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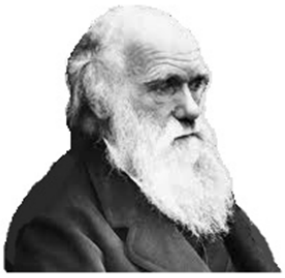

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# Synthesis, spectral study and antimicrobial activity of some new 2-n-butyl-4-chloro-5-formyl imidazole (BCFI) analogues

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**ABSTRACT**

New chalcone derivatives (7a-7j) and thiosemicarbazone derivatives (9a-9j) containing 2-n-Butyl-4-chloro-5-formyl imidazole nucleus have been synthesized and their chemical structure were evaluated using Infrared spectroscopy (IR), Ultra-violet spectroscopy (UV-Vis.), $^{1}$H-NMR spectroscopy and mass spectroscopy. All the synthesized compounds were evaluated for their anti-bacterial activities against Gram-positive bacteria *Bacillus subtilis* & *Staphylococcus epidermidis* and gram-negative bacterial strain *Pseudomonas aeruginosa* & *Porteous vulgaris*. The anti-fungal activity was evaluated against *Aspergillus niger*. The activity of the compounds were compared with known standards such as streptomycin and nystatin. Among the synthesized chalcone derivatives 7d, 7g & 7h are potentially active against bacterial strains & fungi. Among the thiosemicarbazone derivatives 9a, 9g, 9j & 9i are moderately active against bacterial strains. While 9d & 9j shows good anti-fungal activity.

***Keywords*:** 2-n-Butyl-4-chloro-5-formylimidazole (BCFI), Chalcones, Thiosemicarbazones, antimicrobial activity

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## 1. INTRODUCTION

Among the most studied organic compounds [1] characterized each atom of the molecules are joined by ring structure and at least one atom other than carbon namely nitrogen, sulphur, oxygen, etc are present. Formation of such compounds are known as heterocyclic compounds, and they possess diverse physical as well as chemical properties than other class of organic molecules. The class of heterocyclic compounds, specifically those involving nitrogen [2-3] as a heteroatom, is widely studied significantly within organic chemistry. Broad research efforts have been committed to the observation and advancement of novel molecules in this domain. Nitrogen-containing heterocycles play a pivotal role in the synthesis of diverse pharmaceutically active molecules [4-6].

Five membered heterocyclic [7] compound with two nitrogen atoms at 1$^{st}$ and 3$^{rd}$ position known as imidazole [8-10] studied widely among the nitrogen containing molecules. Several natural products [11] including nucleic acids [12], histamine [13], and histidine [14] consist of the imidazole nucleus. The nucleus presents some interesting pharmacological properties like antibacterial [15-17], anti-tubercular [18-19], anticancer [20-23], larvicidal [24], and antifungal [25-26].

In this present research work we have displayed the synthesis, structural characterization and medicinal activity of chalcone derivatives and thiosemicarbazone derivatives from important pharmacological intermediate 2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazole (BCFI) using thiosemicarbazide and various acetophenone derivatives respectively.

## 2. MATERIALS AND METHODS

All the chemicals were purchased from FINAR and SRL chemicals are of AR grade and used directly without purification. Melting points were determined using open glass capillaries, and are not corrected. To check the progress of the reaction, thin-layer chromatography was performed using a 0.2 mm precoated silica gel plate. The UV light (254 nm and 365 nm) visualization was recorded by Shimadzu UV spectrophotometer. The NMR spectra were recorded on a Bruker Advance II (400 MHz) spectrometer after being processed in DMSO-d$^6$. All chemical shifts are expressed as δ ppm downfield from tetramethylsilane (TMS) internal standard. The FT-IR spectra of the compounds were recorded in Bruker Alpha II IR spectroscope. GC-MS QP-2010 mass spectrometer was used to record mass spectroscopy data.

### 2. 1. Experimental Section

#### 2. 1. 1. Synthesis of 2-chloro-N-phenylethanamide (3a)

Aniline **(1a)** (1 mmol) were dissolved in acetone and allowed to react with solution 2-chloroacetyl chloride **(2)** (1.5 mmol) at room temperature for 40 minutes. In order to maintain the neutral pH of the reaction mass, small amount of catalyst $K_2CO_3$ was added and stirred for next 3-4 h. Upon completion of reaction, the product was discharged into chilled water, filtered, dried and re-crystallized using methanol. M.P: 138 °C, Yield: 86%, C: 57.65%, H: 4.43%, N: 7.75%, O: 10.26%, Cl: 20.80%, Mol. Formula: $C_8H_8NOCl$, Calculated: C: 56.65%, H: 4.75%, N: 8.26%, O: 9.43%, Cl: 20.90%.

Subsequently other derivatives **(3a-3j)** were synthesized using same process as reported

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### 2. 1. 2. Synthesis of 2-(2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazol-1'-yl)-N-phenylethanamide (5a)

2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazole (1 mmol) **(4)** in DMF (10 mL) and excess amount of potassium carbonate ($K_2CO_3$) was added in RBF and stirred for 2 h at room temperature. 2-chloro-N-phenylethanamide (1.5 mmol) **(3a)** were added into above mentioned reaction mixture and was refluxed for 3-4 h. The progress of the reaction was observed using TLC. At the end, the reaction mixture was cooled and dumped into ice cold water. The solid crystalline product was filtrated and dried. M.P: 150 °C, Yield: 72%, (Found C: 59.67%, H: 5.09%, N: 13.09%, O: 10.26%, Cl: 11.80%, Mol. Formula: $C_{16}H1_8N_3O_2Cl$, Required: C: 60.09%, H: 5.67%, N: 13.14%, O: 10.01%, Cl: 11.09%).

The synthesis of these compounds is reported in *International Journal of Research and Analytical Reviews,* volume 10, Article number 4(2023) DOI: https://doi.one/10.1729/Journal.3669.i

### 2. 1. 3. Synthesis of 3-(2'-n-Butyl-4'-chloro-1'-(2''-oxo-2''-phenylethyl)-1'H-imidazol-5'-yl)-1-phenylprop-2-en-1-one (7a)

The solution of 2-(2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazol-1'-yl)-N-phenylethanamide (1 mmol) **(5a)** was prepared in 1,4-dioxane (20 mL). To these reaction mass, acetophenone (1.2 mmol) **(6a)** and 10 mL of 20% NaOH solution was added and refluxed at 100 °C for 12 h. Progression of reaction was monitored using TLC. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid product formed was filtrated and recrystallized using methanol. M.P: 284-286 °C, Percentage Yield: 75%.
Similarly other derivatives **(7a-7j)** have been synthesised.

### Spectral Data

White solid, IR (KBr) $cm^{-1}$: 3055 (C-H str. Ar-H), 2955, (C-H str.), 2870, 2723 (C-H str. Ali. $CH_2$), 1743 (C=O str. -$CONH_2$), 1597, 1543 (Ar C=C bend.) 1496, 1442(Ali. C-H bend.), 1033 (C=N, imidazole), 825 (C-Cl str.). $^1$H NMR (DMSO-$d^6$) δ ppm: 10.60 (s, 1H), 7.08-7.95 (m, 13H), 5.12 (s, 2H), 2.67 (t, 2H), 1.62 (m, 2H), 1.39 (m, 2H), 0.90 (t, 3H) MS: m/z; 421.20; Yield: 75 % Calculated: C: 70.84%, H: 5.70% Cl: 8.71%, N: 6.88%, O:7.86%. Mol. Formula: $C_{24}H_{24}ClN_2O_2$, Found: 70.74%, H: 5.80% Cl: 8.86%, N: 6.79%, O:7.81%

### 2. 1. 4. Synthesis of 2-{2'-n-Butyl-5'-[(2''-carbamothioyl hydrazino)methylene]-4'-chloro-1'H-imidazol-1'-yl}-N-phenylethanamide (9a)

A round bottom flask containing a solution of 2-(2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazol-1'-yl)-N-phenylethanamide (1 mmol) **(5a)** in methanol were allowed to react with thiosemicarbazide (2 mmol) **(8)** using 2-3 drops of glacial acetic acid as a catalyst. The whole reaction mass was refluxed for 14 h and TLC was used to monitor the reaction progress. After completion, the reaction mixture was cooled to ambient temperature and the formed solid particles were separated by filtration. The product was dried and re-crystallized using methanol

to remove impurities. M.P: 224-226 °C, Percentage Yield: 62%. Similarly other derivatives **(9a-9j)** have been synthesised.

**Spectral Data Analysis**

Yellow solid, IR (KBr) $cm^{-1}$: 3410 (N-H str.), 3155 (C-H str. Ar-H), 2955, 2650 (C-H str.), 2870, 2723 (C-H str. Ali. $CH_2$), 1689 (C=O str. -$CONH_2$), 1504, 1604 (Ar C=C bend.) 1450, 1350 (Ali. C-H bend.), 1203 (C=N, imidazole), 825 (C-Cl str.). $^1$H NMR (DMSO-$d^6$) δ ppm: 11.32 (s, 1H), 10.29 (s, 1H), 8.08-8.36 (s, 2H), 7.05-7.50 (m, 6H), 5.19 (s, 2H), 2.51 (t, 2H), 1.91 (m, 2H), 1.62 (m, 2H), 1.41 (t, 3H) MS: m/z; 378.30; Yield: 62 % Calculated: C: 51.97%, H:5.39%, Cl:9.02% N:21.39% O: 4.07% S: 8.16%, Mol formula: $C_{17}H_{21}ClN_6OS$ Found: C: 50.95%, H:6.41%, Cl:10.02% N:20.07 % O: 4.16% S: 8.07%.

**Table1.** Physical data of 2-[2'-n-Butyl-4'-chloro-5'-(3"-oxo-3"-arylprop-1'-en-1'-yl)-1'H-imidazol-1'-yl}-N-phenylethanamide derivatives (7a-7j)

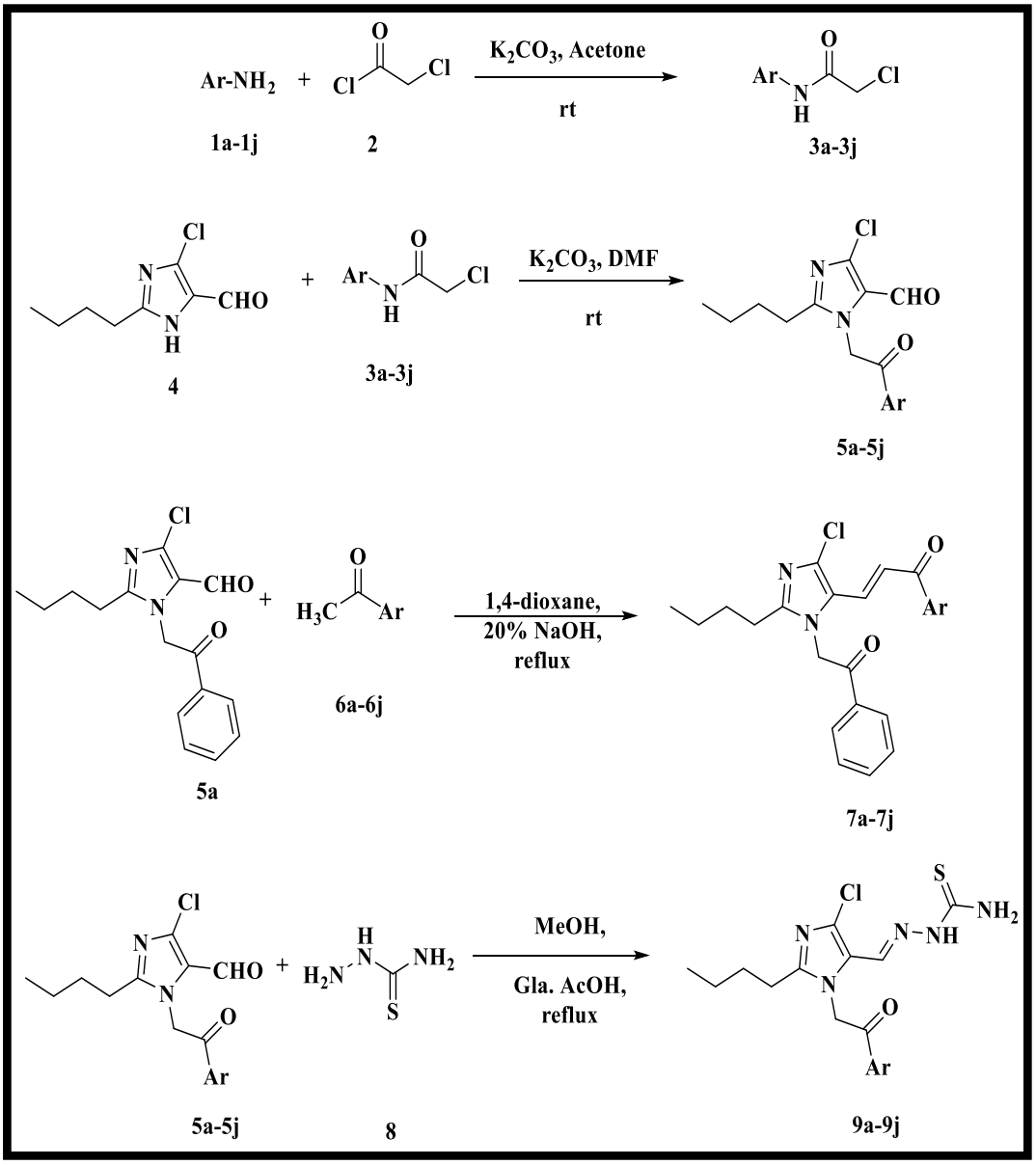
| Code | -Ar | M.F. | M.W. | M.P. | % Yield |
|---|---|---|---|---|---|
| **7a** | $C_6H_5$- | $C_{24}H_{24}ClN_3O_2$ | 421.9 | 284-286 | 75 |
| **7b** | 2-Br-$C_6H_4$- | $C_{24}H_{23}ClBrN_3O_2$ | 500.8 | 220-222 | 58 |
| **7c** | 3-Br-$C_6H_4$- | $C_{24}H_{23}BrClN_3O_2$ | 499.0 | 290-292 | 72 |
| **7d** | 4-Br-$C_6H_4$- | $C_{24}H_{23}BrClN_3O_2$ | 499.1 | 298-300 | 74 |
| **7e** | 2-Cl-$C_6H_4$- | $C_{24}H_{23}Cl_2N_3O_2$ | 456.1 | 294-296 | 62 |
| **7f** | 3-Cl-$C_6H_4$- | $C_{24}H_{23}Cl_2N_3O_2$ | 456.4 | 222-224 | 70 |
| **7g** | 4-Cl-$C_6H_4$- | $C_{24}H_{23}Cl_2N_3O_2$ | 456.4 | 200-202 | 66 |
| **7h** | 4-F-$C_6H_4$- | $C_{24}H_{23}ClFN_3O_2$ | 439.4 | 208-210 | 72 |
| **7i** | 3-$NO_2$-$C_6H_4$- | $C_{24}H_{23}ClN_4O_4$ | 466.9 | 220-222 | 69 |
| **7j** | 4-$NO_2$-$C_6H_4$- | $C_{24}H_{23}ClN_4O_4$ | 466.9 | 210-212 | 69 |

**Table 2.** Physical data of 2-{2'-n-Butyl-5'-[(2"-carbamothioyl hydrazino)methylene]-4'-chloro-1'H-imidazol-1'-yl}-N-arylethanamide derivatives (9a-9j)

| Code | Ar | M.F. | M.W. | M.P | % Yield |
|---|---|---|---|---|---|
| **9a** | $C_6H_5$- | $C_{17}H_{21}ClN_6OS$ | 378.3 | 224-226 | 62 |
| **9b** | 2-$CH_3$-$C_6H_4$- | $C_{18}H_{23}ClN_6OS$ | 406.9 | 240-242 | 66 |
| **9c** | 4-$CH_3$-$C_6H_4$- | $C_{18}H_{23}ClN_6OS$ | 406.9 | 232-234 | 65 |
| **9d** | 4-$OCH_3$-$C_6H_4$- | $C_{18}H_{23}ClN_6O_2S$ | 422.9 | 250-252 | 68 |
| **9e** | 2-Cl-$C_6H_4$- | $C_{17}H_{20}Cl_2N_6OS$ | 427.3 | 242-244 | 61 |

| | | | | | |
|---|---|---|---|---|---|
| **9f** | 3-Cl-$C_6H_4$- | $C_{17}H_{20}Cl_2N_6OS$ | 427.3 | 248-250 | 59 |
| **9g** | 4-Cl-$C_6H_4$- | $C_{17}H_{20}Cl_2N_6OS$ | 427.3 | 252-254 | 69 |
| **9h** | 3-Br-$C_6H_4$- | $C_{17}H_{20}ClBrN_6OS$ | 471.8 | 280-282 | 56 |
| **9i** | 4-F-$C_6H_4$- | $C_{17}H_{20}ClFN_6OS$ | 410.9 | 268-270 | 62 |
| **9j** | 2-$NO_2$-$C_6H_4$- | $C_{17}H_{20}ClN_7O_3S$ | 437.9 | 262-264 | 61 |

## 2. 2. Reaction Scheme



## 3. RESULTS AND DISCUSSION

### 3. 1. Antimicrobial Activity

The evaluation of antibacterial and antifungal properties of the synthesized compounds employs cup plate [27] method to measure the zone of inhibition. The sample is present at a concentration of 100 µg/mL while standard drug present at a concentration of 50 µg /ml, in DMSO serving as the solvent. The anti-bacterial activity was tested using Gram-positive bacteria such as *Bacillus subtilis, Staphylococcus epidermidis* and Gram-negative bacteria such as *Proteus vulgaris, Pseudomonas aeruginosa*. Antifungal activity study was done using fungi *Aspergillus niger*. Here the standard drugs were used for antimicrobial activity are streptomycin as broad spectrum and nystatin as an anti-fungal. The results of antimicrobial activity study in terms of clearance of bacterial and fungi colony (Zone of inhibition) is displayed in table no.3 and 4.

**Table 3.** 2-[2'-n-Butyl-4'-chloro-5'-(3''-oxo-3''-arylprop-1'-en-1'-yl)-1'H-imidazol-1'-yl]-N-phenylethanamide derivatives (7a-7j)

| **Compound ID** | **Antibacterial activity** | | | | **Antifungal Activity** |
|---|---|---|---|---|---|
| | **Gram positive bacteria** | | **Gram negative bacteria** | | **Fungus** |
| | *Bacillus subtilis* | *Staphylococcus epidermidis* | *Proteus vulgaris* | *Pseudomonas aeruginosa* | *Aspergillus niger* |
| **7a** | 10 | 12 | 16 | 5 | 8 |
| **7b** | 15 | 18 | 12 | 5 | 8 |
| **7c** | 14 | 16 | 15 | 6 | 7 |
| **7d** | 20 | 15 | 11 | 16 | 17 |
| **7e** | 11 | 10 | 14 | 8 | 7 |
| **7f** | 12 | 12 | 12 | 5 | 12 |
| **7g** | 21 | 22 | 12 | 17 | 18 |
| **7h** | 12 | 10 | 15 | 12 | 8 |
| **7i** | 13 | 11 | 9 | 13 | 4 |
| **7j** | 14 | 13 | 7 | 15 | 4 |
| **Zone of inhibition in mm** | | | | | |

**Table 4.** Antimicrobial activity data of 2-{2'-n-Butyl-5'-[(2''-carbamothioyl hydrazino)methylene]-4'-chloro-1'H-imidazol-1'-yl}-N-arylethanamide derivatives (9a-9j)

| Compound ID | Antibacterial activity | | | | Antifungal Activity |
|---|---|---|---|---|---|
| | Gram positive bacteria | | Gram negative bacteria | | Fungus |
| | *Bacillus subtilis* | *Staphylococcus epidermidis* | *Proteus vulgaris* | *Pseudomonas aeruginosa* | *Aspergillus niger* |
| **9a** | 21 | 12 | 13 | 12 | 15 |
| **9b** | 18 | 15 | 12 | 14 | 4 |
| **9c** | 17 | 11 | 11 | 5 | 10 |
| **9d** | 15 | 17 | 13 | 8 | 16 |
| **9e** | 13 | 14 | 18 | 7 | 2 |
| **9f** | 11 | 12 | 12 | 2 | 3 |
| **9g** | 22 | 18 | 14 | 3 | 4 |
| **9h** | 14 | 15 | 17 | 12 | 5 |
| **9i** | 12 | 14 | 19 | 14 | 7 |
| **9j** | 3 | 20 | 16 | 14 | 16 |
| **Zone of inhibition in mm** | | | | | |

**Table 5.** Compounds (7a-7j & 9a-9j) showing antibacterial & antifungal activity compare with known standard drugs

| Compound | Antibacterial activity | | | | Antifungal Activity |
|---|---|---|---|---|---|
| | Gram positive bacteria | | Gram negative bacteria | | Fungus |
| | *B. subtilis* | *S. epidermidis* | *P. vulgaris* | *P. aeruginosa* | *A. niger* |
| **(7a-7j) & (9a-9j)** | 7d & 7g<br>9a & 9g | 7g<br>9g & 9j | 9i | 7d & 7g | 7d & 7g<br>9d & 9j |

| Activity of Known Standard Drugs: | | | | | |
|---|---|---|---|---|---|
| Streptomycin | 25 | 25 | 26 | 19 | - |
| Nystatin | - | - | - | - | 22 |
| **Zone of inhibition in mm** | | | | | |

## 4. CONCLUSION

The purpose of the commenced research work was to prepare, structural characterization, and evaluate antimicrobial activity of some new chalcone and thiosemicarbazone derivatives starting from compound 2'-n-Butyl-4'-chloro-5'-formyl-1'H-imidazole to yield the target moieties via reaction with differently substituted acetophenones and thiosemicarbazones respectively. Among the synthesized chalcone molecules **7d, 7g & 7h** are found potent against bacteria and fungi as commenced in table 3 & 4. Among the prepared thiosemicarbazone molecules **9a, 9g & 9j** are found active against gram positive germs, while **9i** only active against gram negative germs. Compound **9d & 9j** are also potent active against fungi as mentioned in table 5.

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