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Original Article

Synthesis and Characterization of Bis-Flavone Imine Derivatives

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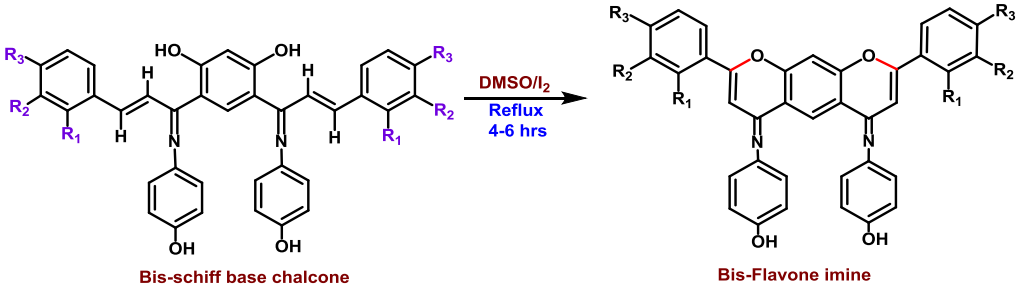
ABSTRACT

For different pharmacological activities to treat various diseases, many naturally occurring and synthesized flavonoid derivatives are explored. Certain molecules have drawn the particular interest because of their possible health advantages, such as the antioxidant capabilities of these polyphenolic compounds. By removing free radicals from the environment or chelating metal ions, the functional hydroxyl groups in flavonoids mediate their antioxidant activities. All of the following features are present: antiviral, anti-inflammatory, hepatoprotective, antioxidant, antithrombotic, vasodilating, and anticarcinogenic, along with a high effectiveness and low toxicity. By refluxing one mole of bis-Schiff base chalcone with two moles of DMSO/I_2, new bis-flavone imine has been synthesized. Synthesized bis-flavone structures were determined by ^{1}H-NMR, ^{13}C-NMR, and Mass spectrum as well as the anticancer activity (MCF-7) of bis-flavone imine.

GRAPHICAL ABSTRACT



1. $R_1 = R_2 = R_3 = H$
2. $R_1 = R_2 = H$, $R_3 = NO_2$
3. $R_1 = R_2 = H$, $R_3 = N(CH_3)_2$
4. $R1 = R_2 = H$, $R_3 = Cl$
5. $R_1 = R_3 = Cl$, $R_2 = H$
6. $R_1 = R_2 = H$, $R_3 = F$
7. $R_1 = R_2 = H$, $R_3 = Br$
8. $R_1 = Cl$, $R_2 = R_3 = H$

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Introduction

The cancer that kills the most women is breast cancer, which accounts for between 30,000 and 45,000 deaths annually in the United States. In addition, it is the most common cancer among women. Numerous factors, including breast lesions, family history, pregnancy, irregular menstruation, and X-rays, are thought to enhance the risk of developing breast cancer in women. However, compared with the earlier times, the use of systemic medicines has considerably decreased disease-related mortality. This is due to factors including improved screening and early detection [1-4]. A family of substances that exist naturally is called flavonoids. Many fruits, vegetables, beverages, and secondary metabolites contain them in significant amounts. Members of the flavonoid family, such as flavones, isoflavones, and neoflavones, have various therapeutic benefits. Different naturally occurring and synthesized flavonoid derivatives are being investigated for a range of pharmacological properties to treat various diseases [5-7]. Different normally and manufactured happening flavonoid subordinates are read up for various pharmacological exercises to treat various illnesses [8]. Due to their potential health advantages, such as the antioxidant properties of certain polyphenolic compounds, these molecules have received particular studies [9]. The functional hydroxyl groups of flavonoids scavenge free radicals or chelate metal ions to mediate their antioxidant properties [10]. Several mesogenic chemicals with intriguing features were created by designing heterocyclic compounds with liquid crystalline qualities. Flavonoid derivatives have become a crucial framework for the intracellular detection of cysteine, demonstrating the potential value of flavones as fluorescent probes [11, 12]. In our prior work, we found that the chalcone-containing chromen-2-one exhibited outstanding mesomorphic characteristics at imine linkages 3 and 4 [13]. Foods like fruits, vegetables, seeds, and flowers generally contain oxygenated heterocyclic compounds called flavones (2-arylchromones) as the secondary metabolites. They are members of the flavonoid group. They have a wide spectrum of biological and pharmacological properties and play significant roles in the growth, reproduction, and defense of plants. This has antiviral, anti-inflammatory, hepatoprotective, antioxidant, antithrombotic, vasodilating, and anticarcinogenic activity and combines the high effectiveness and low toxicity [14-17]. Despite the importance of flavones and chromones in pharmacology, relatively few uses of cross-coupling reactions with palladium on their halides or triflates have been documented so far [18]. The most prevalent naphthoquinonoidal substance extracted from the heart of Bignoniaceae trees is the naturally occurring naphthoquinone lapachol. Due to its significant biological activity, especially its antitumoral properties, this natural substance has received much research [19, 20]. The most advantageous member of the lapachol group is β-lapachone. Some human cancer cells are cytotoxic to it [21], and these cells are inherently more vulnerable to the oxidative damage than the normal cells [22]. A lot of research has been done on β-lapachone recently, and it is currently being tested in phase II clinical trials either alone or in conjunction with the other anticancer medications [23]. On the other hand, the identification of heat shock protein 90 (Hsp 90) as the site of anticancer activity of geldanamycin has generated significant interest in the Hsp 90 suppression as a cancer treatment strategy. Due to this matter, enormous efforts were made to generate tiny Hsp90 inhibitor compounds that were clinically useful and had a wide range of structural diversity, including purine-based analogs (PU3) [24-26]. Coumarins can be produced using various techniques, such as Pechmann condensation [27].

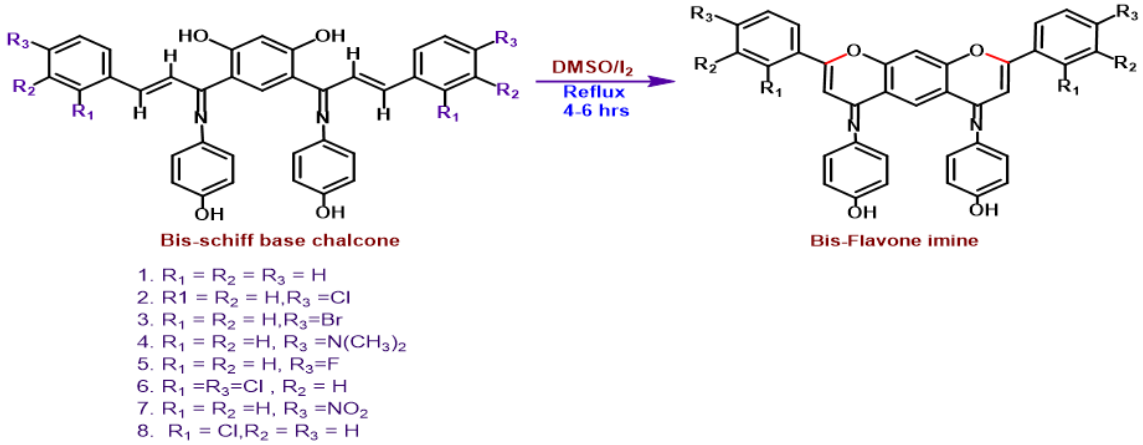
By using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry, synthetic bis-Flavone imine was applied to characterize the structural characteristics of the prepared products. To identify the new anticancer leads, the synthesized compounds were tested for their cytotoxic activities against MCF-7 cancer cell lines.

Materials and Methods

The Fisher-Johns melting point device was used to determine the uncorrected melting points. Using precoated TLC plates, the purity of the compounds was evaluated (Merck, 60F-254). ^{1}H-NMR and ^{13}C-NMR spectra were recorded by Bruker Ascend 400 NMR spectrometer. Mass spectra MS Model: 5973 Network Mass Selective Detector. MCF-7 human breast cancer cell line (ATCC, Manassas, VA, USA)

Synthesis of bis-flavone imine (iodine-mediated cyclization in DMOS) [28]

2,4-Dihydroxy Chalcone bis-Imine (0.01 mol) was dissolved in 15 mL DMSO, and then (0.2 mmol, 0.37 g) iodine was added, while the mixture was being stirred. After that, the mixture was refluxed for 4-6 hours at 130-140 °C on an oil bath, cooled, and neutralized with 10% $Na_2S_2O_3$ to remove unreacted I_2, filtered the precipitate, rinsed with distilled water, and used absolute isopropanol to carry out the recrystallization to get the desired products.



Scheme 1: Iodine-mediated cyclization in DMSO

*4,4'-((2,8-diphenyl-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F1**)*

Beige solid, chemical formula: $C_{36}H_{24}N_2O_4$, molecular weight: 548.60, mp 308-310 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3359, 1598, 1126, 1512. ^{1}H-NMR (500 MHz, DMSO): δ 9.51 (s, 2H), 7.25-7.06 (m, 10H), 6.85-6.66 (m, 10H), 5.57 (d, J = 23.3 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO): δ 165.74, 161.65, 154.09, 147.71, 142.11, 135.34, 121.87, 118.84, 112.85, 99.58, 82.02.

*4,4'-((2,8-bis(4-chlorophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6 diylidene)bis(azaneylylidene))diphenol (**F2**)*

Solid ivory, chemical formula: $C_{36}H_{22}C_{l2}N_2O_4$, molecular weight: 617.48, mp 376-378 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3350, 1595, 1165, 1510, 836. ^{1}H-NMR (500 MHz, DMSO): δ 9.24 (s, 2H), 7.25-7.02 (m, 8H), 7.01-6.66 (m, 10H), 5.75 (d, J = 12.6 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO): δ 170.99, 167.91, 163.60, 151.58, 136.84, 125.19, 124.23, 123.91, 116.12, 113.41, 107.52, and 82.64.

*4,4'-((2,8-bis(4-bromophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F3**)*

Solid peach, yield 74%, chemical formula: $C_{36}H_{22}Br_2N_2O_4$, molecular weight: 706.39, mp 385-388 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3375, 1589, 1512, 1126, 815. ^{1}H-NMR (500 MHz, DMSO): δ 9.81 (s, 2H), 7.3-7.06 (m, 8H), 6.98-6.73 (m, 10H), 6.39 (d, J = 21.3 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO): δ 167.11, 160.08, 153.87, 150.36, 137.74, 132.15, 127.33, 125.38, 117.39, 116.21, 103.95, and 83.38.

*4,4'-((2,8-bis(4-(dimethylamino)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F4**)*

Solid champagne, yield 75%, chemical formula: $C_{40}H_{34}N_4O_4$; molecular weight: 634.74, mp 358-361 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3322, 1599, 1513, 1230, 1125. ^{1}H-NMR (500 MHz, DMSO): δ 9.43 (s, 2H), 7.15-6.91 (m, 8H), 6.66-6.37 (m, 10H), 6.01 (d, J = 25.9 Hz, 2H), 3.24 (s, 12H). ^{13}C NMR (125 MHz, DMSO): δ 169.37, 167.92, 166.38, 155.52, 146.68, 130.93, 123.91, 116.12, 112.28, 104.55, 84.77, and 48.70.

*4,4'-((2,8-bis(4-fluorophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F5**)*

Solid tan, yield 82%, chemical formula: $C_{36}H_{22}F_2N_2O_4$, molecular weight: 584.58, mp 336-340 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3314, 1613, 150., 1162, 840. ^{1}H-NMR (500 MHz, DMSO): δ 9.38 (s, 2H), 7.29-7.01 (m, 8H), 6.95-6.60 (m, 10H), 5.15 (d, J = 18.5 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO): δ 167.88, 165.27, 161.65, 153.67, 148.71, 136.64, 133.24, 123.85, 116.02, 112.63, 104.38, and 84.93.

*4,4'-((2,8-bis(2,4-dichlorophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F6**)*

Solid gray, yield 86%, chemical formula: $C_{36}H_{20}Cl_4N_2O_4$, molecular weight: 686.37, mp 376-379 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3360, 1585, 1512, 1125, 818. ^{1}H-NMR (500 MHz, DMSO): δ 9.59 (s, 2H), 7.25-6.89 (m, 6H), 6.84-6.61 (m, 10H), 5.52 (d, J = 41.4 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO): δ 169.84, 167.71, 163.61, 150.62, 145.34, 142.27, 138.02, 133.53, 128.06, 121.87, 118.64, 105.17, and 84.62.

*4,4'-((2,8-bis(4-nitrophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6 diylidene)bis(azaneylylidene))diphenol (**F7**)*

Solid maroon, yield 80%, chemical formula: $C_{36}H_{22}N_4O_8$, molecular weight: 638.59, mp 349-351 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3339, 1588, 1514, 1508, 1132. ^{1}H-NMR (500 MHz, DMSO): δ 9.54 (s, 2H), 7.2-6.98 (m, 8H), 6.88-6.64 (m, 10H), 5.62 (d, J = 23.3 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO) δ 171.76, 166.96, 159.35, 157.66, 146.07, 135.49, 133.55, 125.37, 123.07, 116.35, 107.45, and 83.65.

*4,4'-((2,8-bis(2-chlorophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-diylidene)bis(azaneylylidene))diphenol (**F8**)*

Dark brown, yield 73%, chemical formula: $C_{36}H_{22}Cl_2N_2O_4$, molecular weight: 617.48, mp 328-331 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3349, 1607, 1511, 1073, 841. ^{1}H-NMR (500 MHz, DMSO): δ 9.06 (s, 2H), 7.27-6.98 (m, 8H), 6.84-6.69 (m, 10H), 5.97 (d, J = 31.1 Hz, 2H). ^{13}C-NMR (126 MHz, DMSO): δ 168.34, 162.99, 161.49, 155.03, 149.00, 140.62, 131.72, 125.50, 123.84, 115.81, 105.65, and 85.48.

MTT cell viability assay in MCF-7 Cells

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (Sigma-Aldrich) assay was used to measure the cell growth and viability. Cells were gathered, trypsinized, and adjusted to 1.4 104 cells/well in density before being seeded into 96-well plates with 200 l of new media for each well and cultivated for 24 hours. Cells were exposed to the substance at a concentration of 100-6.25 g/mL in five serial dilution series in triplicates for 48 hours at 37 °C and 5% CO_2 after they had established a monolayer. After the treatment (24 hours), the supernatant was removed, 200 l/well of MTT solution (0.5 mg/mL in phosphate-buffered saline [PBS]) was added, and then another 4 hours were spent incubating at 37 °C. The monolayer of the culture original plate was not changed.

MTT solution was created by removing the cell supernatant and adding 100 l of dimethyl sulfoxide to each well. Crystals were dissolved in cells after being incubated at 37 °C on a shaker. Utilizing an ELISA reader, absorbance at 570 nm was used to determine the level of cell viability (Model wave xs2, BioTek, USA). Table 1 presents the corresponding dose-response curves that were used to calculate the chemicals' concentration that caused 50% of cell death (IC50).

Table 1: The MTT assay of synthesized compounds (**F1-F8**)

Synthesized compounds	IC50 values µg/mL
F1	104.7
F2	71.59
F3	56.79
F4	40.38
F5	22.61
F6	21.28
F7	93.05
F8	61.41

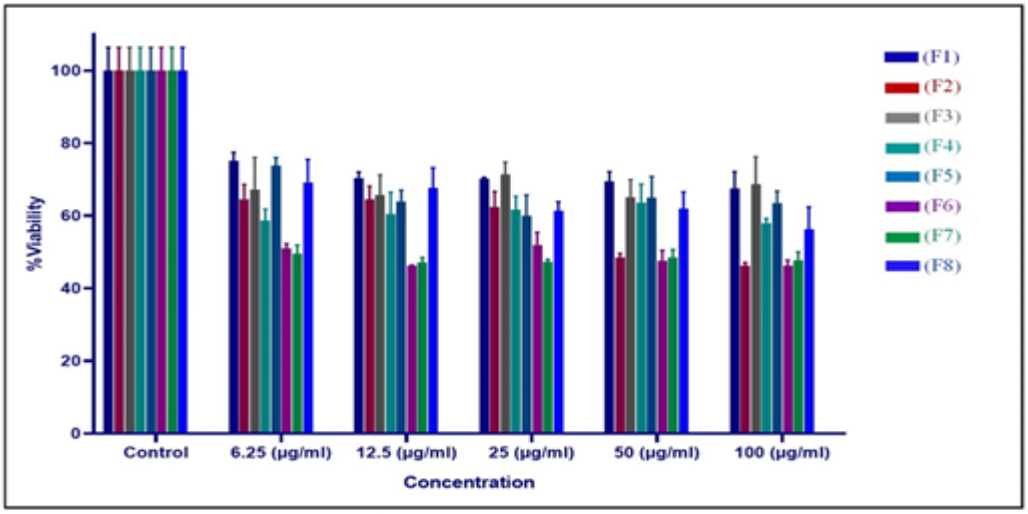


Figure 1: Comparison between cell viability and concentration of Compounds (**F1-F8**)

Results and Discussion

The synthesized compounds (**F1-F8**) were supported by FT-IR spectrum υ(O-H) phenolicat 3314.39- 3360.69cm^{-1}, υ(C=N)imine 1613.6-1585.14 cm^{-1}, υ(C-O) of chromene 1073.88-1165.81 cm^{-1}, υ(C=C) Cyclic1503.66-1513.24 cm^{-1}, ^{1}H-NMR spectrum disappearance of a synthesized bis- flavone imine compounds (**F1-F8**) single peak of proton di hydroxyl groups at 10.50, 10.87, 10.57, 10.47, 10.21, 10.60, 10.48, and 10.58 ppm, respectively. A single peak of proton P-hydroxy aromatic hydroxyl at 9.48, 9.35, 9.83, 9.35, 9.15, 9.84, 9.40, and 9.37 ppm, respectively. ^{13}C-NMR spectra, the peak of a carbon hydroxyl group (-C-OH) disappears at 171.61, 177.40, 172.54, 172.67, 171.60, 176.77, 169.99, and 171.61 ppm, respectively. The molecular mass of all synthesized compounds (**F1-F8**) 549.9, 617.7, 705.7, 634.6, 584.2, 684.1, 639.7, and 616.5 m/z, respectively, corresponds to the molecular weight which refers to the high purity.

The results of the present study in this field were consistant with those of the previous investigations. Most participants in this study had also the elevated CEA marker levels, particularly those who had recurrences. Its consideration can help prevent its return because increasing this marker is a reliable predictor of who will experience a recurrence. The results of this study are consistent with those of other related investigations in every cell line, the median inhibitory concentration (IC_{50}) values were determined (Table 1). The evaluated compounds (**F1-F8**) were found to be significantly cytotoxic to MCF-7 cell lines by the anticancer activity.

Conclusion

The synthesized flavones structures improved by ^{1}H-NMR, and ^{13}C-NMR showed that IC_{50} values compared with the other produced substances in Table 1, derivatives **F4**, **F5**, and **F6** had the highest anticancer efficacy to be significantly

cytotoxic to MCF-7 cell lines by the anticancer activity.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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Supporting Information

Copies of Mass, FT-IR, ^{1}H-NMR (500 MHz, DMSO), and ^{13}C-NMR (125 MHz, DMSO) spectra of synthesized compounds [PDF].

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