

CSBC 2018: The logic of bioactive small molecules: Looking for new drugs for refractory diseases- Makoto Ubukata- Hokkaido University, Japan

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In this Congress, I will outline my way of thinking about biologically active small molecules. We discovered many biologically active small molecules. Ascamycin was Xanthomonas specific antibiotic, cationomycin was a polyether ionophore antibiotic, liposidomycin B was an inhibitor of peptidoglycan biosynthesis, tautomycin and tautomycetin were later put into practical use as biochemical reagents. Reveromycin A also was utilized as a biochemical reagent and a candidate drug for osteoporosis, epiderstatin was discovered as a glutarimide antibiotic, (+)-indocarbazostatin and (–)-indocarbazostatin B are inducers of neurite outgrowth in PC12 cells, (+)-epogymnolactam was discovered as an autophagy inducer isolated from Gymnopus sp. The rediscovery of mycophenolic acid as a latent agonist of PPAR γ led to the development of many interesting inhibitors against HDAC, human IMPDH, and T. congolense IMPDH. The study of TcIMPDH led to the identification of TcGMPR. We recently discovered an existing drug as a potential therapeutic agent for immunodeficient model mouse infected with Cryptosporidium parvum via newly developed high-throughput screening for CpIMPDH inhibitors. A biologically active small molecule may save directly or indirectly a number of people. Even if the molecule has not been used as a therapeutic agent, it can be used as a useful chemical probe for dissecting a living cell into different biochemical pieces. Such biologically active small molecules derived from microorganisms have been primarily found in cultivable microorganisms that make up only 1% of total microbes in nature. If you can cultivate previously uncultured microorganisms that accounting for the other 99% of microorganisms, the possibility to discover new biologically active small molecules will expand. We discovered zinc methylpyrin, zinc coproporphyrin, and coproporphyrin as novel growth factors for uncultured Leucobacter sp. These findings may provide a general strategy for discovering further

biochemical reagents, antibiotics, and therapeutic agents for the treatment of refractory diseases. The principal significant investigation was realized unintentionally that the amide-liquor forerunner of (\pm)-epiderstatin was artificially changed over to an unforeseen nitrile-aldehyde under altered Swern oxidation conditions [23]. The technique, utilizing the enacted DMSO conditions [29], prompted the primary transformation of trifluoroacetamide to trifluoroacetonitrile (bp – 64 °C) at – 78 °C. Accordingly, our gathering endeavored the in situ trap of benzylalcohol to trifluoroacetonitrile at – 78 °C, however the development of imidate was practically nonreproducible and benzaldehyde was the major result. I told an alumni understudy who had directed the examination, "Why not include DBU?" Addition of a solid base, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was powerful for the readiness of benzyl-trifluoroacetimidate. The one-pot technique end up being operationally basic and valuable for the planning of different trifluoroacetimidates or perfluoroimidates. All these trifluoroacetimidates are more steady and simpler to deal with than relating trichloroacetimidates. Benzyl, 4-methoxybenzyl (MPM), and 3,4-dimethoxybenzyl (DMPM) trichloroacetimidates can be supplanted by comparing stable trifluoroacetimidates. 3,3-Sigmatropic revision of allyl trifluoroacetimidate or Lewis corrosive catalyzed reworking of 2,3-epoxy trifluoroacetimidates is a helpful transformation technique to get relating trifluoroacetamide, which can be easily changed over into amine. The stereochemistry of liposidomycin B reasoned from NOE and conformational examination was affirmed by unions of diazepanone ring model mixes by utilizing the above created techniques. Natural science is helpful for the investigation of organically dynamic little particles, and such examination includes knowledge into new natural science, and the new natural science is additionally

valuable for additional exploration on organically dynamic little atom.

Figure 2. Trifluoroacetimidates are more steady and simple to deal with than trichloroacetimidates. During the manufactured investigation of epiderstatin, another change technique for the amide to the nitrile was found. Utilizing a one-pot amalgamation of trifluoroacetimidate, the stereochemistry of liposidomycin was affirmed.

In the lab, we found (+)- indocarbazostatin which has a positive Cotton impact, and (–)- indocarbazostatin B having a negative atropisomeric chirality, from a culture stock of *Streptomyces* sp . What's more, an effective screening framework for the Maillard response inhibitor from regular item removes was set up. When the fluorometric examination of fluorescent material dependent on cutting edge glycation final results (AGEs) was applied to screening for Maillard response inhibitor from plant remove, an alumni understudy experienced an extinguishing impact in a large portion of the characteristic item extricate tried. I let him know, "Why not add TCA to expel such extinguishing and autofluorescent materials from the response blend?", and it worked [38]. Dr Akiko Saito joined my research center as JSPS Fellow and she had accomplished magnificent manufactured examinations for proanthocyanidin . My job was to just give clues, "Why not screen Lewis acids? Why not associate two sections with a linker?" Not just employees and a postdoctoral individual have left from the lab, numerous alumni from the Biotechnology Research Center, Toyama Prefectural University have additionally left and are dynamic in scholarly or industry fields.