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BENZIMIDAZOLE-TRIAZOLE HYBRIDS WITH DIVERSE BIOLOGICAL ACTIVITIES: A SYSTEMATIC REVIEW

Nahana C. P.*[1], Shadiya C. K.[2], Akash Marathakam[3] and Vajid P. K.[4]

[1,2,3,4]Department of Pharmaceutical Chemistry, National College of Pharmacy.

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***Corresponding Author**
Nahana C. P.
Department of Pharmaceutical Chemistry, National College of Pharmacy.

ABSTRACT

Benzimidazole and triazole are important heterocyclic compounds and shown a wide range of pharmacological actions like antimicrobial, anti-inflammatory, antitubercular, anticancer and antiviral. On the other hand, molecular hybridization is a structural modification technique in the design of new ligands which consist of two or more pharmacologically active molecules in one structure. Benzimidazole and triazole can be fused using either functional group or bonds. Researchers hypothesised that these moieties might be joined to produce new or modified hybrid compound. This review summarized to know about the chemistry of benzimidazole-triazole hybrids along with theirpharmacological activities.

KEYWORDS: benzimidazole; triazole; hybrid; anti-cancer; anti-diabetic; anti-fungal.

INTRODUCTION

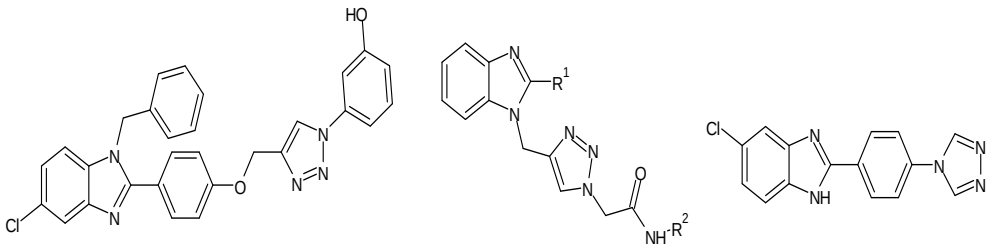
Benzimidazole is a fused heterocyclic ring system consisting of benzene and imidazole ring, it forms an integral part of vit. B_{12}.[1] The benzimidazole ring system is fully planar and in which the benzene ring is fused to the 4,5 position of imidazole ring.[2] The benzimidazole derivatives has wide range of biological activities including anti-arrhythmic, HIV-RT inhibitor[3], analgesic and anti-inflammatory[4], anti-cancer[5], antimicrobial[6], antiviral[7] and antitubercular.[8] To list a few benzimidazole derivatives Omeprazole, Triclabendazole, Mebendazole, Fenbendazole, Thiabendazole, Albendazole, Oxibendazole, Parbendazole, Luxabendazole, which are actively used in pharmacological field.

Although, triazole is a heterocyclic pharmacophore other than benzimidazole, containing three nitrogen atoms and two carbon atoms. Triazole occurs in two isomeric forms: 1,2,3

triazole and 1,2,4 triazole.[9] Triazole derivatives possess a wide range of pharmacological activities such as antibacterial[10,11], anti-cancer[12], antituberculosis[13], and anti-HIV.[14] Numerous triazole based derivatives are offered as medications, for example Fluconazole (antifungal drug), Ribavirin (antiviral drug), Letrozole (anticancer drug).[15]

Molecular hybridisation is a strategy for designing hybrid compound that two or more small molecules are linked together. These hybrid molecules improved the pharmacological activity.[16] Thus, hybrid compound, including benzimidazole and triazole have resulted in new chemical compound with magnified pharmacological activities such as anticancer[35], antidiabetic[43] and antifungal drugs[57] (Figure: 1).

This review is focused on the synthesis of benzimidazole-triazole hybrids with their biological activities such as anticancer, antidiabetic, antifungal and tyrosinase inhibitory activity.



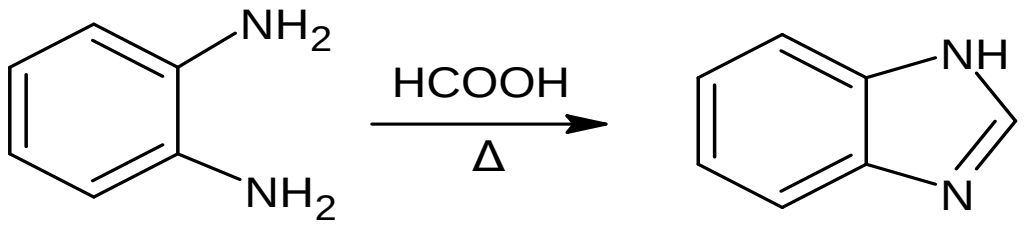
(a) Anticancer Activity (b) Antidiabetic Activity (c) Antifungal Activity

Figure 1:(a) 3-(4-((4-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl) phenoxy) methyl)-1H-1,2,3-triazol-1-yl) phenol, (b) substituted {4-[(1H-benzo-imidazol-1-yl)methyl]-1H-1,2,3-triazol-1-yl}- acetamides, (c)5-chloro-2-[4-(4*H*-1,2,4-triazol-4-yl)phenyl]-1*H*-benzimidazole.

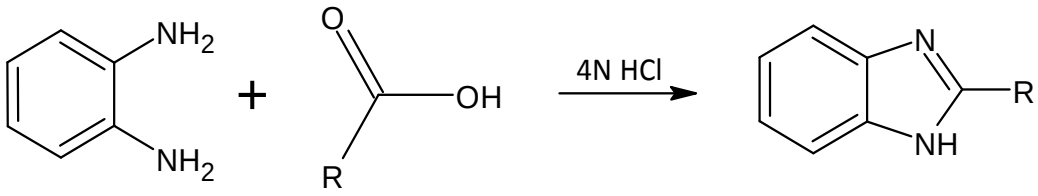
Synthesis of benzimidazole moiety and triazole moiety

During the survey, it was found that more than one fused motif is a powerful tool in research for the development of novel or modified pre-existing compounds. The different reaction procedures are explained in the given below. These reactions were used to synthesise benzimidazole and triazole motif's basic structure to produce a hybrid structure leading to pharmacologically active compound against the targeted disease or disorder.

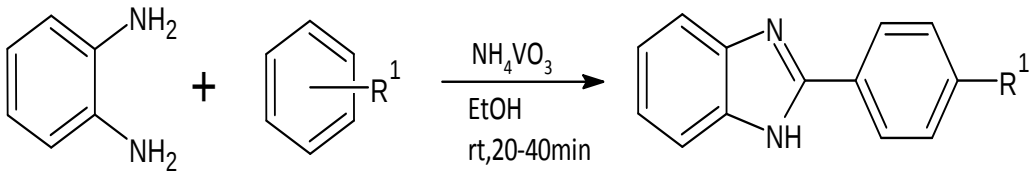
- Various general synthesis reaction of benzimidazole nuclei:



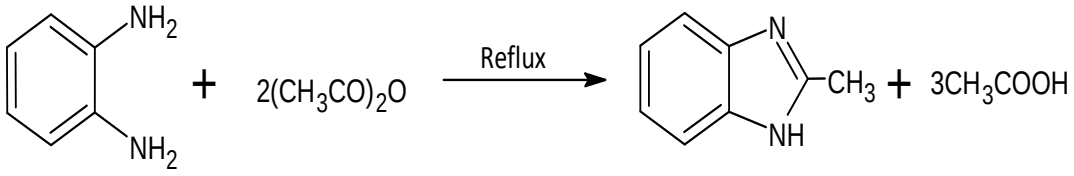
By reaction of o-phenylene diamine with formic acid.[17]



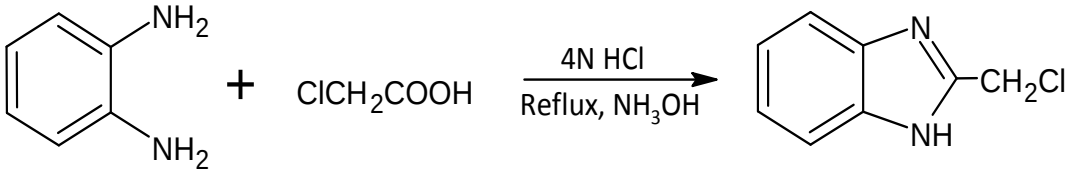
By reaction of o-phenylenediamine with carboxylic acid.[18]



By reaction of o-phenylenediamine with aldehyde.[19]



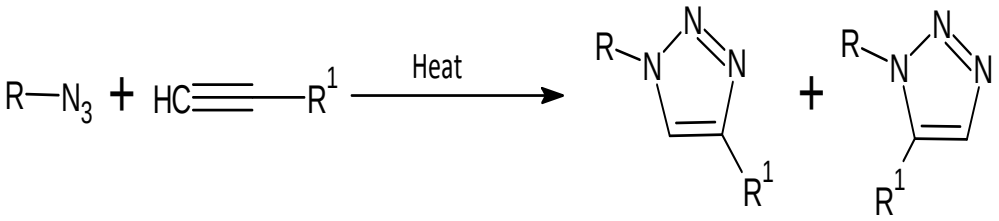
By reaction of o-phenylenediamine with acid anhydride.[20]



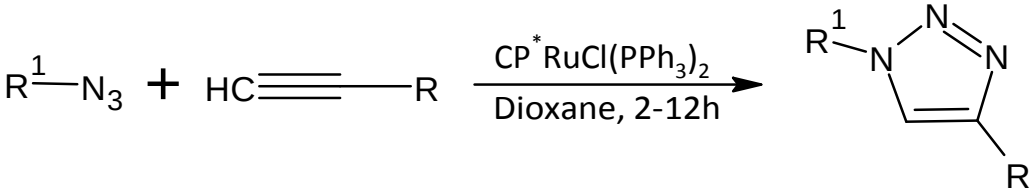
By reaction of o-phenylenediamine with chloroacetic acid.[21]

- Various general synthesis reaction of triazole nuclei:

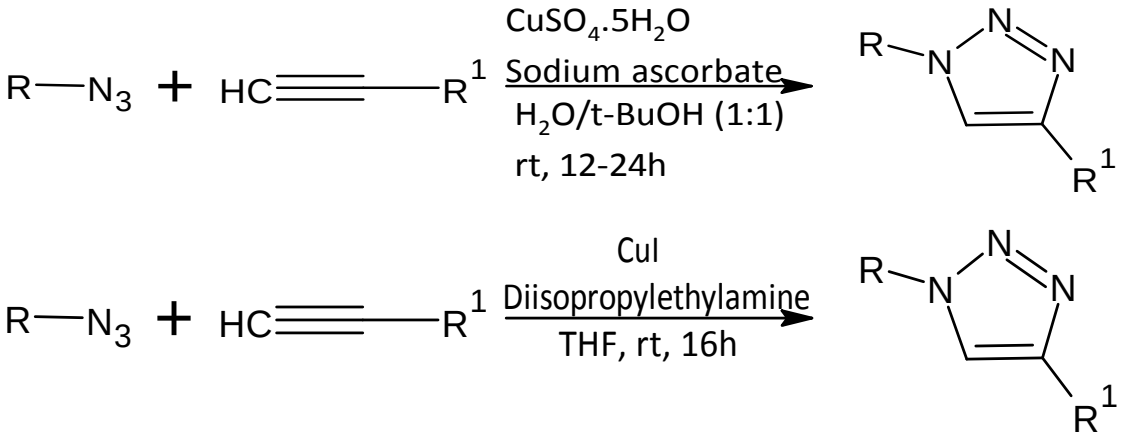
➢ 1,2,3-triazole



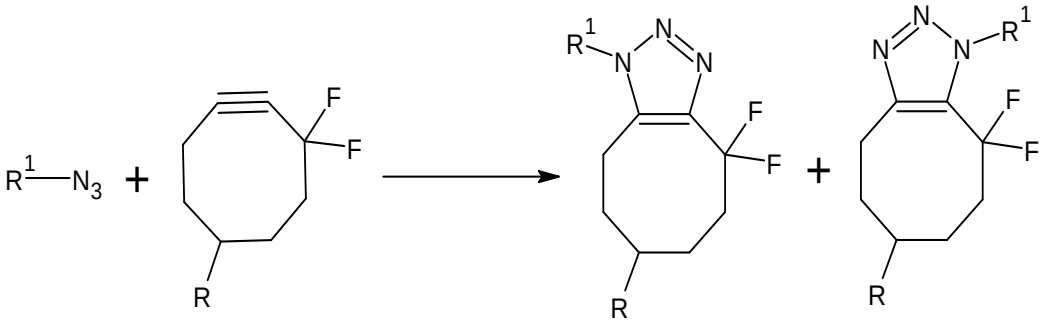
Huisgen azide-alkyne cycloaddition.[22]



Ruthenium catalysed azide-alkyne cycloaddition (RuAAC).[23]

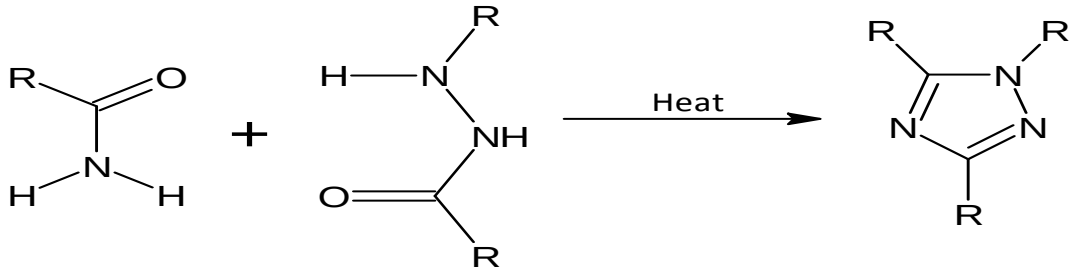


Copper catalysed azide-alkyne cycloaddition (CuAAC).[24]

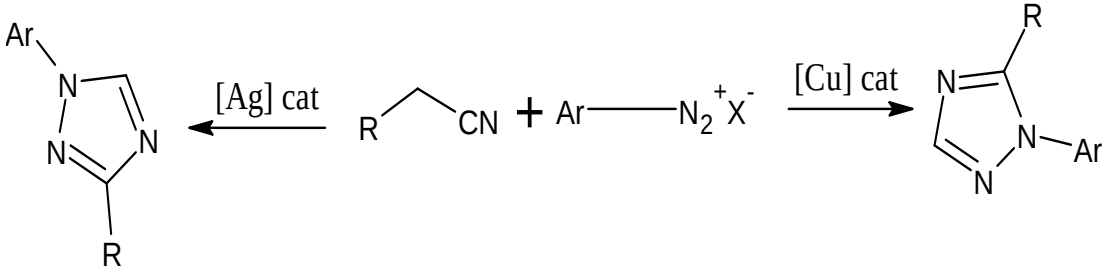


Strain-promoted azide-alkyne cycloaddition (SPAAC).[25]

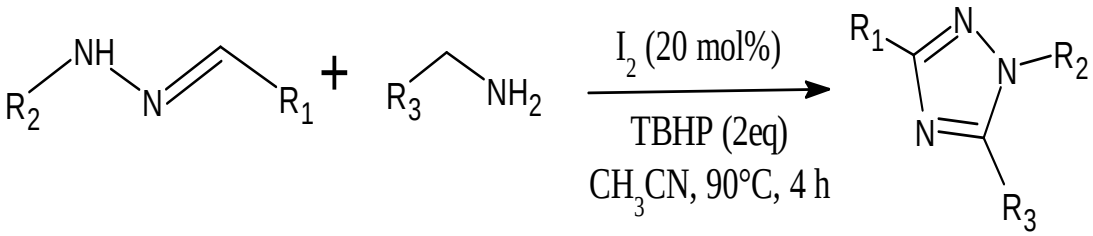
- 1,2,4-triazole



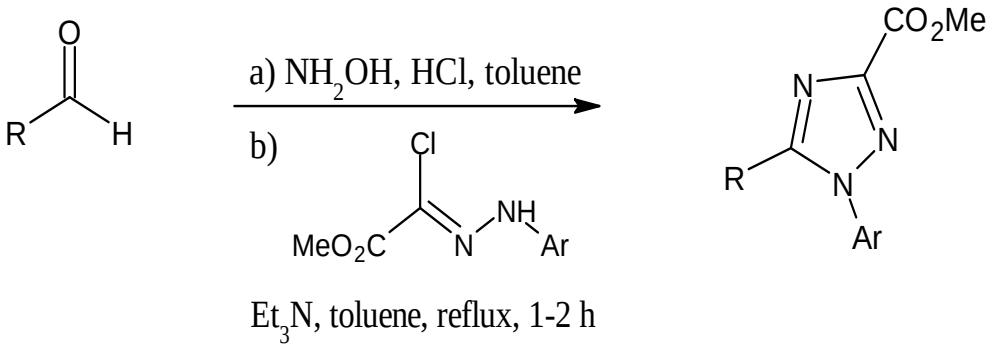
Pellizzari rection.[26]



By aryl diazonium salts and isocyanide [3+2] cycloaddition method.[27]



By reaction of hydrazones with amines.[28]



By reaction of hydrazonoyl hydrochlorides and aldehyde.[29]

Synthesis and pharmacological properties of hybrid of benzimidazole and triazole structure

According to the study of benzimidazole and triazole, it was found that both moieties possessed a vast variety of pharmacological action against many diseases like cancer, fungal

infections, tuberculosis, inflammation, helminths and viral infections. Therefore, combined two dynamic pharmacophores, benzimidazole and triazole, which are necessary to produce a synergistic effect, in order to better understand the subject, enhance the potential of the compounds and find the drug effective against a variety of diseases. Moreover, it is required to understand that the implementation of both the moieties as a hybrid single structure against various diseases (anticancer, antidiabetic, antifungal) with reference to their synthetic scheme and pharmacological activities. So, a brief explanation of the synthesis and activity of hybrid benzimidazole and triazole derivatives is provided below.

Anticancer activity

Cancer is the second major dreadful disease globally and around 1 in 6 persons are being diagnosed with cancer as per recent reports of the world health organisation (WHO).[30] In a molecular state cancer is identified as the conversion of a normal cell to carcinogenic cells, interfering in the cell's normal function like reproduction and apoptosis. These cells exhibit numerous differences in the biological process that result in abnormal cell proliferation when compared to normal cell.[31] The mechanism responsible for the normal cell conversion to cancer cell will be continuously studied in medical research and sciences.[32] The molecular mechanism of cancer cells leads to the tumour cell formation, which is caused by the high regulation of glycolytic catabolism and aerobic glycolysis, a process called "Warburg effect".[33] Despite of biological abnormalities, it is assumed that cancer is also brought on by viruses, radiation, and chemicals.[34] Chemotherapy, radiation and surgery are frequently used in cancer treatment. Chemotherapy is used as the first line treatment for eliminating cancer growth. An effective way to prevent the progression of cancer is to use cytotoxic medication to target cancer cells. Thus, benzimidazole and triazole hybrids are in continuous research for anticancer activity.

Goud NS et al., have synthesised a new series of benzimidazole-triazole hybrids as galectin (gal-1) mediated apoptosis-inducing agents followed by the evaluation of their cytotoxic activity against a panel of human cancer cell lines such as human keratinocyte cancer (HaCaT), lung cancer (A-549 and NCI-H460) and breast cancer (MCF-7 and MDA-MB-231) using MTT assay.[35]

The target benzimidazole-triazole hybrids (7a-t) were Synthesized by utilising Huisgen 1,3-dipolar cycloaddition reaction of terminal alkyne of benzimidazole intermediate (6) with various benzyl or phenyl azides in the presence of copper catalyst (scheme 1). This scheme

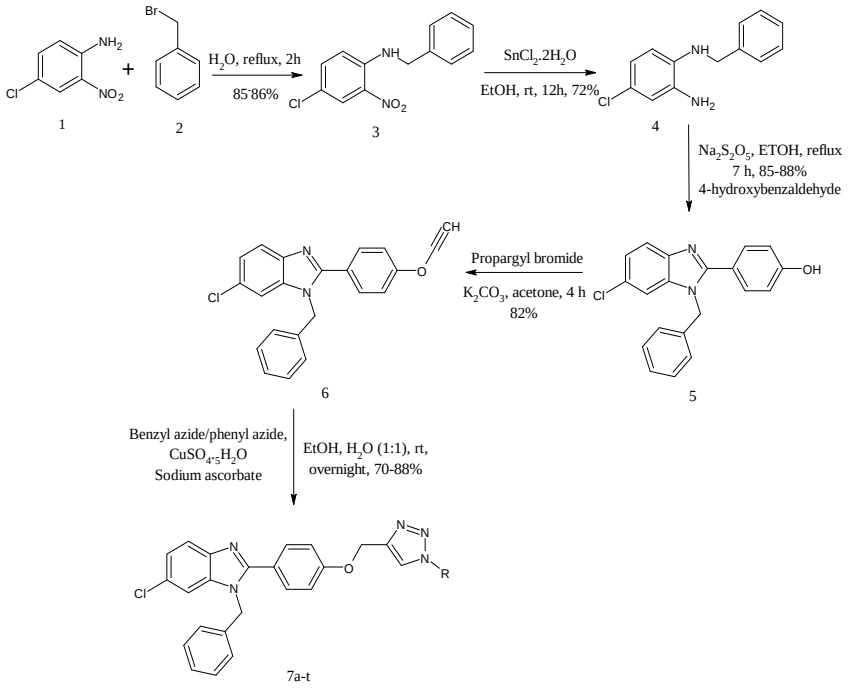
was started with the reaction of 4-chloro-2-nitroaniline and benzyl bromide were used to create N-benzyl-4-chloro-2-nitroaniline (3) in a sustainable manner.Further, the compound (3) was reduced with stannous chloride dehydrate offered N1-benzyl-4-chlorobenzene-1, 2-diamine (4). In the next step, the 4-hydroxy benzaldehyde was reacted with N1-benzyl-4-chlorobenzene-1,2-diamine (4) using ethanol in the presence of sodium metabisulphite furnished 4-(1-benzyl-6-chloro-1H-benzo[d]imidazol-2-yl) phenol intermediate (5), it had further provided 1-benzyl-6- chloro-2-(4-(prop-2-yn-1-yloxy) phenyl)-1H-benzo[d]imidazole (6) upon treatment with propargyl bromide in the presence of potassium carbonate using acetone. Finally, target compounds 7a-t were produced by 1,3-dipolar cycloaddition of benzimidazole intermediate (6) with different benzyl (or) phenyl azides.

Among the synthesized hybrids, compound 7c shown excellent growth inhibition against lung cancer (A-549 and NCI-H460) cells with an IC50 value of 0.63±0.21µm and 0.99±0.01µm respectively. The compound 7c also showed Significant a growth inhibition against breast cancer with IC50 value at 1.3±0.18µm and 0.94±0.02µm concentration in MDA-MB-23 cell lines.

Additionally, the target molecule 7c has been proved as a PET imaging agent by radiochemical synthesis using fluorine-18 radio nuclide in the GE Tracer-lab FX2N module (scheme 2).

Furthermore, JC-1 staining, DAPI staining, annexin V-FITC/PI and flow cytometric analysis were used to confirm that 7c induced apoptosis in lung cancer (A-549) cells as evidenced by a decrease in MMP levels, an increase in the proportion of apoptotic cells and subGI phase arrest.

Using an enzymatic ELISA study, the compound 7c significantly decreased gal-1 protein expression in a dose dependent manner. surface plasmon resonance (SPR) and fluorescence spectroscopy studies also supported the gal-1 interaction with compound 7c. The Possible of binding to the gal-1 was further supported by molecular docking studies.



7a R = Phenyl-

7b R = 2-methoxy Phenyl-

7c R = 3-hydroxy Phenyl-

7d R = 4--methyl Phenyl-

7e R = 4-trifluoro Phenyl-

7f R = 4-fluoro Phenyl-

7g R = 3-fluoro Phenyl-

7h R = 4-bromo Phenyl-

7i R = 4-nitro-2-Chloro Phenyl-

7j R = 3-nitro-4-methyl phenyl-

7k R = 3-nitro phenyl-

7l R = benzyl-

7m R = 2-nitro benzyl-

7n R = 4-nitro benzyl

7o R = 2-fluoro benzyl-

7p R = 3,5-difluoro benzyl-

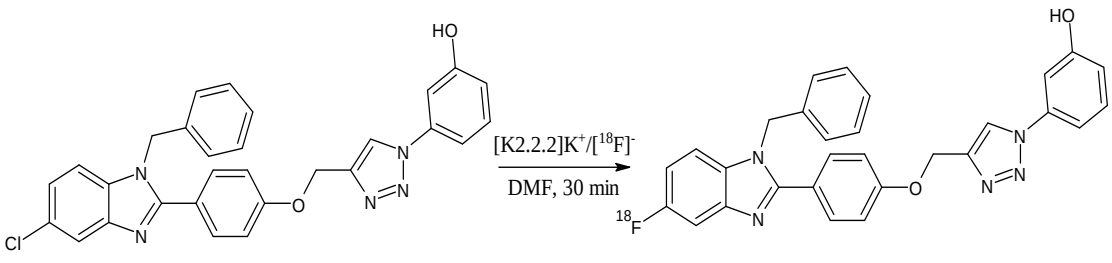
7q R = 4-bromo benzyl-

7r R = 2-bromo benzyl

7s R = 2,3-dimethyl phenyl

7t R = naphthyl-

Scheme 1: synthesis of different benzimidazole-triazole hybrids (7a-t).



compound 7c

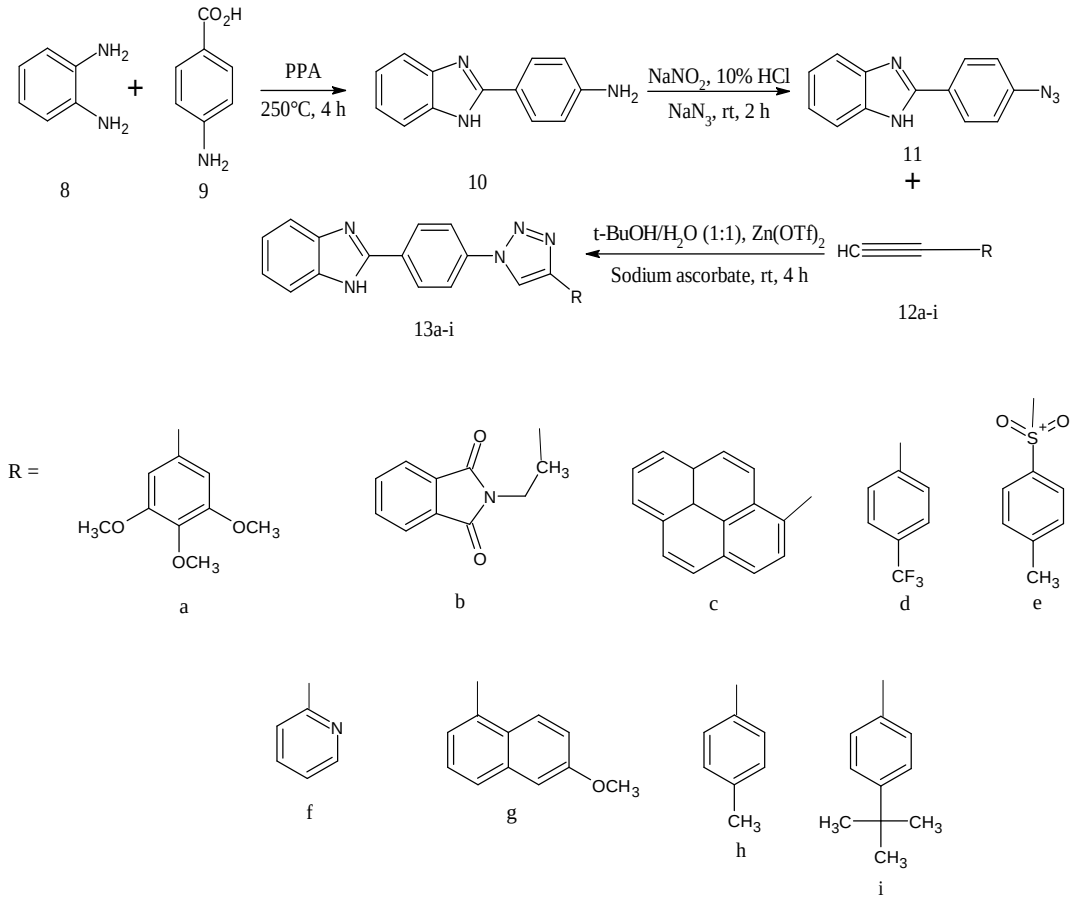
^{18}F-labelled compound ^{18}F-7c

Scheme 2: Radiolabelling of compound 7c with ^{18}F radionuclide.

A Series of benzimidazole-triazole hybrids were Synthesized and tested for their cytotoxity by Harkala KJ et al.[36] The target new benzimidazole linked 1,2,3 triazole congeners were

synthesized through the cyclization of terminal alkynes and azides (scheme 3). In scheme 3, O-phenylenediamine (8), 4-aminobenzoic acid (9), and enough polyphosphoric acid were combined. The resultant mixture was stirred at 250°C for 4 hours to produce compound 10. Compound 10 was diazotizated, followed by azidation, to produce compound 11. Compound 11 was then treated with various terminal alkynes in t-BuOH/H2O, sodium ascorbate, and $Zn(OTf)_2$ to produce further compounds.

Five human cancer cell lines were used to test the cytotoxicity of these synthesised congeners such as A375, B-16, colon-205, MC7-7 and A-549 by using MIT assay. These benzimidazole-triazole derivatives have demonstrated promising activity with IC50 values varying from 0.1 to 43µm. Among them, the compounds (13a,13b,13c and 13e) demonstrated comparable cytotoxicity to the Adriamycin reference drug.

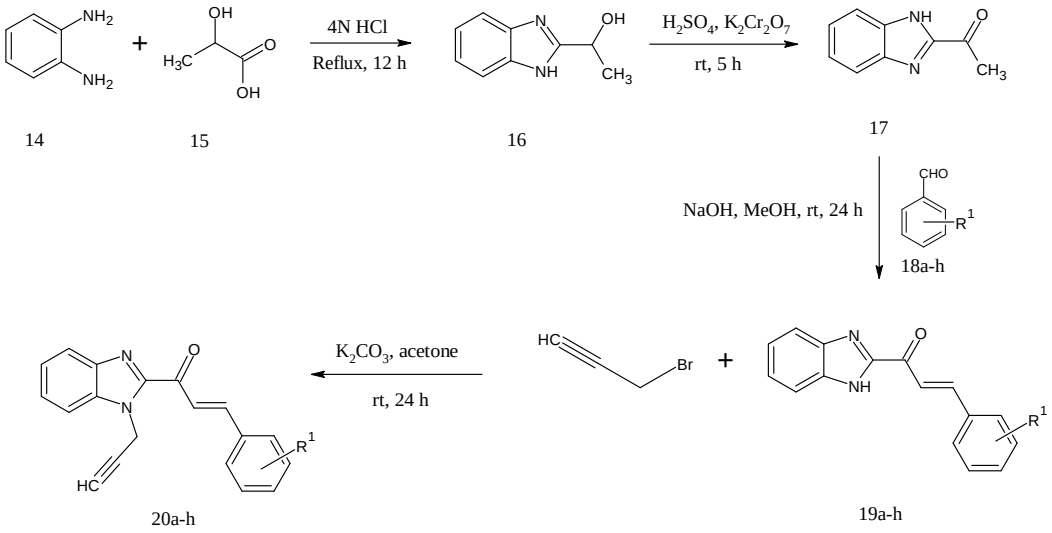


Scheme 3: synthetic scheme for novel benzimidazole linked triazole derivatives (13a-i).

A few years back, the synthesis of hybrids was accomplished by three motifs: benzimidazole, triazole and chalcone. A novel series of triazole-benzimidazole-chalcone hybrids were synthesized via click chemistry by Djemoui A et al.[37] The key intermediates N-propargyl -

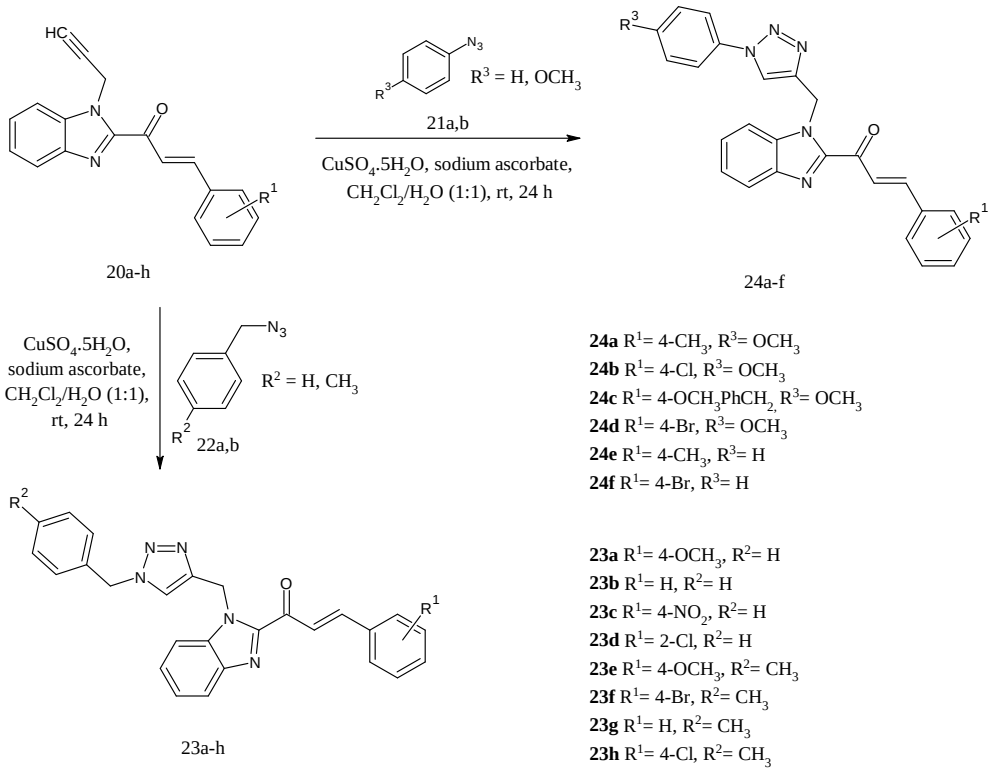
substituted benzimidazole-chalcone (20a-h) has been yielded by four step procedure, initiated by the reaction of o-phenylenediamine (14) with lactic acid (15), which on further reaction with potassium dichromate gives 2-acetyl benzimidazole (17). The compound 17 undergo aldol condensation with a series of substituted aromatic aldehyde (18a-h) gives benzimidazole chalcone derivatives (19a-h). In the final phase of the procedure, benzimidazole-chalcones (19a-h) were alkylated with propargyl bromide to produce N-propargylated compounds (20a-h) in excellent yield (scheme 4). The N-propargylated compounds (20a-h) was treated with the pre-synthetised azide derivatives (21a, b and 22a, b) in dichloromethane/water (1:1) as a solvent system and catalysed by $CuSO_4.5H_2O$ and sodium ascorbate at room temperature, leading to the synthesise of 1,2,3-triazole-benzimidazole-chalcone hybrids (23a-h and 24a-f) in good yield (scheme 3).

The synthesised compounds were screened for their anti-proliferative potential in breast cancer cell lines (T47-D and MDA-MB-231) and prostate cancer cell lines (PC3). Results of in-vitro anticancer activity showed that the presence of choro substituents at the chalcone ring of triazole-benzimidazole-chalcone structure enhanced the cytotoxic effect. The benzyl group linked to the 1,2,3-triazole ring provide more anti-proliferative potential.



14 15 16 17 18a-h 19a-h 20a-h

R^1 = **a)** 4-OCH_3, **b)** 4-Cl, **c)** H, **d)** 4-NO_2 **e)** 2-Cl, **f)** 4-Br **g)** 4-OCH_3PhCH_3, **h)** 4-CH_3



Scheme 4: Synthetic route for the preparation of benzimidazole-chalcone intermediates 20a-h and triazole-benzimidazole-chalcone hybrids 23a-h and 24a-f.

Antidiabetic Activity

Diabetes mellitus is a metabolic ailment which include two primary types: type 1 and type 2. Type 1 of DM is characterised by Insufficient insulin production from the body, whereas type 2 of DM is characterised by sufficient insulin production from the body but inefficient cell utilisation.[38] Injectable insulin is typically used to treat type 1 diabetes, whereas oral blood - glucose-lowering medications are the most common treatment for type 2 diabetes.[39] These drugs are work through Variety of mechanisms, one of the most Significant of these mechanisms is the suppression of carbohydrate-hydrolysing enzymes like glucosidase and amylase, which lowers the intestinal glucose absorption.[40] Acarbose, voglibose and miglitol are the clinically approved mediations in this class, are frequently reported to cause adverse effects such as diarrhoea, abdominal pain and other gastrointestinal Issues.[41] Therefore, designing better drug with low side effect for the treatment of diabetes has been challenging area for medicinal chemist, that leads to the formation of hybrid benzimidazole triazole derivatives.

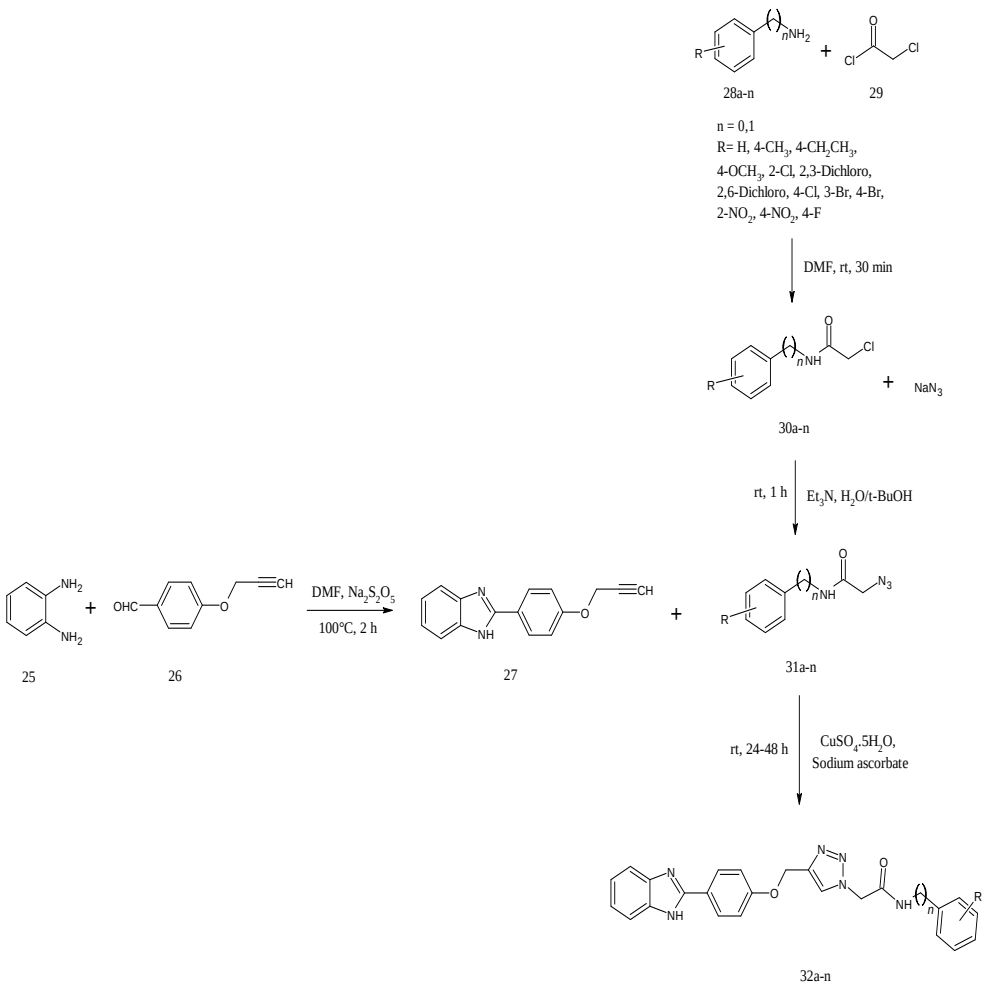
A variety of benzimidazole -triazole hybrids were reported byAsemanipoor N et al.[42] They designed and synthesized a series of benzimidazole -1,2,3-triazole hybrids (32a-n) as a new

α-glucosidase inhibitors. The synthetic route for the synthesis of benzimidazole-triazoles (32a-n) via click reaction has been depicted in scheme 4. In scheme 4, the two different intermediates were synthesized parallelly for the synthesis of the target compounds. 2-(4-(prop-2- ynyloxy)phenyl)-1H-benzo[d]imidazole (27) was synthesised by reaction between o-phenylenediamine (25) and 4-(prop-2- ynyloxy) benzaldehyde (26) in the presence of $Na_2S_2O_5$ in DMF at 100 °C. On the other hand, at room temperature, amines (28a–n) reacted with chloroacetyl chloride (29) in DMF to produce N-phenyl (or benzyl)-2-chloroacetamides (30a-n). In order to produce the appropriate molecules to participate in the click reaction, N-phenyl-2-chloroacetamides (30a-n) and sodium azide reacted in the mixture of H_2O and t-BuOH (1:1) in the presence of triethylamine at room temperature to give azide derivatives (31a-n). Then, to the recently made azide derivatives (31a-n), a mixture of 2-(4-(prop-2-ynyloxy)phenyl)-1H-benzo[d]imidazole (27), sodium ascorbate, and copper(II) sulphate (CuSO4) was added and the reaction was carried out at room temperature for 24-48 hours to produce the target compounds (32a-n).

The synthesized compounds (32a-n) were screened for their in-vitro α-glucosidase inhibition against yeast α-glucosidase. Results of in-vitro α-glucosidase inhibition activity showed that all synthesized compounds had higher inhibitory activity than the standard drug acarbose (IC50 – 750.0±125μm), with IC50 value ranging from 25.2±0.9 to 176±6.7μm and among them, the compounds 32c,32k,32b,32a and 32f are the most potent compounds with IC50 values 25.2±0.9, 35.0±1.0, 43.1±1.5, 51.5±1.8, and 56.6±2.1μm respectively.

They perform enzyme kinetic study on the most potent compound 32c revealed that this compound was a competitive inhibitor into α-glucosidase. Additionally, the docking analysis was conducted to evaluate the interaction modes of the synthesized compounds in the active site of α-glucosidase and to explain structure-activity correlations of the most potent compounds and their corresponding analogues using Autodock Tools (version 15.6).

Furthermore α-amylase inhibition assay on the most active α-glucosidase inhibitors 32c, 32k and 32a was performed and the obtained results revealed that these compounds were inactive against α-amylase (at 300 μm) when compared with acarbose as standard.

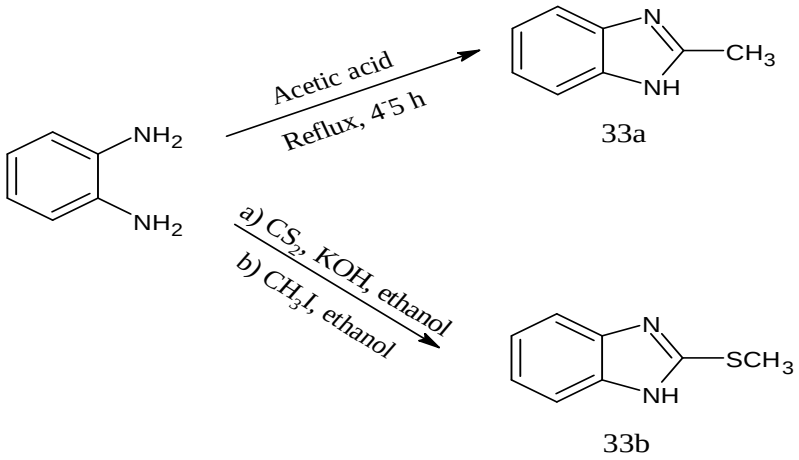


Scheme 5: synthetic scheme for benzimidazole-1,2,3-triazole hybrids (32a-n)

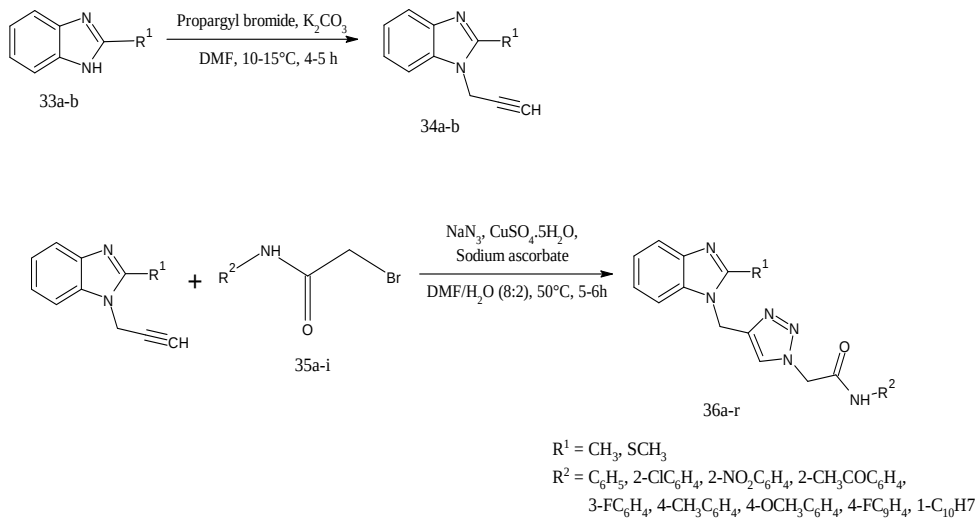
Deswal L et.al., have synthesized some novel benzimidazole tethered 1,2,3 triazole derivatives (25a-r) and evaluated for their antidiabetic activity.[43] The targeted derivatives were synthesized by Cu(I)-catalysed Huisgen 1,3-dipolar cycloaddition reaction between 2-substituted 1-(prop-2-yn-1-yl)-1H-benzo[d] imidazole and in situ azide (scheme 7).

The pre-requisite compounds, 2-methyl-1*H*-benzimidazole (33a) and 2-(methylthio)-1H-benzimidazole (33b) was previously synthesised by reflux of o-phenylenediamine with acetic acid and by reaction of o-phenylenediamine with carbon disulfide and methyl iodide in ethanol respectively (scheme 6), Which later on treatment with propargyl bromide in the presence of potassium carbonate in DMF leads to the formation of 2-substituted 1-(prop-2-yn-1-yl)-1H-benzo[d]imidazoles (34a-b). Further treatment of compounds 34a-b using N-substituted 2-bromoacetamides (35a-i) and sodium azide in the presence of copper sulfate in DMF along with sodium ascorbate, resulted in an target compounds, substituted {4-[(1H-benzoimidazol-1-yl)methyl]-1H-1,2,3- triazol-1-yl}-acetamides (36a–r).

The synthesized compounds were evaluated for their antidiabetic activity using α-amylase inhibition and α-glucosidase inhibition assay. On the biological evaluation of these synthesized compound, the compounds 36e,36g,36n and 36p showed good inhibitory activity against α-amylase and 36e, 36g and 36n were found to be more potent against α-glucosidase. Furthermore, docking studies were used to determine binding conformation of the most active compounds.



Scheme 6: synthesis of compounds 33a and 33b.



Scheme 7: synthetic scheme for substituted {4-[(1H-benzoimidazol-1-yl)methyl]-1H-1,2,3- triazol-1-yl}-acetamides.

Antifungal Activity

Recently, the prevalence of systemic fungal infection has increased and has become a significant source of morbidity and mortality among immunocompromised people, such as those receiving Chemotherapy for cancer or organ transplants or those with AIDS.[44,45]

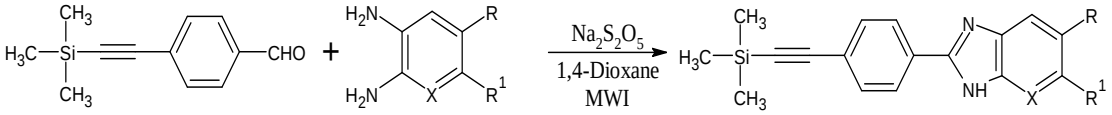
Fungal cells are of two basic morphological types: yeasts (unicellular fungi) and molds (pools of cells containing hyphae). A small number of categorized fungi are responsible for pathological states that cause life-threatening illnesses, despite the fact that most fungal cells are beneficial in many aspects for improved physiological functioning.[46] Candida, Aspergillus, Mucorales, Fusarium and other mould species such as Scedosporium, are among the pathogens that cause fungal infection. The immunological capacity of the patient typically determines how series the fungal infection is in patient.[47] Due to an increase in immunocompromised hosts, the incidence of fungal infection has dramatically increased during the past 20 years.[48] The use of central venous catheters and implantable prosthetic devices, parenteral nutrition, chronic antibiotic use, extended stay in intensive care units, haemodialysis, immunosuppression, organ transplantation, HIV, neutropenia. and the use of glucocorticosteroids, chemotherapeutic agents, and Immunomodulators are among the most frequent cause of this challenge.[49-54] Thus, it is necessary to innovatively synthesize the novel antifungal drugs.

In order to create new antifungal medications, it is important and effective to combine the triazole ring with other pharmacophore like benzimidazole ring. Numerous studies have recently concentrated on this area, leading to the development of numerous novel structural compounds with effective antifungal properties.

A novel series of benzimidazole-1,2,3-triazole hybrid molecules were prepared and tested as antifungal / anti-bacterial agents by Ouahrouch A et al.[55] Three step synthesis was done for the synthesis of targeted derivatives. In the first step involve the condensation of 4 (trimethylsilylethynyl) benzaldehyde (37) with substituted o-phenylenediamine to get 2-(4-(2-(trimethylsilyl)ethynyl)phenyl) benzimidazole derivatives (38a-i) (scheme 8). In second step, the trimethylsilyl group was removed by reacting the products 38a-i with tetrabutylammonium fluoride to obtain the terminal acetylene linked to the benzimidazole core (39a-i) (scheme 9). Next the compounds 39a-i reacted with 2-(azido methoxy) ethyl acetate in Cu alkyne-azide cycloaddition (CUAAC) to generate 1,2,3 triazole ring under microwave irradiation (40a-i). The next step is the cleavage of acetyl group to get the hydroxy group of the corresponding hybrid molecules 41a-h (scheme 10).

The newly synthesized compounds were tested for their in-vitro antimicrobial activity against gram-negative and gram-positive bacteria and also the newly synthesized compounds 41a-h were screened for their in-vitro antifungal activity against two phytopathogenic fungi

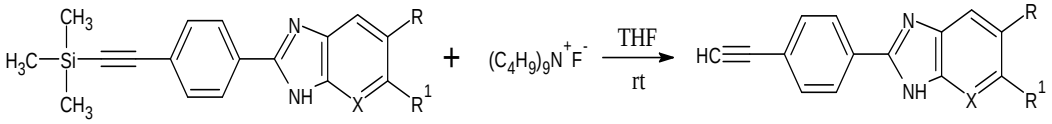
verticillium dahliae kleb (VD) and fusarium oxysporum f. sp. albedinis (foa) by using mycelia linear growth method and sporulation test. The compound 41e showed a moderate inhibition in foa sporulation test.



37 38a-i

a: X=C, R=H, R^1=H **b**: X=C, R=Me, R^1=H **c**: X=C, R=Me, R^1=Me
d: X=C, R=OMe, R^1=H **e**: X=C, R=CF_3, R^1=H **f**: X=C, R=F, R^1=H
g: X=C, R=NO_2, R^1=H **h**: X=N, R=H, R^1=H **i**: X=C, R=Cl, R^1=Cl

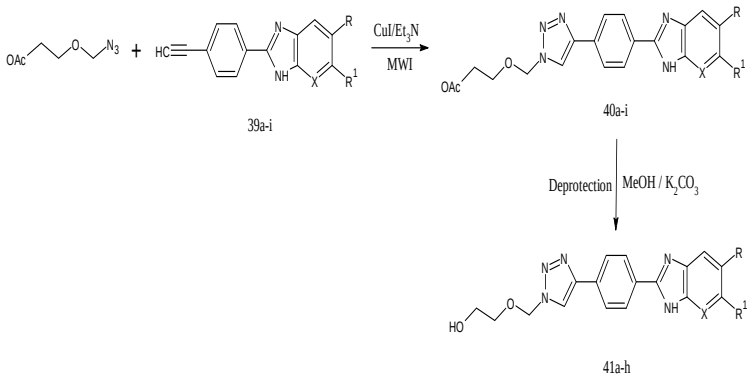
Scheme 8: condensation reaction to 38a–i of 4-(trimethylsilylethynyl)benzaldehyde(37) with substituted o-phenylenediamines.



38a-i 39a-i

a: X=C, R=H, R^1=H **b:** X=C, R=Me, R^1=H **c:** X=C, R=Me, R^1=Me
d: X=C, R=OMe, R^1=H **e:** X=C, R=CF_3, R^1=H **f:** X=C, R=F, R^1=H
g: X=C, R=NO_2, R^1=H **h:** X=N, R=H, R^1=H **i:** X=C, R=Cl, R^1=Cl

Scheme 9: deprotection of 38a-i to obtain free acetylenic compounds 39a-i.



39a-i 40a-i 41a-h

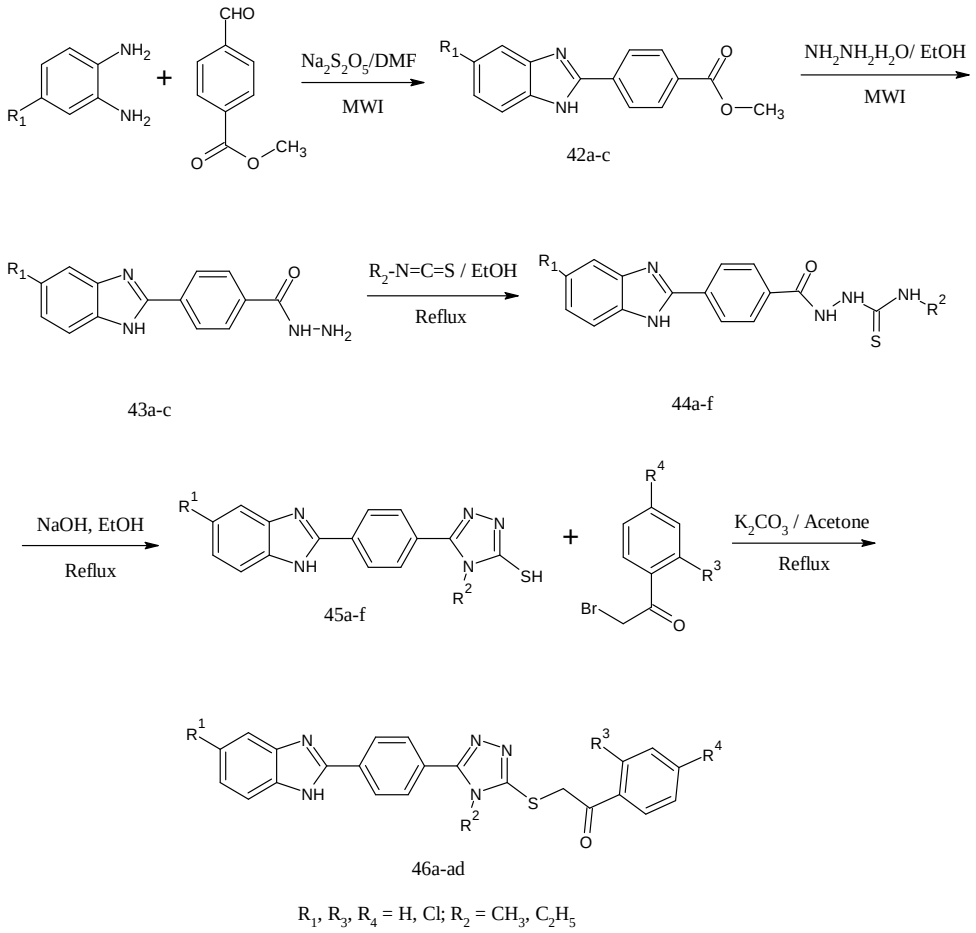
a: X=C, R=H, R^1=H **b:** X=C, R=Me, R^1=H **c:** X=C, R=Me, R^1=Me
d: X=C, R=OMe, R^1=H **e:** X=C, R=CF_3, R^1=H **f:** X=C, R=F, R^1=H
g: X=C, R=NO_2, R^1=H **h:** X=N, R=H, R^1=H **i:** X=C, R=Cl, R^1=Cl

Scheme 10: microwave assisted Cu alkyne–azide cycloaddition to 40a–i followed by deprotection to 41a–h.

Karaca Gençer H et al., have designed a new hybrid compound that consists of benzimidazole ring and 1,2,4-triazole ring.[56] They synthesized a new series of 2-((5-(4-(5- substituted-1H-benzimidazole-2-yl)phenyl)-4-substituted-4H-1,2,4-triazole-3-yl)thio)-1-(substituted

phenyl)ethan-1-one derivatives. The researchers tried to synthesize the hybrid derivatives of benzimidazole-triazole (46a-ad) in accordance with scheme 11. In the beginning, methyl 4-formylbenzoate and the corresponding o-phenylenediamine were reacted in the presence of $Na_2S_2O_5$ to generate methyl 4-(5(6)-substituted-1H-benzimidazol-2-yl)benzoate derivatives(42a-c). In the second reaction step, excess hydrazine hydrate was used to react 4-(5(6)-substituted-1H-benzimidazol-2-yl)benzoate derivatives(42a-c) to produce 4-(5(6)-substituted-1H-benzimidazol-2-yl)benzoic acid hydrazides(43a-c). In the third step, alkyl isothiocyanates were used to treat benzimidazole-hydrazides (43a-c) to produce compounds 44a-f, which were subsequently converted by the action of NaOH into 5-substituted-1,2,4-triazole-3-thiols (34a-f) (45a-f). The target compounds (46a-ad) were produced in the final step via a substitution reaction between 2-bromoacetophenones and compounds 45a-f.

Then, these hybrids were evaluated for anticandidal activity against candida species such as C. albicans (ATCC 24433) C. krusei(ATCC bass), C. parapsikosis (ATCC 22019) and C. glabrata (ATCC 900.30) and also invitro cytotoxic effect of the final compounds were tested by MTT assay. Among the synthesised derivatives, the derivative46w was the active derivative and which displayed antifungal efficacy comparable to that of the standard medication's fluconazole and ketoconazolewith an MIC50 value of 0.75 µg/ml against candidaspecies. With MIC50 values ranging between 0.78-1.56 µg/ml the derivatives 46m, 46r, 46t, 46y, 46ab, and 46ad also shown antifungal activity comparable to that of reference drugs. Cytotoxic evaluation of selected compounds (46m, 46o, 46r, 46w, 46y, 46ab and 46ad) revealed that compounds 46w and 46ad were the least cytotoxic agent. The results of cytotoxicity demonstrate that the antifungal activity of compounds46w and 46ad can be attributed to the selective action against candida species rather than to their general toxicity. They also perform the ergosterol level quantification assay and flow fluorescence microscopy Studies. The findings of these studiesindicated that the compounds mechanism of action is connected to the inhibition of ergosterol biosynthesis, which may subsequently results in altered membrane fluidity, plasma membrane biogenesis and fungi functions.



R_1, R_3, R_4 = H, Cl; R_2 = CH_3, C_2H_5

Scheme 11: synthetic scheme for 2-(5-(4-(5- substituted-1H-benzimidazole-2-yl)phenyl)-4-substituted-4H-1,2,4-triazole-3-yl)thio)-1-(substituted phenyl)ethan-1-one derivatives. (46a-ad)

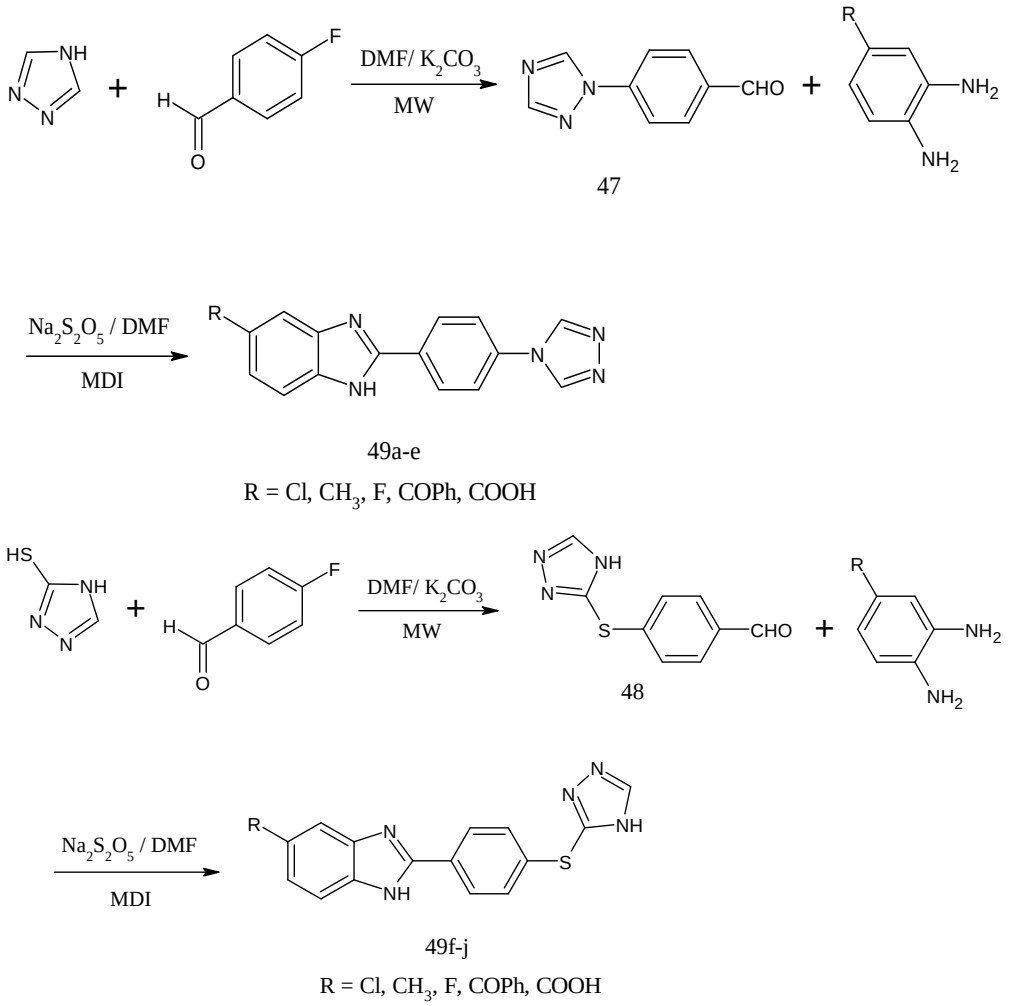
Asaf Evrim Evren etal., synthesized a new benzimidazole-triazole derivativefollowed by the evaluation of their antimicrobial /antifungal activity.[57] In this study, they synthesized target derivatives in two steps. First, 4-benzaldehyde derivatives (47,48) are synthesized by reacting 1,2,4-triazole ring and 4-fluoro benzaldehyde. in the last step, the benzimidazole-triazole derivatives (49a-j) was obtained by the reaction of 4-benzaldehyde derivatives (47,48) with 0-phenylenediamine derivatives under microwave radiation (scheme 12).

The synthesized derivatives are evaluated for their antimicrobial activity against six different types of bacteria (Escherichia coli ATCC 35218, E-coli ATCC 25922, Klebsiella Pneumoniae NCTC 9633, Pseudomonas aeruginosa ATCC 27853, Salmonella typhimurium ATCC 13311, Staphylococcus aureus ATCC 25923) and four different candida species (C.albicans ATCC 24433, C.glabrata ATCC 90030, C.krusei ATCC 6258, C.parapsilosis ATCC 22019). The synthesised compounds showed weak antibacterial activity. Whereas,

antifungal activity assay with candida species, compounds 49a (3.9 µg/ml), 49b (7.8 µg/ml) and 49c (3.9 µg/ml) were used as a standard drug ketoconazole (7.8 µg/mL) showed the same or higher activity.

The Compounds49a, 49b and 49c having chlorine, methyl and fluoro Substituents on the benzimidazole ring draw attention with increased activities when substituents effects on antifungal activity are taken into consideration.

Furthermore, they perform molecular docking of 49a, 49b and 49c compounds with Schrodinger Glide Xp against C.albican's sterol 14-alpha demethylase (CYP51) and estimated ADME calculation were analysed.



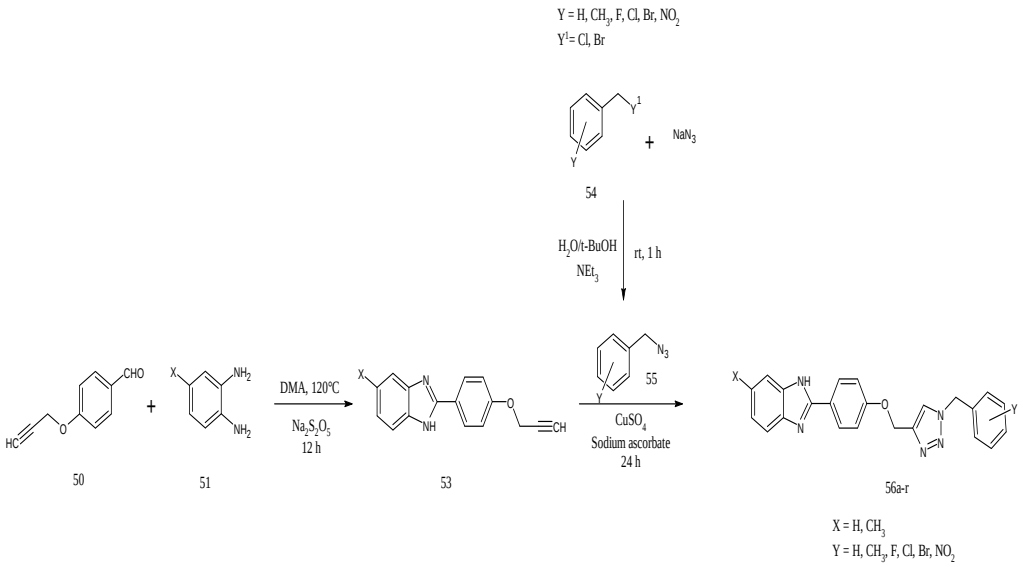
Scheme 12: synthetic scheme for benzimidazole-1,2,4-triazole derivatives (49a-j).

Tyrosinase inhibitor

Tyrosinase (EC 1.14.18.1), a copper containing enzyme and also known as polyphenol oxidase (PPO), is widely distributed in mammals, plants, bacteria and fungi.[58] It catalyses two reactions: hydroxylation of L -tyrosine to 3,4 -dihydroxy phenylalanine (L-DOPA) and oxidation of L -DOPA to dopaquinone.[59] In humans, dopaquinone is converted to melanin by a series of reactions and tyrosinase plays a crucial role in the synthesis of melanin which can cause to hyperpigmentation disorders such as melasma, seborrheic, etc.[60] In addition, tyrosinase is involved in determining the colour of mammalian skin and hair.[61] Tyrosinase is also linked to various neurodegenerative conditions like Parkinson's and Huntington's illnesses.[62,63] Thus, it is necessary to synthesize or identify effective tyrosinase inhibitors.

Mahdavi M et al., designed and synthesised a series of benzimidazole-1,2,3-triazole hybrids containing substituted benzyl moieties and d evaluated for their inhibitory activity against mushroom tyrosinase.[64] The synthetic route for the synthesis of target benzimidazole-1,2,3-triazole hybrids (56a-r) has been depicted in scheme 13. In scheme 13, 4 -(prop-2-yn-1-yloxy)benzaldehyde (50) and o -phenylenediamines(51) were reacted in the presence of $N_2S_2O_5$ in dimethylacetamide (DMA) at 120 °C for 12 h to produce compound 53. The target compounds (56a-r) were synthesized through click reaction. To do this, a variety of organic azides (55) were created by reacting various benzyl chlorides/bromides (54) with sodium azide in the presence of triethylamine (Net_3) in a solution of water and t-butanol at room temperature. The newly synthesised azides (55) were then added to compound 53, sodium ascorbate, and a catalytic quantity of $CuSO_4.5H_2O$ (7 mol%), resulting in the synthesis of various benzimidazole -1,2,3 -triazole hybrids 56a - r.

The synthesized derivatives are evaluated for their inhibitory activity against mushroom tyrosinase. The results of tyrosinase inhibitory activity indicated that 2-(4-((1-(3,4-dichlorobenzyl) -1H-1,2,3-triazol- 4-yl)methoxy)phenyl)-1H-benzo[d]imidazole (56g) and 2-(4-((1-(4-bromobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-benzo[d]imidazole (56h) showed effective inhibitory efficacy with IC50 values of 9.42 and 10.34 μM, respectively, comparable to that of kojic acid as the reference medication (IC50 = 9.28 μM). The researchers carry out kinetic analysis of compound 56g and found mixed-type inhibitory action towards tyrosinase. Additionally, molecular docking analysis was carried out to establish the binding mode of the most potent compounds (56g and 56h) in the tyrosinase active site.



Scheme 13: synthetic route for the synthesis of benzimidazole-1,2,3-triazole hybrids (56a-r).

CONCLUSION

This review explores numerous ways to synthesise benzimidazole and triazole by combining them in a variety of ways. As a result, benzimidazole and triazole are combined to form substituted compounds, which also involve other pharmacophores. Additionally, it has been found that they are effective in showing biological activities such as anticancer, antidiabetic, antifungal and tyrosinase inhibitory effects. As a result, it can provide us a different platform for exploring chemistry in order to synthesise and perhaps conduct investigations for their pharmacological properties.

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