

Evaluation of Novel 2,4-Disubstituted Thiazoles for Antibacterial and Antioxidant Activity

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Abstract:

The biological evaluation of these novel heterocyclic molecules revealed promising biochemical activities. In vitro assays demonstrated significant antimicrobial, anti-inflammatory, and anticancer properties. Several compounds exhibited potent inhibitory effects against key enzymes and cellular pathways associated with these conditions, suggesting their potential as therapeutic agents. The findings of this research highlight the potential of nitrogen-containing heterocyclic compounds in developing new therapeutics. The novel synthetic strategies developed here not only contribute to the field of organic chemistry but also open new avenues for the design of drugs with enhanced efficacy and reduced side effects.

Keywords: Novel, 2,4-Disubstituted, Thiazoles, Antibacterial and Antioxidant Activity

INTRODUCTION

An organic chemical molecule is considered heterocyclic if its rings include an element other than carbon. Hetero-indicates that there are non-carbon atoms, or heteroatoms, in the ring. Conversely, cyclic means that there is a ring structure present. Compounds having a heterocyclic structure resemble those with a cyclic organic structure, such as benzene. Heterocyclic compounds, on the other hand, exhibit unique physical and chemical characteristics due to the presence of heteroatoms.

Many life-sustaining biochemicals are heterocyclic. Heterocyclic unit chains joined by additional components make up nucleic acids, which contain genetic information. Most hallucinogens, colors, vitamins, and antibiotics are heterocyclic.

Modern civilization relies on synthetic heterocycles for pharmaceuticals, insecticides, colors, and plastics.

A significant area of interest for nitrogen-based methods is the synthesis of novel chemicals and composites. heterocyclic chemistry, a distinct field of organic chemistry. The last two decades have seen more attention to these compounds. They developed several organic synthesis procedures and discovered many chemical uses. N-heterocyclic compounds are prevalent in nature and are found in several physiologically significant substances such as vitamins, nucleic acids, medicines, antibiotics, dyes, and agrochemicals. These compounds possess physiological and pharmacological effects. They also make up numerous

pharmacologically active compounds. N-heterocyclic chemicals like purines, pyrimidines, and thymine make up DNA and RNA base pairs.

The pharmaceutical industry, medicinal chemistry, and organic chemistry have all taken an interest in these nitrogen-containing heterocyclic molecules due to their unique characteristics and applications. In addition, the proton-rich nitrogen heterocycle may easily take or give a proton and generate a number of weak interactions. The intermolecular forces, including hydrogen bonding, dipole-dipole interactions, hydrophobic effects, van der Waals forces, and π -stacking interactions, provide nitrogen compounds a substantial impact on medicinal chemistry. Because of how easily they dissolve in water, they form strong binding interactions with enzymes and receptors. Because of this, their offspring have extensive bioactivities, their structural properties are helpful.

Their synthetic worth and the amount of synthetic study on them have led to, heterocyclic molecules are becoming more common. Most disciplines, including medical chemistry and biochemistry, use heterocyclic compounds. "Heteros" means "different" in Greek, therefore heterocyclic. A heterocyclic compound is any organic molecule with one or more hetero atoms, such as nitrogen, oxygen, sulfur, or other atoms. Heterocyclic compounds are the most diverse organic family. Heterocyclic chemistry, a prominent subfield of organic chemistry, studies the synthesis, properties, and uses of heterocycles.

Literature Review

Ruan, Ban-Feng (2022). Many medicinal chemistry applications favour the oxadiazole core. Compounds belonging to the oxadiazole class include 1,2,3,1,2,4, and 1,2,5-oxadiazole. Oxadiazole compounds have shown activity against insects, inflammation, malaria, and cancer.

A large portion of medicinal chemistry's attention has gone into the 1,3,4-oxadiazole class of chemicals. The 1,2,4-, 1,3,4-, and 1,2,5-oxadiazole compounds reported in the last five years and their anti-inflammatory, antibacterial, and anti-cancer activities.

Gajjar, Bhoomika et.al. (2023). Novel therapeutic drug sources in medicinal chemistry include nitrogen-based heterocycle modulators. Roughly three quarters of all FDA-approved drugs include heterocyclic nitrogen compounds. Researchers are developing new heterocyclic compounds with unique properties and potential medical applications. We need heterocyclic compounds based on nitrogen for new medicinal medications. It has been investigated the physiological effects of many new nitrogen-based heterocycles. The novel nitrogen-based heterocycles, their biological actions, and potential medicinal applications are discussed in this article.

Saber, Mohammed. (2023). Naturally occurring N-heterocyclic compounds possess a wealth of pharmacologically active molecules that exert their anti-cancer actions via several antiproliferative mechanisms. This study reviews articles published between 2019 and 2021 that discuss the possible anticancer effects of N-heterocyclic derivatives, their structure-activity relationships, and the mechanisms of action.

Mermer, Arif et.al. (2021). The chemical, biological, and technical characteristics of N-heterocycles make them particularly noteworthy, despite their abundance. They play a crucial role in several areas of biological study, including those pertaining to the battle against cancer, inflammation, bacteria, viruses, tumours, diabetes, and so on. The target of this investigation were synthetic 5- or 6-ring N-heterocyclic compounds synthesized in the previous five years and their antiviral activity as well as their structure-activity

relationships. Researchers in medicinal chemistry, pharmacology, and organic synthesis will find this review useful.

Hamid, Daniah et. al. (2023). Here we see that heterocyclic molecules are present in many fields of biology. These compounds are essential for many technical, medicinal, and biological processes. Structures of heterocyclic compounds may include heteroatoms. They could choose to restate their points or not. Heterocyclic compounds serve several purposes. We include most of the recently

produced or extracted heterocyclic compounds with physiological activity.

Materials and Methods

Flushing equimolar quantities of the starting ingredients with thiosemicarbazide in absolute ethanol. The Furniss et al. 1996 method was used to produce substituted phenacyl bromides (9a-c). Refluxing 3-aryl-1H-thiazole-4-carbaldehyde with pyrazole-4-carbaldehyde thiosemicarbazones (8a-e) yielded **P₂₅₋₃₈** in excellent yield. Fig 1 summarizes the chemical mechanism.

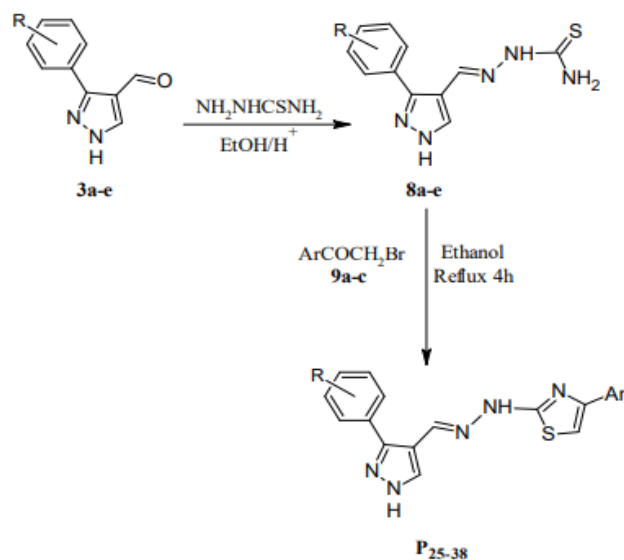


Figure 1: A synthesis process for 2,4-disubstituted thiazole analogues **P₂₅₋₃₈**

If R is a group consisting of hydrogen, 4-chloromethyl, 4-fluoromethyl, 4-chloromethyl, and 2,4-chloromethyl, then Ar = C₆H₅, 4-OCH₃-C₆H₄, 4-F-C₆H₄

Melting points were resolved using open capillary analysis. The infrared spectra were collected using a Thermo Nicolet avatar 330-FT-IR spectrophotometer. A 100 MHz Bruker spectrometer was used to produce the ¹³C NMR spectra, while a 400 MHz Bruker and Varian spectrometer was used to obtain the ¹H-NMR spectra using DMSO-d₆ as the internal standard. Parts per million is the unit of measurement for chemical shift data. The

mass spectra were acquired using an Agilent 1100 series LC-MS. In order to examine the parts, we used a Flash EA 1112 CHNS-O Analyser. In thin layer chromatography (TLC), silica gel 60 F254-coated aluminium sheets were used to guarantee reaction completion. Avoiding purification while using commercial solvents and reagents.

Results and Discussion

Chemistry

Utilizing nuclear magnetic resonance (NMR), infrared, and elemental spectroscopy, the compounds **P₂₅₋₃₈** that were synthesized were examined. Spectra

and analytical information for every single one of the compounds that were made conformed to the models. There were absorption lines at 3320, 3013, 1610, 1485, and 1085. The N-H proton of the pyrazole compound is seen as a singlet with a chemical shift of δ 11.8 in the ¹H-NMR spectra. P25. At δ 8.1, a singlet resonated from an N=CH proton. The proton of thiazole-5H and the proton of pyrazole-5H did not resonate as a pair at δ 7.29 and 8.0, correspondingly. At m/z = 344 (M-1), there peaks in the mass spectra of molecular ions at the P25 level., which matches $C_{19}H_{15}N_5S$. experimental component gives spectrum chemistry and C, H, and N analyses, and Table 1 shows characterizations data.

Processes in biology that are functional

Antibacterial activity evaluated in vitro for testing purposes was carried out using the "well-plate" method on newly synthesized compounds (P25-38). The process of activity was investigated using *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* are the microorganisms that are being discussed here. It is the outcomes of the antimicrobial screening showed that a number of substances inhibited different microbial strains (Table 2). Compared to Streptomycin, P29 and P38 demonstrated outstanding efficacy against all bacterial strains at 1 and 0.5 mg/mL.

Table 1 Information on the chemicals' characteristics P25-38

Compounds	R	Ar	Molecular formula (Mol.wt.)	Yield (%)	M.p. (°C)
P25	H	C ₆ H ₅	C ₁₉ H ₁₅ N ₅ S (345)	86	209-210
P26	4-OCH ₃	C ₆ H ₅	C ₂₀ H ₁₇ N ₅ OS (375)	72	220-221
P27	4-F	C ₆ H ₅	C ₁₉ H ₁₄ FN ₅ S (363)	88	125-127
P28	4-Cl	C ₆ H ₅	C ₁₉ H ₁₄ ClN ₅ S (379)	74	150-152
P29	2,4-Cl	C ₆ H ₅	C ₁₉ H ₁₃ Cl ₂ N ₅ S (414)	87	180-183
P30	H	4-OCH ₃ -C ₆ H ₄	C ₂₀ H ₁₇ N ₅ OS (375)	89	229-231
P31	4-OCH ₃	4-OCH ₃ -C ₆ H ₄	C ₂₁ H ₁₉ N ₅ O ₂ S (405)	85	239-241
P32	4-F	4-OCH ₃ -C ₆ H ₄	C ₂₀ H ₁₆ FN ₅ OS (393)	87	240-242
P33	4-Cl	4-OCH ₃ -C ₆ H ₄	C ₂₀ H ₁₆ ClN ₅ OS (409)	82	243-245
P34	H	4-F-C ₆ H ₄	C ₁₉ H ₁₄ FN ₅ S (363)	84	229-231
P35	4-OCH ₃	4-F-C ₆ H ₄	C ₂₀ H ₁₆ FN ₅ OS (393)	88	241-243
P36	4-F	4-F-C ₆ H ₄	C ₁₉ H ₁₃ F ₂ N ₅ S (381)	85	258-260
P37	4-Cl	4-F-C ₆ H ₄	C ₁₉ H ₁₃ ClFN ₅ S (397)	88	252-254
P38	2,4-Cl	4-F-C ₆ H ₄	C ₁₉ H ₁₂ Cl ₂ FN ₅ S (432)	72	232-233

The compounds P30, P31, P33, P36, and P37 were modestly active against *Pseudomonas aeruginosa* but excellent against *Escherichia coli* and *Staphylococcus aureus*. P34 inhibited *Escherichia coli* more than *E. coli* and *Pseudomonas aeruginosa* is a good

example. It was just P26. modestly active against *Staphylococcus aureus*. The studied microorganisms showed no antibacterial action from compounds P32 and P35.

It was determined whether or not freshly synthesised compounds (P25-38) have

antifungal properties by testing them against *Candida albicans*, *Aspergillus flavus*, and *Chrysosporium keratinophilum*. Fluconazole was the

standard. The concentrations used for the evaluation were 1000 and 500 µg/mL. concentration Table 3 shows antifungal study results.

Table 2 The antibacterial properties of certain substances P25-38

Compound code	Zone of inhibition(mm)					
	<i>Escherichia coli</i>		<i>Staphylococcus aureus</i>		<i>Pseudomonas aeruginosa</i>	
Conc. in µg/mL	1000	500	1000	500	1000	500
P ₂₅	07±0.2	05±0.2	08±0.2	06±0.2	05±0.1	03±0.2
P ₂₆	06±0.1	02±0.2	09±0.2	07±0.2	08±0.2	06±0.1
P ₂₇	09±0.2	06±0.2	06±0.1	04±0.2	07±0.2	05±0.2
P ₂₈	06±0.2	04±0.1	08±0.1	05±0.1	08±0.2	04±0.2
P ₂₉	13±0.2	10±0.2	14±0.1	12±0.1	16±0.1	13±0.1
P ₃₀	10±0.1	07±0.1	11±0.2	08±0.2	10±0.1	08±0.2
P ₃₁	11±0.2	09±0.2	09±0.2	07±0.1	10±0.2	07±0.2
P ₃₂	00	00	00	00	00	00
P ₃₃	10±0.2	07±0.2	10±0.1	08±0.1	07±0.2	03±0.2
P ₃₄	13±0.2	10±0.1	09±0.2	07±0.1	10±0.2	08±0.1
P ₃₅	00	00	00	00	00	00
P ₃₆	10±0.2	08±0.2	08±0.1	06±0.2	09±0.2	07±0.1
P ₃₇	09±0.2	07±0.1	08±0.2	07±0.2	10±0.1	07±0.2
P ₃₈	15±0.2	12±0.2	12±0.1	11±0.2	16±0.2	13±0.1
Streptomycin (Std.)	16±0.2	10±0.1	15±0.2	10±0.2	16±0.2	13±0.2

Results reveal that P29 and P38 have effective efficacy in relation to *Chrysosporium keratinophilum* and *Aspergillus flavus* were measured at values of 1000 and 500 µg/mL, respectively. respectively fluconazole as an example. Only P27 and P36 were

successful. against *Aspergillus flavus* but marginally against the other two fungal species. Some of the produced compounds had similar antifungal properties to Fluconazole against diverse microbial strains, however none were better.

Table 3 Antifungal activity of compounds P25-38

Compound code	Zone of inhibition(mm)					
	<i>Aspergillus flavus</i>		<i>Chrysosporium keratinophilum</i>		<i>Candida Albicans</i>	
Con in µg/mL	1000	500	1000	500	1000	500
P ₂₅	04±0.2	02±0.2	06±0.2	05±0.2	05±0.1	03±0.2
P ₂₆	05±0.1	03±0.1	04±0.2	03±0.1	03±0.1	01
P ₂₇	06±0.1	05±0.2	04±0.1	03±0.1	05±0.1	04±0.1
P ₂₈	06±0.2	04±0.1	05±0.1	03±0.1	04±0.1	03±0.1
P ₂₉	11±0.1	09±0.1	09±0.1	07±0.1	10±0.2	08±0.2
P ₃₀	00	00	00	00	00	00
P ₃₁	03±0.1	01	02±0.1	00	03±0.1	00
P ₃₂	00	00	00	00	00	00
P ₃₃	00	00	00	00	00	00
P ₃₄	04±0.1	01	03±0.1	01	04±0.1	02±0.1
P ₃₅	00	00	00	00	00	00
P ₃₆	06±0.2	05±0.1	04±0.2	03±0.1	05±0.1	03±0.1
P ₃₇	04±0.2	02±0.1	03±0.2	01	05±0.2	02
P ₃₈	10±0.1	08±0.1	09±0.1	07±0.1	11±0.1	08±0.1
Fluconazole (Std.)	13±0.2	10±0.1	17±0.2	15±0.2	22±0.2	20±0.2

Compounds (P25-38) Their antioxidant activity was assessed by scavenging superoxide anion, hydroxyl radical, DPPH, and nitric oxide (Table 4). Except for P27, P28, P29, and P30, all compounds demonstrated >80% DPPH scavenging efficacy in antioxidant experiments. P26,

P34, and P38 have strong nitric oxide, OH radical, and superoxide scavenging activities. P30 compound has substantial nitric oxide and OH radical scavenging action but not super oxide. Figure 1 depicts compound scavenging activity (%).

Table 4 Scavenging activity (%) of compounds P25-38

Compounds	DPPH Assay	Nitric oxide Assay	OH Radical Assay	Superoxide anion scavenging activity
P ₂₅	80.88	60.46	60.46	66.46
P ₂₆	86.69	77.49	77.49	82.49
P ₂₇	68.22	58.22	58.22	62.22
P ₂₈	70.00	60.24	60.24	64.24
P ₂₉	74.55	64.56	64.56	62.32
P ₃₀	76.62	76.62	76.62	68.56
P ₃₁	83.06	61.46	61.46	63.24
P ₃₂	82.56	62.16	62.16	65.16
P ₃₃	84.47	64.42	64.42	60.64
P ₃₄	86.08	72.24	72.24	76.24
P ₃₅	84.10	64.10	64.10	68.46
P ₃₆	85.11	66.11	66.11	66.87
P ₃₇	84.74	62.56	62.56	64.26
P ₃₈	86.18	74.34	74.34	78.56
BHT	92.42	88.56	89.56	85.86

As for the heterocyclic scaffold structure and antibacterial capabilities, P29 and P38's antibacterial activity was enhanced by substituting 2,4-dichloro on the pyrazole ring. activities. For antibacterial action, chloro, methoxy, and fluoro groups on pyrazole and thiazole rings are preferred (P26, P30, P31, P33, P34, P36, and P37), except for P32 and P35. Following OECD recommendations No. 420, substances P29 and P38 were studied

for acute oral toxicity. Experimental investigations showed found a dosage of 2000 mg/kg was safe for the chemicals. Experimental animals revealed no substantial behavioral abnormalities except for the three thousand and four thousand milligrammes per kilogramme of all chemical substances, which showed signs of depression on day one and death the next day.

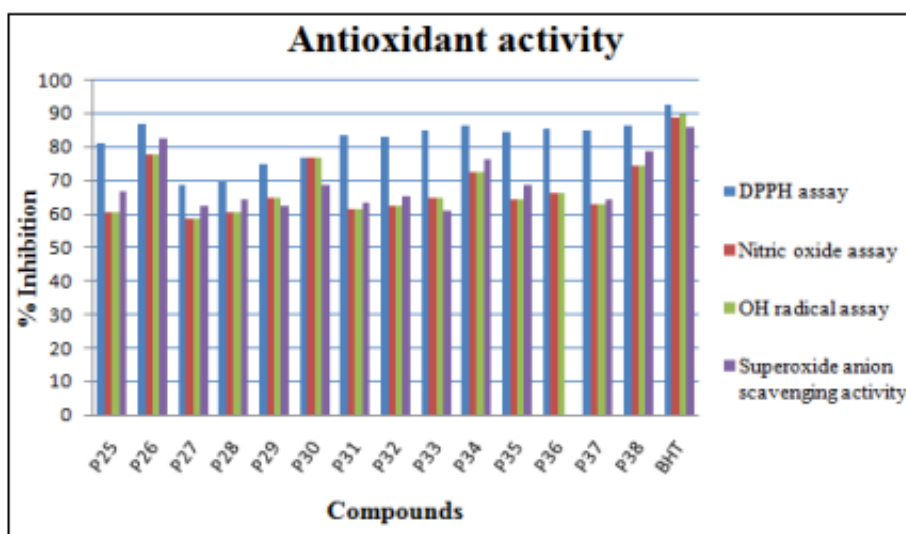


Figure 1 Schematic depicting the percentage of scavenging P25-38

Conclusions

Except for *P*₂₇, *P*₂₈, *P*₂₉ and *P*₃₀, antioxidant investigations demonstrated >80% DPPH activity in all compounds. Nitric oxide, OH radical, and superoxide scavenging activity were considerably elevated in *P*₂₆, *P*₃₄ and *P*₃₈. Three of the six produced compounds—1,3,4-oxadiazoles (*P*₁₁₋₂₄), Thiazoles (*P*₂₅₋₃₈), and Schiff bases (*P*₃₉₋₄₈)—had remarkable antibacterial activity. Compared to conventional medication, 1,3,4-oxadiazoles *P*₁₉, *P*₂₀, thiazoles *P*₂₉, *P*₃₈, and Schiff bases *P*₄₁ and *P*₄₄ have outstanding antibacterial action. Antimicrobial activity of 1,3,4-oxadiazoles is due to 2-chlorophenyl substituent. Thiazoles with 2,4-dichlorophenyl substituents on pyrazole rings enhance antibacterial action. A chemical must

contain hydrogen donor atoms to be antioxidant

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