International Society of Heterocyclic Chemistry
ISHC

Issue 34; August 2019

The ISHC Bulletin

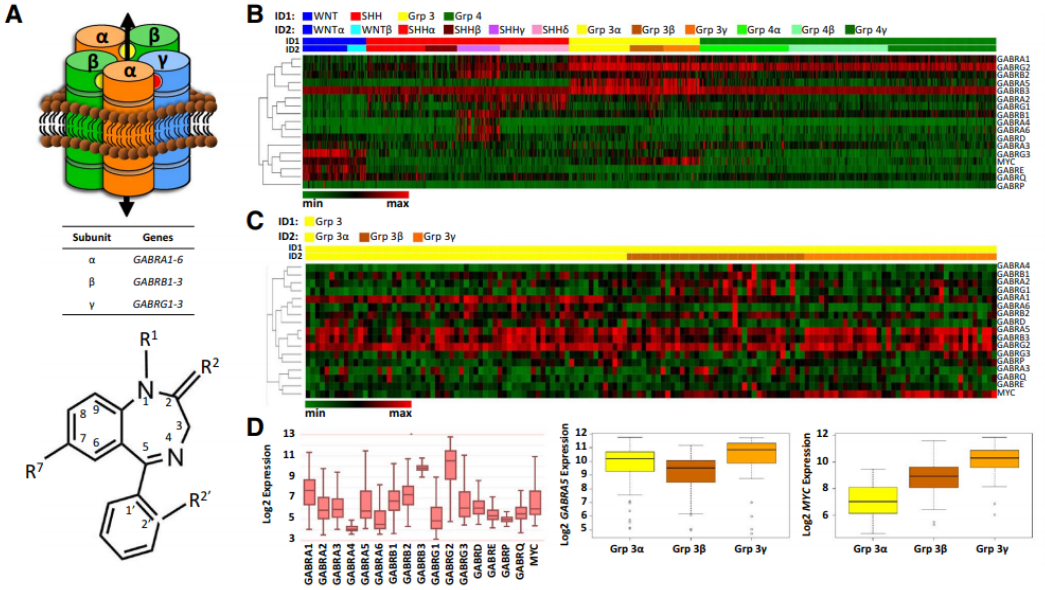
Recent Publications of ISHC Members

Issue 34; August 2019

Modulating Native $GABA_A$ Receptors in Medulloblastoma with Positive Allosteric Benzodiazepine-Derivatives Induces Cell Death

Laura Kallay, Havva Keskin, Alexandra Ross, Manali Rupji, Olivia A. Moody, Xin Wang, Guanguan Li, Taukir Ahmed, Farjana Rashid, Michael Rajesh Stephen, Kirsten A. Cottrill, T. Austin Nuckols, Maxwell Xu, Deborah E. Martinson, Frank Tranghese, Yanxin Pei, James M. Cook,* Jeanne Kowalski, Michael D. Taylor, Andrew Jenkins, Daniel A. Pomeranz Krummel,* and Soma Sengupta (capncook@uwm.edu or pomeranz.krummel@emory.edu or soma.sengupta@emory.edu)

J. Neuro-Oncol. **2019**, *142*, 411–422. **DOI:** 10.1007/s11060-019-03115-0



Abstract: Purpose Pediatric brain cancer medulloblastoma (MB) standard-of-care results in numerous comorbidities. MB is comprised of distinct molecular subgroups. Group 3 molecular subgroup patients have the highest relapse rates and after standard-of-care have a 20% survival. Group 3 tumors have high expression of *GABRA5*, which codes for the α5 subunit of the γ-aminobutyric acid type A receptor ($GABA_AR$). We are advancing a therapeutic approach for group 3 based on $GABA_AR$ modulation using benzodiazepine-derivatives. Methods We performed analysis of *GABR* and *MYC* expression in MB tumors and used molecular, cell biological, and whole-cell electrophysiology approaches to establish presence of a functional 'druggable' $GABA_AR$ in group 3 cells. Results Analysis of expression of 763 MB tumors reveals that group 3 tumors share high subgroup-specific and correlative expression of *GABR* genes, which code for $GABA_AR$ subunits α5, β3 and γ2 and 3. There are ~1000 functional α5-$GABA_ARs$ per group 3 patient-derived cell that mediate a basal chloride-anion efflux of 2×10^9 ions/s. Benzodiazepines, designed to prefer α5-$GABA_AR$, impair group 3 cell viability by enhancing chloride-anion efflux with subtle changes in their structure having significant impact on potency. A potent, non-toxic benzodiazepine ('KRM-II-08') binds to the α5-$GABA_AR$ (0.8 μM EC_{50}) enhancing a chloride-anion efflux that induces mitochondrial membrane depolarization and in response, *TP53* upregulation and p53, constitutively phosphorylated at S392, cytoplasmic localization. This correlates with pro-apoptotic Bcl-2-associated death promoter protein localization. Conclusion *GABRA5* expression can serve as a diagnostic biomarker for group 3 tumors, while α5-$GABA_AR$ is a therapeutic target for benzodiazepine binding, enhancing an ion imbalance that induces apoptosis.

New *N*,*C*-Diaryl-1,2,4-triazol-3-ones: Synthesis and Evaluation as Anticancer Agents

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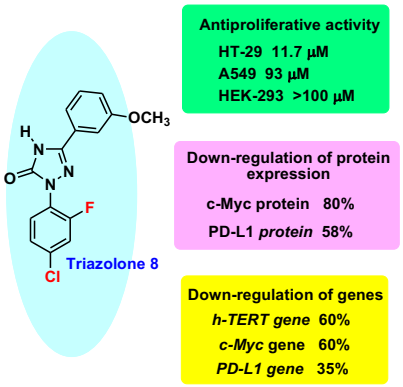
Med. Chem. **2019**, *15*, 360–372. **DOI:** 10.2174/1573406414666180821103604

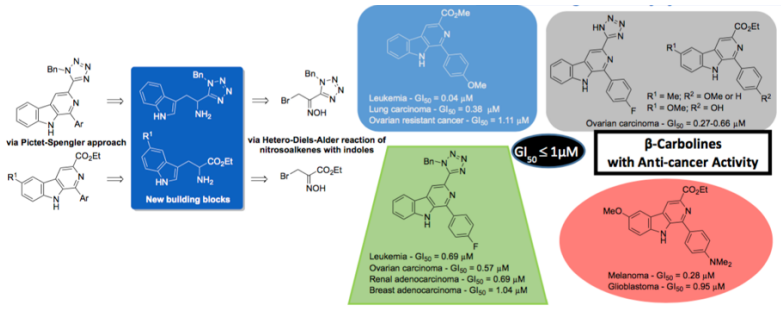


Abstract: A set of ten 2,5-diaryl-1,2,4-triazol-3-ones was synthesized in two steps and evaluated as regards their activity in some relevant biological targets related with cancer. ^{1}H, ^{13}C, ^{15}N and ^{19}F NMR spectroscopy studies proved that all the compounds exist as 4*H*-triazolones, and not as hydroxytriazoles or 1*H*-triazolones. Some showed relatively high activities together with very poor toxicity in non-tumor cell line HEK-293. 2-(2-Fluorophenyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one was particularly active downregulating *c-Myc* and *PD-L1* gene expression although 2-(4-chloro-2-fluorophenyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**8**) is the one that combines the best downregulatory activities in the three genes studied. As regards protein expression the most active compounds are 2-(4-fluorophenyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one and 2-(2,4,6-trifluorophenyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (c-Myc expression) and 2-(2,3,5,6-tetrafluorophenyl)-5-(3-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one and (**8**) (PD-L1 expression).

New 3-Tetrazolyl-β-carbolines and β-Carboline-3-carboxylates with Anti-Cancer Activity

Manuela Ribeiro Panice, Susana M. M. Lopes, Mariana Cecchetto Figueiredo, Ana Lucia T. Goes Ruiz, Mary Ann Foglio, Anelise S. Nazari Formagio, Maria Helena Sarragiotto, Teresa M. V. D. Pinho e Melo* (tmelo@ci.uc.pt)

Eur. J. Med. Chem. **2019**, *179*, 123–132. **DOI:** 10.1016/j.ejmech.2019.05.085

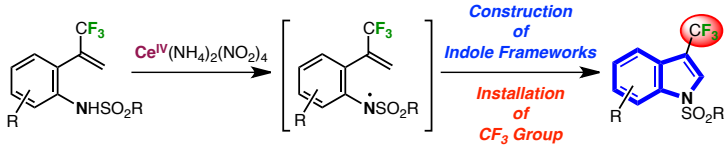


Abstract: New tryptamines have been prepared via hetero-Diels–Alder reaction of nitrosoalkenes with indoles and used to prepare functionalized β-carbolines by the Pictet-Spengler approach. These included 6-substituted-β-carboline-3-carboxylates and 3-(1*H*-tetrazol-5-yl)-β-carbolines, whose synthesis is reported for the first time. Carboline-3-carboxylates derived from *L*-tryptophan methyl ester were also prepared. We have identified at least one β-carboline derivative with $GI_{50} \leq 1\mu M$ for each of the following human tumor cell lines: glioblastoma (U251), melanoma (UACC-61), breast (MCF-7), ovarian expressing multiple-drug-resistance phenotype 4 (NCI-ADR/RES), renal (786-0), lung (NCI-H460), ovarian cancer (OVCAR-3), leukemia (K-562) and colon (HT29). These results demonstrated that the new β-carboline derivatives are very promising anticancer agents.

Synthesis of 3-(Trifluoromethyl)indoles by Oxidative Cyclization of *o*-Sulfonamido-α-(trifluoromethyl)styrenes

Takeshi Fujita, Keisuke Ide, Tanner C. Jankins, Tomoya Nojima, and Junichi Ichikawa* (junji@chem.tsukuba.ac.jp)

Asian J. Org. Chem. **2019**, *8*, 637–640. **DOI:** 10.1002/ajoc.201900061

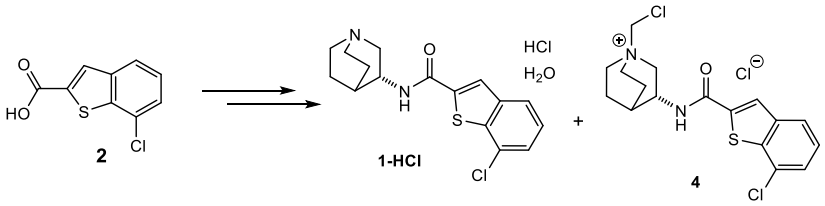


Abstract: We accomplished a microwave-assisted 3-(trifluoromethyl)indole synthesis via oxidative cyclization of α-(trifluoromethyl)styrenes with a sulfonamido group through intramolecular C–H/N–H coupling in the presence of cerium (IV) ammonium nitrate (CAN). This protocol enabled simultaneous construction of indole frameworks and regioselective installation of a trifluoromethyl group via radical 5-*endo-trig* cyclization.

Optimized Synthesis and Solid State Investigations on the Drug Candidate Encenicline Hydrochloride

Gerhard Laus, Sandro Neuner, Ramona Metz, Thomas Müller, Volker Kahlenberg, Thomas Gelbrich, Sven Nerdinger,* Erwin Schreiner, Verena Adamer, Klaus Wurst, and Herwig Schottenberger (sven.nerdinger@sandoz.com)

Heterocycles **2019**, *99*, 1226–1238. **DOI:** 10.3987/COM-18-S(F)97



Abstract: For the production of drug substances a robust, scalable process delivering the active pharmaceutical ingredient (API) in excellent chemical and polymorphic purity is required. For this purpose we developed a novel imidazole-mediated one-pot procedure for the preparation of encenicline hydrochloride monohydrate, which crystallizes directly from the reaction mixture as pure non-hygroscopic polymorph (Form I). Solid state studies revealed a series of additional new physical forms for which crystal structures have been determined by single-crystal X-ray diffraction.

Total Synthesis of the Tetrasubstituted Furan Fatty Acid Metabolite CeDFP *via* Au-Catalyzed Intermolecular Alkyne Hydroarylation

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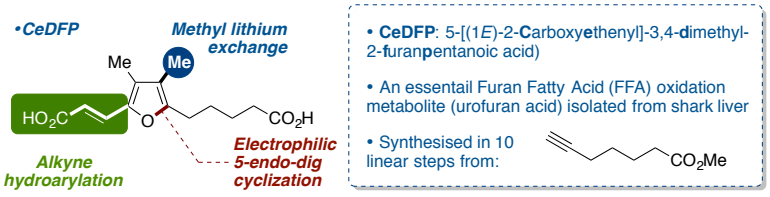
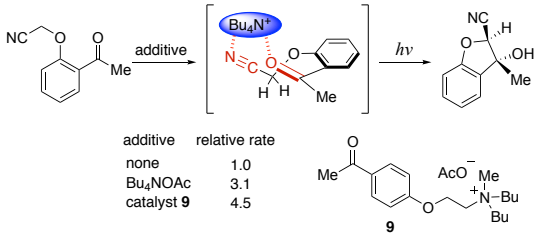
Org. Lett. **2019**, *21*, 4892–4895. **DOI:** 10.1021/acs.orglett.9b01786



Abstract: The first total synthesis of the *tetra* substituted furan fatty acid (FFA) metabolite 5-[(1*E*)-2-carboxyethenyl]-3,4-dimethyl-2-furanpentanoic acid (CeDFP), is reported. CeDFP is a FFA metabolite isolated from shark livers and is related to the known FFA metabolites CMPF and CMPentylF. Key elements of the synthetic route to CeDFP include an iodine promoted 5-*endo-dig* cyclization of a 1,2-akyne diol, a methyllithium mediated insertion of the C_3-methyl group, and an Au(I)-catalyzed intermolecular hydroarylation to introduce the unsaturated ester.

The Tetraalkylammonium-Accelerated Norrish–Yang Photocyclization of 2-Substituted Acetophenones

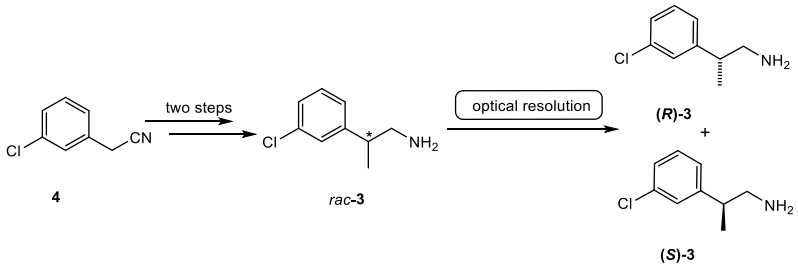
Shinji Yamada,* Yuki Oshima, Yuka Fujita, Seiji Tsuzuki (yamada.shinji@ocha.ac.jp)
Tetrahedron Lett. **2019**, *60*, 1543–1546. **DOI:** 10.1016/j.tetlet.2019.05.005



Abstract: The tetrabutylammonium-accelerated Norrish–Yang cyclization of 2-ethoxycarbonylmethyloxy- and 2-cyanomethyloxyacetophenones afforded *trans*-dihydrobenzofuranols in good stereoselectivities through cation-π interactions between the ammonium and the carbonyl and cyano groups. Furthermore, a new type of organocatalyst possessing both conformation-controlling and triplet-sensitizing units was developed, and was found to be effective in accelerating the Norrish–Yang photocyclization of 2-cyanomethyloxyacetophenone.

A Novel Route to (*R*)-2-(3-Chlorophenyl)propan-1-amine, a Key Intermediate for the Synthesis of Lorcaserin

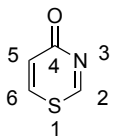
Ivana Gazic Smilovic, Sven Nerdinger,* Sandro Neuner, Herwig Schottenberger, Thomas Gelbrich, and Klaus Wurst (sven.nerdinger@sandoz.com)
Heterocycles **2019**, *99*, 1423–1433. **DOI:** 10.3987/COM-18-S(F)90



Abstract: A new and efficient three-step synthesis of (*R*)-2-(3-chlorophenyl)propan-1-amine is reported, which serves as an intermediate in the synthesis of the antiobesity drug lorcaserin. The key step is a chiral resolution due to the formation of a salt with l-(-)-3-phenyllactic acid. The structure of the relevant salt phase is reported.

Chemistry of 1,3-Thiazin-4-ones and Their Derivatives, 1995 – Mid-2018

Lee J. Silverberg* and Quentin J. Moyer (ljs43@psu.edu)
ARKIVOC **2019**, Part i, 139–227. **DOI:** https://doi.org/10.24820/ark.5550190.p010.788

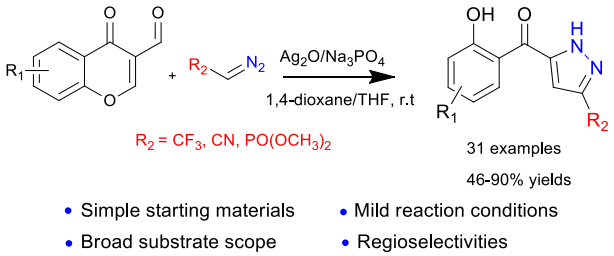


Abstract: This review updates an earlier review published in 1996 by Ryabukhin, Korzhavina, and Suzdalev, which covered the literature through 1994. It deals with the synthesis and reactivity of 1,3-thiazin-4-ones and their derivatives. These include reduced compounds, 2-imino or 2-amino compounds, compounds with fused arenes or heterocycles, bridged compounds, and compounds combining various of these attributes.

Silver-Mediated Synthesis of Novel 3-CF_3/CN/Phosphonate-Substituted Pyrazoles as Pyrrolomycin Analogues from 3-Formyl-chromones and Diazo Compounds

Xiaofeng Peng, Xiaofei Zhang, Shunyao Li, Yunfu Lu, Lefu Lan* and Chunhao Yang* (llan@simm.ac.cn or chyang@simm.ac.cn)

Org. Chem. Front. **2019**, *6*, 1775–1779. **DOI:** 10.1039/C9QO00324J



Abstract: Herein, a simple and regioselective synthesis of (2-hydroxyphenyl)(3-(trifluoromethyl/cyano/phosphonate)-1*H*-pyrazol-5-yl)methanones as pyrrolomycin analogues was reported. This reaction could proceed from 3-formylchromones and corresponding diazo compounds by silver-mediated one-pot cascade reaction under mild conditions with broad substrate scope. Most of all, some products displayed potent antibacterial activities.

Stereocontrol in the Synthesis of β-Lactams Arising from the Interlocked Structure of Benzylfumaramide-Based Hydrogen-Bonded [2]Rotaxanes

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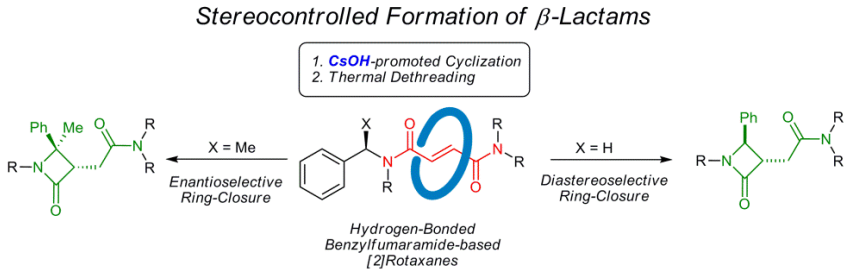
Synlett **2019**, *30*, 893–902. **DOI:** 10.1055/s-0037-1611705



Abstract: β-Lactams are highly valuable compounds due to their antibiotic activity. Among the number of well-established methodologies for building this privileged scaffold, our research group has settled on a novel synthetic approach for their preparation. This Account focuses on our latest progress in the synthesis of these compounds through a novel base-promoted intramolecular cyclization of benzylfumaramide-based rotaxanes. The mechanical bond plays a significant role in the process by activating the cyclization inside the macrocycle void, avoiding the formation of byproducts and fully controlling the diastereoselectivity. Further investigations on this transformation led to the formation of enantioenriched 2-azetidinones. The cyclization of enantiopure interlocked α-methylbenzylfumaramides allows the formation of two new stereogenic centers in the lactamic four-membered ring, one of them a quaternary carbon, keeping the initial configuration of the chiral group of the starting material.