Original Article

Synthesis and Evaluation of New Brominated Azaflavones and Azaflavanone Derivatives as Cytotoxic agents against Breast Cancer Cell Line (MCF-7)

Srujana Muthadi[1], Baswaraju Macha[1] , Prashanthi Mamidi[2], Sravanthi Manchinella[2], Achaiah Garlapati[3], Raghuram Rao Akkinepalli[4]*

[1]Research Scholar, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana,INDIA.
[2]Project fellow, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, INDIA.
[3]Professor, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, INDIA.
[4](Present Address) Director, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Punjab, INDIA.

ABSTRACT

Background: Flavonoids encompasses flavones, isoflavones, flavanones and flavanols each possessing the benzopyranone ring system as the common structural feature, were identified as potent nonsteroidal aromatase inhibitors (NSAIs). **Purpose:** Azaflavones which were isosteric structural scaffolds of flavonoids were also proven to be potent NSAIs. In order to develop new NSAIs as cytotoxic agents for breast cancer, we designed some 6-bromo-2-substituted azaflavanones and azaflavone derivatives. **Method:** Azaflavones and Azaflavononones were synthesized by a reaction of 2-amino-6-bromoacetophenone and various aromatic aldehydes to result in different chalcones (4) using Claisen-Schmidt condensation. Further cyclization of chalcones (4), led to tetrahydroquinoline-4-ones (5) using orthophosphoric acid. In the final oxidative step, the desired dihydroquinoline-4-ones (6) were obtained. **Results:** All the synthesized compounds were characterized by using IR, ^{1}H NMR and ESI-MS data and were evaluated for cytotoxic activity by using MTT assay on MCF-7 cell lines. **Conclusion:** Compounds with furoyl and pyridyl groups as substituents were found to be potent.

Key words: Azaflavones, Azaflavanones, Claisen-Schmidt condensation, Cytotoxicity, MTT assay, FT-IR, NMR.

INTRODUCTION

Worldwide, breast cancer is considered as the leading cause of death among women (accounting for 35% of all cancers and 20% of all cancer deaths).[1-3] In most of the cases breast cancer proved to be hormone-dependent. The tumor progression is dependent on high levels of circulating estrogens, which play a critical role in cancer cell proliferation. Estrogen enhances the growth and proliferation of certain target cells, such as breast epithelial cells and estrogen-dependent mammary carcinoma cells. It also includes the formation and secretion of various growth factors in established human mammary carcinoma cell lines[4-6] such as MCF-7, T4TD and ZR-75-1.

Flavonoids are the plant products present in natural food sources, including fruits, vegetables, legumes, whole grains etc. The classes of flavonoids include flavones, isoflavones, flavanones and flavanols, which posseses the benzopyranone ring system as the common structural moiety. The flavonoids present in soy and in rye flour play a protective role in the incidence of breast cancer, as they show inhibitory activities of the aromatase enzyme,[7,8] thus lowering estrogen biosynthesis and circulating estrogen levels.[9,10]

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Correspondence:
Prof. Raghuram Rao Akkinepalli,
Director, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Punjab, INDIA.
Phone no: 8790432456
E-mail: rrakkinepally@niper.ac.in

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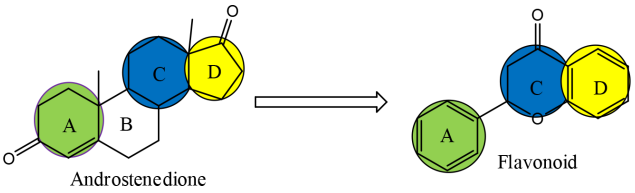

Figure 1: comparison of chemical feature between the model frame work of androstenedione and quinoline-4-one.

Azaflavones, being isosteric structural scaffold of flavonoids, were proven to be potent non-steroidal aromatase inhibitors (NSAIs). Halogenated azaflavones have also been reported to be potent aromatase inhibitors.

Previously, efforts were made to develop novel quinoline derivatives as potent NSAIs[11-14] from these laboratories. Specifically by chemical modifications on the structural scaffold of quinoline. The binding orientation was predicted in which the A, C and D rings of the quinolines mimic the A, C and D rings of the steroid substrate, respectively (Figure 1). The keto group at 4th position of quinoline undergoes keto-enol tautomerisation.

In continuation of our ongoing research to identify the potent molecules having flavonoid scaffold as AIs, an attempt was made to synthesize azaflavanones (tetrahydroquinoin-4-ones) azaflavones (dihydroquinoin-4-ones). For designing these derivatives, we relied on flavonoid skeleton as a structural scaffold for the synthesis of azaflavanones and azaflavones involving bioisosteric modification on ring oxygen with nitrogen. Results are discussed in the present communication.

MATERIALS AND METHODS

All chemicals and solvents were obtained from Sigma Aldrich or Merck, Mumbai and were used without further purification. Melting points were determined using open capillaries on electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on Bruker FTIR spectrophotometer using potassium bromide (KBr) pellet method. Column Chromatography was performed with silica gel G_{60}. ^{1}H NMR spectra were recorded on Bruker AC 400 MHz spectroscopy using DMSO/$CDCl_3$ as solvent and TMS as internal standard (chemicals shifts in .ppm). Triple quadrapole mass spectrometer (LCMS) with an Electrospray ionization (ESI) interface was used to obtain the mass spectra. Progress of the reactions was monitored using Thin Layer Chromatography (TLC) sheets with UV Fluorescence (silica gel Merck 60F 254). Ethylacetate and chloroform were used as solvent system (6:4) and spots were visualized using UV lamp.

Synthesis of 2-acetamido-5-bromoacetophenone(2)[15]

Bromine (0.8 g, 5.6 mM) in glacial acetic acid (10 mL) was added dropwise to a solution of 2-acetamidoacetophenone (**1**) (1 g, 5.6 mM) in glacial acetic acid with stirring at 5-10°C for 45 min. Reaction mixture was kept aside for 30 min at RT with occasional shaking and then poured in to 50 mL of cold water and the solid obtained was filtered and then recrystallized from methanol, to efford compound '2'.

Synthesis of 2-amino-5-bromoacetophenone(3)[16]

2-Acetamido-5-bromoacetopheone (**2,** 0.8 g, 3.1 mM) was dissolved in 5 mL of boiling ethanol and conc. HCl was added by drop wise and heated and refluxed for 20-30 min. After completion of reaction (monitored by TLC), reaction mixture was poured into ice-cold water, 5% NaOH solution was added to make the mixture alkaline. The separated solid was collected and recrystallized from ethanol.

General Procedure for the Synthesis of Chalcones (4a-n): Claisen-Schmidt Condensation

A solution of sodium hydroxide (0.255 g) in 3 mL of water and 4 mL of absolute ethanol was placed in a 100 mL conical flask. The flask was immersed in an ice chest at 0°C. 2-Amino-5-bromoacetophenone **(3,** 0.64 g, 3mmol) was added to the solution and stirred for one hour.[17] Different substituted aryl-aldehydes (3 mmol) in ethanol were added to above solution and stirred for 24-36 h until the reaction was completed (monitored by TLC). The resulting precipitate was separated by filtration, washed with cold water and dried. The crude products were purified by recrystallization from absolute ethanol.

General Procedure for the Synthesis of 6-bromo-2-Substituted Aryl Tetrahydroquinolin-4-ones (5a-n)

To a solution of chalcones (4a-n, 3 mM) in glacial acetic acid (12 ml), orthophosphoric acid (12 ml) was added slowly and refluxed the mixture for 20min. The reaction mixture was poured into cold water (100 ml) after cooling; the resulting precipitate was filtered and purified by recrystallization to get the corresponding tetrahydroquinoli-4-ones (5a-n).

For instance 6-bromo-2-(4-cyanophenyl)-2,3-dihydroquinolin-4(1*H*)-one (5a) was synthesized from 4a (R = 4-cyanophenyl) characterized based on spectral data. Yield: 80%, yellowish solid, mp: 292-294°C.

General Procedure for Synthesis of 6-bromo-2-Substitutedaryldihydroquinolin-4-ones (6a-n)

To a mixture tetrahydroquinolin-4-ones **(5a-n,** 2 mM) and 0.1N KOH in CH_3OH (60 mL, 6 mM) (di-acetoxy-iodo)benzene (0.709 g, 2.2 mM) was added at room temperature, the mixture was heated under reflux at 60°C for 16 h. After completion of reaction (monitored by TLC), CH_3OH was evaporated completely, 0.05N HCl (50 mL) was slowly added to reaction mixture at 0°C.[18] Resulting precipitate was separated by filtration, washed with cold water, and resultant product (6a-n) were recrystallized with methanol and purified by column chromatography.

For instant the 6-bromo-2-(4-cyano phenyl)quinolin-4-ol (6a) was synthesized from 6-bromo-2-(4-cyano phenyl) dihydroquinolin-4-(1H)-one (5a) by adopting the above general procedure. Yield: 68%, yellow solid, mp: 312-314°C.

Cytotoxicity on MCF-7 Cell Lines[19,20]

Cell viability was evaluated by the MTT Assay with three independent experiments with six concentrations of compounds in triplicates. MCF-7 cell lines were trypsinized and performed the tryphan blue assay to know viable cells in cell suspension. Cells were counted by haemocytometer and seeded at density of 5.0×10^3 cells / well in 100 µl media in 96 well plate culture medium and incubated overnight at 37°C. After incubation, the old media was taken off and fresh media (100 µl) with different concentrations of test compound was added in representative wells in 96 plate. After 48 hrs., the drug solution was discarded and fresh media with MTT solution (0.5 mg / mL^{-1}) was added to each well and plates were incubated at 37°C for 3 h. At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilised crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula and concentration of test drug needed to inhibit cell growth by 50 % values is generated from the dose-response curves for each cell line using with origin software.

$$\% \text{ inhibition} = \frac{100\{\text{Control} - \text{Treatment}\}}{\text{Control}}$$

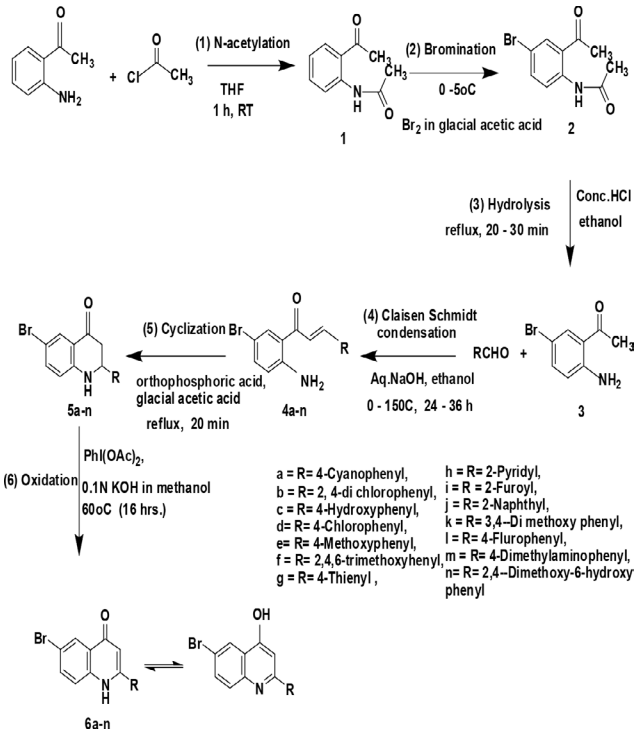

Figure 2: Scheme.

RESULTS AND DISCUSSION

Chemistry

2-Amino acetophenone by reacting with acetyl chloride in the presence of THF for 1 hour at room temperature yields 2-acetamido acetophenone (**1**). Bromine in glacial acetic acid was added drop wise at 5-10°C for 45 mins at RT to give 2-acetamido 5-bromo acetophenone (**2**). The compound (**2**) upon hydrolysis in the presence of Conc. HCl and hot ethanol (98%) gives 2-amino-5-bromo-acetophenone (**3**). This compound (**3**) was treated with different substituted aryl aldehydes in the presence of ethanol and aqueous NaOH at 0-15°C for 24 h (Claisen Schmidt condensation) to get the corresponding chalcones (**4a-n**).

These chalcones (**4a-n**) were cyclised using orthophosphoric acid to give the final product 6-bromo-2-substituted aryl tetrahydro quinoline-4-ones (azaflavanones) (**5a-n**). The compounds (**5a-n**) upon oxidation and by the treatment with 0.1 N KOH in methanol and diacetoxy iodo benzene gave the corresponding 6-bromo-2-substituted aryl dihydro quinoline-4-ones (**6a-n**) (azaflavones).

The final compounds, were purified by recrystallization with methanol or ethanol or by column chromatography. The compounds **(5a-n** and **6 a-n)** were confirmed on the basis of their physical and spectral data. For instance, the IR spectrum of the compound 5a showed NH absorption band at 3343 cm^{-1}, aromatic C-H stretch at 3035 cm^{-1}, an absorption band observed at 2225 cm^{-1} due to CN and carbonyl stretch band was observed at 1674, cm^{-1}. ^1H NMR ($CDCl_3$-d1) showed a singlet at 7.92 assignable to H-5 of quinoline. Two doublets at 7.56 (J= 4.8 Hz) and 7.47 (J= 6.8 Hz) each for two protons are assignable to H-3', H-5' and H-2', H-6' respectively.

Two doublets at 7.36 (*J*= 5.2Hz) and 6.53 (*J*= 4.8 Hz) each for one proton are due to H-7 and H-8 of quinolone. A triplet at 4.52 (*J* =7.2 Hz) for one proton is due to H-2 and a doublet at H-3 of quinoline nucleus. A broad singlet at 4.62 for one proton is assigned to NH. Mass spectrum showed M+ and M++1 peaks at m/z 327 and 328, and thus confirms the formation of 6-bromo-2-(4-cyanophenyl)-2,3-tetrahydroquinoli-4(*1H*)-one.

The IR spectrum of the azaflavones **6(a-n)** showed characteristic stretching absorption bands at 1674-1690 cm^{-1} due to the carbonyl group, at 3343-3361 cm^{-1} due to the presence NH stretching, at 1580-1593 cm^{-1} due to C=C and at 3063-3093 cm^{-1} due to aromatic hydrogens. The ^1H NMR spectra of the compounds 6(a-n) in $CDCl_3$ showed the presence of a single broad peak at 4.6 ppm, integrated to 1 proton, which was assigned to NH proton. In addition to the expected aromatic protons, a sharp singlet for one proton appeared at δ 6.9 ppm assignable to =C-H proton of quinoline ring. All the synthesized compounds showed their molecular ion peaks as base peak in ESI-MS spectra.

Spectral Characterisation of Compounds 5a-n

6-Bromo-2-(4'-cyanophenyl)-1,2,3,4-tetrahydro quinolin-4-one (5a))

Yield: 80%, yellowish solid, mp: 292-293 °C; FT-IR (KBr, cm^{-1}, υ): 3343 cm^{-1} (NH), 3035 cm^{-1} (C=H), 2926 cm^{-1} (C-H), 2225 cm^{-1} (CN), 1674 cm^{-1} (C=O), 1562 cm^{-1} (C=C),; ^1H NMR: ($CDCl_3$-d_1): 7.92 (1H, s, H-5), 7.56 (1H, d, *J* = 4.8 Hz, H-3', H-5'), 7.47 (2H, d, *J* = 6.8 Hz, H-2', H-6'), 7.36 (1H, d, *J* = 2.4 Hz, H-7), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3);ESI-MS [m/z; %]: 327 [M^+] 329(M++2).

6-Bromo-2-(2, 4-chlorophenyl)-1,2,3,4-tetrahydroquinolin-4-one (5b)

Yield: 74%, yellowish orange solid, mp: 285-287 °C; FT-IR (KBr, cm^{-1}, υ): 3425 cm^{-1} (NH), 3025 cm^{-1} (C=H), 2936 cm^{-1} (C-H), 1751 cm^{-1} (C=O), 1565 cm^{-1} (C=C), 761 cm^{-1} (C-Cl); ^1H NMR: ($CDCl_3$-d_1): 7.95 (1H, s, H-5), 7.75 (1H, s, H-3'), 7.41 (1H, d, *J* = 6.8 Hz, H-5'), 7.35 (1H, d, *J* = 2.4 Hz, H-7), 7.08 (1H, d, *J* = 5.2 Hz, H-6'), 6.55 (1H,d, *J* = 4.8 Hz, H-8), 4.5 (1H, t, *J* = 2.4 Hz, H-2), 4.6 (1H, bs, NH), 2.93 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 371 [M^+] 373 (M^++2); 375(M++4).

6-Bromo-2-(4-hydroxyphenyl)-1,2,3,4-tetrahydroquinolin-4-one (5c)

Yield: 78%, pale yellow solid, mp: 291-293 °C; FT-IR (KBr, cm^{-1}, υ): 3415 cm^{-1} (NH), 3036 cm^{-1} (C=H), 2918 cm^{-1} (C-H), 1765 cm^{-1} (C=O), 1551 cm^{-1} (C=C),; ^1H NMR: ($CDCl_3$-d_1): 9.43 (1H, s, OH), 7.94 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 7.15 (2H, d, *J* = 6.4 Hz, H-2', H-6'), 6.72 (2H, d, *J* = 4.2 Hz, H-3', H-5'), 6.55 (1H, *J* = 4.8 Hz, H-8), 4.55 (1H, t, *J* = 7.2 Hz, H-2), 4.64 (1H, bs, NH), 3.2 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 317 [M^+]; 319(M^++2).

6-Bromo-2-(4-chlorophenyl)-1,2,3,4-tetrahydroquinolin-4-one (5d)

Yield: 82%, Light orange solid, mp: 264-266 °C; FT-IR (KBr, cm^{-1}, υ): 3493 cm^{-1} (NH), 3062 cm^{-1} (C=H), 2917 cm^{-1} (C-H), 1721 cm^{-1} (C=O), 1580 cm^{-1} (C=C), 765 cm^{-1} (C-Cl); ^1H- NMR: ($CDCl_3$-d_1): 8.0 (1H, s, H-5), 7.75 (2H, d, *J* = 4.8 Hz, H-3', H-5'), 7.6 (2H, d, *J* = 6.4 Hz, H-2',H-6'), 7.45 (1H, d, *J* = 5.2 Hz, H-7), 6.65 (1H, d, *J* = 4.8 Hz, H-8), 4.8 (1H,t,H-2), 4.6 (1H, bs, NH), 2.8 (2H,d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 336 [M^+] 338 (M^++2); 340(M^++4).

6-Bromo-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-4-one (5e)

Yield: 75%, light yellowish, mp: 295-297 °C; FT-IR (KBr, cm^{-1}, υ): 3323 cm^{-1} (NH), 3026 cm^{-1} (C=H), 2928 cm^{-1} (C-H), 1672 cm^{-1} (C=O), 1565 cm^{-1} (C=C), 1334 cm^{-1} and 1092 cm^{-1} (C-O-C); ^1H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.94 (2H, d, *J* = 2.4 Hz, H-3', H-5'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.85 (3h, s, H-4'), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 332 [M^+] 334(M^++2).

6-Bromo-2-(2,4,6-trimethoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (5f)

Yield: 75%, light brown, mp: 273-275 °C; FT-IR (KBr, cm^{-1}, υ): 3328 cm^{-1} (NH), 3021 cm^{-1} (C=H), 2925 cm^{-1} (C-H), 1675 cm^{-1} (C=O), 1568 cm^{-1} (C=C), 1351 cm^{-1} and 1082 cm^{-1} (C-O-C), ; ^1H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.53 (1H, *J* = 4.8 Hz, H-8), 6.2 (2H, d, *J* = 6.2 Hz, H-3', H-5') 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.83 (9H, s, H-2', H-4', H-6'), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 392 [M^+] 394(M^++2).

6-Bromo-2-(thien-2-yl)-1,2,3,4-tetrahydroquinolin-4-one (5g)

Yield: 70%, light yellow, mp: 254-256 °C; FT-IR (KBr, cm^{-1}, υ): 3322 cm^{-1} (NH), 3018 cm^{-1} (C=H), 2932 cm^{-1} (C-H), 1655 cm^{-1} (C=O), 1555 cm^{-1} (C=C),; ^1H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.42 (1H, d, *J* = 1.2 Hz, H-5'),7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.93(1H, t, *J* = 8.2 Hz, H-4'), 6.85 (1H, d, *J* = 8.6 Hz, H-3') 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 309 [M^+] 311(M^++2).

6-Bromo-2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinolin-4-one (5h)

Yield: 74%, thick orange solid, mp: 225-228 °C; FT-IR (KBr, cm^{-1}, υ): 3321 cm^{-1} (NH), 3020 cm^{-1} (C=H), 2938 cm^{-1} (C-H), 1626 cm^{-1} (C=O), 1601 cm^{-1} (C=N), 1563 cm^{-1} (C=C),; ^{1}H NMR: ($CDCl_3$-d_1): 8.45 (1H, d, *J* = 5.4 Hz, H-6'), 7.96 (1H, s, H-5), 7.75(1H, t, *J* = 6.2 Hz, H- 4'), 7.46 (1H, d, *J* = 2.8 Hz, H-3'), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 7.2 (1H, d, *J* = 4.2 Hz, H-5'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 303 [M^+] 305(M^++2).

6-Bromo-2-(Furo-2-yl)-1,2,3,4-tetrahydroquinolin-4-one (5i)

Yield: 78%, brown colour solid, mp: 175-178 °C; FT-IR (KBr, cm^{-1}, υ): 3315 cm^{-1} (NH), 3035 cm^{-1} (C=H), 2931 cm^{-1} (C-H), 1631 cm^{-1} (C=O), 1558 cm^{-1} (C=C),; ^{1}H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.65 (1H, d, *J* = 5.6 Hz, H-5'), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.53 (1H, *J* = 4.8 Hz, H-8), 6.45 (2H, m, H-3', H-4'), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 292 [M^+] 294(M++2), 296(M^++4).

6-Bromo-2-(naphtha-2-yl)-1,2,3,4-tetrahydroquinolin-4-one (5j)

Yield: 82%, creamish colour solid, mp: 286-288 °C; FT-IR (KBr, cm^{-1}, υ): 3322 cm^{-1} (NH), 3025 cm^{-1} (C=H), 2927 cm^{-1} (C-H), 1628 cm^{-1} (C=O), 1543 cm^{-1} (C=C); ^{1}H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.86 (3H, d, *J* = 7.2 Hz, H-7'), 7.56 (2H, d, *J* = 5. 2 Hz, H-4',H-5'), 7.46 (1H, s, H-2'), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 7.18 (1H, d, *J* = 6.2 Hz, H-8'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 352 [M^+] 354(M^++2).

6-Bromo-2-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroquinolin-4-one (5k)

Yield: 71%, yellowish solid, mp: 172-174 °C; FT-IR (KBr, cm^{-1}, υ): 3348 cm^{-1} (NH), 3032 cm^{-1} (C=H), 2927 cm^{-1} (C-H), 1652 cm^{-1} (C=O), 1547 cm^{-1} (C=C), 1332 cm^{-1} and 1082 cm^{-1} (C-O-C); ^{1}H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.91(1H, s, H-2'), 6.84(1H, d, *J* = 4.8 Hz, H-5'), 6.74 (1H, d, *J* = 1.6 Hz, H-6'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.85 (6H, s, H-3', H-4'), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 362 [M^+] 364(M^++2).

6-Bromo-2-(4-flourophenyl)-1,2,3,4-tetrahydroquinolin-4-one (5l)

Yield: 74%, blackish brown solid, mp: 250-252°C; FT-IR (KBr, cm^{-1}, υ): 3342 cm^{-1} (NH), 3028 cm^{-1} (C=H), 2923 cm^{-1} (C-H), 1646 cm^{-1} (C=O), 1538 cm^{-1} (C=C); ^{1}H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 7.27 (2H, d, *J* = 4.2 Hz, H-2', H-6'), 7.19(2H, d, *J* = 6.3 Hz, H-3', H-5'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 319 [M^+] 321(M++2), 323(M^++4).

6-Bromo-2-(4-dimethyl amino phenyl)-1,2,3,4-tetrahydroquinolin-4-one (5m)

Yield: 80%, orange solid, mp: 278-281°C; FT-IR (KBr, cm^{-1}, υ): 3353 cm^{-1} (NH), 3021 cm^{-1} (C=H), 2932 cm^{-1} (C-H), 1646 cm^{-1} (C=O), 1535 cm^{-1} (C=C); ^{1}H NMR: ($CDCl_3$-d_1): 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 7.11(2H, d, *J*= 3.6 Hz, H-2',H-6'), 6.71 (2H, d, *J*= 3.6 Hz, H-3', H-5'), 6.53 (1H, *J* = 4.8 Hz, H-8), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 345 [M^+] 347(M^++2).

6-Bromo-2-(2,4-dimethoxy-6-hydroxy phenyl)-1,2,3,4-tetrahydroquinolin-4-one (5n)

Yield: 68%, light yellow solid, mp: 145-152°C; FT-IR (KBr, cm^{-1}, υ): 3345 cm^{-1} (NH), 3032 cm^{-1} (C=H), 2928 cm^{-1} (C-H), 1664 cm^{-1} (C=O), 1528 cm^{-1} (C=C); ^{1}H NMR: ($CDCl_3$-d_1): 9.65 (1H, s, H-6'), 7.96 (1H, s, H-5), 7.32 (1H, d, *J* = 2.4 Hz, H-7), 6.53 (1H, *J* = 4.8 Hz, H-8), 6.23 (2H, s, H-3', H-5'), 4.52 (1H, t, *J* = 7.2 Hz, H-2), 4.62 (1H, bs, NH), 3.83 (6H, s, H-2', H-4'), 3.22 (2H, d, *J* = 2.4 Hz, H-3); ESI-MS [m/z; %]: 378 [M^+] 380(M^++2).

Spectral Characterisation of 6-Bromo-2Substituted-aryldihydroquinolin-4-ones (6a-n)÷

6-Bromo-2-(4'-cyanophenyl)-2,3-dihydro quinolin-4(1H)-one (6a)(Figure 3-5)

Yield: 68%, yellow solid, mp: 292-294°C, FT-IR (KBr, cm^{-1}, υ): 3443 cm^{-1} (NH), 2225 (CN), 1674 cm^{-1} (C=O), 1501 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.86 (1H, s, H-5), 7.87 (2H,d, *J* = 3.6 Hz, H-3',H-5'), 7.57 (1H, d, *J* = 5.8 Hz, H-7), 7.45 (2H, d, *J* = 2.8 Hz, H-2', H-6'), 6.54 (1H, d, *J* = 4.4 Hz, H-8), 6.43 (1H, s, H-3), 4.51 (1H, bs, NH); ESI-MS [m/z; %]: 324 (**M**$^+$,326(M++2).

6-Bromo-2-(2,4-dichlorophenyl)-2,3-hydroquinolin-4-one(6b)

Yield: 68%, Pale yellow solid, mp: 319-321°C, FT-IR (KBr, cm^{-1}, υ): 3464 cm^{-1} (NH), 1727 cm^{-1} (C=O), 1590 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.92 (1H, s, H-5), 7.52 (1H, d, *J* = 7.2 Hz, H-7), 7.48(1H, s, H-3'), 7.32 (1H, d, *J* = 5.8 Hz, H-5'), 7.25 (1H, d, *J* = 5.4 Hz, H-6'), 6.93 (1H, s, H-3), 6.56 (1H, d, *J* = 3.6 Hz, H-8), 4.62

(1H, bs, NH); ESI-MS [m/z; %]: 369 (M^+) , 371 (M^++2); 373(M++4)

6-Bromo-2-(4-hydroxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one(6c)

Yield: 75%, Pale yellow solid, mp: 325-327°C, FT-IR (KBr, cm^{-1}, υ): 3464 cm^{-1} (NH), 1727 cm^{-1} (C=O), 1590 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 9.45 (1H, s, OH), 7.86 (1H, s, H-5), 7.65 (1H, d, *J* = 6.2 Hz, H-7), 7.49(2H,d, *J* =7.2 Hz, H-2',H-6'), 7.03 (1H, d, *J* = 5.2 Hz, H-8), 6.65 (2H, d, *J* = 2.4 Hz, H-3', H-5'), 6.55 (1H, s, H-3), 4.62 (1H, bs, NH); ESI-MS [m/z; %]: 315 **(**M^+; 100%), 317 (M^++2).

6-Bromo-2-(4-chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one(6d)

Yield: 74%, Pale yellow solid, mp: 321-323 °C, FT-IR (KBr, cm^{-1}, υ): 3477 cm^{-1} (NH), 1703 cm^{-1} (C=O), 1593 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 8.0 (1H, s, H-5), 7.75 (2H, d, *J* = 6.2 Hz, H-3', H-5'), 7.6 (2H, d, *J* = 2.4 Hz, H-2',H-6'), 7.45 (1H, d, *J* = 5.8 Hz, H-7), 6.98 (1H, s, H-3), 6.65 (1H, d, *J* = 2.2 Hz, H-8), 4.68 (1H, bs, NH); ESI-MS [m/z; %]: 334 **[**M^+; 100%] , 336 [M^++2; 100%]; 338 (M++4).

6-Bromo-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4-one (6e)(Figure 6,7,8)

Yield: 65%, light yellow solid, mp: 347-350°C, FT-IR (KBr, cm^{-1}, υ): 3326 cm^{-1} (NH), 1682 cm^{-1} (C=O), 1525 cm^{-1} (C=C) 1328 cm^{-1} and 1082 cm^{-1} (C-O-C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.82 (1H, s, H-5), 7.57 (1H, d, *J* = 6.2 Hz, H-7), 7.42 (2H, d, *J* = 2.8 Hz, H-2',H-6'), 7.05 (2H, d, *J* = 4.2 Hz, H-3', H-5'), 6.54 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH), 3.82 (3H,s,H-4'); ESI-MS [m/z; %]: 329 **(**M^+), 331(M^++2).

6-Bromo-2-(2,4,6-trimethoxyphenyl)-2,3-dihydroquinolin-4-one (6f)

Yield: 73%, brown solid, mp: 312-315°C, FT-IR (KBr, cm^{-1}, υ): 3342 cm^{-1} (NH), 1654 cm^{-1} (C=O), 1532 cm^{-1} (C=C) 1345 cm^{-1} and 1095 cm^{-1} (C-O-C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.82 (1H, s, H-5), 7.57 (1H, d, *J* = 6.2 Hz, H-7), 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 6.09 (2H, d, *J* = 2.4 Hz, H-3', H-5) 4.55 (1H, bs, NH), 3.85 (9H,s,H-2', H-4', H-6'); ESI-MS [m/z; %]: 389 **(**M^+), 391 (M^++2).

6-Bromo-2-(2-thienyl)-2,3-dihydroquinolin-4-one (6g)

Yield: 75%, yellow solid, mp: 318-320°C, FT-IR (KBr, cm^{-1}, υ): 3346 cm^{-1} (NH), 1664 cm^{-1} (C=O), 1535 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 8.11 (1H, d, *J* = 2.4 Hz, H-5'), 8.03 (1H, d, *J* = 3.6 Hz, H-3'), 7.84 (1H, s, H-5), 7.57 (1H, d, *J* = 6.2 Hz, H-7), 7.43 (1H, t, *J* = 4.2 Hz, H-4'), 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH); ESI-MS [m/z; %]: 305 **(**M^+), 307 (M++2).

6-Bromo-2-(2-pyridyl)-2,3-dihydroquinolin-4-one (6h)

Yield: 68%, orange solid, mp: 283-285°C, FT-IR (KBr, cm^{-1}, υ): 3323 cm^{-1} (NH), 1652 cm^{-1} (C=O), 1541 cm^{-1} (C=C), 1523 (C=N); ^{1}H- NMR: ($CDCl_3$-d_1): 8.45 (1H, d, *J* = 3.8 Hz, H-2', H-6'), 7.84 (1H, s, H-5), 7.57 (1H, d, *J* = 6.2 Hz, H-7), 7.35 (3H, m, H-3', H-4' H-5'), 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH); ESI-MS [m/z; %]: 301 **(**M^+), 303 (M^++2).

6-Bromo-2-(2-furoyl)-2,3-dihydroquinolin-4-one (6i)

Yield: 71%, light brown solid, mp: 210-213°C, FT-IR (KBr, cm^{-1}, υ): 3341 cm^{-1} (NH), 1655 cm^{-1} (C=O), 1545 cm^{-1} (C=C), 1523 (C=N), 1325 cm^{-1} and 1087 cm^{-1}; ^{1}H- NMR: ($CDCl_3$-d_1): 8.62 (2H, d, *J* = 3.8 Hz, H-3', H-5'), 7.82 (1H, s, H-5), 7.52 (1H, d, *J* = 5.2 Hz, H-7), 7.24 (1H, t, *J* = 4.6 Hz, H-4'), 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH); ESI-MS [m/z; %]: 290 **(**M^+), 292 (M++2), 294 (M++4).

6-Bromo-2-(2-naphthyl)-2,3-dihydroquinolin-4-one (6j)

Yield: 73%, light brown solid, mp: 325-327°C, FT-IR (KBr, cm^{-1}, υ): 3345 cm^{-1} (NH), 1643 cm^{-1} (C=O), 1541 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 8.00 (2H, d, *J* = 6.8 Hz, H-3', H-6'), 7.91(1H, s, H-5), 7.83 (1H, s, H-2'), 7.75 (1H, d, *J* = 2.4 Hz, H-7'), 7.57(1H, d, *J* = 6.2 Hz, H-7) 7.47 (3H, m, H-4', H-5', H-8'), 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH); ESI-MS [m/z; %]: 350 **(**M^+), 352 (M^++2).

6-Bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydroquinolin-4-one (6k)

Yield: 75%, light yellow solid, mp: 255-257°C, FT-IR (KBr, cm^{-1}, υ): 3352 cm^{-1} (NH), 1632 cm^{-1} (C=O), 1536 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.85 (1H, s, H-5), 7.52 (1H, d, *J* = 6.8 Hz, H-7), 7.24 (1H, t, *J* = 4.6 Hz, H-2'), 7.05 (2H, d, *J* = 6.4 Hz, H-5', H-6') 6.52 (1H, d, *J* = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH), 3.83 (6H, s, H-3', H-4'); ESI-MS [m/z; %]: 360 **(**M^+), 362 (M^++2).

6-Bromo-2-(4-fluorophenyl)-2,3-dihydroquinolin-4-one (6l)

Yield: 78%, light yellow solid, mp: 312-315°C, FT-IR (KBr, cm^{-1}, υ): 3347 cm^{-1} (NH), 1625 cm^{-1} (C=O), 1528 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.85 (1H, s, H-5), 7.52 (1H, d, *J* = 6.8 Hz, H-7), 7.36(2H, d, *J* = 3.8 Hz, H-2',

H-6'), 7.19 (2H, d, J = 4.2 Hz, H-3', H-5'), 6.52 (1H, d, J = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH); ESI-MS [m/z; %]: 318 (M$^+$), 320 (M$^+$+2).

6-Bromo-2-(4-dimethylaminophenyl)-2,3-dihydroquinolin-4-one (6m)

Yield: 65%, orange solid, mp: 318-320°C, FT-IR (KBr, cm^{-1}, υ): 3327 cm^{-1} (NH), 1631 cm^{-1} (C=O), 1532 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 7.85 (1H, s, H-5), 7.75 (2H, d, J = 6.2 Hz, H-2', H-6'), 7.52 (1H, d, J = 6.8 Hz, H-7), 6.71 (2H, d, J = 3.8 Hz, H-3', H-5'), 6.52 (1H, d, J = 5.8 Hz, H-8), 6.45 (1H, s, H-3), 4.55 (1H, bs, NH), 3.06 (6H, s, N-CH_3); ESI-MS [m/z; %]: 343 (M$^+$), 345 (M$^+$+2).

6-Bromo-2-(2,4-dimethoxy-6-hydroxyphenyl)-2,3-dihydroquinolin-4-one (6n)

Yield: 78%, light yellow solid, mp: 220-228°C, FT-IR (KBr, cm^{-1}, υ): 3345 cm^{-1} (NH), 1645 cm^{-1} (C=O), 1542 cm^{-1} (C=C); ^{1}H- NMR: ($CDCl_3$-d_1): 11.85 (1H, s, OH), 7.81 (1H, s, H-5), 7.55 (1H, d, J = 6.8 Hz, H-7), 6.54 (1H, d, J = 5.8 Hz, H-8), 6.41 (1H, s, H-3), 6.05(2H, d, J = 3.6 Hz,

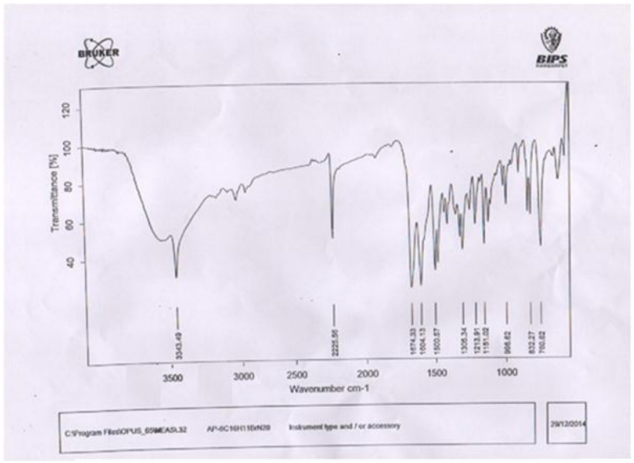

Figure 3: IR spectrum of 6-Bromo-2-(4'-cyano phenyl)-1, 3-dihydroquinoline-4-one (6a).

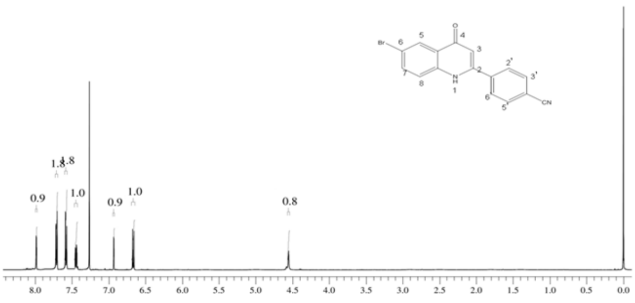

Figure 4: ^{1}H NMR of 6-Bromo-2-(4'-cyano phenyl)-1, 3-dihydroquinoline-4-one (6a).

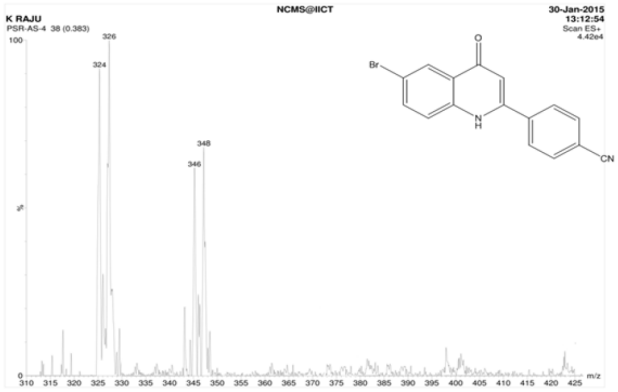

Figure 5: Mass spectrum of 6-Bromo-2-(4'-cyano phenyl)-1, 3-dihydroquinoline-4-one (6a).

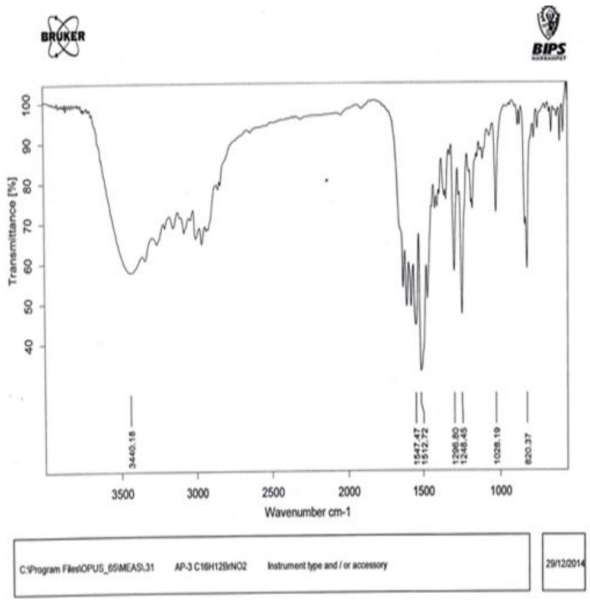

Figure 6: IR spectrum of 6-Bromo-2-(4'-methoxyphenyl)-1, 3-dihydroquinoline-4-one (6e).

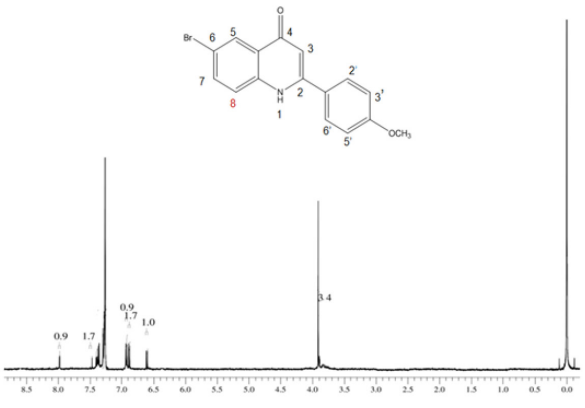

Figure 7: ^{1}H NMR of 6-Bromo-2-(4'-methoxyphenyl)-1, 3-dihydroquinoline-4-one (6e).

H-3', H-5'), 4.55 (1H, bs, NH), 3.83 (6H, s, H-2', H-4'); ESI-MS [m/z; %]: 376 (M$^+$), 378 (M$^+$+1).

Cytotoxicity on MCF-7 Cell Lines

Compounds 5a-n (Figure 9) and 6a-n (Figure 10) were screened for *in vitro* cytotoxic activity (Figure 11) against human breast cancer carcinoma cell lines MCF-7 using MTT assay, where cisplatin was used as a reference. The percentage growth inhibition was calculated and the

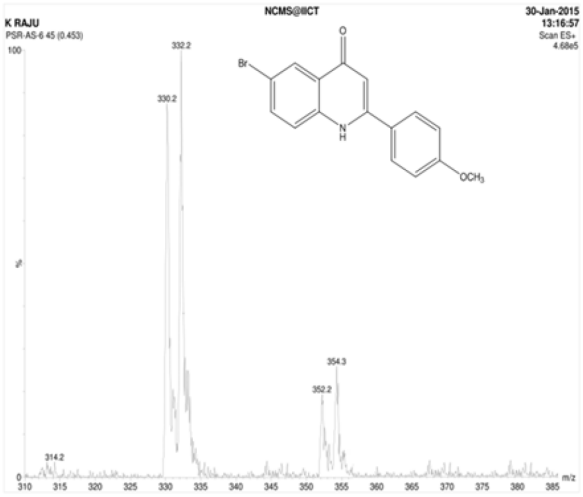

Figure 8: Mass spectrum of 6-Bromo-2-(4'-methoxyphenyl)-1,3-dihydroquinoline-4-one(6e).

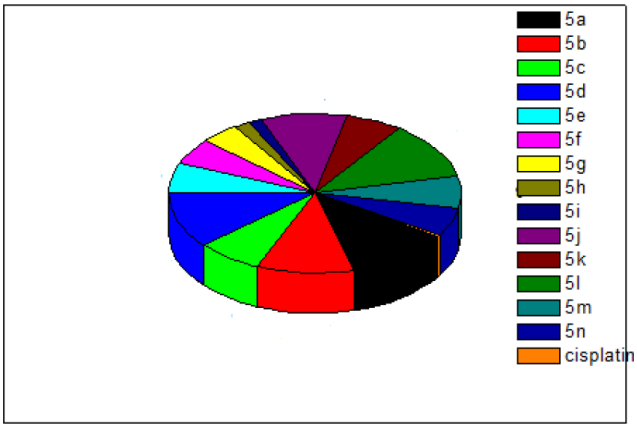

Figure 9: Cytotoxic activity on MCF-7 cell lines for Azaflavanones.

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
5a	76.61±1.64	5h	12.67±1.44
5b	74.5± 1.98	5i	10.39±1.24
5c	50.04± 1.69	5j	64.72 ±1.41
5d	78.63±173	5k	43.13 ±1.91
5e	42.76±1.41	5l	79.42±1.64
5f	36.02± 1.91	5m	46.13 ±1.83
5g	28.27± 1.13	5n	38.02± 1.19

Cisplatin was used as standard (IC_{50} value 3.032 μM).

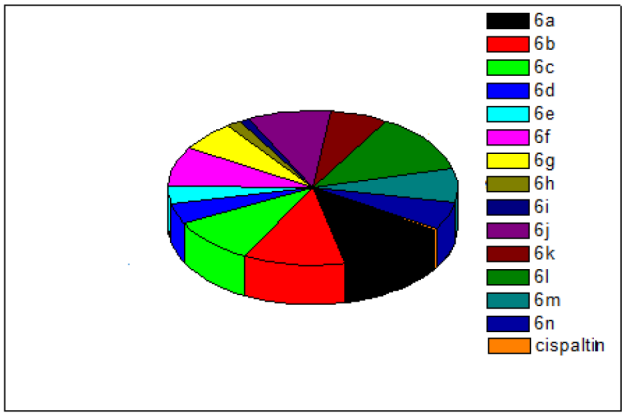

Figure 10: Cytotoxic activity on MCF-7 cell lines for Azaflavones.

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
6a	26.61±1.44	6h	11.38±1.83
6b	69.35±1.98	6i	9.74±1.24
6c	58.41± 1.26	6j	56.75 ±1.38
6d	74.63±0.95	6k	38.64±1.91
6e	21.41±1.41	6l	76.53±1.89
6f	51.3± 1.91	6m	42.27 ±1.35
6g	39.7± 1.13	6n	35.28± 1.57

Cisplatin was used as standard (IC_{50} value 3.032 μM).

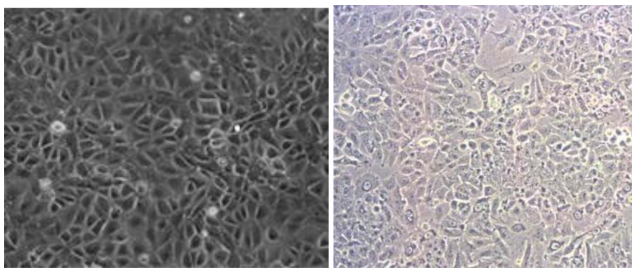

Figure 11: *Invitro* images of compound 5d and 6e.

absorbance was recorded on the ELISA reader at 562 nm wave length. The absorbance of the test compound was compared with that of DMSO control to get the % of inhibition. Compounds bearing furoyl and pyridyl groups on azafalvanone moiety exhibited significant cytotoxic activity [IC_{50} at 10.39 μg/ mL and 12.67 μg/ mL]. Similarly compounds bearing furoyl and pyridyl groups containing azaflavones also exhibited significant cytotoxic activity [IC_{50} at 9.74 μg/ mL and 11.38 μg/ mL] respectively.

CONCLUSION

In conclusion, the proposed 6-bromo-2-substituted azaflavonones and azaflavone derivatives were synthesized successfully and characterized by physical and spectral data. All the compounds were screened for cytotoxic activity

on MCF-7 cell lines. Among them the compounds **5i** (10.39±1.24) and **5h** (12.67 1.44) showed good activity. And the compounds **6i** (IC_{50} = 9.74 μg/mL) and **6h** (IC_{50} = 11.38 μg/mL) also exhibited significant activity. With these results it has been found that these are potential leads for developing new drugs for the treatment of cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

NSAIs: Non steroidal aromatase inhibitors; **FTIR:** Fourier Transform Infrared; **HNMR:** Proton Nuclear Magnetic resonance; **ESI-MS:** Electro Spray Ionization Mass Spectrometry; **TLC:** Thin Layer Chromatography; **TMS:** Tetra Methyl Silane; **IC_{50}:** Inhibitory Concentration 50; **AICTE:** All India Council for Technical Education.

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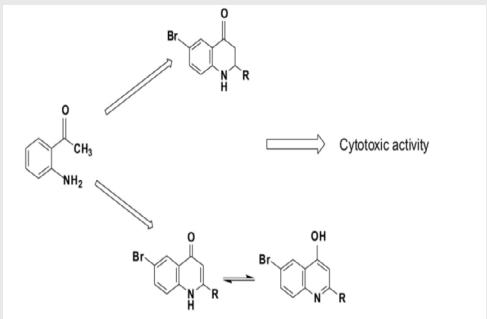
PICTORIAL ABSTRACT



R= 4-Chlorophenyl, 2, 4-di chlorophenyl, 4-Hydroxyphenyl, 4–Cyanophenyl, 4-Methoxyphenyl, 2,4,6-trimethoxyhenyl,4-Thienyl , 2-Pyridyl, 2-Furoyl, 2-Naphthyl, 3,4–Di methoxy phenyl, 4-Flurophenyl, 4-Dimethylaminophenyl, 2,4–Dimethoxy-6-hydroxy phenyl

Summary

In the development of new NSAIs as cytotoxic agents for breast cancer, aza flavones and aza flavanones are proved to be potent NSAIs. By keeping in view of this, we designed and synthesized novel series of aza flavanone and aza flavanone derivatives. These compounds have been characterized by IR, NMR and Mass spectral analysis and they were screened for their cytotoxic activity. Among them, the furoyl and pyridyl compounds were found to potent.

About Authors

Srujana Muthadi: Research Scholar, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India, Area of interest: Pharmaceutical Chemistry

Baswaraju Macha: Research Scholar, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India, Area of interest: Pharmaceutical Chemistry.

Prof. Dr. Achaiah Garlapati: Professor Department of Pharmaceutical Chemistry , University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India. He has 30 years of teaching experience. Area of interest: Design, synthesis and evaluation of New heterocyclic entities as potent Pharmacological agents.

Prof. Dr. Raghuram Rao Akkinepally: Presently working as Director, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Punjab India. He has more than 30 years of teaching and research experience. Area of interest: Design, synthesis and evaluation of New heterocyclic agents for various pharmacological activities.

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