Synthesis and therapeutic potential of imidazole containing compounds

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Abstract: Imidazole is a five-membered heterocyclic moiety that possesses three carbon, two nitrogen, four hydrogen atoms, and two double bonds. It is also known as 1, 3-diazole. It contains two nitrogen atoms, in which one nitrogen bear a hydrogen atom, and the other is called pyrrole type nitrogen. The imidazole name was reported by Arthur Rudolf Hantzsch (1857–1935) in 1887. 1, 3-diazole is an amphoteric in nature i.e. it shows both acidic and basic properties. It is a white or colorless solid that is highly soluble in water and other polar solvents. Due to the presence of a positive charge on either of two nitrogen atom, it shows two equivalent tautomeric forms. Imidazole was first named glyoxaline because the first synthesis has been made by glyoxal and ammonia. It is the basic core of some natural products such as histidine, purine, histamine and DNA based structures, etc. Among the different heterocyclic compounds, imidazole is better known due to its broad range of chemical and biological properties. Imidazole has become an important synthon in the development of new drugs. The derivatives of 1, 3-diazole show different biological activities such as antibacterial, antymycobacterial, anti-inflammatory, antitumor, antidiabetic, anti-allergic, antipyretic, antiviral, antioxidant, anti-amoeobic, antihelminthic, antifungal and ulcerogenic activities, etc. as reported in the literature. There are different examples of commercially available drugs in the market which contains 1, 3-diazole ring such as clemizole (antihistaminic agent), etonitazene (analgesic), astemizole (antihistaminic agent), omeprazole, pantoprazole (antiulcer), thia bendazole (antihelminthic), nocardazole (antimycobacterial), metronidazole, nitroso-imidazole (bactericidal), megalazol (trypanocidal), azathioprine (anti rheumatoid arthritis), dacarbazine (Hodgkin’s disease), tinidazole, ornidazole (antiprotozoal and antibacterial), etc. This present review summarized some pharmacological activities and various kinds of synthetic routes for imidazole and their derived products.

Keywords: 1, 3-diazole, Antibacterial, Antitumor, Antioxidant, Antitubercular

Background
Nowadays, Public health problems were increasing due to AMR in drug therapy. So, there is necessary for the development of a new drug that overcomes the AMR problems [1].

In past, those drugs which contain heterocyclic nuclei give high chemotherapeutic values and act as a remedy for the development of novel drugs [2]. There are lots of heterocyclic compounds that are in clinical use to treat infectious diseases. So, there is a great importance of heterocyclic ring containing drugs [3].

In heterocyclic chemistry, imidazole containing moiety occupied a unique position [4]. It is a five-membered nitrogenous heterocyclic moiety that possesses three carbon, two nitrogen, four hydrogen atoms, and two double bonds having general molecular formula is C₃H₄N₂ (Fig. 1). The nitrogen atoms present at the first and third positions (non–adjacent position) of the ring [5], position four and five are equivalent [6]. It is also known as 1,3-diazole. It contains two nitrogen atoms, one nitrogen bear a hydrogen atom, and the other is called pyrrole type nitrogen [7]. 1,3-diazole ring is a bioester of the pyrazole ring [8]. It is the basic core of some natural products such as histidine, purine, histamine and DNA based structures, etc. [4]. The imidazole name was first reported by Arthur Rudolf Hantzsch (1857–1935) in 1887 [6].
1,3-diazo shows an amphoteric phenomenon i.e. it can behave like acid as well as a base. Two types of lone pair are present in the imidazole ring, delocalized and non-delocalized (non-Huckle) lone pair, i.e. both nitrogen of 1,3-diazo shows different dissociation constant. The dissociation constant (pKa) of delocalized lone pair and non-delocalized lone pair is 7 and 14.9 respectively. 1,3-diazo ring is susceptible to both electrophilic and nucleophilic attacks due to its amphoteric phenomenon [7]. For an acid imidazole, the dissociation constant is 14.5, which makes it less acidic than phenol, imides, and carboxylic acid except for alcohols (which is less acidic than imidazole). For a basic imidazole, the dissociation constant (pKa) is approximately 7 (which makes imidazole 60 times more basic than pyridine). The acidic proton is present on the first nitrogen atom of the imidazole ring [6].

Due to the presence of a positive charge on either of the two nitrogen atoms, 1,3-diazo ring shows two equivalent tautomeric forms (Fig. 2) [9]. The presence of a sextet of π-electrons on the ring makes it an aromatic compound. The nitrogen atom on the third position in the imidazole ring is more reactive to the electrophilic compound due to the availability of unshared pairs of electron on the second nitrogen atom since the second nitrogen is a part of aromatic sextet [6].

It is a white or colorless solid. The imidazole ring shows excellent solubility in water and other polar solvents [10]. The dipole moment, melting point, and boiling point of the imidazole ring is 4.8 D in dioxane [6], 88.9 °C, and 267.8 °C [7] respectively. It possesses intramolecular hydrogen bonding [9].

Imidazole was first named glyoxaline because the first synthesis has been made by glyoxal and ammonia [9]. There is a different kind of synthetic route from which we can synthesize 1,3-diazoles, and its derivatives. Common methods are Debus-Radziszewski synthesis, Wallach synthesis, from dehydrogenation of imidazolines, from alpha halo-ketones, Marckwald synthesis, and amino nitrile [11].

Due to the polar nature of the imidazole ring, the pharmacokinetic parameters of the imidazole containing compounds should be improved to a great extent. Thus, this moiety helps to overcome the solubility problems of poorly soluble drug entities [12].

The 1,3-diazo and its containing compounds shows a lot of therapeutic activities such as analgesics, antifungal, antihypertensive, antiobesity, antioxidant [3], antiviral, antihelminthic, antitubercular [4], antiulcer, antihistaminic [13], anti-inflammatory, antidepressant [14], antidiabetic [15], anticonvulsant [16], antiallergic [7], antihematemic [17], antiasthmatic, alpha-blockers [18], antiprotozoal [19], antiaging, anticoagulant, antimalarial [20], and antiamoebic activity [21] etc.

There are different examples of commercially available drugs which consist 1,3,4-oxadiazole ring (Table 1) such as clemizole (antihistaminic agent), etonitazene (analgesic), enviroxime (antiviral), irtemazole, astemizole (antihistamine), omeprazole, pantoprazole (antiulcer), thiabendazole (antihelminthic), nocardazole (antimetabolot) [22], metronidazole and nitrosoimidazole (bactericidal), megazol (trypanocidal) [12], azathioprime (anti-rheumatoid arthritis), tinidazole, ornidazole (antiprotozoal and antibacterial), satranidazole (amoebiosis), cimetidine (gastric ulcer), carbimazole (against thyroid disorder), tolazoline (vasodilator action), naphazoline (vasoconstrictor), tetrahydrozoline (vasoconstrictor) [16], etomidate, lansoprazole, flumazenil, methimazole, pimobendan (calcium sensitizer and phosphodiesterase inhibitor) [25], fenbendazole [26].

**The mechanism for the formation of 2,4,5-trisubstituted imidazole**
The Debus-Radziszewski reaction mechanism for the formation of the 2,4,5-trisubstituted imidazole is given by (Scheme 1) [27].

**Main text**

**Antibacterial activity**
Jain et al. [28] synthesized 2-(4-substituted phenyl)-1-substituted-4, 5-diphenyl-1H-imidazole (Scheme 2) and evaluated their antimicrobial activity against S. aureus, E. coli, and B. subtilis by cylinder wells diffusion method using Norfloxacin as a reference drug. Among the different derivatives, compounds 1a and 1b showed good antimicrobial potential. The conclusion of antibacterial activity was presented in (Table 2, Jain et al. [28]).
| S. No. | Name      | Structure | Activity                                      |
|-------|-----------|-----------|-----------------------------------------------|
| 1     | Clemizole | ![Clemizole Structure](image1) | Anti-histaminic agent                         |
| 2     | Etonitazene | ![Etonitazene Structure](image2) | Analgesic                                     |
| 3     | Enviroxime | ![Enviroxime Structure](image3) | Antiviral                                     |
| 4     | Irtemazole | ![Irtemazole Structure](image4) | For the promotion of excretion of uric acid |
| 5     | Astemizole | ![Astemizole Structure](image5) | Anti-histaminic agent                         |
| 6     | Omeprazole | ![Omeprazole Structure](image6) | Antiulcer                                     |
| 7     | Pantoprazole | ![Pantoprazole Structure](image7) | Antiulcer                                     |
| 8     | Thiabendazole | ![Thiabendazole Structure](image8) | Anti-helmintic                                |
| 9     | Nocodazole | ![Nocodazole Structure](image9) | Antinematodal                                 |
| 10    | Metronidazole | ![Metronidazole Structure](image10) | Antibacterial                                 |
| 11    | Nitrosoimidazole | ![Nitrosoimidazole Structure](image11) | Antibacterial                                 |
| 12    | Megazol   | ![Megazol Structure](image12) | Trypanocidal                                  |
|   | Chemical Name | Molecular Structure | Function |
|---|---------------|---------------------|----------|
| 13. | Azathioprine | ![Azathioprine](attachment:azathioprine.png) | Anti-rheumatoid arthritis |
| 14. | Tinidazole | ![Tinidazole](attachment:tinidazole.png) | Anti-protozoal and antibacterial |
| 15. | Ornidazole | ![Ornidazole](attachment:ornidazole.png) | Antiprotozoal and antibacterial |
| 16. | Satranidazole | ![Satranidazole](attachment:satranidazole.png) | Anti-amoebic |
| 17. | Cimetidine | ![Cimetidine](attachment:cimetidine.png) | Antiulcer |
| 18. | Carbimazole | ![Carbimazole](attachment:carbimazole.png) | Antithyroid |
| 19. | Tolazoline | ![Tolazoline](attachment:tolazoline.png) | Vasodilator |
| 20. | Naphazoline | ![Naphazoline](attachment:naphazoline.png) | Vaso-constrictor |
| 21. | Tetra-hydrozoline | ![Tetra-hydrozoline](attachment:tetra-hydrozoline.png) | Vaso-constrictor |
| 22. | Etomidate | ![Etomidate](attachment:etomidate.png) | Anesthetic agent |
Narasimhan et al. [1] synthesized pyridin-3-yl (2-(2,3,4,5-tetra substituted phenyl)-1H-imidazol-1-yl) methanone (Scheme 3). The tube dilution method was used for the determination of antimicrobial potential against *S. aureus*, *B. subtilis*, and *E. coli* using ciprofloxacin as a reference drug. The antifungal activity of these derivatives was also evaluated against *A. niger* and *C. albicans* using Fluconazole as a reference standard. The conclusion of antimicrobial potential was presented in (Table 3, Narasimhan et al. [1]).
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Brahmbhatt et al. [2] synthesized 3-(2,4-disubstituted phenyl)-1-(4-substituted phenyl)-4-(4,5-diphenyl-1H-imidazol-2-yl)-1H-pyrazole (Scheme 4). The antibacterial activity of these derivatives was evaluated against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* using amikacin sulfate, ampicillin, and chloramphenicol as a reference drug. Compound 4 h shows the most potent activity compared to the rest of the synthesized compounds. The conclusion of antibacterial activity was presented in (Table 4, Brahmbhatt et al. [2]).

Parab et al. [29] synthesized (Z)-4-((6-Bromo-2-chloroquinolin-3-yl) methylene)-2-phenyl-1-(2, 3, 4-trisubstituted phenyl)-1H-imidazol-5(4H)-one by using Scheme 5. The antibacterial activity of synthesized derivatives was evaluated against *E. coli*, *P. aeruginosa*,

**Scheme 1** Plausible mechanism for the synthesis of imidazoles catalyzed by (4–SB)T(4–SPh)PHSO₄
B. subtilis, and B. megaterium by agar cup borer method using streptomycin as a reference drug. The antymycotic potential was evaluated for these derivatives against Candida albicans and Aspergillus niger using imidil as a reference drug and the conclusion of activity was presented in (Table 5, Parab et al. [29]).

![Scheme 2 Synthesis of 2-(4-substitutedphenyl)-1-substituted-4,5-diphenyl-1H-imidazole](image)

**Compounds**

\[
\begin{align*}
& R_1 = \\
1a &= p-\text{NO}_2 \\
1b &= m-\text{NO}_2 \\
1c &= p-\text{Cl} \\
1d &= o-\text{Cl} \\
1e &= m-\text{Br}
\end{align*}
\]

\[R_2 = \text{Butyl}\]

**Table 2 Antibacterial activity of synthesized derivatives (1a-e)-zone of inhibition (mm,%) Jain et al. [28]**

| Compounds | Zone of inhibition |
|-----------|--------------------|
|           | S. aureus          | B. subtilis       | E. coli          |
|           | 50(µg/mL) 150(µg/mL) | 50(µg/mL) 150(µg/mL) | 50(µg/mL) 150(µg/mL) |
| 1a        | 5 (23.09) 9 (42.85) | 4 (19.04) 8 (38.09) | 7 (33.33) 9 (42.85) |
| 1b        | 3 (14.28) 7 (33.33) | 4 (19.04) 7 (33.33) | 6 (28.57) 9 (42.85) |
| 1c        | 5 (23.09) 6 (28.57) | 6 (28.57) 7 (33.33) | 5 (23.09) 8 (38.09) |
| 1d        | 5 (23.09) 6 (28.57) | 6 (28.57) 6 (28.57) | 5 (23.09) 8 (38.09) |
| 1e        | 4 (19.04) 7 (33.33) | 4 (19.04) 7 (33.33) | 5 (23.09) 8 (38.09) |

**Norfloxacin** Norfloxacin at concentration 50(µg/mL)

Sharma et al. [17] synthesized 2,3-disubstituted-3, 4-dihy droimidazo [4,5-b] indole (Scheme 6) and evaluated for antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebsiella pneumoniae by Kirby-Bauer disc technique using ciprofloxacin as reference drug. The conclusion
Scheme 3 Synthesis of pyridin-3-yl(2-(2,3,4,5-tetrasubstituted phenyl)-1H-imidazol-1-yl)methanone (2a-k)

Table 3 Antimicrobial activity of titled compounds (2a-k) Narasimhan et al. [1]

| Compounds | MIC (µM/mL) | S. aureus | B. subtilis | E. coli | C. albicans | A. niger |
|-----------|-------------|-----------|-------------|---------|-------------|---------|
| 2a        |             | 0.012     | 0.003       | 0.003   | 0.025       | 0.050   |
| 2b        | ND          | ND        | ND          | 0.022   | 0.005       | 0.005   |
| 2c        | ND          | ND        | ND          | 0.005   | 0.005       |         |
| 2d        | 0.044       | 0.044     | 0.044       | 0.022   | 0.044       |         |
| 2e        | 0.022       | 0.044     | 0.006       | 0.022   | 0.044       |         |
| 2f        | 0.044       | 0.044     | 0.011       | 0.342   | 0.044       |         |
| 2g        | ND          | ND        | ND          | 0.004   | 0.019       |         |
| 2h        | 0.010       | 0.010     | 0.040       | 0.020   | 0.040       |         |
| 2i        | 0.040       | 0.002     | 0.040       | 0.020   | 0.040       |         |
| 2j        | 0.013       | 0.005     | 0.002       | 0.025   | 0.025       |         |
| 2k        | 0.002       | 0.002     | 0.002       | 0.020   | 0.040       |         |
| Ciprofloxacin |          | 0.004     | 0.004       | –       | –           | –       |
| Fluconazole |             | –         | –           | 0.005   | 0.005       |         |

MIC Minimum inhibitory concentration, ND not detected
of antimicrobial potential was presented in (Table 6, Sharma et al. [17]).

Ahsan et al. [30] synthesized N-(4-substituted phenyl)-2-(2-(2-(2-hydroxyphenyl)-4, 5-diphenyl-1H-imidazol-1-yl)acetyl) hydrazine carbothioamide (Scheme 7). The antibacterial activity of synthesized derivatives was evaluated against *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus* using Ofloxacin as a reference drug. The antymycotic potential was evaluated for these derivatives against *C. albicans* using Voriconazole as a positive control. Compounds 8a, 8b, and 8d showed good antifungal activity against *C. albicans*. The conclusion of antimicrobial activity was presented in (Table 7, Ahsan et al. [30]).

Bhade et al. [18] synthesized 2,4-dichloro-6-(2-substituted-2,5-dihydro-1H-imidazol-4-yl)phenol, 6-(3, 5-dichloro-2-hydroxyphenyl)-2-substituted-2H-imidazo[1,2-a]imidazol-3(5H)-one, 1-acetyl-4-(3, 5-dichloro-2-hydroxyphenyl)-1H-imidazol-2(5H)-one, (Z)-4-(3,5-dichloro-2-hydroxyphenyl)-1-(3-(2, 3-dichlorophenyl) acryloyl)-1H-imidazol-2(5H)-one and 4-(3,5-dichloro-2-hydroxyphenyl)-1-(5-(2,3-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1H-imidazol-2(5H)-one by using (Scheme 8). The antibacterial activity of these derivatives was evaluated against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella typhi* and *Pseudomonas aeruginosa* using chloramphenicol as a reference control. The conclusion of antimicrobial activity was presented in (Table 8, Bhade et al. [18]).

Desai et al. [31] synthesized (Z)-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)sutituted carbamic (Scheme 9) and evaluated for antimicrobial potential against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* by serial broth dilution method using ampicillin as a reference standard and the results were summarized in (Table 9a, Desai et al. [30]).
Scheme 5 Synthesis of (Z)-4-((6-bromo-2-chloroquinolin-3-yl)methylene)-2-phenyloxazol-5(4H)-one

Table 5 Antimicrobial activity of synthesized compounds (5a-h) Parab et al. [29]

| Compounds | Zone of inhibition (mm) |
|------------|------------------------|
|            | E. coli | P. aeruginosa | B. subtilis | B. megaterium | A. niger | C. albicans |
| 5a         | 15      | 19            | 21          | 19            | 20       | 19          |
| 5b         | 11      | 9             | 19          | 20            | 10       | 11          |
| 5c         | 20      | 22            | 22          | 22            | 13       | 13          |
| 5d         | 11      | 15            | 19          | 13            | 15       | 12          |
| 5e         | 10      | 8             | 15          | 19            | 12       | 9           |
| 5f         | 6       | 18            | 25          | 20            | 14       | 16          |
| 5g         | 14      | 9             | 24          | 15            | 10       | 11          |
| 5h         | 8       | 13            | 21          | 13            | 16       | 17          |
| Streptomycin| 28      | 32            | 31          | 29            | 33       | 33          |
| Imidil     | –       | –             | –           | –             | 34       | 34          |

Antimicrobial activity of compounds at 10 mg% in DMSO
Scheme 6
Synthesis of 2,3-disubstituted-3,4-dihydroimidazo[4,5-b]indole

\[
\text{R-NH}_2 + \text{O-R'} \xrightarrow{a} \text{R-N=C-R'} + \text{CH}_3\text{COONH}_4 + \text{indoline-2,3-dione}
\]

Reagents and conditions: (a) Conv. AcOH, Reflux 5-6 hr, MW: Activated silica gel, 1000 W, 10 min
(b) Ammonium acetate, conv. reflux 12-15 h, MW; 1000 W, 14-22 min.

Scheme 6  Synthesis of 23-disubstituted-3,4-dihydroimidazo[4,5-b]indole
The antimycotic potential of these derivatives was evaluated against *A. niger*, *C. albicans*, and *A. clavatus* using griseofulvin as a reference standard. The results of the activity were summarized in (Table 9b, Desai et al. [31]).

Shobhashana et al. [32] synthesized 6-substituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-2-(4-substituted phenoxy) quinoline by using (Scheme 10) and evaluated for antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, *Clostridium tetani*, *Streptococcus pneumoniae*, and *Salmonella typhi* by using the broth dilution method. Ampicillin, chloramphenicol, and ciprofloxacin were used as a positive control. The antifungal activity of these derivatives was evaluated against *Candida albicans* and *Trichophyton rubrum* using Nystatin and Griseofulvin as reference drugs. The conclusion of antimycotic activity was presented in (Table 10a, b, Shobhashana et al. [32]).

Selvan et al. [33] developed N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)substituted formimidoyl by using (Scheme 11). The disc diffusion technique was used for the determination of antimicrobial activity against *S. aureus* using ciprofloxacin as a positive control. The antimycotic activity of these derivatives was evaluated against *A. niger* using Nystatin as a reference drug and the conclusion of antimicrobial potential was presented in (Table 11, Selvan et al. [33]).

Zala et al. [8] synthesized 2-(substituted amino)-1-(2,4,5-triphenyl-1H-imidazol-1-yl) ethanone (Scheme 12) and evaluated for antimicrobial potential against *Staphylococcus aureus* and *Escherichia coli* using ciprofloxacin as a reference drug. The antimycotic potential of these derivatives was evaluated against *C. albicans* using Clotrimazole as a reference drug. The conclusion of antibacterial activity was presented in (Table 12, Zala et al. [8]).

Yadav et al. [34] synthesized 2-((1H-benzo[d]imidazol-2-yl)thio)-N-(4-oxo-2-(2,3,4,5,6-Penta substituted phenyl)thiazolidin-3-yl)acetamide and 2-((1H-benzo[d]imidazol-2-yl)thio)-N-(2-substituted-4-oxothiazolidin-3-yl) acetamide by using (Scheme 13). The antibacterial activity of these derivatives was evaluated against different bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*) using Norfloxacin as a reference drug. The antimycotic activity of these derivatives was evaluated against different fungal (*Candida albicans* and *Aspergillus niger*) strains using Fluconazole as a reference drug. The conclusion of the activity was presented in (Table 13, Yadav et al. [34]).

**Anticancer activity**

Yurttas et al. [35] developed 2-((1-((4-substituted phenyl) amino)-2,4,5-triphenyl-1H-imidazol-2-yl)thio)-N-(6-substituted phenyl)imidazolidin-2-yl)acetamide and 2-((1-((4-substituted phenyl) amino)-2,4,5-triphenyl-1H-imidazol-2-yl)thio)-N-(2-substituted-4-oxothiazolidin-3-yl)acetamide by using (Scheme 13). The antibacterial activity of these derivatives was evaluated against different bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*) using Norfloxacin as a reference drug. The antimycotic activity of these derivatives was evaluated against different fungal (*Candida albicans* and *Aspergillus niger*) strains using Fluconazole as a reference drug. The conclusion of the activity was presented in (Table 13, Yadav et al. [34]).

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### Table 6 Antimicrobial activity of the synthesized aryl imidazole compounds (7a-t) Sharma et al. [17]

| Compounds | Diameter of zone of inhibition (mm) | Bacterial strains |
|-----------|-----------------------------------|------------------|
|           |                                   | Gram positive bacteria | Gram negative bacteria |
|           |                                   | *S. aureus* | *B. subtilis* | *E. coli* | *K. pneumoniae* |
| 7a        | 5.9 (50)                          | 6.9 (50) | 7.2 (50) | 8.1 (50) |
| 7b        | 5.1 (25)                          | 5.5 (25) | 8.1 (50) | 8.9 (50) |
| 7c        | 8.6 (25)                          | 8.4 (25) | 9.2 (12.5) | 9.5 (12.5) |
| 7d        | 13.1 (50)                         | 12.5 (25) | 11.9 (25) | 12.5 (6.2) |
| 7e        | 9.1 (25)                          | 8.8 (50) | 7.6 (100) | 7.8 (100) |
| 7f        | 5.7 (100)                         | 5.9 (100) | 6.6 (50) | 6.9 (50) |
| 7g        | 12.5 (50)                         | 12.1 (25) | 11.9 (25) | 11.6 (25) |
| 7h        | 11.9 (50)                         | 11.3 (25) | 10.9 (100) | 10.7 (50) |
| 7i        | 12.1 (25)                         | 13.8 (50) | 14.3 (25) | 12.5 (50) |
| 7j        | 13.1 (25)                         | 12.3 (25) | 15.4 (12.5) | 11.8 (25) |
| 7k        | 11.2 (50)                         | 12.4 (25) | 13.5 (12.5) | 9.1 (50) |
| 7l        | 6.2 (100)                         | 7.2 (100) | 9.2 (50) | 7.5 (50) |
| 7m        | 7.2 (100)                         | 8.7 (50) | 10.2 (50) | 10.3 (25) |
| 7n        | 10.3 (25)                         | 12.4 (12.5) | 14.5 (6.2) | 13.3 (12.5) |
| 7o        | 12.3 (50)                         | 13.6 (25) | 14.6 (25) | 14.6 (25) |
| 7p        | 9.1 (100)                         | 8.3 (100) | 9.1 (50) | 10.2 (50) |
| 7q        | 6.1 (100)                         | 7.4 (100) | 8.3 (50) | 6.9 (50) |
| 7r        | 7.3 (100)                         | 7.4 (100) | 9.5 (50) | 9.7 (50) |
| 7s        | 13.2 (25)                         | 14.5 (12.5) | 14.6 (12.5) | 11.5 (25) |
| 7t        | 12.4 (25)                         | 12.7 (25) | 13.1 (50) | 11.1 (50) |
| Ciprofloxacin | 18 (12.5)                   | 19 (6) | 19 (12.5) | 17 (6) |

Values in brackets are MIC values (µg/mL)

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Scheme 7

Scheme 7 Synthesis of $N$-(4-substitutedphenyl)-2-(2-(2-(2-hydroxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)acetyl)hydrazinecarbothioamide (8a-e)

Compounds 8a-e; R =

8a = H, 8b = OCH, 8c = CH, 8d = F, 8e = Cl

Table 7 Antibacterial and antifungal activity of titled compounds (8a-8e) Ahsan et al. [30]

| Compounds | Antibacterial activity | Antifungal activity |
|-----------|------------------------|---------------------|
|           | E. coli | % inhibition | B. subtilis | % inhibition | S. aureus | % inhibition | C. albicans | % inhibition |
| Zone of inhibition (mm) | Zone of inhibition (mm) | Zone of inhibition (mm) | Zone of inhibition (mm) |
| 8a       | 22 | 61.11 | 14 | 43 | 14 | 48 | 20 | 75 |
| 8b       | 22 | 61.11 | 15 | 47 | 21 | 72 | – | – |
| 8c       | 23 | 67 | 15 | 47 | 20 | 69 | 17 | 58.6 |
| 8d       | 22.5 | 62.5 | 20 | 62 | 19 | 65.5 | 20 | 69 |
| 8e       | 19 | 52 | 12 | 50 | 22 | 75 | 20 | 68.5 |
| Ofloxacin | 36 | 100 | 32 | 100 | 29 | 100 | – | – |
| Voriconazole | – | – | – | – | – | – | 29 | 100 |
Scheme 8 Synthesis of imidazole derivatives

1-(3,5-dichloro-2-hydroxyphenyl)ethanone

2-bromo-1-(3,5-dichloro-2-hydroxyphenyl)ethanone

2,4-dichloro-6-(2-substituted-2,5-dihydro-1H-imidazol-4-yl)phenol

R = O, N (9a, 9b)

1-acetyl-4-(3,5-dichloro-2-hydroxyphenyl)-1H-imidazol-2(5H)-one (11a)

6-(3,5-dichloro-2-hydroxyphenyl)-2-substituted-2H-imidazo[1,2-α]imidazol-3(5H)-one

R = H/Me (10a-10b)

(Z)-4-(3,5-dichloro-2-hydroxyphenyl)-1-(3-(2,3-dichlorophenyl)acryloyl)-1H-imidazol-2(5H)-one (12a)

4-(3,5-dichloro-2-hydroxyphenyl)-1-(5-(2,3-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1H-imidazol-2(5H)-one (13a)
| Compounds | Gram negative | Gram positive |
|-----------|---------------|---------------|
|           | *P. aeruginosa* (MTCC-424) | *S. typhi* (ATCC-25812) | *S. aureus* (ATCC-33591) | *S. epidermidis* (MTCC-3086) |
|           | AB | SP | ABSP | CL | AB | SP | ABSP | CL | AB | SP | ABSP | CL | AB | SP | ABSP | CL | AB | SP | ABSP | CL |
| 9a        | 23 | 16 | 26   | 00 | 26 | 19 | 32   | 00 | 16 | 18 | 18   | 00 | 27 | 16 | 28   | 00 | 17 | 20 | 18   | 00 |
| 9b        | 23 | 16 | 26   | 00 | 27 | 18 | 33   | 00 | 17 | 19 | 17   | 00 | 27 | 15 | 29   | 00 | 17 | 15 | 29   | 00 |
| 10a       | 23 | 17 | 26   | 00 | 27 | 17 | 33   | 00 | 17 | 20 | 18   | 00 | 27 | 15 | 29   | 00 | 17 | 20 | 18   | 00 |
| 10b       | 23 | 16 | 25   | 00 | 27 | 18 | 32   | 00 | 17 | 20 | 18   | 00 | 27 | 16 | 28   | 00 | 17 | 17 | 18   | 00 |
| 11a       | 23 | 12 | 24   | 00 | 27 | 16 | 29   | 00 | 17 | 17 | 18   | 00 | 27 | 15 | 28   | 00 | 17 | 17 | 18   | 00 |
| 12a       | 22 | 11 | 23   | 00 | 27 | 16 | 30   | 00 | 17 | 16 | 19   | 00 | 27 | 13 | 27   | 00 | 17 | 16 | 19   | 00 |
| 13a       | 22 | 10 | 23   | 00 | 27 | 15 | 28   | 00 | 16 | 15 | 16   | 00 | 27 | 12 | 28   | 00 | 16 | 15 | 16   | 00 |

Diameter of inhibition zone (mm) AB: Antibiotic Disc (Chloramphenicol-10), SP: Sample, ABSP: Antibiotic + Sample, CL: Control (DMSO), Values were represented as the mean.
Scheme 9 Synthesis of (Z)-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)substitutedcarbamic (14a-l)
Table 9 (a) Antibacterial activity of the synthesized derivatives (14a-l); (b) Antifungal activity of titled compounds (14a-l) Desai et al. [31]

(a)

| Compounds | R           | MIC (µg/mL) ± SD | E. coli MTCC-443 | P. aeruginosa MTCC-1688 | S. aureus MTCC-96 | S. pyogenes MTCC-442 |
|-----------|-------------|-----------------|------------------|--------------------------|------------------|----------------------|
| 14a       | −C₆H₅       | 100 ± 2.03**    | 500 ± 2.64*      | 1000 ± 3.78              | 500 ± 3.64       |
| 14b       | C₆H₅-CH₂-    | 500 ± 3.46*     | 500 ± 3.46       | 250 ± 3.21**             | 250 ± 3.04***    |
| 14c       | −3-Cl-C₆H₄  | 50 ± 2.64***    | 100 ± 1.21**     | 200 ± 2.08*              | 1000 ± 4.51      |
| 14d       | −4-Cl-C₆H₄  | 25 ± 1*         | 100 ± 1.51*      | 200 ± 2.08**             | 250 ± 2.64**     |
| 14e       | −2,5-(Cl)₂-C₆H₃ | 100 ± 1      | 250 ± 2.51**     | 1000 ± 4.04              | 1000 ± 2.51**    |
| 14f       | −4-F-C₆H₄   | 200 ± 1.62*     | 100 ± 1.60       | 100 ± 2.78**             | 1000 ± 3.78**    |
| 14g       | −3-NO₂-C₆H₄ | 100 ± 1**       | 100 ± 1.72       | 500 ± 3.05               | 250 ± 2.51***    |
| 14h       | −4-NO₂-C₆H₄ | 25 ± 1.62***    | 50 ± 1.05*       | 250 ± 2.16*              | 100 ± 1.78**     |
| 14i       | −2-OH-C₆H₄  | 100 ± 2.15*     | 100 ± 1***       | 100 ± 2.04*              | 500 ± 4.50       |
| 14j       | −3-OH-C₆H₄  | 100 ± 2.05*     | 50 ± 1.16**      | 500 ± 4.50               | 200 ± 2.05*      |
| 14k       | −2-OH,4-Cl-C₆H₃ | 200 ± 2.21* | 100 ± 2.15**     | 250 ± 2.64**             | 500 ± 3.08       |
| 14l       | C₅H₄N       | 500 ± 3.05**    | 500 ± 3.78       | 250 ± 3.21*              | 100 ± 1.51*      |
| Ampicillin |             | 100 ± 2.05      | 100 ± 1.0        | 250 ± 1.52               | 100 ± 2.06       |

(b)

| Compounds | R           | MIC (µg/mL) ± SD | C. albicans MTCC-227 | A. niger MTCC-282 | A. clavatus MTCC-1323 |
|-----------|-------------|-----------------|----------------------|-------------------|----------------------|
| 14a       | −C₆H₅       | 500 ± 2.64*     | 500 ± 3.05*          | 1000 ± 3.21       |
| 14b       | C₆H₅-CH₂-    | 1000 ± 1.04**   | 1000 ± 2.51*         | 500 ± 4.05*       |
| 14c       | −3-Cl-C₆H₄  | 100 ± 1.51*     | 1000 ± 4.50          | 100 ± 1.64*       |
| 14d       | −4-Cl-C₆H₄  | 200 ± 2.64*     | 100 ± 1.21**         | 500 ± 4.16        |
| 14e       | −2,5-(Cl)₂-C₆H₃ | 100 ± 2.51**  | 500 ± 2.08***        | 500 ± 3.78**      |
| 14f       | −4-F-C₆H₄   | 100 ± 1.78*     | 1000 ± 3.05          | 100 ± 2.78***     |
| 14g       | −3-NO₂-C₆H₄ | 200 ± 3.51      | 500 ± 4.05*          | 100 ± 1.51*       |
| 14h       | −4-NO₂-C₆H₄ | 100 ± 3.78**    | 100 ± 1***           | 200 ± 3.05**      |
| 14i       | −2-OH-C₆H₄  | 500 ± 4.50*     | 250 ± 3.78**         | 500 ± 4.58        |
| 14j       | −3-OH-C₆H₄  | 1000 ± 2.05***  | 100 ± 2.05***        | 500 ± 3.21**      |
| 14k       | −2-OH,4-Cl-C₆H₃ | 500 ± 2.08   | 250 ± 2.05           | 500 ± 3.46        |
| 14l       | C₅H₄N       | 200 ± 3.51**    | 500 ± 2.64*          | 100 ± 1.12*       |
| Griseofulvin |          | 500 ± 2.58      | 100 ± 1              | 100 ± 1.15        |

± SD = Standard deviation
* Significant P < 0.05
** Moderately significant P < 0.01
*** Extremely significant P < 0.001
Scheme 10  Synthesis of 6-substituted-3-(4,5-diphenyl-1H-imidazol-2-yl)-2-(4-substitutedphenoxy)quinoline

\[
\begin{align*}
\text{R}_1 \quad \text{CHO} & \quad \text{Cl} \quad \text{CHO} \quad \text{R}_1 \quad \text{NH}_4\text{OAC} \\
\text{R}_2 \quad \text{4-substituted phenol} & \quad \text{R}_2 \quad \text{6-substituted-2-(4-substitutedphenoxy) quinoline-3-carbaldehyde} \\
\text{R}_1 = \text{H, CH}_3, \text{OCH}_3 & \\
\text{R}_2 = \text{H, Cl} \\
\text{CAN} & \quad \text{Acetic acid, Reflux} \\
\end{align*}
\]
Table 10 (a) Antibacterial activity of the synthesized compounds (15a-f); (b) Antifungal activity of the synthesized compounds (15a-f) Shobhashana et al. [32]

(a)

| Compounds | Minimum inhibitory concentration in µg/mL |
|-----------|-------------------------------------------|
|           | Antibacterial activity                    |
|           | Gram positive bacteria | Gram negative bacteria |
| 15a       | 100 | 250 | 500 | 100 | 250 | 250 |
| 15b       | 250 | 500 | 250 | 250 | 200 | 500 |
| 15c       | 62.5| 100 | 500 | 62.5| 200 | 250 |
| 15d       | 250 | 100 | 125 | 100 | 125 | 100 |
| 15e       | 500 | 500 | 500 | 250 | 100 | 500 |
| 15f       | 100 | 250 | 100 | 100 | 100 | 250 |
| Ampicillin| 250 | 250 | 100 | 100 | 100 | 100 |
| Chloramphenicol | 50  | 50  | 50  | 50  | 50  | 50  |
| Ciprofloxacin | 50  | 100 | 50  | 25  | 25  | 25  |

(b)

| Compounds | MIC |
|-----------|-----|
|           | C.albicans MTCC227 | T. rubrum MTCC296 |
| 15a       | >1000 | 1000 |
| 15b       | 500   | >1000 |
| 15c       | 1000  | 1000 |
| 15d       | 1000  | 1000 |
| 15e       | 1000  | >1000 |
| 15f       | 500   | 1000 |
| Nystatin  | 100   | 500  |
| Griseofulvin | 500 | 500  |

Scheme 11 Synthesis of N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)substitutedformimidoyl
tutedbenzo[d]thiazol-2-yl)acetamide by using (Scheme 14) and evaluated for antitumor potential by MTT assay against two different cancer cell lines such as C6 (rat glioma) and HepG2 (human liver) using cisplatin as a reference drug. Among the synthesized derivatives compound 20g shows good cytotoxic potential. The conclusion of antitumor potential was presented in (Table 14, Yurttas et al. [35]).

Hsieh et al. [25] synthesized (E)-1-(1-allyl-1H-benzo[d]imidazol-2-yl)-3-(4-substituted phenyl) prop-2-en-1-one by using (Scheme 15) and evaluated for anticancer activity against different cell lines such as A549, MCF-7, HepG2, and OVCAR-3 by MTT assay using cisplatin as a reference drug. The conclusion of anticancer activity was presented in (Table 15, Hsieh et al. [25]).

Roopashree et al. [36] synthesized 2-(5-butyl-3-chloro-1-substituted-1H-pyrrol-2-yl)-1H-benzo[d]imidazole (Scheme 16) and evaluated for antitumor activity against HeLa cancer cell line by using MTT assay. Each compound was tested to calculate the inhibitory concentration and the results of the activity were presented in (Table 16, Roopashree et al. [36]).

Romagnoli et al. [37] developed 2-substituted-1-(3,4,5-trimethoxyphenyl)-1H-imidazole (Scheme 17) and evaluated for anticancer activity against different cancer cell lines such as HeLa, HT-29, A549, MCF-7, Jurkat, and HL-60 using C-A4 as a reference standard. Compounds 28k, 28n, and 28o showed maximum cytotoxicity as compared to others. The conclusion of antitumor potential was presented in (Table 17, Romagnoli et al. [37]).

Rajendran et al. [38] synthesized 1-substituted-2-(5-substituted-1-phenyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazole and 4-(1-chloro-1H-benzo[d]imidazol-2-yl)-6-fluoropyrimidin-2-amine by using (Scheme 18) and evaluated for antitumor potential against different cell lines such as MCF-7 and CaCo-2 using Fluorouracil as reference drug. Each compound was tested to calculate inhibitory concentration and the conclusion of activity was presented in (Table 18a, b, Rajendran et al. [38]).

Meenakshisundaram et al. [39] synthesized 3-(4-substitutedbenzyl)-6,7-disubstituted-2-(4-(6,7-disubstituted-3-(4-substitutedbenzyl)imidazo[1,2-a]pyridin-2-yl)phenyl)imidazo[1,2-a]pyridine, 3-(4-substituted benzyl)-2-(3-(6,7-disubstituted-3-(4-substitutedbenzyl)imidazo[1,2-a]pyridin-2-yl)phenyl)-6,7-disubstitutedimidazo[1,2-a]pyridine and 6,7-disubstituted-3-(4-substitutedbenzyl)-2-phenylimidazo[1,2-a] pyridine (Scheme 19a–c) and evaluated for antitumor potential against different cell lines such as HeLa, MDA-MB-231 and ACHN by SRB method using adriamycin as a reference drug. The conclusion of antitumor potential was presented in (Table 19, Meenakshisundaram et al. [39]).

Sharma et al. [40] synthesized 1,2-disubstituted-4,5-diphenyl-1H-imidazole (Scheme 20), and evaluated for antitumor potential by using the tryphan blue dye exclusion technique against different cancer cell lines such as DLA and EAC at different concentration. The conclusion of antitumor potential was presented in (Table 20, Sharma et al. [40]).

### Antioxidant activity

Naureen et al. [41] synthesized 3-(4,5-diphenyl-1-(substituted phenyl)-1H-imidazol-2-yl)-substituted-2-(substituted phenyl)-1H-indole (Scheme 21) and evaluated for antioxidant potential by DPPH method using Quercetin as reference drug. Compound 61d shows the highest antioxidant activity as compared to others. The conclusion of antioxidant potential was presented in (Table 21, Naureen et al. [41]).

Rajasekaran et al. [42] synthesized (E)-(1H-benzo[d]imidazol-1-yl)(4-((substituted benzylidene)amino)phenyl)methanone (Scheme 22a), 2-(1H-benzo[d]

### Table 11 Antimicrobial activity of titled compounds (16a-b) Selvan et al. [33]

| Compounds | Zone of inhibition in mm | Antibacterial activity | Antifungal activity |
|-----------|--------------------------|------------------------|--------------------|
|           |                          | S. aureus (NCIM-2079)  | A. niger (NCIM-105) |
| 16a       |                         | 22                     | 18                 |
| 16b       |                         | 16                     | 20                 |
| Solvent   |                         | –                      | –                  |
| Ciprofloxacin |                | 35                     | –                  |
| Nystatin  |                         | –                      | 35                 |

Standard—Ciprofloxacin 5 mg/disc for bacteria. Nystatin 100 units/disc for fungi; Solvent-DMSO.
Scheme 12 Synthesis of 2-(chloroamino)-1-(2,4,5-triphenyl-1H-imidazol-1-yl)ethanone

Benzil + Benzaldehyde + NH$_4$OAc $\xrightarrow{\text{Reflux}}$ 2,4,5-triphenyl-1H-imidazole

2-(substitutedamino)-1-(2,4,5-triphenyl-1H-imidazol-1-yl)ethanone

(17a-17f)

Compounds 17a-f; R =

17a

17b

17c

17d

17e

17f

Scheme 12 Synthesis of 2-(chloroamino)-1-(2,4,5-triphenyl-1H-imidazol-1-yl)ethanone
imidazol-1-yl)-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide (Scheme 22b) and 1-(1H-benzo[d]imidazol-1-yl)-2-((substituted-1,3,4-oxadiazol-2-yl)thio)ethanone (Scheme 22c) and evaluated for antioxidant potential by using DPPH assay. All the synthesized derivatives showed good scavenging potential as compared to ascorbic acid (positive control) and the conclusion of activity was presented in (Table 22, Rajasekaran et al. [42]).

Subramaniam et al. [43] synthesized (Z)-3-(2-(5-(3-methyl benzylidene)-4-oxo-2-phenyl-4, 5-dihydro-1H-imidazol-1-yl) ethyl)-2-phenyl quinazolin-4(3H)-one derivatives (Scheme 23) and evaluated for antioxidant potential by using DPPH assay. These compounds showed good scavenging potential as compared to ascorbic acid (positive control). The conclusion of scavenging potential was presented in (Table 23, Subramaniam et al. [43]).

Katikireddy et al. [21] developed (E)-N’-(7-methyl-2-propyl-1H-benzo[d]imidazole-5-carbonyl) substituted formohydrasonoyl (Scheme 24) and evaluated for antioxidant activity using ascorbic acid as a reference drug.

| Compounds | Concentration (µg/mL) | Zone of inhibition (mm) |
|-----------|-----------------------|--------------------------|
|           |                       | S. aureus | E. coli | C. albicans |
| Gram positive | Gram negative |          |          |            |
| 17a       | 750                   | 9         | 10       | 9          |
|           | 500                   | 8         | 9        | 7          |
|           | 250                   | 5         | 6        | 5          |
| 17b       | 750                   | 16        | 15       | 15         |
|           | 500                   | 12        | 11       | 11         |
|           | 250                   | 10        | 8        | 9          |
| 17c       | 750                   | 26        | 25       | 21         |
|           | 500                   | 24        | 23       | 19         |
|           | 250                   | 20        | 19       | 18         |
| 17d       | 750                   | 15        | 16       | 17         |
|           | 500                   | 13        | 14       | 15         |
|           | 250                   | 11        | 10       | 12         |
| 17e       | 750                   | 17        | 13       | 19         |
|           | 500                   | 14        | 11       | 13         |
|           | 250                   | 12        | 9        | 10         |
| 17f       | 750                   | 9         | 10       | 15         |
|           | 500                   | 7         | 8        | 13         |
|           | 250                   | 5         | 6        | 10         |
| Ciprofloxacin | 750       | 27        | 28       | –          |
|           | 500                   | 26        | 27       | –          |
|           | 250                   | 24        | 25       | –          |
| Clofibrate | 750                   | –         | –        | 22         |
|           | 500                   | –         | –        | 20         |
|           | 250                   | –         | –        | 19         |
Scheme 13  Synthesis of benzimidazole-substituted-1,3-thiazolidin-4-ones

Reagents and conditions: (a) EtOH, ethyl chloroacetate, stirring, 24 h, (b) EtOH, NH₂NH₂ H₂O, reflux, (c) Aryl aldehyde, EtOH, glacial acetic acid, (d) Cinnamaldehyde, EtOH, glacial acetic acid, (e) 4-hydroxy-napthaldehyde, EtOH, glacial acetic acid, (f) Dioxane, thioglycollic acid, anhydrous zinc chloride, reflux
Table 13 MIC of benzimidazole-substituted-1,3-thiazolidin4-ones (18a-r) in µM/ml Yadav et al. [34]

| Compounds    | MIC (µM/ml) | S. aureus | B. subtilis | E. coli | C. albicans | A. niger |
|--------------|-------------|-----------|-------------|---------|-------------|---------|
| 18a          | 0.030       | 0.030     | 0.030       | 0.060   | 0.030       |         |
| 18b          | 0.060       | 0.030     | 0.030       | 0.030   | 0.030       |         |
| 18c          | 0.030       | 0.030     | 0.030       | 0.030   | 0.030       |         |
| 18d          | 0.028       | 0.014     | 0.028       | 0.028   | 0.028       |         |
| 18e          | 0.031       | 0.031     | 0.031       | 0.031   | 0.031       |         |
| 18f          | 0.030       | 0.030     | 0.030       | 0.030   | 0.030       |         |
| 18g          | 0.030       | 0.015     | 0.015       | 0.030   | 0.030       |         |
| 18h          | 0.031       | 0.031     | 0.031       | 0.031   | 0.031       |         |
| 18i          | 0.027       | 0.027     | 0.013       | 0.027   | 0.027       |         |
| 18j          | 0.029       | 0.029     | 0.015       | 0.007   | 0.029       |         |
| 18k          | 0.058       | 0.029     | 0.007       | 0.029   | 0.029       |         |
| 18l          | 0.028       | 0.028     | 0.028       | 0.028   | 0.028       |         |
| 18m          | 0.061       | 0.030     | 0.030       | 0.030   | 0.030       |         |
| 18n          | 0.031       | 0.031     | 0.008       | 0.031   | 0.031       |         |
| 18o          | 0.029       | 0.029     | 0.029       | 0.029   | 0.029       |         |
| 18p          | 0.027       | 0.027     | 0.027       | 0.027   | 0.027       |         |
| 18q          | 0.030       | 0.030     | 0.030       | 0.030   | 0.030       |         |
| 18r          | 0.028       | 0.028     | 0.028       | 0.028   | 0.028       |         |
| Norfloxacin  | 0.47        | 0.47      | 0.47        | –       | –           | 0.50    |
| Fluconazole  | –           | –         | –           | 0.50    | 0.50        |         |

Compound 64n shows the most potent antioxidant activity as compared to others and the results of activity were presented in (Table 24, Katikireddy et al. [21]).

Subhashini et al. [44] synthesized 4-((4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1-(2,3,4-trisubstituted phenyl)-1H-1,2,3-triazole derivatives (Scheme 25a, b) and evaluated for antioxidant activity by using four different methods such as Hydrogen peroxide scavenging, Nitric oxide scavenging, DPPH, and FRAP assay. The conclusion of antioxidant potential was presented in (Table 25a–d, Subhashini et al. [44]).

Antihypertensive activity
Navarrete-Vazquez et al. [45] synthesized 5-(trifluoromethyl)-2-(2,3,4-trisubstituted phenyl)-1H-benzo[d] imidazole and 5-nitro-2-(2,3,4-trisubstituted phenyl)-1H-benzo [d] Imidazole (Scheme 26) and evaluated for antihypertensive potential in SHR by using the tail-cuff method and the results of antihypertensive activity were summarized in (Table 26, Navarrete-Vazquez et al. [45]).

Hadizadeh et al. [46] synthesized 2-(2-(1H-imidazol-1-yl)ethyl)-4-(1-benzyl-2-(substituted thio)-1H-imidazol-5-yl)-5-(substituted carbonyl)-6-methyl-1, 4-dihydropyridine-3-substituted carboxylic acid (Scheme 27) and evaluated for antihypertensive potential in rats and the results of antihypertensive activity were summarized in (Table 27, Hadizadeh et al. [46]).

Goyal et al. [22] synthesized 2-substituted-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole derivatives (Scheme 28) and evaluated for antihypertensive potential and the
Antitubercular activity
Amini et al. [47] synthesized N3-(substituted phenyl)-N5-(substituted phenyl)-4-(4,5-dichloro-1H-imidazol-2-yl)-2-methyl-1, 4-dihydropyridine-3,5-dicarboxamide (Scheme 29) and evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* strain using rifampicin as reference drug. The conclusion of the antitubercular activity was presented in (Table 29, Amini et al. [47]).
Scheme 15 Synthesis of imidazole derivatives

Reagents and conditions: (i) Lactic acid, 4N HCl, Reflux (ii) permanganate, solid aluminium oxide, no solvent, r.t. 10 min, (iii) Benzaldehyde, 40% KOH, EtOH, r.t. 10 min, (iv) potassium carbonate, acetonitrile, reflux overnight
Table 15 Anticancer activity of titled compounds (21a-26d) against different cancer cell lines Hsieh et al. [25]

| Compounds | Cancer cells (IC<sub>50</sub> µM) |
|-----------|----------------------------------|
|           | A549    | MCF-7    | HEP-G2    | OVCAR-3    |
| 21a       | 119.3±29.9 | 13.49±0.16  | 24.2±0.32  | 16.91±0.37  |
| 21b       | 19.17±0.43 | 18.09±0.28  | 59.13±0.92  | 24.7±1.69  |
| 21c       | 17.41±0.16 | 16.04±0.24  | 140.85±0.88 | 16.09±0.39  |
| 21d       | 35.89±0.84 | 32.55±3.26  | 36.54±1.35  | 36.48±1.36  |
| 22a       | 12.47±0.18 | 12.12±0.10  | 15.44±0.25  | 16.09±0.39  |
| 22b       | 41.05±1.61 | 53.54±1.12  | 117.28±2.42 | 59.01±8.91  |
| 22c       | >314     | 254.9±13.6  | >314       | 299.52±9.27 |
| 22d       | 15.79±0.49 | 13.42±0.24  | 17.6±0.25  | 16.13±0.32  |
| 23a       | 10.3±0.13 | 9.65±0.06  | 10.16±0.08  | 10.5±0.10  |
| 23b       | 54.12±1.20 | 53.19±0.77  | 64.91±0.24  | 28.71±1.44  |
| 23c       | 56.21±0.96 | 56.09±0.14  | 36.61±1.89  | 11.4±0.24  |
| 23d       | 19.53±0.71 | 14.73±0.09  | 15.49±0.16  | 14.04±0.29  |
| 24a       | 10.73±0.58 | 9.73±0.16  | 10.33±0.06  | 10.34±0.19  |
| 24b       | 11.64±0.25 | 11.14±0.07  | 32.16±1.83  | 12.55±0.12  |
| 24c       | 22.36±0.54 | 21.12±0.53  | 58.74±0.75  | 13.29±0.47  |
| 24d       | 50.45±0.82 | 54.41±0.72  | 56.45±0.86  | 33.13±0.14  |
| 25a       | 14.59±1.20 | 10.38±0.08  | 36.13±0.75  | 22.44±0.47  |
| 25b       | 10.76±0.29 | 10.15±0.06  | 42.05±0.91  | 16.32±0.45  |
| 25c       | 10.27±0.15 | 11.12±0.20  | 50.24±0.88  | 14.88±0.67  |
| 25d       | 24.06±0.08 | 22.93±0.49  | 21.38±0.68  | 0.1422±0.33 |
| 26a       | 9.73±0.07 | 8.91±0.07  | 10.93±0.10  | 10.76±0.12  |
| 26b       | 11.79±0.27 | 11.34±0.17  | 47.88±0.76  | 13.76±0.27  |
| 26c       | 16.92±0.61 | 11.93±0.14  | 32.92±0.38  | 13.4±0.33  |
| 26d       | 81.48±1.40 | 35.69±0.47  | 95.7±2.44  | 42.2±2.43  |
| DOX       | 0.46±0.01 | 0.42±0.01  | 0.72±0.01  | 3.95±0.09  |
| Cisplatin | 7.31±0.44 | 11.7±0.12  | 3.97±0.04  | 16.04±0.74  |

Pandey et al. [48] synthesized (E)-3-(4-(7-substituted-3-(substituted amino)imidazo[1,2-a]pyridin-2-yl)phenyl)-1-(substituted phenyl)prop-2-en-1-one (Scheme 30) and evaluated for anti-tubercular potential against Mycobacterium tuberculosis strain by MB 7H10 agar medium using Ethambutol and Pyrazinamide as a reference drug. The conclusion of the activity was presented in (Table 30, Pandey et al. [48]).

Makwane et al. [49] synthesized 10-(2-(substituted phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-10H-phe-nothiazine by using (L.J) agar method against Mycobacterium tuberculosis H37Rv strain using Isoniazid as reference drug and MIC values of these derivatives were calculated. The conclusion of anti-tubercular activity was presented in (Table 31, Makwane et al. [49]).

Nandha et al. [23] synthesized 2-((1H-imidazol-1-yl) methyl)-6-substituted-5-fluoro-1H-benzo[d]imidazole (Scheme 32) and evaluated for anti-tubercular activity against Mycobacterium tuberculosis strain by MABA assay using Isoniazid as a reference drug. The antitubercular activity by (L.J) agar method against Mycobacterium tuberculosis H37Rv strain using Isoniazid as reference drug and MIC values of these derivatives were calculated. The conclusion of anti-tubercular activity was presented in (Table 31, Pandey et al. [48]).
Scheme 16  Synthesis of 2-(5-butyl-3-chloro-1H-pyrrol-2-yl)-1H-benzo[d]imidazole (27a-j)

Table 16 IC₅₀ values of the synthesized compounds (27a-j) Roopashree et al. [36]

| Compounds | R-X-S     | R(6)       | IC₅₀(µM) ± SD |
|-----------|-----------|------------|--------------|
| 27a       | CH₃I      | CH₃        | > 50         |
| 27b       | EtBr      | Et         | > 50         |
| 27c       | CH₃(CH₂)₂CH₂Br | CH₃(CH₂)₂CH₂ | > 50         |
| 27d       | CH₃(CH₂)₃CH₂Br | CH₃(CH₂)₃CH₂ | 25.3 ± 4.18  |
| 27e       | 3-MeC₆H₄CH₂Br | 3-MeC₆H₄CH₂ | 30.2 ± 2.27  |
| 27f       | 3-MeOC₆H₄CH₂Br | 3-MeOC₆H₄CH₂ | > 50         |
| 27g       | 4-ClC₆H₄CH₂Br | 4-ClC₆H₄CH₂ | > 50         |
| 27h       | 3,4-Cl₂C₆H₄CH₂Br | 3,4-Cl₂C₆H₄CH₂ | 31.9 ± 4.77  |
| 27i       | 4-FC₆H₄CH₂Br | 4-FC₆H₄CH₂ | 30.0 ± 5.12  |
| 27j       | C₆H₅CH₂Br   | C₆H₅CH₂    | > 50         |
| Sorafenib |           |            | 4.1 ± 0.9    |

SD Standard deviation, IC₅₀ Inhibitory concentration 50%
Scheme 17 Synthesis of 2-substituted-1-(3,4,5-trimethoxyphenyl)-1H-imidazole

Reagents and conditions: (a) 1-bromo-3,4,5-trimethoxybenzene, Cs₂CO₃, CuI, DMF, 120°C, 40 h (b) NBS, CH₃CN (c) PdCl₂ (DPPF), ArB(OH)₂, CsF, 1,4-dioxane, 65°C
Table 17 Antitumor activity of the synthesized compounds (28a-q) Romangoli et al. [37]

| Compounds | IC$_{50}$ (µM) | HeLa     | HT-29      | A549       | MCF-7     | Jurkat   | RS4-11    | HL-60     |
|-----------|---------------|----------|------------|------------|-----------|----------|-----------|-----------|
| 28a       | 1260 ± 172    | 1915 ± 354 | 4733 ± 328 | 2800 ± 721 | 760 ± 136 | > 10,000 | 2100 ± 252 |
| 28b       | 1985 ± 126    | 1400 ± 200 | 7000 ± 1153 | 2090 ± 374 | 7569 ± 758 | 5678 ± 259 | 4800 ± 451 |
| 28c       | 337 ± 48      | 330 ± 36  | 5600 ± 352 | 1363 ± 349.8 | 407 ± 24 | 800 ± 58 | 333 ± 41 |
| 28d       | 51 ± 6.5      | 112 ± 15  | 121 ± 56  | 74 ± 17 | 90 ± 23 | 217 ± 46 | 29 ± 9.5 |
| 28e       | 263 ± 39      | 647 ± 83  | 2600 ± 422 | 666 ± 231 | 365 ± 25 | 715 ± 148 | 413 ± 14 |
| 28f       | 330 ± 25      | 377 ± 83  | 4717 ± 509 | 509 ± 25 | 136 ± 38 | 475 ± 106 | 195 ± 27 |
| 28g       | 623 ± 98      | > 10,000 | > 10,000  | > 10,000  | 4933 ± 536 | 2567 ± 784 | > 10,000  |
| 28h       | 9157 ± 1593   | > 10,000 | > 10,000  | > 10,000  | > 10,000  | > 10,000  | 3466 ± 467 |
| 28i       | > 10,000      | > 10,000  | > 10,000  | > 10,000  | > 10,000  | > 10,000  | 3933 ± 517 |
| 28j       | > 10,000      | > 10,000  | > 10,000  | > 10,000  | 6633 ± 338 | > 10,000  | > 10,000  |
| 28k       | 3.7 ± 0.12    | 1.8 ± 0.8 | 1.9 ± 1.0  | 1.5 ± 0.2 | 1.2 ± 0.5 | 34.7 ± 0.0 | 4.8 ± 1.9 |
| 28l       | > 10,000      | > 10,000  | > 10,000  | > 10,000  | > 10,000  | > 10,000  | > 10,000  |
| 28m       | > 10,000      | > 10,000  | > 10,000  | > 10,000  | > 10,000  | > 10,000  | > 10,000  |
| 28n       | 1.5 ± 0.32    | 7.5 ± 1.2 | 14 ± 2.3   | 3.4 ± 0.38 | 12 ± 0.6 | 6.8 ± 1.1 | 3.5 ± 0.73 |
| 28o       | 3.8 ± 0.7     | 0.4 ± 0.06 | 0.57 ± 0.17 | 0.7 ± 0.06 | 0.9 ± 0.2 | 1.2 ± 0.7 | 1.8 ± 0.6 |
| 28p       | 48 ± 2.5      | 174 ± 16  | 228 ± 81  | 69 ± 7.0 | 127 ± 27 | 85 ± 20 | 12 ± 2.5 |
| 28q       | 2.9 ± 0.8     | 15 ± 1.3  | 63 ± 18.1 | 1.7 ± 0.6 | 42 ± 3.9 | 91 ± 8.9 | 63.0 ± 17.6 |
| CA-4      | 4 ± 1         | 180 ± 30  | 3100 ± 100 | 5 ± 0.6  | 0.8 ± 0.2 | 370 ± 100 | 1 ± 0.2 |

Conclusion of anti-tubercular activity was presented in (Table 32, Nandha et al. [23]).

Nandha et al. [50] synthesized 6-(benzo[d][1,3]dioxol-5-yloxy)-2-substituted-5-fluoro-1H-benzo[d] imidazole (Scheme 33) and evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* (ATCC27294) by MABA assay using streptomycin, ciprofloxacin, and pyrazinamide as a reference drug. The conclusion of the activity was presented in (Table 33, Nandha et al. [50]).

Gising et al. [51] synthesized 2,5-disubstituted-4-(6-methoxynaphthalen-2-yl)-1H-imidazole by using (Scheme 34). The anti-tubercular potential of these derivatives was evaluated against *Mycobacterium tuberculosis* strain and MIC values of these derivatives were calculated. The conclusion of anti-tubercular activity was presented in (Table 34, Gising et al. [51]).

Syed et al. [52] synthesized 6-(4-substituted phenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)imidazo [2,1-b][1,3,4] thiadiazole (Scheme 35) and evaluated for anti-tubercular potential against *Mycobacterium tuberculosis* strain. Compounds 80a, 80b, 81a, 82a, and 83a showed the most potent anti-tubercular activity as compared to others. The conclusion of anti-tubercular activity was presented in (Table 35, Syed et al. [52]).
Scheme 18 Synthesis of 1-substituted-2-(5-substituted-1-phenyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazole and 4-(1-chloro-1H-benzo[d]imidazole-2-yl)-6-fluoropyrimidin-2-amine

1-(1-substituted-1H-benzo[d]imidazol-2-yl)ethanone

\[ R = H \]
\[ R = \text{CH}_3 \]

EtOH, KOH \[ \rightarrow \] \( R_1 \)-CHO

(Z)-1-(1-substituted-1H-benzo[d]imidazo 1-2-yl)-3-substitutedprop-2-en-1-one

C\(_6\)H\(_5\)NHNHNH\(_2\)
C\(_2\)H\(_5\)OH \[ \rightarrow \]

1-substituted-2-(5-substituted-1-phenyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazole

\((30\text{a-j})\)

\[ R = \text{H} \]
\[ R = \text{CH}_3 \]

4-(1-substituted-1H-benzo[d]imidazol-2-yl)-6-substitutedpyrimidin-2-amine

\((29\text{a-j})\)
Table 18 (a) IC₅₀ of the titled compounds (29a-j) against of MCF-7 and CaCo-2 cell line—benzo [d] imidazole pyrimidine derivatives; (b) IC₅₀ of the titled compounds (30a-j) against of MCF-7 and CaCo-2 cell line—benzo [d] imidazole pyrazole derivatives Rajendran et al. [38]

| Compounds | Substituent R | Substituent R₁ | Molecular formula | IC₅₀ ± SD (µM) |
|-----------|--------------|----------------|-------------------|----------------|
|           |              |                |                   | MCF-7          | CaCo-2         |
| (a)       |              |                |                   |                |
| 29a       | H            | [苯基]         | C₁₁H₁₁N₅          | 8.22 ± 1.48    | 5.67 ± 1.25    |
| 29b       | H            | [吡啶]         | C₁₆H₁₂N₆          | 10.43 ± 1.45   | 9.56 ± 1.33    |
| 29c       | H            | [甲氧基]        | C₁₉H₁₇N₅O₂        | > 30           | 28.40 ± 2.48   |
| 29d       | H            | [氯]           | C₁₈H₁₄ClN₅O      | 13.05 ± 2.07   | 12.33 ± 1.80   |
| 29e       | H            | [甲基]          | C₂₅H₁₇N₅          | > 30 ± 2.87    | > 30 ± 2.98    |
| 29f       | CH₃          | [苯基]         | C₁₈H₁₃N₅          | > 30 ± 2.66    | > 30 ± 2.43    |
| 29g       | CH₃          | [苯基]         | C₁₉H₁₄N₆          | 18.56 ± 2.82   | 16.23 ± 1.24   |
| 29h       | CH₃          | [氯]           | C₁₉H₁₅ClN₅O      | > 30 ± 2.19    | 25.50 ± 2.74   |
| 29i       | CH₃          | [氯]           | C₂₀H₁₉N₅O₂        | 25.11 ± 2.44   | 21.89 ± 2.35   |
| 29j       | CH₃          | [甲基]          | C₂₆H₁₉N₅          | > 30 ± 2.80    | > 30 ± 2.06    |
| Fluorouracil |       |                |                   | 7.26 ± 2.30    | 5.23 ± 2.36    |
|   |   |   |   |   |
|---|---|---|---|---|
| 30a | H | C_{22}H_{16}N_{4} | 22.65 ± 2.32 | 28.45 ± 2.59 |
| 30b | H | C_{21}H_{15}N_{5} | 12.79 ± 2.20 | 9.788 ± 1.48 |
| 30c | H | C_{13}H_{13}ClN_{4}O | > 30 ± 2.86 | > 30 ± 2.48 |
| 30d | H | C_{24}H_{20}N_{4}O_{2} | 15.34 ± 2.67 | 13.27 ± 1.56 |
| 30e | H | C_{30}H_{20}N_{4} | > 30 ± 2.52 | > 30 ± 2.33 |
| 30f | CH_{3} | C_{33}H_{18}N_{4} | > 30 ± 2.41 | > 30 ± 2.69 |
| 30g | CH_{3} | C_{22}H_{17}N_{5} | 19.04 ± 2.56 | 17.32 ± 2.27 |
| 30h | CH_{3} | C_{24}H_{19}ClN_{4}O | > 30 ± 2.38 | 29.76 ± 2.64 |
| 30i | CH_{3} | C_{25}H_{22}N_{4}O_{2} | 21.73 ± 2.46 | 18.35 ± 2.54 |
| 30j | CH_{3} | C_{31}H_{22}N_{4} | > 30 ± 2.58 | > 30 ± 2.62 |

Fluorouracil

7.26 ± 2.30

5.23 ± 2.36
**Scheme 19**

**a** Synthesis of substituted Schiff base; **b** Synthesis of substituted imidazole derivatives; c. Synthesis of substituted phenyl imidazole pyridine derivatives

**Reagents and conditions:** Ethanol, reflux, 3 hr.

**Reagents and conditions:** (i) p-toluenesulfonyl methylisocyanide, $K_2CO_3$, DMF, 36 hr

**Scheme 19 a** Synthesis of substituted Schiff base, **b** Synthesis of substituted imidazole derivatives, c. Synthesis of substituted phenyl imidazole pyridine derivatives
Scheme 19 continued

Reagents and conditions: (i) EtOH, 10 min, CuSO$_4 \cdot 5$H$_2$O, D-glucose, reflux, 10hr

| 49, 54, 59 | R$_1$, R$_2$, R$_3$ = H  
| 50, 55 | R$_1$ = CH$_3$, R$_2$, R$_3$ = H  
| 51, 56 | R$_2$ = CH$_3$, R$_1$, R$_3$ = H  
| 52, 57 | R$_1$ = Cl, R$_2$, R$_3$ = H  
| 53, 58 | R$_3$ = CH$_3$, R$_1$, R$_2$ = H |
Table 19  Anticancer activity of the synthesized derivatives (31–59) against three different cancer cell lines Meenakshisundaram et al. [39]

| Compounds | HeLa | MDA-MB-231 | ACHN |
|-----------|------|-------------|------|
|           | IC₅₀ (μM) | TGI (μM) | GI₅₀ (μM) | IC₅₀ (μM) | TGI (μM) | GI₅₀ (μM) | IC₅₀ (μM) | TGI (μM) | GI₅₀ (μM) |
| 31        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 32        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 33        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 34        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 35        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 36        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 37        | > 10 | 9.47 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 38        | > 10 | 9.79 | 8.23 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 39        | > 10 | 9.67 | > 10 | > 10 | 8.45 | > 10 | > 10 | > 10 | > 10 |
| 40        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 41        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 42        | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |
| 43        | > 10 | 9.76 | 4.23 | > 10 | > 10 | 5.14 | > 10 | > 10 | 8.24 |
| 44        | > 10 | 9.76 | 1.86 | > 10 | > 10 | 1.16 | > 10 | > 10 | 3.78 |
| 45        | > 10 | > 10 | > 10 | > 10 | > 10 | 6.88 | > 10 | > 10 | 9.88 |
| 46        | > 10 | 9.76 | 6.85 | > 10 | > 10 | 4.26 | > 10 | > 10 | 7.15 |
| 47        | > 10 | > 10 | > 10 | > 10 | > 10 | 1.20 | > 10 | > 10 | 2.24 |
| 48        | > 10 | > 10 | > 10 | > 10 | > 10 | 1.90 | > 10 | > 10 | 3.86 |
| 49        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.43 | > 10 | > 10 | 0.55 |
| 50        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.88 | > 10 | > 10 | 1.16 |
| 51        | > 10 | > 10 | > 10 | > 10 | > 10 | 2.05 | > 10 | > 10 | 1.90 |
| 52        | > 10 | 3.73 | 5.24 | > 10 | > 10 | 4.50 | > 10 | > 10 | 7.72 |
| 53        | > 10 | 9.76 | 0.96 | > 10 | > 10 | 1.30 | > 10 | > 10 | 1.32 |
| 54        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.30 | > 10 | > 10 | 0.38 |
| 55        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.65 | > 10 | > 10 | 0.98 |
| 56        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.58 | > 10 | > 10 | 0.85 |
| 57        | > 10 | 9.74 | 4.00 | > 10 | > 10 | 1.60 | > 10 | > 10 | 1.82 |
| 58        | > 10 | 9.76 | 0.73 | > 10 | > 10 | 1.59 | > 10 | > 10 | 0.62 |
| 59        | > 10 | > 10 | > 10 | > 10 | > 10 | 0.51 | > 10 | > 10 | 0.58 |
| Adriamycin | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 | > 10 |

GI₅₀: Concentration of drug causing 50% inhibition of cell growth
IC₅₀: Concentration of drug causing 50% cell kill
TGI: Concentration of drug causing total inhibition of cell growth
Italic values indicate the activity best compounds
Inhibitory activity was expressed in micromolar
Scheme 20

Synthesis of 1,2-disubstituted-4,5-diphenyl-1H-imidazole

Reagents and conditions:-(a) Conc. AcOH, Reflux 7hr. MW; Activated silica gel, 1000 W, 8 min
(b) Ammonium acetate, conc: Reflux 12 hr. MW; 1000 W, 13-16 min.

1,2-disubstituted-4,5-diphenyl-1H-imidazole

(60a–60j)
Table 20  Antitumor activity of the synthesized derivatives (60a-j) Sharma et al. [40]

| Compounds | Substituent R | Substituent R’ | DLA cells CTC<sub>50</sub> µg/mL | EAC cells CTC<sub>50</sub> µg/mL |
|-----------|--------------|----------------|----------------------------------|----------------------------------|
| 60a       | \(-\text{NH}\) | \(-\text{Me}\)  | 190.26                           | 60.50                            |
| 60b       | \(-\text{NH}\) | \(-\text{OH}\)  | 114.00                           | 240.00                           |
| 60c       | \(-\text{NH}\) | \(-\text{NCH}_{3}\) | 98.56                           | 31.25                            |
| 60d       | \(-\text{NH}\) | \(-\text{Cl}\)  | 309.67                           | 200.22                           |
| 60e       | \(-\text{COOH}\) | \(-\text{NO}_{2}\) | >500                             | 489.34                           |
| 60f       | \(-\text{COOH}\) | \(-\text{Cl}\)  | 207.60                           | 115.31                           |
| 60g       | \(-\text{COOH}\) | \(-\text{Cl}\)  | 238.50                           | 31.25                            |
| 60h       | \(-\text{COOH}\) | \(-\text{OH}\)  | >500                             | >500                             |
| 60i       | \(-\text{OH}\)  | \(-\text{Cl}\)  | 405.68                           | 305.91                           |
| 60j       | \(-\text{OH}\)  | \(-\text{Cl}\)  | 150.26                           | 94.63                            |

CTCs The cytotoxic concentration (which inhibited 50% of total cells)
Scheme 21  Synthesis of 3-(4,5-diphenyl-1-(substitute phenyl)-1H-imidazol-2-yl)-substituted-2-(substituted phenyl)-1H-indole (61a-j)

Table 21  Antioxidant activity of the synthesized derivatives (61a-j)  Naureen et al. [41]

| Compounds | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | Antioxidant activity |
|-----------|-------------|-------------|-------------|----------------------|
|           |             |             |             | Inhibition (%) at 0.5 mM | IC<sub>50</sub> (µM) |
| 61a       | H           | Cl          | CH<sub>3</sub> | 62.58 ± 0.7            | 175.26 ± 1.24 |
| 61b       | H           | Cl          | Br          | 71.74 ± 0.2            | 146.27 ± 1.09 |
| 61c       | Br          | H           | F           | 71.87 ± 0.5            | 181.26 ± 1.1  |
| 61d       | H           | Br          | CH<sub>3</sub> | 90.39 ± 0.5            | 148.26 ± 1.2  |
| 61e       | H           | Br          | Cl          | 20.97 ± 0.5            | –             |
| 61f       | H           | CH<sub>3</sub> | H          | 67.61 ± 0.3            | 162.27 ± 1.2  |
| 61g       | H           | CH<sub>3</sub> | CH<sub>3</sub> | 44.21 ± 0.7            | –             |
| 61h       | H           | CH<sub>3</sub> | Br          | 7.11 ± 0.2             | –             |
| 61i       | H           | CH<sub>3</sub> | F           | 18.91 ± 0.6            | –             |
| 61j       | H           | CH<sub>3</sub> | OCH<sub>3</sub> | 23.03 ± 0.5            | –             |
| Thiourea  | –           | –           | –           | –                     | –             |
| Quercetin | –           | –           | –           | 93.21 ± 0.9            | 16.96 ± 0.1  |
Scheme 22  

a Synthesis of (E)-(1H-benzo[d]imidazole-1-yl)(4-(substituted benzylidene)amino)phenyl)methanone. 
b Synthesis of 2-(1H-benzo[d]imidazole-1-yl)-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide. 
c Synthesis of substituted imidazole linked 1,3,4-oxadiazole derivatives
Table 22  Antioxidant activity of the synthesized compounds (62a-f) Rajasekaran et al. [42]

| Compounds | % Inhibition |
|-----------|-------------|
|           | 10 µg/ml    | 20 µg/ml | 30 µg/ml | 40 µg/ml |
| 62a       | 7.20        | 12.30    | 37.65    | 39.42    |
| 62b       | 34.77       | 34.66    | 37.65    | 39.42    |
| 62c       | 7.08        | 15.61    | 21.04    | 22.26    |
| 62d       | 17.71       | 29.34    | 30.34    | 40.86    |
| 62e       | 34.77       | 37.76    | 47.17    | 52.16    |
| 62f       | 18.98       | 24.67    | 28.90    | 34.34    |
| Ascorbic acid | 56.03    | 58.80    | 65.33    | 68.55    |

Scheme 23  Synthesis of (Z)-3-(2-(5-(benzylidene)-4-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)ethyl)-2-phenylquinazolin-4(3H)-one (63a-e) and 3-(3-mercapto-5-(substituted phenyl)-4H-1,2,4-triazol-4-yl)-2-phenylquinazolin-4(3H)-one (63f-h)
| Compounds | Concentration (μg/ml) | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
|-----------|-----------------------|----|----|----|----|----|----|----|----|----|----|
| 63a       |                       | 2.54 | 8.47 | 14.61 | 20.97 | 27.86 | 33.36 | 42.37 | 45.12 | 51.58 | 56.25 |
| 63b       |                       | 2.11 | 10.06 | 19.17 | 29.34 | 33.15 | 40.57 | 48.62 | 52.43 | 62.5 | 69.70 |
| 63c       |                       | 1.80 | 10.48 | 17.05 | 25.42 | 33.30 | 40.57 | 48.19 | 55.82 | 65.36 | 71.61 |
| 63d       |                       | 1.37 | 7.41 | 15.14 | 20.65 | 27.33 | 33.89 | 39.72 | 47.35 | 51.37 | 59.42 |
| 63e       |                       | 1.80 | 6.88 | 14.83 | 21.29 | 27.22 | 33.47 | 40.25 | 47.98 | 51.48 | 57.83 |
| 63f       |                       | 7.94 | 21.5 | 34.32 | 46.29 | 59.11 | 71.61 | 84.53 | 97.35 | 97.98 | 98.83 |
| 63g       |                       | 12.71 | 27.54 | 40.99 | 55.40 | 73.83 | 84.21 | 93.53 | 94.91 | 95.65 | 96.71 |
| 63h       |                       | 10.91 | 22.77 | 37.07 | 51.16 | 65.14 | 68.32 | 89.72 | 92.37 | 92.69 | 95.85 |
| Standard  | Concentration (μg/ml) | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 |
| Ascorbic acid |                   | 8.76 | 15.34 | 26.08 | 37.65 | 41.23 | 59.29 | 67.43 | 76.53 | 80.21 | 87.76 |
Scheme 24  Synthesis of \((E)-N'-(7\text{-methyl-2-propyl-1H-benzo[}d\text{]imidazole-5-carbonyl})\text{substituted formohydranonoyl (64a-r)}

**Compounds Ar**

\begin{align*}
64a &= C_6H_5  \\
64b &= 4\text{-OCH}_3C_6H_4  \\
64c &= 2\text{-OHC}_6H_4  \\
64d &= 3\text{-ClC}_6H_4  \\
64e &= 3\text{-BrC}_6H_4  \\
64f &= 3\text{-OCH}_3C_6H_4  \\
64g &= 3,4\text{-}(OCH}_3)_3C_6H_3  \\
64h &= 4\text{-CNC}_6H_4  \\
64i &= 2\text{-furyl}  \\
64j &= 2\text{-thienyl}  \\
64k &= 1\text{-napthyl}  \\
64l &= 2\text{-CH}_3C_6H_4  \\
64m &= 4\text{-NO}_2C_6H_4  \\
64n &= 5\text{-Br,2-OHC}_6H_3  \\
64o &= 2,4\text{-}(Cl)_2C_6H_3  \\
64p &= 3,5\text{-Cl}_2,2\text{-OHC}_6H_2  \\
64q &= 4\text{-OH C}_6H_4  \\
64r &= 4\text{-OH,3-OCH}_3C_6H_3
\end{align*}

**Reagents and conditions:** (i) \(Na_2S_2O_4, H_2O\), reflux. 4 h (ii) \(N_2H_4\cdot H_2O\), ethanol, reflux, 10 h (iii) \(Ar\text{-CHO}, gla. AcOH, MeOH\), reflux, 4-6 h.

**Scheme 24**  Synthesis of \((E)-N'-(7\text{-methyl-2-propyl-1H-benzo[}d\text{]imidazole-5-carbonyl})\text{substituted formohydranonoyl}

Patel et al. [53] synthesized 6-(substituted phenyl)-2-(1-methyl-1H-imidazol-2-yl) imidazo [2,1-b] [1,3,4] thiadiazole (Scheme 36) and evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* and MIC values of these derivatives were calculated. The conclusion of anti-tubercular activity was presented in (Table 36, Patel et al. [53]).

Yadav et al. [54] synthesized 2-((1-benzoyl-1H-benzo[d] imidazol-2-yl) thio)-N-(substituted phenyl) acetamide (Scheme 37) and evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* strain and MIC values of these derivatives were calculated. Streptomycin was used as a reference drug and the results of anti-tubercular activity were presented in (Table 37, Yadav et al. [54]).

**Conclusion**

In this present review article, we have summarized different pharmacological activities of 1,3-diazole containing compounds. From this study, we have found that 1,3-diazole containing compounds can be synthesized by various kinds of synthetic routes, and these derivatives having a wide range of biological activities such as antitumor, antitubercular, antimicrobial, antihypertensive and

| Compounds | IC$_{50}$ (μg/ml) |
|-----------|------------------|
| 64a       | 49.28 ± 3.03     |
| 64b       | 32.17 ± 2.87     |
| 64c       | 29.10 ± 1.60     |
| 64d       | 18.31 ± 1.38     |
| 64e       | 26.81 ± 2.10     |
| 64f       | 29.96 ± 2.81     |
| 64g       | 24.79 ± 3.03     |
| 64h       | 30.83 ± 2.93     |
| 64i       | 23.19 ± 1.72     |
| 64j       | 30.08 ± 2.60     |
| 64k       | 20.05 ± 1.27     |
| 64l       | 25.97 ± 2.18     |
| 64m       | 13.60 ± 1.37     |
| 64n       | 9.40 ± 1.04      |
| 64o       | 12.39 ± 1.26     |
| 64p       | 16.27 ± 1.39     |
| 64q       | 24.70 ± 2.29     |
| 64r       | 38.28 ± 3.07     |
| Ascorbic acid | 7.50 ± 0.89 |
Scheme 25  a Synthesis of 4-((4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1-(2, 3, 4-trisubstituted phenyl)-1H-1,2,3-triazole; b Synthesis of 4-((4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)methyl)-1-(2, 3, 4-trisubstituted phenyl)-1H-1,2,3-triazole
Table 25 (a) DPPH radical scavenging activity of (65a-h) and (66a-h); (b) Hydrogen peroxide radical scavenging activity of (65a-h) and (66a-h); (c) Nitric oxide radical scavenging activity of (65a-h) and (66a-h); (d) FRAP oxide radical scavenging activity of (65a-h) and (66a-h) Subhashini et al. [44]

| Compounds | Concentration | 10 μg/ml | 50 μg/ml | 100 μg/ml | 250 μg/ml |
|-----------|---------------|----------|----------|-----------|-----------|
| (a)       |               |          |          |           |           |
| 65a       |               | 57       | 71       | 81        | 94        |
| 65b       |               | 49       | 55       | 59        | 63        |
| 65c       |               | 42       | 53       | 65        | 69        |
| 65d       |               | 53       | 59       | 64        | 93        |
| 65e       |               | 35       | 42       | 55        | 63        |
| 65f       |               | 44       | 61       | 79        | 90        |
| 65g       |               | 41       | 49       | 53        | 61        |
| 65h       |               | 67       | 75       | 83        | 91        |
| 66a       |               | 55       | 63       | 71        | 87        |
| 66b       |               | 60       | 69       | 76        | 89        |
| 66c       |               | 69       | 78       | 81        | 95        |
| 66d       |               | 48       | 67       | 79        | 85        |
| 66e       |               | 71       | 79       | 85        | 96        |
| 66f       |               | 33       | 44       | 55        | 61        |
| 66g       |               | 41       | 47       | 59        | 62        |
| 66h       |               | 66       | 74       | 81        | 90        |
| Standard  |               | 85       | 89       | 93        | 97        |
| (b)       |               |          |          |           |           |
| 65a       |               | 49       | 67       | 75        | 87        |
| 65b       |               | 59       | 73       | 81        | 92        |
| 65c       |               | 40       | 49       | 55        | 57        |
| 65d       |               | 47       | 65       | 72        | 89        |
| 65e       |               | 31       | 43       | 49        | 56        |
| 65f       |               | 52       | 73       | 81        | 92        |
| 65g       |               | 35       | 43       | 51        | 63        |
| 65h       |               | 57       | 68       | 75        | 88        |
| 66a       |               | 51       | 63       | 78        | 91        |
| 66b       |               | 54       | 71       | 82        | 90        |
| 66c       |               | 71       | 88       | 91        | 96        |
| 66d       |               | 57       | 73       | 85        | 94        |
| 66e       |               | 37       | 45       | 52        | 59        |
| 66f       |               | 65       | 78       | 86        | 94        |
| 66g       |               | 38       | 45       | 53        | 55        |
| 66h       |               | 57       | 65       | 78        | 86        |
| Standard  |               | 83       | 91       | 95        | 98        |
| (c)       |               |          |          |           |           |
| 65a       |               | 49       | 55       | 63        | 78        |
| 65b       |               | 54       | 69       | 75        | 89        |
| 65c       |               | 31       | 37       | 44        | 51        |
| 65d       |               | 56       | 68       | 79        | 85        |
| 65e       |               | 29       | 36       | 41        | 47        |
| 65f       |               | 48       | 56       | 67        | 74        |
| 65g       |               | 23       | 32       | 39        | 43        |
| 65h       |               | 61       | 77       | 86        | 95        |
|     | 66a | 65   | 75   | 82   | 89   |
|-----|-----|------|------|------|------|
| 66b | 57  | 69   | 79   |      | 87   |
| 66c | 68  | 79   | 88   |      | 91   |
| 66d | 57  | 68   | 75   |      | 88   |
| 66e | 25  | 37   | 42   |      | 46   |
| 66f | 48  | 55   | 67   |      | 78   |
| 66g | 21  | 27   | 33   |      | 39   |
| 66h | 67  | 65   | 77   |      | 86   |
| Standard | 81 | 86   | 91   |      | 96   |

|     | 65a | 64   | 78   |      | 87   |
|-----|-----|------|------|------|------|
| 65b | 51  | 67   | 79   |      | 93   |
| 65c | 31  | 39   | 43   |      | 47   |
| 65d | 63  | 77   | 83   |      | 92   |
| 65e | 22  | 27   | 32   |      | 38   |
| 65f | 57  | 68   | 77   |      | 85   |
| 65g | 27  | 33   | 40   |      | 45   |
| 65h | 49  | 58   | 69   |      | 87   |
| 66a | 56  | 63   | 75   |      | 89   |
| 66b | 49  | 58   | 67   |      | 85   |
| 66c | 65  | 71   | 84   |      | 97   |
| 66d | 64  | 79   | 86   |      | 91   |
| 66e | 30  | 37   | 45   |      | 50   |
| 66f | 45  | 53   | 62   |      | 85   |
| 66g | 31  | 39   | 42   |      | 48   |
| 66h | 60  | 69   | 78   |      | 87   |
| Standard | 88 | 92   | 95   |      | 99   |
Scheme 26 Synthesis of 5-(trifluoromethyl)-2-(2,3,4-trisubstituted phenyl)-1H-benzo[d] imidazole and 5-nitro-2-(2,3,4-trisubstituted phenyl)-1H-benzo[d]imidazole

Reagents and conditions: (i) H₂, Ni-Raney, EtOH, (ii) Na₂S₂O₅, DMF, reflux, (iii) Na₂S₂O₅, DMF, reflux, mw, 70°C

Table 26 Antihypertensive activity of the synthesized derivatives (67a-o) in SHR Navarrete-Vázquez et al. [45]

| Compounds | R1  | R2  | R3  | R4  | Ex vivo vasorelaxant effect |
|-----------|-----|-----|-----|-----|---------------------------|
|           |     |     |     |     | With endothelium (+E)               |
|           |     |     |     |     | EC₅₀ (μM) | Eₘₐₓ (%) |
| 67a       | −CF₃| −H  | −H  | −H  | 369.37 ± 10.2  | 91.2 ± 1.18 |
| 67b       | −CF₃| −OMe| −H  | −H  | 210.33 ± 11.3  | 75.14 ± 33.5 |
| 67c       | −CF₃| −OEt| −H  | −H  | 548.5 ± 27.8    | 90.97 ± 2.30 |
| 67d       | −CF₃| −NO₂| −H  | −H  | 3.18 ± 0.30     | 93.16 ± 3.52 |
| 67e       | −CF₃| −H  | −H  | −OH | 219.20 ± 14.1   | 51.15 ± 20.6 |
| 67f       | −CF₃| −H  | −H  | −OPr| 524.49 ± 25.4   | 51.0 ± 7.33  |
| 67g       | −CF₃| −H  | −H  | −N (Me)₂| 550.27 ± 30.1  | 63.2 ± 4.81  |
| 67h       | −CF₃| −H  | −OMe| −OH | 34.84 ± 5.43    | 99.55 ± 1.23 |
| 67i       | −CF₃| −H  | −OCH₂O| −   | 38.53 ± 2.35    | 101.17 ± 5.83 |
| 67j       | NO₂ | −H  | −H  | −H  | 4.93 ± 0.30     | 73.82 ± 5.37 |
| 67k       | NO₂ | −OEt| −H  | −H  | 3.71 ± 0.10     | 84.82 ± 3.73 |
| 67l       | NO₂ | −OPr| −H  | −H  | 4.89 ± 0.29     | 80.71 ± 9.41 |
| 67m       | NO₂ | −H  | −OMe| −OH | 1.81 ± 0.08     | 91.74 ± 2.35 |
| 67n       | NO₂ | −H  | −OMe| −OMe| 2.5 ± 0.10      | 75.0 ± 9.35  |
| 67o       | NO₂ | −OMe| −OMe| −OMe| 3.23 ± 0.20     | 90.0 ± 4.56  |
| Pimobendan |     |     |     |     | 4.67 ± 0.83     | 93.22 ± 5.23 |
| Carbachol |     |     |     |     | 0.51 ± 1.9      | 106.3 ± 9.71 |
| Nitrendipine |   |     |     |     | N.T             | N.A         |

NT Not tested, N.A Not active
Scheme 27  Synthesis of 2-(2-(1H-imidazol-1-yl)ethyl)-4-(1-benzyl-2-(substituted thio)-1H-imidazol-5-yl)-5-(substituted carbonyl)-6-methyl-1,4-dihydropyridine-3-substituted carboxylic acid

R₁ = CH₃, C₂H₅, CH₂C₆H₅
R₂ = CH₃, C₂H₅,
### Table 27: Antihypertensive activity of titled compounds (68a-f) in normotensive and hypertensive rats Hadizadeh et al. [46]

| Compounds | MABP fall (SEM) in rats in doses C, in mg/kg b.w., i.v |
|-----------|------------------------------------------------------|
|           | Normotensive                                         | Hypertensive                                        |
|           | 0.3   | 3       | 30      | 0.3   | 3       | 30      |
| 68a       | 26.00(2.00) | 42.00(3.00) | 47.20(3.03) | 38.40(5.37) | 46.40(2.19) | 50.00(2.00) |
| 68b       | Nd    | Nd      | Nd      | Nd    | Nd      | Nd      |
| 68c       | 22.00(2.00) | 42.00(2.00) | 57.2(2.16) | 29.60(4.56) | 54.00(7.79) | 58.00(2.73) |
| 68d       | 18.00(2.00) | 42.00(2.00) | 47.00(1.67) | 22.40(3.58) | 48.00(1.78) | 49.20(1.78) |
| 68e       | Nd    | Nd      | Nd      | Nd    | Nd      | Nd      |
| 68f       | Nd    | Nd      | Nd      | Nd    | Nd      | Nd      |
| 69a       | 17.20(2.68) | 41.60(20.60) | 53.20(2.28) | 28.00(6.20) | 52.80(11.79) | 55.20(2.28) |
| 69b       | 26.40(5.80) | 37.20(1.55) | 38.60(3.83) | 29.00(2.9) | 45.75(8.87) | 50.80(6.60) |
| 69c       | 23.20(7.69) | 44.80(3.34) | 56.80(3.34) | 35.20(3.35) | 56.00(4.00) | 56.80(3.34) |
| 69d       | 27.60(1.82) | 37.40(1.15) | 36.80(3.63) | 29.00(5.10) | 42.00(7.30) | 44.5(7.60) |
| 69e       | 15.40(0.27) | 28.60(1.09) | 33.00(1.41) | 28.00(4.70) | 36.80(1.60) | 51.00(8.70) |
| 69f       | 17.40(1.03) | 26.00(3.19) | 36.80(5.30) | 24.80(4.56) | 42.00(5.40) | 48.00(7.40) |
| Nifedipine| 27.20(2.68) | 59.60(3.84) | Nd       | 42.40(5.36) | 61.20(14.46) | Nd       |
| DMSO      | 12.00(5.65) | 12.00(3.65) | 12.00(5.65) | 14.80(6.72) | 14.80(6.72) | 14.80(6.72) |

MABP: Mean arterial blood pressure fall, SEM: Standard error the mean are indicated in the parenthesis. All results were analyzed for statistically significant differences from control DMSO (0.3 mL/kg b.w., i.v) by analysis of variance and all showed significant difference. (p < 0.05), Nd: not determined.
Scheme 28: Synthesis substituted imidazole derivatives
Table 28  Antihypertensive activity of the synthesized compounds (70a-j) Goyal et al. [22]

| Compounds | SAP (mmHg) | DAP (mmHg) | MAP (mmHg) | HR (bpm) |
|-----------|------------|------------|------------|----------|
| 70a       | B 189±7    | 129±5      | 159±6      | 311±19   |
|           | A 161±9*   | 105±6*     | 121±5*     | 298±11   |
| 70b       | B 189±7    | 124±8      | 154±5      | 310±18   |
|           | A 188±6    | 122±4      | 151±7      | 320±19   |
| 70c       | B 206±15   | 124±8      | 151±6      | 357±15   |
|           | A 198±18   | 119±6      | 146±5      | 337±21   |
| 70d       | B 217±8    | 128±6      | 160±8      | 339±17   |
|           | A 213±7    | 132±8      | 157±9      | 330±14   |
| 70e       | B 221±6    | 130±5      | 157±9      | 363±16   |
|           | A 213±3    | 129±4      | 155±8      | 347±17   |
| 70f       | B 178±2    | 146±7      | 151±6      | 413±28   |
|           | A 176±3    | 144±11     | 148±9      | 402±32   |
| 70g       | B 194±5    | 165±8      | 180±7      | 416±18   |
|           | A 187±7    | 155±6      | 168±6      | 409±11   |
| 70h       | B 158±6    | 151±9      | 155±6      | 453±29   |
|           | A 144±5*   | 141±8*     | 142±9*     | 459±21   |
| 70i       | B 198±7    | 154±7      | 176±7      | 410±19   |
|           | A 197±6    | 148±6      | 183±8      | 405±14   |
| 70j       | B 140±6    | 118±7      | 127±5      | 511±45   |
|           | A 138±5    | 115±4      | 125±4      | 465±28   |
| Control   | B 169±6    | 145±3      | 154±6      | 415±23   |
|           | A 168±9    | 140±4      | 149±7      | 407±29   |
| Prazocin (3 mg/kg) | B 199±7    | 156±6      | 168±6      | 418±17   |
|           | A 176±8*   | 138±4*     | 141±3*     | 411±15   |

Haemodynamic effects shown on systolic blood pressure (SAP), Diastolic blood pressure (DAP), Mean arteriolar pressure (MAP) and Heart rate (HR) on SHRs treated with vehicle control and test compounds. Values were represented as mean ± SEM; n = 5; * p < 0.05
Scheme 29  Synthesis of $N^3$-(substituted phenyl)-$N^5$-(substituted phenyl)-4-(4,5-dichloro-1H-imidazo[2-yl]-2-methyl-1,4-dihydropyridine-3,5-dicarboxamide

Table 29  Antitubercular activity of the synthesized compounds (71a-j) against *Mycobacterium tuberculosis* (H$_3$Rv strain) Amini et al. [47]

| Compounds | R            | Inhibition % |
|-----------|--------------|--------------|
| 71a       | H            | 9            |
| 71b       | 3-F          | 0            |
| 71c       | 4-F          | 13           |
| 71d       | 3-Cl         | 50           |
| 71e       | 4-Cl         | 12           |
| 71f       | 3,4-Cl$_2$   | 34           |
| 71g       | 3-Br         | 1            |
| 71h       | 4-Br         | 0            |
| 71i       | 3-NO$_2$     | 43           |
| 71j       | 4-NO$_2$     | 43           |
| Rifampicin|              | > 98         |
Scheme 30 Synthesis of (E)-3-(4-(7-substituted-3-(substituted amino)imidazo[1,2-α]pyridin-2-yl)phenyl)-1-(substituted phenyl)prop-2-en-1-one

4-substituted pyridin-2-amine  +  4-(diethoxymethyl) benzaldehyde  +  NC

p-TSA, MeOH, r.t, 10-15 h → 7-chloro-2-(4-(diethoxymethyl)phenyl) -N-methylimidazo[1,2-α]pyridin-3-amine

Acetic acid, 90°C, 30 min

KOH, EtOH, r.t, 3-4 h → (E)-3-(4-(7-substituted-3-(substituted amino)imidazo[1,2-α]pyridin-2-yl)phenyl)-1-(substituted phenyl)prop-2-en-1-one

Substituted benzaldehyde

4-(7-chloro-3-(methylamino)imidazo[1,2-α]pyridin-2-yl)benzaldehyde

(72a-q)
Table 30  Antitubercular activity of synthesized compounds (72a-q) against *M. tuberculosis* H37Rv Pandey et al. [48]

| Compounds | Structure | MIC* (μg/mL) | MIC (μM) | CC50 in C1008\(^b\) | CC50 in MBMDMφ\(^c\) | SI\(^d\) | SP* |
|-----------|-----------|--------------|----------|----------------------|-----------------------|--------|-----|
| 72a       | ![Structure](image1) | 3.12 | 7.40 | <25 | ND* | NA | |
| 72b       | ![Structure](image2) | 12.50 | 25.04 | ND | ND | ND | |
| 72c       | ![Structure](image3) | 12.50 | 27.46 | ND | ND | ND | |
| 72d       | ![Structure](image4) | 12.50 | 27.70 | ND | ND | ND | |
| 72e       | ![Structure](image5) | 12.50 | 25.98 | ND | ND | ND | |
| 72f       | ![Structure](image6) | 3.12 | 6.10 | <25 | ND | ND | |
| 7g        | ![Structure](image7) | 25.00 | 53.62 | ND | ND | ND | |
| 72h       | ![Structure](image8) | 12.50 | 28.72 | ND | ND | ND | |
| 72i       | ![Structure](image9) | 25.00 | 48.71 | ND | ND | ND | |
| 72j       | ![Structure](image10) | 12.50 | 23.79 | ND | ND | ND | |
| 72k       | ![Structure](image11) | 12.50 | 26.03 | ND | ND | ND | |
### Table 30 (continued)

| Compound | MIC | C1008 | MBMDMφ | SI | ND |
|----------|-----|-------|---------|----|----|
| 72l      | 3.12| 7.89  | >100    | 47.47 | >10 |
| 72m      | 25.00| 61.09 | ND      | ND  | ND |
| 72n      | 25.00| 58.79 | ND      | ND  | ND |
| 72o      | 6.25 | 13.72 | ND      | ND  | ND |
| 72p      | 3.12 | 6.42  | >100    | <25 | >10 |
| 72q      | 3.12 | 6.59  | >100    | >100| >10 |
| Ethambutol | 2.00 | 9.78  |         |     |    |
| Pyrazinamide | 12.5 | 101.53 |        |     |    |

*MIC: Minimum inhibitory concentration, *C1008: vero cell lines, *MBMDMφ: Mouse bone marrow derived macrophages, *SI: Selectivity index, *ND: not done.
**Scheme 31** Synthesis of 10-(2-(substituted phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-10H-phenothiazine (73a-j)

| Compounds | Ar1          | Antitubercular activity inhibition (%) (ppm) M. tuberculosis H37Rv strain | Antitubercular activity MIC* (μg/mL) M. tuberculosis H37Rv strain |
|-----------|--------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| 73a       | C6H5         | 22                                                                                             | 12                                                               |
| 73b       | 2-ClC6H4     | 32                                                                                             | 7.5                                                              |
| 73c       | 3-ClC6H4     | 36                                                                                             | 6.5                                                              |
| 73d       | 4-ClC6H4     | 32                                                                                             | 7                                                                |
| 73e       | 2-BrC6H4     | 29                                                                                             | 10                                                               |
| 73f       | 3-BrC6H4     | 30                                                                                             | 8.5                                                              |
| 73g       | 4-BrC6H4     | 30                                                                                             | 9                                                                |
| 73h       | 2-NO2C6H4    | 28                                                                                             | 5.5                                                              |
| 73i       | 3-NO2C6H4    | 27                                                                                             | 4                                                                |
| 73j       | 4-NO2C6H4    | 32                                                                                             | 5                                                                |

Table 31. Antitubercular activity of the synthesized compounds (73a-j) Makwane et al. [49]
Scheme 32  Synthesis of 2-((1H-imidazol-1-yl)methyl)-6-substituted-5-fluoro-1H-benzo[d]imidazole

**Compounds R =**

| Compound | MIC (μg/mL) | MABA |
|----------|-------------|------|
| 74a; R = Cl | 100 |  |
| 74b; | 50 |  |
| 74c; | 25 |  |
| 74d; | 50 |  |
| 74e; | 12.5 |  |
| Isoniazid | 0.78 |  |

*MIC Minimum inhibitory concentration, MABA Microplate Alamar Blue Assay (visual)*
Synthesis of 6-(benzo[d][1,3]dioxol-5-yloxy)-2-substituted-5-fluoro-1H-benzo[d]imidazole and 2-(((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)thio)-6-substituted-5-fluoro-1H-benzo[d]imidazole

Scheme 33
Table 33  Antitubercular activity of synthesized derivatives (77a-f) and (78a-i) Nandha et al. [50]

| Compounds | Ar         | MIC (μg/mL) MABA |
|------------|------------|-----------------|
| 77a        |            | 50              |
| 77b        |            | 50              |
| 77c        |            | 50              |
| 77d        |            | 25              |
| 77e        |            | 50              |
| 77f        |            | 50              |
| 78a        | -Cl        | 100             |
| 78b        |            | 50              |
| 78c        |            | 50              |
| 78d        |            | 50              |
| 78e        |            | 50              |
| 78f        |            | 50              |
| 78g        |            | 50              |
| 78h        |            | 25              |
| 78i        |            | 50              |
| Streptomycin|           | 6.25            |
| Pyrazinamide|          | 3.12            |
| Ciprofloxacin|        | 3.12            |

MIC: Minimum inhibitory concentration, MABA: Microplate Alamar Blue Assay (visual).
Reagents and conditions: (a) ethynyltrimethylsilane, Pd(PPh₃)₂Cl₂, CuI, MeCN, diethylamine, microwave 120ºC, 15 min, then K₂CO₃, MeOH, rt, 2h, 85%, (b) bromoaryl/heteroaryl, Pd(PPh₃)₂Cl₂, CuI, MeCN, diethylamine, microwave 80-120ºC, 15 min, 22-63%, (c) KMnO₄, phosphate buffer, (d) aldehyde, ammonium acetate, n-butanol, 50-65ºC, 0.5-5 h, 10-63%.

Scheme 34  Synthesis of 2,5-disubstituted-4-(6-methoxynaphthalen-2-yl)-1H-imidazole
Table 34: Antitubercular activity of synthesized derivatives (79a-m) Gising et al. [51]

| Compounds | R5       | R2       | IC₅₀ (μM)  |
|-----------|----------|----------|------------|
| 79a       | ![Structure](image1) | ![Structure](image2) | 3.1 ± 0.1   |
| 79b       | ![Structure](image3) | ![Structure](image4) | >25         |
| 79c       | ![Structure](image5) | ![Structure](image6) | >25         |
| 79d       | ![Structure](image7) | ![Structure](image8) | >25         |
| 79e       | ![Structure](image9) | ![Structure](image10) | 2.2 ± 0.3   |
| 79f       | ![Structure](image11) | ![Structure](image12) | >25         |
| 79g       | ![Structure](image13) | ![Structure](image14) | >25         |
| 79h       | ![Structure](image15) | ![Structure](image16) | >25         |
| 79i       | ![Structure](image17) | ![Structure](image18) | >25         |
| 79j       | ![Structure](image19) | ![Structure](image20) | >25         |
| 79k       | ![Structure](image21) | ![Structure](image22) | >25         |
| 79l       | ![Structure](image23) | ![Structure](image24) | >25         |
| 79m       | ![Structure](image25) | ![Structure](image26) | >25         |
Scheme 35 Synthesis of substituted phenyl imidazole derivatives

Reagents and conditions: (a) dry ethanol, Na₂CO₃, reflux 12 h, (b) Morpholine, HCHO, AcOH, Methanol, reflux 8 h; (c) pyrrolidine, HCHOIO, AcOH, Methanol, reflux 8 h; (d) piperidine, HCHO, AcOH, methanol, reflux.
This review article established the fact that 1,3-diazole act as useful templates for further modification or derivatization to design more potent biologically active compounds.

**Table 35 Antitubercular activity of synthesized compounds (80a-83e) Syed et al. [52]**

| Compounds | MIC (μg/mL) MABA |
|-----------|------------------|
| 80a       | 10               |
| 80b       | 10               |
| 81a       | 10               |
| 81b       | 25               |
| 82a       | 10               |
| 82b       | 25               |
| 83a       | 10               |
| 83b       | 25               |
| 83c       | 25               |
| 83e       | 25               |
| Streptomycin | 7.5             |

**Abbreviations**

AMR: Antimicrobial resistance; DNA: Deoxyribonucleic acid; DMF: Dimethylformamide; TEBA: Triethyl benzyl ammonium chloride; MTT: 3-(4, 5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; C-A4: Combretastatin-A4; SRB: Sulforhodamine B assay; DLA: Dalton's Lymphoma Ascites cell line; EAC: Ehrlich's ascites carcinoma cell lines; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; FRAP: Ferric reducing ability of plasma; SHR: Spontaneously hypertensive rats; MB: Middlebrook; MABA: Microplate Alamar blue assay; L.J Lowenstein-Jensen; I_{50}: Half maximal inhibitory concentration; HeLa: Henrietta Lacks; TEA: Triethanolamine; DMSO: Dimethyl sulphoxide; MIC: Minimum inhibitory concentration; TBAB: Tetrabutylammonium bromide; NCFT: National Centre of Fungal Taxonomy; MLC: Minimum Lethal concentration; p-TSA: P-Toluenesulfonic acid; MW: Microwave; CAN: Ceric ammonium nitrate; (4-SB) T (4-SPh)PHSO4: (4-Sulfobutytris(4-sulfophenyl) phosphonium hydrogen sulfate.

**Reagents and conditions:** (a) 4-N,N-Dimethylaminopyridine, DMF, Cyanogen bromide, stirred 15 h; (b) thiosemicarbazide, trifluoroacetic acid, reflux 15 h; (c) refluxed in dry ethanol for 18 h.

**Scheme 36** Synthesis of 6-(substituted phenyl)-2-(1-methyl-1H-imidazol-2-yl) imidazo[2,1-b][1,3,4] thiazazole (84a-j)
Table 36  Antitubercular activity of synthesized compounds (84a-j) Patel et al. [53]

| Compounds | R            | Inhibition % | Activity | MIC (μg/mL) | IC<sub>50</sub> | SI   |
|------------|--------------|--------------|----------|-------------|----------------|------|
| 84a        | 3-Nitro      | 91           | +        | 4.34        | 10.56          | 2.43 |
| 84b        | 4-Bromo      | 94           | +        | 5.78        | 11.4           | 1.97 |
| 84c        | 4-Chloro     | 95           | +        | 5.48        | 12.3           | 2.24 |
| 84d        | 4-Fluoro     | 90           | +        | 4.86        | 8.5            | 1.74 |
| 84e        | H            | 16           | −        | >6.25       | −              | −    |
| 84f        | 4-Nitro      | 98           | +        | 3.14        | 9.8            | 3.12 |
| 84g        | 4-Methyl     | 18           | −        | >6.25       | −              | −    |
| 84h        | 3-Methyl     | 30           | −        | >6.25       | −              | −    |
| 84i        | 2,4-Dichloro | 92           | +        | 5.66        | 103            | 1.81 |
| 84j        | 2,4-Dihydroxy| 92           | −        | >6.25       | −              | −    |
| Rifampicin |              |              |          | 0.125–0.25  |                  | >10  |
Scheme 37  Synthesis of 2-((1-benzoyl-1H-benzo[d]imidazol-2-y1)thio)-N-(substituted phenyl) acetamide

\[
\begin{align*}
&\text{Substituted aniline} + \text{ClCH}_2\text{COCl} \xrightarrow{\text{cold condition}} \text{2-chloro-N-}
\end{align*}
\]

\[
\begin{align*}
&\text{(substituted phenyl) acetamide} + \text{1H-benzo[d] imidazole-2-thiol}
\end{align*}
\]

\[
\begin{align*}
&\text{Methanol, KOH}
\end{align*}
\]

\[
\begin{align*}
&\text{CHCl}_3, \text{TEA}
\end{align*}
\]

\[
\begin{align*}
&\text{2-((1-benzoyl-1H-benzo[d]imidazol-2-yl)thio)-N-}
\end{align*}
\]

\[
\begin{align*}
&\text{(substituted phenyl) acetamide (85a-t)}
\end{align*}
\]

| Compounds 85a-t; R = |
|----------------------|
| 85a: R = H           |
| 85b: R = 2-F         |
| 85c: R = 4-F         |
| 85d: R = 2-Cl        |
| 85e: R = 3-Cl        |
| 85f: R = 2-Cl, 5-Cl  |
| 85g: R = 2-Br        |
| 85h: R = 3-Br        |
| 85i: R = 4-Br        |
| 85j: R = 3-NO_2      |
| 85k: R = 2-NO_2, 4-Cl|
| 85l: R = 4-CH_3      |
| 85m: R = 2-CH_3, 6-CH_3|
| 85n: R = 3-OCH_3     |
| 85o: R = 4-Cl        |
| 85p: R = 2-CH_3      |
| 85q: R = 2-OCH_3     |
| 85r: R = 4-OCH_3     |
| 85s: R = 3-CH_3      |
| 85t: R = 2-CH_3, 4-CH_3|
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Authors’ contributions
PKV—endeavored and accomplished the scheme; AS—completed review work and wrote the manuscript. Both authors read and approved the final manuscript.

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Table 37 Antitubercular activity of synthesized compounds (85a-t) Yadav et al. [54]

| Compounds | Diameter of zone of inhibition (mm) against H37Rv (NCFT/TB/537) | MIC (μg/mL) | MLC (μg/mL) |
|-----------|---------------------------------------------------------------|-------------|-------------|
| 85a       | > 20                                                          | 12.5        | 25          |
| 85b       | > 20                                                          | 12.5        | 25          |
| 85c       | > 20                                                          | 12.5        | 25          |
| 85d       | > 20                                                          | 12.5        | 25          |
| 85e       | 08                                                            | 17.8        | 28.12       |
| 85f       | > 20                                                          | 12.5        | 25          |
| 85 g      | 10                                                            | 15          | 28          |
| 85 h      | > 20                                                          | 12.5        | 25          |
| 85 i      | 08                                                            | 17.8        | 28.12       |
| 85 j      | 20                                                            | 12.5        | 25          |
| 85 k      | 10                                                            | 15          | 28          |
| 85 l      | > 20                                                          | 12.5        | 25          |
| 85 m      | > 20                                                          | 12.5        | 25          |
| 85 n      | NA                                                            | NA          | NA          |
| 85 o      | > 20                                                          | 12.5        | 25          |
| 85 p      | 10                                                            | 15          | 28          |
| 85 q      | > 20                                                          | 12.5        | 25          |
| 85 r      | > 20                                                          | 12.5        | 25          |
| 85 s      | NA                                                            | NA          | NA          |
| 85 t      | 10                                                            | 15          | 28          |
| Streptomycin | > 20                                                      | 12.5        | 25          |
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