

The ISHC Bulletin

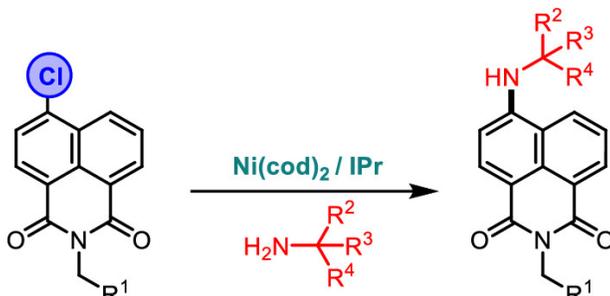
Recent Publications of ISHC Members

Issue 69; July 2022

Nickel-Catalyzed C–N Cross-Coupling of 4-Chloro-1,8-naphthalimide and Bulky, Primary Alkylamines at Room Temperature

Joseph P. Tassone, Travis Lundrigan, Trent D. Ashton, and Mark Stradiotto* (mark.stradiotto@dal.ca)
J. Org. Chem. **2022**, *87*, 6492–6498.

DOI: 10.1021/acs.joc.2c00417

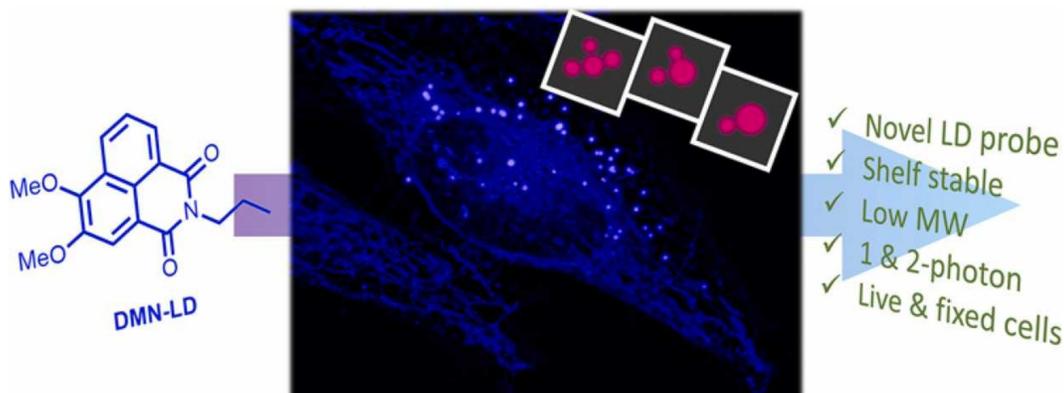


Abstract: 4-Amino-1,8-naphthalimides, potentially useful fluorescent probes in biological applications, are prepared via Ni(cod)₂/IPr-catalyzed cross-couplings between 4-chloro-1,8-naphthalimide electrophiles and α,α,α -trisubstituted, primary alkylamines at room temperature. This method represents the first synthesis of 4-amino-1,8-naphthalimides using Ni-catalyzed C–N cross-coupling and provides the first examples of 4-amino-1,8-naphthalimides incorporating such bulky primary alkylamines, thereby highlighting the utility of Ni-catalyzed processes in synthesizing naphthalimide scaffolds that were inaccessible using established methods (S_NAr; Pd or Cu catalysis).

A 3,4-Dimethoxy-1,8-naphthalimide for Lipid Droplet Imaging in Live and Fixed Cells

Ian R. D. Johnson, Elley E. Rudebeck, Martin J. Sweetman, Alexandra Sorvina, Trent D. Ashton, Frederick M. Pfeffer, Douglas A. Brooks, and Shane M. Hickey* (shane.hickey@unisa.edu.au)
Sens. Actuators, B, **2022**, *365*, 131921 (1–7).

DOI: 10.1016/j.snb.2022.131921



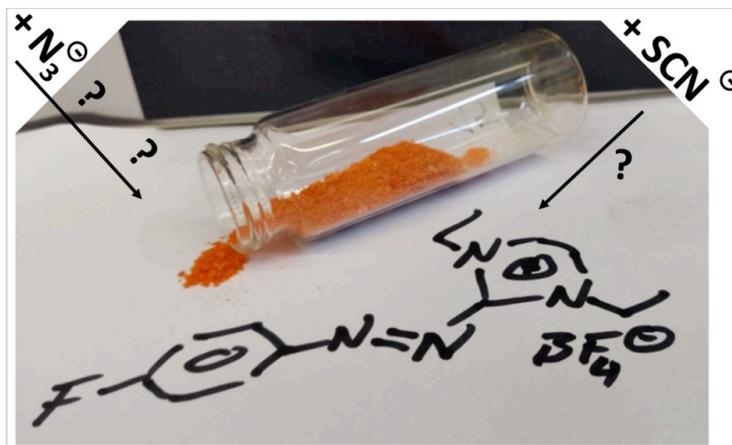
Abstract: Lipid droplets (LDs) are found in most eukaryotic cells and in addition to serving as lipid reservoirs, these highly dynamic organelles play fundamental roles in cell metabolism and growth. The study of LDs and their interactions with other cellular compartments provides new insights into normal cell biology and disease processes such as virus packaging, metabolic disorders, and cancer progression. Here we report the synthesis and comprehensive evaluation of two readily prepared, low molecular weight 3,4-dimethoxy-1,8-naphthalimides, as selective LD stains. The newly synthesised 1,8-naphthalimide derivative (**DMN-LD**), demonstrated impressive versatility compared to currently available options, by staining LDs in both live and fixed cells, as well as a three-dimensional spheroid, using both single and two-photon excitation. This new imaging agent has the potential to further unravel the complex biology of LDs, which are essential to cell survival, and when altered, underpin many disease states.

2-Arylazoimidazoles Revamped by Quarternization or Dimerization; Another Gain in Functionality of an Industrial Dye Family by Task-Specific Side-Chain Substituents

Sandro Neuner, Heidi A. Schwartz, Christoph Kruetz, Thomas Müller, Paul Mayer, Günther Bonn, Thomas Gelbrich, Ulrich J. Griesser, Klaus Wurst, Volker Kahlenberg, Sven Nerdiner,* and Herwig Schottenberger* (sven.nerdinger@sandoz.com or herwig.schottenberger@uibk.ac.at)

Heterocycles **2022**, *105*, 461–476.

DOI: 10.3987/COM-22-S(R)17



Abstract: Based on [(E)-2-(4-fluorophenyl)diazenyl]-1H-imidazole, [210180-24-0], a versatile late stage intermediate for the divergent synthesis of direct dyes, a novel series of N,N'-disubstituted azoimidazolium salts was prepared. In particular, benzylation, 4-vinylbenzylation, phenacylation, sulfopropylation, ethylation, as well as propargylation allowed for the access of derivatives (1-6), which are useful for follow-up conversions, e.g. click reactions, or free radical polymerization. The compounds were routinely characterized spectroscopically. The diethylated tetrafluoroborate salt **5** was additionally analyzed by 19F-NMR. Hot stage microscopy of contact melts of **5** with the less commonly used anionic nucleophiles azide and rhodanide illustrate the rapid formation of deeply colored products confirming the nucleophilic aromatic replacement of fluoride in the 4-fluorophenyl substituent. Remarkably, in addition to the conceived functional quarternizations, a neutral dimer chromophore (**7**) resulted by using epichlorohydrin as a linking agent. For all newly described compounds single crystal X-ray structure determinations are also disclosed.

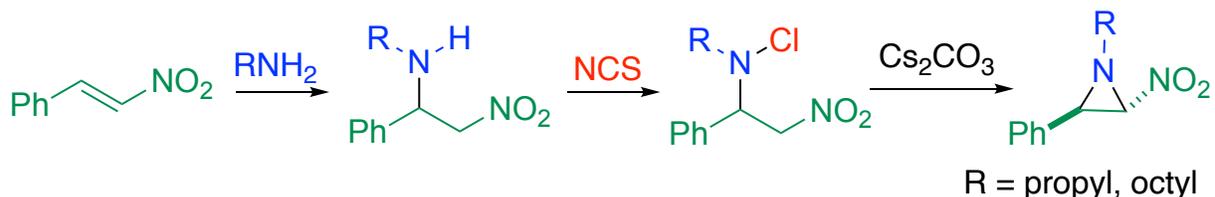
A Mechanistic Study for Aziridination of Nitroalkenes Mediated by N-Chlorosuccinimide

Kento Iwai, Khimiya Wada, Feiyue Hao, Haruyasu Asahara, and Nagatoshi Nishiwaki*

(nishiwaki.nagatoshi@kochi-tech.ac.jp)

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DOI: 10.5650/jos.ess21406



Abstract: Direct aziridination of a nitrostyrene is achieved upon treatment with an alkylamine and N-chlorosuccinimide. The reaction is initiated by the Michael addition of amine to nitroalkene. Subsequent N-chlorination and nucleophilic substitution at the nitrogen atom afford 1-alkyl-2-nitroaziridine diastereoselectively. This reaction mechanism was clarified by NMR studies.

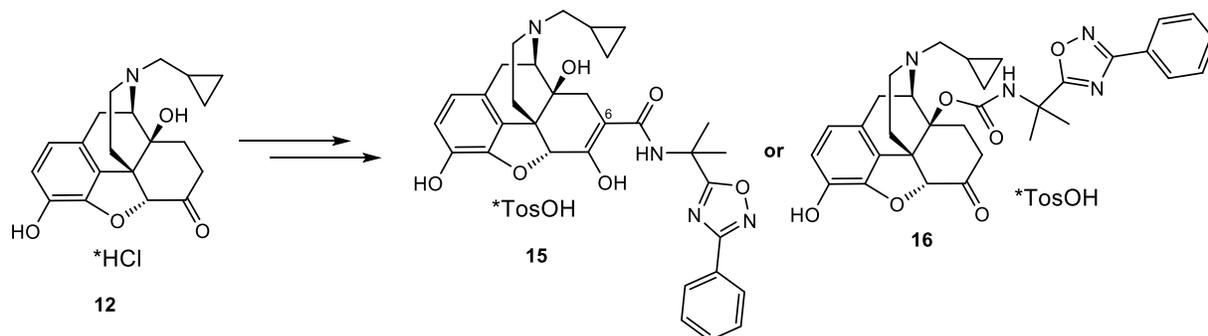
Improved Synthesis of Naldemedine Tosylate and Crystal Structures of Four Related Solid Forms

Josef Spreitz, Thomas Gelbrich, Sven Nerdinger,* Marijan Stefinovic, and Ulrich J. Griesser*

(sven.nerdinger@sandoz.com or ulrich.griesser@uibk.ac.at)

Heterocycles **2022**, *105*, 544–555.

DOI: 10.3987/COM-21-S(R)9



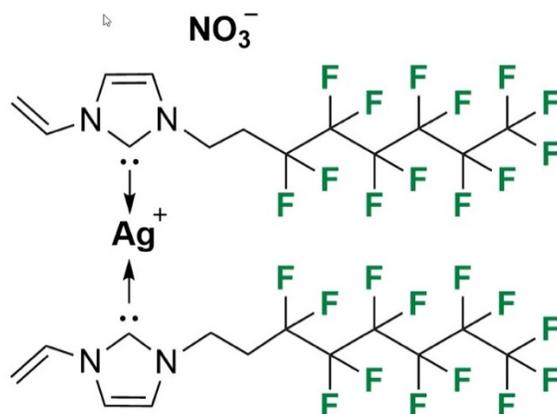
Abstract: The production of drug substances requires a robust and scalable process capable of delivering the active pharmaceutical ingredient (API) in excellent chemical and polymorphic purity. With this goal in mind, we have developed an improved procedure for the preparation of naldemedine tosylate, which crystallizes directly from the reaction mixture as pure polymorph form II. Solid state studies revealed a series of additional new physical forms whose crystal structure have been determined by single-crystal X-ray diffraction.

A Fluoropolytailed NHC–Silver Complex Formed from Vinyl-imidazolium/AgNO₃ under Aqueous–Ammoniacal Conditions

Gabriel Partl, Marcus Rauter, Lukas Fliri, Thomas Gelbrich, Christoph Kreutz, Thomas Müller, Volker Kahlenberg, Sven Nerdinger,* and Herwig Schottenberger* (sven.nerdinger@sandoz.com or herwig.schottenberger@uibk.ac.at)

Molecules **2022**, *27*, 4137 (1–9).

DOI: 10.3390/molecules27134137



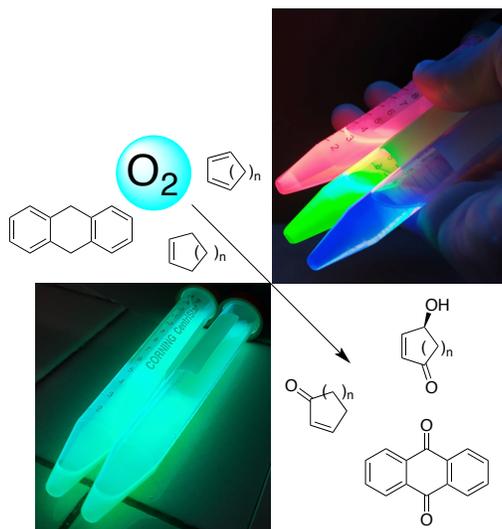
Abstract: 3-(1*H*,1*H*,2*H*,2*H*-Perfluorooctyl)-1-vinylimidazolium chloride [2126844–17–3], a strong fluorosurfactant with remarkably high solubility in water, was expediently converted into the respective doubly NHC-complexed silver salt with nitrate as counter ion in quantitative yield. Due to its vinyl substituents, [bis(3-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-1-vinylimidazol-2-ylidene)silver(I)]nitrate, **Ag(FNHC)₂NO₃**, represents a polymerizable *N*-heterocyclic carbene transfer reagent, thus potentially offering simple and robust access to coordination polymers with crosslinking metal bridges. The compound was characterized by infrared and NMR spectroscopy, mass spectrometry as well as elemental analysis, and supplemented by X-ray single-crystal structure determination. It crystallizes in the monoclinic crystal system in the space group P2₁/c. With 173.3°, the geometry of the Ag-carbene bridge deviates slightly from linearity. The disordered perfluoroalkyl side chains exhibit a helical conformation.

Nanocrystals Perovskites Photocatalyzed Singlet Oxygen Generation for Light-Driven Organic Reactions

Marco Corti, Rossella Chiara, Lidia Romani, Barbara Mannucci, Lorenzo Malavsi,* Paolo Quadrelli* (malalor@unipv.it or paolo.quadrelli@unipv.it)

Photochem. Photobiol. Sci., **2022**, *21*, 613–624.

DOI: 10.1007/s43630-021-00106-x



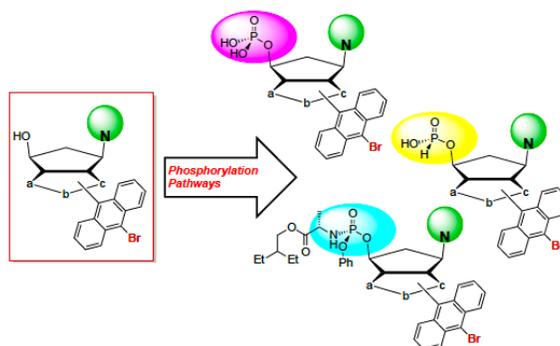
Abstract: Lead halide perovskite nanocrystals were prepared and used as photocatalysts for the *in situ* $^1\text{O}_2$ generation to perform hetero Diels–Alder, ene and oxidation reactions with suitable dienes and alkenes. The methodology has been reasonably standardized and made applicable to a variety of olefinic substrates. The scope of the method is finely illustrated by the results in all the tested reactions, which allowed to obtain desymmetrized hydroxy-ketone derivatives, unsaturated ketones and epoxides. Some limitations were also observed especially in the case of the alkene oxidations as well as poor chemoselectivity was somewhere observed.

Phosphorylation of 10-Bromoanthracen-9-yl-cyclopenta[*d*]isoxazol-6-ols: Chemistry Suitable for Antivirals

Sarbast M. Ahmed, Faiq H. S. Hussain, Marco Leusciatti, Barbara Mannucci, Mariella Mella, and Paolo Quadrelli* (paolo.quadrelli@unipv.it)

Arkivoc **2022**, part v, 174–193.

DOI: 10.24820/ark.5550190.p011.784



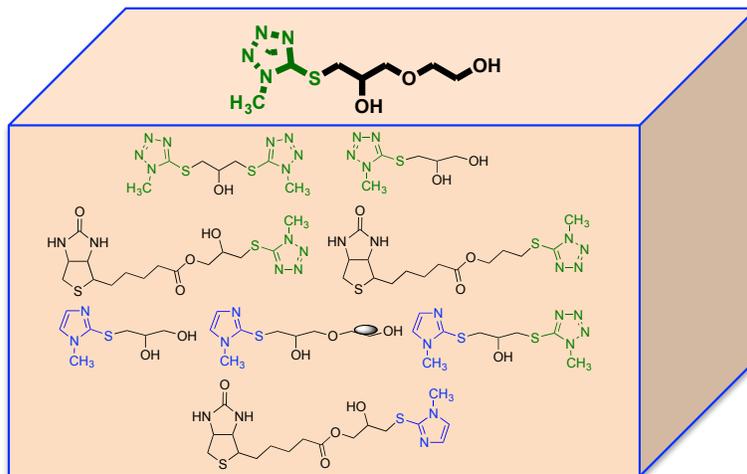
Abstract: Regioisomeric nor-nucleoside analogues, brominated at the anthracene ring, have been prepared and phosphorylated according to different protocols affording a variety of phosphate and phosphonate derivatives. Chiral phosphorus derivatives were also obtained as inseparable mixtures of diastereoisomers. The synthetic methods are described and found to be reliable and robust, affording nor-nucleosides and nor-nucleotides, available in large amounts for *in vitro* antiviral evaluation.

Synthesis of Tetrazole- and Imidazole-Based Compounds: Prophetic Molecules Made Real for Biological Studies

Valentina Pirota, Giovanni D'Acerno, and Paolo Quadrelli* (paolo.quadrelli@unipv.it)

Arkivoc, 2022, part v, 245–258.

DOI: 10.24820/ark.5550190.p011.787



Heterocyclic Box

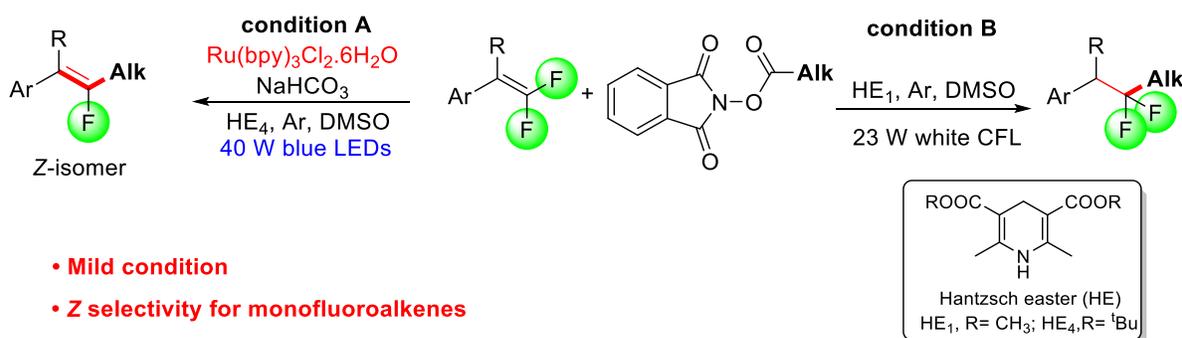
Abstract: The synthesis of tetrazole- and imidazole-based derivatives has been achieved via sulfur nucleophilic ring-opening of 2-oxiranyl-alcohols or chlorides. The derivatives obtained may represent interesting new chemical tools to investigate biological functions and in particular the mitochondrial molecular chaperone TRAP1. The results are discussed in the light of the availability of these molecules according to the proposed synthetic procedures.

Ru-Catalyzed Defluorinative Alkylation or Catalyst-Free Hydroalkylation of *gem*-Difluoroalkenes Enabled by Visible Light

Fangran Liu, Zhen Zhuang, Qun Qian, Xiaofei Zhang,* and Chunhao Yang* (xiaofeizhang@simmm.ac.cn or chyang@simmm.ac.cn)

J. Org. Chem. 2022, 87, 2730–2739.

DOI: 10.1021/acs.joc.1c02662



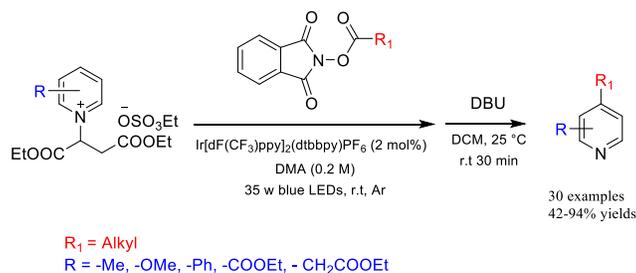
Abstract: A catalyst-induced defluorinative alkylation or metal-free hydroalkylation of *gem*-difluoroalkenes enabled by visible light was developed. This protocol provided a mild and practical approach to important and novel monofluoroalkenes and difluoromethylene-containing compounds with moderate to excellent yields.

Photoredox-Catalysed Regioselective Synthesis of C-4-Alkylated Pyridines with *n*-(Acyloxy) Phthalimides

Zhucheng Zhang, Qian He, Xiaofei Zhang,* and Chunhao Yang* (xiaofeizhang@simmm.ac.cn or chyang@simmm.ac.cn)

Org. Biomol. Chem. **2022**, *20*, 1969–1973.

DOI: 10.1039/d2ob00123c



30 examples
42–94% yields

- oxidant and acid free
- Mild reaction conditions
- Broad substrate scope
- Regioselectivities

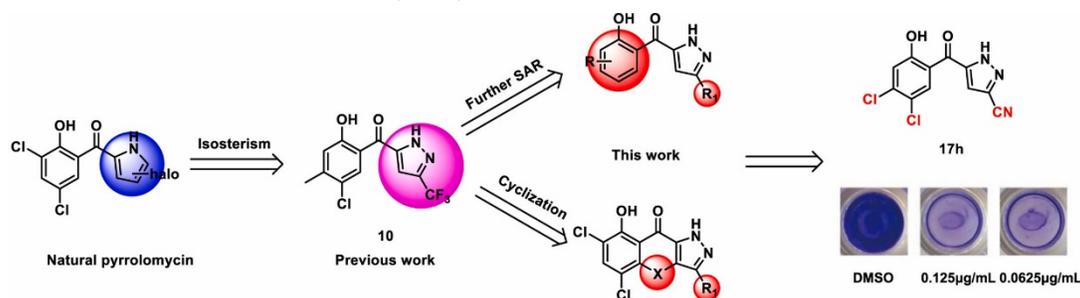
Abstract: A method of direct C-4 selective alkylation of pyridines under visible light irradiation at room temperature has been reported, using simple maleate-derived pyridinium salts as pyridine precursors and the readily available carboxylic acid-derived *N*-(acyloxy)phthalimides as alkyl radical precursors, affording good to excellent yields without using stoichiometric oxidants and acids. A broad range of primary, secondary, and tertiary carboxylates can be used as alkylation reagents. Oxidant and acid-sensitive functional groups can be tolerated well.

Design, Synthesis, and Biological Evaluations of Substituted Pyrazoles as Pyrrolomycin Analogues Against Staphylococcal Biofilm

Xiang Huan, Yanhui Wang, Xiaofeng Peng, Shanshan Xie, Qian He, Xiaofei Zhang,* Lefu Lan,* Chunhao Yang,* (xiaofeizhang@simmm.ac.cn or llan@simmm.ac.cn or chyang@simmm.ac.cn)

Eur. J. Med. Chem. **2022**, *236* 114309 (1–13).

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Abstract: The formation of biofilm enables *Staphylococcus aureus* to resist antibiotics and causes chronic infections. Several compounds of pyrrolomycins are potent antibacterial agents which display inhibition upon staphylococcal biofilms. We designed and synthesized two series of substituted pyrazoles as pyrrolomycin analogues. Compounds **17a**, **17d** and **17h** displayed potent antibacterial activity against various vancomycin-resistant *Enterococcus faecalis* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), and **17d** showed the most potent activity against MRSA (MIC = 0.0625 mg/mL), vancomycin-intermediate *Staphylococcus aureus* (VISA) (MIC = 0.0313 mg/mL). Further study indicated that compound **17h** could significantly reduce the biofilm formation of MRSA and exhibited promising selectivity. *In vitro* liver microsomal stability was also evaluated, and the results manifested that **17h** was metabolically stable in human liver microsomes.