



Anticancer Evaluation of Some Novel 2-Azetidinone Benzothiazole-Derivatives

Bharath Kumar Chagaleti ^a, Pramod N ^b, Ashok Kumar A ^c, Aswani Ankireddy ^c, Gurram Swarupa rani ^d, K. Varalakshmi Devi^{*c}

^a Department of Pharmaceutical Chemistry, Akshaya Institute of Pharmacy, Obulapura post, Tumkur, Karnataka-572106, India.

^b Department of Pharmaceutical Chemistry, KLE Society's College of Pharmacy, Gadag, India.

^c Department of Pharmaceutical Chemistry, SKU College of Pharmaceutical Sciences, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, 515003, India.

^d Department of Pharmaceutical Chemistry, Vikas College of Pharmaceutical Sciences, Rayanigudem, Suryapet, Telangana, India.

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ABSTRACT:

In search of potential therapeutics for cancer, we designed and synthesized some novel 2-azetidinone-benzothiazole derivatives by facile method. These designed series were denoted by PN1-PN5. Physicochemical properties of designed compounds were evaluated by insilico studies with the help of Swiss ADME, and Molinspiration. Lipinski rule of five parameters were predicted by Swiss ADME, and Bioactivity scores were predicted by Molinspiration. The results showed that all compounds demonstrated good drug likeness score. The synthesized compounds were characterized by IR, NMR and Mass spectrometry. Five novel derivatives were screened for invitro anti-cancer activity by MTT assay method. Among all the synthesized compounds compound PN4 showed equipotent activity than standard Gefitinib. This data suggested that these compounds might be promising for further research and development in cancer drug designing.

Introduction:

Cancer is a serious illness that affects millions of people around the world. It's a word that brings fear and uncertainty to many families. Cancer manifests as an abnormal and uncontrolled growth of cells, posing a life-threatening risk as it can infiltrate and spread throughout the body via various mechanisms, affecting individuals of all ages and genders.[1] The World Health Organization (WHO) states that cancer stands as the second leading cause of global mortality, with approximately 1 in 6 patients succumbing to this disease. As per WHO reports that cancer is the second leading cause of death globally, responsible for approximately 9.6 million deaths in 2018 alone. The projected number of cancer cases is estimated to reach 28.4 million by 2040. [2-3] These numbers show us the immense scale of the problem. According to data from

the Globocan report and pharmacoepidemiologic statistics, India reports specific cancer types, with breast cancer (14%), lip and oral cavity cancer (10.4%), cervix cancer (8.4%), lung cancer (5.9%), stomach cancer (5%), and other cancers (56.4%) being prevalent.[4]

Cancer treatments typically involve surgical procedures, radiotherapy, and chemotherapy. However, targeted therapies and immunotherapies are gaining prominence in the medical field. Across various cancer types, inflammation has been consistently linked to all stages of cancer growth and malignant progression. Prolonged inflammation induces immunosuppression, creating an environment conducive to tumorigenesis and subsequent metastasis. [5-6]

Heterocyclic compounds play a crucial role in drug discovery and they provide a wide range of structural diversity in drug molecules. Many naturally



occurring bioactive compounds, such as alkaloids, hormones, and vitamins, contain heterocyclic rings. This makes heterocyclic scaffolds a valuable starting point for designing drugs that interact with specific biological targets, like proteins or enzymes. Their various ring sizes and compositions allow medicinal chemists to create unique and diverse chemical structures, which is essential for developing new drugs. The development of anticancer drugs is not only necessary but also a fundamental component of healthcare and global health security in this era. In the world of making new medicines and finding new ways to treat Cancer and its resistance, scientists are always looking for special compounds that can do different things in our bodies. two of these compounds that has caught their attention is the Benzothiazole and Azetidinone due to having various biological activities. [7-9]

Benzothiazole

Benzothiazole comprising sulfonamide pyrazole derivatives have been synthesized and evaluated for their various activities. The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings.[10] The introduction of trimethaprim and sulphamethoxazole has resulted in increased use of sulfonamide for the treatment of specific microbial infection. Benzothiazoles with sulphonyl group and pyrazole etc were reported to possess various pharmacological activity of clinical importance. The chemistry and pharmacology of benzothiazole have been of great interest because benzothiazole derivatives possess various biological activities like anti-cancer,[11] anti-bacterial,[12] anti-inflammatory,[13] anti-TB,[14] anti-diabetics,[15] and anti-fungal etc. [16]

Azetidinone

2-Azetidinones commonly known as β -lactams are well-known heterocyclic compounds among organic and medicinal chemists. The activity of famous antibiotics such as penicillins, cephalosporins, nocardins and carbapenems are attributed to the presence of 2-azetidinone ring in them. [17-18] Parent heterocyclic ring of azetidinones is azetidine. Azetidine is a 4-member heterocyclic ring system with nitrogen as hetero atom. 2-Azetidinones are also known as β -

lactams and it is one of the most common heterocyclic rings found in antibiotics. 2-Azetidinones consists of a carbonyl group on the second position. [19-20] Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial, antitumor, antitubercular, anticancer, cytotoxic, pesticidal enzyme inhibitors, elastase inhibitors & cholesterol absorption Inhibitors.[21] Recent years have seen a resurgence of interest in the development of stereo and enantio selective methodologies. Due to wide range of pharmacological activities of benzothiazole and azetidinone hence present attempt were made to combine both the nucleus for promising anti-cancer activity. [22-23]

2. METHODOLOGY:

2.1 Materials and methods

All chemicals and solvents were purchased from SD fine and Merck and were used. Clean and sterile laboratory equipment's were used. The melting points of all the reported compounds were determined in open capillaries by using Ana lab melting point apparatus and were uncorrected. The progression of the reaction and homogeneity of the compounds was monitored on silica gel G plates using n-butyl alcohol, ethyl acetate and carbon tetra chloride (1:2:1) as developing solvent system for the purity of the compounds. The IR spectrums of the compounds were recorded using KBr pellets technique on Shimadzu FTIR Spectrophotometer. ¹H Nuclear Magnetic Resonance (NMR) spectra of the pure compounds were recorded on Bruker Advance 400 MHz spectrophotometer. Chemical shift values (δ) were reported in parts per million (ppm). Mass spectral data of the title compounds were recorded on a JEOL JMS-D 300 instrument. Perkin-Elmer 240 analyzers were used for the elemental analysis (C, H, N).

2.2. Chemical Synthesis:

2.2.1. Synthesis of 2-amino-6-fluoro-7-chloro-benzothiazole: (2)

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in water bath and stirred in magnetic stirrer while 1.6ml of bromine in 6ml of glacial acetic acid was added, from a dropping



funnel at such a rate that the temperature never rose beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85⁰c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85⁰c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to p^H 6. A dark yellow precipitate was collected. Recrystallized from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in an oven at 80⁰C, the dry material (1gm 51.02%) melted at 210-212⁰c.

2.2.2. Preparation of p-acetamido benzene sulphonyl chloride: (3)

A 500 ml two necked flask was equipped with a dropping funnel and a reflux condenser, attached the top of the later to calcium guard tube for the absorption of hydrogen chloride. 20g (0.148 mol) of dry acetanilide was placed in the flask and 50 ml (90g, 0.77 mol) of a good grade of chlorosulphonic acid in the dropping funnel. A calcium guard tube was inserted to the later. Chlorosulphonic acid was added in small portions and the contents of flask were shaken from time to time to ensure thorough mixing. When the addition has been made the reaction mixture was heated on a water bath for 1 hr in order to complete the reaction. It was allowed to cool and the oily mixture was poured with stirring into 300g of crushed ice contained in a 1 litre beaker. This operation was carefully carried out in the fume cupboard since the excess of chloro-sulphonic acid reacts vigorously with the water. The flask was rinsed with a little ice water and rinsing was added to the contents of the beaker. The mixture was stirred for several minutes, the solid lump material was broken to obtain even suspension of the granular white solid. The obtained solid p-acetamido benzene sulphonyl chloride was filtered at the pump and washed with cold water. It was pressed and drained well, kept for drying.

2.2.3. Condensation of 2-amino-6-fluoro-7-chloro-benzothiazole and p-acetamido benzene sulphonyl chloride: (4)

2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.013 mol) was taken in pyridine (4 ml) and acetic anhydride (20 ml), to this p-acetamido benzene sulphonyl chloride (0.01 mol) were added and the mixture was kept in water bath for 2 hrs. The reaction mixture then poured in to 20 ml of ice-cold water. The solid obtained was filtered and recrystallized from dil ethanol (80%) to get pure compound 6-fluoro-7-chloro-2-(p-acetamido benzene sulphonamido) (1,3)- benzothiazole.

2.2.4. Hydrolysis of the 6-fluoro-7-substituted-2-(p-acetamido benzene sulphonamido) (1,3) benzothiazoles: (5)

The derivatives obtained were then hydrolyzed by boiling them in 50 ml of 80% acetic acid for 4 to 5 hrs and the contents were poured onto crushed ice. The obtained hydrolyzed derivatives were filtered at suction and dried.

2.2.5. Synthesis of Schiff base by Grind stone method: (7)

Take equimolar benzthiazole derivatives (0.01mol) and Substituted benzaldehyde derivatives (0.01mol) in to a mortar, to this add 2.5mL of lemon juice and 5ml water. The reaction mixture was grounded for 15-30 min. The reaction monitored by TLC. After completion of reaction add 25ml of water and stirred product for 5min. Separated out solid was filtered, washed with water and recrystallized from ethanol to give the corresponding Schiff bases.

2.2.6. Synthesis of Benzthiazole-azetidinone derivatives (PN1 to PN5): (8)

To the benzthiazole Schiff base compounds (0.01mol) in absolute benzene (100 ml), add triethylamine (2-3 drops) and chloroacetylchloride (0.02 mol) were added drop by drop, stirr the mixture for 1hr, further the reaction mixture refluxed for 1 hour. The reaction was monitored by TLC. The reaction mixture was cooled and poured into ice. The solid thus obtained was filtered and recrystallized from ethanol.



2.3. Physical and Spectral data of the compounds:

4-(benzylideneamino)-N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl) benzenesulfonamide (Compound PN-1)

Yield 78%, mp218⁰C. IR Spectrum, ν , cm⁻¹: 3200 NH₂ (3°) stretching, 3000 Ar-CH stretching, 1630 C=O stretching, 1420 Aromatic C=N stretching, 750 Aromatic C-Cl, 620 C-F. ¹HNMR Spectrum, δ , ppm: (CDCl₃): 4.0 s (1H, NH), 7.20-8.09 m (11H, Ar-H), 8.39 s (1H, CH=N). Mass (EI) m/z: 445 (M)⁺, 446 (M+1)⁺. Found %: C 53.84; H 2.95; Cl 7.94; F 4.27; N 9.44; O 7.17; S 14.36. C₂₀H₁₃ClFN₃O₂S₂. Calculated, %: C 53.87; H 2.94; Cl 7.95; F 4.26; N 9.42; O 7.18; S 14.38.

N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-4-(4-chlorobenzylidene) amino benzenesulfonamide (Compound PN-2)

Yield 72%, mp225⁰C. IR Spectrum, ν , cm⁻¹: 3210 3° NH₂ stretching, 3100 Ar-CH stretching, 1620 C=O stretching, 1430 Aromatic C=N stretching, 710 Aromatic C-Cl, 790 p-Cl) ¹HNMR Spectrum, δ , ppm: (CDCl₃): 4.0 s (1H, NH), 7.20-8.09 m (10H, Ar-H), 8.39 s (1H, CH=N). Mass (EI) m/z: 478 (M)⁺, 479 (M+1)⁺. Found %: C 50.00; H 2.51; Cl 14.73; F 3.95; N 8.76; O 6.62; S 13.32. C₂₀H₁₂Cl₂FN₃O₂S₂. Calculated, %: C 50.01; H 2.52; Cl 14.76; F 3.96; N 8.75; O 6.66; S 13.35.

N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-4-((2-hydroxybenzylidene) amino) benzenesulfonamide (Compound PN-3)

Yield 68%, mp227⁰C. IR Spectrum, ν , cm⁻¹: 3300 3° NH₂ stretching, 3100 Ar-CH stretching, 1620 C=O stretching, 3400 -OH, 1480 Aromatic C=N stretching, 720 Aromatic C-Cl) ¹HNMR Spectrum, δ , ppm: (CDCl₃): 4.0 s (1H, NH), 5.0 s (1H, OH) 6.76-8.09 m (10H, Ar-H), 8.39 s (1H, CH=N). Mass (EI) m/z: 461 (M)⁺, 462 (M+1)⁺. Found %: C 52.01; H 2.82; Cl 7.65; F 4.10; N 9.11; O 10.35; S 13.32. C₂₀H₁₃ClFN₃O₃S₂. Calculated, %: C 52.00; H 2.84; Cl 7.68; F 4.11; N 9.10; O 10.39; S 13.35.

N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-4-((4-hydroxy-3-methoxybenzylidene) amino) benzenesulfonamide (Compound PN-4)

Yield 72%, mp215⁰C. IR Spectrum, ν , cm⁻¹: 3200 3° NH₂ stretching, 3100 Ar-CH stretching, 1620 C=O stretching, 1150 -OCH₃, 3600 -OH, 1430 Aromatic C=N stretching, 720 Aromatic C-Cl) ¹HNMR Spectrum, δ , ppm: (CDCl₃): 3.73 s (3H, OCH₃), 4.0 s (1H, NH), 5.0 s (1H, OH) 6.65-8.09 m (9H, Ar-H), 8.39 s (1H, CH=N). Mass (EI) m/z: 491 (M)⁺, 492 (M+1)⁺. Found %: C 51.24; H 3.06; Cl 7.20; F 3.85; N 8.53; O 13.00; S 13.32. C₂₁H₁₅ClFN₃O₄S₂. Calculated, %: C 51.27; H 3.07; Cl 7.21; F 3.86; N 8.54; O 13.01; S 13.35.

N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-4-((4-nitrobenzylidene) amino) benzenesulfonamide (Compound PN-5)

Yield 75%, mp228⁰C. IR Spectrum, ν , cm⁻¹: 3200 3° NH₂ stretching, 3000 Ar-CH stretching, 1630 C=O stretching, 1720 p-NO₂, 1420 Aromatic C=N stretching, 750 Aromatic C-Cl. ¹HNMR Spectrum, δ , ppm: (CDCl₃): 4.0 s (1H, NH), 7.20-8.22 m (10H, Ar-H), 8.39 s (1H, CH=N). Mass (EI) m/z: 489 (M)⁺, 490 (M+1)⁺. Found %: C 48.90; H 2.44; Cl 7.20; F 3.85; N 11.40; O 13.00; S 13.32. C₂₀H₁₂ClFN₄O₄S₂. Calculated, %: C 48.93; H 2.46; Cl 7.22; F 3.87; N 11.41; O 13.04; S 13.35.

2.4. Pharmacological Evaluation:

Anti-Cancer Activity carried by MTT assay

MTT is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, coloured (dark purple) formazan product. The cells are then solubilised with an organic solvent (eg. DMSO, Isopropanol) and the released, solubilised formazan reagent is measured spectrophotometrically. Since reductions of MTT can only occur in metabolically active cells the level of activity is a measure of the viability of the cells.

Materials

A549 (Lung Carcinoma), Dulbecco's Modified Eagle Media (DMEM) with low glucose -Cat No-11965-092 (Gibco, Invitrogen), Fetal bovine serum (FBS) - Cat No



-10270106(Gibco, Invitrogen), Antibiotic – Antimycotic 100X solution (Thermofisher Scientific)- Cat No-15240062

Protocol

Cytotoxicity

The cells were seeded a 96-well flat-bottom micro plate and maintained at 37°C in 95% humidity and 5% CO₂ for overnight. Different concentration (400, 200, 100, 50, 25, 12.5 μg/ml) of samples were treated. The cells were incubated for another 48 hours. The wells were washed twice with PBS and 20 μL of the MTT staining solution was added to each well and plate was incubated at 37°C. After 4h, 100 μL of DMSO was added to each well to dissolve the formazan crystals, and absorbance was recorded with a 570 nm using micro plate reader.

Formulae

Surviving cells (%) = Mean OD of test compound / Mean OD of Negative control × 100

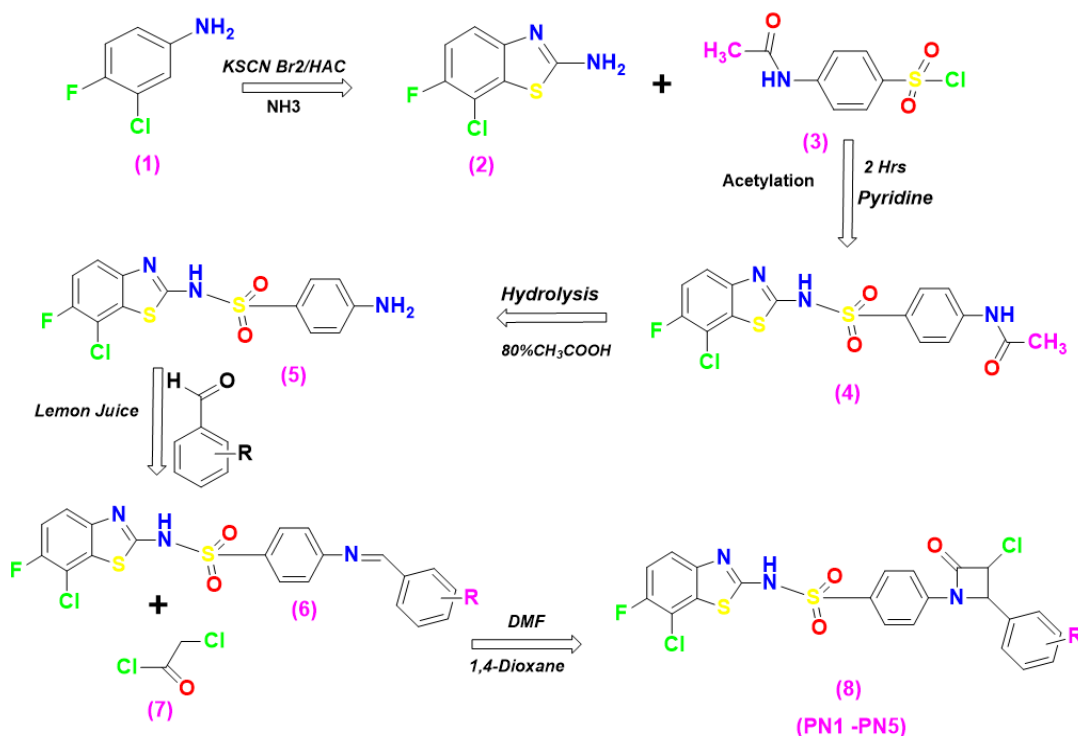
Using graph Pad Prism Version 5.1, we calculate the IC₅₀ of compounds.

3. Results and Discussion

3.1. Chemistry:

Synthesis of 4-(benzylideneamino)-N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl) benzenesulfonamide was achieved with an efficient synthetic route outlined in Scheme 1. The present work involved the reflux of the benzthiazole Schiff base compounds (0.01mol) in absolute benzene (100 ml), and addition of triethylamine (2-3 drops) chloroacetylchloride (0.02 mol) were added drop by drop, stir the mixture for 1hr, to obtain the newer effective compounds. The chemical structures of the title compounds (PN1– PN5) were established using spectroscopic evidences by IR, NMR and Mass. Detailed spectral data is given in experimental protocols.

Scheme-1



**Fig. 1 Synthetic scheme of benzothiazole- azetidinone**

S.no	Compound code	R
1	PN1	-H
2	PN2	p-Cl
3	PN3	o-OH
4	PN4	3-OCH ₃ , 4-OH
5	PN5	p-NO ₂

3.2. In silico studies

3.2.1. Molecular descriptors and drug likeness properties

Some physicochemical parameters of the synthesized compounds were predicted and listed in Table 1. Molecular properties such as partition

coefficient, Molecular weight, H-bond acceptors and donors, Topological polar surface area and Rotatable bonds of a molecule were evaluated by Swiss ADME. From the results obtained, it was found that most of the compounds obeyed Lipinski rule of five by possessing good oral bioavailability.

Table 1: Calculation of physicochemical properties of newly designed benzothiazole- azetidinone analogs

S.no	Compound code	MW	LOGP	TPSA	HBA	HBD	ROTB	N Viol.
1	PN1	445.92	2.92	79.37	5	1	5	0
2	PN2	478.36	2.75	108.04	5	1	5	0
3	PN3	461.92	2.37	128.27	6	2	5	0
4	PN4	491.94	2.65	137.50	7	2	6	0
5	PN5	489.92	2.95	79.37	7	1	6	0

*LOGP- Lipophilicity; TPSA- Topological Surface Area; MW - Molecular Weight; HBA – Hydrogen bond acceptors; HBD – Hydrogen bond donors; N Viol. - Number of Violations; ROTB- Number of Rotatable Bonds.

3.2.2. Bioactivity

The bioactivity scores of the compounds were calculated and reported in Table 2 for their GPCR ligand, kinase inhibitor, protease inhibitor, ion channel inhibitor, nuclear receptor ligand and enzyme inhibitor activities. As a general rule, larger is the bioactivity score, higher is the probability that investigated compound will be active. Therefore, a molecule having bioactivity score more than 0.00 is most likely to

possess considerable biological activities, while values - 0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive. The obtained results revealed that the investigated novel compounds are biological active molecules and will produce the physiological by interacting with GPCR ligands, nuclear receptor ligands, protease inhibitor and other enzymes.

Table 2: Bioactivity scores of benzothiazole- azetidinone derivatives

S.no	Compound code	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor	Protease Inhibitor	Enzyme Inhibitor



1	PN1	-0.26	-0.40	-0.25	-0.50	-0.31	-0.21
2	PN2	-0.26	-0.39	-0.26	-0.49	-0.31	-0.21
3	PN3	-0.26	-0.38	-0.26	-0.41	-0.31	-0.18
4	PN4	-0.26	-0.44	-0.24	-0.43	-0.35	-0.20
5	PN5	-0.26	-0.39	-0.24	-0.48	-0.30	-0.21

3.2.3. Biological Evaluation

The synthesized compounds subjected to MTT and the IC₅₀ Values were shown in Table-3. Among all the

synthesized compounds Compound PN-4 showed good potent activity with having least IC₅₀ Value.

Table 3: IC₅₀ Value of Compounds in µg/ml

Sample code	A549
PN-1	162.24
PN-2	172.21
PN-3	159.27
PN-4	155.39
PN-5	165.43
Gefitinib	151.26

Table 4. Mean Cell Viability of synthesized compounds at Various Concentrations

Concentration µg/mL	PN-1	PN-2	PN-3	PN-4	PN-5	Standard Gefitinib
400.0	27.38	34.64	25.04	21.32	31.54	19.77
200.0	43.65	41.50	39.75	29.12	38.83	22.93
100.0	57.19	47.75	52.45	37.54	42.24	48.58
50.0	62.75	51.15	58.21	42.45	46.32	62.32
25.0	76.24	62.22	70.84	51.58	57.14	74.25
12.5	62.66	77.69	81.26	66.14	71.42	89.28
Negative Control	100					



Conclusion:

The present study reported the successful synthesis of (PN-01 to PN-05) Five novel 2-azetidinone-benzothiazole derivatives by conventional method. The newly synthesized compounds were characterized by Spectral studies [FT-IR, H-NMR & MASS]. All the synthesized derivatives were screened for Invitro anti-cancer activity. Invitro method was assessed by using MTT method by using (A549) Lung Carcinoma cell line. Among the all five derivatives PN-4 exhibited more potent activity with less IC₅₀ values. Further investigations need to be done like Invivo studies and molecular Dynamics to know detailed information about stability of the novel compounds and their relationship between structure and biological activity with living cells.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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