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DESIGN, SYNTHESIS, CHARACTERIZATION OF SUBSTITUTED 3-(BENZOTHIAZOLE)-2-(PHENYL)-THIAZOLIDIN-4-ONE HETEROCYCLIC COMPOUNDS AND ITS BIOLOGICAL EVALUATION

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Benzothiazole, thiazolidin-4-one, anti-oxidant, anti-inflammatory and antimicrobial

ABSTRACT

A new series of bracing thiazolidin-4-one containing substitution at N^3-benzothiazole obtained from azomethine derivatives. The dissimilar azomethine are prepared by reacting substituted 2-amino benzothiazole with aryl aldehyde in ethanol (*et-OH)* media in presence of catalytic glacial acetic acid. Then, the obtain dissimilar azomethine are cyclized with sulfanyl acetic acid in dimethyl formamide/1,4-diaxone medium with anhydrous Zn-chloride as catalyst by conventional way of synthesis to get the title compounds in acceptable yield. All the compounds are re-purified and subjected for structural and biological elucidation. Structure of the compounds was confirmed by spectroscopic analysis and some of the synthesized compounds showed significant to moderate antimicrobial activity over selected microorganism, and few compounds exhibited prominent antioxidant and anti-inflammatory activity and rest all shows satisfactory results.

INTRODUCTION

Drug design and development is an eternal field for contributing a new active chemical compounds over an early ineffective drugs on existing acquired resistance by pathogenic disease causing organism. Its intention is to overcome from plausible side effects, potency and efficacy of the present drugs, so a new entity has to be produced. The free radicals (ROS) are the chemical entities comprise unpaired electron. These are short lived, un-stable, highly reactive undergoes to accept electron to achieve stable configure ration. They acquired electrons from healthy cells in the body and damaging them loses their structure and function. These ROS binds on membrane lipids, nucleic acids, proteins and enzymes and other small molecules which leads to damage the cellular property and major contribute for aging and harmful diseases of aging such as CVS disease, cataracts, cancer, immune system decline, hepatic diseases, DM, inflammation, kidney failure, CNS dysfunction and stress among others. To defend against these radical species the antioxidants are brought in to research which interactively and

synergistically neutralize the ROS before they harm the healthy cells. According to Halliwell *et.al 1995* any substance that when present at low concentrations, compared to those of an oxidizable substrate. Significantly delays or prevents oxidation of that substrate. They undergoes mechanism like Inhibition of generation and scavenging capacity against ROS/RNS (Reactive Nitrogen Species), reducing capacity, metal chelating capacity, inhibition of oxidative enzymes[1]. In view of literature the grandness of thiazolidin-4-one substitute at 2nd, 3rd or 5th position with active group's posses various pharmacological activities like bactericidal ,fungicidal, hypoglycaemia, anti-malarial, immunosuppressive, anticonvulsant, anti-tubercular, anticancer, anti-inflammatory activity, anthalmintic, anti-histaminic and so on [2,3]. These bring on to prepare some active compounds bare the thiazolidin-4-one with active benzothiazole on its surface. Benzothiazole plays a vital role in many diseases. Various marketed formulations such as Ethoxzolomide (diuretic), Frentizole(antiviral and immuno suppressive agents), Riluzole (amyotrophic lateral sclerosis), Zopolrestat(antidiabetic) and several benzothiazole and its derivatives contain benzothiazole nucleus which were reported to exhibit anticancer potential[4,5]. Thiazole orange is an unsym-metrical cynine dye containing benzothiazole nucleus that has been reported to possess DNA intercalating ability [6, 7, 8]. Several tons of new drugs contain benzothiazole have been patented in recent years [9]. In the present research activity a series of new thiazolidin-4-one baring simple/fluoro substituted at benzothiazole at N^3 position have been synthesized to enhance the therapeutic efficacy [10].

MATERIALS AND METHODS: The chemicals and reagents employed in the titled work were purchased from Himedia, Fischer syntifics, Qualigens and Merck chemicals. The melting point for the compounds were determined by open capillary method which are incorrect, all the synthesized compounds are characterized and identified by FT-IR by KBr method using analytical technologies FT-IR spectrophotometer 2202. Some selected compounds were subjected to NMR spectroscopy (^{1}H & ^{13}C) by Bruker AVANCE III 500 MHz using TMS as internal standard in DMSO-d_6 for ^{1}H-NMR and Bruker UXNMR at 100 MHz for ^{13}C-NMR and Mass spectra by GC-MS(EI) for structural confirmation. All compounds are screened for antimicrobial by MIC tube dilution method, antioxidant for hydroxyl radical and hydrogen peroxide scavenging property and *In-vitro* anti-inflammatory by protein denaturation inhibition by using standard procedure with slight modification. From the obtain results it reveals compounds shows prominent activity against bacteria and fungi, few compounds shows significant anti-oxidant & anti-inflammatory activity, rest of the compounds are good to moderate in its activities. Results of the activities exhibited in table 2 & 3, Fig-3 & 4.

EXPERIMENTAL PROCESS:

***Step:1*- Synthesis of Substituted 2-amino benzthiazole[11]:**

The procedure adopted for the synthesis of simple/fluoro substituted 2-amino benzothiazole was discussed elsewhere [11] (Balaji P.N *etal* 2014) and obtained compounds were purified and its M.P are determined.

***Step:2*- Synthesis of azomethine from Simple / Substituted 2-amino benzothiazole[12]:**

An equimolar concentration of above obtain simple/substituted 2-amino benzothiazole (0.01M) with different aryl aldehyde (0.01M) was taken in to 100ml RB flask baring 30 ml of *etOH,* it is condensed over boiling water bath. After30 min to this reacting mixture 2-3 drops of glacial acetic acid/conc. sulphuric acid was added for catalytic purpose and the condensation was continued for ~ 6 hours. Later the mixture was cooled and poured into a crushed ice. The solid was

separated, then filtered, dried and re-crystallized by employing absolute alcohol.

***Step: 3*- Synthesis of title compound 4-thiazolidinone substituted benzothiazole at N^3 [13]:**

Above obtain azomethine of 0.005M was taken with 0.01M of Sulfanyl acetic acid in 30 ml of DMF/diaxone in a 100ml rb flask. To this anhydrous $ZnCl_2$ was added as catalyst and reflexes the mixture on heating mantle for ~12 hours with occasional shaking. Later, cool the mixture and pored it in to an beaker containing 50ml crushed ice (if needed neutralize with Pot. carbonate or Sod. carbonate) and the obtained precipitate was filtered, dried and re-crystallized by absolute alcohol. The reaction scheme is furnished shown in fig 1.

Spectroscopic characterization data of 4-thiazolidinone containing benzothiazole and its derivatives:

BTTz$_1$: 3-(1,3-benzothiazol-2-yl)-2-phenyl-1,3-thiazolidin-4-one :

Mol.formla: $C_{16}H_{12}N_2OS_2$, IR υ_{max}(KBr) cm^{-1}: 790(C-S), 1660(C=O), 1580(C=N), 1260(C-N), 1560(C=C), 3160(C-H Aromatic).

BTTz$_2$: 3-(1,3-benzothiazol-2-yl)-2-[4-(dimethylamino)phenyl]-1,3-thiazolidin-4-one :

Mol.formla: $C_{18}H_{17}N_3OS_2$, IR υ_{max}(KBr) cm^{-1}: 755(C-S), 1610(C=O), 1550(C=N), 1290(C-N), 1580(C=C), 3150 (C-H Aromatic). Mass (m/z) = 355.33

BTTz$_3$: 3-(1,3-benzothiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolidin-4-one :

Mol.formla: $C_{17}H_{14}N_2O_3S_2$, IR υ_{max}(KBr) cm^{-1}: 830 (C-S), 1665(C=O), 1540(C=N), 1180(C-N), 1585(C=C), 3070(C-H Aromatic), 1290(-OCH_3), 3480(-OH). ^{1}H-NMR (δ ppm in DMSO-d_6 solvent) 6.9-7.4(m, 4H, benzothiazole), 7.8-8.1(m, 3H, Ar-H), 2.1(s, 1H, -CH-), 3.45(s, 2H, -CH_2-), 3.85(s, 3H, OCH_3), 12.80(s, 1H, OH). ^{13}C-NMR (δ ppm in DMSO-d_6 solvent) 34.549 (-CH_2-Tzd), 59.98 (-OCH_3), 114.048,123.297,137.329,150.174(Ar-carbons),169.825(C=0).Mass(m/z)=358.18

BTTz$_4$: 3-(1,3-benzothiazol-2-yl)-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{17}H_{14}N_2O_2S_2$, IR υ_{max}(KBr) cm^{-1}: 810 (C-S), 1640(C=O), 1550(C=N), 1235(C-N), 1560(C=C), 3020(C-H Aromatic), 1260(-OCH_3). ^{1}H-NMR (δ ppm in DMSO-d_6 solvent) 7.1-7.3(m, 4H, benzothiazole), 7.5-7.7(m, 4H, Ar-H), 2.0(s, 1H, -CH-), 3.3(s, 2H, -CH_2-), 3.90(s, 3H, OCH_3).

BTTz$_5$: 3-(6-fluoro-1,3-benzothiazol-2-yl)-2-phenyl-1,3-thiazolidin-4-one :

Mol.formla: $C_{16}H_{11}N_2OS_2F$, IR υ_{max}(KBr) cm^{-1}: 815 (C-S), 1090(C-F), 1630(C=O), 1565(C=N), 1150(C-N), 1690(C=C), 3130(C-H Aromatic). Mass (m/z) = 330.76

BTTz$_6$: 2-(4-chlorophenyl)-3-(6-fluoro-1,3-benzothiazol-2-yl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{16}H_{10}ClFN_2OS_2$, IR υ_{max}(KBr) cm^{-1}: 740(C-Cl), 810 (C-S), 1070(C-F), 1640(C=O), 1535(C=N), 1220(C-N), 1565(C=C), 3020(C-H Aromatic). ^{1}H-NMR (δ ppm in DMSO-d_6 solvent) 7.2-7.4(m, 4H, benzothiazole), 7.6-7.8(m, 4H, Ar-H), 1.9(s, 1H, -CH-), 4.23(s, 2H, -CH_2-).^{13}C-NMR(δppm in DMSO-$d_6$solvent) 34.549(-CH_2-Tzd), 118, 123,130,137,150,162,165 (Ar-carbons), 169.82(C=0). Mass (m/z) = 364.87

BTTz$_7$: 3-(1,3-benzothiazol-2-yl)-2-(2-chloro phenyl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{16}H_{11}ClN_2OS_2$, IR υ_{max}(KBr) cm^{-1}: 730(C-Cl), 830 (C-S), 1090(C-F), 1635(C=O), 1560(C=N), 1210(C-N), 1610 (C=C), 3030(C-H Aromatic).

BTTz$_8$: 3-(6-fluoro-1,3-benzothiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{19}H_{17}N_2O_4S_2F$, IR υ_{max}(KBr) cm^{-1}: 800 (C-S), 1110(C-F), 1670(C=O), 1540(C=N), 1240(C-N), 1600 (C=C), 3100(C-H Aromatic), 1310(OCH_3) . ^{1}H-NMR (δ ppm in DMSO-d_6 solvent) 7.6-7.9(m, 3H, benzothiazole), 8.1-8.4(m, 2H, Ar-H), 2.4(s, 1H, -CH-), 3.55(s, 2H, -CH_2-), 3.7, 3.9, 4.1(t, 9H, OCH_3). ^{13}C-NMR (δ ppm in DMSO-d_6 solvent) 24.31(-CH_2-Tzd),68.15(OCH_3),119,124,129,132,134,

151,155,163,175(Ar-carbons),169.85 (C=0).

$BTTz_9$: 3-(6-fluoro-1,3-benzothiazol-2-yl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{17}H_{13}FN_2O_3S_2$, IR υ_{max}(KBr) cm^{-1}: 860 (C-S), 1075(C-F), 1610(C=O), 1565(C=N), 1215(C-N), 1630 (C=C), 3150(C-H Aromatic), 1340(OCH_3), 3385(OH) .

$BTTz_{10}$: 3-(6-fluoro-1,3-benzothiazol-2-yl) -2-(4-methoxyphenyl)-1,3-thiazolidin-4-one:

Mol.formla: $C_{17}H_{13}N_2O_2S_2F$, IR υ_{max}(KBr) cm^{-1}: 810 (C-S), 1100(C-F), 1630(C=O), 1550(C=N), 1200(C-N), 1560(C=C), 3060(C-H Aromatic), 1260(-OCH_3).

Biological Studies:

Determination of minimal inhibitory concentration (MIC)[14]

Dilution susceptibility testing methods were used to determine the minimal concentration of antimicrobial to inhibit or kill the microorganism. This can be achieved by dilution of antimicrobial in either agar or broth media.

Antibacterial activity:

The sterile test tubes containing 1 ml of sterile media were added with 1 ml of different serially diluted test samples. To these tubes, 0.1 ml of suspension of respective microorganism was added in normal saline and incubated at 37 ± 2^0 C for 24 hr.

Anti-fungal activity:

Preparation of suspension of micro-organism

The test organisms (*Aspergillus flavus* and *Candida albicans*) were sub-cultured using potato dextrose agar medium. The tubes containing sterilized medium were inoculated with test fungi and after incubation at 25 °C for 48 hr and they were stored at 4 °C in a refrigerator.

Rest of the procedure did similar to as done with bacterial culture. MIC is expressed as the lowest dilution, which inhibited growth judged by lack of turbidity in the tube.

Antioxidant properties [15, 16]:

Hydrogen peroxide (H_2O_2) scavenging activity:

The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch *et al*. A solution of 30% H_2O_2 (40 mM) was prepared in phosphate buffer (pH 7.4). 50, 100, 150 and 200 µg/ml concentrations of the all test compounds/standard ascorbic acid are prepared by dissolving in suitable solvents. In a test tube add 1ml of different concentration of test and standard are taken to this 3.4 ml phosphate buffer were added and 0.6ml of prepared H_2O_2 solution (40 mM) is added. Keep the mixture for 10 min at room temperature or incubate at 37^0c for 5min. The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated by using Eq. (1).

% of scavenging = [(A control - A sample) / A control] x 100 → Eq. (1)

Hydroxyl (OH^-) radical scavenging activity:

The scavenging activity of hydroxyl radicals was measured with Fenton reaction.

Fe^{2+} -- Oxidized by H_2O_2 ⟹ $Fe^{3+} + OH^- + OH^+$ (1)

Fe^{3+} + 1,10-phenanthroline ⟹ Orange colour (2)

In a test tube containing mixture of 60 µl of 1 mM $FeCl_2$ and 90 µl of 1mM 1,10-phenanthroline, 2.4 ml of 0.2 M phosphate buffer (pH 7.8), 150 µl of 0.17M of H_2O_2 (prepared from 30% H_2O_2) and 1 ml of 50, 100, 150 and 200 µg/ml concentration of test and standard are taken individually in 4 test tubes. Later incubation it at room temperature for 10 min, and measure the absorbance for the color produced in test tube at 560 nm in UV-visible spectrometer. The percentage inhibition of hydroxyl scavenging activity was calculated using the following formula – **Eq-(1)**

Anti-Inflammatory Activity (*In-Vitro* method)[17]:

The standard drug and test compounds were dissolved in minimum amount of dimethyl sulfoxide (DMSO) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMSO in all solutions was less than 2.0%. Test solution (1ml) containing fixed conc. of synthesized compounds/drug (IBF) was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at 370 C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60 0C in water bath for 10 min. After cooling, the turbidity was measured at 660 nm (UV-Visible Spectrophotometer. Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The Ibuprofen is used as standard drug. Results are tabulated in table 2. % of denaturation =

[(Vt – Vc) / Vc] X 100 --- Eq-(2)

Inhibition

Where, Vt = mean absorbance value of test group/std., Vc = mean absorbance value of control group.

RESULT AND DISCUSSION:

Chemistry

A series of new heterocyclic compounds of thiazolid-4-one substituted with benzothiazole at N^3 and its derivatives from a reaction made between simple/substituted 2-amino benzothiazole with different aryl aldehyde in etOH medium under influence of glacial acetic acid to produce azomethine compounds, these azomethine with different substituent's are further under goes cyclo condensation with sulfanyl acetic acid in DMF by catalytic anhydrous zinc chloride to produce the titled compounds $BTTz_{1-10}$. All compounds were purified and subjected to physical and spectroscopic evaluation like melting point carried by open capillary tube method, FT-IR for functional group, NMR for ^1H and ^{13}C determination & mass by GC-MS(EI) method. Evaluated experimental data are depicted in table.1and spectroscopic data. From the data some groups on 4-Thiazolidinone linked benzothiazole shows IR peak at 1640 (C=O), 1535(C=N), 1310(OCH_3), 1070 (C-F), 830(C-S). ^{1}H-NMR interpretation shows 3.3(2H, -CH_2- of Tzd), 3.9(3H, OCH_3), 7.2-.8(Ar-H). ^{13}C-NMR shows 34.55(CH_2-of Tzd), 169.82(C=O), 68.15(OCH_3). Mass of m/z 358.43 expected 358.18 obtained for sample 3. Form these interpreted data it is to be confirms the thiazolidin-4-one, benzothiazole and functional groups are framed.

Biological activity

The synthesized compounds were screened for *In-vitro* antimicrobial, anti-oxidant and anti-inflammatory activity by using standard procedure with slight modification and the obtained values are equated with standard values performed as such done for test. The details are furnished in table 3. The bacterial strains used here are (*S. aureus, B. subtilis, P.aeruginosa and E. coli*) are pre-cultured before using for assay studies and subject it with synthesized compounds and evaluated for MIC by broth dilution method. The compound BTTz-3,6,9 shows significant anti-bacterial property and BTTz- 2,4,6,8 showed significant anti-fungal properties, rest of the compounds are good to moderate in their activity as compared with standard amoxicillin and griseofulvin drugs. Coming to Antioxidant activity the compound BTTz- 6,7,9 & 10 shows significant radical scavenging property compared to ascorbic acid in Fig 3 & 4, rest are shows good to moderate. *In-vitro* activity of the compound BTTz-10,2,4,8 showed prominent for anti-inflammatory activity by inhibiting protein denaturation compared to drug ibuprofen and rest are at accepted range shown in table 2.

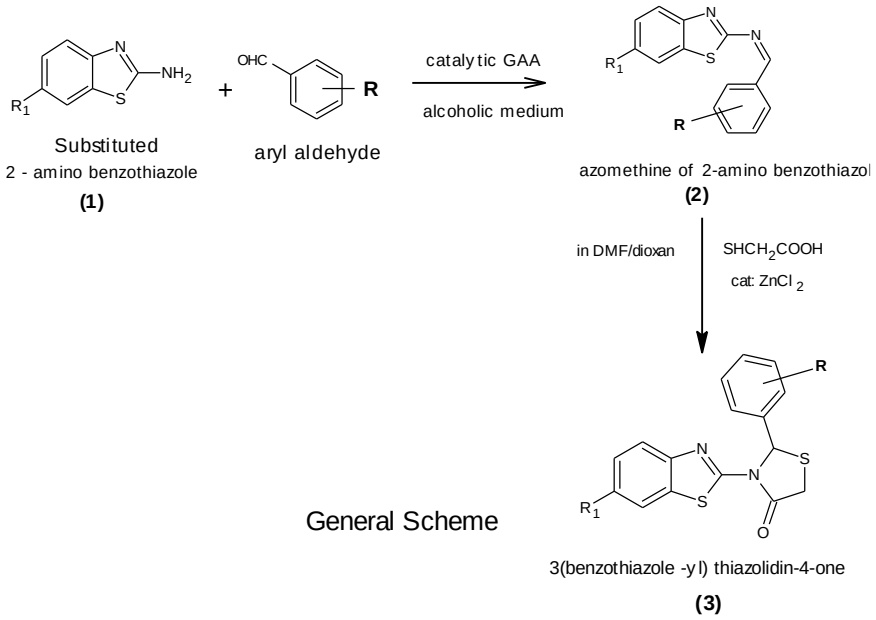


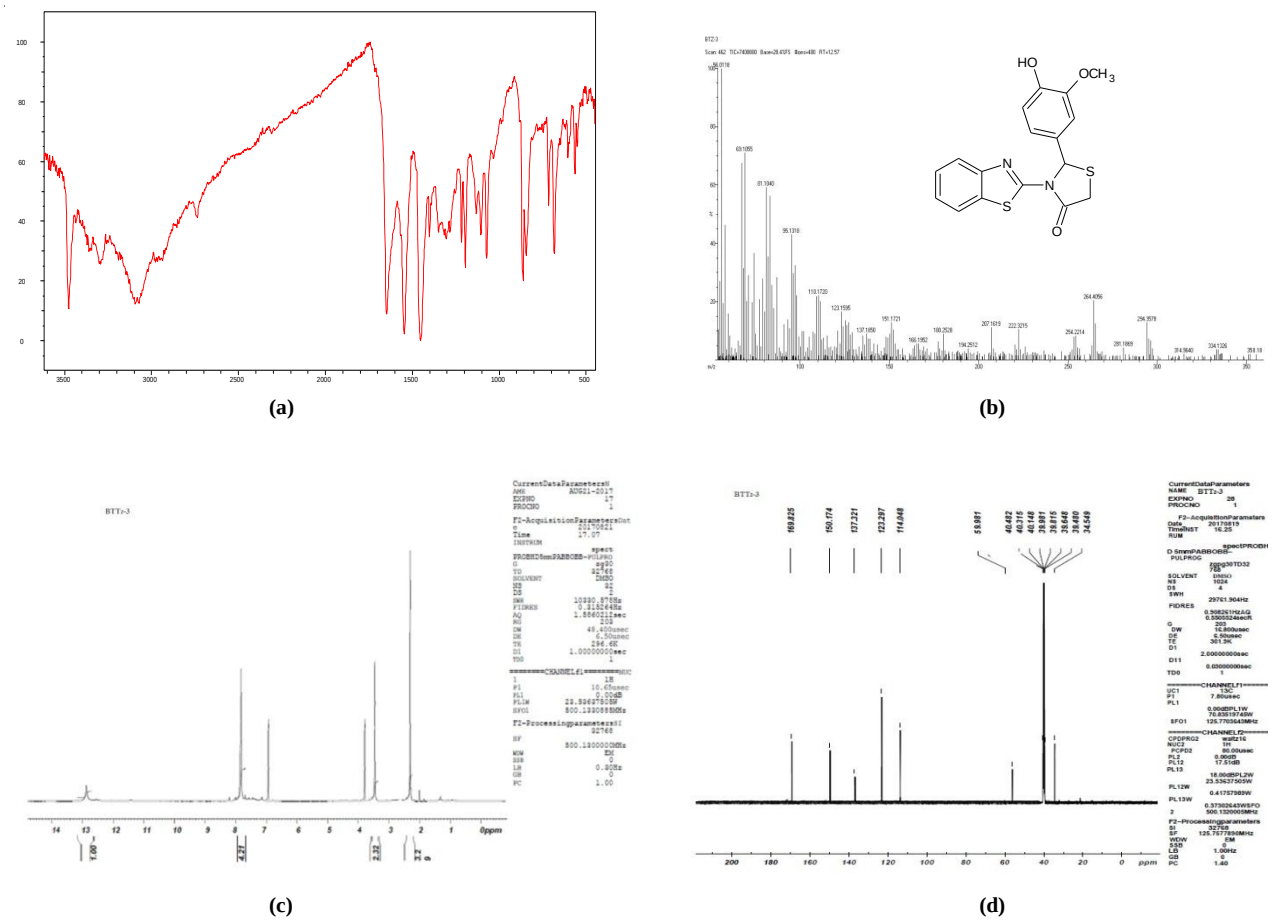
Fig 1: Schematic representation of synthesis of 3-(1,3-benzothiazol-2-yl)-2-phenyl-1,3-thiazolidin-4-one and its derivatives

Table 1: Physical and TLC properties of Thiazolidin-4-one contain benzothiazole

Comp Code	R_1	R	Mol wt	M.P ^{0}c	R_f value		Comp Code	R_1	R	Mol wt	M.P ^{0}c	R_f value
BTTz$_1$	H	H	312.4	198	0.76		**BTTz$_6$**	F	p-Cl	364.84	242	0.76
BTTz$_2$	H	$N(CH_3)_2$	355.47	210	0.70		**BTTz$_7$**	H	o-Cl	346.85	210	0.68
BTTz$_3$	H	p-OH, m-OCH_3	358.43	186	0.88		**BTTz$_8$**	F	3,4,5-tri OCH_3	420.47	202	0.80
BTTz$_4$	H	p- OCH_3	342.43	205	0.93		**BTTz$_9$**	F	o-OH m-OCH_3	376.42	244	0.70
BTTz$_5$	F	H	330.39	180	0.82		**BTTz$_{10}$**	F	p-OCH_3	360.42	219	0.87

Solvent phase - n-Hexane : Chloroform (6.5 : 3.5)

Spectroscopic characterization data of 4-thiazolidinone containing benzothiazole and its derivatives:



(a) **(b)**

(c) **(d)**

Fig 2: Spectroscopy data for the compound

BTTz3: 3-(1,3-benzothiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolidin-4-one

{a. **FT-IR spectroscopy**, **b. Mass spectroscopy by GC-MS(EI)**, **c & d. ^{1}H & ^{13}C – NMR (DMSO-d_6 solvent)}**

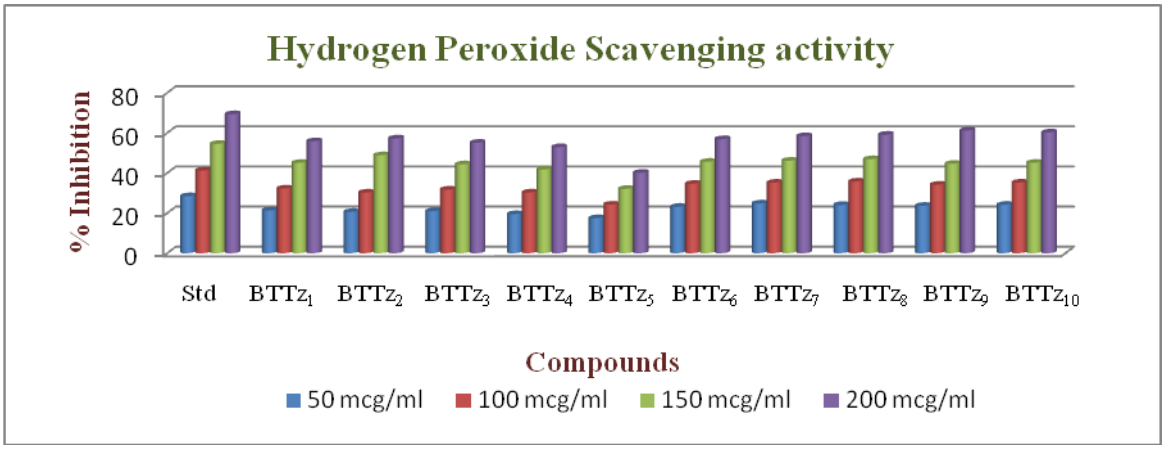
Table.2: *In-vitro* Anti-inflammatory activity of benzothiazole derivatives

Sl.No	Sample	Mean absorbance value ± SEM	% Inhibition of denaturation
1.	Control	0.194 ± 0.03	-
2.	Ibuprofen	0.372 ± 0.02	**91.75 %**
3.	$BTTz_1$	0.318 ± 0.08	63.91 %
4.	$BTTz_2$	0.341 ± 0.05	**75.77 %**
5.	$BTTz_3$	0.280 ± 0.06	44.32 %
6.	$BTTz_4$	0.339 ± 0.05	**74.42 %**
7.	$BTTz_5$	0.322 ± 0.07	65.97 %
8.	$BTTz_6$	0.316 ± 0.02	62.88 %
9	$BTTz_7$	0.292 ± 0.04	50.51 %
10	$BTTz_8$	0.328 ± 0.01	**69.07 %**
11	$BTTz_9$	0.259 ± 0.05	33.50 %
12	$BTTz_{10}$	0.367 ± 0.04	**89.17 %**

Table 3: Anti-microbial activity by MIC (µg/ml) for substituted Thiazolidin-4-one containing benzothiazole

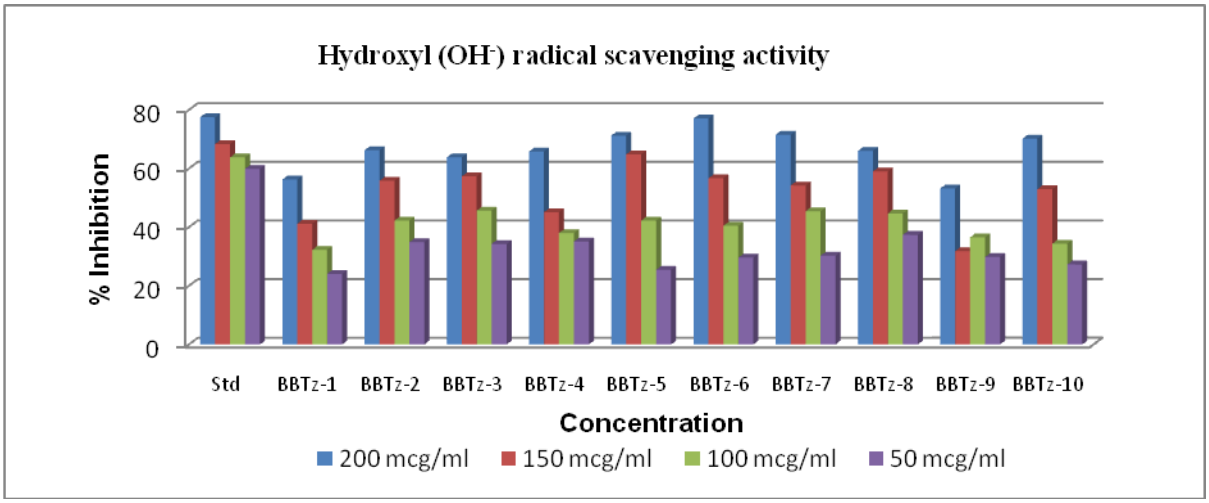
Sl. No.	Compound code	*Minimum inhibitory concentration* (µg/ml)					
		Antibacterial activity				Antifungal activity	
		S. aureus (G+ve)	***B. subtilis***(G+ve)	***P.aeruginosa*** (G-ve)	***E. coli*** (G-ve)	***C. albicans***	***A. flavus***
1	$BTTz_1$	6.25	25	12.5	12.5	12.5	12.5
2	$BTTz_2$	25	25	25	12.5	6.25	3.12
3	$BTTz_3$	6.25	12.5	6.25	6.25	12.5	25
4	$BTTz_4$	12.5	6.25	12.25	6.25	6.25	12.5
5	$BTTz_5$	12.5	12.5	25	25	12.5	25
6	$BTTz_6$	6.25	6.25	12.5	12.5	6.25	12.5
7	$BTTz_7$	6.25	6.25	25	12.5	12.5	25
8	$BTTz_8$	12.5	25	12.5	25	6.25	12.5
9	$BTTz_9$	12.5	6.25	6.25	12.5	12.5	12.5
10	$BTTz_{10}$	6.25	6.25	12.25	25	6.25	25
11	Amoxicillin	**1.56**	**3.12**	**3.12**	**3.12**	-	-
12	Griseofulvin	-	-	-	-	**3.12**	**6.25**

Fig 3: H_2O_2 scavenging property for substituted Thiazolidin-4-one containing benzothiazole



Experiment result performed in triplicate and values are shown in % inhibition

Fig 4: Hydroxyl radical scavenging property for substituted Thiazolidin-4-one containing benzothiazole



Experiment result performed in triplicate and values are shown in % inhibition

CONCLUSION:

A new series of ten thiazolidin-4-one heterocyclic compounds substituted with simple/fluoro benzothiazole scaffold at N^3 position, which is prepared from azomethine of benzothiazole by cyclo condensation with sulfanyl acetic acid in DMF driven by anhydrous zinc chloride as catalyst. All compounds are re-crystallized, structural properties are determined from spectroscopy data and all compounds are evaluated for *In-vitro* models of biological activities like antimicrobial, antioxidant and anti-inflammatory by standard procedure and from the results it is proved the synthesized compounds of 4-thiazolidinone contain benzothiazole posses significant potency compared with standard drug values. This made to prolong the activity study for anti-tubercular by standard method in future days.

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Conflict of interest:

This work is carried by self funding so no conflict of interest.

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