PART I

Studies on compounds containing benzimidazole & 1,3,4-oxadiazole scaffolds
Part I

In part-I, we have incorporated two medicinally important heterocycles like benzimidazole and 1,3,4-oxadiazole. It is our ongoing process to search novel bioactive molecules.

**Introductory features of benzimidazoles**

Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring resulting in benzimidazole (1) and is numbered as follows. Benzimidazoles are also known as benziminazoles and 1,3-benzodiazoles. They possess both acidic and basic characteristics. The NH group present in benzimidazoles is relatively strongly acidic and also weakly basic. Another characteristic of benzimidazoles is that they have the capacity to form salts. Benzimidazoles with unsubstituted NH groups exhibit fast prototropic tautomerism, which leads to equilibrium mixtures of asymmetrically substituted compounds. In 1953, Klaus Hofmann covered the entire chemistry of monocyclic imidazoles and benzimidazoles (1). It was discovered that benzimidazole is an integral part of the structure of vitamin B₁₂.

The benzimidazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as, antioxidant, anti hypertensive, anti-HIV, anti-inflammatory, anticancer, antitrichinellosis, anxiolytic, antiviral, analgesic, antiallergic, antimicrobial, antihelminthic and antiparasitic activity. The optimization of benzimidazole-based structures has resulted in various drugs which are currently in the market. Many reports have revealed that the influence of substitution at 1, 2 and 5 positions of benzimidazole ring is very important for their pharmacological activities. 2-(Substituted phenyl) benzimidazoles with various types of biological activities, such as antibacterial, antiviral, antitumoral and anti-inflammatory have been reported.
Commercially available benzimidazole based analogues

Tautomerism in benzimidazole derivatives

The possibility of tautomerism between 1-unsubstituted benzimidazole-3-oxides and N-hydroxy benzimidazoles (2, 3) is shown. The position of equilibrium between the tautomers has been studied extensively for the parent compound and also for its 2-phenyl and 5-nitro derivatives. In the solid state, comparison of spectroscopic and pKₐ data for benzimidazole-N-oxide with those for N-methoxy benzimidazole (4) and 1-methylbenzimidazole-3-oxide (5) indicates that in aqueous solution the N-oxide tautomer predominates. As the polarity or hydrogen-bonding power of the solvent decreases, the proportions of the N-hydroxy tautomers increase. In solvents, such as acetonitrile, dioxane or chloroform these tautomers predominate. Same trends are apparent in the 5-nitro derivative, although the investigation has been less extensive. 2-Phenyl compound, however, appears to exist predominantly in the N-hydroxy form even
in polar solvents. No conclusive evidence is available regarding the position of equilibrium.

Dall’Oglio E et al\textsuperscript{27} have studied tautomerism of 2,2’-bis-benzimidazoles 5(6),5′(6′)-tetramethyl (6), 5(6),5′(6′)-dimethyl (7a), 5(6),5′(6′)-dichloro (7b), 5(6),5′(6′)-dimethoxy (7c) and 4(7),4′(7′)-dimethyl-2,2’-bis-benzimidazole (8) by means of \textsuperscript{1}H NMR spectroscopy at variable temperatures and the influence of the substituents on the energy barriers for tautomeric interconversion was interpreted with the aid of theoretical calculations.

\textbf{Synthetic study of benzimidazoles}

Most commonly benzimidazoles have been prepared by the reaction of 1,2-diaminobenzene (o-phenylenediamine) with carboxylic acid under harsh dehydrating reaction condition, utilized strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or \textit{p}-toluenesulfonic acid.\textsuperscript{28} On the other hand, the synthesis of benzimidazoles via condensation of 1,2-diaminobenzenes with aldehydes requires an oxidative reagent to generate benzimidazole nucleus. Moreover, a variety of benzimidazoles could also be produced via coupling of 1,2-diaminobenzenes with carboxylic acid derivatives such as nitriles, imidates,
Studies on clinically important nitrogen and sulphur containing heterocyclic compounds

orthoesters, anhydrides or lactones.\textsuperscript{29} In each case, cyclization directly involves a coupling at $\text{o}$-phenylene nitrogen. Therefore, some innovative and improved pathways for synthesis of benzimidazole derivatives have been reported in literature. Among these methods, few selected examples have been highlighted as follows.

Tewari A K and Mishra A\textsuperscript{30,31} have reported the synthesis of $N$-substituted-2-substituted-benzimidazole derivatives by condensing $o$-phenylenediamine and carboxylic acid derivatives in HCl. Whereas, $N$-substituted derivatives have been synthesized by reaction with alkyl/aryl halide in presence of base (sodium hydroxide). These compounds were screened for antiviral activity against Tobacco Mosaic virus\textsuperscript{32} and Sunnhemp Rosette virus.

\begin{equation}
\text{(9)} \quad \text{+} \quad \text{RCOOH} \quad \text{4N HCl} \quad \xrightarrow{} \quad \text{(10)} \quad \text{NaOH} \quad \text{R'X} \quad \xrightarrow{} \quad \text{(11)}
\end{equation}

\begin{align*}
R &= -\text{CH}_2\text{CH}_2\text{COOH}, -\text{C}_6\text{H}_5\text{OH} (\text{o}), -\text{CH} = \text{CH}-\text{C}_6\text{H}_5, R' = -\text{H}, -\text{CH}_2\text{C}_6\text{H}_5
\end{align*}

Mane R B et al\textsuperscript{33} have reported the conventional condensation of 1,2-diaminobenzene (\textbf{12}) with 6-fluoro-3,4-dihydro-$2H$-chroman-2-carboxylic acid (\textbf{13}) under Phillip’s conditions or using Eaton’s reagent (1 : 10 mixture of phosphorus pentoxide/methanesulfonic acid) yielded 2-(6-fluorochroman-2-yl)-$1H$-benzimidazole (\textbf{14}). Some compounds exhibited promising anti-bacterial activity and showed activity against PDE IV for potential anti-asthamatic effect and against DP–IV and PTP 1B for potential anti-diabetic effects was disappointing.
Brain C T and Brunton S A\textsuperscript{34} established a palladium-catalyzed $N$-arylation reaction of novel synthesis of benzimidazoles from ($o$-bromophenyl)amidine precursors (15) under microwave irradiation. The route was found to be flexible with respect to various substituents and allowed for the preparation of highly substituted benzimidazoles, including $N$-substituted examples. Further, Brain C T and Steer J T\textsuperscript{35} modified this method which was later improved and optimized to achieve the rapid formation of benzimidazoles (16) in high yield. It has been found that 50% aqueous dimethyl ether (DME) is an optimal solvent for the reaction and that catalyst loading of palladium can be reduced to 1 mol%.

Ram S et al\textsuperscript{36} have synthesized alkyl-5-\(\text{(alkoxy carbonyl)\text{-1H-benzimidazole-2-carbamates}}\) (17) and related derivatives by reaction of an appropriate alcohol or amine with acid chloride derivatives. These compounds exhibited significant antifilarial and antineoplastic activities. Turconi M et al\textsuperscript{37} have synthesized a series of 2,3-dihydro-2-oxo-1\text{-H-benzimidazole-1-carboxylic acid esters and amides containing a basic azacyclo or azabicyclo alkyl moiety and evaluated for 5-HT\textsubscript{3} antagonistic activity in a binding assay.}

Patel R V et al\textsuperscript{38} have designed a series of benzimidazole based 1,3,4-oxadiazoles (23) were synthesized from $o$-phenylenediamine (19) through intermediate
compounds (20-22) and assessed *in vitro* for their efficacy as antimicrobial agents against eight bacteria, four fungi and mycobacterium tuberculosis H₃⁷Rv. The lipophilicity (LogP) influence on the biological profile (MICs) of the prepared products was also discussed.

Functionalization of C–H bonds of heterocycles to C-arylation is an important synthetic reaction and is used to build important bioactive structures. Palladium catalyst and copper-mediated C-2 arylations of benzimidazole with aryl iodides under ligandless and base-free conditions have been described by Bellina F et al.³⁹

Desai N C et al.⁴⁰ have synthesized some novel 3-(2-(6-methyl-1H-benzo[d]imidazole-2-yl)phenyl)-2-(aryl)thiazolidin-4-ones (31) from Schiff bases of N-arylidenes-
2-(6-methyl-1H-benzo[d]imidazol-2-yl)anilines (30). The Schiff bases (30) were prepared by condensation of different aldehydes with 2-(6-methyl-1H-benzo[d]imidazol-2-yl)aniline (29). The compound (29) was obtained from 2-amino benzoic acid (28) and 4-methylbenzene-1,2-diamine (27). All the synthesized compounds were screened for in vitro antibacterial and antifungal activities on various bacterial and fungal strains.

Pharmacological profile of benzimidazoles

The benzimidazole ring is an important pharmacophore in modern drug discovery. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV, human cytomegalovirus (HCMV) and herpes (HSV-1). Benzimidazole and its derivatives have been used to act as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin II inhibitors, inhibitors of HCMV replication, 5-HT3 antagonists in isolated guinea pig ileum, potential antitumor agents, antimicrobial agents, as factor Xa inhibitors and in diverse areas of chemistry.
Antibacterial and Antifungal Agents

2-substituted benzimidazole derivatives are known to possess varied biological activities. Recently, Desai N C et al. have been established efficient and rapid synthesis of novel benzimidazole containing pyrazoline and pyridines (32). Antimicrobial screening revealed that some compounds exhibited potent antibacterial activity against Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa and Escherichia coli. Moreover, compounds having electron releasing methyl and hydroxy groups exhibited the greatest antifungal activity against all the three fungal strains. In addition, 1-(1H-benzo[d]imidazol-2-yl)ethyldeneamino)-6-(arylideneamino)-4-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (33) were reported to show excellent antibacterial and antifungal activities.

Anti-inflammatory and Antiulcer agents

Structure-activity relationship studies of the 5,6-dialkoxy-2-thiobenzimidazole derivatives (34) have possessed pronounced antiinflammatory properties. Using the carrageenan model, the most significant anti-inflammatory effects were observed for compounds 34a, 34d, 34h, 34i and 34j. While using the bentonite model, the maximum activities were observed for compounds 34e and 34h. These results indicated that benzimidazoles are promising leads for the development of new anti-inflammatory agents. In addition, N-benzyol and N-tosyl benzimidazole compounds (35) showed significant anti-inflammatory activity, as
indicated by ear swelling induced by xylene in mice and their ulcer indices were all lower than those of aspirin.\textsuperscript{57} Furthermore, \textit{N}-morpholinomethylbenzimidazole (36) and its derivatives have been recently reported to show significant anti-inflammatory activity.\textsuperscript{58}

### Cytotoxic and Antitumor agents

Novel bisbenzimidazoles with general formula (37) and (38) incorporating benzimidazole, pyridoimidazole and imidazoquinone moieties as one of the units of bisbenzimidazole with a piperazinyl functional group have been synthesized.\textsuperscript{59} These novel bisbenzimidazoles were found to be actively cytotoxic against many human cancer cell lines, with GI\textsubscript{50} values of between 0.01 and 100 \textmu M, especially in the cases of renal cancer, CNS cancer, colon cancer, melanoma and breast cancer cell lines.
In addition, the alkyl-linked bisbenzimidazole (39) and thiazolylbenzimidazole-4,7-diones (40) exhibited cytotoxic activity against tumor cell lines.

**Introductory features of 1,3,4-oxadiazoles**

Oxadiazoles belong to an important group of heterocyclic compounds having N=C-O linkage. 1,3,4-oxadiazole (41) is a thermally stable aromatic heterocycle and exist in two partially reduced forms; 2,3-dihydro-1,3,4-oxadiazole (1,3,4-oxadiazoline) (42) and 2,5-dihydro-1,3,4-oxadiazole (1,3,4-oxadiazoline) (43) depending on the position of the double bond. The completely reduced form of the 1,3,4-oxadiazole is known as 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazolidine) (44).

Bactericidal and/or fungicidal activity was reported for oxadiazole (45a) and aminooxadiazole (45b). Antiinflammatory, sedative and analgesic properties were reported for aryloxadiazoles (45c). Aminooxadiazoles (45d) showed analgesic activity and aminooxadiazoles (45e) exhibited both antiinflammatory and antiproteolytic properties. Anticonvulsant and nervous system depressant activity was reported for aminooxadiazoles (45f), where R is quinazolin-3-yl group. Aminooxadiazole (45g) showed local anesthetic activity. Insecticidal activity was shown by oxadiazole (45h).
Studies on clinically important nitrogen and sulphur containing heterocyclic compounds

Commercially available 1,3,4-oxadiazole based analogues

Fenadiazole (Hypnotic)

Tiodazosin (antihypertensive)

Furamizole (antibiotics)

Nesapidil (Vaso dilator)

Raltegravir (HIV-integrase inhibitor)
Synthetic study of 1,3,4-oxadiazoles

Bakht M A et al\textsuperscript{68} have investigated a series of oxadiazole analogues (49) derived from chalcone derivatives (48) which were subjected to molecular properties prediction of all synthesized compounds.

Bayrak H et al\textsuperscript{69} have developed 1,3,4-oxadiazole derivatives (52) and (53) obtained from isoniazide (50) through intermediate 1,3,4-oxadiazole compound (51).
Chandrakantha B et al. have synthesized 1,3,4-oxadiazoles (55) by the reaction of hydrazide (54) and aromatic acid in presence of POCl₃. Joshi S D et al. have reported pyrrole clubbed 1,3,4-oxadiazole derivative (57) from corresponding hydrazide (56).

Mogilaiah K and Sakram B have prepared 1,3,4-oxadiazole (59) from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.

Pharmacological profile of 1,3,4-oxadiazoles

El-Essawy F A et al. have synthesized \(5\)-[4,6-dimethyl-1H-[1,2,3]-triazolo \([4,5-d]\)pyrimidine-5,7(4H,6H)-dione]-\{1,3,4-oxadiazol-2-yl\}methyl\} thioglycolyl hydrazide (60) and all the derivatives were tested for antiviral activity against Hepatitis B virus and showed moderate activity. Wagle S et al. have synthesized
some new oxadiazole derivatives 3-methyl-7-substituted-1-\{5-alkylsulfanyl\}-1,3,4-oxadiazol-2-yl|methyl|quinoxalin-2(1H)-ones (61) as potential non-steroidal anti-inflammatory and analgesic agents.

Borzilleri R M et al\textsuperscript{75} have replaced C\textsubscript{6}-ester substituent of the pyrrolo[2,1-\textit{f}][1,2,4]triazine core with substituted 1,3,5-oxadiazoles (62) to afford compounds with excellent oral bioavailability in mice (79%). Significant antitumor efficacy was observed with compounds 62a-c against established L2987 human lung carcinoma xenografts implanted in athymic mice. Ohmoto K et al\textsuperscript{76} have synthesized and biologically evaluated 5-amino-2-phenylpyrimidin-6-ones containing \textit{a}-keto-1,3,4-oxadiazole moiety (63) for both \textit{in vitro} activity and oral activity in an acute hemorrhagic assay and shown to possess a good oral profile.

Desai N C et al\textsuperscript{77} have designed a series of novel \textit{N}-\{5-(4-(((aryl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl\}acetamides (64) and evaluated for their antimicrobial and cytotoxic activity. Jansen M et al\textsuperscript{78} have
synthesized 5-piperidin-4-yl-3H-[1,3,4]oxadiazol-2-one (65a) and 5-piperidin-4-yl-3H-[1,3,4]oxadiazol-2-thione (65b), which were shown to be weak agonists at α2-, α3-, and α5-containing receptors. When coapplied with γ-aminobutyric acid type A receptors (GABA_A), they were antagonistic in α2-, α4-, and α6-containing receptors and potentiated α3-containing receptors.

Almajan G L et al have synthesized novel mercapto 1,3,4-oxadiazoles (66) by various pathways. The heterocyclic mercaptans prepared in this way were assayed as inhibitors of three physiologically relevant isoforms of the zinc enzyme carbonic anhydrase, i.e., the cytosolic CA I and II, and the tumor-associated, transmembrane isozyme CA IX. Interesting biological activity was detected for some of the new mercaptans, with inhibition constants in the low micromolar range.
Plausible mechanistic pathway (section 1-5):

Looking to the literature survey and pharmacological importance of benzimidazole and 1,3,4-oxadiazole, we have synthesized the following hybrid heterocyclic compounds.

**Section 1**: 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(aryl)-1,3,4-oxadiazol-3(2H)-yl)-3-phenylprop-2-en-1-ones.

**Section 2**: 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(aryl)-1,3,4-oxadiazol-3(2H)-yl)-3-(2-chlorophenyl)prop-2-en-1-ones.

**Section 3**: 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(aryl)-1,3,4-oxadiazol-3(2H)-yl)-3-(3-chlorophenyl)prop-2-en-1-ones.

**Section 4**: 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(aryl)-1,3,4-oxadiazol-3(2H)-yl)-3-(4-chlorophenyl)prop-2-en-1-ones.

**Section 5**: 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(aryl)-1,3,4-oxadiazol-3(2H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-ones.
EXPERIMENTAL PROCEDURE

PREPARATION OF 1-(1H-BENZO[d]IMIDAZOL-2-YL)ETHANONE (II)

**Preparation of 1-(1H-benzo[d]imidazol-2-yl)ethanol (I)**

-o-Phenylenediamine (0.04 mol) was condensed with lactic acid (0.03 mol) in 50 mL 4N HCl. The reaction mixture was refluxed for 24 hrs. Compound I was precipitated by adding ammonia solution, filtered, washed with cold water and recrystallized from ethanol (95%). Yield: 78%; m.p.: 80 °C; Anal. calcd. for C₉H₁₀N₂O: C-66.65, H-6.21, N-17.27; Found: C-66.72, H-6.27, N-17.21%.

**Preparation of 1-(1H-benzo[d]imidazol-2-yl)ethanone (II)**

To a solution of compound I (50 mmol) in dil. H₂SO₄ (5%, 40 mL) was added drop wise with stirring a solution of K₂Cr₂O₇ (150 mmol) in aq. H₂SO₄ (25%, 80 mL) at room temperature over a period of 20 min. and then stirred further at room temperature for 2 h. The separated orange solid [which is chromium complex of compound II] was washed with water (30 mL), suspended in water (50 mL) and treated with aq. NH₃ to a pH of 6.5-7.0. The separated solid was filtered, washed with water, dried and recrystallized from ethyl acetate. Yield: 62%; m.p.: 190°C; Anal. calcd. for C₉H₈N₂O: C-67.49, H-5.03, N-17.49; Found: C-67.57, H-5.09, N-17.42%.

The progress of reaction and purity of compounds I and II were checked on TLC [Aluminium sheet silica gel 60 F₂₄₅ [E. Merck]] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
SECTION 1

PREPARATION OF 1-{2-{1H-BENZO[d]IMIDAZOL-2-YL}-2-METHYL-5-{ARYL}-1,3,4-OXADIAZOL-3(2H)-YL}-3-PHENYLPROP-2-EN-1-ONES

SYNTHETIC SCHEME 1

R = -H, -2-Cl, -3-Cl, -4-Cl, -4-F, -2-CH₃, -4-CH₃, -3-NO₂, -4-NO₂, -4-OH, -3-OCH₃, -4-OCH₃, -4-Br
PHYSICAL CONSTANTS OF 1-{2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL)-3-PHENYLPROP-2-EN-1-ONES

![Chemical structure](image)

**R = Different substituents**

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<th>% Hydrogen (Calcd/Found)</th>
<th>% Nitrogen (Calcd/Found)</th>
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**EXPERIMENTAL PROCEDURE**

**N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide (IV)**

Compound 1-(1H-benzo[d]imidazol-2-yl)ethanone (0.01 mol) and benzohydrazide (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture were refluxed for 6 h. After cooling, the crystals formed were filtered and recrystallized from ethanol (95%) to give compound IV. Yield: 74%; m.p.: 178°C; Anal. calcd. for C₁₆H₁₄N₄O: C-69.05, H-5.07, N-20.13; Found: C-69.16, H-5.13, N-20.22%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-ethanone (V)**

Acetic anhydride (0.03 mol) was added to compound N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide (0.01 mol) and refluxed at 90 °C for 4 h. After cooling, the reaction mixture was poured into ice cold water. The precipitates were filtered, washed with water, dried and recrystallized from ethanol (95%) to give compound V. Yield: 71%; m.p.: 231°C; Anal. calcd. for C₁₈H₁₆N₄O₂: C-67.49, H-5.03, N-17.49; Found: C-67.60, H-5.11, N-17.57%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-phenylprop-2-en-1-one (VI) (GK1-1)**

A mixture of intermediate compound 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone (0.01 mol) and benzaldehyde (0.01 mol) was stirred in ethanolic potassium hydroxide for 20 min. at room temperature. After stirring, the reaction mixture was refluxed for 8 h and excess of solvent was distilled out to get final compound VI. Yield: 62%; m.p.: 201°C; Anal. calcd. for C₂₅H₂₀N₄O₂: C-73.51, H-4.94, N-13.72; Found: C-73.61, H-4.84, N-13.81%.

The progress of reaction and purity of compounds IV, V and VI were checked on TLC [Aluminium sheet silica gel 60 F₄₅₅ (E. Merck)] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
SECTION 2

PREPARATION OF 1-(2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL)-3-(2-CHLOROPHENYL)PROP-2-EN-1-ONES

SYNTHETIC SCHEME 2

R = H, -2-Cl, -3-Cl, -4-Cl, -4-F, -2-CH₃, -4-CH₃, -3-NO₂, -4-NO₂, -4-OH, -3-OCH₃, -4-OCH₃, -4-Br
### TABLE 2

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R = Different substituents
**EXPERIMENTAL PROCEDURE**

**N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide (IV)**

Compound 1-(1H-benzo[d]imidazol-2-yl)ethanone II (0.01 mol) and benzohydrazide III (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture were refluxed for 6 h. After cooling, the crystals formed were filtered and recrystallized from ethanol (95%) to give compound IV. Yield: 74%; m.p.: 178ºC; Anal. calcd. for C_{16}H_{14}N_{4}O: C-69.05, H-5.07, N-20.13; Found: C-69.16, H-5.13, N-20.22%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-ethanone (V)**

Acetic anhydride (0.03 mol) was added to compound N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide IV (0.01 mol) and refluxed at 90 ºC for 4 h. After cooling, the reaction mixture was poured into ice cold water. The precipitates were filtered, washed with water, dried and recrystallized from ethanol (95%) to give compound V. Yield: 71%; m.p.: 231ºC; Anal. calcd. for C_{18}H_{16}N_{4}O_{2}: C-67.49, H-5.03, N-17.49; Found: C-67.60, H-5.11, N-17.57%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-(2-chlorophenyl)prop-2-en-1-one (VI) (GK2-1)**

A mixture of intermediate compound 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone V (0.01 mol) and 2-chlorobenzaldehyde (0.01 mol) was stirred in ethanolic potassium hydroxide for 20 min. at room temperature. After stirring, the reaction mixture was refluxed for 8 h and excess of solvent was distilled out to get final compound VI. Yield: 61%; m.p.: 181ºC; Anal. calcd. for C_{25}H_{19}ClN_{4}O_{2}: C-67.80, H-4.32, N-12.65; Found: C-67.68, H-4.40, N-12.74%.

The progress of reaction and purity of compounds IV, V and VI were checked on TLC [Aluminium sheet silica gel 60 F_{245} (E. Merck)] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
SECTION 3

PREPARATION OF 1-{2-{1H-BENZO[d]IMIDAZOL-2-YL}-2-METHYL-5-{ARYL}-1,3,4-OXADIAZOL-3{2H}-YL}-3-{3-CHLOROPHENYL}PROP-2-EN-1-ONES

SYNTHETIC SCHEME 3
Studies on clinically important nitrogen and sulphur containing heterocyclic compounds

PHYSICAL CONSTANTS OF 1-(2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL)-3-(3-CHLOROPHENYL)PROP-2-EN-1-ONES

![Chemical Structure](image)

\[ R = \text{Different substituents} \]

**TABLE 3**

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<th>Sr.No.</th>
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<td>57.55 (57.67)</td>
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**EXPERIMENTAL PROCEDURE**

**N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide (IV)**

Compound 1-(1H-benzo[d]imidazol-2-yl)ethanone II (0.01 mol) and benzohydrazide III (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture were refluxed for 6 h. After cooling, the crystals formed were filtered and recrystallized from ethanol (95%) to give compound IV. Yield: 74%; m.p.: 178°C; Anal. calcd. for C\textsubscript{16}H\textsubscript{14}N\textsubscript{4}O: C-69.05, H-5.07, N-20.13; Found: C-69.16, H-5.13, N-20.22%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-ethanone (V)**

Acetic anhydride (0.03 mol) was added to compound N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide IV (0.01 mol) and refluxed at 90 °C for 4 h. After cooling, the reaction mixture was poured into ice cold water. The precipitates were filtered, washed with water, dried and recrystallized from ethanol (95%) to give compound V. Yield: 71%; m.p.: 231°C; Anal. calcd. for C\textsubscript{18}H\textsubscript{16}N\textsubscript{4}O\textsubscript{2}: C-67.49, H-5.03, N-17.49; Found: C-67.60, H-5.11, N-17.57%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-(3-chlorophenyl)prop-2-en-1-one (VI) (GK\textsubscript{3}-1)**

A mixture of intermediate compound 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone V (0.01 mol) and 3-chlorobenzaldehyde (0.01 mol) was stirred in ethanolic potassium hydroxide for 20 min. at room temperature. After stirring, the reaction mixture was refluxed for 8 h and excess of solvent was distilled out to get final compound VI. Yield: 64%; m.p.: 189°C; Anal. calcd. for C\textsubscript{25}H\textsubscript{19}ClN\textsubscript{4}O\textsubscript{2}: C-67.80, H-4.32, N-12.65; Found: C-67.67, H-4.41, N-12.74%.

The progress of reaction and purity of compounds IV, V and VI were checked on TLC [Aluminium sheet silica gel 60 F\textsubscript{245} (E. Merck)] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
SECTION 4

PREPARATION OF 1-(2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3[2H]-YL)-3-(4-CHLOROPHENYL)PROP-2-EN-1-ONES

SYNTHETIC SCHEME 4
Studies on clinically important nitrogen and sulphur containing heterocyclic compounds

PHYSICAL CONSTANTS OF 1-[2-(1H-BENZO[\text{d}IMIDAZOL-2-YL]-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL]-3-(4-CHLOROPHENYL)PROP-2-EN-1-ONES

![Chemical Structure](image)

R = Different substituents

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TABLE 4
EXPERIMENTAL PROCEDURE

\textbf{N’-}(1\textit{-}(1H-beno[\textit{d}]imidazol-2-yl)ethylidene)benzohydrazide (IV)

Compound \textit{1-}(1H-beno[\textit{d}]imidazol-2-yl)ethanone \textit{II} (0.01 mol) and benzohydrazide \textit{III} (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture were refluxed for 6 h. After cooling, the crystals formed were filtered and recrystallized from ethanol (95%) to give compound \textit{IV}. Yield: 74%; m.p.: 178ºC; Anal. calcd. for C\textsubscript{16}H\textsubscript{14}N\textsubscript{4}O: C-69.05, H-5.07, N-20.13; Found: C-69.16, H-5.13, N-20.22%.

\textit{1-}(2\textit{-}(1H-beno[\textit{d}]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-ethanone (V)

Acetic anhydride (0.03 mol) was added to compound \textit{N’-}(1\textit{-}(1H-beno[\textit{d}]imidazol-2-yl)ethylidene)benzohydrazide \textit{IV} (0.01 mol) and refluxed at 90 ºC for 4 h. After cooling, the reaction mixture was poured into ice cold water. The precipitates were filtered, washed with water, dried and recrystallized from ethanol (95%) to give compound \textit{V}. Yield: 71%; m.p.: 231ºC; Anal. calcd. for C\textsubscript{18}H\textsubscript{16}N\textsubscript{4}O\textsubscript{2}: C-67.49, H-5.03, N-17.49; Found: C-67.60, H-5.11, N-17.57%.

\textit{1-}(2\textit{-}(1H-beno[\textit{d}]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-(4-chlorophenyl)prop-2-en-1-one (VI) (GK4-1)

A mixture of intermediate compound \textit{1-}(2\textit{-}(1H-beno[\textit{d}]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone \textit{V} (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) was stirred in ethanolic potassium hydroxide for 20 min. at room temperature. After stirring, the reaction mixture was refluxed for 8 h and excess of solvent was distilled out to get final compound \textit{VI}. Yield: 62%; m.p.: 221ºC; Anal. calcd. for C\textsubscript{25}H\textsubscript{19}ClN\textsubscript{4}O\textsubscript{2}: C-67.80, H-4.32, N-12.65; Found: C-67.68, H-4.40, N-12.77%.

The progress of reaction and purity of compounds \textit{IV}, \textit{V} and \textit{VI} were checked on TLC [Aluminium sheet silica gel 60 F\textsubscript{245} (E. Merck)] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
SECTION 5

PREPARATION OF 1-(2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL)-3-(4-HYDROXYPHENYL)PROP-2-EN-1-ONES

SYNTHETIC SCHEME 5

R = -H, -2-Cl, -3-Cl, -4-Cl, -4-F, -2-CH₃, -4-CH₃, -3-NO₂, -4-NO₂, -4-OH, -3-OCH₃, -4-OCH₃, -4-Br
**PHYSICAL CONSTANTS OF 1-(2-(1H-BENZO[d]IMIDAZOL-2-YL)-2-METHYL-5-(ARYL)-1,3,4-OXADIAZOL-3(2H)-YL)-3-(4-HYDROXYPHENYL)PROP-2-EN-1-ONES**

![Chemical structure](image)

*R = Different substituents*

**TABLE 5**

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<td>-H</td>
<td>C_{25}H_{20}N_{4}O_{3}</td>
<td>64</td>
<td>232</td>
<td>70.74 (70.62)</td>
</tr>
<tr>
<td>GK5-2</td>
<td>-2-Cl</td>
<td>C_{25}H_{19}ClN_{4}O_{3}</td>
<td>69</td>
<td>201</td>
<td>65.43 (65.54)</td>
</tr>
<tr>
<td>GK5-3</td>
<td>-3-Cl</td>
<td>C_{25}H_{19}ClN_{4}O_{3}</td>
<td>67</td>
<td>217</td>
<td>65.43 (65.32)</td>
</tr>
<tr>
<td>GK5-4</td>
<td>-4-Cl</td>
<td>C_{25}H_{19}ClN_{4}O_{3}</td>
<td>72</td>
<td>231</td>
<td>65.43 (65.55)</td>
</tr>
<tr>
<td>GK5-5</td>
<td>-4-F</td>
<td>C_{25}H_{19}F_{4}N_{4}O_{3}</td>
<td>61</td>
<td>198</td>
<td>67.87 (67.71)</td>
</tr>
<tr>
<td>GK5-6</td>
<td>-2-CH_{3}</td>
<td>C_{26}H_{22}N_{4}O_{3}</td>
<td>65</td>
<td>241</td>
<td>71.22 (71.34)</td>
</tr>
<tr>
<td>GK5-7</td>
<td>-4-CH_{3}</td>
<td>C_{26}H_{22}N_{4}O_{3}</td>
<td>67</td>
<td>254</td>
<td>71.22 (71.35)</td>
</tr>
<tr>
<td>GK5-8</td>
<td>-3-NO_{2}</td>
<td>C_{26}H_{19}N_{5}O_{5}</td>
<td>75</td>
<td>200</td>
<td>63.96 (63.84)</td>
</tr>
<tr>
<td>GK5-9</td>
<td>-4-NO_{2}</td>
<td>C_{26}H_{19}N_{5}O_{5}</td>
<td>71</td>
<td>188</td>
<td>63.96 (63.85)</td>
</tr>
<tr>
<td>GK5-10</td>
<td>-4-OH</td>
<td>C_{26}H_{20}N_{4}O_{4}</td>
<td>67</td>
<td>265</td>
<td>68.17 (68.29)</td>
</tr>
<tr>
<td>GK5-11</td>
<td>-3-OCH_{3}</td>
<td>C_{26}H_{22}N_{4}O_{4}</td>
<td>62</td>
<td>227</td>
<td>68.71 (68.83)</td>
</tr>
<tr>
<td>GK5-12</td>
<td>-4-OCH_{3}</td>
<td>C_{26}H_{22}N_{4}O_{4}</td>
<td>70</td>
<td>209</td>
<td>68.71 (68.84)</td>
</tr>
<tr>
<td>GK5-13</td>
<td>-4-Br</td>
<td>C_{25}H_{19}BrN_{4}O_{3}</td>
<td>77</td>
<td>261</td>
<td>59.65 (59.76)</td>
</tr>
</tbody>
</table>
**EXPERIMENTAL PROCEDURE**

**N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide (IV)**

Compound 1-(1H-benzo[d]imidazol-2-yl)ethanone II (0.01 mol) and benzohydrazide III (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture were refluxed for 6 h. After cooling, the crystals formed were filtered and recrystallized from ethanol (95%) to give compound IV. Yield: 74%; m.p.: 178ºC; Anal. calcd. for C_{16}H_{14}N_{4}O: C-69.05, H-5.07, N-20.13; Found: C-69.16, H-5.13, N-20.22%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-ethanone (V)**

Acetic anhydride (0.03 mol) was added to compound N’-(1-(1H-benzo[d]imidazol-2-yl)ethylidene)benzohydrazide IV (0.01 mol) and refluxed at 90 ºC for 4 h. After cooling, the reaction mixture was poured into ice cold water. The precipitates were filtered, washed with water, dried and recrystallized from ethanol (95%) to give compound V. Yield: 71%; m.p.: 231ºC; Anal. calcd. for C_{18}H_{16}N_{4}O_{2}: C-67.49, H-5.03, N-17.49; Found: C-67.60, H-5.11, N-17.57%.

**1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (VI) (GK5-1)**

A mixture of intermediate compound 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)ethanone V (0.01 mol) and 4-hydroxy-benzaldehyde (0.01 mol) was stirred in ethanolic potassium hydroxide for 20 min. at room temperature. After stirring, the reaction mixture was refluxed for 8 h and excess of solvent was distilled out to get final compound VI. Yield: 63%; m.p.: 232ºC; Anal. calcd. for C_{25}H_{19}ClN_{4}O_{2}: C-67.80, H-4.32, N-12.65; Found: C-67.68, H-4.40, N-12.77%.

The progress of reaction and purity of compounds IV, V and VI were checked on TLC [Aluminium sheet silica gel 60 F_{245} (E. Merck)] plates using chloroform:methanol (9.5:0.5) as an irrigator and plates were visualized with ultraviolet (UV) light, or iodine vapour.
Studies on clinically important nitrogen and sulphur containing heterocyclic compounds

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