INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Triazole-Linked Benzimidazoles as Dual-Action Therapeutics: Antimicrobial and Antiviral Potential

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ARTICLE INFO

Published: 28 July 2025
Keywords:
Triazole-Benzimidazole Hybrids, Antimicrobial Agent, Antiviral Activity
DOI:
10.5281/zenodo.16537472

ABSTRACT

Triazole-benzimidazole conjugate are well-acknowledged cyclic compounds with heteroatoms scaffolds with broad-spectrum biological activities, making them valuable in antimicrobial and antiviral drug development. These structural frameworks have been extensively examined for their competency to target essential biomolecules, thereby disrupting microbial and viral processes. Benzimidazole derivatives exhibit strong antibacterial and antifungal effects, while 1,2,3-triazole-linked compounds have shown notable antiviral potency against pathogens such as influenza and coronaviruses. The combination of these pharmacophores in hybrid molecules has led to the advancement of novel therapeutics with increased potency, selectivity, furthermore a lower risk of resistance. This review provides a meticulous analysis of the model, composition, and structure-activity relationships of benzimidazole-triazole hybrids, focusing on their mechanisms of action and recent advancements in antimicrobial and antiviral research. Furthermore, it explores their therapeutic potential and future applications in addressing drug-resistant diseases and Evolving viral threats. By offering valuable insights into these promising drug candidates, this review aims to support ongoing efforts in developing next-generation antimicrobial and antiviral agents.

INTRODUCTION

Medicinal chemistry heavily relies on heterocyclic compounds for the enhancement of pharmaceuticals for various diseases [1-3]. Of these, benzimidazole is a key player, functioning like a purine-equivalent structural backbone with a remarkably distinct therapeutic profile. Within the scope of pharmaceutical research, nitrogen-containing heterocycles serves a crucial function, exhibiting a comprehensive array of physiological processes [4-7]. Benzimidazole derivatives, for instance, are employed in the evolution of drugs targeting multiple conditions, including bacterial and fungal sepsis, viral diseases, cancer, diabetes, and neurological disorders [8,9] . The structural

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

features of benzimidazoles make them well-suited for interactions within biological systems [10], leading to their classification as important therapeutic agents. This structural compatibility allows their derivatives to exhibit a variety of molecular interactions, such as virucidal, fungicidal , antiproliferative, hypotensive agent , analgesic, anti-swelling agent, antibacterial, and antiparasitic effects [11-18]. Benzimidazole-scaffold can reveal an extensive variety of biological activities; i.e., they are systematic arrangement in opposition to the human cytomegalovirus (HCMV) [19], they have further employed as histamine blocker [20], antibacterial [21], virucidal [22], and herpes antiviral (HSV-1) [23] therapeutics. Likewise, 1,2,3-triazoles are recognized for their therapeutic potential, finding applications in the treatment of microbial infections, tuberculosis, and hypertension, among other conditions [24-29]. Triazoles rings are gaining prominence as adaptable linkers, enabling this creation of innovative bifunctional drugs by connecting two pharmacophores. This capability has significantly increased their utility in the design of bioactive and functional compounds [30-36] 1,2,3-triazoles demonstrate diverse biological activities, encompassing antimicrobial and antitubercular properties, as well as potential inhibition of SARS-CoV-2 and other viruses [37-46]. They also exhibit anti-inflammatory, antitumor, antihypertensive, antioxidant, and antiepileptic effects [47-55]. Furthermore, triazoles are utilized as α-glucosidase inhibitors, analgesics, anticonvulsants, and antimalarial agents [56-60]. Finally, triazole derivatives have shown efficacy in Alzheimer's disease and neuroprotection [61-64]. Given the importance of developing effective antimicrobial agents and our contributions to this field [65-76], we aimed to create an innovative class of molecules. Specifically, we synthesized an unprecedented set of hybrid derivatives that merge the pharmacologically relevant benzimidazole and triazole moieties. The antimicrobial characteristics of these novel categories of molecules were then assessed by test-tube study. The appearance of benzimidazole and triazole rings within established drugs underscores their importance in designing new chemical entities with anti-infective, virus inhibiting agent and parasiticidal abilities . Notably, research has highlighted benzimidazole-triazole mixtures with significant anti-infective and virucidal activities, comprising potential anti-Covid 19 agents [77-81] The recent pandemic has intensified interest in these hybrids, driving research into their integration, anti-infective properties, model-activity associations, and overall biochemical reactions .The benefits of investigating benzimidazole-triazole combination include their extended anti-infective spectrum as well as increased potency, using evidences by lower minimum inhibitory concentrations, alongside the requirement for specialized researchers. This article provides the comprehensive literature review of the assorted biological activities of benzimidazole-1,2,3-triazole mixtures, specifically focusing on antimicrobial, antiviral, antifungal, and antitubercular properties.

Antiviral Activity

There are more than 200 viruses that can make people sick, but medicines are only available for about 10 of these infections. [82,83] In the last ten years, new viruses have shown to be a big danger to the world. One possible solution is to create antiviral drugs that work against many viruses. This method has the benefit of saving time and money in the early stages of making new medicines. It can also lower health risks in later stages of development. [84,85]. Youssif and colleagues declared the creation of benzimidazole-1,2,3-triazole combination, including Compound (1) as well as Compound (2), which represents

strong inhibitory effect on the hepatitis C virus (Figure 1).

Figure 1 Structure of antiviral benzimidazole-1,2,3-triazole hybrids 1 and 2

The substances 1 and 2 acted as evaluated for their skill to stop the hepatitis C virus (HCV). The amount needed to reduce the virus by 50% (EC50) was 7.7 and 7.5 µmol/L, correspondingly. The amount that caused harm to 50% of cells (CC50) was 16.8 and 21.0µmol/L. These findings showed that the chemical group at position 2 of benzimidazole holds key importance in stopping HCV. [86]. The complexes 3a-3e acted as tested for their ability to fight 2 viruses: Japanese encephalitis virus (JEV) , a highly dangerous RNA-based virus, and Herpes virus type-I (HSV-I) , a prevalent virus found in the environment. The results of the virucidal tests are shown in

Table 1 Anti-JEV and anti-HSV activity of compounds 3a-3e

Compd.	In Vitro			In Vivo			
	CT_{50} (µg mL^{-1})	EC_{50} (µg mL^{-1})	TI	CPE Inhibition (%)	Dose (µg per Mouse per Day)	MST (days)	Protection (%)
				Anti-JEV			
3a	125	4	31	30	200	-	-
3b	125	8	16	90	200	4	16
3c	-	-	-	-	-	-	-
3d	125	4	31	30	200	-	-
3e	250	62.5	4	50	200	2	10
				Anti-HSV			
3a	125	62.5	2	33	-	-	-
3b	125	62.5	2	46	-	-	-
3c	-	-	-	-	-	-	-
3d	125	31.25	4	53	200	-	-
3e	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.

Exempt from the associated five tested complexes, only one was inactive against the Japanese encephalitis virus (JEV). Compound **3b** showed strong antiviral activity in lab tests, with a 90% reduction in virus effects at a proportion of 8.1 µg/ml. However, belonging to its effectiveness within living organisms was lower, providing only 16% protection and extending survival by 5 days. The researchers concluded that these formulation work improved against JEV than opposing Herpes virus type-I (HSV-I) because complexes 3b as well as 3e showed measurable activity against JEV in live tests. substances 3c did not work against either virus. The effectiveness against HSV-I was recorded as 33% for 3a, 46% for 3b, 53% for 3d, and 64% for 3e. Since only compound 3e has a methyl group instead of hydrogen at position R1, the study suggests that R1 is not responsible for the

antiviral activity. [87]. Tonelli and colleagues created a sequence of Compounds (4-23) and examined them for virucidal effects contrary to a wide range of viral pathogens with RNA and DNA genome

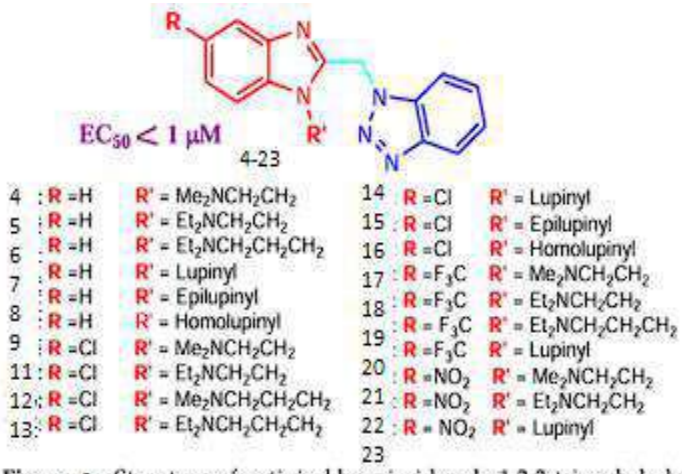


Figure 2 Structure of antiviral benzimidazole-1,2,3-triazole hybrids [4-23]

12 complexes showed strong efficacy in inhibiting Respiratory Syncytial Virus (RSV), within EC50 believed mostly lower than HM. They performed better than the comparator drug 6-azauridine, which was highly toxic to both MT-4 and Vero-76 cell lines (S.I. 16.7). The combinations also had moderate inhibitory effects Bovine Viral Diarrhoea Virus (BVDV), Yellow Fever Virus (YFV), and Coxsackie Virus B2 (CVB2), within EC50 beliefs between 6 and 55 µM for the most effective ones **(Table 2).**

Table 2 RSV, BVDV, YFV, and CVB2 Inhibitory Activity of hybrids 4-23 expressed as EC_{50} (µM).

Compound	Anti-RSV Activity	Anti-BVDV Activity	Anti-YFV Activity	Anti-CVB2 Activity
4	0.7	-	-	-
5	2.3	-	-	-
6	0.7	>100	80	>100
7	0.7	63	>90	>100
8	0.3	53	>70	>100
9	0.15	51	>60	>100
10	0.03	-	-	-
11	0.7	-	-	-
12	0.06	90	>100	>100
13	0.1	72	>54	>100
14	0.9	15	6	40
15	0.05	19	>21	>88
16	0.02	14	>20	26
17	10.0	-	-	-
18	7.0	-	-	-
19	1.9	67	>36	>100
20	>36	15	>18	>36
21	9	-	-	-
22	11	80	>45	>100
23	23.0	80	27	>83
6-Azaurine	1.2	>100	26	>100

Although the suppressive action against BVDV, YFV, and CVB2 is not very strong, it is still important because it could help identify targets for developing broad-spectrum antiviral drugs.

Understanding how these compounds work is essential. Additionally, since their effectiveness depends on the type of chemical groups attached occupying "5" associated the benzimidazole ring, further research on varied substitutions may help improve their activity and reduce toxicity. [88]. Anti-Covid 19 agent and its versions, specifically Omicron, are still a serious danger to physical health.[89]. New alternatives of SARS-CoV-2 are likely to appear in the future. Furthermore, it is important to take broad measures to prevent future outbreaks from animals. Recent studies have shared important and updated information about anti-covid 19 alternatives , virucidal drugs, and vaccines used to fight the virus. [90,91].

Al-Humaidi and colleagues announced the creation of a sequence of benzimidazole--triazole complexes (24-26) **(Figure 25).**

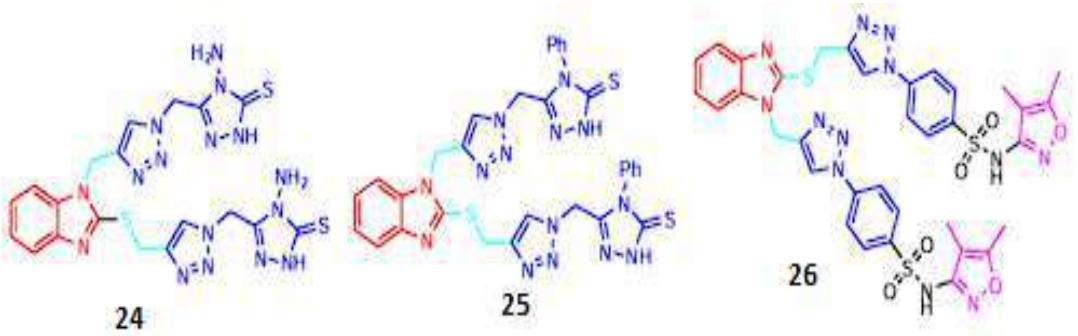


Figure 25 Structure of antiviral benzimidazole-1,2,3-triazole hybrids 24-26

Molecular docking studies and lab tests showed that large portion of the tested complexes had strong binding scores in opposition to anti-covid and Omicron variant spike glycoproteins, performing better than the standard drugs **(Table 3).**

Table 3 Antiviral activity of benzimidazole-1,2,3-triazole hybrids 24-26

Compound	CC_{50} (μg mL^{-1})	EC_{50} (μg mL^{-1})	Selectivity Index (SI)
Ceftazidime	1045.53	85.07	12.29
24	1065.51	155.05	6.87
25	1530.5	306.1	5.0
26	1028.28	80.4	12.78

The information demonstrated that compound 140 had potent activity, within IC50 of 75.97 nm opposing the Omicron variant spike glycoprotein and 74.50 nm against the anti-Covid 19 agent spike protein. The tertiary binding mode of complex 26 is depicted in **(Figure 26).**

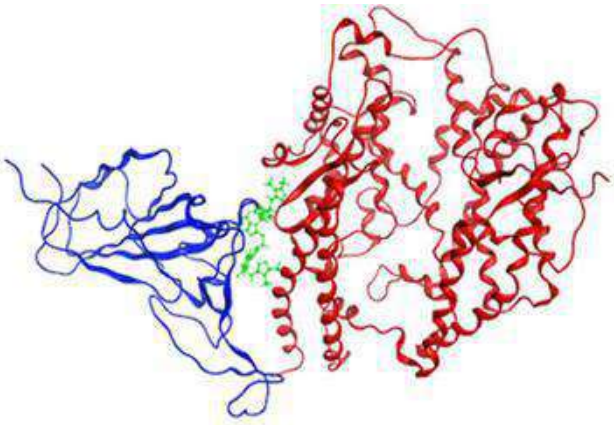


Figure 26 Three-dimensional binding mode of compound **26** (green) at the binding interface between the Omicron S-RBD (red) and human ACE2 (blue) [ ].

Benzimidazole-triazole combinations have the potential to be strong anti-HSV (Herpes simplex virus) agents. These complexes were also tested in opposition to flaviviruses and pestiviruses. Among them, complex 27 displayed potent efficacy against respiratory syncytial virus (RSV) with an EC50 value of 0.03 mm. **(Figure 3)** [92].

27

Figure 3 Structure of antiviral benzimidazole-1,2,3-triazole hybrid 27

Seliem et al. developed and created quinolone-triazole complex to target anti-covid 19 agents. Their study found that 4-((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2-(trifluoromethyl)quinoline as well as 6-fluoro-4-(2-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)ethoxy)-2-(trifluoromethyl)quinoline depicts strong virucidal activity with a high therapeutic selectivity index (SI) in opposition to anti-covid 19 viruses compared to standard drugs. They terminated that the fluorine(F^-) atoms in these compounds played a vital role in their antiviral effects. [93]. El-Sebaey reviewed the importance of the **1,2,4-triazole** ring in antiviral complexes. He highlighted the significance of the chemical groups attached to the triazole core and the crucial role of another heterocyclic structures in the molecule. [94]

Antitubercular Activity

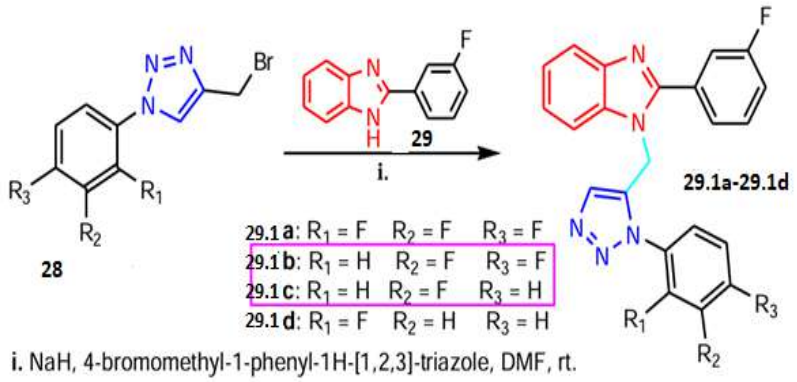
Ashok stated that molecule 26h was the potentially most effective antitubercular drug, suppressing the proliferation of Mycobacterium tuberculosis (MTB) within a minimum inhibitory concentration (MIC) of 3.124 µg/mL (7.1 µM). For comparison, the standard drugs Rifampicin as well as Isoniazid had MIC ethics of 0.04 µg/mL and 0.38 µg/mL, correspondingly. The strong activity of 26h was prone to the nitro group at the ortho position on the aromatic ring.

Other compounds showed moderate tubercular inhibitory activity:

- Complexes 26b (MIC = 6.24 µg/mL, 14.7 µM) with a chlorine substituent

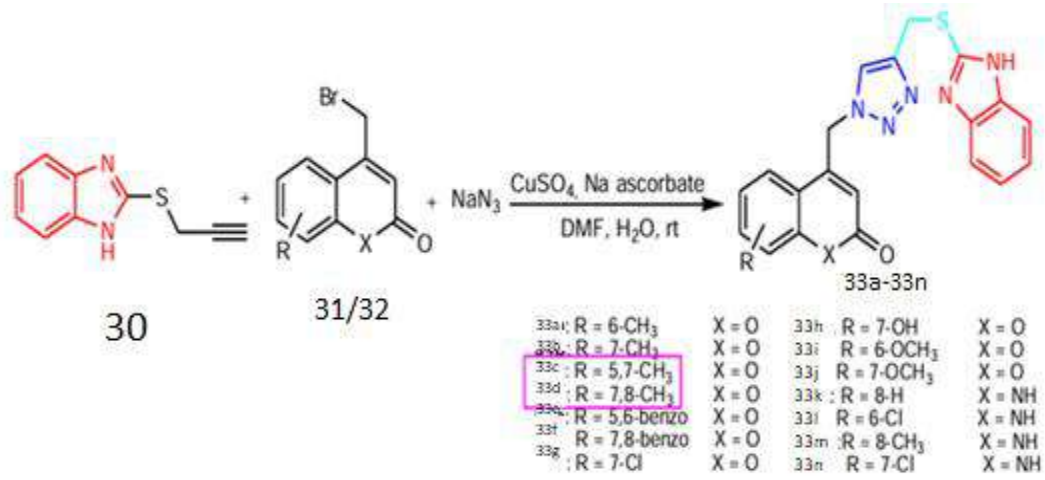
- Complexes 26i (MIC = 6.24 µg/mL, 14.2 µM) with a trifluoromethyl group
- Complexes 26j (MIC = 12.54µg/mL, 28.4 µM) with a benzyl substituent

The study concluded that adding electron-deficient groups like nitro, chlorine, and trifluoromethyl to the aromatic ring significantly improved antitubercular activity. Additionally, theoretical calculations of physicochemical parameters showed that compounds 26a-26j had positive drug scores, indicating their potential as drug candidates. [95]. Gill and colleagues stated the synthesis of mixtures 29.1a-29.1d by reacting Compounds (29) with aromatic ring-substituted Compounds (28) in DMF at ambient temperature. (Scheme 1).



Scheme 1 . Synthesis of benzimidazole-1,2,3-triazoles **29.1a-29.1d**

The trifluoro-substituted compound 51a showed strong anti-mycobacterial activity, inhibiting more than 96% of bacterial growth at a 6.24 µg concentration. Additionally, combinations 51b and 51c demonstrated better anti-infective activity than the other additional evaluated compounds. These two existed as identified as the finest candidates for developing novel derivatives to enhance potency against Endo cellular mycobacteria (macrophages) or in diseased animals. [96]. Anand and team stated a one-pot reaction involving Compounds (30), Compounds (31/32), as well as sodium azide following click chemistry protocols. This reaction selectively produced Compounds (33a-33n). (Scheme 2).



Scheme 2 . Synthesis of benzimidazole-1,2,3-triazoles 33a-33n

Tuberculosis-fighting tests opposing M. tuberculosis (H37Rv), during in silico molecular docking studies, depicted that dimethyl-substituted compounds 33c as well as 33d had potential efficacy with a MIC of 3.8 µM and high C-score values. The Surf Lex-Dock tool was employed to analyse molecular interactions between the ligands and the protein of interest. The three-dimensional structure of the biological protein was obtained from PDB allowance 4FDO. This protein was processed by eliminating the co-crystallized ligand and water molecules as well as adding crucial hydrogen atoms. Every 14 inhibitors (33a-33n) acted to place in the ENR catalytic site using docking analysis. Figure 7a illustrates the docking results, while Figure 7b presents the overlay of compounds 33a and 33d with the reference ligand. [97].

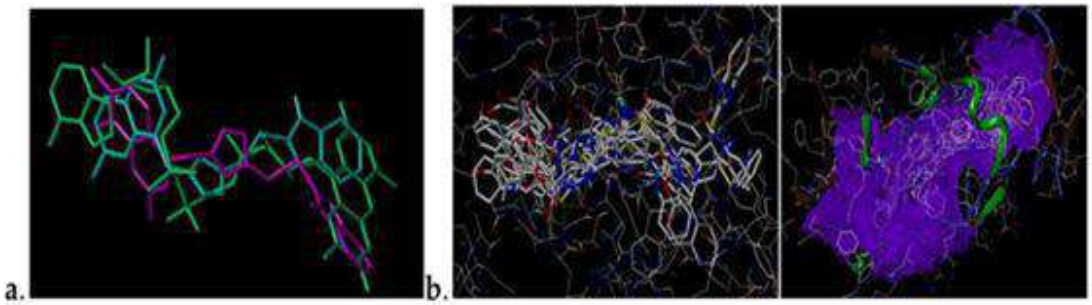


Figure 3 (a). Superimposition of compounds 33a (Cyan color), 33d(Magenta color) with ligand (Green–blue color). (b). All 14 compounds docked into the active site of the enzyme 4FDO. Image adapted from [16].

Khanapurmath and colleagues generated triazoles (34) using a click process (Figure 8a). Among them, benzimidazolone bis-triazoles (34a-34n) depicted good antitubercular action, with MIC values ranging from 2.32 to 18.33 µM. The majority effective complexes were 34h and 34m. Every compound had mild to minimal cytotoxicity, with IC50 data in human embryonic kidney derived cells ranging from 943 to 12,294 µM. None of the 14 compounds showed significant toxicity, indicating their possibility for live model experimentation use as antitubercular agents. Docking studies uncovered an extra interaction of the benzimidazolone oxygen, which may contribute to their biological activity (Figure 8b). [98]

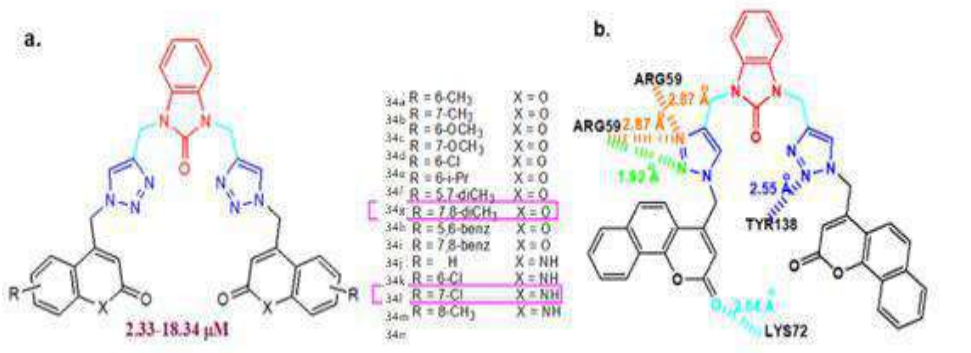
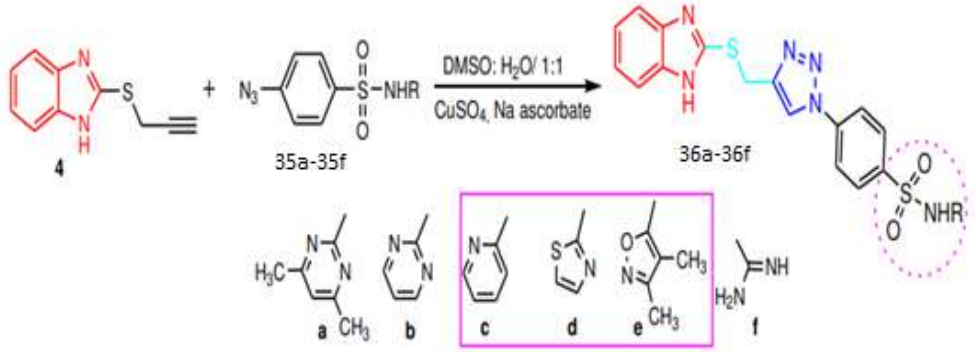


Figure 4 (a). Structure of benzimidazolone bis-1,2,3-triazoles 34a-34n(b). Representation of docked view of compound 34j at the active site of RmlC.

Sharma et al. provided a summary of 1,2,3-triazoles as antitubercular compounds, highlighting various hybrids with benzimidazole, coumarin, isoniazid, quinolines, and other structures. [99].

Antibacterial Activity

Al-Blewi and team utilized a click reaction (Huisgen 1-,3-dipolar cycloaddition) by intermixing thiopropargylated benzimidazole within sulpha entity azides (35a–35f), CuSo4, as well as sodium ascorbate in a DMSO/hydrated solution. This reaction produced benzimidazole-sulphonamide conjugates (36a–36f) in 84–91% yield after 6–7 hours of warming at 80°C.**(Scheme 3).**

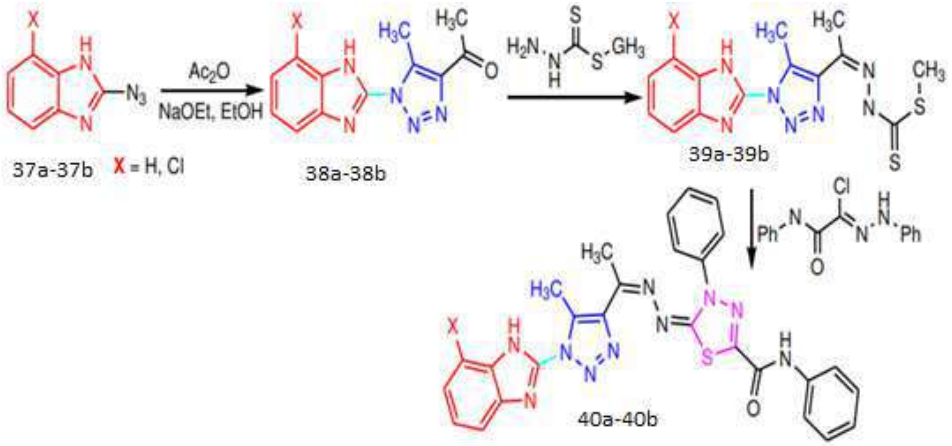


Scheme 3. Synthesis of benzimidazole-1,2,3-triazole hybrids 36a-36f

All complexes were examined for their microbicidal activity (Table 1) in opposition to 4 bacteria

- Gram-positive: Bacillus cereus
- Staphylococcus aureus
- Gram-negative: Escherichia coli
- Pseudomonas aeruginosa two fungi
- Candida albicans ,
- Aspergillus brasiliensis .

According to (Table 1), substance 6a had the greatest antibacterial activity in opposition to Bacillus cereus and Staphylococcus aureus (65 µg/mL). Similarly, substances 6c, 6d, and 6e were the most effective for suppressing Escherichia coli (66 µg/mL). [100] Rashdan et al. created hybrids (40) using Compounds (37a–37b). These compounds bonded with acetylacetone under the influence of sodium ethoxide, forming hybrid molecular entities (38a–38b). These key molecules were then used to produce new carbazone derivatives (39a–39b), which were further reacted along with 2-oxo-N-phenyl-2-(phenyl amino) acetohydrazonoyl chloride into creating respective final hybrid derivatives (40a–40b) (Scheme 4).



Scheme 4 Synthesis of benzimidazole-1,2,3-triazole hybrids 38a-38b,39a-39b and 40a-40b

All substances existed for testing for their antimicrobial activity resisting Staphylococcus aureus, E. coli, Pseudomonas aeruginosa, Aspergillus Niger, and Candida albicans. The outcomes showed that compounds 40a as well as 40b had effective activity opposing all examined microbes. Complexes 38a and 39a were effective merely opposed to Gram-positive and Gram-negative bacteria but had no influence on fungi. Additionally, both within silico and laboratory studies confirmed that substances 40a , 40b were the highly potent against bacterial strains and is capable to be potential microcidal agents.(Table 4).

Hybrids	Inhibition Zone Diameters Using the Agar Diffusion Method (mm)				
	S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
38a	15 ± 0.14	12 ± 1.08	22 ± 1.01	-	-
38b	-	5 ± 0.2	-	30 ± 1.16	27 ± 1.1
39a	23 ± 0.8	-	13 ± 0.65	-	-
39b	-	-	12 ± 0.8	14 ± 0.15	19 ± 1.04
40a	24 ± 0.6	25 ± 0.9	17 ± 0.75	20 ± 0.9	16 ± 0.89
40b	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

The hybrids (38–40) underwent molecular docking studies with DNA gyrase B and showed binding energy ranging from -9.8 to -6.4 kcal/mol, confirming their high potency. Among them, substances 40a as well as 40b had the lowest binding affinity energy (-9.7 and -9.8 kcal/mol), indicating stronger bonding evaluated against the standard drug Ciprofloxacin (-7.45 kcal/mol) in opposition to DNA gyrase B, as shown in [Figure 2]. [101].

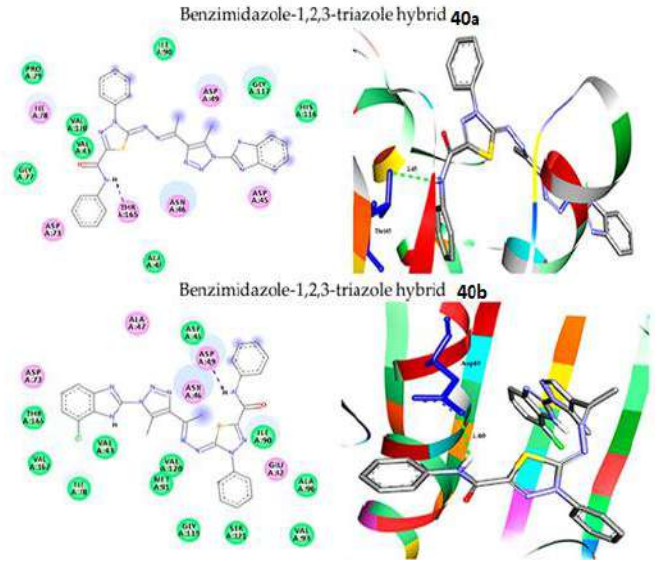
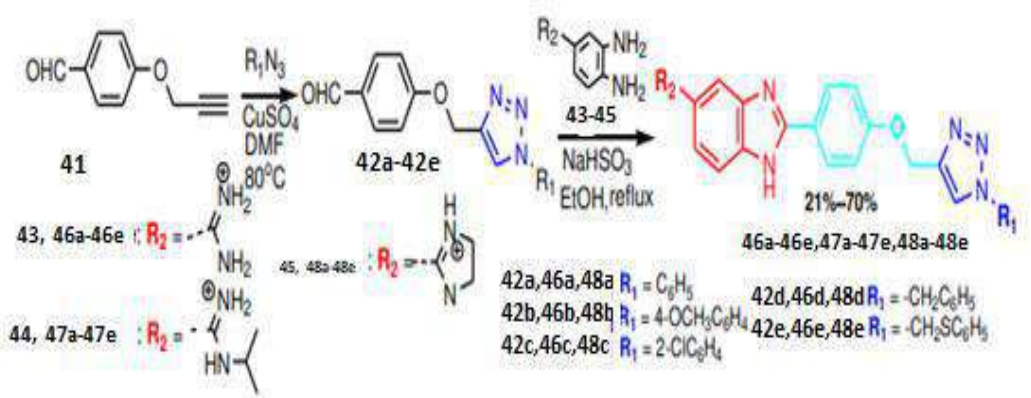


Figure 2 shows the intermolecular interactions of the top-docked compounds (40a as well as 40b) accompanied the marked enzyme DNA gyrase B.

- **Left side (2D view):**
  - By-products are labelled using three-letter codes.
  - Hydrogen bond interaction is shown as green and blue bands.
  - π-interactions are displayed by orange bands.
- **Right side (3D view):**
  - Docked ligands are shown as grey stick representation.
  - Binding site pockets are represented by blue stick representation.
  - H-bond interactions appear as green dashed bands.
  - T-interactions are highlighted in orange bands. [101].

Bistrović et al. synthesized hybrids (46a–46e, 47a–47e, and 48a–48e) in two steps using 4-(prop-2-ynyloxy) benzaldehyde (41) as the starting material (Scheme 4).



Scheme 4 Synthesis of benzimidazole-1,2,3-triazole hybrids 46a-46e,47a-47e,48a-48e

All substances served as tested for their bactericidal activity opposing

Gram-positive bacteria

- (S. aureus ATCC 25923
- methicillin-sensitive S. aureus
- E. faecalis, vancomycin-resistant E. faecium

Gram-negative bacteria

- E. coli ATCC 25925
- P. aeruginosa ATCC 27853
- A. baumannii ATCC 19606
- ESBL-producing K. pneumoniae ATCC 27736).

Key Findings:

- The entities were generally more potent against Gram-positive bacteria than Gram-negative bacteria.
- Compounds 47a–47e showed strong efficacy targeted S. aureus (MIC = 8–32 µg/mL) due to their better binding strength compared to other amidines.
- Compound 46a was the majorly promising against ESBL-producing E. coli (MIC = 4 µg/mL).
- Anti-trypanosome studies revealed that the p-methoxyphenyl group in 46b–48b improved efficacy, with 20b (IC50 = 1.1 mM, IC90 = 3.5 mM) exhibiting greater potency than Nifurtimox.

Interestingly, while there was a relationship linking antimicrobial activity as well as DNA binding, the antiprotozoal effects of 47b failed to align with its DNA affinity strength. [102] Rao and team formulated as hybrids 49a–49b (Fig. 4) utilizing the click chemistry strategy. However, these substances showed weak efficacy supressing Mycobacterium bovis variant (BCG inhibition = 27.3% and 26.2%, correspondingly). [103].

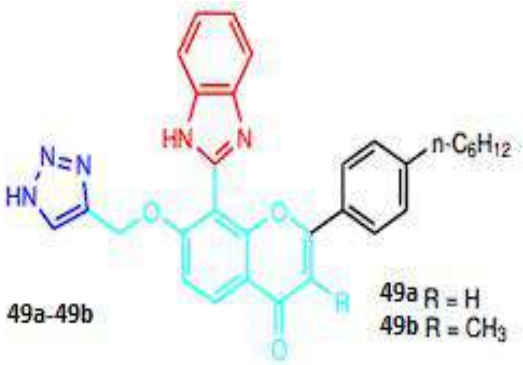
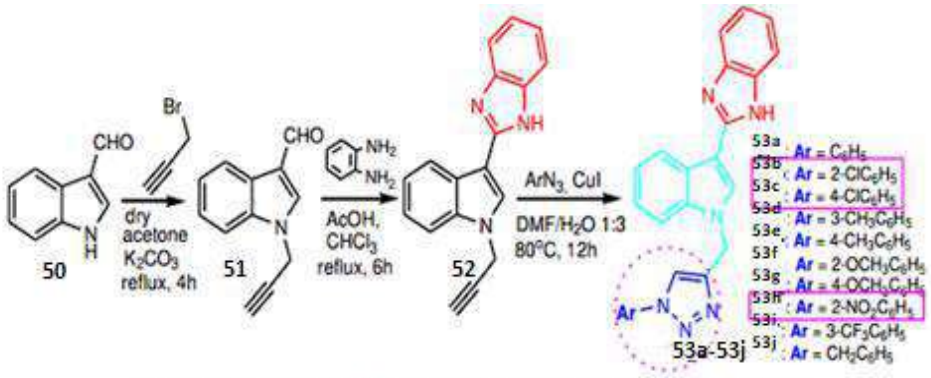


Figure 4. Structure of benzimidazole-1,2,3-triazole hybrids **49a-49b**

Ashok and team formulated hybrids 53a–53j in 3 steps, initiating from 1H-indole-3-carbaldehyde (7) (Scheme 5).



Scheme 5. Synthesis of benzimidazole-1,2,3-triazole hybrids 53a-53j

The compounds were tested for their antimicrobial activity against

Gram-positive bacteria

- (Staphylococcus aureus ATCC 6538
- Bacillus subtilis ATCC 6633

Gram-negative bacteria

- Proteus vulgaris ATCC 29213
- Escherichia coli ATCC 11229

using Gentamicin as the standard drug.

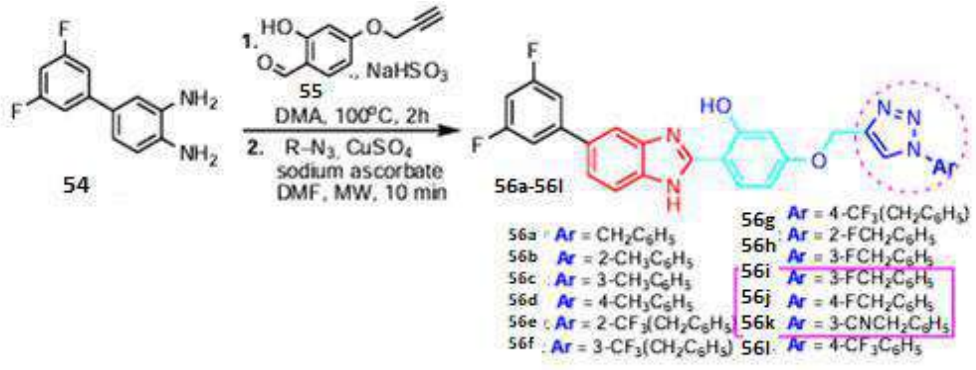
Their fungicidal activity was evaluated opposing Candida albicans as well as Aspergillus Niger using Fluconazole as the reference drug.

Key Findings:

- Substances 53b, 53c, as well as 53h were the most compelling antimicrobial agents, in the presence of a Minimum Inhibitory Concentration of 3.124–6.25 µg/mL . [104].

Mallikanti and team formulated benzimidazole-linked 1,2,3-triazole analogues (29a–29l) in two steps:

1. Generation of benzimidazole intermediate species 4by reacting Compounds (54) with Compounds (55).
2. Microwave-aided copper-catalysed copper(1)-catalysed azide- alkynecycloaddition reaction to obtain the final compounds (Scheme 6).



Scheme 6 Synthesis of benzimidazole-1,2,3-triazole hybrids 56a-56l

Compounds 56a–56l remained investigated for antibacterial activity counteracting Gram-positive

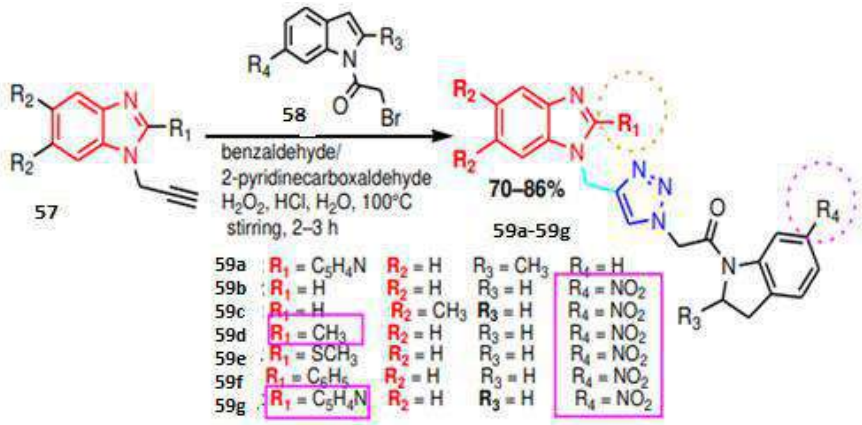
bacteria (S. aureus, B. subtilis) and Gram-negative bacteria (E. coli, P. aeruginosa) adopting Ampicillin as the standard drug.

Key Findings:

- Most compounds demonstrated minimal inhibition zones against every examined bacterial strains.
- Substances 56i as well as 56k exhibited greater efficacy against P. aeruginosa, S. aureus, and B. subtilis than the control standard reference drug.
- Compounds 56a, 56b, 56c, 56d, 56e, 56f, 56g, 56h, 56j, and 56l displayed moderate antibacterial activity.
- Substances 56i, 56j, as well as 56k displayed efficacious antifungal activity in opposition to C. albicans MTCC 183 and A. Niger MTCC 9652, outperforming the control drug Griseofulvin. [105].
- Chandrika and team described hybrids 30–32 with wide ranging-spectrum antifungal activity:
- Against C. albicans: 0.975–3.8 µg/mL
- Against C. parapsilosis: 0.11–0.49 µg/mL (Fig. 2)

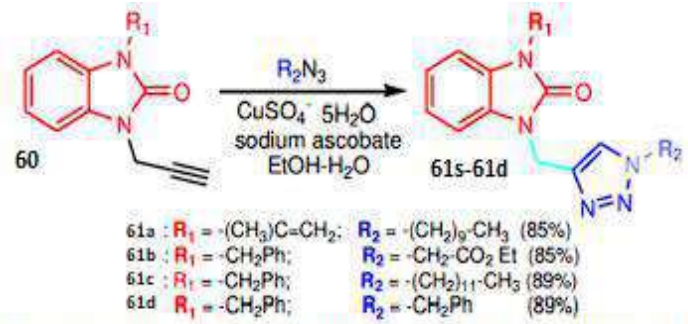
Additionally, these substances revealed strong activity suppressing C. albicans biofilms.[106]

Deswal and team formulated a newly developed series of Compounds (59) using a copper(1)-catalysed azide- alkyne cycloaddition reaction amid substituted Compounds (57) and in situ-generated substituted 2 Compounds (58), yielding the final compounds in mild to favourable yields (Scheme 7).



Scheme 7 Synthesis of benzimidazole-1,2,3-triazole hybrids 59a-59g

The conclusions show that compound 59d has a stronger inhibitory effect on E. coli, while compound 59g effectively inhibits all tested bacteria apart from B. subtilis (Table 3). The strong antimicrobial effect of these compounds is linked to the pyridine aromatic ring at site "2" of benzimidazole and the NO_2 group on the indole aromatic ring. Additionally, laboratory studies glucosidase prevention tests of all formulated compounds found that 59e (IC_{50} = 0.015 ± 0.0003 mol/mL) and 59g (IC_{50} = 0.018 ± 0.0008 mol/mL) are strong inhibitors of α-glucosidase, performing even better than the standard drug Acarbose.[107]Saber et al. created new benzimidazolone derivatives (61a–61d) with 1,4-disubstituted-1,2,3-triazole, utilizing only copper(1)-catalysed azide- alkyne cycloaddition reaction (Scheme 8).

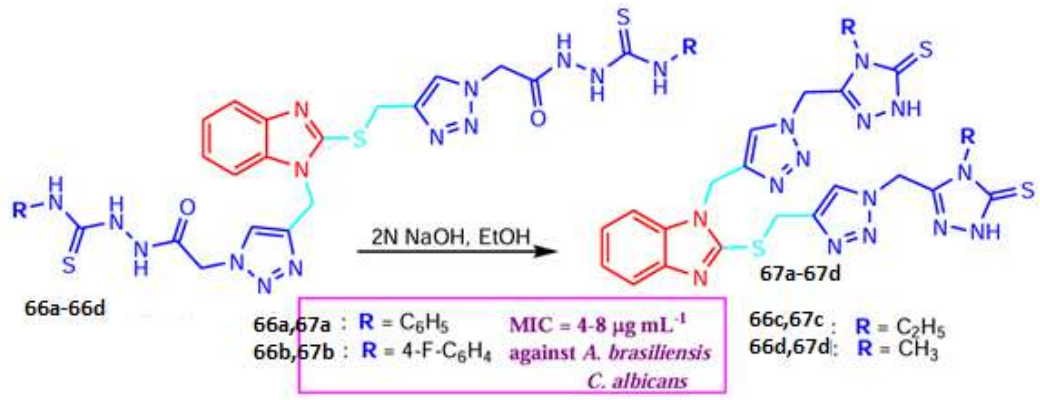


Scheme 8. Synthesis of benzimidazole-1,2,3-triazole hybrids **61a-61d**

All analogues showed antibacterial activity resisting Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. However, compounds 61b and 61d were improved effectiveness resisting the Gram-positive bacterium S. aureus (MIC = 3.124 µg/mL), while 61b had enhanced efficacy against the Gram-negative bacterium E. coli (Minimum Inhibitory Concentration = 3.125 µg/mL), using Chloramphenicol as the standard drug. Mohsen and team prepared hybrids 65a–65e within three steps using benzimidazole (62). The process included 2 alkylation reactions followed by a copper(1)-catalysed azide- alkyne cycloaddition reaction (Scheme 9).

Scheme 9 . Synthesis of benzimidazole-1,2,3-triazole hybrids **65a-65e**

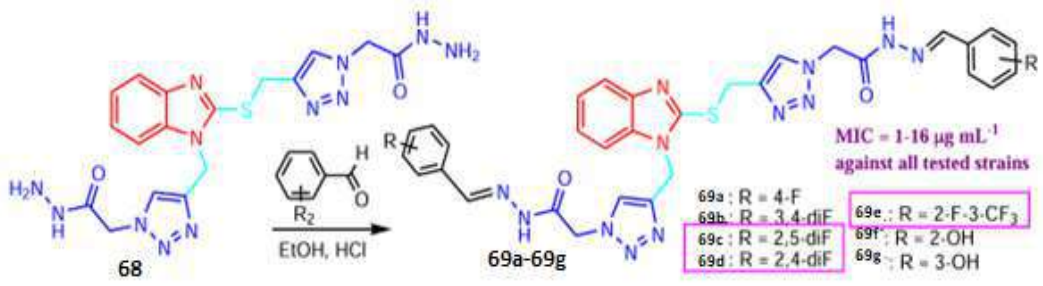
The recently developed derivatives showed significant inhibition zones of 6.8, 5.4, 5.2, 4.5, and 5.4 mm against S. aureus and 5.4, 3.8, 4.2, 3.3, and 4.8 mm against E. coli. This suggests that the 1,2,3-triazole scaffold played a key role in bacterial growth proliferation control. For comparison, Ciprofloxacin exhibited 10.2mm for S. aureus and 10.3mm for E. coli. [108]. Rezki reported the intramolecular cyclization of thiosemicarbazides 66a–66d in refluxing aqueous sodium hydroxide (2N) for 6 hours, leading to the formation of hybrids 67a–67d with yields of 82–86% (Scheme 11).



Scheme 10 Synthesis of benzimidazole-1,2,3-triazoles **67a-67d**

Across all Compounds (67a) and Compounds (67b) were the most effective, with MIC values of 5–9 µg/mL. Additionally, triazoles 67c as well as 67d displayed the maximum inhibition against A. brasiliensis and Candida albicans, within MIC values of 0.5–4 µg/mL, making them more efficient than the standard drug Fluconazole.

Furthermore, the coagulation of compound (68) within various benzaldehydes in recirculating ethanol for 4–6 hours within a catalytic amount of HCl led to the formation of a new category of hybrid Schiff bases (69a–69g) along with yields of 85–87% (Scheme 11).



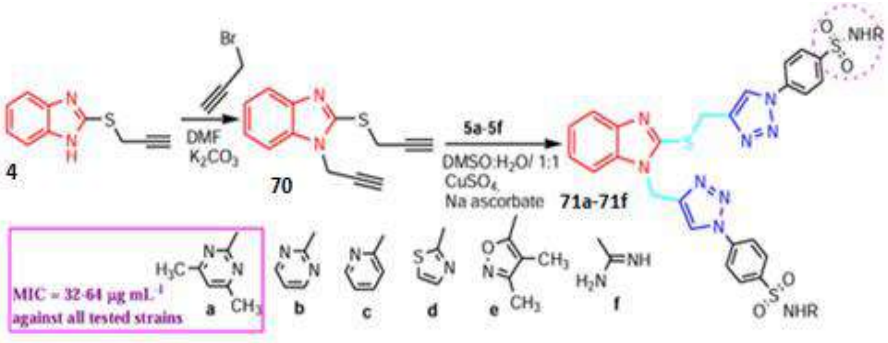
Scheme11. Synthesis of benzimidazole-1,2,3-triazoles **69a-69g**

The antimicrobial bioassay concludes for the Schiff bases 69a–69g showed that all examined compounds were highly effective against all organisms, with MIC values of 1–16 µg/mL. Among them, Schiff bases 69c, 69d, and 69e, which have a fluorine(F^-) atom at position "2", revealed the strongest antibacterial activity with MIC values of 1–8 µg/mL. Additionally, Imine base 69e, consisting of a CF_3 group, exhibited the maximum antifungal activity, with a Minimum Inhibitory Concentration of 1 µg/mL . [109]

Al-Blewi and team formulated triazoles 71a–71f within 2 steps:

1. Region-selective alkylation of compound 4 using two equivalents of propargyl bromide and potassium carbonate like a base catalyst, yielding benzimidazole 70 with 91% yield following overnight shaking at room temperature.

2. Copper-facilitated Huisgen 1,3-dipolar cyclo-addition reaction on Substance 70, resulting in great yields (83–89%) (Scheme 12).



Scheme12. Synthesis of benzimidazole-1,2,3-triazoles **71a-71f**

Typically, bis-1,2,3-triazoles 71a–71f showed stronger bactericidal effects than their mono-1,2,3-triazole scaffolds 6a to 6f. This is because of the combined activity of the sulfonamoyl as well as tethered heterocyclic components, and the better

lipophilicity of the bis-substituted analogues. Across the synthesized compounds, compound 47a was the strongest antimicrobial agent, within Minimum Inhibitory Concentration values amid 31 and 65 µg mL−1 opposing all evaluated strains: B. cereus, S. aureus, E. coli, P. aeruginosa, C. albicans, and A. brasiliensis. Pharmacophore clarification of compounds 47a to 47f must have done on the basis of in silico ADMET assessment of the evaluated compounds. Drug-likeness screening outcomes displayed that all compounds accompany the approved rules, meet the guidelines of drug-likeness, and pursue Lipinski's rule of five. Additionally, toxicity impacts presented that all substances are non-mutagenic and non-carcinogenic. [110] Aparna et al. used a similar strategy to create nine new bis substituted derivatives 72a-72l (Figure 5).

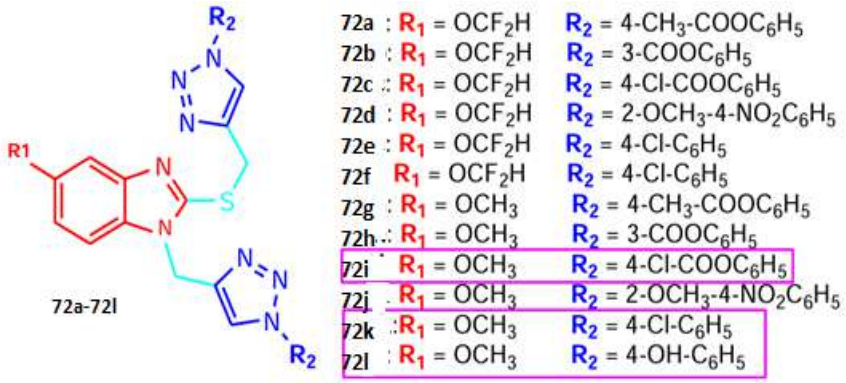


Figure 5. Structure of benzimidazole-1,2,3-triazole hybrids **72a-72l**

Triazole analogues 48 displays average to good antibacterial effectivity against Gram-negative bacteria (E. coli, P. aeruginosa) as well as Gram-positive bacteria (S. aureus). Commodities 72i, 72k, 72l have a wide-ranging spectrum of antibacterial effects at a concentration of 11.2 µg mL−1. The formulated 1,2,3 triazole analogues were researched for their molecular docking on the maximum-resolution X-ray crystal structure of FabI of Staphylococcus aureus (pdb id:4FS3) received from the protein data bank [111] The greatest dock score of -7.68 kcal/mol and the least dock score of -0.943 kcal/mol were found in favour of molecules 72i as well as 72h, correspondingly. [112] Pandey and team formulated hybrids 59a-59e within 3 steps: reaction for 7-hydroxy-4-methyl coumarin along with thiosemicarbazide in order to form triazole intermediary 59, which experienced Mannich reaction with formaldehyde and an amino acid to produce intermediaries 74a-74e. Intermediaries 74a-74e dealt with o-phenylenediamine in pyridine to provide benzimidazole 1,2,4-triazole hybrids in poor(low) output (Scheme 14). Substance 75a revealed promising viricidal activity in opposition to Candida albicans and Cryptococcus himalayensis with Minimum Inhibitory Concentration value of 3.4 µg mL−1 in each case. Compound 75b showed low to moderate antifungal effects against five fungi: Candida albicans, Cryptococcus himalayensis, Sporotrichum schenkii, Trichophyton rubrum, and Aspergillus fumigatus. [113].

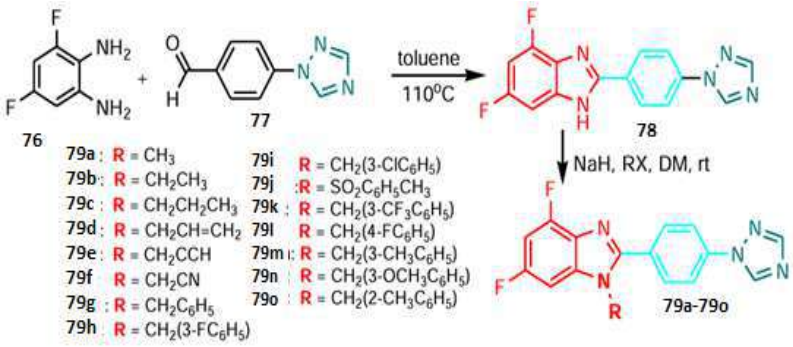
Scheme 14 Synthesis of benzimidazole-1,2,4-triazoles 75a-75e

Barot and colleagues formulated hybrid 64 and tested its bactericidal effects opposing Bacillus cereus, Enterococcus faecalis, S. aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Candida albicans, Aspergillus Niger, as well as Fusarium oxysporum, with Minimum Inhibitory Concentration values of 13-19 μg mL−1. Ofloxacin and Fluconazole were utilized as reference drugs. [114].

Jadhav and team formulated a series of triazolyl-fluorobenzimidazole ring mixture in 2 steps:

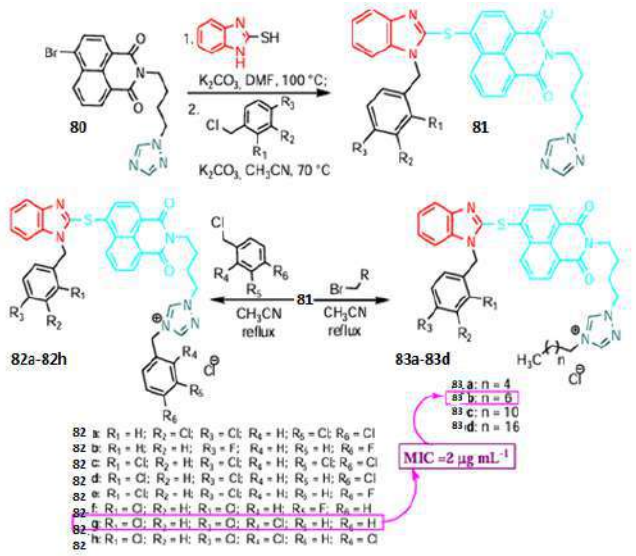
1. Formation of 2-(4-(1H-1,2,4-triazol-1-yl)phenyl)-4,6-difluoro-1H-benzimidazole (compound 78) by interacting compound(76) and compound (77) with toluene at 110°C.

2. Alkylation of substance 78 with DMF at environmental temperature to produce the ultimate hybrids 79a-79o (Scheme 15).



Scheme 15 Synthesis of benzimidazole-1,2,4-triazoles 79a-79o

All single compounds were screened for antimicrobial efficiency opposing various Gram-positive organisms (S. aureus, P. aeruginosa) and Gram-negative organisms (E. coli, S. typhosa) utilizing Gentamycin as a control standard. The data taken from preliminary screening displayed that the compounds presented mild to better antimicrobial activity. Compounds 79a, 79e, 79f, 79h, 79i, and 79l showed the maximum activity. [115]. Luo and team presented a class series of Compounds 82a-82h and the respective triazolium salts 83a-83d, prepared by accessible and productive techniques beginning from Compound 80 (Scheme 16).



Scheme 16. Synthesis of benzimidazole-1,2,4-triazoles 82 and 83

2-Chlorobenzyl triazolium 67g and substance 69b within octyl group showed the maximum bactericidal activities across all the evaluated compounds, especially against S. aureus within a restrictive concentration of 2.1 μg mL−1. This potency was equal to Norfloxacin (MIC = 2.1 μg mL−1) and more active than Chloromycin (MIC = 7.1 μg mL−1). Triazoliums 82g and 82f with 3-fluorobenzyl moiety showed the best antifungal activities (MIC = 2-19 μg mL−1) against all the tested fungal strains: C. albicans ATCC 76615, A. fumigatus, S. cerevisiae, and A. flavus, lacking being toxic into the PC12 cell line within a concentration of 129μg mL−1. Additional studies displayed that complex 82g could integrate into calf thymus DNA to produce the 82g-DNA combination, which could inhibit DNA replication and exert powerful antimicrobial effectiveness. [116]. Benzimidazole-1,2,4-triazole Mannich base 70 was active supressing Bacillus subtilis as well as Bacillus pumilus. The interference zone diameters were 19 mm and 17 mm, correspondingly, compared to Ciprofloxacin with 28 mm and 30 mm, correspondingly. [117] Ahuja and team studied antifungal property of complexes 84a-84c opposing F. verticillioides, D. oryzae, C. lunata, and F. fujikuroi (Figure 16). Every compound has increased potency compared to the reference commercial benzimidazole fungicide, carbendazim (Table 2).

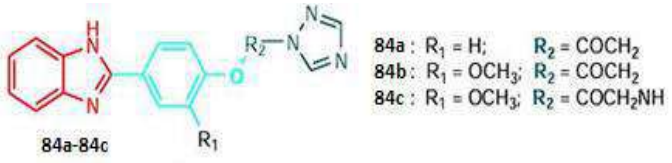
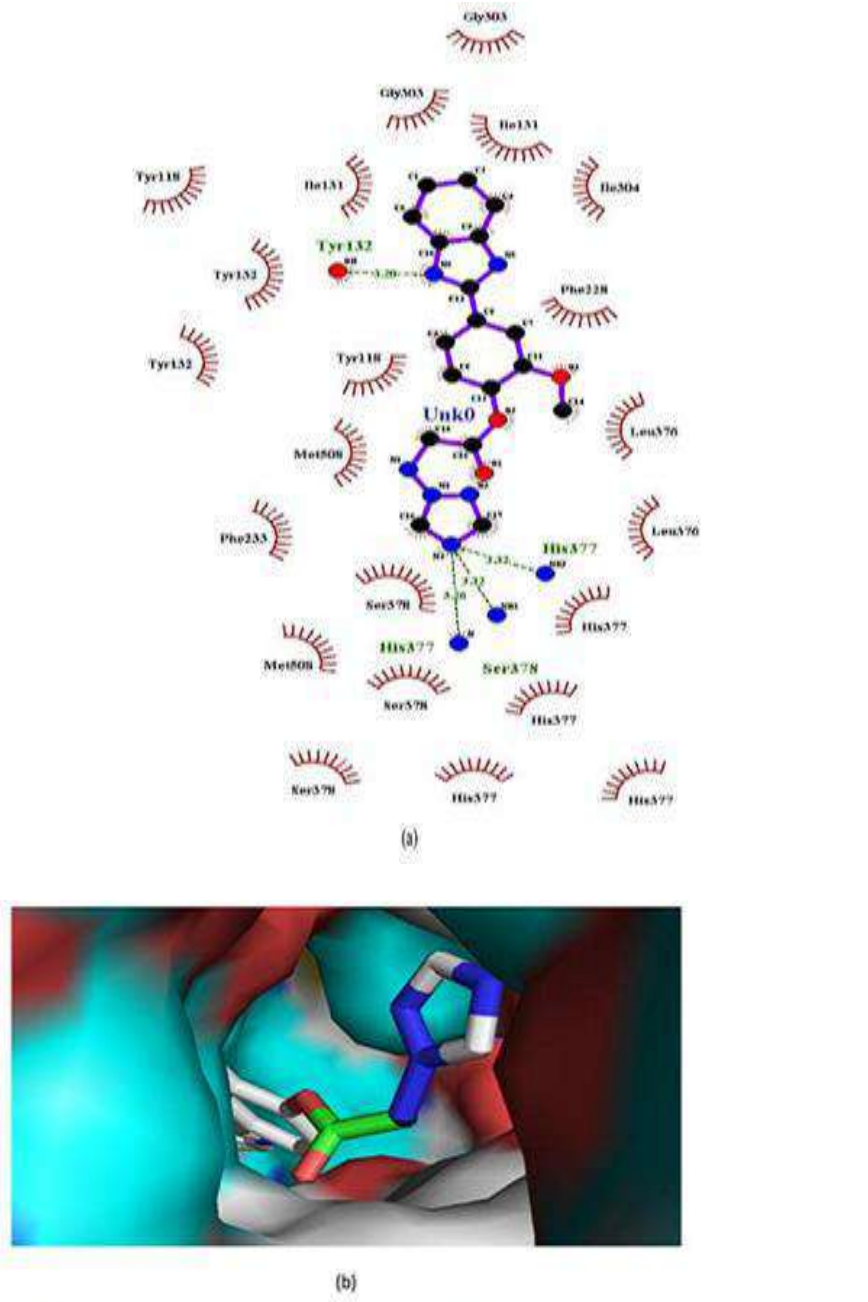


Figure 6. Structure of benzimidazole-1,2,4-triazole hybrids 84a-84c

Table 2. ED_{50} values (μg mL^{-1}) of compounds against test fungi.

Compound	*F. verticillioides*	*D. oryzae*	*C. lunata*	*F. fujikuroi*
84a	35	50	28	45
84b	30	25	18	30
84c	16	12	10	15
Carbendazim	230	-	-	150
Propiconazole	20	25	22	21

Complex 84c showed ED50 values diminished than the triazole fungicide, propiconazole. The conclusions supported the synergistic activity of the benzimidazole as well as 1,2,4-triazole fusion, backed by a computational strategy. Hydrogen bonding inter-relations were more evident in compounds 84a-84c in the linking pockets of each of the two targeted enzymes, compared to references. In complex 84c, two H- linking's were produced with Gln11 in the inter-linking cleft of the active pocket of ß-tubulin (Figure 12). Within all three compounds, the right positions of the N-atoms of each of two 1,2,4-triazole and benzimidazole, and the O-atoms of methoxy as well as carbonyl groups, assisted to strong coupling into the active site of enzymes via H-bonding. [118].



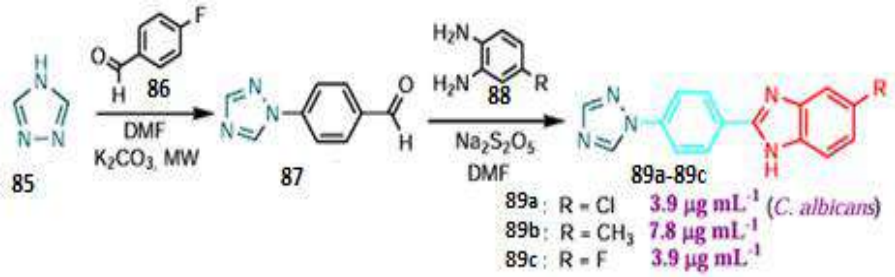
(a)

(b)

Figure 7 Ligand interaction diagram of compound **84c** in lanosterol 14α-demethylase (**a**) 2D and (**b**) 3D view. Image adapted from [27]

Evren and team studied the formulation of compounds 89a-89c in two steps:

1. Chemical reaction of compound 85 with compound 86 within DMF to form compound 87.
2. Chemical reaction of aldehyde 77 along with compound 88 (Scheme 17).



Scheme 17 Synthesis of benzimidazole-1,2,4-triazoles **89a-89c**

Even though the antibacterial activities of compounds 89a-89c opposing Escherichia coli, E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, and Staphylococcus aureus were weak, the fungicidal activities supressing C. albicans was found promising, with Minimum Inhibitory Concentration values of 3.8, 7.9, and 3.8 μg mL−1 respectively, using Ketoconazole as a standard drug (MIC = 7.8 μg mL−1). Protein-ligand connections and coupling poses of the compounds 89a, 89b, as well as 89c upon the CYP51 active site were examined. (Figure 8).

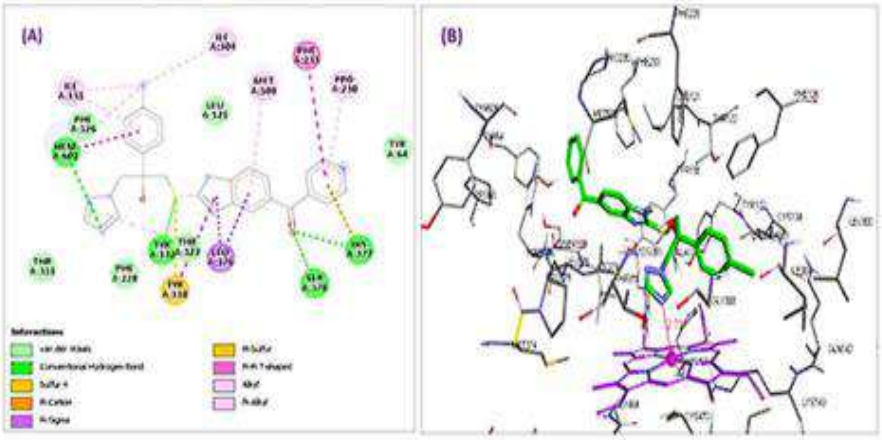


Figure 8 Two-dimensional (**A**) and three-dimensional (**B**) diagrams of compound (*S*)**95 b** (tautomer A) in the active site of CYP51–*C. albicans* (5TZ1.pdb). Image adapted from [28].

An H bonding of 2.11 was found amid compound 79a and Met508, and 7-7 layering interactions within Tyr118, Hie377, and Phe233. Additionally, there were hydrophobic interactions with Pro230, Leu376, Tyr64, Phe228, and Tyr505. Theoretical ADME calculations of compounds 89a, 89b, and 89c were performed, and the compounds were found to have good lipophilicity, moderate water solubility, and were within the limiting rules of Lipinski, Ghose, Veber, Egan, and Muegge (Figure 9).[119]

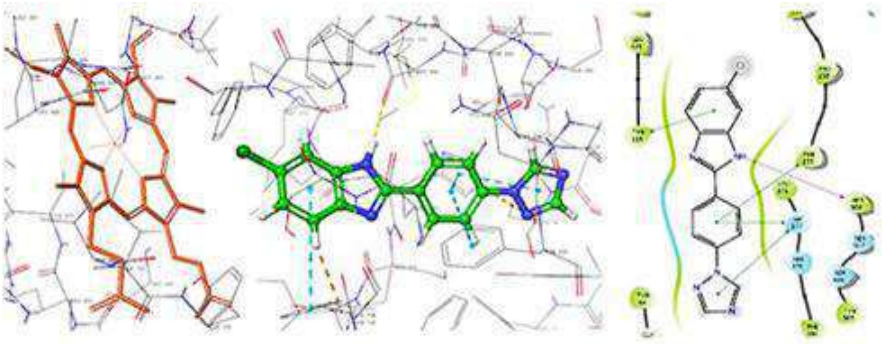
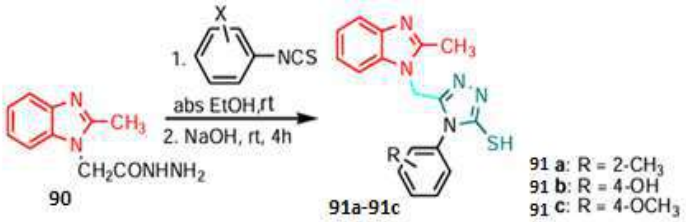


Figure 9. 3D binding picture and 2D schematic protein-ligand interactions of compound **89a**

Ansari and team integrated mixtures 88a-88c in 2 steps from compound 90 (Scheme 18). Normally, all benzimidazole-triazole mixtures revealed low antibacterial activity (Table 3). [120].



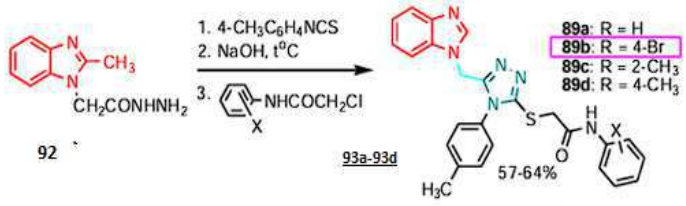
Scheme18. Synthesis of benzimidazole-1,2,4-triazoles **91a-91c**

Table3. Antimicrobial activity of compounds **91a-91c** expressed as MIC in μg mL^{-1}.

Compound	*S. aureus*	*B. subtilis*	*S. mutans*	*P. aeruginosa*	*C. albicans*
91a	NT	NT	16	16	32
91b	8	16	16	16	NT
91c	8	16	32	32	32
Ampicillin	2	2	<1	4	NT
Kanamycin	2	<1	4	2	NT

NT = not tested.

Tien et al. integrated mixtures 93a-93d in three steps from compound 92b (Scheme 23). All compounds appear mycocidal activity opposed to A. Niger (MIC = 50 μg mL−1). Only substance 93b conveyed activity in opposition to F. oxysporum (Table 3).[121].



Scheme 19. Synthesis of benzimidazole-1,2,4-triazoles **93a-93d**

Table 3 The minimum inhibitory concentrations (μg mL^{-1}) of the compounds against fungi.

Compound	Concentration (μg mL^{-1})	*Aspergillus niger*	*Fusarium oxysporum*
93a	50	50	-
93b	50	50	50
93c	50	50	-
93d	50	50	-

Kantar and team announce the bactericidal activity of mixture 94 (Figure 15) opposed to four

Gram-positive bacteria:

- Bacillus cereus 702 Roma (61.5 µg mL−1)
- Staphylococcus aureus (252 µg mL−1)
- Bacillus megaterium (124 µg mL−1)
- Bacillus subtilis (62.55 µg mL−1) And four

Gram-Negative Bacteria:

- Escherichia coli (251 µg mL−1)
- Enterobacter cloacae (126 µg mL−1)
- Pseudomonas aeruginosa (254 µg mL−1)
- Yersinia pseudotuberculosis (126 µg mL−1) [122].

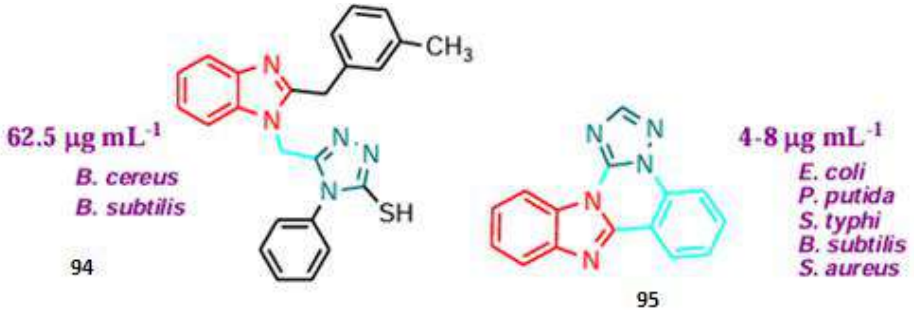
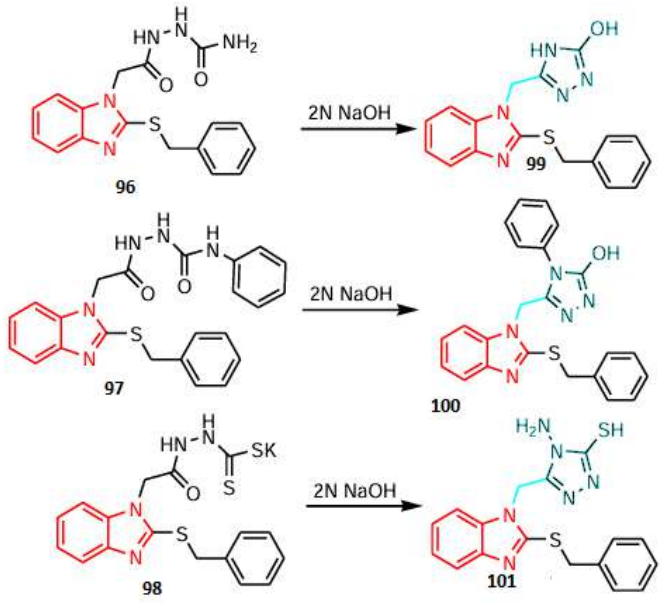


Figure 10. Structure of benzimidazole-1,2,4-triazole hybrids **94** and **95**.

Nandwana and team announced that substance 95 was combined with a great yield of 70% and looked potentially bactericidal activity. The least inhibitory concentration (LIC) values vary from 4-8 µg mL−1 for all tried bacterial strains (*Escherichia coli, Pseudomonas putida, Salmonella typhi, Bacillus subtilis, Staphylococcus aureus*), as collate to the positive control Ciprofloxacin. Additionally, it exhibits pronounced mycocidal activity towards both tested strains, Aspergillus Niger and Candida albicans (Minimum Inhibitory Concentration = 8-17 ng mL−1), as differentiate with Amphotericin B [123]. Al-Majidi and team blend compound derivatives 99, 100, as well as 101 by cyclization of median precursors 97, 98, and 99 under reflow with 2N NaOH (Scheme 20). The compounds normally reveal moderate antimicrobial activity in opposition to all tested strains, as shown in (Table 4) [124].



Scheme 20. Synthesis of benzimidazole-1,2,4-triazoles **96-101**

Table 4 Antimicrobial activity of compounds **99-101**

Compound (800 μg mL^{-1})	*S. aureus*	*P. aerugnosa*	*B. subtilis*	*A. baumannii*	*C. albicans*
99	18	14	15	-	10
100	19	11	12	-	11
101	17	15	14	12	-
Amoxicillin	33	32	33	-	-
Fluconazole	-	-	-	-	25

El-Masry and colleagues generated compounds 102 as well as 103 but establish that they didn't reveal bactericidal activity (Figure 11).[125]

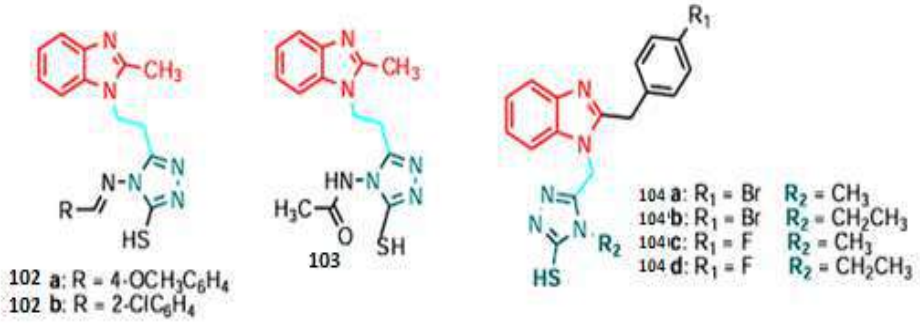
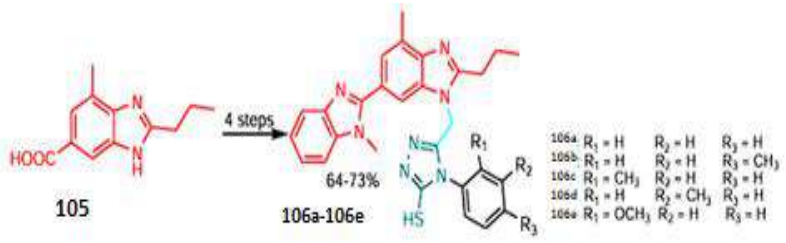


Figure 11. Structure of benzimidazole-1,2,4-triazole hybrids **102-104**

Mentese and colleagues manufactured substances 104a-104d and establish that they had no bactericidal activity in opposed to the ten tested strains.[126].

Karale and team manufactured bis-benzimidazole-1,2,4-triazole mixture 106a-106e (Scheme 21) in 4 steps from compound 105 . Every 106 substances reveal no antimicrobial activity in opposition to C.

albicans, A. fumigatus, S. aureus, and E. coli.[127,128].



Scheme 21 Synthesis of bis-benzimidazole-1,2,4-triazoles **106a-106e**

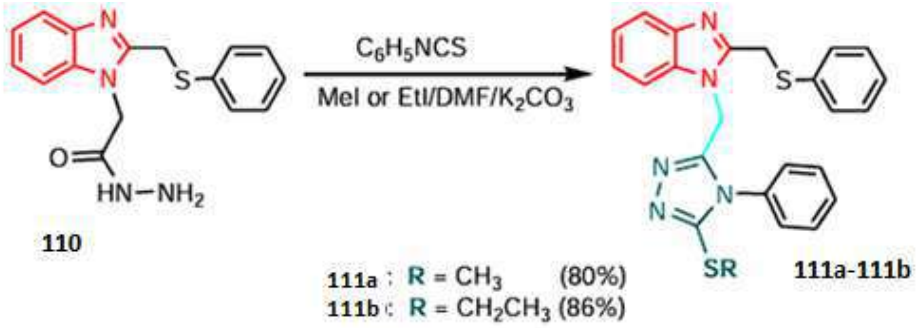
Eisa and team manufactured substances 105a and 105b (Scheme 26, Table 9) in response to 2-(chloromethyl)-1H-benzo[d]imidazole 103 with 4-phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-thiol 104a or 4-phenyl-5-(thiophen-2-yl)-4H-1,2,4-triazole-3-thiol 104b in absolute ethanol at reflow for 12 hours. They also manufactured compounds 105a and 105b from 2-(2-(phenyl Thio-methyl)-1H-benzo[d]imidazol-1-yl) aceto-hydrazide in 2 steps (Scheme 27). Every compound reveals powerful antimicrobial activity in opposition to Escherichia coli, even superior than Gentamicin. However, compound 105a had only average activity in opposed to Staphylococcus aureus.[129].

Scheme 22 Synthesis of benzimidazole-1,2,4-triazoles

Table 5 Antimicrobial activity of compounds **108a-108b** and **109a-109b**

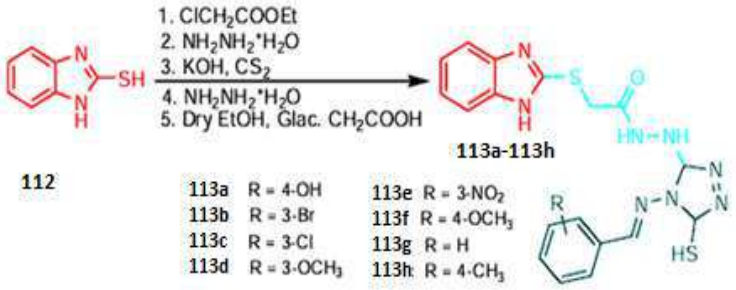
Compound	Minimum Inhibitory Concentrations (μg mL^{-1})			
	Gram-Positive Bacteria		Gram-Negative Bacteria	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*
108a	98	-	52	-
108b	-	-	65	-
109a	75	105	62	-
109b	79	-	72	-
Gentamycin *	64	56	72	48

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



Scheme 23. Synthesis of benzimidazole-1,2,4-triazoles **111a-111b**

Nevade and team make substances 113a-113h in 5 steps from compound 112 (Scheme 24). The bactericidal tests (Table 10) reveal that compounds 113a, 113c, and 113e had positive outcome against S. aureus and E. coli, while compounds 113b, 113f, and 113g reveal average activity in opposed to the same bacteria. The antifungal tests in case of Candida albicans tell that compounds 113a and 113d had the powerful inhibition, even contrast to the standard drug Ketoconazole.[130].



Scheme 24 Synthesis of benzimidazole-1,2,4-triazoles **113a-113h**

Table 6 Antibacterial activity of compounds **113a-113h**

No	Compound	Zone of Inhibition (mm)		
		E. coli	*S. aureus*	*C. albicans*
1	113a	15	13	18
2	113b	13	11	12
3	113c	17	16	14
4	113d	12	13	16
5	113e	13	17	9
6	113f	10	8	11
7	113g	8	11	12
8	113h	12	7	10
9	Ampicilline	24	25	-
10	Ketokonazole	-	-	20

The SAR (Structure-Activity Relationship) analysis of the combined benzimidazole-triazole substances is compiled in Figure 18.

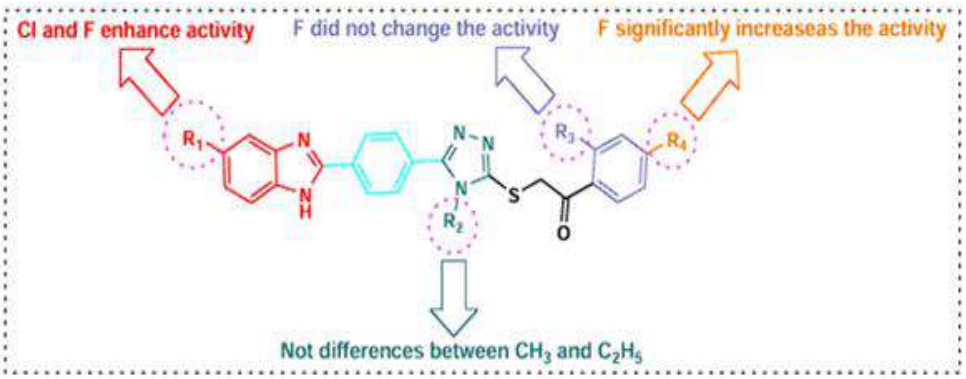
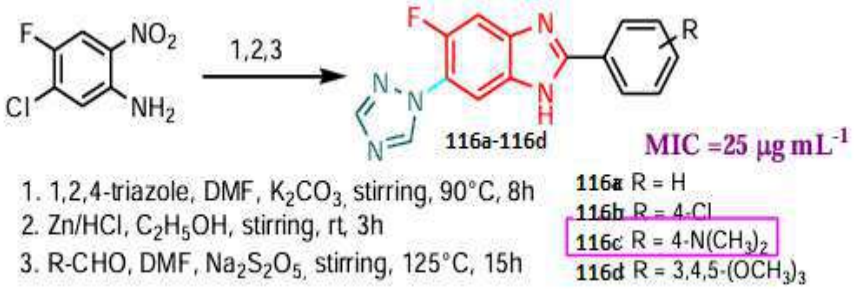


Figure 12. SAR outline of the benzimidazole-1,2,4-triazole hybrids **114a-114i**

It was noticed that adding chlorine or fluorine at the "5" site of benzimidazole and fluorine at the "4" position of phenyl grows antibacterial activity. However, fluorine at the "2" site of phenyl doesn't affect activity, and CH_3 or C_2H_5 groups at position "4" in the triazole nucleus don't change antibacterial activity. Moreover, toxicological and pharmacokinetic profiling verified the relative strength of mixtures 114h and 114i, as stated in the literature.[131-135]. Compound 114i suppressed ergosterol biosynthesis in a dosage dependent manner. The outcomes based on the ergosterol quantification assay and fluorescence microscopy studies revealed that the MOA of these mixtures is connected to the restraint of ergosterol biosynthesis. This could lead to modification in lipid fluidity disruption of plasma membrane generation, and weakened fungal activity. Nandha and team integrated 6-substituted-benzimidazoles with 1-(1,2,4-triazole) (116a-116d) in 3 steps from 5-chloro-4-fluoro-2-nitrobenzenamine. (Scheme 25).

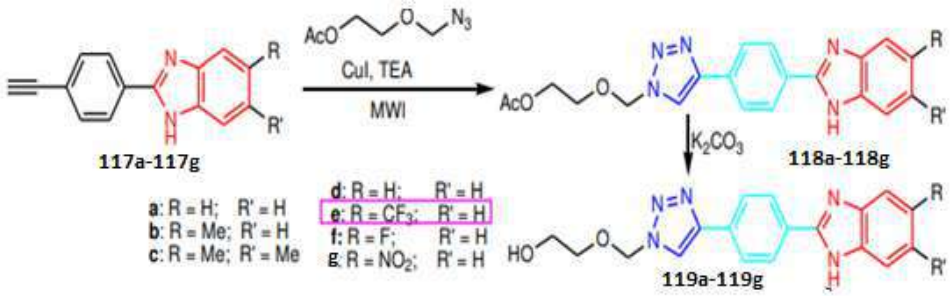


Scheme 25. Synthesis of benzimidazole-triazoles **116a-116d**

All substances were examined contrary to M. tuberculosis and 4 fungal strains: C. albicans, C. glabrata, C. krusei, and C. tropicalis. Substance 115c presented the mightiest activity in opposition to M. tuberculosis and all examined fungal strains, with a Minimum Inhibitory Concentration of 25 µg/mL [136].

Antifungal Activity

Substances 117a–117g, containing mono-substituted alkyne and 2-(azido methoxy) ethyl acetate, were responded employing CuI acting as a catalyst and triethylamine (TEA) exposed to microwave radiation. This process guided to the creation of triazole ring mixtures (118a–118g), which are coupled via a benzene ring to the benzimidazole nuclear region, with abundant returns (70–90%). (Scheme 26).



Scheme 26 Synthesis of benzimidazole-1,2,3-triazole hybrids **119a-119g**

Acetyl moiety attached to the triazole hybrids (118a–118g) was eliminated employing potassium carbonate (K_2CO_3) in methanol, emitting the hydroxy group and forming the respective mixture triazoles (119a–119g) with almost total output.

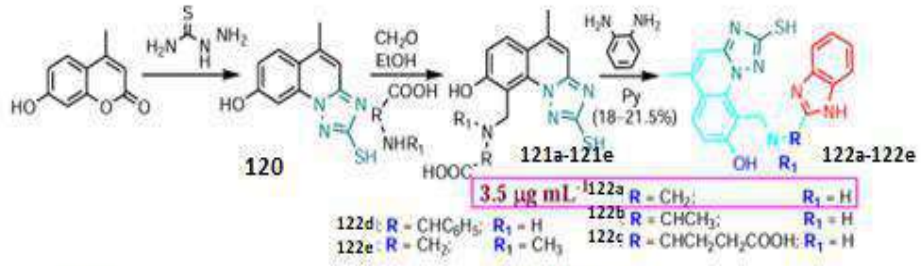
Compounds 119a–119g were examined for in lab analysis mycocidal activity contrary to two phytopathogenic fungi:

- Fusarium oxysporum f. sp. albedinis
- Verticillium dahliae Kleb

These mycelial linear growth rate outcomes reveal that most substances had low inhibition in opposition to both fungi. nevertheless, substance 6e showcased a significantly greater reduction effect of 29.79% contrary to Verticillium dahliae.[137]

Pandey et al. integrated mixtures 122a-122e through a three-step process:

1. Reaction of 7-hydroxy-4-methyl coumarin with thiosemicarbazide, generating the triazole intermediate (120).
2. Mannich reaction of intermediate 120 with formaldehyde and an amino acid, yielding intermediates 121a-121e.
3. Reaction of intermediates 121a-121e alongside o-phenylenediamine in pyridine, producing benzimidazole-triazole mixtures with low output. (Scheme 16).



Scheme 27 Synthesis of benzimidazole-1,2,4-triazoles **122a-122e**

Substance 122a revealed strong mycocidal activity in opposition to Candida albicans and Cryptococcus himalayensis, with a Minimum inhibitory concentration value of 3.54µg/mL for both fungi.

Compound 122b expressed mild to moderate mycocidal activity opposing five fungal species:

- Sporotrichum schenckii
- Aspergillus fumigatus
- Trichophyton rubrum
- Candida albicans

- Cryptococcus himalayensis [138].

Jiang and team informed that mixture 124 reveal mycocidal activity against:

- Trichophyton rubrum
- Aspergillus fumigatus
- Candida albicans
- Cryptococcus neoformans
- Candida tropicalis

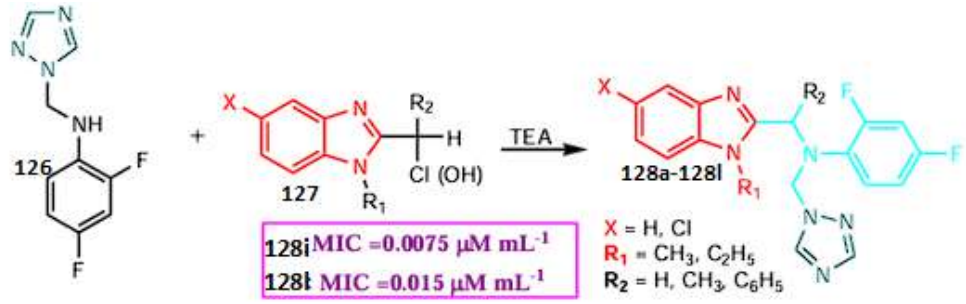
The MIC_{50} values ranged from 1 to 66 µg/mL, with Fluconazole act as the control chemical compound. (Figure 13).

Figure 13 Structure of benzimidazole hybrids 123,124 and 125

From the mycocidal activity data, a tentative structure-activity relationship (SAR) was instituted.

- The amine linker performed a crucial role in antifungal activity.
- Modified piperazine derivatives signified equivalent or better activity than the related N-methyl derivatives.[139].

Kankate and colleagues shared the synthesis of mixtures 128a-128l (Scheme 28).



Scheme 28. Synthesis of benzimidazole-1,2,4-triazoles **128a-128l**

The mycocidal effect of substance 128 was examined on Candida albicans spores in two ways: in vitro (using the turbidimetric method) and in biological system (using the kidney burden test). Substances 128i depicted strong antifungal activity evaluated to 12 other compounds at a very low concentration of 0.0074 µM/mL, which is comparable to the effect of Fluconazole in each of the two tests.

The antifungal power turned weaker when the alkyl chain at N1 of benzimidazole got longer (from methyl to ethyl). This was certified by comparing substance 128i (Minimum Inhibitory Concentration= 0.0074 µM/mL) and substance 128l (Minimum Inhibitory Concentration = 0.014 µM/mL).

To understand how these substances bind to the target enzyme, the ligand fit method was used. This helped forecast how substance 128 mixtures interact with the replicated cytochrome P450 lanosterol 14-α-demethylase enzyme linked to C. albicans. All substances connected to the enzyme's binding site. The triazole ring in compounds 128a-128l was placed nearly perpendicular to the porphyrin plane, having its nitrogen atom linking to the heme [Fe]. (Figure 14) [140,141].

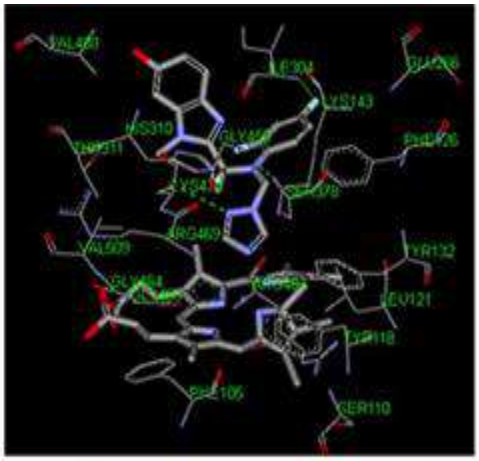


Figure 14 Binding mode of compound **128e** in the active site of modeled CYP51 of *C. albicans*. Image adapted from [145].

Ahuja and team documented that substances 129a-129c reflected antifungal activity contrary to F. verticillioides, D. oryzae, C. lunata, and F. fujikuroi. (Figure 15).

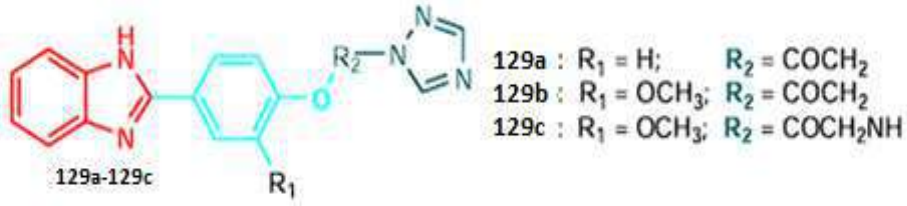


Figure 15. Structure of benzimidazole-1,2,4-triazole hybrids **129a-129c**

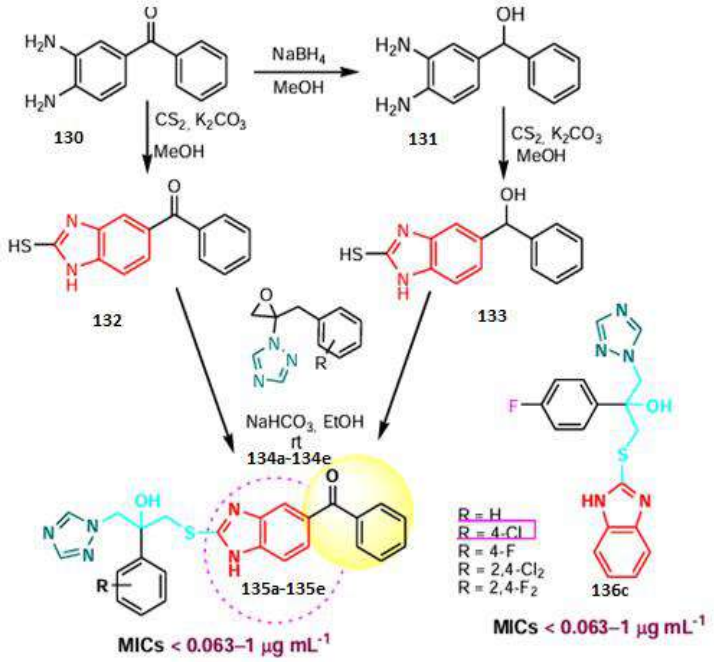
All substances were stronger than the reference commercial benzimidazole mycocide, carbendazim. (Table 11).

Table 11 ED_{50} values (μg mL^{-1}) of compounds against test fungi.

Compound	*F. verticillioides*	*D. oryzae*	*C. lunata*	*F. fujikuroi*
129a	35	50	28	45
129b	30	25	18	30
129c	16	12	10	15
Carbendazim	230	-	-	150
Propiconazole	20	25	22	21

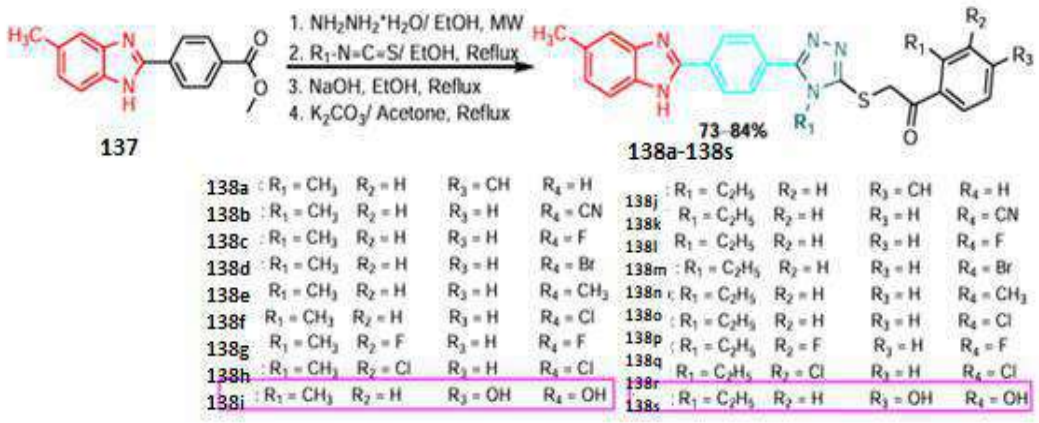
Ghobadi and colleagues uniting the synthesis of substances 135a-135e in 2 ways from 3,4-diaminobenzophenone 80:

1. Generation of 2-mercapto benzimidazole analogue (132, 133).
2. Ring cleavage of different oxiranes (134a-134e) in conjugation with benzimidazoles (132 , 133) using $NaHCO_3$ in ethanol in ambient environment. (Scheme 29).



Scheme 29 Synthesis of benzimidazole-1,2,4-triazoles 135a-135e and compound 136c

Substances 135a-135e, which have a 5-benzoylbenzimidazole mixture, revealed more potent antifungal activity in opposition to Candida spp. and Cryptococcus neoformans measured against to corelated benzimidazole , benzothiazole derivatives. The performance was observed with compound 135b, which had MIC value < 0.062-1 µg/mL. likewise, substance 136c, made in the same way, was just as strong 135b. To understand the antifungal effect, docking experiments were done to study how substance 135b interacts with the binding site of lanosterol 14α-demethylase (CYP51). As illustrated in (Figure 13), the space between the N4 atom of the triazole nucleus of substance 135b and the Fe atom in the heme group of the catalytic site was 2.72 Å and 2.41 Å. A H-bond was similarly observed among Tyr132 as well as the sulphur group of (S)-135b. Assessment in the lab (in vitro) and computer simulations (in silico ADMET) revealed that substance 135b had positive ADMET properties, making it a greater choice than Fluconazole. The docking study supported that the benzimidazol-2-yl-thio group is the key to the powerful antifungal activity of these substances.[142]. Can and team formulated mixtures 138a-138h in 4 steps compound 137. (Scheme 29)



Scheme 30 Synthesis of benzimidazole-1,2,4-triazoles **138a-138s**

All substances were examined for mycocidal activity in opposition to Candida albicans ATCC 24433, Candida glabrata ATCC 90030, Candida krusei ATCC 6258, and Candida parapsilosis ATCC 22019 (Table 12). substances 138i,138s displayed potent suppression in opposition to Candida strains, with MIC_{50} readings intermediate to 0.77 and 1.57 µg/mL.[143].

Table 12 MIC_{50} (µg mL^{-1}) values of compounds **138a-138s**

Compound	*C. albicans*	*G. glabrata*	*C. krusei*	*C. parapsilosis*
138a	12.5	6.25	6.25	12.5
138b	6.25	3.12	6.25	6.25
138c	12.5	6.25	6.25	12.5
138d	6.25	12.5	6.25	6.25
138e	12.5	6.25	12.5	12.5
138f	6.25	3.12	3.12	6.25
138g	3.12	6.25	6.25	6.25
138h	12.5	6.25	12.5	6.25
138i	0.78	1.56	1.56	0.78
138j	12.5	6.25	12.5	12.5
138k	12.5	6.25	12.5	12.5
138l	6.25	12.5	6.25	12.5
138m	3.12	3.12	3.12	6.25
138n	3.12	3.12	1.56	3.12
138o	3.12	3.12	6.25	6.25
138p	12.5	12.52	6.25	6.25
138q	6.25	3.12	3.12	3.12
138r	0.78	1.56	1.56	0.78
138s	0.78	1.56	1.56	1.56
Ketokonazole	0.78	1.56	1.56	0.78
Fluconazole				

Gencer and team effectively created substances 139 with high outputs (77-88%) using a resembling tactic (Figure 15). Microbiological tests revealed that substances 139a-139h had a powerful antifungal effect in opposition to C. albicans, C. krusei, C. glabrata, and C. parapsilosis, with MIC_{50} readings among 0.78 and 1.57 µg/mL.

Substances 139i was the highly efficient and had mycocidal activity comparable to the standard drugs Fluconazole and Ketoconazole.[144].

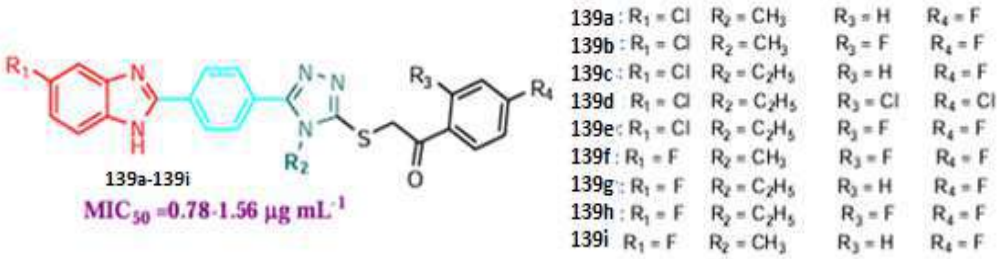
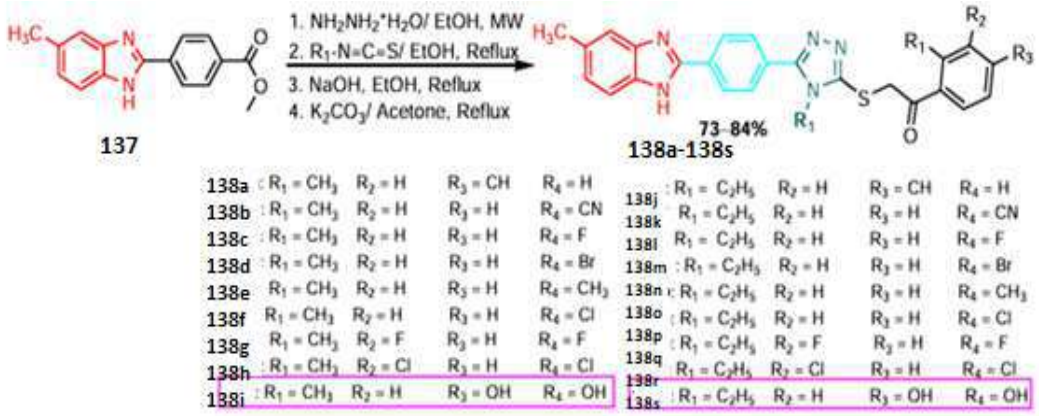


Figure 15 Structure of benzimidazole-1,2,4-triazole hybrids **139a-139i**

Güzel et al. formulated a new series of benzimidazole-1,2,4-triazole derivatives (140a-140l) using the similar procedure described in Scheme 30 (Figure 16) as more potent antifungal agents. All substances were examined for laboratory based antifungal activity in opposition to C. albicans, C. glabrata, C. krusei, and C. parapsilopsis. They showed powerful activity opposed to C. glabrata. Of these, substances 140b, 140i, and 140j were the most efficient, with a Minimum Inhibitory Concentration reading of 0.98 µg/mL . [145].



Scheme 30 Synthesis of benzimidazole-1,2,4-triazoles **138a-138s**

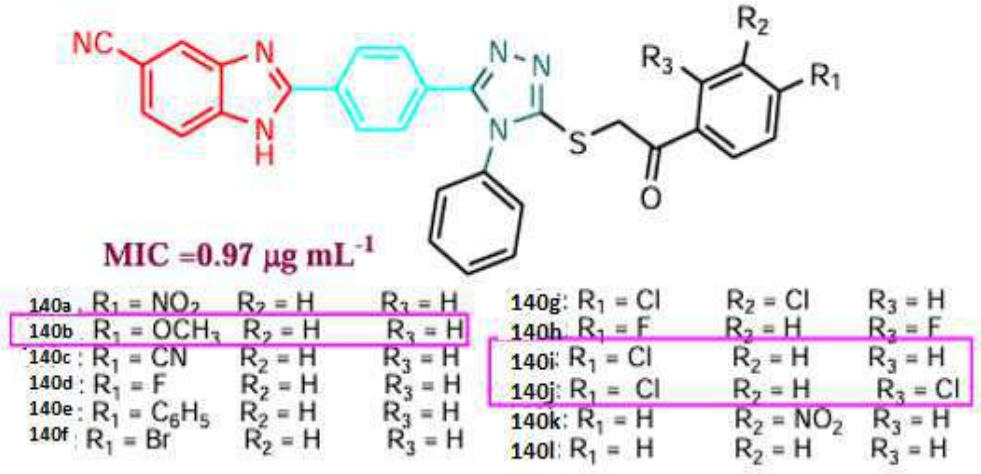


Figure 16. Structure of benzimidazole-1,2,4-triazole hybrids **140a-140l**

Based on the molecular docking study, substances 140b, 140i, and 140j aligned properly into the LDM catalytic pocket. In a prior analysis, comparable results were noted.[146] The Tyr118 amino acid and HEM601 protein were previously identified as essential residues. In this study, the active compounds (140b, 140i, and 140j) showed strong interactions with Tyr118, His377, and HEM601. The engagement with HEM601 have been noticed as π-π interaction and π-cation interactions. Because of this engagement, the mycocidal effects of substances 140b, 140i, and 140j are supposed to result from cell viability disruption because to LDM enzyme inhibition. Additionally, the researchers discovered that substance 6i had increased suppression effect because it formed an H-bond with Tyr132, unlike the other two compounds.

CONCLUSION

This assessment compiles the formulation of benzimidazole-triazole substances documented for their antimicrobial and virus inhibiting effects. This research indicates that specific chemical modifications—such as attaching fluorine, chlorine, bromine, trifluoromethyl, nitro, cyano, amide, aldehyde, hydroxyl, methoxy, dimethylamine, or ester groups, or incorporating other heterocycles like *pyrimidine, pyridine, indole, isoxazole, thiazole, thiadiazol*, or coumarin—significantly enhance the antimicrobial strength of these substances. Key structure-activity relationships (SARs) emerged from the analysed data:[147-154]

- **Benzimidazole Position Effects**: Modifying the benzimidazole ring by adding side groups at the 4th or 5th positions improves its antimicrobial activity.

- **Triazole Phenyl Substituents:** The presence of ortho- or para-substituted phenyl groups at the 1st position of the 1,2,3-triazole ring enhances antimicrobial efficacy.

- **Triazole Attachment**: Whether linked by aliphatic or aromatic radicals, triazoles at the 1st position of benzimidazole improve antimicrobial activity.

- **Linker Atoms:** uniting the benzimidazole and triazole rings with oxygen or sulphur atoms favours antimicrobial activity, with sulphur moreover exhibiting antitubercular potential.[155-159]

- **Multiple Triazoles**: Incorporating additional triazole rings into the hybrid structure further amplifies antimicrobial activity.

- **Antiviral Specificity:** Between the studied substances, only benzimidazole-1,2,3-triazole hybrids have demonstrated antiviral activity.

- **Antiviral Structure**: 2-substituted or 1,2-disubstituted benzimidazoles containing 1,2,3-triazole units display antiviral activity, which is further enhanced by the presence of additional triazole rings.

As observed, the combined presence of benzimidazole and triazole rings in a single molecule significantly enhances antimicrobial activity. Recent ADME and SAR studies are essential for guiding the synthesis of new, property-optimized benzimidazole-triazole hybrids. The dual antimicrobial and antiviral activity of these compounds is highly beneficial from both a therapeutic and economic perspective, meeting current medical demands, particularly in combating SARS-CoV-2. ADME studies confirm these hybrids' potential as effective antimicrobials and antivirals, opening avenues for developing compounds with superior biological properties. Although current research describes fundamental

molecular characteristics like lipophilicity/hydrophilicity, it primarily focuses on liquid formulations. The lack of studies on nanoparticle-based delivery systems to improve bioavailability represents a significant research opportunity. This review aims to serve as a valuable resource for designing and synthesizing novel benzimidazole-triazole hybrids to address the increasing challenge of bacterial and virus induced infections and therapeutic resistance.

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HOW TO CITE: Pavankumar Chopade*, Arya Suresh Bawankar, Aalim Nasir Khan, Triazole-Linked Benzimidazoles as Dual-Action Therapeutics: Antimicrobial and Antiviral Potential, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 7, 3835-3880. https://doi.org/10.5281/zenodo.16537472