Bioactivity Study of Thiophene and Pyrazole Containing Heterocycles

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http://dx.doi.org/10.13005/ojc/370417

(Received: July 17, 2021; Accepted: August 19, 2021)

ABSTRACT

Chalcones 3a-f were prepared by reacting thiophene containing pyrazolyl aldehyde (2) with different 2-hydroxy acetophenones 1a-f. The compounds 3a-f were transformed into different Pyrazolines 4a-f. The formation of chromene derivatives 5a-f occurred from the cyclization of 3a-f, which were then transformed into pyrazole derivatives 6a-f. Newly synthesized compounds have promising antibacterial activity against *S. typhii* and *S. aureus*, while weak activity against *B. subtilis* and *E. coli*. Compounds 5d and 6d had significant antifungal action towards *A. niger*, while most of the compounds were moderately active towards *T. viride*. Some of the synthesized compounds showed promising α-amylase inhibitory activity at 1 mg/mL concentration.

Keywords: 2-Hydroxyacetophenone, Pyrazole, Chromone, Antimicrobial activity.

INTRODUCTION

In the field of medicinal chemistry, most drugs have different heterocyclic scaffolds that show potential biological activities. Microbes are responsible for different human diseases. As these microorganisms develop resistance towards many of the present drug molecules, there is a need for continuous research on developing new potential medicinal agents. The presence of oxygen, sulphur and nitrogen containing heterocyclic nucleus imparts very effective pharmacological properties to therapeutic agents. In these scaffolds, the presence of Fluorine increases bioactivity of molecules several times¹².

Thiophene derivatives have varied therapeutic applications. Thiophene containing heterocyclic compounds have created interest among the researchers owing to their vast spectrum of biological functions including antimicrobial⁴⁻⁵, antiparasitic⁴⁻⁵, antiviral⁷, anticancer⁸⁻⁹, enzyme inhibitors¹⁰⁰, anti-inflammatory and analgesic¹¹ properties. Some of the commercially available drugs that contain thiophene as an integral component are Suprophen and Tiaprofenic acid.
as an anti-inflammatory, Rolaxifene and OSI-930 as an anticancer, Methapyrilene as anti-histamine, Tienilic acid as an antihypertensive, Ticlopidine as antiplatelet, Olanzapine as antisychotic, Etizolam as anti-anxiety and Tigabine as anticonvulsant agents.

In recent years, pyrazole is the most studied heterocycle among the azole family due to its innumerable chemical, agrochemical and pharmacological properties. Pyrazole containing compounds are reported for anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, anti FAAH (Fatty Acid Amide Hydrolase), anti-enzymatic(Anti-S IRT 1 and SIRT 2), analgesic, 5α-Reductase inhibitor, antioxidant, and insecticidal. The Pyrazole scaffold has fascinating medicinal potential and is found as a pharmacophoric group of the drug molecules available on the market such as anti-inflammatory agents Meprizole, Celecoxib and Lonazolac, Rimonabant acts as cannabinoid receptor and used to treat obesity, Difenamizole functions as an analgetic, Fomepizole inhibits alcohol dehydrogenase, Fezolamine acts as antidepressant, CDPPB functions as anti-psychotic and sildenafil inhibits phosphodiesterase (Figure 1).

Chalcones have attracted much attention from medicinal chemists, not only as synthon for biosynthetic perspectives but also as bioactive moiety. Several heterocyclic rings can be obtained from chalcones through ring closure reactions. Chalcone shows diversified medicinal and biological activities such as antimalarial, anticancer, anti-inflammatory, antitubercular, antioxidant, anti-alzheimer, antibacterial and antifungal. In ethanol, the molecule interacts with hydrazine hydrate to produce bipyrazolyl phenols, which can be confirmed by spectral technique. The I.R. Spectrum shows band at 3334 cm\(^{-1}\) and Molecular ion peak at 473.0410 in HRMS validated formation of 4d. The most important confirmation of 4d formation is in \(^1\)HNMR spectra which shows two doublets at 5.88 and 5.09 support the formation of 4a-f. Refluxing chalcone 3a-f in DMSO with a catalytic quantity of iodine yielded 2-substituted chromone 5a-f. The I.R. spectrum at 1653 cm\(^{-1}\)
and the molecular ion peak at 456.9967 verify 5d. 1H NMR spectra validate chromone formation as there is absence of downfield signal above δ 10.0 implies absence of O-H and also singlet at δ 6.80 is due to 3-position proton chromone. Chromones 5a-f when refluxed in ethanol and hydrazine hydrate were transformed into pyrazoles 6a-f. The I.R. Spectrum at 3404 cm⁻¹ and In HRMS molecular ion peaks at 471.0243 supports 6d formation. The most significant confirmation is the presence of a singlet at δ 12.70 in 1H NMR spectra of O-H proton.

Amylase Inhibitory Activity

In a test tube 500 μL of test sample, 500 μL solution of α-amylase whose concentration is 0.5 mg/mL and phosphate buffer of 0.2 mM concentration were mixed and kept undisturbed 10 min at room temperature. Then the contents of the test tube were allowed to react 1% starch solution in phosphate buffer having pH 6.9. Then dinitrosalicylic acid was used to extinguish reaction. After incubation of 5 min test tubes were cooled and the contents were diluted with distilled water. The absorbance of resulting solutions was recorded at the wavelength 540nm. Then the results were compared with well-known inhibitor of the acarbose.

The results are recorded as % inhibition of enzyme activity.

Table II: Amylase inhibitory Activity: (Concentration 1 mg/mL)

| Compound | % Inhibition |
|----------|-------------|
| 6a       | 34          |
| 6b       | 31          |
| 6e       | 09          |
| 6f       | 10          |
| Acarbose | 45          |

Microbial analysis

In vitro tests were performed on the compounds 2, 3a-f, 4a-f, 5a-f, and 6a-j against four bacterial and two fungal strains (Table 1). The agar well diffusion technique was utilized in this experiment. Ciprofloxacin and fluconazole were utilized as antibacterial and antifungal reference drugs respectively, while DMSO was used as a negative control. All compounds are inactive towards Gram-positive bacteria Bacillus subtilis and have modest action against Escherichia coli and Staphylococcus aureus. Compound 3c, 5a and 5b showed good activity against Salmonella typhii while all other compounds have a moderate level of action. Compounds 5d and 6d were shown to have promising action against Aspergillus niger, while others had modest activity against Trichoderma viride. The results were averaged over three experimental sets and reported as zone of inhibition in millimeters.

Table 1: Antimicrobial Activity (Zone of Inhibition at 1 mg/mL in mm)

| Compound | Bacillus subtilis | Staphylococcus aureus | Salmonella typhii | Escherichia coli | Aspergillus niger | Trichoderma viride |
|----------|------------------|----------------------|-------------------|-----------------|------------------|-------------------|
EXPERIMENTAL

Open capillary technique was used for melting points which are uncorrected. IR Affinity-I Fourier transform infrared spectrophotometer (Shimadzu), Bruker Avance II 500 MHz spectrophotometer and Waters SYNAPT G2 HDMS were used to record the IR, 1H NMR and Mass spectra. Samples for NMR were prepared in DMSO-d₆ and TMS was internal reference. Absorption frequencies in terms of chemical shift were expressed in δ ppm. Mass spectra were recorded on.

In 25 mL of ethanol and 12 mL of 30 percent NaOH solution, 2-hydroxyacetophenone 1a (0.015 mol) and 1,3-disubstituted-pyrazole-4-carbaldehyde 2 (0.015 mol) were dissolved and stirred at ambient temperature for 40-48 h with TLC monitoring. The contents were transferred to a beaker containing crushed ice. Then it was acidified using dil. acetic acid and the product was filtered and purified using alcohol to get 3a. The compounds 3b-3f were prepared using the same procedure.

### Table 2: Physical data for synthesized compound

| Compound | R1 | R2 | R3 | R4 | m. p.(°C) | Yield (%) |
|----------|----|----|----|----|----------|----------|
| 3a       | H  | H  | H  | H  | 170      | 65       |
| 3b       | H  | CH₃| H  | H  | 172-174  | 61       |
| 3c       | H  | CH₃| Cl | CH₃| 220-222  | 63       |
| 3d       | H  | H  | Cl | H  | 262-264  | 66       |
| 3e       | Cl | Cl | H  | H  | 280-282  | 68       |
| 3f       | H  | H  | CH₃| H  | 262-264  | 58       |
| 4a       | H  | H  | H  | H  | 176-178  | 84       |
| 4b       | H  | CH₃| H  | H  | 188-190  | 78       |
| 4c       | H  | CH₃| Cl | CH₃| 242-244  | 86       |
| 4d       | H  | H  | Cl | H  | 252-254  | 82       |
| 4e       | Cl | Cl | H  | H  | 294-296  | 84       |
| 4f       | H  | H  | CH₃| H  | 264-266  | 80       |
| 5a       | H  | H  | H  | H  | 206-208  | 76       |
| 5b       | H  | CH₃| H  | H  | 218-220  | 78       |
| 5c       | H  | CH₃| Cl | CH₃| 222-224  | 80       |
| 5d       | H  | H  | Cl | H  | 232-234  | 82       |
| 5e       | Cl | Cl | H  | H  | 256-258  | 78       |
| 5f       | H  | H  | CH₃| H  | 248-252  | 80       |
| 6a       | H  | H  | H  | H  | 196-198  | 82       |
| 6b       | H  | CH₃| H  | H  | 204-206  | 76       |
| 6c       | H  | CH₃| Cl | CH₃| 208-210  | 72       |
| 6d       | H  | H  | Cl | H  | 202-204  | 76       |
| 6e       | Cl | Cl | H  | H  | 218-220  | 82       |
| 6f       | H  | H  | CH₃| H  | 212-214  | 74       |

(2E)-3-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-1-(2-hydroxyphenyl)prop-2-en-1-one, 3a

Yellow Solid, IR (KBr): 3124, 3066, 2926, 1685, 1639, 1514, 831, 748 cm⁻¹; HRMS: m/z 424.8751 (M⁺); ¹H NMR: δ 11.8 (1H, s), 8.89 (1H, s), 7.95 (2H, dd, J=9.12, 4.12Hz), 7.85 (1H, ddd, J=8.86, 2.84Hz), 7.71 (1H, ddd, J=8.92, 8.96, 2.84Hz), 7.46 (2H, t, J=9.12Hz), 7.37 (1H, d), 7.28 (1H, ddd, J=8.96, 8.88, 2.90Hz), 7.21-7.24 (3H, m); 5.92 (2H, q).

3b

Yellow Solid, IR(KBr): 3398, 3132, 3080, 1639, 1573, 1514, 833, 800 cm⁻¹; HRMS: m/z 438.9017(M⁺); ¹H NMR: δ 10.2 (1H, s), 8.81 (1H, s),...
7.87 (2H, dd, J=8.88, 3.88 Hz), 7.71 (1H, dd, J=8.64, 2.58Hz), 7.38 (2H, d, J=8.88Hz), 7.12-7.16 (2H, m), 7.09 (1H, d, J=8.64, 2.56Hz), 5.84 (2H, q), 2.34 (3H, s).

3c

Yellow Solid, IR(KBr): 3532, 3124, 2924, 1672, 1639, 1585, 1514, 831, 752 cm⁻¹; HRMS: m/z 487.3733(M⁺); ¹HNMR: δ 12.4 (1H, t), 8.93 (1H, s), 7.99 (2H, dd, J=9.4Hz), 7.50 (2H, t, J=9.14Hz), 7.41 (1H, d), 7.24-7.28 (2H, m), i5.96i (2H, q), i2.56i(3H, is), i2.48 (3H, is).

3d

Yellow Solid, IR(KBr): 3446; 3132, 3070, 1639, 1573, 1514, 833, 800 cm⁻¹; HRMS: m/z 459.0135 (M⁺); ¹HNMR: δ 11.3 (1H, s), 8.85 (1H, s), 7.91 (2H, dd, J=9.4Hz), 7.79 (1H, d, J=2.7Hz), 7.69 (1H, dd, J=8.8, 2.72Hz), 7.42 (2H, t, J=9Hz), 7.33 (1H, d), 7.17-7.20 (2H, m), 5.88 (2H, AB-Quartet).

3e

Yellow Solid, IR(KBr): 3446; 3130, 3070, 1643, 1570, 1508, 835, 808 cm⁻¹; HRMS: m/z 473.7652(M⁺); ¹HNMR: δ 10.8 (1H, s), 8.79 (1H, s), 7.85 (2H, dd, J=8.86, 3.86 Hz), 7.71 (1H, d, J=2.56Hz), 7.61 (1H, d, J=2.58Hz), 7.36 (2H, t, J=8.86Hz), 7.27 (1H, d), 7.11 (1H, d), 5.82 (2H, q).

3f

Yellow Solid, IR(KBr): 3446; 3134, 1683, 1637, 1560, 1514, 831, 804 cm⁻¹; HRMS: m/z 438.9017(M⁺); ¹HNMR: δ 11.3 (1H, s), 8.91 (1H, s), 7.97 (2H, dd, J=9.06,4.06 Hz), 7.83 (1H, d, J=2.76Hz), 7.73 (1H, d, J=8.86, 2.78Hz), 7.49 (2H, t, J=9.06Hz), 7.39 (1H, d), 7.22-7.26i(2H,im), i5.94i(2H,iq), i2.32i(3H, is).

2-[(3S)-3′-(5-Chlorothiophen-2-yl)-1’-(4-fluorophenyl)-3,4-dihydro-1’H,2H-3,4’-bipyrrozal-5-yl]phenol, 4a

A mixture of 2 mL hydrazine hydrate, 15 mL ethanol and substituted pyrazolyl chalcone 3a (0.0015 mol) was taken in R.B. flask and refluxed for 4 hours. Then by adding 2 mL of glacial acetic acid, heated for further 4 hours. Once the reaction was finished the contents were taken into crushed ice. The resulting product had been filtered. On crystallization from ethanol, pure compound 4a was obtained. The compound 4b-4f were prepared using the same procedure.

4a

Yellow Solid, IR(KBr): 3309, 3084, 1593, 1514, 835, 802 cm⁻¹; HRMS: m/z 438.9050 (M⁺); ¹HNMR: δi12.26 (s, 1H), 8.64i(s,i1H), 7.90-8.01 (m,i3H), 7.37-7.50 (m, 4H), 7.32 (1H, ddd, J=8.84, 8.82, 2.68Hz), 7.22 (1H, d, J=8.92Hz), 7.14 (1H, ddd, J=8.86, 8.80, 2.94Hz), 6.97 (1H, dd, J=8.62, 2.94Hz), 5.13 (1H, t, J=10.12Hz), 3.75 (1H, dd, J=17.02, 10.12Hz), 3.21 (1H, dd, J=17.01Hz, 10.12Hz).

4b

Yellow Solid, IR(KBr): 3361, 3388, 3082, 1593, 1516, 829, 813 cm⁻¹; HRMS: m/z 452.9316 (M⁺); ¹HNMR: δ 11.64i(1H, is), 8.56i(1H, is), T7.84-7.93i(3H, m), 7.29-7.44 (4H, m), 7.13 (1H, d, J=8.68Hz) 7.04 (1H, dd, J=8.62, 2.52Hz), 6.90 (1H, d, J=2.52Hz), 5.05 (1H, t, 9.88Hz), 3.67 (1H, dd, J=17.04, 9.88Hz), 3.13 (1H, dd, J=17.05, 9.88Hz), 2.28 (3H, s).

4c

Yellow Solid, IR(KBr): 3292, 3078, 1514, 835, 802 cm⁻¹; iHRMS: m/z 501.4032 (M⁺); ¹HNMR: δ 10.74 (1H, s), 8.68 (1H, s), 7.94-8.05 (3H, m), 7.41-7.54 (3H, m), 7.27 (1H, d, J=8.94Hz), 7.02 (1H, s), 5.17 (1H, t, J=10.14Hz), 3.79(1H, d), J=16.94, 10.14Hz), 3.25 (1H, dd, J=16.94,i10.14Hz), 2.40i (3H, is), i2.30i(3H, is).

4d

Yellow Solid, IR(KBr): 3334, 3084, 1514, 835, 817 cm⁻¹; HRMS: m/z 473.0410(M⁺); ¹HNMR: δ 11.68 (1H, s), 8.6 (1H, s), 7.86-7.97 (3H, m), 7.33-7.46 (4H, m), 7.27 (1H, dd, J=8.72, 2.56Hz), 7.21 (1H, d, J=8.8Hz), 6.94 (1H, d, J=8.5Hz), 5.09 (1H, t, 10Hz), 3.71 (1H, dd, J=17.01, 10Hz), 3.17 (1H, dd, J=17.01, 10Hz).

4e

Yellow Solid, IR(KBr): 3327, 3080, 1514, 835 cm⁻¹; HRMS: m/z 507.7951 (M⁺); ¹HNMR: δ 12.08 (1H, s), 8.54 (1H, s), 7.80-7.91 (3H, m), 7.27-7.40 (4H, m), 7.21 (1H, d, J=2.42Hz), 7.13 (1H, d, J=8.66Hz), 5.03 (1H, t, 9.86Hz), 3.65 (1H, dd, J=15.97, 9.86Hz), 3.11 (1H, dd, J=15.96, 9.86Hz).

4f

Yellow Solid, IR(KBr): 3277, 3093, 1514, 821, 804 cm⁻¹; HRMS: m/z 452.9316 (M⁺); ¹HNMR: δ 10.14 (1H, s), 8.66 (1H, s), 7.92-8.04 (3H, m), 7.39-7.52 (4H, m), 7.33 (1H, dd, J=8.72, 2.56Hz), 7.25 (1H, d, J=8.8Hz), 7.00 (1H, d, J=8.5Hz), 5.15
(1H, t, J=10Hz), 3.77 (1H, dd, J=17.03, 10Hz), 3.23 (1H, dd, J=17.03, 10Hz), 2.30 (3H, s).

2-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-4H-chromen-4-one, 5a

Substituted pyrazolyl propenone 3a (0.001 mol) was refluxed in 12 mL of DMSO containing 0.2 g iodine at 135-145°C for 3-4 h and kept aside for 24 hours. Then the mixture was transferred to smashed ice and filtered solid was treated with 15% sodium thiosulphate for removal of unreacted iodine. The compound 5a was purified by recrystallizing it from ethanol. The compound 5b-5f were prepared using the same procedure.

5a
Faint Solid, IR(KBr): 3124, 3059, 1653, 1516, 833 cm⁻¹; HRMS: m/z 422.8592 (M⁺); ¹HNMR: δ 8.00-8.05 (4H, m), 7.65 (1H, d, J=8.8 Hz), 7.56 (1H, ddd, J=8.92, 2.88 Hz), 7.49-7.53 (4H, im), 7.29 (1H, d, J=3.92 Hz), 6.84 (1H, s).

5b
Yellowish Brown Solid, IR(KBr): 3122, 3059, 1654, 1516, 833, 800 cm⁻¹; HRMS: m/z 436.8858 (M⁺); ¹HNMR: δ 7.92-7.97 (4H, m), 7.50 (1H, d, J=8.56 Hz), 7.41-7.44 (3H, m), 7.21 (1H, d, J=3.68 Hz), 6.76 (1H, s).

5c
Yellowish Brown Solid, IR(KBr): 3113, 3057, 1645, 1514, 833, 792 cm⁻¹; HRMS: m/z 485.3575 (M⁺); ¹HNMR: δ 8.04-8.09 (3H, m), 7.69 (1H, s), 7.53-7.57 (3H, m), 7.33 (1H, d, J=3.94 Hz), 6.88 (1H, s), 2.60 (3H, is), 2.54 (3H, s).

5d
Faint Yellow Solid, IR(KBr): 3140, 3066, 1653, 1541, 1517, 835, 796 cm⁻¹; HRMS: m/z 456.9967 (M⁺); ¹HNMR: δ 7.96-8.01 (4H, m), 7.61 (1H, d, J=8.8 Hz), 7.45-7.49 (4H, m), 7.25 (1H, d, J=3.8 Hz), 6.80 (1H, s).

5e
Yellow Solid, IR(KBr): 3124, 3074, 1654, 829, 779 cm⁻¹; HRMS: m/z 491.7494 (M⁺); ¹HNMR: δ 8.02-8.07 (4H, m), 7.51-7.55 (4H, m), 7.31 (1H, d, J=3.66 Hz), 6.86 (1H, s).

5f
Yellow Solid, IR(KBr): 3140, 3066, 1653, 1541, 835, 796 cm⁻¹; HRMS: m/z 436.8858 (M⁺); ¹HNMR (DMSO-d₆): δ 7.90-7.96 (4H, m), 7.55 (1H, d, J=8.66 Hz), 7.39-7.43 (4H, m), 7.19 (1H, d, J=3.86 Hz), 6.74 (1H, s), 2.26 (3H, s).

2-[3'-(5-Chlorothiophen-2-yl)-1'-(4-fluorophenyl)-1'H,2H-3,4'-bipyrazol-5-yl]phenol, 6a

In ethanol 2-substituted-chromen-4-one, 5a (0.015 mol) and hydrazine hydrate (0.005 mol) were dissolved and refluxed for 4 hours. TLC was used to monitor the reaction, and once it was finished, the reaction liquid stirred with cold water containing small amount of ice. After that, glacial acetic acid was used to neutralize the resulting mixture. Pure 6a was obtained by filtering the resultant product and recrystallizing it from ethanol. The compound 6b-6f were prepared using the same procedure.

6a
Yellow Solid, IR(KBr): 3336, 3128, 3068, 1514, 835, 800 cm⁻¹; HRMS: m/z 436.8891 (M⁺); ¹HNMR: δ 13.12 (1H, s), 9.04 (1H, s), 8.14 (1H, d, J=2.25 Hz), 7.84-7.95 (3H, m), 7.37-7.49 (5H, m), 7.34 (1H, ddd, J=8.66, 8.48, 2.24 Hz), 7.26 (1H, d, J=9.20, 2.24 Hz), 7.19 (1H, d).

6b
Yellow Solid, IR(KBr): 3421, 3186, 1514, 835, 698 cm⁻¹; HRMS: m/z 450.9157 (M⁺); ¹HNMR: δ 10.95 (1H, s), 8.96 (1H, s), 8.06 (1H, d), 7.84-7.95 (3H, m), 7.47 (1H, ddd, J=8.33, 2.25 Hz), 7.29-7.39 (4H, im), 7.18 (1H, d), 7.13 (1H, d), 7.19 (1H, d), 7.13 (1H, d).
6f

Yellow Solid, IR(KBr): 3292, 3124, 1514, 835, 815 cm\(^{-1}\); HRMS: m/z 450.9157 (M+); \(^1\)H NMR: \(\delta 12.15 (1H, s), 8.94 (1H, s), 8.04 (1H, d), 7.82-7.93 (3H, m), 7.17 (1H, d, \text{J}=9.14 \text{Hz}), 7.09 (1H, d), 2.12 (3H, s).\)

**CONCLUSION**

Flourine and thiophene containing different pyrazolyl compounds were prepared in this present work and spectroscopic evidence strongly supports the suggested compounds. Compound 6a and 6b are promising alpha-amylase inhibitory activity in comparison with reference compound Acarbose. These compounds can be considered as lead compounds as anti-diabetic agents. Results of the antimicrobial study show that all the synthesized compounds can be modified structurally to improve their antimicrobial profile.

**ACKNOWLEDGEMENT**

The authors are thankful to Management of parent institute, Hon. Principal of the college, DST, Government of India for their support. The authors express their gratitude towards the Director, SAIF, Punjab University, Chandigarh, for spectroscopic investigations.

**Conflict of interest**

There are no conflicts of interest declared by the authors.

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