CATALYST FREE MULTI-COMPONENT SYNTHESIS OF 5-AMINO-1,3-DIARYL-*1H*-PYRAZOLE-4-CARBONITRILES IN ENVIRONMENT FRIENDLY MEDIUM AND THEIR BIOLOGICAL EVALUATION

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Abstract: The sequential Knoevengel-cyclo condensation reaction involving aromatic aldehydes, malononitrile, and phenyl hydrazine in water and ethanol at room temperature is described as an efficient, one-pot, three-component synthesis of an extensive variety of heterocyclic compounds that are extremely relevant to the scientific community.

Keywords: Three-component synthesis, Catalyst free, 5-Amino pyrazole, Green chemistry.

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Introduction

The field of science has lately taken an interest in the possible applications of heterocyclic compounds linked by nitrogen. To create these heterocyclic compounds, the cyclization reaction of suitable linear compounds is a common and well-known method [1-3]. Pyrazoles containing heterocyclic compounds were the go-to for the pharmaceutical and agricultural sectors for a long time. These compounds have been found to have a variety of useful properties, including anti-tumor, anti-bacterial, anti-microbial, anti-fungal, anti-inflammatory, analgesic, anti-depressant, anti-convulsant, and antipyretic effects. fights against parasites, malaria, cancer, and viruses [4-10]. Research on pyrazole derivatives is highly valued in the pesticide chemical community because of these molecules' herbicidal and insecticidal effects [11-19]. Coordination chemistry has made extensive use of pyrazole-containing molecules as ligands [20]. Prior research [21, 22] indicated that 5-amino-4-cyanopyrazole derivatives had antibacterial action.

Other routes can be taken to synthesize pyrazole derivatives [23-25]. The two most prevalent ways to create 1,3,4,5-tetrasubstituted pyrazoles are 1,3-dipolar cycloadditions of diazo compounds onto triple bonds [27], and oxidative N-N bond creation of enamines and nitriles [28]. Two other approaches to functionalized prefabricated trisubstituted pyrazoles include nucleophilic substitution and transition metal-catalyzed C-N bond creation. Many heterocyclic compounds can be synthesized using nitriles as an intermediate [30-32]. We have successfully produced novel pyrazole compounds by employing aromatic aldehydes, malononitrile, and phenyl hydrazine derivatives in a tandem Knoevengel cyclo-condensation reaction in water and ethanol at room temperature.

Experimental:

Chemicals and apparatus:

All chemicals were used directly after purchase from Merck or B. L. D. Pharma Companies. Using a **BRUKER AVANCE III HD NMR 500 MHz** spectrometer (in ppm) for ^{1}H NMR. The internal standard was tetramethyl silane (TMS). Singlet (*s*), doublet (*d*), triplet (*t*), quadruplet (*q*), and multiplet (*m*) are the abbreviations for nuclear magnetic resonance (NMR) signals. Uncorrected melting points were measured using an open capillary tube. FT(IR) spectra were recorded on Brucker FT-IR instrument on KBr pellets. Mass spectra of the prepared derivatives were recorded on Bruker IMPACT HD instrument.

General procedure for the preparation of 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile derivatives: An aromatic aldehyde (1 mol), malononitrile (1 mol), and phenyl hydrazine (1 mol) were added to a 50 mL mixture of water and ethanol (1:1) in a 250 mL round-bottomed flask while the ingredients were at room temperature. Once the reaction was complete (as monitored by TLC), crystals of the product were formed. These crystals were recovered via filtration and subsequently recrystallized from ethanol to achieve pure products.

Scheme: Greener Synthesis of 5-amino-3-aryl-1-phenyl-1*H*-pyrazole-4-carbonitrile from phenyl hydrazine, malononitrile, and substituted benzaldehydes

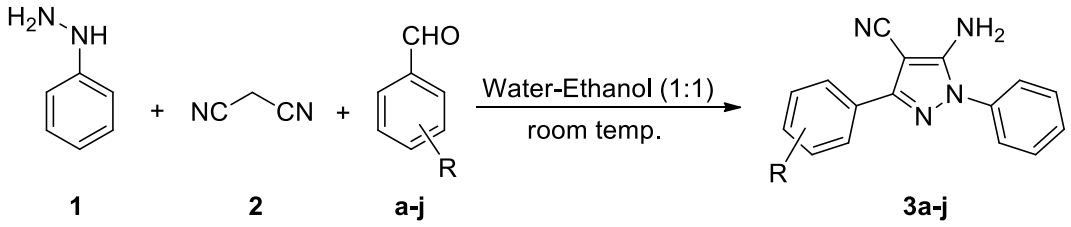
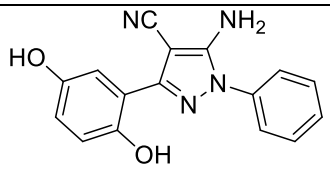
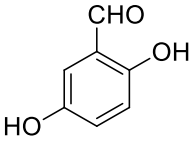
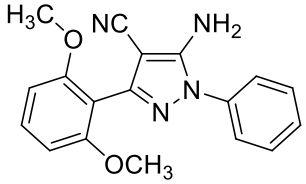
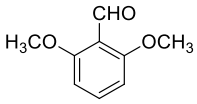
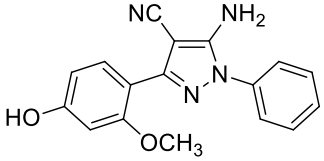
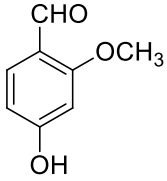
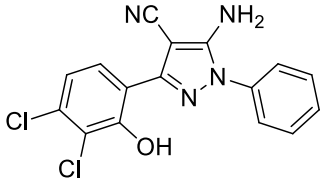
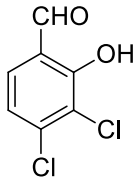
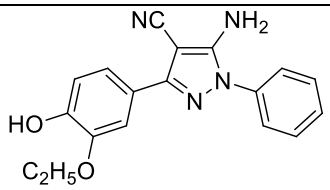
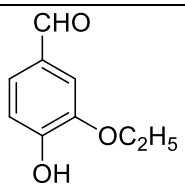
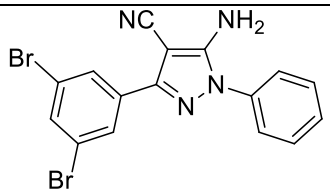
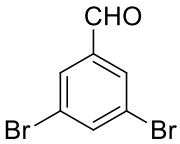
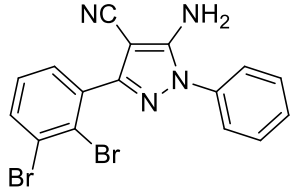
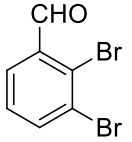
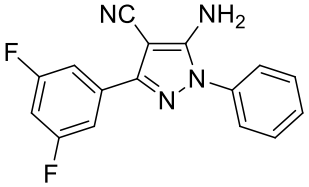
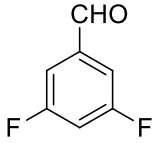
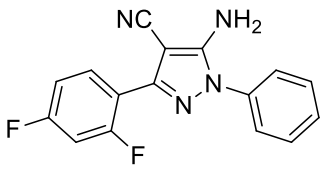
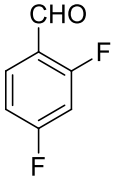
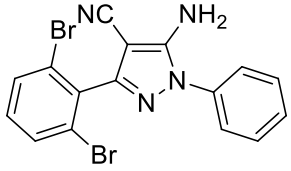
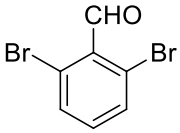


Table 1: Yield, colour, reaction time, and physical constants of the products (**3a-j**)

Products	Aldehyde	Colour	Yield (%)	Reaction time (min.)	m.p. (°C)
 **3a**	 **a**	Yellow powder	76.37	25	207-210
 **3b**	 **b**	Orange powder	73.97	20	194-196
 **3c**	 **c**	Yellow powder	69.78	30	176-178
 **3d**	 **d**	White powder	80.47	45	172-174
 **3e**	 **e**	Red-brown powder	70.36	120	171-173
 **3f**	 **f**	Brown powder	79.19	35	197-199
 **3g**	 **g**	Brown powder	78.74	40	195-197
 **3h**	 **h**	Yellow powder	81.66	20	167-169

 **3i**	 **i**	Yellow powder	79.40	50	170-172
 **3j**	 **j**	Brown powder	73.78	45	197-199

5-Amino-3-(2,4-dihydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3a):
Yellow powder (71.57 %), M.P. = 211^{0}C, FT(IR) spectrum (KBr) 3322, 2953, 2952, 2202, 1684, 1595, 1441, 1250, 737, 683 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 10.19 (s, 1H), 7.84 (s, 1H), 7.34 (d, 2H), 6.73-7.33 (m, 8H). UV spectrum (λ_{nm}) 324, 282. MS (m/z): 290.13 $(M)^+$. (Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17; O, 10.95 %. Found: C, 65.48; H, 4.06; N, 18.72, O, 10.92 %.

5-Amino-3-(2,3-dimethoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3b):
White powder (68.99 %), M.P. = 125 °C, FT(IR) spectrum (KBr) 3292, 2237, 1684, 1248, 736, 684 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.62 (*d*, 2H), 7.62 (*d*, 2H), 6.88-7.60 (*m*, 8H), 3.95-4.01 (*s*, 6H). UV spectrum (λ_{nm}) 355, 270. MS (m/z): 323.10 $(M)^+$. (Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 19.49; O, 9.99 %. Found: C, 66.39; H, 4.99; N, 19.42, O, 9.90 %.

5-Amino-3-(2-hydroxy-4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3c):
White powder (73.53 %), M.P. = 157 °C, FT(IR) spectrum (KBr) 3408, 3290, 2210, 1599, 1250, 735, 685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.84 (*s*, 1H), 4.26-4.27 (*d*, 2H), 6.88-7.65 (*m*, 8H), 1.51-1.55 (*s*, 3H). UV spectrum (λ_{nm}) 363, 277. MS (m/z): 301.08 $(M)^+$. (Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29; O, 10.45 %. Found: C, 66.61; H, 4.59; N, 18.21, O, 10.38 %.

5-Amino-3-(3,4-dichloro-2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3d):
White powder (76.11 %), M.P. = 163 °C, FT(IR) spectrum (KBr) 3444, 3339/3295, 2193, 1645, 1251, 732, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 11.56 (*s*, 1H), 7.66-7.69 (*d*, 2H), 6.94-7.32(*m*, 7H). UV spectrum (λ_{nm}) 383, 318. MS (m/z): 338.34 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4OCl_2$: C, 55.67; H, 2.92; N, 16.23; O, 4.64; Cl, 29.34 %. Found: C, 55.60; H, 2.89; N, 16.16, O, 4.22; Cl, 29.29 %.

5-Amino-3-(3-ethoxy-4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3e):
Red-brown powder (70.36 %), M.P. = 172 °C, FT(IR) spectrum (KBr) 3326, 2192, 1599, 1250, 744, 685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 11.78 (*s*, 1H), 8.173 (*d*, 2H), 7.31-7.93 (*m*, 7H), 7.02-7.11 (*s*, 5H), 3.55 (*s*, 3H). UV spectrum (λ_{nm}) 334, 273. MS (m/z): 332.33 $(M)^+$. (Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76; O, 9.57%. Found: C, 68.00; H, 5.34; N, 16.11, O, 9.49%.

5-Amino-3-(3,4-dibromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3f):
Yellow powder (79.19 %), M.P. = 178 °C, FT(IR) spectrum (KBr) 3306, 1924, 1589, 1252, 749, 653, 633 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.48-7.92 (*d*, 2H), 6.94-7.75 (*m*, 8H). UV spectrum (λ_{nm}) 330, 274. MS (m/z): 418.00 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4Br_2$: C, 45.96; H, 2.41; N, 13.40; Br, 38.22 %. Found: C, 45.69; H, 2.33; N, 13.22; Br, 38.17 %.

5-Amino-3-(2, 5-dibromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3g):
Yellow powder (74.40 %), M.P. = 176 °C, FT(IR) spectrum (KBr) 3302, 2216, 1563, 1252, 752, 693, 635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.20 (*d*, 2H), 6.95-7.96 (*m*, 8H). UV spectrum (λ_{nm}) 337, 309. MS (m/z): 420.95 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4Br_2$: C, 45.96; H, 2.41; N, 13.40; Br, 38.22 %. Found: C, 45.91; H, 2.37; N, 13.27; Br, 38.19 %.

5-Amino-3-(3,4-difluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3h):
Yellow powder (77.51 %), M.P. = 148 °C, FT(IR) spectrum (KBr) 3304, 2233, 1596, 1249, 1250, 753, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm)

7.55-7.63 (*d*, 2H), 6.87-7.54 (*m*, 8H). UV spectrum (λ_{nm}) 336. MS (m/z): 297.09 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4Cl_2$: C, 64.86; H, 3.40; N, 12.62; F, 18.91 %. Found: C, 64.80; H, 3.33; N, 12.55; F, 18.85 %.

5-Amino-3-(2,5-difluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3i):
Yellow powder (79.40 %), M.P. = 151 °C, FT(IR) spectrum (KBr) 3250, 2213, 1594, 1250, 1238, 747, 688 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.68 (*d*, 2H), 6.95-7.75 (*m*, 8H). UV spectrum (λ_{nm}) 333, 287. MS (m/z): 297.08 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4Cl_2$: C, 64.86; H, 3.40; N, 12.62; F, 18.91 %. Found: C, 64.83; H, 3.36; N, 12.57; F, 18.88 %.

5-Amino-3-(2,4-dibromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (3j):
Yellow powder (77.51 %), M.P. = 168 °C, FT(IR) spectrum (KBr) 3396, 2208, 1599, 1247, 750, 693, 639 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.96 (*d*, 2H), 6.95-7.89 (*m*, 8H). UV spectrum (λ_{nm}) 317. MS (m/z): 428.96 $(M)^+$. (Anal. Calcd for $C_{16}H_{10}N_4Br_2$: C, 45.96; H, 2.41; N, 13.40; Br, 38.22 %. Found: C, 45.93; H, 2.37; N, 13.39; Br, 38.19 %.

Antimicrobial Activity:
We used synthetic substances for a variety of fungal and bacterial samples (clinical isolates), and all of the samples were purchased as dry powder for this experiment. Candida albicans MCC1439 and Saccharomyces cerevisiae MCC1033 were among the fungus strains examined. Before being sub-cultured on antimicrobial agent-free potato dextrose agar, the mold isolates were preserved in sterile water to guarantee their vitality and purity. Both Escherichia coli MCC 2412 and Pseudomonas aeruginosa MCC 2080 were Gram-negative bacteria, but Bacillus subtilis MCC 2010 and Staphylococcus aureus MCC 2010 were Gram-positive bacteria. In Pune, India, at the National Centre for Molecular Research, we bought these living organisms. There was no antibacterial action at the concentrations tested when using dimethyl formamide (DMF) to dissolve the compounds and preserve the solution at 4 °C. In contrast to fungi, which can be cultured in potato dextrose agar and Sabaouraud liquid media, bacteria can be grown in nutritional broth (NB; Difco) and nutrient agar (NA).

Antibacterial screening:
To evaluate the antimicrobial efficacy of the produced chemicals, we utilized a panel of four bacteria: two gram-positive (S. aureus MCC 2010 and B. subtilis MCC 2010) and two gram-negative (E. coli MCC2412 and P. aeruginosa MCC2080). Autoclaving the Muller Hilton agar medium at 15 lbs/in2 for 15 minutes was done for the purpose of antibacterial testing. To determine whether newly manufactured antibiotics were effective against bacteria, the disc diffusion method was employed. Floating the culture in sterile distilled water allowed the inoculum to be diluted to a concentration of approximately 108 cfu/mL to test for antibacterial activity. The desired microbial strains were introduced to 20 mL of Muller Hilton agar medium by swabbing it onto petri dishes. Before adding 100 µL of a 4.0 mg/mL solution of each chemical reconstituted in DMSO, 6 mm diameter wells were bored into the pre-inoculated plates using a clean borer. Every plate was incubated for 24 hours at 37 °C. Every plate was incubated for 24 hours at 37 °C. The zone of inhibition surrounding the wells was used to evaluate the antibacterial activity of all produced drugs. The two solvents utilized as controls were streptomycin and dimethyl sulfoxide (DMSO).

Antifungal Activity:
Two different types of fungi were tested using the cup-and-plate technique to see how well the compounds performed. Candida albicans MCC1439 and Saccharomyces cerevisiae MCC1033 were the strains used. The discs were 6 mm in diameter and 1 mm thick. We injected the test fluid into them using a micropipette. After that, the dishes were maintained at 37 °C for an additional 72 hours. The effect of the experimental solution on the implanted fungus's development became obvious during this time. The inhibition ring's size was measured after 36 hours of storage at 37 °C. There have been investigations into the minimum inhibitory doses of chemicals that are believed to possess antifungal properties. After overnight incubation, the minimum inhibitory concentration (MIC) of a fungal medication is defined as the concentration at which noticeable microbial development was inhibited. Clinical laboratories used the minimum inhibitory concentration (MIC) to confirm microbial resistance to existing antimicrobials and to find out how effective new antimicrobials were.

Results and Discussion:
Researchers performed a catalytic screening at room temperature using several catalysts and 1 mmol of aromatic benzaldehyde, phenyl hydrazine, and malononitrile, respectively. There was shown to be no significant effect of catalyst type on pyrazole yield by reaction condition screening. A base catalyst was not necessary to obtain the

desired 5-amino-4-cyanopyrazole derivatives after a remarkable yield was achieved after 2 hours of reaction at room temperature in a solvent mixture of water and ethanol (1:1 v/v).

Consequently, phenyl hydrazine acts as both a nucleophile and a catalyst for the Bronsted base reaction. So, the bases didn't affect the reaction's yield per se. Based on this, we monitored the reaction yield about the phenyl hydrazine concentration. Adding more phenyl hydrazine does not increase the production of 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile. Reducing the amount of phenyl hydrazine did not, however, result in total conversion.

In these ideal circumstances, this three-component process can be extended to include a broad range of aromatic aldehydes, malononitrile, and phenyl hydrazine derivatives. There were high product yields when malononitrile was used. Interestingly, high product yields were achieved with even low nucleophilic malononitrile. Also, dialdehydes were employed to successfully produce bis poly-substituted pyrazoles in large quantities. To further explore the reaction's bounds, aldehydes containing electron-drawing substituents on the aromatic ring were also utilized. The bulky aldehydes that were sterically present were converted into the necessary products with relative ease. To increase the reaction's applicability, researchers looked into using heteroaryl aldehydes.

Findings from experiments evaluating the three-component coupling capability of several aliphatic aldehydes. Aliphatic aldehydes were not effective in this one-pot, catalyst-free reaction, though. Because aromatic aldehydes are more reactive towards nucleophilic addition, this tendency was primarily caused by the fact that aliphatic aldehydes are less reactive. Schematic 1 shows the steps used to synthesize 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile in a very selective manner. In situ preparation of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives is possible, as suggested by this method, by condensation of aromatic aldehyde, phenyl hydrazine, and a very reactive malononitrile.

Since nitrile may be easily transformed into other functional groups, the recently found method offers strong empirical proof of this assertion. Remarkably, a catalyst-free reaction was carried out with remarkable selectivity and minimal atom waste. To our knowledge, no single vessel has ever been used to carry out a Knoevenagel reaction, Michael-type reaction, ring closure, and subsequent aromatization without the need for a catalyst.

The structures of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives were inferred by spectroscopic examinations. Compounds **3a**, **3c**, and **3d** exhibited a wide band in the 3444-3322 cm^{-1} area due to the υ(O-H) stretching of the aromatic hydroxyl groups. The (O-H) group for compound 4a was determined to be represented by bands at 2952 and 1441 cm^{-1}. Bands in the 3350-2953 cm^{-1} area of the infrared spectra of compounds **3a**-**3j** were interpreted as the (N-H) stretching of the grafted amine groups. The FT-IR spectra of all the compounds that were synthesized show the presence of the C=N stretching vibration band between 1684 and 1545 cm^{-1}.

In the ^{1}H NMR spectra of compounds **3a**, **3c**, **3d**, and **3e** ($CDCl_3$, 500 MHz), the presence of an aromatic ring -OH is indicated by the singlet at δ5.84-11.78. The phenyl ring showed a doublet in the range of 6.73 to 7.96. Between 7.34 and 8.20, the NH_2 group added to a 2H singlet. 3H was also given another singlet in the area δ1.54-4.01 because of the methoxy group connected to the aromatic ring.

Antimicrobial evaluation:

The new compounds were evaluated for their antibacterial and antifungal activity against various bacterial and fungal strains in vitro using the broth microdilution method. These strains included Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* (MCC 2010), *Bacillus subtilis* (MCC 2010), *Escherichia coli* (MCC 2412), and *Pseudomonas aeruginosa* (MCC 2080). All bacterial isolates were cultured in nutritional broth for 24 h at 37 °C. Fungal spore suspensions were collected using tween 80 from 7-day-old cultures of fungi cultured on sabouraud dextrose agar at 25 °C for 24 h. The final bacterial and fungal inoculum ODs were 0.2–0.3 and 0.5, respectively. Preparing the stock solutions with DMSO does not affect the measured concentrations. Bacteria and fungi doubled at a concentration of 1000 μg/mL. Powdered medications like fluconazole and streptomycin were commonly used to treat fungal and bacterial infections. After being incubated at 37 °C for 24 h and at 25 °C for 48 hours, antibacterial and antifungal activities were assessed, respectively.

The study's standard treatment was streptomycin, a broad-spectrum antibiotic having a minimum inhibitory concentration (MIC) of 10 mg/mL against the bacterial species. Suppression zones ranged from 12-16 mm for *E. coli* (MCC 2412), 10-12 mm for *B. subtilis* (MCC 2010), 12-15 mm for *P. aeruginosa* (MCC 2080), and 9-13 mm for *S. aureus* (MCC 2010). Compared to other bacterial

species, *S. aureus* was more susceptible to **3a**. It was also discovered that **3e** (19mm) was more effective than the gold standard drug. The effectiveness of the reference medication was found to be lower than **3d** against *P. aeruginosa*. It was shown that **3j** was the most potent chemical against *E. coli*.It was shown that the median inhibition zones for *C. albicans* (MCC1439) and *S. cerevisiae* (MCC1033) were 8-17 mm and 10-17 mm, respectively, when treated with the standard drug *fluconazole* (MIC = 50 µg/ml). The medication is more effective than the gold standard against both *C. albicans* (MCC1439) and *Saccharomyces cerevisiae* (MCC1033), with a minimum inhibitory concentration (MIC) of 54 µg/mL.

Table 2: Antibacterial activities of the product (3a-j)

Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
3a	12	10	15	12
3b	10	12	12	15
3c	9	11	13	13
3d	13	10	14	14
3e	11	12	16	15
3f	12	11	12	12
3g	11	10	15	14
3h	12	12	13	12
3i	13	10	16	15
3j	12	11	15	11
Std	12	11	12	12

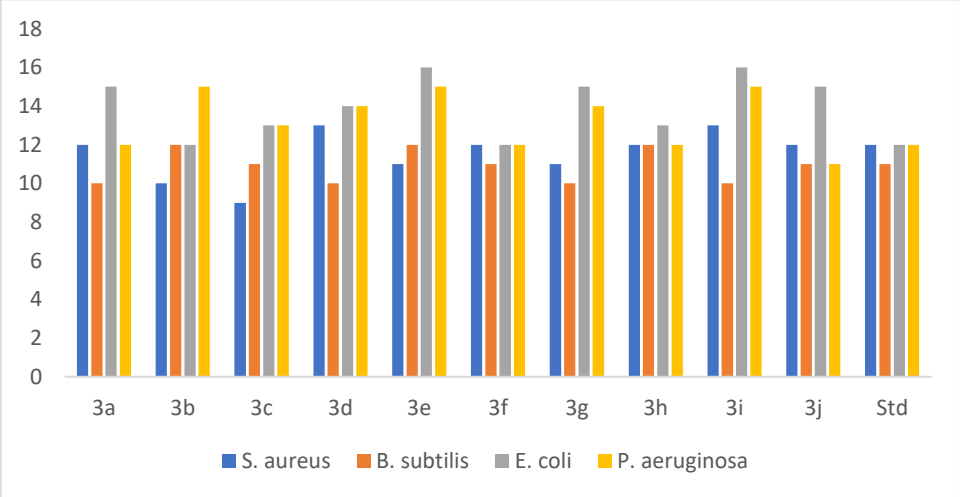


Figure 1: Antibacterial activities of the product (**3a-j**)

Table 3: Antifungal activities of the product (**3a-j**)

Compound	*Candida albicans*	*Saccharomyces cerevisiae*
3a	16	11
3b	10	15
3c	13	16
3d	14	13
3e	8	15
3f	10	12
3g	9	13
3h	8	16
3i	17	17
3j	16	16
Fluconazole	15	11

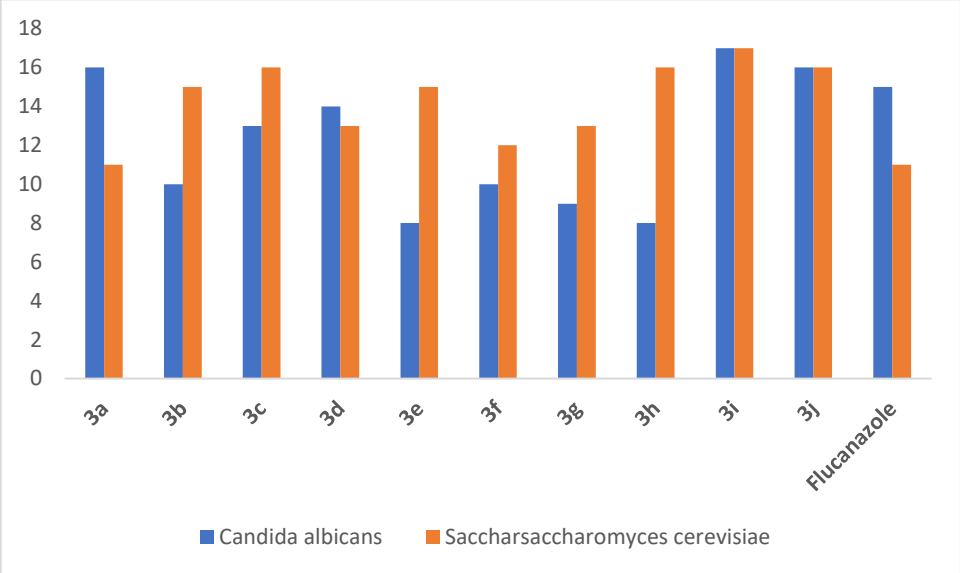


Figure 2: Antifungal activities of the product (**3a-j**)

Conclusions:

Applying a multicomponent reaction method, we have demonstrated the one-step synthesis of poly-substituted amino pyrazole analogs. Fast, good to excellent yields were attained without the need for a catalyst in this reaction, which had additional advantages including easy experimental workup and no hazardous by-products. The use of catalysts, toxic organic solvents, or dehydration is not necessary for the procedure we detail above for dealing with pyrazole systems. An eco-friendly strategy for synthesizing these compounds is presented by this methodology.

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