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SYNTHESIS AND ANTI-CANCER ACTIVITY OF NOVEL QUINAZOLINE DERIVATIVES

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ABSTRACT

Objective: The objective of the present study was to synthesize and screen the in-vitro anticancer activity of quinazoline derivative on MCF 7 Cell line. **Method:** Quinazoline derivatives belonging to the N-containing heterocyclic compounds have caused universal concerns due to their wide and distinct biopharmaceutical activities. The synthesized quinazoline derivatives was screened for anticancer activity against MCF 7 cell line study (via) MTT assay at different concentration level. **Result:** From the investigation of the study nearly 11 compounds were synthesized out of which two compounds such as 4-(2-fluorophenyl)-1,4,5,6 tetrahydro-2-(methyl thio) benzo quinazoline (C1) and 4-(3,4 dimethoxyphenyl)-1,4,5,6-tetrahydro-2-(methylthio) benzo quinazoline (C2) showed anti cancer activity. **Conclusion:** From the studies the results reveals that the compound quinazoline derivatives has significant anticancer activity against breast cancer cell line.

KEYWORDS: Quinazoline derivatives, Anti cancer activity, MCF 7 Cell line.

INTRODUCTION

Cancer is a class of diseases characterized by out-of-control cell growth which harms the body by forming lumps or masses of tissue called tumors.[1] Tumors are invasive, aggressive and mostly metastatic. The adverse effects of oxidative stress on human health have become a serious issue.[2] Under stress, our bodies produce more reactive oxygen species. These Free radicals cause irreversible damage to the DNA and other molecules may lead to cancer. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, structure compound containing benzene fused to pyrimidine.[3,4] Medicinally it has been used in various areas as an analgesic and anti-inflammatory, antihypertensive, antimicrobial, antibacterial, anticonvulsant, anticancer, antimalarial and antidepressant activities. Pyrazole derivatives also exhibit some similar set of activities such as antimicrobial and analgesic, anti-inflammatory.[5,6] It has been reported that substitution pattern by different aryl or heteroaryl moieties at 2/3 position of quinazoline nucleus markedly influences the anti-inflammatory activity.[4] On the other hand, sulphonamides, imidazoles pyrazoles are other important pharmacodynamic heterocyclic nuclei which when incorporated into different heterocyclic templates, have been reported to possess potent anti-inflammatory activity.[7] The observation of the study is to synthesise and screen the in-vitro anti cancer activity of the compound.[8]

MATERIAL AND METHODS

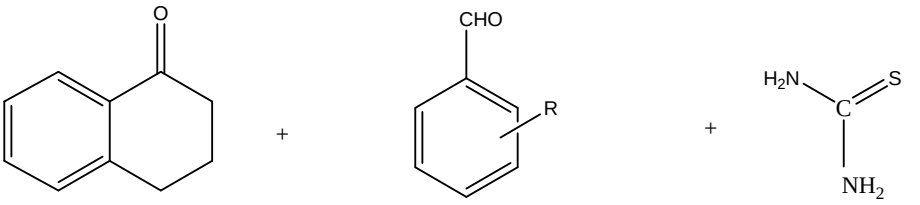
Minimum essential media **(**MEM) was purchased from Hi Media Laboratories Fetal bovine serum (FBS) was purchased from Cistron laboratories Trypsin, methylthiazolyldiphenyl-tetrazolium bromide (MTT), and Dimethyl sulfoxide (DMSO) were purchased from (Sisco research laboratory chemicals Mumbai). All of other chemicals and reagents were obtained from Sigma Aldrich Mumbai. MCF-7 cell lines was obtained from National centre for cell sciences Pune (NCCS).

Synthesis of 4-(2-methoxyphenyl)-3,4,5,6-tetrahydrobenzo [*h*]quinazoline-2(1*H*)-thione

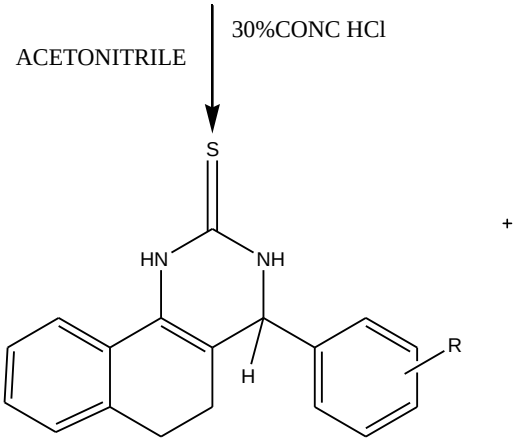
A mixture of alpha-tetralone (0.01 mole, 1.46 g), 4-methoxy benzaldehyde (0.01 mole, 1.36 ml), thiourea (0.01 mole, 0.76 g) and concentrated HCl (3-4 drops) was dissolved in acetonitrile (5 ml) taken in borosil beaker (100 ml) and was irradiated in unmodified domestic microwave at 30% microwave power for 5.00 min.[9] The reaction was monitored by thin layer chromatography (TLC) using silica gel-G plates. Ethyl acetate and n-hexane mixture was used as eluting solvent (1:1).[10,11] After drying the plates, spots were exposed to iodine chamber. The reaction mixture on standing for a

few hours afforded product which was filtered under reduced pressure and recrystallized out of alcohol for 2-3 times to give pure product.[12,13]

STEP 1: Synthesis of 4-substituted phenyl-3,4,5,6 tetrahydrobenzo[h] quinazoline-2(1H)-thiones.



ALPHA TETRALONE SUBS. AROMATIC BENZALDEHYDE THIOUREA

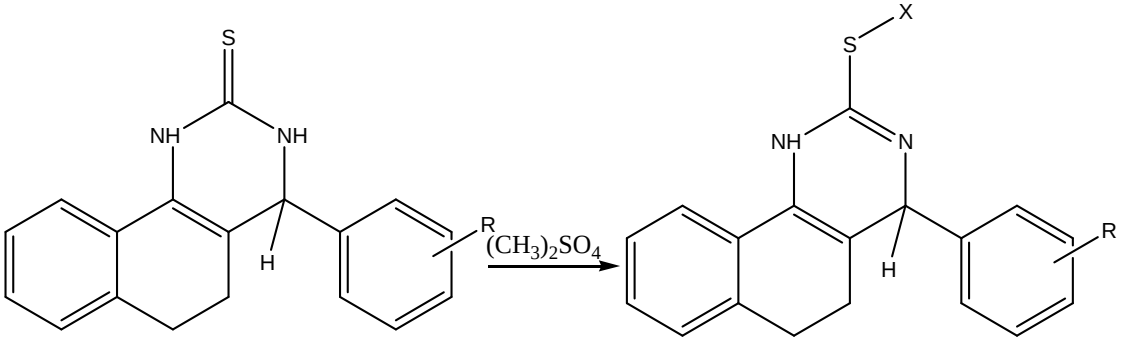


4-SUBSTITUTED PHENYL-3,4,5,6-TETRAHYDROBENZO[h]QUINAZOLINE-2(1H)-THIONES

Synthesis of 4-(2-methoxyphenyl)-2-(methylthio)-1,4,5,6-tetrahydrobenzo[*h*]quinazoline

4-(4-methoxyphenyl)-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione Ia (0.004 mole, 1.288g) was dissolved in 25 ml ethanol.[14] To it, added NaOH solution, which was prepared by dissolving NaOH (0.004 mole, 0.160g) in water (2 ml). The mixture was cooled. To this mixture, dimethyl sulphate (0.5 ml, 0.004 mole) was added dropwise while stirring the mixture continuously.[15,16] The reaction mixture was refluxed for 3 hours. The reaction was monitored by thin layer chromatography (TLC) using silica gel-G plates. Ethyl acetate and n-hexane mixture was used as eluting solvents (1:1) and after drying, the retention factor value is noted.[17,18]

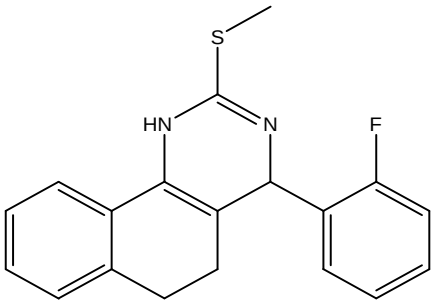
STEP 2: Synthesis of 2-(methyl thio)4-substituted phenyl 1,4,5,6 Tetrahydrobenzo (h)Quinazolines



COMPOUNDS C1 TO C11 COMPOUNDS C1 TO C11

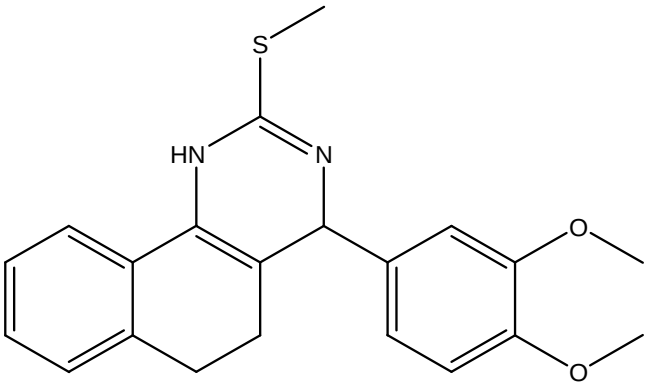
TITLE COMPOUNDS

C1 COMPOUND



4-(2-fluorophenyl)-1,4,5,6-tetrahydro-2-(methylthio)benzo[*h*]quinazoline

C2 COMPOUND



4-(3,4 dimethoxyphenyl)-1,4,5,6-tetrahydro-2-(methylthio)benzo[*h*]quinazoline

Assay for proliferation studies

MTT [(3-(4, 5-dimethyl thiazol-2yl)-2, 5-diphenyl tetrazolium bromide] measures the metabolic activity of the viable cells.[19] The reaction between MTT and mitochondrial dehydrogenase produces water insoluble formazan salt. This method involved culturing the cells in a 96-well microtiterplate, and then incubating them with MTT solution for approximately 2hrs.[20] During incubation period, viable cells convert MTT to a water insoluble formazan dye.[21,22] The formazan dye in the MTP is solubilised and quantified with an ELISE plate reader. The absorbance directly correlates with the cell number. This is applicable for adherent cells cultured in MTP.

Cell line and culture

The cells were maintained in Minimal Essential Media supplemented with 10% FBS, penicillin (100 U/ml), andstreptomycin (100 µg/ml) in a humidified atmosphere of 50 µg/ml CO_2 at 37 °C.[23]

***In vitro* assay for Cytotoxicity activity (MTT assay)**

The Cytotoxicity of samples on MCF-7 was determinedby the MTT assay. Cells (1×10^5/well) were plated in 1ml of medium/well in 24-well plates (Costar Corning, Rochester, NY).[24,25] After 48 hours incubation the cell reaches the confluence. Then, cells were incubated in the presence ofvarious concentrations of the samples in 0.1% DMSO for 48h at 37°C. After removal of the sample solution and washing with phosphate-buffered saline (pH 7.4), 200µl/well (5mg/ml) of 0.5% 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl—tetrazolium bromide cells (MTT) phosphate- buffered saline solution was added.[26,27] After4h incubation, 0.04M HCl/ isopropanol were added. Viable cells were determined by the absorbance at 570nm.[28] Measurements was performed and the concentration required for a 50% inhibition of viability (IC50) was determined graphically. The absorbance at 570 nm was measured with a UV-Spectrophotometer using wells without sample containing cells as blanks.[29] The effect of the samples on the proliferation of MCF-7 was expressed as the % cell viability, using the following formula.[30]

% cell viability = A570 of treated cells / A570 of control cells × 100%.

The results were shown in Table 1-2 and Figure 1-5.

RESULT AND DISCUSSION

Table 1: Anti Cancer effect of C1 on MCF-7 cell line.

S.No	Concentration (µg/ml)	Dilutions	Absorbance(O.D)	Cell viability (%)
1	1000	Neat	0.03	5.76
2	500	1:1	0.10	19.23
3	250	1:2	0.18	34.61
4	125	1:4	0.22	42.3
5	62.5	1:8	0.27	51.92
6	31.2	1:16	0.34	65.38
7	15.6	1:32	0.40	76.92
8	7.8	1:64	0.47	90.38
9	Cell control	-	0.52	100

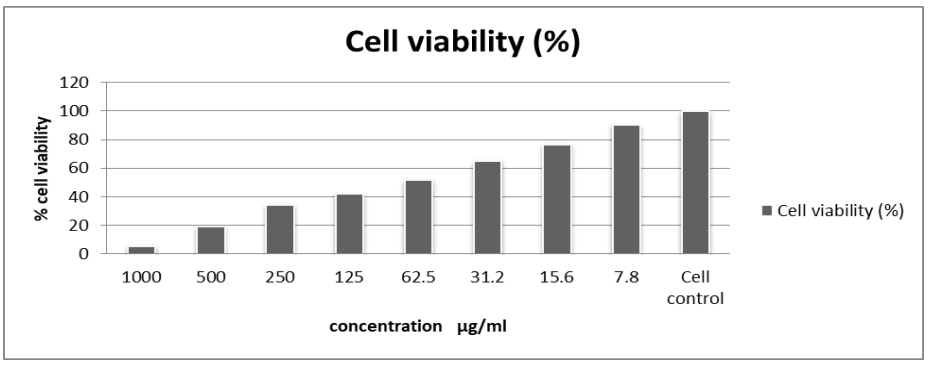


Fig. 1: Percentage cell viability effect of C1 compound on MCF-7 cell line.

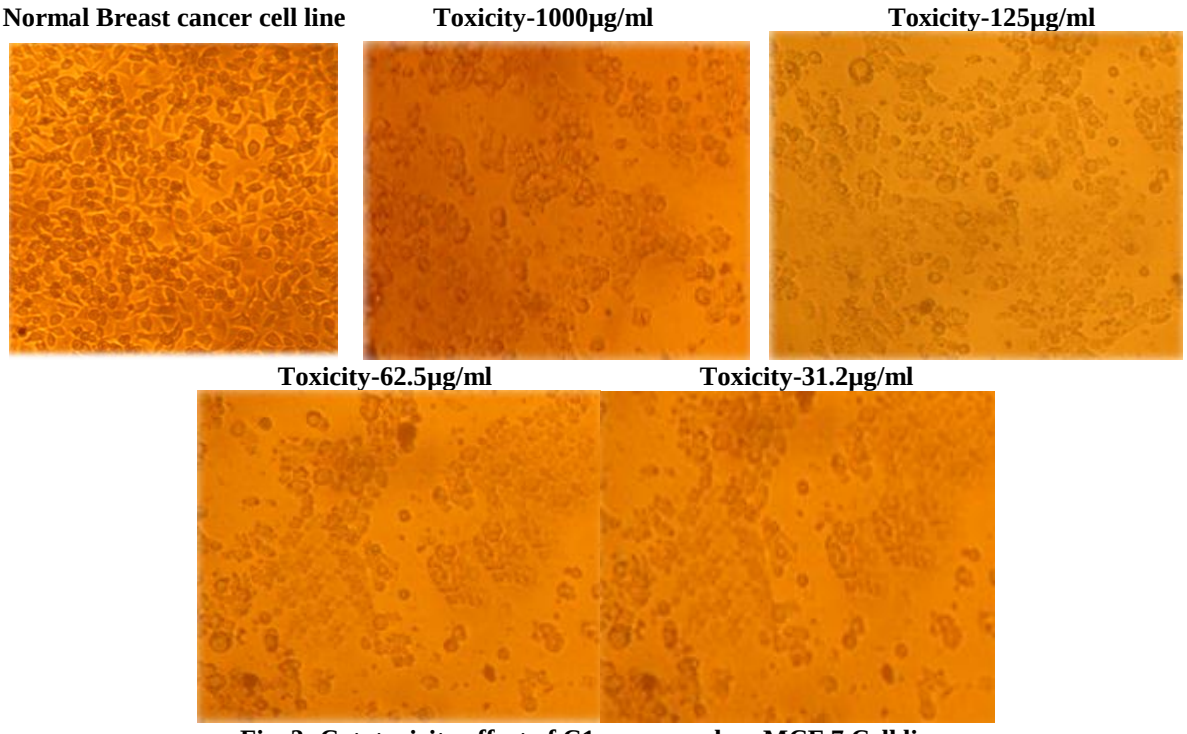


Fig. 3: Cytotoxicity effect of C1 compound on MCF 7 Cell line.

Table 2: Anti Cancer effect of C2 on MCF-7 cell line.

S.No	Concentration (µg/ml)	Dilutions	Absorbance (O.D)	Cell viability (%)
1	1000	Neat	0.06	17.64
2	500	1:1	0.10	29.41
3	250	1:2	0.17	35.29
4	125	1:4	0.21	47.05

5	62..5	1:8	0.25	50.00
6	31.2	1:16	0.32	64.70
7	15.6	1:32	0.39	70.58
8	7.8	1:64	0.40	77.06
8	Cell control	-	0.34	100

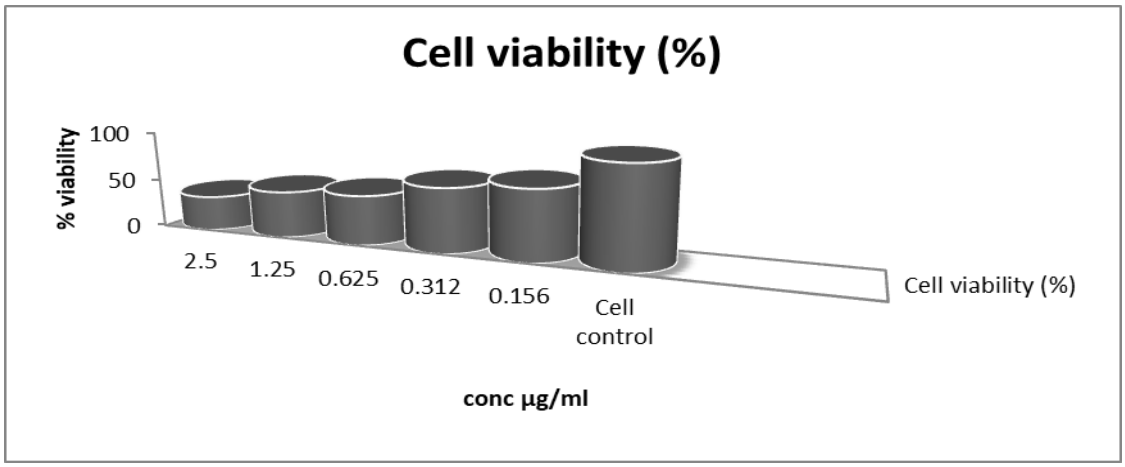


Fig. 4: Percentage cell viability effect of C2 on MCF-7 cell line.

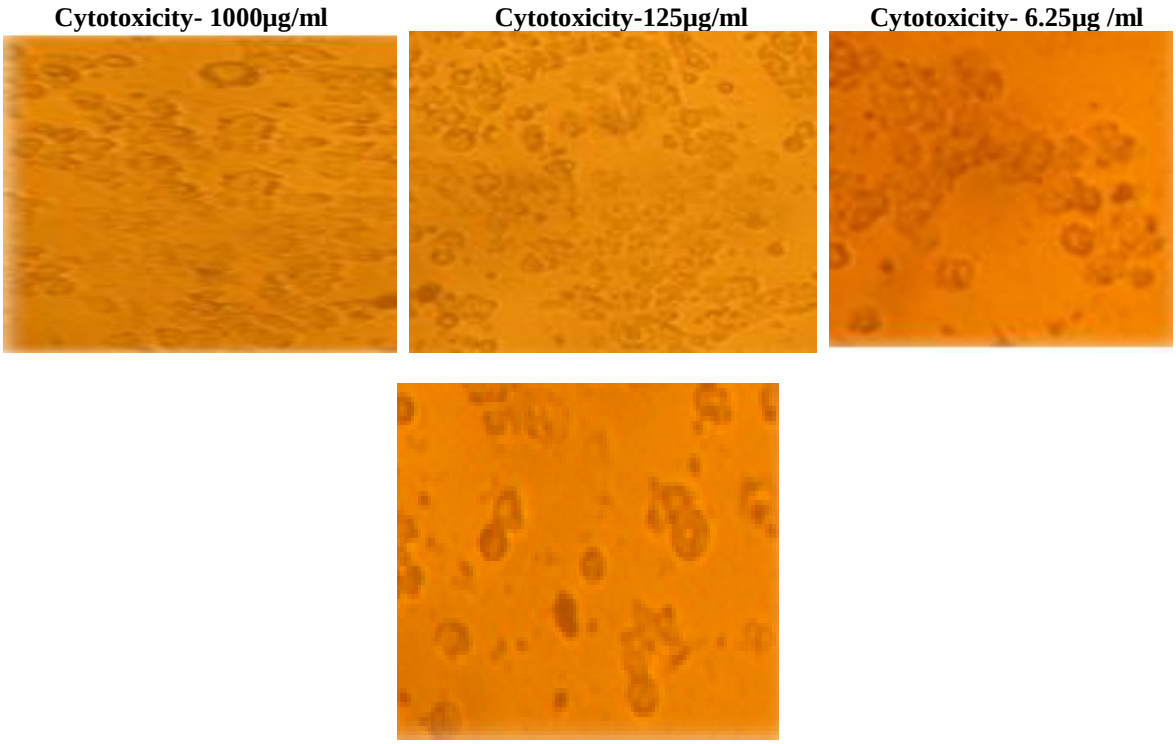


Fig. 5: Cytotoxicity effect of C2 Compound on MCF7 Cell line.

RESULT AND DISCUSSION

A mixture of alpha-tetralone, 4-methoxy benzaldehyde, thiourea and concentrated HCl in presence of acetonitrile which yields 4-substituted phenyl-3,4,5,6 tetrahydrobenzo[h] quinazoline-2(1H)-thiones.

From the quinazoline parent molecule nearly 11 compounds were synthesized out of which 2 compound showed anticancer activities.

The anticancer activity of newly synthesized compound was measured by (MTT) against MCF-7 cell line. The cytotoxicity details of the newly synthesized compound are shown in table 1 and 2. From the data the synthesized compound shows better inhibitory activity towards breast cancer cell line.

The compound C1 has shown an inhibitory action on breast cancer cell line in the range of 51.9% at the concentration of 62.5 (µg/ml) and 90.38% at the

concentration of 7.8(µg/ml). The compound C2 has shown an inhibitory action on breast cancer cell line in the range of 50% at the concentration of 62.5 (µg/ml). 77.06% at 7.8(µg/ml).

From fig 3, and 5 the percentage of cell viability for compound C1 and C2 was achieved by 50% at a concentration of 62.5 (µg/ml) and the lesser cell count was also achieved at this concentration so from the findings its seems that compound C1 is potent than compound C2.

CONCLUSION

From the above results the following observations were noted. The compounds C1 exhibits elevated action compared to compound C2 and in relevance to the literature survey, it was concluded that compared to other Quinazoline derivatives, quinazoline thiones exhibited superior anticancer activity towards cancer cells. Those two compounds were selected in particular, because the anticancer activity of these compounds was excellent which were predicted by PASS Prediction and OSIRIS (molecular property prediction). Even though this recently synthesized molecules represents a fruitful matrix for the development of a new class of biological molecules that would deserve further investigation and derivatization. In future it would be most promising and leading derivatives can act in opposition to malevolent cells.

Conflict of interest

No conflict of interest from authors.

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