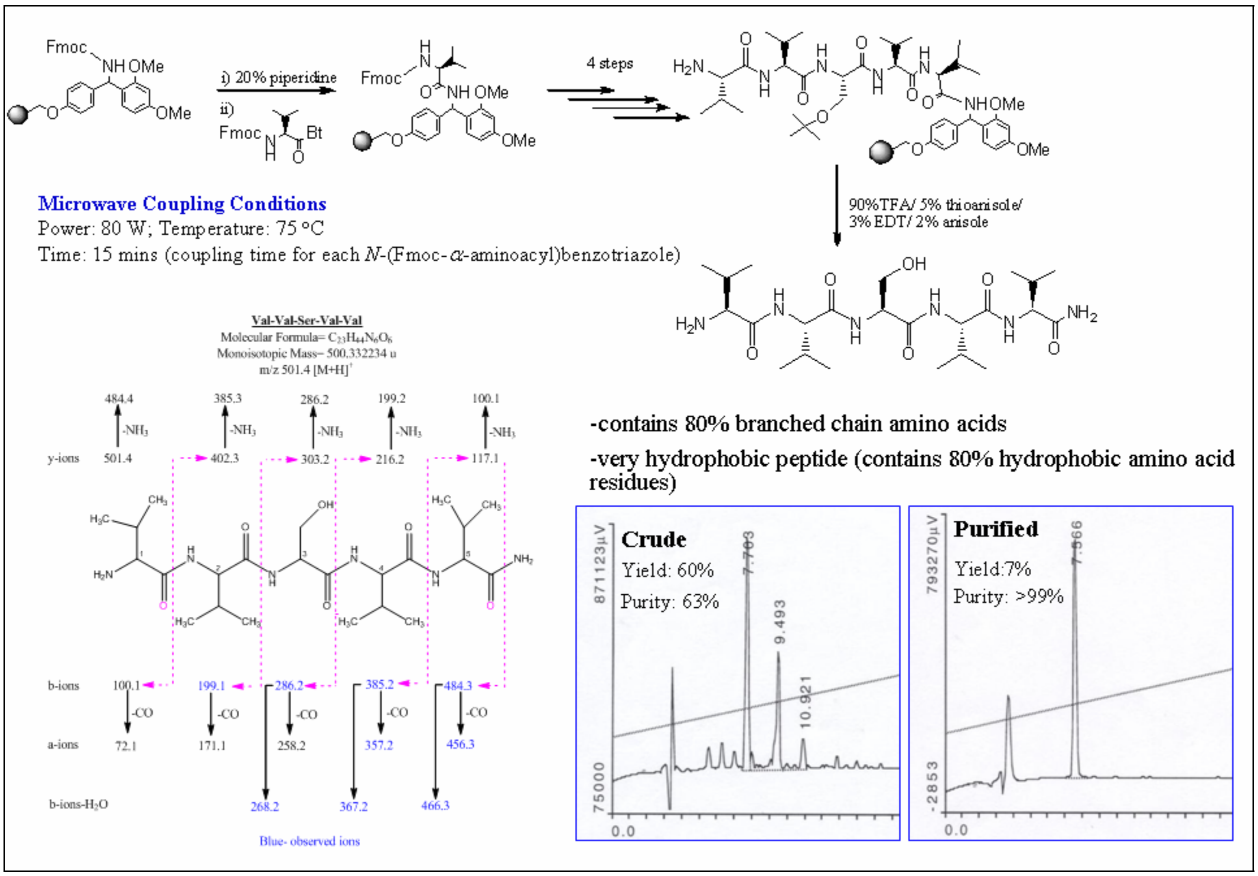


Figure 4. Microwave-assisted solid phase synthesis of a short difficult pentapeptide.[4]

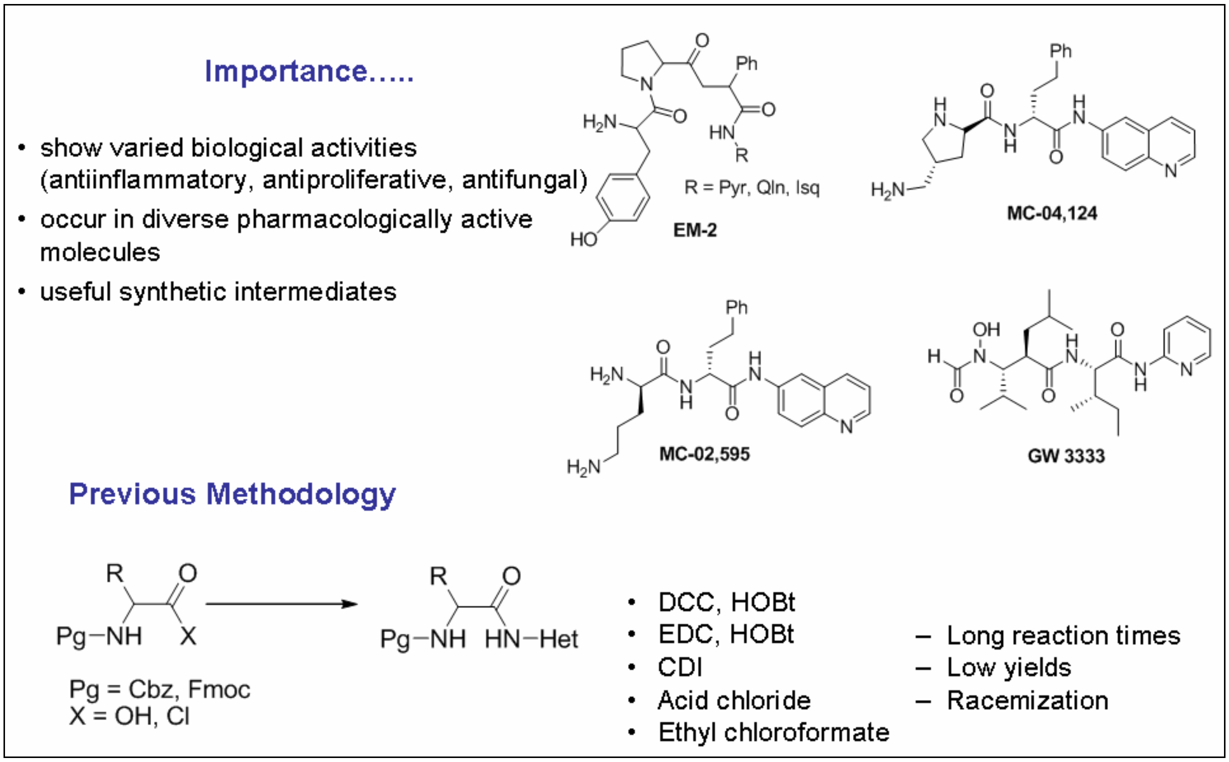


Figure 5. Importance and background for α-aminoacylamino-substituted heterocycles.

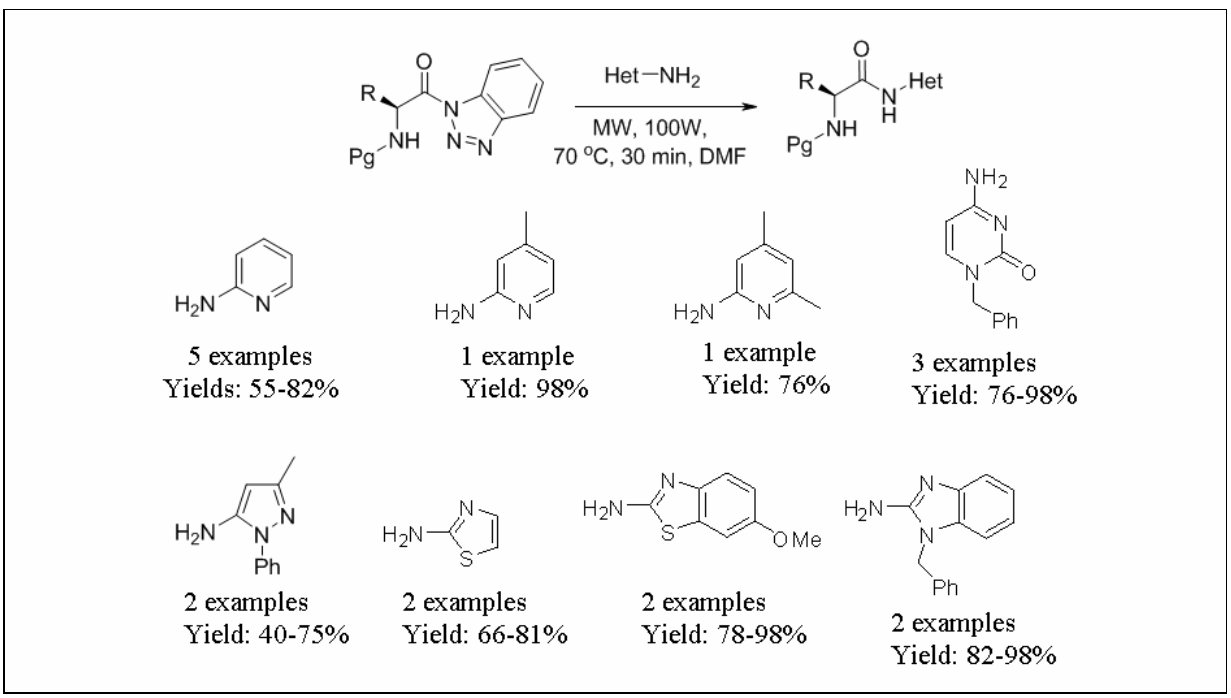
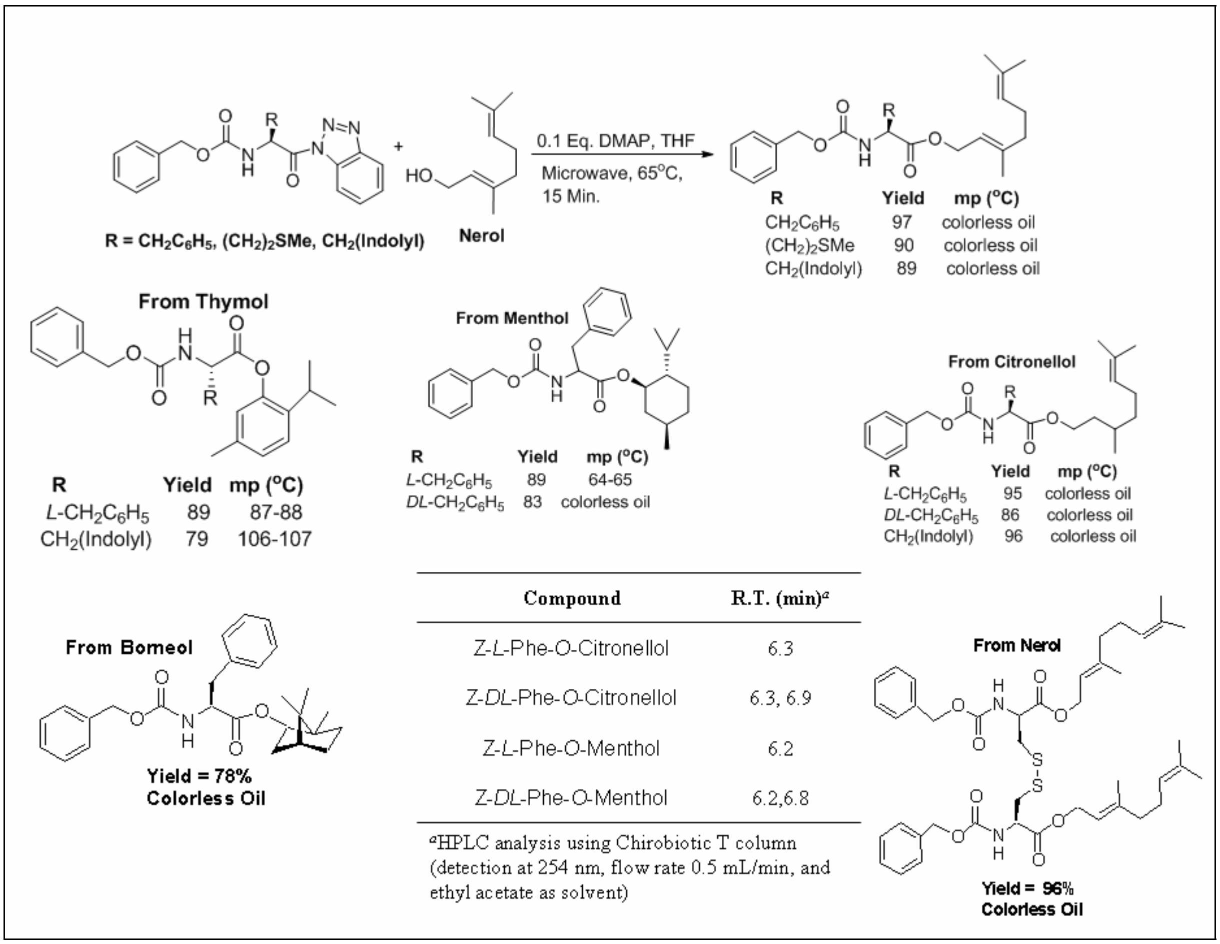


Figure 6. Novel α-aminoacylamino-substituted heterocycles prepared.[5]

Another application[5] is in the preparation of α-aminoacylamino- substituted heterocycles which show many diverse biological activities. Figure 5 shows some examples of this, comparing the new methodology with the old, and resulting in the preparation of a diverse range of such compounds — additional examples of which are shown in Figure 6.

We have linked amino acids with terpenes through hydroxyl groups, as summarized in Figure 7.[6] The data in Figure 7 also demonstrate the fact that chirality is preserved in the preparation and reactions of acylbenzotriazoles. Thus *DL*-Phe-*O*-citronellol shows retention times corresponding to each of the two diastereoisomers, whereas the analogous *L*-phenylalanine product shows only one peak.

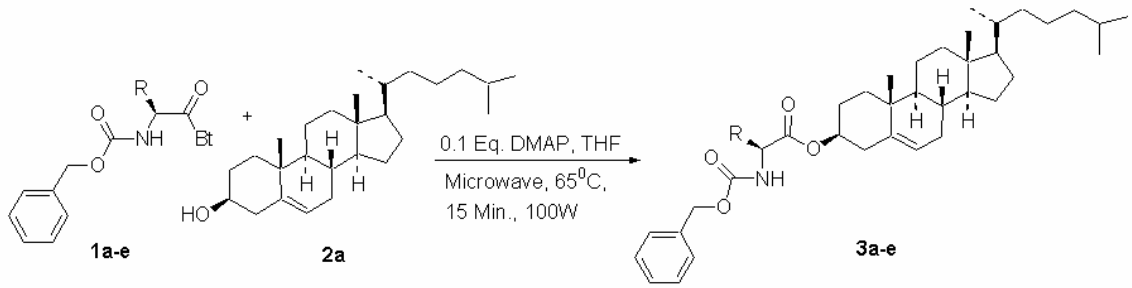


Compound	R.T. (min)[a]
Z-*L*-Phe-O-Citronellol	6.3
Z-*DL*-Phe-O-Citronellol	6.3, 6.9
Z-*L*-Phe-O-Menthol	6.2
Z-*DL*-Phe-O-Menthol	6.2,6.8

[a]HPLC analysis using Chirobiotic T column (detection at 254 nm, flow rate 0.5 mL/min, and ethyl acetate as solvent)

Figure 7. Preparation of *N*-protected (α-aminoacyl)oxy-substituted terpenes.[6]

Similarly amino- acid residues can be linked to steroids: Figure 8 shows some bioconjugates derived from cholesterol linked to a variety of amino acids.[7]



Entry	R	Product	Yield[a] (%)	mp (°C)
1	$-CH_2C_6H_5$ (**1a**)	*Z*-*L*-Phe-*O*-Cholesterol (**3a**)	82	93–94
2	$-CH_2$(Indolyl) (**1b**)	*Z*-*L*-Trp-*O*-Cholesterol (**3b**)*	84	105–106
3	$-CH_2CH_2SMe$ (**1c**)	*Z*-*L*-Met-*O*-Cholesterol (**3c**)	82	96–97
4	$-CH_2C_6H_5$ (**1d**)	*Z*-*D*-Phe-*O*-Cholesterol (**3d**)*	87	96–97
5	$-CH_2CH(CH_3)_2$ (**1e**)	*Z*-*L*-Val-*O*-Cholesterol (**3e**)	87	97–98

[a]Isolated yield; * HPLC analysis using Chirobiotic T column (detection at 254 nm, flow rate 0.5 mL/min, and ethyl acetate as solvent) : Retention Time for **3a**: 9.3 min. and **3d**: 10.1 min.

Figure 8. Microwave- assisted synthesis of *α*-(protected-aminoacyl)oxysteroids.[7]

Isotopic labeling

Stable Isotopic Labeling : labeling by including unusual, stable isotopes in chemical composition
Detection : Mass spectrometry and infrared spectroscopy.
Drawback: Expensive labeling and detection.

Radioisotopic Labeling: Labeled by including radioisotopes in chemical composition.
Radioisotope undergoes radioactive decay, and emits gamma rays and/or subatomic particles.
Detection : By measuring the emitted radiation.
Drawback : Accident or poor disposal can cause a radioactive contamination of the environment.

Fluorescent labeling

Covalently attaching a fluorophore to a biomolecule.
Detection: Labeled molecule is detected via fluorescence microscope or other fluorescence reading instrument.
Common fluorescent dyes: Fluorescein, rhodamine, coumarin, Alexa Fluors, Dylight fluors.
Advantage: Cheap, easy, and very sensitive.

Dye labeling

Introduction of chromophores into the biomolecule.
Being strongly absorbing in the visible region can be used for visual detection or colorimetric probes.
To participate in Fluorescence Resonance Energy Transfer (FRET) as a quencher to develop molecular beacons.
Advantage: Cheap labeling and detection under ambient conditions.

Figure 9. Tagging techniques for molecules.

Tagging has become extremely important for biomolecules (Figure 9).

Azo-dye- labeled *O*-aminoacyl terpenes, -sugars, and -steroids[8] have been prepared by the new technique, as illustrated in Figure 10.

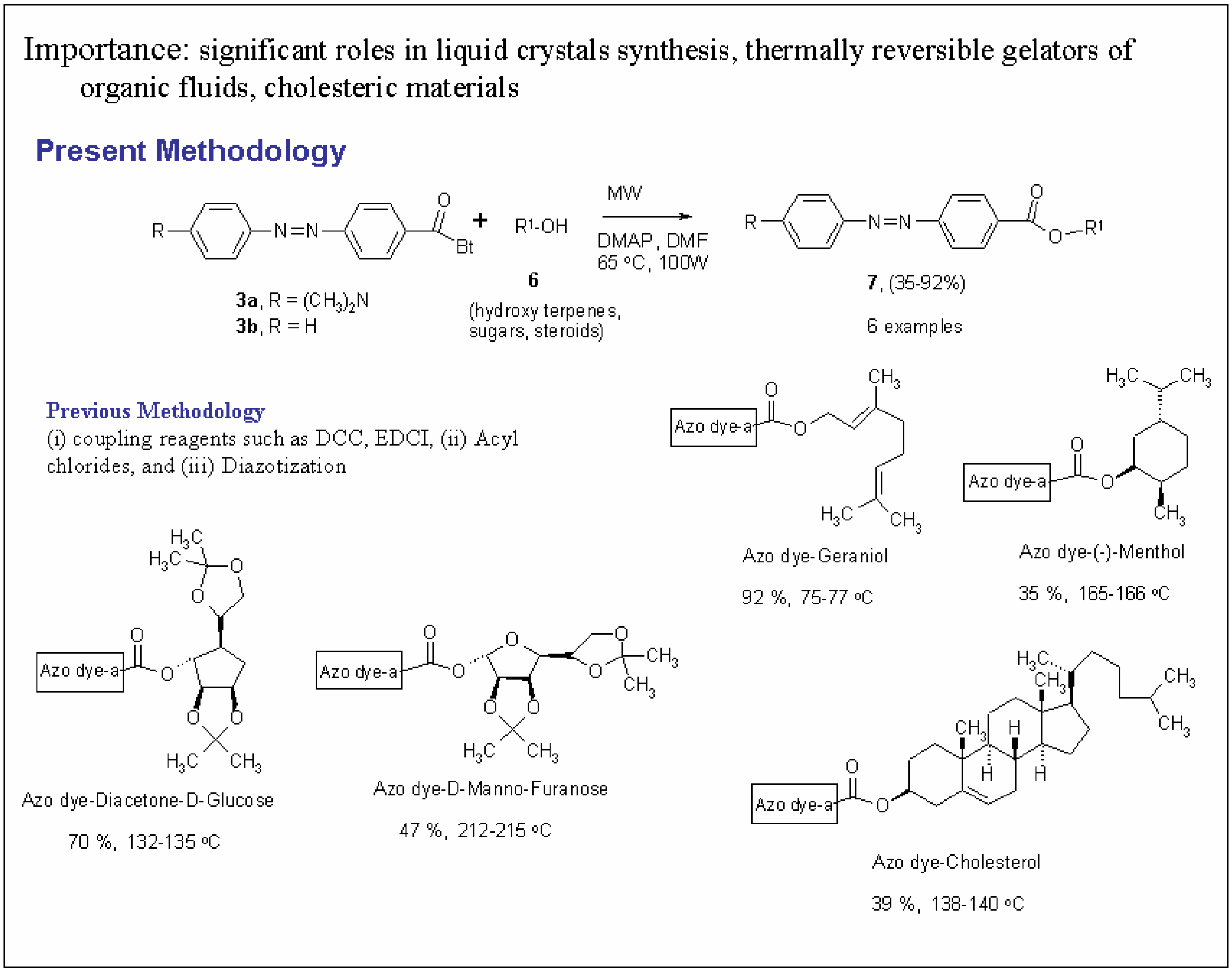


Figure 10. Preparation of azodye labeled terpenes, sugars and steroids.[8]

Fluorescent markers are often even more effective than dye markers. We have shown that coumarin units can be utilized in combination with lysine chemistry to tag a variety of amino acids and peptides[9] (Figure 11).

Incorporation of a sugar unit confers solubility on such compounds and some examples of this technique[10] are shown in Figure 12.

A series of dye- labeled nucleosides[11] is shown in Figure 13.

Similar techniques have been applied to dye- label amino acids and dipeptide amino alcohols,[12] as shown in Figure 14.

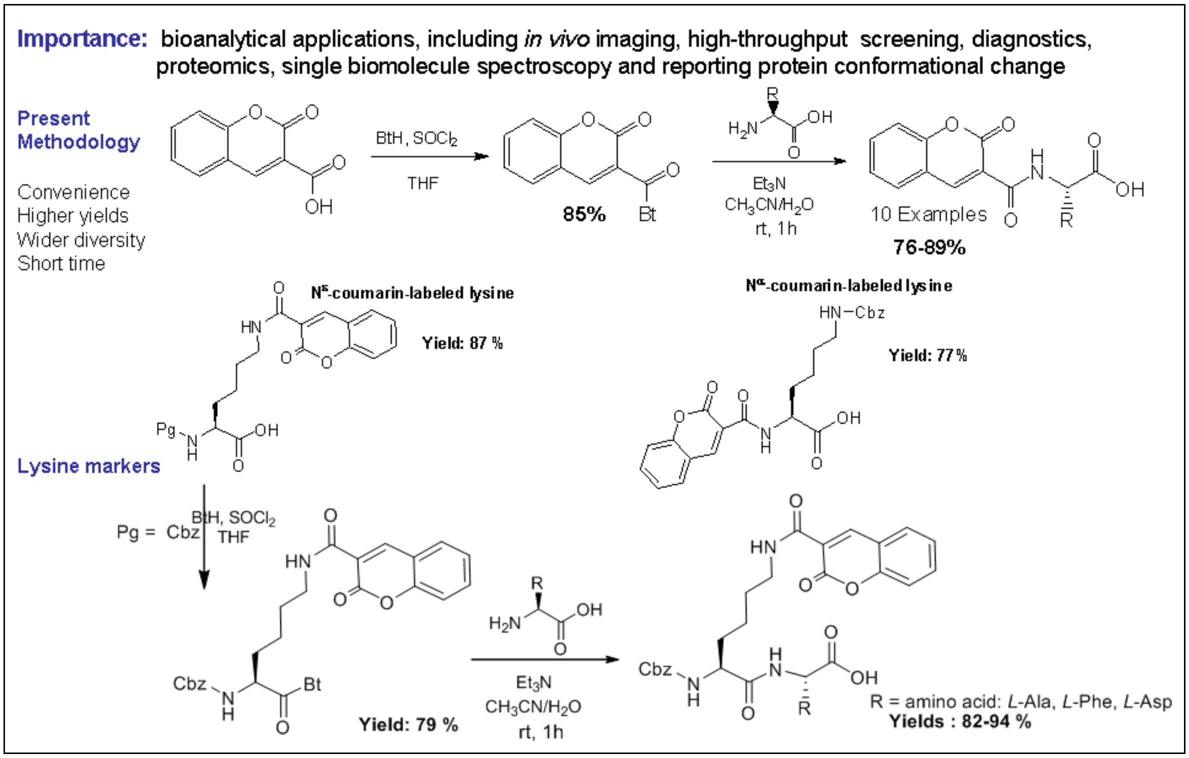


Figure 11. Fluorescent markers for amino acids and dipeptides.[9]

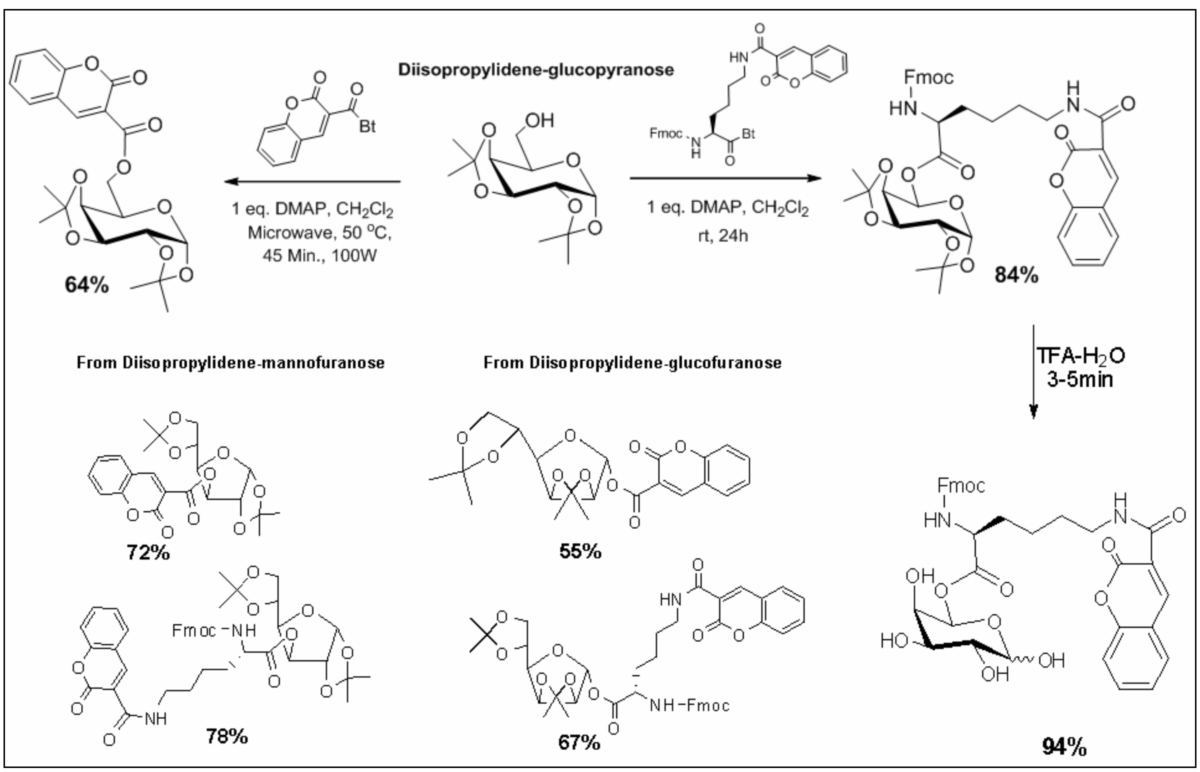


Figure 12. *O*-Labeled sugars and water-soluble fluorescent tags.[10]

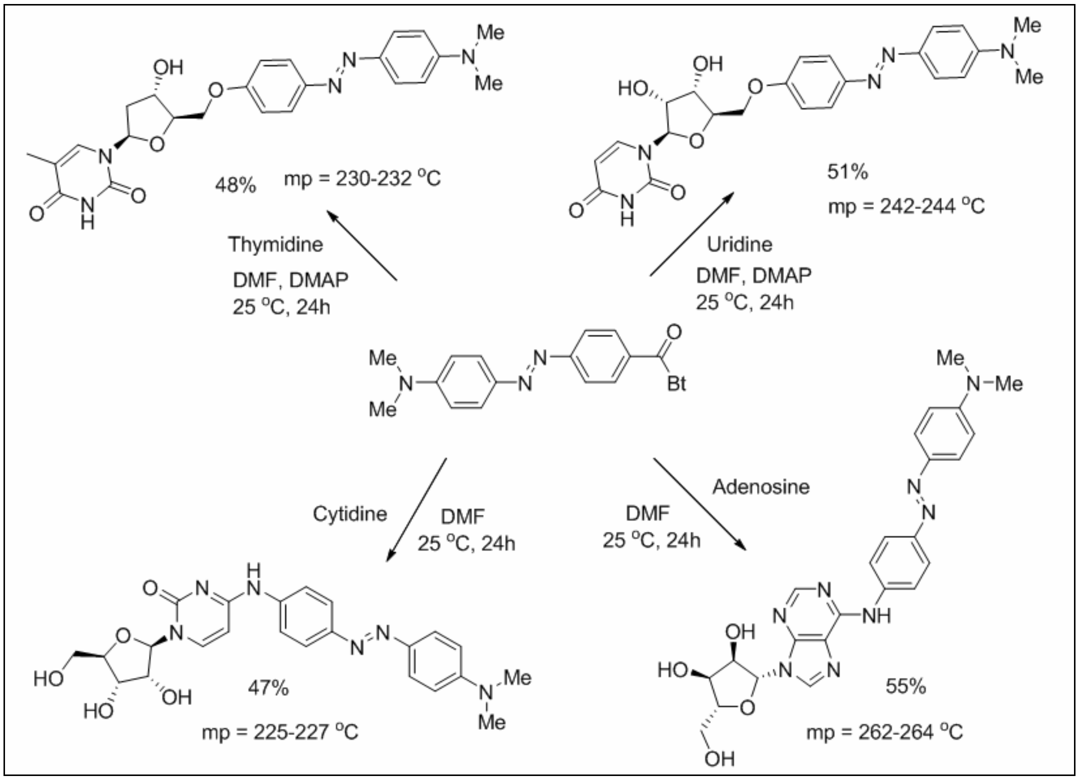


Figure 13. Preparation of dye- labeled nucleosides.[11]

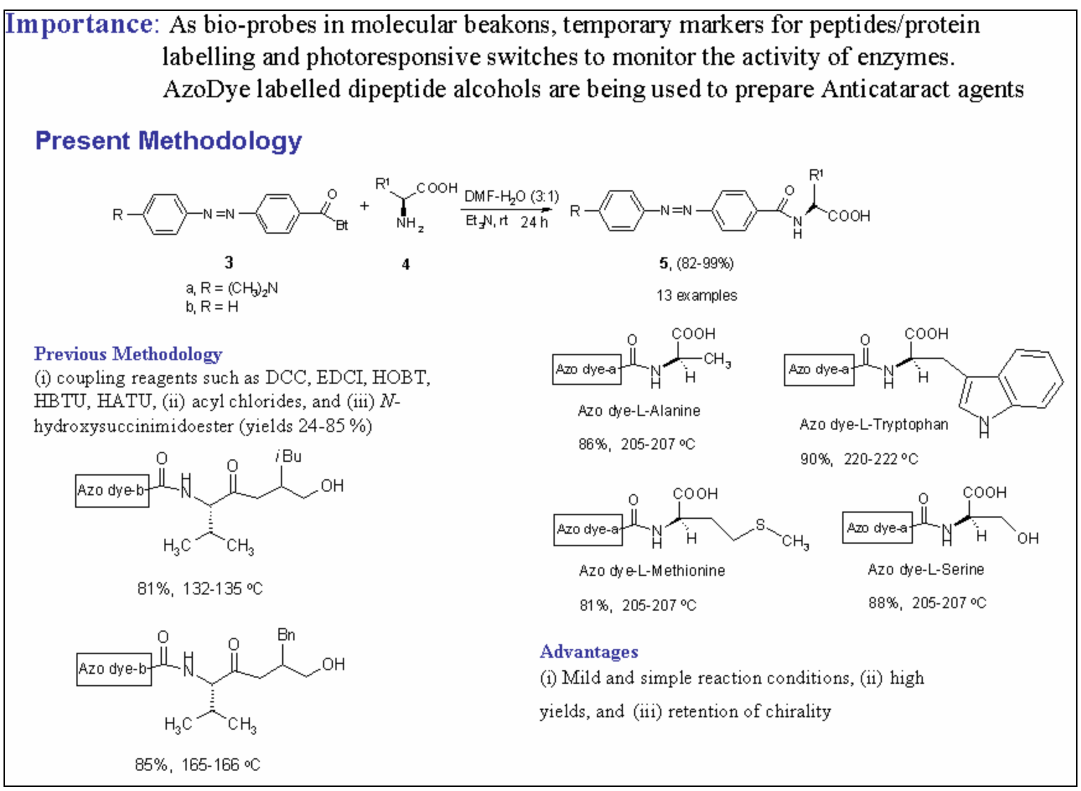


Figure 14. Synthesis of azo-dye- labeled amino acids and dipeptide alcohols.[12]

3. Attempts to help Chemistry in Developing Countries by Innovations in the Publishing and Dissemination of Organic Chemistry Research

The problems faced by libraries in meeting the high subscriptions required by commercial publishers are well known. The subscriptions set by learned societies for access to their publications are also high. This has given rise to the so-called "open access journals" where there is no charge to the reader, but page charges are levied on authors. In these circumstances it was decided eight years ago to launch a new journal with a very different philosophy: it would be free to authors, with no page charges or other fees, and also free to readers with no access or downloading charges. Thus Arkivoc was designed for universal on-demand distribution at no cost to authors or subscribers (see Figure 15).

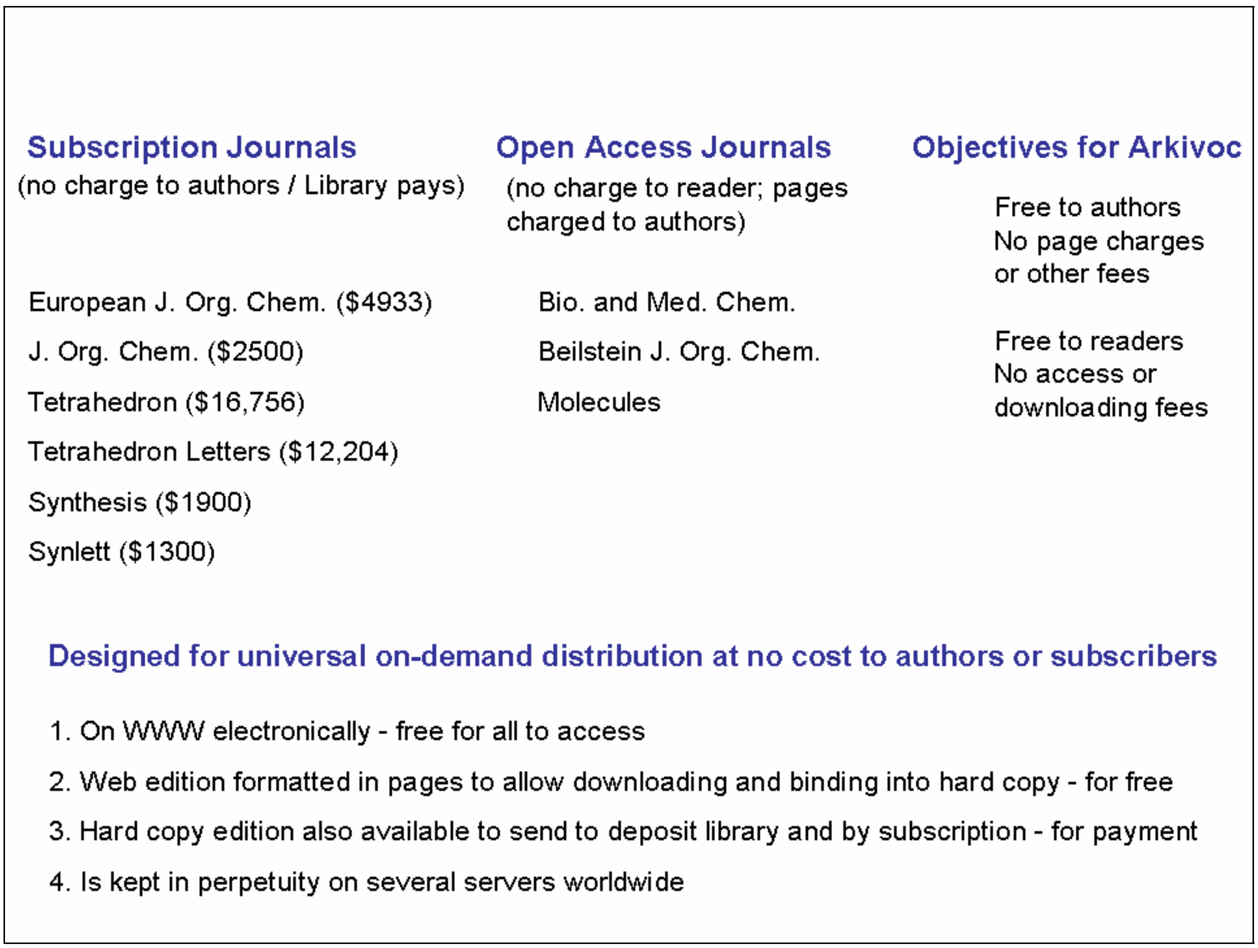


Figure 15. Publishing of chemistry in 2008.

Many of the standard publishing procedures are used in Arkivoc, as detailed in Figure 16, but a major difference is that the "Control Board" which runs Arkivoc is unpaid. The composition of the Control Board as of spring 2008 is shown in Figure 17.

1. Instructions for authors including template available at www.arkat-usa.org
2. Authors contact Coordinating Editor by e-mail with MS title, authors, brief abstract
3. Coordinating Editor designates MS reference number, Scientific Editor, and referees
4. MS sent to Referees by e-mail
5. Referees send reports to Scientific Editor by e-mail
6. Scientific Editor makes decision as to accept the paper as it is, to ask author to amend manuscript, to seek additional Referee comments, or to reject paper
7. Author revises MS to satisfaction of Scientific Editor
8. Scientific Editor corresponds with authors until manuscript is accepted or rejected
9. Accepted manuscript sent to Publishing Editor, who arranges for technical editing and sending in for posting on the web

Figure 16. Submitting, refereeing and editing of manuscripts in ARKIVOC.

Referee Assigners: E. Anders (U. Jena, Germany), A. J. Boulton (also Coordinating Ed, UEA, UK), W. Dolbier (U. Florida, USA), B. Wakefield (U. Leeds, UK)

Scientific Editors: M. Begtrup (Roy. Sch. Pharmacy, Denmark), G. Cirrincione (U. Palermo, Italy), M. A. Iglesias- Arteaga (Nat U Mexico), H. Ila (Indian Inst Sci Kanpur), J. Joule (U. Manchester, UK), A. Kotali (U.Thessaloniki, Greece), P. Krapcho (U. Vermont, USA), B. Maes (U. Antwerp, Belgium), A. Marchand (Coral En, Inc.), R. Muthyala (U. Minnesota, USA), C. Ramsden (Keele U., UK), J. Schantl (U. Innsbruck, Austria), C. Stevens (Ghent U., Belgium), A. Waring (U. Birmingham, UK), V. Zhdankin (U. Minnesota, USA)

Technical Editors: R. Murugan (Vertellus, Indianapolis, USA), A. Sherman (Coll. Notre Dame, Maryland, USA)

Publishing Editor: E. Scriven (U. Florida, USA)

Web Auditor: A. J. Aanonson (Brunel U., UK)
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Figure 17. ARKIVOC organization: Control Board as of March 2008.

We also have a very large Editorial Board of Referees. This has recently been extended significantly, and we now have close to 1,000 members. One difference from most editorial boards of referees is that we have about half our members from outside Western Europe, North America or Japan (see Figures 18 and 19) for representative lists.

During the eight years of existence, Arkivoc has progressed significantly in the number of manuscripts received and published. The number of visitors to its website has also increased dramatically; we now have about 100,000 visitors per month who make more than a million hits per month on the website.

Austria: U. Brinker, J. Froehlich, P. Gaertner, N. Haider, C. O. Kappe, M. D. Mihovilovic, T. Rosenau, M. Schnürch, P. Stanetty
Belgium: K. Abbaspour Tehrani, N. Kimpe, W. Dehaen, M. D'hooghe, R. Dommisse, L.Ghosez, A. Krief, I. Marko, C. Stevens, J. Vanden Eynde, G. Verniest
Canada: E. Buncel, K. Darvesh, T. Fyles, P. Georghiou, J. Kresge, T. Lowary, H. Muchall, T. Ollevier, Thomas Tidwell
Denmark: J. Becher, M. Begtrup, P. Hansen
Finland: K. Klika, M. Oivanen, K. Pihlaja, E. Sievänen
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Netherlands: L. Jenneskens, R. Kellogg
Norway: J. Bakke, P. Carlsen, F. Rise, K. Undheim
Portugal: P. Almeida, A. Lobo,C. Oliveira, A. Oliveira-Campos,A. Silva
Spain: B. Abarca, M. Alvarez, J. Alvarez-Builla, M. Amat, J. Aurrecoechea, F. Aznar, J. Barluenga, J. Fernández Bolaños, J. Bosch, L. Castedo, C. Cativiela, R. Claramunt, D. Diez, E. Díez-Barra, J. Elguero, B. Fontaniella, V. Gotor, C. Lopez, J. Marquet Cortes, J. Menendez, P. Merino, P.Molina, M. Montiel, F. Palacios, C. Palomo, M. Parra, J. Plumet, E. Roman, R. Suau, A. Tárraga, T. Torroba, M. Yus
Sweden: J. Bergman, S. Grivas, T. Janosik, C. Linde, J. Stawinski
Switzerland: H. Heimgartner, C. Jefford
United Kingdom: K. Afarinkia, A. Aitken, D. Allen, S. Allin, R. Bedford, S. Bew, R. Chambers, R. Coombes, M. Cronin, A. de Silva,I. Eggleston, C. Frost, L. Harwood, H. Heaney, W. Horspool,H. Hudson,K. Jones, R. Jones, J. Joule, N. Karodia, D.Kelly, W. Kerr, P. Knowles, B. Linclau, S. Marsden, H. Maskill,T. McKervey, C. Moody, P. Murphy, P.Page, G. Pattenden, M. Plate, C. Ramsden, D. Rees, C. Reese, G. Sandford, J. Shorter, K. Smith, E. Thomas, J. Walton
United States: A.Fattah,R. Abramovitch, P. Angrish, D. Arya, R. Asolkar, W. Bailey, A. Balaban, B.Banik, S. Berthel, N. Bharti, E. Biehl,N. Bodor, D. Bonchev, S. Branz, J. Brown, X. Bu, J. Byers, C. Cantrell, T. Chandra, M. Charton, H. Chen, G. Cherukupalli, S. Chittaboina, M. Chorghade, D. Comins, D. Dalton, S. De, R. Dembinski, S. Deng, G. Dong, A. Dutta, F. Ebetino, L. Echegoyen, E. Enholm, A. Franz, A. Fry, R. Glass, D. Glueck, M. Harmata, T. Harris, L. Hawkins, N. Hebert, R. Hinkle, C. Hulme, M. Ilies, S. Janaswamy, G. Jones, S. Jonnalagadda, F. Kang, A. Katritzky, D. Ketcha, J. Kiely, R. Kinnel, P. Kiprof, K. Kirichenko, H. Kolb, P. Krapcho, S. Kumar, I. Lalezari, H. Lang, V. Lobanov, A. Marchand, A. Martin, T. Masquelin, N. Meanwell, R. Millar, G. Mittapalli, P. Mohapatra, R. Murugan, R. Muthyala, V. Nair, K. Nakanishi, T. Nalli, G. Negrete, G. Newkome, E. Olson, D. Ostercamp, P. Otten, A. PadwaD. Palmer, K. Pankiewicz, C. Parkanyi, A. Pathak, E. Pelkey, D. Pleynet, G. Prakash, M. Quirke, T. Ramachandar, M. Reddy, C. Reddy, M.Mohan Reddy, J. Richard, N. Richards, S. Roy, S. Roy, J. Russel, S. Sabesan, V. Samano, M. Samant, R. Sauers, M. Saulnier, E. Scriven, Y. Sham, I.Shcherbakova, T. Singh, H. Sintim, M. Siskin, K. Smith, X. Song, P. Srirama Sarma, C. Stephens, L. Strekowski, B. Terem, K. Turnbull, A.Vakulenko, C. Verbicky, R. Walczak, M. Walker, A. Wilcox, S. Wiskur, D. Wright, M. Wright, K. Wu, T. Wu, J. Yevich, Y. Yuan, Y. Zhang, Y. Zhang,V. Zhdankin, C. Zhou, P. Zuman

Figure 18. ARKIVOC Editorial Board of Referees: members from W. Europe, N. America, Japan.

Figure 19. ARKIVOC Editorial Board of Referees: members from outside W. Europe, N. America, Japan.

An important part of the philosophy of ARKIVOC is to honor chemists from around the world. Distinguished scientists, including chemists, have long been honored in their own countries and a small number, mainly from a few Western developed countries, are honored internationally. Arkivoc has chosen to recognize chemists from around the world and, so far we have produced 85 commemorative issues (Figure 20).

Country	Year	Chemist
Argentina	2003	Rossi
	2003	Ruveda
	2005	Ledekremer
Austria	2001	Sauter
Australia	2001	Cameron
	2004	Rickards
Belgium	2003	Hoornaert
	2007	Krief
Belarus	2008	Kulinkovich
Bulgaria	2009	Conference
Botswana	2007	Abegaz
Brazil	2004	Gottlieb
Canada	2001	Tee
	2002	Muchowski
	2009	Sorensen
China	2003	Huang
	2004	Yuan
Croatia	2002	Sunko
Finland	2001	Pihlaja
	2009	Lonnberg
France	2006	Lattes
	2008	Queguiner
	2008	Solladie- Cavalle
Germany	2004	Krohn
	2007	Adam
	2007	Anders
	2007	Tietze
Greece	2003	Varvoglis

Country	Year	Chemist
Holland	2004	Zwanenburg
Hungary	2003	Bernath
	2004	Antus
	2008	Szantay
India	2001	Govindachari
	2002	Kessar
	2003	Chatterje
	2004	Sukh Dev
	2005	Narismhan
	2005	Anand
	2005	Rao
	2005	Swaminathan
Israel	2001	Hassner
Italy	2002	Spinelli
	2004	Tortorella
	2006	Bartoli
	2006	ICHC Conf.
	2006	Med. Chem. Conf.
	2009	Vivona
Japan	2003	Fukumoto
	2009	Tomoya
Kuwait	2008	Al- Awadi
Latvia	2006	Lukevics
Mexico	2003	Regional Issue
	2005	Juaristi
	2008	Contreras
NZ	2006	Coxon
Norway	2001	Undheim

Country	Year	Chemist
Pakistan	2007	Rahman
Poland	2004	Makosza
	2007	Epstajn
Romania	2002	Nenitzescu
	2005	Balaban
Russia	2001	Voronkov
	2003	Trofimov
	2004	Chupakhin
	2004	Konovalov
	2005	Minkin
	2005	Zefirov
	2008	Beletskaya
	2009	Pozharskii
Slovakia	2005	Fisera
Slovenia	2001	Tisler
	2003	Stanovnik
S. Africa	2002	Bull
Sweden	2008	Norin
Ukraine	2005	Regional Issue
UK	2000	Jones
	2000	Meth- Cohn
	2002	Lloyd
	2002	Rees
USA	2001	Abramovitch
	2001	Thyagaragan
	2002	Karabatsos
	2002	Padwa
	2003	Shine
	2007	Joulle

Figure 20. 2000- 2009: 85 Chemists honored from 33 countries.

Our impact factor has risen steadily and has now overtaken that of several other journals (Figure 21); while it is still well below that of the best journals in organic chemistry, we hope that the increase in our impact factor will continue.

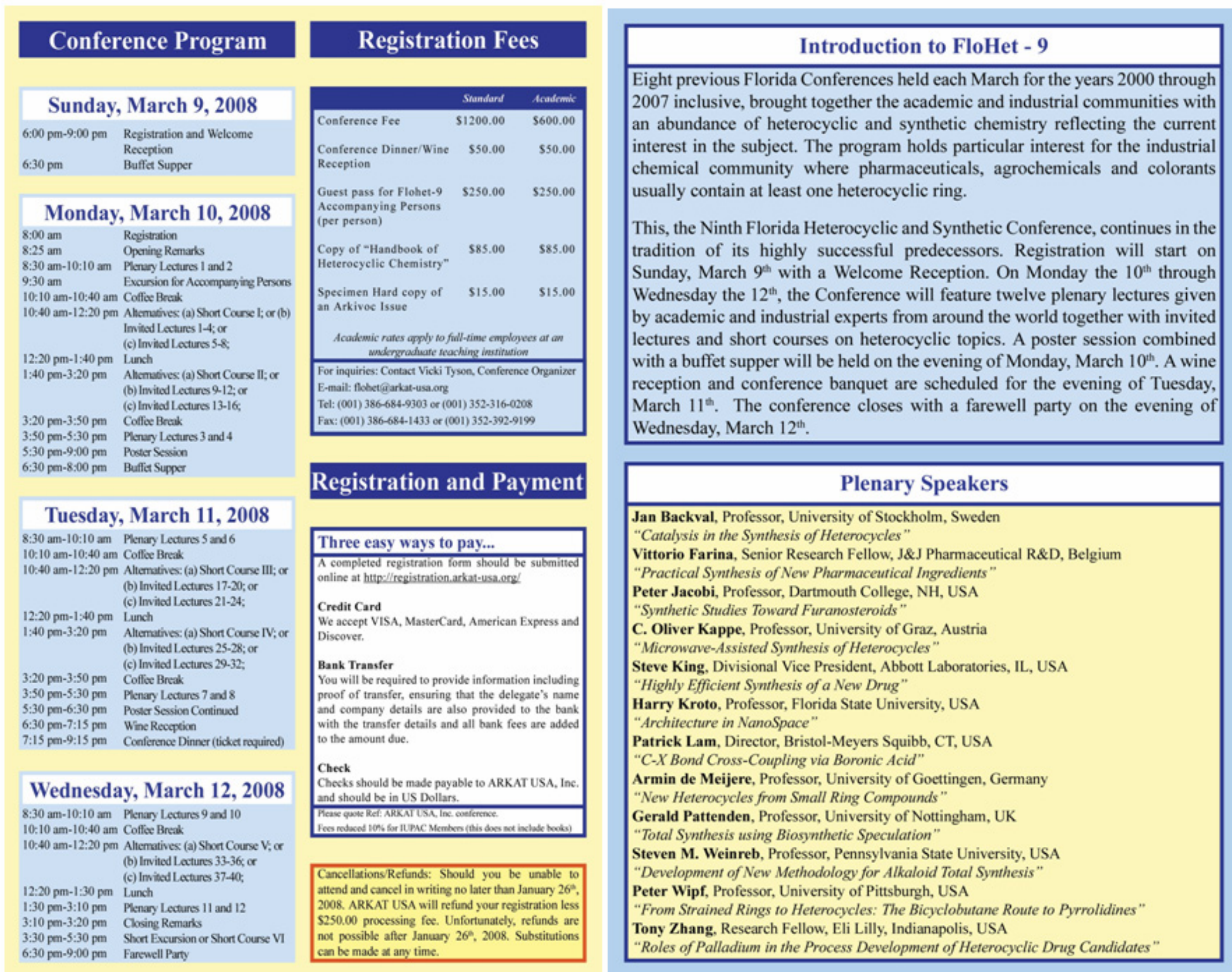
We have also tried to improve contacts between chemists worldwide by running an annual heterocyclic and synthetic conference at the University of Florida. At this conference we offer a dozen plenary lectures from some of the world's most distinguished chemists (Figure 22) together with short courses on various aspects of organic chemistry, 20-30 invited lectures, some 60 posters, and a full social program. Figure 23 shows the program for the 2008 conference.

Year	Arkivoc	Molecules	JHetC	Heterocycles	Synthetic Comm.	Synthesis	JOC
2000	-	0.182	0.781	1.015	0.828	2.193	3.689
2001	-	0.223	0.746	0.970	0.912	1.985	3.280
2002	-	0.408	0.701	1.045	0.802	2.201	3.217
2003	0.392	0.911	0.711	1.082	0.853	2.074	3.297
2004	0.418	0.676	0.814	1.064	0.965	2.203	3.462
2005	0.694	1.113	0.735	1.070	0.860	2.401	3.675
2006	0.800	0.841	0.776	1.077	1.001	2.333	3.790
2007	1.253	0.940	0.813	1.066	0.977	2.257	3.959

Figure 21. ARKIVOC Impact Factor.

Name	Year	Country	Name	Year	Country	Name	Year	Country	Name	Year	Country
E. Anders	2002	Germany	V. Farina	2008	Belgium	G. Mehta	2007	India	J. Schwarz	2006	USA
J.Armstrong	2004	USA	J. Froehlich	2000	Austria	N. Meanwell	2007	USA	E. Scriven	2000	USA
J. Backval	2008	Sweden	G. Fu	2006	USA	B.Maryanoff	2006	USA	J. Sisko	2002	USA
J. Bakke	2003	Norway	A.Furstner	2005/7	Germany	G. Mehta	2006	India	B.Snider	2007	USA
J.Barluenga	2002	Spain	B.Ganem	2006	USA	A. Meijere	2008	Germany	V. Snieckus	2000	Canada
M. Begtrup	2005	Denmark	G.Gribble	2003	USA	O.Meth-Cohn	2000	UK	B. Stanovnik	2001	Slovenia
J.Bergman	2007	Sweden	R. Grigg	2002	UK	V. Minkin	2001	Russia	G.S.R. Rao	2003	India
I.Beletskaya	2002	Russia	R.Grubbs	2003	USA	M. Mitchell	2001	USA	R. Taylor	2006	UK
S. Benner	2001	USA	K. Hafner	2000	Germany	G. Molander	2001	USA	T. Tidwell	2004	Canada
S.Blechert	2003	Germany	S.Hecht	2003	USA	C.J. Moody	2007	UK	L. Tietze	2004	Germany
N. Bodor	2002	USA	P.Hodgson	2005	UK	G.Molander	2005	USA	B. Trofimov	2000	Russia
D. Boger	2005	UK	P. Jacobi	2008	USA	T.Mukaiyaa	2000	Japan	B. Trost	2006	USA
M.Brimble	2005	NZ	G. Johnson	2002	USA	G.Newkome	2001	USA	J. Vollhardt	2007	USA
J. Bristol	2007	USA	J. Joule	2005	UK	P. Ornstein	2004	USA	S. Volante	2006	USA
M. Butters	2003	UK	C. Kappe	2008	Austria	A. Padwa	2004	USA	S. von Unge	2003	Sweden
D. Comins	2000	USA	J. Kiely	2000	USA	G.Pattenden	2008	UK	J. Stoddart	2007	USA
P.Canfalone	2001	USA	S. King	2008	USA	W. Pearson	2002	USA	A. Whittle	2007	UK
D. Curran	2002	USA	P. Knochel	2007	Germany	N.Petasis	2002	USA	S. Weinrab	2008	USA
A. Czarnik	2004	USA	S.Kobayash	2003	Japan	G.Queguine	2004	France	P. Wipf	2008	USA
N. Kimpe	2003	Belgium	H. Kroto	2008	USA	A.V. Rao	2005	India	P. Wuts	2002	USA
M. deLong	2005	USA	P. Lam	2008	USA	C. Ramsden	2001	UK	Y.Yamamoto	2001	Japan
S.Denmark	2005	USA	R. Larson	2007	USA	C. Rees	2004	UK	H. Yamamoto	2006	USA
W. Dolbier	2006	USA	R. Larock	2005	USA	H. Reissig	2007	Germany	M. Yus	2003	Spain
S. Dondoni	2000	Italy	J. Macor	2004	USA	M. Reetz	2006	Germany	T. Zhang	2008	USA
P. Dunn	2001	UK	M. Makosza	2001	Polan	J. Sanders	2004	UK			
J.Ellman	2004	USA	M.Martinelli	2000	USA	J.Schantl	2002	Austria			

Figure 22. Plenary lectures at Flohet, 2000-2008.



Conference Program

Sunday, March 9, 2008

6:00 pm-9:00 pm	Registration and Welcome Reception
6:30 pm	Buffet Supper

Monday, March 10, 2008

8:00 am	Registration
8:25 am	Opening Remarks
8:30 am-10:10 am	Plenary Lectures 1 and 2
9:30 am	Excursion for Accompanying Persons
10:10 am-10:40 am	Coffee Break
10:40 am-12:20 pm	Alternatives: (a) Short Course I; or (b) Invited Lectures 1-4; or (c) Invited Lectures 5-8;
12:20 pm-1:40 pm	Lunch
1:40 pm-3:20 pm	Alternatives: (a) Short Course II; or (b) Invited Lectures 9-12; or (c) Invited Lectures 13-16;
3:20 pm-3:50 pm	Coffee Break
3:50 pm-5:30 pm	Plenary Lectures 3 and 4
5:30 pm-9:00 pm	Poster Session
6:30 pm-8:00 pm	Buffet Supper

Tuesday, March 11, 2008

8:30 am-10:10 am	Plenary Lectures 5 and 6
10:10 am-10:40 am	Coffee Break
10:40 am-12:20 pm	Alternatives: (a) Short Course III; or (b) Invited Lectures 17-20; or (c) Invited Lectures 21-24;
12:20 pm-1:40 pm	Lunch
1:40 pm-3:20 pm	Alternatives: (a) Short Course IV; or (b) Invited Lectures 25-28; or (c) Invited Lectures 29-32;
3:20 pm-3:50 pm	Coffee Break
3:50 pm-5:30 pm	Plenary Lectures 7 and 8
5:30 pm-6:30 pm	Poster Session Continued
6:30 pm-7:15 pm	Wine Reception
7:15 pm-9:15 pm	Conference Dinner (ticket required)

Wednesday, March 12, 2008

8:30 am-10:10 am	Plenary Lectures 9 and 10
10:10 am-10:40 am	Coffee Break
10:40 am-12:20 pm	Alternatives: (a) Short Course V; or (b) Invited Lectures 33-36; or (c) Invited Lectures 37-40;
12:20 pm-1:30 pm	Lunch
1:30 pm-3:10 pm	Plenary Lectures 11 and 12
3:10 pm-3:20 pm	Closing Remarks
3:30 pm-5:30 pm	Short Excursion or Short Course VI
6:30 pm-9:00 pm	Farewell Party

Registration Fees

	Standard	*Academic*
Conference Fee	$1200.00	$600.00
Conference Dinner/Wine Reception	$50.00	$50.00
Guest pass for Flohet-9 Accompanying Persons (per person)	$250.00	$250.00
Copy of "Handbook of Heterocyclic Chemistry"	$85.00	$85.00
Specimen Hard copy of an Arkivoc Issue	$15.00	$15.00

Academic rates apply to full-time employees at an undergraduate teaching institution

For inquiries: Contact Vicki Tyson, Conference Organizer
E-mail: flohet@arkat-usa.org
Tel: (001) 386-684-9303 or (001) 352-316-0208
Fax: (001) 386-684-1433 or (001) 352-392-9199

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Introduction to FloHet - 9

Eight previous Florida Conferences held each March for the years 2000 through 2007 inclusive, brought together the academic and industrial communities with an abundance of heterocyclic and synthetic chemistry reflecting the current interest in the subject. The program holds particular interest for the industrial chemical community where pharmaceuticals, agrochemicals and colorants usually contain at least one heterocyclic ring.

This, the Ninth Florida Heterocyclic and Synthetic Conference, continues in the tradition of its highly successful predecessors. Registration will start on Sunday, March 9th with a Welcome Reception. On Monday the 10th through Wednesday the 12th, the Conference will feature twelve plenary lectures given by academic and industrial experts from around the world together with invited lectures and short courses on heterocyclic topics. A poster session combined with a buffet supper will be held on the evening of Monday, March 10th. A wine reception and conference banquet are scheduled for the evening of Tuesday, March 11th. The conference closes with a farewell party on the evening of Wednesday, March 12th.

Plenary Speakers

Jan Backval, Professor, University of Stockholm, Sweden
"Catalysis in the Synthesis of Heterocycles"
Vittorio Farina, Senior Research Fellow, J&J Pharmaceutical R&D, Belgium
"Practical Synthesis of New Pharmaceutical Ingredients"
Peter Jacobi, Professor, Dartmouth College, NH, USA
"Synthetic Studies Toward Furanosteroids"
C. Oliver Kappe, Professor, University of Graz, Austria
"Microwave-Assisted Synthesis of Heterocycles"
Steve King, Divisional Vice President, Abbott Laboratories, IL, USA
"Highly Efficient Synthesis of a New Drug"
Harry Kroto, Professor, Florida State University, USA
"Architecture in NanoSpace"
Patrick Lam, Director, Bristol-Meyers Squibb, CT, USA
"C-X Bond Cross-Coupling via Boronic Acid"
Armin de Meijere, Professor, University of Goettingen, Germany
"New Heterocycles from Small Ring Compounds"
Gerald Pattenden, Professor, University of Nottingham, UK
"Total Synthesis using Biosynthetic Speculation"
Steven M. Weinreb, Professor, Pennsylvania State University, USA
"Development of New Methodology for Alkaloid Total Synthesis"
Peter Wipf, Professor, University of Pittsburgh, USA
"From Strained Rings to Heterocycles: The Bicyclobutane Route to Pyrrolidines"
Tony Zhang, Research Fellow, Eli Lilly, Indianapolis, USA
"Roles of Palladium in the Process Development of Heterocyclic Drug Candidates"

Figure 23. Conference Program at Flohet in 2008.

We hope that all chemists will help our efforts to extend the hand of friendship to organic chemists all around the world. We now have a rather high rejection rate for Arkivoc, but if you submit a manuscript we will try to provide you with constructive criticism that may be helpful even if it is rejected. We hope that you will access ARKIVOC and, when relevant, cite ARKIVOC; the subject index will help you find suitable papers.

We also hope that you will consider coming to the Flohet conference; it gives excellent value and all profits go to support ARKIVOC. We only regret that we cannot reduce fees or give any awards because the whole operation of ARKIVOC and Flohet occurs without major support and is only made possible by the unstinting efforts of a large number of community-minded chemists.

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