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RESEARCH ARTICLE

SYNTHESIS OF SOME NOVEL BENZOTHIAZOLE ANALOGUES FOR ANTIMICROBIAL, ANTIOXIDANT, AND ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

Benzothiazole analogues have played an important role in the field of medicinal chemistry for current drug discovery and development processes. It becomes a choice of lead compound for new researchers due to its wide variety of pharmacological activities and so on. We have synthesized some novel 7-chloro-6-fluoro benzothiazole analogues keeping the nitro group in their structure as the importance of fluorine and the nitro group has always taken great attention for long for their interesting abilities to enhance the pharmacological activity of the drug.

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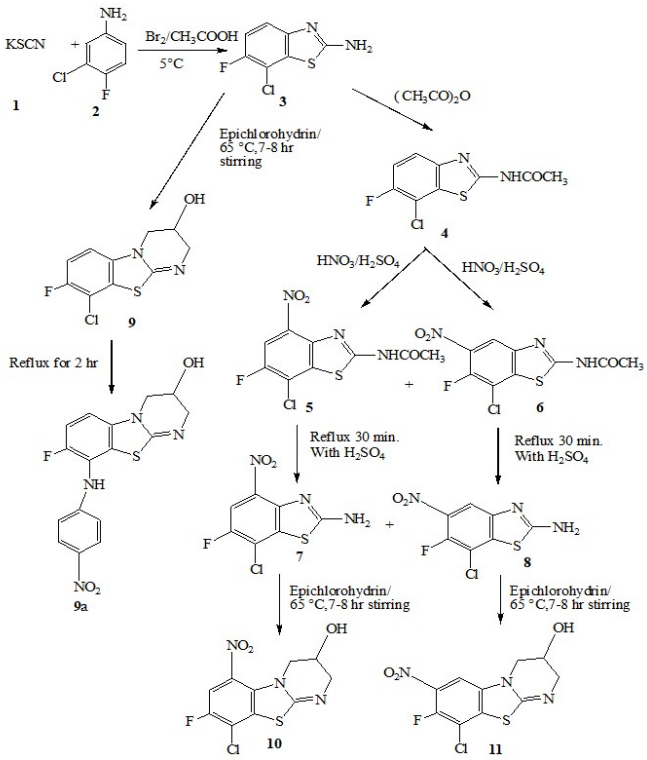
INTRODUCTION

Benzothiazole is a class of nitrogen and sulfur-containing heterocyclic ring system that contains one benzene ring fused to a thiazole ring. The benzothiazole ring system was originally found in various marine and terrestrial natural compounds, which are widely used for anti-viral activity (Sulthana, 2019), anti-inflammatory activity (Gurupadayya, 2011; Reddy, 2013), anti-oxidant activity (Reddy, 2013), anticonvulsant activity (Reddy, 2013), anti-cancer activity (Naresh, 2013; Pathak, 2020), anti-bacterial activity (Catalano, 2021), anti-diabetic activity (Su, 2006), anthelmintic activity (Omar, 2017), anti-tuberculosis activity (Liu, 2021), anti-parkinsonism activity (Hazra, 2011), inhibitors of several enzymes (Hazra, 2011) and so on.Heterocycles containing Fluorine atoms always get great attention due to their unique properties. In fact, in the current drug design and discovery, fluorine is ranked second after nitrogen as the "favorite heteroatom". In medicinal chemistry, the incorporation of fluorine in small molecules instructs a significant enhancement of their biological activities compared to non-fluorinated compounds.

The incorporation of fluorine into pharmaceutical and veterinary drugs to enhance their pharmacological properties has become almost standard practice. In 2006, the best - and the second - best - selling drugs in the world were Lipitor (atorvastatin calcium) by Pfizer and Advair (fluticasone propionate and salmeterol) by GlaxoSmithKline which contain 1 and 3 fluorine atoms, respectively. So many other USFDA-approved drugs are also there which contains fluorine atom in their structure like Mefloquine hydrochloride (anti-malarial), Fluconazole (antifungal) Pantoprazole (antiulcer) etc. The role of the nitro group in medicine has also become a common practice now a day because of its ability to easily undergo reduction at the molecular level where follow-up bond cleavage reactions can generate localized.PA824 (pretomanid), has recently been approved by the FDA for use in combination with bedaquiline and linezolid for the treatment of patients with extensively drug-resistant tuberculosis. Nitrobenzothiazinones like BTZ043 and pBTZ169 have outstanding anti-tuberculosis activity and are currently in advanced clinical trials. PA824 and the BTZs for both of them, the nitro group plays an essential role. It is mostly recognized that the biological activities relate to the reduction properties of the nitro group.

Scheme



MATERIALS AND METHODS

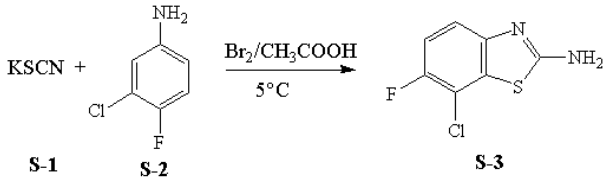
Requirements

Chemicals: Glacial Acetic Acid, Potassium Thiocyanate, 4-Fluoro-3-Chloro Aniline, Bromine, Ammonia Solution, Toluene, Acetic Anhydride, HNO_3, H_2SO_4, Epichlorohydrin, DMF, *P*-Nitro Aniline, Methanol, Cyclohexane, Acetone, Ethyl Acetate, Ethanol.

***All the chemicals used, are from – Sigma-Aldrich and Merck**

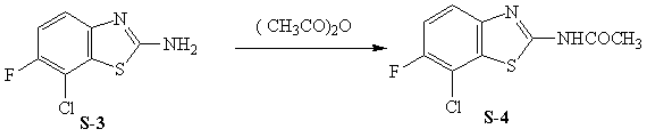
Apparatus: Heating Mantle**,** Magnetic Stirrer with Hot Plate**,** Burette**,** Pipette**,** Beaker**,** Conical Flask**,** Thermometer**,** TLC Plate**,** Funnel**,** Round Bottom Flask, etc.

Methodology



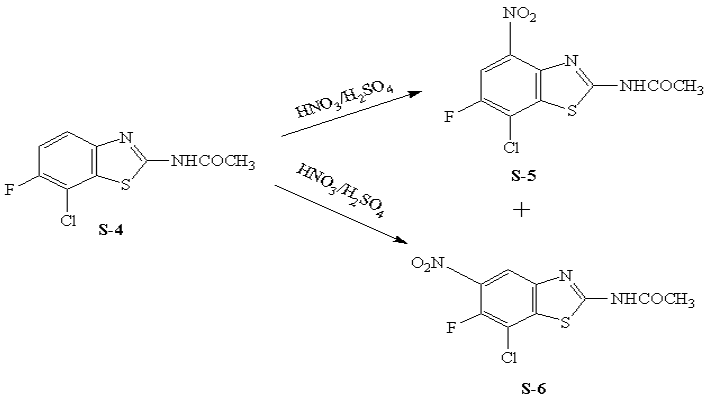
S-1 S-2 S-3

Synthesis of 7-chloro-6-fluorobenzo(*d*)thiazol-2-amine (S-3): To glacial acetic acid (40 mL) precooled at 5ºC were added 40 g (0.4123 mol) potassium thiocyanate and 7.25 g (0.0498 mol) of 4-fluoro-3-chloro aniline. The mixture was stirred, during which 6 mL of bromine in 24 mL of glacial acetic acid was added at such a rate that the temperature was not allowed to rise beyond 5ºC, for a period of 2 h. The stirring was continued for an additional 2 h at the same temperature, and further at room temperature for 10h. It was then kept stand for overnight during which an orange precipitate was settled down at the bottom. 30 mL of water was added and the slurry was heated at 85ºC on a steam bath and filtered hot. The filtrate was cooled and neutralized with a strong ammonia solution to pH 6, and a light yellow precipitate obtained was collected. The resulting product was recrystallized by toluene.

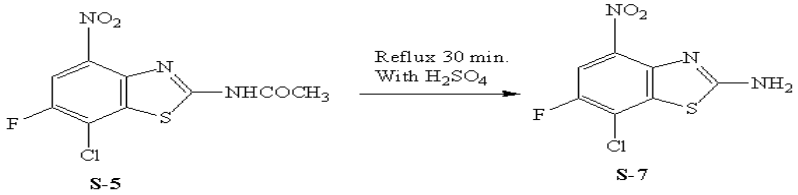


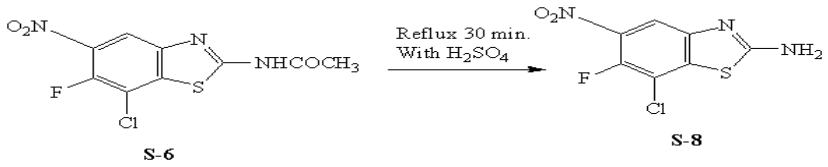
S-3 S-4

Synthesis of N-(7-chloro-6-fluorobenzo(*d*)thiazol-2-yl)-acetamide (S-4): A mixture of compound 3, 2.025 g (0.01 mol), and 10 mL of acetic anhydride was refluxed for 1 h. After that, the reaction mixture was cooled, and the separated solid was heated with water, filtered, and washed with water. The product was then recrystallized in ethanol. Yield 70%, MP 232–233°C, whitish needle-shaped crystal.

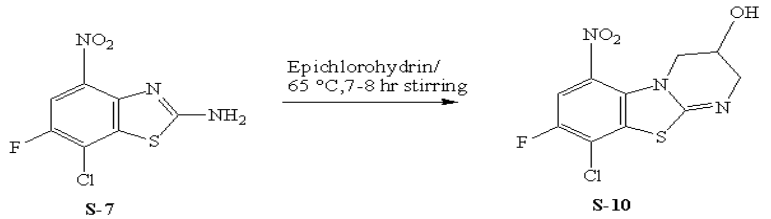


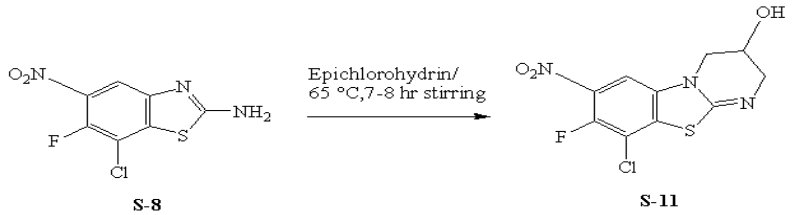
Synthesis of N-(7-chloro-6-fluoro-4-nitrobenzo(d)thiazol-2-yl) acetamide (S-5) & N-(7-chloro-6-fluoro-5-nitrobenzo(d)-thiazol-2-yl)acetamide (S-6): A mixture of compound 5, 100 mg (0.000409 mol), and 0.3 mL of ice-cold conc. H2SO4 was stirred under ice-cooled conditions. To this 0.1 mL conc. HNO3 was added drop-wise and continued to be stirred at room temperature for 2 h. Then, 0.1 mL conc. Stirred overnight after adding HNO3 further to the reaction mixture. The reaction mixture was poured into a large amount of water. The solids obtained were filtered and washed with water thoroughly and dried under a vacuum. The compound obtained was a mixture of 6 & 7, which was separated by column chromatography employing n-hexane/ethyl acetate (9:1) as an eluent.

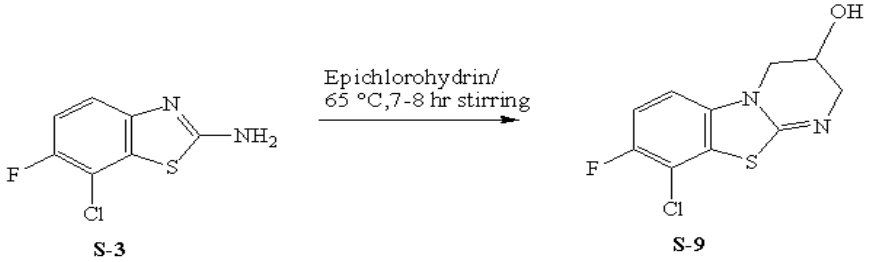




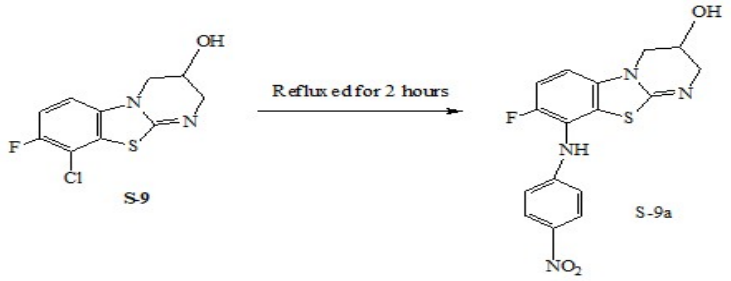
Synthesis of 7-Chloro-6-fluoro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*) thiazole, 7-Chloro- 6-fluoro- 5-nitro-(2,3 (5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole and 7-Chloro-6-fluoro-4-nitro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole (S-9, S-10 &S-11): Epichlorohydrin (20mmol) was added to a solution of amine (10mmol) in glacial acetic acid (15ml) ,then stirred at 65°C for 7hr.The acetic acid was driven off by evaporation, Then add distilled water to the oily residue. The unreacted amine was precipitated and filtered off. The filtrate was evaporated off and the residue was treated with concentrated dry acetone. The residue was filtered off and recrystallized from absolute ethanol.







Synthesis of 7-Chloro-6-fluoro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole derivatives (S-9a): Equimolar quantity of substituted aniline and the synthesized compound S-9 was refluxed for 2 hours in oil bath in presence of DMF. The reaction mixture was cooled and some crushed ice was poured into it. The separated solid product was then filtered off, dried, and crystallized using alcohol and benzene.



Characterization of the Compounds

- **7-chloro-6-fluorobenzo(*d*)thiazol-2-amine (S-3):**Yield 65%; slight yellowish crystalline powder; M.P 180–182ºC; TLC – Cyclohexane: Ethyl acetate (9:1), Rf value- 0.425, IR (ATR) (-C-Cl) 750Cm^{-1}, (-C-F) 1350 Cm^{-1}, (-N-H) 3480 Cm^{-1}.

- **N-(7-chloro-6-fluorobenzo(*d*)thiazol-2-yl)-acetamide (S-4)**:Yield 70%, M.P 232–233^{0}C, whitish needle-shaped crystal; TLC –Acetone:EA (1:1), Rf value- 0.491, IR (ATR) (-C-Cl) 750Cm^{-1}, (-C-F) 1350 Cm^{-1}, (-N-H) 3480 Cm^{-1}(-C=O) 1680Cm^{-1}
- **N-(7-chloro-6-fluoro-4-nitrobenzo(*d*)thiazol-2- yl) acetamide (S-5):**Yield 60%; M.P 267–268ºC; White crystalline solid. TLC – n-Hexane: EA (9:1), Rf value- 0.630. IR (ATR) (-C-Cl) 750Cm^{-1} , (-C-F) 1350 Cm^{-1} , (-N-H) 3480 Cm^{-1} (-C=O) 1680 Cm^{-1} ,(-N=O) 1550 Cm^{-1}

- **N-(7-chloro-6-fluoro-5-nitrobenzo(*d*)- thiazol-2-yl)acetamide (S-6)**:Yield 10%; M.P 273–274ºC; Yellow crystalline solid powder. TLC – n-Hexane: EA (9:1), Rf value- 0.612.IR (ATR) (-C-Cl) 750Cm^{-1}, (-C-F) 1350 Cm^{-1} , (-N-H) 3480 Cm^{-1}, (-C=O) 1680 Cm^{-1},(-N=O) 1550 Cm^{-1}

- **7-chloro-6-fluoro-4-nitrobenzo(*d*)thiazol-2-amine(S-7):**Yield 40%; M.P 277-278^{0}C; White colour crystalline solid. TLC –Chloroform: Methanol(8:2), Rf value- 0.793. IR (ATR) (-C-Cl) 750Cm^{-1} , (-C-F) 1350 Cm^{-1} , (-N-H) 3480 Cm^{-1} ,(-N=O) 1550 Cm^{-1} .

- **7-chloro-6-fluoro-4-nitrobenzo(*d*)thiazol-2-amine(S-8):**Yield 57%; M.P 281–282ºC; Buff colour crystalline solid. TLC –Chloroform: Methanol(8:2), Rf value- 0.811.IR (ATR) (-C-Cl) 750Cm^{-1}, (-C-F) 1350 Cm^{-1} , (-N-H) 3480 Cm^{-1},(-N=O) 1550 Cm^{-1}

- **7-Chloro-6-fluoro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole (S-9):**Yield 70%, M.P , 256–257^{0}C, Light buff colour powder. TLC – Cyclohexane:Ethyl acetate (EA) (9:1), Rf value- 0.649. IR (ATR) (-C-Cl) 750Cm^{-1} , (-C-F) 1350 Cm^{-1} , (-O-H) 3200-3400 Cm^{-1} ,NMR (Solvent DMSO) CH (7.82d, *J*-1.0), CH (8.15d, *J*-1.08), CH_2 (4.48, 4,27 d*J*-1.73, 2.02), CH (3.32 m), CH_2 (1.90, 1.24d) OH (2.01d *J*-1.06)

- **7-Chloro-6-fluoro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole derivatives (S-9a):**Yield 62%, M.P 266-267^{0}C;Greenish yellow colour solid TLC – Cyclohexane: Ethyl acetate(EA) (8:2), Rf value- 0.708. IR (ATR) (-C-F) 1350 Cm^{-1} , (-O-H) 3200-3400 Cm^{-1} ,(-N=O) 1550 Cm^{-1}

- **7-Chloro-6-fluoro-4-nitro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole (S-10):**Yield 61%, M.P-285-286^{0}C, Buff colour , TLC-Chloroform: EA (1:1), Rf value- 0.526. NMR (Solvent DMSO) CH (8.33 s), CH_2 (2.89, 2.68 d), CH (2.33m), CH_2 (1.55, 1.24 d *J*- 3.19, 2.0), OH (1.99 d *J* -2.30)

- **7-Chloro-6-fluoro-5-nitro-(2,3(5-hydroxy-imidazolo))1,3-benzo(*d*)thiazole(S-11):**Yield 48%, M.P-293-294^{0}C, Brownish colour powder, TLC- Chloroform: Methanol (8:2), Rf value- 0.877.NMR (Solvent DMSO) CH (8.14s) CH_2 (2.89, 2.68 d, *J*-3.17, 2.0) CH (2.33m) CH_2 (1.55, 1.24 d , *J*-2.0, 3.17) OH (1.99 d)

Activity: A biological or pharmacological activity describes the beneficial or adverse effects of any drug on living matters. Among the various properties of chemical compounds, pharmacological/biological activity plays a vital role since it suggests the uses of the compounds in medical applications. However, chemical compounds may have some adverse and toxic effects which may inhibit their use in medical practice. Here we have performed 3 different activities - Antimicrobial activity, Anti-oxidant activity, and Anti-inflammatory activity.

Materials and Method

❖Antimicrobial Activity

Requirements: Beef extract (10g), peptone(10g), sodium chloride(5g), distilled water(1000ml), agar(1-2%), conical flask, volumetric flask, glass rod, burner, wire gauge, autoclave, pH meter, microbial inoculum, petri dish, measuring cylinder, needle, inoculating loop, forceps, incubator, drugs, etc.

Methods

Preparation and sterilization of Nutrient Agar media:

- Weigh all the additives separately and add them to a suitable container.
- Dissolve with stirring in hot conditions.
- Add 1-2% agar powder in nutrient broth before sterilization.
- Heat on a water bath with stirring till the agar completely dissolved.

- Filter if necessary in warm conditions.
- Adjust pH 7.2-7.4
- Transfer to a suitable flask and sterilize by autoclave at 15*lb* pressure and 115°C temperature for 30 minutes.

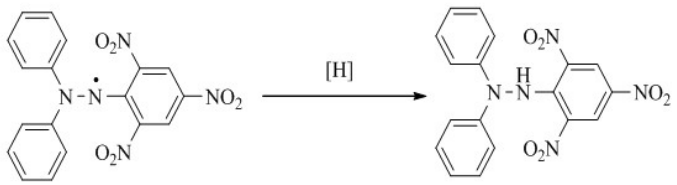
Experimental procedure

This method is based on the diffusion of an antibiotic through the cavity of a solidified agar layer of a petri dish or plate used for the study. Then the growth of inoculated microorganisms is inhibited completely in a round-shaped area 'zone' around the cavity, which contains the solution of antibiotic.

- Prepared microbial suspension and add it with the media on a petri dish and mixed well.
- Prepared the solution of a known antibiotic (Standard) and an unknown drug (Test).
- Then applied the drug solution to the cavities prepared in the agar plate
- Leave all the plates for 1-4 hours at room temperature.
- Incubate the plate at 20-30°C for 18 hours.
- Then observe the zone of inhibition around the cavity.

Anti-Oxidant Activity

DPPH method: DPPH (2,2-diphenyl-1-picryl-hydrazyl) radical scavenging activity (RSA) evaluation is a standard assay in antioxidant activity studies. It deals with a fast technique for screening the radical scavenging activity of particular compounds. A freshly prepared DPPH solution exhibits a deep purple color with an absorption maximum of 517 nm. This purple color usually disappears when an antioxidant remains in the medium. Thus, the antioxidant molecule can quench DPPH free radical (i.e., by providing hydrogen atoms or by electron-donating, conceivable) and convert them to a colorless/bleached product (i.e., 2,2-diphenyl-1-picrylhydrazine, or a substituted analogues hydrazine), outlined in resulting in a decrease in absorbance. The more rapidly the absorbance decrease, the more potent the antioxidant activity of the compounds.



α,α-diphenyl-β-picryl hydrazyl (DPPH) α,α-diphenyl-β-picryl hydrazine

Requirements: DPPH, methanol, ascorbic acid.

Preparation of solutions: DPPH stock solution (100 μM): 39.4 mg of DPPH was dissolved in one liter of analytical grade methanol, and 10 mg of the synthesized compound dissolve into the 10 mL of analytical grade methanol. Ascorbic acid was taken as standard.

Procedure: 5 to 50 μL (5 to 50 μg) of ascorbic acid and synthesized compounds were taken in different test tubes. Then the volume was adjusted to 1000 μL with methanol. To this 4 mL of methanolic solution of DPPH was added, shaken well and the mixture was allowed to stand at room temperature for 20 minutes. The control was prepared as above without compound. The readings were taken for blank (methanol), control, and sample at 517 nm.

Scavenging activity was expressed by way of the inhibition percentage, calculated using the formula,

$$\% \text{ Anti radical activity} = \frac{\text{Control Abs.} - \text{Sample Abs.}}{\text{Control Abs.}} \times 100$$

- **Anti-inflammatory activity**

- ***In vitro* methods:**

Requirements: DMSO, Diclofenac sodium, bovine serum albumin, incubator, water bath, Phosphate buffer, UV-Visible Spectrophotometer.

Denaturation of bovine serum albumin: The synthesized compounds were screened for *in-vitro* anti-inflammatory activity using the Protein denaturation method. The standard drug and test compounds were dissolved in a minimum amount of dimethyl sulfoxide (DMSO) and diluted with phosphate buffer (0.2 M, pH 7.4). The final concentration of DMSO in all solutions was less than 2.0%. Test solution (1 ml) containing different concentrations of the drug was mixed with 1 ml of 1% mm Bovine albumin solution in phosphate buffer and incubated at 270±1°C in an incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 600±1°C in a water bath for 10 min. After cooling the turbidity was measured at 660 nm (UV-Visible Spectrophotometer Shimadzu-1700). Diclofenac sodium was used as a standard drug. The results were tabulated in Table.

$$\% \text{ of inhibition} = \frac{[\text{Abs}_{660\ (\text{Control})} - \text{Abs}_{660\ (\text{Test})}]^* 100}{[\text{Abs}_{660\ (\text{Control})}]}$$

RESULTS

Antibacterial Activity: Synthesized compounds were screened for antibacterial activity using the disc plate method at concentrations 25, 50, and 100µg/ml using gram +ve and gram –ve strains. The strains used for the screening are *Bacillus subtilis*, *Staphylococcus aureus* (gram +ve), *Pseudomonas aeruginosa*, *and Escheria coli* (gram –ve strains). Ciprofloxacin was taken as the standard drug. Among the screened compounds S-9a, S-11, S-2D(iii) and S-2D-(iv) had shown potent activity against the standard.

1.Antibacterial activity of the synthesized compounds

COMPOUNDS	MEAN ZONE OF INHIBITION (mm)											
	B.Subtilis			*S.aureus*			*P.aeruginosa*			*E.Coli*		
	25µg /disc	50µg/disc	100µg/disc	25µg /disc	50µg/disc	100µg/disc	25µg /disc	50µg/disc	100µg/disc	25µg /disc	50µg /disc	100µg/disc
Control	1.0	1.08	1.1	0.8	1.06	1.11	1.4	1.7	2.1	0.7	1.09	1.16
S-9	6.5	6.8	9	8	8.6	11	6	7	9	7	8	10.2
S-9a	7.1	9.9	12	14	17	18	9.9	10	11.5	8.6	9.1	13
S-10	8	8	9.1	7	8	8.3	8	9	9.5	7.9	8.3	9
S-11	9	9.4	10.7	7.9	10.6	11	7	9	10.2	8	9.9	12
Standard	16			21			17			19		

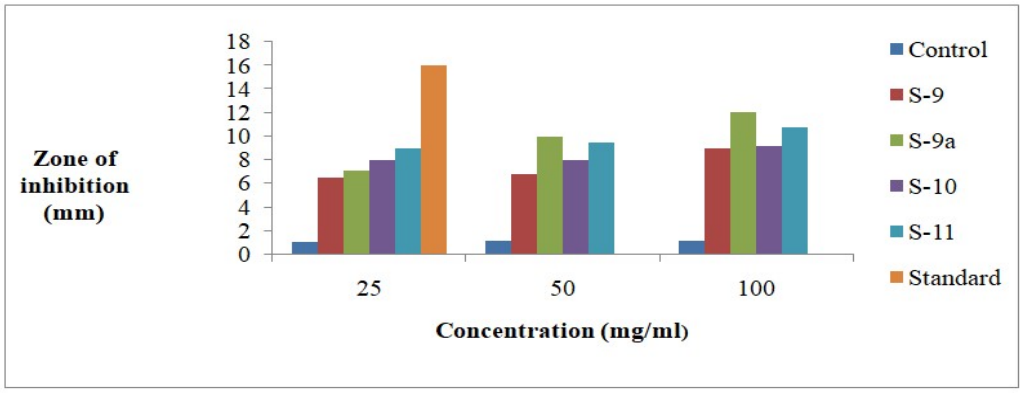


Fig. 1. Antibacterial activity against *Bacillus subtilis*

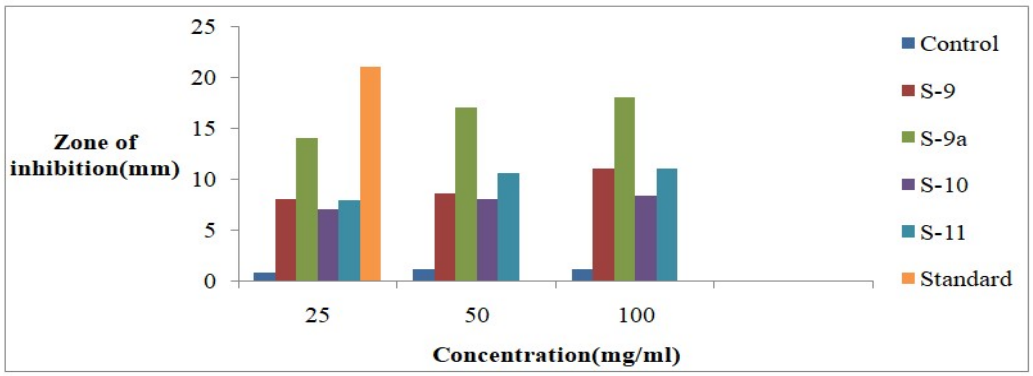


Fig. 2. Antibacterial activities against Staphylococcus aureus

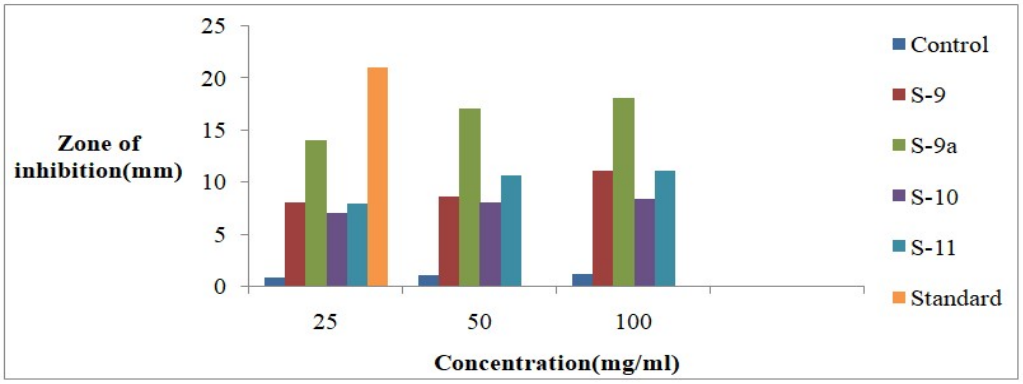


Fig. 3. Antibacterial activities against *Pseudomonas aeruginosa*

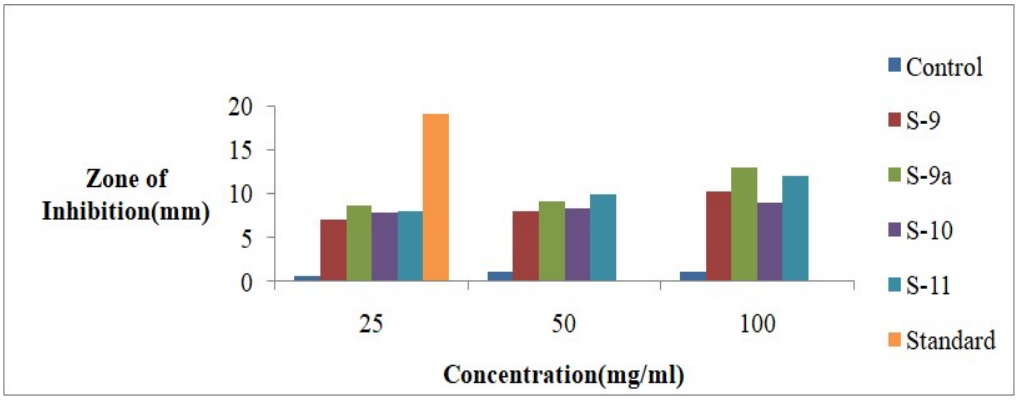


Fig. 4. Antibacterial activities against *Escheria coli*

Anti-Oxidant Activity: All the Synthesized compounds were screened for anti-oxidant activity. Compounds of different concentrations are screened for the activity using Ascorbic acid as standard. The % inhibition of the compounds at various concentrations is calculated from their absorbance values. Among the screened compounds S-9a, S-10, S-11, S-2D(i), S-2D(ii) and S-2D(iv)had shown potent activity against the standard.

Table 2. Anti-Oxidant activity of the synthesized compounds

Compounds	%radical scavenging method Concentrations (mg/ml)					
	0.5	1.0	1.5	2.0	2.5	3.0
Control	0	0	0	0	0	0
S-9	39.08	40.97	43.11	48.57	50.23	60.34
S-9a	33.52	36.38	39.08	47.92	63.99	97.41
S-10	32.09	37.66	40.12	52.00	58.94	90.86
S-11	40.17	44.09	47.88	56.35	71.73	96.03
Standard	54.39	57.56	68.18	79.93	85.97	99.8

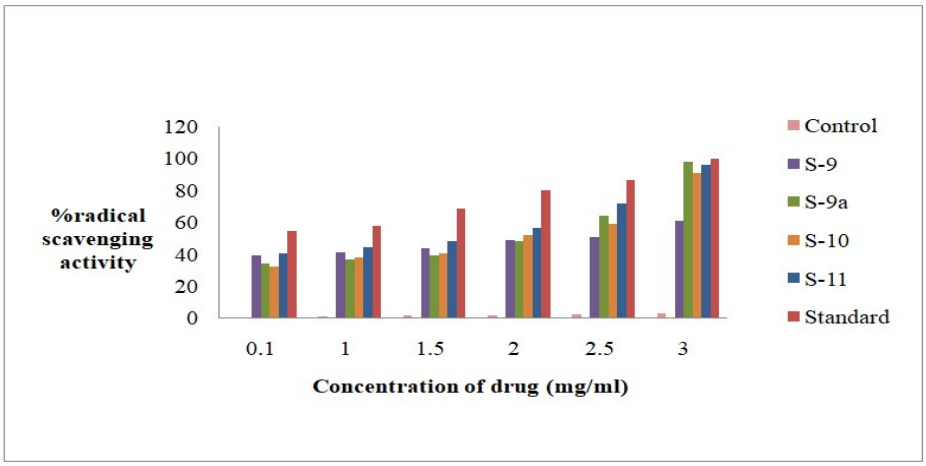


Fig. 5. Antioxidant activities of the synthesized compounds

Table 3. Anti-inflammatory activity of the synthesized compounds

Compounds	Absorbance value	% of denaturation
Control	0.973	0.0
S-9	0. 543	44.19
S-9a	0.197	87.5
S-10	0.321	67
S-11	0.303	66.15
Standard (Diclofenac Sodium)	0.012	84.33

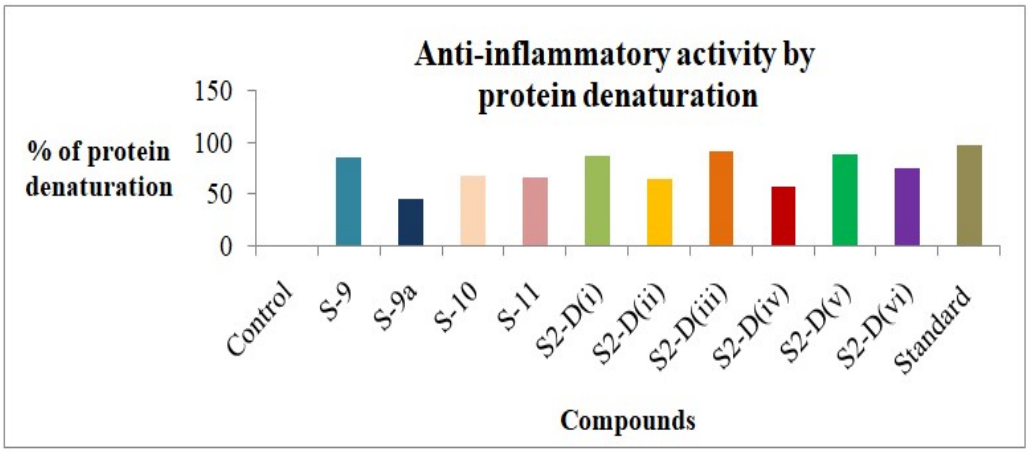


Fig. 6. Anti-inflammatory activities byprotein denaturation

DISCUSSION

Synthesized compounds were screened for antibacterial activity using the disc plate method at concentrations 25, 50, and 100µg/ml using gram +ve and gram –ve strains. The strains used for the screening are *Bacillus subtilis*, *Staphylococcus aureus* (gram +ve), *Pseudomonas aeruginosa*, *and Escheria coli* (gram –ve strains). Ciprofloxacin was taken as the standard drug. Among the screened compounds S-9a and S-11had shown potent activity against the standard drug. All the Synthesized compounds were screened for anti-oxidant activity. Compounds of different concentrations are screened for the activity using Ascorbic acid as standard. The % inhibition of the compounds at various concentrations is calculated from their absorbance values. Among the screened compounds S-9a, S-10, and S-11had shown potent activity against the standard. The synthesized compounds were screened for anti-inflammatory activity by the protein denaturation method. The compound S-9a had shown the most potent activity against the standard drug diclofenac sodium. It was observed that the nitro derivatives had shown a key role in all those different types of activities of the synthesized compounds and give interesting results compared to standard drug.

CONCLUSION

After this research, it can be concluded that the fluorine and nitrogen atom in the world of drug discovery plays a vital role in the inhibition of different microorganisms, inhibition of inflammation, and as antioxidants. The structure of benzothiazole is being using for a long before for its excellent activity with various pharmacological aspects. So we have chosen benzothiazole as a lead molecule for our research and study, keeping nitrogen and fluorine in their structure. We have synthesized 4 different compounds with or without nitro group. The nitro derivatives had shown more potent activity than the non-nitro derivatives compared to standard drug.

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