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Synthesis and *In-Vitro* Anti-bacterial and Anti-fungal Activity of 2-Acetylphenyl Pentafluorobenzoate and 2-acetylphenyl 2, 3, 4, 5-Tetrafluorobenzoate Derivatives

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ABSTRACT

Chromones and Azoles have been reported to play an important role as antibacterial, antifungal and anti-inflammatory activity. Chromones derivatives and Azoles derivatives were synthesized and screened for antibacterial activity and antifungal activity. Some 2-(pentafluorophenyl)-4H-chromone-4-one, 2-[5-(pentafluorophenyl)-1*H*-pyrazol-3-yl] phenol and 2-(2,3,4,5-tetrafluorophenyl)-4H-chromen-4-one, 2-[5-(2,3,4,5-tetrafluorophenyl)-1H-pyrazol-3-yl] phenol were synthesized by a sequence of reactions starting from 2-acetylphenyl pentafluorobenzoate and 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate, respectively and were mentioned in scheme 1 and 2. The antibacterial and antifungal activities of chromones derivatives, azoles derivatives were tested by the cup and plate method by using nutrient agar medium against various microorganisms such as gram positive *Staphylococcus aureus*, gram-negative *Escherichia coli* and the fungi *Aspergillus niger* and *Candida albicans*. Ciprofloxacin and Fluconazole at 50 µg/mL were used as standard drugs for antibacterial and antifungal activities, respectively.

INTRODUCTION

Chromones and pyrazol and its derivatives are important heterocyclic in organic and biochemistry and have been found in many chromones containing natural products such as Khellin, sodium cromoglycate, diosmin, flavones, and flavonoids. There are extensive studies on the synthesis and reactivity of Chromones and pyrazol derivatives. Many Chromones and pyrazol derivatives have shown interesting biological properties such as antibacterial, anti-inflammatory, antioxidant, antitumor, antifungal and immune suppressant activities. Chromones and pyrazol derivatives are prepared by using 1-(2-hydroxyphenyl) ethanone, pentafluorobenzoic acid and 2, 3, 4, 5-tetrafluorobenzoic acid reagent. These pyrrole derivatives and chromones are screened for antibacterial activity and antifungal activity. It reveals that chromones and pyrazol possess broad spectrum activity such as antimicrobial[1-4], anti-inflammatory[5], analgesic[6], antitumorial[7], antihypertensives[8], anticonvulsant and antiviral[9]. Since the past few decades, the literature has been enriched with progressive findings of the synthesis and pharmacological activities of various substituted chromones and pyrazol derivatives. There are antifungal and antibacterial agents having different structures and used in the treatment of fungal and bacterial infection.

MATERIALS AND METHODS

Materials:

1-(2-hydroxyphenyl) ethanone, Pentafluorobenzoic acid, 2,3,4,5-tetraflurobenzoic acid, Pyridine, Hydrazine Hydrate, Guanidine Hydrochloride, Ethanol, Con. Hydrochloric acid phosphorus oxychloride i.e. $POCl_3$ and 2,3,4,5-tetrafluorobenzoic acid etc. All reagents were purchased from Atmaja chemicals, Aurangabad. All chemicals were of analytical grade

Method:

All chromones and Pyrazole derivatives were synthesized by conventional method.

EXPERIMENTAL WORK:

Melting points were determined by open tube capillary method. The purity of the compounds was checked by thin layer chromatography (TLC) plates (silica gel G) in chloroform: acetone

(7:3) and chloroform: methanol (8:2) solvent systems, the spots were located under iodine vapors and UV light. IR spectra were obtained on a 1720 FT-IR spectrometer (KBr pellets). ^{1}H-NMR spectra were recorded by a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d_6/$CDCl_3$ and mass spectra under molecular impact conditions (MI) were recorded at 70 ev ionizing voltage with a VG Prospec instrument and are presented as m/z.

A. General procedure for Synthesis of 2-acetylphenyl pentafluorobenzoate (AA) and 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate (AF):

A mixture of 1-(2-hydroxyphenyl) ethanone (0.5g) and Pentafluorobenzoic acid (0.5g) was reacted with each other in the presence of $POCl_3$ (5 ml) and Pyridine (15 ml) and then stir on magnetic stirrer for 24 hrs, and then it gives solid product after addition of ice cold water and it gives 2-acetylphenyl pentafluorobenzoate (AA).

A mixture of 1-(2-hydroxyphenyl) ethanone (0.5g) and 2,3,4,5-tetrafluorobenzoic acid (0.5g) was reacted with each other in the presence of $POCl_3$ (5 ml) and Pyridine (15 ml) and then stir on magnetic stirrer for 24 hrs, and then it gives solid product after addition of ice cold water and it gives 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate (AF).

B. General procedure for Synthesis of 2-(pentafluorophenyl)-4H-chromone-4-one (AC) and 2-[5-(pentafluorophenyl)-1*H*-pyrazol-3-yl] phenol (AD) (Scheme 1) [4]:

- 2-acetylphenyl pentafluorobenzoate (AA) reacts with potassium hydroxide (0.5g) and pyridine (5 ml) and reflux for 3 hrs and then it gives 1-(2-hydroxyphenyl)-3-(pentafluorophenyl)propane-1,3-dione (AB).
- 1-(2-hydroxyphenyl)-3-(pentafluorophenyl) propane-1,3-dione (AB) reacts with con. Hydrochloric acid (5 ml) and ethanol (5 ml), and reflux for 2 hrs and then it gives 2-(pentafluorophenyl)-4*H*-chromen-4-one (AC).
- 2-(pentafluorophenyl)-4*H*-chromen-4-one (AC) reacts with hydrazine hydrate (5 ml) and ethanol (10 ml) and reflux for 3 hrs and then it gives 2-[5-(pentafluorophenyl)-1*H*-pyrazol-3-yl]phenol (AD).

➢ 2-(pentafluorophenyl)-4*H*-chromen-4-one (AC) reacts with guanidine hydrochloride (5 ml) and it is refluxed for 3 hrs then it gives 2-[2-imino-6-(pentafluorophenyl)-1,2-dihydropyrimidin-4-yl]phenol (AE).

C. General procedure for Synthesis of 2-(2,3,4,5-tetrafluorophenyl)-4*H*-chromen-4-one (AH).and 2-[5-(2,3,4,5-tetrafluorophenyl)-1*H*-pyrazol-3-yl]phenol (AI). (Scheme 2) [5]:

➢ 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate (AF) reacts with potassium hydroxide (0.5 g) and pyridine (5 ml) and reflux for 3 hrs and then it gives 1-(2-hydroxyphenyl)-3-(2,3,4,5-tetrafluorophenyl)propane-1,3-dione(AG).

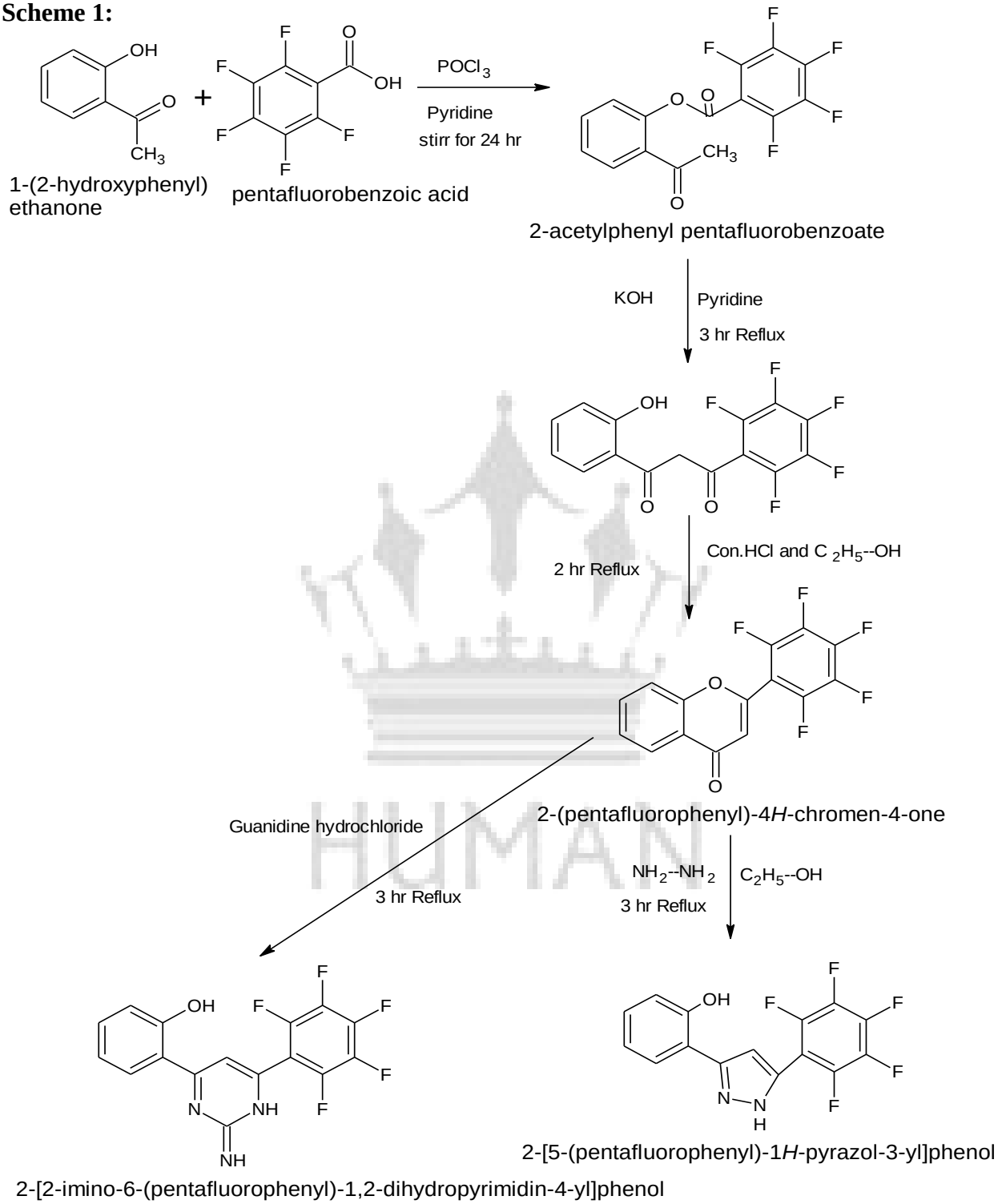
➢ 1-(2-hydroxyphenyl)-3-(2,3,4,5-tetrafluorophenyl)propane-1,3-dione (AG) reacts with con. Hydrochloric acid (5 ml) and ethanol (5 ml), and reflux for 2 hrs and then it gives 2-(2,3,4,5-tetrafluorophenyl)-4*H*-chromen-4-one (AH).

➢ 2-(2,3,4,5-tetrafluorophenyl)-4*H*-chromen-4-one(AH) reacts with hydrazine hydrate (5 ml) and ethanol (10 ml) and reflux for 3 hrs and then it gives 2-[5-(2,3,4,5-tetrafluorophenyl)-1*H*-pyrazol-3-yl]phenol (AI).

➢ 2-(2,3,4,5-tetrafluorophenyl)-4*H*-chromen-4-one(AH) reacts with guanidine hydrochloride (5 ml) and it is refluxed for 3 hrs then it gives 2-[2-imino-6-(2,3,4,5-tetrafluorophenyl)-1,2-dihydropyrimidin-4-yl]phenol (AJ)

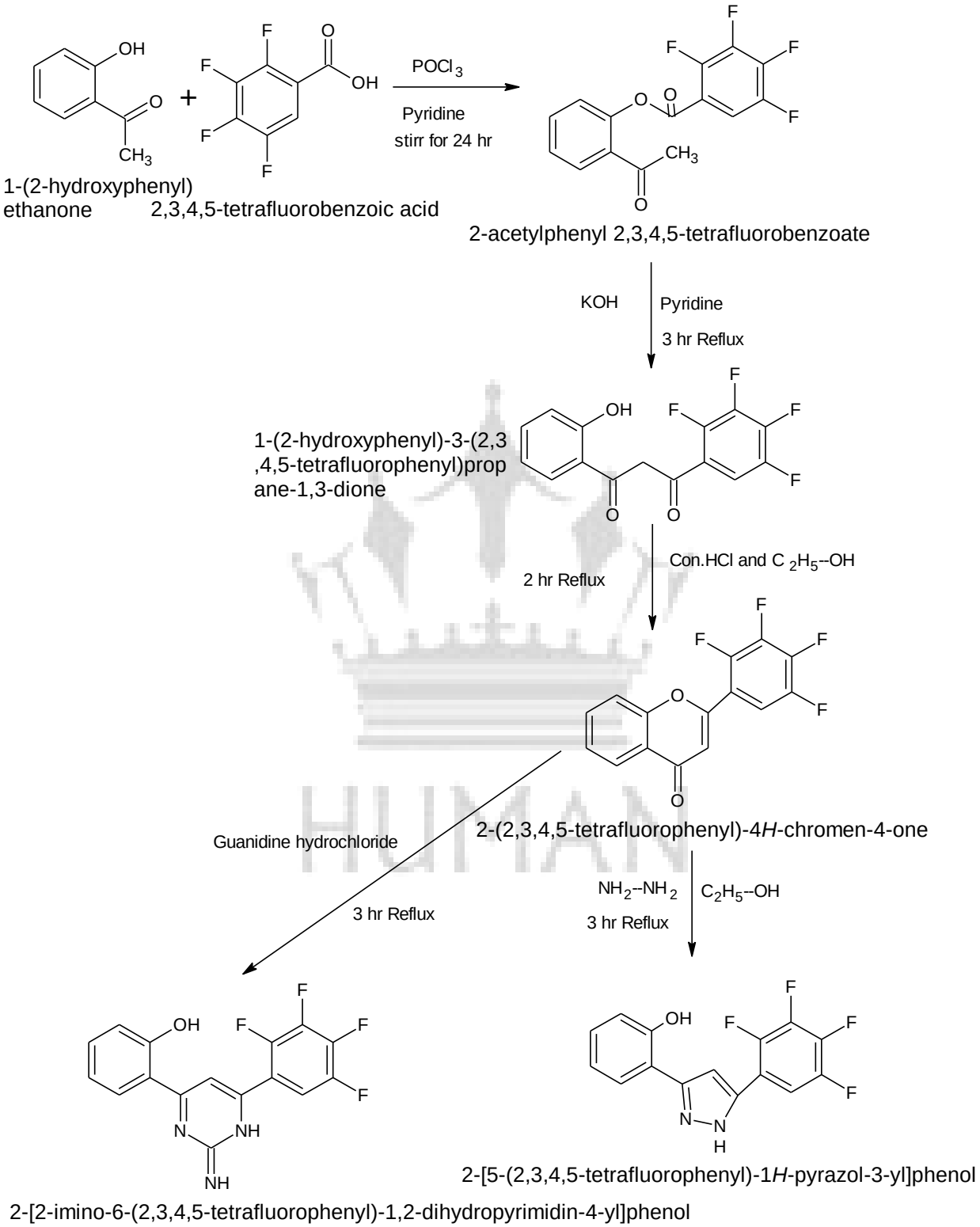
Scheme of reaction:

Scheme 1:



Scheme 1: Synthesis of 2-(pentafluorophenyl)-4H-chromone-4-one (AC) and 2-[5-(pentafluorophenyl)-1*H*-pyrazol-3-yl] phenol (AD) derivatives (AA- AE)

Scheme 2:



Scheme 2: Synthesis of 2-(2,3,4,5-tetrafluorophenyl)-4*H*-chromen-4-one (AH).and 2-[5-(2,3,4,5-tetrafluorophenyl)-1*H*-pyrazol-3-yl]phenol (AI). (AF- AJ)

Data Analysis:

2-acetylphenyl pentafluorobenzoate (AA):

Colorless solid, $C_{15}H_7O_3F_5$; yield 60.84%, mp 286-288°C, R_f 0.9; FTIR (KBr) ν cm^{-1} 3010 (Ar C-H str), 1638 (Ar C=C str), 797 (Ar C-H def), 1158 (Ar C-F str), 1758 (Ester C=O str), 1367 C-O str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 2.34 (s, 3H, CH_3), 7.29-7.86 (m, 4H, aromatic protons), FABMS (m/z) 332(M^+), 333 (M^++1). Mol. Wt.:333.

1-(2-hydroxyphenyl)-3-(pentafluorophenyl) propane-1, 3-dione (AB):

Colorless solid, $C_{15}H_7O_3F_5$; yield 96.07%, mp 312-314°C, R_f 0.92; FTIR (KBr) ν cm^{-1} 3036 (Ar C-H str), 1540 (Ar C=C str), 842 (Ar C-H def), 1161 (Ar C-F str), 1668 (Aryl Ketone C=O str), 1297(C-O str), 3680 (Ar OH str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 3.81 (s, 2H, CH_2), 5.35 (s, 1H, OH), 6.82-7.60 (m, 4H, aromatic protons); FABMS (m/z) 329(M^+), 330 (M^++1). Mol. Wt.:330.

2-(pentafluorophenyl)-4*H*-chromen-4-one (AC):

Colorless solid, $C_{15}H_5O_2F_5$; yield 87.23%, mp 338-340°C, R_f 0.92; FTIR (KBr) ν cm^{-1} 3028 (Ar C-H str), 1525 (Ar C=C str), 807 (Ar C-H def), 1027 (Ar C-F str), 1661 (Aryl Ketone C=O str), 1380 (C-O str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 6.54 (s, 1H, C-H), 7.47-8.08 (m, 4H, aromatic protons); FABMS (m/z) 311(M^+), 312 (M^++1). Mol. Wt.:312.

2-[5-(pentafluorophenyl)-1*H*-pyrazol-3-yl] phenol (AD):

Colorless solid, $C_{15}H_7N_2OF_5$; yield 86.20%, mp 320-322°C, R_f 0.88; FTIR (KBr) ν cm^{-1} 3035 (Ar C-H str), 1631 (Ar C=C str), 747 (Ar C-H def), 1273 (Ar C-F str), 3540 (Ar OH str), 1320 (C-O str) 3385 (N-H str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 7.01-8.26 (m, 4H, aromatic protons) 5.35 (s, 1H, O-H), 6.81 (s, 1H, C-H), 12.62 (s, 1H,N-H); FABMS (m/z) 325 (M^+), 326 (M^++1). Mol. Wt.:326.

2-[2-imino-6-(pentafluorophenyl)-1,2-dihydropyrimidin-4-yl] phenol (AE):

Colorless solid, $C_{15}H_8N_3OF_5$; yield 92.59%, mp 398-400°C, R_f 0.80; FTIR (KBr) ν cm^{-1} 3061 (Ar C-H str), 1618 (Ar C=C str), 754 (Ar C-H def), 1027 (Ar C-F str), 3573 (Ar OH str), 1343 (C-O str) 3390 (N-H str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 7.02-7.66 (m, 4H, aromatic protons) 5.35(s, 1H, O-H), 6.31 (s, 1H, C-H),13.89 (s, 1H,N-H) 13.76 (s, 1H,N-H); FABMS

(m/z) 340(M^+), 341 (M^++1). Mol. Wt.:341.

2-acetylphenyl 2, 3, 4, 5-tetrafluorobenzoate (AF):

Colorless solid, $C_{15}H_8O_3F_4$; yield 76.27%, mp 310-312°C, R_f 0.94; FTIR (KBr) ν cm^{-1} 3025 (Ar C-H str), 1626 (Ar C=C str), 769 (Ar C-H def), 1028 (Ar C-F str), 1786 (Ester C=O str), 1319 (C-O str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 7.37-7.82 (m, 4H, aromatic protons),7.25 (m, 1H, aromatic protons), 2.50 (s, 3H, CH_3); FABMS (m/z) 310 (M^+), 311 (M^++1). Mol. Wt.:311.

1-(2-hydroxyphenyl)-3-(2, 3, 4, 5-tetrafluorophenyl) propane-1, 3-dione (AG):

Colorless solid, $C_{15}H_7O_3F_4$; yield 77.55%, mp 332-334°C, R_f 0.94; FTIR (KBr) ν cm^{-1} 3036 (Ar C-H str), 1607 (Ar C=C str), 880 (Ar C-H def), 1149 (Ar C-F str), 1638 (Aryl Ketone C=O str), 1297(C-O str), 3680 (Ar OH str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 3.81 (s, 2H, CH_2), 5.35 (s, 1H, OH), 6.88-7.47 (m, 4H, aromatic protons), 7.25 (m, 1H, aromatic protons); FABMS (m/z) 310 (M^+), 311 (M^++1). Mol. Wt.:311.

2-(2, 3, 4, 5-tetrafluorophenyl)-4*H*-chromen-4-one (AH):

Colorless solid, $C_{15}H_6O_2F_4$; yield 65.95%, mp 374-376°C, R_f 0.83; FTIR (KBr) ν cm^{-1} 3028 (Ar C-H str), 1529 (Ar C=C str), 846 (Ar C-H def), 1104 (Ar C-F str), 1661 (Aryl Ketone C=O str), 1349 (C-O str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 6.54 (s, 1H, C-H), 7.47-8.06 (m, 4H, aromatic protons), 6.69 (m, 1H, aromatic protons); FABMS (m/z) 293 (M^+), 294 (M^++1). Mol. Wt.:294.

2-[5-(2, 3, 4, 5-tetrafluorophenyl)-1*H*-pyrazol-3-yl] phenol (AI):

Colorless solid, $C_{15}H_8N_2OF_4$; yield 86.53%, mp 354-356°C, R_f 0.93; FTIR (KBr) ν cm^{-1} 3061 (Ar C-H str), 1642 (Ar C=C str), 781 (Ar C-H def), 1222 (Ar C-F str), 3540 (Ar OH str), 1320 (C-O str) 3385 (N-H str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 7.01-8.26 (m, 4H, aromatic protons) 5.35(s, 1H, O-H), 6.81 (s, 1H, C-H),12.62(s, 1H,N-H), 7.25 (m, 1H, aromatic protons); FABMS (m/z) 307 (M^+), 308 (M^++1). Mol. Wt.:308.

2-[2-imino-6-(2, 3, 4, 5-tetrafluorophenyl)-1, 2-dihydropyrimidin-4-yl] phenol (AJ):

Colorless solid, $C_{15}H_9N_3OF_4$; yield 86.53%, mp 354-356°C, R_f 0.93; FTIR (KBr) ν cm^{-1} 3061 (Ar C-H str), 1642 (Ar C=C str), 781 (Ar C-H def), 1222 (Ar C-F str), 3540 (Ar OH str), 1320

(C-O str) 3385 (N-H str); ^{1}H NMR (400 MHz CDCl3 δ ppm) 7.02-7.66 (m, 4H, aromatic protons) 5.35 (s, 1H, O-H), 6.81 (s, 1H, C-H), 13.89 (s, 1H,N-H) 13.76 (s, 1H,N-H), 6.69 (m, 1H, aromatic protons); FABMS (m/z) 334 (M^+), 335 (M^++1). Mol. Wt.:335.

PHARMACOLOGICAL STUDIES [7]

i) Antibacterial Activity

Compounds AA to AJ were evaluated for their *in vitro* antibacterial activity against various microorganisms such as gram positive *Staphylococcus aureus*, gram negative *Escherichia coli* by Cup and Plate method was performed using Nutrient agar medium. Each compound was tested at concentration 50 µg/mL in DMSO. The zone of inhibition was measured after 24 h incubation at 37°C. Standard: Ciprofloxacin (50 µg/mL of DMSO).

Table 1. Antibacterial activity screening result of synthesized compound measuring the zone of inhibition in millimeter

	Diameter of zone of inhibition (mm)			
	Escherichia coli		***Staphylococcus aureus***	
Compd. No.	**50 mg/ml**	**100 mg ml^{-1}**	**50 mg/ml**	**100 mg ml^{-1}**
AA	8.8 ±0.20	14.36±0.15	10.76 ±0.1	16.6±0.20
AB	13.16 ±0.10	15.33±0.20	13.83 ±0.20	20.23±0.20
AC	18.80±0.15	24.26±0.15	19.4±0.10	21.3±0.10
AD	19.83 ±0.25	19.16±0.20	20.63±0.15	22.96±0.15
AE	17.8±0.20	22.13±0.05	19.63±0.05	24.4±0.20
AF	15.63±0.20	12.8±0.10	17.36±0.15	18.6 ±0.20
AG	11.45±0.37	13.45±0.00	12.56±0.05	28.7 ±0.10
AH	16.7±0.30	20.9 ±0.20	19.4±0.20	27.83±0.15
AI	17.16±0.10	21.16±0.10	22.6±0.20	21.86±0.11
AJ	19.36±0.21	20.73±0.25	19.63±0.15	22.71±0.26
Ciprofloxacin	23.32 ±0.20	29.7±0.26	25.63 ±0.15	33.43±0.15

Ciprofloxacin was used as standard drug at 50 mg/ml. All the values are in Mean ± S.D (n=3). Statistical analysis of data was carried out by one-way ANOVA.

ii) Antifungal Activity

Compounds AA to AJ were evaluated for their *in vitro* antibacterial activity against various microorganisms such as *Aspergillus niger* and *Candida albicans* by disc diffusion method was performed using Saboraud's agar medium. Each compound was tested at concentration 600 µg/ml in DMSO. The zone of inhibition was measured after 48 hrs incubation at 37ºC. Standard: Fluconazole (50 µg/mL of DMSO).

Table 2. Antifungal activity screening result of synthesized compound measuring the zone of inhibition in millimeter

	Diameter of zone of inhibition (mm)			
	Candida albicans		*Aspergillus niger*	
Compd. No.	**50 mg/ml**	**100 mg/ml**	**50 mg/ml**	**100 mg/ml**
AA	10.5 ±0.20	11.33 ±0.15	10.76 ±0.1	16.6±0.20
AB	14.7 ±0.10	13.13 ±0.20	13.83 ±0.20	19.23±0.20
AC	19.53±0.15	22.7 ±0.15	21.4±0.10	25.3±0.10
AD	20.6 ±0.25	20.7 ±0.20	20.63±0.15	26.96±0.15
AE	21.16 ±0.20	22.13±0.05	23.63±0.05	24.4±0.20
AF	15.6 ±0.20	17.46 8±0.10	17.36±0.15	11.6 ±0.20
AG	11.23 ±0.37	19.16 ±0.00	12.56±0.05	14.7 ±0.10
AH	19.1 ±0.30	21.23±0.20	19.4±0.20	27.83±0.15
AI	18.0 ±0.10	23.53±0.10	22.6±0.20	29.86±0.11
AJ	21.23±0.21	22.2±0.25	22.63±0.15	28.71±0.26
Fluconazole	24.16±0.20	31.56±0.26	25.63 ±0.15	33.43±0.15

Fluconazole was used as standard at 50 mg/ml. Data are given as Mean ± S.D. (n=3). Statistical analysis of data was carried out by paired t- test

RESULTS AND DISCUSSION

The synthesis of compounds AA-AE and AF-AJ were undertaken as per the **scheme 1** and **2**. The required 2-acetylphenyl pentafluorobenzoate (AA) was prepared by the action of 1-(2-hydroxyphenyl) ethanone and Pentafluorobenzoic acid. The various derivatives of chromones and pyrazol were synthesized by condensation of 2-acetylphenyl pentafluorobenzoate, in a yield ranging between 31 to 68%. Some 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate derivatives (AF) were synthesized by a sequence of reactions starting from 2,3,4,5-tetrafluorobenzoic acid and 1-(2-hydroxyphenyl) ethanone. The various derivatives of chromones and pyrazol were synthesized by condensation of 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate, in a yield ranging between 31 to 68%.^{1}H-NMR, Mass and IR spectra were recorded on Bruker DRX-300 (300 MHz), MS Jeol SX-102 (FAB) and BIORAD FTIR Spectrometer instruments respectively

The results revealed that most of the synthesized compounds showed varying degrees of inhibition of the tested microorganisms. In general, the inhibitory activity against the tested gram-positive bacteria was higher than that of the gram-negative bacteria, and some derivatives showed moderate or weak activity against *C. albicans* and *A. niger*. The results indicated that the nitrogen and oxygen containing compounds, having more antimicrobial activity. However, some compounds exhibited high antifungal activity against *C. albicans*. Moreover, compounds **AC, AD, AE, AH, AI** and **AJ** having the side chain showed higher activity than **AA, AB, AF and AG** against *S. aureus.* The replacement of oxygen to nitrogen resulted in a slightly increased antimicrobial activity. Our study revealed that all the compounds had stronger antibacterial activity against Gram-positive bacteria when compared to Gram-negative bacteria. The antimicrobial activity revealed that newly synthesized compound **AC, AD, AE, AH, AI** and **AJ** showed good significant activity. The results of the preliminary antimicrobial testing of the prepared compounds, the typical broad-spectrum antibacterial drug like Ciprofloxacin (50 µg/mL) and the potent antifungal drug like Fluconazole (50µg/mL) are shown in Table 1 and 2.

CONCLUSION

Various 2-acetylphenyl pentafluorobenzoate was synthesized from the action of 1-(2-hydroxyphenyl) ethanone and Pentafluorobenzoic acid and 2-acetylphenyl 2,3,4,5-tetrafluorobenzoate derivatives were synthesized from the action of 2,3,4,5-tetrafluorobenzoic

acid and 1-(2-hydroxyphenyl) ethanone. The structural antibacterial and antifungal activity relationship of the synthesized compounds was based on the structure of final derivatives. These derivatives possess good antibacterial and antifungal activity. The antimicrobial activities including antibacterial and antifungal properties of the synthesized derivatives showed a significant activity as compared with standard drugs like Ciprofloxacin and Fluconazole.

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