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Synthesis, characterization and anti microbial screening of novel 1-pyrazole acid 2,4,5-tri aryl imidazole derivatives.

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Abstract: An elegant synthesis of novel desired 1-pyrazole acid triphenyl imidazole is described. Cyclization of benzil with appropriate aromatic aldehydes in the presence of ammonium acetate and amino pyrazole yields 1-cyanopyrazole 2-substituted phenyl - 4,5-diphenyl imidazole followed by acid hydrolysis, 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 IP-12 exhibited good better anti-microbial activity against bacterial strains *Staphylococcus aureus, Pseudomonas aeruginosa* and fungal strain *Candida albicans.*
Keywords: 1-pyrazole 2,4,5-trisubstituted imidazoles, Multi-component reactions, *Invitro* antimicrobial activity.

Introduction

Imidazole represents an important class of compounds in pharmaceutical chemistry with potential biological activity[1–5], including antifungal, antimycotic, antibiotic, anti ulcerative and antibacterial activity. The members of this class of compounds are also known to possess NO synthase inhibition and antitumor, CB1 receptor antagonistic activities[6,7] and the core structural skeleton in many important biological molecules like histidine, histamine, and biotin as well as several drug moieties such as Trifenagrel, Eprosartan, and Losartan .

Various substituted imidazoles are found to act as inhibitors of p38 MAP kinase[8a] and B-Raf kinase,[8b] glucagon receptors,[9] plant growth regulators,[10] therapeutic agents,[11] and pesticides.[12] Accordingly, a number of synthetic methods have been reported for the construction of this important structure.

Similarly pyrazole derivatives are well-known and important nitrogen-containing five-membered heterocyclic compounds and have occupied a unique position in the design and synthesis of novel biologically active agents. They display various biological activities such as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal[13-15]. Some of these compounds also possess antioxidant, anti-inflammatory, analgesic properties[16, 17]and cardiovascular agents[17a]. Further, they are also used as chelating agents[18] and inhibitors for the corrosion of the steel [19] Due to these interesting activities of pyrazole derivatives, considerable attention has been focused on this class of compounds. In addition, pyrazoles have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis[20.]

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation.[21] The developing of new MCRs[22] 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.[23] The presence of an imidazole ring in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles.[24] 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.[25,26] 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 temprature. 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.

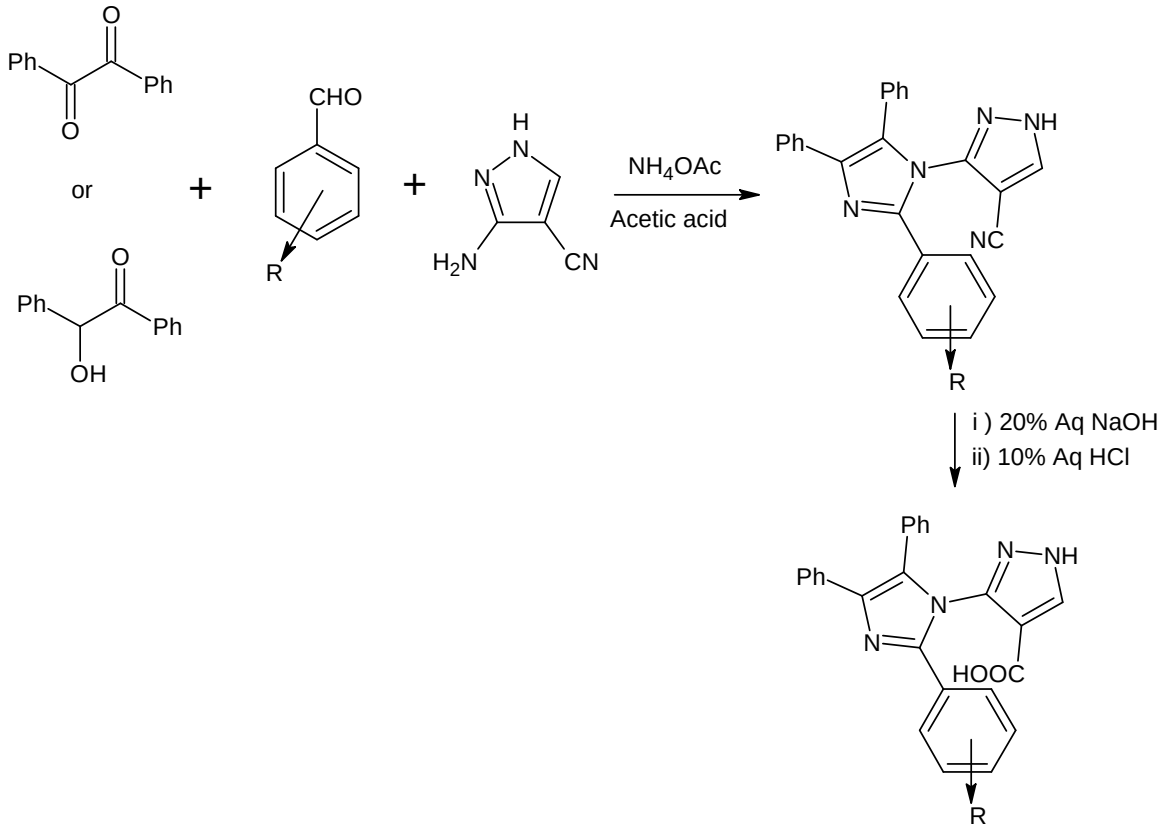
Chemistry

This versatile applicability highlights the importance of access to efficient synthetic routes to well designed 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-Trisubstituted 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-pyrazole 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), pyrazole amine (1 mmol) and ammonium acetate (1 mmol) were stirred in acetic acid (20 ml) at reflux temperature for the stipulated time. The reaction was monitored by TLC. Added 20% Aqueous NaOH solution and stirred for 4-5 hours. Reaction was monitored by TLC. After completion of the reaction, reaction mass was neutralised with 10% HCl. Distilled to residue under vaccum , the reaction mixture was extracted with ethyl acetate (2 X 25 ml) insoluble inorganic was filtered. 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



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

3-[2-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-01)

Yield : 64% IR (KBr) 3400 (N-H) 1603 (C=O) 1538 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 6.91-7.51(m, 15H) MS : m/z 423.1 (M-1)

3-[2-(2-Chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-02)

Yield : 60% IR (KBr) 3398 (N-H) 1648 (C=O) 1558 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 6.82-7.53(m, 15H) MS : m/z 438.9(M-1)

3-[2-(3,4methylenedioxy phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-03)

Yield : 52% IR (KBr) 3294 (N-H) 1620 (C=O) 1588 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 5.94 (s, 2H) δ 6.67-7.50 (m, 14H) MS : m/z 449.1(M-1)

3-[2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid(IP-04)

Yield : 49% IR (KBr) 3378 (N-H) 1609 (C=O) 1577 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 3.7 (s, 3H) δ 6.75-7.51 (m, 15H) MS : m/z 434.0(M-1)

3-[2-(4-trifluromethyl phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-05)

Yield : 58% IR (KBr) 3414 (N-H) 1605 (C=O) 1583 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 7.23-7.64 (m, 15H) MS : m/z 472.9(M-1)

3-[2-(3-hydroxy,4-methyoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid(IP-06)

Yield : 55% IR (KBr) 3352 (N-H) 1618 (C=O) 1564 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 3.92 (s, 3H) δ 9.32 (s,1H) δ 6.89-7.54 (m, 14H) MS : m/z 451.0(M-1)

3-[2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid(IP-07)

Yield : 62% IR (KBr) 3411 (N-H) 1690 (C=O) 1574 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 7.22-7.99 (m, 15H) MS : m/z 450.0(M-1)

3-[2-(4-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid(IP-08)

Yield : 53% IR (KBr) 3414 (N-H) 1644 (C=O) 1570 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 9.41 (s, 1H) δ 7.11-7.78 (m, 15H) MS : m/z 421.0(M-1)

3-[2-(3,4 di hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-09)

Yield : 44% IR (KBr) 3343 (N-H) 1644 (C=O) 1570 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 9.50 (s, 2H) δ 6.81-7.65 (m, 14H) MS : m/z 437.0(M-1)

3-[2-phenyl-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-10)

Yield : 42% IR (KBr) 3343 (N-H) 1623 (C=O) 1572 (C-C arom) cm^{-1}

^1H NMR (δ ppm, DMSO-d_6) δ 7.21-7.52 (m, 16H) MS : m/z 405.1(M-1)

3-[2-(3,4,5 tri methoxy phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-11)

Yield : 61% IR (KBr) 3415 (N-H) 1643 (C=O) 1589 (C-C arom) cm^{-1}

. ^{1}H NMR (δ ppm, DMSO-d_6) δ 3.8 (s, 3H) δ 3.6(s, 6H) δ 6.80-7.68 (m, 13H) MS : m/z 495.1(M-1)

3-[2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-12)

Yield : 57% IR (KBr) 3393 (N-H) 1697 (C=O) 1588 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm , DMSO- d_6) δ 7.21-7.53 (m, 15H) MS : m/z 483.0(M-1)

3-[2-(4-Isoproply phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid(IP-13)

Yield : 62% IR (KBr) 3430 (N-H) 1602 (C=O) 1579 (C-C arom) cm^{-1}

^{1}H NMR (δ ppm, DMSO- d_6) δ 1.25 (d, 6H) δ 2.88 (m, 1H) δ 7.12-7.52(m, 15H)

MS : m/z 447.1(M-1)

3-[2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-pyrazole-4-carboxylic acid (IP-14)

Yield : 61% IR (KBr) 3307 (N-H) 1616 (C=O) 1593 (C-C arom) $cm^{-1.}$

^{1}H NMR (δ ppm, DMSO- d_6) δ 7.23-7.61 (m, 15H) MS : m/z 439.0(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 (IP 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
IP-01	06±0.2	05±0.2	06±0.2	05±0.1	06±0.2	05±0.2
IP-02	07±0.1	05±0.2	08±0.2	06±0.2	06±0.2	04±0.1
IP-03	00	00	00	00	00	00
IP-04	02±0.2	01±0.1	03±0.1	00	03±0.2	01±0.2
IP-05	03±0.2	05±0.1	04±0.1	04±0.1	05±0.2	06±0.2
IP-06	02±0.2	01±0.1	03±0.1	04±0.1	03±0.2	01±0.2
IP-07	04±0.2	02±0.1	01±0.1	03±0.1	01±0.2	02±0.2
IP-08	03±0.2	03±0.1	02±0.1	04±0.2	03±0.2	01±0.2
IP-09	03±0.2	01±0.1	05±0.1	03±0.1	04±0.2	02±0.2
IP-10	02±0.2	01±0.1	02±0.1	00	03±0.2	01±0.2
IP-11	00	00	00	00	00	00
IP-12	07±0.1	05±0.2	08±0.2	06±0.2	06±0.2	04±0.1
IP-13	00	00	00	00	00	00
IP-14	06±0.2	04±0.1	07±0.1	05±0.1	08±0.2	04±0.2
Streptomycin(std)	16±0.2	10±0.1	15±0.2	10±0.2	16±0.2	13±0.2

Antibacterial activity

The antibacterial activities of newly synthesized compounds (IP 01-15) 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 (IP 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
IP-01	06±0.2	01±0.2	04±0.1	03±0.2	05±0.2	04±0.2
IP-02	05±0.1	03±0.2	04±0.2	03±0.2	05±0.2	02±0.1
IP-03	01±0.2	01±0.2	02±0.1	03±0.2	03±0.2	02±0.2
IP-04	00	00	00	00	00	00
IP-05	03±0.2	01±0.1	04±0.1	03±0.1	04±0.1	03±0.1
IP-06	00	00	00	00	00	00
IP-07	04±0.1	03±0.2	06±0.1	05±0.2	04±0.1	02±0.1
IP-08	00	00	00	00	00	00
IP-09	01±0.1	02±0.1	03±0.1	01±0.1	03±0.1	01±0.1
IP-10	00	00	00	00	00	00
IP-11	00	00	00	00	00	00
IP-12	06±0.2	05±0.2	04±0.1	03±0.2	05±0.2	04±0.2
IP-13	02±0.2	01±0.1	03±0.1	02±0.1	03±0.2	01±0.2
IP-14	04±0.2	01±0.1	04±0.1	02±0.1	03±0.2	01±0.2
Fluconazole(Std.)	13±0.2	10±0.1	17±0.2	15±0.2	22±0.2	20±0.2

Antimicrobial activity

The new compounds (**IP 01-15**) 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, **IP-01, IP-02, IP- 07, IP- 08, IP-12** and **IP-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 **IP-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 **IP-01, IP-02, IP-05, IP-07, IP-12, IP-13** and **IP-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-pyrazole 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 **IP-01, IP-02, IP-05, IP-07, IP-12** and **IP-14** showed good antibacterial activity towards all bacterial strains when compared to standard drug streptomycin. **IP-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- pyrazoles was developed. A series of 1,3,4,5-tetrasubstituted Imidazole- pyrazole 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 pyrazole derivative are underway in our laboratory.

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