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Synthesis, Characterization and Antibacterial Activity of Pyrazole Derivatives Featuring Thiazole Frameworks

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Abstract

This work investigates the possible antibacterial characteristics of pyrazole derivatives, including thiazole frameworks. Mass spectrometry, infrared, nuclear magnetic resonance, and other spectroscopic methods were used to confirm the structures of the produced compounds. These compounds' antimicrobial activity was assessed against different bacteria and fungi. A number of the compounds had noteworthy antibacterial and antifungal properties, and several of their derivatives showed increased efficacy in comparison to conventional reference medications. According to a Structure-Activity Relationship (SAR) investigation, the pyrazole and thiazole rings' particular substituents were crucial in boosting the antibacterial activity. According to these results, pyrazole-thiazole hybrids are promising candidates for creating antimicrobial drugs.

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1. Introduction

Drug-resistant bacteria strains are becoming a major worldwide health issue, which makes the ongoing creation of antimicrobial medicines necessary. Modifying pre-existing chemical scaffolds to improve biological activity and get around resistance mechanisms is a viable approach to drug creation [1]. In the past few years, there exists a notable surge in interest in pyrazole derivatives due to their extensive pharmacological activities, including anti-inflammatory properties [2], anticancer [3], and antibacterial qualities [4]. Moreover, thiazole-containing compounds are well-known for their extensive biological activity [6], particularly in medical applications [7]. When combined, two heterocyclic moieties, pyrazole and thiazole, provide a unique opportunity to create compounds with improved antibacterial activity. We present the synthesis and design of pyrazole derivatives with thiazole ring frameworks. These unique compounds were produced to investigate their potential as potent antibacterial agents against various harmful bacteria. Combining the pyrazole and thiazole rings makes sense because of their complimentary biological actions, which may work together to fight microbial diseases [8]. In addition, the synthesized compounds' structure-activity relationship (SAR) was examined to determine the essential structural components behind their antibacterial efficacy. In this survey, we prepared derivative of heterocycles that consist of both pyrazole and thiazole rings, potentially leading to more effective biological actions to aid in the creation of therapeutic agents for the treatment of microbial infections, the following work gives thorough explanations of the synthetic procedures, spectroscopic characterization, and antimicrobial assessment of the recently synthesized pyrazole-thiazole derivatives [9].

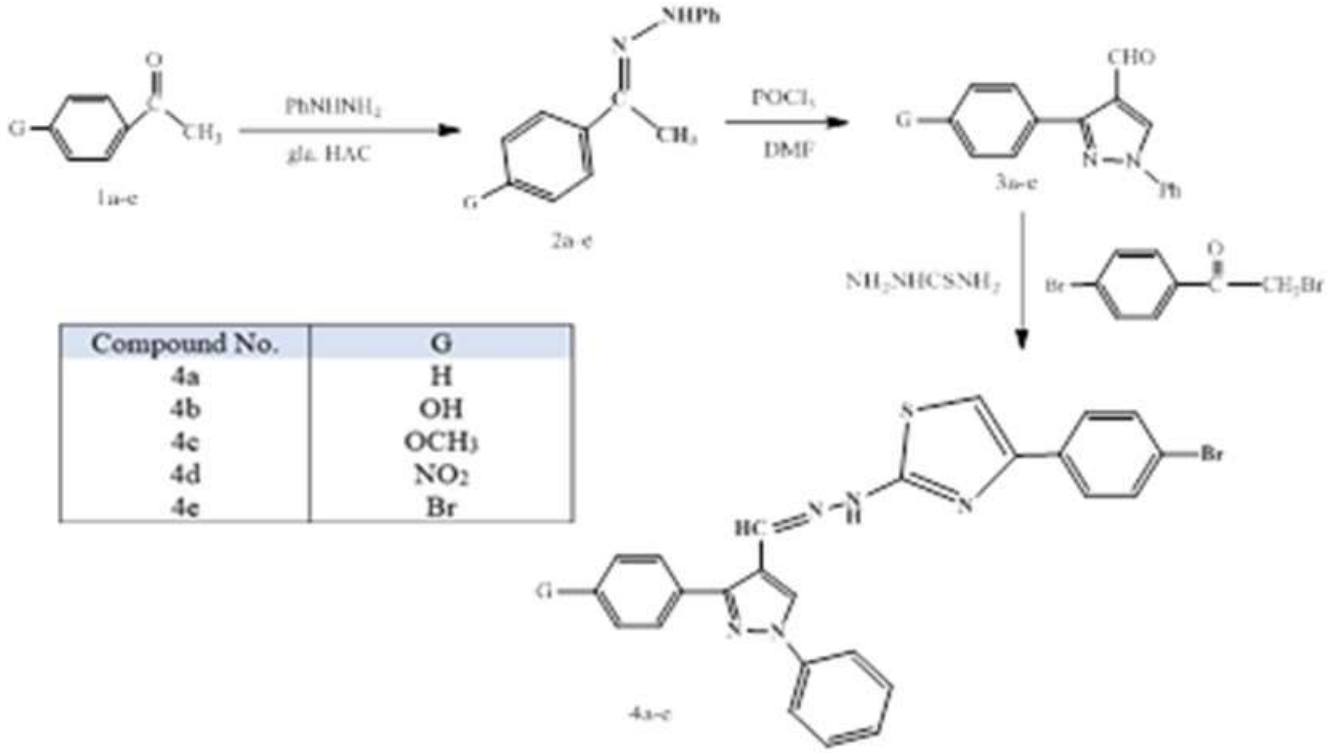
2. Materials and Methods

Every substance used in the experiment was sourced from different companies, including Merck and Fluka.

2.1. General Method of the Synthesis derivatives 2a–e

The condensation of 2 mol of substituted acetophenone 1a-e with 2 mol phenylhydrazine and acetic acid (3 mL) was refluxed in ethyl alcohol (25

mL) for 50 minutes [10]. A mixed solution was cooled to 26 °C when it was completed, as determined by TLC as eluent and iodine as color appearance. The precipitate was purified, washed through aqueous, dried, and recrystallized using ethyl alcohol. Table 1 shows the physical information for compound 2a-e. The solvent system is Hexane: Ethyl Acetate.



Compound No.	G
4a	H
4b	OH
4c	OCH_3
4d	NO_2
4e	Br

Scheme I. Synthetic path of compounds 4a – 4e

Table 1. Physical information 2a–e.

Compound	Color	Melting point (degrees Celsius)	*Rf* Value/Solvent System	Yield percent
2a	reddish orange	133-134	0.1/6:4	90
2b	Yellow light	146-148	0.15/6:4	75
2c	Yellowish green	170-172	0.18/6:4	80
2d	Yellowish green	98-100	0.1/6:4	80
2e	Yellowish green	210-212	0.16 / 6:4	70

2.2. General Method for prepare 1-Pheyl-3-(substiuted-pheyl)-IH-pyrazole-4-carbaldehydes 3a–e

A thoroughly stirred and cold at (1 °C) Dimethylformamide solution (15.5 mL), then 6.5 mL of Phosphoryl chloride distill was added for 1 hour [11]. After adding Phosphoryl chloride, the product was stirred at 0 °C for one hour. Mixture 2a-e (2.5 mol) Dimethylformamide (10.5 ml) was prepared for one and a half hours through stirring and cold-forming. Finally, A solution refluxed for 2 h. A solution of the mixture was poured on shriveled Frezer aqueous and refrigerated all night long, allowing the end product to solidify. A product was pure by filter followed clean by lotion through Na_2CO_3 (7%, 35 mL), and water was then recrystallized from the Dimethylformamide -ethyl alcohol combination. Table 2 contains physical information for compounds 3a-e.

Table 2. Physical information 3a–e.

Compound	Color	Melting point (degrees Celsius)	*Rf* Value/Solvent System	Yield percent
3a	Orange	136-139	0.27.5/7:34	75
3b	Yellow light	148-151	0.31.5/7:33	77
3c	Yellow light	161-163	0.25/7:33	82
3d	Yellow	168-170	0.24/7:32	74
3e	Pale green	189-191	0.25/ 7:3	69

2.3. General Method of prepare of 2,6-Disubstiutde Thizole Derivtives 4a–4e

A combination of aldehyde of pyrazole (2 mmol), Aminothiourea (2 mmol), and α α -haloketoe (2 mmol) in ethyl alcohol via reflex for three hours [12]. A solution of mixture refrigeration at 26 ^{0}C then poured on shrivelled ice. The crystalline material was cleaned and washed with freezing water. The solid was obtained by filtration and recrystallization using a combination of ethanol and dimethylformamide.

3. Results and Discussion

Both Phenyl Hydrazone Derivatives 2a–e and medium pyrazole carbaldehydes 3a–e were synthesized in a recognized manner through the report [13], which were obtained by Vilsmeier-Haack reaction of appropriate phenylhydrazones 2, produced a mix from aryl methyl ketone 1 and phenylhydrazine, as shown in Scheme 1.

The IR bands data at 3361-3120, 1595-1583, and 1622-1612 cm^{-1} indicated the existence of N-H, C=C, and C=N, respectively [14]. The results of ^{1}H NMR (ppm) showed broad data as (s, 1H, NH) at 12.1, a pyrazolyl showed 9.0 - 9.2, a thiazolyl proton showed as a singlet at 7.09, and aromatic protons showed as (m, 14H) at 7.4 to 8.3. The ion peak (M+) of each generated compound was gained utilizing EI-MS, whereas the appearance of M+3 peaks was diagnostic of compounds containing bromide and sulfide atoms. Similarly, each additional substance was analyzed using spectroscopy and analytical methods.

3.1. Spectral Data

The derivative (4a) [15] m.p.: 190-192°C; Infrared (IR) spectroscopy (Potassium bromide, the unit cm^{-1}): 3236 (N-H), 1593 (CH=C), 1612 (CH=NH, which showed δ_H (500 MHz, DMSO): the amine proton showed at 11.4 as singlet, the proton of pyrazlyl showed at 9.4 as singlet, while the protons of thiazlyl at 8.59 as singlet, the proton of imine group showed at 8.3 as singlet, the aromatic protons (5 protons) at 7.3–8.17 as multiplet; (75 MHz, DMSO: 167.3, 151.4, 146.2, 144.0, 138.7, 136.5, 107.1, 114.2, 117.0, 132.0, 125.7, 138.8, 130.3, 128.7, 124.7, 123 .5, [133.5, 133.9, 134.4, 134.8, 127.8, 124.1, 120.5, 116.8, 113.2; MS (EI, 70 eV): m/z (%): 416 (M^+,102); The molecular formula $C_{18}H_{18}BrN_5S$: the carbons% is 51.92; hydrogens is 4.32; nitrogen's 16.82.

The derivative (4b) [16] m.p.: 150-152 °C; IR (Potassium bromide, cm^{-1}): 3176 (OH), 3112 (NH), 1593 (C=C), 3091 (Ar- H), 1614(C=N); ^{1}H-NMR showed the amine proton showed at 11.8 as singlet, in addition to the hydroxyl proton at 10.0 as singlet, while proton of pyrazlyl showed at 9.2 as singlet, while the protons of thiazlyl at 8.6 as singlet, the proton of imine group showed at 8.3 as singlet, while the protons of aromatic protons showed as 7.6-8.5 as multiplet.

MS (EI, 70 eV): m/z (%): 432 (M+, 100); calculate $C_{18}H_{18}N_5OS$: C, 50.00; H, 4.16; N, 16.20; found: C, 50.74; H, 4.08; N, 16.07.

The deriavtive (4c) [15,17] m.p.: 178-179 °C; IR (Potassium bromide, cm^{-1}): 3296 (N-H), 3043 (Ar-H), 1593 (C=C), 1622 (C=N), 2921, 2852 (Aliph. C – H); ^{1}H-NMR showed the amine proton showed at 11.7 as singlet, while proton of pyrazlyl showed at 9.1as singlet, while the protons of thiazlyl at 7.3 as singlet, the proton of imine group showed at 8.3 as singlet, while the protons of aromatic protons showed as 7.1-7.3 as multiplet. The ^{13}C-NMR; 169.3, 152.2, 147.4, 144.5, 142.1, 134.1, 107.2, 114.1, 120.3, 136.2, 127.1, 131.2, 128.7, 129.6, 133.5, 133.9, 134.4, 134.8, 128.0, 124.1, 120.5, 116.8, 113.2; MS (EI, 70 eV): m/z (%): 430 (M+, 100); Molecular formula is $C_{19}H_{20}N_5OS$: Carbons, 53.03; Hydrogens, 4.65; Nitrogens, 16.27; found: Carcons, 53.41; Hhydrogens, 4.48; Nitrogens, 16.41.

The deriative (4d) [16] m.p.: 165-167 °C; ^{1}H-NMR showed the amine proton showed at 12.1 as singlet, proton of pyrazlyl showed at 9.1 as singlet, while the protons of thiazlyl at 6.2 as singlet, the proton of imine group showed at 9.4 as singlet, while the protons of aromatic protons showed as 7.5–7.9 as

multiplet. The ^{13}C-NMR: δc 169.5, 151.0, 148.1, 145.0, 142.4, 138.5, 135.1, 107.4, 1I8.0, 120.5 (2C), 132.3 (2C), 126.3, 127.4 (2C), 126.1 (2C), 123.1 (2C), 135.0 (2C), 134.5 (2C), 133.2, 122.4 (2C); MS (EI, 70 eV): m/z (%): 475 (M+ , 101); Analysis calculated for $C_{18}H_{17}BrN_7O_2S$: Carbons, 45.47; Hydrogens, 3.57; Nitrogens, 20.63; found: Carbons, 45.58; Hydrogens, 3.11; Nitrogens, 20.54.

The derivative (4e) [15,17], Melting point.: 182-185 ◦C; IR showed 3350 for secondary amine peak and 1560 for aromatic (C=C), and 1600 for active group as imine group, the two peaks 1350 and 1540 as nitro groups; 1H-NMR showed the amine proton showed at 12.1 as singlet, proton of pyrazlyl showed at 9.0 as singlet, while the protons of thiazlyl at 7.5 as singlet, the proton of imine group showed at 8.4 as singlet, while the protons of aromatic protons showed as 7.5–7.7 as multiplet. MS (EI, 70 eV): m/z (%): 495 (M+, 100); Molecular formula is $C_{18}H_{17}Br_2N_5S$: C, 43.63; Hydrogens, 3.35; Nitrogens, 14.14; found: Carbons, 43.35; Hydrogens, 3.43; Nitrogens, 14.52.

3.2. The Biological Activity

Compounds on the moiety (N – C = S) relation are reported as irritant agents and fungicides [18]. The series is comprised of numerous basic structures in medicine either to be a part of an open. Using the agar plate diffusion method, some synthesized derivatives were surveyed *in vitro* for antimicribial assay. The zone of inhibition of bacterial increase around the disc was supervised; the screening results given in Table 3 indicated that most derivatives exhibited antibacterial activity against one or the other type of bacteria [19]. Almost all compounds showed more inhibition against (G +ve).

Table 3: The antibacterial activity of synthesized compounds 4b and 4d.

Comp. No.	*Staphylococcus aureus G+ve*	*Escherichia coli aureus*
4a	++	+
4b	+	++
4c	++	++
4d	++	+
4e	+++	+

(-): No inhibition, (+): (5-10) mm, (++): (11-20) mm, (+++): (more than 20mm.

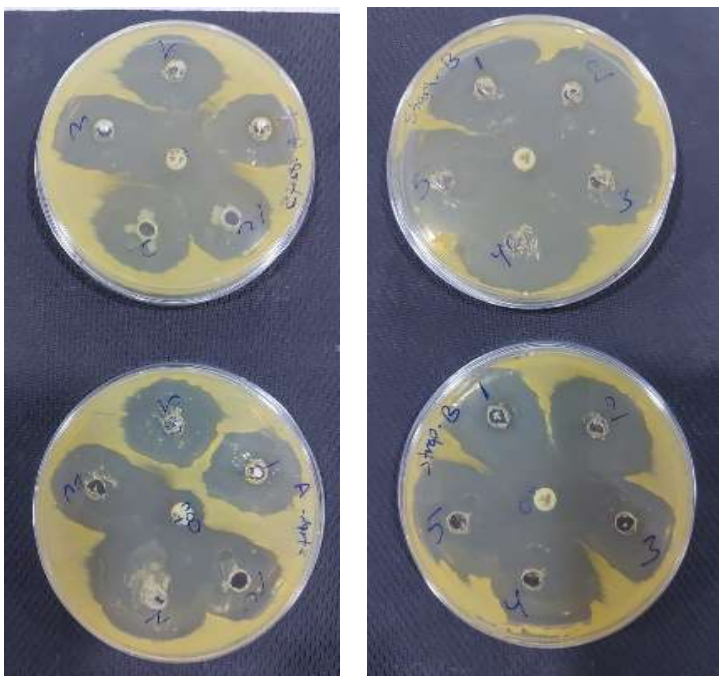


Figure 1: Effect of compounds [4b and 4d] on some types of bacteria.

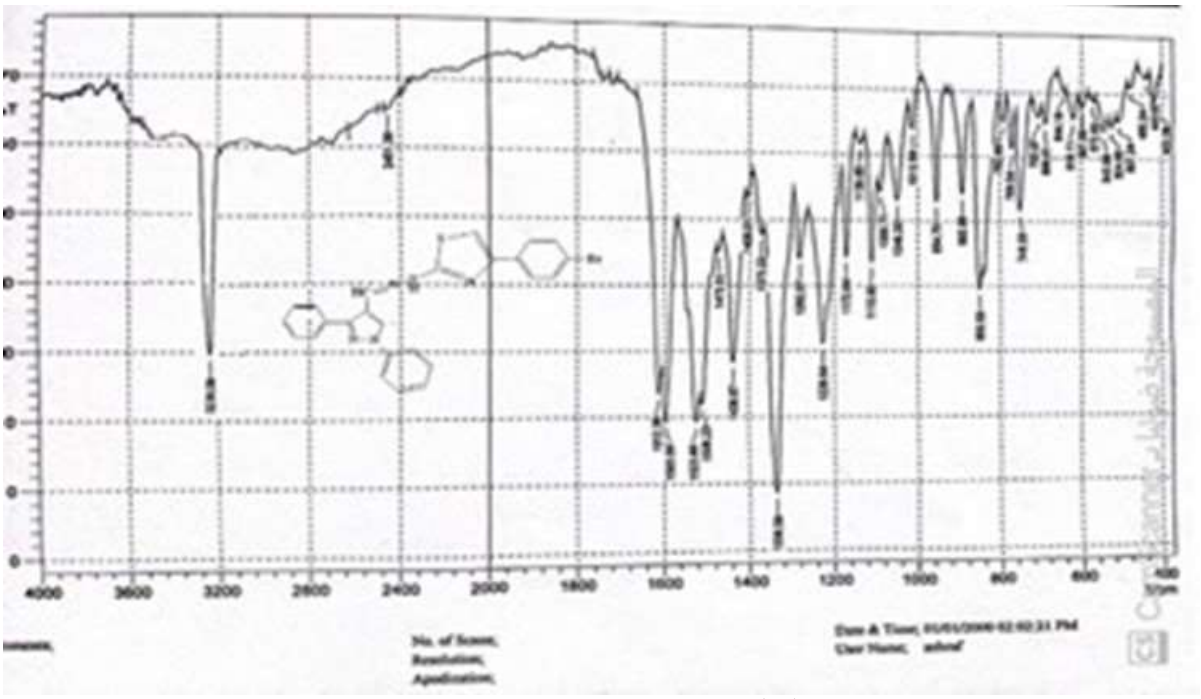


Figure 2: FT-IR of derivative (4a).

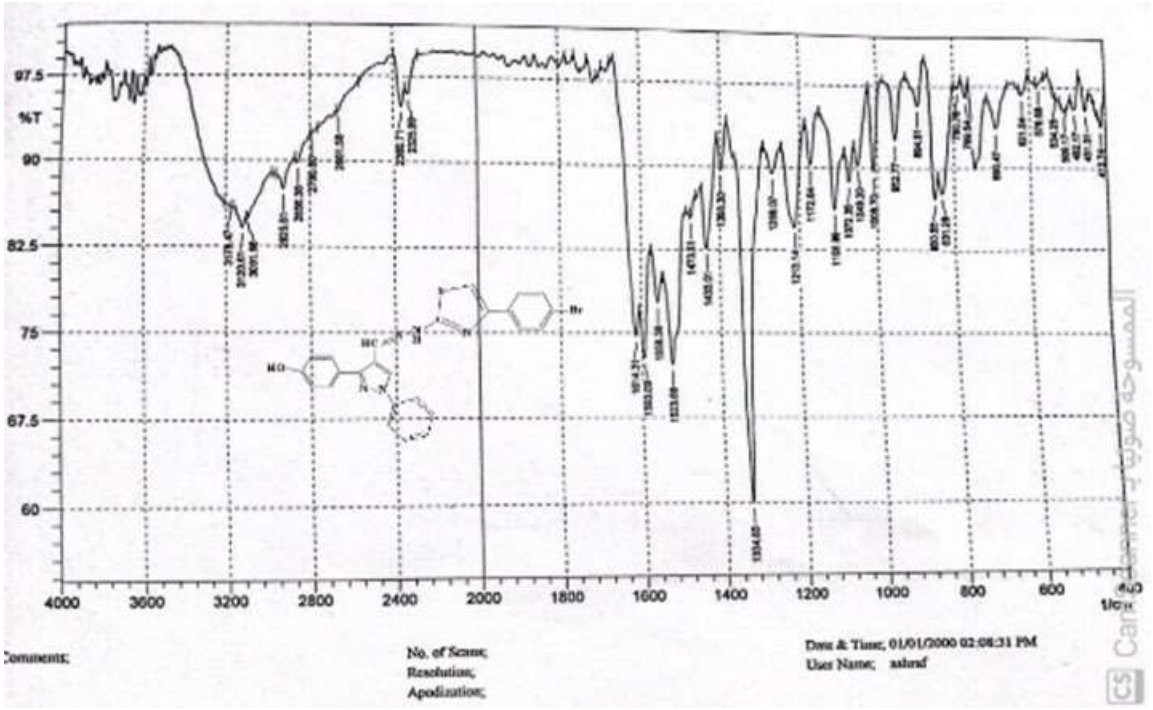


Figure 3: FT-IR of derivative (4b).

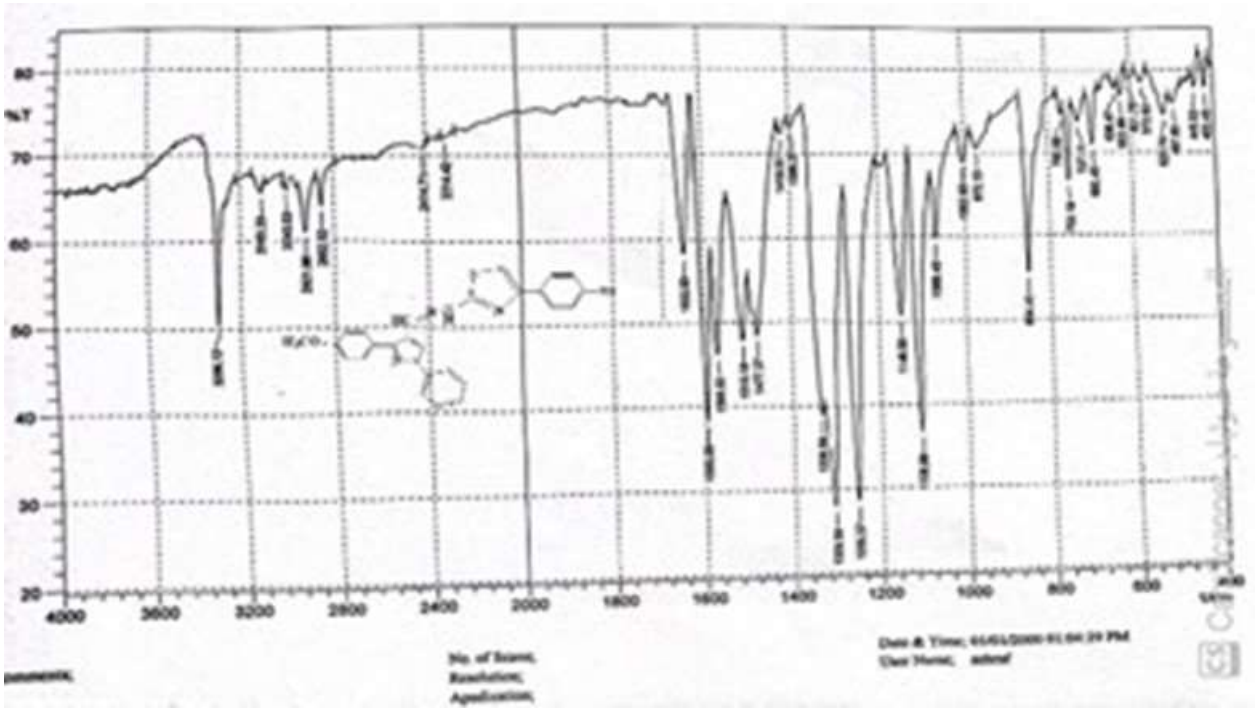


Figure 4: FT-IR of derivative (4c).

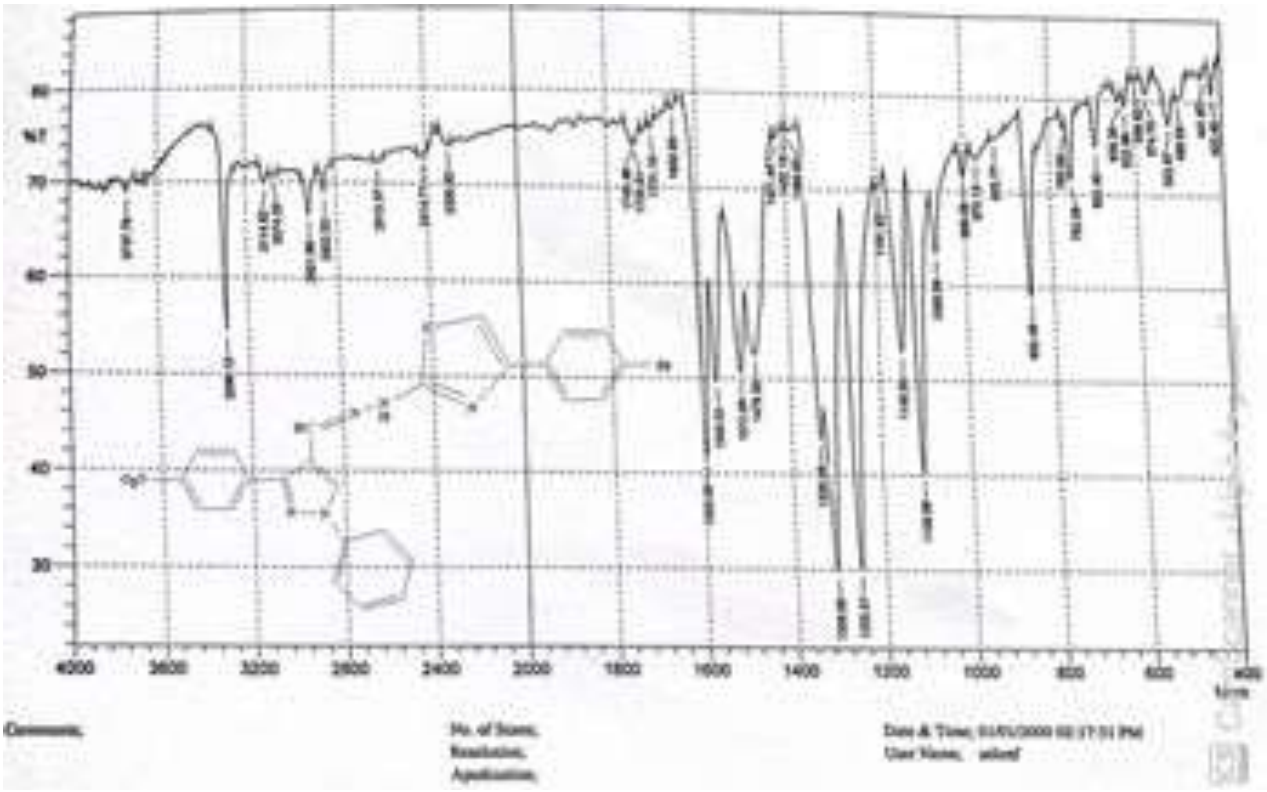


Figure 5: FT-IR of derivative (4d).

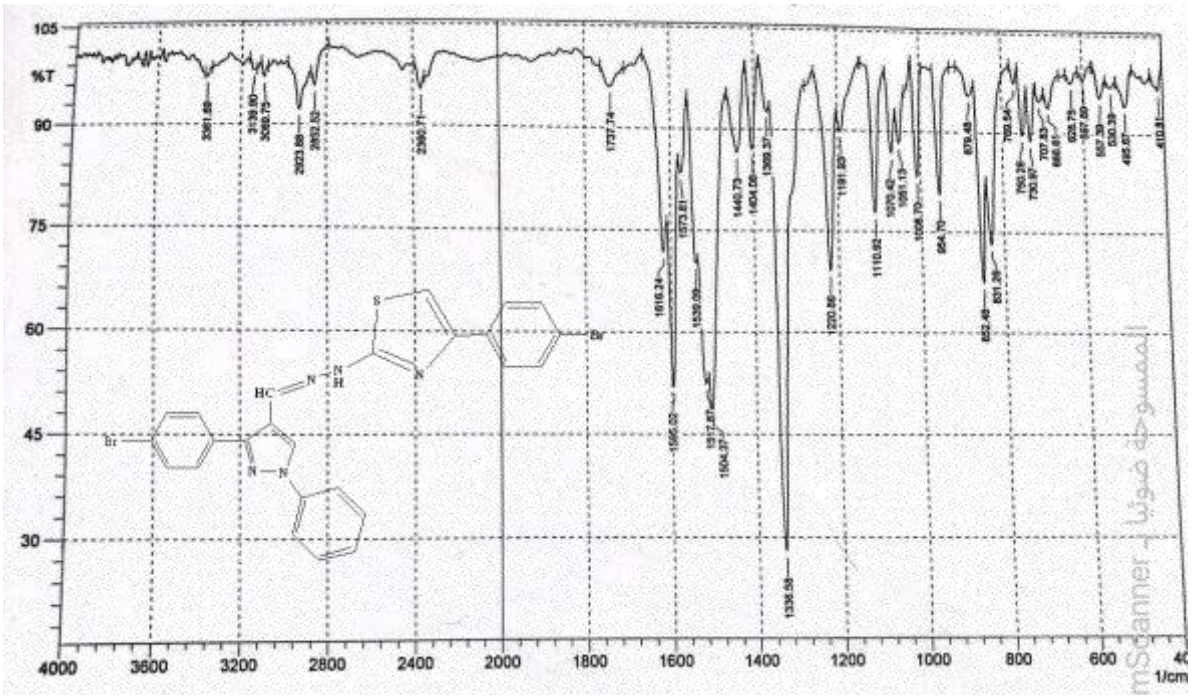


Figure 6: FT-IR of derivative (4e).

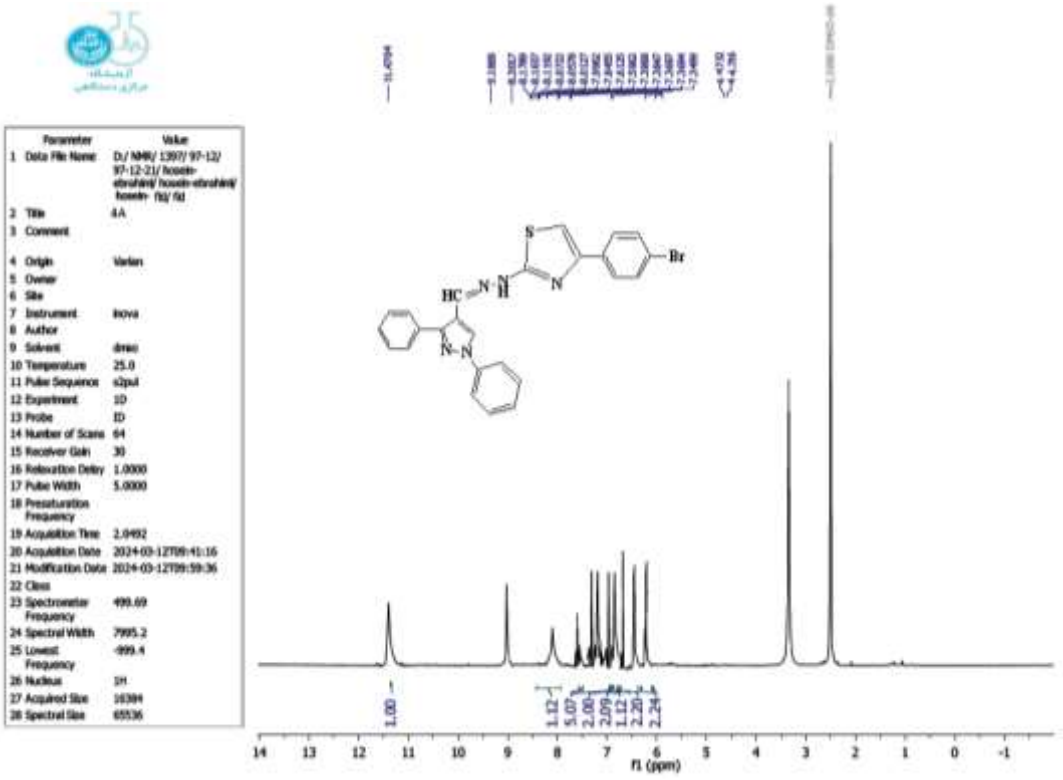


Figure 7: [1]HNMR of derivative 4a.

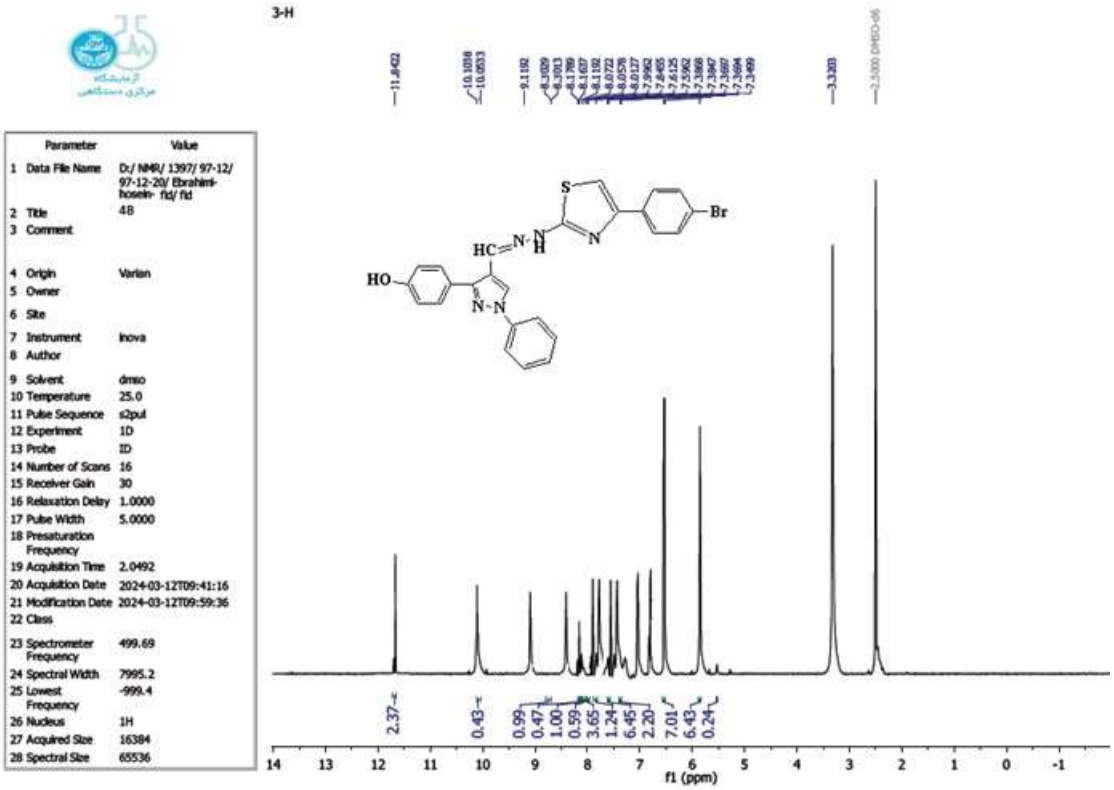


Figure 8: ^{1}HNMR of derivative 4b.

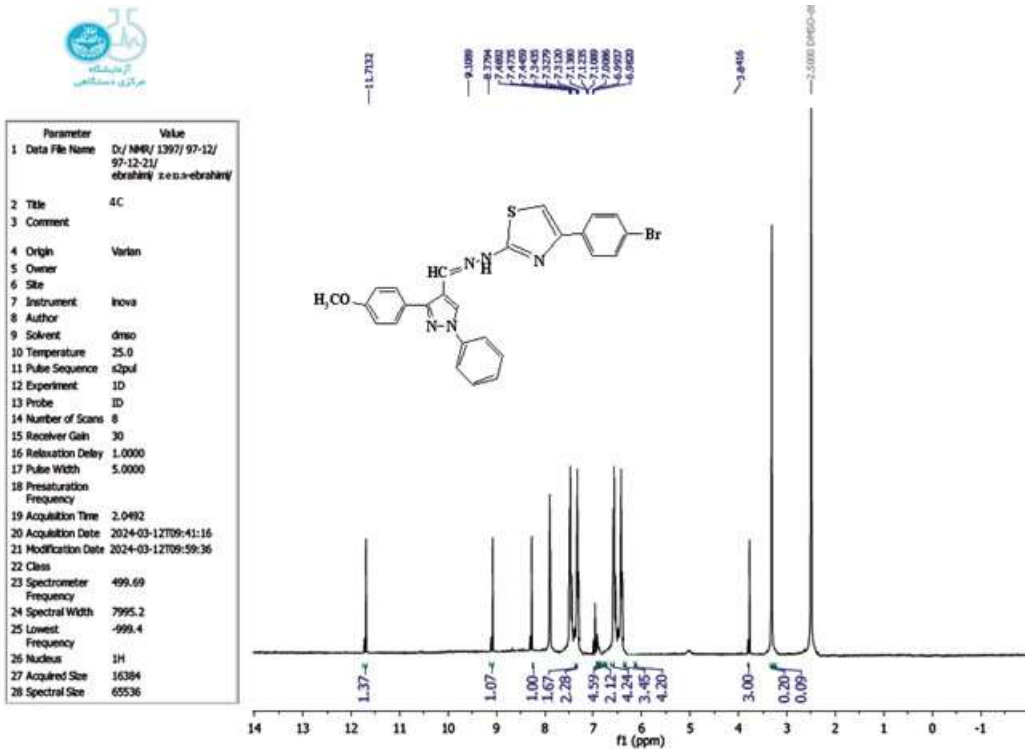


Figure 9: ^{1}HNMR of derivative 4c.

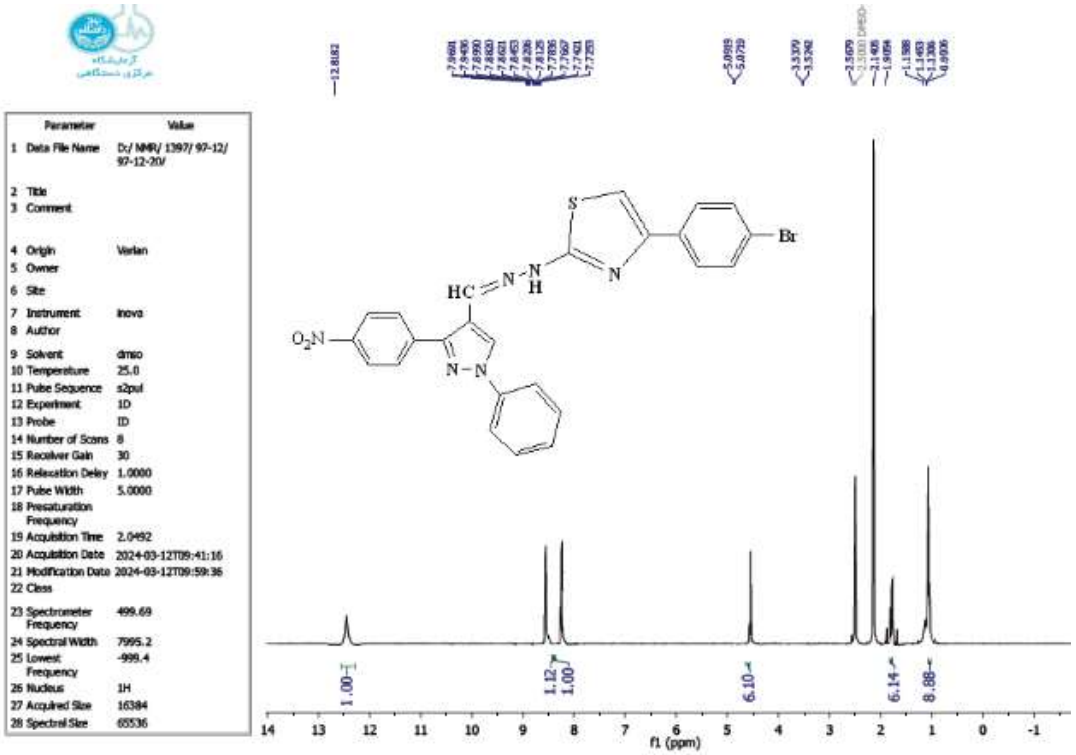


Figure 10: [1]HNMR of derivative 4d.

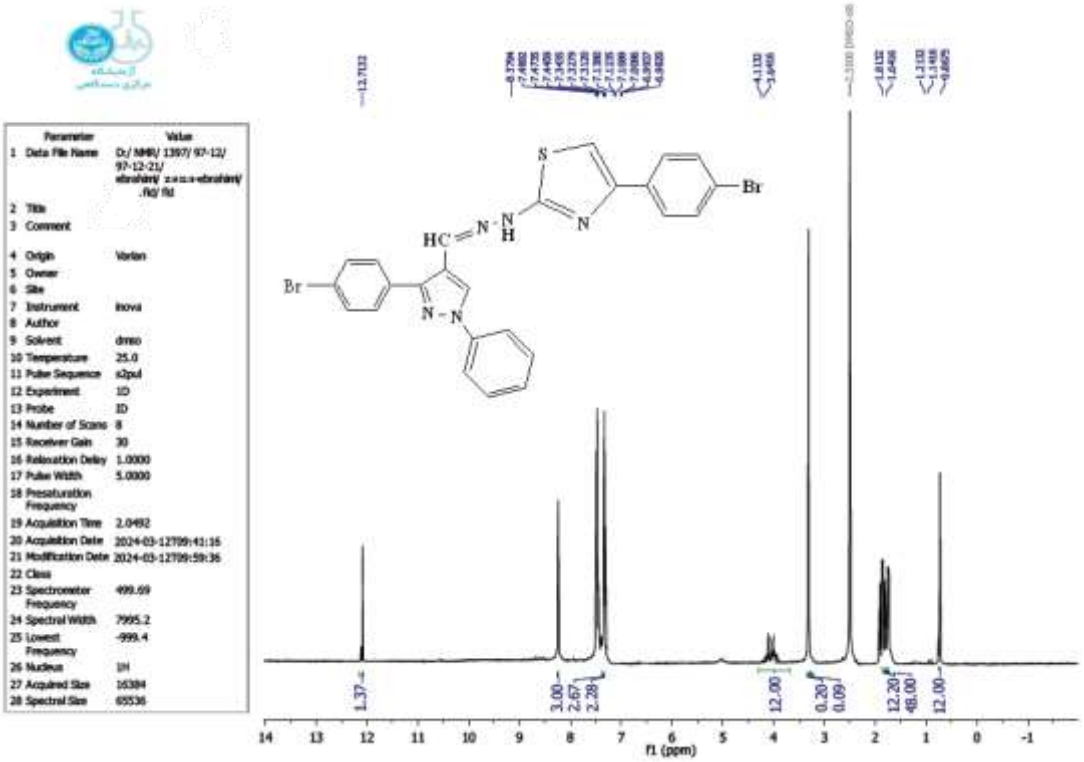


Figure11: [1]HNMR of derivative 4e.

4. Conclusions

In conclusion, we have expanded pyrazole derivatives containing heterocyclic thiazole group. The study revealed that the formulated compounds had superior effectiveness relative to conventional medications. The definition of biological discussion indicates that heterocyclic pyrazole and thiazole groups are significant in the examination of biological activity. Thus, it was worthwhile to search for these azoles for further transformation to develop heterocyclic rings for use as effective drugs.

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