**Research Topic**

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| **Name of the Candidate:** | UJLA DASWANI |
| **Name of Ph.D. registered University:** | Devi Ahilya Vishwavidyalaya, Indore |
| **Name of institute/lab of PhD work** | School of Chemical Sciences |
| **Present position of the candidate** | Research Scholar |
| **Name and address of your PhD supervisor:** | Dr. Ashok Kumar  Professor & Head  School of Chemical Sciences,  Devi Ahilya Vishwavidyalaya, Takshashila Campus, Khandwa Road, Indore (M.P.) |
| **Title of Ph.D. work:** | Synthetic and Electrochemical Studies on Biologically Significant Annelated Azoles and their Precursors |

**Outline of Research Topic**

* **Importance:**

Heterocyclic scaffolds occupy the largest section of organic chemistry and are of enormous significance. One of the reasons for the extensive use of heterocyclic compounds is their skeletal flexibility that can be subtly used to achieve a required modification in functional outcome. Specifically, annelated azoles represent one of the largest chemical families, possessing ample of application profile. They are broadly classified as benzo-1,3-azoles (Fig. 1) and benzo-1,2-azoles (Fig. 2) ca., benzimidazole, benzoxazole, benzothiazole, indazoles, benzisoxazole and benzisothiazole. A thorough elicit of the literature reveals that they have been found to be associated with a number of various biological activities such as gram-positive antibacterial agents, antibiotics, antiparasitic, anti-inflammatory,1 antimicrobial,2 antidiabetic,3,4 anti-stress, anti-ulcerative, anti-HIV,5 antihypertensive activity,6 anti-platelet,7 antiallergic and as enzyme inhibitors.

Particularly, benzoxazoles and benzimidazoles are recognized as important scaffolds in fluorescent probes. Structure of omeprazole contains annelated imidazole as its nucleus; and is known to act as a gastric pump inhibitor which inhibits the common final step in gastric acid secretion and thus is anti-ulcerative. Similarly, benzo-1,2-azoles especially the indazole ring system is known to act as antitumor agent8 and is mostly found in herbicides, dyes and sweeteners.9

Additionally, quantum chemical studies helps in investigating the electronic structure (principally the ground state) of many body systems, in particular atoms, molecules and the condensed phases. Hence, these calculations shed more light on accurate predictions of structural characteristics and fundamental vibrational modes of the compound under study. Thus, one can easily correlate the theoretically predicted parameters with experimental results. Also, these studies help in predicting mechanistic outcome of synthesized compounds on the basis of regioselectivity of the substrates.

* **Noteworthy Contributions in the Field of Proposed Work:**

Most of the annelated azoles are considered as remarkable drugs. A plethora of marketed drugs embracing azole skeleton is shown in Fig. 1.



**Fig. 1.** Marketed drugs with annelated azole as main nucleus

* **A Brief Review of the Work Already Done in the Field**:

Literature encompasses a number of synthetic strategies pertaining to the annelated azoles. However, out of a number of annelated azoles available in the literature, we have paid special focus on benzimidazoles, benzoxazole, benzothiazole and indazole for the sake of present studies.

Basically skeleton of benzimidazole is obtained by the condensation of 1, 2-diaminoarene (o-phenylenediamine) derivatives with carboxylic acid or carbonyl derivatives. Nagawade *et* *al.* has suggested the use of o-phenylenediamine and aldehydes to obtain substituted benzimidazole. It is also synthesized from o-phenylenediamine and mono or di-basic acid. Philips modified this procedure by refluxing the o-phenylenediamine and mono basic acid in 4N hydrochloric acid. Batey’s group has reported the use of palladium and copper-catalyzed intramolecular *N*-arylation starting from o-haloanilines as other alternative. The use of catalysts like SiO2/ZnCl2, cerium (IV) ammonium nitrate (CAN) and solvent-free protocols have also been reported in literature.

Likewise, skeleton of benzoxazole can be synthesized using o-aminophenol and compounds containing acid functional group or by the oxidative cyclization of phenolic Schiff’s bases derived from the condensation of 2-aminophenols and aldehydes, using various oxidants. Synthetic routes for benzoxazole include microwave assisted reaction of *N*-acyl-aminophenol; iron catalysed intramolecular O-arylation of 2-haloacetanilides and cyclization of phenolic Schiff base under UV irradiation.

Conventionally, 2-substituted benzothiazoles are synthesized by the condensation of 2-aminothiophenol with carboxylic acid derivatives. Therefore, 2-aryl benzothiazoles can be prepared by direct coupling of benzothiazoles with aryl bromides or by the cyclization of the intermediate radical formed after initial oxidative coupling between thiophenols and aromatic nitriles.

A classical route to indazoles involves *N*-nitrosation of an acetamide followed by cyclisation onto an ortho alkyl group.

Most of the methods reported in literature suffer from cumbersome approaches such as the prolonged reaction time, limitation of being restricted to only aromatic aldehydes, use of toxic additives, use of hazardous solvents, low yields, operational complexity, formation of by-products and tedious work-up procedure. As a result, search for new alternatives are still an essential experimental challenge to synthetic organic chemists.

* **Work Carried out by Me:**
* To date, synthesis of diverse symmetric and unsymmetric azo benzothiazoles was carried out along with the structural corroboration of the synthesized productsby FT-IR, 1H-NMR, and ESI-MS data. . This protocol has proved to be a better alternative to classical diazotization reactions which usually require harsh reaction conditions, additives and catalysts.
* We havealsofabricated easily recoverable magnetic nanoparticles (CoFe2O4). Catalyst has been characterized using techniques like SEM, EDAX and XRD.
* Theoretically investigation of benzothiazole scaffold on the basis of HF and DFT studies considering 6-31G(d,p) and 6-311++G(d,p) basis sets using Gaussian 03 Program Suite. **(Paper published: “A comprehensive account of spectral, Hartree Fock, and Density Functional Theory studies of 2-chlorobenzothiazole” Daswani, U.; Sharma, P.; Kumar, A. *J. Mol. Struct.* 2015, *1079*, 232-242).**
* Correlation was also established between experimental and theoretical findings of the data deduced from FT-IR, FT-Raman and NMR spectra.
* Electrostatic potential maps have been illustrated in order to visualize reactive site of a molecule in three dimensional ways.
* Total density mapped with electrostatic potential surface (MESP) indicating regions of strongest repulsion to strongest attraction. TD-DFT was also used to predict UV spectral analysis. (**Fig. 3**.)



(a) (b)

**Fig. 3.** (a) Total electron density isosurface mapped with molecular electrostatic potential

(b) Theoretical UV-Visible spectra of 2CBT

* Then similar theoretical investigations were performed on indazole derivative to get deep insight about its thermodynamic properties, vibrational assignments, chemical shifts, and electronic properties (**Fig. 4(a)**).
* Additionally, sites favourable for nucleophilic and electrophilic attack have been calculated by using notion of conceptual density functional theory (**Fig. 4(b)**).

 

(a) (b)

**Fig. 4.** (a) Electronic properties shown by indazole derivative (b) Favourable sites for nucleophilic and electrophilic attack obtained by concept of dual descriptor

* Besides, we have used computational tools to validate stepwise mechanistic aspects of our reaction (**Fig. 5 & 6**).



(a) (b)

**Fig. 5.** (a) Representation of reactive sites for the formation of 2-bromocyclohexanone using frontier orbitals (b) Simple diagrammatic representation showing *in-situ* formation of 2-bromocyclohexanone

 

(a) (b)

**Fig. 6.** (a) Representation of reactive sites using frontier orbitals (b) simple diagrammatic representation showing progress of reaction after addition of urea

* Thus, a facile strategy for the synthesis of 2-aminobenzazoles *via* a reaction of α–halogenated cyclohexanone with guanidine/urea derivatives has been developed in our laboratory.
* This transition metal free protocol uses stoichiometric ratio of *N*-bromosuccinimide (NBS) as brominating agent and oxone as oxidant in which oxone promotes *in situ* halogenations of cyclohexanone, which in turn when allowed to react with guanidine/urea, afforded the 2-aminobenzazoles (**Fig. 7.**). **(Paper published: “A new NBS/oxone promoted one pot cascade synthesis of 2-aminobenzimidazoles/2-aminobenzoxazoles: a facile approach” Daswani, U.; Dubey, N.; Sharma, P.; Kumar, A. *New J. Chem*. 2016, *40*, 8093-8099).**



Thus, keeping in view the diversified importance associated with annelated azoles, it is sought to design,synthesize,and perform theoretical studies on a novel compendium of azoles with potential therapeutic significance.

* **Objective(s):**

In view of the immense importance alluded by the annelated azoles, following objectives are proposed to be undertaken for the sake of present work:

* To develop efficient and convenient methods for the synthesis of some novel annelated azoles and their derivatives *viz*., benzimidazole, benzoxazole, benzothiazole and indazole. The role of catalyst(s) will also be explored in the synthetic methodology, wherever needed.
* To ascertain the structures of all the synthesized heterocycles by elemental, IR, NMR, and Mass-spectral analysis.
* To evaluate the therapeutic potential vis-à-vis to perform comprehensive drug designing of the synthesized compounds.
* To explore the redox behaviour of synthesized heterocycles using electrochemical devices.
* To ascertain the mechanistic findings through theoretical studies using Gaussian 09 Suite.
* **Year Wise Plan of Work:**

**1st Year:**

The proposed studies will be carried out in the following sequential steps:

After designing new synthetic routes, methods and conditions will be optimized to synthesize a number of precursors and target heterocyclic compounds, chosen for the studies. In due course of time, purity of all the synthesized compounds will be routinely checked and their structures will be established on the basis of IR, NMR, and Mass-spectral devices. Evaluation of therapeutic potential studies will be performed on the synthesized heterocycles.

In order to establish structures of synthesized or reported annelated azoles, theoretical studies will also be performed using DFT calculations. Additionally, quantum chemical calculations will also be performed to validate mechanistic details of the synthesized compounds.

**2nd Year:**

In this tenure, efforts will be laid down to correlate the biological activity data with structural features by computer programmed QSAR (Quantitative Structure-Activity Relationship) analysis.s. Finally in order to find out the redox behaviour in qualitative and quantitative manner, comprehensive electroanalytical studies will be performed.

* **Expected Outcome of the Proposed Work:**

The overall outcome of proposed studies will result in innovative approach towards developing new synthetic molecules possessing significant biological activity profile. A complete insight about the structure elucidation of synthesized compounds will be provided. In addition to this, electron transfer process will help in thorough investigation of synthesized compounds. Summarizingly, all these findings will be new to the existing scientific literature.

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Signature of Candidate

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