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IONIC LIQUID / AMBERLYST-15 CATALYSTS SYNTHESIS OF 1H-PYRAZOLE DERIVATIVES AND MICROBIAL EVALUATION

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Abstract:
To explore a conventional eco-friendly approach, we synthesized novel 1H-pyrazole derivatives and conducted biological evaluations of these compounds. We employed a modern method to synthesize acetyl-substituted derivatives **(4a-h),** 2,2,2-trifluoroacetyl derivatives **(5a-h),** and 1-tosyl-1H-pyrazole derivatives **(6a-h),** using Amberlyte-15 and the ionic liquid [bmim][PF_6] / $Cu(OTf)_2$ as catalysts from α,β-unsaturated carbonyl compounds **(3a-h).** Each synthesized compound was tested for antifungal activity against two yeasts (C. albicans and S. cerevisiae) and antibacterial activity against two Gram-negative bacteria (E. coli and P. aeruginosa) as well as two Gram-positive bacteria (S. aureus and B. subtilis). The results indicated that several newly synthesized compounds exhibited potent antimicrobial activity against the different bacterial strains.

Keyword: α,β-unsaturated carbonyl, Amberlyst-15, [bmim][PF_6] ionic liquid, $Cu(OTf)_2$, 1H-pyrazole, microbial evaluation.

Introduction:

Pyrazole is a five-membered ring that contains two adjacent nitrogen atoms, which give it unique physicochemical and biological properties. The structural flexibility of pyrazolines, along with the ease of their synthesis, makes them valuable scaffolds for drug discovery [i-iii]. 1H-Pyrazole is a significant heterocyclic compound with a wide range of applications in medicinal chemistry, materials science, and agrochemicals. Its distinctive five-membered ring structure, which contains two nitrogen atoms, has made it an important scaffold in drug discovery. Derivatives of 1H-Pyrazole exhibit various biological activities, including antimicrobial, anticancer, anti-inflammatory, anti-SARS-Cov-2, and antifungal properties [iv-xv]. In the last decade, the WHO has approved several of pyrazole moieties with pharmacological and biological properties [xvi-xx] shown in Figure 1.

Numerous synthesis strategies for 1H-pyrazoles have been reported in the literature. Researchers have documented protocols that utilise various catalysts and solvents, such as glacial acetic acid under heat or ultrasound irradiation, and sodium hydroxide in ethyl alcohol under ultrasound irradiation [xx-xxii]. Some scientists used K_2CO_3 mediated microwave irradiation, glacial acetic acid and ethanol as solvents, utilising under microwave irradiation

[xxiii-xxvi]. Many scientists use conventional approaches like employing Amberlyst-15, Phosphotungstic acid ($H_3PW_{12}O_4$) and reflux in solvents like Toluene, Ethanol, and Ethyl acetate [xxvii-xxxi].

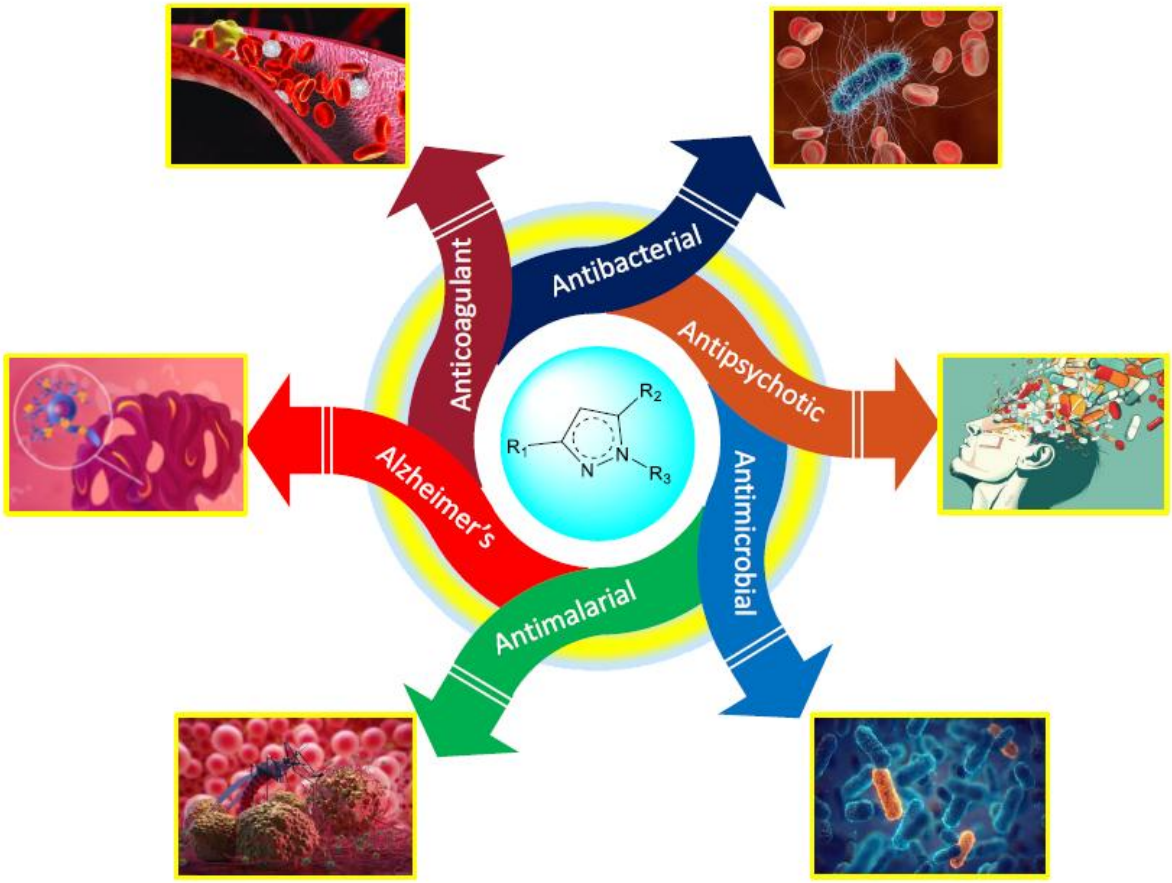


Figure 1: 1H-pyrazole has pharmacological & biological properties.

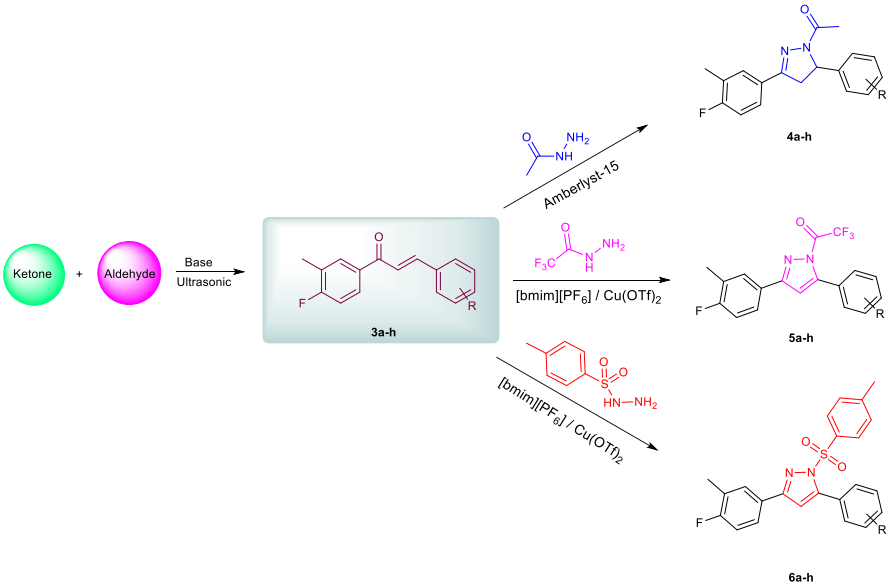
Substituting groups on the pyrazole ring has proven to be an effective method for modulating the compound's biological and chemical properties. Additionally, acetylated and p-tolyl (para-methylphenyl) pyrazoles have demonstrated increased pharmacological activities, including anti-inflammatory, antimicrobial, and anticancer effects [xxxii-xli]. Although this method is effective, it often suffers from issues such as low yields, side reactions, and harsh reaction conditions, which limit its practical application.

Current study we have successfully synthesized some novel 1H-pyrazoles through the condensation of substituted hydrazines with α,β-unsaturated carbonyl compounds. The α,β-unsaturated carbonyl compounds were derived from ketones and aldehydes, using either acidic or basic conditions under ultrasonic conditions [xlii]. Although this method is effective, it often suffers from issues such as low yields, side reactions, and harsh reaction conditions, which limit its practical application.

Acetyl pyrazoline derivatives were synthesized from α and β-unsaturated carbonyl compounds reacted with acetohydrazide using a conventional method. Amberlite-15 was employed as a catalyst in acetonitrile solvent. Additionally, trifluoroacetyl pyrazole and p-tolyl sulphonyl pyrazole derivatives were synthesized using the ionic liquid [bmim][PF_6] and $Cu(OTf)_2$ as catalysts. The novel synthesized derivatives were characterized using various analytical techniques. Synthesized derivatives are evaluated for their Anti-bacterial and Anti-fungal activity against a variety of bacteria[xliii-xlv]. The outcome of this study, that several of the newly synthesised pyrazole derivatives exhibit potent microbial activity properties, was assessed to identify potential candidates for therapeutic applications.

Result and Discussion

Chemistry: The synthesized chalcone derivatives **(3a-h)** were prepared from 4-fluoro-3-methylphenylacetophenone and aromatic aldehydes. Their structures were confirmed using methods described in reference[xlii] including Infrared (IR) spectra, Nuclear Magnetic Resonance (NMR) spectroscopy, and mass spectrometry. Melting points were estimated using the open capillary method, resulting in uncorrected values. The synthesised compounds **(3a-h)** exhibited yields ranging from 65 % to 85 %, demonstrating efficiency and consistency in the synthesis process.



Scheme 1: Reaction for the synthesis of substituted pyrazole derivatives

Acetyl-substituted 1H-pyrazol derivatives **(4a-h)** were obtained from α,β-unsaturated carbonyl compounds **(3a-h)** and acetohydrazide, utilising an environmentally friendly approach with Amberlyst-15 resin in acetonitrile (ACN), general reaction scheme 1. The 1H-pyrazol derivatives **(4a-h)** were verified through NMR spectroscopy, IR spectroscopy, and high-resolution mass spectrometry (HRMS). In the NMR spectra, the transformation from α,β-unsaturated carbonyl compounds to the pyrazole ring was supported by additional signals at δ 2.9-3.3, 3.7-4.0, and 5.50-7.0 ppm, corresponding to the aliphatic pyrazole ring. Additionally, a singlet at δ 2.45 ppm, attributable to the N-acetyl (CH_3) group on the substituted pyrazole, was identified. The HRMS/Mass data confirmed that the synthesized derivatives **(4a-h)** correspond to the intended products.

Trifluoroacetyl pyrazole derivatives **(5a-h)** were prepared by reacting α,β-unsaturated carbonyl compounds **(3a-h)** with trifluoroacetyl hydrazide, using the ionic liquid [bmim][PF_6] along with $Cu(OTf)_2$. This reaction produced the direct oxidation product of aromatic pyrazole, as confirmed by NMR analysis. The signals in the ranges of δ 2.9-3.3 ppm, 3.7-4.0 ppm, and 5.50-7.0 ppm were not observed. Additionally, a singlet in the aromatic region at δ 6.9-7.5 ppm indicates the presence of an aromatic ring, supporting the formation of various substituted pyrazole rings. Infrared (IR) spectroscopy demonstrated characteristic stretching frequencies for the C-F bond and N-acetyl stretching frequencies ranging from 3200 to 3400 cm^-1. High-resolution mass spectrometry confirmed the successful synthesis of the derivatives, as indicated by the M+1 peak observed in their mass spectra.

The synthesis of p-tolyl sulfonyl pyrazole derivatives **(6a-h)** was conducted using α,β-unsaturated carbonyl compounds **(3a-h)** and p-tosylsulfonyl hydrazide. This process transitioned from traditional methods to greener approaches by employing the ionic liquid [bmim][PF_6] in conjunction with $Cu(OTf)_2$, resulting in a one-pot oxidative synthesis of

pyrazole derivatives. To substantiate the synthesized products **(6a-h),** analysis were performed using H1NMR spectroscopy, IR spectroscopy, and high-resolution mass spectrometry (HRMS)/ Mass spectrometry. The NMR spectra revealed a singlet at δ 6.9-7.5 ppm for the aromatic pyrazole, with five additional protons in an aromatic region associated with the p-tolyl sulfonyl group. Furthermore, IR spectroscopy indicated SO_2 stretching in the range of 1150-1350 cm^-1 for all synthesized derivatives **(6a-h).** The HRMS /Mass data displayed an M+1 peak, confirming the successful synthesis of the derivatives **(6a-h)** as outlined in the protocol.

We have synthesized novel 1H-pyrazole analogs with a focus on environmentally friendly methods by utilizing conventional techniques, such as ionic liquids, resins, and ultrasonic conditions. The synthesis successfully generated multiple new pyrazole derivatives from aromatic α,β-unsaturated carbonyl compounds by using acetohydrazide, trifluoroacetyl hydrazide, and p-tosylsulfonyl hydrazide, applying Amberlyst-15 resin and the ionic liquid [bmim][PF_6] in the presence of $Cu(OTf)_2$.

Microbial evaluation (Antibacterial and antifungal activity)

The newly synthesized compounds were tested in vitro (microbial evaluation) for anti-bacterial activity against two Gram-negative bacteria (E. coli and P. aeruginosa) and two Gram-positive bacteria (S. aureus and B. subtilis), as well as for anti-fungal activity against two yeasts (C. albicans and S. cerevisiae). The disc diffusion method was employed to measure the zone of inhibition (ZOI), and the minimum inhibitory concentrations (MIC, in µg/mL) were also determined[xliii-xliv]. The results are summarized below, highlighting the antimicrobial activity of the synthesized compounds against the tested bacterial strains.

The novel 1H-pyrazole derivatives exhibit significantly better microbial activity compared to streptomycin. DMSO served as the control, showing no inhibition of MIC. The synthesized novel acetyl-substituted 1H-pyrazole derivatives **4a-h** were tested against the specified bacteria, using streptomycin as the reference standard. Compounds **4a, 4f, 4g,** and **4h** were identified as active inhibitors against the bacteria Bacillus subtilis. Compounds **4a** and **4c** demonstrated activity against Staphylococcus aureus. Additionally, compounds **4a, 4b, 4c,** and **4f** exhibited good activity against Escherichia coli, while compounds **4b, 4e, 4f,** and **4g** showed maximum activity against P. aeruginosa. Compounds **4d** and **4g** exhibited average activity against the yeast Saccharomyces cerevisiae, and compounds **4a-e** showed maximum inhibition against the yeast C. albicans. The results are summarized in Table 1 and Figure 2.

Table 1: Antimicrobial Activity of Compounds (4a-h),

Comp	Diameter of zone of growth inhibition (mm)					
	Gram-positive bacteria		Gram-negative bacteria		Yeasts	
	S. aureus	B. subtilis	E. coli	P. aeruginosa	S. cerevisiae	C. albicans
4a	11	16	13	14	-	10
4b	9	13	14	15	8	11
4c	13	-	13	12	-	18
4d	11	12	12	14	12	11
4e	8	9	11	17	8	10
4f	11	20	14	29	-	8
4g	-	15	13	21	10	-
4h	9	16	15	22	13	-

Std	15	13	15	14	10	11
DMSO	0	0	0	0	0	0

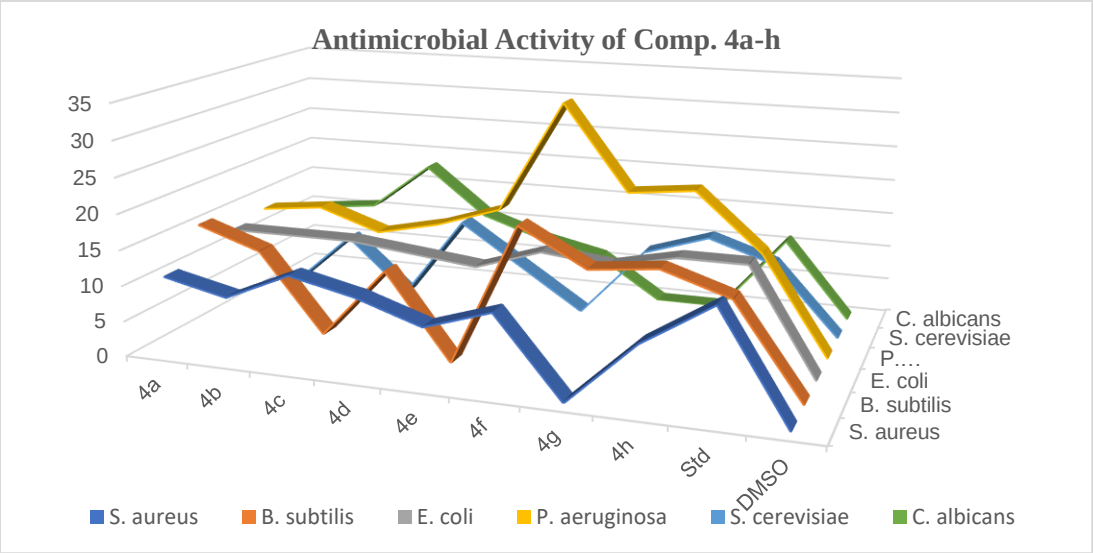


Figure 2: Antimicrobial Activity of Compounds (4a-h),

The novel synthesized 2,2,2-trifluoroacetyl 1H-pyrazole derivatives **5a-h** were tested against specific bacteria, using streptomycin as the reference standard. Compounds **5a, 5b, 5d,** and **5f** were identified as effective inhibitors against the bacteria S. aureus. Compounds **5a, 5b, 5c, 5d,** and **5f** demonstrated activity against B. subtilis. Additionally, compounds **5b, 5c, 5d,** and **5e** showed good activity against E. coli, while compounds **5a, 5c, 5d,** and **5e** exhibited maximum activity against P. aeruginosa. Compounds **5b, 5c, 5d**, and **5e** displayed average activity against the yeast S. cerevisiae, and compounds **5a, 5b, 5d**, and **5e** demonstrated average inhibition against the yeast C. albicans. The results are summarized in Table 2 and Figure 3.

Table 2: Antimicrobial Activity of Compounds (5a-h),

Comp	**Diameter of zone of growth inhibition (mm)**					
	Gram-positive bacteria		**Gram-negative bacteria**		**Yeasts**	
	S. aureus	**B. subtilis**	**E. coli**	**P. aeruginosa**	**S. cerevisiae**	**C. albicans**
5a	16	22	13	14	13	17
5b	18	17	16	11	17	24
5c	12	18	15	15	15	13
5d	23	16	16	14	18	16
5e	11	14	16	19	18	19
5f	14	16	-	12	12	12
Std	17	16	16	20	14	15
DMSO	**0**	**0**	**0**	**0**	**0**	**0**

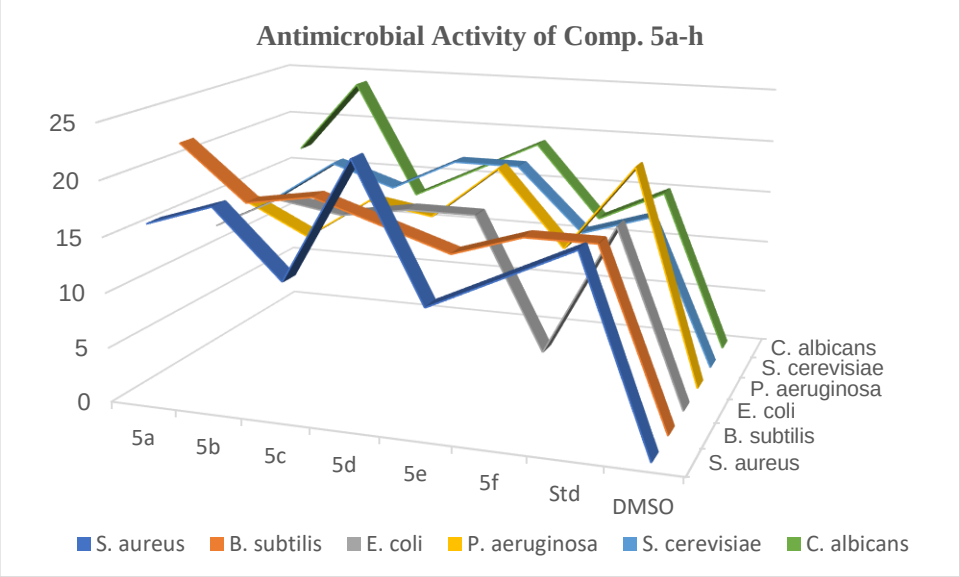


Figure 3: Antimicrobial Activity of Compounds (5a-h),

In contrast, the 1-tosyl-1H-pyrazole derivatives **6a-h** were tested against specific bacteria, with streptomycin serving as the reference standard. Compounds **6a, 6b, 6d,** and **6e** were identified as effective inhibitors of the bacteria S. aureus. Compounds **6a**, **6b, 6d, 6e**, and **6g** exhibited activity against B. subtilis. Additionally, compounds **6a**, **6b, 6d,** and **6e** demonstrated strong activity against E. coli, while compounds **6b, 6d,** and **6e** showed maximum activity against P. aeruginosa. Compounds **6a, 6b, 6d,** and **6g** displayed average activity against the yeast S. cerevisiae, and compounds **6b, 6d,** and **6e** showed promising inhibition of the yeast Candida albicans. The results are summarized in Table 2 and Figure 3.

Table 3: Antimicrobial Activity of Compounds 6a-h,

Comp	**Diameter of zone of growth inhibition (mm)**					
	Gram-positive bacteria		**Gram-negative bacteria**		**Yeasts**	
	S. aureus	**B. subtilis**	**E. coli**	**P. aeruginosa**	**S. cerevisiae**	**C. albicans**
6a	15	18	12	13	19	10
6b	20	18	17	16	14	22
6d	15	15	18	22	14	24
6e	14	14	13	14	9	17
6f	11	13	-	12	12	12
6g	13	15	8	10	14	12
Std	19	16	14	20	14	15
DMSO	0	0	0	0	0	0

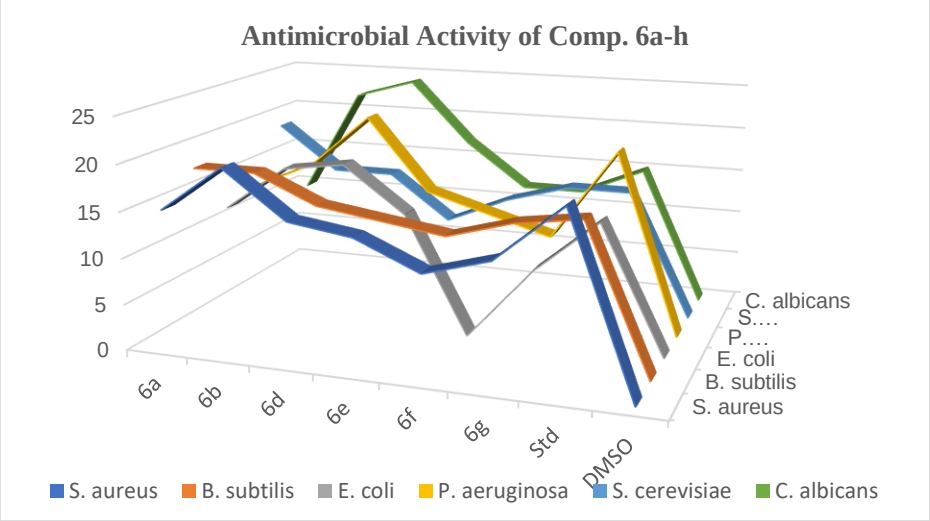


Figure 4: Antimicrobial Activity of Compounds (6a-h),

The results emphasize the promising antimicrobial potential of newly synthesized 1H-pyrazole compounds, particularly those with acetyl, 2,2,2-trifluoroacetyl, and 1-tosyl substitutions. These compounds demonstrate strong activity against both gram-positive and gram-negative bacterial strains. Furthermore, they exhibit notable antifungal activity, which was compared to that of the standard antibiotic streptomycin. This suggests that these compounds could serve as effective alternatives to conventional antibiotics and antifungals agents in the battle against microbial infections.

Experimental

Chemical and Reagent:

All the ingredients, reagents, and solvents are used by commercial providers. Used borosilicate glassware. The open capillary tubes were used to find the uncorrected melting points of the compounds. Brucker FT-IR spectrometer was used for IR of synthesized compound. ^{1}H NMR and ^{13}CNMR spectral analysis was done by using Brucke 400 Hz and 100 Hz instruments. For a mass of synthesized compounds, we used Agilent HRMS analysis.

Microbial Evaluation:

The microbial activity of the synthesized compounds was assessed against four bacterial strains, two Gram-negative bacteria (E. coli and P. aeruginosa) and two Gram-positive bacteria (S. aureus and B. subtilis), as well as for antifungal activity against two yeasts (C. albicans and S. cerevisiae). The antibacterial efficacy was evaluated by determining the zone of inhibition (ZOI) and minimum inhibitory concentration (MIC) values. Dimethylformamide (DMF) was used as the negative control, while streptomycin served as the reference drug. All experiments were conducted in triplicate. For the assays, sterilized bacterial nutrient agar media were poured into autoclaved Petri dishes. Under sterile conditions, 100 µL of each test organism was evenly swabbed onto the agar plates. Wells with a 6 mm diameter were created using a sterile metallic borer and were filled with solutions of the test compounds (128 µg/20 µL). After 48 hours of incubation at 28 °C, the ZOI values were recorded. MIC values were subsequently determined using the broth double-dilution method with 100 µL of each fungal strain, following incubation under identical conditions.

Synthesis of Fluorinated Chalcones (3a-h):

Added (1.0 equiv, 7.89 mmol) of FMAA, (1.0 equiv, 7.89 mmol), mmol of substituted benzaldehydes **(2a-h),** and (1.5 equiv, 11.83 mmol) of NaOH and Ethanol in a 50 ml round-bottom flask. The resulting mixture was brought to room temperature and subjected to ultrasonic agitation until complete conversion to the product was confirmed by TLC. Once the reaction was complete, the solid chalcones **(3a-h)** were obtained [xlii] by cooling the interacting

components in an ice bath and neutralizing them by dil. HCl. The chalcone is recrystallized from alcohol.

Synthesis of Acetyl pyrazoline derivatives (4a-h):

A mixture of chalcones, **(3a-h)** (1.0 equiv, 1.94 mmol), Acetohydrazide (1.1 equiv, 2.13 mmol), and Amberlyst-15 (10%, w/w) in acetonitrile (10 mL) was stirred at room temperature for 1-2 hrs as per protocol [xlvi]. After the completion, the separated solid (catalyst) by filtered. The MLR, solvent was removed under reduced pressure crude compound **(4a-h)** was purified by column chromatography.

Spectral data of synthesized compounds

1-(3-(4-fluoro-3-methylphenyl)-5-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4a): Yellow solid, yield: (74 %), m. p: 178 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, $-CH_3$), 2.45 (s, 3H, Ar-CH_3), 3.09-3.15 (dd, 1H, CH), 3.72-3.80 (dd, 1H, CH), 5.51-5.55 (dd, 1H, CH), 7.05-7.61 (m, 7H, Ar-H); IR (cm-1): 3085.11, 2925.20, 1638.10, 1578.75, 1450.12, 1403.24, 1356.93, 1119.44, 824.00, 754.90; HRMS: MS (ESI, m/z): 315.03 [M+H]; Elemental Analysis: C, 68.78; H, 5.13; F, 12.09; N, 8.91; O, 5.09.

1-(3-(4-fluoro-3-methylphenyl)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4b): Brown solid, yield: (70 %), m. p: 187 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.34 (s, 3H, $-CH_3$), 2.52 (s, 3H, Ar-CH_3), 2.91-3.20 (dd, 1H, CH), 3.84-3.91 (dd, 1H, CH),5.93-5.97 (dd, 1H, CH), 6.98-7.61 (m, 7H, Ar-H); IR (cm-1): 3042.33, 2981.66, 2922.67, 1659.00, 1583.02, 1482.91, 1322.87, 1147.01, 856.84, 756.50; HRMS: MS (ESI, m/z): 315.14 [M+H]; Elemental Analysis: C, 68.78; H, 5.13; F, 12.09; N, 8.91; O, 5.09.

1-(3-(4-fluoro-3-methylphenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4c): Yellow solid, yield: (73 %), m. p: 184 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, $-CH_3$), 2.41 (s, 3H, Ar-CH_3), 3.09-3.15 (dd, 1H, CH), 3.72-3.84 (dd, 1H, CH), 5.52-5.62 (dd, 1H, CH), 6.92-7.63 (m, 7H, Ar-H); IR (cm-1): 3055.69, 2919.63, 1689.63, 1586.70, 1471.52, 1412.27, 1304.60, 1147.51, 851.80, 754.49; HRMS: MS (ESI, m/z): 315.13 [M+H]; Elemental Analysis: C, 68.78; H, 5.13; F, 12.09; N, 8.91; O, 5.09.

1-(3-(4-fluoro-3-methylphenyl)-5-(2,4,6-trifluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4d): Yellow solid, yield: (71 %), m. p: 196 ±1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, $-CH_3$), 2.51 (s, 3H, Ar-CH_3), 3.20-3.29 (dd, 1H, CH), 3.83-3.91 (dd, 1H, CH), 5.60-5.61 (dd, 1H, CH), 7.23-7.74 (m, 5H, Ar-H); IR (cm-1): 3065.31, 2926.20, 1680.90, 1501.83, 1482.25, 1363.03, 1229.30, 1152.10, 893.35, 757.86; HRMS: MS (ESI, m/z): 351.09 [M+H]. Elemental Analysis: C, 61.72; H, 4.03; F, 21.69; N, 8.00; O, 4.57.

1-(5-(3-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4f): Off-white solid, yield: (78 %), m. p: 194 ±1°C ; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 1.85 (s, 3H, $-CH_3$), 2.32 (s, 3H, Ar-CH_3), 2.95-3.02 (dd, 1H, CH), 3.50-3.57 (dd, 1H, CH), 4.96-5.01 (dd, 1H, CH), 7.01-7.73 (m, 7H, Ar-H); IR (cm-1): 3182.22, 3119.16, 1653.10, 1521.99, 1315.44, 1254.26, 1106.31, 832.17, 736.58; HRMS: MS (ESI, m/z): 331.22 [M+H]. Elemental Analysis: C, 65.36; H, 4.88; Cl, 10.72; F, 5.74; N, 8.47; O, 4.84.

1-(5-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4g): Yellow solid, yield: (80 %), m. p: 185 ± 1 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 3H, $-CH_3$), 2.46 (s, 3H, Ar-CH_3), 3.10-3.15 (dd, 1H, CH), 3.77-3.84 (dd, 1H, CH), 5.61-5.65 (dd, 1H, CH), 7.06-7.66 (m, 7H, Ar-H); IR (cm-1): 3098.96, 2923.34, 1590.27, 1571.94, 1497.52, 1408.22, 1372.37, 1118.90, 864.00, 755.77; HRMS: MS (ESI, m/z): 331.34 [M+H]. Elemental Analysis: C, 65.36; H, 4.88; Cl, 10.72; F, 5.74; N, 8.47; O, 4.84.

1-(3-(4-fluoro-3-methylphenyl)-5-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (4h): Off-white, Yield (81 %), m. p: 188 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.33 (s, 3H, $-CH_3$), 2.49 (s, 3H, Ar-CH_3), 3.00-3.06 (dd, 1H, CH), 3.68-3.72 (dd, 1H, CH), 3.88 (s, 3H, OCH_3), 5.85-5.89 (dd, 1H, CH), 6.92-7.6 (m, 7H, Ar-H); (IR (cm-1):3243.77,

3076.00, 2921.72, 1716.60, 1583.96, 1560.55, 1327.70, 1180.33, 824.37, 755.91; HRMS: MS (ESI, m/z): 327.22 [M+H]. Elemental Analysis: C, 69.92; H, 5.87; F, 5.82; N, 8.58; O, 9.80

Synthesis of 2,2,2-trifluoroacetyl pyrazole derivatives (5a-h):

Chalcone **(3a-h)** (1.0 equiv, 1.94 mmol), Trifluoroacetyl hydrazide (1.1 equiv, 2.13 mmol), and [bmim][PF_6] ionic liquid (1.1 equiv, 2.13 mmol), were added to a 50 mL round bottom flask. Added Cu(OTf)$_2$ (0.19 mmol, 0.1 % the reaction mixture was heated at 130°C and stirred for 1-2 hr as per protocol [xlvii]. After completion of the reaction, the crude compound (5a-h) was purified by column chromatography.

Spectral data of synthesized compounds

2,2,2-trifluoro-1-(3-(4-fluoro-3-methylphenyl)-5-(2-fluorophenyl)-1H-pyrazol-1-yl)ethan-1-one (5a): Yellow solid, Yield: (80 %), m. p: 182 ± °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, -CH_3), 7.32-7.37 (d, 1H, Ar-CH), 7.52-7.54 (d, 1H, Ar-H), 7.65-7.67 (d, 1H, Ar-H), 7.91-7.95 (d, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 8.11-8.19 (m, 1H, Ar-H), 8.47 (s, 1H, Ar-H); IR (cm-1): 33233.71, 3142.78, 2990.48, 1734.52, 1597.65, 1485.45, 1323.83, 1227.69, 1157.74, 844.62, 750.78; HRMS: MS (ESI, m/z): 367.12 [M+H]; Elemental Analysis: C, 59.02; H, 3.03; F, 25.93; N, 7.65; O, 4.37.

2,2,2-trifluoro-1-(3-(4-fluoro-3-methylphenyl)-5-(3-fluorophenyl)-1H-pyrazol-1-yl)ethan-1-one (5b): Light yellow solid, Yield: (73%), m. p: 187 ± °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.34 (s, 3H, -CH_3), 6.80-7.02 (d, 1H, Ar-H), 7.06-7.28 (m, 3H, Ar-H), 7.40-7.86 (m, 3H, Ar-H), 7.87 (s, 1H, Ar-H); IR (cm-1): 3268.29, 3137.51, 2994.16, 1574.35, 1535.88, 1487.80, 1325.41, 1154.66, 1043.35, 840.13, 763.74; HRMS: MS (ESI, m/z): 367.08 [M+H]. Elemental Analysis: C, 59.02; H, 3.03; F, 25.93; N, 7.65; O, 4.37.

2,2,2-trifluoro-1-(3-(4-fluoro-3-methylphenyl)-5-(4-fluorophenyl)-1H-pyrazol-1-yl)ethan-1-one (5c): Pale yellow solid, Yield: (72 %), m. p: 190 ± °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 3H, -CH_3), 7.36 (t, 1H, Ar-CH_3), 7.53-7.56 (t, 1H, Ar-H), 7.67-7.69 (d, 1H, Ar-H),7.92-7.96 (d, 1H, Ar-H), 8.09-8.20 (m, 3H, Ar-H), 8.49 (s, 1H, Ar-H); IR (cm-1): 3147.30, 2916.60, 2845.08, 1595.74, 1487.18, 1289.55, 1154.39, 872.11, 748.17; HRMS: MS (ESI, m/z): 367.10 [M+H]. Elemental Analysis: C, 59.02; H, 3.03; F, 25.93; N, 7.65; O, 4.37.

2,2,2-trifluoro-1-(3-(4-fluoro-3-methylphenyl)-5-(2,4,6-trifluorophenyl)-1H-pyrazol-1-yl)ethan-1-one (5d): Pale yellow solid, Yield: (76 %), m. p: 190 ±1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, -CH_3), 7.30-7.35 (m, 1H, Ar-CH_3), 7.56 (s, 1H, Ar-H), 7.96-8.00 (m, 3H, Ar-H),8.00 (d, 1H, Ar-H), 8.13-8.15 (d, 1H, Ar-H); IR (cm-1): 3269.35, 3080.80, 2924.45, 1648.24, 1574.14, 1454.44, 1364.95, 1154.39, 1245.11, 1157.26, 852.64, 739.38; HRMS: MS (ESI, m/z): 403.13 [M+H]. Elemental Analysis: C, 53.74; H, 2.26; F, 33.06; N, 6.96; O, 3.98.

1-(5-(3-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-1H-pyrazol-1-yl)-2,2,2-trifluoroethan-1-one (5f): Yellow solid, Yield: (68 %), m. p: 206 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, -CH_3), 7.34 (m, 2H, Ar-CH_3), 7.60 (s, 1H, Ar-H), 8.01-8.16 (m, 5H, Ar-H); IR (cm-1):3065.31, 2926.20, 1588.75, 1501.83, 1482.25, 1363.03, 1118.72, 893.35, 757.96; HRMS: MS (ESI, m/z): 383.05 [M+H]. Elemental Analysis: C, 56.49; H, 2.90; Cl, 9.26; F, 19.86; N, 7.32; O, 4.18.

Synthesis of p-Tolyl sulphonyl pyrazole derivatives (6a-h):

Chalcone **(3a-h)** (1.0 equiv, 1.94 mmol), p-tosylsulfonyl hydrazide (1.1 equiv, 2.13 mmol), and [bmim][PF_6] ionic liquid (1.1 equiv, 2.13 mmol), were added to a 50 mL round-bottom flask. Added Cu(OTf)$_2$ (0.19 mmol, 0.1 % the reaction mixture was heated at 130°C and stirred for 1-2 hr as per protocol [xlii]. After completion of the reaction, the crude compound **(6a-h)** was purified by column chromatography.

Spectral data of synthesized compounds

3-(4-fluoro-3-methylphenyl)-5-(2-fluorophenyl)-1-tosyl-1H-pyrazole(6a): Yellow solid, Yield: (76 %), m. p: 182 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.20 (s, 3H, Ar-CH_3), 2.36 (s, 3H, Ar-CH_3), 7.13-7.17 (d, 1H, Ar-H), 7.29-7.31 (d, 1H, Ar-H), 7.33-7.35 (s, 1H, Ar-H), 7.50-7.58 (d, 2H, Ar-H), 7.73 (s, 1H, Ar-H), 7.77-7.83 (d, 1H, Ar-H), 7.93-7.95 (m, 2H, Ar-H); IR (cm-1): 3261.41, 3135.42, 1573.06, 1536.93, 1486.19, 1309.23, 1152.61, 838.38, 761.39; HRMS: MS (ESI, m/z): 425.14 [M+H]. Elemental Analysis: C, 65.08; H, 4.27; F, 8.95; N, 6.60; O, 7.54; S, 7.55.

3-(4-fluoro-3-methylphenyl)-5-(3-fluorophenyl)-1-tosyl-1H-pyrazole (4b): Pale yellow solid, Yield: (70 %), m. p: 198 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 6H, Ar-CH_3), 6.75 (s, 1H, Ar-H), 7.05-7.15 (m, 4H, Ar-H), 7.49-7.55 (m, 3H, Ar-H), 7.69-7.73 (m, 3H, Ar-H); IR (cm-1): 3233.71, 3142.78, 2990.48, 1597.65, 1536.29, 1486.45, 1323.83, 1157.74, 844.62, 750.78; HRMS: MS (ESI, m/z): 425.13 [M+H]. Elemental Analysis: C, 65.08; H, 4.27; F, 8.95; N, 6.60; O, 7.54; S, 7.55.

3-(4-fluoro-3-methylphenyl)-1-tosyl-5-(2,4,6-trifluorophenyl)-1H-pyrazole (6d): Yellow solid, Yield: (78 %), m. p: 228 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.38 (s, 6H, Ar-CH_3), 6.90 (s, 1H, Ar-H), 7.06-7.13 (m, 4H, Ar-H), 7.50-7.56 (m, 2H, Ar-H), 7.81-7.87 (m, 2H, Ar-H); IR (cm-1):3510.96, 3190.06, 3106.46, 2953.51, 1664.17, 1589.67, 1475.35, 1357.68, 1286.84, 1183.15, 856.72, 729.09; HRMS: MS (ESI, m/z): 461.51 [M+H]. Elemental Analysis: C, 60.00; H, 3.50; F, 16.50; N, 6.08; O, 6.95; S, 6.96.

5-(2-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-1-tosyl-1H-pyrazole (6e): Light yellow solid, Yield: (84 %), m. p: 199 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 6H, Ar-CH_3), 6.92 (d, 2H, Ar-H), 7.09-7.11 (m, 2H, Ar-H), 7.28 (s, 1H, Ar-H), 7.51-7.53 (m, 4H, Ar-H), 7.59 (d, 1H, Ar-H), 7.65-7.68 (m, 1H, Ar-H), 7.70-7.74 (m, 2H, Ar-H), 7.82 (s, 1H, Ar-H); IR (cm-1): 3197.03, 3079.60, 2978.44 1647.59 1589.67, 1479.54 1351.24, 1214.71, 1159.50, 849.66, 781.06; HRMS: MS (ESI, m/z): 441.14 [M+H]. Elemental Analysis: C, 62.65; H, 4.12; Cl, 8.04; F, 4.31; N, 6.35; O, 7.26; S, 7.27.

5-(3-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-1-tosyl-1H-pyrazole (6f): Light yellow solid, Yield: (79 %), m. p: 204 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 6H, Ar-CH_3), 6.92 (d, 2H, Ar-H), 7.09-7.11 (m, 2H, Ar-H), 7.28 (s, 1H, Ar-H), 7.51-7.53 (m, 4H, Ar-H), 7.59 (d, 1H, Ar-H), 7.65-7.68 (m, 1H, Ar-H), 7.70-7.74 (m, 2H, Ar-H), 7.82 (s, 1H, Ar-H); IR (cm-1): 3196.47, 3114.61, 2978.18, 1719.98, 1598.91, 1570.67, 1436.02, 1350.15, 1173.93, 844.03, 728.64; HRMS: MS (ESI, m/z): 441.17 [M+H]. Elemental Analysis: C, 62.65; H, 4.12; Cl, 8.04; F, 4.31; N, 6.35; O, 7.26; S, 7.27.

5-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-1-tosyl-1H-pyrazole (6g): Yellow solid, Yield: (76 %), m. p: 210 ± 1 °C; H^1NMR (400 MHz, $CDCl_3$, δ ppm): 2.34 (s, 3H, Ar-CH_3), 2.51 (s, 3H, Ar-CH_3), 7.29-7.35 (m, 5H, Ar-H), 7.73-7.77 (s, 1H, Ar-H), 7.90-7.94 (m, 2H, Ar-H), 7.97-8.00 (m, 2H, Ar-H), 8.05-8.07, (d, 1H, Ar-H), 8.14-8.16(m, 1H, Ar-H); IR (cm-1): 3360.80, 3142.89, 3076.73, 2907.65, 1654.01, 1591.45, 1533.84, 1443.28, 1333.91, 1164.61, 1123.53, 864.19, 772.99; HRMS: MS (ESI, m/z): 441.22 [M+H]. Elemental Analysis: C, 62.65; H, 4.12; Cl, 8.04; F, 4.31; N, 6.35; O, 7.26; S, 7.27.

Conclusion:

We are synthesized several novel acetyl-substituted 1H-pyrazole derivatives **4a-h** using a reusable Amberlyst-15 catalyst in acetonitrile as the solvent. Additionally, we developed various novel 2,2,2-trifluoroacetyl derivatives **5a-h** and 1-tosyl-1H-pyrazole derivatives **6a-h** through an efficient and environmentally friendly protocol utilizing the ionic liquid [bmim][PF_6], mediated by $Cu(OTf)_2$. A series of newly synthesized 1H-pyrazole compounds were screened for their in vitro antibacterial and antifungal activity against various bacteria. The novel acetyl derivatives, particularly compounds **4c, 4f,** and **4h,** demonstrated maximum activity against S. aureus, B. subtilis, E. coli, and P. aeruginosa. Similarly, the 2,2,2-

trifluoroacetyl derivatives **5d, 5a, 5b**, and **5e** exhibited promising antibacterial activity against the same bacterial strains. Furthermore, the 1-tosyl-1H-pyrazole derivatives **6a, 6b, 6d**, and **6e** exhibited potent antibacterial properties as assessed in this study. Compounds **4d, 4c, 5d, 5b, 6a**, and **6b** showed maximum fungicidal activity against the fungi S. cerevisiae and C. albicans.

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Confects of Interest

No conflicting interests correspond to the authors

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