Review

Benzimidazole-Triazole Hybrids as Antimicrobial and Antiviral Agents

Maria Marinescu *

Posted Date: 3 July 2023

doi: 10.20944/preprints202307.0093.v1

Keywords: benzimidazole; triazole; hybrids; antimicrobial; antiviral; pharmaceutical properties

Review

Benzimidazole-Triazole Hybrids as Antimicrobial and Antiviral Agents

Maria Marinescu

Department of Organic Chemistry, Biochemistry and Catalysis, Faculty of Chemistry, University of Bucharest, 030018 Soseaua Panduri, Romania; maria.marinescu@chimie.unibuc.ro

Abstract: Bacterial infections have attracted the attention of researchers in recent decades, especially due to the special problems they have faced, such as their increasing diversity and resistance to antibiotic treatment. The emergence and development of the SARS-CoV-2 infection stimulated even more research, to find new structures with antimicrobial and antiviral properties. Among the heterocyclic compounds with remarkable therapeutic properties, benzimidazoles and triazoles stand out, possessing antimicrobial, antiviral, antitumor, anti-Alzheimer, anti-inflammatory, analgesic, antidiabetic, or anti-ulcer activities. In addition, the literature of the last decade reports benzimidazole-triazole hybrids with improved biological properties compared to the properties of simple mono-heterocyclic compounds. This review aims to provide an update on the synthesis methods of these hybrids, along with their antimicrobial and antiviral activities, as well as the structure–activity relationship reported in literature.

Keywords: benzimidazole; triazole; hybrids, antimicrobial, antiviral, pharmaceutical properties

1. Introduction

Heterocyclic compounds have a central place in medicinal chemistry, being used as therapeutic agents to treat most diseases [1-3]. Among these heterocycles, benzimidazole stands out, as a purine-analog pharmacophore, with a wide biological activity, such as antimicrobial [4-8], antiviral [9,10], antihistamine [11,12], anticonvulsant [3,13], antitumor [14-16], proton pump inhibitors [17], antiparasitic [16,18,19], anti-inflammatory [20-22], or antihypertensive [23,24]. Some benzimidazoles are efficient agents in Diabetes mellitus [25-27], while astemizole compounds possess anti-prion activity to treat Creutzfeldt-Jakob disease [5,28]. The literature also reports anti-Alzheimer [29,30], psychoactive, anxiolytic, analgesic [31,32], and anticoagulant properties [33,34] of benzimidazole derivatives. Also, for triazole compounds, the literature mentions a series of therapeutic activities, such as antimicrobial [35-38], antitubercular [39,40], potential inhibitors of SARS CoV-2 [41-43], antiviral [43,44] anti-inflammatory [45,46] antitumor [47-50], antihypertensive [50], antioxidant [47,51,52] and antiepileptic [53,54]. Pharmacological applications of triazoles refer to their activity as α-glucosidase inhibitors [55,56], analgesic [50,57], anticonvulsant [53,58], and antimalarial agents [57,59]. Triazole derivatives are efficient in the treatment of Alzheimer's disease [60,61] and are very effective neuroprotective agents [62,63].

The successive events happened from the spring of 2020 up to and including the present, regarding the emergence and development of the COVID-19 pandemic, have led the scientific world to investigate more closely the possibility of treating this infectious disease with various antiviral [64-66], antimicrobial [67], immunomodulatory [68] or anti-inflammatory drugs [69], therefore, the discovery of new molecules with simple or hybrid structures, with biological properties that satisfy the requirements of the treatment of this condition it is absolutely necessary and constitutes the engine of the development of new effective therapeutic agents.

Classical drugs containing benzimidazole and triazole rings recommend these heterocycles as essential in building new target compounds with antimicrobial, antiviral, antiparasitic, etc. properties (Fig. 1). In addition, the literature mentions a series of benzimidazole-triazole hybrids with remarkable antimicrobial properties, antiviral activities, including new anti-SARS-COV-2 agents [70-74], with particular importance in the context of the recent pandemic, which led to the study of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

synthesis methods, antimicrobial properties, structure-property relationships and their biological activities. As expected, the study refers to both 1,2,3-triazole-benzimidazole hybrids and 1,2,4-triazole-benzimidazole hybrids, even if it seems that the literature is richer in the second category, in terms of antimicrobial activity.

In order to highlight the structures of the heterocycles in the discussed compounds, we colored benzimidazole nucleus with red, 1,2,3-triazole with blue and 1,2,4-triazole with green.

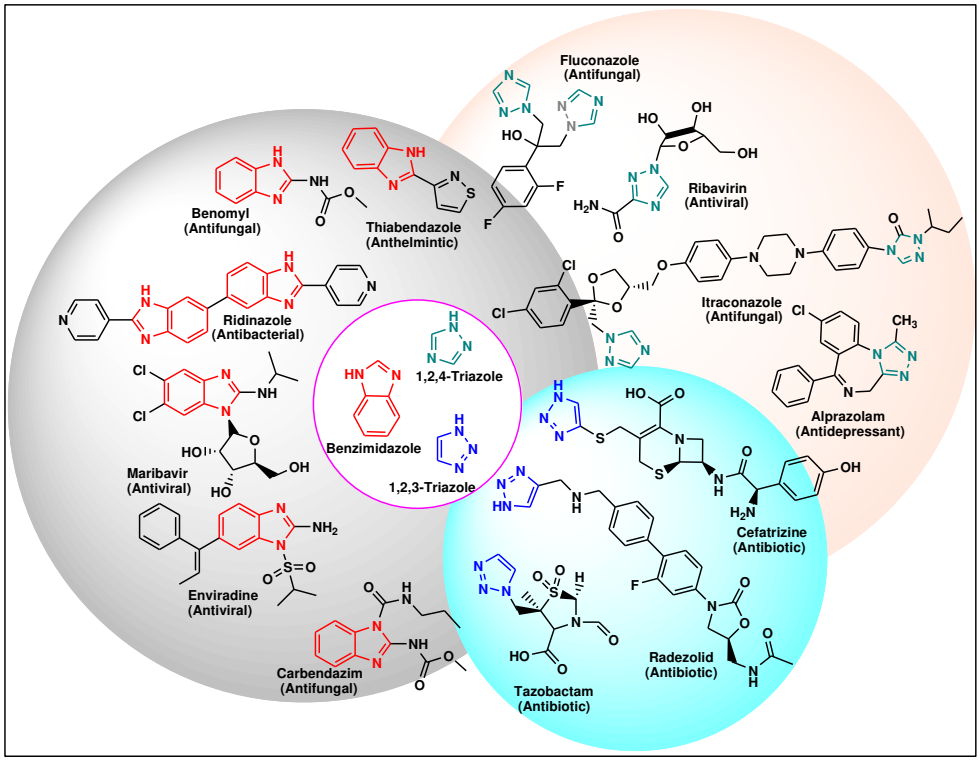


Figure 1. Chemical structures of some benzimidazole, 1,2,3-triazole and 1,2,4-triazole-based marketed drugs

The recent literature marks several strategies for the synthesis of 1,2,3-triazoles, like click reaction [75], Bouiton-Katritzky rearrangement [76], oxidative cyclization of hydrazones [77], post-cycloaddition functionalization [78], alkylation or arylation of triazoles [79]. Also, for benzimidazoles, the literature mentions several methods of synthesis, such as reaction of *o*-phenenediamine with aldehydes or ketones (Phillips-Ladenburg reaction) [3,80-82], with acids or their derivatives (Weidenhagen reaction) [81], or green methods of classic syntheses [80, 83-86].

In the following, we will present syntheses of benzimidazole-triazole hybrids with antimicrobial and antiviral properties.

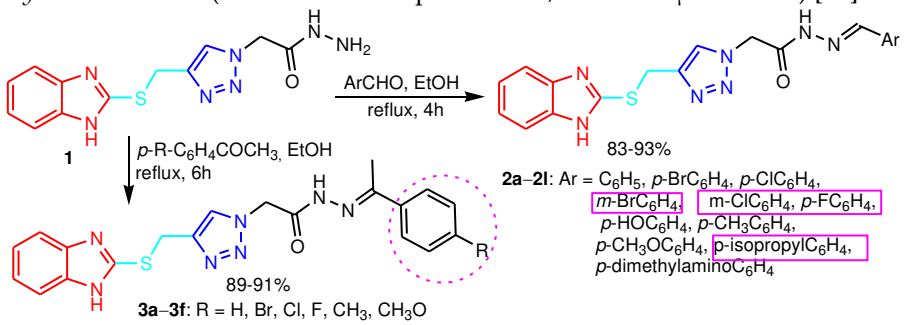
2. Synthesis and antimicrobial activities of benzimidazole-1,2,3-triazoles

2.1. 2-Benzimidazole-R(Ar)-1,4-disubstituted-1,2,3-triazole hybrids

Two series of new hybrids, 2-[4-((1*H*-benzimidazol-2-ylthio)methyl)-1*H*-1,2,3-triazol -1-yl]N`-(arylmethylidene)acetohydrazides (**2a**-**2l**) and 2-[4-((1*H*-benzimidazol-2-ylthio) methyl)-1*H*-1,2,3-triazol-1-yl]N-(α-arylethylidene)acetohydrazides (**3a**-**3f**) were prepared by Youssif et *al*. in two steps starting from 2-[4-((1*H*-benzimidazol-2-ylthio) methyl)-1*H*-1,2,3-triazol-1-yl] acetohydrazide **1** (Scheme 1). Compounds **2a**-**2l** exhibited pronounced antibacterial activity which ranged from 35-75% that of standard drug against *Staphylococcus aureus* and 50-80% that of Ciprofloxacin against *E. Coli* (MIC values of 3.125-12.5 μmol mL^{-1}). Compound **2k** showed the highest activity against *S. aureus* (75% activity, MIC = 12.5 μmol mL^{-1}), while compound **2d** was the most active derivative against *E. Coli* (80% activity, MIC = 3.125 μmol mL^{-1}). All the synthesized compounds were tested as potential antifungal agents against *Candida albicans* using Fluconazole as a reference drug. Compound **1** showed the activity of 48% of that of Fluconazole (MIC = 12.5 μmol mL^{-1}). Compounds **2e** and **2k** displayed the higher antifungal activity among the other derivatives as they showed 75% activity of that of Fluconazole (MIC = 3.125 μmol mL^{-1}). Compounds **3a**-**3f** exhibited moderate to good activity against *E. Coli* and their activity was 50-70% of that of Ciprofloxacin (MIC values of 6.25-12.5 μmol

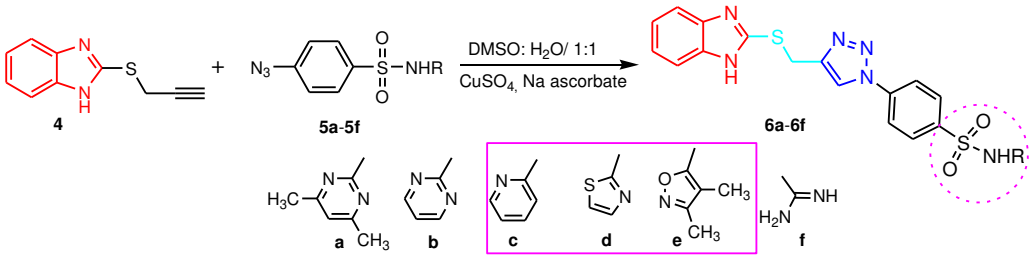
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

mL^{-1}), and that compounds **3a** and **3f** were the most active compounds against *E. coli* as they showed 70% of that of Fluconazole (MIC = 6.25 µmol mL^{-1}) while compound **3b** showed the highest activity against *Staphylococcus aureus* (65% of that of Ciprofloxacin, MIC = 18 µmol mL^{-1}) [87].



Scheme 1. Synthesis of benzimidazole-1,2,3-triazole hybrids **2a**-**2l** and **3a**-**3f**

Al-blewi et *al.* used an azide–alkyne Huisgen cycloaddition reaction carried out by simultaneously mixing thiopropargylated benzimidazole **4** with the appropriate sulfa drug azides **5a–5f**, copper sulfate and sodium ascorbate in DMSO/ H_2O to regioselectively furnish target mono-1,4-disubstituted-1,2,3-triazole tethered benzimidazole-sulfonamide conjugates **6a–6f** with 85–90% yields after 6–8 h of heating at 80 °C (Scheme 2). All compounds were evaluated for their antimicrobial activity (Table 1) against four pathogenic bacterial strains (Gram-positive: *Bacillus cereus* ATTC 10876, *Staphylococcus aureus* ATTC 25923 and Gram-negative: *Escherichia coli* ATTC 25922, *Pseudomonas aeruginosa* ATTC 27853 and two fungal strains, *Candida albicans* ATTC 50193, *Aspergillus brasiliensis* ATTC 16404). As can be seen in Table 1, compound **6a** shown the best antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* (64 µgmL^{-1}) and compounds **6c**, **6d** and **6e** the best antibacterial activity against against *Escherichia coli* (64 µgmL^{-1}) [88].



Scheme 2. Synthesis of benzimidazole-1,2,3-triazole hybrids **6a**-**6f**

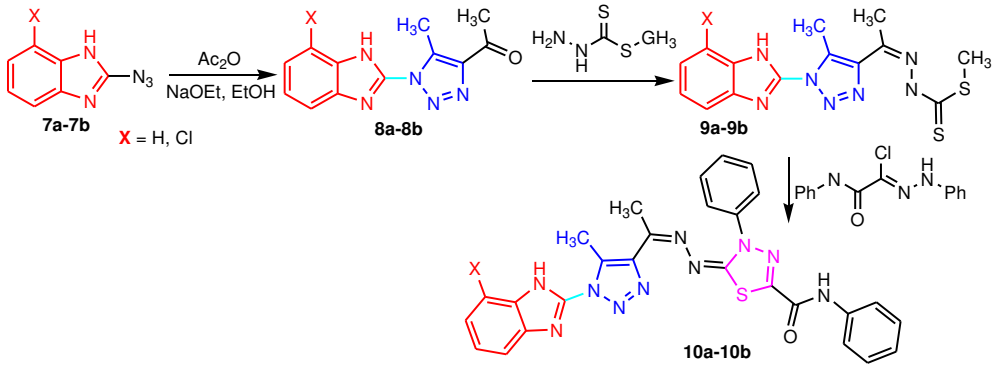
Table 1. Antimicrobial screening results of compounds **6a–6f** presented as MIC (µgmL^{-1}).

Compound	Gram-positive organisms		Gram-negative organisms		Fungi organisms	
	B.c.	*S.a.*	*P.a.*	*E.c.*	*A.b.*	*C.a.*
6a	64	64	256	128	128	128
6b	128	128	128	128	256	256
6c	256	128	256	64	256	156
6d	256	128	256	64	256	256
6e	256	128	256	64	256	256
6f	512	512	256	256	512	512
Ciprofloxacin	8	4	8	4	-	-

Rashdan et *al*. synthesized hybrids **10** starting from 2-azido-1*H*-benzo[d]imidazole derivatives **7a–7b** which reacted with acetylacetone in the presence of sodium ethoxide to obtain hybrids molecules **8a–8b**. The latter acted as a key molecules for the synthesis of new carbazone derivatives **9a–9b** that were submitted to react with 2-oxo-N-phenyl-2 (phenylamino)acetohydrazonoyl chloride to obtain the target hybrid derivatives **10a–10b** (Scheme 3). All compounds were screened for their *in vitro* antimicrobial activity against pathogenic microorganisms *Staphylococcus aureus, E. coli, Pseudomonas aeruginosa, Aspergillus niger*, and *Candida albicans*. The results showed that compounds **10a** and **10b** had strong activity against all the tested pathogenic microbes. Compounds

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

8a and **9a** only showed effects against the Gram-negative and Gram-positive bacteria and had no effect on the tested fungi. In addition, *in silico* and *in vitro* findings showed that compounds **10a** and **10b** were the most active against bacterial strains, and could serve as potential antimicrobial agents (Table 2). The hybrids **8–10** were subjected to molecular docking studies with DNA gyrase B and exhibited binding energy that extended from -9.8 to -6.4 kcal/mol, which confirmed their excellent potency. The compounds **10a** and **10b** were found to be with the minimum binding energy (-9.8 and -9.7 kcal/mol) as compared to the standard drug Ciprofloxacin (-7.4 kcal/mol) against the target enzyme DNA gyrase B [89].

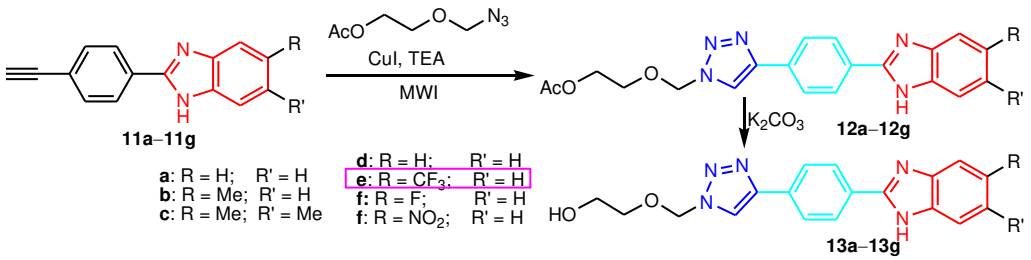


Scheme 3. Synthesis of benzimidazole-1,2,3-triazole hybrids **8a-8b**, **9a-9b** and **10a-10b**

Table 2. In vitro antimicrobial screening of hybrids **8**, **9** and **10** using the agar diffusion method.

Hybrids	Inhibition zone diameters using the agar diffusion method (mm)				
	S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
8a	15 ± 0.14	12 ± 1.08	22 ± 1.01	-	-
8b	-	5 ± 0.2	-	30 ± 1.16	27 ± 1.1
9a	23 ± 0.8	-	13 ± 0.65	-	-
9b	-	-	12 ± 0.8	14 ± 0.15	19 ± 1.04
10a	24 ± 0.6	25 ± 0.9	17 ± 0.75	20 ± 0.9	16 ± 0.89
10b	29 ± 1.2	21 ± 1.14	19 ± 0.79	18 ± 0.12	14 ± 0.58
Ciprofloxacin	20 ± 0.9	23 ± 1.02	21 ± 0.9	-	-
Nystatin	-	-	-	22 ± 0.18	23 ± 1.15

Compounds **11a–11g** with terminal acetylene and 2-(azidomethoxy)ethyl acetate were condensed using CuI as catalyst and triethylamine (TEA) under microwave irradiation, to achieve hybrids 1,2,3-triazole connected *via* benzene to the benzimidazole nucleus **12a–12g** with excellent yields (70-90%)(Scheme 2). The cleavage of the acetyl group using potassium carbonate (K_2CO_3) in methanol liberated the hydroxy group of the corresponding hybrid triazoles **13a–13g** in almost quantitative yields. Compounds **6a–6g** were screened for *in vitro* antifungal activities against two phytopathogenic fungi *Verticillium dahliae* Kleb and *Fusarium oxysporum* f. sp. *albedinis*. The result of the mycelia linear growth rate indicates that some of the compounds show a weak inhibition against the two fungi, the only compound that shows a significantly increased rate is compound **6e** with rate of 29.76% against *Verticillium dahliae* [90].

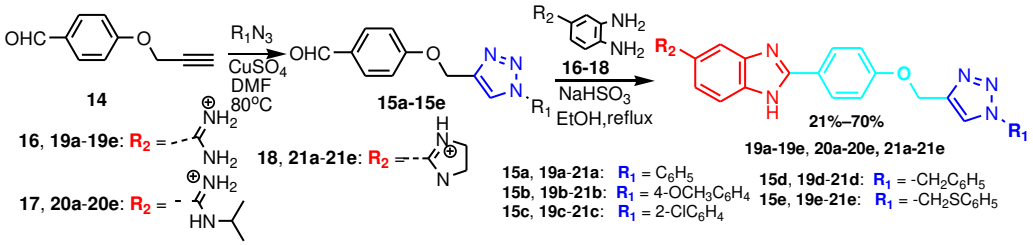


Scheme 4. Synthesis of benzimidazole-1,2,3-triazole hybrids **6a–6g**

Bistrović et *al*. synthesized in two steps hybrids **19a–19e**, **20a–20e** and **21a–21e** starting from 4-(prop-2-ynyloxy)benzaldehyde **14** (Scheme 5). All compounds were evaluated for their *in vitro*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

antibacterial activity against Gram-positive bacteria: *S. aureus* ATCC 25923, methicillin-sensitive *S. aureus*, *E. faecalis,* vancomycin-resistant *E. faecium*, and Gram-negative bacteria: *E. coli* ATCC 25925, *P. aeruginosa* ATCC 27853, *A. baumannii* ATCC 19606 and ESBL-producing *K. pneumoniae* ATCC 27736. Generally, compounds showed better activities against Gram-positive than Gram-negative bacteria. Compounds **20a–20e** with better binding affinity relative to other amidines, were the most active against *S. aureus* (MIC = 8–32 μgmL^{-1}). Compound **19a** was the most promising candidate because of its higher potency (MIC = 4 μgmL^{-1}) against ESBL-producing *E. coli* [91].



Scheme 5. Synthesis of benzimidazole-1,2,3-triazole hybrids **19a–19e**, **20a–20e** and **21a–21e**

Rao et *al.* synthesized hybrids **22a–22b** (Fig. 1), using click chemistry approach. Compounds had weak activity against *Mycobacterium bovis* strain (BCG values % inhibition = 27.3 and 26.2 respectively) [92]. Ashok et *al*. synthesized in three steps hybrids **26a–26j**, starting from 1*H*-indole-3-carbaldehyde **7** (Scheme 6). The compounds were evaluated for their antimicrobial activity against gram-positive *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633 and gram-negative *Proteus vulgaris* ATCC 29213, *Escherichia coli* ATCC 11229 bacteria using Gentamicin as standard. Antifungal activity was tested against *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 9029 strains with standard drug Fluconazole. Compounds **26b**, **26c** and **26h** with with MIC of

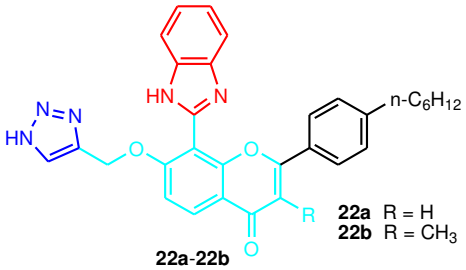
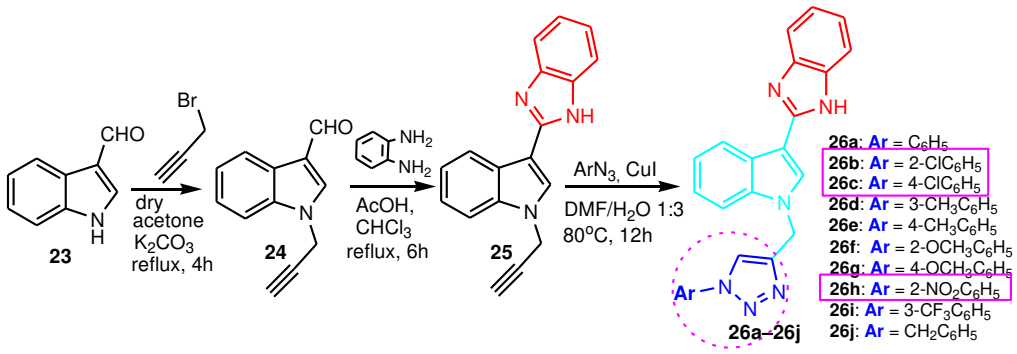


Figure 1. Structure of benzimidazole-1,2,3-triazole hybrids **22a–22b**

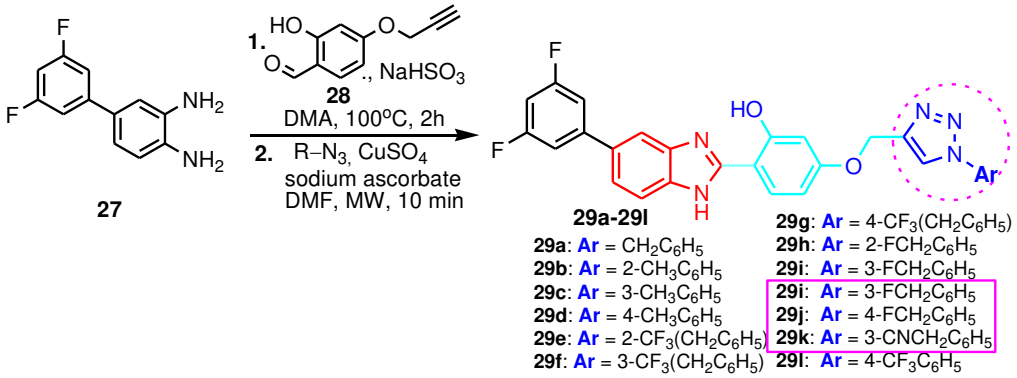


Scheme 6. Synthesis of benzimidazole-1,2,3-triazole hybrids **26a–26j**

3.125–6.25 μgmL^{-1} were found to be the most promising potential antimicrobial molecules [93]. Mallikanti et *al*. synthesized novel benzimidazole-conjugated 1,2,3-triazole analogues **29a–29l** in two steps: 1. formation of benzimidazole intermediate by reaction between 3',5'-difluorobiphenyl-3,4-diamine **27** and 2-hydroxy-4-(prop-2-ynyloxy) benzaldehyde **28**, and 2. microwave-assisted copper-catalyzed click reaction (Scheme 7). Compounds **29a-29l** have shown minimal inhibition zones against all gram positive (*S. aureus, B. subtilis*) and gram-negative (*E. coli, P. aeruginosa*) strains using Ampicillin as standard drug. Among all tested compounds, the **29i** and **29k** have showed greater

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

activity against *P. aeruginosa, S. aureus* and *B. subtilis* than standard reference. Compounds **29a**, **29b**, **29c**, **29d**, **29e**, **29f**, **29g**, **29h**, **29j** and **29l** demonstrated moderate antibacterial activity against the same. Also, compounds **29i**, **29j** and **29k** established potent activity against both fungal strains, *C. albicans* MTCC 183 and *A. niger* MTCC 9652 stains compared to standard drug Griseofulvin [70]. Chandrika et *al.* reported hybrids **30–32** with broad spectrum antifungal activity (0.975-3.9 μgmL^{-1} against *C. albicans*; 0.12-0.48 μgmL^{-1} against *C. parapsilosis*) (Fig. 2). These compounds also displayed good activity against *C. albicans* biofilms [94].



Scheme 7. Synthesis of benzimidazole-1,2,3-triazole hybrids **29a–29l**

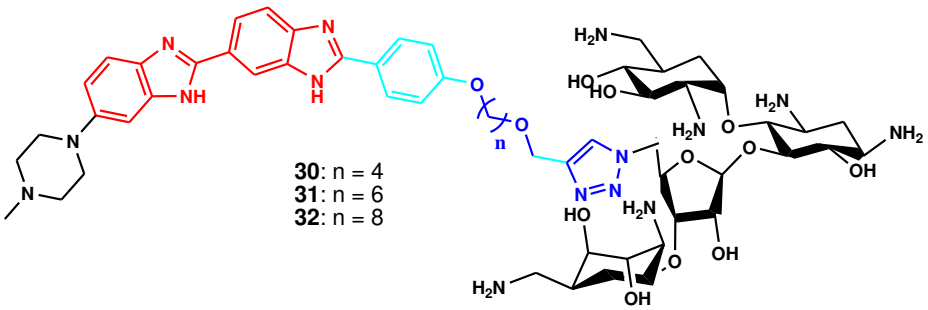
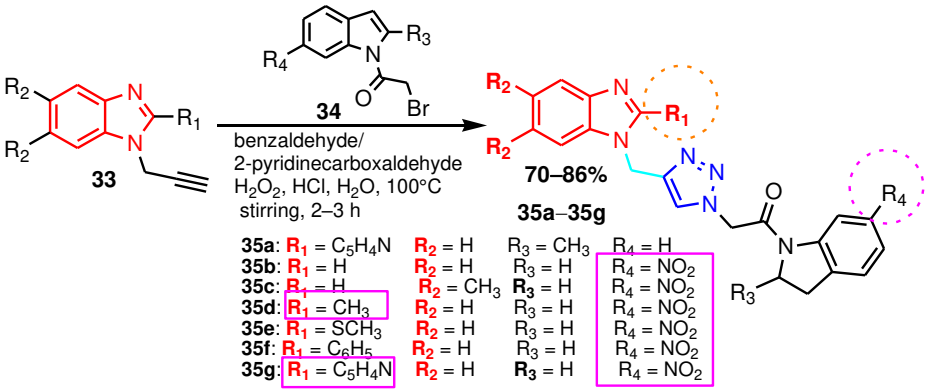


Figure 2. Structure of benzimidazole-1,2,3- hybrids **30–32**

2.2. 1-Benzimidazole-R(Ar)-1,4-disubstituted-1,2,3-triazole hybrids

Deswal et *al.* synthesized a new series of benzimidazole-1,2,3-triazole-indoline derivatives **35** by employing click reaction between substituted N-propargylated benzimidazole derivatives **33** and *in situ* formed substituted 2-azido-1-(indolin-1-yl) ethanone derivatives **34** in moderate to good yields (Scheme 8). The obtained results indicate stronger inhibitory effect of compound **35d** against *E. coli*, while compound **35g** showed good inhibition against all the tested strains except *B. subtilis* (Table 3). The good antimicrobial activity of the compounds was correlated with the presence of the pyridine ring in position "2" of the benzimidazole and the NO_2 group on the indole ring [6].



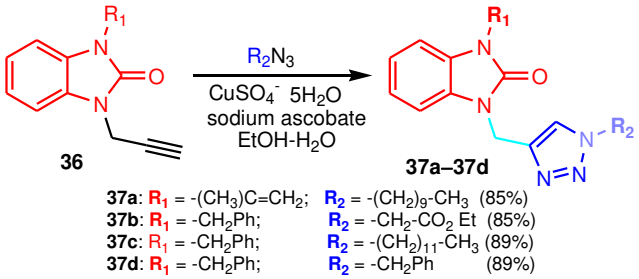
Scheme 8. Synthesis of benzimidazole-1,2,3-triazole hybrids **35a–35g**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

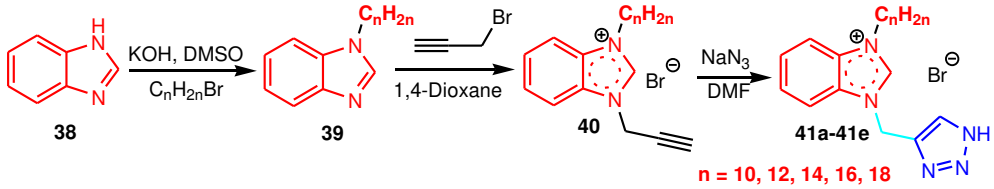
Table 3. Antimicrobial activity of the compounds **35** in terms of MIC (μmol mL^{-1}).

Compound	*S. aureus*	*E. coli*	*B. subtilis*	*S. epidermitis*	*A. niger*	*C. albicans*
35a	0.028	0.056	0.056	0.056	0.056	0.056
35b	0.031	0.062	0.062	0.062	0.062	0.062
35c	0.029	0.058	0.058	0.058	0.058	0.058
35d	0.060	0.030	0.060	0.030	0.060	0.060
35e	0.029	0.056	0.056	0.056	0.056	0.056
35f	0.026	0.052	0.052	0.052	0.052	0.052
35g	0.031	0.026	0.052	0.026	0.026	0.026
Norfloxacin	0.020	0.039	0.039	0.039	-	-
Fluconazole	-	-	-	-	0.04	0.020

Saber et *al.* synthesized new 1,4-disubstituted-1,2,3-triazole containing benzimidazolone derivatives **37a–37d** exclusively using click chemistry (Scheme 9). All derivatives exhibited antibacterial activity against tested strains, *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*, but compounds **37b** and **37d** are more effective against Gram-positive bacterium *S. aureus* (MIC = 3.125 μgmL^{-1}) and **37b** has better activity against Gram-negative bacterium *E. coli* (MIC = 3.125 μgmL^{-1}) with Chloramphenicol as standard drug [95]. Mohsen et *al.* synthesized hybrids **41a–41e** in three steps starting from benzimidazole **38**, namely two alkylation reactions and a click reaction (Scheme 10). New derivatives exhibited good zone inhibition of 6.8, 5.4, 5.2, 4.5, 5.3 mm for *S. aureus* and 5.4, 3.8, 4.2, 3.3, 4.9 mm for *E. coli* strain, indicating that the 1,2,3-triazole core contributed significantly to bacterial growth suppression (Ciprofloxacin showed 10.2 mm for *S. aureus* and 10.4 mm for *E. coli*) [96].



Scheme 9. Synthesis of benzimidazole-1,2,3-triazole hybrids **37a–37d**

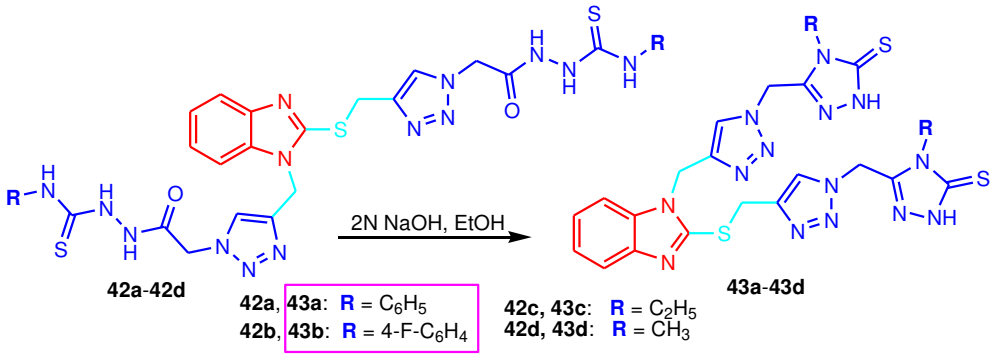


Scheme 10. Synthesis of benzimidazole-1,2,3-triazole hybrids **41a–41e**

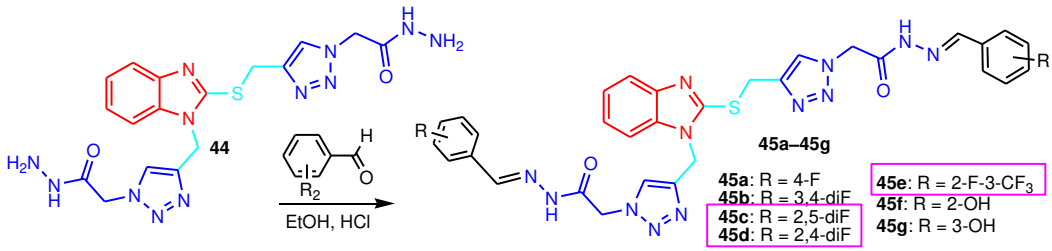
2.3. 1,2-. bis-substitutedBenzimidazoles-R(Ar)-1,4-disubstituted-1,2,3-triazole

Rezki reported the intramolecular cyclization of thiosemicarbazides **42a–42d** in refluxing aqueous sodium hydroxide (2N) for 6 h with the formation of hybrids **43a–43d** with yields of 82–86% (Scheme 11). Among all the 1,2,4-triazole derivatives, N4-phenyl and N4-(4-fluorophenyl) derivatives **43a** and **43b** were found the most potent with MIC values of 4–8 μg mL^{-1}. Also, triazoles **43a** and **43b** exerted the best inhibition against both tested fungal strains, *A. brasiliensis* and *Candida albicans*, with MIC values ranging from 0.5–4 μg mL^{-1}, more potent than the reference drug Fluconazole. Condensation of compound **44** with several benzaldehydes in refluxing ethanol for 4–6 h with a catalytic amount of HCl produced a new class of hybrid Schiff bases **45a–45g** with yields of 84–86% (Scheme 12). The antimicrobial bioassay results for the synthesized Schiff bases **45a–45g** revealed that all of the tested compounds were more effective towards all of the organisms, with MIC values of 1–16 μg mL^{-1}. Among them, Schiff bases **45c**, **45d** and **145e** with a fluorine atom at position "2" exhibited the highest antibacterial inhibition potency at MIC 1–8 μg mL^{-1}. The Schiff base **45e** containing a CF_3 group exerted the highest antifungal inhibition activity with MIC of 1 μg mL^{-1} [97].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



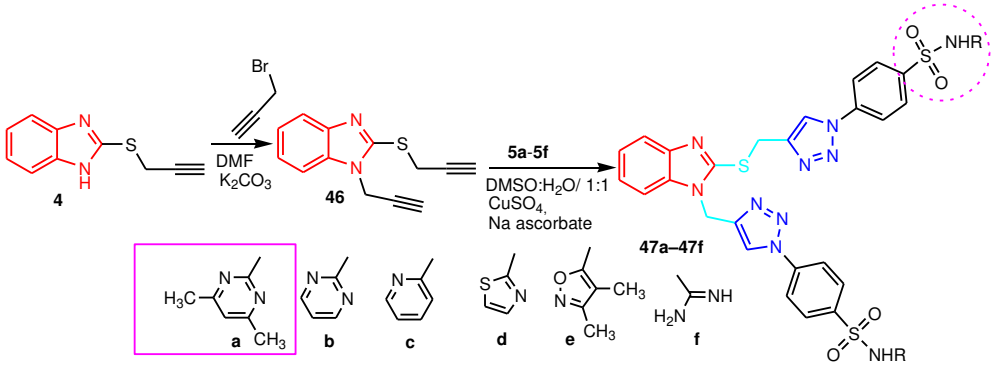
Scheme 11. Synthesis of benzimidazole-1,2,3-triazoles **43a-43d**



Scheme 12. Synthesis of benzimidazole-1,2,3-triazoles **45a-45g**

Al-blewi et *al*. synthesized triazoles **47a–47f** in two steps: i. regioselective alkylation of **4** with two equivalents of propargyl bromide in the presence of two equivalents of potassium carbonate as a base catalyst to afford benzimidazole **46** with 91% yield after stirring at room temperature overnight; ii. Copper-mediated Huisgen 1,3-dipolar cycloaddition reaction on compound **46** in good yields (82–88%) (Scheme 13). In general, bis-1,2,3-triazoles **47a–47f** exhibited more potent antimicrobial activities than their mono-1,2,3-triazole derivatives **6a-6f**. This was attributed to the synergistic effect of the sulfonamoyl and tethered heterocyclic components in addition to the improved

lipophilicity of the bis-substituted derivatives. Among the synthesized compounds, compound **47a** was the most potent antimicrobial agent with MIC values ranging between 32 and 64 μgmL^{-1} against all tested strains *B. cereus, S. aureus, E. coli P. aeruginosa, C. albicans*, and *A. brasiliensis* [88].



Scheme 13. Synthesis of benzimidazole-1,2,3-triazoles **47a-47f**

Aparna et *al*. used a similar strategy for obtaining nine new bis-1,2,3-triazol-1*H*- 4-yl-substituted arylbenzimidazole-2-thiol derivatives **48a-48l** (Fig. 3). Antibacterial activity of triazole derivatives **48** demonstrates moderate to good activity against gram negative (*E. coli, S. typhy, P. aeruginosa*) and gram positive (*S. aureus)* bacterial strains. The products **48i**, **48k**, and **48l** characterized by a broad spectrum of antibacterial activity at concentration of 10 μgmL^{-1}. The derivative **48l** displays the highest dock score of –7.69 kcal/mol and the least dock score of –0.942 kcal/mol is obtained for **48h** [98].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

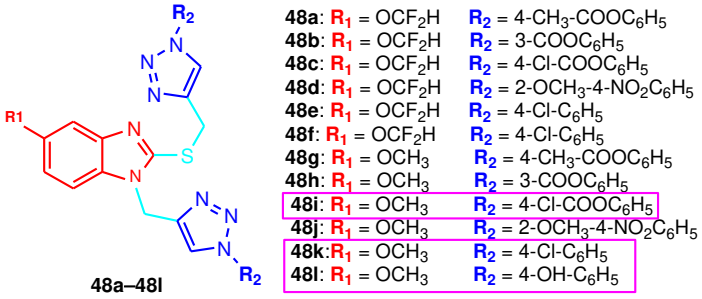
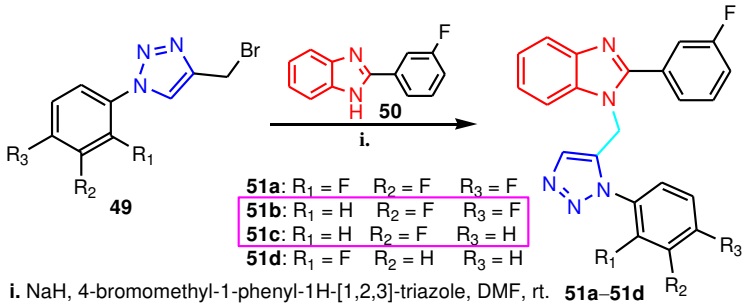


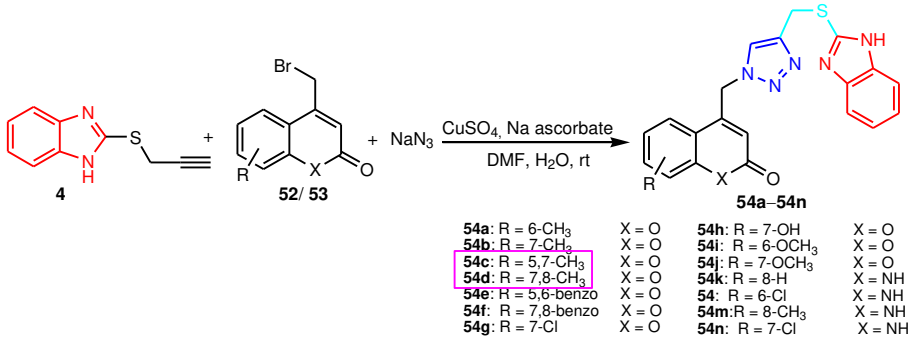
Figure 3. Structure of benzimidazole-1,2,3-triazole hybrids **48a–48l**

2.4. Benzimidazole-R(Ar)-1,2,3-triazole hybrids as antitubecular agents

Ashok reported compound **26h** as best antitubercular drug candidate by inhibiting the growth of the MTB (*Mycobacterium tuberculosis*) strain with MIC = 3.125μ mL^{-1} (7.1 μM) (control Rifampicin MIC = 0.04μgmL^{-1} and isoniazid MIC = 0.38μgmL^{-1}). The best antitubercular activity of **26h** may be attributed to the presence of nitro group on phenyl ring at *ortho* position. Compound **26b** (MIC = 6.25 μg mL^{-1} (14.7μM)) with chlorine substituent, compound **26i** (MIC = 6.25 μgmL^{-1}(14.2 μM)) with trifluoromethyl substituent and compound **26j** (MIC = 12.5 μgmL^{-1} (28.4μM)) with benzyl substituent exhibited moderate antitubercular activity. Therefore, incorporation of the electron-withdrawing nitro group, electronegative chlorine and trifluoromethyl groups on the phenyl ring was highly favored for antitubercular activity [93]. Gill et *al.* reported synthesis of hybrids **51a–51d** by reaction between 2-(3-fluorophenyl)-1*H*-benzo[d]imidazole **50** and phenyl-substituted 4-(bromomethyl)-1-phenyl-1*H*-1,2,3-triazole **49** in DMF at room temperature (Scheme 14). Trifluorosubstituted-compound **51a** possessed enhanced anti-mycobacterial activity, > 96% of inhibition at 6.25 μg concentration. Also, compounds **51b** and **51c**, which had antimicrobial activities superior to the other compounds, were reported as the best choice for the preparation of new derivatives in order to improve effectiveness on intracellular mycobacteria (macrophage) or in infected animal [99]. Anand et *al*. reported one pot reaction between 2-propargylthiobenzimidazole **4**, 4-bromomethyl coumarins/1-aza-coumarins **52/53** and sodium azide under click chemistry conditions to give exclusively 1,4-disubstituted triazoles **54a–54n**. Anti-tubercular assays against *M. tuberculosis* (H37Rv) coupled with in silico molecular docking studies indicated that dimethyl substituents **54c** and **54d** showed promising activity



Scheme 14. Synthesis of benzimidazole-1,2,3-triazoles **51a-51d**



Scheme 15. Synthesis of benzimidazole-1,2,3-triazoles **54a-54n**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

(MIC = 3.8 μMol L^{-1}) with higher C-score values [100]. Khanapurmath et *al*. synthesized triazoles **55** by click reaction (Fig. 4A). Benzimidazolone bis-triazoles **55a**–55**n** showed better activity with MIC in the range 2.33–18.34 μM and most active compounds were **55h** and **55**m. All compounds exhibited moderate to low levels of cytotoxicity with IC_{50} values of the human embryonic kidney cells in the range of 943–12294 μM, and none of 14 compounds exhibited any significant cytotoxic effects, suggesting huge potential for their *in vivo* use as antitubercular agents. Docking studies revealed an additional interaction of benzimidazolone oxygen in these compounds (Fig. 4B) [101]. Also, Sharma et *al*. summarizes 1,2,3-triazoles as antitubercular compounds, and various hybrids with benzimidazole, coumarin, isoniazid, quinolines, etc [39].

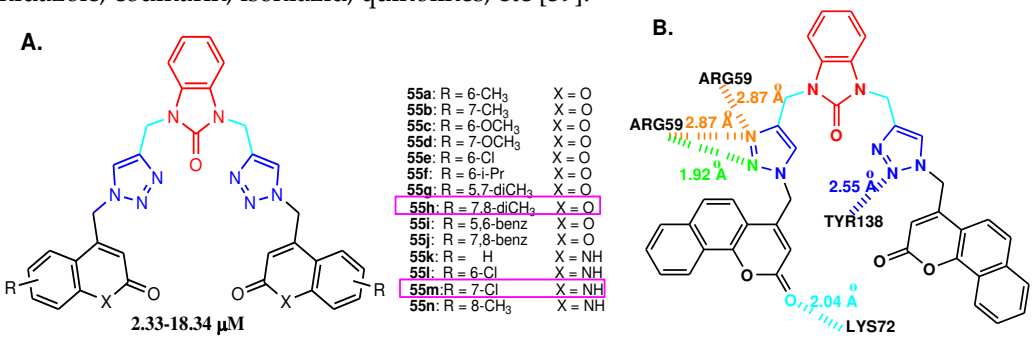
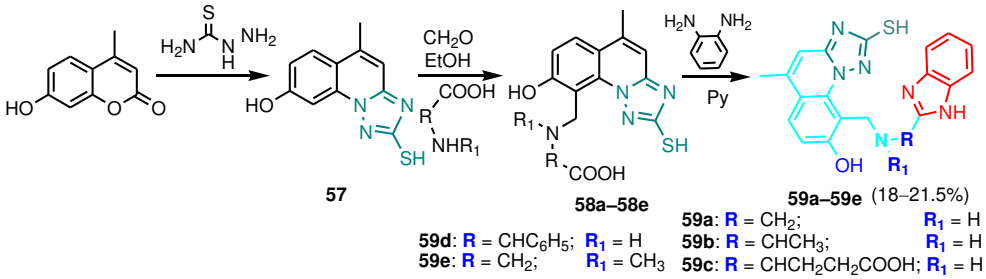


Figure 4. A. Structure of benzimidazolone bis-1,2,3-triazoles **55a**–**55n**. B. Representation of docked view of compound **55j** at the active site of RmlC.

3. Synthesis and antimicrobial activities of benzimidazole-1,2,4-triazoles

3.1. 2-Benzimidazole-R(Ar)-1-(1,2,4-triazole)

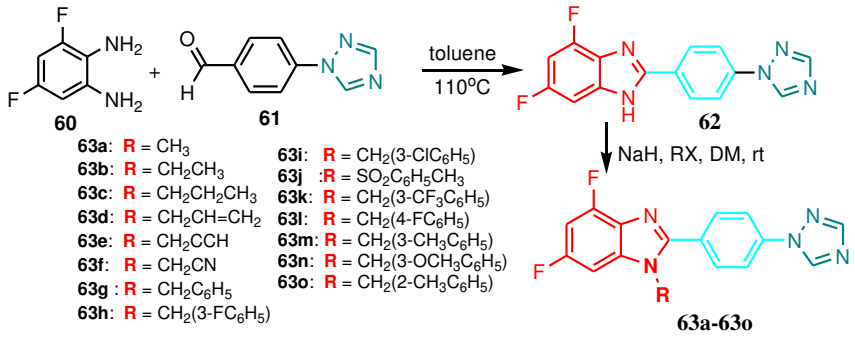
Pandey et *al*. synthesized hybrids **59a**–**59e** in three steps: reaction of 7-hydroxy-4-methyl coumarin with thiosemicarbazide to form triazole intermediate57**1**, which underwent Mannich reaction with formaldehyde, and an amino acid to form intermediates **58a**–**58e**, which gave benzimidazolo-1,2,4-triazole hybrids in poor yields by reaction with *o*-phenylenediamine in pyridine (Scheme 16). Compound **59a** displayed promising antifungal activity against *Candida albicans* and *Cryptococcus himalayensis*, since the MIC value in each case was found to be 3.5 μg mL^{-1}. Compound **59b** showed low to moderate antifungal activity against all the five fungi, *Candida albicans, Cryptococcus himalayensis, Sporotrichum schenkii, Trichophyton rubrum* and *Aspergillus fumigatus* [102].



Scheme 16. Synthesis of benzimidazole-1,2,4-triazoles **59a-59e**

Jadhav et *al*. synthesed a series of hybrids 1,2,4-triazolyl-fluorobenzimidazoles in two steps: i. synthesis of 2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-4,6-difluoro-1*H*-benzo [d]imidazole **62** by reaction between 3,5-difluorobenzene-1,2-diamine **60** and 4-(1*H*-1,2,4- triazol-1-yl)benzaldehyde **61** in toluene at 110°C, and ii. alkylation of compound **62** in DMF at room temperature, with the formation of the final hybrids **63a**-**63o** (Scheme 17). All compounds were screened for the antimicrobial activity against different gram positive organisms *S. aureus, P. aeruginosa* and gram negative organisms *E. coli* and *S. typhosa* using Gentamycin as a reference standard. The data generated from preliminary screening showed that compounds displayed moderate to better antimicrobial activity. Compounds **63a**, **63e**, **63f**, **63h**, **63i**, and **63l** displayed maximum activity (Table 4)[103].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 17. Synthesis of benzimidazole-1,2,4-triazoles **63a-63e**

Barot et *al*. synthesized hybrid **64** and determined its antimicrobial activity against *Bacillus cereus* MTCC-430, *Enterococcus faecalis* MTCC-493, *S. aureus* MTCC-737, *Escherichia coli* MTCC-1687, *Pseudomonas aeruginosa* MTCC-2642, *Klebsiella pneumonia* MTCC-109, *Candida albicans* MTCC-3017, *Aspergillus niger* MTCC-1344 and *Fusarium oxyspora* MTCC-1755, of MIC = 13-18 µg ml^{-1}, with Ofloxacine and Fluconazole as standard drugs [104]. Also, Jiang et *al.* reported antifungal activity for hybrid **65** against *Candida albicans, Candida tropicalis, Cryptococcus neoformans, Trichophyton rubrum*, and *Aspergillus fumigatus*, of MIC_{80} = 1-64 µg mL^{-1} considering Fluconazole as standard drug (Fig. 5) [105]. Luo et *al.* reported a series of naphthalimide benzimidazole-1,2,4-triazole hybrids **68a–68h** and the corresponding triazoliums salts **69a–69d** prepared by convenient and efficient procedures starting from naphthalimide triazole **66** (Scheme 18). 2-Chlorobenzyl triazolium **68g** and compound **69b** with octyl group exhibited the best antibacterial activities among all the tested compounds, especially against *S. aureus* with inhibitory concentration of 2 µgmL^{-1} which was equipotent potency to Norfloxacin (MIC=2 µgmL^{-1}) and more active than Chloromycin (MIC= 7 µgmL^{-1}). Triazoliums **68g** and **68f** bearing 3-fluorobenzyl moiety displayed the best antifungal activities (MIC=2-19 µgmL^{-1}) against all the tested fungal strains, *C. albicans* ATCC 76615, *A. fumigatus* ATCC 96918, *C. utilis, S. cerevisia* and *A. flavus*, without being toxic to PC12 cell line within concentration of 128 µg mL^{-1}. Further investigations showed that compound **68g** could intercalate into calf thymus DNA to

form the **68g**-DNA complex which could block DNA replication, exerting powerful antimicrobial activities. [106]. Benzimidazole-1,2,4-triazole Mannich base **70** was active against *Bacillus subtilis* and *Bacillus pumilus* (inhibition zone diameters being 19 and 17 mm, respectively, compared to Ciprofloxacin with 28 and 30 mm, respectively) [107]. Kankate et *al*. reported synthesis of the hybrids **73a–73l** (Scheme 19). Antifungal activity of compounds **73a** was tested against *Candida albicans* spores *in vitro* (turbidimetric

Table 4. Antimicrobial activity of the compounds **63a-63o** using the agar diffusion method

Compound	Inhibition zone diameters using the agar diffusion method (mm)			
	S. aureus	*P. aeruginosa*	*E. coli*	*S. typhosa*
63a	28	26	21	19
63b	23	18	16	14
63c	21	23	18	19
63d	20	22	23	23
63e	25	23	21	24
63f	27	26	24	20
63g	19	20	15	13
63h	29	26	22	24
63i	26	22	19	18
63j	14	12	16	16
63k	22	21	20	18
63l	25	23	19	21
63m	21	18	18	16
63n	24	22	22	21
63o	19	21	18	14
Gentamycin	34	35	31	30

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

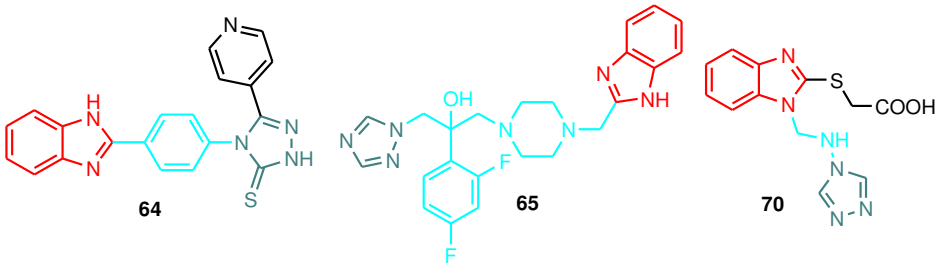
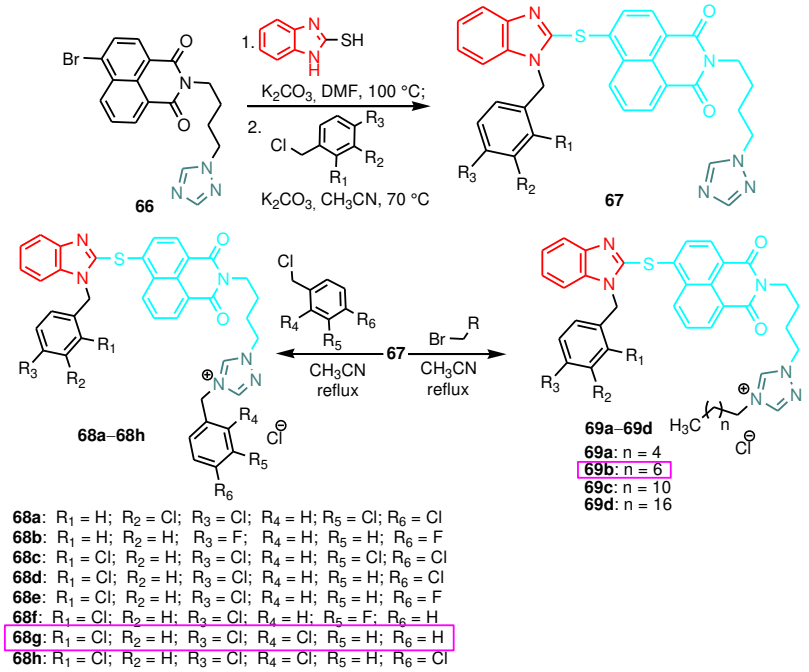


Figure 5. Structure of benzimidazole hybrids **64, 65** and **70**

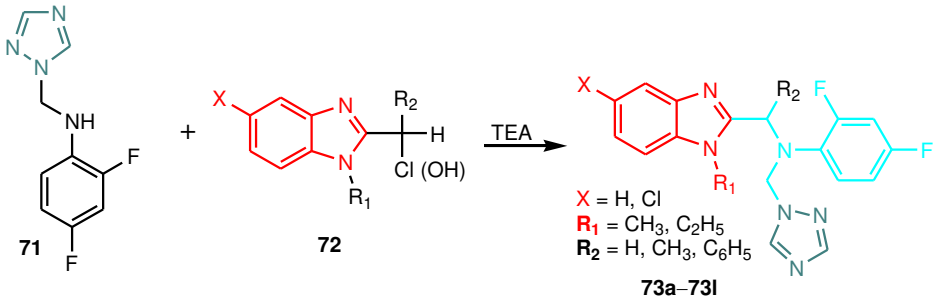


Scheme 18. Synthesis of benzimidazole-1,2,4-triazoles **68** and **69**

method) and *in vivo* (kidney burden test). Compound **73i** had a good antifungal activity as compared with the other twelve compounds at 0.0075 μmole ml^{-1} which is equivalent to Fluconazole activity both *in vitro* and *in vivo* [108]. Ahuja et *al.* reported antifungal activity of compounds **74a–74c** against *F. verticillioides, D. oryzae, C. lunata* and *F. fujikuroi* (Fig. 6). All compounds had increased potency than the standard commercial benzimidazole fungicide, carbendazim (Table 5). Compound **74c** exhibited ED_{50} values lower than triazole fungicide, propiconazole. The results reinforced the synergistic effects of benzimidazole and 1,2,4-triazole combination supported by computational approach [109]. Evren et *al*. reported synthesis of the compounds **79a–79c** in two steps: i. reaction of 1,2,4-triazole **75** with 4-fluorobenzaldehyde **76** in DMF with the formation of 4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde **77**; ii. reaction of aldehyde **77** with 1,2-phenylene diamines **78** (Scheme 20). Although the antibacterial activities of compounds **79a–79c** against *Escherichia coli* ATCC 35218, *E. coli* ATCC 25922, *Klebsiella pneumoniae* NCTC 9633, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* ATCC 13311, and Staphylococcus aureus ATCC 25923, were weak, the antifungal activities against *C. albicans* were found promising, with MIC values of 3.9, 7.8, and 3.9 μg mL^{-1} respectively, using as reference drug Ketokonazole (MIC = 7.8 μgmL $^{-1}$). Theoretical ADME calculations of the **79a**, **79b**, and **79c** were made, and the compounds were found to have good lipophilicity, moderate water solubility, and within the limiting rules of Lipinski, Ghose, Veber, Egan, and Muegge [110]. Ghobadi et *al.* reported synthesis of compounds **85a**-**85e**, in two different ways, from 3,4-diaminobenzophenone **80**, i. formation of 2-mercapto benzimidazole derivatives **82**, **83**, and ii. nucleophilic ring opening of various oxiranes **84a**-**84e** with benzimidazoles **82** and **83** using $NaHCO_3$ in ethanol at room temperature (Scheme 21). Compounds **85a**-**85e**, containing 5-benzoylbenzimidazole scaffold showed better antifungal activity against *Candida* spp. and *Cryptococcus neoformans* than related benzimidazole and benzothiazole derivatives. The better results were obtained with the 4-chloro-derivative **85b** displaying MICs < 0.063–1 μgmL^{-1}. Also, compound

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

86c, synthesized analogously, is as potent as compound **85b**. In vitro and in silico ADMET evaluations of the most promising compounds **85b** indicated that the selected compounds have desirable ADMET properties in comparison to standard drug Fluconazole. Docking simulation study demonstrated that the benzimidazol-2-yl-thio moiety is responsible for the potent antifungal activity of these compounds [72].



Scheme 19. Synthesis of benzimidazole-1,2,4-triazoles **73a–73l**

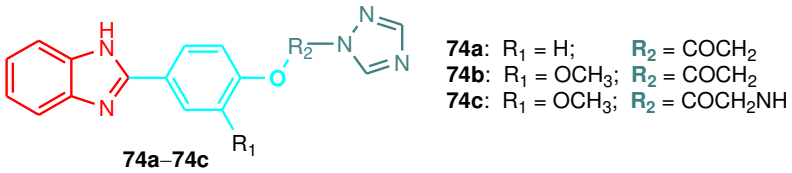
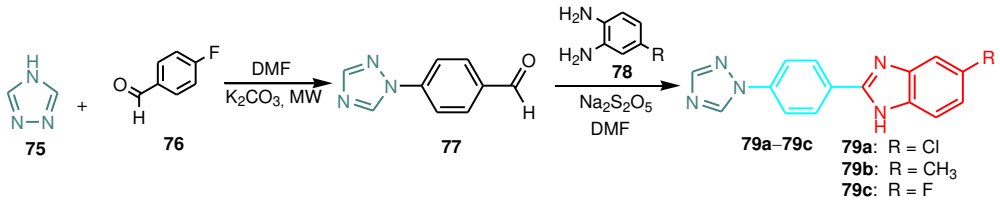


Figure 6. Structure of benzimidazole-1,2,4-triazole hybrids **74a–74c**

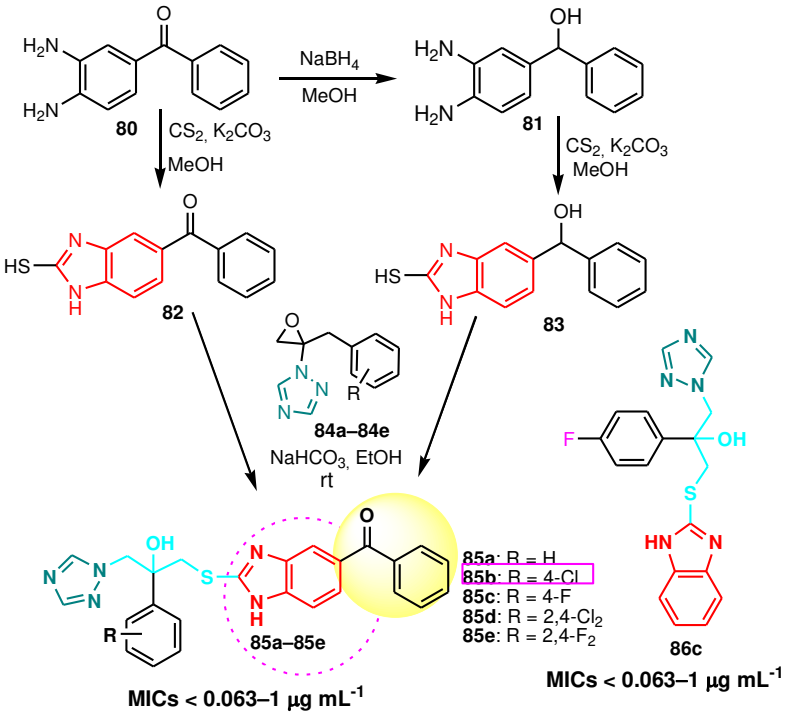
Table 5. ED_{50} values (μg mL^{-1}) of compounds against test fungi.

Compound	*F. verticillioides*	*D. oryzae*	*C. lunata*	*F. fujikuroi*
74a	35	50	28	45
74b	30	25	18	30
74c	16	12	10	15
Carbendazim	230	-	-	150
Propiconazole	20	25	22	21



Scheme 20. Synthesis of benzimidazole-1,2,4-triazoles **79a–79c**

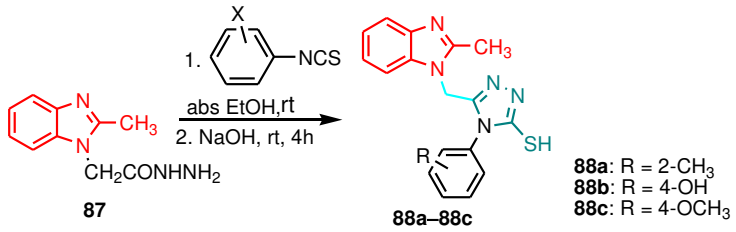
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 21. Synthesis of benzimidazole-1,2,4-triazoles **85a–85e** and compound **86c**

3.2. 1-Benzimidazole-R(Ar)-2-1,2,3-triazole

Ansari et *al.* synthesized hybrids **88a–88c** in two steps from 2-(2-methyl-1*H*-benzo [d]imidazol-1-yl)acetohydrazide **87** (Scheme 22). Generally, all benzimidazole-triazole hybrids showed low antimicrobial activity (Table 6) [111]. Tien et *al.* synthesized hybrids **89a–89d** in three steps from 2-(2-methyl-1*H*-benzo[d]imidazol-1-yl)acetohydrazide **87b** (Scheme 23). All compounds exhibited antifugal activity against *A. niger* (MIC = 50 μg mL^{-1}). Only compound **89b** exhibited activity against *F. oxysporum* (Table 7) [112]. Kantar et *al.* reported antimicrobial activity of hybrid **90** (Fig. 7) against four Gram-positive, *Bacillus cereus* 702 Roma (62.5 μg mL^{-1}), *B. megaterium* DSM-32 (125 μg mL^{-1}), *B. subtilis* ATCC 6633 (62.5 μg mL^{-1}), *Staphylococcus aureus* ATCC 25923 (250 μg mL^{-1}), and four



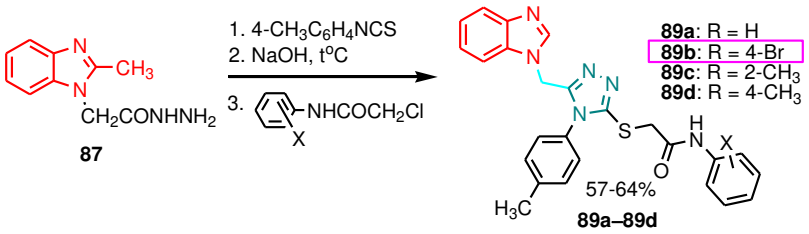
Scheme 22. Synthesis of benzimidazole-1,2,4-triazoles **88a–88c**

Table 6. Antimicrobial activity of compounds **88a–88c** expressed as MIC in μg mL^{-1}

Compound	*S. aureus,*	*B. subtilis*	*S. mutans*	*P. aeruginosa*	*C. albicans*
88a	NT	NT	16	16	32
88b	8	16	16	16	NT
88c	8	16	32	32	32
Ampicillin	2	2	< 1	4	NT
Kanamycin	2	< 1	4	2	NT

NT = not tested

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 23. Synthesis of benzimidazole-1,2,4-triazoles **89a–89c**

Table 7. The minimum inhibitory concentrations (μg mL^{-1})) of the compounds against fungi.

Compound	Concentration (μg mL^{-1})	*Aspergillus niger*	*Fusarium oxysporum*
89a	50	50	-
89b	50	50	50
89c	50	50	-
89d	50	50	-

Gram-negative bacteria, *Escherichia coli* ATCC 25922 (250 μg mL^{-1}), *Enterobacter cloaceae* ATCC13047 (125 μg mL^{-1}), *Pseudomonas aeruginosa* ATCC 27853 (250 μg mL^{-1}), and *Yersinia pseudotuberculosis* ATCC 911 (125 μg mL^{-1}) bacteria [113]. Nandwana et *al*. reported compound **91** synthesized in good yield (70%) with promising antibacterial activity, with minimum inhibitory concentration (MIC) values of 4–8 μg mL^{-1} for all bacterial tested strains (*Escherichia coli, Pseudomonas putida, Salmonella typhi, Bacillus subtilis, Staphylococcus aureus*), as compared to the positive control Ciprofloxacin, and also with pronounced antifungal activity against both tested strains, *Aspergillus niger* and *Candida albicans* (MIC = 8–16 μg mL^{-1}) as compared with Amphotericin B [114]. Al-Majidi et *al*. synthesized 2-mercaptobenzimidazole derivatives **95**, **96** and **97** by cyclization of intermediate precursors **93**, **94** and **95** under reflux with 2N NaOH (Scheme 24). The compounds generally showed a moderate antimicrobial activity against all tested strains, as can be seen in Table 8 [115]. El-masry et *al.* synthesized compounds **98** and **99** and found that they did not exhibit antimicrobial activity (Fig. 8) [116]. Menteşe et *al*. synthesized compounds **100a–100d**, for which they found no antimicrobial activity on the ten strains tested [117]. Karale et al. synthesized bis-benzimidazole-1,2,4-triazole hybrids **102a**-**102e** in four steps, from 7-methyl-2-propyl-3*H*-benzo[d]imidazole-5-carboxylic acid. All compounds **102** did not show antimicrobial activity against the strains tested, *C. albicans, A. fumigatus, S. aureus* and *E. coli* [118,119].

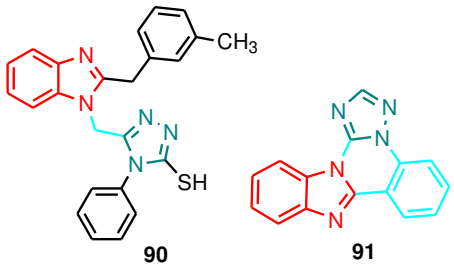
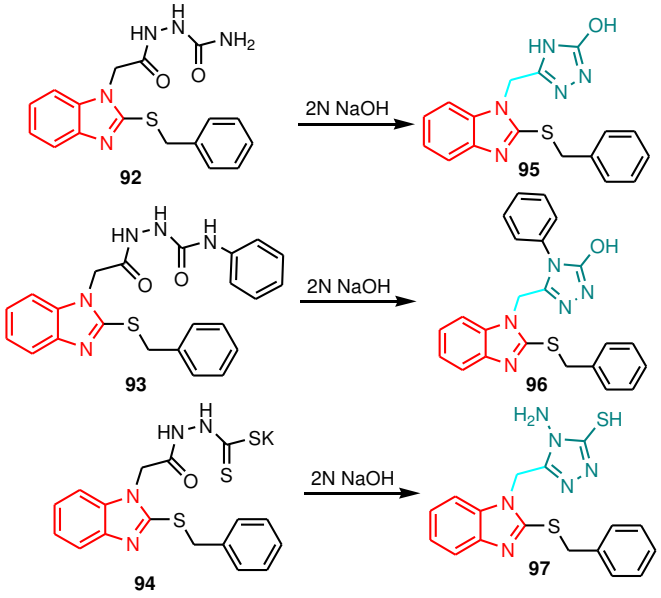


Figure 7. Structure of benzimidazole-1,2,4-triazole hybrids **90** and **91**

Table 8. Antimicrobial activity of compounds **89a–89c**

Compound (800 μg mL^{-1})	*S. aureus*	*P. aerugnosa*	*B. subtilis*	*A. baumannii*	*C. albicans*
95	18	14	15	-	10
96	19	11	12	-	11
97	17	15	14	12	-
Amoxicillin	33	32	33	-	-
Fluconazole	-	-	-	-	25

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 24. Synthesis of benzimidazole-1,2,4-triazoles **95–97**

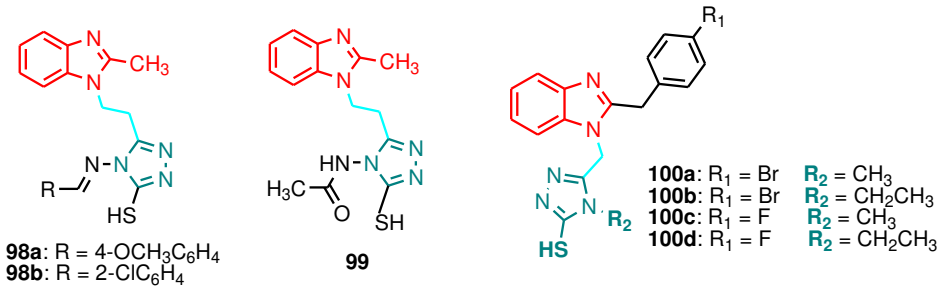
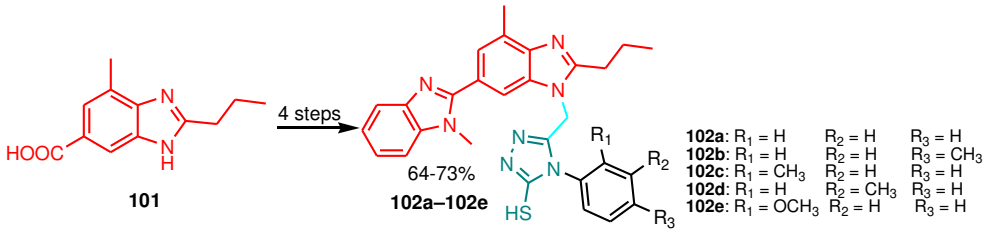


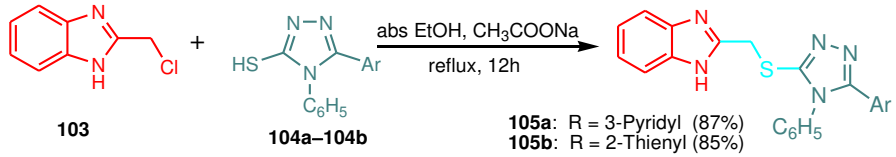
Figure 8. Structure of benzimidazole-1,2,4-triazole hybrids **98–100**



Scheme 25. Synthesis of bis-benzimidazole-1,2,4-triazoles **102a-102e**

3.3. *2-Benzimidazole-R(Ar)-2-1,2,4-triazole*

Eisa et *al.* synthesized compounds **105a** and **105b** by the reaction between 2-(chloromethyl)-1*H*-benzo[d]imidazole **103** and 4-phenyl-5-(pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol **103** and 4-phenyl-5-(pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol **104a** or 4-phenyl -5-(thiophen-2-yl)-4*H*- 1,2,4-triazole-3-thiol **104b**, at reflux in absolute ethanol, for 12 hours. Also, they reported synthesis of the compounds **107a** and **107b** from 2-(2-(phenylthiomethyl)-1*H*-benzo[d]imidazol-1-yl) acetohydrazide in two steps (Scheme 27). All compounds showed antimicrobial activity against *Escherichia coli* superior to that of standard Gentamicin. Compound **107a** exhibited only a moderate activity against *Staphylococcus aureus* [120].



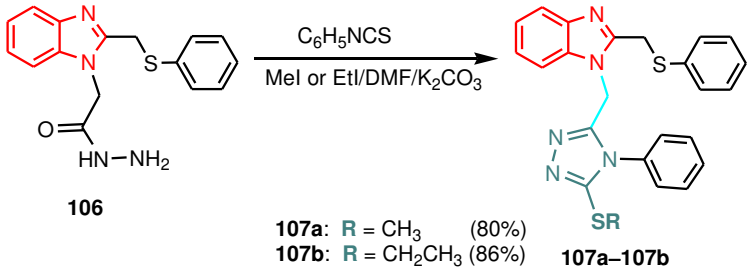
Scheme 26. Synthesis of benzimidazole-1,2,4-triazoles **105a-105b**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

Table 9. Antimicrobial activity of compounds **105a–105b** and **107a–107b**

Compound	Minimum inhibitory concentrations (μgmL^{-1})			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	***S. aureus***	***E. coli***	***P. aeruginosa***
105a	98	-	52	-
105b	-	-	65	-
107a	75	105	62	-
107b	79	-	72	-
Gentamycin*	64	56	72	48

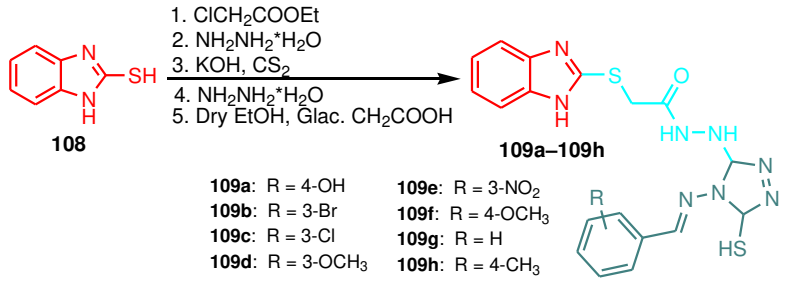
* Concentration of Gentamycin = 30 μg mL^{-1}



Scheme 27. Synthesis of benzimidazole-1,2,4-triazoles **107a-107b**

Nevade et *al.* synthesized compounds **109a–109h** in five steps from 1*H*-benzo[d]imidazole-2-thiol **108** (Scheme 28). The antimicrobial screening results presented in Table 10 reveal that compounds **109a**, **109c**, **109e** exhibited satisfactory effect against *S.aureus* and *E.coli*, while the compounds **109b**, **109f, 109g** have shown the moderate activity against the same microbes. Also antifungal activity of these compounds was screened against *Candida albicans*. Compounds **109a** and **109d** showed highest degree of inhibition against *C.albicans* when compared with the Standard drug Ketoconazole [121]. Can et *al.* synthesized hybrids **111a–111h** in four steps from methyl 4-(5-methyl-1*H*-benzo[d]imidazol-2-yl)benzoate **110** (Scheme 29). All compounds were screened for antifungal activity against *Candida albicans* ATCC 24433, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 (Table 11). Compounds **111i** and **111s** exhibited significant inhibitory activity against *Candida* strains with MIC_{50} values ranging from 0.78 to 1.56 μg mL^{-1} [122]. Gencer et *al.* synthesized compounds **112** in good yields (77-88%) using a similar strategy (Fig. 9). Microbiological studies revealed that compounds **112a**, **112b**, **112c**, **112e**, **112f**, **112g** and **112h** possess a good antifungal profile against all tested strains, *C. albicans, C. glabrata, C. krusei, C. parapsilopsis*, with MIC_{50} = 0.78-1.56 μg mL^{-1}. Compound **112i** was the most active derivative and showed comparable antifungal activity to those of reference drugs Ketoconazole and Fluconazole [123]. The SAR (Structure–activity relationship) on the synthesized benzimidazole-triazole compounds are summarized in Fig. 10. It is observed that the presence of chlorine or fluorine in the "5" position of benzimidazole, as well as the presence of fluorine in the "4" position of phenyl increase the antibacterial activity, while the presence of fluorine in the "2" position of phenyl does not change the activity, and the presence of groups CH_3 or C_2H_5 in position "4" in the triazole nucleus does not bring any change in the antibacterial activity of the compounds. Güzel et *al.* synthesized a new series of benzimidazole-1,2,4-triazole derivatives **113a–113l** using the same procedure described in Scheme 29 as potential antifungal agents. All the compounds were screened for their *in vitro* antifungal activity against four fungal strains, namely, *C. albicans, C. glabrata, C. krusei*, and *C. parapsilopsis* and were found to exhibit excellent activity against *C. glabrata*. Especially, compounds **113b, 113i**, and **113j** were found to be the most effective

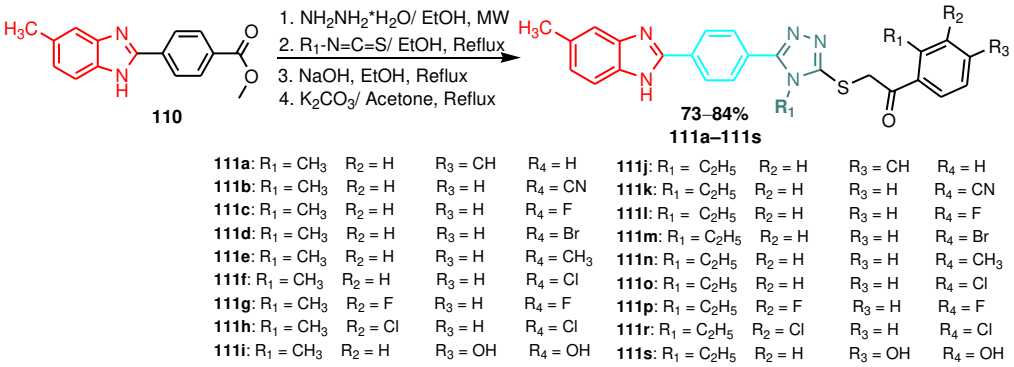
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 28. Synthesis of benzimidazole-1,2,4-triazoles **109a-109h**

Table 10. Antibacterial activity of compounds s **109a-109h**

No	Compound	Zone of inhibition (mm)		
		E. coli	*S. aureus*	*C. albicans*
1	**109a**	15	13	18
2	**109b**	13	11	12
3	**109c**	17	16	14
4	**109d**	12	13	16
5	**109e**	13	17	9
6	**109f**	10	8	11
7	**109g**	8	11	12
8	**109h**	12	7	10
9	Ampicilline	24	25	-
10	Ketokonazole	-	-	20



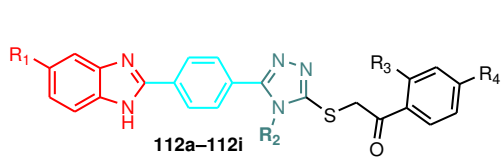
Scheme 29. Synthesis of benzimidazole-1,2,4-triazoles **111a-111s**

Table 11. MIC_{50} ($\mu g\ mL^{-1}$) values of compounds **111a–111s.**

Compound	*C. albicans*	*G. glabrata*	*C. krusei*	*C. parapsilosis*
111a	12.5	6.25	6.25	12.5
111b	6.25	3.12	6.25	6.25
111c	12.5	6.25	6.25	12.5
111d	6.25	12.5	6.25	6.25
111e	12.5	6.25	12.5	12.5
111f	6.25	3.12	3.12	6.25
111g	3.12	6.25	6.25	6.25
111h	12.5	6.25	12.5	6.25
111i	0.78	1.56	1.56	0.78
111j	12.5	6.25	12.5	12.5
111k	12.5	6.25	12.5	12.5
111l	6.25	12.5	6.25	12.5
111m	3.12	3.12	3.12	6.25
111n	3.12	3.12	1.56	3.12
111o	3.12	3.12	6.25	6.25
111p	12.5	12.52	6.25	6.25
111r	6.25	3.12	3.12	3.12
111s	0.78	1.56	1.56	0.78
Ketokonazole	0.78	1.56	1.56	1.56

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

Floconazole	0.78	1.56	1.56	0.78



112a: R_1 = Cl R_2 = CH_3 R_3 = H R_4 = F
112b: R_1 = Cl R_2 = CH_3 R_3 = F R_4 = F
112c: R_1 = Cl R_2 = C_2H_5 R_3 = H R_4 = F
112d: R_1 = Cl R_2 = C_2H_5 R_3 = Cl R_4 = Cl
112e: R_1 = Cl R_2 = C_2H_5 R_3 = F R_4 = F
112f: R_1 = F R_2 = CH_3 R_3 = F R_4 = F
112g: R_1 = F R_2 = C_2H_5 R_3 = H R_4 = F
112h: R_1 = F R_2 = C_2H_5 R_3 = F R_4 = F
112i: R_1 = F R_2 = CH_3 R_3 = H R_4 = F

Figure 9. Structure of benzimidazole-1,2,4-triazole hybrids **112a–112i**

compounds in the series with an MIC value of 0.97 μg mL^{-1} [71]. Aryal et *al*. reported synthesis of new 2-substituted benzimidazole containing 1,2,4-triazoles **114a** and **114b** (Fig. 12). The compounds did not show antimicrobial activity against the tested strains *Staphylococcus aureus* ATCC 6538P and *Staphylococcus epidermidis* ATCC 1228 [124]. Kazeminejad et *al*. did a study on 1,2,4-triazoles as well as structure-activity relationships (SAR) [125].

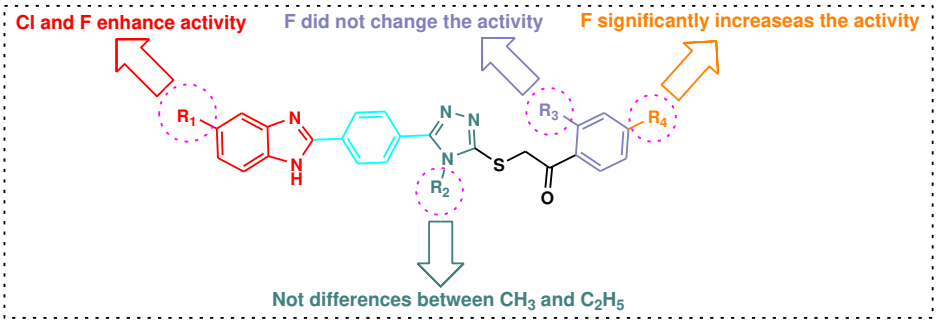
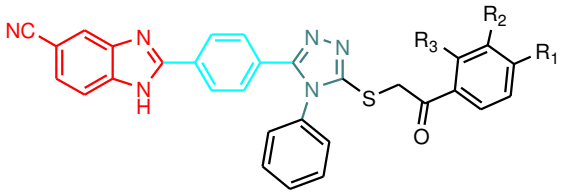
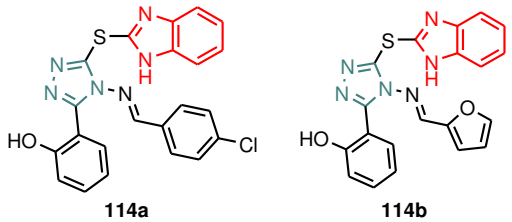


Figure 10. SAR outline of the benzimidazole-1,2,4-triazole hybrids **112a–112i**



113a: R_1 = NO_2 R_2 = H R_3 = H
113b: R_1 = OCH_3 R_2 = H R_3 = H
113c: R_1 = CN R_2 = H R_3 = H
113d: R_1 = F R_2 = H R_3 = H
113e: R_1 = C_6H_5 R_2 = H R_3 = H
113f: R_1 = Br R_2 = H R_3 = H
113g: R_1 = Cl R_2 = Cl R_3 = H
113h: R_1 = F R_2 = H R_3 = F
113i: R_1 = Cl R_2 = H R_3 = H
113j: R_1 = Cl R_2 = H R_3 = Cl
113k: R_1 = H R_2 = NO_2 R_3 = H
113l: R_1 = H R_2 = H R_3 = H

Figure 11. Structure of benzimidazole-1,2,4-triazole hybrids **113a–113l**



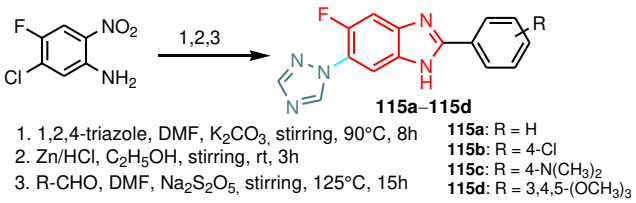
114a **114b**

Figure 12. Structure of benzimidazole-1,2,4-triazole hybrids **114a–114l**

3.4. 6-substituted-Benzimidazole-R(Ar)-1-1,2,4-triazole

Nandha et *al*. reported synthesis of 6-substituted-benzimidazoles with 1-(1,2,4-triazole) **115a--115d** in three steps from 5-chloro-4-fluoro-2-nitrobenzenamine (Scheme 30). All compounds were screened against *M. tuberculosis* and four fungal strains, *C. albicans, C. glabrata, C. krusei* and *C. tropicalis*. Compound **115c** was the most active against *M. tuberculosis* and all tested fungal strains (MIC = 25 μg mL^{-1}) [126].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1



Scheme 30. Synthesis of benzimidazole-triazoles **115a-115d**

4. Synthesis and antiviral activities of benzimidazole-triazoles

Youssif et *al*. reported synyhesis of benzimidazole-1,2,3-triazole hybrids 2-{4-[(1-benzoylbenzimidazol-2-ylthio)methyl]-1H-1,2,3-triazol-1-yl}-N-(p-nitro--phenyl)-acetamide **116** and 2-(4-{[1-(p-chlorobenzoyl)-benzimidazol-2-ylthio)methyl]-1H-1,2,3-triazol -1-yl}-N-(p-nitrophenyl)-acetamide **117** which showed significant activity against hepatitis C virus (HCV) (Fig. 13). Thus, fifty percent effective concentrations (EC_{50}) of HCV inhibition for compounds **116** and **117** were 7.8 and 7.6 µmol L^{-1}, respectively, and the 50 % cytotoxic concentrations (CC_{50}) were 16.9 and 21.1 µmol L^{-1}.The results gave an insight into the importance of the substituent at position 2 of benzimidazole for the inhibition of HCV [73].

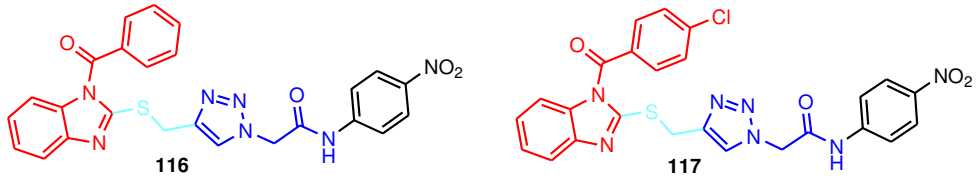


Figure 13. Structure of antiviral benzimidazole-1,2,3-triazole hybrids **116** and **117**

Antiviral activity of compounds **59a–59e** was tested against two viruses, viz., *Japanese encephalitis virus* (JEV) (P20778), a RNA virus of higher pathogenicity, and *Herpes simplex virus* type-I (HSV-I) (753166), the most common virus present in the environment. The antiviral activity of the compounds data are given in Table 12. All but one of the five compounds were found active against JEV. Compound **59b** displayed 90% CPE (cytopathic effect) *in vitro* with an effective concentration of 8 µg mL^{-1} while its *in vivo* activity was less significant (16% protection with a MST of 4 days). The authors sugested that that these compounds are better anti-JEV agents than anti-HSV agents, since two such compounds, namely **59b** and **59e**, also displayed a measurable degree of anti-JEV activity *in vivo*. Compound **59c** was found antivirally inactive against both viruses. The anti HSV-I activity was found to be in the order of 33, 46, 53 and 64% for compounds **59a**, **59b**, **59d** and **59e**, respectively. Since among compounds **59a** to **59e** only compound **59e** contains a methyl group instead of H as R_1, it follows that R_1 does not seem to be responsible for the biological activity [87].

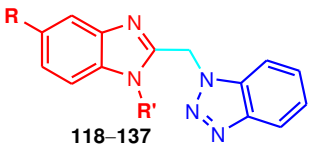
Table 12. Anti-JEV and anti-HSV activity of compounds **59a–59e.**

Compd.	*In vitro*		TI	*In vivo*			
	CT_{50} (µg mL^{-1})	EC_{50} (µg mL^{-1})		CPE Inhibition (%)	Dose (µg per mouse per day)	MST (days)	Protection (%)
				Anti-JEV			
59a	125	4	31	30	200	-	-
59b	125	8	16	90	200	4	16
59c	-	-	-	-	-	-	-
59d	125	4	31	30	200	-	-
59e	250	62.5	4	50	200	2	10
				Anti-HSV			
59a	125	62.5	2	33	-	-	-
59b	125	62.5	2	46	-	-	-
59c	-	-	-	-	-	-	-
59d	125	31.25	4	53	200	-	-
59e	250	7.8	32	64	200	-	-

CT_{50} – 50% cytotoxic concentration, *EC_{50}* – 50% effective concentration, *TI* –therapeutic index (*TI*= CT_{50}/EC_{50})
CPE - cytopathic effect, *MST* – mean survival time

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

Tonelli et *al*. synthesized a series of 1-substituted 2-[(benzotriazol-1/2-yl)methyl] benzimidazoles **118-137** and tested for antiviral activity against a large panel of RNA and DNA viruses (Fig. 14). Twelve compounds exhibited high activity against RSV (Respiratory Syncytial Virus), with EC_{50} values in most cases below 1 μM, comparing favorably with the reference drug 6-azauridine, which, moreover, exhibited a high toxicity against both the MT-4 and Vero-76 cell lines (S.I. =16.7). The observed activity against BVDV, YFV, and CVB2 is moderate, with EC50 values in the range of 6 – 55 μM for the best compounds (Table 13)[127].



118–137

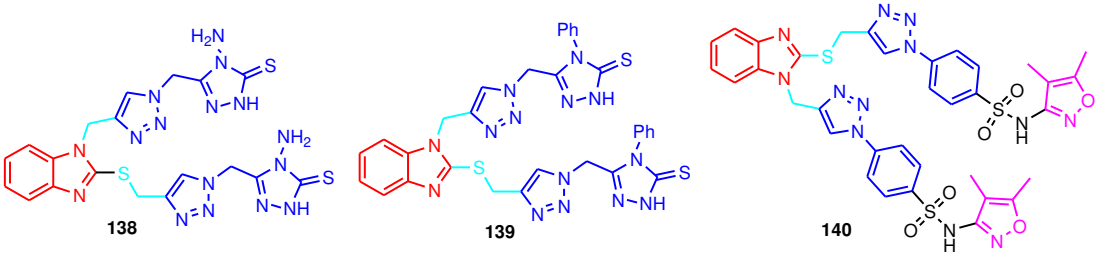
118: R =H R' = $Me_2NCH_2CH_2$
119: R =H R' = $Et_2NCH_2CH_2$
120: R =H R' = $Et_2NCH_2CH_2CH_2$
121: R =H R' = Lupinyl
122: R =H R' = Epilupinyl
123: R =H R' = Homolupinyl
124: R =Cl R' = $Me_2NCH_2CH_2$
125: R =Cl R' = $Et_2NCH_2CH_2$
126: R =Cl R' = $Me_2NCH_2CH_2CH_2$
127: R =Cl R' = $Et_2NCH_2CH_2CH_2$
128: R =Cl R' = Lupinyl
129: R =Cl R' = Epilupinyl
130: R =Cl R' = Homolupinyl
131: R =F_3C R' = $Me_2NCH_2CH_2$
132: R =F_3C R' = $Et_2NCH_2CH_2$
133: R = F_3C R' = $Et_2NCH_2CH_2CH_2$
134: R =F_3C R' = Lupinyl
135: R =NO_2 R' = $Me_2NCH_2CH_2$
136: R =NO_2 R' = $Et_2NCH_2CH_2$
137: R = NO_2 R' = Lupinyl

Figure 14. Structure of antiviral benzimidazole-1,2,3-triazole hybrids **118-137**

Table 13. RSV, BVDV, YFV, and CVB2 Inhibitory Activity of hybrids **118-137** expressed as EC_{50} (μM)

Compound	Anti-RSV activity	Anti-BVDV activity	Anti-YFV activity	Anti-CVB2 activity
118	0.7	-	-	-
119	2.3	-	-	-
120	0.7	> 100	80	> 100
121	0.7	63	> 90	> 100
122	0.3	53	> 70	> 100
123	0.15	51	> 60	> 100
124	0.03	-	-	-
125	0.7	-	-	-
126	0.06	90	> 100	> 100
127	0.1	72	> 54	> 100
128	0.9	15	6	40
129	0.05	19	> 21	> 88
130	0.02	14	> 20	26
131	10.0	-	-	-
132	7.0	-	-	-
133	1.9	67	> 36	> 100
134	> 36	15	> 18	> 36
135	9	-	-	-
136	11	80	> 45	> 100
137	23.0	80	27	> 83
6-Azaurine	1.2	> 100	26	> 100

SARS-CoV-2 and its variants, especially the Omicron variant, remain a great threat to human health. Al-Humaidi et al. reported synthesis a series of benzimidazole-1,2,3-triazoles **138–140** (Fig. 15). Molecular docking studies and *in vitro* enzyme activity revealed that most of the investigated compounds demonstrated promising binding scores against the SARS-CoV-2 and Omicron spike proteins, in comparison to the reference drugs (Table 14).



138 **139** **140**

Figure 15. Structure of antiviral benzimidazole-1,2,3-triazole hybrids **138-140**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 July 2023 doi:10.20944/preprints202307.0093.v1

Table 14. Antiviral activity of benzimidazole-1,2,3-triazole hybrids **138-140**

Compound	CC_{50} (mg mL^{-1})	EC_{50} (mg mL^{-1})	Selectivity Index (SI)
Ceftazidime	1045.53	85.07	12.29
138	1065.51	155.05	6.87
139	1530.5	306.1	5.0
140	1028.28	80.4	12.78

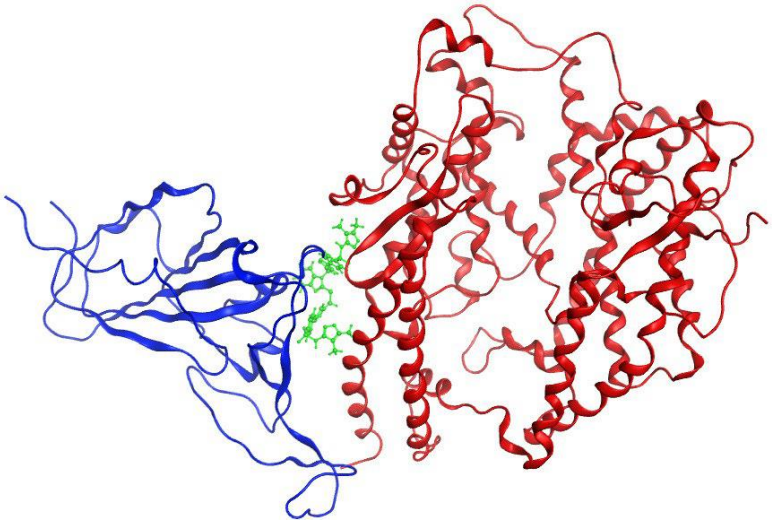
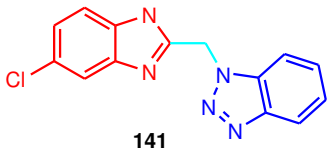


Figure 16. Three-dimensional binding mode of compound **140** (green) at the binding interface between the Omicron S-RBD (red) and human ACE2 (blue)

Three-dimensional binding mode of compound **140** is shown in Fig. 16 [74]. Benzimidazole-1,2,3-triazole hybrids can be potent anti-HSV (Herpes simplex virus) agents. These compounds were screened against flaviviruses and pestiviruses. Compound **141** showed excellent activity against respiratory syncytial virus (RSV) with an EC_{50} value of 0.02 mM (Fig. 17) [128].



141

Figure 17. Structure of antiviral benzimidazole-1,2,3-triazole hybrid **141**

5. Conclusions

This review summarizes the syntheses of benzimidazole–triazole compounds with antimicrobial an antiviral properties mentioned in the literature. The presence of certain groups grafted on the benzimidazole and trizole nuclei, such as -F, -Cl, -Br, $-CF_3$, $-NO_2$, -CN, -NHCO, -CHO, -OH, OCH_3, $-N(CH_3)_2$, $COOCH_3$, as well as other heterocycles in the molecule (pyridine, pyrimidine, thiazole, indole, isoxazole, thiadiazole, coumarine), increases the antimicrobial activity of the compounds [4,5,83,84,129-131]. From the presented literature data, we can highlight some aspects related to the correlation structure - antimicrobial properties.

- The presence of substituents in the "4" or "5" positions of the benzimidazole nucleus can increase the antimicrobial activity of the benzimidazole-triazole hybrids (compounds **12**, **13**, **19**, **20**, **35**).

- The presence of the *ortho* or *para* substituted phenyl substituent in the "1" position of 1,2,3-triazoles in benzimidazole-triazole hybrids can increase their antimicrobial activity.

- In the case of benzimidazoles substituted in the "1" position with triazoles, the presence of an aliphatic or aromatic radical substituent increases the antimicrobial activity of the hybrids.

- The presence of the oxygen atom in the bridge that connects the benzimidazole and triazole rings is favorable to the antimicrobial activity of the hybrids (compounds **19**, **20**, **21**, **29**, **30**)

- The presence of the sulfur atom in the bridge that connects the benzimidazole and triazole rings is favorable to the antimicrobial activity of the hybrids, and even to the antitubercular activity (**95-97**, **105**, **107**).

- The presence of a supplementary triazole ring in benzimidazole-triazole hybrids improves their antimicrobial activity (compounds **43**, **45**, **47**).

- The presence of the benzoyl substituent in the "5" position of the benzimidazole in the benzimidazole-1,2,4-triazole hybrids clearly improves their antimicrobial activity (compounds **85a-85e**).

- The phenyl nucleus as a spacer between the "1" position of 1,2,4-triazole and the "2" position of benzimidazole favors the formation of antimicrobial compounds, and the substituents in the "5" position of the benzimidazole nucleus increase the antimicrobial activity (compounds **79**, **111**, **112**, **113**).

- Only benzimidazole-1,2,3-triazole hybrids are mentioned in the literature as having antiviral properties.

- 2-Substituted or 1,2-disubstituted benzimidazoles with 1,2,3-triazoles are mentioned as antiviral compounds and the presence of an additional triazole ring improves the antiviral activity (compound **140**).

We hope that this review will be useful for the design and synthesis of new benzimidazole-triazole hybrids with antimicrobial and antiviral properties in the context of exacerbation of microbial and viral infections and of resistance to treatments with drugs known on the market.

Author Contributions: Conceptualization, M.M.; methodology, M.M.; software, M.M.; validation, M.M. and C.-V.P.; resources, C.-V.P.; data curation, M.M.; writing—review and editing original draft preparation M.M. and C.-V.P., visualization, M.M.; supervision, M.M. All authors have read and agreed to the published version of the manuscript.

Funding: Please add: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The author is thankful to Department of Organic Chemistry, Biochemistry and Catalysis, for providing necessary facilities to carry out this research work.

Conflicts of Interest: The authors declare no conflict of interest."

References

1. Kabir, E.; Uzzaman,M. A review on biological and medicinal impact of heterocyclic compounds. *Results in Chemistry* **2022**, 100606. https://doi.org/10.1016/j.rechem.2022.100606
2. Nishanth Rao, R.; Jena, S.; Mukherjee, M.; Maiti, B; Chanda, K. Green synthesis of biologically active heterocycles of medicinal importance: a review. *Environ. Chem. Lett.* **2021**, *19*, 3315–3358. https://doi.org/10.1007/s10311-021-01232-9
3. Ebenezer, O.; Oyetunde-Joshua, F.; Omotoso, O.D.; Shapi, M. Benzimidazole and its derivatives: Recent Advances (2020–2022). *Results in Chemistry* **2023**, *5*, 100925. https://doi.org/10.1016/j.rechem.2023.100925
4. Bansal, Y.; Kaur, M.; Bansal, G. Antimicrobial Potential of Benzimidazole Derived Molecules. *Mini. Rev. Med. Chem.* **2019**, 19 (8), 624-646. DOI: 10.2174/1389557517666171101104024
5. Marinescu, M. Synthesis of Antimicrobial Benzimidazole–Pyrazole Compounds and Their Biological Activities. *Antibiotics* **2021**, *10*, 1002. https://doi.org/10.3390/antibiotics10081002
6. Deswal, L.; Verma, V.; Kumar, D.; Deswal, Y.; Kumar, A.; Kumar, R; Parshad, M.; Bhatia, M. Synthesis, antimicrobial and α-glucosidase inhibition of new benzimidazole-1,2,3-triazole-indoline derivatives: a combined experimental and computational venture. *Chem. Pap.* **2022**, 76, 7607–7622. https://doi.org/10.1007/s11696-022-02436-1
7. Raducka, A.; Świątkowski, M.; Korona-Głowniak, I.; Kaproń, B.; Plech, T.; Szczesio, M.; Gobis, K.; Szynkowska-Jóźwik, M.I.; Czylkowska, A. Zinc Coordination Compounds with Benzimidazole Derivatives: Synthesis, Structure, Antimicrobial Activity and Potential Anticancer Application. *Int. J. Mol. Sci.* **2022,** *23*, 6595. https://doi.org/10.3390/ijms23126595
8. Zalaru, C.; Dumitrascu, F.; Draghici, C.; Tarcomnicu, I.; Marinescu, M.; Nitulescu, G.M.; Tatia, R.; Moldovan, L.; Popa, M.; Chifiriuc, M.C. New Pyrazolo-Benzimidazole Mannich Bases with Antimicrobial and Antibiofilm Activities. *Antibiotics* **2022**, 11, 1094. https://doi.org/10.3390/antibiotics11081094
9. Chen, M.; Su, S.; Zhou, Q.; Tang, X.; Liu, T., Peng, F.; He, M.; Luo, H.; Xue, W. Antibacterial and antiviral activities and action mechanism of flavonoid derivatives with a benzimidazole moiety. *J. Saudi Chem. Soc.* **2021**, *25,* 101194. https://doi.org/10.1016/j.jscs.2020.101194

10. Kanwal, A.; Ahmad, M.; Aslam, S.; Naqvi, S.A.R.; Jawwad Saif, M.J. Molecular-biological prolems of drug design and mehanism of drug action. Recent advances n antiviral benyimidayole derivatives: a mini review. *Pharm. Chem. J.* **2019**, 53 (3), 179-187. https://doi.org/10.1007/s11094-019-01976-3
11. Brishty, S.R.; Hossain, Md. J.; Khandaker, M.U.; Faruque, M.R.I.; Osman, H.; Rahman, S.M.A. A Comprehensive Account on Recent Progress in Pharmacological Activities of Benzimidazole Derivatives. *Front. Pharmacol.* **2021**, *12*, 762807. https://doi.org/10.3389/fphar.2021.762807
12. Yhou, S.; Huang, G. Synthesis of anti-allergic drugs. *RSC Adv.* **2020**, *10*, 5874. https://doi.org/10.1039/C9RA10659F
13. Vasil'ev, P. M. ; Kalitin, K. Yu.; Spasov, A. A.; Grechko, O. Yu.; Poroikov, V. V.; Filimonov, D. A.; Anisimova, V. A. Search for new dugs prediction and study of anticonvulsant properties of benzimidazole derivatives. *Pharm. Chem. J.* **2017**, *50* (12), 775-780. https://doi.org/10.1007/s11094-017-1530-6
14. Lee, Y.T.; Tan, YJ.; OOn, C.E. Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine. *Acta Pharmaceutica Sinica B* **2023**, *13* (2), 478-497. https://doi.org/10.1016/j.apsb.2022.09.010
15. Satija, G.; Sharma, B.; Madan,A.; Iqubal, A; Shaquiquzzaman, M.; Akhter, M.; Parvez, S.; Khan, M.A.; Alam, M.M. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. *J. Heterocyclic. Chem.* **2021**, *59* (1), 22-66. https://doi.org/10.1002/jhet.4355
16. Song, B.; Park, E.Y.; Kim, K.J.; Ki, S.H. Repurposing of Benzimidazole Anthelmintic Drugs as Cancer Therapeutics. *Cancers* **2022**, *14*, 4601. https://doi.org/10.3390/cancers14194601
17. Chen, W.L.; Li, D.D.; Chen, X.; Wang, Y.Z.; Xu, J.-J.; Jiang, Z.-Y.; You, Q.-D.; Guo, X.-K. Proton pump inhibitors selectively suppress MLL rearranged leukemia cells via disrupting MLL1-WDR5 protein-protein interaction. *Eur. J. Med. Chem.* **2020**, *188*, 112027. https://doi.org/10.1016/j.ejmech.2019.112027
18. Argirova,M.A.; Georgieva, M.K.; Hristova-Avakumova, N.G.; Vuchev, D.I.; Popova-Daskalova, G.V.; Anichina, K.K.; Yancheva, D.Y. New 1*H*-benzimidazole-2-yl hydrazones with combined antiparasitic and antioxidant activity. *RSC Adv.* **2021**, *11*, 39848–39868. https://doi.org/10.1039/D1RA07419A
19. Valderas-García, E.; Häberli, C.; Álvarez-Bardón, M.; Escala, N.; Castilla-Gómez de Agüero, V.; de la Vega, J.; del Olmo, E.; Balaña-Fouce, R.; Keiser, J.; Martínez-Valladares, M. Benzimidazole and aminoalcohol derivatives show in vitro anthelmintic activity against Trichuris muris and Heligmosomoides polygyrus. *Parasites & Vectors* **2022**, *15*, 243. https://doi.org/10.1186/s13071-022-05347-y
20. Kamat, V.; Yallur , B.C.; Poojary, B.; Patil, V.B.; Nayak, S.P.; Krishna, P.M.; Joshi , S.D. Synthesis, molecular docking, antibacterial, and anti-inflammatory activities of benzimidazole-containing tricyclic systems. *J. Chin. Chem. Soc.* **2021**, *68* (6), 1055-1066. https://doi.org/10.1002/jccs.202000454
21. Moharana, A.K.; Dash, R.N.; Mahanandia, N.C.; Subudhi, B.B. Synthesis and anti-inflammatory activity evaluation of some benzimidazoled erivatives. *Pharm. Chem. J.* **2022**, *56* (8), 1070-1074. https://doi.org/10.1007/s11094-022-02755-3
22. Veerasamy, R.; Roy, A.; Karunakaran, R.; Rajak, H. Structure–Activity Relationship Analysis of Benzimidazoles as Emerging Anti-Inflammatory Agents: An Overview. *Pharmaceuticals* **2021**, *14*, 663. https://doi.org/10.3390/ph14070663
23. Iqbal, H.; Verma, A.K.; Yadav, P.; Alam, S.; Shafiq, M.; Mishra, D.; Khan, F.; Hanif, K.; Negi, A.S.; Chanda, D. Antihypertensive Effect of a Novel Angiotensin II Receptor Blocker Fluorophenyl Benzimidazole: Contribution of cGMP, Voltage-dependent Calcium Channels, and BKCa Channels to Vasorelaxant Mechanisms. *Front. Pharmacol.* **2021**, *30* (12), 611109. https://doi.org/10.3389/fphar.2021.611109
24. Tajane, P. S., Sawant, R. L. An updated review on benzimidazole derivatives as potential antihypertensive agents. *Int. J. Health Sci.* **2022**, 6(S1), 7169-7179. https://doi.org/10.53730/ijhs.v6nS1.6543
25. Aboul-Enein, H.Y.; El Rashedy, A.A. Benzimidazole Derivatives as Antidiabetic Agents. *Med. Chem.* **2015**, *5* (7), 318-325. doi: 10.4172/2161-0444.1000280
26. Dik, B.; Coşkun, D.; Bahcivan, E.; Unez, K. Potential antidiabetic activity of benzimidazole derivative albendazole and lansoprazole drugs in different doses in experimental type 2 diabetic rats. *Turk. J. Med. Sci.* **2021**, *51*, 1578-1585. DOI: 10.3906/sag-2004-38.
27. Farid, S.M.: Noori, M.; Montazer, M.N.; Ghomi, M.K.; Mollazadeh, M.; Dastyafteh, N.; Irajie C.; Zomorodian, K.; Mirfazli, S.S.; Mojtabavi, S.; Faramarzi, M.A.; Larijani, B.; Iraji, A.; Mahdavi, M. Synthesis and structure–activity relationship studies of benzimidazole-thioquinoline derivatives as α-glucosidase inhibitors. *Sci. Rep.* **2023**, *13*, 4392. https://doi.org/10.1038/s41598-023-31080-2
28. Stanton, J.B.; Schneider, D.A.; Dinkel, K.D.; Balmer, B.F.; Baszler, T.V.; Mathison, B.A.; Boykin, D.W.; Kumar, A. Discovery of a Novel, Monocationic, Small-Molecule Inhibitor of Scrapie Prion Accumulation in Cultured Sheep Microglia and Rov Cells. *Plos One* **2012**, *7* (11), | e51173. https://doi.org/10.1371/journal.pone.0119084
29. Dinparast, L.; Zengin, G.; Bahadori, M.B. Cholinesterases Inhibitory Activity of 1H-benzimidazole Derivatives. *Biointerface Res in Appl. Chem.* **2021**, *11* (3), 10739 - 10745. https://doi.org/10.33263/BRIAC113.1073910745

30. Adalat, B.; Rahim, F.; Taha, M.; Alshamrani, F.J.; Anouar, E.H.; Uddin, N.; Shah, S.A.A.; Ali, Z.; Zakaria, Z.A. Synthesis of Benzimidazole–Based Analogs as Anti Alzheimer's Disease Compounds and Their Molecular Docking Studies. *Molecules* **2020**, *25*, 4828. https://doi.org/10.3390/molecules25204828
31. Cheretaev, I. V.; Korenyuk, I. I.; Nozdrachev, A.D. Neurotropic, Psychoactive, and Analgesic Properties of Benzimidazole and Its Derivatives: Physiological Mechanisms. *Neurosci. Behav. Physiol.* **2018**, *48* (7), 848-853. https://doi.org/10.1007/s11055-018-0639-8
32. Maltsev, D.V.; Spasov, A.A.; Vassiliev, P.M.; Skripka, M.O.; Miroshnikov, M.V.; Kochetkov, A.N.; Eliseeva, N.V.; Lifanova, Y.V.; Kuzmenko, T.A.; Divaeva, L.N.; Morkovnik, A.S. Synthesis and Pharmacological Evaluation of Novel 2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole Derivatives as Promising Anxiolytic and Analgesic Agents. *Molecules* **2021**, *26*, 6049. https://doi.org/10.3390/molecules26196049
33. Yen, T.L.; Wu, .P.; Chng, C.L.; Yang, W.B.; Jayakumar, T.; Geraldine, P.; Chou, C.M.; Chang, C.Y.; Lu, W.J.; Sheu, J.R. Novel synthetic benzimidazole-derived oligosaccharide, M3BIM, prevents ex vivo platelet aggregation and in vivo thromboembolism. *J. Biomed. Sci.* **2016**, *23*, 26. https://doi.org/10.1186/s12929-016-0245-4
34. Zhang, T.; Liu, Q.; Ren, Y. Design, synthesis and biological activity evaluation of novel methyl substituted benzimidazole derivatives. *Tetrahedron* **2020**, *76* (13), 131027. https://doi.org/10.1016/j.tet.2020.131027
35. Zhang, B. Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids. *Eur. J. Med. Chem.* **2019**, *168*, 357-372. https://doi.org/10.1016/j.ejmech.2019.02.055
36. Strzelecka, M.; Świątek, P. 1,2,4-Triazoles as Important Antibacterial Agents. *Pharmaceuticals* **2021**, *14*, 224. https://doi.org/10.3390/ph14030224
37. Patil, S.A.; Nesaragi, A.R.; Rodríguez-Berrios, R.R.; Hampton, S.M.; Bugarin, A.; Patil, S.A. Coumarin Triazoles as Potential Antimicrobial Agents. *Antibiotics* **2023**, *12*, 160. https://doi.org/10.3390/antibiotics12010160
38. Kazeminejad, Z.; Marzi, M.; Shiroudi, A.; Kouhpayeh, S.A.; Farjam, M.; Zarenezhad, E. Novel 1, 2, 4-Triazoles as Antifungal Agents. Review. *BioMed Res. Int.* **2022**, 4584846, 1-39. https://doi.org/10.1155/2022/4584846
39. Sharma, A.; Agrahari, A.K.; Rajkhowa, S.; Tiwari, V.K. Emerging impact of triazoles as anti-tubercular agent. *Eur. J. Med.Chem.* **2022**, *238*, 114454. https://doi.org/10.1016/j.ejmech.2022.114454
40. El-Shoukrofy, M.S.; Atta, A.; Fahmy, S.; Sriram, D.; Mahran, M.A.; Labouta, I.M. New tetrahydropyrimidine-1,2,3-triazole clubbed compounds: Antitubercular activity and Thymidine Monophosphate Kinase (TMPKmt) inhibition. *Bioorg. Chem.* **2023**, *131*, 106312. https://doi.org/10.1016/j.bioorg.2022.106312
41. Ravisankar N.; Sarathi, N.; Maruthavanan, T.; Ramasundaram, S.; Ramesh, M.; Sankar, C.; Umamatheswari, S.; Kanthimathi, G.; Oh, T.H. Synthesis, antimycobacterial screening, molecular docking, ADMET prediction and pharmacological evaluation on novel pyran-4-one bearing hydrazone, triazole and isoxazole moieties: Potential inhibitors of SARS CoV-2. Synthesis, antimycobacterial screening, molecular docking, ADMET prediction and pharmacological evaluation on novel pyran-4-one bearing hydrazone, triazole and isoxazole moieties: Potential inhibitors of SARS CoV-2. *J. Mol. Struct.* **2023**, *1285*, 135461. https://doi.org/10.1016/j.molstruc.2023.135461
42. Musa, A.; Abulkhair, H.S.; Aljuhani, A.; Rezki, N.; Abdelgawad, M.A.; Shalaby, K.; El-Ghorab, A.H.; Aouad, M.R. Phenylpyrazolone-1,2,3-triazole Hybrids as Potent Antiviral Agents with Promising SARS-CoV-2 Main Protease Inhibition Potential. *Pharmaceuticals* **2023**, *16*, 463. https://doi.org/10.3390/ph16030463
43. Seliem, I.A.; Panda, S.S.; Girgis, A.S.; Moatasim, Y.; Kandeil, A.; Mostafa, A.; Ali, M.A.; Nossier, E.S.; Rasslan, F.; Srour, A.M.; Sakhuja, R.; Ibrahim, T.S.; Abdel-samii, Z.K.M.; Al-Mahmoudy, A.M.M. New quinoline-triazole conjugates: Synthesis, and antiviral properties against SARS-CoV-2. *Bioorg. Chem.* **2021**, *114*, 105117. https://doi.org/10.1016/j.bioorg.2021.105117
44. Venkatesham, P.; Schols, D.; Persoons, L.; Claes, S.; Sangolkar, A.A.; Chedupaka, R.; Vedula, R.R. Synthesis of novel thioalkylated triazolothiazoles and their promising in-vitro antiviral activity. *J. Mol. Struct.* **2023**, *1286*, 135573. https://doi.org/10.1016/j.molstruc.2023.135573
45. Pinheiro, N.G.; Gonzaga, D.T.G.; da Silva, A.R.; Fuly, A.C.; von Ranke, N.L.; Rodrigues, C.R.; Magalhães, B.Q.; Pereira, J.S.; Pacheco, P.A.F.; Silva, A.C.; Ferreira, V.F.; de Carvalho da Silva, F.; Faria, R.X. Triazoles with inhibitory action on P2X7R impaired the acute inflammatory response in vivo and modulated the hemostatic balance in vitro and ex vivo. *Inflamm. Res.* **2023**, *72*, 237–250. https://doi.org/10.1007/s00011-022-01664-1
46. Demchenko, S.; Lesyk, R.; Yadlovskyi, O.; Holota, S.; Yarmoluk, S.; Tsyhankov, S.; Demchenko, A. Fused Triazole-Azepine Hybrids as Potential Non-Steroidal Antiinflammatory Agents. *Sci. Pharm.* **2023**, *91*, 26. https://doi.org/10.3390/scipharm91020026
47. Bozorov, K.; Zhao, J.; Aisa, H.A. 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview. *Bioorg. Med. Chem.* **2019**, *27*, 3511–3531. https://doi.org/10.1016/j.bmc.2019.07.005
48. Hashem, H.E.; Amr, A.E-G.E.; Nossier, E.S.; Anwar, , M.M.; Azmy, E.M. New Benzimidazole-1,2,4-Triazole-, and 1,3,5-Triazine-Based Derivatives as Potential EGFRWT and EGFRT790M Inhibitors:

Microwave-Assisted Synthesis, Anticancer Evaluation, and Molecular Docking Study. *ACS Omega* **2022**, *7* (8), 7155-7171. https://doi.org/10.1021/acsomega.1c06836

49. Othman, D.I.A.; Hamdi, A.; Tawfik, S.S.; Elgazar, A.A.; Mostafa, A.S. Identification of new benzimidazole-triazole hybrids as anticancer agents: multi-target recognition, in vitro and in silico studies. *J. Enzyme Inhib. Med. Chem.* **2023**, *38* (1), 2166037. https://doi.org/10.1080/14756366.2023.2166037
50. Gupta, O.; Pradhan, G, T. Chawla, G. An updated review on diverse range of biological activities of 1,2,4-triazole derivatives: Insight into structure activity relationship. *J. Mol. Struct.* **2023**, *1274*, Part 2, 134487. https://doi.org/10.1016/j.molstruc.2022.134487
51. Abu-Melha, S.; Azher, O.A.; Alaysuy, O.; Alnoman, R.B.; Abualnaja, M.M.; Althagafi, I.; El-Metwaly, N.M. Synthesis, molecular modeling and antioxidant activity of new thiadiazolyl-triazole analogues. *J. Saudi. Chem. Soc*. **2023**, *27* (2), 101596. https://doi.org/10.1016/j.jscs.2022.101596
52. Dawbaa, S.; Nuha, D.; Evren, A.E.; Cankiliç, M.Y.; Yurttaş, L.; Turan, G. New oxadiazole/triazole derivatives with antimicrobial and antioxidant properties. *J. Mol. Struct*. **2023**, *1282*, 135213. https://doi.org/10.1016/j.molstruc.2023.135213
53. Zhao, W.; Song, M.; Hua, Y.; Zhu, Y.; Liu, W.; Xia, Q.; Deng, X.; Huang, Y. Design, Synthesis, and Pharmacology of New Triazole-Containing Quinolinones as CNS Active Agents. *Molecules* **2023**, *28*, 1987. https://doi.org/10.3390/molecules28041987
54. Dixit, D.; Verma, P.K.; Marwaha, R.K. A review on 'triazoles': their chemistry, synthesis and pharmacological potentials. *J. Iran. Chem. Soc*. **2021**, *18*, 2535–2565. https://doi.org/10.1007/s13738-021-02231-x
55. Fallah, Z.; Tajbakhsh, M.; Alikhani, M.; Larijani, B.; Faramarzi, M.A.; Hamedifar, H.; Mohammadi-Khanaposhtani, M.; Mahdavi, M. A review on synthesis, mechanism of action, and structure-activity relationships of 1,2,3-triazole-based α-glucosidase inhibitors as promising anti-diabetic agents. *J. Mol. Struct.* **2022**, *1255*, 132469. https://doi.org/10.1016/j.molstruc.2022.132469
56. Rahim, F.; Ullah, H.; Hussain, R.; Taha, M.; Khan, S.; Nawaz, M.; Nawaz, F.; Gilani, S.J.; Bin Jumah, M.N. Thiadiazole based triazole/hydrazone derivatives: Synthesis, in vitro α-glucosidase inhibitory activity and in silico molecular docking study. *J. Mol. Struct*. **2023**, 1287,135619. https://doi.org/10.1016/j.molstruc.2023.135619
57. Kumar, S.; Khokra, S.L.; Yadav, A. Triazole analogues as potential pharmacological agents: a brief review. *Future J. Pharm. Sci*. **2021**, *7*, 106. https://doi.org/10.1186/s43094-021-00241-3
58. Kaproń, B.; Łuszczki, J.J.; Siwek, A.; Karcz, T.; Nowak, G.; Zagaja, M.; Andres-Mach, M.; Stasiłowicz, A.; Cielecka-Piontek, J.; Kocki, J.; Plech, T. Preclinical evaluation of 1,2,4-triazole-based compounds targeting voltage-gated sodium channels (VGSCs) as promising anticonvulsant drug candidates. *Bioorg. Chem.* **2020**, 94, 103355. https://doi.org/10.1016/j.bioorg.2019.103355
59. Chu, X.M.; Wang, C.; Wang, W.-L.; Liang, L.L.; Liu, W.; Gong, K.K.; Sun, K.L. Triazole derivatives and their antiplasmodial and antimalarial activities. *Eur. J. Med. Chem*. **2019**, *166*, 206-223. https://doi.org/10.1016/j.ejmech.2019.01.047
60. Xu, M.; Peng, Y.; Zhu, L.; Wang, S.; Ji, J.; Rakesh, K.P. Triazole derivatives as inhibitors of Alzheimer's disease: Current developments and structure-activity relationships. *Eur. J. Med. Chem.* **2019,** *180*, 656-672. https://doi.org/10.1016/j.ejmech.2019.07.059
61. Khan, S.A.; Akhtar, M.J.; Gogoi, U.; Meenakshi, D.U.; Das, A. An Overview of 1,2,3-triazole-Containing Hybrids and Their Potential Anticholinesterase Activities. *Pharmaceuticals* **2023**, *16*, 179. https://doi.org/10.3390/ph16020179
62. Sooknual, P.; Pingaew, R.; Phopin, K.; Ruankham, W.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. Synthesis and neuroprotective effects of novel chalcone-triazole hybrids. *Bioorg. Chem.* **2020**, *105*, 104384. https://doi.org/10.1016/j.bioorg.2020.104384
63. Manzoor, S.; Almarghalani, D.A.; James, A.W.; Raza, Md K.; Kausar, T.; Nayeem, S.M.; Hoda, N.; Shah, Z.A. Synthesis and Pharmacological Evaluation of Novel Triazole-Pyrimidine Hybrids as Potential Neuroprotective and Anti-neuroinflammatory Agents. *Pharm. Res*. **2023**, 40,167–185. https://doi.org/10.1007/s11095-022-03429-1
64. Li, G.; Hilgenfeld, R.; Whitley, R; De Clercq, E. Therapeutic strategies for COVID-19: progress and lessons learned. *Nat. Rev. Drug. Discov.* **2023**, 1-27. https://doi.org/10.1038/s41573-023-00672-y
65. Panahi, Y.; Gorabi, A.M.; Talaei, S.; Beiraghdar, F.; Akbarzadeh, A.; Tarhriz, V.; Mellatyar, H. An overview on the treatments and prevention against COVID-19. *Virol. J.* **2023**, *20* (1), 23. https://doi.org/10.1186/s12985-023-01973-9
66. Uematsu, T.; Takano, T.; Matsui, H.; Kobayashi, N.; Ōmura, S.; Hanaki, H. Prophylactic administration of ivermectin attenuates SARS-CoV-2 induced disease in a Syrian Hamster Model. The *Journal of Antibiotics* **2023**, 1-8. https://doi.org/10.1038/s41429-023-00623-0
67. Shukla, A.K.; Misra, S. Antimicrobials in COVID-19: strategies for treating a COVID-19 pandemic. *J. Basic Clin. Physiol. Pharmacol*. **2022**, 1-16. https://doi.org/10.1515/jbcpp-2022-0061

68. McCarthy, M.W. Current and emerging immunomodulators for treatment of SARS-CoV2 infection (COVID-19). *Expert Opin. Pharmacother.* **2022**, 1–6. https://doi.org/10.1080/14656566.2022.2035360
69. Fazio, S.; Bellavite, P. Early Multi-Target Treatment of Mild-to-Moderate COVID-19, Particularly in Terms of Non-Steroidal Anti-Inflammatory Drugs and Indomethacin. *BioMed* **2023**, *3*, 177-194. https://doi.org/10.3390/biomed3010015
70. Mallikanti, V.; Thumma, V.; Matta, R.; Valluru, K.R.; Sharma Konidena, L.N.; Boddu, L.S.; Pochampally, *J. Chem. Data Collections* **2023**, *45*, 101034. https://doi.org/10.1016/j.cdc.2023.101034
71. Güzel, E.; Çevik, U.A.; Evren, A.E.; Bostancı, H.E.; Gül, U.D.; Kayış, U.; Özkay, Y.; Kaplancıklı, Z.A. Synthesis of Benzimidazole-1,2,4-triazole Derivatives as Potential Antifungal Agents Targeting 14α-Demethylase. *ACS Omega* **2023**, *8* (4), 4369–4384. https://doi.org/10.1021/acsomega.2c07755
72. Ghobadi, E.; Hashemi, S.M.; Fakhim, H.; Hosseini-khah, Z.; Badali, H.; Emami, S. Design, synthesis and biological activity of hybrid antifungals derived from fluconazole and mebendazole. *Eur. J. Med. Chem.* **2023**, *249*, 115146. https://doi.org/10.1016/j.ejmech.2023.115146
73. Youssif, B.G.M.; Mohamed, Y.A.M.; Salim, M.T.A.; Inagaki, F.; Mukai, C.; Abdu-Allah, H.H.M. Synthesis of some benzimidazole derivatives endowed with 1,2,3-triazole as potential inhibitors of hepatitis C virus. *Acta Pharm.* **2016**, *66*, 219–231. https://doi.org/10.1515/acph-2016-0014
74. Al-Humaidi, J.Y.; Shaaban, M.M.; Rezki, N.; Aouad, M.R.; Zakaria, M.; Jaremko, M.; Hagar, M.; Elwakil, B.H. 1,2,3-Triazole-Benzofused Molecular Conjugates as Potential Antiviral Agents against SARS-CoV-2 Virus Variants. *Life* **2022**, *12*, 1341. https://doi.org/10.3390/life12091341
75. Kondengadan, S.M.; Bansal, S.; Yang, C.; Liu, D.; Fultz, Z.; Wang, B. Click chemistry and drug delivery: A bird's-eye view. *Acta Pharm. Sin. B*. **2023**, *13* (5), 1990-2016. https://doi.org/10.1016/j.apsb.2022.10.015
76. de Souza, R.O.M.A.; de Mariz Miranda, L.S. Strategies Towards the Synthesis of N2-Substituted 1,2,3-Triazoles. *An. Acad. Bras. Ciênc*. **2019**, *91*(Suppl. 1), e20180751. http://orcid.org/0000-0003-0634-5846
77. Dai, J.: Tian, S; Yang, X.; Liu, Z. Synthesis methods of 1,2,3-/1,2,4-triazoles: A review. *Front. Chem*. **2022**, *10*, 891484. https://doi.org/10.3389/fchem.2022.891484
78. De Nino, A.; Maiuolo, L.; Costanzo, P.; Algieri, V.; Jiritano, A.; Olivito, F.; Tallarida, M.A. Recent Progress in Catalytic Synthesis of 1,2,3-Triazoles. *Catalysts* **2021**, *11*, 1120. https://doi.org/10.3390/catal11091120
79. Koranne, A; Kurrey, K.; Kumar, P.; Gupta, S.; Jha, K.V.; Ravi, R.; Sahu, K.P.; Anamika; Jha, A.K. Metal catalyzed C–H functionalization on triazole rings. RSC Adv. 2022, 12, 27534. https://doi.org/10.1039/D2RA05697F
80. Marinescu, M. Chemistry and Applications of Benzimidazole and its Derivatives; Publisher: IntechOpen London, GB, 2019; pp. 1-213.
81. Marinescu, M. Chiral benzimidazoles in medicinal chemistry: syntheses and applications. In *Benzimidazole: Preparation and Applications*. Vestergaard, A.A. Ed. Publisher: New York, USA, 2020; pp. 87–112.
82. Zalaru, C.-M.; Marinescu, M. Benzimidazole compounds with anti-tumor and antibacterial activities. In Benzimidazole: Preparation and Applications. Vestergaard, A.A. Ed. Publisher: New York, USA, 2020; pp. 221-250.
83. Marinescu, M.; Tudorache, D.G.; Marton, G.I.; Zalaru, C.M.; Popa, M.; Chifiriuc, M.C.; Stavarache, C.E.; Constantinescu, C. Density functional theory molecular modeling, chemical synthesis, and antimicrobial behaviour of selected benzimidazole derivatives. *J. Mol. Struct*. **2017**, 463-471. https://doi.org/10.1016/j.molstruc.2016.10.066
84. Marinescu, M.; Cinteza, L.O.; Marton, G.I.; Chifiriuc, M.C.; Popa, M.; Stanculescu, I.; Zalaru, C.M.; Stavarache, C.E. Synthesis, density functional theory study and *in vitro* antimicrobial evaluation of new benzimidazole Mannich bases. *BMC Chemistry* **2020**, 14 (1), 45. https://doi.org/10.1186/s13065-020-00697-z
85. Marinescu, M. Nitrogen-containing heterocycles as corrosion inhibitors. In *Corrosion Inhibitors: An Overview*. Wilkerson, R. Ed. Publisher: New York, USA, 2020; pp. 161–201.
86. Qiu, J.; Zou, Y.; Li, S.; Yang, L.; Qiu, Z.; Kong, F.; Gu, X. Discovery of benzimidazole substituted 1, 2, 4-oxadiazole compounds as novel anti-HBV agents with TLR8-agonistic activities. *Eur. J. Med. Chem.* **2022**, *244*, 114833. https://doi.org/10.1016/j.ejmech.2022.114833
87. Youssif, B.G.M.; Abdel-Moty, S.G.; Sayed, Y.B. Synthesis and biologicalevaluation of some novel 1,2,3-triazol-N-arylidene acetohydrazide incorporating benzimidazole ring moiety as potential antimicrobial agents. *J. Curr. Chem. Pharm. Sc.* **2014**, *4(2),* 54-64.
88. Al-blewi, F.F.; Almehmadi, M.A.; Aouad, M.R.; Bardaweel, S.K.; Sahu, P.K.; Messali, M.; Rezki, N.; El Ashry, L.S.H. Design, synthesis, ADME prediction and pharmacological evaluation of novel benzimidazole-1,2,3-triazole-sulfonamide hybrids as antimicrobial and antiproliferative agents. *Chem. Cent. J.* **2018**, *12*, 110. https://doi.org/10.1186/s13065-018-0479-1
89. Rashdan, H.R.M.; Abdelmonsef, A.H.; Abou-Krisha, M.M.; Yousef, T.A. Synthesis, Identification, Computer-Aided Docking Studies, and ADMET Prediction of Novel Benzimidazo-1,2,3-triazole Based Molecules as Potential Antimicrobial Agents. *Molecules* **2021**, *26*, 7119. https://doi.org/10.3390/molecules26237119

90. Ouahrouch, A.; Ighachane, H.; Taourirte, M.; Engels, J.W.; Sedra, M.H.; Lazrek, H.B. Benzimidazole-1,2,3-triazole Hybrid Molecules: Synthesis and Evaluation for Antibacterial/Antifungal Activity. *Arch. Pharm. Chem. Life Sci.* **2014**, *347*, 748–755. https://doi.org/10.1002/ardp.201400142
91. Bistrović, A.; Krstulović, L.; Stolić, I.; Drenjancević, D.; Talapko, J.; Taylor, M.C.; Kelly, J.M.; Bajić, M.; Raic-Malić, S. Synthesis, anti-bacterial and anti-protozoal activities of amidinobenzimidazole derivatives and their interactions with DNA and RNA. *J. Enzyme Inhib. Med. Chem*. **2018**, *33*, (1), 1323–1334. https://doi.org/10.1080/14756366.2018.1484733
92. Rao, Y.J.; Sowjanya, T.; Thirupathi, G.; Murthy, N.Y.S.; Kotapalli, S.S. Synthesis and biological evaluation of novel flavone/triazole/ benzimidazole hybrids and flavone/isoxazole-annulated heterocycles as antiproliferative and antimycobacterial agents. *Mol. Div.* **2018**, *22*, 803-814. https://doi.org/10.1007/s11030-018-9833-4
93. Ashok, D; Gundu, S.; Aamate, V.K.; Devulapally, M.G. Conventional andmicrowave-assisted synthesis of new indole-tethered benzimidazole-based 1,2,3-triazoles and evaluation of their antimycobacterial, antioxidant and antimicrobial activities. *Mol. Div*. **2018**, *22*, 769-778. https://doi.org/10.1007/s11030-018-9828-1
94. Chandrika, N.T.; Shrestha, S.K.; Ranjan, N.; Sharma, A.; Arya, D.P.; Garneau-Tsodikova, S. New Application of Neomycin B−Bisbenzimidazole Hybrids as Antifungal Agents. *ACS Infect. Dis.* **2018**, *4*, 196−207. https://doi.org/10.1021/acsinfecdis.7b00254
95. Saber, A.; Anouar, E.H.; Sebbar, G.; El Ibrahimi, B.; Srhir, M.; Hökelek, T.; Mague, J.T.; El Ghayati, L.; Sebbar, N.K.; Essassi, E.M. New 1,2,3-triazole containing benzimidazolone derivatives: Syntheses, crystal structures, spectroscopic characterizations, Hirshfeld surface analyses, DFT calculations, anti-corrosion property anticipation, and antibacterial activities. *J. Mol. Struct*. **2021**, *1242*, 130719. https://doi.org/10.1016/j.molstruc.2021.130719
96. Mohsen, D.H.; Radhi, A.J.; Shaheed, D.Q.; Abbas, H.K. Synthesis New Benzimidazole Derivatives as Antibacterial. *J. Pharm. Negative Results* **2022**, *13* (3), 893-898. DOI: 10.47750/pnr.2022.13.S03.137
97. Rezki, N. Green Microwave Synthesis and Antimicrobial Evaluation of Novel Triazoles. *Org. Prep. Proc. Int.* **2017**, *49*, 525–541. https://doi.org/10.1080/00304948.2017.1384262
98. Aparna, Y.; Nirmala, G.; Subhashini, N.J.P.; Sharada, L.N.; Sreekanth, S. Synthesis and Antimicrobial Activity of Novel Bis-1,2,3-triazol-1H-4-yl-substituted Aryl Benzimidazole-2-thiol Derivatives. *Russ. J. Gen. Chem.* **2020**, *90* (8), 1501–1506. https://doi.org/10.1134/S1070363220080186
99. Gill, C.; Jadhav, G.; Shaikh, M.; Kale, R.; Ghawalkar, A.; Nagargoje, D.; Shiradkar, M. Clubbed [1,2,3] triazoles by fluorine benzimidazole: A novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 6244–6247. https://doi.org/10.1016/j.bmcl.2008.09.096
100. Anand, A.; Kulkarni, M.V.; Joshi, S.D.; Dixit, S.R. One pot Click chemistry: A three component reaction for the synthesis of 2-mercaptobenzimidazole linked coumarinyl triazoles as anti-tubercular agents. *Bioorg. Med. Chem. Lett*. **2016**, 4709–4713. https://doi.org/10.1016/j.bmcl.2016.08.045
101. Khanapurmath, N. Kulkarni, M.V.; Joshi, S.D.; Kumar, G.N.A. A click chemistry approach for the synthesis of cyclic ureido tethered coumarinyl and 1-aza coumarinyl 1,2,3-triazoles as inhibitors of *Mycobacterium tuberculosis* H37Rv and their in silico studies. *Biorg. Med. Chem*. **2019**, 115054. https://doi.org/10.1016/j.bmc.2019.115054
102. Pandey, V.K.; Upadhyay, M.; Upadhyay, M.; Gupta, V.D.; Tandon, M. Benzimidazolyl quinolinyl mercaptotriazoles as potential antimicrobial and antiviral agents. *Acta Pharm.* **2005**, *55*, 47–56.
103. Jadhav, G.R.; Shaikh, M.U.; Kale, R.P.; Shiradkar, M.R.; Gill, C.H. SAR study of clubbed [1,2,4]-triazolyl with fluorobenzimidazoles as antimicrobial and antituberculosis agents. *Eur. J. Med. Chem*. **2009**, *44*, 2930–2935. https://doi.org/10.1016/j.ejmech.2008.12.001
104. Barot, K.P.; Manna, K.S.; Ghate, M.D. Design, synthesis and antimicrobial activities of some novel 1,3,4-thiadiazole, 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole. *J. Saudi Chem. Soc*. **2017**, *21*, S35–S43. http://dx.doi.org/10.1016/j.jscs.2013.09.010
105. Jiang, Z.; Wang, Y.; Wang, W.; Wang, S.; Xu, B.; Fan, G.; Dong, G.; Liu, Y.; Yao, J.; Miao, Z.; Zhang, W. Discovery of highly potent triazole antifungal derivatives by heterocycle-benzene bioisosteric replacement. *Eur. J. Med. Chem.* **2013**, *64*, 16-22. http://dx.doi.org/10.1016/j.ejmech.2013.04.025
106. Luo, Y.-L; Baathulaa, K.; Kannekanti, V.K.; Zhou, C.-H.; Cai, G.-X. Novel benzimidazole derived naphthalimide triazoles: synthesis, antimicrobial activity and interactions with calf thymus DNA. *Science China Chem*. **2015**, *58* (3), 483–494. https://doi.org/10.1007/s11426-014-5296-3
107. Ahmadi, A. Synthesis an antibacterial evaluation of ome novel Mannich bases of benzimidazole derivatives. *Bull. Chem. Soc. Ethiop*. **2016**, *30* (3), 421-425. http://dx.doi.org/10.4314/bcse.v30i3.10
108. Kankate, R.S.; Gide, P.S.; Belsare, D.P. Design, synthesis and antifungal evaluation of novel benzimidazole tertiary amine type of fluconazole analogues. *Arab. J. Chem.* **2019**, *12*, 2224–2235. http://dx.doi.org/10.1016/j.arabjc.2015.02.002

109. Ahuja, R.; Sidhu, A.; Bala, A.; Arora, D.; Sharma, P. Structure based approach for twin-enzyme targeted benzimidazolyl-1,2,4-triazole molecular hybrids as antifungal agents. *Arab. J. Chem.* **2020**, *13*, 5832–5848. https://doi.org/10.1016/j.arabjc.2020.04.020
110. Evren, A.E.; Celik, I.; Akar Cevik, U. Synthesis, molecular docking, in silico ADME and antimicrobial activity studies of some new benzimidazole-triazole derivatives. *Cumhuriyet Sci. J.* **2021**, *42* (4), 795-805. http://dx.doi.org/10.17776/csj.1014986
111. Ansari, K.F.; Lal, C.; Khitoliya, R.K. Synthesis and biological activity of some triazole-bearing benzimidazole derivatives. *J. Serb. Chem. Soc.* **2011**, *76* (3) 341–352. doi: 10.2298/JSC100301029A
112. Tien, C.N.; Cam, D.T.T.; Manh, H.B.; Dang, D.N. Synthesis and Antibacterial Activity of Some Derivatives of 2-Methylbenzimidazole Containing 1,3,4-Oxadiazole or 1,2,4-Triazole Heterocycle. *J. Chem.* **2016**, *2016*, 1507049. http://dx.doi.org/10.1155/2016/1507049
113. Kantar, G.K.; Mentese, E.; Beris, F.S.; Şasmaz, S.; Kahveci, B. Synthesis and antimicrobial activity of some new triazole bridged benzimidazole substituted phthalonitrile and phthalocyanines. *Rev. Roum. Chim*. **2018**, *63* (1) 59-65.
114. Nandwana, N.K.; Singh, R.P.; Patel, O.P.S.; Dhiman, S.; Saini, H.K.; Jha, P.N.; Kumar, A. Design and Synthesis of Imidazo/Benzimidazo[1,2-c] quinazoline Derivatives and Evaluation of Their Antimicrobial Activity. *ACS Omega* **2018**, *3*, 16338−16346. https://pubs.acs.org/doi/10.1021/acsomega.8b01592
115. Al-Majidi, S.M.H.; Ibrahim, H.A.R.; AL-issa, A.H. Synthesis and Identification of Some New Derivatives of ([Benzyl Thio) Benzimidazole N-(Methylene-5-Yl)]-4,5-Di Substituted 1,2,4-Triazole and Evaluation of Their Activity as Antimicrobial and Anti-Inflammatory Agents. *Iraqi J. Sci.* **2021**,*62* (4), 1054-1065. DOI: 10.24996/ijs.2021.62.4.2
116. El-masry, A.H.; Fahmy, H.H.; Ali Abdelwahed, S.H. Synthesis and Antimicrobial Activity of Some New Benzimidazole Derivatives. *Molecules* **2000**, *5*, 1429-1438. https://doi.org/10.3390/51201429
117. Menteşe, E.; Ülker, S.; Kahveci, B. Synthesis and study of α-glucosidase inhibitory, antimicrobial and antioxidant activities of some benzimidazole derivatives containing triazole, thiadiazole, oxaiazole and morpholine rings. *Chem. Heterocycl. Comp*. **2015**, *50* (12), 1671-1682. https://doi.org/10.1007/s10593-015-1637-1
118. Karale, B.K.; Nirmal, P.R.; Akolkar, H.N. Synthesis and in vitro biological screening of some benzimidazolyl anchored azoles. *Ind. J. Chem*. **2015**, 54B, 399-405.
119. Madawali, I.M.; Gaviraj, E.N; Kalyane, N.V.; Shivakumar, B. A Review On Substituted Benzimidazoles: Biologically Active Compounds. *Am. J. Pharm. Tech. Res*. **2019**, *9* (03), 256-274.
120. Eisa, H.M.; Barghash, A.-e.M.; Badr, S.M.; Farahat, A.A. Synthesis and antimicrobial activity of certain benzimidazole and fused benzimidazole derivatives. *Ind. J. Chem*. **2010**, **49B**, 1515-1525.
121. Nevade, S.A.; Lokapure, S.G.; Kalyane, N.V. Synthesis and Pharmacological Evaluation of Some Novel 2-Mercapto Benzimidazole Derivatives. *Kor. Che. Soc*. **2013**, *57* (6), 755-760. http://dx.doi.org/10.5012/jkcs.2013.57.6.755
122. Can N.O.; Çevik, U.A.; Saglik, B.N.; Levent, S.; Korkut, B.; Özkay, Y.; Kaplancikli, Z.A.; Koparal, A.S. *J. Chem*. **2017**, 9387102. https://doi.org/10.1155/2017/9387102
123. Karaca Gençer, H.; Acar Çevik, U.; Levent, S.; Sağlık, B.N.; Korkut, B.; Özkay, Y.; Ilgın, S.; Öztürk, Y. New Benzimidazole-1,2,4-Triazole Hybrid Compounds: Synthesis, Anticandidal Activity and Cytotoxicity Evaluation. *Molecules* **2017**, *22*, 507. https://doi.org/10.3390/molecules22040507
124. Aryal, P.; Shakya, B. J. Synthesis, Cytotoxicity, Antibacterial and Antioxidant Activity of New 2-Substituted Benzimidazole Containing 1,2,4-Triazoles. *Nepal Chem. Soc.* **2023**, *43* (2), 34-45. DOI: https://doi.org/10.3126/jncs.v43i2.53339
125. Kazeminejad, Z.; Marzi, M.; Shiroudi, A.; Kouhpayeh, S.A.; Farjam, M.; Zarenezhad, E. Novel 1,2,4-Triazoles as Antifungal Agents. *BioMed Res. Int.* **2022**, 4584846. https://doi.org/10.1155/2022/4584846
126. Nandha, B.; Nargund, L.V.G.; Nargund, S.L. Design and synthesis of some new imidazole and 1,2,4-triazole substituted fluorobenzimidazoles for antitubercular and antifungal activity. *Der Pharma Chem*. **2013**, 5 (6), 317-327.
127. Tonelli, M.; Paglietti, G.; Boido. V.; Sparatore, F.; Marongiu, F.; Marongiu, E.; La Colla, P.; Loddo, R. Antiviral Activity of Benzimidazole Derivatives. I. Antiviral Activity of1-Substituted-2-[(Benzotriazol-1/2-yl)methyl]benzimidazoles). *Chem. Biodivers.* **2008**, 5, 2386-2401. https://doi.org/10.1002/cbdv.200890203
128. Kanwal, A.; Ahmad, M.; Aslam, S.; Raza Naqvi, S.A.; Saif, M.J. Recent advances in antiviral benzimidazole derivatives: a mini review. *Pharm. Chem. J*. **2019**, *15* (3), 179-187. https://doi.org/10.1007/s11094-019-01976-3
129. Ion, V.; Matei, A.; Constantinescu, C.; Ionita, I.; Marinescu, M.; Dinescu, M.; Emandi, A. Octahydroacridine thin films grown by matrix-assisted pulsed laser evaporation for non linear optical applications. *Mater. Science Semicond. Process*. **2015**, 36, 78-83. https://doi.org/10.1016/j.mssp.2015.02.06
130. Zalaru, C.; Dumitrascu,F.; Draghici, C.; Tarcomnicu, I.; Tatia, R.; Moldovan, L.; Chifiriuc, M.C.; Lazar, V.; Marinescu, M.; Nitulescu, M.G.; Ferbinteanu, M. Synthesis, spectroscopic characterization, DFT study and antimicrobial activity of novel alkylaminopyrazole derivatives, *J. Mol. Struct.* **2018**, 1156,12-21. https://doi.org/10.1016/j.molstruc.2017.11.073

 doi:10.20944/preprints202307.0093.v1

131. Zalaru, C.; Dumitrascu, F.; Draghici, C.; Iovu, M.; Marinescu, M.; Tarcomnicu, I.; Nitulescu, G.M. Synthesis and biological screening of some novel 2-(1*H*-pyrazol-1-yl)-acetamides as lidocaine analogue, *Ind. J. Chem. B* **2014**, 53 B (06), 733-739.