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Synthesis, characterization and anti microbial screening of novel 1*H*-2,4triazole 2,4,5-tri aryl imidazole derivatives

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Abstract : A multi component synthesis of novel desired 1*H*-2,4 triazole triphenyl imidazole is described. Cyclization of benzil with appropriate aromatic aldehydes in the presence of ammonium acetate and amino triazole yields 1*H*-2,4 triazole 2-substituted phenyl - 4,5-diphenyl imidazole afforded the title compounds. The newly synthesised compounds have been established on the basis of their physical and spectral data. All the newly synthesised heterocycles have been screened for antimicrobial activities. Among all the synthesized compounds, the compound IA-12 exhibited better anti-microbial activity against bacterial strains *Staphylococcus aureus, Pseudomonas aeruginosa* and fungal strain *Candida albicans.*
Keywords : 1*H*-2,4 triazole 2,4,5-trisubstituted imidazoles, Multi-component reactions, *In vitro* antimicrobial activity.

Introduction

In the field of five membered heterocyclic structures imidazole nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, beta-lactamase inhibitors, 20-HETE (20-Hydroxy- 5,8,11,14- eicosatetraenoic acid) synthase inhibitors, carboxy peptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial[1-14]. This group presents in azoles antifungal which inhibit the accumulation of methylated sterols destroy the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters [15-16]. The substituted imidazole derivatives are valuable in treatment of many systemic fungal infections. Imidazoles are found in many antifungal drugs, which include ketoconazole, miconazole, and clotrimazole.

The chemistry and pharmacology of benzimidazoles are also of great interest to medicinal chemistry[17-18] because its derivatives possessed various biological activities such as antioxidant [19-20], antimicrobial [21-26], antihelmintic [27-29], anticancer [30], antihypertensive [31], antineoplastic [32], anti-inflammatory [33-34], analgesic [35], antiprotozoal [36] and anti-hepatitis B virus activity[37]. A variety of benzimidazole is also in use, like thiabendazole and flubendazole as anthelmintic, omeprazole and lansoprazole as antiulcerative and astemizole as antihistaminic.

Triazole and its derivatives have occupied an unique position in heterocyclic chemistry due to their biological activities. 1,2,4-Triazoles as antibacterial agents can be grouped according to the mode of action, i.e. the ability to inhibit the synthesis of the cell wall, cell membrane, proteins and nucleic acids of bacteria. The syntheses of 1,2,4-triazoles has also attracted wide spread attention due to the diverse agricultural and industrial activities, including antibacterial[38-40], antimycobacterial[41-42], antimycotic[43], antifungal[44-45], antidepressive[46], and cardiotonic[47] activity shown by these compounds. Recent research has also established for these heterocycles as an analgesic [48] and anti-inflammatory [49-50] activities. Meanwhile, N-acylated amino acids are known for their hepatoprotective[51], antimicrobial[52-53] and antitumor action[54-55]. The drugs in this class offer activity against many fungal pathogens without the serious nephrotoxic effects observed with amphotericin B. Newer azole agents have emerged as first-line therapies for several severe fungal diseases, such as invasive aspergillosis, for which voriconazole has become the standard of care. The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole. The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole and flusilazole. Additionally, there are triazoles with nonfungicidal applications e.g., azocyclotin is used as an acaricide, paclobutrazole as a growth regulator, carfentrazone as a herbicide, and isazophos as an insecticide.

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation [56]. The developing of new MCRs [57] and improving known multi-component reactions are an area of considerable current interest. One such reaction is the synthesis of imidazoles. Tetrasubstituted imidazole is a core section in many biological systems such as Losartan and Olmesartan[58]. The presence of an imidazole ring in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles [59]. However, despite intensive efforts, only a handful of general methods exist for the construction of tetrasubstituted imidazoles.

In 1882, Radziszewski and Japp reported the first synthesis of the highly substituted imidazole from a 1,2-dicarbonyl compound, different aldehydes, and ammonia[60-61]. Also a number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and 2,4,5-trisubstituted imidazoles. The syntheses of 1, 2, 4, 5-tetrasubstituted imidazoles are carried out by four-component condensation of a 1,2-diketone / a-hydroxyketone with an aldehyde, primary amine, and ammonium acetate.

Experimental section

All the chemicals and reagents were procured from Sigma Aldrich lab grade source. All the solvents used were from commercial source and redistilled before use. Melting points were determined on Buchi apparatus and are uncorrected. The Infrared spectra (in KBr pellets) were recorded on a JOSCO spectrometer and frequencies are expressed in $cm^{-1.}$ Mass spectra (CG/MS) were recorded on a Agilent MSD VL mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker Advance 400 spectrometer operating at 400.00 MHz. The chemical shifts are reported in ppm (δ) relative to tetra methyl silane proton and carbon spectra were typically obtained at room temperature. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using Ethyl acetate: Hexane or Methylene dichloride: Methanol as eluent and spots were developed in UV.

Chemistry

This versatile applicability highlights the importance of access to efficient synthetic routes to well design highly substituted imidazole derivatives. A number of methods have been developed for the synthesis of 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles. 1,2,4,5-Tetra substituted imidazoles are generally synthesized by three component cyclo condensation of a 1,2-diketone, a-hydroxyketone with an aldehyde and ammonium acetate, which comprise refluxing in acetic acid. We next examined a wide variety of aromatic aldehydes and 1, 2-diketones to establish the scope of this transformation. A broad range of aromatic aldehydes bearing electron donating and electron withdrawing substituents underwent this one-pot, three-component cyclo condensation to furnish 1*H*-2,4 triazole 2,4,5-trisubstituted imidazoles in good yields. Aliphatic aldehyde afforded the corresponding imidazoles in moderate yields. Various functional groups were found to be compatible under the reaction conditions.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles:

In a 50 ml round-bottom flask, 1,2-diketone (1 mmol), aldehyde (1 mmol), 3 amino -(1H,2,4- triazole) amine (1 mmol) and ammonium acetate (15 mmol) were stirred in acetic acid (20 ml) at reflux temperature for the 6 to 8 hours. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 X 25 ml). The organic layer was dried over Na_2SO_4 and concentrated. The products were separated and purified by column chromatography on silica gel (60–120 mesh) using Ethyl acetate/Hexane mixture as an eluent to afford pure tetra substituted imidazoles

Scheme

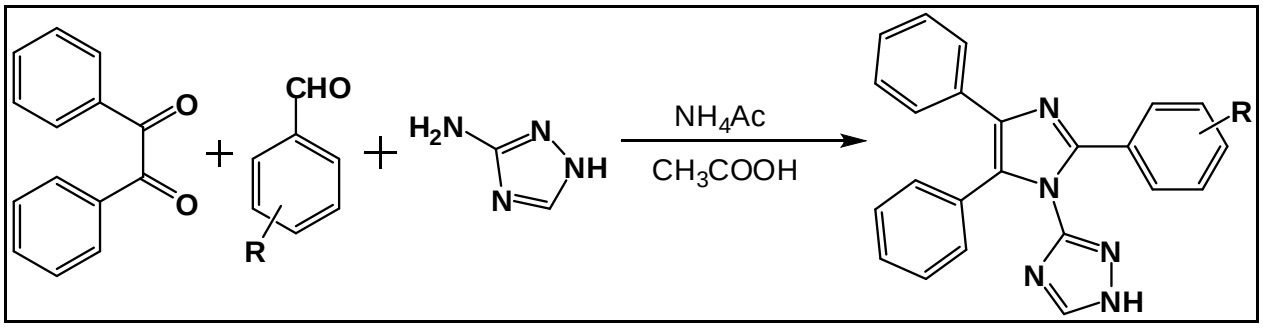

Table 1. List of Imidazole- triazole compounds

SNO	Entry	R
1	IA-01	4F
2	IA-02	2Cl
3	IA-03	OCH_2O
4	IA-04	4OMe
5	IA-05	$4CF_3$
6	IA-06	3OH, 4OMe
7	IA-07	$3NO_2$
8	IA-08	4OH
9	IA-09	3,4OH
10	IA-10	Ph
11	IA-11	3,4,5 OMe
12	IA-12	4Br
13	IA-13	4-IPA
14	IA-14	4Cl

3-[2-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-01)

Yield : 56% IR (KBr) 3413 (N-H) 1602 (C=O) 1543 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 7.01-7.34 (m, 4H) δ 7.36-7.47(m, 6H) δ 7.51-8.32(m, 4H) δ 8.41(d, 1H) δ 10.87(s, NH) MS : m/z 380.1 (M-1)

3-[2-(2-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4triazole (IA-02) Yield : 67% IR (KBr) 3430 (N-H) 1602 (C=O) 1584 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 6.94-8.26(m, 14H) δ 8.38(d, 1H) δ 10.64(s, NH)

MS : m/z 396.1 (M-1)

3-[2-(3,4methylenedioxy phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-03)

Yield : 57% IR (KBr) 3433 (N-H) 1602 (C=O) 1578 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 5.92 (s, 2H) δ 6.55-7.91 (m, 14H) δ 10.66(s, NH) MS : m/z 406.1(M-1)

3-[2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-04)

Yield : 45% IR (KBr) 3429 (N-H) 1604 (C=O) 1587 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 3.72 (s, 3H) δ 7.09-7.54 (m, 12H) δ 7.57-7.72 (m, 2H) δ 8.36 (d, 1H) δ 10.65 (s, NH) MS : m/z 392.1 (M-1)

3-[2-(4-trifluromethyl phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-05)

Yield : 60% IR (KBr) 3428 (N-H) 1605 (C=O) 1583 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 6.99-8.15 (m, 15H) δ 10.66(s, NH) MS : m/z 430.0 (M-1)

3-[2-(3-hydroxy,4-methyoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-06)

Yield : 54% IR (KBr) 3413 (N-H) 1693 (C=O) 1524 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 3.90 (s, 3H) δ 9.31 (s,1H) δ 7.08-7.78 (m, 14H) δ 10.65(s, NH) MS : m/z 408.4 (M-1)

3-[2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-07)

Yield : 70% IR (KBr) 3569 (N-H) 1666 (C=O) 1599 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 7.12-7.21 (m, 6H) δ 7.32-7.42 (m, 5H) δ 7.44-7.78 (m, 3H) δ 8.43(d, 1H) δ 10.72(s, NH) MS : m/z 407.4 (M-1)

3-[2-(4-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-08)

Yield : 66% IR (KBr) 3541 (N-H) 1691 (C=O) 1589 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm,DMSO-d_6) δ 9.39 (s, 1H) δ 6.79-8.50 (m, 15H) δ 10.65(s, NH) MS : m/z 378.1 (M-1)

3-[2-(3,4 di hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-09)

Yield : 58% IR (KBr) 3430 (N-H) 1613 (C=O) 1579 (C-C arom) cm^{-1}

$^{.1}$H NMR (δ ppm, DMSO-d_6) δ 9.51 (s, 2H) δ 6.78-8.48 (m, 14H) δ 10.66(s, NH) MS : m/z 394.4 (M-1)

3-[2-phenyl-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-10)

Yield : 62% IR (KBr) 3430 (N-H) 1603 (C=O) 1585 (C-C arom) cm^{-1}

$^{.1}$H NMR (δ ppm, DMSO-d_6) δ 6.58-7.41 (m, 3H) δ 7.44-7.56(m, 6H) δ 7.58-7.62 (m, 3H) δ 8.28-8.34 (m, 3H) δ 10.66(s, NH) MS : m/z 362.1(M-1)

3-[2-(3,4,5 tri methoxy phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-11)

Yield : 58% IR (KBr) 3413 (N-H) 1602 (C=O) 1588 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO-d_6) δ 3.82 (s, 3H) δ 3.61(s, 6H) δ 7.02-7.31 (m, 13H) δ 10.87(s, NH) MS : m/z 452.5 (M-1)

3-[2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-12)

Yield : 69% IR (KBr) 3413 (N-H) 1604 (C=O) 1550 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm , DMSO- d_6) δ 7.07-7.17 (m, 3H) δ 7.36-7.46 (m, 3H) δ 7.53 (s, 1H) δ 7.58-7.62 (m, 2H) δ 7.74 (s, 1H) δ 7.85-7.87 (m, 2H) δ 7.99-8.02 (m, 2H) δ 8.39-8.41 (d, 1H) δ 10.64(s, NH) MS : m/z 440.0 (M-1)

3-[2-(4-Isoproply phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-13)

Yield : 64% IR (KBr) 3316 (N-H) 1558 (C=O) 1526 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO- d_6) δ 1.24 (s, 6H) δ 2.89 (m, 1H) δ 7.21-8.09(m, 15H) δ 10.66(s, NH)

MS: m/z 404.4 (M-1)

3-[2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4 triazole (IA-14)

Yield : 46 % IR (KBr) 3413 (N-H) 1584 (C=O) 1524 (C-C arom) $cm^{-1.}$

^{1}H NMR (δ ppm, DMSO- d_6) δ 7.32-7.46 (m, 6H) δ 7.47 (m, 2H) δ 7.56-7.66 (m, 2H) δ 7.87-7.98 (m, 2H) δ 7.99-8.22 (m, 2H) δ 8.4 (m, 1H) δ 10.65 (s, NH) MS : m/z 396.1 (M-1)

Antimicrobial activity

The following bacteria and fungi were used for screening. Bacteria: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853. All bacterial strains were maintained on nutrient agar medium at ±37°C. Fungi: *Aspergillus flavus*, *Chrysosporium keratinophilum* and *Candida albicans MTCC 227* are also used in this study. All fungi strains were maintained on potato dextrose agar (PDA) at ±25 °C.

Table 2. Antibacterial activity of compounds (IA 01-14) (*Zone of inhibition in mm*).

Compound code	**Escherichia coli**		**Staphylococcus aureus**		**Pseudomonas aeruginosa**	
Concentration in µg/ml	1000	500	1000	500	1000	500
IA-01	09±0.2	05±0.2	08±0.2	06±0.1	10±0.2	06±0.2
IA-02	08±0.2	05±0.1	09±0.1	05±0.2	09±0.2	07±0.1
IA-03	02±0.1	03±0.2	04±0.1	03±0.1	04±0.2	01±0.2
IA-04	00	00	00	00	00	00
IA-05	07±0.1	06±0.1	07±0.1	05±0.1	07±0.1	04±0.1
IA-06	03±0.2	01±0.1	05±0.2	04±0.1	06±0.1	03±0.1
IA-07	06±0.1	04±0.1	12±0.2	10±0.1	08±0.1	04±0.2
IA-08	04±0.2	03±0.1	06±0.1	04±0.1	07±0.1	05±0.2
IA-09	04±0.1	03±0.1	04±0.1	03±0.1	08±0.1	06±0.2
IA-10	00	00	00	00	00	00
IA-11	03±0.1	01±0.1	05±0.1	03±0.1	04±0.1	02±0.2
IA-12	10±0.1	06±0.1	15±0.1	13±0.1	12±0.1	10±0.1
IA-13	04±0.1	03±0.2	02±0.1	02±0.1	07±0.2	06±0.1
IA-14	09±0.2	05±0.1	08±0.1	06±0.1	12±0.2	08±0.2
Steptomycin(std) 30µg/mL	16±0.2		15±0.2		16±0.2	

Antibacterial activity

The antibacterial activities of newly synthesized compounds (IA 01-14) were determined by well plate method in Mueller-Hinton Agar. The compounds were tested against a panel of pathogenic microorganisms, including *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Microorganism strains were maintained on nutrient agar medium at 37°C. The cultures were inoculated in fresh 10 mL Nutrient Broth to yield an initial suspension of approximately 10–100 cfu/mL. All broths were then incubated statically at the afore mentioned temperatures for microorganisms, for 18-24 h so that all cells were in the stationary phase. Susceptibility of the test organism to the compounds was also determined by employing the well plate

technique. The bacterial suspensions were diluted tenfold in distilled water, and 0.1 mL from the appropriate dilution was spread plated on nutrient agar in order to give a population of approximately 10^6 cfu/plate. The wells were dug in each Petri dish by sterilized cork borer. The compounds were dissolved in DMSO and appropriate dilutions were made (1mg/mL and 0.5mg/mL). The same procedure was repeated for different micro-organisms. Each experiment was carried out in triplicate. After the inoculation of organism and compound, the Petri dishes were incubated for 24 hrs at 37^{o}C. After the incubation, the inhibition zone was measured and the values for Dimethylsulphoxide (DMSO) were subtracted to get the actual values. Streptomycin was used as standard drug.

Antifungal activity

The fungal strains used in this study were *Aspergillus flavus*, *Chrysosporium Keratinophilum* and *Candida albicans*. The required amounts of each fungal strain were removed from the stock and suspended in 5mL of distilled water with 2 drops of Tween 80. This suspension was uniformly spread on Petri plates containing Potato dextrose agar media using sterile swabs. After applying the samples into the wells formed by using the same technique for tests on bacteria, the plates were incubated at 25 °C for 3 days. The plates were then examined for the presence of zones of inhibition and the results were recorded. Fluconazole was used as a standard drug.

Table 3. Antifungal activity of compounds (IA 01-14) (*Zone of inhibition in mm*).

Compound code	**Aspergillus Flavus**		**Chrysosporium Keratinophilum**		**Candida Albicans**	
Concentration in µg/ml	1000	500	1000	500	1000	500
IA-01	08±0.2	06±0.2	10±0.1	08±0.2	16±0.2	13±0.2
IA-02	10±0.1	07±0.1	09±0.1	08±0.1	07±0.1	06±0.1
IA-03	02±0.1	02±0.2	04±0.1	03±0.1	03±0.2	02±0.2
IA-04	00	00	00	00	00	00
IA-05	09±0.1	06±0.1	08±0.1	05±0.2	08±0.1	10±0.1
IA-06	05±0.2	04±0.2	03±0.1	03±0.2	03±0.2	02±0.2
IA-07	09±0.1	07±0.2	14±0.1	12±0.2	14±0.1	08±0.1
IA-08	05±0.1	04±0.1	06±0.1	03±0.1	07±0.1	06±0.1
IA-09	06±0.1	04±0.1	07±0.1	04±0.2	08±0.1	07±0.1
IA-10	00	00	00	00	00	00
IA-11	04±0.2	03±0.1	06±0.1	03±0.1	04±0.1	03±0.2
IA-12	09±0.1	03±0.1	11±0.1	10±0.1	16±0.1	12±0.1
IA-13	04±0.2	03±0.2	04±0.1	02±0.2	02±0.2	01±0.2
IA-14	10±0.2	07±0.2	10±0.1	08±0.2	12±0.2	10±0.2
Fluconazole(Std.)	13±0.2		17±0.2		22±0.2	

Antimicrobial activity

The new compounds (**IA 01-14**) were tested for their antibacterial activity (*in vitro)* at a concentration of 1000 and 500 µg/mL against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and their activity was compared to a well-known commercial antibiotic, streptomycin. The results were recorded for each tested compound as the average diameter of inhibition zones of bacterial growth surrounding the well in millimetres. The newly synthesized compounds exhibited variable antibacterial activity against the above tested bacterial strains. The results indicated that among the tested compounds, **IA-01, IA-02, IA- 05, IA- 07, IA- 12** and **IA-14** showed good antibacterial activity towards all bacterial strains at concentrations of 1000 and 500 µg/mL when compared with standard drug. Rest of compounds showed fair or poor activity. Results of

Antibacterial studies have been presented in **Table 2**.

All the synthesized compounds were also tested for its antifungal activity (*in vitro)* against *Aspergillus flavus*, *Chrysosporium keratinophilum* and *Candida albicans* by measuring its average zone of inhibition.

Fluconazole was used as standard for antifungal activity. Among the synthesized, compound **IA-12** showed good activity against *Aspergillus Flavus* at concentrations of 1000 and 500 µg/mL compared to standard drug fluconazole (**Table 3)**.

The result of antimicrobial study reveals that presence of substituent on the phenyl ring attached to the 2-position of imidazole ring plays important role. The enhanced activity of **IA-01, IA-02, IA- 05, IA- 07, IA-12** and **IA-14 is** due to the presence of groups like F, Cl, $4CF_3$, NO_2, Br and isopropyl attached to phenyl rings of imidazole ring. This is also supported by the previous reports. However, in general, compounds containing a halogen substituents showed better antibacterial activity than the compounds with other substituent. The absence of such pharmacophore on phenyl ring fails to exhibit both antibacterial as well as antifungal activity. From the antimicrobial results we can conclude that, synthesized compounds are specific antibacterial agents. A combination of two different heterocyclic systems namely pyrazole and imidazole has enhanced the harmacological effect and hence they are ideally suited for further modifications to obtain more efficacious antibacterial compounds.

Conclusion

In the present work, a series of novel 1*H*-2,4 triazole 2,4,5-trisubstituted imidazoles derivatives were synthesized and characterized by IR, 1H NMR,and mass analyses. All the compounds were screened for its antimicrobial activity. Antibacterial results indicated that the compounds **IA-01, IA-02, IA- 05, IA- 07, IA- 12** and **IA-14 showed** good antibacterial activity towards all bacterial strains when compared to standard drug streptomycin. **IA-12** showed good antifungal activity whereas remaining compounds showed moderate to poor antifungal activity compared to other synthesized compound.

In conclusion, an efficient, one-pot, three-step synthesis of substituted Imidazole- triazole was developed. A series of 1,3,4,5-tetrasubstituted Imidazole- triazole derivatives were synthesized in good yields. This efficient and highly modular one-pot procedure methodology to other interesting is practical and useful. Further studies on the biological activities of the products and application of this triazole derivative are underway in our laboratory.

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