Dr. Sandip B. Bharate

b) In order of importance, list of ten best papers of the candidate, highlighting the important discoveries/contributions described in them briefly (not to exceed 3000 words)

Sr No	Paper	Important discovery/ contribution in the paper
1	**Bharate SB;*** Kumar V; Jain SK; Mintoo NJ; Guru SK; Nuthakki VK; Sharma M; Bharate SS; Gandhi SG; Mondhe DM; Bhushan S; Vishwakarma RA. Discovery and Preclinical Development of IIIM-290, an Orally Active Potent Cyclin-dependent Kinase Inhibitor. *J. Med. Chem.* ***2018,*** 61, 1664-1687	Four series of rohitukine derivatives were prepared and screened for Cdk inhibition and cellular antiproliferative activity. The 2,6-dichloro-styryl derivative IIIM-290 (11d) showed strong inhibition of Cdk-9/T1 (IC50 1.9 nM) kinase and Molt-4/MIAPaCa-2 cell growth (GI50 < 1.0 μM) and was found to be highly selective for cancer cells over normal fibroblast cells. It inhibited the cell growth of MIAPaCa-2 cells via caspase-dependent apoptosis. It achieved 71% oral bioavailability with in vivo efficacy in pancreatic, colon, and leukemia xenografts at 50 mg/kg, po. **All the chemistry work, including the drug design, synthesis, SAR, pilot scale synthesis was done in my lab.**
2	Nuthakki VK, Choudhary S, Reddy CN, Bhatt S, Jamwal A, Jotshi A, Raghuvanshi, R, Sharma A, Thakur S, Jadhav H, Bharate SS, Nandi U, Kumar A, **Bharate SB***. Design, Synthesis, and Pharmacological Evaluation of Embelin-Aryl/alkyl amine Hybrids as Orally Bioavailable Blood-Brain Barrier Permeable Multitargeted Agents with Therapeutic Potential in Alzheimer's Disease: Discovery of SB-1448. *ACS Chem Neurosci.* ***2023,*** *14, 6, 1193–1219 [IF = 5.8].*	We synthesized a series of embelin−aryl/alkyl amine hybrids to improve its physicochemical properties and therapeutic potency against targeted enzymes. The most active derivative, 9j (SB-1448), inhibits human acetylcholinesterase (hAChE), human butyrylcholinesterase (hBChE), and human BACE-1 (hBACE-1) with IC50 values of 0.15, 1.6, and 0.6 μM, respectively. It inhibits both ChEs noncompetitively with *k*i values of 0.21

		and 1.3 μM, respectively. It is orally bioavailable, crosses blood−brain barrier (BBB), inhibits Aβ self-aggregation, possesses good ADME properties, and protects neuronal cells from scopolamine-induced cell death. The oral administration of 9j at 30 mg/kg attenuates the scopolamine-induced cognitive impairments in C57BL/6J mice. **In this paper, all the chemistry, design, SAR development, all in vitro biochemical assays, BBB-PAMPA assay were done in my lab.**
3	Bhurta D, Hossain MM, Bhardwaj M, Showket F, Nandi U, Dar MJ, **Bharate SB*** Orally Bioavailable Styryl Derivative of Rohitukine-N-oxide Inhibits CDK9/T1 and the Growth of Pancreatic Cancer cells. *Eur. J. Med. Chem.* ***2023****, 258, 115533 [IF = 7.1].*	We report isolation, biological evaluation, and synthetic modification of rohitukine *N*-oxide for CDK9/T1 inhibition and antiproliferative activity in cancer cells. Rohitukine *N*-oxide (**2**) inhibits CDK9/T1 (IC50 7.6 μM) and shows antiproliferative activity in the colon and pancreatic cancer cells. The chloro-substituted styryl derivatives, **2b**, and **2l**, inhibit CDK9/T1 with IC50 values of 0.17 and 0.15 μM, respectively. These derivatives display cellular antiproliferative activity in HCT 116 (colon) and MIA PaCa-2 (pancreatic) cancer cells with GI50 values of 2.5–9.7 μM with excellent selectivity over HEK293 (embryonic kidney) cells. Both analogs induce cell death in MIA PaCa-2 cells *via* inducing intracellular ROS production, reducing mitochondrial membrane potential, and inducing apoptosis. These analogs are metabolically stable in liver microsomes

		and have a decent oral pharmacokinetics in BALB/c mice. **All chemistry, design, in-vitro CDK assays, docking, MD simulation is done in my lab.**
4	Bhurta D, **Bharate SB*** Discovery of Pongol, the Furanoflavonoid, as an Inhibitor of CDK7/Cyclin H/MAT1, and its Preliminary Structure-Activity Relationship. *ACS Omega,* **2023**, 8 (1), 1291–1300 *[IF = 4.1].*	We screened a small library of pure natural products in an ADP-Glo CDK7/H kinase assay that yielded a series of furano- and naphthoflavonoids among actives. Pongol (SBN-88), the hydroxysubstituted furanoflavonoid, inhibits CDK7/H as well as CDK9/T1 with IC50 values of 0.93 and 0.83 μM, respectively, and >20-fold selectivity over CDK2/E1 (IC50 > 20 μM). The molecular docking and molecular dynamics simulation revealed that the presence of phenolic −OH in pongol is vital for kinase inhibition, as its absence resulted in a significant loss in activity (e.g., lanceolatin B). **We established CDK7 and CDK9 assays in the lab, and screened a library of ~100 NPs in these assays. Docking and MD simulation was also done in our lab.**
5	Sharma A, Nuthakki VK, Gairola S, Singh B, **Bharate SB.*** A Coumarin-donepezil Hybrid as a Blood-brain Barrier Permeable Dual Cholinesterase Inhibitor: Isolation, Synthetic Modifications and Biological Evaluation of Natural Coumarins. *ChemMedChem*, **2022**, 17 (8), e202200300 *[IF = 3.54].*	Herein, we undertook the phytochemical investigation of *Nardostachys jatamansi* (D.Don) DC. rhizomes followed by semisynthetic modifications to discover cholinesterase (ChE) and beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) inhibitors. The 8-acetyl-7-hydroxycoumarin isolated from the bioactive extract moderately

		inhibits acetylcholinesterase (AChE) and BACE-1 with IC50 values of 22.1 and 17.7 μM, respectively. The semisynthetic trifluoromethyl substituted coumarin chalcone display a 5-fold improvement in BACE-1 inhibition (IC50 3.3 μM). Another semisynthetic derivative, a coumarin-donepezil hybrid, exhibits dual inhibition of both ChEs with IC_{50} values of 1.22 and 3.09 μM, respectively. **In this paper, all the work presented is done in our lab** (except the collection and authentication of the plant material).
6	Shah K, Maradana MR, Delás MJ, Metidji A, Graelmann F, Llorian M, Chakravarty P, Li Y, Tolaini M, Shapiro M, Kelly G, Cheshire C, Bhurta D, **Bharate SB**, Stockinger B. Cell-intrinsic Aryl Hydrocarbon Receptor signalling is required for the resolution of injury-induced colonic stem cells. *Nature Commun*. **2022**, 13 (1), 1827 [IF = 17.7].	Here we show that AHR is important for the termination of the regenerative response and the reacquisition of mature epithelial cell identity post injury in vivo and in organoid cultures in vitro. Using an integrative multi-omics approach in colon organoids, we show that AHR is required for timely termination of the regenerative response through direct regulation of transcription factors involved in epithelial cell differentiation as well as restriction of chromatin accessibility to regeneration-associated Yap/Tead transcriptional targets. **In this paper, we contributed in synthesis of a tool compound (a khellin derivative, CYP1A1 inhibitor) that was used in in-vivo mice model.**
7	Raghuvanshi R, Nuthakki VK, Singh L, Singh B, Bharate SS, Bhatti R, **Bharate SB*** Identification of Plant-based Multitargeted Leads for Alzheimer's Disease: In-vitro and In-vivo Validation of *Woodfordia fruticosa* (L.) Kurz.	A library of plant extracts was screened for inhibition of acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and beta-site amyloid precursor protein cleaving enzyme 1 **(**BACE-1). Among the library of 105 extracts, *Woodfordia*

	Phytomedicine, **2021**, 91, 153659 [IF = 7.9]	*fruticosa* (SBE-80) and *Bergenia ciliata* (SBE-65) extracts displayed significant inhibition of all three enzymes. The *W. fruticosa* extract SBE-80 at the dose of 25 mg/kg QD × 9 (PO) displayed memory-enhancing activity in Morris Water Maze and Passive Avoidance Test in Swiss albino mice. **The natural products chemistry, and all in vitro biology is done in my lab.**
8	Abdullaha M, Ali M, Kour D, Mudududdla R, Khajuria P, Kumar A, **Bharate SB.*** Tetramethoxystilbene Inhibits NLRP3 Inflammasome Assembly via Blocking the Oligomerization of Apoptosis-associated Speck-like Protein Containing Caspase Recruitment Domain: In-Vitro and In-Vivo Evaluation. *ACS Pharmacol. Trans. Sci.* ***2021****,* 4, 1437-1448 [IF = 6.1]	The structure-guided design and synthesis of a series of methoxystilbenes and methoxy-2-phenylnaphthalenes identified new inhibitors of NLRP3 inflammasome complex. The tetramethoxystilbene 4o and trimethoxy 2-phenylnaphthalene 1t inhibit the release of a mature form of IL-1β in J774A.1 cells with IC50 values of 1.39 and 2.07 μM, respectively. Mechanistic investigation revealed that tetramethoxystilbene 4o blocks the oligomerization of apoptosis-associated speck-like protein (ASC), which is the vital step in the formation of NLRP3 inflammasome assembly, thus preventing the activation of caspase-1 and the IL-1β release. Treatment of LPS+ATP challenged mice with 20 mg/kg of 4o significantly suppressed the levels of IL-1β. **The drug design, synthesis and docking studies done in my lab.**
9	Kumar V; Bharate SS; Bhurta D; Gupta M; Gandhi SG; Singh D; Jaglan S; Kumar A; Vishwakarma RA; **Bharate SB*.**	Herein we report the discovery and preclinical development of rohitukine-enriched fraction of *D. binectariferum* as a phytopharmaceutical lead candidate.

	Evaluation of rohitukine-enriched fraction of *Dysoxylum binectariferum* Hook.f. (leaves) as Anti-arthritic Phytopharmaceutical Candidate: Chemical Standardization, In-vivo validation, Formulation Development and Oral Pharmacokinetics. *J. Ethnopharmacol.,* ***2020****, 254, 112758 [IF=5.19]*	The in-vivo efficacy is validated in collagen-induced arthritis in DBA/1J mice. **All the natural products chemistry, phytopharmaceutical lead identification, quantification is done in my lab.** **All GLP-Tox is completed and GMP batches are prepared. This phytopharmaceutical lead is now being submitted as an IND application to the CDSCO.**
10	Abdullaha M; Mohammed S; Ali M; Kumar A; Vishwakarma RA; **Bharate SB*** Discovery of quinazolin-4(3H)-ones as NLRP3 inflammasome inhibitors: computational design, metal-free synthesis and in-vitro biological evaluation. *J. Org. Chem.*, **2019**, *84*, 5129-5140 [IF= 4.35]	Herein, computationally designed series of quinazolin-4(3H)-ones were synthesized using iodine-catalyzed coupling of arylalkynes (or styrenes) with O-aminobenzamides. The nitro-substituted quinazolin-4(3H)-one 2k inhibited NLRP3 inflammasome (IC50 5 μM) via the suppression of IL-1β release from ATP-stimulated J774A.1 cells. **All the chemistry work including computational homology modeling is done in my lab.**