Synthesis and Identification of Some Imino Chalcone Derivatives with Evaluating their Anti-oxidant Activity

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Abstract

This work involves the preparation of high yield iminochalcon compounds (B1-B15) through two parts. The first part involves the preparation of 2,4-dihydroxy Chalcone (A1-A15) by the condensation of 2,4-dihydroxy aceto phenone with aryl aldehyde in the presence of sodium hydroxide (40%) as a catalyst. The second part includes the preparation of iminochalcon from the condensation of p-hydroxy aniline with 2,4-dihydroxy chalcone derivatives (A1-A15) in the presence of some drops of conc. H2SO4. Thin-layer chromatography (TLC) was used to control the chemical reaction. These new derivatives were characterized by using FT-IR and 1H-NMR spectroscopy. These synthesized compounds were also assessed by the DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical method, through which the compounds (B1-B15) were evaluated for their antioxidant activity. The compound B3 was found to have the strongest antioxidant activity (IC50=23.91 μg/mL) as compared to that of the common standard of ascorbic acid (IC50=31.95 μg/mL).

Keywords: iminochalcone, 2,4-dihydroxy chalcone, aniline, antioxidant activity.

1. Introduction

Schiff bases are prepared through the condensation between equimolaris of primary amine (aromatic, aliphatic, or related derivatives) and carbonyl compounds (aldehydes or ketones, aromatic, ...
aliphatic, or related derivatives) using basic or acidic media in alcoholic solvent [1]. They are characterized by the \( \text{N} = \text{CH} \) bond, which is essential in the process of transamination and racemization in biologic structures [2]. They are used in various biochemical and biological activities, such as antitumor [3], anticancer and anti-tubercular [4], antimicrobial [5], antibacterial [6], and anti-biofilmformation in methicillin-resistant staphylococcus aureus [7]. Chalcones have a \( \text{C}^{\text{A}}\text{N}(\text{A})-\text{CO}-\text{CH} = \text{C}^{\text{B}} \) (B) structure, where two aromatic rings (A and B) are bound by an aliphatic three carbon chain [8]. Chalcone condenses in ethanol with substituted aniline in the presence of 2.3 drops of \( \text{H}_2\text{SO}_4 \) to provide chalcone imine. Chalcones and their derivatives hold a special significance among pharmaceutical and synthetic compounds [9]. The chalcone nuclei are important components of several drugs [10]. The synthesis of imines from the condensation of carbonyl compounds (aldehydes or ketones) with amines as a nucleophile is typically used to prepare chalcones and Schiff bases [11]. Chalcone (1,3-diaryl-2-prapen-1-one) and Schiff bases (substituted benzylidene aniline) belong to the commonly used compounds in companies of natural intermediates. They have broad spectrums of biological activities, such as those of antioxidants [12], anti leshmanial [13], antifungal [14], and antimicrobial [15], \( \alpha,\beta \)-Unsaturated ketimines, which are obtained from chalcone and amine condensation, possess different pharmacological properties [16]. Both chalcones and Schiff bases are essential for the synthesis of different active organic compounds, such as flavones [17], indazol-3-one and thioxo pyrimidines [18], pyrazoloins [19], \( \beta \)-lactams [20], sulfonamide derivatives [21], and metal complexes [22]. They are also used to minimize photosensitivity of photographic emulsions in color photography [23] and mesomorphic properties of dimer containing chalcone [24].

2. Materials and Methods

Chemicals used in this work are supplied from Sigma Fluka, MERCK, BDH and CDH and are used without further purification.

2.1 Instruments

The melting points of the compounds prepared were determined using the SMP30 melting point instrument. The uncorrected FT-IR spectra were recorded on SHMADZU FT-IR 8400Series Japan using the KBr disk method. TLC was performed for silica gel G and spots were visualized by \( \text{I}_2 \) vapors. The H1-NMR spectra were obtained using DMSO as a solvent and TMS as an internal standard with NMR spectrometer (Bruker, Ultra Shield 400 MHZ, Switzerland).

2.2 Synthesis of Chalcone Derivatives [25] (A1-A15)

A total of 40 \% \( \text{NaOH}(10 \text{mL}) \) and 0.01mol of 2,4-dihydroxy acetophenone (1.52gm) were added to 15 ml absolute \( \text{EtOH} \) in 100ml round bottom flask with 30 minutes of stirring. The substituted aldehyde (0.01 mol) heated at 40-45 \(^\circ\text{C} \) on water bath for 4-5 hours. The precipitate formed was left for overnight. The reaction mixture was completed by TLC using petroleum ether: ethylacetate (4:1), then washed with water and ethanol. Crushed ice was acidified with 45\% (50ml) \( \text{HCl} \) and added. The precipitate was filtered and washed with 1\% \( \text{NaHCO}_3 \) solution and water. The precipitate (yellow – orange product) was crystallized from \( \text{EtOH} \). Its physical properties are shown in Table-1.

2.3 Synthesis of imino chalcone derivative [26] (B1-B15)

In a round bottom flask, equimolar quantities of substituted 2,4-dihydroxy chalcone (0.01 moles) and aromatic amines (p-hydroxy aniline, 1.091g, 0.01 moles) were dissolved in ethanol (20ml) and 2, 3 drops of Conc. \( \text{H}_2\text{SO}_4 \) was added. The mixture was heated at 70-80 \(^\circ\text{C} \) in a water bath for 4-5 hours. TLC control (ethylacetate: methanol) (4:1) was used to complete the reaction. The reaction mixture was diluted with ice cold water. Solid substituted 2, 4-dihydroxy -N-hydroxy phenyl chalcone imines were obtained. These were purified, washed, and recrystallized from absolute ethanol. Their physical properties are shown in Table-2.
### Table 1 - Physical properties of Chalcone compounds (A1-A15).

| Com. NO. | Molecular Formula | R' | Color | Melting point °C | Yield% | Retention factor | Petroleum ether: ethylacetate (TLC) |
|----------|-------------------|----|-------|------------------|--------|-------------------|------------------------------------|
| A1       | C_{15}H_{12}O_{3} |    | Orange| 148-150          | 92     | 0.94              | (1:3)                              |
| A2       | C_{16}H_{14}O_{4} |    | crystal orange| 192–194 | 67     | 0.89              | (1:4)                              |
| A3       | C_{15}H_{12}O_{4} |    | Light brown| 175-178 | 64     | 0.68              | (2:3)                              |
| A4       | C_{17}H_{14}O_{6} |    | Light yellow| 117-118 | 60     | 0.54              | (1:9)                              |
| A5       | C_{17}H_{13}NO_{3} |     | Wine red| 180–182 | 62     | 0.59              | (2:3)                              |
| A6       | C_{18}H_{16}O_{7} |    | Yellowish brown| 135-137 | 65     | 0.71              | (1:5)                              |
| A7       | C_{15}H_{11}ClO_{3} |  | Light yellow| 156–158 | 87     | 0.74              | (2:3)                              |
| A8       | C_{15}H_{11}NO_{5} |  | Brown| 210-212 | 75     | 0.93              | (2:3)                              |
| A9       | C_{13}H_{10}O_{4} |    | White yellow crystals| 71-74 | 73     | 0.93              | (2:3)                              |
| A10      | C_{23}H_{20}O_{5} |    | Yellowish orange thick| 186-187 | 82     | 0.77              | (1:5)                              |
| A11      | C_{17}H_{15}NO_{5} |  | Pale yellow needles| 113-114 | 67     | 0.65              | (1:8)                              |
| A12      | C_{16}H_{14}O_{4} |    | Orangish yellow| 166-168 | 68     | 0.66              | (2:3)                              |
| A13      | C_{18}H_{12}N_{4}O_{3} | | Yellow| 178–180 | 58     | 0.73              | (4 : 1)                            |
| A14      | C_{22}H_{18}O_{4} |    | Orange thick| 188-189 | 81     | 0.66              | (1:4)                              |
| A15      | C_{18}H_{12}ClN_{3}O_{3} | | Pale yellow| 312-314 | 78     | 0.51              | (4 : 1)                            |
Table 2-Physical properties of iminochalcone compounds (B1-B15).

| Compound | Molecular Formula | R’ | Color | Melting point °C | Yield % | Retention factor | ethylacetate:methanol (TLC) |
|----------|------------------|----|-------|------------------|--------|----------------|-----------------------------|
| B1       | C21H17NO3        |    | Light brown | 171-173        | 63     | 0.69           | (4:1)                       |
| B2       | C22H19NO4        |    | Pale yellow  | 208-206        | 57     | 0.77           | (4:1)                       |
| B3       | C21H17NO4        |    | Pale yellow  | 192-193        | 64     | 0.75           | (4:1)                       |
| B4       | C23H19NO6        |    | White shiny crystals | 184-186 | 69     | 0.68           | 3:2                         |
| B5       | C23H32N2O3       |    | Dark brown   | 216-214        | 54     | 0.57           | (4:1)                       |
| B6       | C24H21NO7        |    | Light brown white | 178-180      | 64     | 0.62           | 3:2                         |
| B7       | C21H16ClNO3      |    | Dark orange  | 118-120        | 86     | 0.81           | 4:1                         |
| B8       | C21H16N2O5       |    | Yellowish cream solid | 184-186 | 90     | 0.66           | 4:1                         |
| B9       | C19H15NO4        |    | Brown        | 131-132        | 73     | 0.74           | 4:1                         |
| B10      | C29H25NO5        |    | Light yellow | 162-163        | 76     | 0.67           | 3:2                         |
| B11      | C23H20N2O5       |    | Red          | 126-128        | 60     | 0.57           | 3:2                         |
| B12      | C22H19NO4        |    | Pale orange  | 152-150        | 68     | 0.78           | (4:1)                       |
| B13      | C24H17N5O3       |    | Pale green needles | 261-263    | 66     | 0.53           | n-hexane:CHCl3 1:1          |
| B14      | C28H23NO4        |    | White cream  | 156-158        | 75     | 0.73           | 4:1                         |
| B15      | C24H17ClN2O3     |    | Dark yellow  | 237-239        | 82     | 0.70           | n-hexane:CHCl3 1:1          |

3. Results and Discussion
The formation of Schiff bases from an aldehyde (or) ketone is a reversible reaction and usually occurs under acid (or) base catalysis or heating. The formation is usually powered by the separation of
the liquid or water removal, or both, from the campsite. Replaced 2, 4-dihydroxychalcones imine (B1–B14) was synthesized from the substitution of 2,4-dihydroxy chalcone with p-hydroxy aniline, using H₂SO₄ as a catalyst, with a yield of 54-90%. The reaction sequences are outlined in schemes 1.1 and 1.2.

Scheme 1.1 - Synthesis of chalcone from 2,4-dihydroxy acetophenone (A1-A15).

Scheme 1.2 - Synthesis of imino chalcone derivatives from chalcone (B1-B15).
The mechanism of the preparation of α, β-unsaturated ketimines from aldehydes (or) ketones was developed in an acid-catalyzed process which begins with the addition of the primary amine to the carbonyl group by nucleophile [27], as shown in scheme 1.3.

Scheme 1.3-Mechanism of Schiff’s base synthesis (acid-catalyzed)

The FT-IR spectra of the prepared compounds (B1-B15), which are listed in Table-3, did not show the band assigned to the $\nu$ (C=O) of chalcone derivative at (1674-1647) cm$^{-1}$. The absorption bands of C=N at (1590-1630) cm$^{-1}$ were observed. The stretching vibration of C=N was moved to low due to the conjugation of the C=N bond with the aromatic ring [28]. A wide band of the hydrogen-bonded phenolic hydroxyl group (bonding O-H) was observed at (3307-3417) cm$^{-1}$. The $\nu$ (C=O, aromatic two peaks at (1489-1586) cm$^{-1}$ were also shown. Two bands of absorption appeared at (3050-2959) cm$^{-1}$ belonging to (C-H, stretching) of the aromatic and aliphatic groups, respectively, and a (C-N) appeared at a stretching frequency of (1230-1020)cm$^{-1}$, as shown in Figures-(1-6).

The $^1$H-NMR data for some compounds (B8, B10, and B14) were recorded using DMSO as a solvent. The results showed: ($\delta$ 9.16-9.92)ppm of (S,1H,OH at position C4), ($\delta$ (S,1H,OH at position C2), (6.17-6.45)ppm of (α-H), (6.73-6.99) ppm of (β-H), (7.22-8.17) ppm of aromatic protons and (-OCH$_3$) at (3.97) ppm, as shown in Figures-(7-10).

Table 3 - Characterization of FT-IR absorption bands of compounds (B1-B15).

| Compound | R$'$ | $\nu$ CH$_{ar}$ | $\nu$ CH$_{aliph}$ | $\nu$ C=N | $\nu$ OH | $\nu$ C=O,C-N | $\nu$C=C$_a$
|----------|------|----------------|----------------|--------|--------|-------------|--------|
| B1       |      | 3005          | 2982           | 1634   | 3308   | 1229,11    | 1574  |
|          |      |               |                |        |        | 30,1257,13 | 1509  |
| B2       |      | 3081          | 3004           | 2900   | 1623   | 1236,11    | 1577  |
|          |      |               |                |        |        | 29,1264,13 | 1509  |
| B3       |      | 3068          | 2996           | 1628   | 3355   | 1213,11    | 1587  |
|          |      |               |                |        |        | 47,1254,13 | 1504  |
|   | Structure | 1H-NMR Data | Chemical Shift Data |
|---|-----------|-------------|---------------------|
| B4 | ![Structure](https://via.placeholder.com/150) | 3057 3025 2931 2833 1621 3310 1236,11 77 1283 1578 1600 | \( \nu \) (OH)acid (2583-3500) \( \nu \) C=O acid 1725 |
| B5 | ![Structure](https://via.placeholder.com/150) | 3042 2949 2842 1627 3432 3312 1215,11 76 1258,13 31 1587 - |
| B6 | ![Structure](https://via.placeholder.com/150) | 3069 2917 2806 1625 3427 1229,11 73 1262,13 06 1513 1571 | \( \nu \) (OH)acid (2498-3127) \( \nu \) C=O acid 1729 |
| B7 | ![Structure](https://via.placeholder.com/150) | 3070 - 1629 3308 1216,11 27 1228,13 67 1573 1508 | \( \nu \) C-Cl : 776 |
| B8 | ![Structure](https://via.placeholder.com/150) | 3069 2910 1624 3337 1217,11 78 1256,13 94 1573 1600 | m-NO2 (str.): 1494,1337 (N=O, symmetric) |
| B9 | ![Structure](https://via.placeholder.com/150) | 3068 3027 2896 2837 1633 3304 1212,12 88 1358 1597 1558 | \( \nu \) C-O cyclic: 1026 |
| B10 | ![Structure](https://via.placeholder.com/150) | 3082 3052 2907,280 0 1630 3483 1208,11 78 1294,13 33 1603 1572 | - |
| B11 | ![Structure](https://via.placeholder.com/150) | 3033 2827 1621 3526 1233,11 50 1341 1567 | \( \nu \) (OH)acid (2487, 3500) \( \nu \) C=O acid 1716 \( \nu \) (NH) :3233 |
| B12 | ![Structure](https://via.placeholder.com/150) | 3013 2970 2945 1626 3460 1228,12 10 1265,13 67 1571 1610 | - |
| B13 | ![Structure](https://via.placeholder.com/150) | 3006 2970,296 0 2868 1616 3307 1217,11 60 1368 1573 - |
| B14 | ![Structure](https://via.placeholder.com/150) | 3005 2970 2917 1626 3390 3307 1230,11 60 1254,13 27 1573 1505 | - |
| B15 | ![Structure](https://via.placeholder.com/150) | 3047 2970 1633 3308 1256,11 50 1367 1574 1507 | \( \nu \) C-Cl : 616 |

**Table 4**-Chemical shift data of \(^1\)H-NMR spectra of some chalcone imine derivatives
1H-NMR (δ=ppm) = (δR/Co)mpound

| Compound | R' | 1H-NMR (400MHz-DMSO-d6, solvent), (δ=ppm): |
|----------|----|-----------------------------------------------|
| B8       |    | 6.44(d,1Hα), 6.99(d,1Hβ), 2.51(DMSOd6, solvent), 13.22 (S,1H, OH at C2), 9.16(S,1H,OHatC4), 7.85- 8.17 (m, 11H, Ar - H), 8.39(S,1H, OH at C4) |
| B10      |    | 6.31(d,1Hα), 6.92(d,1Hβ), 2.51(DMSOd6, solvent), 4.97(S,2H, O-CH2), 11.53 (S,1H, OH at C2), 9.92 (S,1H, OH at C4), 3.97 (S,3H, OCH3), 7.56-8.17 (m, 15H, Ar - H), 8.408(S,1H, OH at C4) |
| B14      |    | 5.29 (S, 2H, O-CH2), 11.29 (S,1H, OH at C2), 9.16 (S,1H, OH at C4), 7.37-7.63(m,16H,Ar-H), 8.71(S,1H, OH at C4) |
| B15      |    | 6.49(d,1Hα), 6.73(d,1Hβ), 2.51(DMSOd6, solvent), 11.99 (S,1H, OH at C2), 9.57 (S,1H, OH at C4), 7.22-8.15 (m,12H,Ar-H), 8.76(S,1H, OH at C4) |

Figure 1- FT-IR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl)imino)-3-phenylallyl) benzene-1,3-diol (B1).
Figure 2-FT-IR spectrum of 2-((1E,2E)-3-(4-hydroxy-3-methoxyphenyl)-1-((4-hydroxyphenyl)imino)allyl)benzene-1,3-diol (B2).

Figure 3-FT-IR spectrum of 2-(4-((1E)-3-(2,4-dihydroxyphenyl)-3-((4-hydroxyphenyl)imino)prop-1-en-1-yl)-2-methoxyphenoxy)acetic acid (B6).
Figure 4-FT-IR spectrum of 4-((2E)-3-(4-benzyloxy)-3-methoxyphenyl)-1-((4-hydroxyphenyl)imino)allyl)benzene-1,3-diol (B9).

Figure 5-FT-IR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl)imino)-3-(4-methoxy phenyl) allyl) benzene-1,3-diol (B11).
Figure 6- FT-IR spectrum of 4-((2E)-3-(4-(benzyloxy)phenyl)-1(4-hydroxyphenyl) iminoallylbenzene 1,3diol (B13).

Figure 7- H\textsuperscript{1}-NMR spectrum of 2-((1E,2E)-1-((4-hydroxyphenyl) imino)-3-(3-nitrophenylallyl)benzene 1,3diol (B8).
Figure 8: $^1$H-NMR spectrum of (4-((1E)-3-(2,4-dihydroxyphenyl)-3-((4-hydroxy phenyl)imino)prop-1-en-1-yl)phenyl)glycine (B10).

Figure 9: $^1$H-NMR spectrum of 4-((2E)-3-(4-(benzyloxy)phenyl)-1(4-hydroxyphenyl)iminoallylbenzene1,3diol (B14).
Figure 10-H$^1$-NMR spectrum of 4-((2E)-3-(2-chloroquinolin-3-yl)-1(4-hydroxyphenyl) iminooallylbenzene1,3diol (B15).

3.1 Antioxidant Activities of the Prepared Compounds[29]

DPPH (1.3mg / ml) was prepared as a normal solution in methanol 100μl DPPH was added in 3ml of methanol and absorbance at 517 nm was noted. Various compound concentrations (25, 50, 75, and 100 μg / ml) were prepared. Sample (1 ml) was diluted to 3 ml and 100 μl of DPPH was applied. Test tubes were placed in light for 30 minutes to complete the reaction. Absorbance of each test tube was measured after 30min at 517 nm on UV-VIS spectrophotometer against methanol as a blank, as in Figures- (11, 12, 13).

The results of antioxidant activity are shown in Table-5 and indicate that the majority of the synthesized compounds displayed moderate to strong antioxidant activity in comparison to normal (ascorbic acid) activity (IC50=31.95 μg / mL). The highest activity was attributed to the p-OH group on the ring B in compounds B3 and B2 (IC50= 23.91 μg / ml and 28.82 μg / ml, respectively). Conversely, compound B8 showed a low activity of m-NO$_2$ (IC50=123.87 μg / mL). For this reason, the (OH) ring in groups A and B confers high antioxidant activity. The p-OH group in B2 and B3 displayed greater free radical scavenging behavior than that of the m-NO$_2$ group of B8 compound.

The standard reference made of ascorbic acid showed IC50 value of 31.95 μM. Compared to the reference, the strength of antioxidant functions of the tested compounds are in the following order: ascorbic acid >B3>B2>B6>B1>B11>B4>B10>B7>B9>B13>B12> B15> B14>B5>B8.

Table 5-Observation of in-vitro antioxidant activities of the synthesized compounds

| con. c. μg/ml | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 | B1 0 | B1 1 | B1 2 | B1 3 | B1 4 | B1 5 | STD (Ascorbic acid) |
|--------------|----|----|----|----|----|----|----|----|----|------|------|------|------|------|------|---------------------|
| 25           | 47.76 | 48.41 | 50.34 | 40.44 | 25.16 | 45.35 | 39.42 | 27.21 | 40.32 | 41.08 | 37.24 | 44.03 | 40.43 | 30.51 | 36.21 | 46.12               |
| 50           | 49.83 | 57.42 | 57.21 | 52.25 | 52.32 | 58.22 | 45.63 | 36.22 | 47.14 | 45.36 | 56.52 | 48.85 | 45.67 | 37.22 | 39.22 | 60.14               |
| 75           | 53.77 | 60.26 | 66.23 | 62.32 | 78.25 | 56.58 | 39.43 | 56.85 | 59.23 | 63.17 | 52.63 | 55.47 | 47.61 | 43.04 | 65.01 |
|       | 100 | 65.21 | 69.44 | 72.11 | 69.65 | 60.35 | 68.18 | 65.22 | 44.13 | 60.62 | 68.04 | 70.81 | 56.01 | 61.52 | 56.32 | 64.11 | 78.3 |
|-------|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| IC50  | 44.09| 28.82 | 23.91 | 46.72 | 88.12 | 33.24 | 56.28 | 123.87 | 58.22 | 53.45 | 46.11 | 60.13 | 60.09 | 82.66 | 74.95 | 31.95 |
| µg/ml |      |       |       |       |       |       |       |       |       |       |       |       |       |       |       |      |

**Figure 11**- Graph showing DPPH scavenging activities of chalcones (B1-B5).

**Figure 12**- Graph showing DPPH scavenging activities of chalcones (B6-B10).
Figure 13-Graph showing DPPH scavenging activities of chalcones (B11-B15).

Conclusions
In the present study, substituted 2,4-dihydroxy–N-hydroxyl phenyl chalcone imines were synthesized with a percentage yield range of 54-90%. The structures of all these synthesized compounds were established on the basis of spectral data (FT-IR and 1H-NMR). It is also interesting to note that the synthesized chalcone imines had strong antioxidant activities.

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