

Ultrasound-assisted Synthesis of Auxiliary Pyrazoline Integrated Thiazole, Thiazolone Derivative and Their Biological Evaluation

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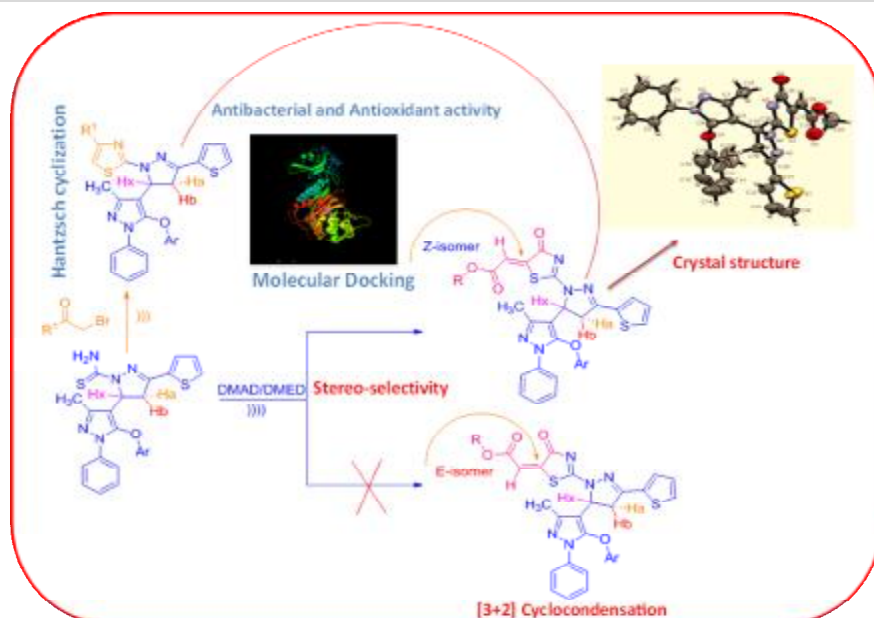
Antibacterial

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ABSTRACT

In this paper, we describe a simple catalyst-free protocol for the synthesis of thiazole, thiazolone integrated pyrazole derivatives, under ultra-sonication technique. Thiazolone derivatives (**5a**, **5e**, **5i**, **5d**, **5h**, **5l**) were derived from [3+2] cyclocondensation reaction between carbothioamide pyrazoline (**4a-c**) as S-N bi-nucleophile with DMAD/DEAD. The target molecules (**5b**, **5f**, **5j**, **5c**, **5g**, **5k**) were synthesized by the reaction of (**4a-c**) with the substituted bromoethanone. Formation of the products was confirmed by FT-IR, ¹H-NMR, ¹³C-NMR, LC-MS analysis. Docking studies were carried out against the antimicrobial target (Acinetobacterbaumannii penicillin) to know the interaction of the molecules (ligands) with the docked target. Among the docked compounds thiazolone derivative (**5d**) showed the minimum binding energy of -9.08 kJ/mol with ligand efficiency of -0.23. All the synthesized compounds were examined primarily for their *in-vitro* antibacterial and antioxidant activity (IC₅₀). Compound (**5g**)(18±0.0) and (**5d**)(19.5±0.5) showed significant bacterial inhibition against *E.coli* and *S.aureus*. Compound (**5k**) (16.57) showed substantially DPPH free radical inhibition activity as compared to the reference drug Ascorbic acid.

GRAPHICAL ABSTRACT



1. Introduction

The importance of heterocycles and modified heterocycles in living system is well known for curing many chronic diseases.

¹⁻² Nowadays the treatment of bacterial and fungal infectious diseases remains a challenging problem because of the

increasing number of multi-drug resistant microbial pathogens. Designing new compounds with an active nucleus to deal with multidrug-resistant bacteria are one of the challenging work for the chemist in the field of medicinal chemistry, among them, heterocycles are the fundamental core for the inhibition of many fatal diseases.³⁻⁴ Incorporation

of five-membered heterocycles is always a fascinating work for the chemist, due to its potentiality as a therapeutic agent. Among the five-membered heterocyclic templates, nitrogen and sulfur-containing heterocycles such as pyrazole, thiophene, pyrazoline, thiazole, and thiazolone have shown a broad spectrum of biological activities like anticancer,⁵ antidiabetics,⁶ antimicrobial,⁷⁻⁸ tubercular,⁹ antioxidant,¹⁰ anti-inflammatory¹¹ etc. Among these, thiazole and thiazolone are building blocks for several natural products as they are mainly found in Vitamin B₁ (thiamine). They are also found in many biological active drugs such as sulfathiazole (anti-microbial), abafungin (antifungal), meloxicam (anti-inflammatory), tiazofurin (anti-neoplastic). Pharmacological studies showed that incorporation of thiazole nucleus increases the biological activity.¹²⁻¹³ Apart from thiazole/thiazolone, drugs bearing pyrazole, pyrazoline, and thiophene showed enhanced activity after the introduction of these heterocycles¹⁴⁻¹⁵. Ultrasound-mediated organic synthesis has had a significant impact on synthetic chemistry like reduction in reaction time, increase in the product yield and suppression of side product formation over the conventional thermal method¹⁶⁻¹⁷. Prompted by these observations and in our search for green techniques¹⁸⁻²⁰, we prepared twelve new heterocyclic hybrid-templates carrying thiazole, thiazolone, pyrazole, pyrazoline, thiophene and sydnone moieties by catalyst-free ultra-sonication technique. All newly synthesized compounds (**4a-c**) and (**5a-l**) were initially assessed for their interaction with the antimicrobial target (*Acinetobacterbaumannii* penicillin) and we further evaluated for their *in-vitro* antibacterial activity against clinical isolates. Radical scavenging ability of the compounds was also carried out against DPPH radical. The structure of the newly synthesized compounds were established on the basis of FT-IR, ¹H-NMR, ¹³C-NMR, LC-MS data and X-ray analysis.

2. Experimental

2.1 Material, Methods and Instrumentation

All the chemicals were purchased from Sigma-Aldrich or Hi-Media and used after distillation/ recrystallization. The ultrasound-assisted synthesis was carried out using catalyst system Mini-M operator. ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz Bruker Avance II NMR spectrometer with CDCl₃ (Deuterated chloroform) and TMS (tetramethylsilane) as an internal standard. Mass spectra were recorded on LC-MS (SHIMADZU LCMS-8030) operating at 70 eV. The X-ray diffraction of compound (**5e**) obtained with Rigaku Saturn724+ diffractometer with graphite monochromated MoK α radiation at 296 K. Melting points was observed with Innovative DTC-967A digital melting point device. FT-IR spectra were recorded by dispersing the compounds in potassium bromide pellets on a Shimadzu FT-IR 157 spectrophotometer. The molecular docking was performed and analyzed using AutoDock 4.2. The Bacterial isolates *Staphylococcus aureus* (NCIM-5021), *Bacillus subtilis* (NCIM-2197), *Escherichia coli* (NCIM-2931), and *Pseudomonas aeruginosa* (NCIM-2036) were obtained from the National collection of industrial microorganisms, Pune, India. The purity of the compounds was checked on silica gel plates (Merck) and visualized under ultraviolet lamp using ethyl acetate: hexane (3:7) as a mobile phase.

General procedure for the synthesis 3-(3-methyl-5-aryloxy-1-phenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one (**3a-c**)

To a mixture of 3-methyl-5-aryloxy-1-phenyl-1H-pyrazole-4-carbaldehyde (**1 a-c**)²¹⁻²² (0.01 mol) and acetyl thiophene (**2**) (0.01 mol) in 25 mL of ethanol, potassium hydroxide (0.5g, 0.01 mol) in 5 mL ethanol was added drop wise under ice bath, and the mixture was stirred for 4 hours. After the completion of the reaction (monitored by TLC), the solid product separated was filtered, washed with water, dried and recrystallized from ethanol: dimethylformamide mixture.

(3a): 3-(3-methyl-5-phenoxy-1-phenyl-1H-pyrazol-4-yl)-1-(thiophene-2-yl)prop-2-en-1-one: m.p: 152-154 °C, Yield 84%.

(3b): 3-(3-methyl-5(2,4-dichlorophenoxy)-1-phenyl-1H-pyrazol-4-yl)-1-(thiophene-2-yl)prop-2-en-1-one: m.p: 128-132 °C, Yield 84%.

(3c): 3-(3-methyl-5(2,4-dichlorophenoxy)-1-phenyl-1H-pyrazol-4-yl)-1-(thiophene-2-yl)prop-2-en-1-one: m.p: 167-168 °C, Yield 77%.

General procedure for the preparation 5-(3-methyl-5-aryloxy-1-phenyl-1H-pyrazol-4-yl)-3-(thiophen-2-yl)-4,5-dihydro pyrazole-1-carbothioamide (**4a-c**).

To a mixture of 3-(3-methyl-5-aryloxy-1-phenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one (**3a-c**) (0.01 mol) and thiosemicarbazide (0.02 mol) in ethanol (25 mL), potassium hydroxide (5 mL, 30%) was added and the mixture was stirred for 4 hours at 80 °C. The solid obtained was filtered, washed thoroughly with water and recrystallized from ethanol to get pure 5-(3-Methyl-5-aryloxy-1-phenyl-1H-pyrazol-4-yl)-3-(thiophen-2-yl)-4,5-dihydro pyrazole-1-carbothioamide (**4a-c**). Compounds prepared according to this procedure are given in (Table 1).

General procedure for the preparation 2-(2-(5-(3-methyl-5-aryloxy-1-phenyl-1H-pyrazol-4-yl)-3-(thiophen-2-yl)-4,5-dihydropyrazol-1-yl)-4-oxothiazol-5(4H)-ylideneacetate (**5a, 5e, 5i, 5d, 5h, 5l**)

A mixture of thiocarboamide (**4a-c**) (0.01 mol) and DMAD (dimethyl acetylenedicarboxylates) or DMED (diethyl acetylenedicarboxylates) (0.01 mol) was taken in 50 mL of round-bottomed flask and added 25 mL of ethanol. The resulting mixture was treated under ultra-sonication for the appropriate time (Table 1). The solid product separated was filtered, washed with water, dried and recrystallized from ethanol-dimethylformamide mixture.

General procedure for the preparation 5-(1-phenyl-3-methyl-5-aryloxy-1H-4-pyrazolyl)-3-(2-thiophenyl)-1-(4-substituted-thiazole-2-yl)-4,5-dihydro-1H-pyrazol (**5b, 5f, 5j, 5c, 5g, 5k**)

A mixture of compounds (**4a-c**) and p-bromophenyl bromide/ 4-bromoacetyl-3-(p-tolyl) sydnone (0.01 mol) was taken in 50 mL round-bottomed flask and dissolved by adding 25 mL of ethanol. The resulting mixture was treated under ultrasonication for the appropriate time (Table 1). The solid product was separated, filtered, washed with water and dried and, then the obtained products were further purified by recrystallization from aqueous ethanol: DMF mixture. The

structure of the newly synthesized compounds is given in (Table 1).

Table 1. Characterization data of carbothioamide (4a-c) thiazole/thiazolone(5a-l).

Compound	Ar	Time (h=hour, min=minutes)	M. P (°C)	Yield
4a	phenyl	4h	223	64
4b	o-tolyloxy	4h	207-208	69
4c	2,4 di-chloro phenyl	4h	216	65
5a	phenyl	6 min	207	67
5b	phenyl	6.5 min	216-218	77
5c	phenyl	6.5 min	168	71
5d	phenyl	7.0 min	245-248	79
5e	o-tolyloxy	7.0 min	216-218	68
5f	o-tolyloxy	8.5 min	189	74
5g	o-tolyloxy	7.5 min	272	70
5h	o-tolyloxy	8.0 min	278	67
5i	2,4 di-chloro phenyl	6.5 min	251-252	76
5j	2,4 di-chloro phenyl	7.0 min	216	73
5k	2,4 di-chloro phenyl	7.5 min	139-144	78
5l	2,4 di-chloro phenyl	7.0 min	254-256	72

3. Biological Activity

3.1 Antioxidant activity

The free radical scavenging activity of the title compounds is measured by using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) method²³. 0.2mM solution of DPPH in methanol was prepared, and 100µl of this solution was added to various concentrations of title compounds at the concentrations of 10, 20, 30, 40, 50 µg/ml. After 30 minutes, absorbance was measured at 517nm. Ascorbic acid was used as the reference material. All the tests were performed in triplicate and percentage of inhibition was calculated by comparing the absorbance values of the control and test samples.

3.2 Antibacterial activity

The antibacterial activity of the synthesized thiocarbamide intermediate (4a-c), thiazole and thiazolone derivatives (5a-l) was tested against bacterial isolates *Staphylococcus aureus*(NCIM-5021), *Bacillus subtilis* (NCIM-2197) (Gram-positive bacteria), *Escherichia coli* (NCIM-2931), and *Pseudomonas aeruginosa* (NCIM-2036) (Gram-negative bacteria) by cup-plate method²⁴ at 50 µg/mL concentration. The sterilized nutrient agar medium was distributed 100 mL each in two 250 mL conical flasks and allowed to cool to room temperature. To these media, 18-24 hr grown bacterial sub-cultures were added and shaken thoroughly to ensure uniform distribution of organism throughout the medium. Then, this agar medium was distributed in equal portions, in sterilized Petri dishes, ensuring that each Petri dish contains about 45-50 mL of the medium. The medium was then allowed for solidification. Then, cups were made with the help of a sterile cork borer (6

mm diameter) punching into the set of agar media. The solutions of required concentrations (50 µg/mL) of test compounds were prepared by dissolving the compounds in DMF and were filled into the cups with 1mL of particular solution. Then, the Petri dishes were kept for incubation in an inverted position for 48 hr at 37 °C in an incubator. When growth inhibition zones were developed surrounding each cup, their diameter in mm was measured and compared with that of the standard drug Ciprofloxacin.

3.3 Molecular Docking Studies

Energy minimization for ligands was carried out using Dundee PRODRG server²⁵⁻²⁶ and the protein target which was retrieved from the RCSB protein data Bank (PDB Code 3UDI) served as a docking receptor. The binding interaction between macromolecule and ligands was done using AutoDock 4.2. The molecular docking was performed and analyzed using AutoDock 4.2. A Lamarckian genetic algorithm method implemented in the program suite was employed to identify appropriate binding modes and conformation of the ligand molecules. Gasteiger charges were added, and the AutoDock tools set the rotatable bonds, and all torsions were allowed to rotate. Polar hydrogen atoms were added, and Kollaman charges were assigned to the protein using AutoDock tools (ADT).

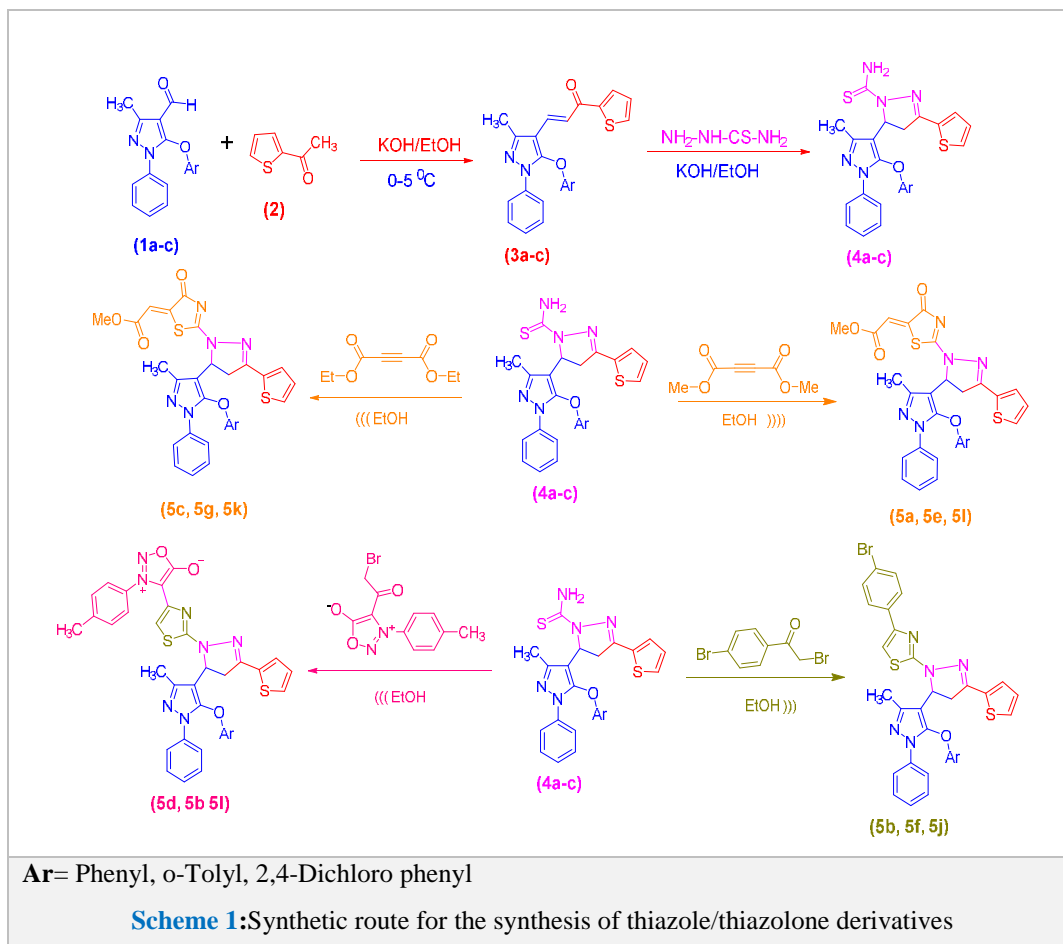
4. Result and Discussion

4.1 Chemistry

The synthetic route for thiazole, thiazolone integrated pyrazole pyrazoline, and thiophene derivative is limned in (Scheme 1). Reaction of 5-(3-methyl-5-aryloxy-1-phenyl-1H-

pyrazol-4-yl)-3-(thiophen-2-yl)-4,5-dihydropyrazole-1-carbothioamide (**4a-c**) with DMAD (dimethyl-acetylenedicarboxylates) or DMED (diethyl-acetylenedicarboxylates) underwent [3+2] cyclocondensation reaction in ethanol under ultra-sonication method to form new

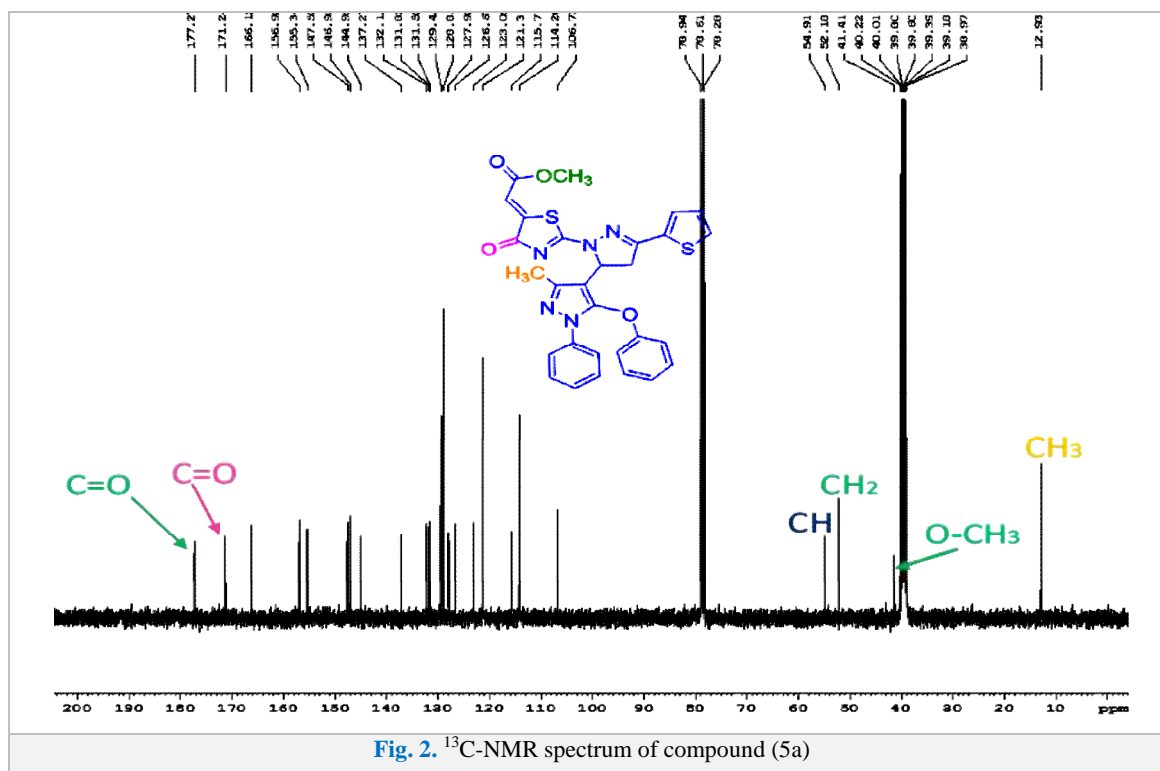
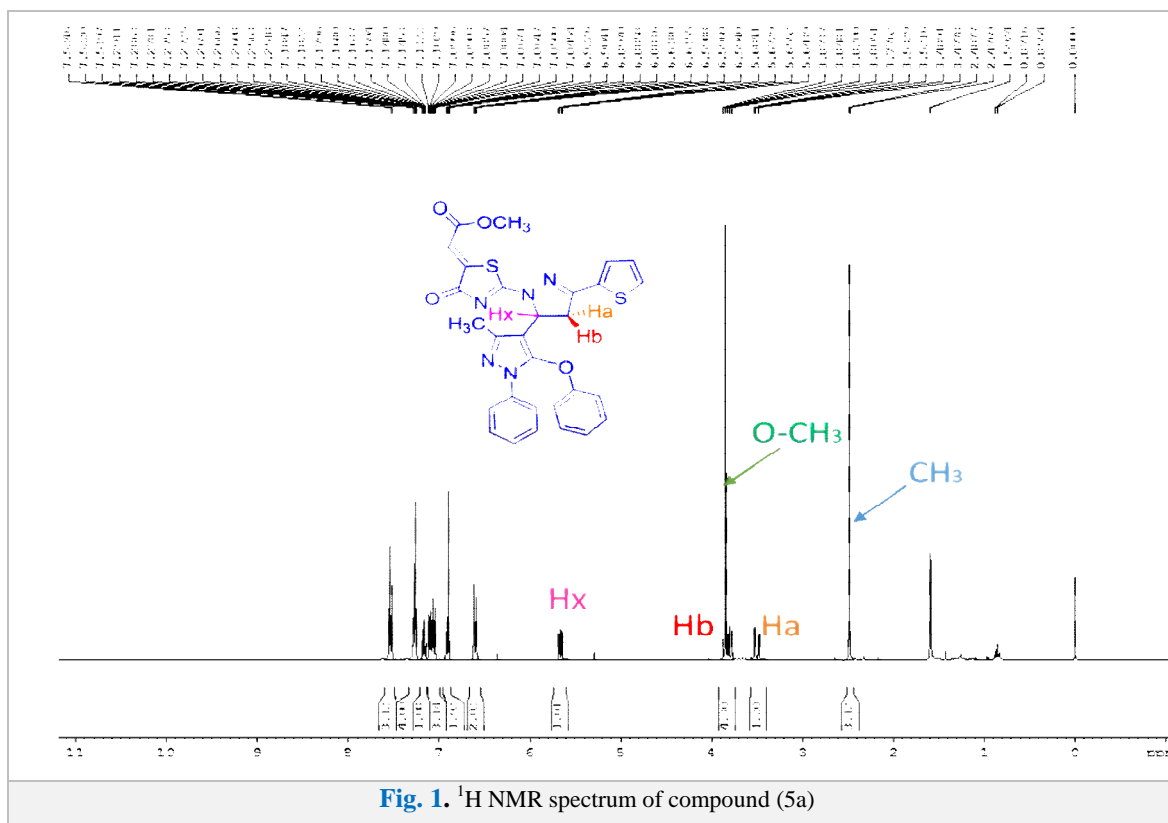
thiazolone derivatives (**5a**, **5e**, **5i** and **5d**, **5h**, **5l**). Also, compounds (**4a-c**) on treatment with p-bromophenylbromide and 4-bromoacetyl-3-(p-tolyl) sydnone lead to the formation of thiazole derivatives (**5b**, **5f**, **5j**) and (**5e**, **5g**, **5k**) in moderate to excellent yield under ultra-sonication method



Formation of thiazole and thiazolone hybrid from pyrazoline carbothioamide (**4a-c**) was confirmed by the changes observed in the $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, LC-MS, FT-IR, Mass and X-ray analysis. In the FT-IR spectrum of compound (**5a**), the absence of NH band at 3398 cm^{-1} and disappearance of C=S stretching vibration at 1373 cm^{-1} firmly indicate the formation of cyclized product (**5a**). It is also supported by the appearance of strong stretching bands around 1738 cm^{-1} & 1698 cm^{-1} for ester carbonyl, as well as cyclic ring carbonyl in the compounds, that confirm the formation of [3+2] cyclocondensation product (**5a**). In the FT-IR spectrum of compound (**5b**) absence of NH_2 , C=S and C=O stretching indicate the formation thiazole nucleus. Molecules carrying mesoionic compounds (**5c**) shows a strong peak at 1729 cm^{-1} corresponding to the lactone ring in sydnone moiety.

Formation of title compounds was also confirmed by the $^1\text{H-NMR}$ spectrum (**Fig. 1**). The signal due to the NH_2 protons of

carbothioamide intermediate (**4a**) disappeared in the spectrum of compounds (**5a**). In the target compound (**5a**) the singlet at 3.84 ppm integrating for 3 protons indicates the presence of methoxy protons and confirms the [3+2] cyclocondensation with dimethyl acetylene dicarboxylate (DMAD). The peaks at 2.48 ppm as singlet corresponding to the pyrazole methyl protons. The proton in pyrazoline ring displayed **ABX** pattern of signals corresponding to diastereotopic methylene and chiral methine protons. The geminal protons H_A and H_B appeared in the region 3.47 and 3.77 ppm as two doublet of the doublet. The chiral proton showed vicinal coupling with magnetically non-equivalent geminal protons in the region 5.64 ppm as doublet of doublet. The C2-H proton of thiophene appeared as a doublet at 6.59 ppm. The aromatic protons appeared in the region 6.88-7.55 ppm as multiplet.



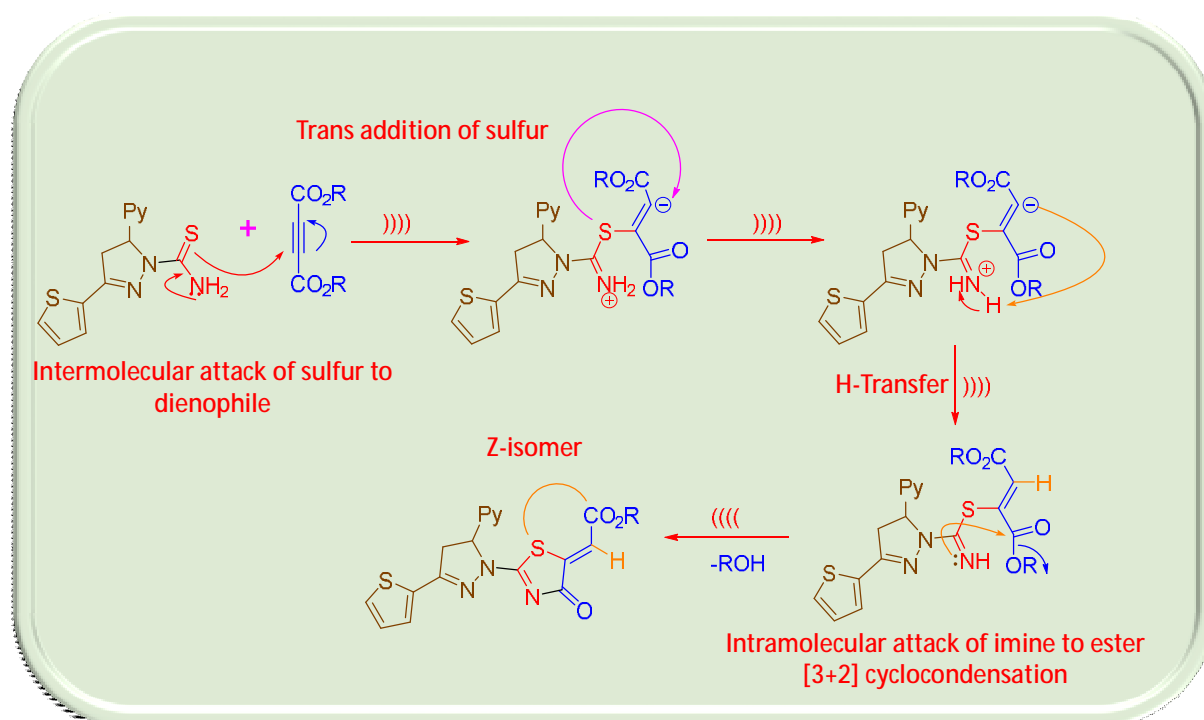
The ¹³C-NMR and LC-MS analysis further confirmed the structure of the thiazole and thiazolone derivatives. In ¹³C-NMR spectra of title compounds (5a) (Fig. 2) absence of a characteristic C=S signal at 175.48 ppm which is present in the key intermediate (4a) confirms the cyclization. The carbonyl carbon present in the ring, exocyclic to the thiazole ring, appeared at 177.27 ppm and 166.12 ppm, respectively.

The characteristic signals of the N=C=N which were present in thiazole were observed at 171.24 ppm. The signals at 41.41 ppm and 52.18 ppm were assigned for methylene (CH₂) and chiral methine (CH) carbon in the pyrazoline ring. The peak at 12.93 ppm is assigned to pyrazole methyl carbon. The aromatic carbon peaks appeared in the range of 106.75-156.92 ppm, respectively. The mass spectrum (ESI-MS) of (5a)

shows a protonated molecular ion peak ($M^+ + 1$) with m/z value of 570.21, which confirms the formation of the product.

The formation of the products (**5a-l**) were also supported by the single crystal X-ray diffraction method. The thiazolone derivative (**5e**) were crystallized into a single crystal by the slow evaporation technique. The crystal structure of compound (**5e**) provides solid evidence for the stereoselectivity (**Z**-isomer) in the reaction. During the cycloaddition between dienophile (DMAD/DMED) with S-N bi-nucleophile, the thiocarbamide sulfur was added to dienophile in trans manner and finally the proton transfer to the formed carbanion resulted in the formation of free imine.

The intramolecular attack of imine to one of the ester group (since it is symmetrical alkyne) under ultrasonication resulted in the formation of thiazolone derivatives (**5a-l**) with stereoselectively **Z**-configuration of the exocyclic double bond. The stereoselectivity is believed due to the trans addition of SH group (**Scheme. 2**) to the triple bond in DMAD/DMED. The ortep diagram of the compound is given in (**Fig. 3**). The details of crystal structure and data refinement are given in (**Table 2**).



Scheme 2: A reasonable mechanism for the stereoselectivity in the reaction (**Z**-isomer)

Table 2. Crystal data and structure refinement (**5e**)

Identification code	5e
Empirical formula	$C_{30}H_{25}N_5O_4S_2$
CCDC	1588961
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/n$

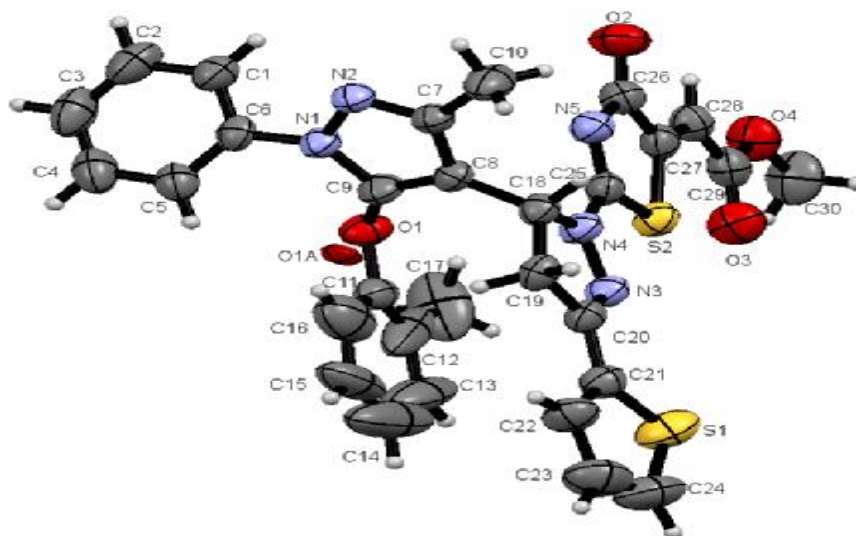


Fig. 3. Single crystal X-ray structure of compound (5e) showing the atomic numbering system. Displacement ellipsoids are drawn at the 50% probability.

4.2 Antioxidant activity

The results obtained from the DPPH radical inhibition assay are presented in the (Table 3). Compound (5k)(16.57) exhibited excellent radical inhibition activity, even greater

than standard ascorbic acid (18.21). As compared to key intermediates (4a-c), DPPH radical inhibition activity was enhanced by the introduction of thiazole and thiazolone derivatives (5a-l).

Table 3. Antioxidant activity of the synthesized compounds(4a-c) and (5a-l)

Compound	% of DPPH inhibition (IC ₅₀)
4a	59.84
4b	56.18
4c	48.26
5a	41.28
5b	42.56
5c	43.02
5d	42.54
5e	44.47
5f	27.96
5g	28.55
5h	37.93
5i	25.12
5j	24.62
5k	16.57
5l	25.27
STD (Ascorbic acid)	18.21

4.3 Antibacterial activity

All thiazole and thiazolone (5a-l) derivatives showed moderate to good antibacterial activity as compared to the intermediate (4a-c) as shown in (Table 4). Among the tested compounds, (5d)(19.5±0.5) and(5g)(18±0.0) showed

prominent bacterial inhibition against *S. aureus* and *E.coli*. All other compounds in this series exhibited moderate bacterial inhibition. Thiocarbamide derivatives (4a-c) showed negligible antibacterial activity but soon after cyclization to the correspondingthiazole and thiazolone hybrids bacterial inhibition activity was enhanced. The result indicates the apparent importance of thiazole, thiazolone integrated

multicomponent heterocyclic systems in antibacterial inhibition.

Table 4. Antibacterial activity of the synthesized compounds (4a-c) and (5a-l)

Sample Nor	Diameter of zone of inhibition (in mm) at 50 µg/mL			
	<i>Bacillus Subtilis</i>	<i>Escherichia coli</i>	<i>Staphylococcus Aureus</i>	<i>Pseudomonas Aeruginosa</i>
4a	11.5±0.5	12.5±0.5	11.5±0.5	9.5±0.5
4b	12±0.0	12.5±0.5	12.5±0.5	10±0.0
4c	10.5±0.5	10.5±0.5	11.5±0.5	12±1.0
5a	10.2±0.5	13.5±1.0	10±0.5	11.5±0.5
5b	10.5±0.5	11.5±0.5	11±0.0	9.5±0.5
5c	10.5±0.5	9.5±0.5	15.5±0.5	9.5±0.5
5d	15±0.0	14.5±0.5	19.5±0.5	9.5±0.5
5e	14.5±0.5	14±1.0	12.5±0.5	11.5±0.5
5f	9.5±1.5	12.5±0.5	11±1.0	9.5±0.5
5g	12.5±0.5	18±0.0	10.5±1.5	12±0.0
5h	14.5±0.5	14±0.5	11.5±0.5	10.5±0.5
5i	11±1.0	11.5±0.5	10±0.0	11.5±0.5
5j	13±0.0	21±1.0	11.5±0.5	12.5±0.5
5k	10.5±0.5	13.5±0.5	14±1.0	11±1.0
5l	12.5±0.5	13±1.0	13±0.0	11.5±0.5
STD (Ciprofloxacin)	23.5± 0.7	22.5± 0.7	23.5± 0.7	22.5± 0.7

4.4 Molecular Docking

In molecular docking study, all of the compounds (4a-c) and (5a-l) were found to have minimum binding energy ranging from -4.17 to -9.08 kJ/mol. Among the molecules tested for docking study, (5d) showed the minimum binding energy of -9.08 kJ/mol with ligand efficiency of -0.23. Most of the residues that are near the inhibitor are hydrophobic in nature. The ligand molecules, (5h)(5l) and (5a) revealed binding energy of -8.08, -8.00 and -7.76 kJ/mol, with ligand efficiency of -0.20, -0.19 and -0.19, respectively. These molecules were wrapped entirely by active site amino acid residues at the active site pocket region (Fig S 1. Supplemental materials). Similarly, molecules (5d, 5e, 5a) and (4c) were found to show

hydrogen bond interaction with active site amino acid residues, THR670, THR672, GLY709, THR670, THR672, LYS669, THR670 and TYR485, THR670, at a distance of (1.86, 2.24) (1.72, 2.14), (1.78, 2.11) and (2.154, 2.159) Å, respectively as depicted in (Fig. 2). The docking study results showed that the molecules (5a-l) and (4a-c) have an excellent inhibition constant, vdW + Hbond + dissolve energy with best RMSD value. Docking studies showed that thiazole, thiazolone derivatives are an excellent inhibitor of the bacterial target. The details of docked score results of the molecules with antimicrobial protein target (PDB Code: 3UDI) are given in (Table S 1 supplemental materials) and binding mode of molecules presented in (Fig S 2. Supplemental materials)



Fig 2. Fig (a) and (b) represents the H-bond interaction of ligand molecules 5d, 5h, with 3UDI.

5. Conclusions

In summary, we have reported eco-friendly synthesis of thiazole and thiazolone derivatives through [3+2] cyclocondensation and Hantzsch cyclization. The structures of these compounds were confirmed by analytical, spectral and X-ray crystallographic analysis. Docking studies showed their suitability as antibacterial agents, this was in turn supported by *in-vitro* antibacterial activity. Antioxidant studies showed that some of the synthesized compounds exhibited excellent DPPH radical inhibition activity comparable to that of standard ascorbic acid. The overall study manifests the importance of modified heterocyclic systems in biological activity (antibacterial and antioxidant activity).

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References

- H. S. Gold, R. C. Moeller, *New England J. Med.*, **335** (1996) 1445.
- K. Nepali, S. Sharma, M. Sharma, P.M.S. Bedi, K.L. Dhar, *Eur. J. Med. Chem.*, **77** (2014) 422.
- M. H. Cohen, J. R. Johnson, R. Justice, *Pazdur. Oncologist*, **13** (2008) 709.
- O.I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini, A. A. Rashad, *Eur. J. Med. Chem.*, **44** (2009) 3746.
- K. M. Cheng, Y. Y. Huang, J. J. Huang, K. Kaneko, M. Kimura, H. Takayama, S. H. Juang, F. F. Wong, *Bioorg. Med. Chem. Lett.*, **20**, (2010) 6781.
- M. Hassan, M. M. Faidallah, A. Mohammadi, A. Khalid, K. A. J. Alamry, Khan, *Enzyme. Inhib. Med. Chem.*, **31**, (2016) 1475.
- Asma, B. Kalluraya, N. Manju, Chandra, M. Mahendra, B. C. Revanasiddappa, *J. Med. Chem. Drug. Des.*, **1**, (2018) 1.
- M. A. Gouda, M. A. Berghot, A. I. Shoeib, A.M. Khalil. *Eur. J. Med. Chem.*, **45**, (2010) 1843.
- V. H. S. Jois, B. Kalluraya, K. S. Girisha, *J. Seb. Chem. Soc.*, **79**, (2014) 1469
- N. Manju, B. Kalluraya, Asma, Madan S Kumar, *Indian J. Heterocycl. Chem.*, **28**, (2018) 426.
- K. S. Girisha, B. Kalluraya, V. Narayana, Padmashree. *Eur. J. Med. Chem.*, **45**, (2010) 4640.
- S. A. F. Rostom, I. M. El-Ashmawy, H. A. Abd El Razik, M. H. Badr, M. A. Ashour. *Bioorg. Med. Chem.*, **17**, (2009) 882.
- S. Bondock, W. Fadaly, A. M. Mohamed, A. M. *Eur. J. Med. Chem.*, **45**, (2010) 3692.
- H. Dmytro, R. Olexandra, L. Roman. *Eur. J. Med. Chem.*, (2016) DOI: 10.1016/j.ejmech.2016.02.030
- S. S. Sulthan, S. A. Antony, C. Balachandran, S. S. Syed. *Bioorg. Med. Chem.*, **25**, (2015) 2753.
- S. M. Gomha, D. K. Khaled. *Molecules*, **17**, (2012) 9335.
- Asma, B. Kalluraya, Manju. N, A. V. Adhikari, Chandra, M. Mahendra. *Indian J. Heterocycl. Chem.*, **28**, (2018) 335.
- N. M. Abd EL-Rahaman, T. S. Saleh, M. F. Mady, *Ultrason. Sonochem.*, **16**, (2009) 70.
- B. Kalluraya, R. Ganesh. *Indian. J. Chem.*, **42B**, (2003) 2556.
- B. Kalluraya, R. Ganesh. *Synth. Commun.*, **33**, (2003) 3583.
- S. M. Anush, B. Vishalakshi, B. Kalluraya, N. Manju, *Int. J. Biol. Macromol.*, **119**, (2018) 446.
- N. Manju, B. Kalluraya, Asma, *Heterocyclic Lett.*, **8**, (2018) 366.
- S. K. Mondal, G. Chakraborty, M. Gupta, U. K. Mazumder. *Ind. J. Exp. Biol.*, **44**, (2004) 39.
- S. B. Rose, R. B. Miller. *J. Bacteriol.*, **38** (1939) 525.
- A. W. Schuttelkopf, D. M. F. Van Aalten. *Acta. Cryst.*, **D60** (2004) 1355.
- J. K. Gerard, *Acta. Cryst.*, **D63** (2007) 94.

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