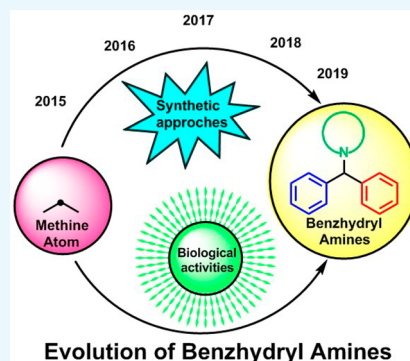


# Benzhydryl Amines: Synthesis and Their Biological Perspective

Deblina Roy and Gautam Panda\*

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, Uttar Pradesh, India

**ABSTRACT:** The current review describes the recent progress in the chemistry and biology of the benzhydryl amines where the central carbon atom is directly attached to the nitrogen atom of one ring and which have published in the last five years (2015–2019). Both metal and metal-free racemic and asymmetric synthetic approaches along with their activities as anti-leishmanial, antiviral, antibacterial, and anti-aromatase and other miscellaneous properties are discussed.



## INTRODUCTION

Benzhydryl amines, broadly belonging to Triarylmethanes (TRAMs) or Trisubstituted Methanes (TRSMs), are privileged architectural patterns where the central  $sp^3$ -hybridized methine atom is attached to three similar or different types of groups. Depending on the type of substitution attached, these benzhydryl amines could be symmetrically or asymmetrically substituted. Due to their distinctive chemical as well as pharmaceutical properties, they have gained conspicuous attention in organic chemistry (Figure-1).

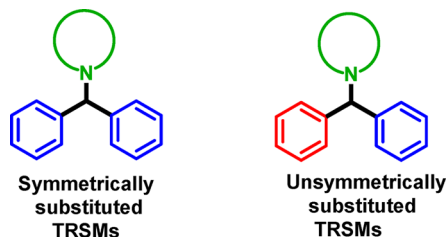


Figure 1. Symmetrically and unsymmetrically substituted TRSMs.

The triarylmethanes or trisubstituted methanes play an important role in dyes, pharmaceutical chemistry, materials science, as well as in organic synthesis. They have shown activity against intestinal helminthes, filariae, trichomonads, as well as trypanosomes. Their hydroxy analogs exhibit antioxidant and antitumor activities and also inhibit many protein kinases. Some of the important triaryl methanes like malachite green, crystal violet, sunset orange, pararosanilin, and victoria blue are used in dye industry. The ortho-substituted triarylmethanes showed chiral helical conformation and find uses in theoretical and conformational studies. The electron and  $\pi$ -electron donor properties come from the sulfur atom and heteroaromatic rings of trithienylmethanes, respectively. Moreover, the trityl group

originating from triarylmethanes has versatile uses as a protecting group in carbohydrate, peptide, and nucleoside chemistry due to the stability of the carbocations. However, triarylmethanols are used as chiral catalysts in diverse organic transformations like Mukaiyama aldol reactions and allylations of the aldehydes with allyl tributyl stannane.

Diarylmethylamine units are widely found in various biologically active compounds like anticancer, anti-tubercular, antimalarial, antiviral, potent and selective nonsteroidal aromatase inhibitors (NSAIs), and anti-HCV (Hepatitis C Virus) agents. Though such compounds have wide areas of applicability, to the best of our knowledge the synthesis and biomedical perspectives of benzhydryl amines have not been reviewed. We will discuss the synthesis and the biomedical application of benzhydryl amines in the pharmaceutical area from 2015–2019, leaving behind the reports that have already been published in the previous reviews.

## RESULTS AND DISCUSSION

**1. Synthesis of Benzhydryl Amines.** Due to the flexibility of TRSMs in diverse areas of research, synthetic organic chemists have become interested in synthesizing benzhydryl amines, a class of TRSMs utilizing diverse types of routes. In this review, we have categorized and discussed several approaches for the synthesis of diaryl methyl amine scaffold which will allow the readers to gain an impression of the different synthetic routes to access them, which have been categorized into the following classes:

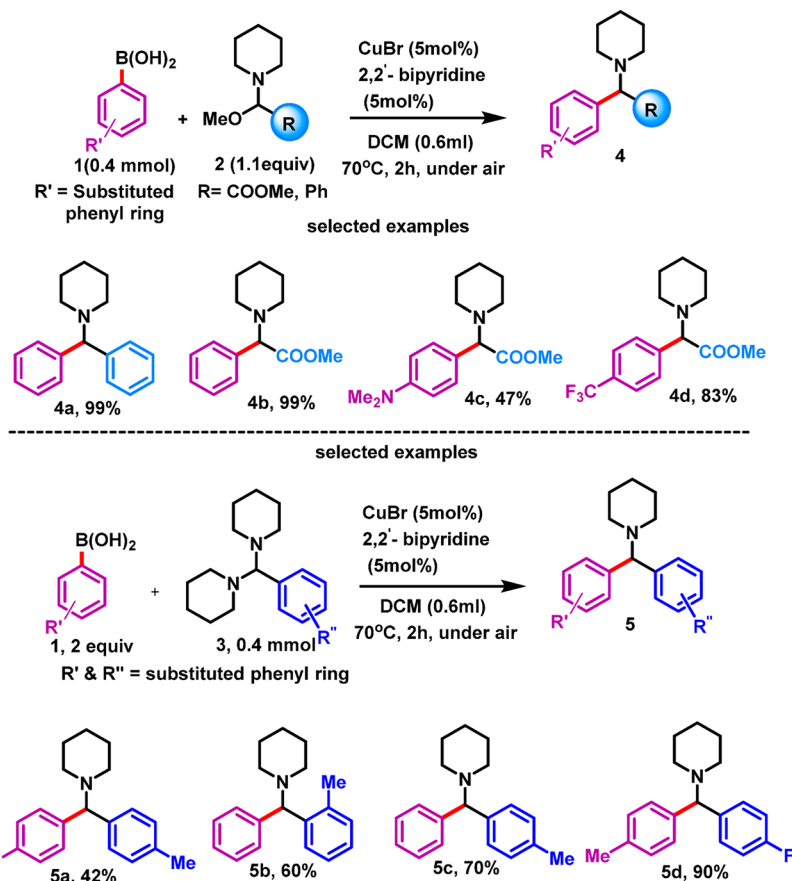
- 1.1. Metal catalyzed reactions for the synthesis of benzhydryl amines
- 1.2. Multicomponent reactions (MCR)

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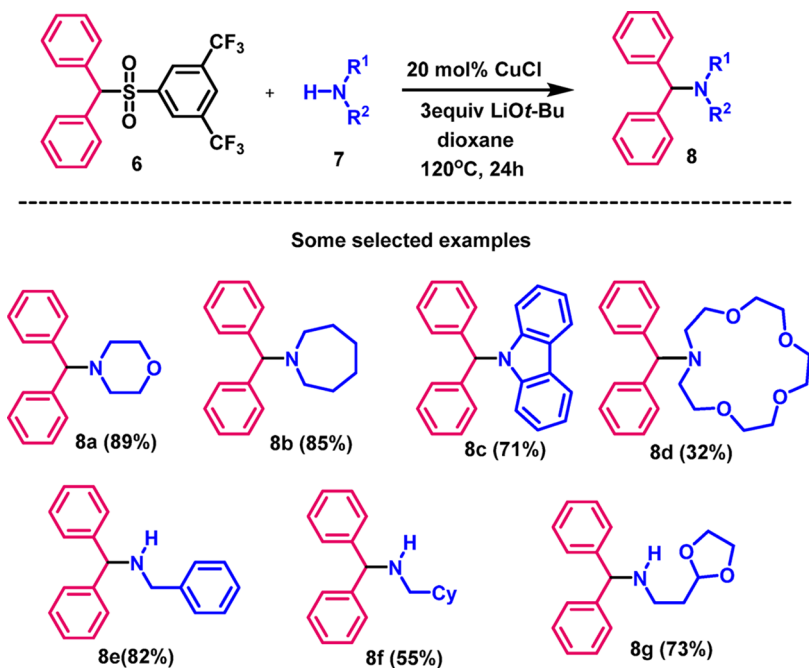
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Scheme 1. Copper(I)-Catalyzed Coupling Reaction of Aryl Boronic Acids with N,O-Acetals and N,N-Aminals



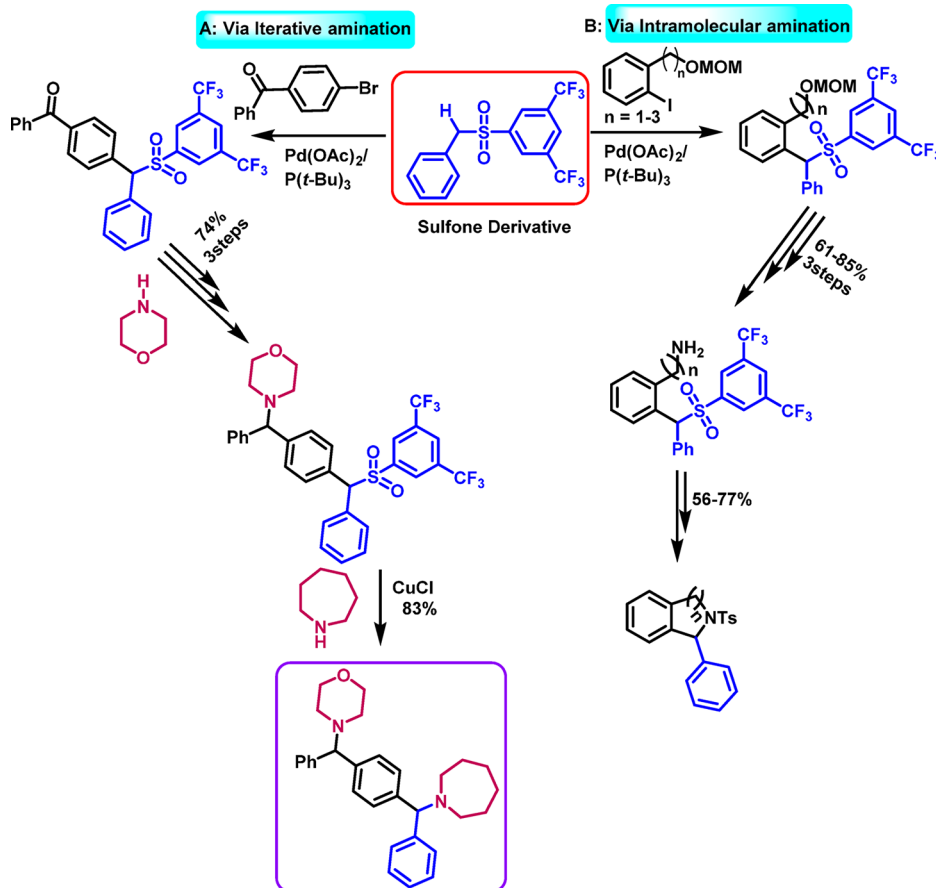
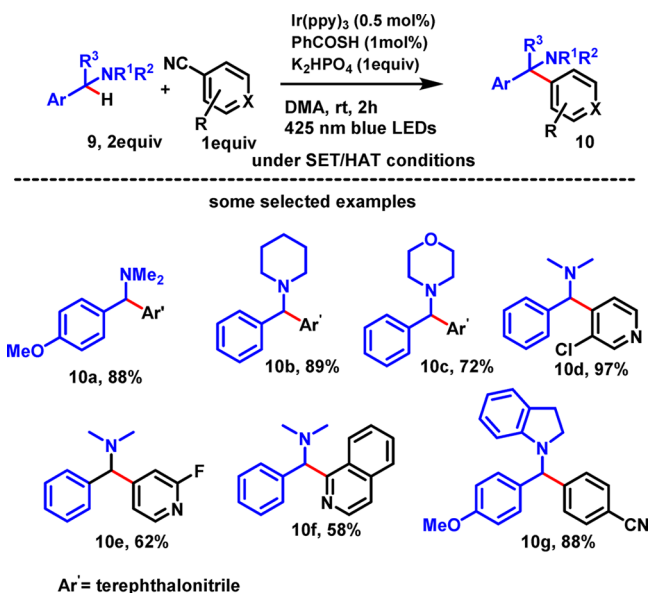
Scheme 2. Cu-Catalyzed Desulfonylative Amination for the Synthesis of Diaryl Methyl Amines



- 1.2.a. Noble metal nanoparticles catalyzed MCRs
- 1.2.b. Metal free MCRs
- 1.3. Enantioselective synthesis of benzhydryl amines
- 1.3.a. Organocatalyzed enantioselective synthesis
- 1.3.b. Metal catalyzed enantioselective synthesis

- 1.4. Miscellaneous methods
- 1.1. Metal Catalyzed Reactions for the Synthesis of Benzhydryl Amines. Sakai et al. in 2015 reported a coupling reaction of aryl boronic acids (1) with N,O-acetals (2) and N,N-aminals (3) with copper(I) as catalyst leading to the formation

Scheme 3. Iterative and Intramolecular Aminations

Scheme 4. Ir(ppy)<sub>3</sub> and PhCOSH (HAT Catalyst) Catalyzed Regio- and Chemoselective C–H Arylation

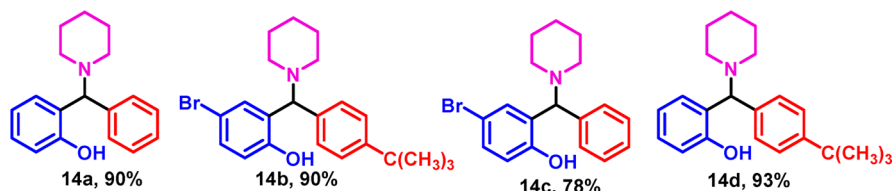
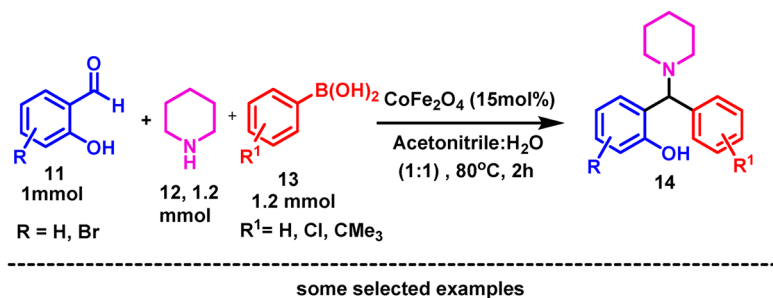
of  $\alpha$ -aryl glycines (4) and diarylmethylamines (10) (Scheme 1).<sup>2</sup> The authors observed that this catalyst successfully activated both the C(sp<sup>3</sup>)-O bond of N,O-acetals as well as the C(sp<sup>3</sup>)-N bond of N,N-aminals, but in the absence of any coordinating substituent, the C(sp<sup>3</sup>)-O bond of the N,O-acetal particularly gets activated.

Nambo et al. in 2018 reported a novel route for desulfonylative transformation for benzhydryl amines (8) from the reaction between easily available sulfones (6) and amines (7) using copper chloride as a catalyst (Scheme 2).<sup>3</sup>

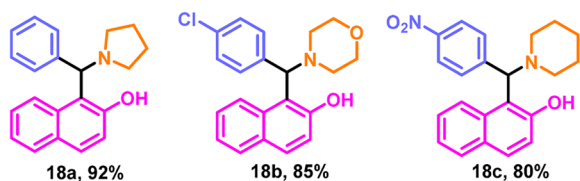
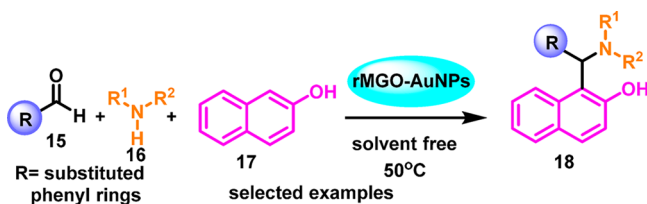
They found that the desulfonylative amination catalyzed by Cu furnishes structurally varying benzhydryl amines in reasonable yields as well as provides iterative and intramolecular aminations (Scheme 3). From several control experiments, authors observed that the reaction proceeds through generation of a Cu-carbene complex derived from stable sulfone derivatives.

In 2018, Ide et al. published a novel approach for the regio- and chemoselective Csp<sup>3</sup>-H arylation of benzylamines (9) by employing single electron transfer (SET)/hydrogen atom transfer (HAT) synergistic catalysis using Ir(ppy)<sub>3</sub> as a photoredox catalyst (Scheme 4).<sup>4</sup> Interestingly, it was found that the reaction occurred at the N-methyl and/or cyclic N-methylene positions through an aminium radical cation intermediate under SET catalysis only, whereas in contrast, synergistic SET and HAT catalysis reversed the regioselectivity. The reaction was finished within a very short time with 0.5 mol % of the Ir complex and 1 mol % of PhC(O)SH as a HAT catalyst, and diverse 1,1-diarylmethylamines (10) were synthesized in reasonable to excellent yields (56–98%). From a mechanistic point of view, the role of PhC(O)SH as a HAT catalyst is delineated like this: Favorable oxidation of PhC(O)-SK has effectively stopped SET oxidation of the tertiary amines and the C–H bonds was selectively abstracted by the resulting sulfur radical to give N-benzyl radicals.

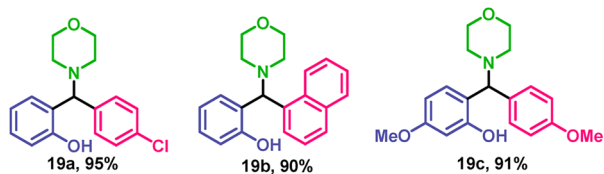
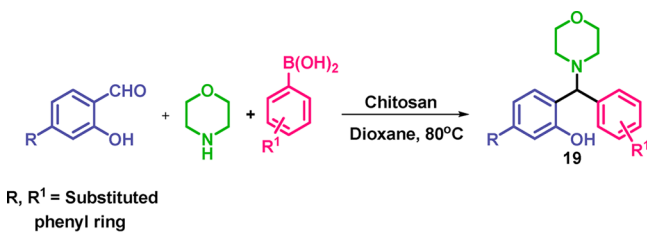
**1.2. Multicomponent Reactions (MCR) for the Synthesis of Benzhydryl Amines. 1.2.a. Noble Metal Nanoparticle**

Scheme 5. (CoFe<sub>2</sub>O<sub>4</sub>, NPS) Catalyzed Petasis–Borono–Mannich (PBM) Reaction

Scheme 6. rMGO-Au NPs Catalyzed Betti Reaction

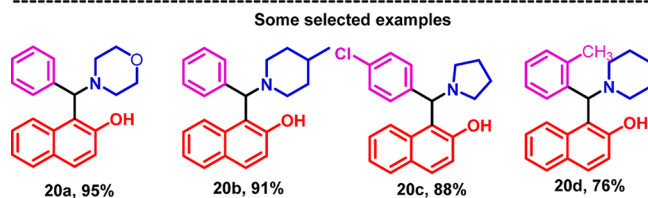
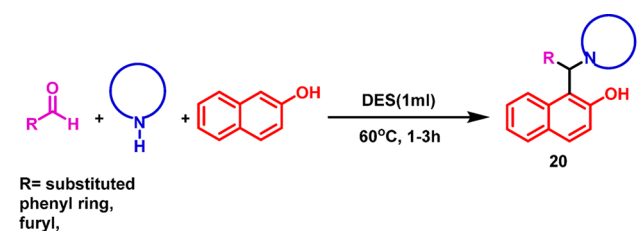


Scheme 7. Chitosan-Catalyzed Three-Component PBM Reactions



**Catalyzed MCRs.** Noble metal nanoparticles have huge potential for application as catalysts. In 2015, Kulkarni et al. indicated cobalt ferrite nanoparticles catalyzed a three-component Petasis–Borono–Mannich reaction between aryl boronic acids (11), salicylaldehydes (12), and secondary amines (13) to furnish alkylaminophenols (14) within a very short time period (Scheme 5).<sup>5</sup> Surprisingly, the catalyst (CoFe<sub>2</sub>O<sub>4</sub>, NPS)

Scheme 8. DES Catalyzed MCR for the Synthesis of Betti Bases

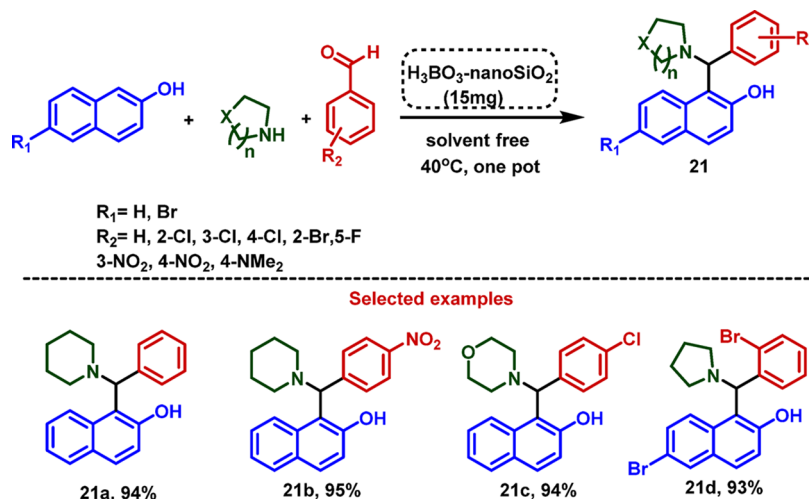


could be recycled and reused up to five consecutive cycles without appreciable loss in its activity, thus further demonstrating the importance of the methodology.

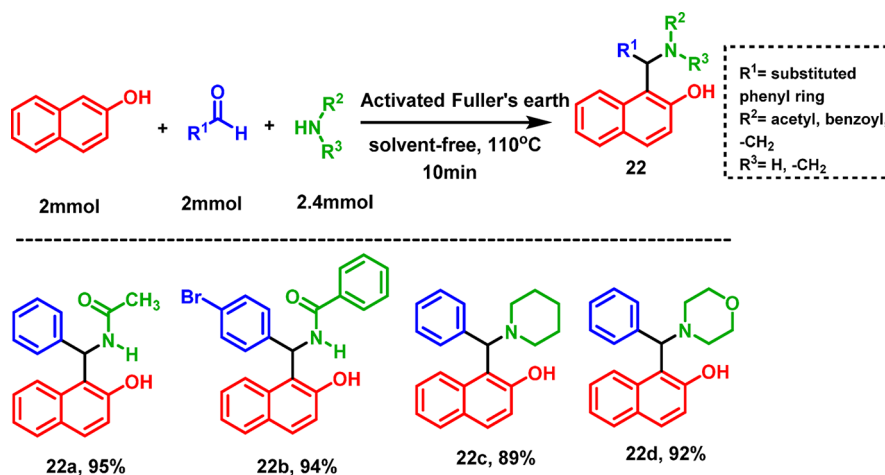
Later on, in 2018 Fathalipour et al. developed a solvent-free one-pot approach for the synthesis of 1-( $\alpha$ -amino alkyl)-2-naphthols (18) using biocompatible, reduced modified graphene oxide (rMGO)-Au NPs as catalyst (Scheme 6).<sup>6</sup> Noble metal nanoparticles were synthesized by the reduction of Au(III) complex by sodium citrate with the use of covalent modified graphene oxide and diacid polyethylene glycol. Catalyst recyclability, reasonable yield, short reaction times, and easy workup procedure and purification are the salient features of the reaction.

**1.2.b. Metal-Free MCRs.** In 2015, Reddy et al. reported a green approach for the synthesis of alkylaminophenols (19) using Chitosan as a biopolymer catalyst via a three-component Petasis borono-Mannich reaction in very good to excellent yield (Scheme 7).<sup>7</sup> Short reaction time, no purification, and recycled and reusable catalyst are the key features of this approach.

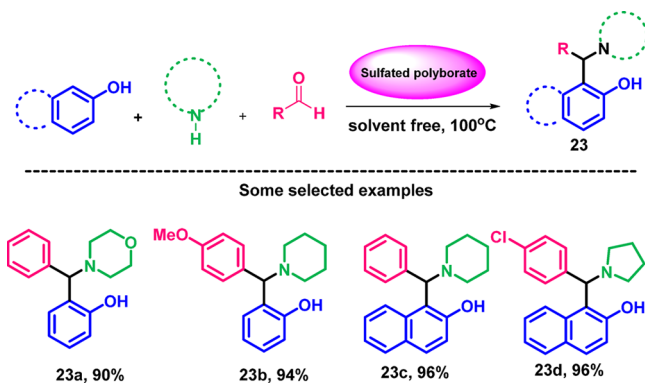
In 2016, Azizi and co-workers developed a green, one-pot approach for the synthesis of alkylaminophenols (20) in biodegradable choline-chloride-based deep eutectic solvent in very good to excellent yield (Scheme 8).<sup>8</sup> They prepared the

Scheme 9.  $\text{H}_3\text{BO}_3$ -nano- $\text{SiO}_2$  Catalyzed the Direct Synthesis of Aminonaphthols

Scheme 10. Activated Fuller's Earth Catalyzed MCR



Scheme 11. Sulfated Polyborate Catalyzed One-Pot Three-Component Reactions for the Synthesis of Betti Bases



catalyst by refluxing urea and choline chloride at 60 °C. Deep eutectic solvent (DES) could be readily recycled at least four times without loss of catalytic activity.

In 2017, Teimuri-Mofrad et al. reported a multicomponent reaction between aldehydes, amines, and 2-naphthol with nano- $\text{SiO}_2$ - $\text{H}_3\text{BO}_3$  as catalyst for the synthesis of Betti bases (21) under solvent-free conditions (Scheme 9).<sup>9</sup> Nano- $\text{SiO}_2$ - $\text{H}_3\text{BO}_3$  catalyst was generated by mixing nanosilica and  $\text{H}_3\text{BO}_3$  in

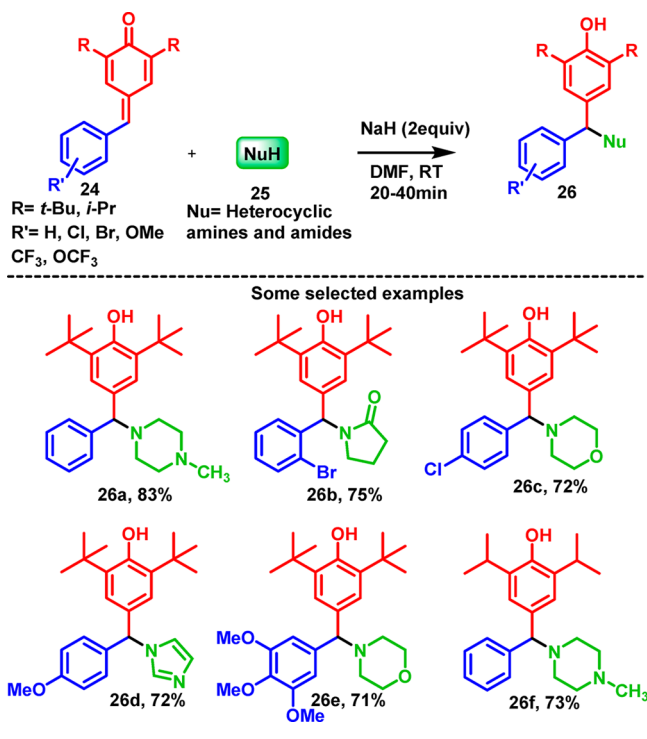
ethanol, and the recovered catalyst was reused for four catalytic cycles without loss of any efficacy.

In 2018, Rekunge et al. reported a cost-effective, solvent-free, green protocol for the synthesis of 1-(amido/amino) alkyl-2-naphthols (22) using activated Fuller's earth as a heterogeneous reusable catalyst via multicomponent reaction of an aldehyde, 2-naphthol or phenol, and amides or amines with excellent to good yields (Scheme 10).<sup>10</sup>

Afterward, in 2018 Patil et al. (same group) reported an expeditious, practical, and environmentally benign approach for the synthesis of Betti bases (1-aminoalkyl-2-phenols) (23) via a multicomponent reaction using sulfated polyborate catalyst under solvent-free conditions (Scheme 11).<sup>11</sup> The catalyst was prepared by dehydration of boric acid followed by sulfonation, and the recovered catalyst was reused up to four times without loss of any catalytic activity.

In 2019, our group described a base-mediated 1,6-conjugate addition of heterocyclic amines and amides (25) to substituted *para*-quinone methides (24) to give unsymmetrical benzhydryl amine (26) in moderate to very good yields (up to 83%) in one pot (Scheme 12).<sup>12</sup> This methodology could further be elaborated for the synthesis of the biologically important first-generation antihistamines meclizine, hydroxyzine, and cetirizine like scaffolds, highlighting the utility of the work.



Scheme 12. Base-Mediated 1,6-Conjugate Addition to *p*-QMs

**1.3. Enantioselective Synthesis of Benzhydryl Amines.** Benzhydryl amines belong to an significant class of chiral hydrocarbons having diverse medicinal properties. In today's

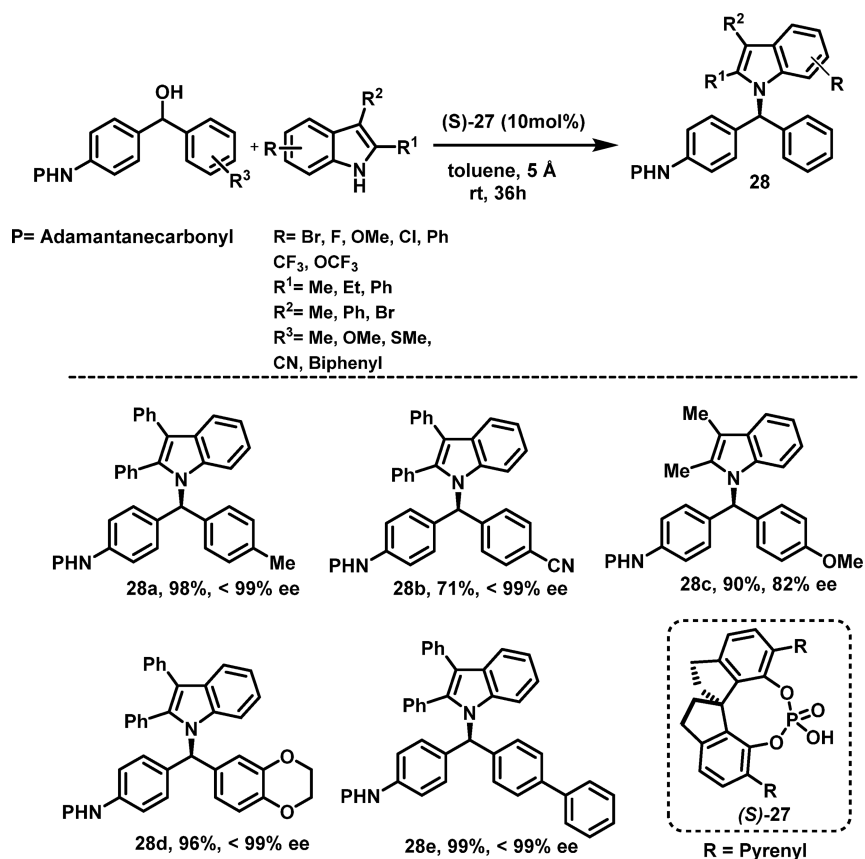
drug discovery process, chirality and activity derived from single enantiomer play important roles. Thus, developing new asymmetric methods for chiral diarylmethylamine will be very challenging. Despite having a variety of racemic routes, enantioselective or enantiospecific methods to this important class of chiral molecule are very scarce.

**1.3.a. Organocatalyzed Enantioselective Synthesis.** In 2017, the Sun group observed a new organocatalytic method for the efficient N-alkylation of indoles (28) and carbazoles via *in situ* generated aza-*para*-quinone methides using SPINOL-derived chiral phosphoric acid catalyst (27) (Scheme 13).<sup>13</sup> From control experiments, it was established that chiral acid catalyst acts as a promoter for *in situ* formation of the crucial aza-*para*-quinone methide intermediate and a bifunctional catalyst in the upcoming enantio-determining step.

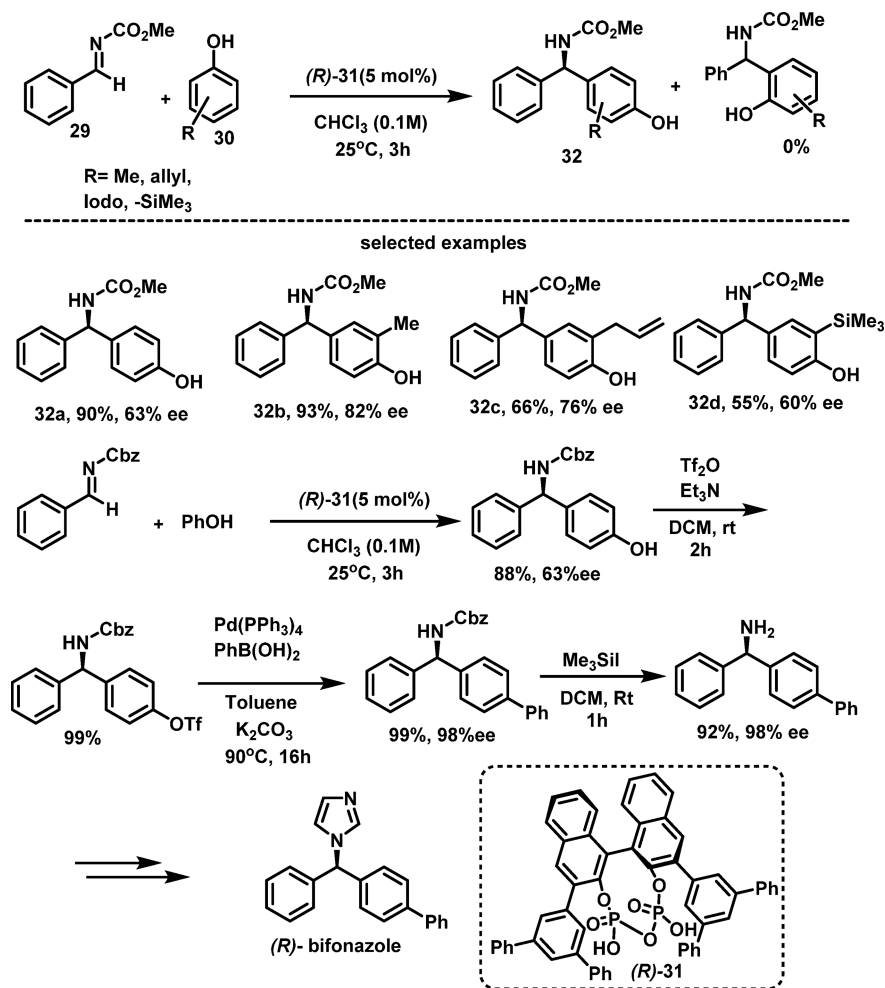
Later on, in 2018 Okamoto and co-workers demonstrated a regio- and enantioselective aza-Friedel–Crafts reaction of phenols (30) with aldimines (29) using BINOL-derived chiral pyrophosphoric acid catalyst (31) for the synthesis of diarylcarbamate derivatives (32) (Scheme 14).<sup>14</sup> *ortho/para*-Directing phenols could react at a *para*-position with moderate to good enantioselectivity. The Sakakura group further extended this methodology for the enantioselective synthesis (*R*)-bifonazole.

**1.3.b. Metal-Catalyzed Enantioselective Synthesis.** In 2015, Wang et al. demonstrated a highly enantioselective pinacolboronyl addition of N-Boc-imines (33) using a chiral sulfoxide-dialkylphosphine (SOP) as ligand (34) and copper(I) as catalyst to form enantio-enriched N-Boc- $\alpha$ -amino boronic compounds (35) (Scheme 15).<sup>15</sup> They next explored the synthetic utility of

Scheme 13. SPINOL-Derived Chiral Phosphoric Acid Catalyzed 1,6-Conjugate Addition



Scheme 14. BINOL-Derived Chiral Pyrophosphoric Acid Catalyzed aza-Friedel–Crafts Reaction



enantio-enriched N-Boc- $\alpha$ -amino boronic esters and presented a new route to the synthesis of antihistamine (*R*)-cetirizine (Zyrtec).

In 2017, Syu et al. developed Rh(I)-catalyzed enantioselective addition of arylboronic acids to *N*-diphenylphosphinyl (N-DPP)-protected aldimines (36) using chiral bicycle [2.2.1] heptadiene ligands (37) bearing aryl and secondary amido groups to furnish optically active N-DPP protected amines (38) with 31–99% yields and up to 91–99% ee (Scheme 16).<sup>16</sup> They have designed and synthesized the ligand. This protocol was also extended to access antifungal agent, bifonazole.

In 2018, Jiang et al. reported iridium-catalyzed asymmetric (4 + 3) cyclization of vinyl aziridines (39) with *ortho*-hydroxy-substituted *para*-quinone methides (40) for seven-membered benzoxazepine scaffolds (42) in good to outstanding yields (40% to 96%) and moderate diastereoselectivities (73:27 to 91:9 dr) and high enantioselectivities (92:8 to 96:4 ee) using a chiral ligand (41) (Scheme 17).<sup>17</sup>

**1.4. Miscellaneous Method.** In 2015, Borukhova et al. reported a simplification and acceleration of chemical reactions to make meclizine, commercially available cyclizine and cinnarizine, and a buclizine derivative from diphenylmethanol using microflow technology.<sup>18</sup>

**2. Biomedical Application of Benzhydryl Amines.** In the last couple of decades, there has been a thunder in the utilization of diarylmethylamine derivatives in the biomedical field. The diarylmethylamine derivatives displays diverse

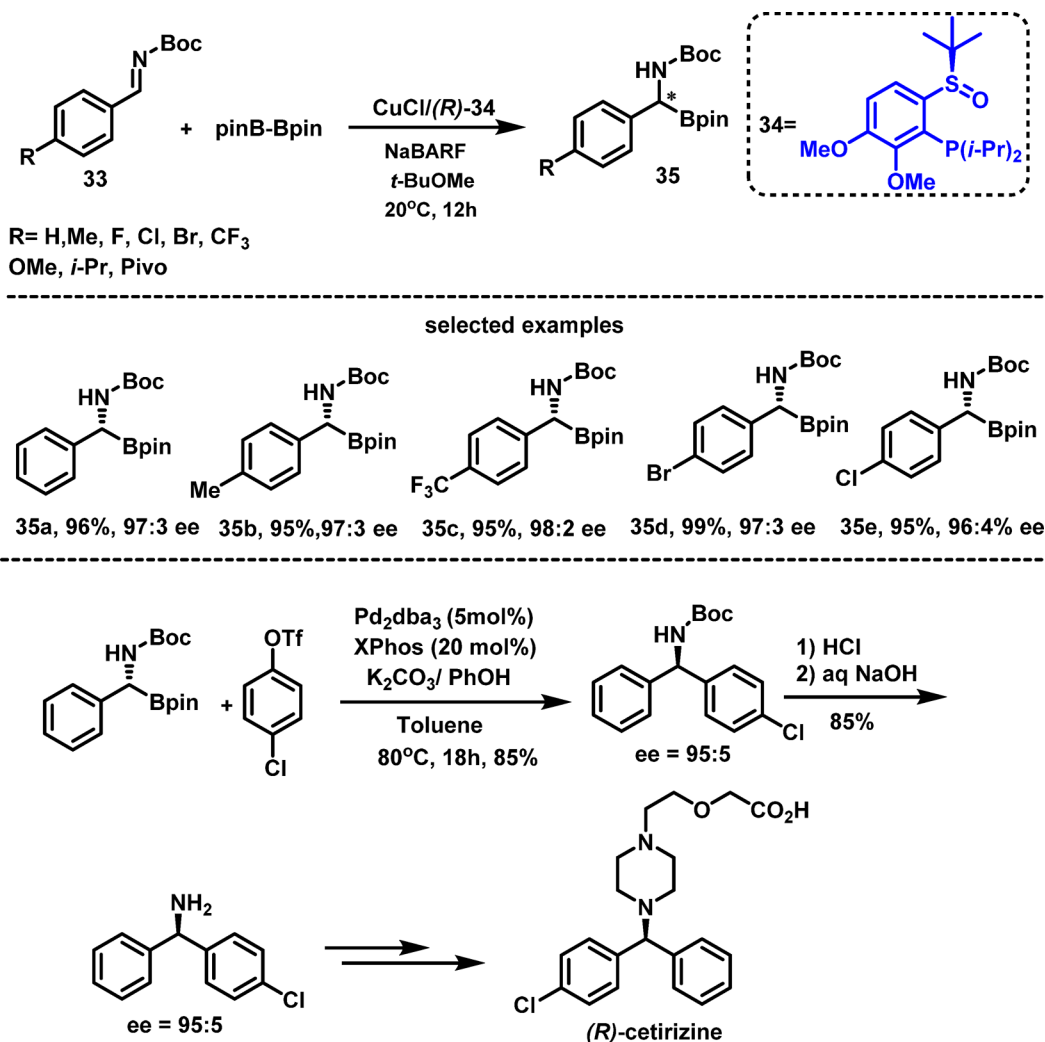
bioactivities like as anticancer, anti-muscarinic, antimalarial, and antiviral and antihistamine agents. We will be covering the biomedical applications of diarylmethylamine derivatives that were reported during 2015–2019.

**2.1. Diarylmethylamine Derivatives as Potent Aromatase Inhibitors.** In 2016, Ghodsi et al. reported diarylalkylimidazole and diarylalkyltriazole derivatives as potent aromatase inhibitors based on Quantitative Structure Activity Relationship (QSAR) analysis (Figure 2).<sup>19</sup> Their study indicated that lipophilicity can be one of the effective factors for the strong binding to aromatase. SAR study confirmed that with the replacement of the imidazole group by a triazole moiety, *in vitro* inhibition was reduced and activity was increased *in vivo* because of enhanced metabolic stability of the triazole derivatives.

**2.2. Diarylmethylamine Derivatives as Antibacterial Agents.** In a study directed toward developing new and selective agents with potential utility in the treatment of antibacterial activity against Gram-positive pathogens and methicillin-resistant *S. aureus* (MRSA), a series of 1-aminoalkylated 2-naphthols was prepared by Roman and co-workers in 2016 (Figure 3).<sup>20</sup> All of the Mannich bases having a thiophen-2-yl ring in their structure showed good activity against Gram-positive bacteria, without consideration of the nature of the amino moiety by SAR analysis.

**2.3. Diarylmethylamine Derivatives as Antiviral Agents.** In 2016, He et al. reported a structural modification study that furnished optimized, achiral, well-tolerated Chlorcyclizine

Scheme 15. Copper(I)-Catalyzed Asymmetric Pinacolboronyl Addition



## Formal synthesis of (R)-cetirizine

analogues with advanced anti-HCV potency and good pharmacokinetic properties in the liver at very reasonable doses (Figure 4).<sup>21</sup> From SAR study, they concluded that hydroxyl or amino groups at the chain terminal position of chlorcyclizine derivatives showed high anti-HCV activity and moderate cytotoxicity. Removal of the *para*-chloro substituent reduced the activity and introduction of an extra *para*-chloro substituent in the other ring marginally increased the activity. Next, structural modifications to the piperazine ring expressed that compounds having one carbon extension of the piperazine ring maintained the activity but led to increased cytotoxicity. The swap of the piperazine ring with other rings led to a remarkable loss of activity.

Later on, in 2018 Schafer et al. suggested that first-generation antihistamines as excellent postulants can be repurposed as antifilovirus therapeutics and can be further optimized for removal of unwanted histamine or muscarinic receptor interactions without loss of antifilovirus efficacy. They reported that among all zinc related antihistamines, chlorcyclizine (Ahist) could be a potential candidate for repurposing as an antifilovirus agent in both human immortalized cell lines and human primary cells (Figure 5).<sup>22</sup> Docking studies proved the potential for these drugs to bind directly to the Ebola virus-glycoproteins (EBOV-

GP) at the same site as toremifene. SAR studies disclosed that loss of the chlorine group (Cyclizine) led to a notable depletion in Marburg virus (MARV) inhibition but not EBOV inhibition, and bulky substitutions at the terminal amine group (bucizine and meclizine) generally led to a diminution in efficacy against both EBOV and MARV inhibitions.

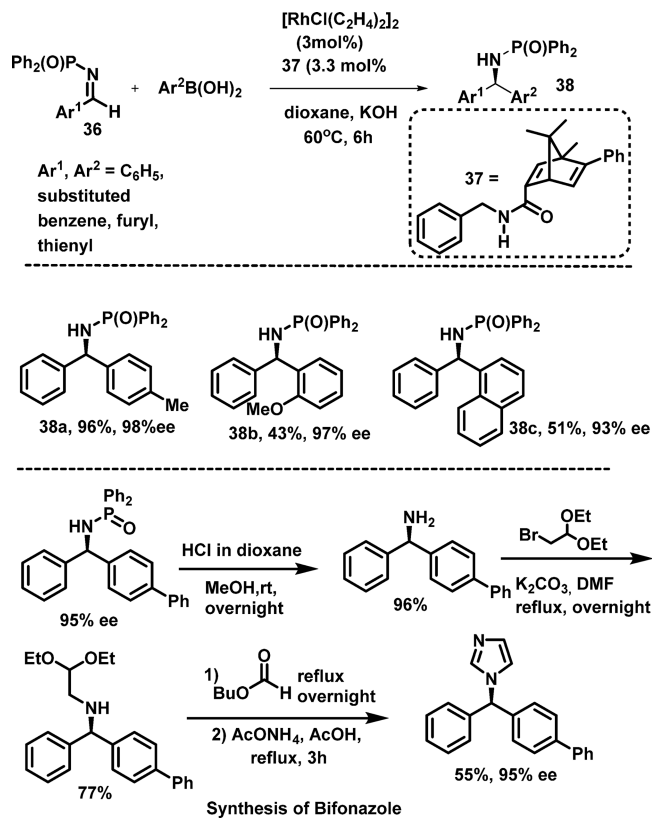
**2.4. Diarylmethylamine Derivatives as Anti-Leishmanial Agents.** In 2019, Mendes et al. reported that the H1-antihistamines cinnarizine and meclizine could be explored as new routes of cellular death in the parasite, and the determination of molecular target would contribute to understanding the potential of these drugs as anti-leishmanial agents. However, cetirizine failed to show significant anti-leishmanial activity (Figure 6).<sup>23</sup> Cinnarizine and meclizine showed activity against promastigotes as well as intracellular amastigotes with  $\text{IC}_{50}$  values 10–29  $\mu\text{M}$  and 20–35  $\mu\text{M}$ .

**2.5. Miscellaneous Bioactivities of Compounds Containing Diarylmethylamine Core.** A considerable amount of research has been carried out over the past few years aimed at the preparation of a new drug of different activity based on the analogues of meclizine.

Foo et al. reported meclizine, a pregnane X receptor agonist, directly inhibited testosterone  $6\beta$ -hydroxylation catalyzed by



## Scheme 16. Rh(I)-Catalyzed Enantioselective Arylation



human liver microsomes, recombinant CYP3A4, and recombinant CYP3A5 (Figure 7).<sup>24</sup> Meclizine inhibited human liver microsomal testosterone 6 $\beta$ -hydroxylation by a mixed mode and with an apparent  $K_i$  of  $31 \pm 6 \mu\text{M}$ . The authors concluded that meclizine inhibited human CYP3A enzymes by both direct

## Scheme 17. Iridium Catalyzed Asymmetric (4 + 3) Cyclization

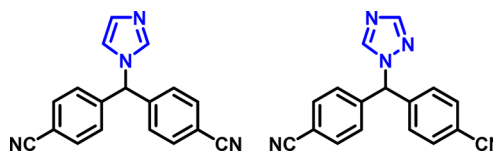
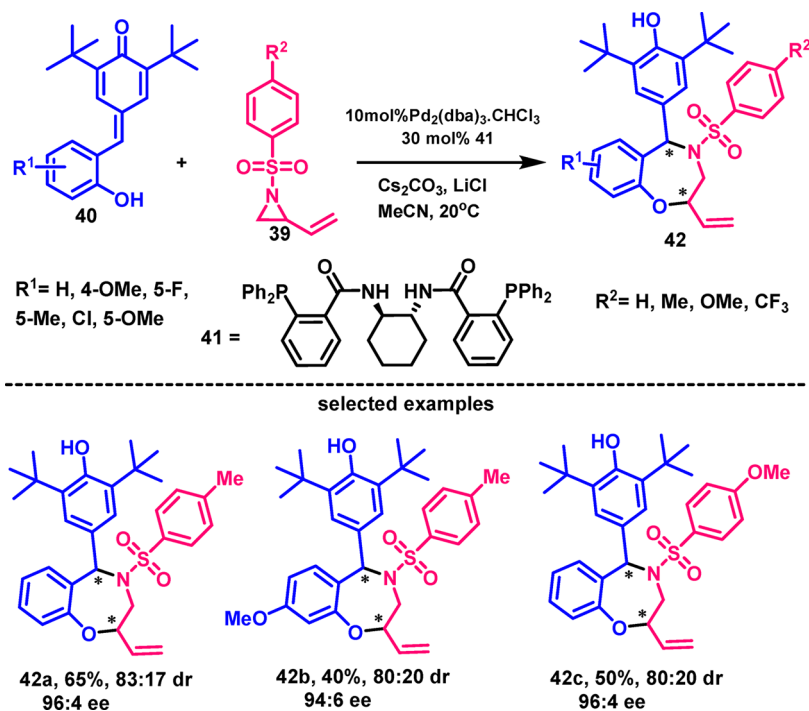


Figure 2. Structure of diarylalkylimidazole and diarylalkyltriazole derivatives.

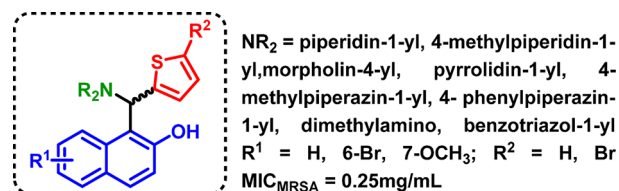


Figure 3. 1-Aminoalkylated 2-naphthol derivatives as antibacterial agents.

inhibition and mechanism-based inactivation, but norchlorcyclizine is a direct inhibitor but not a mechanism-based inactivator.

In 2016, Gorgun et al. observed in the mitochondria-rich dorsal root ganglion (DRG) neurons that meclizine reduces cisplatin-induced mitochondrial compromise via elevation of the pentose phosphate pathway and repletion of nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione stores (Figure 7).<sup>25</sup> The authors also proposed that Meclizine-mediated preservation of redox balance sustains mitochondrial respiration, which supports execution of cellular processes, including timely removal of cisplatin cross-links from nuclear DNA, thereby attenuating cisplatin toxicity in the DRG neuron.

Later on, in 2017 Guo et al. reported that meclizine has a remarkable inhibitory effect on osteoclastogenesis and ovariectomy-induced bone loss. *In vitro* and *in vivo* study revealed that meclizine prevents osteoclastogenesis via regulation of

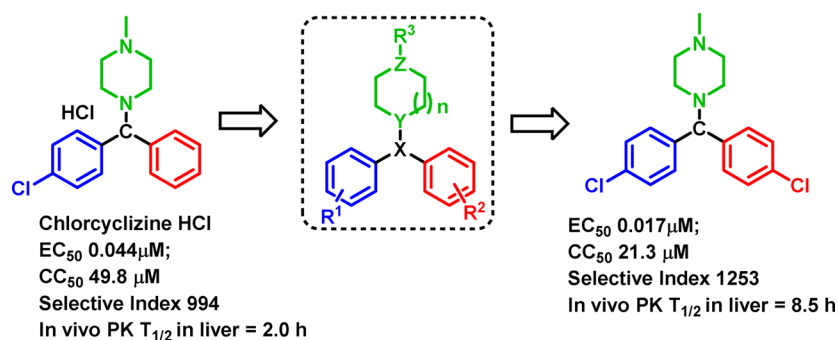


Figure 4. Chlorcyclizine analogues as antiviral agents.

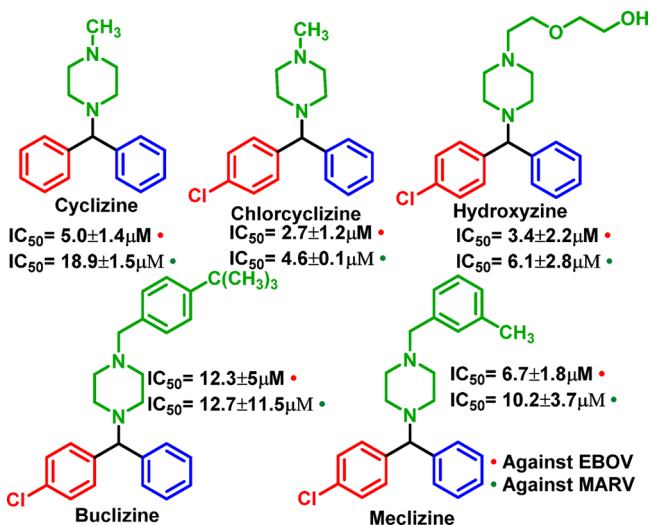


Figure 5. Piperazine based diarylmethylamines as antiviral agents.

several receptor activators of nuclear factor- $\kappa$ B ligand (RANKL) signaling pathways, and Pregnane X receptor (PXR) was involved in the processes (Figure 7).<sup>26</sup>

Recently, Hussein et al. investigated *in vitro/in vivo* study of meclizine floating microspheres to control nausea and vomiting during pregnancy (Figure 7).<sup>27</sup> They have prepared meclizine floating microspheres by an emulsion solvent evaporation method and characterized them as well. Pharmacokinetic studies confirmed that the optimized formula of meclizine floating microsphere could attain prolonged and/or controlled release, in tandem with exhibiting enhanced systemic bioavailability, compared to the plain drug.

In 2018, Durham et al. determined the effectiveness and safety of cetirizine compared with diphenhydramine for the prevention of chemotherapy-related infusion like flushing, itching, alter-

ations in heart rate and blood pressure, etc.<sup>28</sup> They will establish the role of cetirizine and discuss its adverse effect profile in comparison with diphenhydramine in the future with various studies.

## FUTURE PERSPECTIVE

While there are plenty of literature reports on the synthesis of racemic and asymmetric triarylmethanes and trisubstituted methanes, the articles originating from benzhydryl amines, a class of TRSM, are scarce. Careful analysis of the nitrogen part of TRSM reveals that mostly acyclic and cyclic aliphatic and aromatic nucleophiles with nitrogen have been used for synthesis of a large variety of this class of molecule. In some cases, their asymmetric versions originating from the central methine atom are also reported. Among the abundant chiral natural products containing nitrogen are amino acids where the nitrogen group can be utilized as a suitable nucleophile for the construction of a large array of benzhydryl amines having already built-in chirality and providing an ample scope of generation of a mixture of diastereomers which may exhibit specific biological properties. Moreover, a large number of amino acids with fixed absolute configuration and variety of functional groups will give a fine balance of hydrophobicity and hydrophilicity among the synthesized benzhydryl amines.

## CONCLUSION

The current review discusses the recent developments in the chemistry and biology of the benzhydryl amine derivatives that has been reported in the last five years (2015–2019) and hence can be a thrust for the further elaboration of this family of molecules toward small molecules as therapeutic agents. The significant advantage of this class of molecules has created a high insistence for their effective synthesis and thus led to various improvements in synthetic organic chemistry.

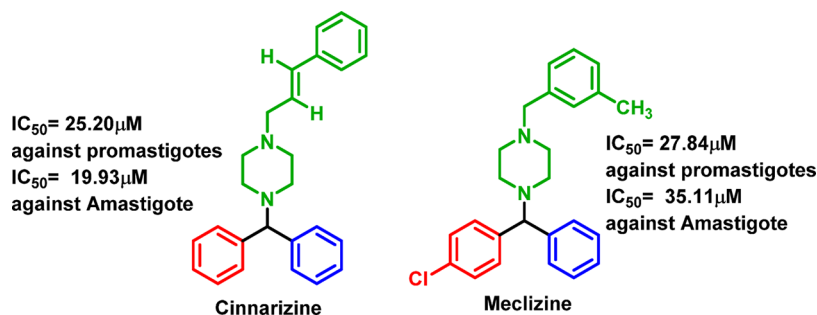


Figure 6. Piperazine based diarylmethylamines as anti-leishmanials.

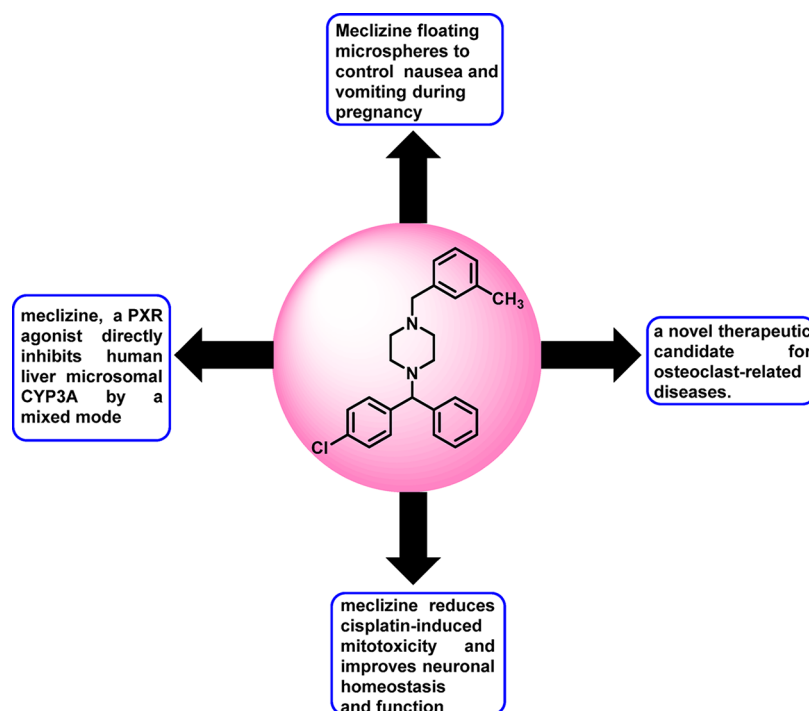


Figure 7. Meclizine as a versatile therapeutic agent.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [gautam.panda@gmail.com](mailto:gautam.panda@gmail.com), [gautam\\_panda@cdri.res.in](mailto:gautam_panda@cdri.res.in). Phone: 915222772450, ext 4659. Fax: 915222771941.

### ORCID

Gautam Panda: 0000-0003-4248-4579

### Notes

The authors declare no competing financial interest.

### Biographies



**Deblina Roy** was born in West Bengal. She joined CSIR Central Drug Research Institute, Lucknow to work on a project funded by Ministry of Earth Sciences (MoES), New Delhi on 21st April, 2016 under the supervision of Dr Gautam Panda after completing her M.Sc. degree in chemistry in 2013 from University of Burdwan. Currently she is working as project JRF in Board of Nuclear Sciences (BRNS) funded project entitled “Amino acids derived steroidal and nonsteroidal Ligands as inhibitors of steroid 5- $\alpha$ -reductase in cancer”.



**Gautam Panda** was raised from West Bengal, India. He completed a Ph.D. working with Prof. Goverdhan Mehta at University of Hyderabad on classical synthesis of bucky-bowls in 1999 after completing a M.Sc. in Chemical Sciences from IIT Kharagpur in 1993. Later he had a postdoctoral stint as NSERC visiting fellow in the lab of Prof. Howard Alper, University of Ottawa and Dr. Prabhat Arya, National Research Council, Ottawa, Canada from 2000–2001. He started his independent career at CSIR-Central Drug Research Institute, Lucknow in 2002 where currently he is a senior principal scientist. His research interests centered around finding new chemical entities in treating tuberculosis and breast cancer through the synthesis of natural products and like molecules from chiral amino acids and trisubstituted methanes (TRSMs).

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