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Editorial

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Editorial: Medicinal Chemistry Research in India

India rejoined the international product patent regime in 2005 after a gap of 35 years. In the interim period (1970−2005), only process patents were allowed and Indian companies were free to produce and market patented drugs from other territories (US, Europe etc.). After promulgation of product patent regulations in 2005, medicinal chemistry research has taken a positive turn in India and a number of productive research groups have come up in the past decade, both in academic as well as industrial laboratories. Consequently, the funding ecosystem has also significantly improved and a number of Indian Government agencies, such as the Department of Science & Technology (DST), Department of Biotechnology (DBT), and Council of Scientific and Industrial Research (CSIR), are investing substantial financial resources. A number of Indian pharmaceutical companies and International Charities (Gates Foundation, Global TB Alliance, and Wellcome Trust) are also investing in NCE discovery and preclinical and clinical development. In addition to this, a number of CROs providing valuable services in PK-ADME and preclinical development are filling the expertise gap in lead optimization and selection.

Against this backdrop, it is heartening that the two most important global platforms (*Journal of Medicinal Chemistry* and *ACS Medicinal Chemistry Letters*) decided to highlight medicinal chemistry research in India. In the past 2 years (2015−16), 35 articles have been published in *Journal of Medicinal Chemistry* from India wherein 18 articles have corresponding authors based in India. In *ACS Medicinal Chemistry Letters*, 23 articles have been published during 2015−16 wherein 20 articles have corresponding authors based in India. The disease areas of interest in India are also fairly broad, including infectious diseases, oncology, inflammation, Alzheimer's, diabetes, cardiac, and neglected diseases (malaria, filariasis, and leishmaniasis). This joint virtual issue comprises selected original research articles published in the last two years and authored by groups primarily working in India in diverse areas of medicinal chemistry. A fair representation of articles from academic as well as industrial laboratories has been given.

In the area of infectious diseases, the challenge being faced is emergence of resistance, and therefore, identification and generation of new leads with alternative mechanisms of action is highly desirable. In this direction, Panda and co-workers from AstraZeneca have identified 3-cyanopyridones and 1,6-naphthyridin-2-ones as the first hits against *M. tuberculosis* thymidylate kinase, an important enzyme which is involved in DNA synthesis and represents a novel and essential target for the survival of mycobacterium. Structure guided lead optimization study led to the generation of nanomolar potent inhibitors.[1] Similarly, Haldar and co-workers have designed and synthesized novel biocides which showed antibacterial activity against wild-type bacteria as well as showing excellent activity against drug-resistant bacteria including MRSA and VRE.[2] Degani and co-workers have designed and synthesized a focused library of diamino triazines as potential inhibitors against *Mycobacterium tuberculosis* dihydrofolate reductase, wherein one of the molecules has shown good selectivity in the enzyme assay and potent MIC in whole cell assays well as exhibited synergy with the second-line anti-TB agent aminosalicylic acid.[3] Gill's group reported a benzo[*b*]thiophene derivative that was active against MTB H37Ra and resistant MTB strains along with a good safety index. The authors also presented insight regarding their mechanism of action through a computational study, wherein these derivatives have shown a high binding affinity toward the active site of DprE1 (decaprenylphosphoryl-β-D-ribose-2′-epimerase).[4] Hameed et al. from AstraZeneca have designed novel bacterial topoisomerase inhibitors displaying potent antimycobacterial activity and improved selectivity against hERG cardiac channel binding. The best identified compound also inhibits Mtb DNA gyrase. The compound has shown anti-TB activity in an acute mouse model of TB following oral administration of a compound.[5] Singh and co-workers did extensive medicinal chemistry on the 6-nitro-2,3-dihydroimidazooxazole scaffold with the aim to produce a compound with enhanced solubility and generated a series of polar functionalities containing 6-nitro-2,3-dihydroimidazooxazole analogues. The optimized compound has shown good activity against sensitive and resistant (Rif^R and MDR) and dormant strains of MTB along with a good safety index. In addition, the best compound has also shown high microsomal stability, high solubility, and favorable oral in vivo pharmacokinetics and in vivo efficacy.[6] Reddy and co-workers have performed extensive medicinal chemistry and developed new generation silicon incorporated oxazolidinone antibiotics, wherein the best compound has shown a 30-fold higher brain/plasma ratio as compared to linezolid and represents potential for curing brain infections.[7]

In the area of oncology, Batra and co-workers reported β-carboline-based *N*-heterocyclic carbenes as new anticancer agents. These compounds also show anti-invasive and anti-migratory activity against human breast cancer cells.[8] Sreedhar and co-workers have investigated the anticancer activity of mononuclear copper(II) polypyridyl complexes. These complexes showed inhibition of endothelial cell proliferation, indicating their antiangiogenic activity.[9] The scaffold-hopping of bioactive natural product aurones was done by Guchhait and co-workers[10] to discover topoisomerase IIα -targeting anticancer compounds. The identified compounds exhibited topoisomerase II-selective poison activity with efficiency more than etoposide. Dugar and co-workers reported an orally bioavailable PI3K-α inhibitor based on the indazole substituted morpholino-triazine scaffold.[11] In a fundamental study, Muniyappa and co-workers reported the role of G-rich sequences to form G-quadruplex structures and regulation of normal DNA transactions. This study has revealed a novel regulatory mechanism of ACC1 gene expression.[12]

For anti-inflammatory diseases, Singh and co-workers, through rational design, have identified a small peptide showing optimal inhibition of COX-2. In acute toxicity studies, this

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peptide was found to be safe up to 2000 mg/kg dose.[13] Yadav and co-workers have prepared hybrids of donepezil and diarylthiazole and explored their ability to modulate multiple targets involved in the pathogenesis of Alzheimer's disease.[14] Agarwal and co-workers from Cadila Healthcare[15] discovered 3-(4-aryloxyaryl)propanoic acid derivatives as orally efficacious GPR40/FFAR1 receptor agonists.

Thomas and co-workers developed a highly potent pharmacophore from an inactive diarylpyridine-2-amine scaffold via extensive synthesis and SAR analysis. This work led to identification of pyridin-2(1H)-one based potent, selective, and orally active PDE10A inhibitors possessing good efficacy in selected rodent models of psychosis.[16]

Dhavale and co-workers reported indolizidine and indolizidone iminosugars as potential immunostimulating agents and as glycosidase inhibitory compounds. In their study, these compounds showed potent inhibitory activity against various glycosidase enzymes having K_i and IC_{50} values in the micromolar/nanomolar concentration range.[17] Sampath Kumar and co-workers screened a focused library of benzyloxyalkyl-substituted 1,2,3-triazolyl α-GalCer analogues for immunomodulatory activity.[18] Bharate and co-workers discovered 7-(prolinol-N-yl)-2-phenylamino-thiazolo[5,4-*d*]-pyrimidines as a novel chemotype of non-nucleoside partial agonists of the A2A adenosine receptor. The molecular-modeling studies indicated that the prolinol moiety mimics the interactions of the ribose moiety of adenosine, a natural agonist of the A2A receptor, suggesting that this class of compounds could have good agonistic properties. The molecular modeling predictions were validated by in vitro binding and functional assays. The best compound displayed promising A2A agonism, selectivity, and physicochemical properties.[19]

Tandon and co-workers reported 1,2-dihydroisoquinolines as HIV-1 integrase inhibitors. These compounds inhibit HIV integrase and reduce the level of p24 viral antigen.[20]

The diversity of the publications highlighted above indicates that there are a number of active research groups in India pursuing cutting-edge medicinal chemistry integrating screening, modeling, design, synthesis, and pharmacokinetics of NCEs. Interestingly, there is greater propensity for collaboration between academic laboratories and homegrown pharmaceutical companies and start-ups, amply supported by generous federal funding. However, for the successful translation of discovery leads, there are a number of skillsets and types of expertise (PK, metabolism, off-target profiling, formulation, and IND enabling studies) critical for preclinical and clinical development, which are suboptimal and therefore require special attention by institutions, funding bodies, and policy leaders. Also there is greater need and opportunity for international collaboration. It is hoped that this ecosystem will take shape in India sooner than later, enabling India to discover and market new therapeutics for alleviating the global disease burden.

The Guest Editor is grateful to the Editors and Associate Editors of *Journal of Medicinal Chemistry* and *ACS Medicinal Chemistry Letters* for conceiving the idea to showcase medicinal chemistry research in India in this joint virtual issue, perhaps at the most suitable time when new drug discovery in India is trying to make its mark on the global scene. It is hoped that this special spotlight will encourage further work and support from funding agencies.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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