Egypt. J. Chem. **54**, No. 5, pp. 609- 622 (2011)

Antimicrobial Activities of Some Novel Synthesized Aryl-pyrazole, Isoxazole, Pyran and Pyridine Derivatives from 3-Aryl-1- (2-naphthyl) Prop-2-en-1-ones

E. R. Kotb, M. A. El-Hashash[*], M.A. Salama[#] and N. A. M. Abdel Wahed[**]

Photochemistry Department, National Research Centre, [*]Chemistry Department, Faculty of Science, Ain Shams University and [**]Natural and Microbial Products Department, National Research Centre, Cairo, Egypt.

3-ARYL-1-(2-naphthyl)prop-2-en-1-ones (1) were reacted with hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride as nitrogen nucleophiles and with malononitrile, cyclohexanone, cyclopentanone as carbon nucleophiles to afford the corresponding dihydropyrazole 2,3and isoxazole 4 derivatives successively. Furthermore, cyanoamino pyran 5 and cyanoamino pyridine 6 derivatives were obtained. Additionally, a novel series of 1,5- diketone derivatives 7 and 8 were obtained, synthesized by base catalysed addition of cyclohexanone or cyclopentanone to compound 1. The latter compounds 7 and 8 were reacted with hydrazine hydrate to afford the respective hydrazide 9 and 10. Some of these compounds have been screened for antimicrobial activities. The structure assignments are based on the analytical and spectroscopic results.

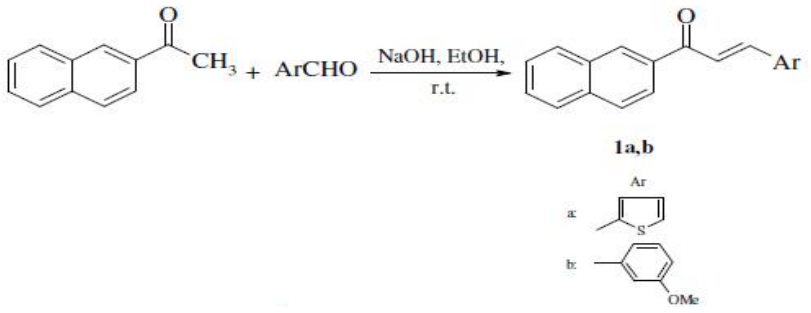
Keywords: α,β-Unsaturated ketones, 1,5-Diketones, Nicotinonitriles, Pyrazole, Isoxazole, Pyran and pyridine derivatives and Antimicrobial activity.

In a previous work it was reported that certain substituted pyridines have antidepressant, antimicrobial, anticancer, analgesic and anticonvulsant activities[(1-7)]. Also it was reported recently that N-acetylated pyrazoles are inhibitors of kinesin spindle protein, potentially useful for the treatment of cancer[(8,9)]. α,β-Enones are widely used as versatile precursors for the synthesis of several types of heterocyclic compounds such as isoxazoles[(10)], thiazoles[(11)], thiadiazoles [(12)], oxazolopyridines, pyran, pyridines, pyrimidines [(13,14)], triazine[(15)] and flavonoids [(16)]. In view of these observations and as a continuation of our previous work in heterocyclic chemistry[(17-19)], we synthesized some new aryl heterocyclic derivatives and tested their and antimicrobial activities.

[#]Corresponding author, e-mail: mowafsalam@yahoo.com

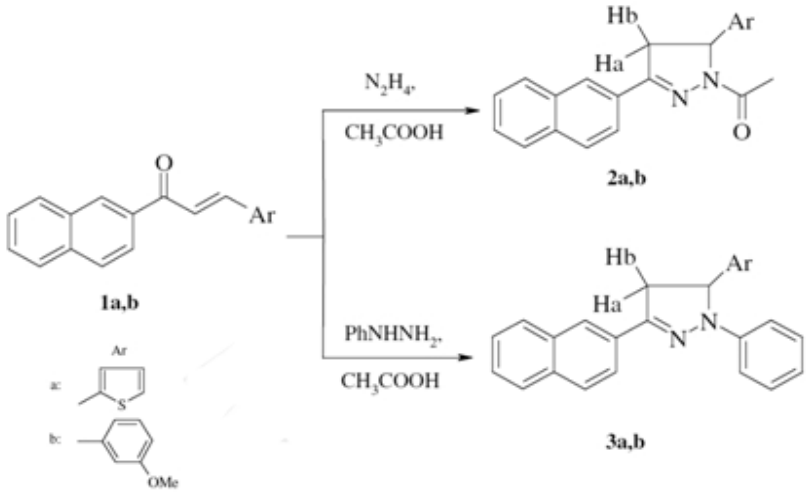
Results and Discussion

The general synthetic strategy employed to prepare novel 3-aryl-1-(2-naphthalen-2-yl)prop-2-en-1-ones (1a,b) derivatives was based on Claisen Schmidt condensation, which was reported previously[19] as shown in Scheme 1.



Scheme 1

Compounds 1a,b were identified via their melting points [19,20]. Behavior of α,β-enones 1a,b towards hydrazine hydrate, phenyl hydrazine and hydroxylamine depended on the reaction conditions. Thus, when compounds 1a,b were reacted with hydrazine hydrate in glacial acetic acid,the corresponding 1-[4,5-dihydro-3-(naphthalen-2-yl)-5-(thienyl-2-yl)-pyrazol-1-yl]ethanone (2a) and 1-[4,5-dihydro-5-(3-methoxyphenyl)-3-(naphthalen-2-yl)pyrazol-1-yl) ethanone (2b) were obtained ,respectively (Scheme 2).



Scheme 2

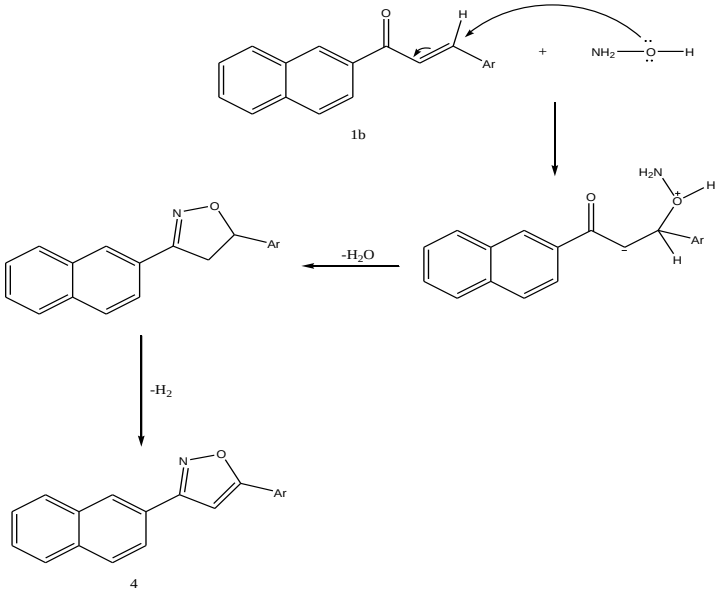
IR spectrum of compound 2a as an example showed absorption bands at 1665 cm^{-1} (C=O), 1590 cm^{-1} (C=N) and absence of any bands characterized to (NH)

group. ^{1}HNMR spectrum (DMSO-d_6, δ ppm) of compound 2a showed signals at 1.86 (s, 3H, CH_3), 2.85 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 3.16 (dd, J = 3.0/3.0 Hz, 1H, Hb of CH_2), 5.33 (m, 1H, pyrazole-H), 6.32 (d, J = 5.4 Hz, 1H, thiophen-H), 6.45 (d, 1H, thiophen-H), 6.56 (m, 1H, thiophen-H), 7.95-8.25 (m, 7H, Ar-H). Its mass spectrum showed the molecular ion peak at m/z (%) 320 (M^+, 33) (*c.f.* experimental).

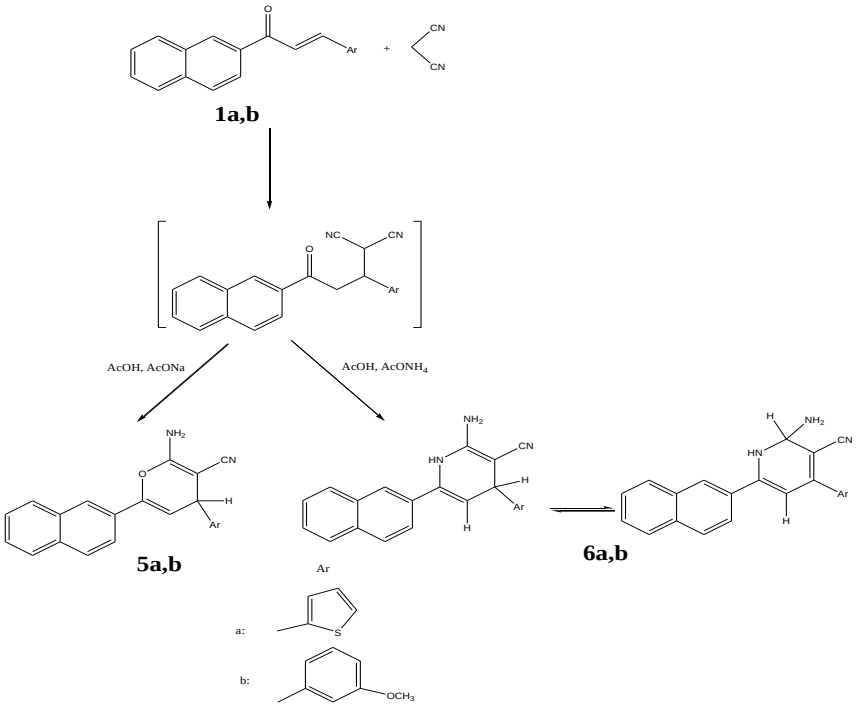
Similarly α,β-enones 1 condensed with phenyl hydrazine in acetic acid on boiling to yield the corresponding 4,5-dihydro-3-(naphthalen-2-yl)-1-phenyl-5-(thiophen-2-yl) pyrazole (3a) and 4,5- dihydro-5- (3-methoxyphenyl)-3-(naphthalen-2-yl)-1-phenyl-pyrazole (3b) (Scheme 2). Besides, the correct analytical data of compounds 3a and 3b, IR spectrum of compound 3a as an example showed absorption bands at 3100, 2923 and 1596 cm^{-1} characteristic of the CH aromatic, CH aliphatic and C=N, respectively. ^{1}HNMR spectrum ($CDCl_3$, δ ppm) of compound 3a showed signals at 3.62 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 4.12 (dd, J = 3.0/3.0 Hz, 1H, Hb of CH_2), 5.80 (m, 1H, pyrazole-H), 6.80-7.00 (m, 3H, Ar-H), 7.25-7.60 (m, 3H, Ar-H), 7.58-8.00 (m, 7H, Ar-H), 8.25-8.40 (m, 2H, Ar-H). Its mass spectrum showed the molecular ion peak at m/z (%) 354 (M+, 70) (*c.f.* experimental). IR spectrum of compound 3b showed absorption bands at 3100, 2920 and 1597 cm^{-1} characteristic of the CH aromatic, CH aliphatic and C=N absorption , respectively. ^{1}HNMR spectrum (DMSO-d_6, δ ppm) of compound 3b showed signals at 3.35 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 3.91 (s, 3H, OCH_3), 4.01 (dd, J = 3.0/3.0 Hz, 1H, Hb of CH_2), 5.35 (m, 1H, pyrazole-H), 6.92-7.00 (m, 4H, Ar- H), 7.04-7.38 (m, 3H, Ar-H), 7.57-7.95 (m, 7H, Ar-H), 8.26-8.29 (m, 2H, Ar-H). Its mass spectrum showed the molecular ion peak at m/z 378 (M^+, 66%) (*c.f.* experimental).

Reaction of α,β-enones 1b with hydroxylamine hydrocholoride in pyridine under reflux gave 5-(3-methoxyphenyl)-3-naphthalen-2-yl-isoxazole(4) (Scheme 3). The IR spectrum of compound 4 showed absorption bands at 2937, 1619 and 1590 cm^{-1}characteristic of CH ,C=N and C=C ,respectively.^{1}HNMR spectrum ($CDCl_3$,δ ppm) of compound 4 showed signals at 3.81 (s,3H,OCH_3)and 6.49-8.03(m,12H,Ar-H+1H isoxazole).Mass spectrum of compound 4 showed molcular ion peak M^+ at m/z 301 (52%) $C_{20}H_{15}NO_2$ (*c.f.* experimental).This result is in accordance with previous literature results [21-24] . The mechanism depicted here accounts for the formation of compound 4.

Moreover, condensation of compound 1 with malononitrile in acetic acid under reflux in the presence of anhydrous sodium acetate or ammonium acetate afforded the corresponding 2- amino-6-(naphthalen-2-yl)-4-(thien-2-yl)-4-*H*-pyran-3-carbonitrile (5a), 2-amino-4-(3- methoxyphenyl)-6-(naphthalen-2-yl)-4-H-pyran-3-carbonitrile (5b), 2-amino-6-(naphthalen-2-yl)-4- (thien-2-yl)-2,3-dihydropyridine-3- carbonitrile (6a) and 2-amino-4- (3methoxyphenyl)-6-(naphthalen-2-yl) -2,3-dihydro pyridine -3-carbonitrile (6b), respectively (Scheme 4).

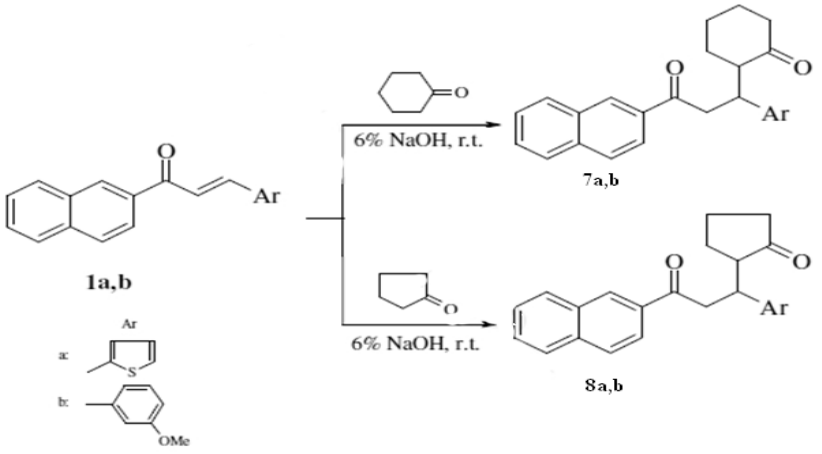


Scheme 3



Scheme 4

The structures of the synthesized compounds were confirmed on the basis of their elemental analyses and spectral data. IR spectrum of compound 5b as an example displayed absorption bands near 3453-3215 cm^{-1} (NH_2) and 2205 cm^{-1} (CN). Its ^{1}HNMR spectrum (DMSO-d_6, δ ppm) showed signals at 3.86 (s, 3H, OCH_3), 3.91 (d, J = 4.5 Hz, 1H, pyran-H4), 6.98 (d, J = 4.5 Hz, 1H, pyran- H5), 7.10-7.53 (m, 6H, Ar-H), 7.60-7.97 (m, 4H, 2Ar-H + NH_2, D_2O exchangeable), 8.15-8.50 (m,2H, Ar-H), 8.94 (s, 1H, Ar-H). Mass spectrum of compound 5b showed the molecular ion peak at m/z 354 (M+, 41%) (*c.f.* experimental). IR spectrum of compound 6b showed absorption bands near 3363, 3199 cm^{-1} (NH_2) and 2202 cm^{-1} (CN). Its ^{1}HNMR spectrum (DMSO-d_6, δ ppm) showed signals at 3.86 (s, 3H, OCH_3), 6.93 (s, 2H, NH_2, D_2O exchangeable), 7.15 (s, 1H, pyridine-H5), 7.33-7.50 (m, 6H, Ar-H), 8.03-8.29 (m, 4H, Ar-H), 8.76 (s, 1H, Ar-H). Mass spectrum of compound 6b showed the molecular ion peak at m/z 353 (M^+, 100%) (*c.f.* experimental). A novel series of 1,5-diketones 7a,b and 8a,b were prepared by base catalyzed Michael addition of cyclohexanone or cyclopentanone on 1a,b. (Scheme 5).



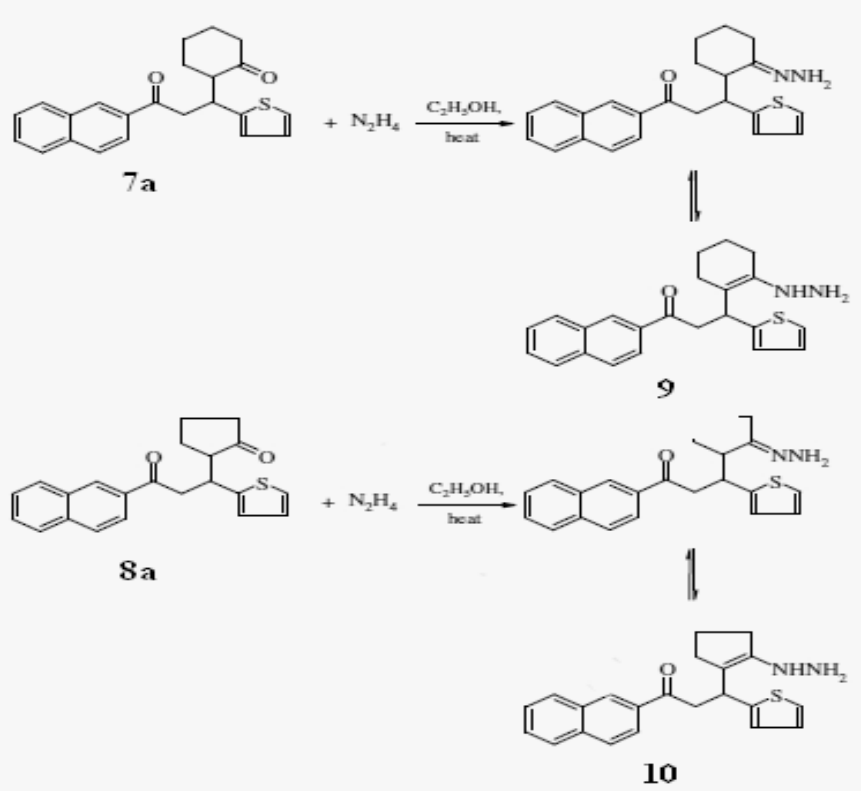
Scheme 5

Thus, 2-[3-(naphthalen-2-yl)-3-oxo-1-(thienyl-2-yl)propyl] cyclohexanone 7a, 2-[1-(3-methoxyphenyl) -3-(naphthalen-2-yl) 3-oxopropyl] cyclohexanone 7b, 2-[3-(naphthalen-2-yl) -3-oxo- 1-(thienyl-2-yl) propyl]cyclopentanone 8a and 2-[1-(3-methoxyphenyl)-3-(naphthalen-2 yl) 3-oxopropyl]cyclopentanone 8b were obtained successively.

The diketones were obtained in yields of 50-70%. The structures of novel series of 1,5-diketones 7a,b and 8a,b were determined on the basis of spectral data (IR, ^{1}HNMR, ^{13}CNMR, Ms and elemental analysis). IR spectrum of compound 7a as an example showed bands at 1726 and 1676 cm^{-1} (2C=O). ^{1}HNMR spectrum of compounds 7a,b and 8a,b assigned their structure (*c.f.* experimental).

Reaction of compounds 7a and 8a with hydrazine hydrate in ethanol under reflux led to the formation of the corresponding novel derivatives 9 and 10, respectively (Scheme 6).

The structures of the novel synthesized compounds were confirmed on the basis of their elemental analysis and their spectral data (*c.f.* experimental).



Scheme 6

Antimicrobial activity

The target compounds were tested for their antimicrobial activity against *Esherichia coli NRRLB-210* (Gram-negative bacteria), *Bacillus subtilis NRRLB-543* (Gram-positive bacteria), *Aspergillus niger* (Yeast) and *Candida albicans NRRLY-477* (Fungi). These microorganisms were obtained from Northern Utilisation Research and Development Division, U.S. Department of Agriculture, Peoria, Illinois, USA. Chloromphenicol and Fluconazole were purchased from Egyptian market and used at the concentration of 25 mg/ml as references for antibacterial and antifungal activities. These compounds were assayed by the agar diffusion method.20 The assay medium flasks containing 50 ml of nutrient agar medium for bacteria and Czapeks-Dox agar media for fungi, respectively were allowed to reach 40-50°C and then incoulated with 0.5 ml of the last organism cell suspension.

The flasks were mixed well and then the content of each flask was poured into a petri dish and allowed to solidify. Thereafter, holes (1 cm diameter) were made in the agar plate by the aid of a sterile carkborer. In these holes 100µL of the 1.8 mg/ml DMSO of each compound was placed using an automatic micropipette. The petri dish was left at 5°C for 1 hr to allow diffusion of the samples through the agar medium and retard the growth of the test organism, and then incubated at 30°C for 24 hr for bacteria and 72 hr of incubation at 28°C for fungi. The diameter of the resulted inhibition zone was measured in cm.

Results

Results of antibacterial activity test aganist *Esherichia coli* (Gram-positive bacteria), *Bacillus subtilis* (Gram-negative bacteria) showed that compounds 3a, 3b, 4b, 7a, 8a and 9 have an antibacterial activity. While the other tested compounds were generally inefficient (Table 1).

TABLE 1. *In vitro* antimicrobial activity by agar diffusion method of tested compounds *

Tested compounds & Standards	**Inhibition Zone (mm)**			
	Microorganism			
	Bacteria			
	Gram positive	**Gram negative**	**Yeast**	**Fungi**
	Esherichia coli	***Bacillus subtilis***	***Aspergillus niger***	***Candida albicans***
Chloromphenicol	+++	+++	+	+
Fluconazole	-	-	+++	+++
2a	-	-	-	-
2b	-	-	-	-
3a	-	++	-	-
3b	-	++	-	-
4b	++	++	-	-
5a	-	-	-	-
6b	-	-	-	-
7a	++	-	-	-
7b	++	++	-	-
8a	++	-	-	-
8b	++	-	-	-
9	++	++	++	++

***+++ Highly sensitive (inhibition zone = 21-25 mm),++ Fairly sensitivity (inhibition zone = 16-20 mm),+ Slightly sensitivity (inhibition zone = 10-15 mm), - No sensitivity.

Antifungal activity

The prepared compounds were evaluated in vitro against two strains of fungi, *Candida albicans* and *Aspergillus niger* (Yeast). Result of antifungel activity showed that compound 9 has an antifungal activity. While the other compounds were generally inefficient.

Experimental

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin- Elmer 1650 Spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}HNMR and ^{13}CNMR spectra were determined on a Jeol-Ex-300 NMR spectrometer (Jeol, Tokyo, Japan) and chemical shifts were expressed as part per million (ppm) (δ values) against TMS as internal reference. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA).

Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Centre, Cairo, Egypt and the results were within the accepted range of the calculated values. Follow up the reactions and checking the purity of the compounds was made by TLC on silica gel-precoted aluminium sheets (Type 60 F254, Merck, Darmstadt, Germany).Compounds 1a (m.p. 105-107) and 1b (m.p. 102-103) were prepared as reported in the literature [19,20].

General procedure for the synthesis of compounds 2a,b and 3a,b

A solution of compounds 1 (0.01 mol) and hydrazine hydrate and/or phenyl hydrazine (0.01 mol) in acetic acid (30 ml) was refluxed for 6hr, then left to cool, poured onto water. The obtained precipitate was filtered off, washed several times with water, recrystallized from acetic acid to afford the corresponding pyrazole derivatives 2a,b and 3a,b, respectively.

1-[4,5-Dihydro-3-(naphthalen-2-yl)-5-(thiophen-2-yl)pyrazol-1-yl]ethanone(2a)

Yield (75%), m.p. 115-116°C; IR (KBr) □max/ cm^{-1}: 1665 (C=O), 1590 (C=N). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.86 (s, 3H, CH_3), 2.85 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 3.16 (dd, J = 3.0/3.0 Hz, 1H, Hb of CH_2), 5.33 (m, 1H, pyrazole-H), 6.32 (d, J = 5.4 Hz, 1H, thiophen-H), 6.45 (d, 1H, thiophen-H), 6.56 (m, 1H, thiophen-H), 7.95-8.25 (m, 7H, Ar-H). MS, m/z (%) 320 (M+, 32.89). Anal. calcd for $C_{19}H_{16}N_2OS$: C, 71.25; H, 5.00; N, 8.75; S, 10.00. Found: C, 71.31; H, 4.95;N, 8.81; S, 9.97.

1-[4,5-Dihydro-5-(3-methoxyphenyl)-3- (naphthalen-2-yl) pyrazol-1-yl] ethanone (2b)

Yield (65%), m.p. 130-131°C; IR (KBr) □max/ cm^{-1}: 1668 (C=O), 1585 (C=N). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 2.53 (s, 3H, CH_3), 3.26 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 3.37 (dd, J= 3.0/3.0 Hz, 1H, Hb of CH_2), 3.79 (s, 3H, OCH_3), 5.61 (m, 1H, pyrazole-H), 6.83-8.11 (m, 11H,Ar-H). MS, m/z (%) 345 (M+, 100). Anal. calcd for $C_{22}H_{21}N_2O_2$: C, 76.52; H, 6.08; N, 8.11. Found:C, 76.60; H, 6.00; N, 8.07.

4,5-Dihydro-3-(naphthalen-2-yl)-1-phenyl-5-(thiophen-2-yl)-1H-pyrazole(3a)

max/ Yield (75%), m.p. 180-181°C; IR (KBr) cm–1: 3100 (CH aromatic), 2923 (CH aliphatic) and 1596 (C=N). ^{1}HNMR (CDC_{l3}, δ ppm) 3.62 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 4.12 (dd, J =3.0/3.0 Hz, 1H, Hb of CH_2), 5.80 (m, 1H, pyrazole-H), 6.80-7.00 (m, 3H, Ar-H), 7.25-7.60 (m, 3H,Ar-H), 7.58-8.00 (m, 7H, Ar-H), 8.25-8.40 (m, 2H, Ar-H). ^{13}CNMR (62.9MHz, CDC_{l3}, δ ppm):43.7, 60.5, 105.1, 113.8, 119.6, 123.4, 124.1, 124.8, 125.2, 126.3, 126.4 (2C), 126.9, 127.8, 128.1(2C), 128.2 (2C), 128.8 (2C), 144.8, 145.9, 147.3. MS m/z (%) 354 (M+, 70). Anal. calcd for $C_{23}H_{18}N_2S$: C, 77.93; H, 5.12; N, 7.90; S, 9.04. Found: C, 77.88; H, 5.34; N, 7.85; S, 9.00.

4,5-Dihydro-5-(3-methoxyphenyl)-3-(naphthalen-2-yl)-1-phenyl-1H-pyrazole (3b)

Yield (72%), m.p. 115-116°C; IR (KBr) max/ cm^{-1}: 3110 (CH aromatic), 2920 (CH aliphatic) and 1589 (C=N). ^{1}HNMR (CDC_{l3}, δ ppm) 3.35 (dd, J = 2.5/2.5 Hz, 1H, Ha of CH_2), 3.91 (s, 3H, OCH_3), 4.01 (dd, J = 3.0/3.0 Hz, 1H, Hb of CH_2), 5.35 (m, 1H, pyrazole-H), 6.92-7.00 (m, 4H, Ar-H), 7.04-7.38 (m, 3H, Ar-H), 7.57-7.95 (m, 7H, Ar-H), 8.26-8.29 (m, 2H, Ar-H). ^{13}CNMR (62.9MHz, CDC_{l3}, δ ppm): 160.6, 147.3, 145.2, 144.7, 133.8 (2C), 133.7 (2C), 130.7, 129.4, 128.6,128.5, 128.2 (2C), 125.5 (2C), 123.9, 128.5, 113.9, 111.8, 77.8, 77.5, 77.1, 65.1, 55.6 and 43.9. MSm/z (%) 378 (M+, 66). Anal. calcd for $C_{26}H_{22}N_2O$: C, 82.53; H, 5.82; N, 7.40. Found: C, 82.48; H,5.88; N, 7.36.

General procedure for the synthesis of compound 4

A solution of compounds 1b (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in pyridine (20 ml) was refluxed for 10hr, then left to cool. The cooled reaction mixture was acidified with cold dilute hydrochloric acid. The separated solid was filtered off, dried and recrystallized from benzene/petroleum ether to afford compound 4 .

5-(3-Methothoxyphenyl)-3-naphthalen-2-yl-isoxazole (4)

Yield (72%), m.p. 110-111°C; IR (KBr) max/ cm^{-1}: 2937 (CH), 1619(C=N) and 1596 (C=C). ^{1}HNMR ($CDCl_3$, δ ppm) 3.81 (s, 3H, OCH_3) 6.49-8.03 (m, 12H, Ar-H + isoxazole-H). MS m/z 301 (M+, 52). ^{13}CNMR (62.9MHz, CDC_{l3}, δ ppm): 159.7, 157.7, 139.6, 136.9, 129.5,128.6, 128.2 (2C), 127.5, 126.5, 126.2 (2C), 120.1, 119.4, 117.2, 115.1, 114.6, 112.09, 111.4, and55.1. MS m/z (%) 301 (M+, 52). Anal. calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.61; N, 4.65. Found: C,79.01; H, 5.56; N, 4.68.

General procedure for the synthesis of compounds 5a,b and 6a,b

A mixture of compounds 1a,b (0.01 mol) and malononitirile (0.01 mol) and anhydrous sodium acetate and/or anhydrous ammonium acetate in glacial acetic acid (50 ml) was refluxed for 6hr, left to cool and poured onto water with stirring the formed solid was filtered off and crystallized from acetic acid to give compounds 5a,b and 6a,b, respectively.

2-Amino-6-(naphthalen-2-yl)-4-(thiophen-2-yl)-4H-pyran-3-carbonitrile (5a)

Yield (55%), m.p. 250-251°C; IR (KBr) max/ cm^{-1}: 3453-3215 (NH_2), 2205 (CN). ^{1}HNMR (DMSO-d_6, δ ppm) 3.80 (d, J= 4.2 Hz, 1H, pyran-H4), 6.95 (d, J =

4.5 Hz, 1H, pyran-H5), 7.53 (d, J= 5.40 Hz, 1H, thiophen-H), 7.60-8.00 (m, 9H, 7Ar-H + NH_2, D_2O exchangeable), 8.30 (m, 1H, thiophen-H), 8.94 (s, 1H, Ar-H). MS m/z (%) 330 (M+, 12.5). Anal. calcd for $C_{20}H_{14}N_2OS$: C, 72.73;H, 4.24; N, 8.48; S, 9.70. Found: C, 72.70; H, 4.20; N, 8.52; S, 9.76.

2-Amino-4-(3-methoxyphenyl)-6-(naphthalen-2-yl)-4-H-pyran-3-carbonitrile (5b)

Yield (70%), m.p. 255-256°C (acetic max/ cm□acid); IR (KBr) $^{-1}$: 3450-3200 (NH_2), 2205 (CN). ^{1}HNMR (DMSO-d_6, δ ppm) 3.86 (s, 3H, OCH_3), 3.91 (d, J= 4.5 Hz, 1H, pyran-H4), 6.98 (d, J= 4.5 Hz, 1H, pyran-H5), 7.10-7.53 (m, 6H, Ar-H), 7.60-7.97 (m, 4H, 2Ar-H + NH_2, D_2O exchangeable), 8.15-8.50 (m, 2H, Ar-H), 8.94 (s, 1H, Ar-H). MS m/z (%) 354 (M+, 41). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.79; H, 5.08; N, 7.91. Found: C, 77.71; H, 5.08; N, 7.92.

2-Amino-6- (naphthalen -2-yl) -4- (thiophen-2-yl) -3,4- dihydropyridine -3-carbonitrile (6a)

Yield (55%), m.p. 255-257°C (acetic max/ cm□acid); IR (KBr) $^{-1}$: 3453-3205 (NH_2), 2206 (CN). ^{1}HNMR (DMSO-d_6, δ ppm) 6.62 (s, 2H, NH_2, D_2O exchangeable), 7.25 (d, J = 4.5 Hz, 1H,pyridine-H5), 7.60 (d, J= 5.04 Hz, 1H, thiophen-H), 7.90-8.25 (m, 7H, 7Ar-H), 8.35 (m, 1H, thiophen-H), 8.91 (s, 1H, Ar-H). MS m/z (%) 327 (M+, 100). Anal. calcd for $C_{20}H_{13}N_3S$: C, 73.40;H, 3.70; N, 12.84; S, 9.77. Found: C, 73.45; H, 3.66; N, 12.66; S, 9.77.

2-Amino-4- (3-methoxyphenyl) -6- (naphthalen-2-yl) -3,4- dihydropyridine-3-carbonitrile (6b)

Yield (68%), m.p. 260-262°C; IR (KBr) max/ cm□$^{-1}$: 3363-3199 (NH_2), 2202 (CN). ^{1}HNMR (DMSO-d_6, δ ppm) 3.86 (s, 3H, OCH_3), 6.93 (s, 2H, NH_2, D_2O exchangeable), 7.15 (s, 1H, pyridine-H5), 7.33-7.50 (m, 6H, Ar-H), 8.03-8.29 (m, 4H, Ar-H), 8.76 (s, 1H, Ar-H). MS m/z (%) 353 (M+,100). Anal. calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.27; H, 5.33; N, 11.99.

General procedure for the synthesis of compounds 7a,b and 8a,b

A mixture of chalcone 1 (0.01 mol), cyclohexanone and/or cyclopentanone (0.02 mol), solid NaOH (0.06) in ethanol (20 ml) was added and stirred for 10hr. at room temperature. Then the mixture was extracted with chloroform (20 ml) and dried over sodium sulphate anhydrous after the solvent removed in vacua, the product was precipitated in CCl4/hexane (3:1) and crystallized from acetic acid to give compounds 7a,b and 8a,b respectively.

2-[3-(Naphthalen-2-yl)-3-oxo-1-(thiophen-2-yl)propyl]cyclohexanone (7a)

Yield (75%), m.p. 150-152°C □max/ cm (benzene/petroleum ether); IR (KBr)$^{-1}$: 1720 (C=O), 1677 (C=O). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.20-1.28 (m, 3H), 1.60-1.88 (m, 5H), 2.25 (m,1H), 2.50 (dd, 1H, J = 11.66/2.60 Hz, propyl-H), 2.80 (dd, 1H, J = 12.90/3.27 Hz, propyl-H), 3.75(m, 3H, propyl-H), 7.26 (d, 1H, J = 5.40 Hz, thiophen-H), 7.59-8.01 (m, 6H, Ar-H), 8.22-8.12 (m,2H, Ar-H), 8.73 (s, 1H, Ar-H). MS, m/z (%) 362 (M+, 10). Anal. calcd for $C_{23}H_{22}O_2S$: C, 76.24; H,6.08; S, 8.84. Found: C, 76.00; H, 6.11; S, 8.80.

2-[1-(3-Methoxyphenyl)-3-(naphthalen-2-yl)3-oxopropyl]cyclohexanone (7b)

max/ Yield (55%), m.p. 90-91°C; IR (KBr) cm^{-1}: 1725 (C=O), 1676 (C=O). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.22-1.28 (m, 1H), 1.56-1.88 (m, 5H), 2.70 (dd, 1H, J = 11.88/3.00 Hz,propyl-H), 2.38-2.82 (m, 2H), 2.79 (m, 1H), 2.90 (dd, 1H, J = 12.94/3.25 Hz, propyl-H), 3.50 (m,1H, propyl-H), 3.83 (s, 3H, OCH_3), 7.21-7.40 (m, 6H, Ar-H), 8.01-8.28 (m, 4H, Ar-H), 8.62 (s, 1H,Ar-H). ^{13}CNMR (62.9 MHz, CDC_{l3}, δ ppm): 215.5, 200.6, 161.7, 143.9, 135.6,134.5, 132.5, 129.8,129.5, 128.7, 128.5, 128.2, 126.5, 124.5, 120.5 (2C), 122.5, 113.3, 55.9, 55.5, 54.5, 46.8, 41.3, 24.9(2C), 22.9. MS, m/z (%) 386 (M+, 100). Anal. calcd for $C_{26}H_{26}O_3$:C, 80.82; H, 6.74. Found: C, 80.85; H, 6.78.

2-[3-(Naphthalen-2-yl)-3-oxo-1-(thiophen-2-yl)propyl]cyclopentanone (8a)

Yield (50%), m.p. 150-152°C; IR (KBr) max/ cm^{-1}: 1720 (C=O), 1675 (C=O). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.63-1.92 (m, 4H), 2.11 (m, 2H), 2.40 (m, 1H), 2.60 (dd, 1H, J = 11.44/2.60 Hz, propyl-H), 2.70 (dd, 1H, J = 12.85/3.50 Hz, propyl-H), 3.55 (m, 3H, propyl-H), 7.08(d, 1H, J = 5.41, thiophen-H), 7.25-7.84 (m, 6H, Ar-H), 8.12-8.20 (m, 2H, Ar-H), 8.71 (s, 1H, Ar-H). MS, m/z (%) 348 (M+, 4). Anal. calcd for $C_{22}H_{20}O_2S$: C, 75.86; H, 5.73; S, 9.20. Found: C, 75.50; H, 5.80; S, 9.00.

2-[1-(3-Methoxyphenyl)-3-(naphthalen-2-yl)3-oxopropyl]cyclopentanone (8b)

Yield (40%), m.p. 100-102°C; IR (KBr) max/ cm^{-1}: 1735 (C=O), 1678 (C=O). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.21-1.23 (m, 2H), 1.45-1.47 (m, 2H), 1.88-1.90 (m, 2H), 2.68 (m, 1H), 3.15-3.32 (m, 2H, propyl-H), 3.85 (s, 3H, OCH_3), 4.08 (m, 1H, propyl-H), 7.00-7.32 (m, 6H, Ar-H), 7.40-7.90 (m, 4H, Ar-H), 8.56 (s, 1H, Ar-H). MS, m/z (%) 372 (M+, 40). Anal. calcd for $C_{25}H_{24}O_3$: C, 80.64; H, 6.45. Found: C, 80.00; H, 6.66.

General procedure for the synthesis of compounds 9 and 10

A mixture of compounds 8a or 9a (0.01 mol), hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 3hr, then left cool, the obtained precipitate was filtered off, recrystallized from acetic acid to give compounds 9 and 10, respectively.

E-3-(2-Hydrazinocyclohexen-yl)-1-(naphthalen-2-yl)-3-(thiophen-2-yl) propan-1-one (9)

Yield (60%), m.p. 195-196°C; IR (KBr) max/ cm^{-1}: 3250-3160 (NH_2, NH), 1715 (C=O).^{1}HNMR spectrum (DMSO-d_6, δ ppm) 1.52-1.83 (m, 4H), 2.35-2.52 (m, 4H), 2.90 (dd, 1H, J = 16/9.6 Hz, propyl-H), 3.05 (dd, 1H, J = 16.1/3.9 Hz, propyl-H), 3.8 (dd, 1H, propyl-H), 5.91 (s, 2H, NH_2, D_2O exchangeable), 6.97-7.98 (m, 10H, 7Ar-H + 3 thiophen-H), 10.22 (s, 1H, NH, D_2O exchangeable). MS, m/z (%) 376 (M+, 1.07). Anal. calcd for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44; S, 8.52. Found: C, 73.25; H, 6.51; N, 7.57; S, 8.32.

E-3-(2-Hydrazinocyclopenten-yl)-1-(naphthalen-2-yl)-3-(thiophen-2-yl)propan-1-one (10)

Yield (60%), m.p. 190-191°C; IR (KBr) max/ cm^{-1}: 3250-3130 (NH_2, NH), 1711 (C=O). ^{1}HNMR spectrum (DMSO-d_6, δ ppm) 2.30-2.35 (m, 4H), 1.95 (m,

2H), 2.80 (dd, 1H, propyl-H), 3.11 (dd, 1H, propyl-H), 3.80 (dd, 1H, propyl-H), 3.85 (dd, 1H, propyl-H), 5.82 (s, 2H, NH_2, D_2O exchangeable), 6.87-6.92 (m, 3 thiophen-H), 7.52-7.75 (m, 6H, 6Ar-H), 8.25(d, 1H, Ar-H), 10.11 (s, 1H, NH, D_2O exchangeable). MS, m/z (%) 362 (M+, 2.06). Anal. calcd for $C_{22}H_{22}N_2OS$: C, 72.89; H, 6.12; N, 7.73; S, 8.85. Found: C, 72.83; H, 6.21; N, 7.70; S, 8.8.

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(*Received* 27/11/2011;
accepted 28/2 /2012)

تخليق مشتقات أريل البيرازول والأيزوكزازول والبيران والبيريدين الجديدة من -٣-أريل -١ -(٢-نافثيل) بروبين-١-أون ذات نشاط بيولوجى

إيمان قطب ،ماهر الحشاش*،موافية عبد الرحمن سلامه و نيرةعبد الواحد**
قسم الكيمياء الضوئية – المركز القومى للبحوث ،*قسم الكيمياء - كلية العلوم- جامعة عين شمس و**قسم المنتجات الطبيعية والميكروبية – المركز القومى للبحوث - القاهرة - مصر.

في هذا البحث تم تحضير مركبات حلقية غير متجانسة جديدة من مشتقات -٣-أريل-١-(٢-نافثيل) بروبين-١-أون وذلك بتفاعله مع هيدرازين هيدريت ،فينيل هيدرازين وهيدروكسيل أمين الهيدروكلوريد ككواشف نيوكليوفيلية نيتروجينية. وايضا مع مالونونيتريل، سيكلوهيكسانون ، سيكلوبنتانون ككواشف نيوكليوفيلية كربونية لتعطى مشتقات (ثنائى هيدروالبيرازول ٢،٣ وأيزوكزازول ٤) علي التوالى. وايضا مشتقات (سيانو امينو بيران ٥ و سيانو امينو بيريدين ٦) . بالأضافة إلى سلسلة جديدة من المشتقات الجديدة ١،٥-ثنائى الكيتون ٧،٨. وبتفاعل المركبين الأخيرين ٧،٨ مع هيدرازين هيدريت أعطيا المركبين المناظرين ٩،١٠. وقد أظهرت بعض هذه المركبات المنتقاة نتائج بيولوجية ممتازة.