Nanotechnology Perceptions
ISSN 1660-6795
www.nano-*ntp.com*

Synthesis, Characterization, And Antioxidant Evaluation Of Some Novel Substituted Benzothiazole–Pyrazole Hybrid Derivatives

Suraj Mishra*, Namita Arora[1], Sujeet Kumar Gupta[2], Bhumika Yogi[2] and Pankaj Arora[1]

** Research Scholar, Department of Pharmacy, Lords University, Alwar-Bhiwadi Highway, Chikni, Alwar, Rajasthan – 301028*
[1]Faculty of Pharmacy, Lords University, Alwar-Bhiwadi Highway, Chikni, Alwar, Rajasthan – 301028
[2]J.S. Singh Institute of Pharmacy, Parasarai, Dhondi, Sitapur - 261207
Corresponding Author:
Suraj Mishra
Research Scholar, Department of Pharmacy, Lords University,
Alwar-Bhiwadi Highway, Chikni, Alwar, Rajasthan – 301028
Email Id. surajmishranh24@gmail.com

In the present study, a series of novel pyrazole–benzothiazole hybrid molecules (compounds 17–24) were synthesized via a multistep reaction pathway involving hydrazone formation and subsequent cyclization. The final compounds were structurally characterized using FTIR, ^{1}H NMR spectroscopy, elemental analysis, and chromatographic techniques. These hybrids were evaluated for their in vitro antioxidant potential using the 2,2-Diphenyl-1-picrylhydrazyl free radical scavenging assay. Among the synthesized derivatives, compounds bearing electron-donating groups such as hydroxyl (compound 20) and amino (compound 17) demonstrated the most potent antioxidant activity, with IC_{50} values of 17.2 µg/mL and 19.8 µg/mL, respectively, compared to the standard ascorbic acid (IC_{50} = 12.4 µg/mL). The results suggest that the antioxidant activity is significantly influenced by the nature and position of substituents on the aromatic ring. The designed molecules offer promising scaffolds for further development of antioxidant agents based on molecular hybridization strategies.

Keywords: Pyrazole, Benzothiazole, Hybrid molecules, Antioxidant activity, DPPH assay.

1. Introduction

Heterocyclic compounds constitute a fundamental and expansive cornerstone of modern medicinal chemistry. Their unparalleled prevalence in pharmaceuticals stems from inherent versatility: serving as essential pharmacophores, engaging in diverse molecular interactions with biological targets, and offering significant synthetic flexibility for modulating critical physicochemical properties like solubility, lipophilicity, and metabolic stability.[1] Within this diverse chemical landscape, the benzothiazole and pyrazole scaffolds emerge as particularly privileged heterocyclic structures, each possessing a rich history of demonstrated biological significance and therapeutic application.

The benzothiazole nucleus exemplifies this privilege, serving as a cornerstone pharmacophore.[2,3] Its planar, electron-rich structure facilitates potent interactions with diverse biological targets, underpinning a broad spectrum of pharmacological activities. Benzothiazole derivatives are recognized as promising anticancer agents (inhibiting tubulin polymerization[4], kinases[5], or topoisomerases), effective antimicrobials (against bacteria, fungi, and viruses)[6], anti-inflammatory agents, and central nervous system modulators (e.g., neuroprotective[7], anticonvulsant). This therapeutic utility is clinically validated by key marketed drugs. Riluzole, the first FDA-approved drug for Amyotrophic Lateral Sclerosis (ALS), relies on its benzothiazole core to inhibit glutamate release and block sodium channels.[8] Similarly, Methimazole, a mainstay in hyperthyroidism treatment, inhibits thyroperoxidase[9], highlighting the scaffold's relevance in endocrine disorders. Furthermore, derivatives like Thioflavin T are vital diagnostic tools in neuroscience for detecting amyloid fibrils.[10] Complementing benzothiazole's versatility, the pyrazole ring, a five-membered diazole, stands as another highly privileged scaffold in drug design.[11] Its inherent stability, capacity for both hydrogen bond donation and acceptance, and ease of functionalization contribute to remarkably wide-ranging bioactivity. Pyrazole derivatives are prominent as anti-inflammatory and analgesic agents (notably selective COX-2 inhibitors)[12], anticancer drugs (targeting kinases[13], inducing apoptosis), antimicrobials[14], antidiabetics, and agrochemicals, while also exhibiting significant intrinsic antioxidant potential.[15] The prominence of pyrazole is powerfully demonstrated by its inclusion in numerous marketed therapeutics across diverse areas. Key examples include the anti-inflammatory agents Celecoxib (a widely used COX-2 inhibitor for arthritis)[12] and Lonazolac (an NSAID)[16], alongside Crizotinib, a potent ALK and ROS1 inhibitor highlighting the scaffold's critical role in oncology for treating specific lung cancers.[13]

Faced with persistent challenges in drug discovery such as complex diseases, evolving resistance, and the demand for safer, more efficacious therapies—the strategy of molecular hybridization has gained significant traction.[17] This approach rationally fuses two or more distinct pharmacophoric units, each with established biological relevance, into a single novel chemical entity.[18] The goal transcends mere additive effects; hybrids aim for synergy, potentially enhancing potency and efficacy through multi-target engagement or stronger binding, overcoming resistance via novel structures, improving pharmacokinetic profiles, and reducing off-target effects through increased selectivity. Designing such hybrid molecules, particularly by combining well-validated scaffolds like benzothiazole and pyrazole, represents a cutting-edge trend for generating superior new chemical leads.[18]

The compelling rationale for focusing on antioxidant activity in this research stems directly from the central pathological role of oxidative stress.[19] An imbalance between damaging reactive oxygen species (ROS) generation and endogenous antioxidant defenses acts as a critical mediator in the development and progression of a vast array of chronic conditions.[20] This pervasive mechanism significantly contributes to neurodegeneration (e.g., Alzheimer's, Parkinson's)[21], cardiovascular dysfunction (e.g., atherosclerosis)[22], metabolic disorders (e.g., diabetes mellitus)[20], carcinogenesis[19], chronic inflammatory states (e.g., arthritis, IBD), and the aging process itself. The resulting oxidative damage to lipids, proteins, and DNA forms a common link between these diverse pathologies. Consequently, the development of effective antioxidant therapeutics remains a crucial pharmaceutical objective, driving the exploration of novel hybrid structures like those combining benzothiazole and pyrazole motifs.

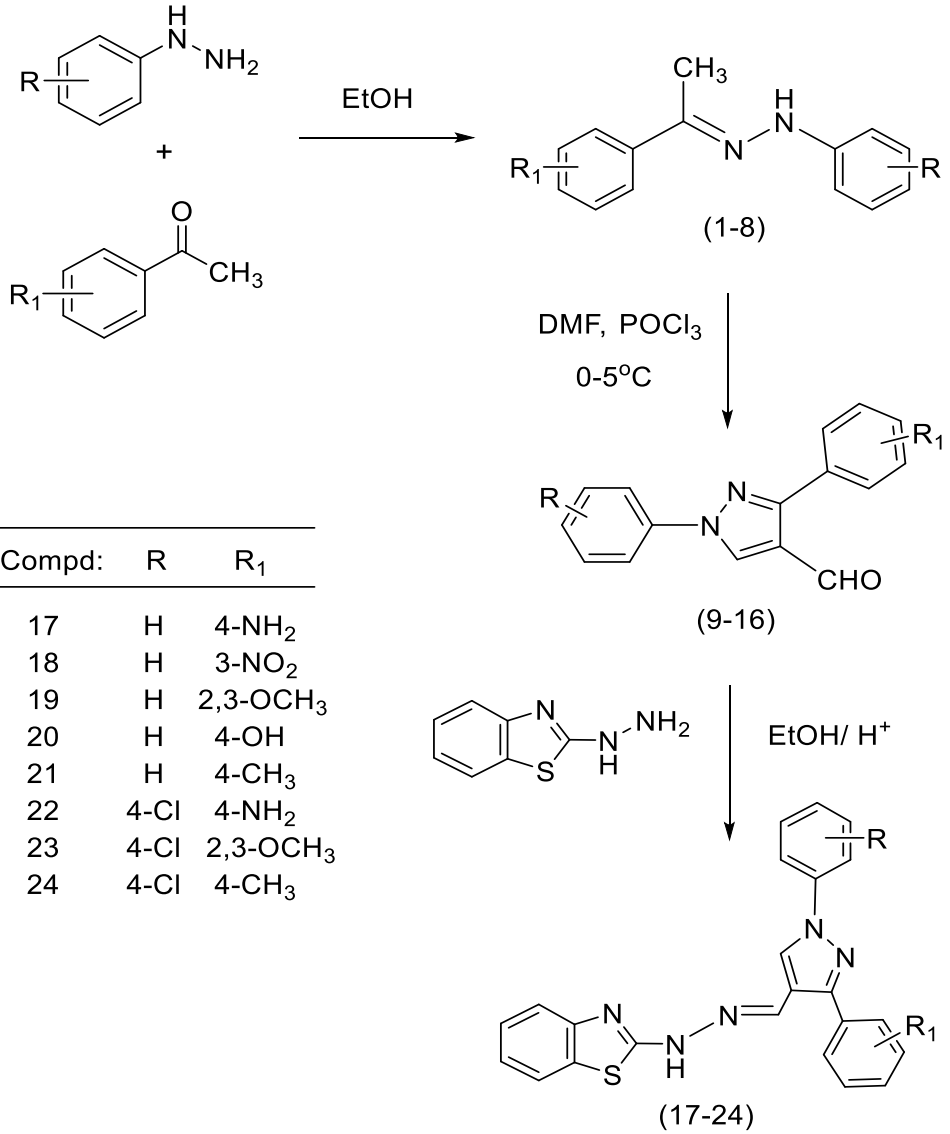
2. Material and Method

All synthesized compounds underwent comprehensive structural characterization employing standard analytical methods. Uncorrected melting points were determined using a calibrated digital melting point apparatus. Fourier Transform Infrared (FTIR) spectra were acquired on a Shimadzu IR Affinity-1S

spectrometer. Nuclear Magnetic Resonance (NMR) analysis confirmed molecular structures: ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance Neo spectrometer, utilizing deuterated solvents (DMSO-d_6/$CDCl_3$) with tetramethylsilane (TMS) as the internal reference standard.

2.1 Synthesis

The target benzothiazolylpyrazole derivatives (17-24) were synthesized via a two-step sequence. Initially, substituted acetophenones underwent acid-catalyzed condensation with arylhydrazines to generate key phenylethylidene hydrazone intermediates (1-8). Subsequently, these hydrazone precursors underwent intramolecular cyclization under dehydrating conditions, facilitating ring closure to afford the final pyrazole-fused benzothiazole scaffolds (17-24).



Compd:	R	R_1
17	H	4-NH_2
18	H	3-NO_2
19	H	2,3-OCH_3
20	H	4-OH
21	H	4-CH_3
22	4-Cl	4-NH_2
23	4-Cl	2,3-OCH_3
24	4-Cl	4-CH_3

Fig.1 Synthesis of Pyrazole-Benzothiazole scaffold

2.1.1 Synthesis of Substituted Acetophenone Phenylhydrazones (1-8)

Equimolar quantities (0.014 mol) of substituted acetophenone derivatives and phenylhydrazine were dissolved in anhydrous ethanol (20 mL) in a 50 mL round-bottom flask. The reaction was catalyzed by adding glacial acetic acid (2–3 drops) under continuous stirring. The mixture was initially maintained at 0°C for 15 minutes, then gradually warmed to 60°C and refluxed for 2.5–3 hours. Reaction progression was monitored at 30-minute intervals using TLC (ethyl acetate/hexane, 3:7). Upon completion, the homogeneous solution was quenched by pouring into ice-cold distilled water (100 mL). The precipitated crystalline solid was vacuum-filtered, washed with cold water (3 × 10 mL), and desiccated to constant weight.

2.1.2 Synthesis of 2-(Substituted Phenylethylidene)hydrazine Derivatives (9-16)

A solution of phenylethylidene hydrazine intermediate (12 mmol) in anhydrous DMF (40 mmol) was chilled in an ice-salt bath (–5°C). Phosphorous oxychloride (40 mmol) was added dropwise over 20 minutes with vigorous stirring, maintaining the temperature below 5°C. The reaction assembly was then transferred to an oil bath and heated at 60°C under reflux for 6 hours. After confirming cyclization by TLC, the cooled mixture was carefully decanted onto crushed ice (150 g). The pH was adjusted to 7.0–7.5. The resulting suspension was stirred for 30 minutes, filtered, and the collected solid sequentially washed with ice water (50 mL) and cold ethanol (10 mL). Purification was achieved by recrystallization from hot ethanol (95%).

2.1.3 Synthesis of Pyrazole-Benzothiazole Conjugates (17-24)

Equimolar quantities of functionalized pyrazole carbaldehyde and 2-hydrazinocarbonylbenzothiazole were dissolved in absolute ethanol (30 mL). Catalytic concentrated H_2SO_4 (4 drops) was introduced, and the mixture was refluxed at 70±2°C for 3 hours with vigorous stirring. Condensation progress was tracked by TLC (dichloromethane/methanol, 9:1). The reaction was quenched by pouring onto crushed ice (100 g) with rapid agitation. The precipitated Schiff base was isolated by Buchner filtration, washed with cold ethanol-water (1:1, 20 mL), and dried at 40°C. Final purification involved recrystallization from ethanol to afford crystalline hybrids.

(E)-4-(4-((2-(benzo[d]thiazol-2-yl) hydrazineylidene) methyl)-1-phenyl-1H-pyrazol-3-yl) aniline (17)

White solid. Yield: 92%. M.P: 216–218 °C. Rf = 0.56 (n-hexane: ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3235.97 (Ar C-NH_2), 3011.36 (Ar C-H), 1621.66 (Benzothia C=N), 1466.05 (Azole C=N), 1411.05 (Ar C=C), 1345.06(N-N), 1120.10 (Benzothia C-N), 700.70(C-S). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.30 (m, 6H, Ar), 7.00 (s, 1H, NH), 7.23–6.52 (m, 4H, Ar), 4.00 (d, 2H, NH). Elemental Analysis: Calculated for $C_{23}H_{18}N_6S$: C, 67.30; H, 4.42; N, 20.47; S, 7.81%. Found: C, 67.27; H, 4.45; N, 20.42; S, 7.87%.

(E)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazineyl) benzo[d] thiazole (18)

Yellow solid. Yield: 88%. M.P: 227–229 °C. Rf = 0.74 (n-hexane: ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3100.80 (Ar C-H), 1615.06 (Benzothia C=N), 1556.05 (Ar C=C), 1530.01 (Ar C-NO2), 1411.05 (Azole C=N), 1246.72 (N-N), 1165.09 (Benzothia C-N),710.05(C-S).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.41–7.58 (m, 4H, Ar), 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.30 (m, 6H, Ar), 7.00 (s, 1H, NH).

Elemental Analysis: Calculated for $C_{23}H_{16}N_6O_2S$: C, 62.72; H, 3.66; N, 19.08; S, 7.28%. Found: C, 62.71; H, 3.67; N, 19.09; S, 7.28%.

(E)-2-(2-((3-(2,3-dimethoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazineyl) benzo [d]thiazole (19)

Pale yellow solid. Yield: 89%. M.P: 190–191 °C. Rf = 0.68 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr, cm-1): 3020.04 (Ar C-H), 2850.27 (Ar C-OCH3), 1619.23 (Benzothia C=N), 1517.45 (Ar C=C), 1405.25(Azole C=N), 1348.08 (N-N), 1219.56 (Benzothia C-N), 771.94 (C-S).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.30 (m, 6H, Ar), 7.00 (s, 1H, NH), 6.93–6.62 (m, 3H, Ar), 3.73 (m, 6H, OCH_3).

Elemental Analysis: Calculated for $C_{25}H_{21}N_5O_2S$: C, 65.92; H, 4.65; N, 15.37; S, 7.04%. Found: C, 65.90; H, 4.67; N, 15.38; S, 7.03%.

(E)-4-(4-((2-(benzo[d] thiazol-2-yl) hydrazineylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)phenol (20)

Off-white solid. Yield: 91%. M.P: 258–260 °C. Rf = 0.60 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3095.39 (Ar C-H), 1617.00 (Benzothia C=N), 1585.44 (Ar C=C), 1460.12 (Azole C=N), 1385.74 (N-N), 1311.87 (Benzothia C-N), 1242.578 (Ar C-OH), 695.86 (C-S).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.30 (m, 6H, Ar), 7.00 (s, 1H, NH), 7.31–6.79 (m, 4H, Ar), 6.00 (s, 1H, OH).

Elemental Analysis: Calculated for $C_{23}H_{17}N_5OS$: C, 67.13; H, 4.16; N, 17.02; S, 7.79%. Found: C, 67.11; H, 4.18; N, 17.04; S, 7.76%.

(E)-2-(2-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)hydrazineyl) benzo[d]thiazole (21)

Yellow solid. Yield: 89%. M.P: 240–242 °C. Rf = 0.88 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3090.40 (Ar C-H), 2926.82 (Ar C-CH3), 1628.03 (Benzothia C=N), 1591.15 (Ar C=C), 1512.81 (Azole C=N), 1268.93 (N-N), 1134.17 (Benzothia C-N), 752.72 (C-S). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.36–7.12 (m, 4H, Ar), 7.80–7.20 (m, 5H, Ar), 7.00 (s, 1H, NH), 2.35 (m, 3H, CH_3).

Elemental Analysis: Calculated for $C_{24}H_{19}N_5S$: C, 70.39; H, 4.68; N, 17.10; S, 7.83%. Found: C, 70.29; H, 4.78; N, 17.08; S, 7.85%.

(E)-4-(4-((2-(benzo[d]thiazol-2-yl)hydrazineylidene)methyl)-1-(4-chlorophenyl)-1H-pyrazol-3-yl)aniline (22)

Off-white solid. Yield: 92%. M.P: 217–219 °C. Rf = 0.84 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3262.83 (Ar C-NH2), 3012.27 (Ar C-H), 1609.85 (Benzothia C=N), 1544.40 (Azole C=N), 1504.81 (Ar C=C), 1462.61 (N-N), 1142.73 (Benzothia C-N), 667.97 (Ar C-Cl), 1582.02 (C-S). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.20 (m, 5H, Ar), 7.00 (s, 1H, NH), 7.23–6.52 (m, 4H, Ar), 4.20 (d, 2H, NH_2).

Elemental Analysis: Calculated for $C_{23}H_{17}ClN_6S$: C, 62.09; H, 3.85; N, 18.89; S, 7.21%. Found: C, 62.07; H, 3.87; N, 18.90; S, 7.22%.

(E)-2-(2-((1-(4-chlorophenyl)-3-(2,3-dimethoxyphenyl)-1H-pyrazol-4-yl)methylene)hydrazineyl)benzo[d]thiazole (23)

Yellow solid. Yield: 88%. M.P: 257–259 °C. Rf = 0.90 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr, cm-1): 3011.36 (Ar C-H), 2810.19 (Ar C-OCH3), 1621.66 (Benzothia C=N), 1544.01 (Ar C=C), 1466.05 (Azole C=N), 1345.06 (N-N), 1246.72 (Benzothia C-N), 822.96 (Ar C-Cl), 700.70(C-S).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.20 (m, 5H, Ar), 7.00 (s, 1H, NH), 6.93–6.62 (m, 3H, Ar), 3.73 (m, 6H, OCH_3).

Elemental Analysis: Calculated for $C_{25}H_{20}ClN_5O_2S$: C, 61.28; H, 4.11; N, 14.29; S, 6.54%. Found: C, 61.25; H, 4.15; N, 14.31; S, 6.56%.

(E)-2-(2-((1-(4-chlorophenyl)-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)hydrazineyl) benzo[d]thiazole (24)

Light yellow solid. Yield: 80%. M.P: 204–206 °C. Rf = 0.68 (n-hexane:ethyl acetate, 7:3 v/v). IR (KBr,cm-1): 3087.17 (Ar C-H), 2810.19 (Ar C-CH3), 1638.05 (Benzothia C=N), 1590.24 (Ar C=C), 1447.92 (Azole C=N), 1280.71 (N-N), 1115.17 (Benzothia C-N), 836.61 (C-S), 724.16 (Ar C-Cl).^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.23–7.55 (m, 4H, Ar–H, benzotriazole), 7.50 (s, 1H, Ar–H), 7.80–7.20 (m, 5H, Ar), 7.00 (s, 1H, NH), 7.36–7.12 (m, 4H, Ar), 2.35 (m, 3H, CH_3).

Elemental Analysis: Calculated for $C_{24}H_{18}ClN_5S$: C, 64.93; H, 4.09; N, 15.78; S, 7.22%. Found: C, 64.88; H, 4.07; N, 15.79; S, 7.29%.

2.2 Biological Activity

Antioxidant Activity

The antioxidant potential of the synthesized compounds was determined via a stable DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method. A 0.1 mM DPPH solution was prepared freshly in methanol and stored in the dark to prevent degradation. Sample solutions were prepared at varying concentrations (10–100 µg/mL) by dissolving the test compounds in methanol.

To each test solution (2 mL), an equal volume (2 mL) of the DPPH reagent was added. The mixtures were shaken gently and kept aside at ambient temperature in the dark for 30 minutes to allow for the reaction. After the incubation period, absorbance was recorded at 517 nm using a UV-Vis spectrophotometer against a blank.

A control solution containing only DPPH and methanol (without sample) was used for baseline correction. Ascorbic acid served as the reference standard under identical conditions. All determinations were carried out in triplicate for accuracy.

The free radical scavenging efficiency was expressed as a percentage inhibition, calculated using the following expression:

$$\% \text{ inhibition } = \left(\frac{A_0 - A_1}{A_0}\right) \times 100$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the test sample.

Compound	10 µg/mL	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
17	**32.6 ± 0.42**	**47.2 ± 0.35**	**62.5 ± 0.47**	**74.3 ± 0.40**	**84.1 ± 0.38**
18	18.5 ± 0.33	28.4 ± 0.36	41.9 ± 0.41	55.7 ± 0.39	68.2 ± 0.37
19	**30.3 ± 0.29**	**43.6 ± 0.33**	**59.8 ± 0.45**	**72.1 ± 0.42**	**81.4 ± 0.40**
20	**36.7 ± 0.35**	**52.4 ± 0.42**	**68.9 ± 0.49**	**80.7 ± 0.40**	**89.2 ± 0.36**
21	26.4 ± 0.38	39.5 ± 0.41	55.0 ± 0.44	66.3 ± 0.39	76.8 ± 0.33
22	28.2 ± 0.31	42.1 ± 0.35	57.6 ± 0.38	69.9 ± 0.41	79.5 ± 0.35
23	24.1 ± 0.36	36.8 ± 0.30	50.5 ± 0.40	62.8 ± 0.42	74.0 ± 0.38
24	21.3 ± 0.34	32.7 ± 0.33	45.6 ± 0.37	58.9 ± 0.40	70.1 ± 0.39
Std (AA)	40.5 ± 0.28	58.6 ± 0.36	75.4 ± 0.40	86.3 ± 0.35	93.6 ± 0.30

Table.1: Percentage Inhibition of DPPH Radical by Compounds 17–24

Compound	IC_{50} (µg/mL) ± SEM
17	19.8 ± 0.27
18	42.3 ± 0.35
19	21.6 ± 0.31
20	17.2 ± 0.22
21	26.9 ± 0.30
22	24.4 ± 0.25
23	28.7 ± 0.28
24	33.5 ± 0.33
Std (AA)	12.4 ± 0.20

Table.2: IC_{50} Values of Synthesized Compounds

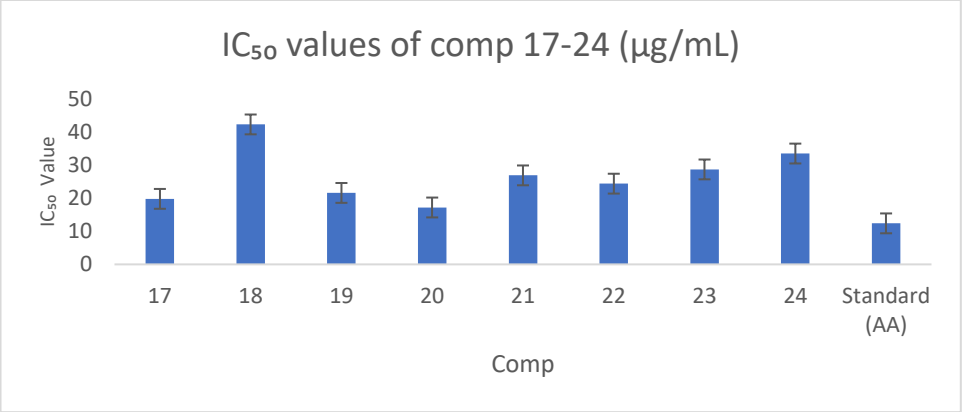


Fig.2. Graph represents IC_{50} Values of Synthesized Compounds

Conclusion

This research successfully synthesized and characterized a new series of pyrazole–benzothiazole hybrids with diverse substituents and evaluated their antioxidant properties using the DPPH assay. The results demonstrated that compounds possessing electron-donating groups such as –OH, $–NH_2$, and $–OCH_3$ exhibited stronger free radical scavenging activity than those with electron-withdrawing substituents. Compound 20 emerged as the most potent antioxidant, closely followed by compounds 17 and 19. The observed structure–activity relationship highlights the potential of benzothiazole–pyrazole hybrids as promising templates for designing effective antioxidant agents. These findings support further exploration of such hybrids in medicinal chemistry for oxidative stress–related disorders.

Acknowledgement

The authors are grateful to Lords University, Alwar and Management of J.S. Singh Institute of Pharmacy, for providing the necessary research facilities and academic support throughout the study. The technical assistance and encouragement received from the university's faculty and staff are also sincerely acknowledged.

Conflict of Interest

The authors declare no conflict of interest related to the publication of this research work.

References

1. Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs: Miniperspective. J. Med. Chem. 2014, 57 (14), 5845–5859.
2. Kamal, A.; Ashwini Kumar, B.; Sridevi, B.; Sravanthi, G.; Manasa, N. Benzothiazole: A Privileged Scaffold in Drug Discovery. Asian J. Chem. 2013, 25 (14), 7591–7599.
3. Bradshaw, T. D.; Wrigley, S.; Shi, D.-F.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. 2-(4-Aminophenyl)benzothiazoles: Novel Agents with Selective Profiles of In Vitro Anti-Tumour Activity. Br. J. Cancer 1998, 77 (5), 745–752.
4. Romagnoli, R.; Baraldi, P. G.; Carrion, M. D. et al. Design, Synthesis, and Biological Evaluation of 2-(3′,4′,5′-Trimethoxybenzoyl)-3-Amino 5-Aryl Thiophenes as Tubulin Inhibitors. J. Med. Chem. 2008, 51 (5), 1464–1468.
5. Yurttaş, L.; Özkay, Y.; Kaplancıklı, Z. A. et al. Synthesis and Anticancer Activity Evaluation of New Benzothiazole-Piperazine Derivatives. J. Enzyme Inhib. Med. Chem. 2014, 29 (2), 175–184.
6. Chhajed, S. S.; Shinde, S.; Padvi, S. A. et al. Synthesis and Antimicrobial Evaluation of Novel 2-Substituted Benzothiazole Derivatives. J. Heterocycl. Chem. 2016, 53 (6), 1853–1857.
7. Lee, H. S.; Park, J. H.; Kim, S. J.; Jang, C. G. Neuroprotective Effect of KR-33028, a Benzothiazole Derivative, Against Glutamate-Induced Neuronal Cell Death. Brain Res. 2006, 1117 (1), 42–50.
8. Hubert, J. P.; Delumeau, J. C.; Glowinski, J.; Prémont, J.; Doble, A. Antagonism by Riluzole of Entry of Calcium Evoked by NMDA and Veratridine in Rat Cultured Granule Cells. Br. J. Pharmacol. 1994, 113 (1), 261–267.
9. Engler, H.; Taurog, A.; Luthy, C.; Dorris, M. L. Reversible and Irreversible Inhibition of Thyroid Peroxidase-Catalyzed Iodination by Thioureylene Drugs. Endocrinology 1983, 112 (1), 86–95.
10. LeVine, H. Thioflavine T Interaction with Synthetic Alzheimer's Disease β-Amyloid Peptides. Protein Sci. 1993, 2 (3), 404–410.
11. Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. Chem. Rev. 2011, 111 (11), 6984–7034.
12. Gupta, S. K., Khanal P., Srivastava, N., Yogi, B., Sinha, A., "Synthesis, characterization & screening of pyrazole derivatives as potent anti-inflammatory agents" Anti-inflammatory & Anti-Allergy agents in medicinal chemistry, 2018, 17, 1-7.

13. Christensen, J. G.; Zou, H. Y.; Arango, M. E. et al. Cytoreductive Antitumor Activity of PF-2341066 (Crizotinib), a Novel Inhibitor of ALK and c-Met, in Experimental Models of Anaplastic Large-Cell Lymphoma. Mol. Cancer Ther. 2007, 6 (12), 3314–3322.
14. Bekhit, A. A.; Ashour, H. M. A.; Ghany, Y. S. A. et al. Synthesis and Biological Evaluation of Some Thiazolyl and Thiadiazolyl Derivatives of 1H-Pyrazole as Antimicrobial Agents. Eur. J. Med. Chem. 2008, 43 (3), 456–463.
15. Yogi B, Mishra A. Hepatoprotective effects and antioxidant potential of polyherbal formulation against CCl_4-induced hepatic injury in albino rats. Curr Tradit Med. 2016;2(1):42–49.
16. Schillinger, E.; Prior, G.; Speckenbach, A.; Löw, M. Lonazolac and Its Metabolites: Potent Inhibitors of Prostaglandin Biosynthesis. Agents Actions 1981, 11 (6–7), 729–734.
17. Meunier, B. Hybrid Molecules with Dual Mode of Action: Dream or Reality? Acc. Chem. Res. 2008, 41 (1), 69–77.
18. Singh, M.; Kaur, M.; Chadha, N.; Silakari, O. Hybrids of Oxindole and Benzothiazole: Design, Synthesis, and Anti-Proliferative Activity. Med. Chem. Commun. 2015, 6 (6), 1104–1116.
19. Trachootham, D.; Alexandre, J.; Huang, P. Targeting Cancer Cells by ROS-Mediated Mechanisms: A Radical Therapeutic Approach? Nat. Rev. Drug Discov. 2009, 8 (7), 579–591.
20. Evans, J. L.; Goldfine, I. D.; Maddux, B. A.; Grodsky, G. M. Oxidative Stress and Stress-Activated Signaling Pathways: A Unifying Hypothesis of Type 2 Diabetes. Endocr. Rev. 2002, 23 (5), 599–622.
21. Barnham, K. J.; Masters, C. L.; Bush, A. I. Neurodegenerative Diseases and Oxidative Stress. Nat. Rev. Drug Discov. 2004, 3 (3), 205–214
22. Madamanchi, N. R.; Vendrov, A.; Runge, M. S. Oxidative Stress and Vascular Disease. Arterioscler. Thromb. Vasc. Biol. 2005, 25 (1), 29–38.