International Society of Heterocyclic Chemistry
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Issue 92 November 2024

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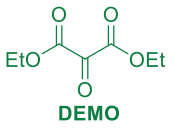
Diethyl Mesoxalate, A Representative Tricarbonyl Compound – A Useful Synthetic Tool Possessing Diverse Reactivities

Nagatoshi Nishiwaki

European Journal of Organic Chemistry **2024**, e202400823. DOI:https:// doi.org/10.1002/ejoc.202400823



Diethyl mesoxalate, a vicinal tricarbonyl compound, possesses multiple functionalities that facilitate diverse chemical conversions. The central carbonyl group with two ester functionalities exhibits high electrophilicity to accept nucleophilic attacks of various reagents. This unusual electrophilicity enables the reaction with acid amides that are not common nucleophiles in organic syntheses. Condensation with active methylene compounds or amines leads to electron-deficient alkenes and imines, respectively, which can be transformed into more complex polyfunctionalized compounds by a second nucleophilic addition. Chemical transformations between the central and adjacent ester carbonyls furnish new ring systems that are useful in material and pharmaceutical sciences. The central carbonyl group can also be built into a ring system by reacting with reagents possessing nucleophilic and electrophilic sites. Furthermore, the central carbonyl serves as a dienophile that undergoes cycloaddition to form functionalized heterocyclic compounds in a single step.

Repurposed Drugs during the Outbreak of Pandemic COVID-19: A

Mini-Review on Their Molecular Structures and Hit-and-Trial Results

Thangjam Linda Devi, Mayanglambam Maneeta Devi, Monika Okram, and Okram Mukherjee Singh*

ACS Omega **2024**, *9*, 36858−36864

One of the most significant threats to global public health in the 21st century is the novel coronavirus disease (COVID-19) caused by SARS-CoV- 2. It rapidly turned into a global pandemic after it was identified in late 2019, and the World Health Organization announced the end of the pandemic on May 5, 2023. Current strategies for managing this disease include vaccination and repurposing antimalarial and antibiotic medications to alleviate symptoms like fever and throat pain, which are associated with acute respiratory distress syndrome (ARDS). Antiviral drugs such as chloroquine, hydroxychloroquine, azithromycin, remdesivir, and favipiravir have been repurposed for the treatment of COVID-19. They were previously recommended for treating SARS-CoV and MERS-CoV. However, the inefficacy and adverse side effects of these repurposed drugs led to a decrease in their widespread use in treating COVID-19 patients. The lack of approved drugs for combating this coronavirus and its unpredictable variants remains a significant challenge.

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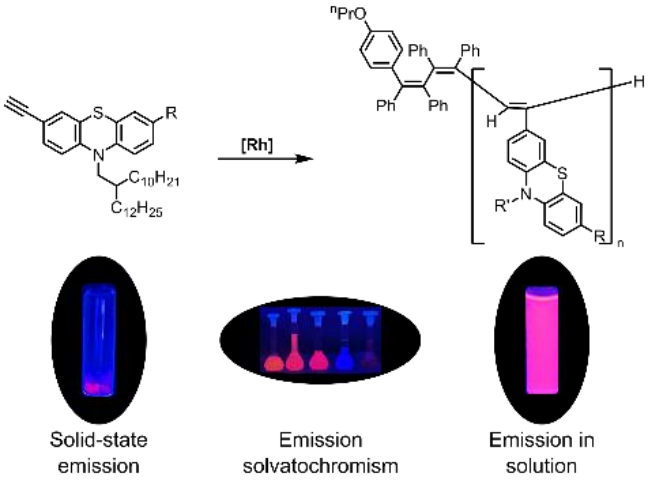
Synthesis and Photophysical Properties of Luminescent Phenothiazinyl Merocyanine Substituted Polyacetylenes

W. Pisetsky, P. Budny, T. J. J. Müller

Angew. Chem. Int. Ed. **2024**, *63*, e202316246. DOI: 10.1002/anie.202316246

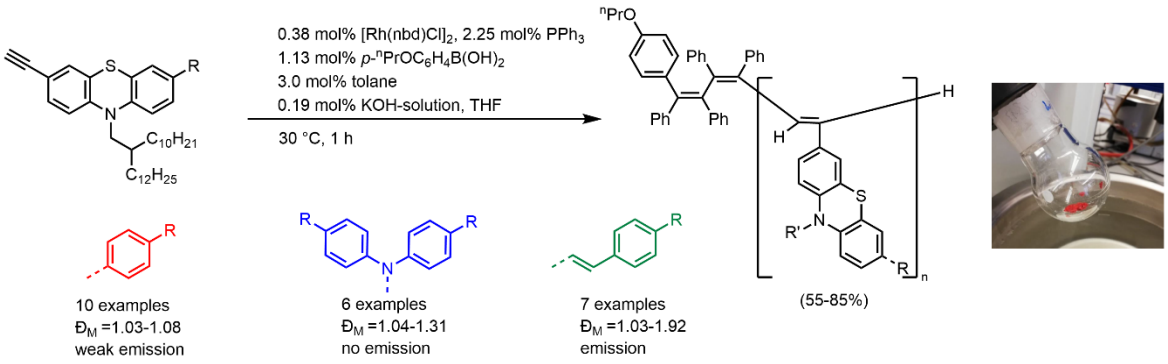


A new generation of soluble phenothiazinyl merocyanine substituted polyacetylenes can be readily synthesized by rhodium-catalyzed polymerization of the corresponding 3-ethynyl phenothiazines, accessible by Sonogashira coupling and Knoevenagel condensation. UV/Vis and fluorescence spectroscopy of 7-acceptorsubstituted phenothiazinyl polyacetylenes reveal that these polyacetylenes with conjugatively ligated merocyanines are luminescent in solution with positive emission solvatochromism and, in some cases, with distinct solid state luminescence.

Polyacetylenes with (Hetero)Aryl-, Styryl-, and Amino-Phenothiazinyl Sidechains – Synthesis and Photophysics.

W. Pisetsky, T. J. J. Müller

RSC Adv. **2024**, *14*, 10638-10643. DOI: 10.1039/d4ra01912a



A novel generation of 7-aryl phenothiazinyl substituted polyacetylenes is readily accessible via controlled rhodium-catalyzed polymerization of the corresponding 3-ethynyl 7-aryl phenothiazines. The monomers are synthesized by Suzuki coupling, Heck coupling, or Buchwald–Hartwig amination, and Bestmann–Ohira reaction. This allows for the introduction of electron donating and releasing substituents with different ligation patterns. The obtained polymers display narrow molecular weight distributions, with very few exceptions, and are soluble in many organic solvents. The photophysical properties of novel monosubstituted polyacetylenes and corresponding monomers were compared. While the monomers exhibit strong emission in solution with quantum yields of up to 0.84 only selected polymers are luminescent (Ff = 0.06) and display moderate Stokes shifts and positive emission solvatochromism.

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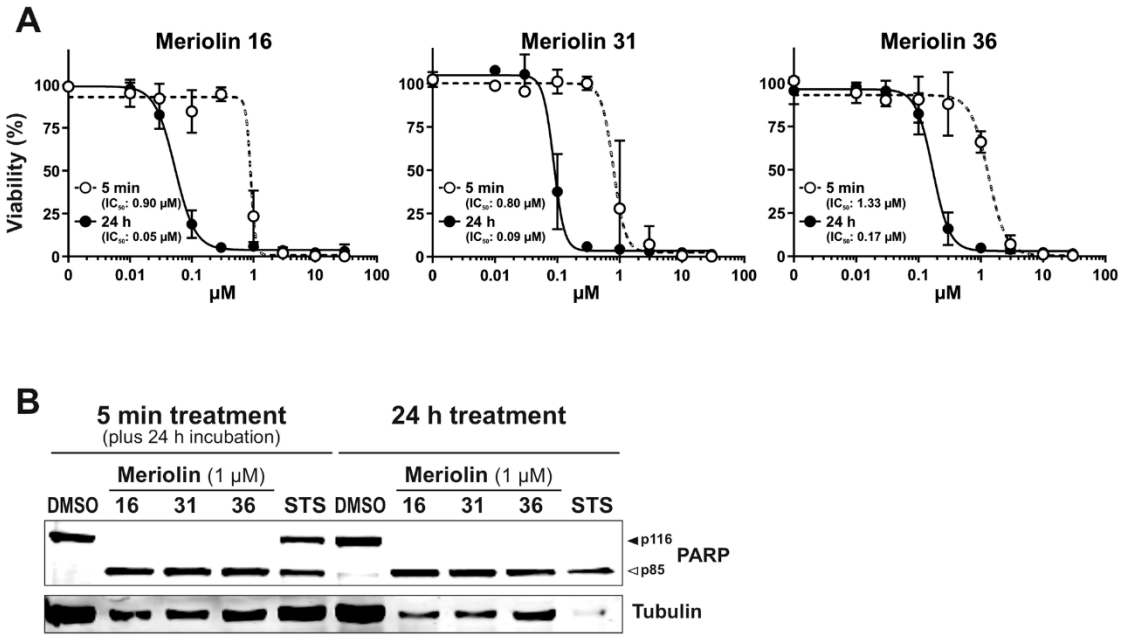
Novel meriolin derivatives activate the mitochondrial apoptosis pathway in the presence of antiapoptotic Bcl-2

L. Schmitt, I. Hinxlage, D. Drießen, H. Flores-Romero, M. Skowron, M. Sekeres, J. Hoppe, K. Krings, C. Peter, B. Stork, S. Bhatia, D. Nettersheim, G. Fritz, A. García-Sáez, T. J. J. Müller, S. Wesselborg

Cell Death Dis. **2024**, *10*, 125. DOI: 10.1038/s41420-024-01901-y



Meriolin derivatives represent a new class of kinase inhibitors with a pronounced cytotoxic potential. Here, we investigated a newly synthesized meriolin derivative (termed meriolin 16) that displayed a strong apoptotic potential in Jurkat leukemia and Ramos lymphoma cells. Meriolin 16 induced apoptosis in rapid kinetics (within 2–3 h) and more potently (IC50: 50 nM) than the previously described derivatives meriolin 31 and 36 [1]. Exposure of Ramos cells to meriolin 16, 31, or 36 for 5 min was sufficient to trigger severe and irreversible cytotoxicity. Apoptosis induction by all three meriolin derivatives was independent of death receptor signaling but required caspase-9 and Apaf-1 as central mediators of the mitochondrial death pathway. Meriolin-induced mitochondrial toxicity was demonstrated by disruption of the mitochondrial membrane potential (ΔΨm), mitochondrial release of proapoptotic Smac, processing of the dynamin-like GTPase OPA1, and subsequent fragmentation of mitochondria. Remarkably, all meriolin derivatives were able to activate the mitochondrial death pathway in Jurkat cells, even in the presence of the antiapoptotic Bcl-2 protein. In addition, meriolins were capable of inducing cell death in imatinib-resistant K562 and KCL22 chronic myeloid leukemia cells as well as in cisplatin-resistant J82 urothelial carcinoma and 2102EP germ cell tumor cells. Given the frequent inactivation of the mitochondrial apoptosis pathway by tumor cells, such as through overexpression of antiapoptotic Bcl-2, meriolin derivatives emerge as promising therapeutic agents for overcoming treatment resistance.

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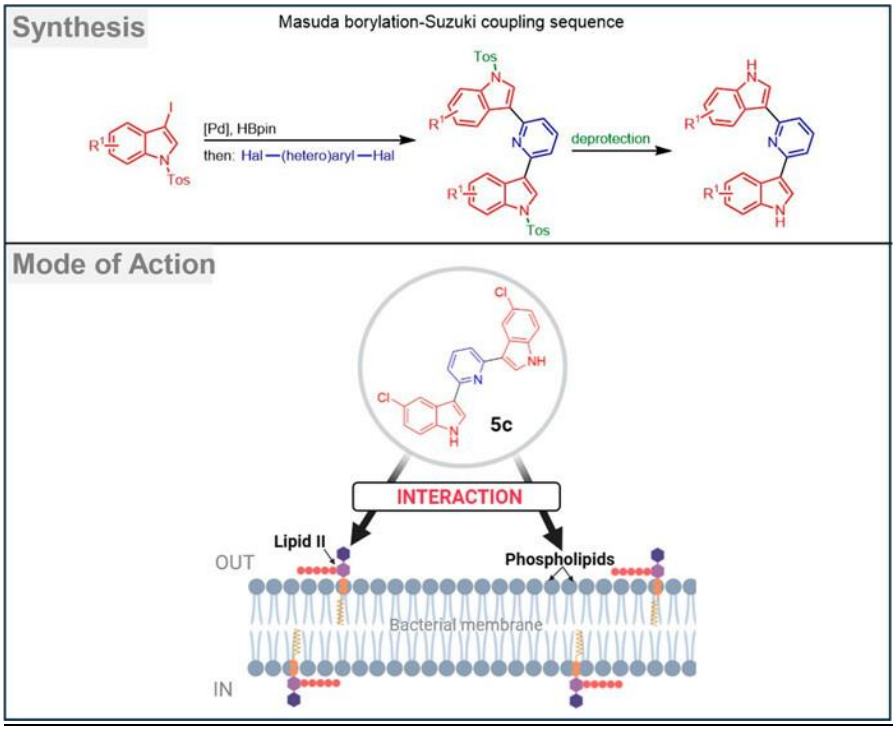
Synthesis of novel bisindole alkaloids and their mode of action against methicillin-resistant *Staphylococcus aureus*

E. Adeniyi, M. Kruppa, S. DeBenedetti, K. Ludwig, V. Krisilia, T. Wassenberg, M. Both, T. Schneider, T. J. J. Müller, R. Kalscheuer,
ACS Infect. Dis. **2024**, *10*, 1958–1969. DOI: 10.1021/acsinfecdis.3c00657



About 100,000 deaths are attributed annually to infections with methicillin-resistant *Staphylococcus aureus* (MRSA) despite concerted efforts toward vaccine development and clinical trials involving several preclinically efficacious drug candidates. This necessitates the development of alternative therapeutic options against this drug-resistant bacterial pathogen. Using the Masuda borylation-Suzuki coupling (MBSC) sequence, we previously synthesized and modified naturally occurring bisindole alkaloids, alocasin A, hyrtinadine A and scalaradine A, resulting in derivatives showing potent *in vitro* and *in vivo* antibacterial efficacy. Here, we report on a modified one-pot MBSC protocol for the synthesis of previously reported and several undescribed *N*-tosyl-protected bisindoles with anti-MRSA activities and moderate cytotoxicity against human monocytic and kidney cell lines. In continuation of the mode of action investigation of the previously synthesized membrane permeabilizing hit compounds, mechanistic studies reveal that bisindoles impact the cytoplasmic membrane of Gram-positive bacteria by promiscuously interacting with lipid II and membrane phospholipids while rapidly dissipating membrane potential. The bactericidal and lipid II-interacting lead compounds 5c and 5f might be interesting starting points for drug development in the fight against MRSA.

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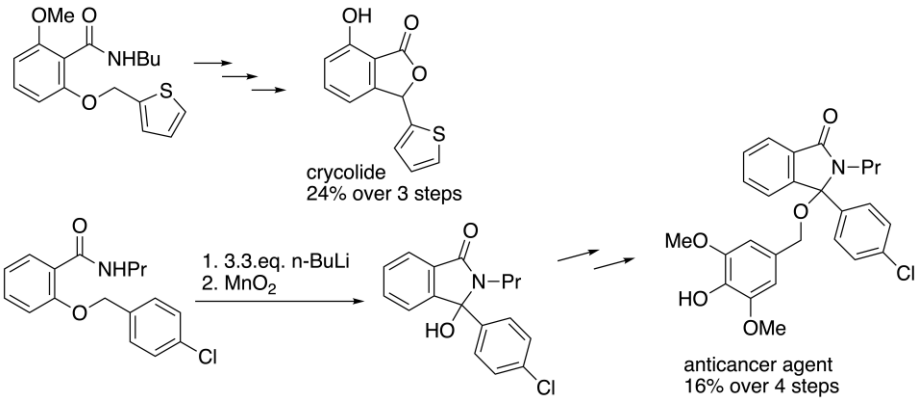
Application of the Wittig Rearrangement of *N*-Butyl-2-benzyloxybenzamides to Synthesis of Phthalide Natural Products and 3-Aryl-3-benzyloxyisoindolinone Anticancer Agents

R. Alan Aitken, Francesca K. Cooper, Andrew D. Harper, Ryan A. Inwood, Elizabeth A. Saab and Ewan J. Soutar

Molecules **2024**, *29*, 4722 (1–16). DOI: 10.3390/molecules29194722

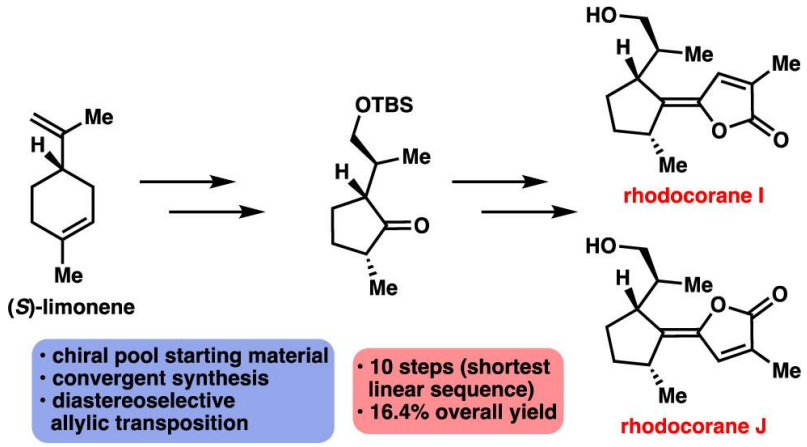


Application of the [1,2]-Wittig rearrangement and cyclisation approach to 3-arylphthalides has been evaluated for the synthesis of three bioactive natural products. While this is successful in the case of crycolide, providing the second synthesis of this compound, the more sterically demanding targets isopestacin and cryphonectric acid prove not to be amenable to this approach, with the 2,6-disubstituted aryl groups causing the failure of the rearrangement and alkylation steps, respectively. Direct oxidation of the substituted benzhydrols resulting from [1,2]-Wittig rearrangement using MnO_2 provides a new route to 3-aryl-3-hydroxyisoindolinones, and this method has been used in the synthesis of two 3-aryl-3-benzyloxyisoindolinone anticancer agents.

Stereoselective Total Synthesis of Rhodocoranes I and J

Cooper A. Vincent, Vaishnavi N. Nair, and Uttam K. Tambar*

Org. Lett. **2024**, *40*, 8453-8456 DOI: 10.1021/acs.orglett.4c02764



We report the stereoselective total synthesis of rhodocoranes I and J in 10 steps and 16.4% overall yield from (*S*)-limonene. The synthesis was accomplished through the convergent assembly of a highly substituted chiral cyclopentanone and a lithiated furanyl silyl ketene acetal. The requisite cyclopentanone framework was strategically constructed from the chiral pool, (*S*)-limonene, through a sequence of steps that included a hydroboration/oxidation, ozonolysis, aldol condensation, reduction, and palladium-catalyzed diastereoselective allylic transposition. This study provides a general approach to the synthesis of the rhodocorane family, known for their antibacterial, antifungal, and cytotoxic properties.

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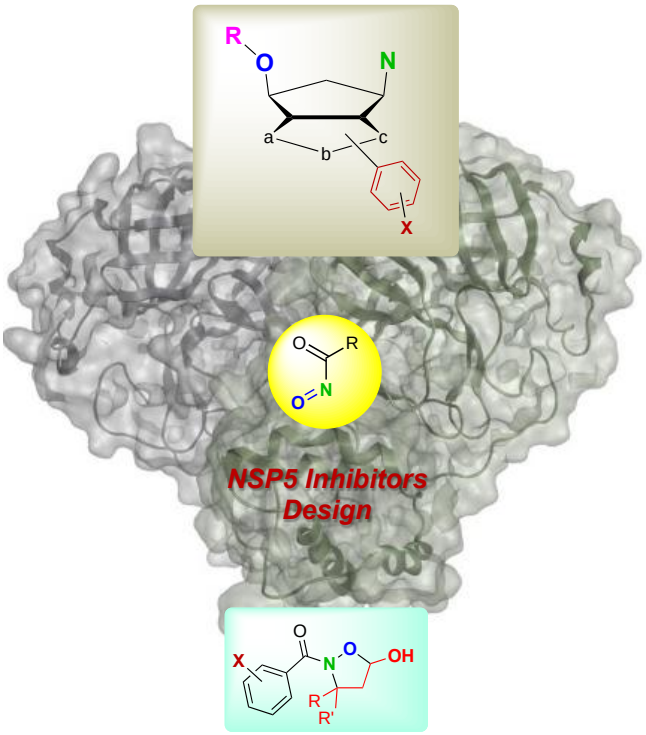
Inhibition of the SARS-CoV-2 Non-structural Protein 5 (NSP5) Protease by Nitrosocarbonyl-Bases Small Molecules

Marco Leusciatti, Beatrice Macchi, Francesca Marino-Merlo, Valeria Stefanizzi, Antonio Mastino, Giulia Morra and Paolo Quadrelli

ACS Omega, **2024***, 9,* 41599−41615. 10.1021/acsomega.4c05480



In the present work, we have designed and synthesized potential NSP5 protease allosteric inhibitors exploiting both docking and molecular dynamic data on SARS-CoV-2. The chemical protocols were developed on the basis of 1,3-dipolar cycloaddition reactions as well as the chemistry of nitrosocarbonyl intermediates. Computational studies were first conducted for determining the best candidate for SARS-CoV-2 NSP5 protease inhibition. Selected compounds were submitted to biological tests, showing low cytotoxicity and moderate activity.