Received: 23 December 2019 | Revised: 20 April 2020 | Accepted: 24 April 2020

DOI: 10.1002/jhet.4018

Check for updates

WILEY

ARTICLE

Synthesis and antioxidant activity study of carbothioamide and their corresponding thiazole derivatives

Asma | Balakrishna Kalluraya | Nagaraja Manju | Chigahally Lakshmegowda Sharath

Department of Chemistry, Mangalore University, Mangalagangothri, India

Correspondence
Balakrishna Kalluraya, Department of Chemistry, Mangalore University, Mangalagangothri 574199, Karnataka, India.
Email: bkalluraya@gmail.com

Abstract

A novel series of 5-(p-(prop-2-ynyloxy)phenyl)-3-aryl-4,5-dihydropyrazole-1-carbothioamides **2a-f** and functionalized 2-(3-(aryl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-arylsydnone-4-yl)thiazoles **4a-l** were synthesized. The newly synthesized compounds were elucidated by analytical and spectral analysis. From the single-crystal X-ray diffraction method, it was observed that **2d** crystallizes in a monoclinic crystal system with *P21/n* space group. The compounds **2d** crystallized with cell parameters a = 15.0614 (19) Å, b = 6.0805 (7) Å, c = 20.903 (7) Å, α = 114.136 (6)°, β = 110.709 (14) °, γ = 96.553 (5) °, V = 1790.6 (4) Å^3, Z = 4. From the Hirshfeld surface computational method, the major intercontacts present in these molecules are H...H (31.6%), C...H (18.2%) and S...H (12.2%), respectively. The newly synthesized compounds were tested for their ability to bleach 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical using DPPH scavenging assay. Among the synthesized compounds carbothioamide compounds **2c** (90.7%) and **2b** (89.8%) exhibited good DPPH scavenging activity compared to the rest of the compounds. Most of the synthesized carbothioamide molecules (**2a-f**) found to be potent compared to the thiazole derivatives (**4a-l**).

1 | INTRODUCTION

Sydnone is the privileged member of the mesoionic heteroaromatic compounds, which undergoes a wide variety of functionalization reaction.[1] One of the well-known reaction of sydnone is intermolecular 1,3-dipolar cycloaddition. In presence of dipolarophiles like acetylene or ethylenic sydnone readily undergoes cyclo-addition which can be catalyzed thermally,[2,3] or photochemically.[4,5] In particular, terminal acetylene (dipolarophile) is one of the best precursors for the synthesis of various aromatic/heteroaromatic rings through cycloaddition reaction, for example, azide-alkyne cycloaddition,[6,7] and Diels alder reaction,[8] etc. Terminal acetylene is also found to be a very important scaffold in the field of medicinal chemistry, as they occur in some pharmaceuticals,[9,10] including the contraceptive noretynodrel.[11]

In synthetic and medicinal chemistry field, the combination of heterocyclic moiety such as such as sydnone, pyrazoles, and thiazoles (Figure 1) have attracted a special status due to their easy synthetic procedure and a wide spectrum of pharmacological applications.[12–16]

On the other hand, the effect of free radicals on humans and in industrial sectors is increasing day by day. The free radical not only cause premature ageing and wrinkles but also is the primary cause of cancer and other chronic diseases.[17] In industrial sectors like food, petroleum and rubber and oil are also severely affected by free radicals.[18]

Over the past two decades, there has been growing demand to find novel antioxidants to eradicate these

 © 2020 Wiley Periodicals LLC.

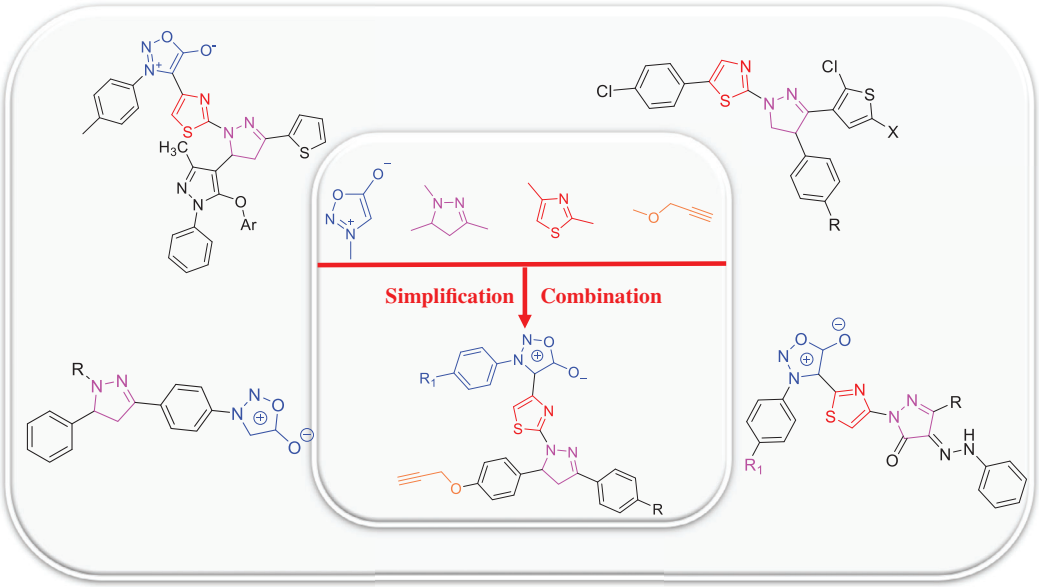
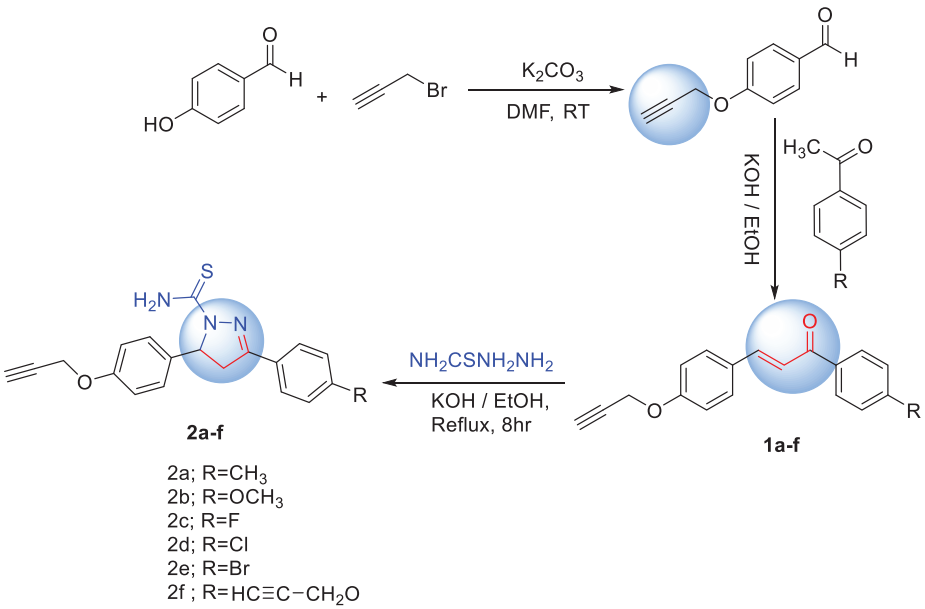


FIGURE 1 Some of the biologically potent molecules bearing sydnone, pyrazole, and thiazole rings



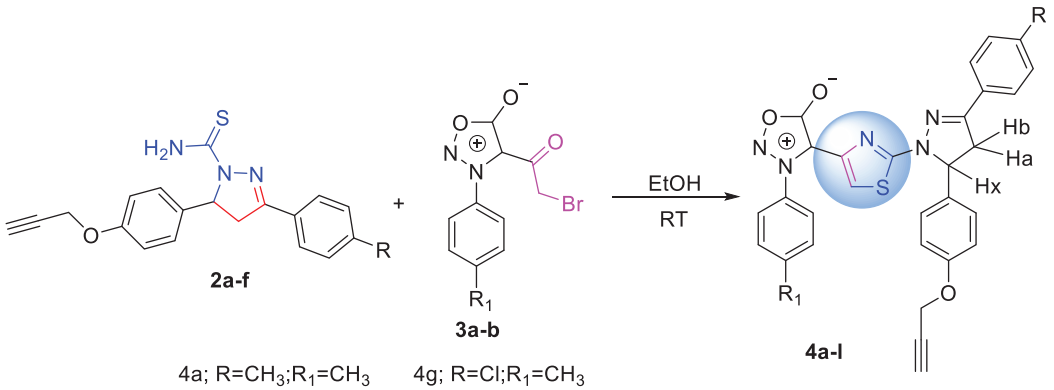
SCHEME 1 Synthetic route for the synthesis of pyrazoline carbothioamide **2a-f**

problems, majorly many attempts were made to synthesize novel heterocyclic based antioxidants, in particular, thiol (thiourea)-based heterocyclic compounds exhibited good radical scavenging activity.[19–21]

Prompted by the above observations and in continuation of our research work on the synthesis of biologically active heterocycles, herein we report the total approach towards the synthesis of thiazole-integrated pyrazole carrying sydnone with functionalized acetylene in a single molecular frame and evaluated for their antioxidant activity. Apart from antioxidant activity, intercontacts in the crystal structure were quantified and visualized by using Hirshfeld surface.

2 | RESULT AND DISCUSSION

In the present work, we hereby report the synthesis of functionalized acetylene bearing multicomponent heterocyclic hybrid is as shown in Scheme 1 to Scheme 2. The required starting compounds 5-(4-(prop-2-ynyloxy)phenyl)-3-aryl-4,5-dihydropyrazole-1-carbothioamide (**2a-f**) were synthesized by the base-catalyzed cyclization of 1-(p-substituted-phenyl)-3-(4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one[22,23] (**1a-f**) with thiosemicarbazide in presence of catalytical amount of potassium hydroxide (Scheme 1). The Hantzsch cyclization of precursor **2a-f** and 4-bromoacetyl-3-(aryl) sydnone[24] (**3a-b**) in ethanol medium



4a; R=CH_3;R_1=CH_3 4g; R=Cl;R_1=CH_3
4b; R=CH_3;R_1=H 4h; R=Cl;R_1=H
4c; R=OCH_3;R_1=CH_3 4i; R=Br;R_1=CH_3
4d; R=OCH_3;R_1=H 4j; R=Br;R_1=H
4e; R=F;R_1=CH_3 4k; R= $HC{\equiv}C-CH_2O$;R_1=CH_3
4f; R=F;R_1=H 4l; R= $HC{\equiv}C-CH_2O$;R_1=H

SCHEME 2 Synthetic route for the synthesis of thiazole hybrid **4a-l**

afforded the formation of thiazole, pyrazoline, and sydnone heterocycles in single molecular framework **4a-l** (Scheme 2). Though acetylene is better dienophile, the thiosemicarbazide (S-N bi-nucleophile) is selectively reacted with α, β unsaturated ketone (chalcone) in presence of a mild base. However, the newly synthesized moiety can be utilized for the synthesis of various heterocycles, for example, 1,2,3-triazole can be synthesized through copper-catalyzed cycloaddition of organic azide.[25] Moreover, terminal acetylene can act as the best dienophile towards the various nucleophiles.[26,27]

The structures of newly synthesized thiazole hybrids **4a-l** were explicated using analytical and spectral data (IR, ^{1}H-NMR, ^{13}C- NMR, CHN analysis and mass spectroscopy) and they are in consistency with the proposed structure. Thus, in the IR spectrum of thiazole hybrid **4k** showed a sharp band at 1732/cm due to sydnone C=O stretching, whereas the absorption band due to ≡C-H stretch was seen at 3286/cm. The bands due to C≡C stretching and C=N stretching were seen at 2182 and 1606/cm.

In the ^{1}H-NMR spectrum of **4k**, the peaks due to magnetically non-equivalent N-H disappeared while a singlet at δ = 6.72 assigned to thiazole ring proton appeared which confirmed the formation of product (Figure S1**)**. Methyl protons of p-tolyl ring attached to sydnone appeared as a singlet at δ = 2.32, whereas two triplets were seen at δ = 2.47 (J = 2.28 Hz) and δ = 2.53 (J = 2.32 Hz) which is attributed to acetylenic protons. The diastereotopic protons (Ha and Hb) and chiral (Hx) proton of pyrazoline ring appeared as three doublet of doublets at δ = 3.24, δ = 3.78, and δ = 5.58 with coupling constant J_{ab} = 17.40 Hz, J_{ax} = 11.92 Hz and J_{bx} = 6.6 Hz integrating for one proton each. Aliphatic -OCH_2 protons appeared as a doublet at δ = 4.64 (J = 2.32 Hz) and δ = 4.72 (J = 2.08 Hz). Ortho and meta protons of p-tolyl ring came into resonance as two doublets at δ = 6.92 (J = 8.68 Hz) and δ = 7.34 (J = 8.68 Hz), while the aromatic protons attributed to the p-propynyloxy phenyl ring appeared as two doublets at δ = 6.99 (J = 8.84 Hz) and δ = 7.56 (J = 8.08 Hz).

Similarly, ^{13}C-NMR also avouches the formation of the product by furnishing expected peaks. The presence of methylene (CH_2) and methine carbon (CH) of the pyrazoline ring appeared at δ 42.57 and δ 61.64 ppm. The signals at δ 55.44, 55.71 ppm were observed for O-CH_2 carbons, respectively. The appearance of a peak at 166.80 ppm indicated the presence of lactone ring in the moiety (ester of sydnone). Furthermore, the appearance of a molecular ion peak at m/z: 588.1 (M^++1), also provided the evidence for the formation of products.

2.1 | Crystallography

One of the synthesized compound **2d** was recrystallized by slow evaporation method and resolved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* program.[28,29] The geometrical calculations were carried out using the program *PLATON*.[30] The molecular structure and packing diagrams were generated with the help of *MERCURY* software[31]. Crystallographic data for the compounds **2d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1857199, copies of this information may be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336 033; e-mail: deposit@ccdc.cam.ac.uk).

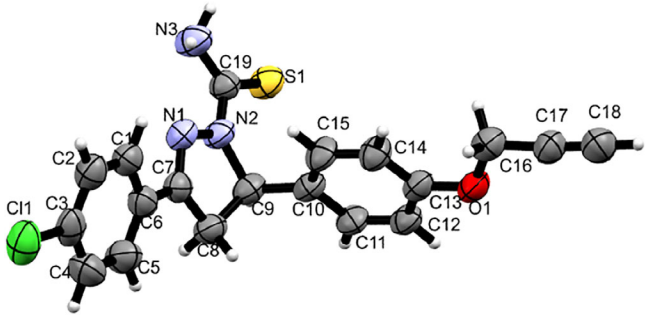


FIGURE 2 Single crystal X-ray structure of compound **2d** showing the atomic numbering system. Displacement ellipsoids are drawn at the 50% probability

Synthesized compound **2d** was crystallized in a monoclinic crystal system with P21/n space group (Figure 2**).** The X-RD data of the compound **2d** are given in (Table S1**).**

2.2 | Hirshfeld surface

The intercontacts observed in the crystal structure of compound **2d** were quantized using the Hirshfeld surface analysis and were presented in the following figures (Figure 3A-C).

The dark-red spots on the d_{norm} surface arise as a result of the short interatomic contacts, that is, strong hydrogen bonds, while the other intermolecular interactions appeared as light-red spots (Figure 3B). The two-dimensional (2D)-fingerprint plots were used to plot intercontacts with respect to d_i and d_e (Figure 3A). The electrostatic potential is mapped on Hirshfeld surfaces using Hartree-Fock (STO-3G basis set) theory over the range of −0.30 a.u. to +0.30 a.u. (Figure 3B). The electrostatic potential surfaces were plotted (Figure 3C) with the red region, which is a negative electrostatic potential (hydrogen acceptors) and blue region, which is a positive electrostatic potential (hydrogen donor)[32,33].

The intercontacts were found to be Cl...H (10.9%), C...H (18.2%), Cl...S (0.8%), Cl...N (1.0%), Cl...C (1.8%), H...H (31.6%), N...C (1.4%), N...H (4.2%), O...C (O.6%), S...H (12.2%), O...H (4.8%) (Figure 3A(i-xi)).

From the 2D Fingerprint plots, it was observed that the major contributions are from H...H (31.6%), and C...H (18.2%) when compared to other intercontacts. Electrostatic potential over the Hirshfeld surfaces is shown in Figure 3C.

2.3 | Antioxidant studies

"The newly synthesized dihydropyrazole-1-carbothioamide (**2a-f)** and thiazole derivatives (**4a-l)** were evaluated for their ability to bleach 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical at the concentration of 100 μg/mL using modified DPPH method[34] in dimethyl sulfoxide (DMSO) solvent. Butylated hydroxyanisole (BHA) was taken as standard". The in vitro antioxidant activity results are presented as a bar diagram in Figure 4. All the experiments were performed in triplicate, and the results are expressed as their mean values.

The precursor 5-(4-(prop-2-ynyloxy)phenyl)-3-(aryl)-4,-5-dihydropyrazole-1-carbothioamide (**2a-f)** exhibited DPPH scavenging activity varying from 90.7% to 77.18%, whereas the product 2-(3-(aryl)-5-(4-(prop-2-ynyloxy)phenyl)-4,-5-dihydropyrazol-1-yl)-4-(3-arylsydnone-4-yl)thiazole (**4a-l)** showed DPPH scavenging activity varying from 74.7% to 4.6%. The standard BHA showed 88.4% inhibition (Figure 4**)**. Compound 5-(4-(prop-2-ynyloxy) phenyl)-3-(p-fluorophenyl)-4,5-dihydropyrazole-1-carbothioamide **2c** and 5-(4-(prop-2-ynyloxy) phenyl)-3-(p- anisyl)-4,5-dihydropyrazole-1-carbothioamide (**2b)** showed radical scavenging activity higher than the standard used, that is, 90.7% and 89.8%, while 2-(3-(p-tolyl)-5-(4-[prop-2-ynyloxy] phenyl)-4,-5-dihydropyrazol-1-yl)-4-(3-phenyl sydnone-4-yl)thiazole (**4b)** displayed the least DPPH scavenging activity of 4.6%. Since the carbothioamide(thiole/thione tautomerization)[35] has a better electron-donating capacity over thiazole derivatives, it rapidly reduces the DPPH radical and showed better DPPH inhibition compared to thiazole derivatives. The overall study clearly manifests the importance of electron donor molecules in the DPPH inhibition activity.

2.4 | Experimental

Thin layer chromatography (TLC) was used for checking the progress and purity of the synthesized compounds (ethyl acetate: hexane (1:9)/ (3:7) mobile phase). IR were obtained in KBr discs (Shimadzu-8400 FTIR spectrophotometer). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 400 MHz Bruker Avance spectrometer with DMSO-d_6 (Deuterated Dimethyl sulfoxide) using TMS as an internal standard. CHN analysis was carried out on the ElementarVario-EL III model analyzer. The X-ray diffraction of compound **2d** obtained with Rigaku Saturn724+ diffractometer with graphite monochromated MoKa radiation at 296 K. Melting point was observed by open glass capillary method and were uncorrected.

2.5 | General procedure for the synthesis of 5-(4-(prop-2-ynyloxy) phenyl)-3-aryl-4,5-dihydropyrazole-1-carbothioamide (2a-f)

A mixture of 1-(p-substituted phenyl)-3-(4-(prop-2-ynyloxy) phenyl)prop-2-en-1-one (1a-f) (1 mmol) and thiosemicarbazide (0.7 g, 2 mmol) were taken in 50 mL of rb flask, 0.2 g of potassium hydroxide in ethanol (10 mL) was added to it

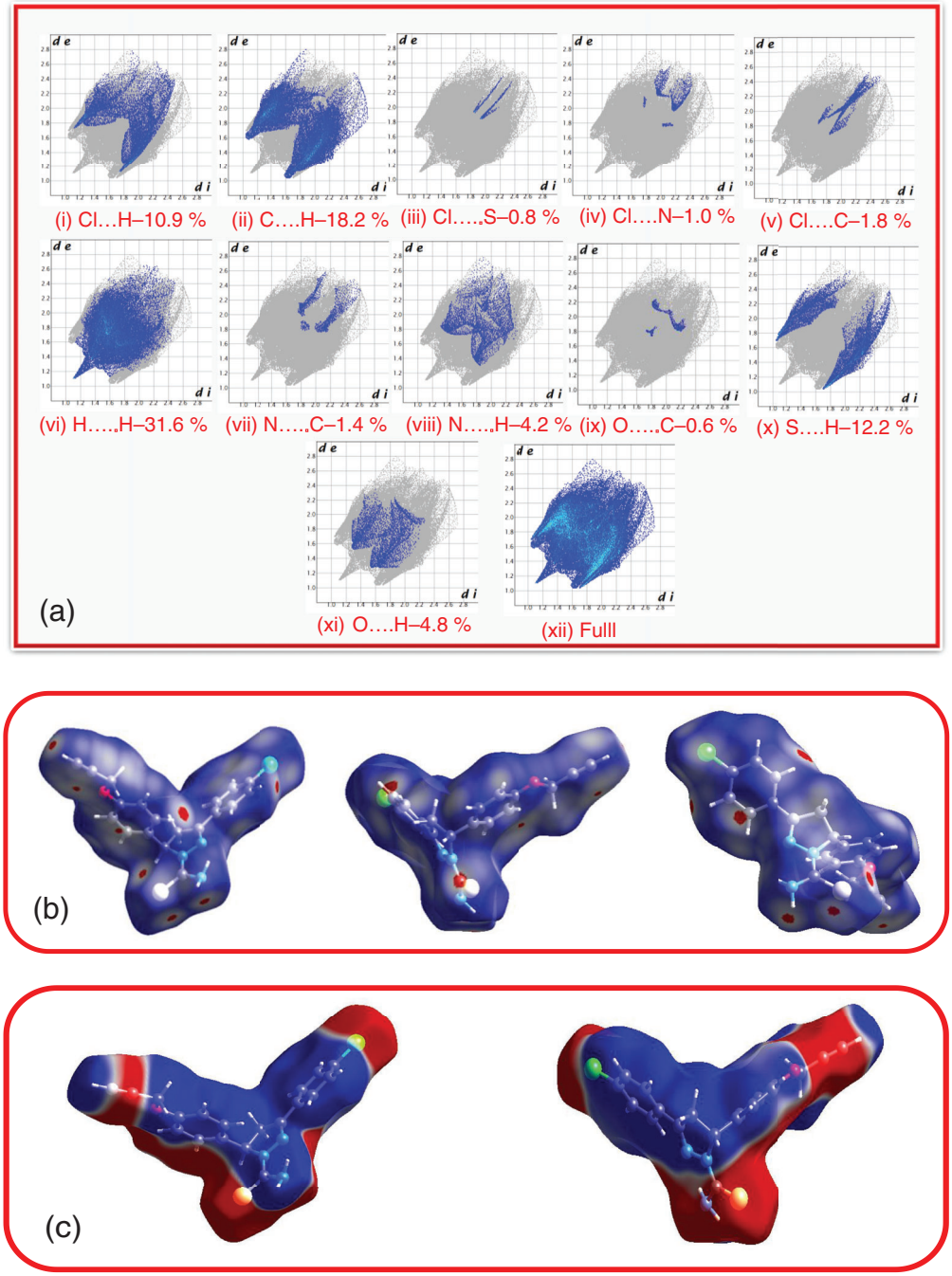


FIGURE 3
(A) Fingerprint plots: The outline of the full fingerprints are shown in gray (a (i-xi)), d_i is the closest internal distance from a given point on the Hirshfeld surface, and d_e is the closest external contacts. (B): The d_{norm} mapped on the Hirshfeld surface for visualizing the intercontacts of the compound **2d.** (C): Electrostatic potential mapped on the Hirshfeld surface (different orientation) with ±0.30 au. The blue region corresponds to positive electrostatic potential and red region to negative electrostatic potential

and refluxed in an oil bath at 80°C for 6 hours. After the reaction completion (monitored by TLC), the contents were cooled to room temperature (Scheme 1). The solid product obtained was filtered, washed with water, dried and recrystallized from ethanol-dimethylformamide mixture.

2.6 | 5-(4-(Prop-2-ynyloxy)phenyl)-3-(p-tolyl)-4,5-dihydropyrazole-1-carbothioamide (2a)

mp 168-170°C; yield 74%; white powder; IR: νmax/cm (KBr): 3442 (N-H), 3285 (≡C-H), 3153 (Ar C-H), 2125 (C≡C), 1598 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.35 (3H, *s*, CH_3), 3.06 (dd, 1H, J_{bx} = 3.4 Hz, J_{ba} = 18 Hz, Hb), 3.72 (*t*, 1H, *J* = 2.28 Hz, ≡C-H), 3.76 (dd, 1H, J_{ax} = 11.56 Hz, J_{ab} = 17.88 Hz, Ha), 4.69 (*d*, 2H, *J* = 2.28 Hz, OCH_2), 5.87 (dd, 1H, J_{xb} = 3.24 Hz, J_{xa} = 11.36 Hz, Hx), 6.87 (*d*, 2H, *J* = 8.68 Hz, ortho protons of p-propynyloxy phenyl ring), 7.08 (*d*, 2H, *J* = 8.64 Hz, meta protons of p-propynyloxy phenyl ring), 7.21 (*d*, 2H, *J* = 8.08 Hz, ortho protons of p-tolyl ring), 7.64 (bs, 1H, N-H), 7.70 (*d*, 2H, *J* = 8.08 Hz, meta protons of p-tolyl ring), 7.89 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 21.31, 43.84,

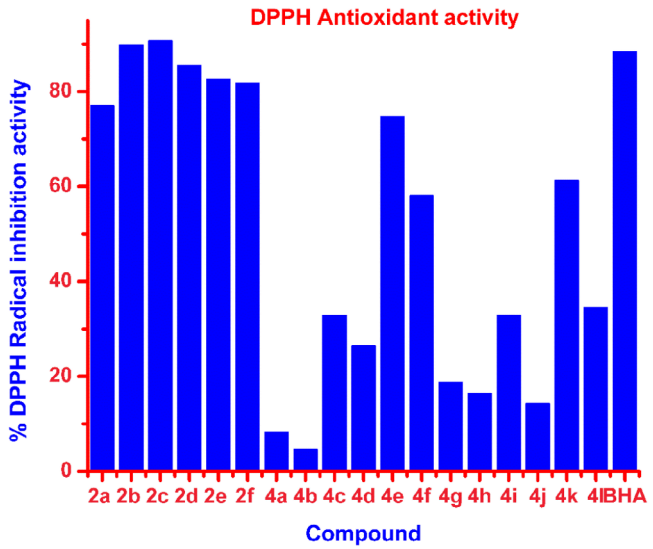


FIGURE 4 Antioxidant activity data of compound 2a-f and 4a-l

58.46, 67.51, 77.20, 77.42, 77.64, 78.20, 78.28, 114.30, 114.62, 123.82, 126.42, 127.74, 135.42, 144.53, 153.14, 158.98, 175.74 (C=S); Mass spectrum, m/z: 350 (M^++1); Elemental *Anal*. Calcd (%) for $C_{20}H_{19}N_3OS$: C, 68.68; H, 5.50; N, 12.04. Found C, 68.74; H, 5.48; N, 12.02.

2.7 | 5-(4-(Prop-2-ynyloxy) phenyl)-3-(p-anisyl)-4,5-dihydropyrazole-1-carbothioamide (2b)

mp: 149-150°C; yield 79%; pale yellow powder; IR: νmax/cm (KBr): 3339 (N-H), 3269 (≡C-H), 3106 (Ar C-H), 2120 (C≡C), 1574 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.09 (dd, 1H, J_{bx} = 3.24 Hz, J_{ba} = 18 Hz, Hb), 3.69 (*t*, 1H, *J* = 2.32 Hz, ≡C-H), 3.71 (dd, 1H, J_{ax} = 11.52 Hz, J_{ab} = 17.80 Hz, Ha), 3.78 (*s*, 3H, OCH_3), 4.52 (*d*, 2H, *J* = 2.32 Hz, OCH_2), 5.76 (dd, 1H, J_{xb} = 3.20 Hz, J_{xa} = 11.32 Hz, Hx), 6.75 (*d*, 2H, *J* = 8.84 Hz, ortho protons of p-propynyloxy phenyl ring), 7.02 (*d*, 2H, *J* = 8.88 Hz, meta protons of p-propynyloxy phenyl ring), 7.13 (*d*, 2H, *J* = 8.24 Hz, ortho protons of p-anisyl ring), 7.59 (bs, 1H, N-H), 7.63 (*d*, 2H, *J* = 8.08 Hz, meta protons of p-anisyl ring), 7.94 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 45.55, 59.76, 62.13, 76.47, 77.55, 77.27, 79.86, 78.34, 115.42, 115.87, 124.60, 125.74, 126.83, 137.96, 147.54, 158.22, 158.78, 175.34 (C=S); Mass spectrum, m/z: 365.8 (M^++1); Elemental *Anal*. Calcd (%) for $C_{20}H_{19}N_3O_2S$: C, 65.72; H, 5.20; N, 11.52. Found C, 65.79; H, 5.24; N, 11.50.

2.8 | 5-(4-(Prop-2-ynyloxy) phenyl)-3-(p-fluoro phenyl)-4,5-dihydropyrazole-1-carbothioamide (2c)

mp: 152-154°C; yield 73%; white powder; IR: νmax cm^{-1} (KBr): 3426 (N-H), 3291 (≡C-H), 3113 (Ar C-H), 2127 (C≡C), 1583 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.07 (dd, 1H, J_{bx} = 3.20 Hz, J_{ba} = 17.84 Hz, Hb), 3.66 (*t*, 1H, *J* = 2.28 Hz, ≡C-H), 3.80 (dd, 1H, J_{ax} = 11.58 Hz, J_{ab} = 17.94 Hz, Ha), 4.68 (*d*, 2H, *J* = 2.32 Hz, OCH_2), 5.78 (dd, 1H, J_{xb} = 3.34 Hz, J_{xa} = 11.52 Hz, Hx), 6.82-7.59 (*m*, 5H, Ar-H), 7.61 (bs, 1H, N-H), 7.67 to 7.73 (*m*, 3H, Ar-H), 7.79 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 45.18, 58.42, 62.88, 76.32, 77.47, 77.12, 78.76, 78.63, 114.82, 114.97, 123.17, 125.74, 126.89, 135.96, 148.05, 157.18, 162.88, 176.64 (C=S); Mass spectrum, m/z: 354 (M^++1); Elemental *Anal*. Calcd (%) for $C_{19}H_{16}FN_3OS$: C, 64.58; H, 4.54; N, 11.90. Found C, 64.57; H, 4.60; N, 11.86.

2.9 | 5-(4-(Prop-2-ynyloxy) phenyl)-3-(p-chloro phenyl)-4,5-dihydropyrazole-1-carbothioamide (2d)

mp: 148°C; yield 81%; yellowish brown powder; IR: νmax/cm (KBr): 3440 (N-H), 3265 (≡C-H), 3147 (Ar C-H), 2123 (C≡C), 1591 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.09 (dd, 1H, J_{bx} = 3.32 Hz, J_{ba} = 18 Hz, Hb), 3.72 (*t*, 1H, *J* = 2.36 Hz, ≡C-H), 3.84 (dd, 1H, J_{ax} = 11.48 Hz, J_{ab} = 18 Hz, Ha), 4.56 (*d*, 2H, *J* = 2.36 Hz, OCH_2), 5.73 (dd, 1H, J_{xb} = 3.28 Hz, J_{xa} = 11.52 Hz, Hx), 6.65 (*d*, 2H, *J* = 8.64 Hz, ortho protons of p-propynyloxy phenyl ring), 7.10 (*d*, 2H, *J* = 8.68 Hz, meta protons of p-propynyloxy phenyl ring), 7.19 to 7.22 (*m*, 4H, *J* = 8.08 Hz, Ar-H), 7.52 (bs, 1H, N-H), 7.73 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 43.90, 56.48, 62.62, 77.32, 77.47, 77.69, 78.28, 78.47, 114.49, 114.67, 123.87, 126.55, 127.82, 135.47, 144.61, 153.24, 159.06, 175.48 (C=S); Mass spectrum, m/z: 370 (M^++1), 371.8 (M^++3); Elemental *Anal*. Calcd (%) for $C_{19}H_{16}ClN_3OS$: C, 61.72; H, 4.38; N, 11.34. Found C, 61.70; H, 4.41; N, 11.39.

2.10 | 5-(4-(Prop-2-ynyloxy) phenyl)-3-(p-bromo phenyl)-4,5-dihydropyrazole-1-carbothioamide (2e)

mp: 182-184°C; yield 71%; white powder; IR: νmax/cm (KBr): 3414 (N-H), 3276 (≡C-H), 3222 (Ar C-H), 2126 (C≡C), 1599 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.09 (dd, 1H, J_{bx} = 3.4 Hz, J_{ba} = 18 Hz, Hb), 3.32 (*t*, 1H, *J* = 2.24 Hz, ≡C-H), 3.80 (dd, 1H, J_{ax} = 11.52 Hz, J_{ab} = 17.96 Hz, Ha), 4.70 (*d*, 2H, *J* = 2.24 Hz, OCH_2), 5.89

(dd, 1H, J_{xb} = 3.24 Hz, J_{xa} = 11.32 Hz, Hx), 6.88 (*d*, 2H, *J* = 8.64 Hz, ortho protons of p-propynyloxy phenyl ring), 7.07 (*d*, 2H, *J* = 8.64 Hz, meta protons of p-propynyloxy phenyl ring), 7.58 (*d*, 2H, *J* = 8.48 Hz, ortho protons of p-bromo phenyl ring), 7.60 (bs, 1H, N-H), 7.77 (*d*, 3H, *J* = 8.56 Hz, meta protons of p-bromo phenyl ring and N-H), 8.00 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 44.11, 57.24, 63.32, 76.88, 77.34, 77.24, 78.28, 78.47, 113.12, 113.67, 122.92, 125.79, 126.82, 135.47, 144.41, 153.10, 158.58, 176.64 (C=S); Mass spectrum, m/z: 414 (M^++1), 416 (M^++3); Elemental *Anal*. Calcd (%) for $C_{19}H_{16}BrN_3OS$: C, 55.10; H, 3.90; N, 10.17 Found C, 55.15; H, 3.90; N, 10.14.

2.11 | 5-(4-(Prop-2-ynyloxy) phenyl)-3-((4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazole-1-carbothioamide (2f)

mp: 215-217°C; yield 79%; white powder; IR: νmax/cm (KBr): 3399 (N-H), 3246 (≡C-H), 3209 (Ar C-H), 2124 (C≡C), 1607 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.08 (dd, 1H, J_{bx} = 3.32 Hz, J_{ba} = 17.84 Hz, Hb), 3.21 (*t*, 1H, *J* = 2.36 Hz, ≡C-H), 3.27 (*t*, 1H, *J* = 2.32 Hz, ≡C-H), 3.77 (dd, 1H, J_{ax} = 11.36 Hz, J_{ab} = 17.8 Hz, Ha), 4.69 (*d*, 2H, *J* = 2.36 Hz, OCH_2), 4.80 (*d*, 2H, *J* = 2.40 Hz, OCH_2), 5.87 (dd, 1H, J_{xb} = 3.08 Hz, J_{xa} = 11.16 Hz, Hx), 6.87 (*d*, 2H, *J* = 11.32 Hz, ortho protons of p-propynyloxy phenyl ring), 7.01 (*d*, 2H, *J* = 8.88 Hz, ortho protons of p-propynyloxy phenyl ring), 7.08 (*d*, 2H, *J* = 8.72 Hz, meta protons of p-propynyloxy phenyl ring), 7.58 (bs, 1H, N-H), 7.77 (dd, 2H, *J* = 11.32 Hz, meta protons of p-propynyloxy phenyl ring), 7.83 (bs, 1H, N-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 42.46, 55.27, 55.48, 62.08, 77.18, 77.56, 78.15 to 78.19, 78.52 to 78.67, 78.72 to 78.85, 114.49, 114.79, 123.88, 126.45, 128.43, 135.49, 154.55, 156.14, 158.99, 175.75 (C=S); Mass spectrum, m/z: 390 (M^++1); Elemental *Anal*. Calcd (%) for $C_{22}H_{19}N_3O_2S$: C, 67.88; H, 4.84; N, 10.88 Found C, 67.83; H, 4.92; N, 10.79.

2.12 | General procedure for the synthesis of 2-(3-(aryl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-arylsydnone-4-yl)thiazole (4a-l)

A mixture of 5-(4-(prop-2-ynyloxy) phenyl)-3-aryl-4,-5-dihydropyrazole-1-carbothioamide (2a-f) (1 mmol) and 4-bromoacetyl-3-(aryl) sydnone (3a-b) (1 mmol) in ethanol (10 mL) was taken in a round-bottomed flask and stirred at room temperature for 10 to 12 hours (Scheme. 2). The solid mass obtained was filtered, washed with ethanol, dried and recrystallized from ethanol.

2.13 | 2-(3-(p-Tolyl)-5-(4-[prop-2-ynyloxy] phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl)thiazole (4a)

mp: 196-198°C; yield 74%; yellow powder; IR: νmax cm^{-1} (KBr): 3119 (≡C-H), 3278 (Ar C-H), 2120 (C ≡ C), 1735 (C=O), 1608 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.37 (*s*, 3H, CH_3), 2.49(*s*, 3H, CH_3), 2.51 (*t*, 1H, *J* = 2.4 Hz, ≡C-H), 3.11 (dd, 1H, J_{bx} = 5.4 Hz, J_{ba} = 17.44 Hz, Hb), 3.72 (dd, 1H, J_{ax} = 11.96 Hz, J_{ab} = 17.32 Hz, Ha), 4.66 (*d*, 2H, *J* = 2.4 Hz, OCH_2), 4.98 (dd, 1H, J_{xb} = 5.44 Hz, J_{xa} = 11.92 Hz, Hx), 6.75 (*d*, 2H, *J* = 8.8 Hz, ortho protons of p-tolyl ring), 7.30 (*d*, 2H, *J* = 8.4 Hz, meta protons of p-tolyl ring), 7.57 (*d*, 2H, *J* = 8.16 Hz, Ar-H), 7.47 (*s*, 1H, thiazole-5H); ^{13}C-NMR (DMSO-d_6, δ ppm): 21.37, 21.79, 43.72, 56.41, 63.65, 78.20, 78.46, 78.76, 78.84, 79.09, 103.81, 110.61, 122.17, 125.26, 127.12, 128.71, 128.18, 131.44, 131.78, 133.12, 135.29, 137.08, 152.27, 156.61, 164.21, 165.76; Mass spectrum, m/z: 547.8 (M^++1); Elemental *Anal*. Calcd (%) for $C_{31}H_{25}N_5O_3S$: C, 68.04; H, 4.68; N, 12.80 Found C, 67.99; H, 4.60; N, 12.88.

2.14 | 2-(3-(p-Tolyl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(phenyl) sydnone-4-yl)thiazole (4b)

mp: 170 tc172°C; yield 68%; orange powder; IR: νmax/cm (KBr): 3103 (≡C-H), 3283 (Ar C-H), 2120 (C≡C), 1731 (C=O), 1598 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.35 (*s*, 3H, CH_3), 2.52 (t, 1H, *J* = 2.36 Hz, ≡C-H), 3.14 (dd, 1H, J_{bx} = 5.56 Hz, J_{ba} = 17.62 Hz, Hb), 3.71 (dd, 1H, J_{ax} = 11.88 Hz, J_{ab} = 17.56 Hz, Ha), 4.62 (*d*, 2H, *J* = 2.4 Hz, OCH_2), 4.90 (dd, 1H, J_{xb} = 5.40 Hz, J_{xa} = 11.80 Hz, Hx), 6.69 (*d*, 2H, *J* = 8.8 Hz, ortho protons of p-tolyl ring), 6.78 to 7.19 (*m*, 7H, Ar-H), 7.22 (*d*, 2H, *J* = 8.8 Hz, meta protons of p-tolyl ring), 7.39 (*d*, 2H, *J* = 8.12 Hz, Ar-H), 7.48 (*s*, 1H, thiazole-5H); ^{13}C-NMR (DMSO-d_6, δ ppm): 15.28, 44.71, 56.21, 62.39, 77.97, 78.83, 79.69, 79.91, 80.10, 105.53, 107.68, 113.71, 124.85, 127.23, 127.61, 128.45, 128.97, 130.10, 131.69, 131.90, 133.54, 134.67, 137.14, 154.28, 163.12, 166.22; Mass spectrum, m/z: 534 (M^++1); Elemental *Anal*. Calcd (%) for $C_{30}H_{23}N_5O_3S$: C, 67.62; H, 4.38; N, 13.14 Found C, 67.53; H, 4.34; N, 13.19.

2.15 | 2-(3-(p-Anisyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl)thiazole (4c)

mp: 188 to 190°C; yield 77%; yellow powder; IR: νmax/cm (KBr): 3288 (≡C-H), 3128 (Ar C-H), 2159

(C≡C), 1735 (C=O), 1609 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.49 (*s*, 3H, CH_3), 2.51 (*t*, 1H, J = 2.36 Hz, ≡C-H), 3.10 (dd, 1H, J_{bx} = 5.44 Hz, J_{ba} = 17.36 Hz, Hb), 3.71 (dd, 1H, J_{ax} = 11.88 Hz, J_{ab} = 17.32 Hz, Ha), 3.78 (*s*, 3H, OCH_3), 4.66 (*d*, 2H, *J* = 2.36 Hz, OCH_2), 4.96 (dd, 1H, J_{xb} = 5.36 Hz, J_{xa} = 11.80 Hz, Hx), 6.75 (*d*, 2H, *J* = 8.8 Hz, ortho protons of p-tolyl ring), 6.80 (*d*, 2H, *J* = 8.8 Hz, meta protons of p-tolyl ring), 6.89 (*d*, 2H, *J* = 8.88 Hz, ortho protons of p-propynyloxy phenyl ring), 7.17 (*d*, 2H, *J* = 8.2 Hz, ortho protons of p-anisyl ring), 7.30 (*d*, 2H, *J* = 8.36 Hz, meta protons of p-anisyl ring), 7.46 (*s*, 1H, thiazole-5H), 7.61 (*d*, 2H, *J* = 8.84 Hz, meta protons of p-propynyloxy phenyl ring); ^{13}C-NMR (DMSO-d_6, δ ppm): 21.28, 55.45, 56.54, 63.12, 77.28, 77.80, 78.13, 78.26, 78.64, 104.54, 104.91, 110.17, 110.64, 126.32, 127.88, 130.43, 130.91, 134.47, 134.82, 135.25, 135.70, 136.42, 152.28, 159.67, 161.38, 162.64, 165.33; Mass spectrum, m/z: 564.15 (M^++1); Elemental *Anal*. Calcd (%) for $C_{31}H_{25}N_5O_4S$: C, 66.10; H, 4.49; N, 12.52 Found C, 66.06; H, 4.47; N, 12.43.

2.16 | 2-(3-(p-Anisyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(phenyl) sydnone-4-yl)thiazole (4d)

mp: 205 to 207°C; yield 82%; yellow powder; IR: νmax/cm (KBr): 3279 (≡C-H), 3198 (Ar C-H), 2142 (C≡C), 1737 (C=O), 1598 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.53 (*t*, 1H, *J* = 2.36 Hz, ≡C-H), 3.16 (dd, 1H, J_{bx} = 5.56 Hz, J_{ba} = 17.32 Hz, Hb), 3.69 (dd, 1H, J_{ax} = 11.80 Hz, J_{ab} = 17.32 Hz, Ha), 3.73 (*s*, 3H, OCH_3), 4.58 (*d*, 2H, *J* = 2.32 Hz, OCH_2), 4.91 (dd, 1H, J_{xb} = 5.40 Hz, J_{xa} = 11.88 Hz, Hx), 6.69 (*d*, 2H, *J* = 8.84 Hz, ortho protons of p-tolyl ring), 6.76 (*d*, 2H, *J* = 8.88 Hz, meta protons of p-tolyl ring), 6.83 to 7.57 (*d*, 9H, Ar-H), 7.59 (*s*, 1H, thiazole-5H); ^{13}C-NMR (DMSO-d_6, δ ppm): 43.81, 55.51, 56.60, 63.30, 77.86, 77.98, 78.22, 78.44, 79.12, 105.17, 105.62, 110.12, 110.86, 125.27, 127.80, 130.42, 130.89, 133.44, 133.44, 133.76, 135.17, 135.08, 136.17, 152.18, 159.62, 161.62, 162.66, 165.18; Mass spectrum, m/z: 549.75 (M^++1); Elemental *Anal*. Calcd (%) for $C_{30}H_{23}N_5O_4S$: C, 65.62; H, 4.28; N, 12.82 Found C, 65.56; H, 4.22; N, 12.74.

2.17 | 2-(3-(p-Fluorophenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl)thiazole (4e)

mp: 208 to 210°C; yield 77%; yellow powder; IR: νmax/cm (KBr): 3286 (≡C-H), 2974 (Ar C-H), 2136 (C≡C), 1733 (C=O), 1589 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.32 (*s*, 3H, CH_3), 2.48 (*t*, 1H, *J* = 2.36 Hz, ≡C-H), 3.25 (dd, 1H, J_{bx} = 6.72 Hz, J_{ba} = 17.44 Hz, Hb), 3.80 (dd, 1H, J_{ax} = 12 Hz, J_{ab} = 17.44 Hz, Ha), 4.65 (*d*, 2H, *J* = 2.4 Hz, OCH_2), 5.60 (dd, 1H, J_{xb} = 6.68 Hz, J_{xa} = 11.88 Hz, Hx), 6.74 (*s*, 1H, thiazole-5H), 6.92 to 7.75 (*m*, 12H, Ar-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 15.28, 43.32, 55.67, 62.90, 77.81, 78.60, 79.08, 79.44, 79.92, 104.22, 107.41, 114.32, 124.12, 126.48, 127.40, 128.79, 128.96, 132.40, 132.80, 133.13, 133.42, 137.25, 152.33. 164.54, 165.28, 166.45; Mass spectrum, m/z: 552 (M^++1); Elemental *Anal*. Calcd (%) for $C_{30}H_{22}FN_5O_3S$: C, 65.38; H, 4.08; N, 12.82 Found C, 65.32; H, 4.02; N, 12.70.

2.18 | 2-(3-(p-Fluorophenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(phenyl) sydnone-4-yl)thiazole (4f)

mp: 189 to 191°C; yield 74%; yellow powder; IR: νmax/cm (KBr): 3299 (≡C-H), 2965 (Ar C-H), 2127 (C≡C), 1735 (C=O), 1603 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.45 (t, 1H, *J* = 2.36 Hz, ≡C-H), 3.29 (dd, 1H, J_{bx} = 6.68 Hz, J_{ba} = 17.40 Hz, Hb), 3.75 (dd, 1H, J_{ax} = 12 Hz, J_{ab} = 17.44 Hz, Ha), 4.64 (*d*, 2H, *J* = 2.8 Hz, OCH_2), 5.57 (dd, 1H, J_{xb} = 6.64 Hz, J_{xa} = 11.96 Hz, Hx), 6.76 (*s*, 1H, thiazole-5H), 6.88-7.26 (*m*, 8H, Ar-H), 7.31 to 7.69 (*m*, 5H, Ar-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 43.12, 55.64, 62.98, 77.82, 78.64, 79.02, 79.41, 79.89, 104.94, 108.30, 114.64, 124.04, 126.42, 127.37, 128.31, 128.91, 131.43, 131.86, 133.39, 135.21, 136.27, 152.39, 164.55, 165.14, 166.70; Mass spectrum, m/z: 538 (M^++1); Elemental *Anal*. Calcd (%) for $C_{29}H_{20}FN_5O_3S$: C, 64.84; H, 3.82; N, 13.07 Found C, 64.79; H, 3.75; N, 13.03.

2.19 | 2-(3-(p-Chloro phenyl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl)thiazole (4 g)

mp: 154 to 156°C; yield 80%; orange powder; IR: νmax/cm (KBr): 3298 (≡C-H), 2956 (Ar C-H), 2131 (C≡C), 1736 (C=O), 1594 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.34 (*s*, 3H, CH_3), 2.49 (*t*, 1H, *J* = 2.36 Hz, ≡C-H), 3.06 (dd, 1H, J_{bx} = 5.44 Hz, J_{ba} = 17.92 Hz, Hb), 3.75 (dd, 1H, J_{ax} = 11.96 Hz, J_{ab} = 18 Hz, Ha), 4.78 (*d*, 2H, *J* = 2.32 Hz, OCH_2), 4.99 (dd, 1H, J_{xb} = 5.36 Hz, J_{xa} = 11.96 Hz, Hx), 6.63 (*d*, 2H, *J* = 8.68 Hz, ortho protons of p-chloro phenyl ring), 6.73 (*s*, 1H, thiazole-5H), 6.79 (*d*, 2H, *J* = 8.56 Hz, meta protons of p-propynyloxy phenyl ring), 7.21 (*d*, 2H, *J* = 8.76 Hz, ortho protons of p-tolyl ring) 7.28 (*d*, 2H, *J* = 8.28 Hz, meta protons of p-chloro phenyl ring), 7.42 (*d*, 2H, *J* = 8.8 Hz, meta protons of p-tolyl ring), 7.51 (dd, 2H, *J* = 7.6 Hz, ortho protons of

p-propynyloxy phenyl ring);^{13}C-NMR (DMSO-d_6, δ ppm): 44.15, 56.17, 63.22, 77.94, 78.62, 79.33, 79.81, 80.15, 105.63, 108.14, 113.80, 124.89, 127.14, 127.39, 128.44, 128.98, 129.12, 132.11, 131.89, 133.24, 135.17, 137.04, 153.11, 162.60, 165.40; Mass spectrum, m/z: 568 (M^++1), 570 (M^++3); Elemental *Anal*. Calcd (%) for $C_{30}H_{22}ClN_5O_3S$: C, 63.48; H, 3.92; N, 12.30 Found C, 63.43; H, 3.90; N, 12.33.

2.20 | 2-(3-(p-Chlorophenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(phenyl) sydnone-4-yl)thiazole (4 hours)

mp: 169°C; yield 79%; yellow powder; IR: νmax/cm (KBr): 3277 (≡C-H), 2987 (Ar C-H), 2359(C≡C), 1733 (C=O), 1587 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.53 (t, 1H, J = 2.36 Hz, ≡C-H), 3.18 (dd, 1H, J_{bx} = 5.44 Hz, J_{ba} = 17.96 Hz, Hb), 3.86 (dd, 1H, J_{ax} = 12 Hz, J_{ab} = 17.96 Hz, Ha), 4.71 (*d*, 2H, J = 2.36 Hz, OCH_2), 5.01 (dd, 1H, J_{xb} = 5.28 Hz, J_{xa} = 11.84 Hz, Hx), 5.61 (*s*, 1H, thiazole-5H), 6.69 (*d*, 2H, J = 8.72 Hz, ortho protons of p-chloro phenyl ring), 6.80 (*d*, 2H, J = 8.76 Hz, meta protons of p-propynyloxy phenyl ring), 7.33 (*d*, 2H, J = 8.28 Hz, meta protons of p-chloro phenyl ring), 7.42 to 7.46 (*m*, 5H, Ar-H), 7.71 (dd, 2H, J = 6.8 Hz, ortho protons of p-propynyloxy phenyl ring); ^{13}C-NMR (DMSO-d_6, δ ppm): 43.97, 57.01, 61.23, 79.36, 79.62, 79.79, 80.07, 82.71, 103.21, 105.79, 113.29, 126.01, 126.97, 127.33, 128.25, 128.77, 129.21, 130.09, 130.66, 133.54, 134.93, 137.21, 154.06, 163.17, 165.56; Mass spectrum, m/z: 553.8 (M^++1), 556 (M^++3); Elemental *Anal*. Calcd (%) for $C_{29}H_{20}ClN_5O_3S$: C, 62.89; H, 3.60; N, 12.62 Found C, 62.87; H, 3.64; N, 12.65.

2.21 | 2-(3-(p-Bromophenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl)thiazole (4i)

mp: 179 to 181°C; yield 75%; yellow powder; IR: νmax/cm (KBr): 3290 (≡C-H), 3136 (Ar C-H), 2159 (C≡C), 1736 (C=O),1610 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.42 (*s*, 3H, CH_3), 2.51 (*t*, 1H, J = 2.36 Hz, ≡C-H), 3.29 (dd, 1H, J_{bx} = 6.68 Hz, J_{ba} = 17.48 Hz, Hb), 3.84 (dd, 1H, J_{ax} = 11.92 Hz, J_{ab} = 17.44 Hz, Ha), 4.68 (*d*, 2H, J = 2.36 Hz, OCH_2), 5.57 (dd, 1H, J_{xb} = 6.64 Hz, J_{xa} = 11.88 Hz, Hx), 6.81 (*s*, 1H, thiazole-5H), 6.96 (*d*, 2H, J = 8.72 Hz, ortho protons of p-bromo phenyl ring), 7.24 (*d*, 2H, J = 7.36 Hz, ortho protons of p-propynyloxy phenyl ring), 7.36 (*d*, 2H, J = 8.68 Hz, meta protons of p-bromo phenyl ring), 7.44 (*d*, 2H, J = 8.52 Hz, ortho protons of p-tolyl ring), 7.55 (*d*, 2H, J = 8.52 Hz, meta protons of p-tolyl ring), 7.66 (*d*, 2H, J = 8.12 Hz, meta protons of p-propynyloxy phenyl ring); ^{13}C-NMR (DMSO-d_6, δ ppm): 15.46, 41.45, 54.79, 62.36, 77.61, 77.48, 78.32, 78.69, 79.28, 105.80, 107.52, 112.60, 124.67, 124.89, 126.18, 127.94, 128.88, 131.63, 132.12, 132.79, 134.86, 135.42, 153.34, 155.72, 165.33, 166.41; Mass spectrum, m/z: 612.6 (M^++1); Elemental *Anal*. Calcd (%) for $C_{30}H_{24}BrN_5O_3S$: C, 58.69; H, 3.99; N, 11.40 Found C, 58.64; H, 3.94; N, 11.40.

2.22 | 2-(3-(p-Bromophenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-(phenyl) sydnone-4-yl)thiazole (4j)

mp: 216 to 218°C; yield 86%; orange powder; IR: νmax/cm (KBr): 3265 (≡C-H), 2988 (Ar C-H), 2117 (C≡C), 1726 (C=O),1589 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.51 (*t*, 1H, J = 2.36 Hz, ≡C-H), 3.17 (dd, 1H, J_{bx} = 5.36 Hz, J_{ba} = 18.04 Hz, Hb), 3.85 (dd, 1H, J_{ax} = 12.04 Hz, J_{ab} = 18.08 Hz, Ha), 4.73 (*d*, 2H, J = 2.36 Hz, OCH_2), 4.94 (dd, 1H, J_{xb} = 5.2 Hz, J_{xa} = 11.88 Hz, Hx), 6.65 (*d*, 2H, J = 8.72 Hz, ortho protons of p-bromo phenyl ring), 6.80 (*d*, 2H, J = 8.72 Hz, meta protons of p-bromo phenyl ring), 7.43 (*s*, 1H, thiazole-5H), 7.57 to 7.71 (*m*, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6, δ ppm): 42.77, 55.29, 62.90, 77.81, 78.48, 78.81, 78.89, 79.14, 104.90, 108.22, 114.54, 123.41, 125.56, 127.14, 128.13, 128.78, 131.43, 131.62, 133.40, 135.02, 136.32, 152.24, 156.42, 164.13, 165.90; Mass spectrum, m/z: 598 (M^++1); Elemental *Anal*. Calcd (%) for $C_{29}H_{20}BrN_5O_3S$: C, 58.15; H, 3.42; N, 11.71 Found C, 58.20; H, 3.37; N, 11.70.

2.23 | 2-(3-(4-(Prop-2-ynyloxy) phenyl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydro pyrazol-1-yl)-4-(3-(p-tolyl) sydnone-4-yl) thiazole (4 k)

mp: 188°C; yield 85%; yellow powder; IR: νmax/cm (KBr): 3286 (≡C-H), 2987 (Ar C-H), 2182 (C≡C), 1732 (C=O), 1606 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.32 (*s*, 3H, CH_3), 2.47 (*t*, 1H, J = 2.28 Hz, ≡C-H), 2.53 (*t*, 1H, J = 2.32 Hz, ≡C-H), 3.24 (dd, 1H, J_{bx} = 6.6 Hz, J_{ba} = 17.4 Hz, Hb), 3.78 (dd, 1H, J_{ax} = 11.92 Hz, J_{ab} = 17.4 Hz, Ha), 4.64 (*d*, 2H, J = 2.32 Hz, OCH_2), 4.72 (*d*, 2H, J = 2.08 Hz, OCH_2), 5.58 (dd, 1H, J_{xb} = 6.56 Hz, J_{xa} = 11.76 Hz, Hx), 6.72 (*s*, 1H, thiazole-5H), 6.92 (*d*, 2H, J = 8.68 Hz, ortho protons of p-tolyl ring), 6.99 (*d*, 2H, J = 8.84 Hz, ortho protons of p-propynyloxy phenyl ring), 7.10 (*d*, 2H, J = 8.00 Hz, ortho protons of p-propynyloxy

phenyl ring), 7.34 (*d*, 2H, J = 8.68 Hz, meta protons of p-tolyl ring), 7.56 (*d*, 2H, J = 8.08 Hz, meta protons of p-propynyloxy phenyl ring), 7.69 (*d*, 2H, J = 8.76 Hz, meta protons of p-propynyloxy phenyl ring); ^{13}C-NMR (DMSO-d_6, δ ppm): 21.26, 42.57, 55.44, 55.71, 61.64, 77.28, 77.66, 78.32 to 78.41, 78.55 to 78.69, 78.70 to 78.83, 114.40, 114.72, 123.89, 126.47, 127.18, 128.37, 128.64, 135.62, 135.78, 136.51, 139.40, 140.81, 152.62, 158.37, 160.26, 162.44, 166.80; Mass spectrum, m/z: 588.1 (M^++1); Elemental *Anal*. Calcd (%) for $C_{33}H_{25}N_5O_4S$: C, 67.49; H, 4.32; N, 12.02 Found C, 67.45; H, 4.29; N, 11.92.

2.24 | 2-(3-(4-(Prop-2-ynyloxy)phenyl)-5-(4-(prop-2-ynyloxy)phenyl)-4,5-dihydro pyrazol -1-yl)-4-(3-(phenyl) sydnone-4-yl) thiazole (4l)

mp: 155 to 157°C; yield 79%; yellow powder; IR: νmax/cm (KBr): 3312 (≡C-H), 3290 (Ar C-H), 2136 (C≡C), 1731 (C=O) and 1608 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 3.13 (dd, 1H, J_{bx} = 5.28 Hz, J_{ba} = 17.84 Hz, Hb),δ 3.29 (*t*, 1H, J = 2.4 Hz, ≡C-H), 3.31 (*t*, 1H, J = 2.28 Hz, ≡C-H), 3.81 (dd, 1H, J_{ax} = 11.88 Hz, J_{ab} = 17.8 Hz, Ha), 4.71 (*d*, 2H, J = 2.36 Hz, OCH_2), 4.80 (*d*, 2H, J = 2.36 Hz, OCH_2), 4.91 (dd, 1H, J_{xb} = 5.12 Hz, J_{xa} = 11.72 Hz, Hx), 6.67 (*d*, 2H, J = 8.72 Hz, ortho protons of p-propynyloxy phenyl ring), 6.79 (*d*, 2H, J = 8.76 Hz, meta protons of p-propynyloxy phenyl ring), 7.02 (*d*, 2H, J = 8.92 Hz, ortho protons of p-propynyloxy phenyl ring), 7.39 (*s*, 1H, thiazole-5H), 7.54-7.69 (*m*, 7H, meta protons of p-propynyloxy phenyl ring and protons of phenyl ring); ^{13}C- NMR (DMSO-d_6, δ ppm): 42.42, 55.28, 55.42, 62.22, 77.24, 77.67, 78.24 to 78.28, 78.50 to 78.64, 78.70-78.83, 114.39, 114.64, 123.82, 126.39, 127.22, 128.12, 128.47, 135.52, 135.88, 136.64, 139.26, 140.21, 152.61, 158.28, 160.51, 162.24, 166.75; Mass spectrum, m/z: 574 (M^++1); Elemental *Anal*. Calcd (%) for $C_{32}H_{23}N_5O_4S$: C, 67.08; H, 4.12; N, 12.22 Found C, 67.00; H, 4.04; N, 12.21.

3 | CONCLUSION

In summary, a novel series of thiazole bearing terminal acetylene were prepared by Hantzsch cyclization. Majority of the synthesized carbothioamide molecules **2a-f** exhibited excellent DPPH scavenging activity varying from 90.7% to 77.18%, in particular, compounds **2c** (90.7%) and **2b** (89.8%) exhibited excellent DPPH scavenging activity which is higher than the standard used BHA. The high pronounced activity of the carbothioamide (**2a-f**) derivative might be due to the ability of molecule to undergo amine/imine tautomerization.

Soon after the cyclization of carbothioamide into thiazole derivatives, the DPPH activity was reduced. The less pronounced radical inhibition activity of thiazole derivatives (**4a-l**) majorly attributed to the lack of electron/ proton donor capacity in the synthesized molecules. Further with the help of Hirshfeld surface computational method short contacts in the crystal structure are quantified and visualized (2D fingerprint plot) and major intercontacts present in compound **2d** are H...H (31.6%), C...H (18.2%).

ACKNOWLEDGMENTS

The authors are thankful to SAIF Punjab University, PURSE laboratory Mangalore University for providing the facility for spectral analysis. Asma is thankful to UGC, New Delhi for Maulana Azad National Senior Research Fellowship (MANF).

ORCID

Balakrishna Kalluraya https://orcid.org/0000-0003-0442-7178

REFERENCES

[1] D. L. Browne, J. P. A. Harrity, *Tetrahedron. Lett.* **2010**, *66*, 553.
[2] G. Rai, V. G. Puranik, B. Kalluraya, J. C. Hedge, *Synth. Commun.* **2006**, *36*, 1285.
[3] E. M. Chang, T. H. Chen, F. F. Wong, E. C. Chang, M. Y. Yeh, *Syn Lett.* **2006**, *6*, 901.
[4] K. Butković, N. Basarić, K. Lovreković, Ž. Marinić, A. Višnjevac, B. Kojić-Prodić, M. Šindler-Kulyk, *Tetrahedron Lett.* **2004**, *45*, 9057.
[5] U. Mazzucato, D. Pannaci, M. Sindler-Kulyk, K. Butkovic, J. Spalleti, *Photochem. Photobiol. A. Chem.* **2018**, *351*, 124.
[6] W. Xu, W. Zhang, F. Zhang, *Heterocycl. Commun.* **2016**, *22*, 165.
[7] N. Manju, B. Kalluraya, M. Asma, S. K. Madan, *Heterocyclic. Lett.* **2018**, *8*, 619.
[8] A. Srinivas, M. Sunitha, R. Vasumathi, P. Karthik, G. Rajesh Kumar, *J. Heterocycl. Chem.* **2018**, *55*, 1564.
[9] A. Meyer, C. P. Bagowski, M. Kokoschka, M. Stefanopoulou, H. Alborzinia, S. Can, D. H. Vlecken, W. S. Sheldrick, S. Wölfl, I. Ott, *Angew. Chem. Int. Ed.* **2012**, *51*, 8895.
[10] J. S. Suzanne, A. L. Petr, S. G. Sudagar, B. C. Ian, L. S. Merrill, E. M. David, S. B. Gurdyal, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 373.
[11] M. Lara, *Sexual Chemistry: A History of Contraceptive Pill*, *Yale University Press*, New Haven, Connecticut. **2010**, 74–75. https://books.google.com/books?id=_i-s4biQs7MC&pg=PA75.
[12] T. Tasneem, R. K. Ravindra, B. M. Sheetal, *J. Heterocycl. chem.* **2014**, *51*, 323.
[13] N. Manju, B. Kalluraya, M. S. K. Asma, B. C. Revanasiddappa, *J. Med. Chem.Sci.* **2019**, *2*, 101.
[14] K. S. Girish, B. Kalluraya, V. Naryana, Padmashree, *Eur. J. Med. Chem.* **2010**, *45*, 4640.
[15] N. C. Desai, D. Panday, D. Vaja, *Med. Chem. Res.* **2018**, *27*, 52.

[16] N. C. Desai, H. V. Vaghani, B. Y. Patel, T. J. Karkar, *Indian. J. Pharm. Sci.* **2018**, *80*, 242.
[17] R. Mills, G. Wu, *J. Pharm. Sci.* **2004**, *93*, 1320.
[18] H. H. Hussain, G. Babie, T. Durst, J. S. Wright, M. Flucraru, A. Chichrau, L. I. Chapelev, *J. Org. Chem.* **2003**, *68*, 7023.
[19] Y. Dong, T. Venkatachalam, R. Narla, V. Trieu, E. Sudbeck, F. Uckun, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 87.
[20] M. A. A. Hana, *J. Heterocyclic. Chem.* **2020**, *57*, 1. https://doi.org/10.1002/jhet.3820.
[21] B. V. Kopylova, R. G. Gasanov, R. K. Friedlina, *Russ. Chem. Bull.* **1981**, *30*, 1059.
[22] P. Yadav, K. Lal, A. Kumar, S. K. Guru, S. Jaglan, S. Bhushan, *Eur. J. Med. Chem.* **2017**, *126*, 944.
[23] B. Yu, P.-P. Qi, X. J. Shi, R. Huang, H. Guo, Y. C. Zheng, D. Q. Yu, H. M. Liu, *Eur. J. Med. Chem.* **2016**, *117*, 241.
[24] H. J. Tien, K. Kanda, A. Chinone, M. Ohta, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3304.
[25] P. C. Shyma, B. Kalluraya, S. K. Peethambar, A. M. Vijesh, *Med. Chem. Res.* **2016**, *25*, 2680.
[26] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689.
[27] K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46.
[28] G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Crystallogr.* **2017**, *64*, 112.
[29] N. Manju, B. Kalluraya, Asma, S. M. Kumar, *J. Mol. Struct.* **2019**, *1193*, 386.
[30] A. L. Spek, *Acta Crystallogr. Sect. A Found. Crystallogr.* **1990**, *46*, 34.
[31] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Monge, R. Taylor, P. A. Wood, *J. Appl. Crystallogr.* **2008**, *4a*, 466.
[32] J. J. McKinnon, M. A. Spackman, A. S. Mitchell, *Acta. Crystallogr. B.* **2004**, *60*, 627.
[33] M. A. Spackman, J. J. McKinnon, D. Jayatilaka, *Cryst. Eng. Commun.* **2008**, *10*, 377.
[34] L. I. Mensor, F. S. Menezes, G. G. Lietao, A. S. Reis, T. Don Santos, C. S. Coube, S. Lietao, *Phytother. Res.* **2001**, *15*, 127.
[35] A. Y. Wageeh, A. R. Noorsaadha, A. Azhar, H. Sharifah Bee Abd, A. A. Abeer, A. K. Frakaad, Y. Marzieh, *Eur. J. Med. Chem.* **2015**, *101*, 295.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Asma, Kalluraya B, Manju N, CL Sharath. Synthesis and antioxidant activity study of carbothioamide and their corresponding thiazole derivatives. *J Heterocyclic Chem*. 2020;1–11. https://doi.org/10.1002/jhet.4018