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Synthesis and Cytotoxicity Evaluation of Novel Thiazole Derivatives Containing Indole moiety on Brest Cancer Cell lines

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ABSTRACT

*A series of new thiazole derivatives containing indole moiety were designed and prepared. The structure of newly synthesized compounds were characterized by spectral data's and screened for their cytotoxic activity against barest cancer cell lines. The study showed that some of the compounds **(3a** and **4e)** were found to be moderately cytotoxic, but not effective as control substance.*

Keywords: Indole, Thiazole, Amino cyanothiazole, Cytotoxcity, Anticancer.

INTRODUCTION

Nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals. In the field of heterocyclic structures indole and thiazole pharmacophores have significant therapeutic values in medicinal chemistry.

Indole is an aromatic heterocyclic bicyclic organic compound, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Many naturally occurring alkaloids found to contain indole heterocyclic moiety and the marked physiological action is due the indole nucleus [1]. Indole derivatives are an important class of heterocyclic compounds with a wide range of biological activities. Indole is a sub structural element of many natural products [2], and is widely used as a scaffold in agricultural and medicinal chemistry. The prominent alkaloids containing indole moiety are, Ajmalicine [3], Reserpine [4], Vindoline [5], and Yohimbine [6]. The chemistry of Indole derivatives continues to draw attention of synthetic organic chemist due to various biological activities such as, antibacterial [7], antioxidant [8], antifungal [9], antiviral [10], herbicidal [11] and anti-convulsant [12] etc. Furthermore, one of the active positions in indole is 3rd position. Some of active molecules like Serotonin [13], Psilocybin [14], DMT [15], Indomethacin [16] and Auxin [17] etc. are vital in pharmacology and are found to be substituted at 3rd position of Indole moiety.

Thiazole is another important class of heterocyclic compound contains two hetero atoms nitrogen and sulfur in the ring. Thiazoles attracted a great deal of attention from synthetic community due to diverse type of biological and pharmacological properties such as antidiabetic [18], antibacterial [19], antifungal [20], herbicidal [21], Cox-2 inhibitor [22] etc.

These properties of indoles and thiazoles with numerous pharmacological and physiological activities encouraged us to develop new scaffold of molecules to synthesize novel compounds. The development of new and efficient methodologies for synthesis of potentially bioactive indole-thiazole derivatives is important. Compounds of the nature shown in figure 1 revealed the framework of indole-thaizole pharmacophoric component systems.

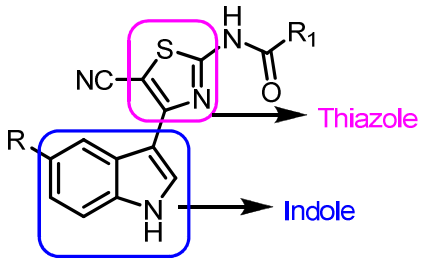


Fig.1. Indole-Thiazole scaffold

Currently cancer is one of the most deadly diseases and requires chemotherapy for the treatment [23]. Chemotherapeutic compounds are drugs that are used to destroy cancer cells. The study of destroying the cancer cell is called cytotoxicity. The cytotoxicity study is important to know about the toxic nature of compounds on cell lines. In this research we choose breast cancer lines for our studies against indole-thiazole scaffold molecules. For preliminary research we choose un-substitution and fluoro substitution on indole ring at 5^{th} position and amides on thiazole ring. The synthesized new molecules are characterized by spectral data's like Mass, IR, NMR and physical constants and subjected to cytotoxic studies on breast cancer cells.

MATERIALS AND METHODS

All chemicals used for the synthesis were of reagent grade and were procured from Sigma Aldrich Chemical Co, Bangalore; SDFCL, Mumbai; and the intermediates were prepared as per the known literature procedure. NMR spectra were recorded on 400 MHz Varian-AS NMR spectrometer using TMS as an internal standard. IR spectra were recorded by using PerkinElmer Spectrum 100 Series FT-IR spectrometer. Mass spectra were recorded on Waters Micro mass Q-Tof Micro, equipped with electro spray ionization (ESI). Melting points were determined by using Buchi melting point B-545 instrument and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) using pre-coated silica 60 F254, 0.25 mm aluminum plates (Merck). The crude compounds were crystallized with appropriate solvents.

General procedure for 3-(1*H*-indole-3-yl)-3-oxopropanenitrile derivatives (2a-b) [24]
The mixture of cyanoacetic acid (0.1 mol) and acetic anhydride (25 ml) was heated to 50 °C and maintained for 15 min. To this mixture added indole (0.1 mol) at 50 °C and continued heating to 80 °C for 10 min; the progress of the reaction was monitored by TLC (20% ethyl acetate in hexane). After completion of reaction, cooled the reaction mixture to room temperature, the precipitated product was filtered, washed initially with water, followed by slurry wash with n-heptane gives titled compounds.

3-(1*H*-indole-3-yl)-3-oxopropanenitrile (2a) Pale yellow solid; Yield: 91%; m. p.: 242-246 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.18 (s, 1H, NH), 8.37 (d, *J*=3.2, 1H, Ar-H), 8.14-8.12 (m, 1H, Ar-H), 7.52-7.49 (m, 1H, Ar-H), 7.28-7.21 (m, 2H, Ar-H), 4.50 (s, 2H, CH_2); MS (m/z): 184 [M+].

3-(5-fluoro-1*H*-indole-3-yl)-3-oxopropanenitrile (2b) Pale yellow solid; Yield: 86%; m. p.: 275-280 °C; 1H NMR (DMSO-d6, 400 MHz) δ: 12.29 (s, 1H, NH), 8.43 (d, *J*=3.2, 1H, Ar-H), 7.81-7.78 (m, 9.6, 1H, Ar-H), 7.55-7.51 (m, 1H, Ar-H), 7.14-7.09 (m, 1H, Ar-H), 4.51 (s, 2H, CH_2); MS (m/z): 202 [M+].

General procedure for the synthesis of 2-amino-4-(1*H*-indole-3-yl) thiazole-5-carbonitrile derivatives (3a-b)
To the solution indole derivative **2a** or **2b** (27 mmol) in ethanol (50 ml), was added pyridine (135 mmol), thiourea (54 mmol) and iodine (27 mmol) slowly, portion wise maintaining the temperature at below 40 ^{o}C. After completion of addition, the resulting solution was heated to reflux for 12 h, the progress of reaction was monitored by using TLC (20% ethyl acetate in hexane). After completion of reaction, the mixture was quenched with ice cold water (250 ml), filtered the precipitated product, washed with saturated sodium metabisulphate solution and water. The crude product was purified by column chromatography using ethyl acetate and hexane (30-40%) as mobile phase to obtain the pure product as pale brown solid.

2-amino-4-(1*H*-indole-3-yl) thiazole-5carbonitrile (3a); Yield: 61%; Pale brown solid; m. p.: 200-205 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 11.7 (s, 1H, NH), 8.26 (d, *J*=7.6, 1H, Ar-H), 8.14 (s, 2H, NH_2), 8.04 (d, *J*=2.4, 1H, Ar-H), 7.47 (d, *J*=8.4, 1H, Ar-H), 7.20-7.16 (m, 1H, Ar-H), 7.13-7.09 (m, 1H, Ar-H); MS (m/z): 240 [M+].

2-amino-4-(5-fluoro-1*H*-indole-3-yl) thiazole-5carbonitrile (3b) Yield: 56%; Pale brown solid; m. p.: 256-262 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 11.81 (s, 1H, NH), 8.18 (s, 2H, NH_2), 8.13 (d, *J*=2.8, 1H, Ar-H), 8.01 (dd, *J*=2.4, 1H, Ar-H), 7.50-7.47 (dd, *J*= 4.8, 1H, Ar-H), 7.04 (td, *J*=2.8, 1H, Ar-H), MS (m/z): 258 [M+].

General procedure for the synthesis of N-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl) substituted amides (4a-l)
To a solution of thiazole amine derivative **3a** or **3b** (2.08 mmol) in dichloromethane (10 ml) was added pyridine (10.4 mmol), to this mixture was added a solution of carboxylic acid chloride (4.16 mmol) in dichloromethane (5 ml) at 5-10 °C and allowed to 25-30 °C. The progress of reaction was monitored by TLC (20% ethyl acetate in hexane). After completion of reaction, the mixture was quenched with water and extracted the product with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, dried with anhydrous sodium sulphate, concentrated to get the residue. The crude product was crystallized with 2-propanol to obtain the desired pure products (Table 2).

***N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl) acetamide (4a)** Yield: 83 %; Off white solid; m. p.: 262-268; MS (ESI) m/z=282 [M+]; IR (KBr) cm^{-1}: 3420, 3172 2(NH), 2988 (Ar-CH), 2200 (CN), 1707 (C=O), 1533 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.91 (s, 1H, N-H), 11.82 (s, 1H, N-H), 8.34 (d, *J*=8.4, 1H, Ar-H), 8.14 (d, *J*=2.4, 1H, Ar-H), 7.51 (d, *J*=8, 1H, Ar-H), 7.24-7.15 (m, 2H, Ar-H), 2.26 (s, 3H, CH_3).

***N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl) hexaneamide (4b)** Yield: 89 %; Off white solid; m. p.: 262-268 °C; MS (ESI) m/z=338 [M+]; .IR (KBr) cm^{-1}: 3559, 3326 (2NH), 2956 (Ar-CH), 2205 (CN), 1670 (C=O), 1529 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.84 (s, 1H, N-H), 11.78 (s, 1H, N-H), 8.33 (d, *J*=7.6, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 7.50 (d, *J*=7.6, 1H, Ar-H), 7.23-7.13 (m, 2H, Ar-H), 1.64 (t, 2H, CH_2), 1.32-1.29 (m, 6H, CH_2), 0.88 (t, 3H, CH_3).

***N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl) benzamide (4c)** Yield: 78 %; Off white solid; m. p.: 263-266 °C; MS (ESI) m/z= 344 [M+]; .IR (KBr) cm^{-1}: 3417, 3290 (2NH), 3056 (Ar-CH), 2198 (CN), 1660 (C=O), 1523 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.80 (s, 1H, N-H), 8.54 (s, 1H, N-H), 8.38 (d, *J*=8.4, 1H, Ar-H), 8.20 (d, *J*=2.8, 1H, Ar-H), 7.99 (d, *J*=8.4, 2H, Ar-H), 7.68 (t, 1H, Ar-H), 7.60 (t, 2H, Ar-H), 7.47 (d, *J*=6.8, 1H, Ar-H), 7.36-7.21 (m, 2H, Ar-H).

***N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl)-4-methyl benzamide (4d)** Yield: 81 %; Off white solid; m. p.: 266-272 °C; MS (ESI) m/z= 358 [M+]; .IR (KBr) cm^{-1}: 3636, 3346 (2NH), 2734 (Ar-CH), 2204 (CN), 1656 (C=O), 1551 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.23 (s, 1H, N-H), 11.81 (s, 1H, N-H), 8.60-8.58 (m, 1H, Ar-H), 8.47 (d, *J*=7.6, 1H, Ar-H), 8.18 (d, *J*=3.2, 1H, Ar-H), 8.11 (d, *J*=8.4, 2H, Ar-H), 7.80 (tt, *J*=7.4, 1H, Ar-H), 7.53 (d, *J*=8, 1H, Ar-H), 7.43 (d, *J*=8.0, 1H, Ar-H), 7.41-7.38 (m, 2H, Ar-H), 7.27-7.18 (m, 2H, Ar-H); 2.44 (s, 3H, CH3).

***N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl)-4-methoxy benzamide (4e)** Yield: 76 %; Off white solid; m. p.: 235-240 °C; MS (ESI) m/z=374 [M+]; IR (KBr) cm^{-1}: 3521, 3318 (2NH), 3054 (Ar-CH), 2974 (Ar-CH), 2205 (CN), 1664 (C=O), 1541 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.12 (s, 1H, N-H), 11.78 (s, 1H, N-H), 8.45 (d, *J*=7.6, 1H, Ar-H), 8.19 (d, *J*=8.8, 2H, Ar-H), 8.15 (d, *J*=2.8, 1H, Ar-H), 7.51 (d, *J*=8.0, 1H, Ar-H), 7.25-7.16 (m, 2H, Ar-H), 7.13 (d, 2H, Ar-H); 3.88 (s, 3H, OCH3).

4-chloro-*N*-(5-cyano-4-(1*H*-indole-3-yl) thiazol-2-yl) benzamide (4f) Yield: 73 %; Off white solid; m. p.: 266-270 °C; MS (ESI) m/z= 378 [M+]; IR (KBr) cm^{-1}: 3373, 3219 (2NH), 3050 (Ar-CH), 2976 (Ar-CH), 2210 (CN), 1664 (C=O), 1546 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.41 (s, 1H, N-H), 11.84 (s, 1H, N-H), 8.45 (d, *J*=7.6, 1H, Ar-H), 8.21-8.17 (m, 3H, Ar-H), 7.70 (d, *J*=7.6, 2H, Ar-H), 7.52 (d, *J*=7.6, 1H, Ar-H), 7.26-7.17 (m, 2H, Ar-H).

***N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl) acetamide (4g)** Yield: 82 %; Off white solid; m. p.: 318-324 °C; MS (ESI) m/z=300 [M+]; IR (KBr) cm-1: 3313, 3146 (2NH), 2961 (Ar-CH), 2877 (Ar-CH), 2288 (CN), 1772 (C=O), 1593 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.89 (s, 1H, N-H), 11.92 (s, 1H, N-H), 8.22 (d, *J*=2.8, 1H, Ar-H), 8.09 (d, *J*=2.4, 1H, Ar-H), 7.52 (dd, *J*=4.4, 1H, Ar-H), 7.11-7.08 (td, *J*=2.8, 1H, Ar-H), 2.26 (s, 3H, CH_3).

***N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl) hexaneamide (4h)** Yield: 86 %; Off white solid; m. p.: 237-240 °C; MS (ESI) m/z=356 [M+]; IR (KBr) cm^{-1}: 3466, 3186 (2NH), 2957 (Ar-CH), 2867 (Ar-CH), 2206 (CN), 1694 (C=O), 1580 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.81 (s, 1H, N-H), 11.87 (s, 1H, N-H), 8.18 (d, *J*=2.8, 1H, Ar-H), 8.06 (dd, *J*=2.4, 1H, Ar-H), 7.48 (dd, *J*=4.4, 1H, Ar-H), 7.04 (td, *J*=2.4, 1H, Ar-H), 2.50 (t, *J*=7.2, 2H, CH2), 1.61 (t, *J*=7.2, 2H, CH2), 1.32-1.22 (m, 4H, CH2), 0.84 (t, J=6.8, 3H, CH_3).

***N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl) benzamide (4i)** Yield: 77 %; Off white solid; m. p.: 285-290 °C; MS (ESI) m/z=362 [M+]; IR (KBr) cm^{-1}: 3344, 3260 (2NH), 3050 (Ar-CH), 2961 (Ar-CH), 2205 (CN), 1660

(C=O), 1565, 1540 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.27 (s, 1H, N-H), 11.90 (s, 1H, N-H), 8.24-8.21 (m, 2H, Ar-H), 8.14 (d, *J*=7.2, 2H, Ar-H), 7.69 (t, *J*=7.2, 1H, Ar-H), 7.59 (t, *J*=8, 2H, Ar-H), 7.50 (dd, *J*=4.4, 1H, Ar-H), 7.06 (td, *J*=2.4, 1H, Ar-H).

***N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl)-4-metyl benzamide (4j)** Yield: 75 %; Off white solid; m. p.: 285-290 °C; MS (ESI) m/z= 376 [M+]; IR (KBr) cm^{-1}: 3649, 3491 (2NH), 2961 (Ar-CH), 2202 (CN), 1655 (C=O), 1531 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.17 (s, 1H, N-H), 11.90 (s, 1H, N-H), 8.27-8.24 (m, 2H, Ar-H), 8.08 (d, *J*=8, 2H, Ar-H), 7.52 (dd, *J*=4.8, 1H, Ar-H), 7.42 (d, *J*=8, 2H, Ar-H), 7.08 (td, *J*=2.4, 1H, Ar-H), 2.42 (s, 3H, CH_3).

***N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl)-4-methoxy benzamide (4k)** Yield: 71 %; Pale yellow solid; m. p.: 278-280 °C; MS (ESI) m/z=392 [M+]; IR (KBr) cm^{-1}: 3524, 3318 (2NH), 2961 (Ar-CH), 2203 (CN), 1667, 1608 (C=O), 1543 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.11 (s, 1H, N-H), 11.97 (s, 1H, N-H), 8.25 (m, 2H, Ar-H), 8.18 (d, *J*=8.8, 2H, Ar-H), 7.53 (dd, *J*=4.8, 1H, Ar-H), 7.14 (d, *J*=8.8, 2H, Ar-H), 7.09 (td, *J*=2.4, 1H, Ar-H), 3.9 (s, 3H, OCH_3).:

4-chloro-*N*-(5-cyano-4-(5-fluoro-1*H*-indole-3-yl) thiazol-2-yl) benzamide (4l) Yield: 78 %; Pale yellow solid; m. p.: 314-318 °C; MS (ESI) m/z= 396 [M+]; IR (KBr) cm^{-1}: 3372, 3218 (2NH), 3050 (Ar-CH), 2976 (Ar-CH), 2209 (CN), 1662 (C=O), 1598 (C=C); ^{1}H NMR (DMSO-d6, 400 MHz) δ: 13.38 (s, 1H, N-H), 11.95 (s, 1H, N-H), 8.26-8.17 (m, 4H, Ar-H), 7.70 (d, *J*=8, 1H, Ar-H), 7.53 (dd, *J*=4.4, 2H, Ar-H), 7.09 (td, *J*=2.4, 1H, Ar-H)

BIOLOGICAL ACTIVITY.

Cytotoxicity activity:

The cytotoxic activities of newly synthesized compounds **3(a-b)** and **4(a-l)** were studied by MTT assay method [25]. The MTT system is a means of measuring the activity of living cells via mitochondrial dehydrogenases. This viability assay is based on the color change of the MTT molecule into insoluble purple formazan by cleavage of the tetrazolium ring by mitochondrial dehydrogenase enzymes of viable cells when it is exposed to viable cells. The water insoluble formazan can be solubilized using DMSO. Measurement of the absorbance, which is proportional to the number of viable cells, and comparison to untreated controls, enables assessment of the cell growth inhibition capabilities of the compound tested.

Procedure:

Breast cancer cell lines (MDA-MB-231) were grown in T25 flasks and trypsinized after 70-80% confluent growth and checked for the viability by trypan blue dye exclusion method. Cells (50,000 cells / well) were seeded in a 96 well plate and incubated for 24 hrs at 37 °C in a humidified (5 % CO2) incubator. Compounds **3(a-b)** and **4(a-l)** were tested from 0-100 µM [2 fold variations] in RPMI media without FBS are incubated for 24 hr. After incubation with compounds, the media is removed from the wells and MTT (100 µl /well, 0.5mg/mL) is added. Post incubation with MTT reagent for 3 to 4 hours, the media is removed from the wells and formazan is solubilized with 100 µl of DMSO and absorbance at 590 nm is recorded. The percentage inhibition was calculated by using the following formula.

$$\% \text{ Inhibition} = 100 - \frac{\text{Sample}}{\text{Control}} \text{X } 100$$

All experiments were performed in triplicate, and the relative cell viability (%) was expressed as a percentage relative to the untreated control cells. The results were tabulated in table-1.

Table 1. Cytotoxicity of tested compounds against Breast Cancer cells (MDA-MB-231)

Test Compounds	Concentration (µM)	Absorbance 590nm	% Inhibition (n=3)
0	0	0.392	0.00
3a	100	0.4856	23.73
3b	100	0.6036	5.20
4a	100	0.6204	2.56
4b	100	0.5392	15.31
4c	100	0.5522	13.27
4d	100	0.5235	17.78
4e	100	0.5114	19.68
4f	100	0.5321	16.43
4g	100	0.5226	17.92
4h	100	0.5206	18.23
4i	100	0.5211	18.16
4j	100	0.5458	14.28
4k	100	0.5384	15.44
4l	100	0.5463	14.2

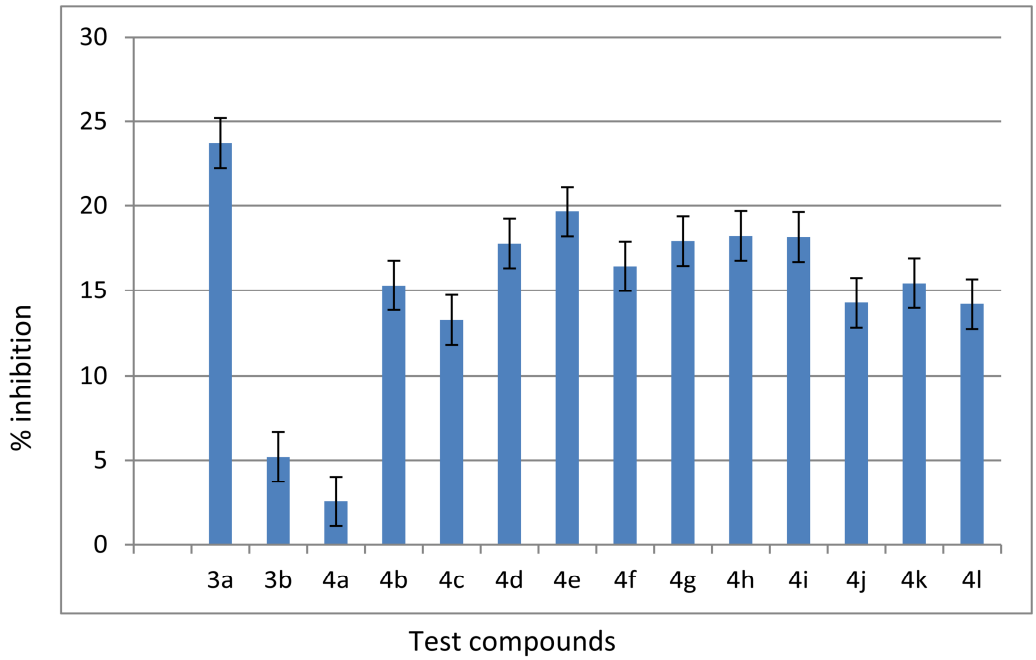


Fig.2. Cytotoxcity of test compounds against Breast Cancer (MDA-MB-231 cells)

Comments:
The test sample namely 3a and 3b and 4a-4l treatment, among them 3a has more percent of inhibition of growth of MDA MB 231 cells. The % of inhibition values are shown in the table.

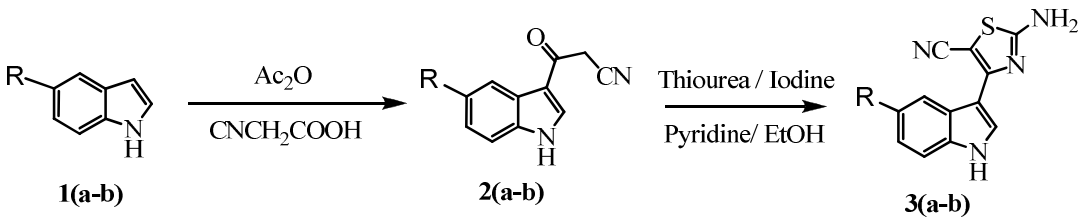
Drug likeness of compounds
In addition to Cytotoxcity studies, the evaluation of drug likeness of compounds according to Lipinski's rule of five is done which states that, in general, an orally active drug has not more than 5 hydrogen bond donors (OH and NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P less than 5. Almost all compounds **3a** and **3b** and **4a-4l** obey Lipinski's rule and is of druggable nature (Table 2).

Table 2. Drug like properties of indole containing thiazole derivatives

Compound	MW	Log P	nON	nOHON
3a	240.29	2.29	4	3
3b	258.28	1.46	4	3
4a	282.33	2.03	5	2
4b	338.44	4.44	5	2
4c	344.40	3.70	5	2
4d	358.43	4.15	5	2
4e	374.43	3.76	6	2
4f	378.84	4.38	5	2
4g	300.32	1.19	5	2
4h	356.43	3.60	5	2
4i	362.39	2.87	5	2
4j	376.42	3.31	5	2
4k	392.42	2.92	6	2
4l	396.83	3.54	2	2

RESULTS AND DISCUSSION

Chemistry
The intermediate for the synthesis of indole-thiazole amide derivatives (**4a-l**) is indole substituted 2-Amino-4-(1H-indol-3-yl)-thiazole-5-carbonitrile which were prepared as per the scheme-1



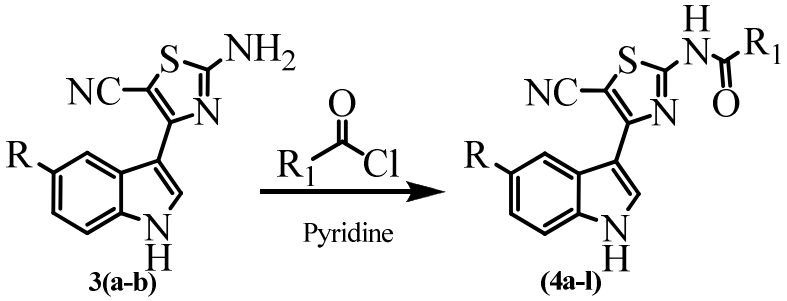
3a= R= H

3b= R= F

Scheme-1: Preparation of 2-Amino-4-(1*H*-indol-3-yl)-thiazole-5-carbonitriles

Electrophilic acylation of unprotected indoles **1(a-b**) with acetic anhydride and cyanoacetic acid resulted in 3-(1H-Indol-3-yl)-3-oxo-propionitriles **2(a-b)**. The compounds were characterized by mass and NMR spectra. The mass spectra of **2a** and **2b** were matches with the molecular weight of the structure showing m+1 mass. The NMR spectra's showed the indole NH proton at around 12 ppm and the disappearance of the proton of 3rd position of indole in NMR shows the substitution at that position.

The compounds **2a** and **2b** were reacted with thiourea in presence of pyridine and iodine gives the intermediated **3a** and **3b**. The NMR spectrum shows the presence of NH_2 protons at 8.14 -8.18 ppm and disappearance of the CH_2 protons of **2a** and **2b** shows the cyclization to triazole ring. The mass spectra's matches with the molecular weight of the structures and thus confirms the structures.



4a= R= H, R_1= $-CH_3$,

4b= R=H, R1= $-(CH_2)_4-CH_3$

4c= R= H, R_1=

4d=R=H, R_1=

4e= R= H, R_1=

4f = R= H, R_1=

4g= R= F, R_1=$-CH_3$,

4h= R= F, R1= $-(CH_2)_4-CH_3$

4i= R= F, R_1=

4j= R= F, R_1=

4k =R= F, R_1=

4l = R= F, R_1=

Scheme-2: Preparation of indole-thiazole amides 4(a-l)

The amino thiazole derivatives were reacted with different acid chlorides in presence of pyridine as base to get the targeted compounds **4(a-l).** The compounds were confirmed by mass, IR and NMR spectra's. The mass spectra's shows the m+1 masses w.r.t to the molecular weights of the structures. The IR spectrum shows the absorbance at around 3420 for NH group, 2200 for cyano, amide keto at 1707. Also the NMR spectrum shows indole NH at 12.91

ppm and the amide NH at around 11.82 ppm. The aromatic protons matches with their multiplicities and thus confirms the structures.

Biology:
The cytotoxicity study for the synthesized compounds against Breast Cancer (MDA-MB-231) cells shows that the compounds are not so active except compound **3a** and **4e** showed 23.73 % inhibition and 19.68 % inhibition. When the amino group of **3a** is protected with acid chlorides, the cytotoxicity decreases, while the compounds with fluoro substitution on indole ring with amine group on thiazole ring at 2-position having activity 5.2 % inhibition and the protected compounds with acid chloride shows increase in inhibition. Also it is noted that the compounds with aryl substitution found to be inhibitorier than the alkyl substitution. The results showed that the compounds are not highly toxic towards breast cancer cell lines.

CONCLUSION

In conclusion, we have efficiently synthesized new scaffold of indole-based thiazole derivatives, which are to be an area of intensive investigation in medicinal chemistry The synthesized indole-thiazole derivatives were evaluated for cytotoxicity effect on breast cancer cells and found that, compounds (**3a** and **4e**) are moderately toxic and the others are less toxic to the breast cancer cells and the fact that the compounds prepared in this study are chemically unrelated to the current medication suggests that the further work is clearly warranted and to be explored.

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