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Convenient synthesis of some new thiazolidin-4-one, chromen-2-imine and pyrrol-2-one derivatives containing thiophene moiety

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Abstract: In the present study, 2-amino-4-methyl-5-(pyridin-2-ylcarbamoyl)thiophene-3-ethylcarboxylate (2) has been achieved using Gewald's methodology between 3-oxo-N-(pyridin-2-yl)butanamide (1), ethyl 2-cyanoacetate and elemental sulfur in refluxing ethyl alcohol containing a catalytic amount of morpholine. This 2-aminothiophene derivative was served as key synthon for the synthesis of new thiazolidin-4-one, chromen-2-imine and pyrrol-2-one derivatives via its reactions with the convenient chemical reagents. The mechanistic aspects for the achievement of the new thiophene derivatives were also discussed

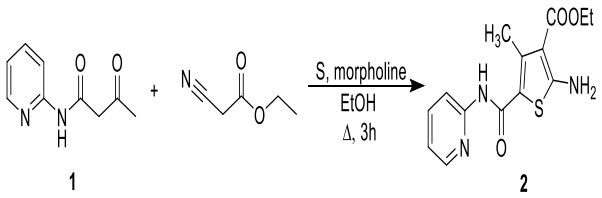
keywords: Thiophene; thiazolidinone; chromene; pyrrolone; Gewald's methodology**.**

1.Introduction

Aryl thiophenes are substantial heterocycles found in various bioactive compounds as herbicides [1], antibacterial [2], antifungal [3] and antileishmanial [4] and also used as precursors in numerous agrochemicals [5]. Thiophene scaffold is the backbone of many vital products as dyes [6] and numerous natural products [7]. Recently, the synthesis of thiophene derivatives has attracted a great interest because many of them are agonist allosteric enhancers at the adenosine receptor A1 [8, 9] and possess anthelmintic activity against *Haemonchus contortus*[10]. Alkyl thiophene-carboxylates are versatile synthetic intermediates for the preparation of polycyclic systems [11] and have been used as monomers for the synthesis of the corresponding polymers by direct coupling polymerization [12]. In addition, complexes of 2-(3-mercapto-3-cyano-2-(arylamino)acrylamido)-4,5,6,7-tetrahydrobenzothiophene-3-ethylcarboxylate are potent analogues as anti-rheumatic agents [13]. In the light of the immense biological significance of thiophene derivatives, we have undertaken in this study the synthesis of novel thiazolidin-4-one, chromen-2-imine and pyrrol-2-one derivatives containing thiophene nucleus derived from 2-aminothiophene **2**.

2. Results and Discussion

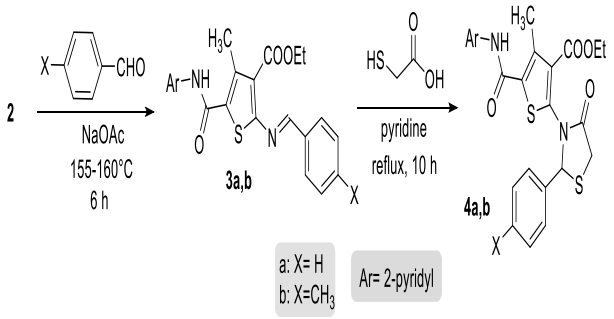
The key compound, 2-aminothiophene **2** was synthesized from readily attainable reagents through Gewald condensation of pyridine derivative **1** with ethyl 2-cyanoacetate and elemental sulfur in refluxing ethyl alcohol containing morpholine (few drops), in a good yield as outlined in **Scheme 1**.



Scheme 1. Synthesis of 2-aminothiophene **2**.

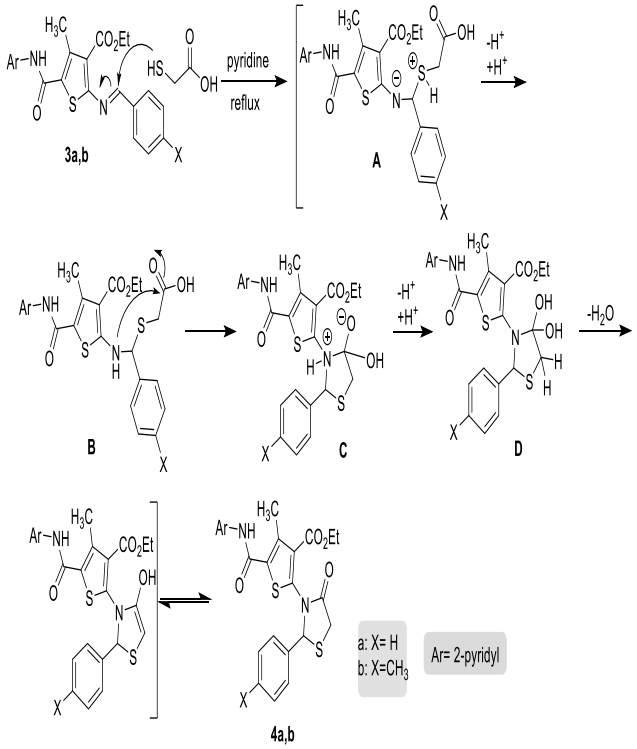
Schiff bases are compounds incorporating a parent azomethine group and having various synthetic applications such as catalysts, dyeing processes, synthetic intermediates, polymer stabilizers and metal corrosion inhibitors. In addition, these compounds have shown diverse, potent and remarkable biological performance when applied in the medical field [14]. Therefore, condensation of 2-aminothiophene **2** with aromatic aldehydes at 155-160^{o}C in the presence of freshly melted NaOAc provide a facile route to yield the corresponding Schiff bases **3a,b**. Subsequent cyclocondensation reactions of mercaptoacetic acid with each of

Schiff bases **3a,b** afforded the desired thiazolidin-4-ones **4a,b**, respectively (**Scheme 2**).



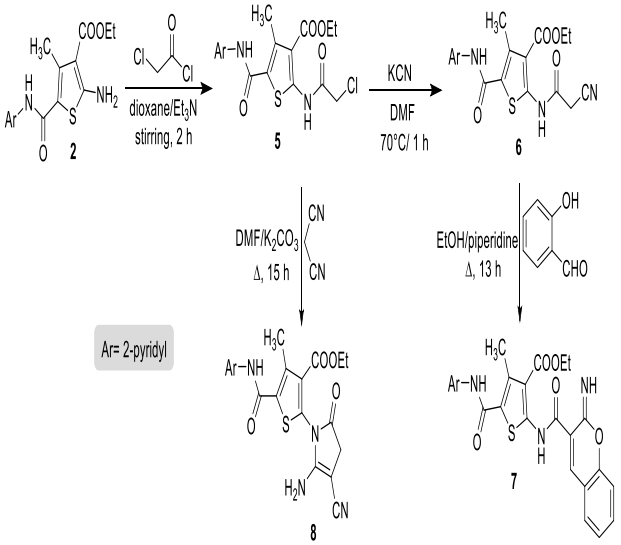
Scheme 2. Synthesis of thiazolidin-4-ones **4a,b**.

The reactions of Schiff bases **3a,b** with mercaptoacetic acid were progressed initially through the nucleophilic attack of sulfur atom of mercaptoacetic acid to the C=N group of Schiff bases followed by intramolecular cyclization with the loss of H_2O molecule (Scheme 3).



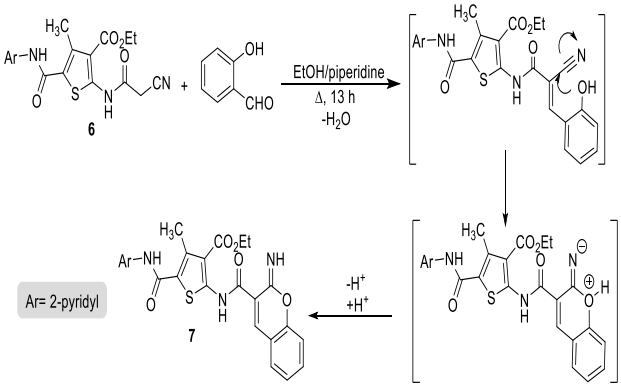
Scheme 3. The suggested mechanism for the synthesis of thiazolidin-4-ones **4a-d**.

Cyanoacetamides were applied as versatile synthetic intermediates for the synthesis of diverse dyes, biologically active components, and agrochemical analogues [15]. On the other side, the researcher's interest in the synthesis of coumarin heterocycles has been increased in the last decades due to their remarkable biological impacts [16]. Thus, treatment of 2-aminothiophene **2** with chloroacetyl chloride in dioxane catalyzed by Et_3N afforded the desired chloroacetamide **5**. Heating of **5** with potassium cyanide in DMF yielded the corresponding cyanoacetamide **6** through nucleophilic substitution step. Cyanoacetamide **6** reacted with salicylaldehyde in refluxing ethanol containing piperidine to give the chromene **7** (Scheme 4).



Scheme 4. Synthesis of chromene **7** and pyrrol-2-one **8**.

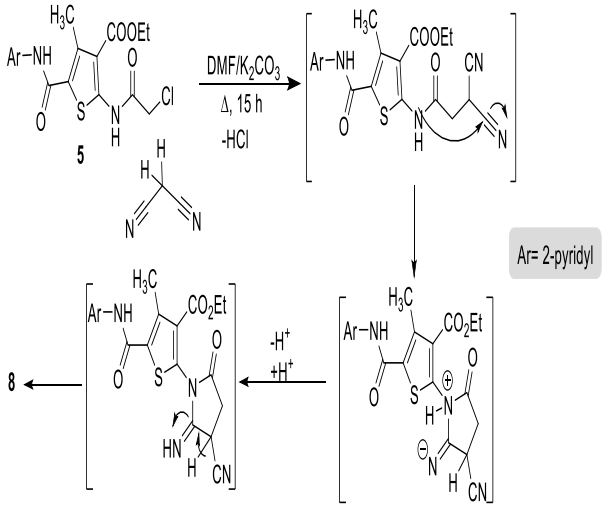
The mechanism for the formation of chromene **7** was projected as outlined in Scheme 5.



Scheme 5. The projected mechanistic route for the synthesis of chromene **7**.

α-Haloketones have been applied in a wide range in synthetic organic researches considering their high reactivity as intermediates in the preparation of various classes of heterocyclic systems [17]. chloroacetamide **5** reacted with malononitrile in refluxing DMF and potassium carbonate as a basic medium to give the respective pyrrol-2-one derivative **8** (Scheme 4). The mechanism

for the formation of pyrrol-2-one **8** was projected as outlined in Schemes 6.



Scheme 6. The estimated mechanistic route for the synthesis of pyrrol-2-one **8**.

3. Materials and Methods

Melting points (uncorrected) were achieved on Gallenkamp electric melting point apparatus in degree Celsius. The IR (υ cm^{-1}) (KBr) were achieved on a Mattson 5000 FTIR Spectrometer (USA). The ^{1}H-NMR spectra (DMSO-d_6/400 MHz) were recorded on a Bruker Avance III spectrophotometer. The mass spectra were recorded by EI mode with ionizing voltage 70 eV on Kratos MS (Kratos Analytical Instrument, Ramsey, NJ) apparatus. Carbon, hydrogen and nitrogen elemental analyses were run on Perkin-Elmer 2400 Instruments, Shelton, CT.

2-Amino-5-(pyridin-2-ylcarbamoyl) -4-methyl-thiophene-3-ethyl carboxylate (2)

A mixture of pyridine derivative **1** (8.90 g, 0.05 mol), ethyl cyanoacetate (5.65 g، 0.05 mol) and sulphur (1.60 g, 0.05 mol) catalyzed by morpholine (4.35 g, 0.05 mol) were heated in ethyl alcohol for 3 h. Cool the mixture at 25^{o}C and then diluted with water. The 2-aminothiophene that formed was picked up by filtration, then finally recrystallized by heating in ethyl alcohol. Grey needles; yield 62%; mp 212-214ºC. IR (KBr, cm^{-1}): 3407 (NH), 2984 (C-H, aliphatic), 3300-3230 (NH_2), 1681 (C=O of ester), 1662 (C=O, amidic), 1588 (C=C), 1626 (C=N). ^{1}H-NMR δ (ppm): 10.49 (s, 1H, NH), 7.74 (s, 2H, NH_2), 8.19-7.22 (m, 4H, Ar-H), 4.30 (q, 2H, ester, $\underline{CH_2}$-CH_3, *J* = 7.5 *Hz*), 2.64 (s, 3H, methyl), 1.33 (t, 3H, ester, CH_2-$\underline{CH_3}$, *J* = 7.5 *Hz*). MS: (*m/z*, %): 305.13 (M^+, 11.34). Elemental analyses for $C_{14}H_{15}N_3O_3S$ (305.35), calcd: C, 55.07; H, 4.94; N, 13.74%. Found: C, 55.09; H, 4.96; N, 13.73%.

Reaction of 2-aminothiophene 2 with aromatic aldehydes (General procedure)

2-Aminothiophene **2** (1.525 g, 0.005 mol), benzaldehyde and/or 4-methylbenzaldehyde (0.005 mol) and melted NaOAc (0.41 g, 0.005 mol) were fused at 155-160°C for 6 h. After fulfillment of the reaction using TLC, the crude was left to cool and the product was recrystallized from ethyl alcohol.

2-(Aminobenzylidene)-4-methyl-5-(pyridin-2-ylcarbamoyl)thiophene-3-ethyl carboxylate (3a)

Brown power; yield 44%; mp 182-184ºC. IR (KBr, cm^{-1}): 3355 (NH), 1678 (CO, ester), 1600 (C=N), 1588 (C=C), 1643 (CO, amidic). ^{1}H-NMR δ (ppm): 8.34 (s, 1H, CH=N), 10.81 (s, 1H, NH), 8.21-7.33 (m, 9H, Ar-H), 4.31 (q, 2H, ester, $\underline{CH_2}CH_3$, *J* = 7.5 *Hz*), 2.60 (s, 3H, CH_3), 1.22 (t, 3H, ester, CH_2-$\underline{CH_3}$, *J* = 7.5 *Hz*. MS: (*m/z*, %): 393.54 (M^+, 12.28). Elemental analyses for $C_{21}H_{19}N_3O_3S$ (393.46), calcd: C, 64.11; H, 4.87; N, 10.68%; Found: C, 64.22; H, 4.92; N, 10.74%.

Ethyl.4-methyl2((4methylbenzylidene)amino)-5-(pyridin-2-ylcarbamoyl)thiophene-3-carboxylate (3b)

Brown power; yield 51%; mp 166-168ºC. IR (KBr, cm^{-1}): 3300 (NH), 1668 (CO, ester), 1653 (CO, amidic), 1619 (C=N), 1589 (C=C). ^{1}H-NMR δ (ppm): 10.72 (s, 1H, NH), 8.28 (s, 1H, CH=N), 8.11-7.22 (m, 8H, Ar-H), 4.30 (q, 2H, CH_2-ester, *J* = 7.5 *Hz*), 2.62 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.25 (t, 3H, CH_3-ester, *J* = 7.5 *Hz*). MS: (*m/z*, %): 407.11 (M^+, 5.76). Elemental analyses for $C_{22}H_{21}N_3O_3S$ (407.49), calcd: C, 64.85; H, 5.19; N, 10.31%; Found: C, 64.90; H, 5.23; N, 10.36%.

Synthesis of thiazolidin-4-ones 4a and 4b (General procedur)

A solution of equimolar ratios of 2-mercaptoacetic acid (0.18 g, 0.002 mol) and Schiff bases **3a,b** (0.002 mol) in 20 mL pyridine was heated for 10 h. Pour onto ice-cold water after the mixture was cooled and the obtained thiazolidin-4-ones were filtered off and recrystallized from ethyl alcohol.

***Ethyl.2-(2-phenyl-3-thiazolidin-4one)4methyl-5-(pyridin-2-ylcarbamoyl)thiophene-3-carboxylate* (4a)**

Yellow power; yield 40%; mp 155-157ºC. IR (KBr, cm^{-1}): 3311 (NH), 1675 (CO, ester), 1653 (2 CO, amidic), 1619 (C=N), 1590 (C=C). ^{1}H-NMR δ (ppm): 10.43 (s, 1H, NH), 8.26-7.22 (m, 9H, Ar-H), 6.00 (s, 1H, CH), 4.31 (q, 2H, ester, $\underline{CH_2}$-CH_3), 3.57 (s, 2H, H5), 2.62 (s, 3H, methyl), 1.25 (t, 3H, ester, $CH_2\underline{CH_3}$). MS: (*m/z*, %): 467.09 (M^+, 9.21). Elemental analyses for $C_{23}H_{21}N_3O_4S_2$ (467.56), calcd: C, 59.08; H, 4.53; N, 8.99%; Found: C, 59.14; H, 4.58; N, 9.06%.

***Ethyl.2-(2-(ptolyl)thiazolidin4one)4methyl-5-(pyridin-2-ylcarbamoyl)thiophene-3-carboxylate* (4b)**

Yellow power; yield 45%; mp 190-192ºC. IR (KBr, cm^{-1}): 3288 (NH), 1680 (CO, ester), 1665 (2 CO, amidic), 1623 (C=N), 1611 (C=C). ^{1}H-NMR δ (ppm): 10.43 (s, 1H, NH), 8.26-7.22 (m, 8H, Ar-H), 4.31 (q, 2H, ester, $\underline{CH_2}$-CH_3), 5.80 (s, 1H, CH), 3.57 (s, 2H, H5), 2.62 (s, 3H, methyl), 2.11 (s, 3H, methyl), 1.24 (t, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 481.77 (M^+, 23.30). Elemental analyses for $C_{24}H_{23}N_3O_4S_2$ (481.59), calcd: C, 59.86; H, 4.81; N, 8.73%; Found: C, 59.90; H, 4.86; N, 8.80%.

***4-Methyl-5-(pyridin-2-ylcarbamoyl) 2-(2-chloroacetamido)-thiophene-3-ethyl carboxylate* (5)**

To a stirred cold solution of 2-aminothiophene **2** (0.611 g, 0.002 mol) and 1 mL of triethylamine, in 20 mL dioxane, 2-Chloroacetyl chloride (0.23 g, 0.002 mol) was added and then stirring was resumed for further 2h at 25°C. The 2-chloroacetamide derivative that formed was picked up by filtration and finally purified by boiling in DMF. Yellow needles; yield 72%; mp 235-237°C. IR (KBr, cm^{-1}): 3381, 3373 (2 NH), 2969 (C-H, aliphatic), 1705 (C=O, ester), 1670, 1601 (C=N), 1583 (C=C), 1656 (2 C=O, amidic). ^{1}H-NMR δ (ppm): 11.09 (s, 1H, NH), 10.81 (s, 1H, NH), 8.08-7.10 (m, 4H, Ar-H), 4.30 (q, 2H, CH_2-ester, *J* = 7.2 *Hz*), 4.25 (s, 2H, CH_2Cl), 2.68 (s, 3H, methyl), 1.35 (t, 3H, CH_3-ester, *J* = 7.2 *Hz*). MS: (*m/z*, %): 384.15 (M^++2, 12.72), 381.53 (M^+, 38.85). Elemental analyses for $C_{16}H_{16}ClN_3O_4S$ (381.83), calcd: C, 50.33; H, 4.22; N, 11.01%. Found: C, 50.30; H, 4.20; N, 11.04%.

***4.Methyl5(pyridin2ylcarbamoyl)2(2Cyanoacetamido)-thiophene-3-ethyl carboxylate* (6)**

A solution of 2-chloroacetamide **5** (1.91 g, 0.005 mol) and KCN (0.325 g, 0.005 mol) in 30 mL DMF was heated at 70 °C for 1 h. Pour onto cold water with continuous stirring. The precipitated cyanoacetamide was filtered off and recrystallized by heating in DMF.

Pale yellow power; yield 88%; mp 203-205°C. IR (KBr, cm^{-1}): 3359, 3346 (2 NH), 2213 (CN), 1694 (C=O, ester), 1600 (C=N), 1587 (C=C), 1670, 1664 (2 C=O, amidic). ^{1}H-NMR δ (ppm): 11.05 (s, 1H, NH), 10.62 (s, 1H, NH), 8.08-7.20 (m, 4H, Ar-H), 4.31 (q, 2H, ester, $\underline{CH_2}$-CH_3), 3.11 (s, 2H, CH_2-CN), 2.62 (s, 3H, methyl), 1.30 (t, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 372.16 (M^+, 27.00). Elemental analyses for $C_{17}H_{16}N_4O_4S$ (372.40), calcd: C, 54.83; H, 4.30; N, 15.00%; Found: C, 54.90; H, 4.37; N, 15.10%.

***4-Methyl-5-(pyridin-2-yl-carbamoyl)-2-(2-iminochromene-3-carboxamido) thiophene-3-ethyl carboxylate* (7)**

To an equimolar amounts of 2-cyanoacetamide **6** (1.11 g, 0.003 mol) and 2-hydroxybenzaldehyde (0.36 g, 0.003 mol) in 25 mL ethanol, five drop of piperidine was added and heated for 13 h. Left to stand overnight at 25°C and poured onto cold water. The obtained chromene was filtered and recrystallized by boiling in methanol. Pale yellow power; yield 88%; mp 203-205°C. IR (KBr, cm^{-1}): 3346, 3334 (2NH, amidic), 3155 (NH), 1709 (CO, ester), 1629 (C=N), 1585 (C=C), 1663, 1653 (2CO, amidic). ^{1}H-NMR δ (ppm): 11.05 (s, 1H, NH), 10.65 (s, 1H, NH), 9.54 (s, 1H, NH), 8.23 (s, 1H, CH=C), 8.03-7.10 (m, 8H, Ar-H), 4.31 (q, 2H, ester, $\underline{CH_2}$-CH_3), 2.64 (s, 3H, methyl), 1.30 (t, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 476.14 (M^+, 6.62). Elemental analyses for $C_{24}H_{20}N_4O_5S$ (476.51), calcd: C, 60.50; H, 4.23; N, 11.76%; Found: C, 60.55; H, 4.30; N, 11.80%.

***4-Methyl-5-(pyridin-2-yl-carbamoyl)2-(4-amino-5-cyano-2,3-dihydro-1H-pyrrol-2-one) thiophene-3-ethylcarboxylate* (8)**

To a mixture of 2-chloroacetamide **5** (1.143 g, 0.003 mol) and malononitrile (0.198 g, 0.003

mol) in 20 mL DMF, K_2CO_3 (0.69 g, 0.005 mol) was added and heated for 15 h, then left to cool. Pour onto cold water and the obtained pyrollone was filtered and recrystallized by heating in methyl alcohol. Yellow power; yield 42%; mp 178-280°C. IR (KBr, cm^{-1}): 3301 (NH), 3261-3200 (NH_2), 2201 (CN), 1688 (CO, ester), 1664 (2CO, amidic), 1620 (C=N), 1571 (C=C). ^{1}H-NMR δ (ppm): 10.43 (s, 1H, NH), 8.06-7.19 (m, 6H, Ar-H, NH_2), 4.31 (q, 2H, ester, CH_2-CH_3), 2.72 (s, 2H, H3), 2.62 (s, 3H, methyl), 1.22 (t, 3H, ester, CH_2-CH_3). MS: (*m/z*, %): 412.87 (M^+ +1, 32.10), 411.03 (M^+, 23.60). Elemental analyses for $C_{19}H_{17}N_5O_4S$ (411.44), calcd: C, 55.45; H, 4.14; N, 17.00%; Found: C, 55.52; H, 4.23; N, 17.13%.

In summary, the results of the current consideration mention that 2-aminothiophene **2** is a convenient synthon for the preparation of novel thiazolidin-4-one, chromen-2-imine and pyrrol-2-one derivatives *via* its reactions with the convenient chemical reagents.

4. References

1 Abbas, S. E.; Gawad, N. M. A.; George, R. F.; Akar, Y. A (2013). *Eur. J. Med. Chem.*, *65*, 195.

2 Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A. (2003) *Eur. J. Med. Chem.*, *38*, 851.

3 Bozorov, K.; Nie, L. F.; Zhao, J.; Aisa, H. A. (. 2017) *Eur. J. Med. Chem*, *140*, 465.

4 Ram, V. J.; Goel, A.; Shukla, P. K.; Kapil, A. Bioorg. (1997),Med. Chem. Lett. *7*, 3101.

5 Ozcan, B.; Esen, M.; Caliskan, M.; Mothana, R. A.; Cihan, A. C.; Yolcu, H. Eur. Rev. (2011),Med. Pharmacol. Sci. *15*, 900.

6 Abdou, M. M. Am. (2013) *J. Chem*., *3*, 126.

7 Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. Org. Lett. (1999) , *1*, 197.

8 Mabkhot, Y. N.; Kaal, N. A.; Alterary, S.; Mubarak, M. S.; Alsayari, A.; Muhsinah, A. B. (2019), *J. Heterocyclic Chem.* DOI 10.1002/jhet.3688.

9 Musayeib, N. M.; Mothana, R. A.; Gamal, A. A.; AlMassarani, S. M.; Maes, L. (2013) Molecules, *18*, 9207.

10 Mothana, R. A. (2012) ,Records Natural Prod. *6*, 189.

11 Mabkhot, Y. N.; Alatibi, F.; El-Sayed, N. N. E.; Al-Showiman, S. S.; Kheder, N. A.; Ghabbour, H. A(2017). *J. Mol. Structure*, *1149*, 736.

12 Deng, L.; Zhang, Q.; Zhao, L.; Lu, Y. (2018), *Eur. Polymer J. 109*, 72.

13 Sherif, Y. E.; Hosny, N. M. (2014), *Eur. J. Med. Chem. 83*, 338.

14 Kajal, A.; Bala, S.; Kamboj, S.; Sharma, N.; Saini, V2013. *J. Catal.*, 2013, 1.

15 Fadda, A. A.; Bondock, S.; Rabie, R.; Etman, H. A. Turk (2008),. *J. Chem*. *32*, 259.

16 Ghate, M.; Kusanur, R. A.; Kulkarni, M. V.(2005) *Eur. J. Med. Chem.*, *40*, 882.

17 Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules* (2003), *8*, 793