

## Ten Best Papers of Professor Diwan S Rawat

1. Woori Kim<sup>+</sup>, Mohit Tripathi<sup>+</sup>, 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](#)<sup>\*</sup>, Kwang-Soo Kim,<sup>\*</sup> 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).

**Contribution:** Design, synthesis and characterization was carried out by Prof Rawat's research group.

**Patent Nos:** 20220008418 (Publication date: January 13, 2022); 11026943 (Publication date: June 8, 2021); 20170209441 (Publication date: July 27, 2017); 9567316 (Publication date: February 14, 2017); 20150023930 (Publication date: January 22, 2015).

**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 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 and improves both motor and non-motor olfactory deficits without side-effects such as dyskinesia-like behaviors. Furthermore, 4A7C-301 significantly ameliorates neuropathological abnormalities and improves motor and olfactory dysfunctions in AAV2-mediated human  $\alpha$ -synuclein (both wild-type and hA53T mutant)-overexpressing mouse models, with reduced  $\alpha$ -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.

2. Shashikant Tiwari, [Diwan S. Rawat](#)<sup>\*</sup> 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 regiodivergent synthesis of crucial six or eight substituted indolizine 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 to afford biologically active compounds.

3. 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](#)<sup>\*</sup>, **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 by 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 and the activity was found to be 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.

4. 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 Ponnann, Thirumurthy Velpandian, Ujjalkumar Das, **Diwan S. Rawat\*** *ACS Med. Chem. Lett.* 10, 714–719 (2019), **Impact factor: 4.345. Citation: 19**

**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.

5. 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: 136**

**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 to give propargylamine *via* 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 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.

6. 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 the synthesis of biologically important 3-substituted indoles.

7. 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: 45

**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 for five times without significant loss in its catalytic activity. The anomalous selectivity in the formation of aminoindolizines and chalcones was dependent of solvents and secondary amines used for the reaction. The present methodology is facile and follows green principles with higher atom economy (94%), smaller E-factor (0.06).

8. 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: 93 (Invited review on TB: Med. Res. Rev. 41, 2565-2581 (2021). Impact Factor: 13.59)

**Summary:** A molecular hybrids consisting of isoniazid and 1,2,3-triazoles were synthesized and evaluated for antimycobacterial activity. Most of the compounds exhibited potent activity against *Mycobacterium tuberculosis* H37Rv strain with MIC<sub>99</sub> values ranging from 0.195 to 1.56  $\mu$ M *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  $\mu$ M concentration. *In vivo* activity of the best compound in murine model of tuberculosis significantly reduced bacillary load in both lungs and spleen at 10 weeks post-treatment.

9. 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: 147.  
(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* in comparison 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 did not show any cytotoxicity up to a high concentration (60  $\mu$ M), others exhibited mild toxicities but the selective index for the antimalarial activity was very high for most of these hybrids. Two compounds selected for in vivo evaluation have shown excellent activity (p.o.) in a mouse model of *P. berghei* without any apparent toxicity. X-ray crystal structure of one of the compound was also determined.

***Molecule has been taken up by NURRON Pharmaceuticals, Boston for development as anti-Parkinson drug.***

10. N. Agarwal, R. Kumar, P. Dureja, [Diwan S. Rawat](#)\* "Schiffs bases as potential fungicides and nitrification inhibitors" **J. Agric. Food Chem.** 57, 8520-8525 (2009). **Impact Factor: 5.279.**

**Summary:** The Schiff bases were synthesized and for their antifungal activity in vitro against pathogenic fungi, namely, *Sclerotium rolfii* and *Rhizoctonia bataticola*, and for their effect on nitrification inhibition under laboratory conditions. Some of the compounds showed antifungal activity against these two strains at low nano-molar range.



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