Synthesis, in silico studies and biological screening of (E)-2-(3-(substituted styryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives as an anti-oxidant, anti-inflammatory and antimicrobial agents

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Abstract
A new series of (E)-2-(3-(substituted styryl)-5-(substituted phenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives was synthesized and the chemical structures of synthesized compounds were deduced by IR and NMR spectral tools. These compounds were synthesized via aldol condensation reaction of substituted benzaldehydes and acetone in alkaline ethanolic solution and their in vitro anti-oxidant, anti-inflammatory and antimicrobial activities were investigated. All the synthesized compounds displayed anti-oxidant potential with IC₅₀ values ranging from 0.13 to 8.43 µmol/ml. The compound Z₁₃ exhibited potent anti-inflammatory activity with IC₅₀ value of 0.03 µmol/ml compared with the standard ibuprofen, which showed IC₅₀ value of 0.11 µmol/ml. On the other hand, most of the compounds had a certain antibacterial potential particularly against P. aeruginosa and among these derivatives, compound Z₂ exhibited the highest potential against P. aeruginosa with MIC value of 0.0069 µmol/ml. The analysis of docking results demonstrated the binding affinity and hydrogen bond, electrostatic and hydrophobic interactions of all the synthesized compounds with their respective targets. In silico ADMET studies were carried out for the synthesized compounds and most of the compounds exhibited good ADMET profile.

Keywords: Dibenzalacetones, Antimicrobial, Anti-inflammatory, DPPH assay, Molecular docking, ADMET

Introduction
The evolution of medicines, drug discovery, and medicinal chemistry are all intertwined [1]. Medicinal chemistry continues to play an important part in drug discovery, utilising improved methodologies and a better understanding of other fields of related sciences [2]. Dibenzalacetone is an unsaturated organic compound with the chemical formula: C₆H₅CH=CHCOCH=CHC₆H₅. Dibenzalacetone is also known by the acronym's DBA and dibenzylideneacetone. It is pale yellow solid in nature that is insoluble in water but generally soluble in alcohol [3]. The IUPAC name of dibenzalacetone is 1,5-diphenylpenta-1,4-dien-3-one. It interacts with metals and aids in the formation of a stable chemical structure and it is employed as a component in sunscreens and some commercial organometallic compounds. It’s a symmetrical, non-polar molecule. The dibenzalacetone can show cis–trans geometrical isomerism due to the presence of a double bond. DBA and its analogs can be synthesized via a classic Claisen-Schmidt (cross-aldol) condensation reaction of acetone and benzaldehyde derivatives.

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Aldol condensation reaction is usually performed to synthesize unsaturated α-carbonyl compounds with various advantages such as chalcone, benzalacetone, etc. [5] Heterocyclic compounds have a cyclic structure in which the ring encompasses two or more distinct groups of atoms. The quantity and diversity of heteroatoms in the rings of known compounds has grown over time, indicating a continuous transition to incorporate the growing domain of heterocyclic systems. The number of conceivable heterocyclic systems is essentially endless since rings may be of any size, from three-member upwards, and heteroatom’s can be drawn in practically any combination from a huge number of elements (though nitrogen, oxygen, and sulphur are still by far the most frequent) [6]. There are a huge number of heterocyclic compounds known, and the number is continually growing. Molecules containing benzothiazole moiety have broad range of biological action, encompassing antiviral [7], antibacterial [8, 9], anti-inflammatory [10], antidiabetic [11], analgesic [12], antioxidant [13, 14], antidepressant [15], anticonvulsant [16], antianginal [17], anticancer [18], immunomodulatory characteristics [19], antihelmintic [20], antimalarial [21], fungicidal [22–24], insecticidal (Melaku et al. [25]) and herbicidal properties [26–28].

Antioxidants have the ability to protect organisms and cells from the damage caused by oxidative stress, and as a result, much studies have been done to investigate this property [29, 30]. There are several mediators that control inflammation, among them the prostaglandins (PGs) which play a key role in the process. PGs are synthesized from arachidonic acid (AA) via the COX enzyme (cyclooxygenase isoenzymes). COX-1 is a constitutive type that protects cells in the GI tract from damage, while COX-2 is an inducible version that increases PG synthesis during inflammation [31]. At therapeutic levels, most non-steroidal anti-inflammatory medications (NSAIDs) suppress both COX-1 and COX-2. Antimicrobials are anticipated as one of the leading kind of chemotherapy

![General synthetic scheme for the synthesis of (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives](image-url)
in medical history [32]. Antibiotics are antimicrobial substances that are efficacious against bacterial, parasitic and fungal infections [33]. Antibiotic drugs are extensively employed in the treatment and prevention of bacterial infections since they are the representative form of antibacterial agent [1]. Antibiotics are essential in contemporary medicine, and antibiotic resistance is a serious global health problem. Both at the general level and in an individual, the link between drug exposure and antibiotic resistance is unmistakable [34]. Antibiotic resistance can only be mitigated by reducing needless antibiotic use. In order to tackle microbial resistance, there has been an increasing interest in investigating and creating novel antimicrobial agents from diverse sources [35]. As a result, approaches for screening and measuring antimicrobial activity have received more attention. In view of all these facts the present study was undertaken to synthesize and evaluate of (E)-2-(3-(substituted styryl)-5-(substituted phenyl)-4,5-dihydropyrazol-1-yl)benzo[d] thiazole derivatives as anti-oxidant, anti-inflammatory and antimicrobial agents.

Results and discussion
Chemistry
The synthesis of (E)-2-(3-(substituted styryl)-5-(substituted phenyl)-4,5-dihydropyrazol-1-yl)benzo[d] thiazole derivatives (VI) was accomplished as presented in Fig. 1. The compound (1E,4E)-1,5-bis(substituted phenyl) penta-1,4-dien-3-ones (III) was prepared by aldol condensation reaction of substituted benzaldehydes and acetone in alkaline ethanolic solution. From IR spectra, the appearance of peaks at 1651.66 cm\(^{-1}\) confirmed the presence of α, β unsaturated ketone of synthesized compound III. The aromatic C–H stretching (3027 cm\(^{-1}\), 1495 cm\(^{-1}\), 1448 cm\(^{-1}\), aliphatic CH stretching (2950 cm\(^{-1}\), 2835 cm\(^{-1}\), aromatic C–H stretching (2950 cm\(^{-1}\), 2835 cm\(^{-1}\), aromatic C–C stretching (1495 cm\(^{-1}\), 1448 cm\(^{-1}\), aliphatic C–C stretching (1595 cm\(^{-1}\), CH=CH trans (982 cm\(^{-1}\)) were found in IR spectra of synthesized compound III. 1-(Benzo[d]thiazol-2-yl)hydrazine (V) was synthesized from benzothiazole amine by reaction with hydrazine hydrate in the presence of ethylene glycol. FTIR spectra depicted the presence of NH stretching at 3449 cm\(^{-1}\), aromatic CH str. at 3064 cm\(^{-1}\), 1900 cm\(^{-1}\), C=N str at 1560 cm\(^{-1}\), C–N str at 1282 cm\(^{-1}\), C=S-C at 757 cm\(^{-1}\), C≡N stretching band at 1601–1660 cm\(^{-1}\), the existence of C=N functional group. The existence of C=N was demonstrated by the presence of stretching band at 1177–1384 cm\(^{-1}\). The FTIR spectrum exhibited characteristics peaks for aromatic CH and aliphatic CH stretching at 3000–3084 cm\(^{-1}\) and 2834–2872 cm\(^{-1}\), respectively. C–Cl stretching, C–F stretching and C–Br stretching peaks appeared at 692–722 cm\(^{-1}\), 1250–1280 cm\(^{-1}\) and 593–617 cm\(^{-1}\), respectively. Presence of methoxy group was confirmed by stretching around 1030–1046 cm\(^{-1}\). Hydroxy group stretching peak were observed at 3400–3500 cm\(^{-1}\) and NO2 group exhibited asymmetrical and symmetrical stretching at 1500–1570 cm\(^{-1}\) and 1300–1350 cm\(^{-1}\), respectively. 1HNMR peaks of Hα, Hβ, and Hγ of pyrazole ring appeared at δ 2.13–3.45, 2.39–3.90 and 6.42–5.88 ppm, respectively. The 1HNMR spectrum of compounds showed doublet at around δ 6–7 ppm (J = 16 MHz) indicating the ethylene moiety in trans confirmation.

General structure of target compounds

| Compound | R₁ | R₂ | R₃ | R₄ | R₅ |
|---------|----|----|----|----|----|
| Z₁      | H  | H  | Cl | H  | H  |
| Z₂      | H  | Cl | H  | H  | H  |
| Z₃      | H  | NO₂| H  | H  | H  |
| Z₄      | H  | H  | NO₂| H  | H  |
| Z₅      | NO₂| H  | H  | H  | H  |
| Z₆      | Cl | H  | H  | H  | H  |
| Z₇      | H  | OH | H  | H  | H  |
| Z₈      | H  | H  | OH | H  | H  |
| Z₉      | H  | H  | Br | H  | H  |
| Z₁₀     | H  | H  | CH₃| H  | H  |
| Z₁₁     | H  | H  | OCH₃| H  | H  |
| Z₁₂     | H  | H  | H  | H  | H  |
| Z₁₃     | H  | H  | F  | H  | H  |
| Z₁₄     | H  | OCH₃| H  | H  | H  |
| Z₁₅     | OCH₃| H  | H  | H  | H  |
| Z₁₆     | H  | Br | H  | H  | H  |
| Z₁₇     | Cl | Cl | H  | H  | H  |
| Z₁₈     | Cl | H  | H  | H  | Cl |
| Z₁₉     | OCH₃| H  | H  | OCH₃| H  |
| Z₂₀     | H  | OCH₃| OCH₃| OCH₃| H  |
In vitro biological evaluation

Anti-oxidant activity

All the synthesized compounds were evaluated for anti-oxidant activity via DPPH assay method. Compound Z1 (R=4-Cl) showed maximum anti-oxidant potential with IC$_{50}$ value of 0.13 µmol/ml (85.54±0.22% inhibition at 500 µg/ml) in comparison to standard compound (0.50 µmol/ml) as presented in Table 1. Compound Z13 (R=4-F) also displayed higher anti-oxidant activity with IC$_{50}$ value of 0.44 µmol/ml. Compounds Z16 (R=3-Br), Z11 (R=4-OCH$_3$), Z3 (R=3-NO$_2$) were observed as least active compounds amongst the synthesized compounds with IC$_{50}$ values of 8.43, 4.80 and 2.03 µmol/ml, respectively.

Anti-inflammatory activity

All the synthesized compounds [(E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-di-hydroxyrazol-1-yl)benzo[d]thiazole derivatives] were evaluated for their in vitro anti-inflammatory potential by egg albumin assay method as presented in Table 2. Compound Z13 (R=4-F) was found to be most potent compound with IC$_{50}$ value of 0.03 µmol/ml (79.26±0.13% inhibition at 500 µg/ml) as compared to standard compound ibuprofen (IC$_{50}$=0.11 µmol/ml). Compound Z3 (R=3-NO$_2$) gave 2nd highest activity with IC$_{50}$ value of 0.05 µmol/ml. Compound Z8 (R=4-OH) and Z10 (R=4-CH$_3$) showed less inhibitory potential with IC$_{50}$ value 3.08 and 1.30 µmol/ml, respectively in comparison with other synthesized compounds.

Antimicrobial activity

The synthesized derivatives were tested against Gram positive B. subtilis (MTCC 441), S. aureus (MTCC 3160), and Gram negative E. coli (MTCC 16,521), P. aeruginosa (MTCC 647) for antibacterial activity and C. albicans (MTCC 183) and R. oryzae (MTCC 262) for antifungal activity by serial dilution method. Compound Z6 (R=2-Cl) exhibited most potent antibacterial activity against B. subtilis with MIC value of 0.0069 µmol/ml as compared to ciprofloxacin (0.0075 µmol/ml). Compound Z13 (R=4-F) was found as the second most active compound against B. subtilis with MIC value of 0.0150 µmol/ml. Compound Z14 (R=3-OCH$_3$), Z5 (R=2-NO$_2$) and Z12 (R=H) were observed as the least active compounds and showed antibacterial activity against B. subtilis with MIC values of 0.0566, 0.0530, 0.0328 µmol/ml, respectively.

Compounds Z17 (R=2,3-diCl) and Z18 (R=2,6-diCl) among the synthesized compounds showed good antibacterial activity against E. coli with MIC value of 0.0241 µmol/ml. Compounds Z8 (R=4-OH), Z10 (R=4-CH$_3$), Z11 (R=4-OCH$_3$), Z14 (R=3-OCH$_3$) and Z15 (R=2-OCH$_3$) were found to be least active compounds against E. coli. Compounds Z20 (R=3,4,5-tri-OCH$_3$), Z9 (R=4-Br) and Z16 (R=3-Br) displayed good antibacterial activity against S. aureus with MIC values of 0.0223, 0.0232 and 0.0232 µmol/ml, respectively. Compound Z14 (R=3-OCH$_3$) was found as least active compound. Compound Z2 (R=3-Cl) revealed maximum inhibitory potential against P. aeruginosa with MIC value of 0.0069 µmol/ml. Compounds Z11 (R=4-OCH$_3$), Z15 (R=2-OCH$_3$), Z13 (R=4-F), Z12 (R=H) also showed good antibacterial activity against P. aeruginosa with MIC values of 0.0140, 0.0140, 0.0149 and 0.063 µmol/ml, respectively. Compounds Z14 (R=3-OCH$_3$) and Z10 (R=4-CH$_3$) showed minimum inhibitory potential against P. aeruginosa.

In case of Gram positive bacterial strain, study indicated that compound Z20 (R=3,4,5-tri-OCH$_3$) showed better antibacterial potential towards both B. subtilis and S. aureus with MIC value of 0.223 µmol/ml. Compounds Z14 (R=3-OCH$_3$) and Z12 (R=H) were found to have minimum inhibitory potential against Gram positive bacterial strains. In case of Gram negative strains synthesized compounds such as Z2 (R=3-Cl), Z11 (R=4-OCH$_3$), Z15 (R=2-OCH$_3$), Z13 (R=4-F), Z12 (R=H) showed maximum inhibitory potential against P. aeruginosa. Compounds Z9 (R=4-Br), Z16 (R=3-Br), Z20 (R=3,4,5-tri-OCH$_3$) exhibited good antifungal potential against both fungal strains.

Compounds Z9 (R=4-Br), Z16 (R=3-Br) and Z20 (R=3,4,5-tri-OCH$_3$), demonstrated good antifungal activity against C. albicans with MIC values of 0.223, 0.0232 and 0.232 µmol/ml. Compounds Z14 (R=3-OCH$_3$) and Z17 (R=2,3-di-Cl) displayed minimum inhibitory potential against C. albicans. Compounds Z7 (R=3-OH), Z20 (R=3,4,5-tri-OCH$_3$) displayed maximum antifungal activity against R. oryzae with MIC values of 0.0151 and 0.0223 µmol/ml. Compounds Z12 (R=H) and Z10 (R=4-CH$_3$) were observed as least active compound against R. oryzae. The antimicrobial study revealed that the synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-di-hydroxyrazol-1-yl)benzo[d]thiazole derivatives exhibited most potent antibacterial potential against P. aeruginosa as shown in Table 3.

Structure Activity Relationship can be summarized as follows: (Fig. 2)

Molecular docking

Molecular docking is appraised as remarkable tool to explore the binding affinity and binding interactions of synthesized compounds with active binding sites of corresponding proteins. In the present study all the
Table 1  Anti-oxidant activity (µmol/ml) of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl) benzo[d]thiazole derivatives (VI)

| Comp | Conc | %Inhibition ± SEM | IC₅₀ | Comp | Conc | %Inhibition ± SEM | IC₅₀ |
|------|------|--------------------|------|------|------|--------------------|------|
| Z1   | 500  | 85.54 ± 0.22**     | 0.13 | Z11  | 500  | 51.75 ± 0.12**     | 4.8  |
| 250  | 76.10 ± 0.04**     | 125  | 62.54 ± 0.29**     | 250  | 40.67 ± 0.04**     | 125  | 31.30 ± 0.05**     |
| 62.5 | 49.84 ± 0.05**     | 62.5 | 29.17 ± 0.02**     | 31.25| 35.33 ± 0.13***    | 25.66±0.03** |
|      |      | 31.25 | 21.72 ± 0.02**     |      |      | 31.25 | 36.96 ± 0.02**     |
| Z2   | 500  | 96.89 ± 0.02**     | 0.71 | Z12  | 500  | 86.59 ± 0.21**     | 1.68 |
| 250  | 71.08 ± 0.02**     | 125  | 50.46 ± 0.29**     | 250  | 62.82 ± 0.09**     |
| 125  | 30.57 ± 0.03**     | 125  | 48.03 ± 0.01***    | 62.5 | 40.12 ± 0.03**     |
|      | 125  | 21.72 ± 0.02**     |      |      | 31.25 | 31.25 | 18.54 ± 0.01**     |
| Z3   | 500  | 72.67 ± 0.02**     | 2.03 | Z13  | 500  | 56.07 ± 0.02**     | 0.44 |
| 250  | 52.30 ± 0.00**     | 125  | 37.38 ± 0.02**     | 250  | 48.56 ± 0.00**     |
| 125  | 29.39 ± 0.01**     | 125  | 36.70 ± 0.04**     | 62.5 | 29.54 ± 0.09**     |
|      | 125  | 23.70 ± 0.07**     |      |      | 31.25 | 31.25 | 24.50 ± 0.01**     |
| Z4   | 500  | 68.26 ± 0.07**     | 0.61 | Z14  | 500  | 53.00 ± 0.94**     | 5.41 |
| 250  | 53.70 ± 0.09**     | 125  | 39.35 ± 0.06**     | 250  | 39.13 ± 0.34**     |
| 125  | 28.11 ± 1.05**     | 125  | 29.63 ± 0.00**     | 62.5 | 22.58 ± 0.00**     |
|      | 125  | 22.01 ± 0.00**     |      |      | 31.25 | 31.25 | 18.54 ± 0.01**     |
| Z5   | 500  | 70.82 ± 0.4**      | 1.05 | Z15  | 500  | 55.37 ± 0.11**     | 0.86 |
| 250  | 57.59 ± 0.07**     | 125  | 45.80 ± 0.04**     | 250  | 43.49 ± 0.13**     |
| 125  | 39.61 ± 0.30**     | 125  | 32.89 ± 0.03**     | 62.5 | 28.20 ± 0.04**     |
|      | 125  | 34.40 ± 0.18**     |      |      | 31.25 | 31.25 | 24.37 ± 0.00**     |
| Z6   | 500  | 28.96 ± 0.03**     | 0.74 | Z16  | 500  | 68.22 ± 0.00**     | 8.43 |
| 250  | 25.85 ± 0.03**     | 125  | 22.16 ± 0.00**     | 250  | 54.48 ± 0.01**     |
| 125  | 19.99 ± 0.00**     | 125  | 43.37 ± 0.00**     | 62.5 | 37.93 ± 0.00**     |
|      | 125  | 17.53 ± 0.02**     |      |      | 31.25 | 31.25 | 32.39 ± 0.01**     |
| Z7   | 500  | 86.39 ± 0.04**     | 0.71 | Z17  | 500  | 39.80 ± 0.33**     | 0.54 |
| 250  | 65.10 ± 0.00**     | 125  | 50.44 ± 0.00**     | 250  | 34.61 ± 0.18**     |
| 125  | 30.83 ± 0.01**     | 125  | 26.75 ± 0.04**     | 62.5 | 23.96 ± 0.03**     |
|      | 125  | 23.81 ± 0.02**     |      |      | 31.25 | 31.25 | 18.91 ± 0.04**     |
| Z8   | 500  | 83.87 ± 0.01**     | 0.50 | Z18  | 500  | 86.11 ± 0.3**      | 1.75 |
| 250  | 64.66 ± 0.07**     | 125  | 27.30 ± 0.02**     | 250  | 49.05 ± 0.00**     |
| 125  | 21.53 ± 0.00**     | 125  | 31.67 ± 0.05**     | 62.5 | 26.63 ± 0.01**     |
|      | 125  | 19.83 ± 0.16**     |      |      | 31.25 | 31.25 | 23.13 ± 0.01**     |
| Z9   | 500  | 64.36 ± 0.03**     | 0.70 | Z19  | 500  | 50.57 ± 0.1**      | 0.58 |
| 250  | 49.79 ± 0.00**     | 125  | 34.62 ± 0.01**     | 250  | 38.53 ± 0.31**     |
| 125  | 23.35 ± 0.00**     | 125  | 28.53 ± 0.07**     | 62.5 | 22.92 ± 0.00**     |
|      | 125  | 12.81 ± 0.02**     |      |      | 31.25 | 31.25 | 21.84 ± 0.04**     |
| Z10  | 500  | 61.12 ± 0.06**     | 0.87 | Z20  | 500  | 52.64 ± 0.01**     | 0.88 |
| 250  | 47.88 ± 0.00**     | 125  | 36.72 ± 0.09**     | 250  | 42.45 ± 0.01**     |
| 125  | 26.70 ± 0.03**     | 125  | 32.53 ± 0.01**     | 62.5 | 26.87 ± 0.01**     |
|      | 125  | 20.95 ± 0.01**     |      |      | 31.25 | 31.25 | 21.62 ± 0.04**     |
|      |      | STD               | 500  | 99.92 ± 0.03       | 0.50 |
|      |      |                  | 250  | 88.95 ± 0.00       |
|      |      |                  | 125  | 74.33 ± 0.24       |
|      |      |                  | 62.5 | 55.31 ± 0.30       |
|      |      |                  | 31.25| 40.18 ± 0.51       |

This data is represented as Mean ± SEM, n = 3, values are significantly different as compared to positive control (STD) Ascorbic acid (500 µg/ml) (“P < 0.01”.)
Table 2  Anti-inflammatory activity (µmol/ml) of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl) benzo[d]thiazole derivatives (VI)

| Comp | Conc | %Inhibition ± SEM | IC₅₀ | Comp | Conc | %Inhibition ± SEM | IC₅₀ |
|------|------|------------------|------|------|------|------------------|------|
| Z1   | 500  | 46.38 ± 0.19**   | 0.54 | Z11  | 500  | 31.00 ± 0.00**   | 0.16 |
| 250  | 42.52 ± 0.06** | 250  | 28.72 ± 0.11** |
| 125  | 38.07 ± 0.43** | 125  | 26.26 ± 0.06** |
| 62.5 | 33.51 ± 0.25** | 62.5 | 21.92 ± 0.02** |
| 31.25| 31.69 ± 0.11** | 31.25| 18.47 ± 0.07** |
| Z2   | 500  | 70.42 ± 0.07 ns  | 0.41 | Z12  | 500  | 82.53 ± 0.28**   | 0.23 |
| 250  | 58.88 ± 0.07** | 250  | 75.28 ± 0.06** |
| 125  | 40.54 ± 3.07** | 125  | 62.96 ± 0.01** |
| 62.5 | 33.39 ± 0.01** | 62.5 | 54.98 ± 0.29** |
| 31.25| 27.21 ± 0.07** | 31.25| 43.97 ± 0.38** |
| Z3   | 500  | 71.11 ± 0.03 ns  | 0.05 | Z13  | 500  | 79.26 ± 0.13**   | 0.03 |
| 250  | 65.23 ± 0.05** | 250  | 77.17 ± 0.03** |
| 125  | 57.86 ± 0.05** | 125  | 73.51 ± 0.04** |
| 62.5 | 46.00 ± 0.02** | 62.5 | 63.28 ± 0.04** |
| 31.25| 34.71 ± 0.00** | 31.25| 42.12 ± 0.00** |
| Z4   | 500  | 42.26 ± 0.00**   | 0.13 | Z14  | 500  | 29.58 ± 0.17**   | 0.17 |
| 250  | 38.37 ± 0.00** | 250  | 26.98 ± 0.29** |
| 125  | 35.91 ± 0.02** | 125  | 24.54 ± 0.33** |
| 62.5 | 29.49 ± 0.00** | 62.5 | 20.04 ± 0.10** |
| 31.25| 25.14 ± 0.00** | 31.25| 16.73 ± 0.09** |
| Z5   | 500  | 44.16 ± 0.07**   | 0.27 | Z15  | 500  | 39.57 ± 0.33**   | 0.19 |
| 250  | 41.06 ± 0.01** | 250  | 36.83 ± 0.00** |
| 125  | 36.32 ± 0.07** | 125  | 34.62 ± 0.00** |
| 62.5 | 32.92 ± 0.01** | 62.5 | 29.58 ± 0.00** |
| 31.25| 29.15 ± 0.02** | 31.25| 26.53 ± 0.01** |
| Z6   | 500  | 77.70 ± 0.32**   | 0.42 | Z16  | 500  | 57.24 ± 0.07**   | 1.20 |
| 250  | 62.26 ± 0.09** | 250  | 45.39 ± 0.14** |
| 125  | 42.24 ± 0.19** | 125  | 37.15 ± 0.10** |
| 62.5 | 28.67 ± 0.07** | 62.5 | 28.20 ± 0.15** |
| 31.25| 22.17 ± 0.34** | 31.25| 24.06 ± 0.05** |
| Z7   | 500  | 50.23 ± 0.09**   | 0.28 | Z17  | 500  | 71.05 ± 0.03 ns  | 0.61 |
| 250  | 42.92 ± 0.02** | 250  | 60.72 ± 0.14** |
| 125  | 37.68 ± 0.25** | 125  | 51.87 ± 0.27** |
| 62.5 | 26.65 ± 0.13** | 62.5 | 43.38 ± 0.01** |
| 31.25| 22.15 ± 0.03** | 31.25| 38.31 ± 0.35** |
| Z8   | 500  | 48.57 ± 1.34**   | 3.08 | Z18  | 500  | 51.07 ± 0.00**   | 0.43 |
| 250  | 35.98 ± 0.06** | 250  | 46.05 ± 0.05** |
| 125  | 27.95 ± 0.02** | 125  | 37.66 ± 0.01** |
| 62.5 | 20.48 ± 1.35** | 62.5 | 35.63 ± 0.01** |
| 31.25| 17.30 ± 0.79** | 31.25| 31.12 ± 0.01** |
| Z9   | 500  | 86.05 ± 0.02**   | 0.90 | Z19  | 500  | 58.11 ± 0.02**   | 0.14 |
| 250  | 64.45 ± 0.02** | 250  | 54.56 ± 0.11** |
| 125  | 49.63 ± 0.09** | 125  | 48.08 ± 0.05** |
| 62.5 | 33.12 ± 0.03** | 62.5 | 36.74 ± 0.31** |
| 31.25| 26.53 ± 0.04** | 31.25| 26.95 ± 0.63** |
| Z10  | 500  | 80.14 ± 0.02**   | 1.30 | Z20  | 500  | 32.22 ± 0.02**   | 0.15 |
| 250  | 55.13 ± 0.05** | 250  | 30.19 ± 0.04** |
| 125  | 38.64 ± 0.03** | 125  | 27.25 ± 0.00** |
| 62.5 | 28.13 ± 0.05** | 62.5 | 24.24 ± 0.02** |
| 31.25| 24.72 ± 0.08** | 31.25| 21.26 ± 0.01** |
| STD  | 500  | 70.53 ± 0.03     | 0.11 | 250  | 69.11 ± 0.01     |
| 125  | 66.53 ± 0.03     |
| 62.5 | 60.46 ± 0.03     |
| 31.25| 50.55 ± 0.14     |

This data is represented as Mean ± SEM, n = 3, values are significantly different as compared to positive control (STD) ibuprofen (500 µg/ml) (**P < 0.01); ns- non-significant
synthesized compounds were subjected to molecular docking studies with respect to their target proteins. Binding score of all the synthesized compound against target protein PDB:2CAG is represented in Table 4. Compound Z1 exhibited hydrophobic interactions with amino acid residues of marked protein PDB: 2CAG (Catalase compound II) (Fig. 3). Para chlorostyryl ring created pi-pi stacked interaction with Tyr:337 (4.59 Å) residue. Phenyl ring of benzothiazole displayed pi-pi stacked interaction with Tyr:343 (5.21 Å) and amide-pi-stacked interaction with AspA:339 (5.07 Å) amino acid residue. Pi-pi T shaped interaction was induced by para chloro substituted phenyl ring with Phe:140 amino acid residue. Pi-pi T shaped interaction was induced by para chloro substituted phenyl ring with Phe:140 amino acid residue with bond length of 5.78 Å. Alkyl and pi-alkyl interactions were observed with Val:125, Ala:112, Pro:141, Phe:140, Pro:141, His:145, Arg:52, Ala:340 and Phe:313 amino acid residues. Thiazole ring of benzothiazole was engaged in pi-sigma interaction with Ala:340 amino acid residue. Compound Z16 displayed four pi-pi stacked and three pi-alkyl and one alkyl interaction with target residue. Compound Z11 the second least active compound created two hydrogen bonds, one pi-pi stacked, alkyl and pi-alkyl interactions with target residue. Ascorbic acid displayed three hydrogen bond and one pi-donor hydrogen bond interaction with PheA:313, AlaA:311, ArgA:344 and HisA:54 amino acid residues of the target protein.

All the synthesized compounds showed binding affinity values ranging between $-7.8$ to $-11.3$ kcal/mol against target protein PDB:6COX (Table 4). Compound Z13 exhibited hydrogen bonding, hydrophobic (pi-pi-T-shaped, amide-pi-stacked, pi-sigma, pi-alkyl), electrostatic (pi-cation, pi-anion) and halogen bond interactions with target residues of PDB:6COX [Cyclooxygenase-2 (prostaglandin synthase 2)] (Fig. 4). Tyr:A115 amino acid was involved in hydrogen bond interaction with N of pyrazoline ring at a distance of 2.26 Å. The phenyl ring of benzothiazole contributed pi-cation interaction with Arg:120 amino acid residue (3.37 Å). Para fluoro substituted phenyl ring established pi-anion interaction with Glu:A254 residue (4.03 Å). Amide-pi-stacked interaction was introduced by Leu:A82 amino acid residue with para fluorostyryl ring (4.68 Å) whereas para fluoro substituted phenyl ring fascinated pi-pi-T shaped interaction with Tyr:A122 amino acid residue with bond length of 5.56 Å. Para fluorostyryl ring and para fluoro substituted phenyl ring also prompted pi-sigma interactions with Val:A89 and LysA:79, LeuA:82, LysA:83, ValA:89, TyrA:122 and ArgA:120 amino acid residues.

### Table 3 Antimicrobial activity (µmol/ml) of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives

| Comp | B. subtilis | S. aureus | E. coli | P. aeruginosa | C. albicans | R. oryzae |
|------|-------------|-----------|---------|---------------|-------------|-----------|
| Z1   | 0.0278      | 0.0278    | 0.0278  | 0.0278        | 0.0278      | 0.0278    |
| Z2   | 0.0278      | 0.0278    | 0.0555  | 0.0069        | 0.0278      | 0.0278    |
| Z3   | 0.0265      | 0.0265    | 0.0265  | 0.0265        | 0.0265      | 0.0265    |
| Z4   | 0.0265      | 0.0265    | 0.0530  | 0.0265        | 0.0265      | 0.0265    |
| Z5   | 0.0530      | 0.0265    | 0.0530  | 0.0265        | 0.0265      | 0.0265    |
| Z6   | 0.0069      | 0.0278    | 0.0555  | 0.0278        | 0.0278      | 0.0278    |
| Z7   | 0.0302      | 0.0302    | 0.0302  | 0.0302        | 0.0302      | 0.0151    |
| Z8   | 0.0302      | 0.0302    | 0.0605  | 0.0302        | 0.0302      | 0.0302    |
| Z9   | 0.0232      | 0.0232    | 0.0464  | 0.0232        | 0.0232      | 0.0232    |
| Z10  | 0.0305      | 0.0305    | 0.0610  | 0.0305        | 0.0305      | 0.0305    |
| Z11  | 0.0283      | 0.0283    | 0.0566  | 0.0142        | 0.0283      | 0.0283    |
| Z12  | 0.0328      | 0.0328    | 0.0328  | 0.0164        | 0.0328      | 0.0328    |
| Z13  | 0.0150      | 0.0299    | 0.0299  | 0.0150        | 0.0299      | 0.0299    |
| Z14  | 0.0566      | 0.0566    | 0.0566  | 0.0566        | 0.0566      | 0.0566    |
| Z15  | 0.0283      | 0.0283    | 0.0566  | 0.0142        | 0.0283      | 0.0283    |
| Z16  | 0.0232      | 0.0232    | 0.0464  | 0.0232        | 0.0232      | 0.0232    |
| Z17  | 0.0241      | 0.0241    | 0.0241  | 0.0241        | 0.0481      | 0.0241    |
| Z18  | 0.0241      | 0.0241    | 0.0241  | 0.0241        | 0.0241      | 0.0241    |
| Z19  | 0.0249      | 0.0249    | 0.0498  | 0.0249        | 0.0249      | 0.0249    |
| Z20  | 0.0223      | 0.0223    | 0.0445  | 0.0223        | 0.0223      | 0.0223    |
| STDa | 0.0075      | 0.0075    | 0.0075  | 0.0075        | 0.0040      | 0.0040    |

*a Ciprofloxacin (antibacterial), Fluconazole (antifungal)*
residues induced pi-alkyl interactions with compound Z13. The second least active compound Z8 displayed lesser interactions such as two hydrogen bonds, one pi-cation, two pi-sigma, one alkyl and one pi-alkyl interaction with target residues. The least active compound Z10 showed one pi-cation and five pi-alkyl interactions with target residues. The reference compound ibuprofen showed one hydrogen bond, one pi-sigma, alkyl and pi-alkyl interactions with target residues i.e. MetA:522, ValA:523, AlaA:516, HisA:90, ArgA:513 and LeuA:352.

In case of antibacterial activity, all the synthesized compounds exhibited binding affinity in the range of -6.9 to -9.3 kcal/mol (Table 4). In compound Z2, nitrogen of benzothiazole ring established hydrogen bond interaction with AsnA:112 amino acid residue at a distance of 2.56 Å (Fig. 5). Meta chlorostyryl ring created pi-cation interaction with ArgA:198 whereas meta chloro substituted phenyl ring displayed pi-anion interaction with GluA:164 residue. Pi-pi-T shaped interaction was formed by meta chlorostyryl ring (4.76 Å) with HisA:140 amino acid residue and meta chloro substituted phenyl ring showed pi-pi stacked interaction with HisA:144 (4.57 Å) amino acid residue. The chloro group of synthesized compounds interacted with target protein (ValA:222, IleA:186, ValA:137) via alkyl interaction. Pi-alkyl interactions exhibited by compound Z2 with LeuA:197, HisA:140, HisA:223 and TyrA:155 amino acid residue. Meta chlorostyryl ring was also engaged in pi-sigma interaction with ValA:137 amino acid residue of target protein. The least active compound Z14 showed two hydrogen bond, three pi-pi-T shaped, three pi-alkyl and one pi-sigma interaction with target residues. The reference compound ciprofloxacin showed three hydrogen bond, one pi-anion, one pi-pi-T shaped, two pi-pi stacked, one alkyl, two pi-alkyl and one halogen bond with target residues like ValA:222, HisA:223, GluA:164, TrpA:115, TyrA:155, HisA:144 and GluA:148.

Molecular docking studies for fungal studies depicted the binding affinity ranging from -9.9 to 11.3 kcal/mol (Table 4) and binding interactions of all the synthesized compounds with target protein PDB:1EA1. Compound Z20 created hydrophobic and carbon hydrogen bond interactions with target amino acid residues (Fig. 6). The benzothiazole ring was engaged in two pi-pi-T shaped interactions with Tyr:76 amino acid residue with bond length of 4.91 and 5.782 Å. Two pi-sigma interactions were formed by benzothiazole ring at a distance of 3.59 and 3.94 Å. The carbon of methoxy group of trimethoxystyryl ring formed pi-sigma interaction with PheA:399 amino acid residue with bond length of 3.70 Å. Pi-alkyl interactions were created by compound Z20 with Cys:394, Ala:256, Leu:321 and Met79 amino acid residues. Carbon-hydrogen bond were induced with ProA:386, HisA:392, AlaA:256, HisA:101 and LeuA:100 amino acid residues. The second active compound Z9 displayed hydrogen bond interaction, pi-pi T shaped, amide-pi-stacked, pi-sigma interactions with Arg:96, Tyr:76, Phe:387, Leu:321, Cys:394, Leu:105, Ala:256,
Leu:321 and Met79 target residues. The least active compound Z14 displayed one pi-pi-T shaped, two alkyl, two pi-sigma, five pi-alkyl interactions with target residues. The standard drug fluconazole exhibited two hydrogen bond, two pi-pi-T shaped, one pi-sigma, one pi-cation, pi-alkyl and one halogen bond interaction with target residues.

**Drug likeness parameters**

Molinspiration online tool kit and OSIRIS property explorer was used for the evaluation of drug like characteristics. According to the law, molecular weight < 500 Daltons, hydrogen bond donors < 5 and hydrogen bond acceptors < 10 and log P not be higher than 5 [36]. If more than two criteria are violated then these rules highlight possible bioavailability problem. The intestinal absorption, oral bioavailability, and blood brain barrier penetration of the drug molecules are influenced by optimum value of descriptor like polar surface area. The compounds with TPSA value < 140 Å² possess better intestinal absorption, molecules with a polar surface area > 140 Å² be likely to be poor at permeating cell membrane and TPSA of < 60 Å² signifies sufficient bioavailability and generally the compounds penetrate the blood brain barrier. The results presented in Table 5 depicted that compounds Z1, Z2, Z3, Z6, Z7, Z9 and Z13 met all the rules of Lipinski. Agreeing to Veber’s rule there must be number of rotatable bonds 10 or < 10 and TPSA equal to or < 140Å² which is also supporting the synthesized compounds [37, 38].

| Comp | PDB:2CAG | PDB:6Cox | PDB:1U4G | PDB:1EA1 |
|------|-----------|-----------|-----------|-----------|
| Z1   | −9.8      | −8.6      | −7.8      | −10.5     |
| Z2   | −11.3     | −10.0     | −8.7      | −10.4     |
| Z3   | −9.2      | −10.8     | −9.2      | −11.3     |
| Z4   | −10.8     | −9.0      | −8.8      | −10.6     |
| Z5   | −10.5     | −9.7      | −7.9      | −10.4     |
| Z6   | −9.1      | −9.2      | −9.3      | −10.6     |
| Z7   | −9.9      | −11.1     | −8.1      | −9.9      |
| Z8   | −10.5     | −9.1      | −8.6      | −10.5     |
| Z9   | −10.1     | −8.8      | −7.9      | −10.0     |
| Z10  | −9.9      | −10.7     | −8.8      | −10.7     |
| Z11  | −9.2      | −8.1      | −7.7      | −10.0     |
| Z12  | −9.2      | −9.4      | −7.6      | −10.4     |
| Z13  | −10.6     | −10.0     | −8.2      | −11.0     |
| Z14  | −10.6     | −10.3     | −9.0      | −10.4     |
| Z15  | −9.8      | −9.0      | −8.0      | −10.6     |
| Z16  | −8.3      | −9.1      | −9.1      | −10.5     |
| Z17  | −9.2      | −9.1      | −7.9      | −10.9     |
| Z18  | −9.4      | −8.7      | −7.6      | −10.6     |
| Z19  | −7.8      | −8.4      | −7.2      | −10.0     |
| Z20  | −9.0      | −7.4      | −6.9      | −10.0     |
| STD  | −6.1      | −7.2      | −6.6      | −7.2      |

**Table 4** Binding affinity of synthesized (E)-2-(3-(substituted styryl)-5-(substituted phenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives against its respective targets (Kcal/mol)

PDB:2CAG (Catalase compound II); PDB:6Cox (Cyclooxygenase-2 (prostaglandin synthase-2) complexed with a selective inhibitor, SC-558 IN I222 space group); PDB:1U4G (Elastase of P. aeruginosa with an inhibitor); PDB:1EA1 (cytochrome P450 14 alpha-sterol demethylase (CYP51) from Mycobacterium tuberculosis in complex with fluconazole)

Fig. 3 a 3D illustration of compound Z1 in the active site of catalase enzyme (PDB:2CAG). b 2D illustration of compound Z1 in the active site of catalase enzyme (PDB:2CAG)
ADMET study

Pre-ADMET online server was utilized for estimation of pharmacokinetic parameters. The HIA value ranging 0 and 20% specifies poor absorption, 20–70% moderate absorption, and 70–100% indicates well absorption.

In case of Caco-2 cell permeability, the value < 4 shows low permeability, 4–70 moderate permeability, and > 70 high permeability. MDCK cell system may be used as a sensible tool for rapid permeability screening and the value < 25 indicates low permeability, 25–500 moderate...
permeability, and > 500 high permeability. The percentage of drug bind to plasma protein is another remarkable factor, the value < 90% indicates weak binding and > 90% indicates strong binding to plasma proteins. The blood–brain barrier (BBB) penetration is symbolized as \( \frac{\text{BB}}{\text{Brain}} \div \frac{\text{BB}}{\text{Blood}} \). The value < 0.1 indicates low absorption, 0.1–2.0 moderate absorption, and > 2.0 higher absorption to CNS [38].

The human intestinal absorption values were observed in range of 96.02–98.48% which recognised as the absorption capacity of synthesized compounds. The in vitro Caco-2 cell permeable property in the range of 1.01–57.80 nm/s, in vitro MDCK cell permeability in range of 0.02–63.42 nm/s designated low to moderate permeability of target compounds with the concerned cell line. The synthesized compounds displayed values in range of 90.12–100% which assured its strong binding capacity with proteins. The in vivo blood brain barrier penetration ranges from 0.32 to 3.62 facilitated its distribution in vivo with medium to good penetration capacity (Table 6) [38].

Bioactivity and toxicity risk
The bioactivity and toxicity risks of synthesized compounds were estimated by Molinspiration online server and Osiris property explorer, respectively (Table 7).

Conclusion
\( (E)-2-(3-(\text{Substitutedstyril})-5-(\text{substitutedphenyl})-4,5-\text{dihydropyrazol-1-yl})\text{benzo[d]thiazole derivatives} \) were synthesized and evaluated for their anti-oxidant, anti-inflammatory and antimicrobial potential. Compound Z1 showed the maximum anti-oxidant potential and exhibited hydrophobic interactions with target residues of respective protein. Compound Z13 was observed as the most potent anti-inflammatory compound and established hydrogen bond, electrostatic, halogen and hydrophobic interactions with amino acid residues of target protein. Compound Z2 revealed maximum inhibitory potential against \( \text{P. aeruginosa} \) and formed hydrogen bond, hydrophobic and electrostatic interaction with target protein. Compound Z20 showed good antifungal activity and binding interactions with target residues. Molecular docking studies and pharmacokinetic analysis also supported the in vitro results.

Materials and methods
Chemical and instruments
The analytical grade chemicals and reagents were utilized by itself in experiments without any purification. Decibel melting point apparatus was adapted for monitoring the melting point of the synthesized compounds and are expressed as uncorrected. The thin-layer chromatography (TLC) was fascinated for observing the
reaction progress. FT-IR (Diffuse Reflectance Method (DRS) -8000A, Shimadzu, Japan) spectrophotometer was utilized for recording infrared spectra and the Bruker Avance III, 400 MHz NMR spectrometer was employed for nuclear magnetic resonance spectra (1H NMR, 13C NMR, Chemical shift δ values- ppm). DPPH (High Media), Nutrient broth and Sabouard dextrose broth (Hi-Media) have been used for in vitro biological studies.

General procedure for synthesis of (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d] thiazole derivatives (Z1-Z20)

First of all, 40 mmol benzaldehyde (II) was taken in a round bottom flask and 20 ml of ethanol was added. After dissolution, 20 mmol acetone (I) was added in above mixture. The solution was vigorously stirred for 15 min on magnetic stirrer. RBF was placed in an ice bath for maintaining temperature 1–4 °C and 20 ml of a freshly prepared 20% sodium hydroxide solution was added drop by drop into the solution with continuous stirring. After complete addition of 20% sodium hydroxide solution, the resulting mixture was continuously stirred for 1 h. The resultant product was neutralized by 10% HCl solution (approximately 50–70 ml). After neutralization the separated product was filtered, washed with water and then dried at room temperature [4].

Synthesis of 1-(benzo[d]thiazol-2-yl)hydrazine (V)
1.5 ml of hydrazine hydrate (99%) was taken in a 50 ml round bottom flask and 1.5 ml concentrated HCl was added drop by drop with stirring the flask at 5–10 °C temperature. After complete addition of conc. HCl, 15 ml of ethylene glycol was added slowly, mixed and 0.75 g of benzo[d]thiazol-2-amine was added. Then flask was vigorously shaken and refluxed for 3 h. Mixture was cooled at room temperature and the mixture was poured drop

| Comp | miLog P<sup>a</sup> | Log S<sup>b</sup> (mol/L) | TPSA<sup>c</sup> (Å²) | MW<sup>d</sup> | nON<sup>e</sup> | nOHNH<sup>f</sup> | nviolatio<sup>g</sup> | nrot<sup>h</sup> |
|------|----------------|-----------------|-----------------|----------|---------|---------|----------|---------|
| Z1   | 4.01           | − 7.13          | 27.97           | 454.43   | 3       | 0       | 0        | 4       |
| Z2   | 4.88           | − 7.13          | 28.49           | 450.39   | 3       | 0       | 0        | 4       |
| Z3   | 4.44           | − 6.582         | 120.14          | 471.50   | 9       | 0       | 0        | 6       |
| Z4   | 6.49           | − 6.582         | 120.14          | 471.50   | 9       | 0       | 0        | 6       |
| Z5   | 6.21           | − 6.582         | 120.14          | 471.50   | 9       | 0       | 1        | 6       |
| Z6   | 4.65           | − 7.134         | 28.49           | 450.39   | 3       | 0       | 0        | 4       |
| Z7   | 4.57           | − 5.07          | 68.95           | 413.50   | 5       | 2       | 0        | 4       |
| Z8   | 5.61           | − 5.07          | 68.95           | 413.50   | 5       | 2       | 1        | 4       |
| Z9   | 4.18           | − 7.33          | 28.49           | 539.30   | 3       | 0       | 1        | 4       |
| Z10  | 7.47           | − 6.35          | 28.49           | 409.56   | 3       | 0       | 0        | 4       |
| Z11  | 6.69           | − 5.698         | 46.96           | 441.56   | 5       | 0       | 1        | 6       |
| Z12  | 6.57           | − 5.662         | 28.49           | 381.50   | 3       | 0       | 1        | 4       |
| Z13  | 3.90           | − 6.29          | 28.49           | 417.48   | 3       | 0       | 0        | 4       |
| Z14  | 4.43           | − 5.698         | 46.96           | 441.56   | 5       | 0       | 1        | 6       |
| Z15  | 6.41           | − 5.698         | 46.96           | 441.56   | 5       | 0       | 1        | 6       |
| Z16  | 8.13           | − 7.33          | 28.49           | 539.30   | 3       | 0       | 1        | 4       |
| Z17  | 8.65           | − 8.606         | 28.49           | 519.28   | 3       | 0       | 2        | 4       |
| Z18  | 8.65           | − 8.606         | 28.49           | 519.28   | 3       | 0       | 2        | 4       |
| Z19  | 6.48           | − 5.734         | 65.43           | 501.61   | 7       | 0       | 2        | 8       |
| Z20  | 5.83           | − 5.77          | 83.90           | 561.66   | 9       | 0       | 2        | 10      |

| Table 5 | Drug likeness characteristics of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d] thiazole derivatives |

<sup>a</sup> miLog P Logarithm of partition coefficient between n-octanol and water  
<sup>b</sup> LogS Solubility  
<sup>c</sup> TPSA Topological polar surface area  
<sup>d</sup> MW Molecular weight  
<sup>e</sup> nON Number of hydrogen bond acceptor  
<sup>f</sup> nOHNH Number of hydrogen bond donor  
<sup>g</sup> nviolations Number of violations  
<sup>h</sup> nrot Number of rotatable bonds
by drop into crushed ice to obtain solid precipitate, which were filtered off and dried [26].

**Synthesis of (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives (Z1-Z20) (VI)**

2 mmol of (1E,4E)-1,5-bis (substitutedphenyl)penta-1,4-dien-3-one (III) was taken in a 50 ml round bottom flask and 15 ml of glacial acetic acid was added and shaken vigorously to dissolve completely. Then 2 mmol of 1-(benzo[d]thiazol-2-yl)hydrazine (V) was added in the solution and refluxed until the completion of reaction monitored by TLC. The reaction was cooled at room temperature and pour the solution into crushed ice, drop by drop, to obtain solid precipitate. The product was filtered and washed with cold water and dried [4].

**Physicochemical and spectral characterization**

*(E)-2-(3-(4-Chlorostyryl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z1): Yield: 66.6%; m.p.: 129–132 ºC; Rf: 0.7 (Benzene:Chloroform 5:5); FT-IR (KBr), νmax (cm⁻¹): 2923.36, 2857 (C–H stretching aliphatic), 1650.30 (C= N stretching), 1536.28 (C=C stretching aliphatic), 1490.68 (C=C stretching aromatic), 1327.02 (C=N stretching), 753.74 (C=S–C stretching), 710 (C–Cl stretching); 1H NMR (400 MHz, CDCl₃, δ ppm): 7.69–7.73 (d, 2H, C₄ʺ of benzothiazole ring), 7.56–7.58 (d, 2H, C₇ʺ of benzothiazole ring), 7.40–7.43 (t, 3H, C₅ʺ and C₆ʺ of benzothiazole ring), 7.30–7.31 (d, 2H, C₃ and C₅ of phenyl ring A), 7.15–7.17 (d, 2H, C₃ and C₅ of phenyl ring B), 7.12–7.14 (d, 2H, C₂ and C₆ of phenyl ring B), 7.04–7.08 (d, 2H, C₂ and C₆ of phenyl ring A), 6.69–6.75 (dd, 2H, J 16 MHz, ethylene group), 5.79–5.84 (dd, Hₓ, C₄ʹ of pyrazole ring), 3.78–3.85 (dd, 1Hb, C₃ʹ of pyrazole ring), 3.14–3.19 (dd, 1Ha, C₃ʹ of pyrazole ring). 13C NMR (300 MHz, CDCl₃, δ ppm), 188.47 (N=C=S-N), 142.08 (C=N), 140.21 (C=S), 138.72 (C=N, pyrazoline), 136.53 (C=N, benzothiazole), 135.11 (C=S of pyrazole ring), 3.14–3.19 (dd, 1Hₓ, C₃ʹ of pyrazole ring).

**Table 6** ADME analysis of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives by Pre ADMET online server

| Comp  | Human intestinal absorption (HIA, %) | In vitro Caco‑2 cell permeability (nm/s) | In vitro MDCK cell permeability (nm/s) | In vitro plasma protein binding (%) | In vivo blood brain barrier penetration (C.brain/C. blood) | Pgp_inhibition |
|-------|-------------------------------------|-----------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------------|---------------|
| Z1    | 98.23                               | 57.80                                   | 0.177                                  | 100                               | 0.41                                      | Inhibitor     |
| Z2    | 98.23                               | 57.03                                   | 28.85                                  | 97.62                             | 0.82                                      | Inhibitor     |
| Z3    | 98.48                               | 01.82                                   | 0.04                                   | 93.74                             | 0.32                                      | Inhibitor     |
| Z4    | 98.48                               | 01.08                                   | 0.04                                   | 94.60                             | 0.52                                      | Inhibitor     |
| Z5    | 98.48                               | 01.01                                   | 0.04                                   | 93.74                             | 0.57                                      | Inhibitor     |
| Z6    | 98.23                               | 56.83                                   | 12.79                                  | 97.67                             | 0.51                                      | Inhibitor     |
| Z7    | 96.02                               | 29.91                                   | 0.19                                   | 95.10                             | 0.59                                      | Inhibitor     |
| Z8    | 96.02                               | 39.58                                   | 0.04                                   | 95.28                             | 0.44                                      | Inhibitor     |
| Z9    | 98.27                               | 56.27                                   | 0.02                                   | 100                               | 0.41                                      | Inhibitor     |
| Z10   | 97.95                               | 38.08                                   | 0.37                                   | 93.08                             | 0.80                                      | Inhibitor     |
| Z11   | 97.68                               | 44.87                                   | 0.04                                   | 91.56                             | 1.97                                      | Inhibitor     |
| Z12   | 97.86                               | 37.63                                   | 63.42                                  | 94.17                             | 2.18                                      | Inhibitor     |
| Z13   | 97.87                               | 53.83                                   | 0.05                                   | 96.94                             | 0.46                                      | Inhibitor     |
| Z14   | 97.68                               | 34.80                                   | 1.32                                   | 91.32                             | 3.62                                      | Inhibitor     |
| Z15   | 97.68                               | 36.02                                   | 0.05                                   | 91.64                             | 2.02                                      | Inhibitor     |
| Z16   | 98.35                               | 56.16                                   | 0.02                                   | 100                               | 0.74                                      | Inhibitor     |
| Z17   | 98.37                               | 56.16                                   | 0.05                                   | 100                               | 0.60                                      | Inhibitor     |
| Z18   | 98.37                               | 56.64                                   | 0.07                                   | 100                               | 0.60                                      | Inhibitor     |
| Z19   | 97.69                               | 33.42                                   | 0.04                                   | 90.39                             | 2.81                                      | Inhibitor     |
| Z20   | 98.27                               | 36.86                                   | 0.04                                   | 90.12                             | 2.41                                      | Inhibitor     |

Caco-2- Cells derived from human colon adenocarcinomas; MDCK- Medin-Darbey Canine Kidney Epithelial Cells; Pgp- P-glycoprotein (plasma membrane protein)
Table 7  Bioactivity and toxicity risks of synthesized (E)-2-(3-(substitutedstyryl)-5-(substitutedphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole derivatives

| Comp | GPCR ligand | Ion channel modulator | Kinase inhibitor | Nuclear receptor ligand | Protease inhibitor | Enzyme inhibitor | Mutagenic | Tumorigenic | Reproductive effective | Irritant |
|------|-------------|-----------------------|-----------------|-------------------------|-------------------|-----------------|-----------|------------|------------------------|----------|
| Z1   | -0.22       | -0.33                 | -0.51           | -0.67                   | -0.38             | -0.16           | None      | None       | None                   | None     |
| Z2   | -0.37       | -0.48                 | -0.57           | -0.53                   | -0.56             | -0.31           | None      | None       | None                   | None     |
| Z3   | -0.46       | -0.48                 | -0.58           | -0.53                   | -0.58             | -0.35           | None      | None       | None                   | None     |
| Z4   | -0.45       | -0.48                 | -0.59           | -0.53                   | -0.58             | -0.34           | None      | None       | None                   | None     |
| Z5   | -0.43       | -0.45                 | -0.69           | -0.52                   | -0.67             | -0.36           | None      | None       | None                   | None     |
| Z6   | -0.40       | -0.53                 | -0.73           | -0.49                   | -0.62             | -0.37           | None      | None       | None                   | None     |
| Z7   | -0.34       | -0.46                 | -0.52           | -0.39                   | -0.52             | -0.24           | None      | None       | None                   | None     |
| Z8   | -0.34       | -0.45                 | -0.51           | -0.40                   | -0.52             | -0.24           | None      | None       | None                   | None     |
| Z9   | -0.46       | -0.55                 | -0.58           | -0.61                   | -0.62             | -0.34           | None      | None       | None                   | None     |
| Z10  | -0.41       | -0.55                 | -0.58           | -0.54                   | -0.57             | -0.33           | None      | None       | None                   | None     |
| Z11  | -0.39       | -0.52                 | -0.54           | -0.49                   | -0.54             | -0.30           | None      | None       | None                   | None     |
| Z12  | -0.40       | -0.52                 | -0.58           | -0.55                   | -0.56             | -0.30           | None      | None       | None                   | None     |
| Z13  | -0.37       | -0.50                 | -0.52           | -0.49                   | -0.55             | -0.29           | None      | None       | None                   | None     |
| Z14  | -0.39       | -0.53                 | -0.55           | -0.49                   | -0.55             | -0.31           | None      | None       | None                   | None     |
| Z15  | -0.40       | -0.53                 | -0.57           | -0.51                   | -0.57             | -0.32           | None      | None       | None                   | None     |
| Z16  | -0.47       | -0.56                 | -0.60           | -0.62                   | -0.64             | -0.35           | None      | None       | None                   | None     |
| Z17  | -0.37       | -0.47                 | -0.71           | -0.46                   | -0.58             | -0.35           | None      | None       | None                   | None     |
| Z18  | -0.43       | -0.53                 | -0.59           | -0.42                   | -0.53             | -0.32           | None      | None       | None                   | None     |
| Z19  | -0.37       | -0.51                 | -0.53           | -0.44                   | -0.52             | -0.29           | None      | None       | None                   | None     |
| Z20  | -0.33       | -0.65                 | -0.49           | -0.52                   | -0.47             | -0.32           | None      | None       | None                   | None     |

**GPCR ligand:** G-Protein coupled receptor ligand property
(E)-2-(3-(3-Nitrostyryl)-5-(3-nitrophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z3): Yield: 43.1%; m.p.: 102–105°C; Rf: 0.6 (Toluene: Methanol 7:3); FT-IR (KBr), νmax (cm⁻¹): 3084.43 (C–H stretching aromatic), 2924.2, 2926.85 (C–H stretching aliphatic), 1630.89 (C=N stretching), 1564.41 (Assym. NO2 stretching), 1526.81 (C=C stretching aliphatic), 1478.26 (C=C aromatic stretching), 1351.48 (Sym. NO2 stretching), 1203.43 (C–S–C stretching); 1HNMR (400 MHz, DMSO-d6, δ, ppm): 7.56–7.60 (d, 1H, C7 of phenyl ring A and B), 7.73–7.84 (t, 2H, C5 and C6 of benzothiazole ring), 7.95–7.99 (d, 1H, C6 of phenyl ring A and B), 8.41–8.44 (d, 1H, C4 of phenyl ring A), 8.26–8.30 (t, 1H, C5 of phenyl ring B), 8.20–8.21 (d, 1H, C6 of phenyl ring B), 7.95–7.99 (d, 1H, C6 of phenyl ring A and B), 7.73–7.84 (t, 2H, C5 and C6 of benzothiazole ring), 7.69–7.73 (d, 1H, C4 of pyrazole ring), 7.56–7.60 (d, 1H, C4 of benzothiazole ring), 6.00–6.05 (dd, 2H, J 12 Hz, ethylene group), 5.69–5.76 (dd, H6, C6′ of pyrazole ring), 3.40–3.45 (dd, 1H, C3′ of pyrazole ring), 3.26–3.32 (dd, 1H, C3′ of pyrazole ring).

(E)-2-(3-(4-Nitrostyryl)-5-(4-nitrophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z6): Yield: 36.8%; m.p.: 167–170°C; Rf: 0.5 (Toluene: Methanol 7:3); FT-IR (KBr), νmax (cm⁻¹): 2924.28 (C–H stretching aliphatic), 1631.46 (C–N stretching), 1201.05 (C–N aromatic stretching), 1344.93 (Sym. NO2 stretching), 1210.05 (C–N stretching), 748.79 (C=C aromatic stretching).

(E)-2-(3-(2-Nitrostyryl)-5-(2-nitrophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z7): Yield: 75.6%; m.p.: 157–160°C; Rf: 0.9 (Toluene: Methanol 7:3); FT-IR (KBr), νmax (cm⁻¹): 3436.49 (OH str.), 2965.4, 2826.5 (C–H stretching aliphatic), 1660.66 (C=N stretching), 1565.52 (C=C aliphatic stretching), 1471.72 (C=C aromatic stretching), 1316.26 (C=N stretching), 752.45 (C=C aromatic stretching), 692.04 (C=Cl stretching).

(E)-2-(3-(3-Hydroxyphenyl)-5-(3-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z8): Yield: 53.7%; m.p.: 197–200°C; Rf: 0.8 (Toluene: Methanol 7:3); FT-IR (KBr), νmax (cm⁻¹): 3454.05 (OH str.), 2928.1, 2850.2 (C–H stretching aliphatic), 1384.87 (C=C aromatic stretching), 1450.39 (C=C aromatic stretching), 1264.79 (C–N stretching), 752.98 (C=C aromatic stretching).

(E)-2-(3-(4-Hydroxyphenyl)-5-(4-hydroxyphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z9): Yield: 58.9%; m.p.: 148–151°C; Rf: 0.8 (Benzenes: Chloroform 5:5); FT-IR (KBr), νmax (cm⁻¹): 3291.28, 2853.6 (C–H stretching aliphatic), 1648.04 (C=C aromatic stretching), 1564.19 (C=C aliphatic stretching), 1486.95 (C=C aromatic stretching), 1325.34 (C–N stretching), 754.57 (C=C aromatic stretching), 593.40 (C=Br stretching).

(E)-2-(3-(4-Methylstyryl)-5-(4-methylphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z10): Yield: 35.8%; m.p.: 134–146°C; Rf: 0.62 (Benzenes: Chloroform 5:5); FT-IR (KBr), νmax (cm⁻¹): 2918, 2853.6 (C–H stretching aliphatic), 1621.40 (C–N stretching), 1540.90 (C=C aromatic stretching), 1442.87 (C=C aromatic stretching), 1228.88 (C–N stretching), 749.58 (C=C aromatic stretching); 1HNMR (400 MHz, CDCl3, δ, ppm): 7.72–7.76 (d, 4H, C3, C5 of phenyl ring A and B), 7.38–7.40 (d, 2H, C3, C5 of phenyl ring A), 7.05–7.28 (m, 4H, of benzothiazole ring), 6.70–6.76 (dd, 2H, J 16 Hz, ethylene group), 5.69–5.76 (dd, H6, C6′ of pyrazole ring), 3.76–3.83 (dd, 1H, C3′ of pyrazole ring).
(E)-2-(3-(4-Fluorostyryl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z12): Yield: 55.2%; m.p.: 101–104 °C; Rf: 0.67 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3060.55, 3016.2 (C–H stretching aromatic), 2972.2, 2926.16 (C–H stretching aliphatic), 1617.02 (C=C aliphatic stretching), 1466.39 (C=C aromatic stretching), 1364.16 (C–N stretching), 752.39 (C–S–C stretching), 617.41 (C–Br stretching).

(E)-2-(3-(2-Methoxystyryl)-5-(2-methoxyphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z13): Yield: 73.9%; m.p.: 95–98 °C; Rf: 0.74 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3063.51, 3002.6, 3063.6 (C–H stretching aromatic), 2941.3, 2841.12 (C–H stretching aliphatic), 1617.02 (C=C aliphatic stretching), 1447.94 (C=C aromatic stretching), 1195.50 (C–N stretching), 762.34 (C–S–C stretching).

(E)-2-(3-(4-Fluorostyryl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z14): Yield: 95.9%; m.p.: 205–208 °C; Rf: 0.52 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3063.6 (C–H stretching aromatic), 2931.5, 2860.4 (C–H stretching aliphatic), 1618.00 (C=C aliphatic stretching), 1450.93 (C=C stretching aliphatic), 1411.07 (C=C aromatic stretching), 1181.02 (C–N stretching), 749.52 (C–S–C stretching), 722.10 (C–Cl stretching).

(E)-2-(3-(2,6-Dichlorostyryl)-5-(2,6-dichlorophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z15): Yield: 82%; m.p.: 100–103 °C; Rf: 0.72 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3070.4 (C–H stretching aromatic), 2931.5, 2860.4 (C–H stretching aliphatic), 1615.96 (C=C aliphatic stretching), 1437.90 (C=C stretching aliphatic), 1427.31 (C=C aromatic stretching), 1177.26 (C–N stretching), 718.76 (C–Cl stretching), 746.32 (C–S–C stretching); 1HNMR (400 MHz, CDCl₃, δ, ppm): 7.82–7.87 (d, 2H, C₃ of pyrazole ring B), 7.69–7.71 (d, 2H, C₃ of pyrazole ring A), 7.36–7.42 (t, 1H, C₄ of benzothiazole ring), 6.85–6.90 (dd, 2H, J 16 MHz, ethylene group), 5.78–5.83 (dd, 2H, C₃ of pyrazole ring), 3.38–3.87 (dd, 1H, C₃ of pyrazole ring), 3.19–3.25 (dd, 1H, C₃ of pyrazole ring).

(E)-2-(3-(3-Bromostyryl)-5-(3-bromophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z16): Yield: 73.9%; m.p.: 205–208 °C; Rf: 0.67 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3060.55, 3016.2 (C–H stretching aromatic), 2972.2, 2926.16 (C–H stretching aliphatic), 1617.02 (C=C aliphatic stretching), 1466.39 (C=C aromatic stretching), 1364.16 (C–N stretching), 752.39 (C–S–C stretching), 617.41 (C–Br stretching).

(E)-2-(3-(2,6-Dichlorostyryl)-5-(2,6-dichlorophenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z17): Yield: 95.9%; m.p.: 205–208 °C; Rf: 0.52 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3063.6 (C–H stretching aromatic), 2931.5, 2860.4 (C–H stretching aliphatic), 1618.00 (C=C aliphatic stretching), 1450.93 (C=C stretching aliphatic), 1411.07 (C=C aromatic stretching), 1181.02 (C–N stretching), 749.52 (C–S–C stretching), 722.10 (C–Cl stretching).

(E)-2-(3-(2,5-Dimethoxystyryl)-5-(2,5-dimethoxyphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z18): Yield: 73.9%; m.p.: 95–98 °C; Rf: 0.74 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3063.6 (C–H stretching aromatic), 2941.3, 2841.12 (C–H stretching aliphatic), 1617.02 (C=C aliphatic stretching), 1437.90 (C=C stretching aliphatic), 1427.31 (C=C aromatic stretching), 1177.26 (C–N stretching), 718.76 (C–Cl stretching), 746.32 (C–S–C stretching); 1HNMR (400 MHz, CDCl₃, δ, ppm): 7.82–7.87 (d, 2H, C₃ of pyrazole ring A), 7.69–7.71 (d, 2H, C₃ of pyrazole ring B), 7.36–7.42 (t, 1H, C₄ of benzothiazole ring), 6.85–6.90 (dd, 2H, J 16 MHz, ethylene group), 5.78–5.83 (dd, 2H, C₃ of pyrazole ring), 3.38–3.87 (dd, 1H, C₃ of pyrazole ring), 3.19–3.25 (dd, 1H, C₃ of pyrazole ring).

(E)-2-(3-(3-Trimethoxystyryl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z19): Yield: 95.9%; m.p.: 137–140 °C; Rf: 0.57 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 3002.6, 3063.6 (C–H stretching aromatic), 2941.3, 2934.73 (C–H stretching aliphatic), 1615.19 (C=C aliphatic stretching), 1446.47 (C=C aromatic stretching), 1420.51 (C=C aromatic stretching), 1178.12 (C–N stretching), 1021.77 (OCH₃ stretching), 747.32 (C–S–C stretching).

(E)-2-(3-(3,4,5-Trimethoxystyryl)-5-(3,4,5-trimethoxystyryl)-4,5-dihydropyrazol-1-yl)benzo[d]thiazole (Z20): Yield: 97.7%; m.p.: 95–98 °C; Rf: 0.74 (Benzene:Chloroform 5:5); FT-IR (KBr), v_max (cm⁻¹): 2995.9 (C–H stretching aromatic), 2939.94, 2838.24 (C–H stretching aliphatic), 1619.76 (C=C aliphatic stretching), 1538.45, 1455.37 (C=C stretching aliphatic), 1418.06 (C=C aromatic stretching), 1245.62 (C–N stretching), 1025.38 (OCH₃ stretching), 751.56 (C=C–C stretching).
In vitro biological evaluation

Anti-oxidant activity

The different concentrations (500, 250, 125, 62.5 and 31.25 µg/ml) of synthesized compounds (Z1–Z20) in DMSO were prepared and 1 ml of sample was taken in a test tube, 1 ml of DPPH solution was added in each test tube and a purple color was observed. The test tubes were placed in dark chamber for 30 min, purple color changed into yellow and after 30 min absorbance was determined by UV spectroscopy at 517 nm wavelength. DMSO was used as blank to set zero [39].

Anti-inflammatory activity

The synthesized compounds (Z1–Z20) were used for the preparation of different concentrations (500, 250, 125, 62.5 and 31.25 µg/ml) in DMSO and 1 ml of each resulting solutions was taken in different test tubes. Then 1.4 ml of freshly prepared phosphate buffer (pH 6.4) and 0.1 ml egg albumin from fresh egg was transferred in each test tube containing different solutions for determining anti-inflammatory activity. The resulting mixtures in test tubes were incubated in a BOD for 15 min at 37 ± 2 ºC and then heated for 5 min at 70 ºC temperature. The mixture of test tubes was cooled at room temperature and absorbance was determined by UV spectroscopy at 660 nm wavelength [40].

Antimicrobial activity

1 ml of test sample was taken in a test tube having 1 ml of nutrient medium and serial dilutions of 50, 25, 12.5, 6.25 and 3.125 µg/ml were prepared. Then inoculation of test strains was done by micropipette and incubated at 37 ºC for 24 h for bacterial strains and 48 h for C. albicans and 120 h for R. oryzae. Results were calculated by visual turbidity observed in test tubes. MIC was calculated by using lowest concentration that inhibits microbial growth [41, 42].

Molecular docking

AutoDock Vina, the advanced docking program was employed to estimate the binding characterstics of synthesized compounds into the active sites of target protein [38, 43]. The crystal structures of PDB: 6COX Cyclooxygenase-2 (prostaglandin synthase-2) complexed with a selective inhibitor, SC-558 IN I222 space group [44], PDB: 2CAG (Catalase compound II) [13], PDB:1U4G, Elastase of P. aeruginosa with an inhibitor [45] and PDB:1EA1 (cytochrome P450 14 alpha-sterol demethylase (CYP51)) from Mycobacterium tuberculosis in complex with fluconazole [46] were retrieved from the protein data bank (www.rcsb.org). AutoDock tools were utilized for the enlightenment of A chain of the proteins in pdbqt format. Water molecules which did not participate in interactions were removed and polar hydrogen atoms were introduced. The 2D structures of ligands were figured in MarvinSketch and saved in mol2 format, and then AutoDock tools were utilized to convert into pdbqt format. Energy minimization was accomplished using MMFF94 force field. The docking studies were executed according to requisite conditions of grid box by AutoDock tools. The search grid was identified as center_x = 21.72, center_y = 23.606, center_z = 47.846 (PDB:6COX); center_x = 58.613, center_y = 15.29, center_z = 16.972 (PDB:2CAG); center_x = 19.067, center_y = 26.357, center_z = −4.427 (PDB:1U4G); center_x = −16.172, center_y = −5.396, center_z = 62.468 (PDB:1EA1), for target proteins with dimension size_x = 60, size_y = 60, size_z = 60, respectively. The exhaustiveness was set to be 8. The results were visualized using PyMol and Discovery studio visualizer [47].

Pharmacokinetic parameters

ADMET analysis of synthesized compounds was performed by Molinspiration online tool kit, OSIRIS property explorer and Pre ADMET online server [48–50].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-022-00901-2.

Additional file 1: Fig. S1. IR spectra of compound Z1 [[(E)-2-3-(4-chlorostyryl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl]benzo[d]thiazole]. Fig. S2. 1H NMR spectra of compound Z1 [((E)-2-(3,4-dichlorostyryl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl]benzo[d]thiazole]. Fig. S3. 13C NMR spectra of compound Z1 [[(E)-2-(3,4-dichlorostyryl)-5-(4-chlorophenyl)4,5-dihydropyrazol-1-yl]benzo[d]thiazole]. Fig. S4. IR spectra of compound Z2 [(E)-2-(3-(3-chlorostyryl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl]benzo[d]thiazole]. Fig. S5. 1H spectra of compound Z3 [(E)-2-(3-(3-nitrostyryl)-5-(3-nitrophenyl)-4,5-dihydropyrazol-1-yl]benzo[d]thiazole]. Fig. S6. 1H NMR spectra of compound Z3.

(C–C aromatic stretching), 1187.75 (C–N Stretching), 1040.88 (OCH3 stretching), 757.07 (C–S–C stretching); 1HNMR (400 MHz, CDCl3, δ, ppm):7.67–7.71 (t, 1H, C6″ of benzothiazole ring), 7.57–7.59 (1H, C4″ of benzothiazole ring), 7.14–7.16 (t, 1H, C5″ of benzothiazole ring), 6.98–7.02 (d, 1H, C7 of benzothiazole ring), 6.87 (s, 2H, C2 and C6 of phenyl ring B), 6.70–6.76 (dd, 2H, J 16 MHz ethylene group), 6.56 (s, 2H, C2 and C6 of phenyl ring A), 5.70–5.74 (dd, Hx, C4 of pyrazole ring), 3.94 (s, OCH3 group), 3.89–3.90 (dd, 1Hb, C3 of pyrazole ring), 3.83–3.84 (dd, 1Hv, C3 of pyrazole ring).
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