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Microwave Assisted Synthesis, Characterization and Biological Study of Some Heterocyclic Derived from Chalcone compounds.

Suha K. Al-Mosawi[1]*, Hanan A. Al-Hazam[2], and Abbas F. Abbas [2].

[1]Department of pharmaceutical chemistry, College of Pharmacy, University of Basrah, Basrah-Iraq
[2]Department of Chemistry, College of Science, University of Basrah, Basrah-Iraq

ABSTRACT

A number of heterocyclic compounds were prepared by condensing of chalcones in ethanollic NaOH solutions. These Heterocyclic were immediately reacted with phenyl hydrazine, hydrazine hydrate, hydroxylamine hydrochloride and thiourea to obtain the corresponding phenyl pyrazole (A1-A10)), pyrazole acetate (B1-B10), oxazole (C1-C10) and thiopyrimidine (D1-D10) compounds. The synthesized heterocycles were characterized on the basis of their chemical properties and spectroscopic data (IR, NMR and MS). These compounds were tested for antimicrobial and fungal activity against a variety of test organisms: Escherichia coli, Staphylococcus aureus, *Pseudomonas aeruginosa*, *Bacillus cereus*, *aspergillus niger* and *Candida albicans*.

Keywords: microwave, chalcone, antimicrobial, antifungal.

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Corresponding author

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INTRODUCTION

Pyrazoles, Oxazoles and thiopyrimidines are five and six-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family. Indeed, a huge variety of synthesis methods and synthetic analogues have been reported over the years.

The presence of the Heterocyclic nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant as well as antiviral agents [1,2].

Nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities [3–10].

In this review, we present descriptions and discussions on the most relevant synthesis methods and biological properties of pyrazole, oxazole and thiopyrimidines derived chalcone system.

EXPERIMENTAL WORK

Melting point were determined in Buchi thermal point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in Costech ESC4010 CHNSO in University of Tehran in Iran. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk in the range 40-4000cm^{-1}. ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker spctrospin ultra shield magnets 400MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d_6 as a solvent in university of university of Tehran. The compounds were synthesized by microwave type Panasonic microwave instrument (Malaysia), NN-SN382, compact 20L, power1200 Watt and frequency 2450 MHz, by using turntable system with different powers between 90-300W. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck Company.

Synthesis of Compounds

Synthesis of (Pyrazoles, Oxazole and Thiopyrimidine) Derivatives [11, 12]

A mixture of chalcone [13-15] (0.01 mole), (phenyl hydrazine, hydrazine hydrate, hydroxylamine hydrochloride and thiourea) respectively (0.01 mole) and 3ml (40%) KOH in 10 ml ethanol. The contents were thoroughly mixed. The reaction mixture under went to microwave irradiation in a commercially available domestic microwave oven having a maximum power output of 480W operating at 2450 Hz intermittently at 30 seconds intervals for 3-6 min on a completion of reaction as monitored by TLC. It was then cooled and poured in cold water acidified with dil. HCl. Filtered, washed and dried. The product was recrystallized from ethanol to get product. The purity of the compound was checked with TLC using eluent n-hexane: ethyl acetate (3:7) respectively, the products were obtained in 70-89%. Physical properties of chalcone compounds as shown in Table (1)-(4) and chemical structure in figure (1)

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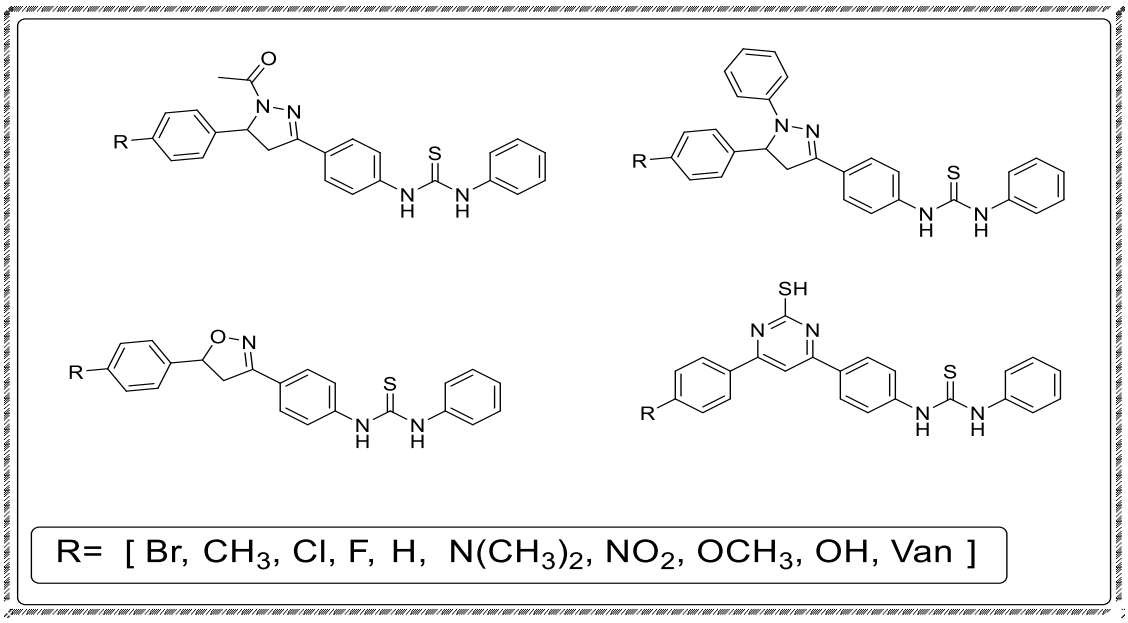

Figure 1: Substituents Chalcone Derivatives Compounds

Table 1: Some Physical Data of Phenyl Pyrazole Compounds

Symbol of Pyrazole Acetate	Name of Phenyl Pyrazole	Colour	Melting Point (^{0}C)	Yield (%)	R_f
A1 (4-Br)	*1-{4-(1-phenyl-5-(4-bromophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	161-163	87	0.85
A2 (4-CH_3)	*1-{4-(1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	orange	145-147	80	0.74
A3 (4-Cl)	*1-{4-(1-phenyl-5-(4-chlorophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	189-191	88	0.77
A4 (4-F)	*1-{4-(1-phenyl-5-(4-fluorophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	154-156	89	0.63
A5 (H)	*1-{4-(1,5-diphenyl -4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow pale	182-183	83	0.76
A6 4-N(CH_3)$_2$	*1-{4-(1-phenyl-5-(4-N,N-dimethylphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	164-166	77	0.77
A7 (4-NO_2)	*1-{4-(1-phenyl-5-(4-nitrophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow pale	279-281	88	0.81
A8 (4-OCH_3)	*1-{4-(1-phenyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	160-161	79	0.72
A9 (4-OH)	*1-{4-(1-phenyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	187-189	77	0.69
A10 (Van)	*1-{4-(1-phenyl-5-(4-hydroxy-2-methoxyphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	170-172	70	0.72

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Table 2: Some Physical Data of Pyrazole Acetate Compounds

Symbol of Pyrazoles	Name of Pyrazole Acetate	Colour	Melting Point (^{0}C)	Yield (%)	R_f
B1 (4-Br)	*1-{4-(1-acetyl-5-(4-bromophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	181-183	84	0.79
B2 (4-CH_3)	*1-{4-(1-acetyl-5-(p-tolyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	190-192	78	0.86
B3 (4-Cl)	*1-{4-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	Pale yellow	166-168	85	0.73
B4 (4-F)	*1-{4-(1-acetyl-5-(4-fluorophenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	192-194	88	0.69
B5 (H)	*1-{4-(1-acetyl-5-phenyl-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow dark	166-167	76	0.64
B6 4-N(CH_3)$_2$	*1-{4-(1-acetyl-5-(4-N,N-dimethylphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	140-142	71	0.78
B7 (4-NO_2)	*1-{4-(1-acetyl-5-(4-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea nitrophenyl)-4,5-ه*	yellow	222-224	86	0.76
B8 (4-OCH_3)	*1-{4-(1-acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	157-159	70	0.70
B9 (4-OH)	*1-{4-(1-acetyl-5-(4-hydropxyhenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	119-121	70	0.65
B10 (Van)	*1-{4-(1-acetyl-5-(4-hydropxy-3-methoxyphenyl)-4,5-dihydro-1H-Pyrazol-3-yl)phenyl}-3-phenylthiourea*	yellow	157-159	65	0.72

Table 3: Some Physical Data of Oxazole compounds

Symbol of Oxazoles	Name of Oxazole	Colour	Melting Point (^{0}C)	Yield (%)	R_f
C1 (4-Br)	*1-{4-(5-(4-bromophenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	yellow	136-138	79	0.77
C2 (4-CH_3)	*1-{4-(5-(p-tolyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	187-189	75	0.81
C3 (4-Cl)	*1-{4-(5-(4-chlorophenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	150-152	86	0.72
C4 (4-F)	*1-{4-(5-(4-fluorophenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	116-118	82	0.89
C5 (H)	*1-{4-(5-diphenyl -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	177-179	75	0.75
C6 4-N(CH_3)$_2$	*1-{4-(5-(4-N,N-dimethylphenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	198-200	75	0.73
C7 (4-NO_2)	*1-{4-(5-(4-nitrophenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	235-237	80	0.74
C8 (4-OCH_3)	*1-{4-(5-(4-methoxyphenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	188-190	71	0.68

C9 (4-OH)	*1-{4-(5-(4-hydroxyphenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	yellow	194-196	70	0.82
C10 (Van)	*1-{4-(5-(4-hydroxy-2-methoxyphenyl) -4,5-dihydro-1isoxzol-3-yl)phenyl}-3-phenylthiourea*	orange	170-172	69	0.81

Table 4: Some Physical Data of Thiopyrimidine Compounds

Symbol of Thiopyrimidine	Name of Thiopyrimidine	Colour	Melting Point (^{0}C)	Yield (%)	R_f
D1 (4-Br)	*1-{4-(2-mercapto-6-(4-bromophenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	dark yellow	126-128	77	0.73
D2 (4-CH_3)	*1-{4-(2-mercapto-6-(p-tolyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	deep yellow	135-136	70	0.68
D3 (4-Cl)	*1-{4-(2-mercapto-6-(4-chlorophenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	pale yellow	170-172	83	0.59
D4 (4-F)	*1-{4-(2-mercapto-6-(4-fluorophenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	pale yellow	147-149	80	0.65
D5 (H)	*1-{4-(2-mercapto-6-phenylpyrimidine- 4-yl)phenyl}-3-phenylthiourea*	pale yellow	158-160	70	0.63
D6 4-N(CH_3)$_2$	*1-{4-(2-mercapto-6-(4-N,N-dimethylphenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	brawn	186-187	69	0.80
D7 (4-NO_2)	*1-{4-(2-mercapto-6-(4-nitrophenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	orange	240-242	86	0.62
D8 (4-OCH_3)	*1-{4-(2-mercapto-6-(4-methoxyphenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	yellow	188-190	70	0.72
D9 (4-OH)	*1-{4-(2-mercapto-6-(4-hydroxyphenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	pale yellow	140-142	71	0.63
D10 (Van)	*1-{4-(2-mercapto-6-(4-hydroxy-2-methoxyphenyl)pyrimidine- 4-yl)phenyl}-3-phenylthiourea*	yellow	163-165	68	0.66

RESULT AND DISCUSSION

The compounds were synthesized by the reaction of 0.01 mole of (phenyl hydrazine, hydrazine hydrate, hydroxylamine hydrochloride and thiourea) respectively with 0.01 mole of appropriate chalcones by using 40% KOH in absolute ethanol. Using microwave irradiation in power 270W (3-6 min.) at a different time. All the reactions were monitored by TLC.

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Table 5: The Percentage of Yield and Reaction Time of Some Phenyl Pyrazole Compounds

Compounds	R	Yield (%)	Reaction time (min.)
A1	(4-Br)	87	3
A2	(4-CH_3)	80	5
A3	(4-Cl)	88	2
A4	(4-F)	89	2
A5	(H)	83	3
A6	$N(CH_3)_2$	77	5
A7	(NO_2)	88	3
A8	(4-OCH_3)	79	5
A9	(OH)	77	4
A10	(Van)	70	6

Table 5: The Percentage of Yield and Reaction Time of Some Pyrazoles Acetate Compounds

Compounds	R	Yield (%)	Reaction time (min.)
B1	(4-Br)	84	3
B2	(4-CH_3)	78	5
B3	(4-Cl)	85	3
B4	(4-F)	88	4
B5	(H)	76	5
B6	$N(CH_3)_2$	71	5
B7	(NO_2)	86	3
B8	(OCH_3)	70	4
B9	(OH)	70	4
B10	(Van)	65	5

Table 7: The Percentage of Yield and Reaction Time of Some Oxazole Compounds

Compounds	R	Yield (%)	Reaction time (min.)
C1	(4-Br)	79	3
C2	(4-CH_3)	75	4
C3	(4-Cl)	86	3
C4	(4-F)	82	3
C5	(H)	75	3
C6	$N(CH_3)_2$	75	4
C7	(NO_2)	80	3
C8	(OCH_3)	71	4
C9	(OH)	70	5
C10	(Van)	69	5

Table 8: The Percentage of Yield and Reaction Time of Some Thiopyrimidine compounds

Compounds	R	Yield (%)	Reaction time (min.)
D1	(4-Br)	77	4
D2	(4-CH_3)	70	5
D3	(4-Cl)	83	3
D4	(4-F)	80	3
D5	(H)	70	4
D6	$N(CH_3)_2$	69	3
D7	(NO_2)	86	4
D8	(OCH_3)	70	5
D9	(OH)	71	4
D10	(Van)	68	6

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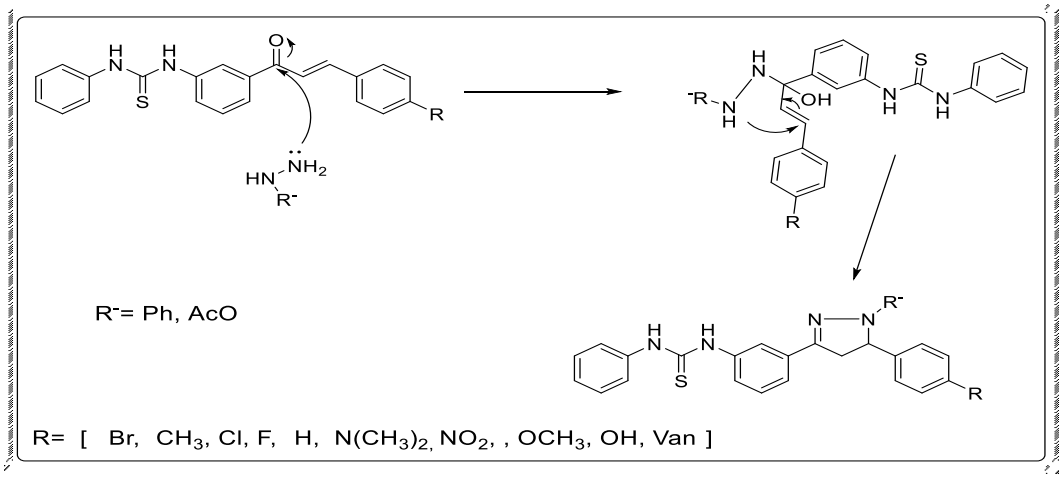
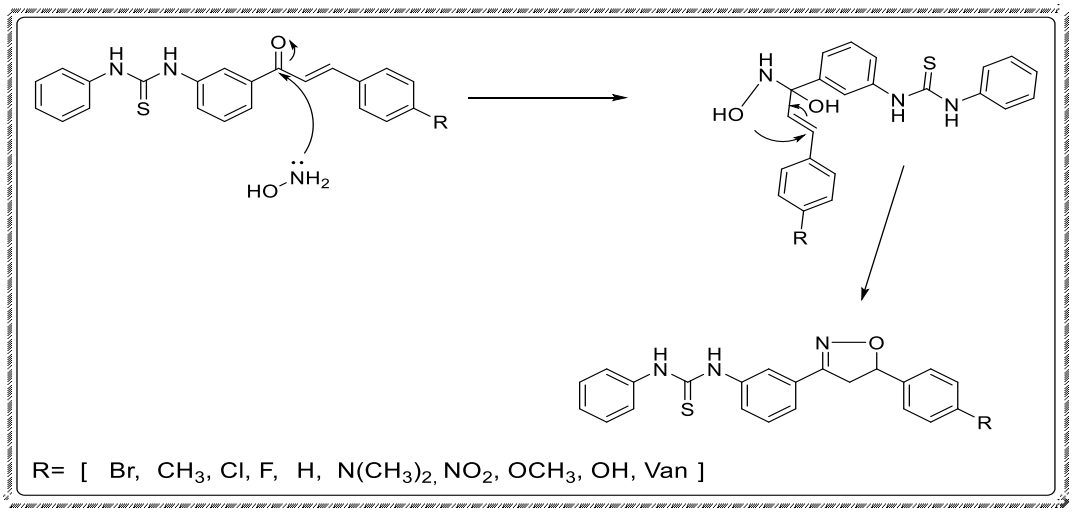
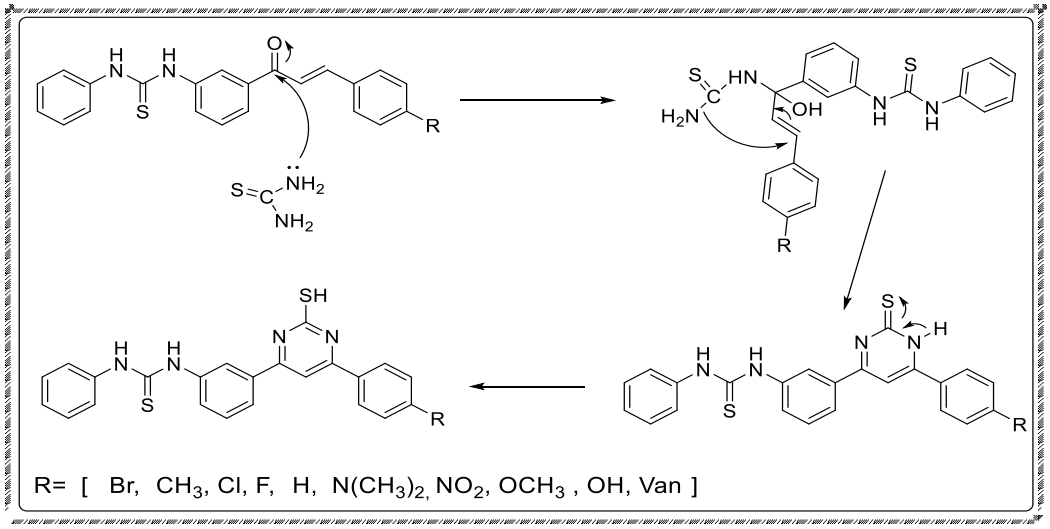
The mechanism of reactions can be explained by means of nucleophilic attack of amino group related to (phenyl hydrazine, hydrazine hydrate, hydroxylamine hydrochloride and thiourea) followed by cyclization.



Scheme 1: Formation of Pyrazole Compounds



Scheme 2: Formation of Oxazole Compounds



Scheme 3: Formation of Thiopyrimidine Compounds

The IR spectra of substituent heterocyclic[16-19] compounds were characterized by the disappearance of the absorption band that was assign to the (C=O) stretching which appeared at (1631-1683) cm^{-1} due to the chalcone compounds, these fact certain the correct expected chemical structure of these compounds.

The IR spectra of substituent heterocyclic compounds showed strong absorption bands in the range (1579-1629) cm^{-1} due to (C=N) stretching of azomethane group. In addition to these absorption bands, weak bands appeared in the region (1436-1523) cm^{-1} which were attributed to the (C=C) aromatic group. However, the IR spectra of compounds (B5, B7, and B8) showed that strong absorption bands appeared in the region (1666-1688) cm^{-1} due to stretching of (C=O) acetate group in pyrazole compounds. Also, strong absorption bands appeared between the range (1207-1357) cm^{-1} due to the stretching of the (C=S) group. Moreover, all these spectra appeared that the weak absorption bands, which appeared in the range (3022-3107) cm^{-1}, were due to the stretching of aromatic (-CH). In addition to these absorption bands, all the IR spectra of heterocyclic compounds showed weak bands between the region (2916-2999) cm^{-1} and (823-887) cm^{-1} which were attributed to the (-CH) or (CH_3) and C-X (X= Cl, Br, F) groups respectively. The strong absorption bands appeared between the range (2511-2576) cm^{-1} due to the stretching of the (S-H) group in thiopyrimidines (D3, D5 and D7). The IR spectra of these compounds showed a strong absorption band in the region between (3224-3394) cm^{-1} due to NH stretching exist in skeleton of all heterocyclic compounds.

Most of the synthesized substituent Heterocyclic compounds were characterized by ^{1}HNMR spectroscopy, which showed similar patterns of the heterocyclic scaffold and characterized by the presence of aromatic protons.

The ^{1}HNMR spectra of substituent heterocyclic compounds were characterized by the disappearance band with in the range (4.86-6.00) ppm due to (C=CH). This fact confirmed the correct expected chemical structure of these compounds.

The ^{1}HNMR spectra of A3, A5, A8, B5, B7, B8, C3, C7, C8, D3, D5 and D7 substituent heterocyclic compounds showed multiplet signal within the region (6.04-8.41) ppm due to aromatic rings system. The protons of methyl group in B5, B7 and B8 appeared at (1.11-1.81) ppm. In addition, the ^{1}HNMR spectrum of B7 and C3 compounds showed singlet signals at the chemical shift (3.4) ppm due to the three-proton equivalent of methoxy groups. The spectra of A3, A5, A8, B5, B7, B8, C3, C7, C8, were characterized by the show of the protons that was attributed to the (CH_2 and CH) which appeared at (2.22-2.77) ppm in Pyrazoles[20-22] and oxazole[23-26]. The low field singlets at the region (9.01-9.72) ppm were referred to thiol (SH) signals in thiopyrimidines [27, 28] D3, D5 and D7 compounds. In addition, the low field singlets at the region (9.19-9.72) ppm were assigned to secondary amine signals in these compounds.

The ^{13}CNMR spectra of (A3-D7) substituent heterocyclic compounds showed several signal, phenyl pyrazole compounds (A3, A5 and A8) appears (20-21)signals within the region (120-163) ppm due to C_1, C_2, C_3 , C_4, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14},C_{15},C_{16},C_{17},C_{18},C_{19} and C_{20} for aromatic rings system including the substituents (Cl, H and OCH_3) respectively. While the signals of azomethane (C=N) in pyrazole ring [22, 23] appearance in the region (146-157) ppm. In addition, the signal of methoxy group in A8 compounds appearance in the region (55.1) ppm.

Pyrazole acetate compounds (B3, B5 and B8) appears (18-19) signal according to the carbon atoms exist in the structure. The lines in the region (115-146) ppm due to C_1, C_2, C_3 , C_4, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14},C_{15} and C_{16} for aromatic rings system including the substituents (Cl, H and OCH_3) respectively. While the signals of azomethane (C=N) in pyrazole ring appearance in the region (135-160) ppm. Also, the signal of methoxy group in A8 compounds appearance in the region (61.8) ppm. In addition, the C12 and C17 showed the signals in the region (158-161)-(161-163) for the (C=O) and (C=S) respectively.

Oxazole compounds (C3, C7 and C8) appears (16-17) signals within the region (120-163) ppm due to C_1, C_2, C_3 , C_4, C_8, C_9, C_{10}, C_{13}, C_{14},C_{15} and C_{16} for aromatic rings system including the substituents (H, NO_2 and OCH_3) respectively. The signals of azomethane (C=N) in pyrazole ring appearance in the region (158) ppm. In addition, the signal of methoxy group in A8 compounds appearance in the region (62.8) ppm. Also the C_{12} showed the signal in the region (161) ppm for the (C=S).

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Thiopyrimidine compounds (D3, D5 and D7) appears (17-18) signal according to the carbon atoms exist in the backbone structure. signals within the region (105-147) ppm due to C_1, C_2, C_3 , C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{13}, C_{14},C_{15} and C_{16} for aromatic rings system including the substituents (Cl, H and OCH_3) respectively. While the signal of methoxy group in D8 compounds appearance in the region (62.7) ppm. In addition, the C_{12} showed the signal in the region (161) ppm for the (C=S) respectively.

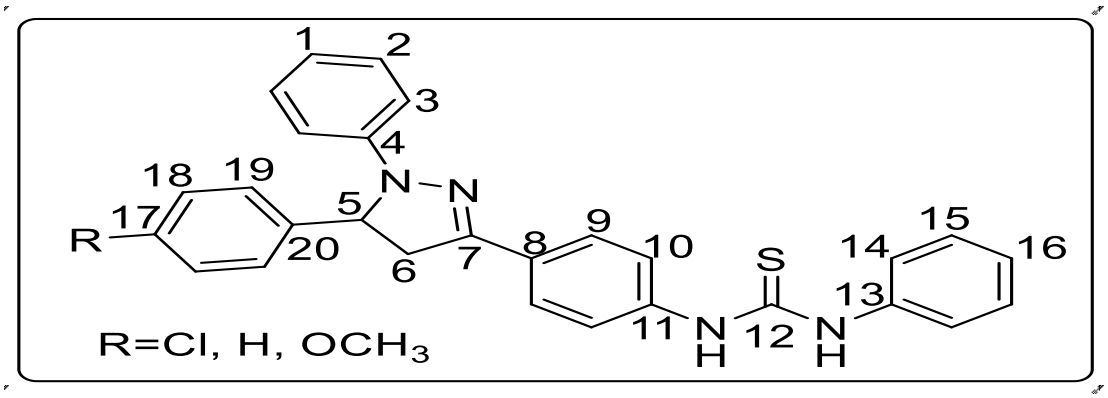

Figure 2: Numbering Carbon Atoms of Phenyl Pyrazole Compounds

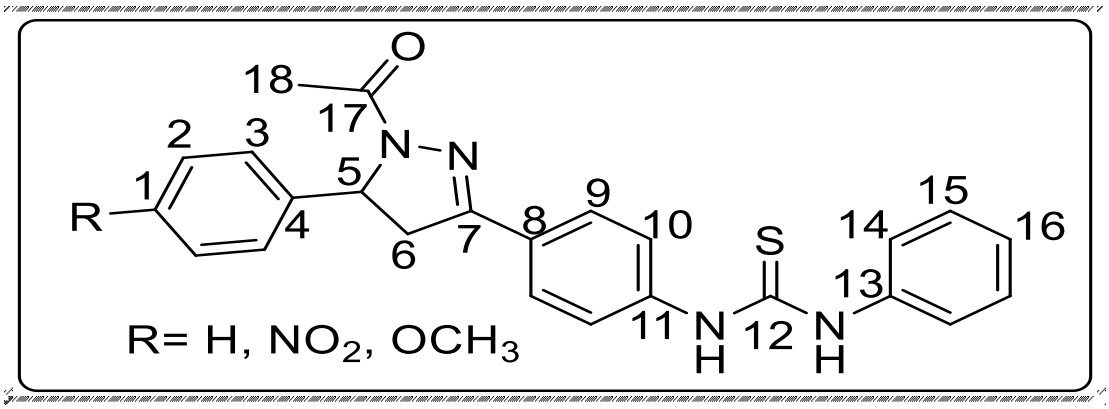

Figure 3: Numbering Carbon Atoms of Pyrazole Acetate Compounds

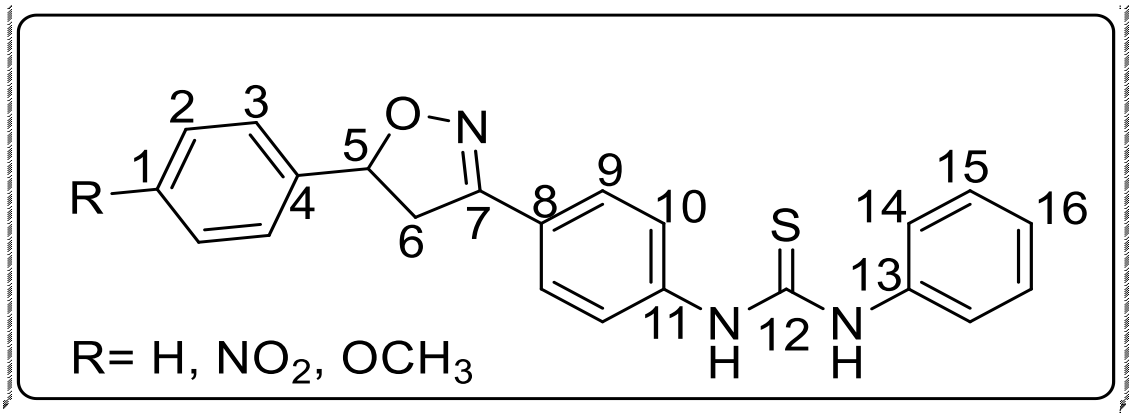

Figure 4: Numbering Carbon Atom of Oxazole Compounds

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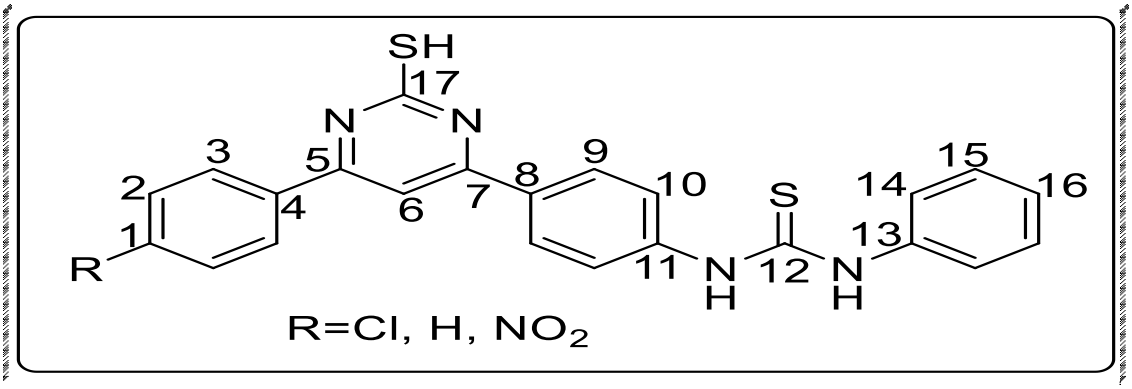

Scheme 5: Numbring Carbon Atoms of Thiopyramidine Compounds

The mass spectra [30-31] of the synthesized substituent heterocyclic compounds are represented in Figures (3-108)-(3-111) and Table (3-22). From the mass spectra, it was observed that the peak at (m/z = 448, 414, 418, and 414) represented the molecular ion [M^+] for (A5, B5, C7, and D5) compounds, respectively. These peaks indicated that the structures of the synthesized compounds in this study were as expected.

All synthesized substituent heterocyclic compounds had similar fragment mechanisms. as shown in Table (9).

Table 9: The Major Fragment Ions of Substituent Heterocyclic Compounds

Sym.	M1 *Inte. (%)*	2 *Inte. (%)*	3 *Inte. (%)*	4 *Inte. (%)*	5 *Inte (%)*	6 *Inte (%)*	7 *Inte (%)*	8 *Inte. (%)*
A5	448 *96*	370 66	355 50	313 76	298 46	279 26	144 50	77 78
B5	414 *97*	372 70	336 48	321 78	278 34	268 22	264 58	186 84
C7	418 97	325 25	295 35	283 61	268 13	204 38	190 14	123 12
D5	414 28	382 12	321 74	264 52	253 30	187 20	177 12	163 10

The antibacterial and fungal [32-33] activities of the series have been carried out against some strain of bacteria. The result (Table 10) showed that some prepared compounds are toxic against the bacteria. The compounds were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with Amoxicillin and Nystatin shows that these compounds have almost similar activity. The bacterial cultures for *S. aurous* , *E. coli*, *P. aeruginosa and B. cereus* and the fungal, *C. albicans* and *A. niger* were obtained from Department of biology University of Basrah. Iraq. The bacterial cultures were incubated at 30°C for 24 hours by inoculation into nutrient agar. Heterocyclic compounds were stored dry at room temperature and dissolved 20mg/ml in dimethyl sulfoxide (DMSO). Antibacterial activities of each compound were evaluated by the agar disc-diffusion method. Mueller Hinton Agar Media (15 cm^3) kept at 45°C was poured in the petridishes and allowed to solidify. Poured Petri plates [9 cm] were incubated with 50µL of normal saline solution of above culture media (105-106 bacteria per ml). Discs injected with prepared chalcones ([50µL) were applied on the solid agar medium by pressing tightly. The Petri plates were placed at 37°C for 24 hours. At the end of period, the inhibition zones formed on media were measured with a zone reader in millimeters.

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Table 10: inhibition zone for type's bacteria and fungi

Code	*E. Coli*	*S. aureus*	*P. aeruginosa*	*B. cereus*	*C. albicans*	*A. niger*
A3	8	13	zero	zero	20	zero
A5	8	10	16	11	10	20
A7	10	10	zero	zero	15	20
B3	zero	zero	18	zero	13	20
B5	10	12	9	15	18	22
B7	15	25	13	zero	25	20
C3	zero	10	15	15	30	22
C5	15	20	20	17	10	20
C7	15	15	26	16	10	16
D3	30	30	zero	zero	10	18
D5	10	12	9	15	18	22
D7	15	25	13	zero	25	20
Nystatin	------	------	------	------	50	50
Amoxicillin	50	50	50	50	------	------

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