ORGANIC SYNTHESIS FOR HEALTHCARE AND SOCIETAL BENEFITS

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Abstract

Since decades, Bio-Science group in BARC has been instrumental in contributing to the healthcare department and societal benefits via various routes. In this aspect, synthetic organic chemistry has immensely contributed towards the development of diverse bioactive molecules via environment friendly green routes, and their applications in the fields of agriculture, bioremediation, catalysis, radiopharmaceutical ligands, targeted chemotherapeutics and advanced drug intermediates. These research activities have led to different in-house developed products which have been used very regularly in agricultural and clinical practices. This book chapter provides glimpses of the activities in the field of synthetic organic chemistry over the last few decades and acknowledges the efforts and hard work of all the members of the group who has worked with sincerity and dedication towards achieving their goals related to DAE activities, societal benefits, national interests, novel science and modern technologies.

1. Introduction

Since its inception, synthetic organic chemistry in Bio-Science Group, BARC has played an indispensable part in DAE (Department of Atomic Energy) activities through its contribution in high quality basic research and development of organic and bio-materials. Organic multistep syntheses have been instrumental in development of novel strategies to synthesize highly modular synthetic building blocks which are applied in various research projects, from macromolecular and materials science to chemical biology. The

division's research group has pioneered and mastered the multistep organic syntheses in BARC through its highly motivated and well-organized research projects, many of which have found applications towards healthcare and societal benefits.

Over the years, the mandate of the research activities in the division has been motivated by the contemporary departmental and societal needs. During the 70´s, the research focus was mainly directed towards better crop protection strategies and plant biotechnology, leading to the development of several plant-based formulations/compounds for the purpose, with some spin-offs like anti-hepatitic herbal preparations, anti-cancer agents etc. However, with the growing societal need of insect pheromones in the next decade, the research focus was diverted to the syntheses of insect pheromones. In India, our division was one of the first few laboratories to initiate enantiomeric synthesis (1984). This paradigm resulted in major and pioneering contributions from the division in developing short and economical routes for chiral drugs and other bioactive molecules. Several synthetic strategies, including bio-catalysis, organo-catalysis, transition-metal catalysis, solid phase synthesis etc. were developed for this purpose. These strategies were used to synthesize several multi-functional intermediates with multiple stereocenters, and a diverse array of molecules such as macrolides, lactones, spiroketals, fused furanomacrolides, iminosugars, hydroxystilbenes etc. The expertise in organic multistep synthesis was further extended to the in-house synthesis of radiopharmaceutical ligands/carriers, which, in turn, led to the in-house development of several clinically used diagnostic and therapeutic nuclear medicines.

2. Asymmetric Synthesis

The undeniable role of stereocenters in determining the bioactivities of molecules is well documented and warrants the search for new synthetic tools to instil chirality in a molecule. One of the biggest challenges in the asymmetric syntheses of complex organic molecules lies in the design and development of short, simple and flexible strategies. Hence, fundamental and original contributions have been invoked in chemical asymmetric syntheses, by designing several new chiral catalysts as well as synthetic strategies for enantioselective reactions.

To this end, reusable natural sources like terpenoids, steroids, and sugar derivatives (especially (*R*)-cyclohexylideneglyceraldehyde from mannitol) have been used both as chiral pool materials and templates for the enantiomeric syntheses of multitude of target molecules as well as designing new asymmetric synthetic reactions. Formulaion of (i) asymmetric dihydroxylation (ADH) of homoallylic alcohols without the need of expensive ADH reagents; (ii) tuning of diastereoselectivity of Barbier-type reactions by suitable choice of metal-solvent combinations were among some notable achievements in chiral template driven enantioselective reactions. Optimization of chiral template driven enantioselective reactions viz. (i) asymmetric dihydroxylation (ADH) of homoallylic alcohols without the need of expensive ADH reagents; (ii) tuning of diastereoselectivity of Barbier-type reactions by suitable choice of metal-solvent combinations were among some notable achievements. Using either Barbier or Reformatsky or Grignard protocol,

diastereoslective addition of alkyl- and allylic organometallic reagents, in particular, to enantio-pure (*R*)-cyclohexylideneglyceraldehyde was optimised with respect to the metals, solvents, reagents, and additives. These new synthetic protocols were further explored for the enantiomeric syntheses of various enzyme inhibitors, immunosuppressants, chemotherapeutics, nucleosides, herbicidal agents etc. Different bioactive molecules like the anti-AIDS drug (AZT) and its precursors (2,5-disubstituted tetrahydrofurans) and/ or congeners (3′*S*,5′*S*)-isodideoxynucleosides (2-C-branched 2-deoxypentofuranoses), (-)-prelactone (polyketide macrolide with a δ-lactone moiety), octalactin lactone (a polyketide marine metabolite), hapalosin (multidrug-resistance reversing depsipeptide), SPIKET-P (tubulin-binding anti-cancer agent), (*S*)-2-cyclohexyl-2-phenylglycolic acid (component of anticholinergic, oxybutynin), sulfobacin A (an antagonist for von Willebrand factor (WF) receptor) etc. were synthesized in high-yielding protocols (**Fig. 1**). A chiral template-directed enantioselective construction of tertiary carbinols also formed the basis of several medicinal compounds. In a significant study, an asymmetric synthesis of herbarumin III, a phytotoxic macrolide, was developed using (*R*)-cyclohexylideneglyceraldehyde as the chiral template. This report (*Tetrahedron Asymmetry* 2006, *17*, 325-329) was well appreciated globally and was among the most cited paper in 2006-2009. In addition, interest in aliphatic polyhydroxy acids as immunomodulatory, anti-inflammatory, and anti-neoplastic agents prompted to develop the first asymmetric synthesis of oxylipin, an established and important mediator during inflammation, using the same chiral template. Chiral material driven synthesis was further extended to the synthesis of *β*-hydroxy derivatives of L -glutamic acid, L -glutamine and L-proline, useful for peptide/protein studies. A divergent asymmetric synthesis of iminosugars was also accomplished starting from D -glucose. Other chiral templates like citronellal had also been used in asymmetric synthesis of medicinally important trans/cis octahydroacridines, and most importantly for trogodermal (a pheromone, used against stored grain, khapra beetle).

In another innovative effort, it was demonstrated for the first time that cyclopentylmagnesium bromide (CPMB) acts exclusively as an inexpensive and safe reducing agent with aryl and alkyl aldehydes/ketones/esters, and was used for the diastereoselective reduction of various cyclic/polycyclic ketones including steroids, flavanones and terpenes. The reagent was also used for substrate-controlled reduction of chiral oxygenated ketones to furnish chiral alcohols. Notably, CPMB functioned as a normal nucleophile to transfer the cyclopentyl moiety to the ketones in the presence of $ZnCl_2$ (catalytic). This strategy was further utilized for the synthesis of a medicinally important compound (+)-*α*-conhydrine (a hemlock alkaloid) and also a key chiral segment of the muscarinic receptor antagonist (*S*)-2-(cyclopentyl-2-phenylglycolic acid (better efficacy than the widely used drug oxybutynin, highlighting the importance of chiral drugs).

Along with that, desymmetrization of prochiral anhydrides was also investigated as a strategy for stereoselective organic syntheses. Compared to the conventional methods of diastereoselective differentiation where costly and irrecoverable chiral reagents are used,

this unique method using the lithium salt of Evans' oxazolidinone could be efficiently employed for the economic and operationally simple desymmetrization of σ-symmetric anhydrides on a preparative scale. This method was further applied to the stereoselective total synthesis of (1)-preussin via desymmetrisation of σ-symmetric 3-dimethyl(phenyl)silyl substituted glutaric anhydride.

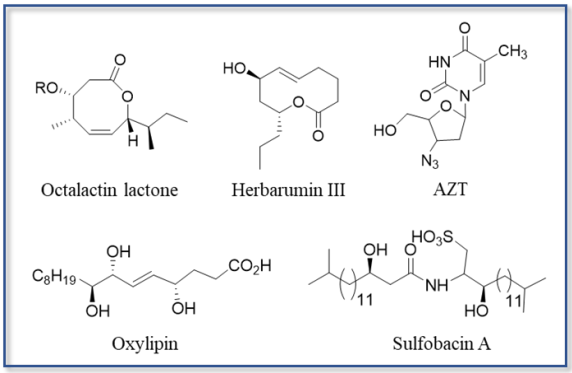

Fig. 1: Some representative bioactive molecules synthesized in the laboratories

In a seminal work, highly regio- and stereoselective vinylogous Horner-Wadsworth-Emmons (HWE) reaction (**Fig. 2**) of aldehydes with allylic phosphonates generated in situ from α-cyanovinylphosphonates, yielding stereochemicallypure 1,3-dienes with a trisubstituted double bond, was developed (*Angew. Chem. Int. Ed.* 2007, *46*, 2348-2348). In a similar line, Horner-Wadsworth-Emmons reaction was utilized to construct reactive dendralenes, which finally led to the syntheses of highly functionalised cyclohexenes with very high regio- and stereoselectivity.

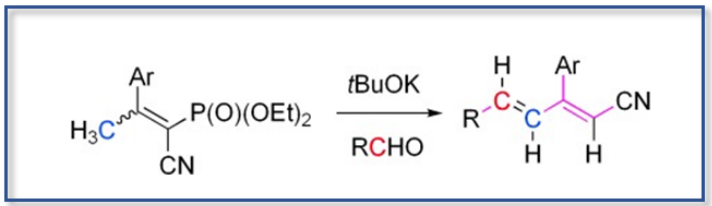

Fig. 2: Vinylogous HWE route to densely substituted 1,3-butadienes

Pioneering contributions were also made in introducing several new concepts for tuning reactivity of the low-valent-titanium (LVT) reagents using various additives (inorganic salts like NaCl vs CsCl; s vs p-donors like (polyaromatic hydrocarbons, I_2, NaCl, CsCl etc.), that helps in carrying out McMurry coupling of carbonyls (i) up to pinacol stage & controlling the stereoselctivity [stereoselective construction of pinacols using covalently-linking ligands/auxiliaries at low temperatures (*J. Am. Chem. Soc.* 1996, *118*, 5932-5937)]; (ii) demethoxylation of aromatics (for phenthrene synthesis), (iii) carrying out McMurry coupling at low temperature for better diasterecocontrol, and/ or proceeding to

alkene stage (for substituted diarylalkanes, hydroxystilbenoids, benzopyrans etc.). In particular, the new LVT reagents, containing LVT or LVT-alkali metal salts or I_2 [generating Ti-Grignard reagents] were found to be hyperactive in single electron transfer (SET) processes, which was useful for carbon-heteroatom bond cleavages at a faster rate and at a low temperature in high yields. In addition, several synthetic utility of low-valent titanium (LVT) reagents were also demonstrated. One such effort was an efficient and short synthesis of benzofurans from ortho-aroyloxyacetophenone using $TiCl_4$-Zn-THF reagent via intramolecular reductive deoxygenation. A remarkable application of LVT reagents for synthesis of polycyclic aromatic hydrocarbons (PAHs) from ortho-alkoxy aromatic aldehydes/ketones was established. It was found that pyridine-stabilized LVT has the highest potential to increase the yield of PAHs from *ortho*-alkoxy aromatic aldehydes. Utility of the LVT reagents were further explored for deprotection of allyl, benzyl and propargyl ethers as well as cleavage of N-allyl/benzyl/aryl/propargyl bonds. In continuation, this method was also utilised for the synthesis of substituted diarylalkanes, hydroxystilbenoids, benzopyrans etc.

Continuing our endeavour towards development of new synthetic methodologies, copper(II) bromide was found to be an effective catalyst for the imino Diels-Alder reaction, conjugate addition of indoles to α,β-enones, conjugate addition of pyrroles to α,β-unsaturated, monobromination of aromatic compounds and deprotection of tert-butyldimethysilyl ethers. In addition, copper(II) bromide was utilized in efficient one-pot synthesis of phenyl substituted benzo[b]furans from styrlphenols. Further, antimony(III) chloride ($SbCl_3$), a group 15 metal containing Lewis acid, was utilised as a catalyst for direct alkylation of electron-rich arenes/heteroarenes with benzylic alcohol under microwave-irradiation. The ortho-alkenyl phenols thus obtained were utilized in synthesis of biologically important functionalized oxygen-heterocycle, 4-phenylchroman. Later, $SbCl_3$ was utilised for solvent-free Friedel–Crafts reaction of phenols with mandelic acids to yield 3-aryl benzofuran-2(3*H*)-ones, which were further utilised for the syntheses of highly functionalized 3-substituted-3-arylbenzofuran-2(3*H*)-ones. Use of camphor-10-sulphonic acid (CSA) as a organo-catalyst to realize different organic transformations was also explored. In a notable effort, CSA was efficiently used as a catalyst for solvent-free direct three component one-pot Mannich-type reactions to afford *β*-amino ketones with good diasteroselectivity. Later, application of this methodology towards synthesis of 4-aminochroman was successfully accomplished. Synthesis of another important class of oxygen heterocycle, 14-aryl/alkyl-14H-dibenzo[a,j]xanthene was also realized by using CSA as catalyst.

Basic research with the stereoelectronic effects of organosilicon compounds in directing regio- and stereoselectivities of organic transformations lead to several complex biologiocally relevant natural products and their congeners. Stereoselective total synthesis of (+)-preussin (antifungal), (+)-carpamic acid (a medicinal alkaloid), fagomine (glycosidase inhibitor) etc. were achieved using this strategy. A one-pot self-regulated approach for the synthesis of amides/peptides based on two reduction–oxidation (redox) reactions was developed from azidotrimethylsilane and alkyl azides/*α*-azido acid

derivatives, and was applied for the synthesis of methionine enkephalin, an endogeneous neuropeptide. In addition, a highly regio- and stereoselective Heck reaction of iodoarenes with vinylated malonates, generated in situ by fluoride-induced protiodesilylation of alkenylsilanols/disiloxanes was developed, and was used for short synthesis of a structurally challenging lignan, (±)-matairesinol, a potential therapeutic for muscle contraction, muscle spasms and other disorders such as epilepsy. Silyl alkylidenes and related compounds were also utilised as a Michael acceptor to construct functionalised and enantiomerically enriched *β*-silyl ketones, vinyl silanes, styrenes, cyclopropanes, cyclobutanes. Additionally, a silicon directed Baeyer–Villiger oxidation on solid-phase was explored to achieve the synthesis of a *β*-silylethanol anchoring group. Efficient and short syntheses of enantiomerically pure enantiomers of 2,6-dioxabicyclo[3.3.0]octane-3,7-dione were achieved from the bis-silylated adipic acid derivatives using Fleming-Tamao oxidation.

The versatile use of organosilicon compounds led researchers to look for improved and green synthetic methods for its synthesis. Towards this, very recently, a method involving visible-light-induced organophotocatalyzed ring-opening followed by remote Giese addition of tertiary cycloalkanols with *β*-silylmethylene malonates was developed under mild reaction conditions, and was utilised for the synthesis of several structurally and electronically challenging organosilicon derivatives.

3. Green Protocols

3.1. Organocatalysis

Organocatalysis is the field wherein small organic molecules efficiently and selectively catalyse organic transformations in metal-free environments. To this end, several organocatalysts were designed to achieve many difficult organic transformations which led to the easy, short and enantioselective syntheses of many bioactive molecules with varied stereochemistry.

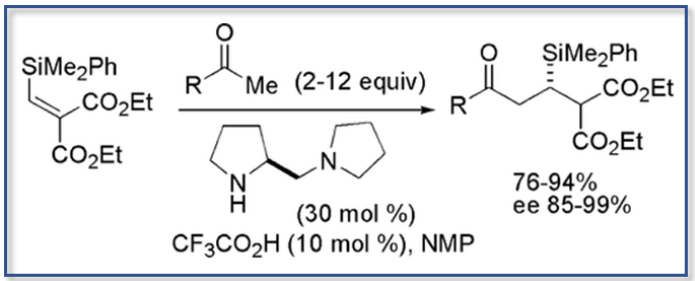

Fig. 3: Organocatalytic conjugate addition of alkyl methyl ketones to a *β*-silylmethylene malonate

The organocatalytic enantioselective direct conjugate addition of alkyl methyl ketones and enolizable aldehydes to dimethyl(phenyl)silylmethylene malonate was reported for the first time (**Fig. 3**). Synthetic manipulation of the resultant products led to the formal

and total syntheses of various *O*-and *N*-heterocyclic natural products [(+)-preussin, (*S*)-hexadecanolide, (–)-tetrahydrolipstatin, (+)-simplactone B, (+)-γ-caprolactone, (+)-methylenolactocine, (-)-quercus lactone, etc.]. Enantioenriched organosilanes bearing a nitro group were also synthesized, which gave access to the nootropic drug (*R*)-oxiracetam, sila-analogue of PAR-2 agonist AC-264613, (*R*)-N-benzyl-4-hydroxy-pyrrolidin-2-one etc.

Incorporation of a silyl group into known drugs /bioactive molecules is known to improve their biological properties. Towards this, highly enantioselective asymmetric catalytic Michael addition of 4-unsubstituted pyrazolin-5-ones to β-silylmethylene malonates was disclosed on applying a chiral H-bonding organocatalyst to incorporate the target organosilanes appendage with a pyrazole moiety.

An alternative reaction concept for the cycloaddition reactions of enone and nitrodienes was explored *via* an endo [4 + 2] "on water''cycloaddition reaction of enones and nitrodienes. In a similar line, a novel organocatalytic asymmetric formal [3+2] cycloaddition of 3-isothiocyanato oxindoles and arylidene malonates was also disclosed using a cinchona derived tertiary amine-thiourea-based bifunctional organocatalyst. This allowed access to pharmaceutically important and highly functionalized 3,2'-pyrrolidinyl spirooxindole derivatives.

A biomimetic asymmetric organocatalyzed decarboxylative aldol reaction of β-ketoacids with α-ketophosphonates yielded biologically important γ-carbonyl tertiary α-hydroxyphosphonates with a hydroxyl and phosphonate bearing chiral quaternary centers. Further to construct a chiral pyrazolone derivative with all-carbon quaternary stereocenters, a one-pot synthesis of 4-monosubstituted pyrazolones was achieved with high yields and stereoselectivities via a primary amine organocatalyzed conjugate addition of 4-monosubstituted pyrazolones to enones.

Apart from that, the increasing importance of Deuterium-labeled biologically active compounds because of their better metabolic stability and bioavailability, led the researchers to develop methods for D-labelling of organic molecules at specific positions. A highly regioselective and enantioselective direct Michael addition of methyl-d3 alkyl ketones to dimethyl(phenyl)silylmethylene malonate, catalyzed by (*S*)-*N*-(2-pyrrolidinylmethyl) pyrrolidine/trifluoroacetic acid/ D_2O combination was achieved with high yield and isotopic purity, and was utilised to synthesize dideuterated silylated tetrahydropyran-2-one, which is an advanced intermediate for *gem*-dideutero (-)-tetrahydrolipstatin and (+)-δ-hexadecanolide syntheses.

3.2. Biocatalysis

A systematic research on biocatalysis was initiated in India, in the early 90's that was furthered to make remarkable contributions in organic syntheses. Creation of new and small chiral intermediates with multiple stereogenic centers and high functional density using inexpensive, operationally simple, scalable and novel enantioselective strategies has been one of the happy hunting grounds since then. These chirons are instrumental in the syntheses of a platter of bioactive compounds *viz*. macrolides, polyhydroxy compounds, plant-growth regulators, pheromones, marine sponge-metabolites and many

more natural products often displaying impressive anti-cancer, antiviral, antifungal, bacteriostatic and vaccine adjuvant activities.

Using commercially available isolated enzymes (lipases)

A lipase-catalysed protocol for synthesis of medium to large ring macrolides even containing chemically fragile 1,4-dienoic compounds was devised. This was extended to control stereogenicity of multiple stereogenic centers by a single macrolactonization step. The researchers also introduced the concept of inter-facial lipase activation by carrying out reactions with immobilized substrates rather than in solution phase that also helped in acetylating hydrophilic molecules like sugars and glycerols. Further, it was demonstrated that the enantioselectivity of the lipase catalysed acylation can be tailored by changing the nucleophile. A few examples are discussed below:

Our tryst with enzymatic protocols dates back to 1993 with lipase catalysed acetylation of some pentose and hexose sugars in organic solvents. The primary motivation of the work stemmed from the utilities of the products for the manufacture of low calorific sweeteners, biosurfactants etc. The existing enzymatic methodologies of sugars acylation in polar solvents suffered from poor product solubility and enzyme deactivation. These limitations were innovatively offset by immobilising the carbohydrates on an inert support when the regioselective acetylation could be accomplished with porcine pancreatic lipase (PPL) in an environmentally safe, hydrophobic media. A highly regioselective esterification strategy for the aliphatic ω, α-dicarboxylic acids in n-butanol, and a chemoselective esterification of a saturated acid moiety in presence of a conjugated acid function were accomplished. Around the same time, the enzymatic resolution of alkyn-3-ols *viz.* racemic 1-octyn-3-ol and 1-nonyn-3-ol in non-aqueous media were established, since the acetylenic unit in such compounds can serve as an intermediate for conversion to alkaloids, prostaglandins, pyrethroids, pheromones, vitamins, steroids and antibiotics. Likewise, a lipase catalysed transesterification strategy for the resolution of alkan-2-ols was formulated after extensive screening of enzymes, solvents and optimization of reaction conditions.

Several of the above enzymatic strategies paved the way for efficient enantiomeric synthesis of a host of bioactive compounds of diverse skeletons (**Fig. 4**). Some examples include ferrulactone II (insect pheromone) and (2*E*)-9-hydroxydecenoic acid (mandibular gland secretion of queen bees, *Apis mellifera L.*)**,** (*R*)-patulolide (anti-microbial macrolide), (*R*)- phoracantholide I and few enantiomers of the antifungal and antibacterial principles of *Sporothrix* species, wherein PPL (porcine pancreatic lipase)-catalysed enantioselective reactions provided the key steps. Similar lipase catalysed protocols were applied for the synthesis of an array of marine sponge components *viz.* (4*E*,7*S*)-7-methoxytetradec-4-enoic acid (antimicrobial), 1-tert-butyldimethylsilylpenta-1,4-diyn-3-ol, (15*E*,*R*,*R*)-duryne, (*S*)-eicos-(4*E*)-en-1-yn-3-ol (cytotoxic), (2*R*,5*Z*,9*Z*)-2-methoxyhexacosa-5,9-dienoic acid and the hydroxy acid segment of schulzeines B and C.

In a remarkable effort, a novel lipase-catalyzed protocol was formulated for the simultaneous enantiocontrol of three stereogenic centers in a flexible acyclic system to

achieve an enantioselective synthesis of tetrahydrolipstatin (anti-obesity). The first asymmetric synthesis of (6*S*,13*R*)-6,13-dihydroxytetradeca-(2*E*,4*E*,8*E*)-trienoate (component of *Mycosphaerella rubella*) and diastereomers of pinellic acids were also developed using an efficient lipase-catalyzed acylation strategy. Later, syntheses and biological evaluation of all possible stereoisomers of a 16-membered macrolide antibiotic (-)-A26771B was achieved *via* lipase (Novozym 435®) catalysed acylation routes. Herein, the lipase was used both for kinetic resolution of a methylcarbinol $CH_3CH(OH)$ moiety and its chemoselective acrylation (using a non-traditional acyl donor, ethyl acrylate) over a secondary allylic alcohol unit. Similarly, a lipase catalysed acylation was used to accomplish the asymmetric synthesis of the C22-trihydroxy fatty acid component of the 42-membered antiviral macrodiolide, macroviracin A

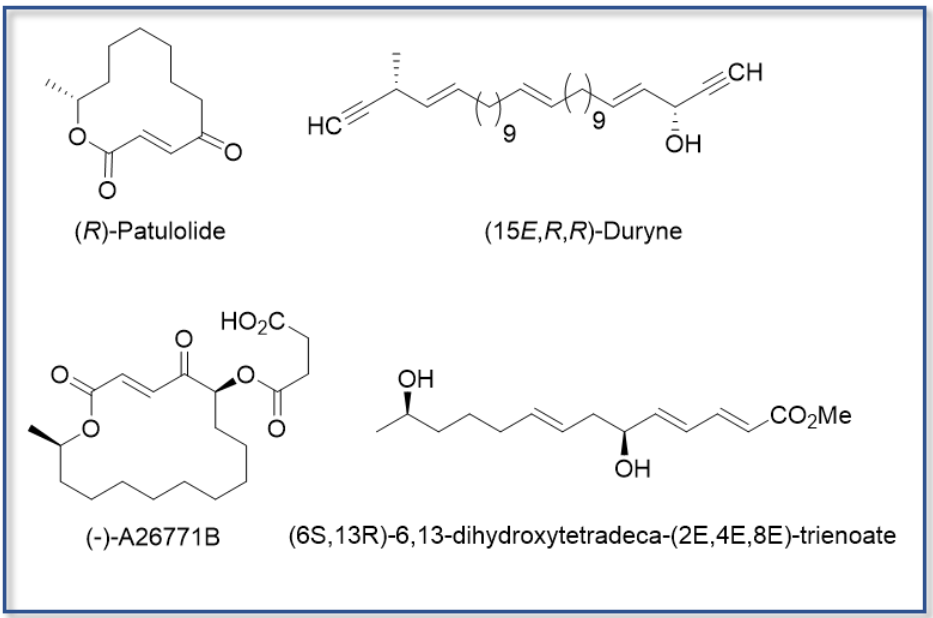

Fig. 4: Some representative bioactive molecules synthesized using biocatalytic route

With the ongoing quest for divergent synthesis of potential anti-cancer and immunomodulatory agents, researchers identified a common structural motif hept-6-ene-2,5-diol found in several bioactive compounds *viz*. decarestrictine (cholesterol biosynthesis inhibitor), pyrenophorol (antimicrobial), acremodiol (antimicrobial), clonostachydiol (cytotoxic), stagonolide (phytotoxin) and nonenolide (anti-malarial), which were synthesized in all its enantiomeric forms using two Novozyme-435® catalysed acylation steps (**Fig. 5**). Similarly, a ceramide trafficking inhibitor HPA-12 was synthesized using an efficient and highly enantioselective lipase-catalyzed acylation in a hydrophobic ionic liquid, [bmim][PF_6]. In continuation of the endeavours to synthesize bioactive compounds, few bioactive diarylheptanoids (from *Alpinia* officinarum) were

synthesized using *PS Amano Lipase* catalysed kinetic resolution, and their antiproliferative properties were tested in-vitro, where one of the compounds showed impressive anticancer effect.

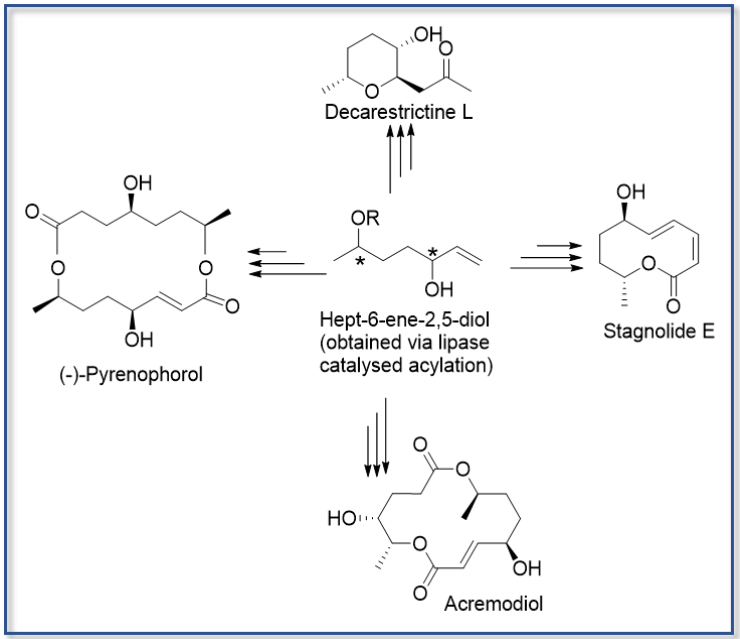

Fig. 5: Divergent synthesis of potential anti-cancer and immunomodulatory agents developed.

Using whole cell enzymatic reactions and potential uses of spent biomass

Unlike the commercially available lipases/proteases, use of whole cell systems offers an economical alternative biocatalytic protocols, especially with cofactor-requiring enzymes (oxido-reductases, oxynitrilase etc.). The microorganisms are available with a wide variety, show broad substrate specificities and possess built-in co-factor regenerating systems. The whole cell plants and microbial systems were extensively used for asymmetric reduction of ketones and hydrolysis of secondary carbinol esters by tuning the enantioselectivity via subtle structural modifications of the substrates. The reaction rates and selectivities were correlated with steric and electronic parameters of the substitutions of the aryl/alkyl and heteroaryl/alkyl substrates. *Rhizopus arrhizus* mediated microbial reduction of a series of arylalkanones, with varying spacer length between the aryl and carbonyl groups, were investigated for the first time, which demonstrated an 'enantio-switch' in the course of microbial reduction. Moreover, the spent (dead and dried) *Rhizopus arrhizus* biomass, obtained from microbial reduction of aryl alkanones, was further evaluated as a potential biosorption material for treatment of waste water containing toxic azo dyes *viz*., amaranth, fast red A, congo red, tartrazine, metanil yellow

and sunset yellow FCF (**Fig. 6**). On a similar line, *Rhizopus arrhizus* biomass was also demonstrated for the removal of dye erythrosine B from aqueous solution (**Fig. 6**).

Fig. 6: Biosorption of Erythrosine B by *Rhizopus arrhizus* biomass.

Plausible applications of biosorption in nuclear waste management motivated us to carry out sorption studies of various radionuclides *viz*. ^{233}U, ^{239}Pu, ^{241}Am, ^{144}Ce, ^{147}Pm, $^{152/154}Eu$ and ^{95}Zr from aqueous nitrate medium using the dead *Rhizopus arrhizus* biomass. The biomass showed selective adsorption capacity for U/Pu and trivalent actinides depending on the pH of the solution. Later on, the said biomass was immobilized by crosslinking with 15% formaldehyde/0.1 M HCl solution, leading to better mechanical strength, rigidity and chemical stability. This showed a sorption capacity of 65 mg/g for Am and U ions, and hence could be utilized for the removal of radionuclides from radioactive waste effluents. As a follow-up study, a highly radiolytically stable biosorbent based on wild-type *R. arrhizus* biomass was employed for separation of Am^{3+} and Eu^{3+}.

3.3. Room Temperature Ionic Liquids

Room temperature ionic liquids (RTILs) are regarded as a greener alternative to traditional volatile organic solvents. BSG has pioneered the use of an inexpensive and hydrophilic RTIL, [bmim][Br] for activation of metals (Ga, In, Bi metals) without the need of any acid, additive or additional energy source (microwave irradiation, heating and ultrasonication) that facilitated Barbier-type allylation/crotylation reactions of aldehydes and even ketones. The activation of Ga was shown to follow a novel mechanism, involving a Ga-NHC intermediate via an unprecedented oxidative formation of [bmim] diradicals. The first report of the synthesis of a Ga-NHC complex with the imidazole-containing RTIL under a hydrous, aerobic and moderate condition has far reaching consequences in organic synthesis. With the aim of tuning the reaction diastereoselectivity of asymmetric crotylation, a *syn*-selective crotylation strategy of aldehydes in [bmim][Br] was established. This strategy was further utilized for the syntheses of C1–C9 segment of dictyostatin, the octadienoic ester fragment of the

desoxycryptophycins, and (+)-*cis*-aerangis lactone. Subsequently, the In metal-catalysed Barbier type allylation of aldehydes in [bmim][Br] was reported with detailed mechanistic studies, which was recognised as a VIP publication by European Chem. Soc. (*Eur. J. Org. Chem.* 2018, 1333-1341). Most importantly, the Barbier type carbonyl allylation could accomplished using catalytic (for In), sub-stoichiometric (for Ga) and stoichiometric (for Bi) quantities of the metal as well as reusing the RTIL several times – key attributes towards development of a green synthesis. With substantial knowledge and experience in handling RTILs, a Bronsted acidic RTIL, [bmim][HSO_4], was synthesized and used for the targeted α-regioselective Barbier-type carbonyl crotylation, yielding α-homoallylic alcohols. The department's contribution in activation of metals by RTIL has been highly appreciated by peers.

4. Organics for Agriculture

Since the beginning, the department has been actively involved in research and development of molecules which play important roles to improve agricultural productivity *viz*. pheromones or plant growth regulators etc. Plant agents like garlic oil was found to destroy aphids, cabbage-white butterfly caterpillars, and *Colorado beetle* larvae, and hence was envisaged as an effective larvicide and pesticide. In one of the earliest ventures (*Science* 1971, *174*, 1343-1344), researchers were able to isolate the hitherto unknown components *viz*. diallyl sulphide, diallyl disulphide, diallyl trisulphide and diallyl tetrasulphide, present in garlic oil. This was accomplished via steam distillation using garlic cloves. These components were tested for larvicidal activity, and it was found that diallyl disulphide and triallyl disulphide alone or in mixture even at a concentration of 5 ppm were highly effective. Later, a plant was set up for the large-scale syntheses of the garlic oil components for field applications.

India is the second largest producer of silk globally and sericulture is an important industry in our country. With the aim to increase silk productivity and decrease the production costs, plant-based moulting hormone (MH) preparations were developed that promote silkworm maturation. The low-cost preparation enhances silkworm larvae maturity, generating better quality of reelable silk in a shorter time-span. Notably, the preparation, which is an import substitute for the silk industry was commercialized (MoU between BARC and Indian Agriculture & Sericulture Institute, Mysore (under IACR)).

To meet the never-ending demand for food and tackle the paucity of cultivable land due to global population burst, plant growth regulators (PGR) play a significant role. In this context, the first synthesis of the racemic and enantiomers of 3-methylnonacosanol (PGR from Indian medicinal shrub *Lowsoni ainermis*, traditionally used for treatment of jaundice, leprosy, skin diseases and enlargement of liver and spleen) and its PGR bioassay *vis-à-vis* the stereochemistry was accomplished in the late nineties.

Pheromones

In view of their extreme potency, species-specificity, non-toxicity, biodegradability and requirement of very small concentrations, insect pheromones offer an eco- and

environment friendly pest management strategy sparing the beneficial insects. However, implementation of a successful insect pheromone technology demands a viable synthesis, development of a slow releasing formulations followed by field trials.

Usually pheromones are medium to long chain aliphatic alcohols or their derivatives, having one or several double bonds where the chain length, functionalites as well as the numbers, positions and geometries of the double bonds confer them the species-specificity. Using the core competence in acetylenic chemistry and Wittig reaction, coupled with the expertise on multistep organic synthesis, syntheses of various insect pheromones were accomplished.

For example, syntheses of 6,8-dioxabicyclo[3.2.1]octanes, *viz*. (±)-frontalin and (±)-brevicomins, the aggregation pheromone components of bark beetles, were achieved from pent-4-en-1-ol and pent-4-yn-1-ol. Likewise, synthesis of gossyplure, the pink bollworm pheromone, was achieved using a stereocontrolled Wittig reaction.

The production of sweet potato is often affected by the ubiquitous sweet potato weevils (SPW), rendering the roots unfit for consumption. Pheromones offer an eco-friendly way to manage this pest. To accomplish that, a practical synthesis of the sweet potato weevil pheromone was developed using a *cis*-selective Wittig reaction. Further, an integrated pest management (IPM) strategy was developed using a combination of weevil-free planting material, re-ridging, mass trapping of males through sex pheromone traps, preservation of biocontrol agents, disposal of harvest residues and early harvesting (**Fig. 7**). A number of experiments and observations were carried out over a period of 10 years, and was successfully used for pest management in farmers' fields across India.

Fig. 7: Field use of in-house synthesized sweet potato weevil (SPW) pheromone, A. SPW pheromone dispenser and trap, and B. Catch of SPW in a pheromone-baited trap

India is the second-largest producer of cotton worldwide. However, the production gets hampered due to the presence of several cotton pests, which are difficult to control using conventional pest management methods. BSG steered the idea of using cotton pest pheromones in pest management by accomplishing a practical synthesis of the cotton pest pheromones, particularly the pheromones of one of the major pests *viz*. American

ballworm. In field trials using the mating disruption technique, the pheromone could effectively control the cotton pest. Variations in dose led to the use of this pheromone in both mating disruption and mass trapping techniques, making it one of the most useful pheromones for cotton pest management. These are regularly used in Northern India for cotton pest management.

Until the early 80s, it was believed that biological recognition of pheromones was dictated by alkyl chain length, number, position and geometry of the double bonds present in the molecule, and not by the stereochemistry present in the molecule. Later on, it was observed that the stereochemistry (orientation in three dimensional space) of a chiral pheromone also plays a very important role in its activities. Over the years, a large number of pheromones were isolated from various insects, and the chirality present in them showed profound impact on their physiological action. Hence, synthesis of chiral pheromones *viz*. 4-dodecanolide, trogodermal (dermestid beetle), (*R*)-japonilure (sex pheromones of Japanese beetle) were accomplished using chiral templates like (*R*)-2,3-isopropanedioxyglyceraldehyde, (*R*)-pulegone etc. (*R*)-2,3-cyclohexylideneglyceraldehyde was used as a divergent chiral template for the syntheses of (6*S*)-acetoxy-(5*R*)-hexadecanolide, an oviposition deterring pheromone of the mosquito *Culex pipensfatigans*, which is a possible vector of filarial diseases.

Chirality due to methyl branching is abundant amongst several insect pheromones, many of which are of economic significance. To synthesize such chiral pheromones, a convenient chemoenzymatic protocol was optimised, starting from the castor oil-derived, 10-undecenoic acid, and was utilised for the synthesis of the gypsy moth sex pheromone. Using the same precursor, syntheses of the pheromones of the destructive pests of cash crops and fruits *viz*. (11*Z*)-hexadecenal, (3*Z*,13*Z*)-octadecadienyl acetate and its 3*E*-isomer and (2*E*,13*Z*)-octadecadienyl acetate were realised in good yields. In addition, chemoenzymatic synthesis of a pheromone antipode of stored grain pests (khapra beetle) was accomplished via a baker's yeast mediated asymmetric carbonyl reduction. Similarly, enantioselective chemical and chemoenzymatic approaches were also employed to synthesize pheromones of cucujid grain beetles, rice moth, southern corn rootworm, spice pest *Dichocrocis punctiferalis*, square-necked grain beetle, bark beetle, *Crematogaster* ants, *Drosophila mulleri* flies, cotton pests, peach tree borer and cherry tree borer etc.

Asymmetric synthesis using biocatalysts was also exploited successfully in the synthesis of insect pheromones. To this end, enzymatic acylation of 2-alkanols was extensively studied by optimizing the effects of solvent hydrophobicity, degree of conversion, alkyl chain length and presence of unsaturation on the course of the reaction. Using this optimized protocol, syntheses of (6*R*)-6-methyl-3-octanone, the alarm pheromone of *Crematogaster* and *Myrmecine* ants, were accomplished in a more practical and enantioselective way.

5. Organics for Health

5.1. Radiopharmaceutical Ligands

A radiopharmaceutical (RPh) delivers a radionuclide to a diseased site using a targeted vehicle, resulting in precise diagnostics or therapy. Unlike conventional drugs, they do not show pharmacological effects as such, and are used in trace amounts. Diagnostic RPhs use γ or positron emitters for imaging *via* SPECT or PET, ^{99m}Tc being the most commonly used radionuclide. PET-CT is more sensitive than SPECT-CT, using positron emitters like ^{18}F and ^{68}Ga. Therapeutic RPhs use β- or α-emitters to treat diseases, especially metastatic cancers. Theranostics combines diagnostics and therapy, as exemplified by [^{68}Ga/^{177}Lu] DOTATATE for tumors and [$^{123/131}$I]mIBG for neuroblastoma. The researchers have pioneered the in-house syntheses of several targeted vehicles, called radiopharmaceutical ligands, and in collaboration with Radiopharmaceuticals Division (RPhD), BARC; Board of Radiation and Isotope Technology (BRIT) and Radiation Medicine Centre (RMC) helped to develop affordable radiopharmaceuticals, which, after proper validation and DAE-Radiopharmaceutical Committee (DAE-RPC) approval, were provided to hospitals pan-India through BRIT. Synthesis of several radiopharmaceutical ligands such as the import substitute cardiac diagnostic precursor, tetrakis(2-methoxyisobutylisonitrile)Copper(I) tetrafluroborate ([Cu(MIBI)$_4$]BF$_4$) and prostate-targeting ligands (PSMA-617 and PSMA-11) have been accomplished (**Fig. 8**).

[Cu(MIBI)$_4$]BF$_4$ is a precursor of [^{99m}Tc(MIBI)$_6$]BF$_4$, a myocardial perfusion imaging agent for evaluating and risk stratifying patients with known or suspected coronary artery disease. As a cationic complex, it passively diffuses through capillary and cell membranes and is captured by myocyte cells in the heart. Myocardial perfusion imaging, primarily used to diagnose ischemic heart diseases, relies on [^{99m}Tc(MIBI)$_6$]BF$_4$ in over 75% of cases. The radiopharmaceutical freeze-dried kit containing [Cu(MIBI)$_4$]BF$_4$, is radiolabeled with ^{99m}Tc using a ^{99}Mo/^{99m}Tc generator for clinical use. A multistep organic synthesis of the key component, [Cu(MIBI)$_4$]BF$_4$ and its purification was accomplished, and delivered to BRIT for preparation of kits. In view of its increasing demand in hospitals performing MIBI scans, the synthesis of [Cu(MIBI)$_4$]BF$_4$ was modified and scaled up to 10 g per batch. This is used to make approximately 7000 kits per year (BRIT code: TCK-50), and benefits over 25000 patients in more than 65 hospitals pan India.

Diagnosis and treatment of prostate cancer, which accounts for nearly 10% of all male tumors, is one of the most challenging jobs in radiomedicines. Clinically, ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 are used for diagnosis and therapy for prostate cancer, respectively. However, due to their high cost and irregular availability in India, a cost-effective synthetic route is warranted. The challenging tasks of synthesizing PSMA-617 and PSMA-11 where accomplished using commercially available amino acid derivatives. In collaboration with BRIT, the ligands were radiolabelled and evaluated for their efficacy. Finally, both the in-house developed radiopharmaceuticals were approved by RPC for clinical use. The in-house made ^{177}Lu-PSMA-617 KIT (BRIT code: LUM-5) has been in clinical use, and caters >4000 patients in different Indian hospitals. This is one of the

most important advancement for treating metastatic castration-resistant prostate cancer (mCRPC) using radiopharmaceuticals.

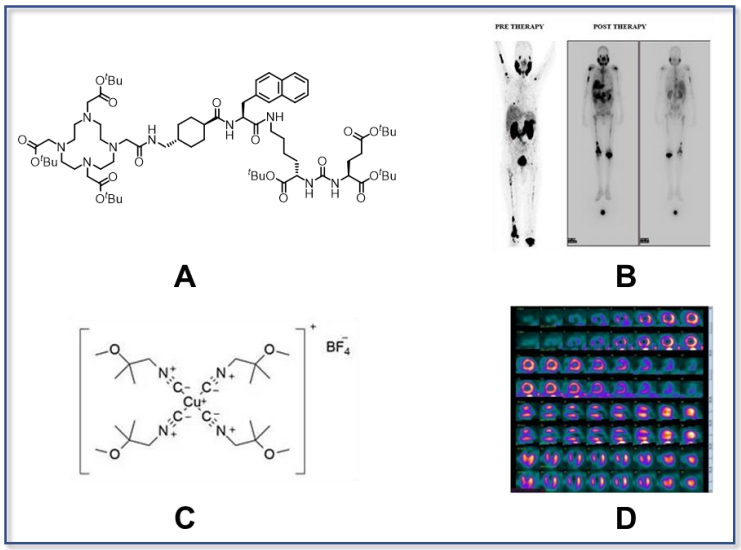

Fig. 8: Chemical structure and clinical use of in-house synthesized radiopharmaceutical ligands. A. PSMA-617; B. Prostate cancer patient images before and after treatment with in-house developed ^{177}Lu-PSMA-617; C. [Cu(MIBI)$_4$]BF$_4$ and, D. Myocardial scan images using in-house developed [^{99m}Tc(MIBI)$_6$]BF$_4$

With an endeavour to further develop in-house synthesis of ligands for other diagnostic and therapeutic radiopharmaceuticals, a protocol for an efficient and economically viable synthesis of three [^{18}F]FLT precursors was indigenously developed using a chiral template (*R*)-2,3-cyclohexylideneglyceraldehyde-directed asymmetric reaction followed by thymidine attachment. [^{18}F]FLT is widely used as a PET radiotracer for disease diagnosis. In addition, mIBG hemisulfate, used as a ligand for [$^{123/131}$I]mIBG preparation, used for imaging and therapy of neuroblastomas, was synthesized using an in-house developed protocol. Similarly, hynic-PSMA, a ligand used in the preparation of [^{99m}Tc]hynic-PSMA, used for SPECT diagnosis of prostate cancer has also been synthesized.

5.2. Targeted therapeutics

Of late, development of targeted therapeutics has become one of the cornerstones in medical sciences, mainly with the aim to deliver chemotherapeutics exclusively at the disease site, so as to reduce the drug dose and generate no/less side effects. Towards this, promising contributions have been made to formulate new compositions as anti-cancer chemotherapeutics and targeted therapeutics for iron overload diseases. Iron-overload has been proven to be detrimental for patients having β-Thalassemia, hereditary hemochromatosis etc. The group's scientists have been instrumental in synthesis and evaluation of targeted iron chelators designed for iron overload therapy. Imidazole based

vectors with varied hydrophobicities and zwitterionic carbon nanodots were synthesized and were coupled separately with an FDA approved chelator, Deferoxamine®, to achieve targeted iron chelators with improved characteristics. Regarding targeted chemo-therapeutics, *N*-succinyl chitosan-based hydrogel beads, stabilized with glycopolymeric network (NSC/Glc-gel) was developed and evaluated for controlled release of the anticancer drug doxorubicin, specifically in a tumor microenvironment (**Fig. 9A**). Recently, a GSH-responsive, Doxorubicin loaded, self-sufficient, metal-organic framework (MOF) based anti-cancer agent chemotherapeutic has been synthesized as a combined chemo-chemodynamic agent, and evaluated *in vivo* in a rodent model (**Fig. 9B**). NET-expressive-neuroblastoma targeting anti-cancer chemotherapeutic has been synthesized and screened for their targeting potential.

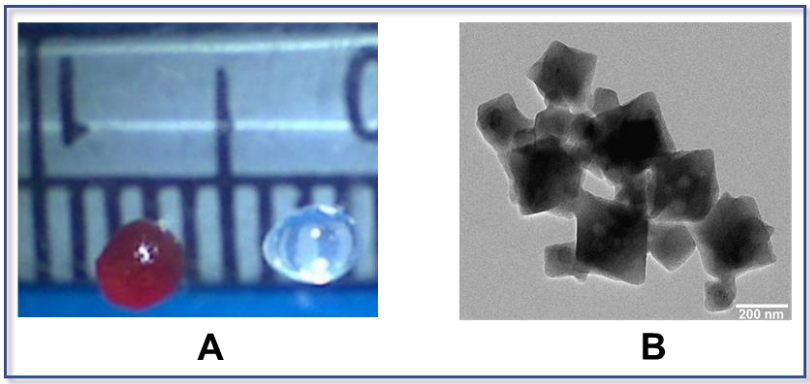

Fig. 9: In-house synthesized drug delivery agents. A. Doxorubicin® loaded NSC/Glc-gel beads, and, B. TEM images of doxorubicin loaded Cu-MOF

5.3. Advanced Drug Intermediates

Although, India is one of the largest manufacturers of bulk drugs, and contributes to approximately 3.5% of the global manufacturing of bulk drugs, it is heavily dependent on other countries for the import of advanced intermediates and key starting materials. One such intermediates, *o*-tolylbenzonitrile (OTBN), an advanced drug intermediate for the -sartan group of drugs, used for treatment of hypertension and heart failures, is extensively imported in a very high volume (>200 MT/year costing >250 million INR/year). In an effort to curb import dependency, and promote local bulk manufacturing of OTBN, a unique method was developed involving the preparation of an organometallic Grignard reagent followed by utilizing a cross-coupling methodology to selectively heterocouple two chemically differentiated aromatic partners using a novel *in-situ* generated catalyst. Our accomplishments for OTBN synthesis include (i) developing an economical, industry-friendly synthetic route using Suzuki-Miyura coupling, (ii) recovery of costly solvent, (iii) avoidance of heavy and toxic palladium metal catalyst, (iv) low amount of waste generation and (v) minimum environmental pollution. Till date, this popular technology named "*A process for synthesis of o-tolylbenzonitrile (OTBN), an*

advanced intermediate for anti-hypertensive -sartan group of drugs, [CH38BOD]" has been transferred to multiple private entrepreneurs for bulk manufacturing.

6. Way Forward

In modern changing era, the national requirements in areas of organic chemistry will gradually grow both in nuclear science programmes and material science (for human benefits). The way ahead will be primarily motivated by excellence in global research in bio-organic chemistry and will be dedicated to modern science and departmental relevance, especially in the field of targeted therapeutics and radiopharmaceutical ligands/carriers. This warrants extensive basic research and development with culmination of multi-disciplines to identify and deliver novel molecules of relevance. By tailoring the molecular structures of the target molecules, one can achieve better targeting of anti-cancer chemotherapeutics with minimal side effects, particularly for those cancers with high prevalence and high mortality rates. Along with that, newer radiopharmaceutical ligands will increase the spectrum of treatments currently offered via nuclear medicine, and will pave the way for improving diagnostic and therapeutic potentials. Solution to challenges like population growth and complexity of modern diseases (including life-style related) seem daunting, and synthetic organic chemistry is bound to play a pivotal role in achieving these solutions. The gathered experience in organic chemistry is indeed and will always be an inexhaustible platform for designing new molecular structures and assemblies, aimed at satisfying the ever-growing societal needs.

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