Curriculum vitae

Dr. SUNIL KUMAR RAI (Ph.D)
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Education

Ph.D., (2016), Banaras Hindu University, India: Title of the thesis "Synthesis of 2-Pyridone Derivatives, and Their Structural and Biological Evaluation".

M.Sc., (2011), Banaras Hindu University, India: Organic Chemistry.

B.Sc., (2009), Banaras Hindu University, India: B. Sc. (Honors) Chemistry.

Professional Positions

August 2021 – Continued: Deputy Manager at Sai Life Sciences Pvt. Ltd. Hyderabad, India. Here, I my work covers the support to MedChem and PR&D department for high soluble salt preparation of discovery and developmental molecules, polymorphs screening, particle property improvement and impurity purging through crystallization. The analytical techniques which I am using to characterize the compounds are DSC, TGA, PXRD, NMR, LC-MS, GC-MS, TG-MS etc. The special tools which I use for crystallization are Carousel, poly-blocks, EasyMax, Mya4, Radley reactor, etc. Here, I am engaged in proposal and report preparation for internal and clients followed by taking knowledge sharing sessions.

April 2019 – September 2020: Postdoctoral Fellow at Tata Institute of Fundamental Research. I was working on "Synthesis and characterization of small molecule inhibitors of the AF6 PDZ-domain" and solid forms (polymorphs) characterization using solid-state NMR fast MAS. Further, we were using double-quantum/single-quantum (DQ/SQ) ^{1}H-^{1}H, ^{1}H-^{13}C and ^{1}H-^{15}N 2D ssNMR to full evaluation of structures and interactions.

February 2017 – February 2019: Science and Engineering Research Board (SERB) National Postdoctoral fellow at Council of Scientific and Industrial Research (CSIR) National Chemical Laboratory (NCL), Pune. Project title "High-Throughput Screening and Cocrystallization of Anticancer APIs-Excipients for Successful Drug Delivery: Perspective of Multi-Component Pharmaceutical Materials". Under this project, I prepared several polymorphs, salts and cocrystals to improve the physicochemical properties of APIs. At NCL-Pune, I established my own laboratory where multiple projects are still running.

Research Areas of Interest

- Medicinal Chemistry: Synthesis of biologically relevant flexible analogues and their Structure-activity relationships (SAR) analysis.
- Pharmaceutical Crystal-engineering: Polymorphs, salts and Co-crystals screening of active pharmaceutical ingredients (APIs) to improve the solubility, dissolution and bioavailability. Improving particle properties through agglomeration, impurities purging and improving filtration rate through crystallization techniques.
- Supramolecular Chemistry: Experimental and Computational studies on small and medium size flexible molecules to understand the role of Inter- and intramolecular Interactions on conformational preferences.

Research Skills

- Synthesis of small and medium size organic molecules using one pot multicomponents and via multi-steps. Purification of more than two components mixture using column chromatography and crystallization techniques.
- Crystallization of single component, multi-component and host-gust type organic compounds using solvent evaporation, cooling, diffusion and antisolvent techniques.
- Improving particle properties, filterability, flowability, and purity using crystallization.
- Crystal structure determination from SC-XRD data using WinGX and OLEX software (Along with BRUKER Instrument handling).
- Evaluation of structure and conformation using various NMR techniques.
- Analysis of XRPD, DSC and TGA data (Along with Instrument handling).
- Use of Easymax, Carousel, Mya4 and Radley reactor.
- Polarizing optical microscope (POM) analysis for texture analysis of polymorphs.
- Analysis of SEM, TEM and AFM data.
- Application of UV, Fluorescence, IR, Raman, MS, HPLC (Along with Instrument handling).
- Use of Gaussian software for the computational purpose.
- Technical writing of scientific reports.
- Managing team and guiding junior researchers.

Publications

1. Manish K. Bommaka, M. K. Chaitanya Mannava, **Sunil K. Rai**, Kuthuru Suresh, Ashwini K. Nangia,* *Entacapone Polymorphs: Crystal Structures, Dissolution, Permeability, and Stability*, ***Cryst. Growth Des.***, 2021 21, 10, 5573–5585.
2. **Sunil K Rai,*** Debjani Baidya, Ashwini K Nangia,* *Salts, Solvates and Hydrates of Multi-kinase Inhibitor Drug Pazopanib with Hydroxybenzoic Acids*, ***CrystEngComm***, 2021, 23, 5994-6011 (Highlighted on cover page and part of the themed collections).
3. **Sunil K Rai,** Suryanarayana Allu, Ashwini K Nangia,* *Salts and Cocrystal of Etodolac: Advantage of Solubility, Dissolution and Permeability*, ***Cryst. Growth Des.***, 2020, 20, 7, 4512–4522.
4. **Sunil K. Rai,** Anilkumar Gunnam, MK Chaitanya Mannava, Ashwini K. Nangia,* *Improving the Dissolution Rate of Anticancer Drug Dabrafenib*, ***Cryst. Growth Des.***, 2020, 20, 2, 1035-1046.
5. Sunil K. Pandey, Seema Pratap,* **Sunil K. Rai,** Gaetano Marverti, *Structural, Hirshfeld surface and in vitro cytotoxicity evaluation of five new N-aryl-N'-alkoxycarbonyl thiocarbamide derivatives*, ***Phosphorus, Sulfur, and Silicon and the Related Elements***, 2020, 195 (10), 812-820.
6. Sunil K. Pandey, Seema Pratap,* **Sunil K. Rai**, Gaetano Marverti, Manpreet Kaur, Jerry P Jasinski, *Synthesis, characterisation, Hirshfeld surface and in vitro cytotoxicity evaluation of new N-aryl-N'-Alkoxycarbonyl thiocarbamide derivatives*, ***J. Mol. Struct.***, 2020, 1202, 127269.
7. Sunil K. Pandey, Seema Pratap,* **Sunil K. Rai**, Gaetano Marverti, Manpreet Kaur, Jerry P. Jasinskid, *Synthesis, characterization, Hirshfeld surface, cytotoxicity, DNA damage and cell cycle arrest studies of N, N-diphenyl-N'-(biphenyl-4-carbonyl/4-chlorobenzoyl) thiocarbamides*, ***J. Mol. Struct.***, 2019, 1186, 333-344.
8. **Sunil K. Rai**, Tomasz Sierański, Shaziya Khanam, Krishnan Ravi Kumar, Balasubramanian Sridhar, Ashish K. Tewari*, *Quantitative Analysis of Intermolecular Interactions in 3-Cyano-2-Pyridones: Evaluation through Single Crystal X-ray Diffraction and Density Functional Theory*, ***ChemistrySelect***, 2018, 3 (21), 5864 – 5873.
9. **Sunil K. Rai**, ShaziyaKhanam, Ashish K. Tewari*, *Study of Conformational and Supramolecular Structural Stability of Propylene-Bridged 2-Pyridone Dimers*, ***ChemistrySelect***, 2018, 3 (1), 12273-12278.
10. S. Khanam, S. K. Pandey, **Sunil K. Rai**, D. Verma, J. P. Jasinski, S. Pratap, A. K. Tewari*, *Synthesis of N,N-Bis-Sulfonylated and N-Alkyl-N-Sulfonylated G1 Dendrimers via Click Reaction: Application of Thiocarbamide based Cu(I) Catalysts*, ***ChemistrySelect***, 2017, 2, 6370 – 6374.

11. Shaziya Khanam, **Sunil K Rai**, A K Tewari*, *Advancement in the sulfone-based dendrimers: From synthesis to application*, ***Advanced Materials Letters***, 2017, 8, 1005-1019.

12. Ranjana Singh, **Sunil Kumar Rai**, Manish Kumar Tiwari, Anurag Mishra, Ashish K Tewari, Phool Chand Mishra, Ranjan K Singh,* *An excellent stable fluorescent probe: Selective and sensitive detection of trace amounts of Hg^{+2} ions in natural source of water*, ***Chemical Physics Letters***, 2017, 676, 39-45.

13. **Sunil K. Rai**, Praveen Singh, Shaziya Khanam and Ashish K. Tewari*, *Polymorphic Study and Anti-inflammatory Activity of 3-Cyano-2-pyridone Based Flexible Model*, ***New J. Chem.***, 2016, 40, 5577−5587.

14. Shaziya Khanam, **Sunil K Rai**, Deepshikha Verma, Ranjana S Khanna, Ashish K Tewari*, *An efficient and controlled synthesis of persulfonylated G1 dendrimers via click reaction*, ***RSC Adv.***, 2016, 6, 56952-56962.

15. **Sunil K. Rai**, Praveen Singh, Ranjeet Kumar, Ashish K. Tewari*, Jiří Hostaš, Ramachandran Gnanasekaran, and Pavel Hobza*, *Experimental and Theoretical Study for the Assessment of the Conformational Stability of Polymethylene-Bridged Heteroaromatic Dimers: A Case of Unprecedented Folding*, ***Cryst. Growth Des.***, 2016, 16, 1176−1180.

16. **Sunil K. Rai**, Shaziya Khanam, Ranjana S. Khanna and Ashish K. Tewari*, *Design and Synthesis of 2-Pyridone Based Flexible Dimers and Their Conformational Study through X-ray Diffraction and Density Functional Theory: Perspective of Cyclooxygenase-2 Inhibition*, ***Cryst. Growth Des.***, 2015, 15, 1430 −1439.

17. **Sunil Kumar Rai**, Priyanka Srivastava, Hariom Gupta, Maria del C. Puerta, Pedro Valerga, Ashish Kumar Tewari,* *Unusual reverse face-to-face stacking in propylene linked pyrazole system: perspective of organic materials*, ***StructChem***, 2015, 26, 555–563.

18. Ranjeet Kumar, **Sunil K Rai**, Praveen Singh, Archana Gaurav, Pratima Yadav, Ranjana S. Khanna, Hariom Gupta, Ashish K. Tewari*, *Face-to-Face Stacking in Sulfonamide Based Bis-ethylene Bridged Heteroaromatic Dimers*, ***RSC Adv.***, 2015, 5, 97205 – 97211.

19. **Sunil K. Rai**, Shaziya Khanam, Ranjana S. Khanna and Ashish K. Tewari*, *Cascade synthesis of 2-pyridones using acrylamides and ketones*, ***RSC Adv.***, 2014, 4, 44141–44145.

Book Chapter

1. **Sunil Kumar Rai**, Ashish Kumar Tewari, *Dual role of drugs: beneficial and harmful aspects*, Synthesis of Medicinal Agents from Plants, Elsevier, 2018; (ISBN 9780081022740).

Conferences, Workshops and Training Visits

1. Participated and presented a poster in "Applied Pharmaceutical Analysis (APA) – India 2020". Conference was held at the Courtyard by Marriott, Ahmedabad, India on 23-25 February 2020.
2. Participated and presented a poster in "26th International Conference & Meeting of Magnetic Resonance Society on NMR from Molecules to Human Behaviour and Beyond". Conference was held at the Department of Chemistry, Saurashtra, Rajkot, India on 18-21 February 2020.
3. Actively participated in two days' workshop titled "GastroPlus™ Pharmaceutical Development'. Workshop was held at Hotel Sahara Star, Mumbai, India on 27th and 28th September, 2018.
4. Participated in "Applied Pharmaceutical Analysis (APA) – India 2018" conference held at the Westin, Pune, India on 25-27 February 2018.
5. Actively participated in a workshop on "Introduction to Gaussian: Theory and Practice" conducted by SCUBE Scientific Software Solutions (P) Ltd in Delhi, India on January 8-12, 2018.
6. Participated in the National conference on "Climate Change and Its Vast Impact on Human Life and Society". Conference was held at the Dr. P. S. Mukherjee government degree college, Bhadohi, India on 17-18 February 2017.
7. Participated and presented a paper in the National conference on "Energy, Environment and Impact on Society". Conference was held at the K. N. government post graduate college, Gyanpur, Bhadohi, India on 19-20 January 2017.
8. Participated and presented a poster in "17th CRSI National Symposium in Chemistry". Conference was held at the CSIR National Chemical Laboratory, Pune, Maharashtra, India on 06-07 February 2015.
9. Participated and presented a poster in "International Conference on Frontiers of Spectroscopy". Conference was held at the Department of Physics, Banaras Hindu University, Varanasi, India on 10-12 January 2015.
10. Participated and presented a poster in "20th ISCB International Conference on Chemistry and Medicinal Plants in Translational Medicine for Healthcare". Conference was held at the Department of Chemistry, University of Delhi, Delhi, India on 1-4 March 2014.

11. Participated and presented a poster in "16th CRSI National Symposium in Chemistry". Conference was held at the Indian Institute of Technology Bombay, Mumbai, Maharashtra, India on 07-09 February 2014.

12. Participated and presented a poster in "15th CRSI National Symposium in Chemistry". Conference was held at the Department of Chemistry, Banaras Hindu University, Varanasi, India on 01-03 February 2013.

13. Participated and presented a poster in "Mid Year Meeting of the Chemical Research Society of India". Conference was held at the CSIR Central Drug Research Institute, Lucknow, India on 21-22 July 2012.

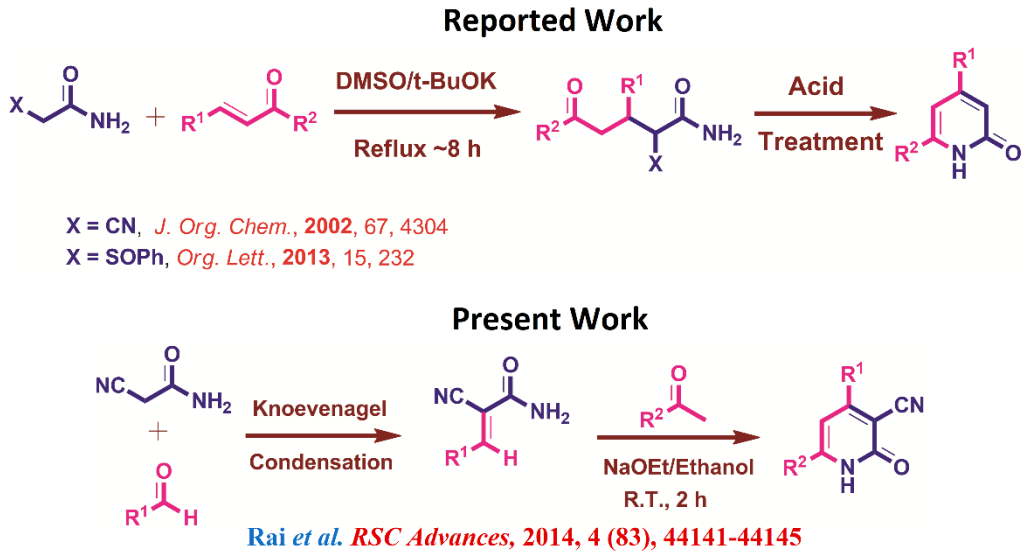
14. Participated in "Workshop on Technical Communication for Research Scholars". Conference was held at the Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India on 05-11 May 2012.

15. Participated in "International Workshop on Spectroscopic Signatures of Molecular Complexes/Ions in Our Atmosphere and Beyond". Conference was held at the Department of Applied Physics, Indian Institute of Technology, Banaras Hindu University, Varanasi, India on 07-10 February 2012.

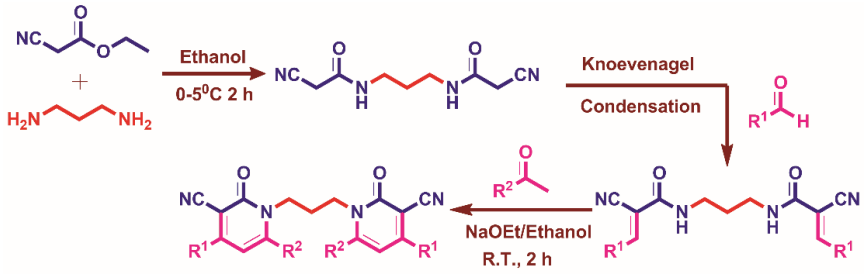
Research Summary

My research work covers a wide range of chemistry especially organic synthesis, medicinal chemistry, crystal engineering and physical organic chemistry. In my Ph. D., I have synthesized heteroaromatic compounds for their structural and biological evaluations. In my first postdoctoral project at CSIR-NCL Pune, I was working in the field of pharmaceutical crystal engineering. However, at TIFR Hyderabad, I was dealing with both organic synthesis and crystal engineering along with solid form characterization using fast MAS solid-state NMR. Further, I got experience in handling numerous analytical tools and techniques to characterize the organic molecules and to analysed their physicochemical properties. For instance, X-ray diffraction (both single crystal and powder forms), solid-state/solution phase 1D/2D nuclear magnetic resonance (NMR) analysis, mass spectrometry, differential scanning calorimetry (DSC) analysis and thermogravemetric analysis (TGA), etc.

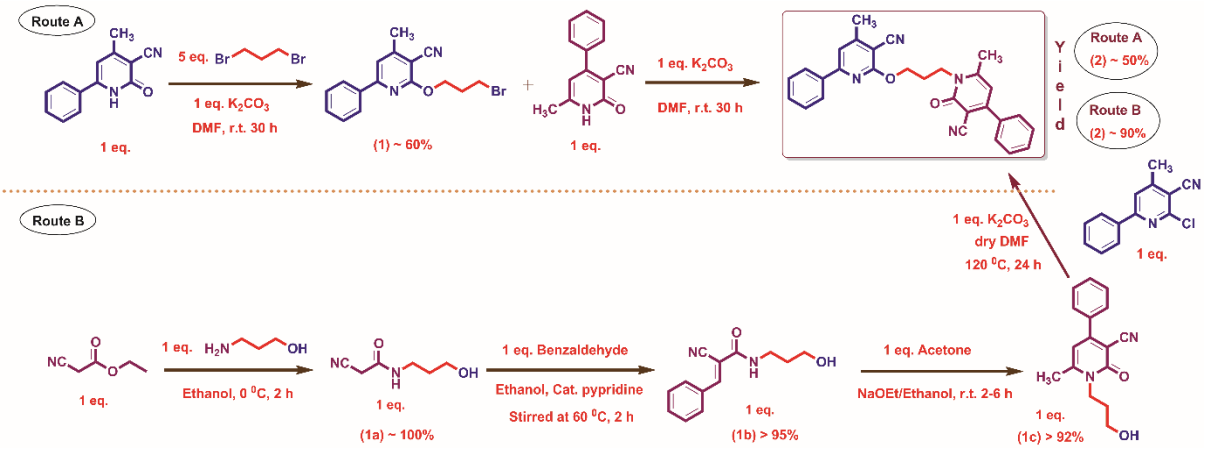
Ph. D. Work: Our aim was to synthesize 3-cyano-2-pyridone derivatives and their flexible isomeric dimers (i.e. O/O, N/O and N/N) linked with alkyl chain (i.e. C3) for their biological evaluations. To deal with complications in N/N dimer synthesis, a novel method was developed for the synthesis of 3-cyano-2-pyridone derivatives (Scheme 1), by virtue of which most of the desired N/N dimer molecules were synthesized (Scheme 2). Subsequently, we develop a new route to obtain N/O hetero dimers in excellent yield (Scheme 3). Since the developed methodology enabled us to synthesize the dimers of our interest, we did the conformational analysis of various dimers through the computational techniques using DFT methods. The *in-silico* structure activity relationship (SAR) analysis was performed for the specific receptors using Auto Dock 4 software (***Crystal Growth & Design***, 2015, 15 (3), 1430-1439). After getting the molecular hierarchy, we synthesized a series of 3-cyano-2-pyridone based dimers. Effort was to crystallize most of the dimers to get direct evidence of their stable conformation. Eventually, some interesting results were screened for *in-vivo* biological activity with our collaborators (***New J. Chem.***, 2016, 40, 5577-5587).



Scheme 1. Reported synthetic route for 2-pyridones under harsh conditions and modified route for the synthesis of 3-cyano-2-pyridones under ambient conditions.



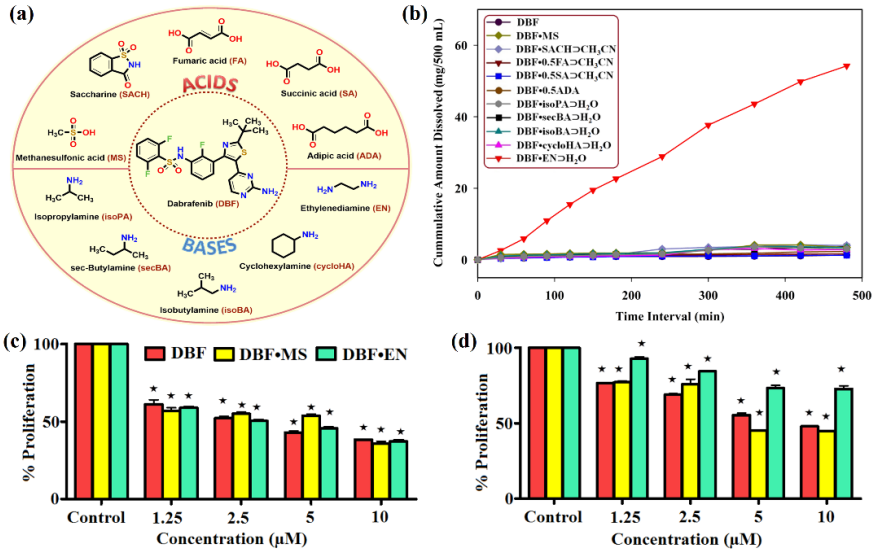
Scheme 2. Synthesis of N/N dimers of 3-cyano-2-pyridones.



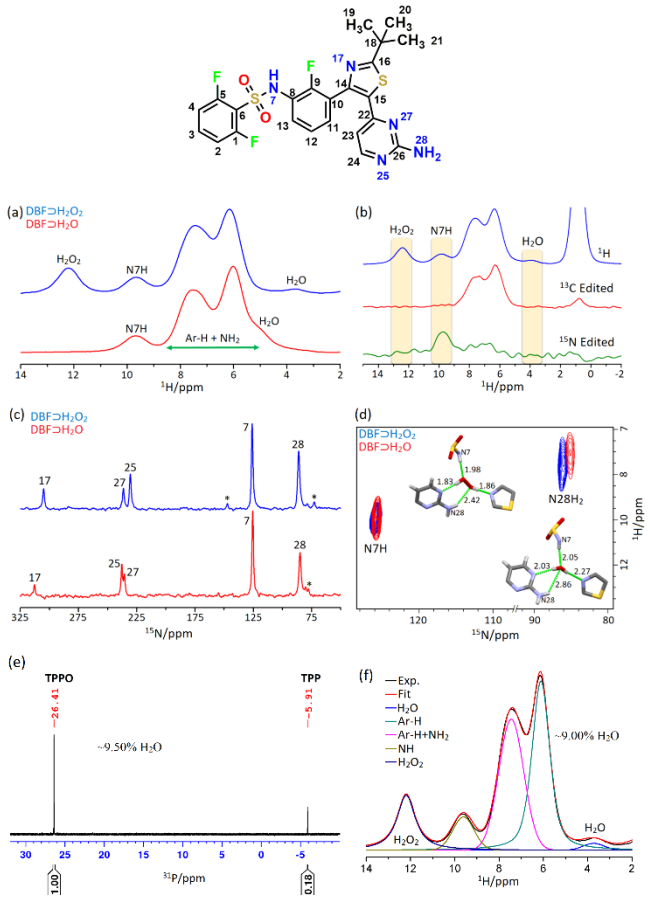
Scheme 3. Synthesis of N/O hetero dimer of 3-cyano-2-pyridones.

Postdoctoral Work: At NCL, Pune, my work was focused on the improvement of physicochemical properties of active pharmaceutical ingredients (APIs) through salts, cocrystals, and polymorphs preparation. So far, I have been successful in improving the physicochemical properties of Dabrafenib (Scheme 4, ***Crystal Growth & Design***, 2020, 20, 4512–4522), Etodolac (***Crystal Growth & Design***, 2020, 20, 1035-1046), and Pazopanib (***CrystEngComm***, 2021, 23, 5994-6011), however, some other drugs have also been investigated for salt/cocrystal/polymorphs. Further, I was able to develop 14 polymorphs of dabrafenib, that include four neat polymorphs, one hydrate, one perhydrate and eight solvatomorphs.

At TIFR Hyderabad, I was working on the characterization of an isostructural hydrate/perhydrate of dabrafenib, where, a local difference in the crystal structures were probed by solid-state NMR techniques. Initially, it was fully characterized by ^{1}H, ^{13}C, and ^{15}N SSNMR followed by HETCOR and double quantum-single quantum (DQ-SQ) correlations. Subsequently, the acidic proton signals of sulfonamide and hydrogen peroxide were unambiguously characterized. Some selected SSNMR spectra have been shown in Scheme 5 which played the key role in discrimination of hydrate and perhydrate, and quantitative analysis of residual water in the mixed perhydrate.

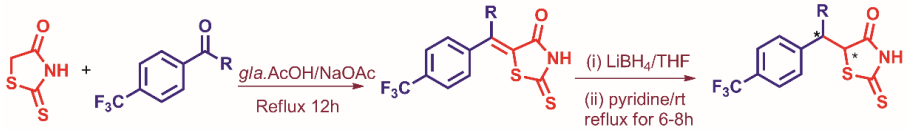


Scheme 4. (a) Synthesis of salts and cocrystals of DBF, (b) dissolution profile of synthesized salts and cocrystals at pH 1.2 over 8 h, (c) histogram representing a decrease in proliferation of SK-MEL-28 cells and (d) histogram representing a decrease in proliferation of HEK-293 cells on treatment with DBF, DBF·MS, and DBF·EN⊃H_2O for 72 h. Cytotoxicity was measured using the MTT assay.



Scheme 5. (a) Stack plot of ^{1}H SSNMR spectra of DBF⊃H_2O (red) and DBF⊃H_2O_2 (blue) acquired at 70 kHz MAS frequency, (b) stack plot of ^{1}H SSNMR and ^{13}C/^{15}N edited ^{1}H SSNMR for DBF⊃H_2O_2 acquired at 60 kHz MAS frequency, (c) stack plot of ^{15}N SSNMR spectra of DBF⊃H_2O (red) and DBF⊃H_2O_2 (blue) acquired at 8 kHz MAS frequency, (d) overlay of ^{1}H–^{15}N HETCOR spectra of DBF⊃H_2O (red) and DBF⊃H_2O_2 (blue) acquired at 8 kHz MAS frequency, (e) ^{31}P NMR spectra of DBF⊃H_2O_2 (mixed perhydrate) after reaction with triphenylphosphine (TPP) in dry acetonitrile at 300 MHz spectrometer and (f) deconvolution analysis of ^{1}H NMR of DBF⊃H_2O_2 to quantify the water which shows ~9% of water content.

In another project, I have synthesized 2-thioxo-4-thiazolidinone derivatives as low molecular-weight ligands for the AF6 PDZ domain. Unlike usual condensation of aldehydes with molecules having active hydrogen in presence of piperidine, 2-thioxo-4-thiazolidinone showed substitution of sulfure atom by piperidine molecule. Therefore, an alternate method was used to get the desired product where, glacial acetic acid and sodium acetate were used at refluxed temperature. Subsequently, selective hydrogenation of newly formed C=C bond was done through $LiBH_4$. All products, byproducts and intermediates were characterized by LC-MS spectra, ^1H and ^{13}C NMR spectra and single crystal X-ray diffraction analysis. Some representative LC-MS spectra, ^1H and ^{13}C NMR spectra are shown in Figures 1-5.



Scheme 6. Synthesis of 2-thioxo-4-thiazolidinone derivatives as low molecular-weight ligands for the AF6 PDZ domain.

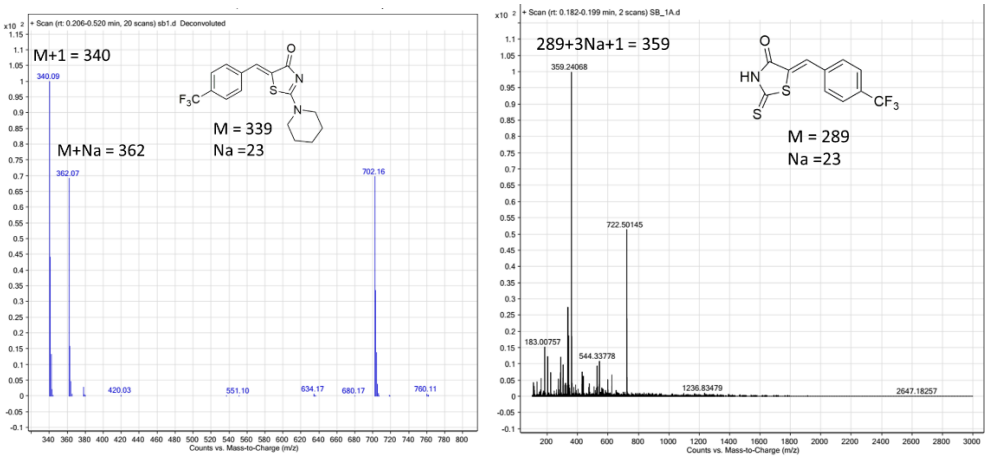


Figure 1. LC-MS spectra of byproduct formed by substitution with piperidine (left) and desired product (right).

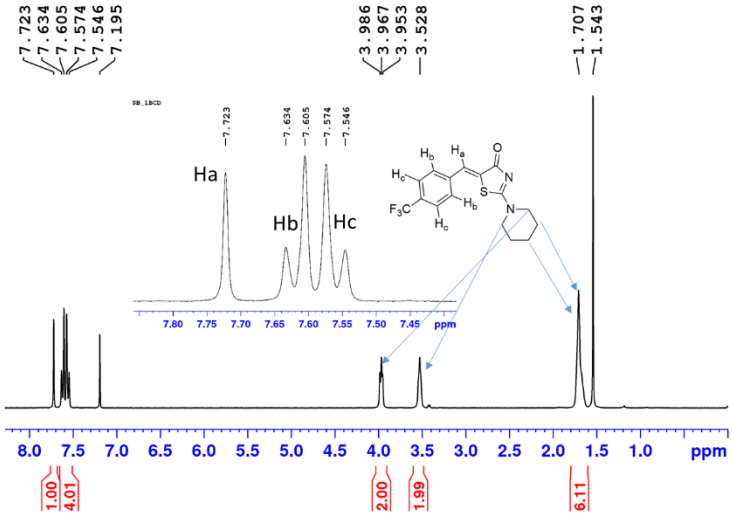


Figure 2. ^1H NMR spectrum of side product formed by substitution with piperidine.

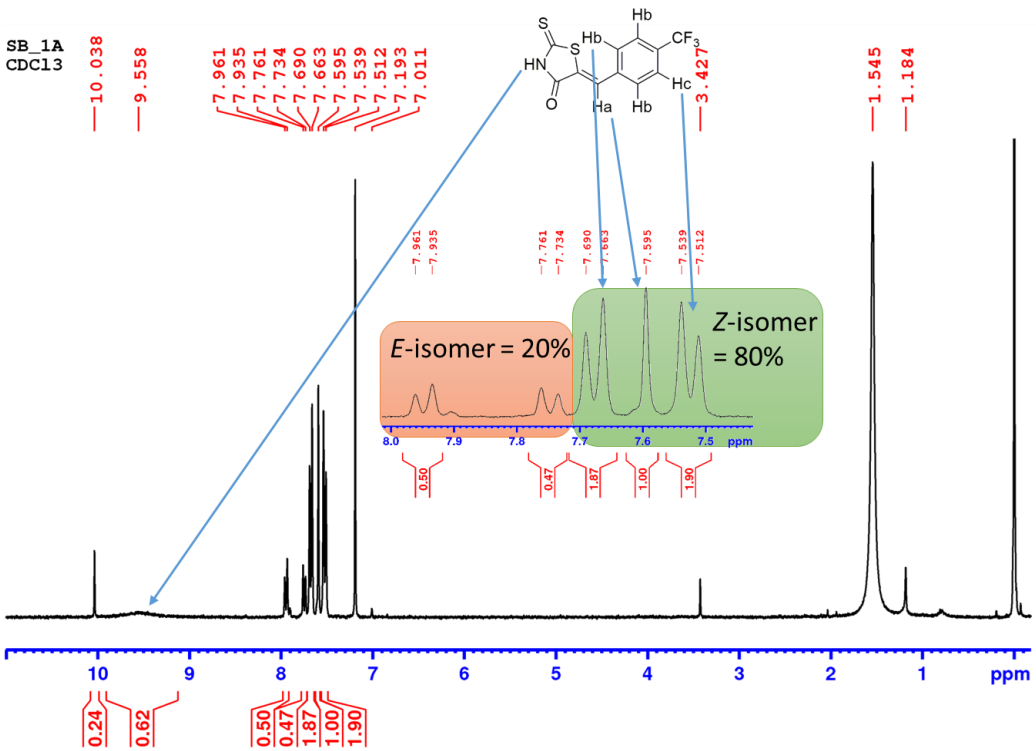


Figure 3. [1]H NMR spectrum of crude desired product showing *E*- and *Z*- isomers.

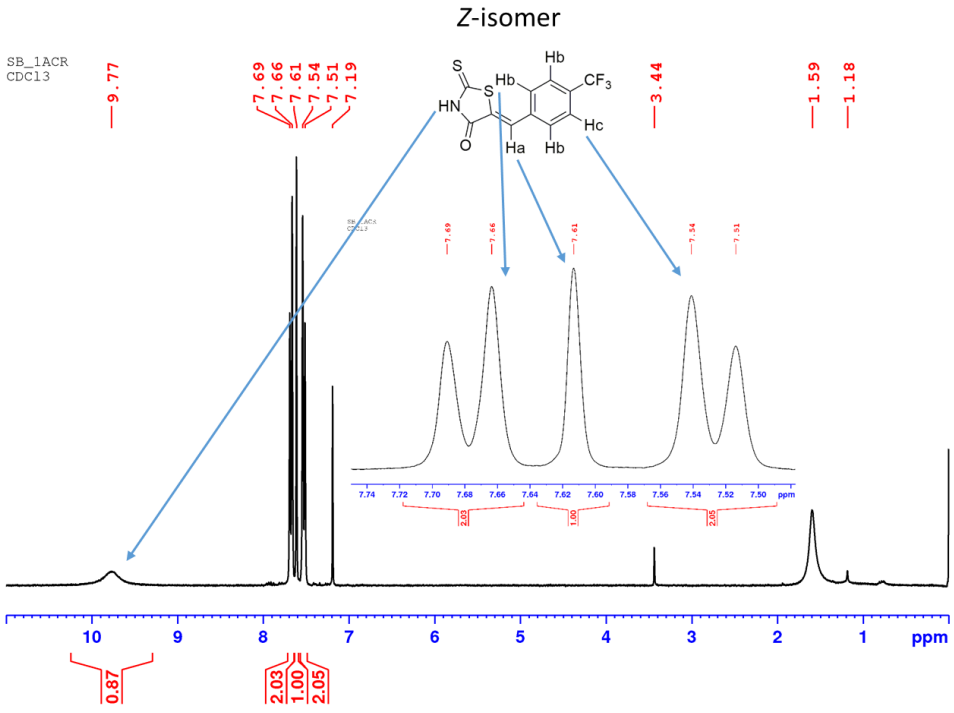


Figure 4. [1]H NMR spectrum of recrystallized desired product in water-methanol mixture (4:6) showing only *Z*- isomers.

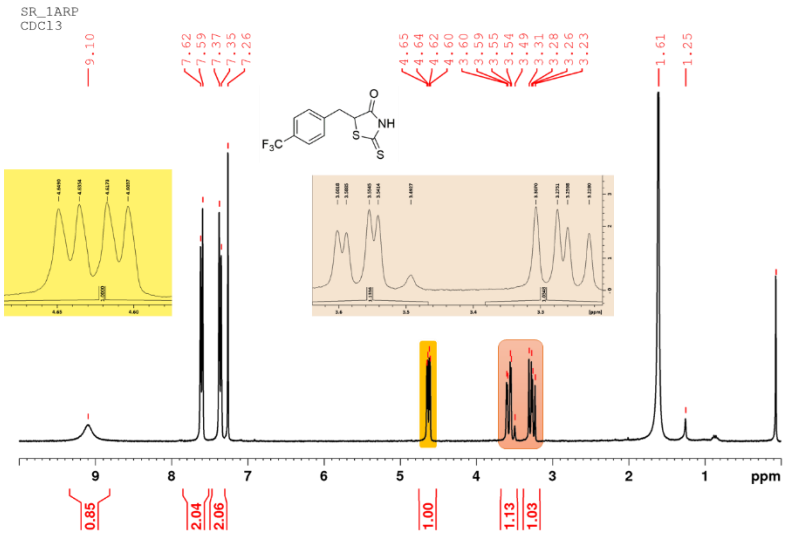


Figure 5. ^{1}H NMR spectrum of final product (after hydrogenation of C=C).