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Green Synthesis and Spectroscopic Study of New Heterocyclic Compounds Derived from Ethyl Coumarilate

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Abstract:
The common starting compound ethyl coumarilate and substituted (1,2,3) prepared by the reaction of substituted salicylaldehydes with ethyl chloroacetate in the presence of base the treatment of (1,2,3) with hydrazine hydrate give 2,3a-dihydro-3H-benzofuro[3,2-c]pr azol-3-one (4, 11&18) derivative. But when the ester (1,2,3) reacted with phenyl hydrazine form 2-phenyl-2,3a-dihydro-3H-benzofuro[3,2-c) pyrazol-3-one (5, 12&19). Similar type of reaction occurs with urea, thiourea, guanidine, semicarbazide, thiosemicarbazide, to produce benzofuro [3,2-d] pyrimidine-2,4(3H,4aH)-Dione (6, 13&20). 2-thioxo-2,4a-dihydrobenzofuro [3,2-d] pyrimidin-4(3H)-one (7, 14&21). 2-imino-2,4a-dihydrobenzofuro [3,2-d] pyrimidin-4(3H)-one (8, 15&22), 3-oxo-3,3a-dihydro-2H-benzofuro [3, 2-c] pyrazole-2-carboxamide (9, 16&23), 3-oxo-3,3a-dihydro-2H-benzofuro[3,2-c] pyrazole-2-carbothioamide (10, 17&24) derivatives were synthesized in good to excellent yield under ultrasonic irradiation. The structures of all synthesized compounds in this study have been established by using FT-IR, 1H NMR, and 13C NMR techniques

Keywords: Pyrazole, Pyrimidine, Ethyl coumarilate, Ultrasonic technique

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Introduction

Benzofuran derivatives incorporating diazole and pyrimidine moieties have emerged as novel compounds with significant biological potential. These compounds are of great interest due to their diverse range of biological activities and potential therapeutic applications [1]. The biological evaluation of these benzofuran derivatives has revealed promising results across various areas. Let's explore some of the key biological activities associated with these compounds, anti-inflammatory [2], anti- bacterial [3], antitumor [4], and antioxidant [5]. Some benzofuran derivatives have been developed as drugs for the treatment of diseases such as cancer [6], Alzheimer's disease [7], HIV [8], and asthma disease [9] . The combination of benzofuran with diazole (a five-membered aromatic heterocycle containing two nitrogen atoms) and pyrimidine (a six-membered aromatic heterocycle containing two nitrogen atoms) introduces unique structural features and functional groups that contribute to their biological properties [10]. Represents a promising avenue in the search for novel therapeutic agents. These compounds possess unique chemical structures and exhibit a wide range of biological activities, making them attractive candidates for drug development to the discovery of new drugs for the treatment of various diseases. All the synthesized compounds have been supported by their spectral data.

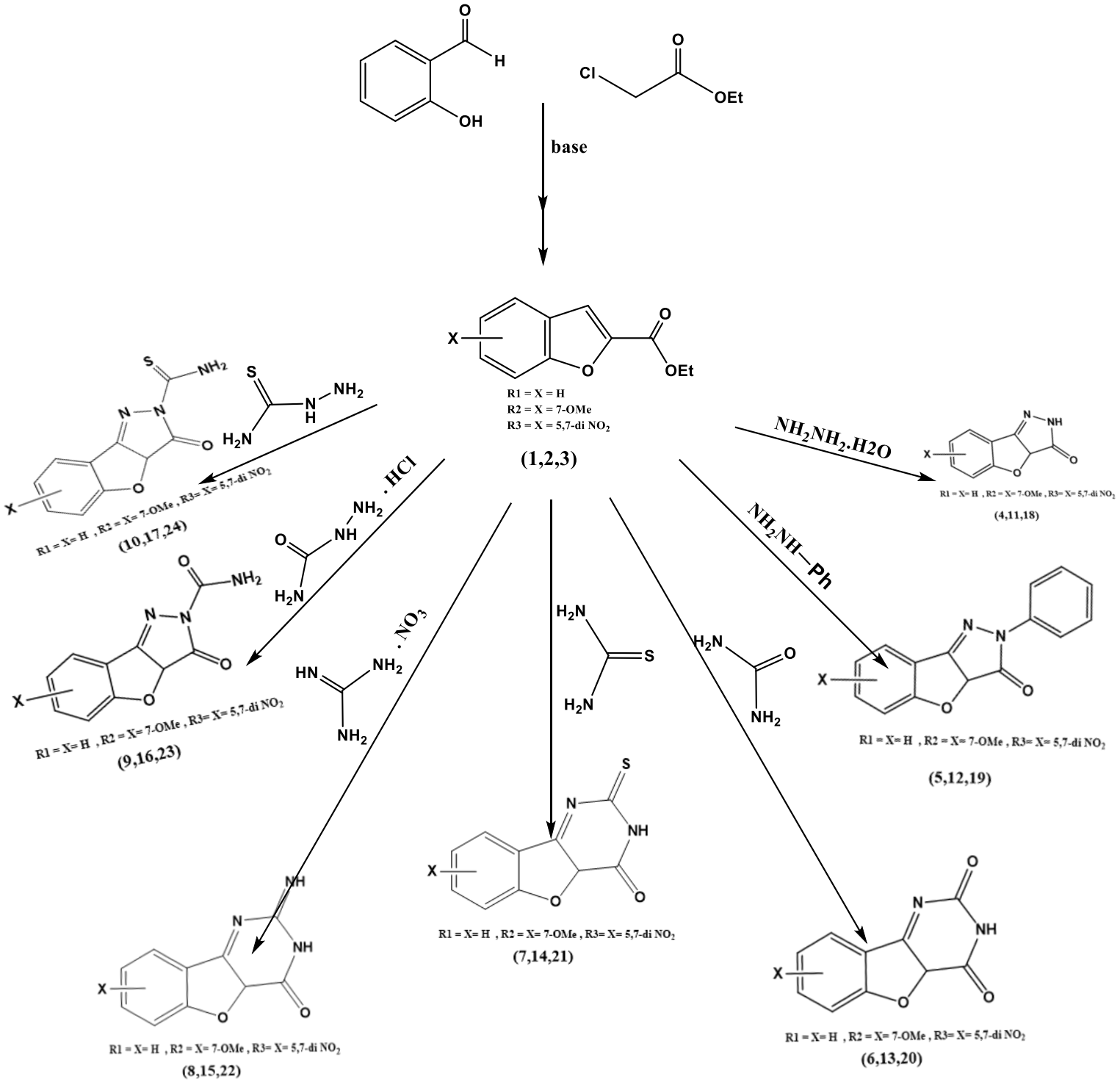


Figure 1: Synthesis Compound

Experimental work

Melting points were measured on Electrothermal Gallen Kamp melting points and were uncorrected. Infrared (FT.IR.) spectra was recorded as (KBr) disk using a Brucker FT.IR. spectrophotometer. 1HNMR spectra was recorded using Inova 500 MHz by using DMSO - d6 as solvent, and using TMS as internal standard in University of Basrah, Iraq

Preparation of Ethyl coumarilate (1, 2, 3) [11]

Preparation of Ethyl coumarilate ester (1, 2, 3) a mixture of salicylaldehyde (0.05 mmol) and ethyl chloroacetate (0.05 mmol) in the presence of acetone (45ml) and catalyst anhydrous K2CO3 (0.075 mol), at 100 °C for 8-10 h respectively. After reflux the round bottom flask was cooled to room temperature and the acetone evaporated by rotary evaporator, then add H2O (50 ml) and chloroform (50 ml) was added to round bottom flask and the layers were separated. The aqueous layer was extracted with K2CO3 . The organic layer was dried with MgSO4 and the solvent was removed by rotary evaporator give the desired ester (63 %) as a clear green-black oil.

R1 = X= H , R2 = X= 7-OMe , R3= X= 5,7-di NO_2

R1 = X= H , R2 = X= 7-OMe , R3= X= 5,7-di NO_2

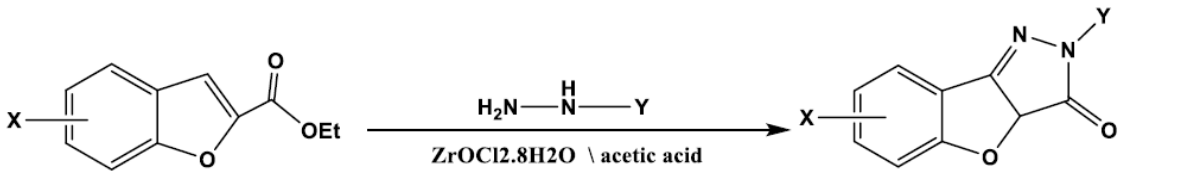
(1, 2, 3)

Table (1): physical properties of starting compound

NO.	X	B.P °C	Yield %	Color	Molecular weight	Molecular formula
1	H	274°C	75	Green	190.20	$C_{11}H_{10}O_3$
2	7-OMe	316°C	73	yellow	220.22	$C_{12}H_{12}O_4$
3	5,7-$(NO_2)_2$	298 °C	77	Orange	280.19	$C_{11}H_8N_2O_7$

Preparation of 2,3a-dihydro-3H-benzofuro[3,2-c]pyrazol-3-one and 3-oxo-3,3a-dihydro-2H-benzofuro[3,2-c]pyrazole-2-carbothioamide (4,10,11,17,18,24) [12-13]

A mixture of ester [1,2,3] (1 mmole) and hydrazine hydrate (99%) (5 mmole) in glacial acetic acid (15 ml) The reaction mixture was heated for (3 hrs) at (70C°) in Ultrasonic technique with small amount of zirconyl chloride octahydrate ZrOCl2.8H2O as a catalyst. Then, (50 ml) of water was added to the crude mixture and the solid was collected by vacuum filtration, washed with warm water. The product was recrystallized from EtOH and dried under room temperature to give compounds (4,10,11,17,18,24).



R1 = X= H , R2 = X= 7-OMe , R3= X= 5,7-di NO_2

Y= H , $CSNH_2$

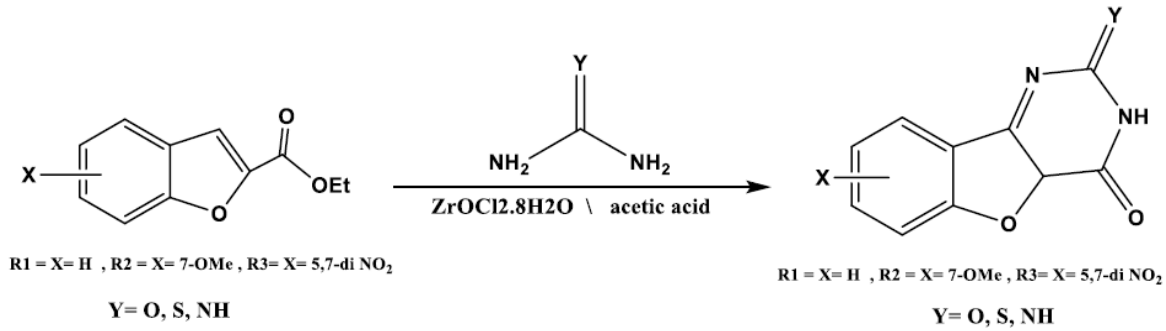
R1 = X= H , R2 = X= 7-OMe , R3= X= 5,7-di NO_2

Y= H , $CSNH_2$

Preparation of benzofuro[3,2-d]pyrimidine-2,4(3H,4aH)-dione and 2-thioxo-2,4a-dihydrobenzofuro[3,2-d]pyrimidin-4(3H)-one and 2-imino-2,4a-dihydrobenzofuro[3,2-d]pyrimidin-4(3H)-one (6,7,8,13,14,15,20,21,22) [14-15-16]

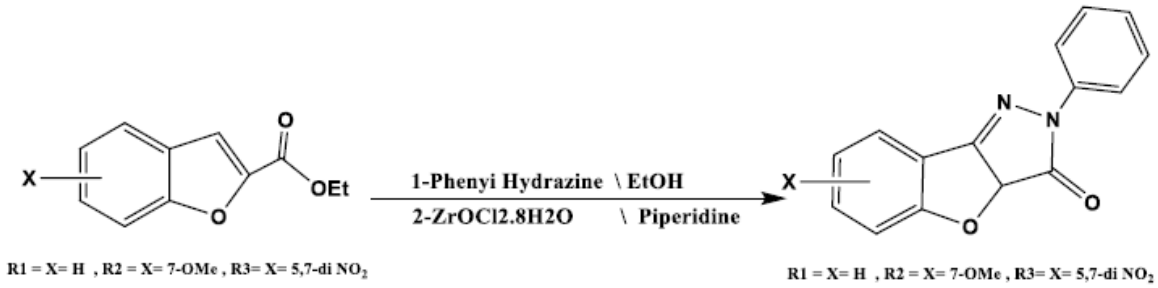
A mixture of ester [1,2,3] (1 mmole) and Urea, Thiourea, and Guanidine (5 mmole) in glacial acetic acid (15 ml) The reaction mixture was heated for (3 hrs) at (70C°) in Ultrasonic technique with small amount of zirconyl chloride octahydrate ZrOCl2.8H2O as a catalyst. Then, (50 ml) of water was added to the crude mixture and the

solid was collected by vacuum filtration, washed with warm water. The product was recrystallized from EtOH and dried under room temperature to give compounds (6,7,8,13,14,15,20,21,22).



Preparation of 2-phenyl-2,3a-dihydro-3H-benzofuro[3,2-c]pyrazol-3-one (5,12,19) [17]

A mixture of ester [1,2,3] (1 mmole) was dissolved with phenyl hydrazine hydrochloride (5 mmole) in dimethyl sulfoxide (DMSO) (10 ml). To this mixture Piperidine (5ml) were added dropwise. The reaction mixture was heated for (3 hrs) at (70C°) in Ultrasonic technique with small amount of zirconyl chloride octahydrate ZrOCl2.8H2O as a catalyst. Then, (50 ml) of water was added to the crude mixture and the solid was collected by vacuum filtration, washed with warm water. The product was recrystallized from EtOH and dried under room temperature to give compounds (5,12,19).



***Preparation of 3-oxo-3,3a-dihydro-2H-benzofuro[3,2-c]pyrazole-2-carboxamide* (19,16,23) [18]**

A mixture of ester [1,2,3] (1 mmole) was dissolved with semicarbazide hydrochloride (5 mmole) in ethanol (25 ml). was treated with a few drops of cone HCl. The reaction mixture was heated for (3 hrs) at (70C°) in Ultrasonic technique with small amount of zirconyl chloride octahydrate ZrOCl2.8H2O as a catalyst. Then, (50 ml) of water was added to the crude mixture and the solid was collected by vacuum filtration, washed with warm water. The product was recrystallized from EtOH and dried under room temperature to give compounds (19,16,23).

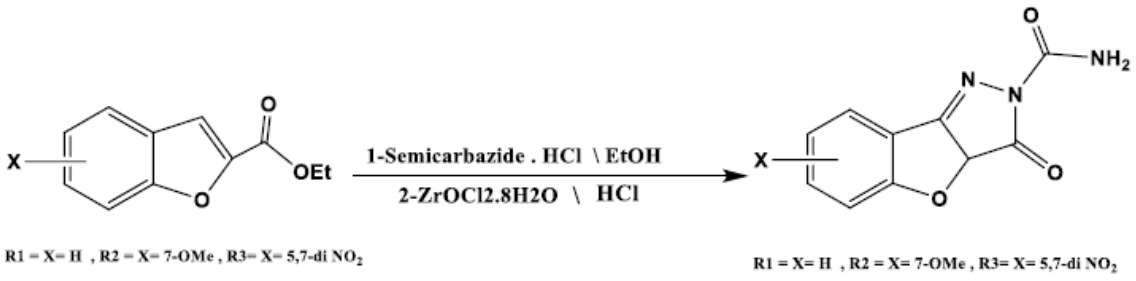


Table 2: the physical properties & IR of synthesized compounds

Compound No.	M.P.(°C)	Yield %	IR(KBr)Vcm-1			
			C=O	C=N	C-O-C	Other
4	210-212	70	1618	1600	1195 Ass	NH , 3380
5	104-106	84	1658	1600	1254 Ass	
6	114-116	71	1640	1599	1207 Ass	NH , 3326
7	95-97	65	1600	1539	1112 Sy	NH , 3305 C=S , 1201
8	88-90	63	1686	1665	1196 Ass	NH , 3357 NH , 3249
9	200-203	82	1685	1622	1199 Ass	NH2 , 3345
10	89-90	80	1615	1590	1215 Ass	NH2 , 3428 C=S , 1232
11	225-227	68	1666	1622	1214 Ass	NH , 3382
12	110-112	69	1603	1589	1167 Sy	
13	118-120	65	1648	1588	1178 Sy	NH , 3349
14	120-122	72	1677	1607	1196 Ass	NH , 3323 C=S , 1239
15	70-72	60	1690	1667	1195Ass	NH , 3516 NH , 3367
16	192-194	71	1695	1661	1183 Ass	NH2 , 3461
17	150-152	73	1643	1620	1181 Ass	NH2 , 3455 C=S , 1256
18	200-202	61	1654	1602	1205 Ass	NH , 3215 NO2 , 1340 , Sy
19	254-256	88	1599	1599	1213 Ass	NO2 , 1339 , Sy
20	96-100	63	1669	1601	1196 Ass	NH , 3338 NO2 , 1489 , Ass
21	133-135	70	1625	1600	1117 Sy	NH , 3184 C=S , 1198 NO2 , 1488 , Ass
22	112-116	60	1684	1951	1204 Ass	NH , 3366 , 3251 NO2 , 1537 , Ass
23	204-206	66	1643	1603	1110 Sy	NH2 , 3470 NO2 , 1346 , Sy
24	168-170	70	1682	1599	1197 Ass	NH2 ,3431, C=S 1256, NO2,1486 As

The reaction of ester (1, 2, 3) with five equivalent moles of Hydrazine hydrate or thiosemecarbazide and present of ZrOCl2.8H2O gave pyrazolines compound (4, 10,11, 17, 18, 24) respectively, the scheme 2 showed these reactions.

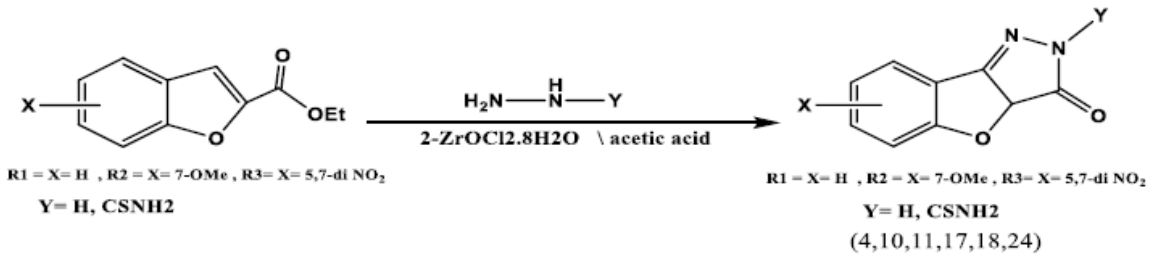


Table 3: the ^{1}H-NMR & ^{13}C-NMR Spectrum of synthesized Compounds

NO.	^{1}HNMR, DMSO-d6, δ (ppm)	^{13}C-NMR, DMSO-d6, δ (ppm)
4	4.966 (1H, S, H1), 11.438 (1H, S, H2), 6.806-8.987 (4H, m, Aromatic protons)	117.00-118.66-120.07-133.54-133.71 (C- aromatic rings); 159.11(C=N); 163.48(C=O amide); 169.01(HC=C--O); 84.88(CH);
10	4.871 (1H, S, H1), 9.888 (2H, S, H2), 6.796-8.465 (4H, m, Aromatic protons)	113.17-116.50-119.74-130.09-130.23 (C- aromatic rings); 156.64(C=N); 169.01(C=O amide); 169.12(HC=C--O); 79.92(CH); 179.13(C=S);
11	4.752 (1H, S, H1), 10.905 (1H, S, H2), 3.838 (3H, S, H3), 6.765-7.923 (3H, m, Aromatic protons)	118.85-119.02-122.57-124.98 (C- aromatic rings); 159.01(C=N); 163.50(C=O amide); 85.32(CH); 56.16(O-CH3); 148.03(HC=C--O); 148.47(HC=C—O-CH3);
17	4.694 (1H, S, H1), 9.208(2H, S, H2), 4.160 (3H, S, H3), 6.749-8.631 (3H, m, Benzylic ring)	114.58-114.97-119.69-121.19 (C- aromatic rings); 158.23(C=N); 170.14(C=O amide); 79.87(CH); 169.12(HC=C--O); 152.14 (HC=C—O-CH3); 56.33(O-CH3); 178.42(C=S);
18	4.961 (1H, S, H1), 11.983(1H, S, H2), 6.906-7.395 (2H, m, Aromatic protons)	121.09-124.78-126.38-130.32-131.00 (C- aromatic rings); 157.71(C=N); 168.44(C=O amide); 72.37(CH); 163.70(HC=C--O);
24	4.924 (1H, S, H1), 9.932 (2H, S, H2), 8.110-8.458 (2H, m, Aromatic protons)	118.53-121.32-126.52-132.38-138.93(C- aromatic rings); 158.85(C=N); 169.04(C=O amide); 78.59(CH); 162.52(HC=C--O); 182.54C=S);

The reaction of ester (1, 2, 3) with five equivalent moles of Urea, Thiourea, and Guanidine the present of ZrOCl2.8H2O gave pyrimidine compound (6,7,8,13,14,15,20,21,22) respectively, the scheme 3 showed this reaction.

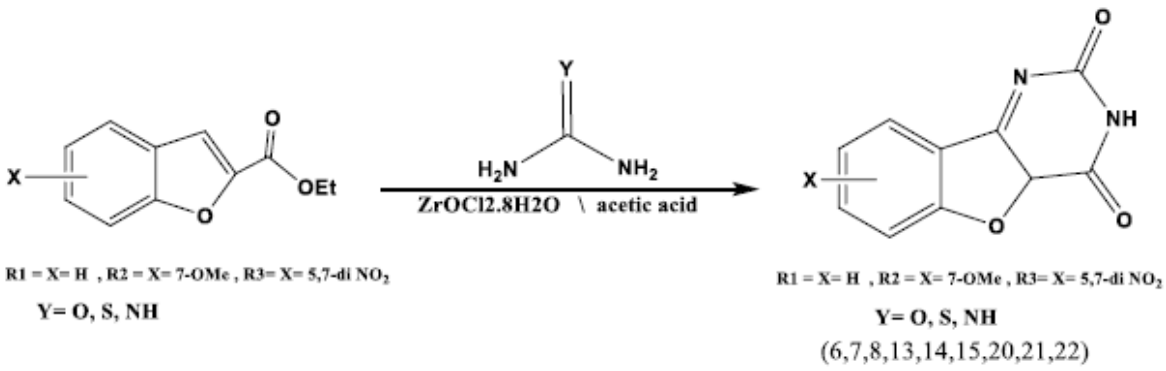
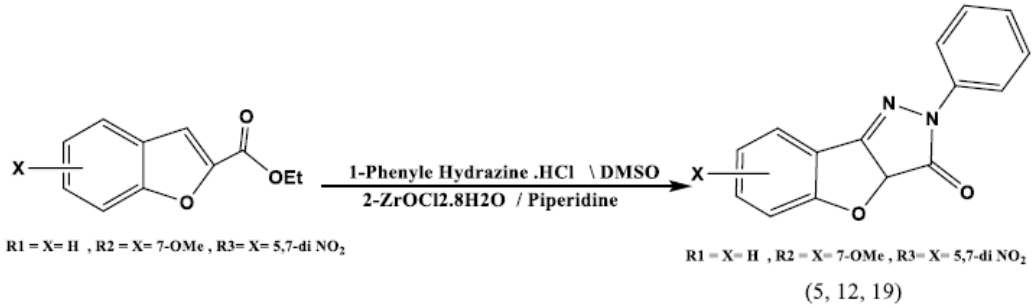


Table 4: the 1H-NMR & 13C-NMR Spectrum of synthesized Compounds

NO.	^{1}HNMR, DMSO-d6, δ (ppm)	^{13}C-NMR, DMSO-d6, δ (ppm)
6	4.870 (1H, S, H1), 10.321 (1H, S, H2), 6.809-7.269 (4H, m, Aromatic protons)	115.32-117.71-121.88-129.38-129.73 (C- aromatic rings); 159.11(C=N); 163.48(C=O amide); 169.01(HC=C--O); 84.88(CH); 160.31(C=O pyrimidin ring);
7	4.201 (1H, S, H1), 15.296 (1H, S, H2), 6.809-7.334 (4H, m, Aromatic protons)	114.52-122.00-129.39-132.33-132.56 (C- aromatic rings); 158.88(C=N); 169.33(C=O amide); 171.52(HC=C--O); 78.96(CH); 187.88(C=S);
8	4.211 (1H, S, H1), 10.448 (1H, S, H2), 9.212 (1H, S, H3), 6.980-8.433 (4H, m, Aromatic protons)	113.32-114.47-118.93-136.40-136.71 (C- aromatic rings); 160.55(C=N); 166.13(C=O amide); 168.93(HC=C--O); 78.84(CH); 154.54(C=NH);
13	4.590 (1H, S, H1), 10.312 (1H, S, H2), 3.854 (3H, S, H3), 6.788-7.097 (3H, m, Aromatic protons)	112.51-119.60-124.71-124.87(C- aromatic rings); 169.47(C=N); 172.53(C=O amide); 83.56(CH); 56.23(O-CH3); 146.34(HC=C--O); 151.86(HC=C—O-CH3);

		156.75(C=O pyrimidin ring);
14	4.764 (1H, S, H1), 14.752 (1H, S, H2), 3.864 (3H, S, H3), 6.910-7.235 (3H, m, Aromatic protons)	119.64-119.83-121.85-124.62 (C- aromatic rings); 169.36(C=N); 172.50(C=O amide); 69.75(CH); 56.46(O-CH3); 148.41(HC=C--O); 152.09(HC=C—O-CH3); 184.31(C=S);
15	4.887 (1H, S, H1), 10.520 (1H, S, H2), 9.012(1H, S, H3), 3.967 (3H, S, H3), 7.195-7.404 (3H, m, Aromatic protons)	118.43-119.31-124.93-129.68 (C- aromatic rings); 165.34(C=N); 169.66(C=O amide); 69.42(CH); 56.63(O-CH3); 150.03(HC=C--O); 152.29(HC=C—O-CH3); 153.32(C=NH);
20	4.857 (1H, S, H1), 9.389 (1H, S, H2), 6.533-7.245 (2H, m, Benzylic ring)	121.83-126.26-127.31-128.57-130.95(C- aromatic rings); 156.10(C=N); 169.12(C=O amide); 83.01(CH); 155.17(HC=C--O); 154.79(C=O pyrimidin ring);
21	4.952 (1H, S, H1), 14.981 (1H, S, H2), 6.894-7.259 (2H, m, Aromatic protons)	118.93-122.31-129.31-136.56-142.12 (C- aromatic rings); 168.13(C=N); 174.56(C=O amide); 77.84(CH); 162.94(HC=C--O); 186.31(C=S);
22	4.881 (1H, S, H1), 10.448 (1H, S, H2), 9.122 (1H, S, H3), 6.913-7.401 (2H, m, Aromatic protons)	118.46-119.34-124.94-129.70-135.96 (C- aromatic rings); 162.63(C=N); 169.65(C=O amide); 74.46(CH); 152.30(HC=C--O); 150.05(C=NH);

The reaction of ester (1, 2, 3) with five equivalent moles of Phenyl hydrazine hydrochloride and present of ZrOCl2.8H2O gave pyrazolines compound (5, 12, 19) respectively, the scheme 4 showed these reactions.

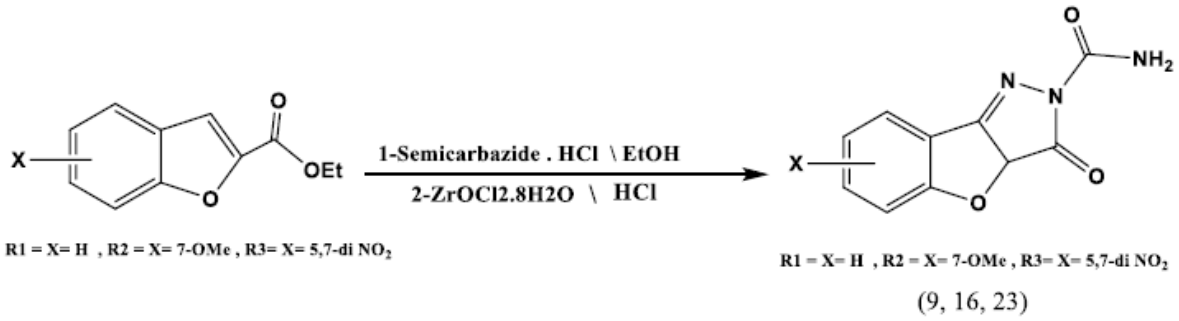


(5, 12, 19)

Table 5: the 1H-NMR & 13C-NMR Spectrum of synthesized Compounds

NO.	^{1}HNMR, DMSO-d6, δ (ppm)	^{13}C-NMR, DMSO-d6, δ (ppm)
5	4.563 (1H, S, H1), 6.773-8.171 (9H, m, Aromatic protons)	112.16-116.30 -119.37 -119.82 -121.00-127.65-131.61-132.09-137.55 (C- aromatic rings); 163.35(C=N); 171.01(C=O amide); 177.32(HC=C--O); 76.56(CH);
12	4.523 (1H, S, H1), 3.835(3H, S, H2), 6.953-7.34 (8H, m, Aromatic protons)	114.73-114.93-120.94-121.96-125.34-129.43-131.35-140.01(C- aromatic rings); 156.87(C=N); 171.31(C=O amide); 80.01(CH); 59.85(O-CH3); 146.00(HC=C--O); 152.35(HC=C—O-CH3);
19	4.771 (1H, S, H1), 8.254 (1H, S, H2), 10.241 (1H, S, H3), 6.636-7.306 (5H, m, Aromatic protons)	114.90-121.91-124.01-124.48-128.88-129.01-129.42-130.25-139.64-141.83-146.03(C- aromatic rings); 155.21(C=N); 169.87(C=O amide); 75.56(CH); 165.35(HC=C--O);

The reaction of ester (1, 2, 3) with five equivalent moles of semicarbazide hydrochloride and present of ZrOCl2.8H2O gave pyrazolines compound (9,16,23) respectively, the scheme 5 showed these reactions.



(9, 16, 23)

Table 6: the 1H-NMR & 13C-NMR Spectrum of synthesized Compounds

NO.	^{1}HNMR, DMSO-d6, δ (ppm)	^{13}C-NMR, DMSO-d6, δ (ppm)
9	4.203 (1H, S, H1), 4.876 (2H, S, H2), 6.463-8.262 (4H, m, Aromatic protons)	113.01-116.44-119.67-130.55-130.64 (C- aromatic rings); 156.33(C=N); 155.97(C=O amide); 170.58(HC=C--O); 79.80(CH); 169.05(C=O imidazoline ring);
16	4.686 (1H, S, H1), 6.577 (2H, S, H2), 4.163 (3H, S, H3), 7.056-8.271 (3H, m, Aromatic protons)	117.83-124.14-124.52-157.23 (C- aromatic rings); 157.23(C=N); 152.12(C=O amide); 169.42(C=O imidazoline ring); 170.58(HC=C--O); 151.99(HC=C—O-CH3); 80.71(CH); 56.28(O-CH3);
23	4.870 (1H, S, H1), 6.989 (2H, S, H2), 8.009-8.231 (2H, m, Aromatic protons)	112.81-120.04-123.65-130.59-135.35 (C- aromatic rings); 157.26(C=N); 156.09(C=O amide); 170.55(C=O imidazoline ring); 165.89(HC=C--O); 78.86(CH);

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