SYNTHESIS REACTIONS AND ANTIOXIDANT ACTIVITY OF SOME NEW HETEROCYCLES DERIVED FROM 2-ACETYLNAPHTHALENE

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ABSTRACT :

2-Methyl-4-(1-(naphthalen-2-yl)ethylidene)oxazol-5(4*H*)-one **2** was used as precursor for the preparation of some novel (1-(4-substituted)-2-methyl-4-(1-naphthalen-2-yl)ethylidene)-1*H*-imidazol-5(4*H*)-one derivatives **4a, b** and other derivatives **3a,b, 5-12.** Furthermore, the preparation of thieno[2,3-d]pyrimidin-4(3*H*)-one derivative **16**,**17** and 4-iminothieno[2,3-d] pyrimidin-3-ylamine derivative **18, 19** is described starting from 2-aminothiophen-3-carbonitrile derivative **15a.** Some of the prepared products revealed a promising antioxidant activity by using 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) method.

Keywords: Imidazoles, thienopyrimidines, Antioxidant activity.

INTRODUCTION :

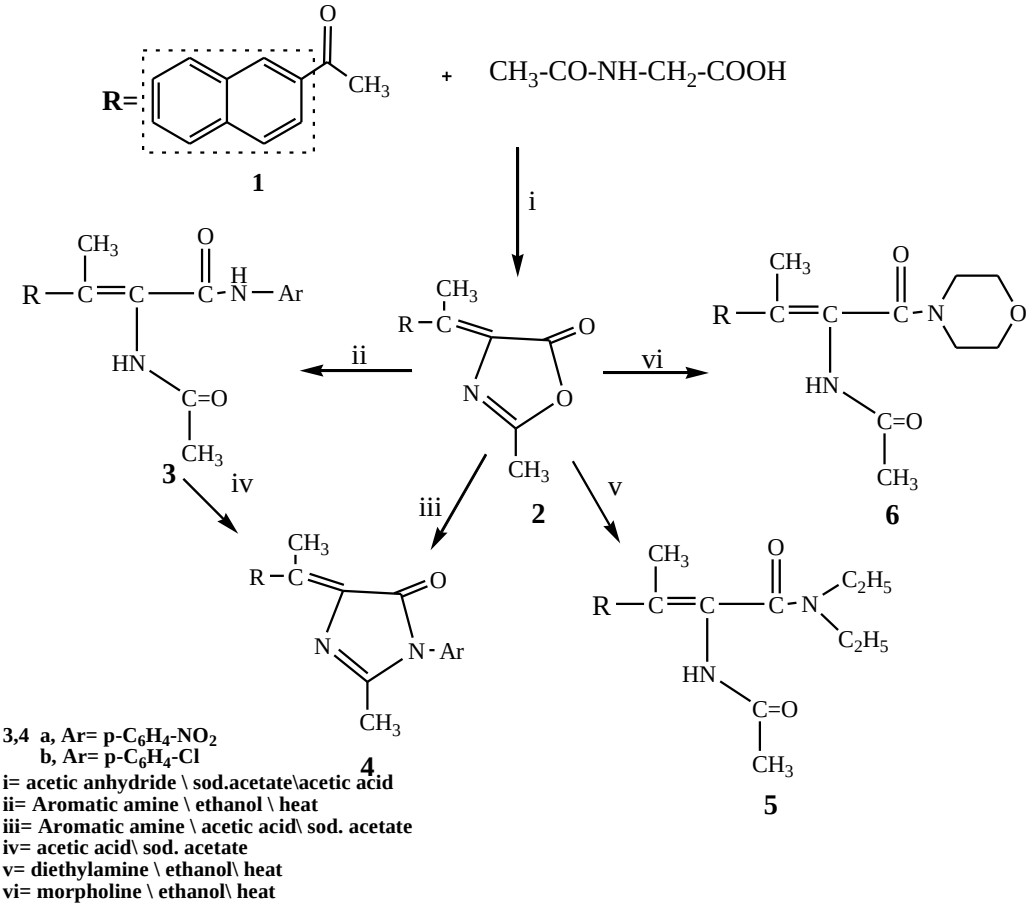
For a long time heterocyclic compounds have constituted one of the largest areas of research in organic chemistry. Heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities attributed to heterocyclic systems known today. Among different nitrogen heterocycles, the imidazole ring which acts as a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Imidazoles and their derivatives have demonstrated a diverse set of biological activities such as antibacterial **(Maddila, *et al.*, 2010; Kumari, *et al.*, 2010; Rajasekaran, *et al.*, 2010; Nanda, *et al.*, 2010; Ingle, *et al.*, 2011; Shailesh, *et al.*, 2012),** anticancer **(Li, *et al.*, 2003, Mahboobi, *et al.*, 2006; Chuu, *et al.*, 2007; Hait, *et al.* 2009; Kanthou, *et al.*, 2009; De Rychker, *et al.*, 2009; Sanchila, *et al.*, 2010; Wen-Tai, *et al.*, 2010; Soroor, *et al.*, 2012),** anti-inflammatory **(Achar, *et al.*, 2010; Shailesh, *et al.*, 2012),** antitumor **(Liberatore, *et al.*, 2008),** antioxidant **(Maddila, *et al.*, 2010; Rajasekaran, *et al.*, 2010)** activities**.** Also, prominent biological activities have been reported for fused thienopyrimidine derivatives **(Hegab, *et al.*, 2007; Shamrokh, *et al.*, 2010; Marzouk, *et al.*, 2011).** In connection with our research program for the synthesis of different heterocyclic compounds, we describe here the synthesis of some new imidazole derivatives hopping to show promising antioxidant activity.

RESULTS AND DISCUSSION

The interaction of 2-acetylnaphthalene **1** with acetyl glycine in acetic anhydride and in the presence of fused sodium acetate effected cyclization and afforded the corresponding 2-methyl-4-(1-(naphthalen-2-yl)ethylidene)oxazol-5(4*H*)-one **2** (scheme 1). The structure of the oxazolinone derivative **2** was confirmed by elemental analysis and spectral data. The IR spectrum showed absorption band at 1668.9 cm^{-1} (C=O); moreover, ^{1}H-NMR spectrum exhibited signals at δ2.05, 2.70 ppm for two methyl groups and 7.60-8.15 for six aromatic protons, 8.47 (s, 1H, C_{-1}naphthyl) and its mass spectrum afforded a molecular ion peak M^{+} at m/z 251 (3.82%). The behaviour of oxazolinone derivative **2** towards some nucleophilic

reagents was discussed under different conditions, as well as its transformation into the corresponding imidazolinone derivatives. Thus, interaction of **2** with p-nitroaniline or p-chloroaniline in ethanol with boiling led to ring opening and gave the corresponding 2-acetamido-N-substituted-3-(naphthalen-2-yl)but-2-enamides **3a,b** which underwent heterocyclization by heating with acetic acid in the presence fused sodium acetate and produced imidazolinone derivatives **4a,b** in 70% yield (scheme 1). On the other hand, compound **4a,b** could be obtained in one step and better yield by direct reaction of **2** with p-nitroaniline or p-chloroaniline under reflux in acetic acid and fused sodium acetate (89% yield) (scheme 1).

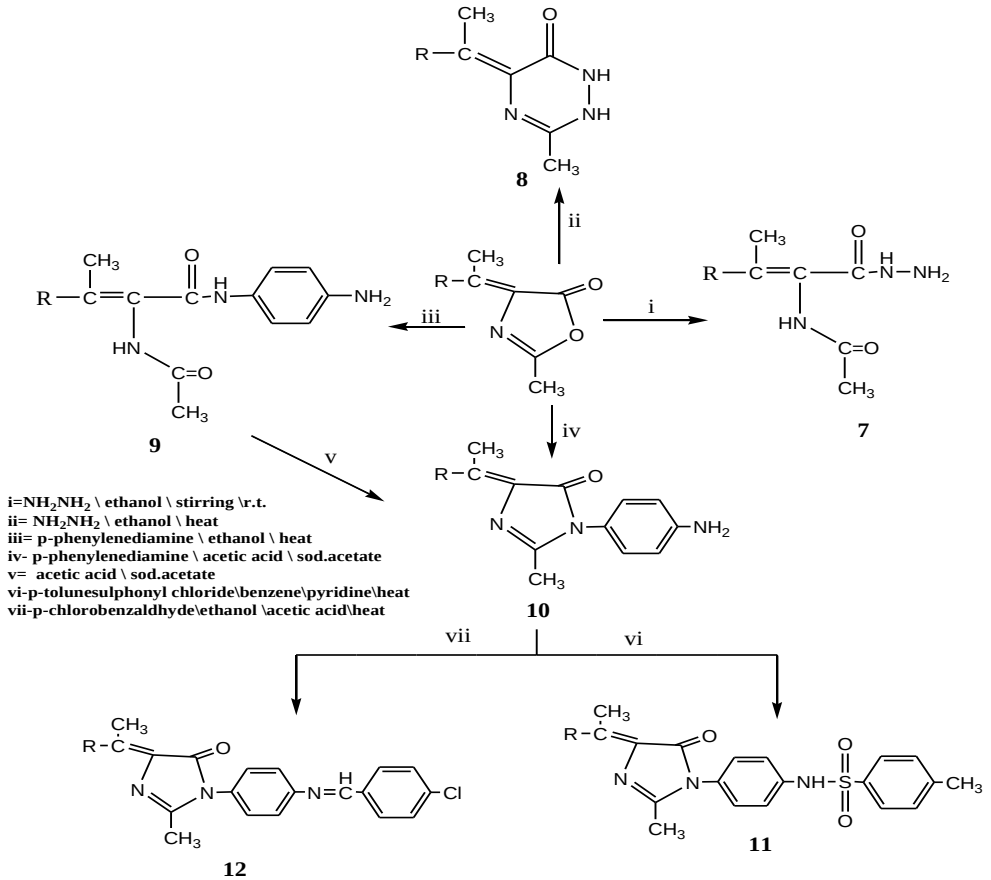
The structures of compounds **3** and **4** were deduced from elemental analysis and spectral data. IR spectra of **3** which showed absorption bands characteristic for 2NH groups while IR spectrum of **4** showed the absence of this absorption bands (c.f. exp.) Similarly, the reaction of oxazolinone **2** with secondary amines in ethanol or acetic acid led to ring opening to produce the corresponding acetamido compounds without transmitting into imidazolinone as in the case of primary amines. When compound **2** was treated with N,N-diethylamine or morpholine in ethanol under reflux, the corresponding 2-acetamido-N,N-diethyl-3-(naphthalen-2-yl)but-2-enamide **5** and N-1-morphoilino-3-naphthalen-2-yl)-1-oxobut-2-en-2-yl)acetamide **6**, were produced, respectively (scheme 1). The IR spectra of **5** and **6** showed characteristic absorption bands for (2C=O) and (NH) groups. Also ^{1}HNMR spectra (δ, ppm) revealed signals at 1.01 (t, J=7.5Hz, 6H, $2CH_3$), 3.51 (q, J=7.5H, 4H, $2CH_2$) for compound **5** and for compound **6** revealed signals at 3.24-3.70 (m, 8H, $4CH_2$, morphilino) (c.f. exp.)



scheme 1

Also, the behaviour of oxazolinone ring towards binucleophile reagent such hydrazine hydrate and phenylenediamine was studied hoping to prepare different heterocyclic of five and six membered ring hoping to have good pharmacological activity. Thus, interaction of oxazolinone **2** with hydrazine hydrate in ethanol under stirring at room temperature caused ring opening to give the corresponding hydrazide derivative **7**, while the product that isolated from the reaction of **2** with hydrazine hydrate in ethanol with boiling for 2h was formulated as the triazine derivative **8** (scheme 2). The structures of compounds **7** and **8** were deduced from elemental analysis and spectral data. The ^{1}H-NMR spectrum of compound **7** (δ, ppm) reaveled signals at 3.72 (br, 2H, NH_2), 9.25, 9.51 (2s, 2H, 2NH) exchangeable with D_2O, while mass spectrum of compound **8** exhibited a molecular ion peak at m/z = 265 (18.67%) (c.f. exp.).

Moreover, interaction of oxazolinone **2** with p-phenylenediamine in ethanol consumed one mole of oxazolinone and produce 2-acetamido-N-(4-aminophenyl)-3-(naphthalen-2-yl)but-2-enamide **9** which under-went heteocyclization by heating with acetic acid in the presence fused sodium acetate and produced imidazolinone derivative **10** (scheme 2). The proposed structures of compounds **9** and **10** was confirmed by elemental analysis and spectral data (c.f. exp.). Treatment of the later compound with p-toluene sulphonyl chloride or p-chlorobenzaldehyde afforded the corresponding sulfonamide derivative **11** and the Schiff base **12**, respectively. Inspection of the IR spectrum of the reaction product **11** revealed absorption bands characteristic for (NH), (C=O) groups at 3432,, 1671 and (SO_2) group at 1187, 1361cm^{-1} ; ^{1}H-NMR spectrum showed signals (δ, ppm) at 1.22, 1.52, 2.57(3s, 9H, 3CH_3), and 7.25 (s, 1H, NH, exchangeable with D_2O), while for compound **12** the ^{1}H-NMR spectrum revealed a signal at 9.83ppm characteristic for (–CH=N–) (c.f. exp.).

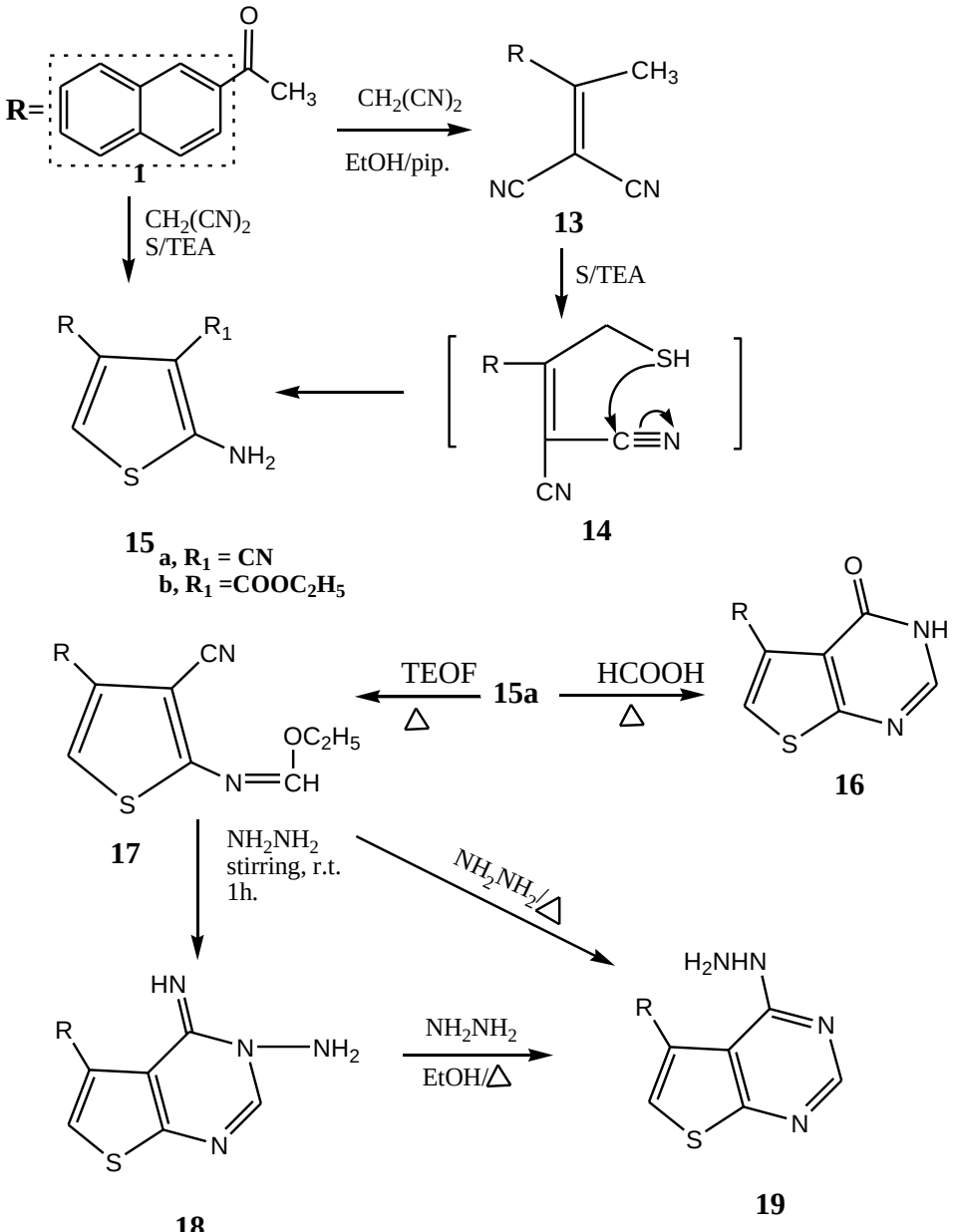


Scheme 2

It was reported **(Hessien, *et al.*, 2009; Hafez, *et al.*, 2010)** that various activated nitriles and enaminonitriles were used as intermediates for the syntheses of thieno derivatives and thienopyrimidine derivatives. Thus, condensation of 2-acetyl naphthalene **1** with malononitrile in ethanolic–piperidine solution under reflux gave the corresponding ethylidinemalononitrile derivative **13**. IR spectrum showed sharp absorption bands at 2210 and 1589 characteristic for (2C≡N) group and (C=C), respectively and the MS spectrum showed a molecular ion peak at m/z = 218 (M^+, 100%). Treatment of **13** with elemental sulfur under Gewald reaction conditions (**Gewald**, **1965)** furnished 2-aminothiophene-3-carbonitrile derivatives **15a**. The formation of compound **15a** occurred via thiation of methyl group in compound **13** to give **14** as an intermediate followed by intramolecualr cyclization (scheme 3). Compound **15a** was also obtained directly by interaction of ketone **1** with a mixture of malononitrile and elemental sulfur in the presence of few drops of triethylamine. The obtained product **15a** through out the two pathways was checked by TLC and mixed m.p which showed no depression.

Similarly, when compound **1** was treated ethyl cyanoacetate and elemental sulfur under Gewald reaction conditions **(Gewald, 1965)** gave the corresponding ethyl-2-aminothiophen-3-carboxylate derivative **15b** (scheme 3). The IR spectra showed absorption bands (υ, cm^{-1}) at 2206 (C≡N) and 3202 & 3322 (NH_2) groups for **15a** while for **15b** showed (C=O) at 1721 and NH_2 at 3200, 3321 (c.f. exp.)

The 4-pyrmidinone derivative was prepared by reacting compound **15a** with formic acid under reflux to give derivative **16** (scheme 3). Product **16** was formed presumably via intermediacy of the corresponding oxazinimine derivative **(Abdelrazek, *et al.*, 1996; Hegab, *et al.*, 2007)** which then rearranged under the conditions of the reaction. On the other hand, when compound **15a** was refluxed with triethyl orthoformate, it afforded derivative **17.** When the ethanolic solution of the later compound was stirred at room temperature with hydrazine hydrate, it afforded 4-iminopyrimidin-3-ylamine derivative **18**. the structures of compounds **16-18** were deduced from elemental analysis and spectral data. IR spectra showed the absence of cyano group for **16** and **18,** while ^{1}H-NMR spectrum revealed signals characteristic for ethyl group for **17** (c.f. exp.). However, the pyrmidin-4-ylhydrazine derivative **19** was obtained by treatment of compound **17** with hydrazine hydrate under reflux (scheme 3). Also, compound **18** was isomerized to corresponding more stable 4-hydrazino derivative **19** upon reflux in ethanol in the presence of hydrazine hydrate. Actually, hydrazine hydrate acts as a base in this Dimroth type of rearrangement, which involves a sequence of ring opening and ring closure reaction **(Mohamed, *et al.*, 2005; Rashad, *et al.*, 2005; Hegab *et al.*, 2007).**



Scheme 3

Antioxidant activity.

RESULTS:

The provided compounds showed different antioxidant activity using 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) radical scavenging method compared to ascorbic acid standard as shown by the following table :

Table I . Antioxidant activity of some synthesized compounds

Compound No.	DDPH radical scavenging Activity
3a	+
3b	+
5	+++
6	+
7	+
8	++
9	+
10	+
11	+
12	+++

\+ : Weak
++ : Moderate
+++ : Good
++++ : Strong
\- : No activity

Comment : Qualitative analysis are recommended for the promising result.

Table II: Physical data of the new synthesized compounds

Compd. No.	M.P.[°C]	Yield[%] solvent	Mol. Formula/Mol.wt.	(Calcd./Found)%			
				C	H	N	Cl,S,
2	78-79	80 Pet.E 40-60	$C_{16}H_{13}NO_2$ 251.28	76.48 76.51	5.21 5.19	5.57 5.54	--
3a	105-107	85 B	$C_{22}H_{19}N_3O_4$ 389.4	67.86 67.83	4.92 4.91	10.79 10.77	
3b	200-202	80 D	$C_{22}H_{19}ClN_2O_2$ 378.85	69.75 69.73	5.05 5.07	7.39 7.41	9.36 9.31 (Cl)
4a	115-116	87 E	$C_{22}H_{17}N_3O_3$ 371.39	71.15 71.17	4.61 4.65	11.31 11.37	
4b	210-211	70 B	$C_{22}H_{17}ClN_2O$ 360.84	73.23 73.25	4.75 4.72	7.76 7.79	9.83 (Cl)
5	110-112	95 B	$C_{20}H_{24}N_2O_2$ 324.42	74.04 74.06	7.46 7.43	8.64 8.60	--
6	50-51	90 Pet.E	$C_{20}H_{22}N_2O_3$ 338.4	70.99 70.97	6.55 6.57	8.28 8.27	--
7	180-182	70 M	$C_{16}H_{17}N_3O_2$ 283.33	67.83 67.86	6.05 6.02	14.83 14.85	--
8	155-156	85 M	$C_{16}H_{15}N_3O$ 265.31	72.43 72.41	5.70 5.69	15.84 15.81	--
9	120-121	75 B	$C_{22}H_{21}N_3O_2$ 359.42	73.52 73.49	5.89 5.91	11.69 11.71	--
10	210-212	75 M	$C_{22}H_{19}N_3O$ 341.41	77.40 77.47	5.61 5.59	12.31 12.29	--
11	50-51	85 Pet.E 40-60	$C_{29}H_{25}N_3O_3S$ 495.59	70.28 70.25	5.08 5.11	8.48 8.46	6.47 6.51 (S)
12	70-71	80 B	$C_{29}H_{22}N_3ClO$ 463.96	75.07 75.11	4.78 4.77	9.06 9.03	7.64 7.62 (Cl)
13	78-79	80 B	$C_{15}H_{10}N_2$ 218.25	82.55 82.53	4.62 4.66	12.84 12.85	--
15a	120-121	85 B	$C_{15}H_{10}N_2S$ 250.32	71.97 71.91	4.03 4.05	11.19 11.21	12.81 12.85 (S)
15b	45-46	55 Pet-E 40-60	$C_{17}H_{15}NO_2S$ 297.37	68.66 68.63	5.08 5.09	4.71 4.69	10.78 10.81 (S)
16	220-222	70 E	$C_{16}H_{10}N_2OS$ 278.33	69.04 69.05	3.62 3.60	10.06 10.08	11.52 11.58 (S)
17	165-166	70 B	$C_{18}H_{14}N_2OS$ 306.38	70.56 70.60	4.61 4.69	9.14 9.10	10.47 10.42 (S)
18	238	75 D	$C_{16}H_{12}N_4S$ 292.36	65.73 65.74	4.14 4.15	19.16 19.19	10.97 10.99
19	>260	70 D	$C_{16}H_{12}N_4S$ 292.36	65.73 65.75	4.14 4.17	19.16 19.14	10.97 10.93

Solvent of crystallization : Pet.E: petroleum ether; B : Benzene; D: dioxan ; M : Methanol ; E : Ethanol

Experimental

Melting points were recorded on an electrothermal IA 9100 digital melting point apparatus and were uncorrected. IR spectra (V_{max} in cm^{-1}) were recorded on a Shimadzu FT-IR 8300 spectrophotometer using KBr pellets technique. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using Bruker WM-400 spectrophotometer using DMSO-d_6 as the solvent and TMS as the internal reference (chemist shifts in ppm). The mass spectra were run at 70 eV with a finnigan SSQ7000 spectrophotometer (thermo-instrument system incorporation, USA) Elemental analysis were operated using Mario El Mentar apparatus, Organic microanalysis unit. Elemental analysis and the above spectra were measured the at National Research Center. Pharmacology was carried out in the Regional Center for Mycology & Biotechnology, Al-Azhar University.

2-Methyl-4-(1-naphthalen-2-yl)ethylidene)oxazol-5-(4*H*)-one (2).

A mixture of compound **1** (0.01 mol), acetyl glycine (0.01 mol) and 2 gm of fused sodium acetate in (10 mL) of acetic acid and 5 mL of acetic anhydride was refluxed for 1h. The reaction mixture was allowed to cool and then poured into cold water, the product obtained was filtered, dried and recrystallized to give **2.** IR (cm^{-1}, υ): 1668.9 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm) 2.05, 2.70 (2s, 6H, $2CH_3$), 7.60-8.15 (m, 6H, ArH), 8.47(s, 1H, C_{-1}ArH); MS: m/z(%): 251[M^+, 3.82].

General procedure for the preparation of the compounds 3a,b,5,6,8 and 9.

To a solution of oxazolinon-5-one (0.01 mol) in ethanol (30 mL) **,** the request amine (p-nitroaniline, p-chloroaniline, diethylamine, morpholine, hydrazine hydrate or p-aminoaniline (0.01 mol) was added. The reaction mixture was heated under reflux for 2h. after cooling precipitate was filtered, dried and recrystallized from the appropriate solvent to give **3a,b**, **5,6,8** and **9**, respectively

2-Acetamido-N-(4-nitrophenyl)-3-(naphthalen-2-yl)but-2-enamide (3a).

IR(cm^{-1}, υ): 1309, 1552 (NO_2) 1663 (br, 2C=O), 3354, 3472(2NH) groups; ^{1}H-NMR ($CHCl_3$, δ, ppm): 2.38, 2.67 (2s, 6H, $2CH_3$), 6.59, 6.64 (2s, 2H, 2NH, exchangeable with D_2O), 7.25-8.07(m,10H,ArH),8.3(s,1H,C_{-1}ArH).

2-Acetamido-N-(4-chlorphenyl)-3-(naphthalen-2-yl)but-2-enamid (3b).

IR(cm^{-1}, υ): 1627 (br, 2C=O), 3308, 3476 (2NH) groups; MS: m/z (%)378: [M^+, 27.11]

2-Acetamido-N,N-diethyl-3-(naphthalen-2-yl)but-2-enamide (5).

IR(cm^{-1}, υ): 1667 (br,2C=O), 3399, (NH + enaolic OH) groups; ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.01 (t, J=7.5Hz, 6H, $2CH_3$), 1.67, 2.72 (2s, 6H, $2CH_3$), 3.51 (q, J=7.5 Hz, 4H, $2CH_2$),7.60-8.01 (m, 6H, ArH), 8.31 (s, 1H, C_{-1}ArH), 8.96 (s, 1H, NH, exchangeable with D_2O).

N-1-Morpholino-3-(naphthalen-2-yl)-1-oxobut-2-en-2-yl)acetamide (6).

IR(cm^{-1}, υ): 1669 (br, 2C=O), 3389(NH + enolic OH) groups; ^{1}HNMR ($CHCl_3$, δ ppm): 2.22, 2.54 (2s, 6H, $2CH_3$), 3.24-3.70(m, 8H, $4CH_2$, morpholino), 7.55-8.02 (m, 6H, ArH), 8.30 (s, 1H, C_{-1} ArH), 9.43(br, 1H,NH, exchangeable with D_2O).

1,2-Dihydro-3-methyl-5-(1-(naphthalen-2-yl)ethylidene)-1,2,4-triazin-6(5*H*)-one (8).

IR(cm^{-1}, υ): 1676(C=O), 3123(2NH) groups; MS: m/z(%): 265 [M^+, 18.67).

2-Acetamido-N-(4-aminophenyl)-3-naphthalen-2-yl)but-2-enamide (9).

IR(cm^{-1},υ): 1664(br,2C=O), 3167, 3301, 3445(NH_2/NH) groups. ^{1}H-NMR ($CHCl_3$, δ, ppm): 2.22, 2.46 (2s, 6H, $2CH_3$), 3.48 (s, 2H, NH_2, D_2O exchangeable), 7.55-8.04 (m, 10H, ArH), 8.47 (s, 1H,C_{-1}ArH), 9.44 (s, 2H, 2NH, exchangeable with D_2O).

General procedure for the preparation of the compounds 4a,b and 10.

Procedure 1:

A solution of compound **2** (0.01 mol) in acetic acid (20 mL) was treated with 1gm of fused sodium acetate and (0.01 mol) of (p-nitroaniliine, *p*-chloroaniline,or *p*-aminoaniline). The mixture was heated for 3h, the solid obtained was collected and recrystallized to give **4a,b** and **10.**

Procedure 2:

A mixture of (compound **3a,3b, or 9)**(0.01 mol) and 1gm of fused sodium acetate in acetic acid (20 mL) was refluxed for 2h. After cooling, the product formed was filtered off, air dried and recrystallized to give **4a,b** and **10**.

1-(4-Nitrophenyl)-2-methyl-4-(1-naphthalen-2-yl)ethylidene)-1*H*-imidazole-5(4*H*)-one (4a).

IR (cm^{-1}, υ): 1677 (C=O), 1619(C=N), 1505, 1332 (NO_2); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.86, 2.71 (2s, 6H, $2CH_3$), 7.51-8.01) (m, 10H, ArH), 8.11(s, 1H, C_{-1}naphthalene).

1-(4-Chlorophenyl)-2-methyl-4-(1-(naphthalen-2-yl) ethylidene)-1*H*-imidazol-5(4*H*)-one (4b).

IR (cm^{-1}, υ): 1629(C=N); 1672 (C=O), MS: m/z (%) : 360[M^+, 5.21].

1-(4-Aminophenyl)-2-methyl-4-(1-(naphthalene-2-yl)ethylidene)-1H-imidazol-5(4*H*)-one (10).

IR(cm^{-1}, υ) 1632(C=N), 1669 (C=O), 3180, 3305 (NH_2) groups; ^{1}H-NMR(DMSO-d_6, δ ppm): 1.66, 2.24(2s, 6H, $2CH_3$), 7.25(s, 2H, NH_2, exchangeable with D_2O), 7.57-8.02 (m, 10H,ArH), 8.46(s, 1H, C_{-1} naphthalene).

2-Acetamido-3-(naphthalen-2-yl)but-2-enehydrazide (7).

A mixture of oxazolinone **2** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was stirred at room temperature for 2h. The product obtained was filtered and recrystallized to give **7**. IR (cm^{-1}, υ): 1691 (br, C=O), 3131, 3210, 3363(NH_2/NH) groups; ^{1}H-NMR ($CHCl_3$, δppm): 1.63, 2.73 (2s, 6H, $2CH_3$), 3.72(s, 2H, NH_2, exchangeable with D_2O). 7.52-7.92 (m, 6H, ArH), 8.25 (s, 1H,C_{-1} naphthalene).9.25, 9.51(2s, 2H, 2NH, exchangeable with D_2O).

1-[(4-Tolylsulfonamido)phenyl)]-2-methyl-4-(1-(naphthalen-2-yl)ethylidene)-1*H*-imidazol-5(4*H*)-one (11).

A mixture of compound **10** (0.01 mol) and p-toluene sulphonyl chloride (0.01 mol) in benzene/pyridine (20/10 mL) was heated under reflux for 3h. The reaction mixture was cooled and the product obtained was filtered off, dried and recrystallized to give **11**.

IR (cm^{-1}, υ): 1187, 1361 (SO_2–N), 1620 (C=N) 1671 (C=O), 3432(NH) groups; ^{1}H-NMR ($CHCl_3$, δ, ppm), 1.22, 1.52, 2.57 (3s, 9H, $3CH_3$), 7.25 (s, 1H, NH, exchangeable with D_2O), 7.55-7.97 (m, 14H, 3ArH), 8.47 (s,1H, C_{-1}naphthalene).

1-[4-(4-Chlorobenzylidine)aminophenyl)]-2-methyl-4-(1-(naphthalen-2-yl) ethylidine)-1H-imidazole-5(4H)-one 12.

To a solution of compound **10(**0.0 mol) in ethanol, 4-chloro- benzaldehdye (0.01 mol) was added followed by addition of 2-3 drops glacial acetic acid, then, the reaction mixture was heated under reflux temperature for 2h, the solid obtained after cooling was filtered, dried and recrystallized to give **12**. IR (cm^{-1}, υ): 1599(HC=N–), 1664(C=O) groups; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.00, 2.71 (2S, 6H, $2CH_3$), 7.46-7.98 (m, 14H, 3ArH), 8.67(s, 1H, C_{-1} naphthalene), 9.83 (s, 1H, CH=N–).

1-(Naphthalen-2-yl)ethylidenemalononitrile 13.

A mixture of compound **10** (0.0l mol) and malononitrile was heated under refluxed in ethanolic piperidine for 2h. the solid obtained after cooling was filtered, dried and recrystallized to give **12.** IR (cm^{-1}, υ): 1589 (C=C), 2210(2C≡N); MS: m/z (%): 218 (M^+, 100).

2-Amino-4-(naphthalen-2-yl)thiophen-3-carbonirtrile (15a).

Procedure A:

A solution of ethylidenemalononitrite **13** (0.01 mol) and sulfur powder (0.01 mol) in ethanol (30 mL) containing few drops of piperidine, was refluxed for 3h. The solid product was filtered and recrystallized to give **15a.**

Procedure B: For preparation of 15a and 15b:

A mixture of compound **1** (0.01 moL), malononitrile or ethyl cyanoacetate (0.01 moL) and sulfur powder (0.01 moL) was refluxed in ethanol containing few drops of triethylamine for 2h. the solid formed after filtration and cooling was crystallized to give **15a** and **15b** respectively.

2-Amino-4-(naphthalen-2-yl)thiophene-3-carbonitrile (15a).

IR (cm^{-1}, υ): 2206(C≡N), 3202, 3322 (NH_2) groups; ^{1}H-NMR(DMSO-d_6, δ,ppm): 3.74(br., 2H, NH_2, exchangeable with D_2O), 6.68 (s, 1H, C_{-5}thiophene), 7.15-7.99 (m, 6H, ArH), 8.68 (s, 1H, C_{-1} naphthalene).

Ethyl-2-amino-4-(naphthalen-2-yl) thiophen-3-carboxylate (15b).

IR (cm^{-1}, υ): 1721(C=O), 3200, 3321 (NH_2) groups; ^{1}HNMR (DMSO-d_6,δ, ppm): 1.49(t, = 8.5 Hz, 3H, CH_3) 3.39 (br, 2H, NH_2, exchangeable with D_2O), 3.75(q, J= 7.5Hz, 2H, CH_2), 6.67(s, 1H, C_{-5} thiophene), 7.60-8.01 (m, 6H, ArH), 8.68 (s, 1H, C_{-1} naphthalene).

5-(Naphthalen-2yl)thieno[2,3-d]pyrimidin-4(3H)-one (16).

Compound **15a** (0.01 mol) was heated under reflux temperature in 20 mL formic acid for 6h. The reaction mixture was cooled, poured into water, filtered dried and the residue was recrystallized to give **16**.

IR (cm^{-1}, υ): 1596 (C=N), 1697 (C=O), 3211 (NH); ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.7(s, 1H, C_{-6}H),7.20-7.97 (m, 7H, ArH+NH), 8.15(s, 1H, C_{-2}H), 8.31 (s, 1H, C_{-1} naphthalene).

Ethyl N-[4-(naphthalen-2yl)]-3-cyanothieno-2-yl) methanimidate (17).

A mixture of compound **15a** (0.01 mol) and 20 mL triethyl orthoformate was heated under reflux temperature for 4h, then evaporated and the residue was recryustallized to give compound **17**.

IR (cm^{-1}, υ): 2211 (C≡N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.23 (t, 8.5Hz, 3H, CH_3), 3.75 (q, J= 7.50, 2H, CH_2), 6.71 (s, 1H, thiophene), 7.25-7.81 (m, 6H, ArH), 8.21 (s, 1H, C_{-1} naphthalene), 8.51 (s,1H, N= CHOEt).

4-Imino-5-(naphthalen-2yl)thieno[2,3-d]pyrimidin-3-ylamine (18).

A mixture of compound **17** (0.01) dissolved in 20 mL of absolute ethanol and 3 mL of hydrazine hydrate (99%), was stirred for 1h at room temperature. The solid that formed was filtered, washed with a little amount of methanol dried, and recrystallized to give compound **18**. IR (cm^{-1}, υ): 1645 (C=N), 3111, 3220, 3250 (NH_2/NH) groups.; MS: m/z (%): 292 (M^+, 100)

5-(Naphthalene-2-yl)thieno[2,3-d]pyrimidin-4-yl-hydrazine (19):

Method A:

Compound **17** (0.01 mol) was dissolved in 20 mL absolute ethanol, then 2 mL of hydrazine hydrate (99%) were added, and the reaction mixture was heated under reflux temperature for 3h; it was evaporated and the residue was recrystallized to give **19**. IR (cm^{-1}, υ): 3180, 3210, 3310 (NH_2/NH).; MS: m/z (%): 292 (M^+, 71)

Method B: Isomerization of 18 to 19.

Compound **18** (0.01 mol) was dissolved in 20 mL ethanol and then drops of hydrazine hydrate were added, then the reaction mixture was heated under reflux temperature for 2h and evaporated under reduced pressure to give compound **19.** Product **19** which was obtained from this isomarization is identical in all respects (physical and spectral data) to those prepared by method A.

Antioxidant Assay:

The antioxidant activity of extract was determined by the DPPH free radical scavenging assay method **(Sonia, *et al.*, 2008)** in triplicate and average values were considered.

DPPH antioxidant assay

Freshly prepared (0.004%w/v) methanol solution of 2,2-diphenyl-l-picrylhydrazyl (DPPH) radical was prepared and stored at 10°C in the dark. A methanol solution of the test compound was prepared. A 40ul aliquot of the methanol solution was added to 3ml of DPPH solution. Absorbance measurements were recorded immediately with a Milton Roy Spectronic 201 UV-visible spectrophotometer. The decrease in absorbance at 515 nm was determined continuously, with data being recorded at 1 min intervals until the absorbance stabilized (16 min). Tocopherol was used as a reference standard and dissolved in distilled water to make the stock solution with the same concentration. The absorbance of the DPPH radical without antioxidant was also measured as control and 95% methanol was used as blank. All the determinations were performed in three replicates and averaged.

% Scavenging of the DPPH free radical was measured using the following equation: % DPPH radical-scavenging = [(Absorbance of control - Absorbance of test Sample)/ (Absorbance of control)] x 100 .

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تشييد، تفاعلات ومضادات الأكسدة لبعض الحلقات الغير متجانسة الحلقة الجديدة المشيدة من ٢- أستيل نفثالين

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في هذا البحث تم استخدام ٢-ميثيل-٤(١-نفثالين-٢-يل) ايثيليدين أكسازول–(4H)5-أون **2** في تحضير بعض مشتقات ١-(٤-مستدبل)-٢-ميثيل-٤-(١-نفثالين–٢-يل) ايثيليدين)–1H – ايميدازول– (4H) 5 أون **$4_{a,b}$** وبعض المشتقات الأخرى **5-12 ,$3_{a,b}$**. كما تم تحضير مشتق ثيينو [2,3-d] بريمدين (3H) 4–أون **16**، **17** ومشتق ٤-إيمينوثييينو [2,3-d] بريمدين -٣- يل **18**و **19** من تفاعل مشتق ٢- أمينوثيوفين -٣- كاربونيتريل **15a**. وعلاوة على هذا تم اختبار النشاط المضاد للأكسدة وأعطت بعض هذه المركبات فاعلية كمضادات للأكسدة.