Ten Best Papers of Professor Diwan S Rawat

1. Shashikant Tiwari, Manisha Kumari, **Diwan S Rawat***, Air induced phosphoryl radical mediated stereoselective hydrosulfonylation of alkynes via halogen atom transfer (XAT): Ingress of Z-vinyl sulfones, **Organic Letters, 6, 2303–2308 (2024). Impact Factor: 6.072.**

   Summary: This study demonstrated that phosphoryl radicals participate in halogen atom transfer (XAT) with electron-deficient vinyl halides instead of in a facile addition reaction. This protocol allows direct hydrosulfonylation of numerous internal and terminal alkynes to get various biologically relevant Z-vinyl sulfones under environmentally benign conditions. Generation of the phosphoryl radical in the open air, water as a solvent, excellent functional group compatibility, and exceptional chemoselectivity are the attractive features of the present methodology.

2. Woori Kim[+], Mohit Tripathi[+], Chunhyung Kim, Satyapavan Vardhineni, Young Cha, Shamseer Kulangara Kandi, Melissa Feitosa, Rohit Kholiya, Eric Sah, Anuj Thakur, Yehan Kim, Sunny Manohar, Youngbin Kong, Gagandeep Sindhu, Yoon-Seong Kim, Bruce Cohen, **Diwan S Rawat*,** Kwang-Soo Kim,* An optimized Nurr1 agonist provides disease-modifying effects in Parkinson's disease models, **Nature Communications 14:4283 (https://doi.org/10.1038/s41467-023-39970-9). (2023). Impact Factor: 17.694. ([+]WK and MT contributed equally to this study). Citations: 4**

   Contribution: Prof Rawat`s research group designed, synthesized, and characterized the study.

   Patent Nos: ES2899730T3 (2022); CA3175047A1 (2022); EP3971178A1 (2022); US20170209441A1 (2021); PT2822936T (Portugal, 2021); US9567316B2 (2017); IN 283657 (2017); WO 2013 134047A3 (20213)

   Summary: The nuclear receptor, Nurr1, is critical for both the development and maintenance of midbrain dopamine neurons (mDANs) and protects them from neuroinflammation. In this communication, we reported the results of an extensive medicinal chemistry search in which over 570 4A7C-derivatives were generated and characterized for their ability to activate Nurr1. In support of the hypothesized SAR, multiple compounds enhanced Nurr1's transcriptional activity, leading to the identification of an optimized, brain-penetrant agonist, 4A7C-301, that exhibits robust neuroprotective effects using in vitro models (e.g., mDA cell lines and primary mDAN-glia co-cultures) with enhanced expression of mDAN-specific markers along with suppression of microglial activation. In addition, 4A7C-301 protects against the loss of mDANs in the MPTP-induced mouse model of PD. It improves motor and non-motor olfactory deficits without side effects such as dyskinesia-like behaviours. Furthermore, 4A7C-301 significantly ameliorates neuropathological abnormalities and improves motor and olfactory dysfunctions in AAV2-mediated human α-synuclein (both wild-type and hA53T mutant)-overexpressing mouse models, with reduced α-synuclein accumulation and increased dopamine production. These substantial disease-modifying properties of 4A7C-301 may warrant clinical evaluation of this or analogous compounds for the treatment of patients with PD.

3. Shashikant Tiwari, **Diwan S. Rawat*** Regiodivergent synthesis of densely functionalized indolizines" **J. Org. Chem. 88, 6805–6815 (2023). Impact Factor: 4.192.**

   Summary: A novel metal and additive-free, atom-economic method for the regio divergent synthesis of crucial six or eight substituted indolizines from meta-amide substituted pyridine and alkyne *via* a [2+2+1] cycloaddition is developed. The reaction proceeds through the cleavage of the carbon-carbon triple bond. The synthesized product contains an important amide group that can be further functionalized for biologically active compounds.

4. Synthesis of novel monocarbonyl curcuminoids, evaluation of their efficacy against MRSA, including ex vivo infection model and their mechanistic studies, Gagandeep, Prince Kumar, Shamseer Kulangara Kandi, Kasturi Mukhopadhyay, **Diwan S. Rawat***, **Eur. J. Med. Chem. 195, 112276 (2020).** ***Impact Factor:*** **7.088.**

   Summary: A series of novel monocarbonyl curcuminoids were synthesized, and these compounds showed potent antibacterial activity against both methicillin-sensitive and methicillin-resistant strains of *S. aureus* with MIC values 2-8 and 4-16 mg/mL, respectively. They also exhibited moderate potency against *E. coli* strains. And these compounds were non-hemolytic, and non-toxic toward mammalian cells up to 150 mg/mL concentration. Mechanistic studies revealed that these curcuminoids displayed potent bactericidal activity targeting cell membranes. In an *ex vivo* mammalian co-culture infection model study, two of the compounds were able to clear the internalized bacteria in mammalian cells. The activity was superior to conventional antibiotics such as vancomycin and linezolid. These water-soluble, non-toxic curcuminoids may serve as a lead molecule for development as antibacterial agents against MRSA infections.

5. Hybridization of fluoro-amodiaquine (FAQ) with pyrimidines: Synthesis, *in vitro* and *in vivo* antimalarial potency of FAQ-pyrimidines; Mohit Tripathi, Dale Taylor, Shabana I. Khan, Babu L. Tekwani, Prija Ponnan, Thirumurthy Velpandian, Ujjalkumar Das, **Diwan S. Rawat*** **ACS Med. Chem. Lett.** 10, 714–719 **(2019), Impact factor: 4.345. Citation: 21**

   Summary: To evade the possible toxicity associated with the formation of quinone-imine metabolite in amodiaquine (AQ), the para –hydroxyl group was replaced with a –F atom and the resulting 4'-fluoro-amodiaquine (FAQ) was hybridized with substituted pyrimidines. The synthesized FAQ-pyrimidines displayed better in vitro potency than chloroquine (CQ) against the resistant P. falciparum strain (Dd2), exhibiting up to 47.3-fold better activity (IC_{50}: 4.69 nM) than CQ (IC_{50}: 222 nM) and 2.8-fold better potency than artesunate (IC_{50}: 13.0 nM). Twelve compounds exhibited better antiplasmodial activity than CQ against the CQ-sensitive (NF54) strain. Two compounds were evaluated in vivo against a P. berghei-mouse malaria model and displayed better activity than CQ and comparable to AQ at 33.3 mg/Kg dose. Mechanistic heme-binding studies and computational docking against Pf-DHFR was performed for the best molecules of the series to correlate their high antiplasmodial activities.

6. U. Chinna Rajesh, Upasana Gulati and **Diwan S. Rawat*** Cu(II)-Hydromagnesite catalyzed synthesis of tetrasubstituted propargylamines and pyrrolo[1,2-a]quinolines *via* KA2, A3 couplings and their decarboxylative versions, **ACS Sustainable Chem. Eng. 4, 3409 – 3419 (2016). Impact Factor: 9.224. Citations: 170**

   Summary: A novel copper supported on hydromagnesite (Cu/HM) nanomaterial was prepared by a simple impregnation method at room temperature and this material was used in the three-component coupling of ketone and amine with alkyne to afford

tetrasubstituted propargylamine via KA2 coupling. Under similar reaction conditions, the three-component reaction of aldehydes and amine with alkyne gives propargylamine via an A3-coupling reaction. The high catalytic activity of Cu/HM in the A3 coupling strategy to afford propargylamine intermediate is due to the synergistic effect of both Cu^{2+} and Mg^{2+} active sites. The versatility of Cu/HM catalyst was also studied for the decarboxylative A3 and KA2 coupling strategies. The present method offers several advantages, such as the simple procedure for the catalyst preparation, versatile catalytic applications, cheap precursors, higher yield of products in short reaction time, recovery and reusability of the catalyst, and this methodology can be utilized in the preparation of industrially important chemicals.

7. U. Chinna Rajesh, Jinfeng Wang, Stuart Prescott, Takuya Tsuzuki, **Diwan S. Rawat***, RGO/ZnO nanocomposite: An efficient sustainable heterogeneous amphiphilic catalyst for the synthesis of 3-substituted indoles in water. **ACS Sustainable Chem. Eng.** 3, 9 – 18 (**2015**) **[Highlighted in the Cover Page]. Impact Factor: 9.224. Citation: 129.**

Summary: A nanocomposite consisting of reduced graphene oxide and zinc oxide nanoparticles (RGO/ZnO) with unique structural features was developed as a highly efficient reusable heterogeneous amphiphilic catalyst for the synthesis of various 3-substituted indoles in aqueous medium. The catalyst was recycled six times without significant loss of the catalytic activity. The higher environmental compatibility and sustainability factor, such as smaller E-factor and higher atom economy, makes the present methodology a true green process for synthesizing biologically important 3-substituted indoles.

8. U. Chinna Rajesh, Gunjan Purohit, **Diwan S. Rawat*** Facile one-pot synthesis of N-heterocycles using CuI/CSP composites as efficient recyclable nanocatalysts with anomalous selectivity under green conditions, **ACS Sustainable Chem. Eng.** 3, 2397 – 2404 (**2015**). **Impact Factor: 9.224; Citation: 52**

Summary: CuI/CSP nanocomposites were developed as efficient and recyclable nanocatalysts for one-pot synthesis of aminoindolizines *via* A3 coupling reaction in the presence of ethylene glycol (EG) as a recyclable solvent. In contrast, chalcones were isolated when the reaction was performed in the presence of secondary amines such as piperidine, 3-methylpiperidine, pyrrolidine, and piperazine under solvent-free conditions. The CuI/CSP was recycled five times without significant loss in its catalytic activity. The anomalous selectivity in the formation of aminoindolizines and chalcones was dependent on solvents and secondary amines used for the reaction. The methodology is facile and follows green principles with a higher atom economy (94%) and a smaller E-factor (0.06).

9. Deepak Kumar, Beena, Garima Khare, Saqib Kidwai, Anil K. Tyagi, Ramandeep Singh, **Diwan S Rawat***, Synthesis of novel 1,2,3-triazole derivatives of isoniazid and their *in vitro* and *in vivo* antimycobacterial activity evaluation, **Eur. J. Med Chem.** 81, 301 – 313 (**2014**). ***Impact Factor:* 7.088. Citation: 103 (Invited review on TB: Med. Res. Rev. 41, 2565–2581 (2021). Impact Factor: 13.59)**

Summary: A molecular hybrids of isoniazid and 1,2,3-triazoles were synthesized and evaluated for antimycobacterial activity. Most compounds exhibited potent activity against *Mycobacterium tuberculosis* H37Rv strain with MIC_{99} values ranging from 0.195 to 1.56 μM *in vitro*. One compound showed better *in vitro* activity than the reference, whereas five compounds were equally potent to the reference compound isoniazid without any observed toxicity even at 50 μM concentration. *In vivo*, activity of the best

compound in the murine model of tuberculosis significantly reduced bacillary load in both lungs and spleen at 10 weeks post-treatment.

10. Novel 4-aminoquinoline-pyrimidine based hybrids with improved *in vitro* and *in vivo* antimalarial activity, Sunny Manohar, U. Chinna Rajesh, Shabana I. Khan, Babu L. Tekwani, **Diwan S. Rawat***, **ACS Med. Chem. Lett.** 3, 555-559 (**2012**). **Impact factor: 4.345. Citations: 157.**
(**Patents on Anti-Parkinson activity of these compounds**: US 2017/0209441 A1; EP. 13758678, PCT/US2013/28329, WO2013134047 A3, PCT/US2013/028329).

Summary: A class of hybrid molecules consisting of 4-aminoquinoline and pyrimidine were synthesized and tested for antimalarial activity against both chloroquine (CQ)-sensitive (D6) and chloroquine (CQ)-resistant (W2) strains of Plasmodium falciparum through an in vitro assay. Eleven hybrids showed better antimalarial activity against both CQ-sensitive and CQ-resistant strains of P. falciparum compared to standard drug CQ. Four molecules were more potent (7-8 fold) than CQ in D6 strain and eight molecules were found to be 5-25 fold more active against resistant strain (W2). Several compounds showed no cytotoxicity up to a high concentration (60 μM), while others exhibited mild toxicities. Still, most of these hybrids' selective index for the antimalarial activity was very high. Two compounds selected for in vivo evaluation have shown excellent activity (p.o.) in a mouse model of P. berghei without any apparent toxicity. The X-ray crystal structure of one of the compounds was also determined.

The molecule has been taken up by NURRON Pharmaceuticals, Boston, for development as an anti-Parkinson drug.

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