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SYNTHESIS AND EVALUATION OF NITROGEN ANALOGUES OF FLAVANONES-TETRAHYDROQUINOLONES AS CYTOTOXIC AGENTS

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ABSTRACT

Studies by Kellies and Vickery[1] showed that several naturally occurring and synthetic flavonoids were found to inhibit aromatase. The present investigation includes synthesis and evaluation of novel tetrahydroquinolones (nitrogen analogues of flavanones) for their cytotoxic activity on hormone dependent human cancer cell lines including breast (MCF-7), ovarian (OVC-AR) and prostate (DU-145). The compounds synthesized (7a-j) showed potent cytotoxic effects in micromolar range. Among the compounds tested 7d & 7j exhibited good cytotoxic activites with IC_{50} values of 4 & 3 µM against MCF-7 and 7 & 3 µM against OVC-AR and 11 & 8 µM against DU-105 cell lines respectively.

KEY WORDS

Flavonoids, Cytotoxic activity, Tetrahydroquinolones.

INTRODUCTION:

Flavonoids are one of the secondary metabolites of plants. Flavonoids have been shown to possess anti-inflammatory[2], anti-allergic[3], antiviral[4] and cytotoxic activities[5]. Furthermore, some of these compounds were found to have estrogenic[6], anti estrogenic[7] as well as aromatse inhibitory activity. Studies by several groups of researchers postulates that flavonoids present in soy and whole grain may be responsible for lower incidence of breast cancer in women of certain regions of the world. The present investigation involves synthesis of nitrogen analogues of flavanones (tetrahydroquinolin-4-ones) and evaluation of the synthesized compounds for their cytotoxic activities on hormone dependant human cancer cell lines (breast, ovarian and prostate).

RESULTS AND DISCUSSION:

Chemistry:

Tetrahydroquinolin-4-one derivatives were prepared from 2-amino-5-nitroacetophenone 4. Scheme 1 includes the synthesis of 2-amino-5-nitroacetophenone. Acetylation of 2-aminoacetophenone gave 2-acetylamidoacetophenone. Nitration of 2-acetylamidoacetophenone followed by hydrolysis gave the compound 4. The IR spectra of the compound 4 revealed absorption bands at 1348, 1695 and 3345 cm-1 characteristics for the nitro, keto and amine groups respectively. 1H NMR revealed the characteristic singlets for methyl (δ 2.51 ppm) and amine (δ 4.46 ppm) group protons. Scheme 2 shows the synthesis of tetrahydroquinolin-4-ones from 2-amino-5-nitroacetophenone. Clasien-Schmidt condensation of 4 with the appropriate aryl aldehydes (5a-j) followed by acid catalyzed cyclization gave the final compounds (7a-j). Final compounds (7a-j) characterized using I.R, NMR

and mass spectral techniques. IR stretching frequencies in the range of 1340-1365, 1680-1710, 3050-3100 and 3300-3355 were indicative of nitro, keto, aliphatic and amine functionalities. ^{1}H NMR spectrum of final compounds revealed quartets at 2.64-2.85 ppm, 4.60-4.68 ppm and singlet at 4.43-5.01 ppm which further confirmed the presence of tetrahydroquinoline nulcues.

Cytotoxic activity:

Final compounds (7a-j) were screened for their *invitro* cytotoxicity against three hormone dependant human cancer cell lines including breast (MCF-7), ovarian (OVC-AR) and prostate (DU-145). Sulphorhodamine B assay utilized for the screening. All the compounds synthesized displayed significant cytotoxic activity in micromolar range, compounds 7j found to the potent one with IC_{50} values of 2 µM, 3 µM and 8 µM against MCF-7, OVC-AR & DU-105 cell lines respectively. Compound 7d was next in order with IC_{50} values of 4 µM, 7 µM and 11 µM against MCF-7, OVC-AR & DU-105 cell lines respectively. In relation of SAR information, compounds substituted at 4' position with CN, OCF_3, Cl and Br were more active than those substituted with methoxy and hydroxyl groups. Compounds 7d and 7j with respective trifluoromethoxy group and thienyl ring were found to most potent ones.

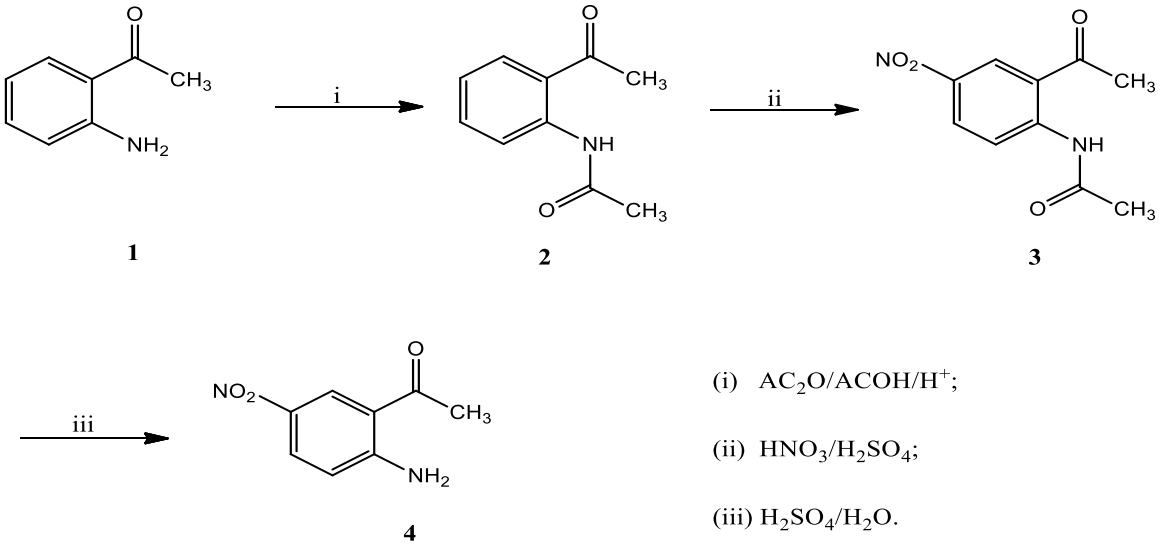
Biological Assay:

The invitro cytotoxicity assay was carried out according to the procedures described in Skehan et al.[8] using SRB (sulphorhodamine B) assay. Stock solutions of the drugs were prepared in DMSO and diluted to produce a final concentration of < 2% DMSO (V/V), a concentration which is non-toxic to cell proliferation. The human tumor cell line panel constituted three hormone dependent cancer cell lines including breast (MCF-7), ovarian (OVC-AR) and prostate (DU-145). Cells were grown in RPMI-1640 containing fetal bovine serum (5%) and L-glutamine (2 mM). these cell lines were incubated with five concentrations of final compounds in a humidified atmosphere at 37^{0}C containing 5% CO_2. After 24 h incubation, the absorbances were read at 540 nm and used to plot dose-response curve. Three response parameters, TGI (total growth inhibition), LC_{50} and IC_{50} were calculated for each cell line.

EXPERIMENTAL:

Chemistry: Melting points were recorded on Buchi melting point apparatus and were uncorrected. The IR spectra were recorded on Bruker FT-IR analyzer using the KBr pellets. ^{1}H NMR spectra were read on Bruker DPX-400 FT NMR spectrometer using TMS (tetramethyl silane) as internal standard. Splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet. Mass spectra were recorded on Agilent LC-MS 6120 single quard. Elememtal analysis was performed on a 2400 Perkin Elmer series analyzer and the found values were within ± 0.4% of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds was made by TLC on silica gel G F_{250} sheets.

Scheme 1: Synthesis of 2-amino-5-nitroacetophenone (4)



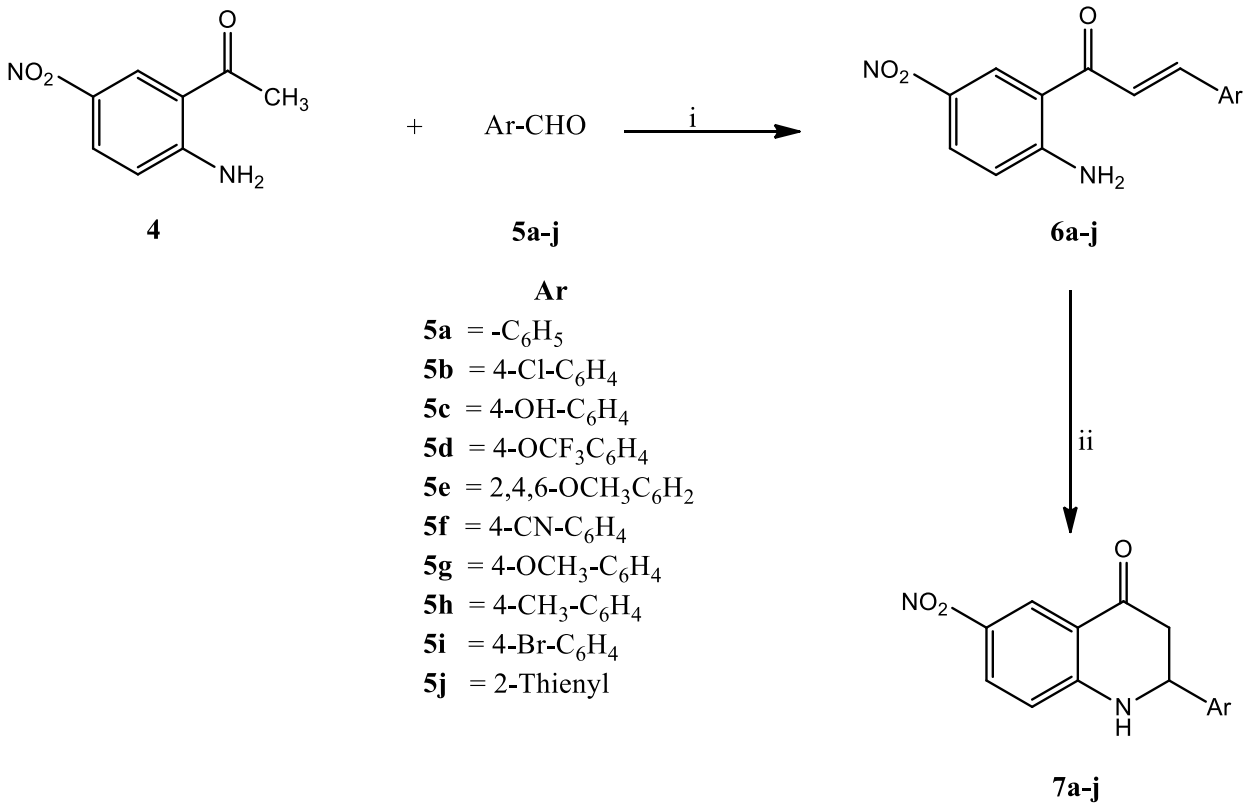
1 2 3 4

(i) $AC_2O/ACOH/H^+$;

(ii) HNO_3/H_2SO_4;

(iii) H_2SO_4/H_2O.

Scheme 2: Synthesis of 2-aryl-5-nitrotetrahydroquinolinones (7a-j)



2.2.1: 2-acetamidoacetophenone (**2**):

2-aminoacetophenone 1 (2.7 g, 0.02 moles) and acetic anhydride (5 ml) were refluxed for 30 min[9]. The mixture was cooled, poured onto crushed ice. The separated solid was washed with water, dried and recrystalized from hot water.

Yield: 65%, mp: 121-123^{0}C, IR (KBr, cm^{-1}): 1690, 3250, 2860. ^{1}H NMR (δ ppm): 2.30 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.16-7.21 (m, 2H, $C_{4,5}$-H), 7.57-7.59 (d, 1H, C_3-H) 7.63-7.65 (d, 1H, C_6-H), 9.10 (s, 1H, NH), MS m/z: 177 (M^+): Anal. Cald. For $C_{10}H_{11}NO_2$ (177): C, 67.79; H, 6.21; N, 7.90. Found: C, 67.92; H, 6.13; N, 7.95

2.2.2: 5-nitro-2-acetamidoacetophenone (**3**):

Finely powdered 2-acetamidoacetophenone (6.54 g, 0.037 moles) dissolved in glacial acetic acid in a 50 ml beaker; introduced into the well stirred mixture 18.4 g (10 ml) of concentrated sulphuric acid[10]. The mixture became warm and a clear solution resulted. The beaker surrounded with a freezing mixture of ice and salt. A cold mixture of 3.1 g (2.2 ml) of concentrated nitric acid and 2.5 g (1.4 ml) of concentrated sulphuric acid added using a separating funnel. After all the mixed acid has been added, the beaker removed from the freezing mixture and allowed to stand at room temperature for 1 hr. The reaction mixture then poured onto crushed ice. The crude 5-nitro-2-acetamidoacetophenone precipitated was filtered, collected and recrystalized using alcohol and dried.

Yield: 52%, mp: 221-223^{0}C, IR (KBr, cm^{-1}): 1350, 1685, 2885, 3210. ^{1}H NMR (δ ppm): 2.32 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.23-7.26 (m, 2H, $C_{3,4}$-H), 7.83 (s, 1H, C_6-H), 9.15 (s, 1H, NH),. MS m/z: 222 (M^+): Anal. Cald. For $C_{10}H_{10}N_2O_4$ (222): C, 54.05; H, 4.50; N, 12.61. Found: C, 54.13; H, 4.43; N, 12.57

5-nitro-2-aminoacetophenone (**4**):

A mixture of 5-nitro-2-acetamido acetophenone (3.684 g, 0.0166 moles) and 15 ml of 70% W/W sulphuric acid boiled under a reflux condenser for 20-30 min. The reaction mixture was poured into 50 ml of cold water. The 5-nitro-2-aminoacetophone which present as the sulphate salt was precipitated by adding excess of 10%

NaOH solution. The yellow precipitate was filtered and dried[11].

Yield: 75%, mp: 152-154^{0}C, IR (KBr, cm^{-1}): 1348, 1695, 3335. ^{1}H NMR (δ ppm): 2.51 (s, 3H, CH_3), 4.46 (s, 2H, NH_2), 7.26-7.31 (m, 2H, $C_{3,4}$-H), 7.86 (s, 1H, C_6-H). MS m/z: 180 (M^+): Anal. Cald. For $C_8H_8N_2O_3$ (180): C, 53.33; H, 4.44; N, 15.55. Found: C, 53.13; H, 4.49; N, 15.32

5-nitro-2-aminoacetophnone chalcones (**6a-j**):

A solution of sodium hydroxide (1.425 g) in 11.55 ml of water and 5.2 ml of absolute ethanol placed in a 100 ml conical flask. The flask immersed in an ice chest at 0^{0}C. 5-nitro-2-aminoacetophnone (4.65 g, 0.025 moles) was added into the solution and stirred on a magnetic stirrer for one hr. Different substituted aryl aldehydes (5 mM) in ethanol were then added and stirred for 24-36 hr until the reaction was complete. The resultant precipitate was separated by filtration washed with cold water and dried. The crude products recrystalized using appropriate solvents[12].

E-1-(5-nitro-2-aminophenyl)-3-phenylprop-2-en-1-one (**6a**):

Yield: 75%, mp: 173-175^{0}C, IR (KBr, cm^{-1}): 1680, 3050, 3315. ^{1}H NMR (δ ppm): 4.52 (s, 2H, NH_2), 7.32-7.34 (d, 1H, olefinic), 7.41-7.47 (m, 5H, $C_{2'',3'',4'',5'',6''}$-H), 7.53-7.55 (m, 2H, $C_{3',4'}$-H), 7.61 (s, 1H, C_6'-H), 8.01-8.05 (d, 1H, olefinic). MS m/z: 268 (M^+): Anal. Cald. For $C_{15}H_{12}N_2O_3$ (268): C, 67.16; H, 4.47; N, 10.44. Found: C, 67.23; H, 4.52; N, 10.38.

6-nitro-2-aryl-1,2,3,4-tetrahydroquinolin-4-ones (**7a-j**):

5-nitro-2-aminoacetophnone chalcones 6a-j (0.003 moles) were dissolved in glacial acetic acid (12 ml) and orthophosphoric acid (12 ml) was added slowly into the solution. Reaction mixture was then heated at 100^{0}C for 20 min. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, added to ice cold water (100 ml) to precipitate crude solid. The product separated by filtration and recrystalized using appropriate solvents[12].

2-phenyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7a**):

Yield: 72%, mp: 238-240^{0}C, IR (KBr, cm^{-1}): 1352, 1695, 3080, 3325. ^{1}H NMR (δ ppm): 2.69-2.71 (q, 1H, C_3-H), 2.73-2.75 (q, 1H, C_3-H), 4.46 (s, 1H, NH), 4.62-4.64 (q, 1H, C_2-H), 6.71-6.73 (d, 1H, C_8-H), 6.83-6.85 (d, 1H, C_7-H), 7.30-7.36 (m, 5H, $C_{2',3',4',5',6'}$-H), 7.74 (s, 1H, C_5-H). MS m/z: 268 (M^+): Anal. Cald. For $C_{15}H_{12}N_2O_3$ (268): C, 67.16; H, 4.47; N, 10.44. Found: C, 67.19; H, 4.51; N, 10.37.

2-(4'-chlorophenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7b**):

Yield: 68%, mp: 262-264^{0}C, IR (KBr, cm^{-1}): 1356, 1691, 3100, 3352. ^{1}H NMR (δ ppm): 2.70-2.72 (q, 1H, C_3-H), 2.74-2.76 (q, 1H, C_3-H), 4.43 (s, 1H, NH), 4.60-4.62 (q, 1H, C_2-H), 6.77-6.79 (d, 1H, C_8-H), 6.91-6.93 (d, 1H, C_7-H), 7.31-7.33 (d, 2H, $C_{2',6'}$-H),7.56-7.58 (d, 2H, $C_{3',5'}$-H), 7.75 (s, 1H, C_5-H). MS m/z: 302 (M^+): Anal. Cald. For $C_{15}H_{11}N_2O_3Cl$ (302): C, 59.50; H, 3.63; N, 9.25. Found: C, 59.61; H, 3.67; N, 9.29.

2-(4'-hydroxyphenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7c**):

Yield: 68%, mp: 212-214^{0}C, IR (KBr, cm^{-1}): 1345, 1682, 3095, 3350. ^{1}H NMR (δ ppm): 2.64-2.66 (q, 1H, C_3-H), 2.70-2.72 (q, 1H, C_3-H), 4.49 (s, 1H, NH), 4.63-4.65 (q, 1H, C_2-H), 6.74-6.75 (d, 1H, C_8-H), 6.91-6.93 (d, 1H, C_7-H), 7.29-7.31 (d, 2H, $C_{2',6'}$-H),7.49-7.52 (d, 2H, $C_{3',5'}$-H), 7.71 (s, 1H, C_5-H), 10.25 (s, 1H, OH). MS m/z: 284 (M^+): Anal. Cald. For $C_{15}H_{12}N_2O_4$ (284): C, 63.38; H, 4.22; N, 9.85. Found: C, 63.43; H, 4.26; N, 9.79.

2-(4'-trifluoromethoxyphenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7d**):

Yield: 75%, mp: 266-268^{0}C, IR (KBr, cm^{-1}): 1350, 1680, 3085, 3345. ^{1}H NMR (δ ppm): 2.73-2.75 (q, 1H, C_3-H), 2.78-2.80 (q, 1H, C_3-H), 4.82 (s, 1H, NH), 4.67-4.69 (q, 1H, C_2-H), 6.71-6.73 (d, 1H, C_8-H), 6.88-6.90 (d, 1H, C_7-H), 7.26-7.28 (d, 2H, $C_{2',6'}$-H),7.46-7.48 (d, 2H, $C_{3',5'}$-H), 7.65 (s, 1H, C_5-H). MS m/z: 352 (M^+): Anal. Cald. For $C_{16}H_{11}N_2O_4F_3$ (352): C, 54.54; H, 3.12; N, 7.95. Found: C, 54.61; H, 3.08; N, 7.99.

2-(2',4',6'-trimethoxyphenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7e**):

Yield: 82%, mp: 236-238^{0}C, IR (KBr, cm^{-1}): 1350, 1710, 3095, 3335. ^{1}H NMR (δ ppm): 2.69-2.71 (q, 1H, C_3-H), 2.74-2.76 (q, 1H, C_3-H), 3.91 (s, 6H, OCH_3), 3.97 (s, 3H, OCH_3), 4.66-4.68 (q, 1H, C_2-H), 5.01 (s, 1H, NH), 6.70-6.72 (d, 1H, C_8-H), 6.83-6.85 (d, 1H, C_7-H), 7.41 (s, 2H, $C_{3',5'}$-H), 7.61 (s, 1H, C_5-H). MS m/z: 358 (M^+). Anal. Cald. For $C_{18}H_{18}N_2O_6$ (358): C, 60.33; H, 5.02; N, 7.82. Found: C, 60.16; H, 5.12; N, 7.89.

2-(4'-cyanophenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7f**):

Yield: 76%, mp: 263-265^{0}C, IR (KBr, cm^{-1}): 1357, 1705, 3090, 3300. ^{1}H NMR (δ ppm): 2.71-2.73 (q, 1H, C_3-H), 2.76-2.78 (q, 1H, C_3-H), 4.48 (s, 1H, NH), 4.66-4.68 (q, 1H, C_2-H), 6.76-6.78 (d, 1H, C_8-H), 6.92-6.94 (d, 1H, C_7-H), 7.27-7.29 (d, 2H, $C_{2',6'}$-H),7.43-7.45 (d, 2H, $C_{3',5'}$-H), 7.69 (s, 1H, C_5-H). MS m/z: 293 (M^+). Anal. Cald. For $C_{16}H_{11}N_3O_3$ (293): C, 65.52; H, 3.75; N, 14.33. Found: C, 65.55; H, 3.81; N, 14.28.

2-(4'-methoxyphenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7g**):

Yield: 59%, mp: 228-230^{0}C, IR (KBr, cm^{-1}): 1365, 1690, 3100, 3355. ^{1}H NMR (δ ppm): 2.72-2.74 (q, 1H, C_3-H), 2.78-2.80 (q, 1H, C_3-H), 3.85 (s, 3H, CH_3), 4.43 (s, 1H, NH), 4.63-4.65 (q, 1H, C_2-H), 6.74-6.76 (d, 1H, C_8-H), 6.81-6.83 (d, 1H, C_7-H), 7.19-7.21 (d, 2H, $C_{2',6'}$-H),7.36-7.38 (d, 2H, $C_{3',5'}$-H), 7.66 (s, 1H, C_5-H). MS m/z: 298 (M^+). Anal. Cald. For $C_{16}H_{14}N_2O_4$ (298): C, 64.42; H, 4.69; N, 9.39. Found: C, 64.46; H, 4.66; N, 9.45.

2-(4'-methylphenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7h**):

Yield: 63%, mp: 218-220^{0}C, IR (KBr, cm^{-1}): 1353, 1700, 3075, 3350. ^{1}H NMR (δ ppm): 2.23 (s, 3H, CH_3), 2.69-2.71 (q, 1H, C_3-H), 2.76-2.78 (q, 1H, C_3-H), 4.49 (s, 1H, NH), 4.60-4.62 (q, 1H, C_2-H), 6.71-6.73 (d, 1H, C_8-H), 6.84-6.86 (d, 1H, C_7-H), 7.27-7.29 (d, 2H, $C_{2',6'}$-H), 7.41-7.43 (d, 2H, $C_{3',5'}$-H), 7.69 (s, 1H, C_5-H). MS m/z: 282 (M^+). Anal. Cald. For $C_{16}H_{14}N_2O_3$ (282): C, 68.08; H, 4.96; N, 9.92. Found: C, 68.04; H, 4.89; N, 9.89.

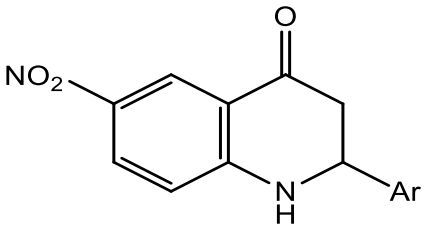
2-(4'-bromophenyl)-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7i**):

Yield: 61%, mp: 283-285^{0}C, IR (KBr, cm^{-1}): 1350, 1685, 3055, 3315. ^{1}H NMR (δ ppm): 2.76-2.78 (q, 1H, C_3-H), 2.82-2.84 (q, 1H, C_3-H), 4.56 (s, 1H, NH), 4.65-4.67 (q, 1H, C_2-H), 6.73-6.75 (d, 1H, C_8-H), 6.86-6.88 (d, 1H, C_7-H), 7.39-7.41 (d, 2H, $C_{2',6'}$-H), 7.50-7.52 (d, 2H, $C_{3',5'}$-H), 7.78 (s, 1H, C_5-H). MS m/z: 347 (M^+). Anal. Cald. For $C_{15}H_{11}N_2O_3Br$ (347): C, 51.87; H, 3.17; N, 8.06. Found: C, 51.59; H, 3.09; N, 8.13.

2-thienyl-6-nitro-1,2,3,4-tetrahydroquinolin-4-one (**7j**):

Yield: 71%, mp: 192-194^{0}C, IR (KBr, cm^{-1}): 1348, 1695, 3100, 3345. ^{1}H NMR (δ ppm): 2.77-2.79 (q, 1H, C_3-H), 2.83-2.85 (q, 1H, C_3-H), 4.49 (s, 1H, NH), 4.61-4.63 (q, 1H, C_2-H), 6.78-6.80 (d, 1H, C_8-H), 6.85-6.87 (d, 1H, C_7-H), 7.30-7.32 (dd, 1H, $C_{4'}$-H), 7.43-7.45 (d, 1H, $C_{3'}$-H), 7.73 (s, 1H, C_5-H), 7.79-7.80 (d, 1H, $C_{5'}$-H MS m/z: 274 (M^+). Anal. Cald. For $C_{13}H_{10}N_2O_3S$ (274): C, 56.93; H, 3.64; N, 10.21. Found: C, 56.95; H, 3.69; N, 10.23.

Physical and biological data of tetrahydroquinolones: (**7a-j**) (**Table 1**):



7a-j

Compound	Ar	m.p (^{0}C)	Yield (%)	Cytotoxicity (μM) MCF-7	OVC-AR	DU-145
7a	-C_6H_5	238-240	72	23	25	29
7b	4-Cl-C_6H_4	262-264	68	15	16	20
7c	4-OH-C_6H_4	212-214	68	24	26	31
7d	4-OCF_3-C_6H_4	266-268	75	4	7	11
7e	2,4,6-OCH_3-C_6H_2	236-238	82	17	19	21
7f	4-CN-C_6H_4	263-265	76	11	14	15
7g	4-OCH_3-C_6H_4	228-230	59	19	20	23
7h	4-CH_3-C_6H_4	218-220	63	21	23	25
7i	4-Br-C_6H_4	283-285	61	19	22	26
7j	2-Thienyl	192-194	71	2	3	8
8	Adriamycin (Standard)			0.01	0.01	0.02

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