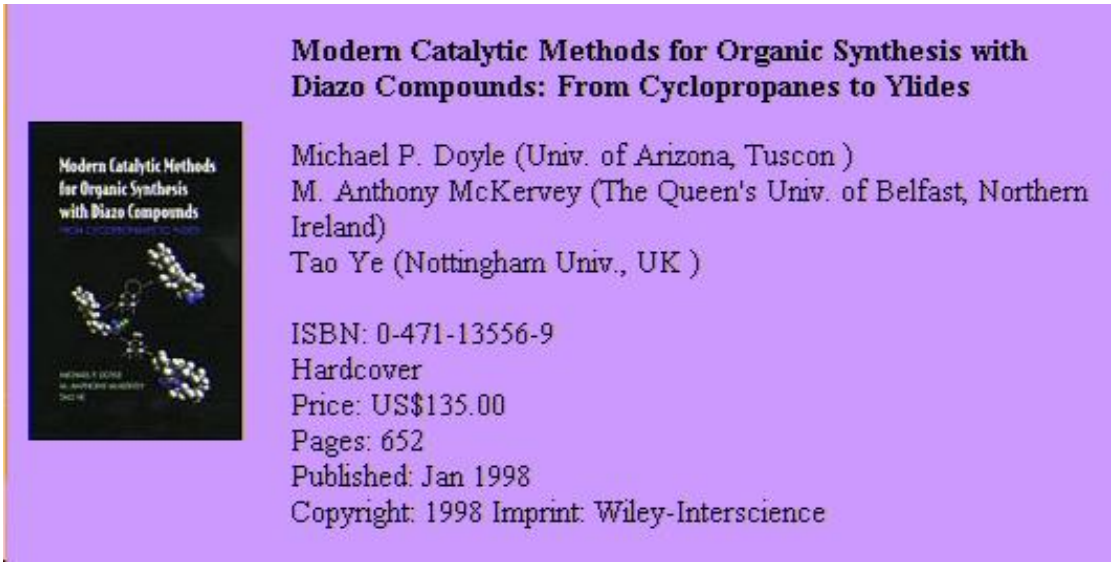
List of Publication

Book and Book Chapters

1. *"Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides"* (652 pages), Michael. P. Doyle, M. Anthony McKervey, Tao Ye, John Wiley & Sons, Inc., New York. **1998**



2. Zhengshuang Xu, Tao Ye "Chapter 12, Thiazoline/thiazole and their derivatives" Pages: 459–505, in "Heterocycles in Natural Product Synthesis" Ed. by Majumdar & Chattopadhyay, WILEY-VCH, Verlag GmbH & Co. KGaA, Weinheim, **2011**.

3. Siti Mariam, Zhengshuang Xu, Tao Ye "Chapter 16, Bioactive Macrocyclic Natural Products", Pages: 569–619, in "Heterocycles in Natural Product Synthesis" Ed. by Majumdar & Chattopadhyay, WILEY-VCH, Verlag GmbH & Co. KGaA, Weinheim, **2011**.

4. "Metal Catalysed Cyclopropanation" Tao Ye, M. Anthony McKervey, Chapter 11 in "*The Chemistry of Cyclopropyl Group*", Vol. 2; page 657-706, Rappoport, Z., Ed.; John Wiley & Sons Ltd., Chichester, **1995**.

5. "Doubly Bonded Metalloid Functions (Si, Ge, B)" Tao Ye, M. Anthony McKervey, Chapter 3.14 in book: "*Comprehensive Organic Functional Group Transformation*", Vol. 3, page 501-505, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon, Oxford, **1995**.

6. "Doubly Bonded Metal Functions" Tao Ye, M. Anthony McKervey, Chapter 3.15 "*Comprehensive Organic Functional Group Transformation*", Vol. 3, page

507-523, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon, Oxford, **1995**.

Publications in peer-reviewed journals:

7. "Total synthesis of antiallergic bicyclic peptide seongsanamide A" Feipeng Han, Yian Guo, Tao Ye *Organic Chemistry Frontiers*, **2020**, 7, 1658-62
   Abstract: The first total synthesis of antiallergic depsipeptide seongsanamide A has been achieved and also confirmed the relative and absolute stereochemistry of the natural product. Highlights of the convergent route include the use of Miyuara borylation, Chan-Evans-Lam coupling for the effective assembly of isodityrosine subunit and the identification of an effective macrocyclization site in very high conversion. The longest linear sequence leading to seongsanamide A was 12 steps, with an overall yield of 12.7%.
8. "Nine-Step Total Synthesis and Biological Evaluation of Rhizonin A" Qingchao Liu, Langlang Liu, Ranjala Ratnayake, Hendrik Luesch, Yian Guo, Tao Ye *Chinese Journal of Chemistry* **2020**, *38*, 1280-4
   Abstract: We have achieved the total synthesis of an architecturally and biologically intriguing cyclic polypeptide, rhizonin A (1), in an exceptionally concise and convergent fashion. The strategic route entails 9 longest linear steps to elaborate commercially available materials into the natural product with an overall yield of 9.7%. The brevity of sequence and high overall yield was fueled by the judicious selection of chemical tactics. Rhizonin A (1) showed weak inhibitory effects on the cell viability of HCT116 colorectal cancer cells and this activity was dependent on hypoxia-inducible factors.

9. "Asymmetric Total Syntheses of Kopsane Alkaloids via a $PtCl_2$-Catalyzed Intramolecular [3+2] Cycloaddition" Xuelei Jia, Honghui Lei, Feipeng Han, Tao Zhang, Ying Chen, Zhengshuang Xu, Pratanphorn Nakliang, Sun Choi, Yian Guo, Tao Ye *Angew. Chem. Int. Ed.* **2020**, 59, 12832-6
   Abstract: A concise and asymmetric total synthesis of five kopsane alkaloids which share a unique heptacyclic caged ring system was accomplished. The key transformation in our sequence involved a remarkable PtCl2 catalyzed intramolecular [3+2] cycloaddition, which allowed for the rapid assembly of pentacyclic carbon skeletons bearing 2,3-quaternary functionalized indoline. Expeditious construction of diverse indoline scaffolds with excellent control of diastereoselectivity demonstrated the broad scope and versatility of this key transformation

10. "Total Synthesis and Biological Evaluation of Kakeromamide A and Its Analogues" Meng Zhao, Yi Xiao, Satoshi Otsuka, Yoichi Nakao, Yian Guo1, Tao Ye *Frontiers in Chemistry* **2020**, 8, doi: 10.3389/fchem.2020.00410

Abstract: Kakeromamide A (**1**), the first marine cyclopeptide inducing neural stem cells differentiation into astrocytes, was synthesized in 12 longest linear steps and 14% overall yield. Using this synthetic approach, four analogues of kakeromamide A were prepared and evaluated for neural differentiation-modulating activity.

11. "Proteomic study reveals the involvement of energy metabolism in the fast antidepressant effect of (2R, 6R)-hydroxy norketamine" Shafiq Ur Rahman, Qiang Hao, Kaiwu He, Yumeng Li, Xifei Yang, Tao Ye, Tahir Ali, Qiang Zhou, Shupeng Li, *Proteomics - Clinical Applications*, **2020**, https://doi.org/10.1002/prca.201900094
Abstract: Depression is a major disabling psychiatric disorder, causes severe financial burden and social consequences worldwide. Recently, (2R, 6R)-hydroxynorketamine (HNK), a metabolite of ketamine, showed strong antidepressant effects through an N-methyl-D aspartate (NMDA) antagonizing independent mechanism. In the current study we tried to identify the potential intracellular molecules and pathways that might be involved in different therapeutic effects underlying HNK as compared to NMDA antagonist MK-801.

12. "Total Synthesis of Dysoxylactam A" Mingze Yang, Wenquan Peng, Yian Guo, Tao Ye *Org. Lett.* **2020**, *22*, 1776-9
Abstract: The total synthesis of a potent multi-drug-resistant reverser, dysoxylacatam A (**1**), was achieved in a highly efficient and stereocontrolled fashion. The highlights of the strategy enlisted an iterative combination of lithiation−borylation tactics including Aggarwal homologation and Matteson homologation, Brown crotylation, Krische allylation, and ring-closing metathesis to forge the macrocycle.

13. "Reductase of Mutanobactin Synthetase Triggers Sequential C−C Macrocyclization, C−S Bond Formation, and C−C Bond Cleavage" Min Wang, Zhoujie Xie, Shoubin Tang, Ee Ling Chang, Yue Tang, Zhengyan Guo, Yinglu Cui, Bian Wu, Tao Ye, Yihua Chen *Org. Lett.* **2020**, *22*, 960-4
Abstract: Mutanobactins (MUBs) and their congeners that contain a macrocycle and/or a thiazepane ring are lipopeptides from Streptococcus mutans, a major causative agent of dental caries. Here we show that the C-terminal reductase domain of MubD releases the lipohexapeptide intermediates in an aldehyde form, which enables a spontaneous C−C macrocyclization. In the presence of a thiol group, the macrocyclized MUBs can further undergo spontaneous C−S bond formation and C−C bond cleavage to generate diverse MUB congeners.

14. "Total Synthesis of Hoiamide A Using an Evans-Tishchenko Reaction As a Key Step" Yian Guo, Jingjing Zhou, Bowen Gao, Meng Zhao, Jia-Lei Yan, Zhengshuang Xu, Sun Choi, Tao Ye *Org. Lett.* **2019**, *21*, 5471-4

Abstract: The first total synthesis of neurotoxic cyclodepsipeptide hoiamide A (1) has been accomplished. The synthesis features the use of an Evans-Tishchenko fragment coupling between a five-stereogenic-center-containing β-hydroxyketone and a chiral aldehyde derived from threonine.

15. "Total Synthesis of Psymberin (Irciniastatin A)" Jie Yu, Mingze Yang, Yian Guo, Tao Ye
Org. Lett. **2019**, *21*, 3670-3673
Abstract: A convergent, stereocontrolled total synthesis of psymberin, an architecturally complex marine antitumor agent, has been achieved in 27 steps from the known aldehyde 8. Highlights of this synthesis include a novel and efficient transannular Michael addition/lactone reduction sequence to construct the highly substituted 2,6-trans-tetrahydropyran, a diastereoselective IBr-induced iodocarbonate cyclization to introduce the C(17) stereogenic center, and a Diels-Alder/aromatization reaction to install the highly substituted aromatic ring.

16. "Discovery of Amantamide, a Selective CXCR7 Agonist from Marine Cyanobacteria" X. Liang, D. Luo, J. Yan, M. A. Rezaei, L. A. Salvador-Reyes, S. P. Gunasekera, C. Li, Tao Ye, V. J. Paul, H. Luesch, *Org. Lett.* **2019**, *21*, 1622–1626
Abstract: CXCR7 plays an emerging role in several physiological processes. A linear peptide, amantamide (**1**), was isolated from marine cyanobacteria and the structure determined by NMR and mass spectrometry. The total synthesis was achieved by solid-phase method. After screening two biological target libraries, **1** was identified as a selective CXCR7 agonist. The selective activation of CXCR7 by **1** could provide the basis for developing CXCR7 targeted therapeutics and deciphering the role of CXCR7 in different diseases.

17. "Isolation, Structure Elucidation and Biological Evaluation of Lagunamide D: A New Cytotoxic Macrocyclic Depsipeptide from Marine Cyanobacteria" D. Luo, M. Y. Putra, Tao Ye, V. J. Paul, H. Luesch, *Mar. Drugs* **2019**, *17*, 83; doi:10.3390/md17020083
Abstract: LagunamideD, a new cytotoxic macrocyclic depsipeptide, was discovered from a collection of marine cyanobacteria from Loggerhead Key in the Dry Tortugas, Florida. An intramolecular ester exchange was observed, where the 26-membered macrocycle could contract to a 24-membered compound via acyl migration at the 1,3-diol unit, and the transformation product was named lagunamide D'. The planar structures of both compounds were elucidated using a combination of nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectroscopy (HRMS). The absolute configurations were determined on the basis of enantioselective analysis, modified Mosher's analysis, Kishi NMR database, and direct comparison with lagunamide A, a structure closely resembling lagunamide D. Lagunamides A

and D displayed low-nanomolar antiproliferative activity against A549 human lung adenocarcinomacells, while the structural transformation from the 26-membered lagunamide D macrocycle to the 24-membered ring structure for lagunamide D' led to a 9.6-fold decrease in activity. Lagunamide D also displayed potent activity in triggering apoptosis in a dose- and time-dependent manner. Further investigation on the mechanism of action of the lagunamide scaffold is needed to fully explore its therapeutic potential as an anticancer agent.

18. "Chemical and Metagenomic Studies of the Lethal Black Band 2 Disease of Corals Reveal Two Broadly Distributed, Redox-Sensitive 3 Mixed Polyketide/Peptide Macrocycles" S. P. Gunasekera, J. L. Meyer, Y. Ding, K. A. Abboud, D. Luo, J. E. Campbell, A. Angerhofer, J. L. Goodsell, L. J. Raymundo, J. Liu, Tao Ye, H. Luesch, M. Teplitski, V. J. Paul, *J. Nat. Prod.* **2019**, *82*, 111-121

Abstract: Black band disease (BBD), a lethal, polymicro bial disease consortium dominated by the cyanobacterium Roseofilum reptotaenium, kills many species of corals worldwide. To uncover chemical signals or cytotoxins that could be important in proliferation of Roseofilum and the BBD layer, we examined the secondary metabolites present in geographically diverse collections of BBD from Caribbean and Pacific coral reefs. Looekeyolide A (1), a 20-membered macrocyclic compound formed by a 16-carbon polyketide chain, 2 deamino-2-hydroxymethionine, and D-leucine, and its autoxidation product looekeyolide B (2) were extracted as major compounds (∼1 mg g^{-1} dry wt) from more than a dozen field-collected BBD samples. Looekeyolides A and B were also produced by a nonaxenic R. reptotaenium culture under laboratory conditions at similar concentrations. R. reptotaenium genomes that were constructed from four different metagenomic data sets contained a unique nonribosomal peptide/polyketide biosynthetic cluster that is likely responsible for the biosynthesis of the looekeyolides. Looekeyolide A, which readily oxidizes to looekeyolide B, may play a biological role in reducing H_2O_2 and other reactive oxygen species that could occur in the BBD layer as it overgrows and destroys coral tissue.

19. "Solution-Phase Total Synthesis of Teixobactin" B. Gao, S. Chen, Y. Hou, Y. Zhao, T. Ye, Z. Xu, *Org. Biomol. Chem.* **2019**, *16*, 1141-1153

Abstract: The first solution-phase total synthesis of the cyclic depsipeptide teixobactin is described. Stereoselective construction of L-allo-enduracididine was established, the protective groups for peptide coupling reactions and conditions for fragments assembly were also optimised. The total synthesis featured by 20-step longest linear steps from the known Lcis-4-hydroxyproline derivative in 5.6% overall yield. This solution-phase total synthesis could serve as complement for current solid-phase synthesis of teixobactin.

20. "Total Synthesis of Asperphenins A and B" Jia-Lei Yan, Yingying Cheng, Jing Chen, Ranjala Ratnayake, Long H. Dang, Hendrik Luesch, Yian Guo, Tao Ye *Org. Lett.* **2018**, *20*, 6170-3

Abstract: The first total synthesis of asperphenins A and B has been accomplished in a concise, highly stereoselective fashion from commercially available materials (15 steps, 9.7% and 14.2% overall yields, respectively). The convergent route featured the judicious choice of protecting groups, fragment assembly strategy and a late-stage iron-catalyzed Wacker-type selective oxidation of an internal alkene to the corresponding ketone.

21. "Total Synthesis of Anti-tuberculosis Natural Products Ilamycins E1 and F" Yingying Cheng, Shoubin Tang, Yian Guo, Tao Ye *Org. Lett.* **2018**, *20*, 6166-9;

Abstract: The first total synthesis of the potent antituberculosis cyclopeptide natural products ilamycins E1 and F was achieved. This highly convergent strategy consists of the synthesis of the two units 10 and 11 and linking them together to form the macrocyclic lactam 31. The upper unit 10 was prepared from tryptophan in five steps, and the lower unit 11 was prepared from glutamic acid in thirteen steps. Conversion of ilamycin F, the most abundant of the cyclopeptides, into the more active congener, ilamycin E1, was also accomplished. This would provide sufficient material of ilamycin E1 for more extensive biological studies.

22. "Sameuramide A, a new cyclic depsipeptide isolated from an ascidian of the family Didemnidae" Koshi Machida, Daisuke Arai, Ryosuke Katsumata, Satoshi Otsuka, Jun K. Yamashita, Tao Ye, Shoubing Tang, Nobuhiro Fusetani and Yoichi Nakao *Bioorg. Med. Chem.* **2018**, *26*, 3852-3857

Abstract: Sameuramide A (1), a new cyclic depsipeptide encompassing one each of alanine, N-methyl alanine, N-methyl dehydroalanine, N,O-dimethyl threonine, phenyllactic acid, three β-hydroxy leucines, and two propionates, was isolated from a didemnid ascidian collected at the northern part of Japan. The planar structure was established based on the interpretation of MS and NMR data. The absolute configuration of the subunits was determined by the advanced Marfey's method and the chiral LC-MS analysis. Compound 1 exhibited the activity of maintaining colony formation of murine embryonic stem (mES) cells without leukemia inhibitory factor (LIF). Down regulation of the gene expression of Krüppel-like transcription factor 4 (Klf4) indicated that 1 itself was not able to maintain the undifferentiated state of the mES cells. However, the expression levels of the marker genes (Nestin, T, Sox17) for three germ layers were upregulated in embryoid bodies (EBs) after treatment of 1 together with LIF, suggesting that 1 plays a supportive role for LIF in maintaining the multipotency of mES cells .

23. “Discovery and Characterization of Brintonamides A–E, Novel Dual Protease and GPCR Modulators from a Marine Cyanobacterium Targeting Breast Cancer Metastasis” Fatma H. Al-Awadhi, Bowen Gao, Mohammad A. Rezaei, Jason C. Kwan, Chenglong Li, Tao Ye, Valerie J. Paul, Hendrik Luesch, *J. Med. Chem.* **2018**, *61*, 6364−6378

Abstract: Five novel modified peptides named brintonamides A–E (1–5) were discovered from a marine cyanobacterium collected from Brinton Channel, Florida. The total synthesis of 1–5 in addition to two other structurally related analogues (6 and 7) was pursued, which provided more material to allow rigorous biological evaluation and SAR studies. Initial protease profiling identified KLK7 as a hit; however, due to the weak enzymatic activity and lack of SAR among brintonamides, we applied for the first time GPCR profiling as an orthogonal platform which enabled the identification of five additional targets. The best hit identified was CCR10 which was inhibited by submicromolar IC50 of 4. We also carried out in silico modeling to understand the structural basis underlying the differences in the antagonistic activity among brintonamides towards CCR10. Due to the significance of KLK7 and CCR10 in cancer progression and metastasis we demonstrated the ability of brintonamide D (4) at 10 μM to significantly target downstream cellular substrates of KLK7: Dsg-2 and E-cad, CCL27 induced proliferation, and the migration of highly invasive breast cancer cells.

24. “Kakeromamide A, a new cyclic pentapeptide inducing astrocyte differentiation isolated from the marine cyanobacterium Moorea bouillonii” Fumiaki Nakamura, Hiroshi Maejima, Midori Kawamura, Daisuke Arai, Tatsufumi Okino, Meng Zhao, Tao Ye, Jungyeol Lee, Young-Tae Chang, Nobuhiro Fusetani, Yoichi Nakao *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2206-2209

Abstract: Kakeromamide A (**1**), a new cyclic pentapeptide encompassing a thiazole ring moiety and a β-amino acid, was isolated from the marine cyanobacterium Moorea bouillonii. Its structure was elucidated by the spectral analysis and the modified Marfey’s method. Compound 1 induced differentiation of neural stem cells into astrocytes at the concentration of 10 μM.

25. “Studies toward the Synthesis of Iriomoteolide-2a: Construction of the C(6)−C(28) Fragment” Lushun Wang, Fusong Wu, Xuelei Jia, Zhengshuang Xu, Yian Guo, Tao Ye *Org. Lett.* **2018**, *20*, 2213-15

Abstract: The synthesis of an appropriately functionalized advanced C(6−28) fragment (3) of the marine macrolide iriomoteolide-2a (1) has been achieved in a highly efficient manner. The C(6)−C(18) fragment of 1 is prepared via a radical cyclization of a vinyl ether intermediate and palladium-promoted hydrostannylation/iodination. Paterson aldol reaction and Peterson olefination are used to construct the C(19)−C(28) fragment. The union of the C(6)−C(18)

and C(19)−C(28) fragments is accomplished via a Suzuki−Miyaura coupling reaction.

26. "Formal Synthesis of Kanamienamide" Yang Li, Yian Guo, Zhengshuang Xu, Tao Ye, *Synlett*, **2018**, *29*, 964-8
Abstract: A formal total synthesis of the anticancer natural product kanamienamide has been accomplished. This communication describes two approaches to the macrocyclic core of the natural product. The key features of the route include an efficient macrolactamization, a Corey–Bakshi–Shibata asymmetric reduction, and a Stork–Zhao–Wittig olefination.

27. "Total Synthesis of Luteoalbusin A and Formal Synthesis of T988 C" Lushun Wang, Xuelei Jia, Honghui Lei, Zhengshuang Xu, Tao Ye, *Synlett*, **2018**, *29*, 613-6
Abstract: An efficient total synthesis of luteoalbusin A was achieved in nine linear steps and in 17% overall yield from the known and easily accessible 3a-(3-indolyl)-hexahydropyrrolo[2,3-b]indole. A formal synthesis of (+)-T988 C through manipulation of the key intermediate is also reported.

28. "Genome Mining and Assembly-Line Biosynthesis of the UCS1025A Pyrrolizidinone Family of Fungal Alkaloids" Li Li, Man-Cheng Tang, Shoubin Tang, Shu-Shan Gao, sameh.S.Msoliman, Leibniz Hang, Wei Xu, Tao Ye, Kenji Watanabe, Yi Tang, *J. Am. Chem, Soc.* **2018**, *140*, 2067-2071.
Abstract: UCS1025A is a fungal polyketide/alkaloid that displays strong inhibition of telomerase. The structures of UCS1025A and related natural products are featured by a tricyclic furopyrrolizidine connected to a trans-decalin fragment. We mined the genome of a thermophilic fungus and activated the ucs gene cluster to produce UCS1025A at a high titer. Genetic and biochemical analysis revealed a PKS-NRPS assembly line that activates 2S,3S-methylproline derived from l-isoleucine, followed by Knoevenagel condensation to construct the pyrrolizidine moiety. Oxidation of the 3S-methyl group to a carboxylate leads to an oxa-Michael cyclization and furnishes the furopyrrolizidine. Our work reveals a new strategy used by nature to construct heterocyclic alkaloid-like ring systems using assembly line logic.

29. "Total synthesis of amphidinins E, F and *epi*-amphidinin F" Kai Chen, Zhengshuang Xu, Tao Ye *Org. Chem. Front.* **2018**, *5*, 629-632
Abstract: A unified approach leading to the total synthesis of amphidinins E, F and epi-amphidinin F of a new structural class of linear marine polyketides is described.

30. "Regio- and Stereospecific Construction of 3a-(1H-Indol-3-yl)pyrrolidinoindolines and Application to the Formal Syntheses of

Gliocladins B and C" Honghui Lei, Lushun Wang, Zhengshuang Xu, Tao Ye, *Org. Lett.* **2017**, *19*, 5134−5137;
Abstract: A one-pot regio- and stereospecific strategy for the construction of 3a-(3-indolyl)-hexahydropyrrolo[2,3-b]indoles based on the condensation of an indole and an in situ generated cyclopropylazetoindoline has been developed. This unified strategy works with a variety of substituted indoles to produce 3a-(3-indolyl)-hexahydropyrrolo[2,3-b]indole products in high yields. The utility of this transformation was highlighted in the formal total syntheses of gliocladins B and C.

31. "Total syntheses of smenothiazoles A and B" Xiao Ma, Yajie Chen, Sigui Chen, Zhengshuang Xu, Tao Ye, *Org. Biomol. Chem.* **2017**, *15*, 7196-7203;
Abstract: Concise total syntheses of smenothiazoles A (1) and B (2), two distinguished vinyl chloride containing natural products isolated from the marine sponge S. aurea, have been developed. Silastannation, Stille reaction and a carefully controlled desilylchlorination were employed as key steps to construct unique polyketide acid fragments, and the optimized reaction conditions avoided migration of 2,5-diene to a 2,4- conjugated system. This report unambiguously confirmed the structures of both natural products.

32. "Are there limits to rational chemical synthesis?" ZhengShuang Xu, Tao Ye, *Chinese Science Bulletin* **2017**, *62*, 2313-2322;
Abstract: Chemical synthesis is the purposeful execution of one or more reactions to obtain a product, or several products, which could modify the existing molecular frameworks, or make a complex (often natural) molecule from simple reagents. There are several possible reasons to make complex molecules by total chemical synthesis. A century ago the aim was often to identify a molecular structure. With the advent of routine X-ray crystallography and high-field FT NMR in the late 1960s, total chemical synthesis served as a necessary structural confirmation became much less compelling. Another reason that chemists synthesized natural products was because of their useful properties. In some cases, molecules could be cheaper to make from scratch than to obtain from nature source. The history of chemistry is essentially the history of finding out the structure of molecules and of developing new and efficient methods of making them. Putting these molecules to new uses is what underpins our modern world, but it was really a secondary goal for most of chemistry's history. Great synthetic chemists of the mid-to-late twentieth century are revered not so much for what they made but for how they made it. Synthesis cultivates an understanding of the basic principles of chemistry: how and why reactions occur, the relationships between molecular shape and function, and so on. Today, synthetic chemists still need to pursue "ideality" in the way molecules are synthesized, and total synthesis should be able to provide large quantities of complex natural products with a minimum amount of labor and material expense. In future years, the emphasis of synthetic chemistry, also

natural product synthesis, will shift from delivering structures to delivering functions. Natural products will continue to serve a central role in the discovery and development of pharmaceutical agents as well as the elucidation of new biological targets of therapeutic relevance. Synthetic chemists are in a unique position to define those very important molecules that we want, which allow us to access to non-natural derivatives that may offer superior biological and physical properties in comparison to the natural material. The research in natural products synthesis has indeed been the impetus for many fundamental discoveries and could also motivate future research in chemistry and biology.

33. "Total Synthesis and Stereochemical Assignment of Actinoranone" Yi-an Guo, Meng Zhao, Zhengshuang Xu, Tao Ye, *Chem. Eur. J.* **2017**, *23*, 3572–3576

Abstract: The total synthesis of four actinoranone stereoisomers led to unambiguous assignment of relative and absolute stereochemistry of the natural product. Key features of the convergent, fully stereocontrolled route include the use of a Negishi carbozirconation/iodination, a Friedel–Crafts cyclization, a Felkin-controlled addition reaction, a Mitsunobu reaction, and a late-stage C H oxidation.

34. "Total Synthesis and Stereochemical Assignment of Nostosin B" Xiaoji Wang, Junmin Feng, Zhengshuang Xu, Tao Ye, Yi Meng, Zhiyu Zhang, *Marine Drugs*, **2017**, *15*, 59; doi:10.3390/md15030058

Abstract: Nostosins A and B were isolated from a hydrophilic extract of Nostoc sp. strain from Iran, which exhibits excellent trypsin inhibitory activity. Nostosin A was the most potent natural tripeptide aldehyde as trypsin inhibitor up to now. Both R‐ and S‐2‐hydroxy‐4‐(4‐hydroxy phenyl) butanoic acid (Hhpba) were prepared and incorporated into the total synthesis of nostosin B, respectively. Careful comparison of the NMR spectra and optical rotation data of synthetic nostosin B (1a and 1b) with the natural product led to the unambiguous identification of the R‐configuration of the Hhpba fragment, which was further confirmed by co‐injection with the authentic sample on HPLC using both reversed phase column and the chiral AD‐RH column.

35. "Concise Total Synthesis of Nannocystin A", Linping Liao, Jingjing Zhou, Zhengshuang Xu, Tao Ye *Angew. Chem. Int. Ed.* **2016**, *55*, 13263-13266. **This paper has been featured by SYNFACTS Highlights in Current Synthetic Organic Chemistry 2016, 12, 1228**

Abstract: Nannocystin A, a structurally unique 21-membered macrocyclic depsipeptide with low nanomolar inhibitory activity against elongation factor-1A, was synthesized according to a strategy employing vinylogous Mukaiyama aldol reaction, Sharpless epoxidation, Brown crotylation, olefin metathesis

reaction, Mitsunobu reaction, and a palladium-catalyzed intramolecular Suzuki coupling of a highly complex cyclization substrate. The overall synthesis is efficient (17.3% overall yield for 10 linear steps) and paves the way for efficient preparation of analogues for drug development efforts.

36. "Total Synthesis and Stereochemical Assignment of Callyspongiolide" Jingjing Zhou, Bowen Gao, Zhengshuang Xu, Tao Ye, *J. Am. Chem. Soc.* **2016**, *138*, 6948-6951

Abstract: Total synthesis of four callyspongiolide stereoisomers led to unambiguous assignment of relative and absolute stereochemistry of the natural product. Key features of the convergent, fully stereocontrolled route include the use of Krische allylation, Kiyooka Aldol reaction, Kociénski−Julia olefination, Still-Gennari olefination, Yamaguchi macrocy-clization and Sonogashira coupling reaction. Biological eval-uation of the synthesized compounds against an array of cancer cells revealed that the stereochemistry of the macro-lactone core played an important role.

37. "Discovery, Total Synthesis and Key Structural Elements for the Immunosuppressive Activity of Cocosolide, a Symmetrical Glycosylated Macrolide Dimer from Marine Cyanobacteria" S. P. Gunasekera, Yang Li, Ranjala Ratnayake, Danmeng Luo, Jeannette Lo, Joseph H. Reibenspies, Zhengshuang Xu, Michael J. Clare-Salzler, T. Ye, V. J. Paul, H. Luesch, *Chem. Eur. J.* **2016**, *22*, 8158-8166

Abstract: A new dimeric macrolide xylopyranoside, cocosolide (1), was isolated from the marine cyanobacterium preliminarily identified as Symploca sp. from Guam. The structure was determined by a combination of NMR spectroscopy, HRMS, X-ray diffraction studies and Mosher's analysis of the base hydrolysis product. Its carbon skeleton closely resembles that of clavosolides A–D isolated from the sponge Myriastra clavosa, for which no bioactivity is known. We performed the first total synthesis of cocosolide (1) along with its [a,a]-anomer (26) and macrocyclic core (28), thus leading to the confirmation of the structure of natural 1. The convergent synthesis featured Wadsworth–Emmons cyclopropanation, Sakurai annulation, Yamaguchi macrocyclization/dimerization reaction, a-selective glycosidation and b-selective glycosidation. Compounds 1 and 26 potently inhibited IL-2 production in both T-cell receptor dependent and independent manners. Full activity requires the presence of the sugar moiety as well as the intact dimeric structure. Cocosolide also suppressed the proliferation of anti-CD3-stimulated Tcells in a dose-dependent manner.

38. "Towards theory driven structure elucidation of complex natural products: mandelalides and coibamide A" K. M. Snyder, J. Sikorska, Tao Ye, L. Fang,

W. Su, R. G. Carter, K. L. McPhail, P. H.-Y. Cheong, *Org. Biomol. Chem.*, **2016**,*14*, 5826–5831.

Abstract: The effectiveness of computational tools in determining relative configurations of complex molecules is investigated, using natural products mandelalides A–D and coibamide A, towards a generalized recipe for the scientific community at large. Ultimately, continuing efforts in this vein will accelerate and strengthen relative structure elucidation of complex molecules, such as natural products. Molecular mechanics conformational search, quantum mechanical NMR chemical shift predictions, and DP4 analyses led to confirmation of the revised structures of mandelalides A–D and coibamide A. All chiral centers in the northern hemisphere of mandelalides A–D are inverted with respect to the originally proposed structures, in agreement with recent total syntheses of mandelalide A by Ye, Fürstner & Carter. In the case of coibamide A, it was found that Fang & Su's revision, in which both the macrocycle [MeAla11] and the side chain [HIV2] residues are inverted from L to D, was consistent with the authentic natural product and computations.

39. "Discovery of Mandelalide E and Determinants of Cytotoxicity for the Mandelalide Series" M. Nazari, J. D. Serrill, J. Sikorska, T. Ye, J. E. Ishmael, K. L. McPhail, *Org. Lett.* **2016**, *18*, 1374-1377.

Abstract: Recollection of the tunicate source of the mandelalides has provided new and known analogues that have facilitated expanded analyses of the disputed cancer cytotoxicity of mandelalide A following a number of recent reported total syntheses. Using newly characterized mandelalide E, reisolated natural mandelalides B and C, and synthetic mandelalide A, the cytotoxicity of the mandelalides is demonstrated to be strongly influenced by compound glycosylation and assay cell density. Glycosylated mandelalides reduced the viability of human cancer cells cultured at a high starting density with a rank order of potency A > B >> E, yet display dramatically reduced cytotoxic efficacy against low density cultures.

40. "The total synthesis and stereochemical assignment of scytonemin A", Junyang Liu, Lei Wang, Juefei Zhang, Zhengshuang Xu, Tao Ye *Chem. Commun.*, **2016**, 52, 1002-1005

Abstract: The total synthesis of scytonemin A and its C-9 epimer, as well as elucidation of the absolute stereochemistry of natural scytonemin A is described.

41. "Synthesis of Lysine Methyltransferase Inhibitors" Chunngai Hui, Tao Ye *Front. Chem., 23 July* **2015**, http://dx.doi.org/10.3389/fchem.2015.00044

Abstract: Lysine methyltransferase which catalyze methylation of histone and nonhistone proteins, play a crucial role in diverse biological processes and has

emerged as a promising target for the development of various human diseases, including cancer, inflammation, and psychiatric disorders. However, inhibiting lysine methyltransferases selectively has presented many challenges to medicinal chemists. During the past decade, lysine methyltransferase inhibitors covering many different structural classes have been designed and developed. In this review, we describe the development of selective, small-molecule inhibitors of lysine methyltransferases with an emphasis on their discovery and chemical synthesis. We highlight the current state of lysine methyltransferase inhibitors and discuss future directions and opportunities for lysine methyltransferase inhibitor discovery.

42. "Total synthesis of the putative structure of the proposed Banyasin A" Xuguang Gao, Qi Ren, Sun Choi, Zhengshuang Xu, Tao Ye, *Front. Chem.*, 17 March **2015**; DOI:10.3389/fchem.2015.00019
Abstract: The first total synthesis of four possible isomers of a molecule possessing the configuration proposed for banyasin A is described. The structure synthesized appears to be different from that of the natural product.

43. "Studies toward the Total Synthesis of Itralamide B and Biological Evaluation of Its Structural Analogs" Xiaoji Wang, Chanshan Lv, Junmin Feng, Linjun Tang, Zhuo Wang, Yuqing Liu, Yi Meng, Tao Ye, Zhengshuang Xu, *Marine Drugs*, **2015**, *13*, 2085-2104.
ABSTRACT: Itralamides A and B were isolated from the lipophilic extract of Lyngbya majuscula collected from the eastern Caribbean. Itralamide B (1) showed cytotoxic activity towards human embryonic kidney cells (HEK293, IC50 = 6 μM). Preliminary studies disapproved the proposed stereochemistry of itralamide. In this paper, we will provide a full account of the total synthesis of four stereoisomers of itralamide B and the results derived from biological tests of these structural congeners.

44. "Total Synthesis of Largamide B" Shiwei Qu, Ying Chen, Xiaoji Wang, Shipeng Chen, Zhengshuang Xu, Tao Ye, *Chem. Commun.* **2015**, *51*, 2510-2513. **This paper has been featured on the intra-front cover of issue 13, volume 51 (2015) of Chemical Communications.**
Abstract: Total synthesis of the cyanobacterial metabolite largamide B and the disapproval of its originally assigned stereochemistry as well as confirmation of the revised stereochemistry are reported

45. "Total Synthesis and Stereochemical Reassignment of Mandelalide A", Honghui Lei, Jialei Yan, Jie Yu, Yuqing Liu, Zhuo Wang, Zhengshuang Xu, Tao Ye *Angew.Chem. Int. Ed.*. **2014**, *53*, 6533-

6537. This paper has been selected as a “HOT PAPER” by Angewandte Chemie International Edition.

Abstract: Total synthesis of the tunicate metabolite mandelalide A and the correction of its originally assigned stereochemistry are reported. Key features of our convergent, fully stereocontrolled route include the use of Prins cyclization for the diastereoselective construction of the tetrahydropyran subunit, Rychnovsky-Bartlett cyclization for the preparation of the tetrahydrofuran moiety, Suzuki coupling reaction, Horner-Wadsworth-Emmons macrocyclization and glycosylation to append the L-rhamnose-derived pyranoside.

46. "Grassypeptolides as Natural Inhibitors of Dipeptidyl Peptidase 8 and T-Cell Activation", Jason C. Kwan, Yanxia, Liu,; Ranjala Ratnayake, Ryo Hatano, Akiko Kuribara, Chiko Morimoto, Kei Ohnuma, Valerie J. Paul, Tao Ye, Luesch, Hendrik, *ChemBioChem*, **2014**, *15*, 799-804.

Abstract: Natural products made by marine cyanobacteria are often highly modified peptides and depsipeptides that have the potential to act as inhibitors for proteases. In the interests of finding new protease inhibition activity and selectivity, grassypeptolide A (1) was screened against a panel of proteases and found to inhibit DPP8 selectively over DPP4. Grassypeptolides were also found to inhibit IL-2 production and proliferation in activated T-cells, consistent with a putative role of DPP8 in the immune system. These effects were also observed in Jurkat cells, and DPP activity in Jurkat cell cytosol was shown to be inhibited by grassypeptolides. In silico docking suggests two possible binding modes of grassypeptolides—at the active site of DPP8 and at one of the entrances to the internal cavity. Collectively these results suggest that grassypeptolides might be useful tool compounds in the study of DPP8 function.

47. "Total Synthesis of the Proposed Structure for Itralamide B", Xiaoji Wang, Chanshan Lv, Junyang Liu, Linjun Tang, Junmin Feng, Shoubin Tang, Zhuo Wang, Yuqing Liu, Yi Meng, Tao Ye, Zhengshuang Xu *Synlett*, **2014**, *25*, 1014-1018.

Abstract: A stereocontrolled total synthesis of the cyclodepsipeptide, itralamide B has been achieved. Both *R*- and *S*-stereomers of the side chain were attached to the macrocyclic ring. The structure synthesized appears to be different from that of the marine natural product.

48. "LSD1 Regulates Pluripotency of Embryonic Stem/Carcinoma Cells through HDAC1-mediated Deacetylation of Histone H4 at Lysine 16", Feng Yin, Rongfeng Lan, Xiaoming Zhang, Linyu Zhu, Fangfang Chen, Zhengshuang Xu, Yuqing Liu, Tao Ye, Hong Sun, Fei Lu and Hui Zhang, *Mol. Cell. Biology* **2014**, *34*, 158-179

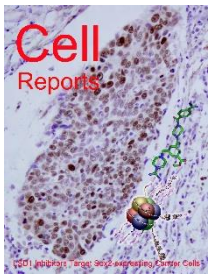
Abstract: LSD1 is essential for the maintenance of pluripotency of embryonic stem (ES) or embryonic carcinoma/teratocarcinoma (EC) cells. We have previously developed novel LSD1 inhibitors that selectively inhibit ES/EC cells. However,

the critical targets of LSD1 remain unclear. Here, we found that LSD1 interacts with HDAC1 to regulate the proliferation of ES/EC cells through H4K16 acetylation, which we showed is a critical substrate of HDAC1. The LSD1 demethylase and HDAC1 deacetylase activities were both inactivated if one of them in the complex was chemically inhibited in ES/EC cells or in reconstituted protein complexes. Loss of HDAC1 phenocopied the selective growth inhibitory effects and increased levels of H3K4 methylation and H4K16 acetylation of LSD1 inactivation on ES/EC cells. Reduction of acetylated H4K16 by ablation of acetyltransferase MOF is sufficient to rescue the growth inhibition induced by LSD1 inactivation. While LSD1 or HDAC1 inactivation caused the down-regulation of Sox2 and Oct4 and induction of differentiation genes such as FOXA2 or BMP2, depletion of MOF restored the levels of Sox2, Oct4 and FOXA2 in LSD1 deficient cells. Our studies reveal a novel mechanism by which LSD1 acts through the HDAC1- and MOF-mediated regulation of H4K16 acetylation to maintain the pluripotency of ES/EC cells.

49. "Cross-Metathesis Approach for Stereocontrolled Synthesis of the C1–C15 Fragment of Rhizopodin", Honggang Gui, Junyang Liu, Liankai Song, Chunngai Hui, Junmin Feng, Zhengshuang Xu, Tao Ye *Synlett*, **2014**, *25*, 138-142

Abstract: The C1–C15 fragment of rhizopodin was synthesized through either Suzuki coupling reaction of vinyl iodide and vinyl boronate or cross-metathesis of a terminal olefin and a diene adduct in the presence of Hoveyda–Grubbs II catalyst.

50. "Pluripotent Stem Cell Protein Sox2 Confers Sensitivity towards LSD1 Inhibition in Cancer Cell", Xiaoming Zhang, Fei Lu, Jing Wang, Feng Yin, Zhengshuang Xu, Dandan Qi, Xianhui Wu, Yuwen Cao, Weihua Liang, Yuqing Liu, Hong Sun, Tao Ye and Hui Zhang *Cell Reports*, **2013**, *5*, 445-457.



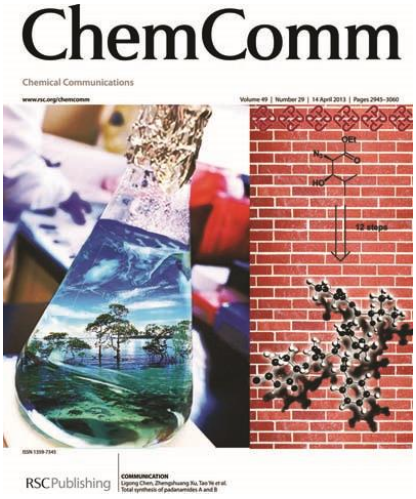
Abstract: The gene amplification of Sox2 at 3q26.33 is a common event in squamous cell carcinomas (SCCs) of lung, esophagus, and several other cancers. Here, we show that the expression of LSD1/KDM1 histone demethylase is significantly elevated in Sox2-expressing lung SCCs. LSD1-specific inhibitors selectively impair the growth of Sox2-expressing lung SCC cells but not that of Sox2-negative cells. Sox2 expression is associated with the sensitivity towards LSD1 inhibition in lung, breast, ovarian, and other carcinoma cells. Inactivation of LSD1 reduces Sox2 expression, promotes G1 cell cycle arrest, and induces genes for differentiation by selectively modulating methylations of histone H3 at lysines 4 (H3K4) and 9 (H3K9). Reduction of Sox2 further suppresses Sox2-dependent lineage-survival oncogenic potential, elevates trimethylation of histone H3 at lysine 27 (H3K27), and enhances growth arrest and cellular differentiation. Our studies

suggest that LSD1 serves as a selective and specific epigenetic target for the therapy of Sox2-expressing cancers.

51. "Synthesis of the Macrocyclic Core of Rhizopodin" Liankai Song, Junyang Liu, Honggang Gui, Chunngai Hui, Jingjing Zhou, Yian Guo, Pengpeng Zhang, Zhengshuang Xu, Tao Ye *Chem. Asian J.* **2013**, *8*, 2955-2959.
Abstract: Rhizing star: A stereoselective synthesis of the fully functionalized macrocyclic core of rhizopodin, a cytotoxic 38-membered macrolide, has been disclosed. The key steps involve Sharpless epoxidation, Robinson–Gabriel oxazole synthesis, olefin cross-metathesis, Suzuki coupling, Yamaguchi esterificationn, and Shiina macrolactonization.

52. "Total Synthesis and Biological Evaluation of Grassypeptolide A" Hui Liu, Yuqing Liu, Zhuo Wang, Xiangyou Xing, Anita R. Maguire, Hendrik Luesch, Hui Zhang, Zhengshuang Xu, Tao Ye *Chem. Eur. J.* **2013**, *19*, 6774-6784.
Abstract: Herein, we describe in full our investigations into the synthesis of grassypeptolide A (1) in 17 linear steps with an overall yield of 11.3 %. In particular, this work features the late-stage introduction of sensitive bis(thiazoline) heterocycles and 31-membered macrocyclization conducted at the sterically congested secondary amide site in superb conversion (72 % yield). Biological evaluation indicated that grassypeptolide A significantly inhibited cancer cell proliferation in a dose-dependent manner. It induced cancer cell apoptosis, which was associated with increased cleavage of poly(ADP-ribose) polymerase (PARP) and decreased expression of bcl-2 and bcl-xL. Furthermore, grassypeptolide A also caused cell cycle redistribution by increasing cells in the G1 phase and decreasing cells in the S and G2 phases. In addition, cell cycle arrest was correlated with downregulation of cyclin D and upregulation of p27 and p21.

53. "Total Synthesis of Padanamides A and B", Bohua Long, Shoubin Tang, Ligong Chen, Shiwei Qu, Bo Chen, Junyang Liu, Anita R. Maguire, Zhuo Wang, Yuqing Liu, Hui Zhang, Zhengshuang Xu and Tao Ye, *Chem. Commun.* **2013**, *49*, 2977-2979.
This paper has been featured on the intra-front cover of issue 29, volume 49 (2013) of Chemical Communications. This cover image contains PolyU's Logo.
Abstract: The first total syntheses of padanamides A and B have been achieved, unambiguously confirming their structures.



54. "A Novel CyclinE/CyclinA-CDK2 Inhibitor Targets p27(Kip1) Degradation, Cell Cycle Progression and Cell Survival: Implications in Cancer Therapy" Lu Dai, Yuqing Liu, Junyang Liu, Xiaoming Wen, Zhengshuang Xu, Zhuo Wang, Hong Sun, Shoubin Tang, Anita R Maguire, Junmin Quan, Hui Zhang, Tao Ye *Cancer Letters*, **2013**, *333*, 103-112.
Abstract: p27(Kip1) (p27) binds and inhibits the cyclin E- or cyclin A-associated cyclin-dependent kinases (CDKs)2 and other CDKs, and negatively regulates G1-G2 cell cycle progression. To develop specific CDK inhibitors, we have modeled the interaction between p27 and cyclin A-CDK2, and designed a novel compound that mimics p27 binding to cyclin A-CDK2. The chemically synthesized inhibitor exhibited high potency and selective inhibition towards cyclin E/cyclin A-CDK2 kinase in vitro but not other kinases. To facilitate permeability of the inhibitor, a cell penetrating peptide (CPP) was conjugated to the inhibitor to examine its effect in several cancer cell lines. The CPP-conjugated inhibitor significantly inhibited the proliferation of cancer cells. The treatment of the inhibitor resulted in the increased accumulation of p27 and p21(Cip1/Waf1) (p21) and hypo-phosphorylation of retinoblastoma protein (Rb). The degradation of p27, mediated through the phosphorylation of threonine-187 in p27, was also inhibited. Consequently, exposure of cells to the inhibitor caused cell cycle arrest and apoptosis. We conclude that specific cyclinE/cyclin A-CDK2 inhibitors can be developed based on the interaction between p27 and cyclin/CDK to block cell cycle progression to prevent tumor growth and survival.

55. "A Histone Deacetylase Inhibitor, Largazole, Decreases Liver Fibrosis and Angiogenesis by Inhibiting Transforming Growth Factor-beta and Vascular Endothelial Growth Factor Signalling " Yuqing Liu, Zhuo Wang, Jianing Wang, Wingchi Lam, Shuqin Kwong, Furong Li, Scott L. Friedman, Shuyan Zhou, Qi Ren, Zhengshuang Xu, XinGen Wang, Ling Ji, Shoubin Tang, Hui Zhang, Eric L. Lui and Tao Ye *Liver International*, **2013**, *33*, 504-515.
Abstract: Largazole is a novel histone deacetylase (HDAC) inhibitor. This study investigated the effects of largazole against liver fibrosis. METHODS: The in vitro effects of largazole were examined using hepatic stellate cells (HSCs). In vivo effects of largazole were studied using a mouse liver fibrotic model induced by CCl(4). RESULTS: Largazole augmented acetylation of histone H3 (H3) and histone H4 (H4) in HSCs. It directly inhibited the activation of HSCs owing to HDAC inhibitory activity as the antifibrotic effect of largazole was significantly decreased in cells with HDAC1, HDAC2 and HDAC3 knockdown. Largazole also induced apoptosis of HSCs. Largazole not only inhibited the expression of TGFbetaR2, but also reduced phosphorylation of Smad2 and Akt induced by TGF-beta1. Largazole also inhibited the expression of vascular endothelial growth factor (VEGF) and its receptor. VEGF-induced proliferation

of HSCs and activation of Akt and p38MAPK were also suppressed by largazole. In vivo, largazole reduced the expression of collagen I, alpha-smooth muscle actin and tissue inhibitor of metalloproteinase-1 in CCl(4) -induced fibrosis, and these antifibrotic effects were associated with increased acetylation of H3 and H4. Largazole also induced HSCs to undergo apoptosis in vivo, which was correlated with downregulation of bcl-2 and bcl-xL. Furthermore, largazole inhibited angiogenesis in vivo as evidenced by reduced expression of CD34, VEGF and VEGFR. In addition to its antifibrotic activity, the drug reduced inflammatory activity in CCl(4) -induced liver fibrosis. CONCLUSIONS: Our findings revealed a novel role of largazole in the treatment of liver fibrosis. Through multiple mechanisms, largazole could be a potentially effective antifibrotic agent.

56. "Superoxide constitutes a major signal of mitochondrial superoxide flash"
Xing Zhang, Zhanglong Huang,Tingting Hou, Jiejia Xu,Yanru Wang, Wei Shang, Tao Ye, Heping Cheng, Feng Gao, Xianhua Wang, *Life sciences*, **2013**, *93*, 178-186.

Abstract: AIMS: Mitochondrial flashes detected with an N- and C-terminal circularly- permuted yellow fluorescent protein (cpYFP) have been thought to represent transient and quantal bursts of superoxide production under physiological, stressful and pathophysiological conditions. However, the superoxide nature of the cpYFP-flash has been challenged, considering the pH-sensitivity of cpYFP and the distinctive regulation of the flash versus the basal production of mitochondrial reactive oxygen species (ROS). Thus, the aim of the study is to further determine the origin of mitochondrial flashes.

MAIN METHODS: We investigated the origin of the flashes using the widely-used pH-insensitive ROS indicators, mitoSOX, an indicator for superoxide, and 2, 7-dichlorodihydrofluorescein diacetate (DCF), an indicator for H_2O_2 and other oxidants.

KEY FINDINGS: Robust, quantal, and stochastic mitochondrial flashes were detected with either mitoSOX or DCF in several cell-types and in mitochondria isolated from the heart. Both mitoSOX-flashes and DCF-flashes showed similar incidence and kinetics to those of cpYFP-flashes, and were equally sensitive to mitochondria-targeted antioxidants. Furthermore, they were markedly decreased by inhibitors or an uncoupler of the mitochondrial electron transport chain, as is the case with cpYFP-flashes. The involvement of the mitochondrial permeability transition pore in DCF-flashes was evidenced by the coincidental loss of mitochondrial membrane potential and matrix-enriched rhod-2, as well as by their sensitivity to cyclosporine A.SIGNIFICANCE: These data indicate that all the three types of mitochondrial flashes stem from the common physiological process of bursting superoxide and ensuing H_2O_2 production in the matrix of single mitochondrion.

57. "First Total Synthesis and Stereochemical Revision of Laxaphycin B and Its Extension to Lyngbyacyclamide A." France Boyaud, Zahia Mahiout, Christine Lenoir, Shoubin Tang, Joanna Wdzieczak-Bakala, Anne Witczak, Isabelle Bonnard, Bernard Banaigs, Tao Ye, Nicolas Inguimbert, *Org. Lett.* **2013**, *15*, 3898-3901.

Abstract: The first total synthesis of laxaphycin B was accomplished through stepwise automated Solid Phase Peptide Synthesis (SPPS), leading to the structural revision of its stereochemistry especially with regard to the configuration of one of the two 3-hydroxyleucines of this cyclic dodecapeptide of marine origin. The analogous Lyngbyacyclamide A was obtained by an extension of this synthesis.

58. "NuRD Blocks Reprogramming of Mouse Somatic Cells into Pluripotent Stem Cells" Min Luo, Te Ling, Wenbing Xie, He Sun, Yonggang Zhou, Qiaoyun Zhu, Meili Shen, Le Zong, Guoliang Lyu, Yun Zhao, Tao Ye, Jun Gu, Wei Tao, Zhigang Lu, Ingrid Grummt, *Stem Cells*, **2013**, *31*, 1278-86.

Abstract: Reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) by overexpression of a defined set of transcription factors requires epigenetic changes in pluripotency genes. Nuclear reprogramming is an inefficient process and the molecular mechanisms that reset the epigenetic state during iPSC generation are largely unknown. Here, we show that downregulation of the nucleosome remodeling and deacetylation (NuRD) complex is required for efficient reprogramming. Overexpression of Mbd3, a subunit of NuRD, inhibits induction of iPSCs by establishing heterochromatic features and silencing embryonic stem cell-specific marker genes, including Oct4 and Nanog. Depletion of Mbd3, on the other hand, improves reprogramming efficiency and facilitates the formation of pluripotent stem cells that are capable of generating viable chimeric mice, even in the absence of c-Myc or Sox2. The results establish Mbd3/NuRD as an important epigenetic regulator that restricts the expression of key pluripotency genes, suggesting that drug-induced downregulation of Mbd3/NuRD may be a powerful means to improve the efficiency and fidelity of reprogramming.

59. "Role of histone deacetylase inhibitors in the aging of human umbilical cord mesenchymal stem cells." Yunshuai Wang, Tao Chen, Hongjie Yan, Hui Qi, Chunyan Deng, Tao Ye, Shuyan Zhou, FuRong Li, *J. Cell. Biochem.* **2013**, *114*, 2231-2239.

Abstract: Mesenchymal stem cells (MSCs) are self-renewing cells that exhibit differentiation capacity and immune regulation ability. These versatile cells have a wide range of potential applications. However, the spontaneous differentiation and aging of MSCs during long-term culturing restrict the amount of cells available for therapies and tissue engineering. Thus, maintaining the biological characteristics of MSCs during long-term culturing is crucial. Chromatic modification via epigenetic regulatory mechanisms (e.g., histone acetylation, deacetylation, and methylation) is crucial in stem cell

pluripotency. We investigated the effects of largazole or trichostatin A (TSA), a novel histone deacetylase inhibitor (HDACi), against human umbilical cord (hUC)-MSCs aging. Results show that low concentrations of largazole or TSA can significantly improve hUC-MSCs proliferation and delay hUC-MSCs aging. Largazole can better improve MSCs proliferation than TSA. HDAC is modulate histone H3 acetylation and methylation in the telomerase reverse-transcriptase, octamer-binding transcription factor 4, Nanog, C-X-C chemokine receptor 4, alkaline phosphatase, and osteopontin genes. HDACis can promote hUC-MSCs proliferation and suppress hUC-MSCs spontaneous osteogenic differentiation. HDACis can affect histone H3 lysine 9 or 14 acetylation and histone H3 lysine 4 dimethylation, thus increasing the mRNA expression of pluripotent and proliferative genes and suppressing the spontaneous differentiation of hUC-MSCs.

60. "Synergistic Triggering of Superoxide Flashes by Mitochondrial Ca^{2+} Uniport and Basal Reactive Oxygen Species Elevation", Tingting Hou, Xing Zhang, Jiejia Xu, Chongshu Jian, Zhanglong Huang, Tao Ye, Keping Hu, Ming Zheng, Feng Gao, Xianhua Wang and Heping Cheng, *J. Biol. Chem.* **2013**, *288*, 4602–4612.

Abstract: Mitochondrial superoxide flashes reflect a quantal, bursting mode of reactive oxygen species (ROS) production that arises from stochastic, transient opening of the mitochondrial permeability transition pore (mPTP) in many types of cells and in living animals. However, the regulatory mechanisms and the exact nature of the flash-coupled mPTP remain poorly understood. Here we demonstrate a profound synergistic effect between mitochondrial Ca2+ uniport and elevated basal ROS production in triggering superoxide flashes in intact cells. Hyperosmotic stress potently augmented the flash activity while simultaneously elevating mitochondrial Ca2+ and ROS. Blocking mitochondrial Ca2+ transport by knockdown of MICU1 or MCU, newly identified components of the mitochondrial Ca2+ uniporter, or scavenging mitochondrial basal ROS markedly diminished the flash response. More importantly, whereas elevating Ca2+ or ROS production alone was inefficacious in triggering the flashes, concurrent physiological Ca2+ and ROS elevation served as the most powerful flash activator, increasing the flash incidence by an order of magnitude. Functionally, superoxide flashes in response to hyperosmotic stress participated in the activation of JNK and p38.Thus, physiological levels of mitochondrial Ca2+ and ROS synergistically regulate stochastic mPTP opening and quantal ROS production in intact cells, marking the flash as a coincidence detector of mitochondrial Ca2+ and ROS signals.

61. "Total Synthesis and Stereochemical Revision of Lagunamide A" Lu Dai, Bo Chen, Honghui Lei, Zhuo Wang, Yuqing Liu, Zhengshuang Xu, Tao Ye *Chem. Commun.* **2012**, *48*, 8697-8699.

Abstract: A revised configurational assignment for the marine metabolite lagunamide A is proposed and validated by total synthesis.

62. "Total Synthesis and Absolute Configuration of Nocardioazine B" Mingzhong Wang, Xiangyang Feng, Liangzhen Cai, Zhengshuang Xu and Tao Ye, *Chem. Commun.* **2012**, *48*, 4344 - 4346.
Abstract: The first total synthesis of the indole alkaloid nocardioazine B was accomplished in 10 steps with an overall yield of 11.8%, establishing the absolute stereochemistry of the natural product.

63. "Total Synthesis and Stereochemical Revision of Burkholdac A" Junyang Liu, Xiao Ma, Yuqing Liu, Zhuo Wang, Shuqin Kwong, Qi Ren, Shoubin Tang, Yi Meng, Zhengshuang Xu, Tao Ye, *Synlett*, **2012**, *23*, 783-787.
Abstract: A stereocontrolled total synthesis of burkholdac A was completed, leading to a revision of the reported stereochemistry.

64. "Novel Histone Demethylase LSD1 InhibitorsSelectively Target Cancer Cells with Pluripotent Stem Cell Properties" Jing Wang, Fei Lu, Qi Ren, Hong Sun, Zhengshuang Xu, Rongfeng Lan, Yuqing Liu, David Ward, Junmin Quan, Tao Ye, Hui Zhang, *Cancer Research*, **2011**, *71*, 7238-7249. **This paper was highlighted by *NATURE* (China).** For details, please see (http://www.nature.com/nchina/2012/120104/full/nchina.2012.1.html)

Abstract: Histone modification determines epigenetic patterns of gene expression with methylation of histone H3 at lysine 4 (H3K4) often associated with active promoters. LSD1/KDM1 is a histone demethylase that suppresses gene expression by converting dimethylated H3K4 to mono- and unmethylated H3K4. LSD1 is essential for metazoan development, but its pathophysiologic functions in cancer remain mainly uncharacterized. In this study, we developed specific bioactive small inhibitors of LSD1 that enhance H3K4 methylation and derepress epigenetically suppressed genes in vivo. Strikingly, these compounds inhibited the proliferation of pluripotent cancer cells including teratocarcinoma, embryonic carcinoma, and seminoma or embryonic stem cells that express the stem cell markers Oct4 and Sox2 while displaying minimum growth-inhibitory effects on nonpluripotent cancer or normal somatic cells. RNA interference–mediated knockdown of LSD1 expression phenocopied these effects, confirming the specificity of small molecules and further establishing the high degree of sensitivity and selectivity of pluripotent cancer cells to LSD1 ablation. In support of these results, we found that LSD1 protein level is highly elevated in pluripotent cancer cells and in human testicular seminoma tissues that express Oct4. Using these novel chemical inhibitors as probes, our findings establish LSD1 and histone H3K4 methylation as essential

cancer-selective epigenetic targets in cancer cells that have pluripotent stem cell properties..

65. "Total Synthesis of Hoiamide C" Lei Wang, Zhengshuang Xu, and Tao Ye *Org. Lett.* **2011**, *13*, 2506-2509.
Abstract: Hoiamide C was synthesized in 16 steps with an overall yield of 1.8% starting from homoallylic alcohol 18, unambiguously confirming its structure.

66. "Inhibition of PDGF, TGF-β and Abl Signaling and Reduction of Liver Fibrosis by the Small Molecule Bcr-Abl Tyrosine Kinase Antagonist Nilotinib", Yuqing Liu, Zhuo Wang, Shu Qin Kwong, Eric Lik Hang Lui, Scott L. Friedman, Fu Rong Li, Reni Wing Chi Lam, Guo Chao Zhang, Hui Zhang, and Tao Ye, *J. Hepatology*, **2011**, *55*, 612-625.
Abstract: BACKGROUND & AIMS: Nilotinib is a novel tyrosine kinase inhibitor of Bcr-Abl and other kinases. In this study, we have examined its activity as an anti-fibrotic agent. METHODS: The in vitro effect of Nilotinib on rat and human HSCs was assessed using proliferation assays and Western blotting. The in vivo antifibrotic efficacy of Nilotinib was assessed in mice with liver fibrosis induced by CCl(4) and bile duct ligation (BDL). RESULTS: Nilotinib inhibited proliferation, migration, and actin filament formation, as well as the expression of α-SMA and collagen in activated HSCs. Nilotinib induced apoptosis of HSCs, which was correlated with reduced bcl-2 expression, increased p53 expression, cleavage of PARP, as well as increased expression of PPARγ and TRAIL-R. Nilotinib also induced cell cycle arrest, accompanied by increased expression of p27 and downregulation of cyclin D1. Interestingly, Nilotinib not only inhibited activation of PDGFR, but also TGFRII through Src. Nilotinib significantly inhibited PDGF and TGFβ-simulated phosphorylation of ERK and Akt. Furthermore, PDGF- and TGFβ-activated phosphorylated form(s) of Abl in human HSCs were inhibited by Nilotinib. In vivo, Nilotinib reduced collagen deposition and α-SMA expression in CCl(4) and BDL-induced fibrosis. These beneficial effects were associated with suppressed expression of procollagen-(I), TIMP-1, CD31, CD34, VEGF, and VEGFR. Nilotinib could induce HSC undergoing apoptosis in vivo, which was correlated with downregulation of bcl-2. We also observed reduced expression of phosphorylated ERK, Akt, and Abl in the Nilotinib-treated CCl(4) and BDL livers. In addition to its antifibrotic activity, the drug was hepatoprotective and reduced the elevations of ALT and AST after CCl(4) and BDL. CONCLUSIONS: These studies uncover a novel role of Bcr-Abl activity in treatment of liver fibrosis through multiple mechanisms and indicate that Nilotinib represents a potentially effective antifibrotic agent.

67. "Development of an Oral Form of Azacytidine: 2'3'5'triacetylazacytidine" Amy Ziemba, Eugene Hayes, Burgess B. Freeman III, Tao Ye and Giuseppe

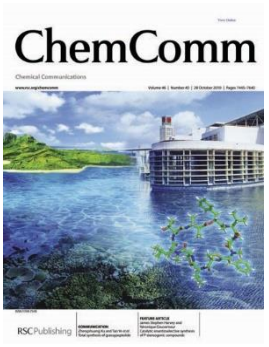
Pizzorno1, *Chemotherapy Res. Prac.*, **2011** 965826, 9 pp. DOI: 10.1155/2011/965826

Abstract: Myelodysplastic syndromes (MDSs) represent a group of incurable stem-cell malignancies which are predominantly treated by supportive care. Epigenetic silencing through promoter methylation of a number of genes is present in poor-risk subtypes of MDS and often predicts transformation to acute myelogenous leukemia (AML). Azacitidine and decitabine, two FDA-approved DNA methyltransferase (DNMT) inhibitors, are able to improve overall response although their oral bioavailability complicates their clinical use. This study evaluated 2', 3', 5'-triacetyl-5-azacitidine (TAC) as a potential prodrug for azacitidine. The prodrug demonstrated significant pharmacokinetic improvements in bioavailability, solubility, and stability over the parent compound. In vivo analyses indicated a lack of general toxicity coupled with significantly improved survival. Pharmacodynamic analyses confirmed its ability to suppress global methylation in vivo. These data indicate that esterified nucleoside derivatives may be effective prodrugs for azacitidine and encourages further investigation of TAC into its metabolism, activity, and possible clinical evaluation.

68. "Superoxide Flashes Early Mitochondrial Signals for Oxidative Stress-induced Apoptosis", Qi Ma, Huaqiang Fang, Wei Shang, Lei Liu, Zhengshuang Xu, Tao Ye, Xianhua Wang, Ming Zheng, Quan Chen and Heping Cheng, *J. Biol. Chem.* **2011**, 286, 27573-27581.

Abstract: Irreversible mitochondrial permeability transition and the resultant cytochrome c release signify the commitment of a cell to apoptotic death. However, the role of transient MPT (tMPT) because of flickering opening of the mitochondrial permeability transition pore remains elusive. Here we show that tMPT and the associated superoxide flashes (i.e. tMPT/superoxide flashes) constitute early mitochondrial signals during oxidative stress-induced apoptosis. Selenite (a ROS-dependent insult) but not staurosporine (a ROS-independent insult) stimulated an early and persistent increase in tMPT/superoxide flash activity prior to mitochondrial fragmentation and a global ROS rise, independently of Bax translocation and cytochrome c release. Selectively targeting tMPT/superoxide flash activity by manipulating cyclophilin D expression or scavenging mitochondrial ROS markedly impacted the progression of selenite-induced apoptosis while exerting little effect on the global ROS response. Furthermore, the tMPT/superoxide flash served as a convergence point for pro- and anti-apoptotic regulation mediated by cyclophilin D and Bcl-2 proteins. These results indicate that tMPT/superoxide flashes act as early mitochondrial signals mediating the apoptotic response during oxidative stress, and provide the first demonstration of highly efficacious local mitochondrial ROS signaling in deciding cell fate.

69. "Total Synthesis of Grassypeptolide", Hui Liu, Yuqing Liu, Xiangyou Xing, Zhengshuang Xu, Tao Ye, *Chem.Commun.* **2010**, *46*, 7486-7488. **This paper was featured on the intra-front cover of issue 40, volume 46, (2010) of Chemical Communications and highlighted by *NATURE* (China).** For details, please see:



(http://www.nature.com/nchina/2010/101103/full/nchina.2010.121.html)

Abstract: The first total synthesis of grassypeptolide (I), an anticancer cyclodepsipeptide isolated from marine cyanobacteria, has been achieved in 17 steps and an overall 11.3% yield.

70. "Synthesis of the Macrocyclic Core of Iriomoteolide-1a", Shuo Li, Zheng Chen, Zhengshuang Xu, Tao Ye, *Chem. Commun.* **2010**, *46*, 4773-4775.

Abstract: The fully functionalized macrocyclic core (I) of the marine natural product iriomoteolide-1a has been successfully constructed in a convergent and enantioselective manner. Key steps include 1,5-anti aldol reaction, Yamaguchi esterification, Kocienski-Julia olefination and ring-closing metathesis.

71. "Total Synthesis and Stereochemical Reassignment of Bisebromoamide", Xuguang Gao, Yuqing Liu, Shuqin Kwong, Zhengshuang Xu and Tao Ye, *Org. Lett.* **2010**, *12*, 3018-3021.

Abstract: A revised configurational assignment for the thiazoline moiety of the marine peptide bisebromoamide is proposed and validated by total synthesis.

72. "Synthesis of the C9−C23 (C9'-C23') Fragment of the Dimeric Natural Product Rhizopodin", Zheng Chen, Liankai Song, Zhengshuang Xu, Tao Ye, *Org. Lett*. **2010**, *12*, 2036-2039.

Abstract: A stereoselective assembly of the C9−C23 (C9′−C23′) fragment of rhizopodin, a 38-membered bis-lactone natural product, has been developed. A highly efficient approach to this fragment assembles >50% of the carbon skeleton and the stereochemical elements present in the natural product.

73. "Total Synthesis of Sintokamide C", Ying Jin, Yuqing Liu, Zhuo Wang, Shuqin Kwong, Zhengshuang Xu and Tao Ye, *Org. Lett*. **2010**, *12*, 1100-1103.

Abstract: A convergent stereoselective synthesis of sintokamide C was accomplished in 14 steps with an overall yield of 3.8% starting from Garner's aldehyde, unambiguously confirming its structure.

74. "Towards the Stereochemical Assignment of Natural Lydiamycin A", Bo Chen, Lu Dai, Hui Zhang, Wenfei Tan, Zhengshuang Xu and Tao Ye, *Chem. Commun.* **2010**, *46*, 574-576.
Abstract: A convergent approach leading to the stereoselective synthesis of four diastereomers of lydiamycin A has been established and verified.

75. "Total Synthesis of Largamide H", Shuo Liang, Zhengshuang Xu, Tao Ye, *Chem. Commun.* **2010**, *46*, 153-155.
Abstract: Total synthesis of largamide H has been completed, utilising the oxidative elimination reaction of enantiomerically pure 2-amino-3-(phenylselenyl)butanoic acid residues to stereospecifically install both (Z)- and (E)-2,3-dehydro-2-aminobutanoic moieties.

76. "Progress towards the Total Synthesis of Scytonemin A: Asymmetric Synthesis of (2S,3R,4R)-4-Hydroxy-3-methylproline" Lei Wang, Junyang Liu, Hui Zhang, Zhengshuang Xu, Tao Ye, *Synlett*, **2010**, 563-566.
Abstract: During the total synthesis of the novel cyclopeptide scytonemin A, the fragment containing two (2S,3R,4R)-4-hydroxy-3-methylproline units was successfully prepared. Two approaches leading to (2S,3R,4R)-4-hydroxy-3-methylproline have been explored. They involve the following key transformations: asymmetric crotylation, Sharpless epoxidation-subsequent epoxide opening, intramolecular amidomercuration-oxidation.

77. "Nuclear Entry of Active Caspase-3 Is Facilitated by Its P3-Recognition-Based Specific Cleavage Activity", Min Luo, Zhiyong Lu, He Sun, Kehu Yuan, Quancang Zhang, Sha Meng, Fangxun Wang, Hongchun Guo, Xiaofang Ju, Yuqing Liu, Tao Ye, Zhigang Lu and Zhonghe Zhai, *Cell Res.*, **2010**, *20*, 211-222.
Abstract: As a critical apoptosis executioner, caspase-3 becomes activated and then enters into the nucleus to exert its function. However, the molecular mechanism of this nuclear entry of active caspase-3 is still unknown. In this study, we revealed that caspase-3 harbors a crm-1-independent nuclear export signal (NES) in its small subunit. Using reverse-caspase-3 as the study model, we found that the function of the NES in caspase-3 was not disturbed by the conformational changes during induced caspase-3 activation. Mutations disrupting the cleavage activity or p3-recognition site resulted in a defect in the nuclear entry of active caspase-3. We provide evidence that the p3-mediated specific cleavage activity of active caspase-3 abrogated the function of the NES. In conclusion, our results demonstrate that during caspase-3 activation, NES is constitutively present. p3-mediated specific cleavage activity abrogates the NES function in caspase-3, thus facilitating the nuclear entry of active caspase-3.

78. "Stereoselective Synthesis of C1-C12 Fragment of Thuggacins", Shoubin Tang, Zhengshuang Xu, Tao Ye, *Tetrahedron: Asymmetry*, **2009**, *20*, 2027-32.

Abstract: A concise asymmetric synthesis of the C1–C12 fragment of the antibacterial natural product thuggacins has been achieved. The stereochemistry of this fragment was established efficiently via stereoselective reduction and Evans-aldol condensation. Hanztsch's method and a Horner–Wadsworth–Emmnons reaction were employed for thiazole formation and the construction of the E-α,β-unsaturated double bond.

79. "Total Synthesis of Emericellamides A & B" Shuo Li,Shuo Liang,Wenfei Tan, Zhengshuang Xu, Tao Ye, *Tetrahedron* **2009**, *65*, 2695-2702.

Abstract: The total synthesis of emericellamides A and B is reported. A convergent, flexible strategy employing peptide chemistry, asymmetric alkylations, and culminating in macrolactamization is described. The previously reported structure of both compounds is confirmed.

80. "Therapeutic targeting of the PDGF and TGF-beta-signaling pathways in hepatic stellate cells by PTK787/ZK22258", Yuqing Liu, Xiao Ming Wen, Eric Lik Hang Lui, Scott L Friedman, Wei Cui, Nancy Pei Shan Ho, Lei Li, Tao Ye, Sheung Tat Fan, Hui Zhang, *Laboratory Investigation* **2009**, *89*, 1152–60.

Abstract: Stimulation of hepatic stellate cells (HSCs) by platelet-derived growth factor (PDGF) and transforming growth factor-beta1 (TGF-beta1) is an essential pathway of proliferation and fibrogenesis, respectively, in liver fibrosis. We provide evidence that PTK787/ZK222584 (PTK/ZK), a potent tyrosine kinase inhibitor that blocks vascular endothelial growth factor receptor (VEGFR), significantly inhibits PDGF receptor expression, as well as PDGF-simulated HSC proliferation, migration and phosphorylation of ERK1/2, Akt and p70S6 kinase. Interestingly, PTK/ZK also antagonizes the TGF-beta1-induced expression of VEGF and VEGFR1. Furthermore, PTK/ZK downregulates TGF-beta receptor expression, which is associated with reduced Akt, ERK and p38MAPK phosphorylation. Furthermore, PDGF-induced TGF-beta1 expression is inhibited by PTK/ZK. These findings provide evidence that PTK/ZK targets multiple essential pathways of stellate cell activation that provoke proliferation and fibrogenesis. Our study underscores the potential use of PTK/ZK as an antifibrotic drug in chronic liver disease.

81. "PTK787/ZK22258 Attenuates Stellate Cell Activation and Hepatic Fibrosis in vivo by Inhibiting VEGF Signaling", Yuqing Liu, Eric Lik Hang Lui, Scott L Friedman, Lei Li, Tao Ye, Yongjun Chen, Ronnie T Poon, Jana Wo, Tsz Wai Kok, Sheung Tat Fan *Laboratory Investigation* **2009**, *89*, 209–221.

Abstract: Liver fibrosis due to hepatic stellate cell (HSC) activation represents a common response to chronic liver injury. PTK787/ZK222584 (PTK/ZK) is a

pan-VEGFR tyrosine kinase inhibitor. The aim of this study was to examine the effect of PTK/ZK in liver fibrosis. In primary HSCs, PTK/ZK inhibited the expression of alpha-smooth muscle actin (alpha-SMA), collagen, tissue inhibitor of metalloproteinase-1 (TIMP-1), as well as cell proliferation, migration and actin filament formation. PTK/ZK-induced apoptosis of HSCs, which was correlated with increased caspase-3 activation and suppressed Bcl-2 expression. PTK/ZK also induced cell cycle arrest, accompanied by increasing the expression of p27(Kip1) and downregulation of cyclin D1 and cyclin E. PTK/ZK significantly inhibited vascular endothelial growth factor (VEGF) expression, as well as VEGF-simulated cell proliferation and phosphorylation of Akt in activated HSCs. In a murine fibrotic liver, PTK/ZK attenuated collagen deposition and alpha-SMA expression in carbon tetrachloride-induced fibrosis in both a 'prevention' and 'treatment' dosing scheme. These beneficial effects were associated with reduced phosphorylation of Akt and suppressed mRNA expression of procollagen-(I), TIMP-1, matrix metalloproteinase-9 and CD31. These findings provide novel insights into the potential value of blocking VEGF signaling by a small molecule tyrosine kinase inhibitor in treating hepatic fibrosis.

82. “Total Synthesis of Largazole” Qi Ren, Lu Dai, Hui Zhang, Wenfei Tan, Zhengshuang Xu, Tao Ye, *Synlett*, **2008**, 2379-83.

Abstract: The stereocontrolled total synthesis of largazole was accomplished, unambiguously confirming its structure. Key steps included the use of the Nagao thiazolidinethione auxiliary for a diastereoselective acetate aldol reaction, thiazoline- thiazole formation, and macrolactamization by use of the Mukaiyama reagent.

83. “Total Synthesis of the Proposed Structure of LL15G256γ” Shuo Li, Shuo Liang, Zhengshuang Xu, Tao Ye, *Synlett*, **2008**, 569-74.

Abstract: Total synthesis of the proposed structure of LL15G256 gamma|antifungal agents; cyclodepsipeptide; LL15G256 gamma; total synthesis; benzylic oxidation; macrolactamization|The first total synthesis of a molecule possessing the stereochemistry proposed for LL15G256 gamma is described. The structure synthesized appears to be different from that of the marine natural product.

84. “The First Total Synthesis of Aeruginosamide” Zhiyong Chen, Tao Ye, *New J. Chem.* **2006**, *30*, 518-20.

Abstract: Synthesis of aeruginosamide, a metabolite of the cyanobacterium Microcystis aeruginosa, required overcoming difficulties encountered in a convergent route and an interesting change in conformation of the product governed by the conditions for the final step.

85. "CUL4-DDB1 ubiquitin ligase interacts with multiple WD40-repeat proteins and regulates histone methylation" Leigh Ann Higa, Min Wu, Tao Ye, Ryuji Kobayashi, Hong Sun and Hui Zhang, *Nature Cell Biology* **2006**, *8*, 1277-83.

Abstract: The CUL4-DDB1-ROC1 ubiquitin E3 ligase regulates cell-cycle progression, replication and DNA damage response. However, the substrate-specific adaptors of this ligase remain uncharacterized. Here, we show that CUL4-DDB1 complexes interact with multiple WD40-repeat proteins (WDRs) including TLE1-3, WDR5, L2DTL (also known as CDT2) and the Polycomb-group protein EED (also known as ESC). WDR5 and EED are core components of histone methylation complexes that are essential for histone H3 methylation and epigenetic control at K4 or K9 and K27, respectively, whereas L2DTL regulates CDT1 proteolysis after DNA damage through CUL4-DDB1 (ref. 8). We found that CUL4A-DDB1 interacts with H3 methylated mononucleosomes and peptides. Inactivation of either CUL4 or DDB1 impairs these histone modifications. However, loss of WDR5 specifically affects histone H3 methylation at K4 but not CDT1 degradation, whereas inactivation of L2DTL prevents CDT1 degradation but not histone methylation. Our studies suggest that CUL4-DDB1 ligases use WDR proteins as molecular adaptors for substrate recognition, and modulate multiple biological processes through ubiquitin-dependent proteolysis.

86. "L2DTL/CDT2 and PCNA Interact with p53 and Regulate p53 Polyubiquitination and Protein Stability through MDM2 and CUL4A/DDB1 Complexes", Damon Banks, Min Wu, Leigh Ann Higa, Nadia Gavrilova, Junmin Quan, Tao Ye, Ryuji Kobayashi, Hong Sun, Hui Zhang, *Cell Cycle* **2006**, 15, 1719-29.

Abstract: The CUL4-ROC1 E3 ligase complex regulates genome stability, replication and cell cycle progression. A novel WD40 domain-containing protein, L2DTL/CDT2 and PCNA were identified as proteins associated with CUL4/DDB1 complexes. Inactivation of CUL4A, L2DTL, PCNA, DDB1 or ROC1 induced p53 stabilization and growth arrest. L2DTL, PCNA and DDB1/CUL4A complexes were found to physically interact with p53 tumor suppressor and its regulator MDM2/HDM2. The isolated CUL4A complexes display potent and robust polyubiquitination activity towards p53 and this activity is dependent on L2DTL, PCNA, DDB1, ROC1 and MDM2/HDM2. We also found that the interaction between p53 and CUL4 complex is regulated by DNA damage. Our data further showed that MDM2/HDM2 is rapidly proteolyzed in response to UV irradiation and this process is regulated by CUL4/DDB1 and PCNA. Our studies demonstrate that PCNA, L2DTL and the DDB1-CUL4A complex play critical and differential roles in regulating the protein stability of p53 and MDM2/HDM2 in unstressed and stressed cells.

87. "Total Synthesis of *Lyngbyabellin A*", Heungwing Pang, Zhengshuang Xu, Zhiyong Chen and, Tao Ye, *Lett. Org. Chem.***2005**, *2*, 699-702

Abstract: The total synthesis of lyngbyabellin A, a biologically active metabolite from the marine cyanobacterium Lyngbya majuscula, is reported. There is flexibility in the approach which can readily allow structural modifications to be introduced.

88. "Enantiocontrol in Intermolecular Cyclopropanations: Use of Diazosulphonate Esters" Tao Ye, Congying Zhou, *New J. Chem.* **2005**, *29*, 1159-63.

Abstract: The novel use of α-diazosulfonate esters as alternative cyclopropanating agents to diazoacetates is investigated. The effects of structure of both substrate and ligand on diastereo- and enantioselectivity are studied, and the catalytic ability of different metals is compared.

89. "Synthesis of 2,4,5-Trisubstituted Thiazoline *via* a Novel Stereoselective Intramolecular Conjugate Addition" Zhengshuang Xu, Tao Ye *Tetrahedron: Asymmetry*, **2005**, 16, 1905-12.

Abstract: A convenient stereoselective preparation of 2,4,5-trisubstituted thiazolines is reported. The procedure involves the cyclisation of an unsaturated thioamide under mildly acidic conditions, and proceeds with excellent stereocontrol. A range of substrates are presented, and an explanation of the stereochemical outcome discussed.

90. "The Total Synthesis and Reassignment of Stereochemistry of Dragonamide" Hongliang Chen, Yaqing Feng, Zhengshuang Xu, Tao Ye, *Tetrahedron* **2005**, *61*, 11132- 40

Abstract: The first total synthesis of dragonamide is reported. The synthesis has led to a reassignment of the configuration at the stereogenic centre on the alkyne-bearing fragment of the molecule.

91. "Diastereoselective Synthesis of the Acyl Side-Chain and Amino Acid (2*S*,3*R*)-3- Hydroxy-3-Methylproline Fragments of *Polyoxypeptin A*", Zhiyong Chen, Tao Ye, *Synlett*. **2005**, 2781-85.

Abstract: Synthesis of the acyl side-chain and amino acid (2S,3R)-3-hydroxy-3- methylproline units of the potent depsipeptide poly-oxypeptin A, is described. Key intermediates were secured via dia-stereoselective addition involving a homoenolate ion and allylation of an aminoketone, respectively.

92. "Total Synthesis of *Pitipeptolide A*" Yungui Peng, Heungwing Pang, Zhengshuang Xu and, Tao Ye, *Lett. Org. Chem.* **2005**, *2*, 703-6.

Abstract: An efficient synthesis of the marine cyanobacterium metabolite pitipeptolide A is presented. The approach incorporates a variety of peptide coupling methods, asymmetric synthesis and macrocyclization. The route is versatile and allows scope for structural modification.

93. "Synthesis of the Polyketide Segment of Apratoxin A" Zhengshuang Xu, Zhiyong Chen, Tao Ye, *Tetrahedron: Asymmetry*, **2004**, *15*, 355-63.

Abstract: Apratoxin A 1 is a potent cytotoxic agent extracted from a marine cyanobacterium. We report the results of our synthetic approaches to the polyketide segment 3-OTBS-7-OPMB-2,5,8,8-tetramethylnonanoic acid 4, and the scope and limitations of these approaches.

94. "Stereocontrolled Synthesis of Onchidins" Yungui Peng, Heung Wing Pang, Tao Ye *Organic Lett.* **2004**, *6*, 3781-84.

Abstract: The first total synthesis of a molecule possessing the stereochemistry proposed for onchidin is described. The structure synthesized appears to be different from that of the marine natural product.

95. "Total Synthesis and Biological Testing of Isomers of Onchidin" Yungui Peng, Heung Wing Pang, Yuqing Liu, Tao Ye, *Peptides* **2004**, 291-92.

96. "Total Synthesis of *cis, cis*-Ceratospongamide" Zhiyong Chen, Jingen Deng, Tao Ye *ARKIVOC* Vol. **2003**, Part VII, page 268-285, invited paper

Abstract: A total synthesis of cis, cis-ceratospongamide 1 was accomplished via 4+3 fragment condensation, macrolactamization and subsequent cyclodehydration. Macrolactamization of both linear peptides 4a & 4b produced the corresponding cyclopeptide 3 as a mixture of two conformational isomers (cis, cis 3a and cis, trans 3b). Further oxazoline ring closure furnished the *cis*, *cis*-ceratospongamide 1 which is identical to the natural product.

97. "The Total Synthesis and Stereochemical Revision of Yanucamide A" Zhengshuang Xu ,Yungui Peng, Tao Ye*, *Organic Lett.* **2003**, *5*, 2821-24.

Abstract: The first total synthesis of yanucamide A is reported via amide and ester couplings of the key components. This synthesis has established the configuration at the previously ambiguous 3-position, and also revised the stereochemistry at the 22-position, to give 3S,12S,17S,22S for the natural product.

98. "Total Synthesis of (+)-Phorboxazole A, a Potent Cytostatic Agent from the Sponge *Phorbas* Sp." Gerald Pattenden, Miguel A. González, Paul B. Little, David S. Millan, Alleyn T. Plowright, James A. Tornos and Tao Ye, *Organic and Biomolecular Chemistry* **2003**,*1*, 4173-208.

Abstract: A convergent total synthesis of phorboxazole A (1a), from the C(3-19), C(20-27) and C(33-46) fragments 5, 4 and 91, respectively, concentrating on stereocontrolled formation of the bonds at C(2-3), C(19-20) and C(27-28), is described. Although a coupling reaction between a macrolide ketone and the side chain substituted sulfone, at C(27-28) was not successful, a Wadsworth-Emmons olefination involving the oxane methyl ketone 4 and an oxazole

produced the oxane 90 which was next coupled to 91 leading to the C(20-46) unit 100. A further coupling of 100 to 71c at C(19-20) then led to 105, ultimately, and the synthesis was completed by a macrocyclisation reaction from 105, at the C(2-3) alkene bond, followed by deprotection of 106.

99. "Highly Efficient and Practical Resolution of 1,1'-Spirobiindane-7,7'-diol by Inclusion Crystallization with N-Benzylcinchonidium Chloride", Ju-Hua Zhang, Jian Liao, Xin Cui, Kai-Bei Yu, Jin Zhu, Jin-Gen Deng, Shou-Fei Zhu, Li-Xin Wang, Qi-Lin Zhou, Lung Wa Chung, Tao Ye, *Tetrahedron: Asymmetry* **2002**, *13*, 1363-66.
Abstract: The chiral spirobiindane ligand, 1,1′-spirobiindane-7,7′-diol has been resolved efficiently by inclusion complexation with commercially available *N*-benzylcinchonidinium chloride. The resolved complex was studied by X-ray crystallography in order to characterize the intermolecular interactions and recognition nature.

100. "Total Synthesis of (+)-Curacin A, a Novel Antimitotic Metabolite from a Cyanobacterium" James C. Muir, Gerald Pattenden, Tao Ye, *J. Chem. Soc., Perkin Trans. 1*, **2002**, (20), 2243 – 50.
Abstract: A concise total synthesis of (+)-curacin A, a potent antimitotic agent isolated from the cyanobacterium Lyngbya majuscula, is described. The synthesis features a new strategy to the 2-cyclopropyl-4-alkenyl substituted thiazoline unit in the natural product involving facile and selective thioacylation of the amino-alcohol 10 with the benzotriazole derived thioamide 11, leading to 28, as a key step. Cyclodehydration of 28 using Burgess' reagent then completed the synthesis of curacin A1.

101. "New Cycloartane Glycosides from *Cimicifuga Dahurica*" Wencai Ye, Jingwen Zhang, Chun-Tao Che, Tao Ye, Shouxun Zhao, *Planta Medica* **1999**, *65*, 770-72.
Abstract: Two new cylcoartane glycosides along with a known compound, 12beta-hydroxycimigenol 3- O-alpha- L-arabinopyranoside, were isolated from the rhizomes of Cimicifuga dahurica (Ranunculaceae). The structures of the new compounds were elucidated as cimigenol 3- O-alpha- L-arabinopyranoside and 25- O-acetylcimigenol 3- O-alpha- L-arabinopyranoside on the basis of chemical and spectral evidence.

102. "Synthetic Studies towards Phorboxazole A. A Concise Stereoselective Synthesis of the C20-C26 Pentasubstituted Oxane Ring Unit" Tao Ye, Gerald Pattenden, *Tetrahedron Lett*. **1998**, *39*, 319-22.
Abstract: A stereoselective synthesis of the 2,6-cis oxane unit, accommodating five contiguous asymmetric centres, found in the novel marine natural product phorboxazole A1, is described.

103. "A Concise Total Synthesis of (+)-Curacin A, A Novel Cyclopropyl-Substituted Thiazoline from the Cyanobacterium Lyngbya Majuscula" James C. Muir, Gerald Pattenden, Tao Ye, *Tetrahedron Lett.* **1998**, *39*, 2861-64.

Abstract: A total synthesis of (+)-curacin A 1 which features a facile and selective thioacylation of the polyene amino-alcohol 2 with the benzotriazole-derived cyclopropyl thioamide 3, leading to 15, as a key step is described.

104. "Synthetic Studies towards Phorboxazole A. A Convergent Synthesis of the C31-C46 Polyene Oxane-Hemiacetal Side Chain" Gerald Pattenden, Alleyn T Plowright, James A Tornos, Tao Ye, *Tetrahedron Lett.* **1998**, 39, 6099-102.

Abstract: A convergent and stereoselective synthesis of the C31-C46 side chain unit in the marine natural product phorboxazole A, which accommodates five asymmetric centres, three carbon-to-carbon double bonds and an oxane-hemiacetal unit, is described. A concise approach to the C31-C46 side chain of phorboxazole A is described

105. "Triterpenoids from *Pulsatilla Chinensis*" Wen-Cai, Nine-Ning Ji, Shou-Xun Zhao, Jing-Han Liu, Tao Ye, M. Anthony McKervey, Paul Stevenson, *Phytochemistry* **1996**, *42*, 799-802.

Abstract: A new lupane type triterpenic acid, pulsatillic acid, and two new lupane type triterpenoid glycosides, pulsatilloside A and B, along with the known 23-hydroxybetulinic acid were isolated from the roots of Pulsatilla chinensis. Their structures were characterized as 3-oxo-23-hydroxy-lup-20(29)-en-28-oic acid, 3β, 23-dihydroxy-lup-20(29)-en-28-oic acid View the MathML source and 3β, 23-dihydroxy- lup-20(29)-en-28-oic acid View the MathML source on the basis of hydrolysis and spectral evidence including two-dimensional relay HOHAHA, one-dimensional multiple relay COSY and ROESY NMR techniques. Pulsatillic acid exhibited cytotoxic activities against P-388, Lewis lung carcinoma and human large-cell lung carcinoma.

106. "Asymmetric Catalysis of Intramolecular N-H Insertion reactions of alpha-Diazo carbonyls." Concepción Fernández García and M. Anthony McKervey, Tao Ye *Chem. Commun.* **1996**, 1465-66.

Abstract: Intramolecular N–H insertion reactions of α-diazocarbonyl substrates are catalysed by rhodium(II) carboxylates with catalyst-dependent competition with C–H insertion and β-elimination; asymmetric N–H insertion leading to a pipecolic acid derivative with ee up to 45% is achieved using chiral catalysts.

107. "Palladium-Catalysed Hydrostannylation of 1-Bromoalkynes. A Practical Synthesis of (*E*)-1-Stannylalk-1-enes", Christopher D. J. Boden, Gerald Pattenden, Tao Ye, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417-19.

Abstract: A practical synthesis of (E)-1-stannylalk-1-enes containing a range of oxygen and nitrogen functionality is highlighted, involving hydrostannylation followed by palladium-catalysed carbon–bromine bond cleavage reactions of 1-bromoalkynes.

108. "Synthesis of Biologically Active Molecules from Enantiopure Amino Acid and Peptide Glyoxals", Paul A. Darkins, Noreen McCarthy, M Anthony McKervey, Hazel M. Moncrieff, Brian Walker, Tao Ye "Peptides: Chemistry, Structure and Biology" page 98-99, Pravin T. P. Kaumaya, Robert S. Hodges (Eds.); Mayflower Scientific Ltd., **1996**.

109. "Patensin, A Saponin from *pulsatilla patens var. multifida*", Wen-Cai Ye, Bo-Xin Ou, Nine-Ning Ji, Shou-Xun Zhao, Tao Ye, M. Anthony McKervey, Paul Stevenson, *Phytochemistry* **1995**, *39*, 937-39.

Abstract: Patensin, a new triterpenoid glycoside, was isolated from the ethanolic extraction of the roots of Pulsatilla patens var. multifida. Its structure was established as hederagenin View the MathML source on the basis of hydrolysis and spectral evidence including 1D and 2D NMR techniques.

110. "Chemoselectivity and Stereoselectivity of Cyclisation of α-Diazocarbonyls Leading to Oxygen and Sulphur Heterocycles Catalysed by Chiral Rhodium and Copper Catalysts" Tao Ye, Concepción Fernández García and M. Anthony McKervey *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373-79.

Abstract: Good levels of enantioselectivity have been achieved in intramolecular C–H insertion reactions of α-diazocarbonyl compounds leading to six-membered oxygen heterocycles (chromanones) through the use of chiral rhodium(II) carboxylates as catalysts. Competition between C–H insertion and sigmatropic rearrangement, the latter leading to five-membered oxygen heterocycles (furanones), was observed with precursors containing a proximal O-allyl side chain. Whereas rhodium carboxylates produced C-H insertion products predominantly, a copper catalyst produced sigmatropic rearrangement products exclusively. A precursor with an S-allyl side chain exhibited cyclisation via sigmatropic rearrangement with both copper and rhodium catalysts.

111. "The Synthesis of Optically Active Thiazoline and Thiazole Derived Peptides from *N*- Protected α-Amino Acids" Christopher D. J. Boden, Gerald Pattenden, Tao Ye, *Synlett* **1995**, 417-9.

Abstract: The scope and limitations of the available methods for the synthesis of optically active thiazoline and thiazole-derived amino acids and peptides are compared and contrasted.

112. "First Synthesis of Enantiomerically Pure *N*-Protected Beta-Amino-Alpha-Keto Esters from Alpha-Amino-Acids and Dipeptides", Paul Darkias,

Noreen McCarthy, M. Anthony McKervey' Kevin O'Donnell and Tao Ye, *Tetrahedron: Asymmetry* **1994**, *5*(2), 195-8.

Abstract: A racemization-free route from N-protected α-amino acids and dipeptides to N-protected β-amino-α-keto esters is described, involving the sequence: diazoketone formation, Wolff rearrangement in methanol, diazo transfer, and oxidation with dimethyldioxirane.

113. "Stereoselective Synthesis of Disubstituted 3(2*H*)-Furanones *via* Catalytic Intramolecular C-H Insertion Reactions of alpha-Diazo-beta-Keto Esters Including Asymmetric Induction" Tao Ye, M. Anthony McKervey, Bridget D. Brandes, Michael P. Doyle, *Tetrahedron Lett.* **1994**, *35*, 7269-72.

Abstract: Rhodium(II) catalysed decomposition of γ-alkoxy-α-diazo-β-ketoesters produce cis-2,5-disubstituted -3(2H)-furanones with high (>97%) stereoselectivity. The combination of a chiral auxiliary in the ester moiety of the diazo precursor and a chiral catalyst can lead to asymmetric synthesis with diastereoselectivities up to 61% de.

114. "Organic Synthesis with α-Diazocarbonyl Compounds" Tao Ye, M. Anthony McKervey, *Chemical Reviews* **1994**, *94*, 1091-160.

115. "Oxidation of α-Diazoketones Derived from L-Amino Acids and Dipeptides Using Dimethyldioxirane. Synthesis and Reactions of Homochiral *N*-Protected α-Amino Glyoxals." Paul Darkins, Noreen McCarthy, M. Anthony McKervey, Tao Ye, *J. Chem. Soc. Chem. Commun.* **1993**, 1222-3.

Abstract: Homochiral N-protected α-amino glyoxals are readily accessible by oxidation of α-diazoketones derived from natural amino acids and dipeptides using dimethyldioxirane in acetone; the glyoxals can be trapped efficiently in reactions such as Wittig olefination and condensation with amines and vicinal diamines.

116. "Peptidyl Glyoxals - A Novel Class of Inhibitor for Serine and Cysteine Proteinases"

Brian WALKER, Noreen MCCARTHY, Adrienne HEALY, Tao YE and M. Anthony McKERVEY, *Biochem. J.* **1993**, *293*, 321-3.

Abstract: A series of novel synthetic dipeptides, containing a C-terminal glyoxal grouping (-COCHO), have been tested as inhibitors against typical members of the serine- and cysteine-proteinase families. For example, the sequences benzyloxycarbonyl (Cbz)-Pro-Phe-CHO (I) and Cbz-Phe-Ala-CHO (II), which fulfil the known primary and secondary specificity requirements of chymotrypsin and cathepsin B respectively, have been found to be potent reversible inhibitors of their respective target proteinase. Thus was found to inhibit chymotrypsin with a Ki of approximately 0.8 microM, whereas II exhibits a Ki of approximately 80 nm against cathepsin B. These Ki values are some 10-fold and 3-fold lower than those reported for the corresponding peptide-aldehyde inhibitors of chymotrypsin and

cathepsin B upon which the peptidyl-glyoxals were fashioned. Unexpectedly, the sequence Cbz- Pro-Ala-CHO, which was designed to inhibit elastase-like proteinases, exhibited no inhibitory activity towards porcine pancreatic elastase, even when used at concentrations as high as 200 microM.

117. "Asymmetric Synthesis of Substituted Chromanones *via* C-H Insertion Reactions of α-Diazoketones Catalysed by Homochiral Rhodium (II) Carboxylates" M. Anthony McKervey, Tao Ye, *J. Chem. Soc. Chem. Commun*. **1992**, 823-4.

Abstract: High levels of regio-, stereo- and enantio-selectivity are achieved in the asymmetric synthesis of six-membered oxygen heterocycles via intramolecular C–H insertion reactions of α-diazoketones catalysed by chiral rhodium(II) carboxylates.

118. "Synthesis of Chiral *N*-Protected α-Amino-β-diketones from α-Diazoketones Derived from Natural Amino Acids" Tao Ye, M. Anthony McKervey, *Tetrahedron* **1992**, *48*, 8007-22.

Abstract: *α*-Diazoketols, prepared by condensation of aldehydes or ketones with lithiated optically active α-diazoketones derived from natural amino acids, rearrange to homochiral α-amino-β-diketones on treatment with rhodium(II) acetate. Optically active α-amino-β-diketones were prepared via a diazo aldol reaction with subsequent rhodium-catalysed rearrangement.

119. "A New Rhodium(II) Phosphate Catalyst For Diazocarbonyl Reactions Including Asymmetric-Synthesis" Noreen McCarthy, M. Anthony McKervey, Tao Ye, Malachy McCann, Eamonn Murphy, M. P. Doyle, *Tetrahedron Lett*. **1992**, *33*, 5983-6.

Abstract: A new homochiral Rh(II) complex, Rh{HCO3}2{(+)-phos}2 • $5H_2O$, where (+)-phosH represents (S)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, has been prepared and used as a catalyst for reactions of diazocarbonyl compounds leading to enantioselective 2,3-sigmatropic rearrangement (first example), C- H insertion and aromatic cycloaddition.

Published Abstracts in Journals

120. "Total Synthesis of Marine Cyclodepsipeptides" Ye, T. *J. Pep. Sci*. **2014**, *20*, S1, Pages: S73-S74

121. "Structural Revisions/Assignments of Marine Natural Products by Total Synthesis" Ye, T. *Planta Med*. **2013**; *79*, 816

122. "Synthetic Studies toward the Total Synthesis of Hoiamides" *Planta Med*. **2013**, *79*, 846

123. "Total Synthesis of Marine Cyclopeptide Scytonemin A" Junyang Liu, Lei Wang, Zhengshuang Xu, Tao Ye, *J. Pep. Sci.* **2012**, 18, S32

124. "Design, Synthesis, and Evaluation of alpha-Helix Mimetics Targeting PCNA-p53 Interaction", Tao Ye, *J. Pep. Sci.* **2010**, 16, S105. (one page abstract)

125. "The first total synthesis of LL-15G256gamma" Tao Ye , Shuo Li, Shuo Liang, *J. Peptide Sci.* **2006**, 12, 135

126. "Total Synthesis of the Proposed Structure of Onchidin" Yungui Peng, Heung Wing Pang, Tao Ye, *J. Peptide Sci.* **2004**, 10, S138

127. "Studies toward the total synthesis of anticancer marine natural product Apratoxin A", Zhengshuang Xu, Zhiyong Chen, Tao Ye, *Abs. Papers of Am. Chem. Soc.* **2003**, Vol. 225, Pages: U350-U350.

Patents and Provisional Patents

The work leading to the filing/issuing of the following patents were derived from the drug discovery programs under my direction and conducted at PolyU's Shenzhen Research Institute. These projects were supported by pharmaceutical companies under the agreement signed between PolyU and USA-based companies.

128. "Preparation of steroidal CYP11B, CYP17, and/or CYP21 inhibitors for treating androgen-dependent conditions" (558pp) Daniel Chu, Bing Wang, Tao Ye **PCT Int. Appl. (2012), WO 2012083112 A2 20120621**

Abstract: The invention reports the prepn. of steroidal CYP11B, CYP17, and CYP21 inhibitors. For example, reacting acetate I with 5-methylpyridin-3-ylboronic acid gave the corresponding 17-pyridyl substituted compd., which was hydrolyzed to the alc., followed by oxidn. of the alc. to the ketone, conversion of the ketone to the oxime, which was treated with SOCl2/THF to give ring expanded steroid II. Also described herein are pharmaceutical compns. that include at least one of the prepd. compds. to treat androgen-dependent diseases, disorders and conditions.

129. "Histone demethylase inhibitors and uses thereof for treatment of cancer" Hui Zhang, Tao Ye, Junmin Quan, Jing Wang, **PCT Int. Appl. (2012), WO 2012071469 A2 20120531**.

Abstract: The invention provides histone demethylase inhibitory compds. of formula I [R1 = H, carboxamide, acyl, alkylsulfonyl, arylsulfonyl, guanidine etc.; R2 = H, alkyl, nitro, sulfonamide, carboxyalkyl etc.; R3 = aryl,

heteroaryl, cycloalkyl etc.; X = CH2, S, NH, SO2; Y, Z = N, CH2] or pharmaceutically acceptable salts thereof for treatment of cancer.

130. "Novel semi-synthetic glycopeptides as antibacterial agents" (227 pages) Daniel Chu, Tao Ye, Bing Wang, **US Patent Application: 20120252741**, Publication Date: 2012- 10-04

Abstract: Provided herein are semi-synthetic glycopeptides having antibacterial activity. The semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety with certain acyl groups; conversion of the amide group in amino acid-3 to various acylamide, acylsulfonamide, acylsulfonylurea derivatives; aminomethylation with substituent containing sulfonamide or acylsulfonamide group on amino acid-7 through Mannich reaction; and conversion of the acid moiety on the macrocyclic ring to certain substituted amides. Also provided herein are pharmaceutical compositions comprising the semi-synthetic glycopeptides, and methods of use of the semi-synthetic glycopeptides for the treatment and/or prophylaxis of diseases, especially bacterial infections.

131. "Novel semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, **US Patent Application 20120129763**, Publication Date: 2012-05-24

Abstract: Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate or carrying a Hofmann degradation of the primary amide of the 3rd amino acid asparagines with phenyl-bis-trifluoroacetate to give the primary amine. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

132. "NOUVEAUX GLYCOPEPTIDES SEMI-SYNTHÉTIQUES COMME AGENTS ANTIBACTÉRIENS" Daniel Chu, Bing Wang, Tao Ye, **EP2373694 (A1)—**2011-10- 12; Application number: EP20090830765 20090901, Publication Date: 2011-10-12

Abstract not available for EP2373694 (A1) Abstract of corresponding document: GB2465863 (A)

133. "NOVEL CYP17 INHIBITORS" Daniel Chu, Bing Wang, Tao Ye, **US Patent Application 20110178065**; Publication Date: 2011-07-21

Abstract: Provided herein are inhibitors of CYP17 enzyme. Also described herein are pharmaceutical compositions that include at least one compound described herein and the use of a compound or pharmaceutical composition described herein to treat androgen-dependent diseases, disorders and conditions.

134. "Semi-synthetic heptapeptidic glycopeptides for the treatment of bacterial infections" Daniel Chu, Bing Wang, Tao Ye **JP2012510999 (A);** Application number: JP20110539532, 20090901; Publication date: 2012-05-17; Abstract not available for JP2012510999 (A) Abstract of corresponding document: GB2465863 (A)

135. "Novel Semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, Bing Wang, **CN102307903 (A) —** 2012-01-04; Application number: CN20098156149 20090901; Publication date: 2012-01-04;

Abstract : Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi not synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

136. "Novel Semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, Bing Wang, **KR20110099028 (A);** Application number: KR20117015395 20090901 Publication date: 2011-09-05;

Abstract not available for KR20110099028 (A) Abstract of corresponding document: GB2465863 (A)

137. “Preparation of steroid derivatives as CYP17 inhibitors for the treatment of cancer” (248 pages), Daniel Chu, Bing Wang, Tao Ye, **PCT Int. Appl. (2011), WO 2011088160 A2 20110721**.

Abstract: Steroids, e.g. of formula I [R = $(CH_2)_p$; T = $(CH_2)_q$; p, q = 0-1; W = O, NR^1, N-acyl, absent, etc.; V = (substituted) CH_2, O, NR^1, etc.; A = heteroaryl; R^1 = H, alkyl, cycloalkyl, etc.; R^2 = H, halo, alkyl, cyano, nitro, alkoxy, OH, etc.; R^3 = H, halo, alkyl, cycloalkyl, cyano, OH, etc.; R^5, R^6 = H, halo, alkyl, alkoxyalkyl] are prepd. as inhibitors of CYP17 enzyme. Also described herein are pharmaceutical compns. that include at least one compd. described herein and the use of a compd. or pharmaceutical compn. described herein to treat androgen-dependent diseases, disorders and conditions. Thus, II was prepd. starting from androstenedione.

138. "Novel semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, **AU2009322925 (A1)**, Application no.: AU20090322925 20090901; Publication Date: 2011-06-30

Abstract: Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi not synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

139. "Semi-synthetic heptapeptidic glycopeptides for the treatment of bacterial infections" Daniel Chu, Bing Wang, Tao Ye **AR075354 (A1),** Application number: AR2009P103380 20090902 ; Publication date: 2011-03-30; Abstract not available for AR075354 (A1) Abstract of corresponding document: GB2465863 (A)

140. "Novel semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, **US Patent Application 20110015119**, Publication Date: 2011-01-20

Abstract: Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B,

Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

141. "Preparation of semi-synthetic glycopeptides as antibacterial agents." (96 pages), Daniel Chu, Tao Ye, **Patent Number: US 2010216699 A1** 20100826; Publication date: 2010-08-26;

Abstract: The invention relates to compds. of formulas I and II [R^A is H, Me, C_{2-12} alkyl; R^1 is H, alkyl, cycloalkyl, etc.; R^2 is H, alkyl, cycloalkyl, heterocyclyl, etc.; R^3 is OH, 1- or 2-adamantanamino, amino groups, etc.; R^4 is aminomethyl substituted by sulfonylaminoalkyl or carboxyalkyl groups; X is H or Cl; T is H, sulfonyl, acyl, carbamoyl, thiocarbamoyl, or sulfonylcarbamoyl groups] and their pharmaceutically- acceptable salts, esters, alkylated quaternary ammonium salts, stereoisomers, tautomers and prodrugs for use as antibacterial agents. Also described are processes for prepg. semi-synthetic glycopeptides by chem. modification of a glycopeptide or the monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid of the parent glycopeptide in mild acidic medium to give the amino acid monosaccharide, protection of the amino groups in the mol., and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Also included are the process of conversion of the amide group in amino acid on these scaffolds to various acylureas, acylamide, acylsulfonamide, acylsulfonylurea derivs. and aminomethylation with substituent contg. sulfonamide or acylsulfonamide group on amino acid through Mannich reaction procedures. Pharmaceutical compns. and methods of using these compds. are given for the treatment and/or prophylaxis of diseases, including bacterial infections. Thus, compd. I (R^A = Me; R^1, R^4 = H; R^3 = 2-adamantylamino; X = Cl, T = C_8H_{17}) was prepd. from vancomycin and its antibacterial activity compared to that of vancomycin.

142. "Novel Semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, Bing Wang, **TW201021805 (A);** Application number: TW20090129618 20090902 Publication date: 2010-06-16;

Abstract: Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B,

Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

143. "Novel Semi-synthetic glycopeptides as antibacterial agents" Daniel Chu, Tao Ye, Bing Wang, **CA2745446 (A1)**; Application number: CA20092745446 20090901; Publication date: 2010-06-10;

Abstract : Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi not synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

144. "Preparation of semi-synthetic glycopeptides as antibacterial agents" (154 pages), Daniel Chu, Tao Ye, Bing Wang, **Patent Number: WO 2010065174 A1 20100610**; Publication date: 2010-06-10;

Abstract: The invention is related to the prepn. of a semi-synthetic glycopeptide as antibacterial agent, for e.g. of formula I [R^A = H, Me, C_{2-12} alkyl; R^3 = OH, 1-adamantanamino, 2-adamantanamino, 3-amino-1-adamantanamino, 1-amino-3-adamantanamino, 3-loweralkylamino-1-adamantanamino, 1-loweralkylamino-3-adamantanamino, NH_2 and derivs.; R, R^C = independently H, heterocycloalkyl, (un)substituted alkyl, etc.; R^4 = H, $CH_2NHCH_2PO_3H_2$, $CH_2NHCHR^{15}(CH_2)_pCONHSO_2R^B$, etc.; p = 0-6; R^{15} = H, lower alkyl; R^B = (un)substituted (hetero)cycloalkyl, (hetero)aryl, alkyl; at least two of A^{1-3} = H; when two of A^{1-3} = H, the other is $C(Z)NHR^B$, $C(Z)NHCHR^{15}(CH_2)_mNHCONHR^B$, $C(Z)NHCHR^{15}(CH_2)_mR^B$ or $C(Z)NHCHR^{15}(CH_2)_mNHSO_2R^B$; Z = O, S; m = 1-

6 and R^{15} = H or loweralkyl; when A^{1-3}, R^C, R^D = H, then R^4 is not hydrogen] and its pharmaceutically acceptable salts, esters, solvates, alkylated quaternary ammonium salts, stereoisomers, tautomers and prodrugs, by: (a) hydrolysis of the disaccharide moiety of the amino acid-4 of a glycopeptide; (b) conversion of the monosaccharide to the amino-sugar deriv.; (c) acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and (d) conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compd. with isocyanate. Thus, II [R^A = H; R^3 = 2-adamantanamino; R = R^C = R^4 = A^2 = A^3 = H; A^1 = octylaminocarbonyl] was prepd. from vancomycin and displayed antibacterial activity in vitro against Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Enterococcus faecium, etc. I are useful in treatment and/or prophylaxis of diseases, esp. bacterial infections. Pharmaceutical compns. contg. I are also described

145. "Semi-synthetic heptapeptidic glycopeptides for the treatment of bacterial infections" (154 pages), Daniel Chu, Tao Ye, Bing Wang, **UK patent Application: GB2465863 (A)**; Publication date: 2010-06-9; CROSS-REFERENCE: This application claims the benefit of U.S. provisional application Ser. No. 6 1/220,167, filed June 24, 2009 and PCT Patent Application No. PCT/US2008/0857 16, filed December 5, 2008, both of which are incorporated by reference in their entirety. FIELD OF THE INVENTION: Described herein are semi-synthetic glycopeptides having antibacterial activity, pharmaceutical compositions comprising these compounds, and methods of treatment using semi-synthetic glycopeptides.

146. "Semi-synthetic heptapeptidic glycopeptides for the treatment of bacterial infections" (154 pages), Daniel Chu, Tao Ye, Bing Wang, **Patent Number: GB2464617 (A);** Publication date: 2010-04-28;

The invention relates to the semisynthesis of glycopeptides, e.g., those of formula I, where R^A is H, Me, or C_2-C_{12} alkyl; X is H or Cl; T is a sulfonyl, acyl, or aminocarbamoyl group; R is H, (un)substituted alkyl, cycloalk(en)yl, carboxy or an ester, or carbamoyl group; R^3 is OH, 1- or 2-adamantanamino, 3-(alkyl)amino-1- adamantanamino, NH_2 or substituted amino; and R^4 is H, $CH_2NHCH_2PO_3H_2$, substituted aminoalkyl, or sulfonylamino-, sulfonylcarbamoyl-, or carboxy- functionalized alkylaminomethyl group, and including pharmaceutically-acceptable salts, esters, solvates, alkylated quaternary ammonium salts, stereoisomers, tautomers and prodrugs, which are useful for the treatment and/or prophylaxis of diseases such as bacterial infections. Also outlined are methods for the synthesis of these compds. and pharmaceutical compns. which comprise them. Thus, glycopeptide I (R^A = Me, X = Cl, T = p-butoxyphenylsulfonyl, R = R^4 = H, R^3 = 1-adamantanamino) was prepd. from vancomycin and displayed antibacterial activity (MIC range 0.01 < to ≤ 0.5

μg/mL) against Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, etc.