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Heterocyclization of polarized system: synthesis, antioxidant and anti-inflammatory 4-(pyridin-3-yl)-6-(thiophen-2-yl) pyrimidine-2-thiol derivatives

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Abstract

Background: Chalcones are intent in the daily diet as a favorable chemotherapeutic compound; on the other hand thiophene moiety is present in a large number of bioactive molecules having diverse biological efficiency.

Results: Our current goal is the synthesis of (*E*)-1-(pyridin-3-yl)-3-(thiophen-2-yl) prop-2-en-1-one **3** that's used as a starting compound to synthesize the novel pyrimidine-2-thiol, pyrazole, pyran derivatives. Chalcones **3** was prepared by condensation of 3-acetylpyridine with thiophene 2-carboxaldehyde which reacted with thiourea to obtain pyrimidinthiol derivative **4**. Compound **4** was allowed to react with hydrazine hydrate to afford 2-hydrazinylpyrimidine derivative **5**. Compound **5** was used as a key intermediate for a facile synthesis of the targets **6** and **7**. In contrast, pyranone **8** was obtained by transformation of compound **5**. Using as a precursor for the synthesis of new pyrazolo pyrimidine derivatives **9**–**10**. The major incentive behind the preparation of these compounds was the immense biological activities associated to these heterocyclic derivatives.

Conclusions: The newly synthesized compounds (**1**–**4**) showed potent anti-inflammatory activities both in vitro and in vivo. They also exhibited promising antioxidant vitalities against α, α-diphenyl-β-picrylhydrazyl scavenging activity and lipid peroxidation. In conclusion, compound **1** showed a hopefully anti-inflammatory and antioxidant activities.

Keywords: Pyrazolopyrimidine, Thiophene, Chalcone, Pyrazol, Pyranone, Anti-inflammatory-antioxidant-cycloxygenase-5-LOX-DPPH

Introduction

Chalcones are distinguished by their easy synthesis from Claisen-Schmidt condensation. The chemical structure of chalcones formed of two aromatic rings joined by a thee carbon, α, *β*-unsaturated carbonyl system (1, 3-diphenyl-prop-2-en-1-one) [1, 2]. They have been authenticated with diverse biological efficiency including antibacterial [3–8], anti-inflammatory [9–12], antioxidant [13–16], anti-tumor effects [17–22]. Also, pyridine derivatives of different heterocyclic nucleus have shown potent pharmacological properties like cytotoxic activity [23, 24]. Recent studies have demonstrated that chalcones are target in the daily diet as a favorable chemotherapeutic compounds [25] and anti-proliferative activity [26]. On the other hand thiophene moiety is present in a large number of bioactive molecules having diverse biological activities such as anti-inflammatory [27], anticonvulsant [26], antimicrobial [27] and antitumor [28]. Moreover, thiophene moiety is a well-known isostere for benzene; for example, the replacement of benzene ring of the antidepressant drug, Viloxazine led to a prolongation of the half-life [29]. Recently we were concerned with the synthesis of polyfunctional heterocyclic compounds, where the (*E*)-1-(pyridin-3-yl)-3-(thiophen-2-yl) prop-2-en-1-one **3** was used as a starting compound. The remarkable

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biological activity of the polycyclic heterocyclic compounds encouraged us to continue our previous work on the synthesis of fused pyrimidine [30–33] and their applications, by designing a polycyclic heterocyclic compounds containing five and/or six rings fused with each other to develop a superior biological activity.

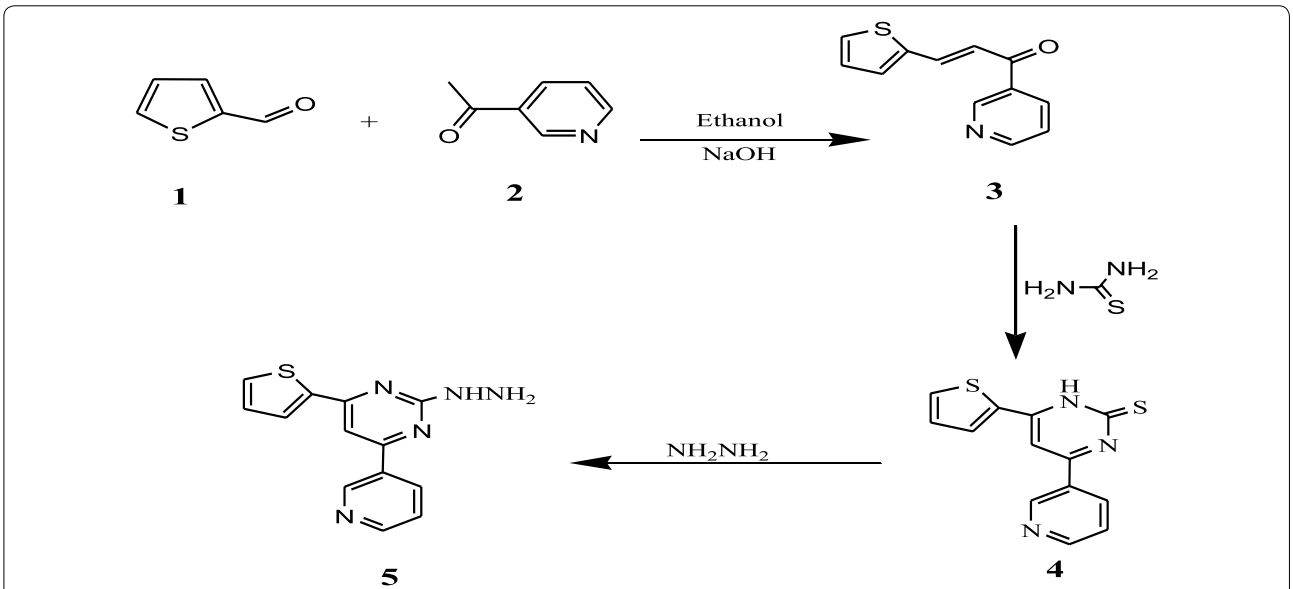
Results and discussion

Chemistry

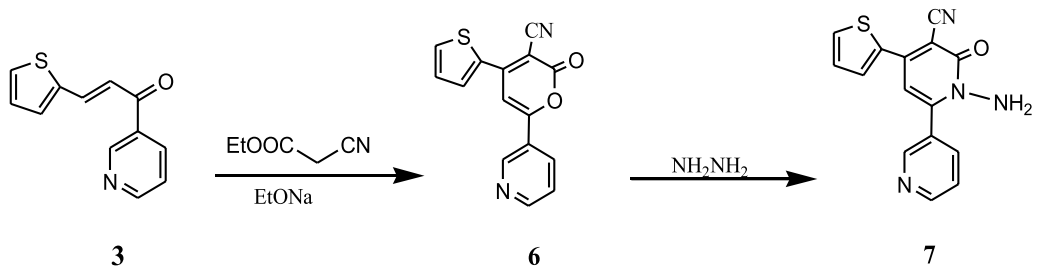
Aldol condensation reaction of 3-thiophenecarboxaldehyde **1** with 3-acetylpyridine **2** in ethanolic NaOH solution afforded chalcone **3**. The structure of compound **3** was elucidated by its IR, ^{1}H NMR and ^{13}C NMR. Its IR spectrum showed a characteristic peak for a conjugated carbonyl group at 1633 cm^{-1}, and by its ^{1}H NMR which gave signals at δ 7.53 (d, 1H, J = 12.9 Hz, (CH=C–C=O), and 7.92 (d, 1H, J = 12.9 Hz (CH=C–C=O) and two doublet signals at δ = 7.28 and 7.94 due to thiophenyl-C_4H and thiophenyl-C_3H and another at 8.11 owing to thiophenyl-C_5H whereas, the ^{13}C NMR spectrum showed a signal at (δ in ppm) 123 caused by ethylene group and 125, 126, 135, 149 and a signal due to C=O groups at 193. [3 + 3] base induced cycloaddition of chalcone **3** with thiourea gave 4-(pyridin-3-yl)-6-(thiophen-2-yl) pyrimidine-2(1H)-thione **4**. IR spectra of compounds **4** showed the presence of a C=S band at 1270 cm^{-1} and an absorption band in the range 3433–3490 cm^{-1} attributed to the amine (NH). The ^{1}H NMR spectrum of compound **4** two doublet signals at δ = 7.28 and 7.94 due to thiophenyl-C_4H and thiophenyl-C_3H and another at 8.11 as a result of thiophenyl-C_5H. The spectra displayed a singlet at 8.82 for NH, respectively. The hydrazinopyrimidine derivative **5** was synthesized by condensation of the thiopyrimidinone **4** with hydrazine hydrate in refluxing alcohol, the structure of compound **5** was confirmed by the IR, ^{1}H NMR and elemental analysis, where its IR revealed the absorption bands at ν max = 3212 for the NH_2 and 3184 cm^{-1} for the NH group, ^{1}H NMR spectrum gave the signals at δ = 8.93–8.95 as a broad singlet for NH_2, hydrazine NH, respectively (Scheme 1).

Cyclocondensation of chalcone **3** and ethyl cyanoacetate in the presence of sodium ethoxide under the reflux conditions [33] gave pyranone derivative **6**. Condensation with hydrazinehydrate [34, 35] in refluxing ethanol leads to ring transformation producing corresponding pyridinones **7**. The structure of the target **7** was confirmed from its spectral data, where is IR spectra showed absorption bands in the region 2222 and 1688 cm^{-1} characteristic for C≡N and carbonyl group, respectively (Scheme 2).

The hydrazinopyrimidine derivative **5** was used as a precursor for the synthesis of some heterocyclic compounds. The hydrazinopyrimidine derivative **5** reacted with ethyl acetoacetate in excess manner to afford compound **8**. The formation of **8** may be proceeds via the formation of pyrazolone derivative **9** followed by the attack of methylene anion of pyrazolone to ketonic function of ethyl acetoacetate followed by pyran cyclization. IR spectrum of compound **8** revealed the absorption peaks at 1715 cm^{-1} characteristic of C=O groups respectively, ^{1}H NMR exhibited the two singlets at δ = 2.25 and 2.32 for 2 CH_3 protons and a singlet at δ = 5.60 ppm for pyranone H. Furthermore, the pyrimidine pyrazolone compound

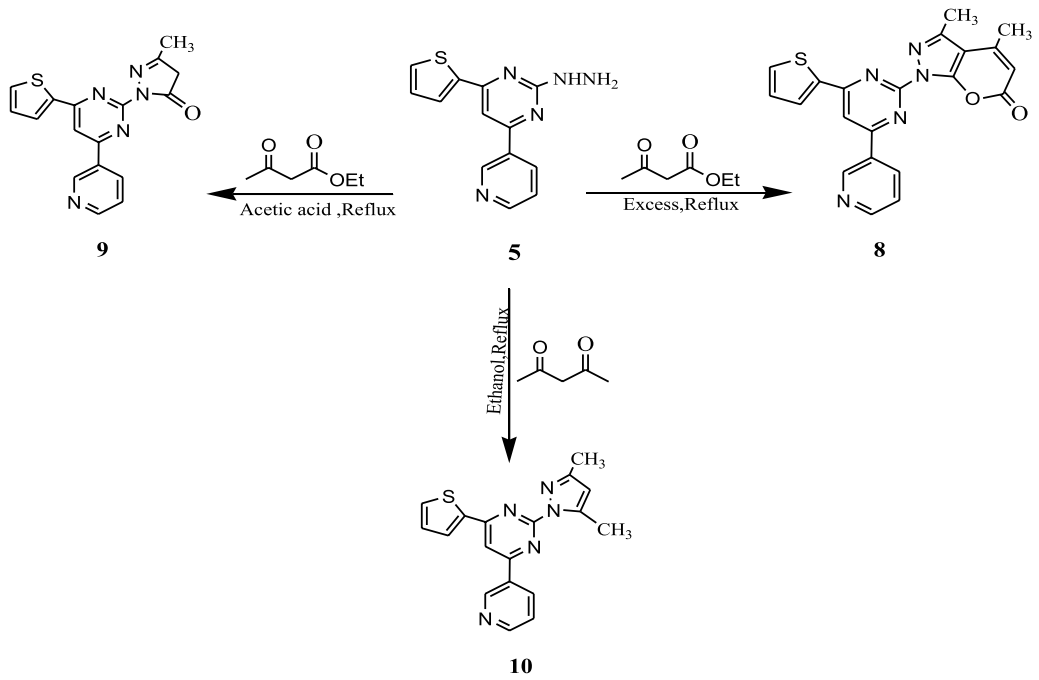


Scheme 1 Synthesis of pyrimidine derivatives



3 **6** **7**

Scheme 2 Synthesis of pyranone and pyridinones derivatives



9 **5** **8**

10

Scheme 3 Synthesis of isolated and fused pyrimidine derivatives

9 was obtained as a result of attack of hydrazinofunction of **5** to ethyl acetoacetate. The pyrazolo pyrimidine **10** was synthesized by heating an alcoholic solution of compound **5** (10.0 mmol.) with acetylacetone (10.0 mmol.) at reflux temperature for 5 h. The IR spectra of **9** and **10** showed the disappearance of the hydrazine group where the ^{1}H NMR spectrum showed singlet pyrimidine H at $\delta = 8.95$ ppm and two singlets for the two CH_3 protons, respectively (Scheme 3).

Biological activity studies

In vitro anti-inflammatory activity

In vitro COX-1 and COX-2 inhibition Compounds (**3**–**6**) were calorimetrically evaluated for their anti-inflammatory activities in vitro for COX-1 and COX-2 at 590 nm using ovine COX-1/COX-2 inhibitor screening assay kit [36]. Celecoxib was used as a standard reference drug.

In vitro 5-LOX inhibition A bnova 5 lipoxygenase inhibitor screening assay was used [37]. Meclofenamate sodium was used as a standard reference drug. Results were expressed in Table 1 as IC $_{50}$ as means of thee determinations the selectivity index was calculated also as IC_{50} (COX-1)/IC_{50} (COX-2).

In vivo anti- inflammatory activity

Carrageenan induced rat paw edema in rats: Fifty rats were divided into ten groups (i.e., each group, five rats). The first group (control), received carboxymethyl cellulose. The second group was given diclofenac sodium as a standard anti-inflammatory drug. Groups (3–10) were

Table 1 Display the anti-inflammatory activity of the newly synthesized compounds as IC $_{50}$, μM for COX-1, COX-2 and 5-LOX

Group	IC $_{50}$ (μM) COX-1	IC $_{50}$ (μM) COX-2	COX-1/COX-2	IC 50 (μM) 5 LOX
Celecoxib	5.47	0.86	7.91	N.D
Meclofenamate sodium	ND	ND	ND	6.15
Compound **3**	3.7	0.39	9.49	4.71
Compound **4**	4.02	0.44	9.13	4.91
Compound **5**	4.60	0.87	5.29	6.98
Compound **6**	4.95	0.84	5.89	7.65

orally given the newly synthesized compounds (**3**–**6**) in two dosages (5 and 10 mg/kg). Results were expressed as rat paw edema percent. One hour later after administration of tested doses, carrageenan was injected sub planter in the left hind footpad of each rat as 0.05 ml of 1% solution in sterile distilled water. Plethysmometer was used to measure paw edema volume from 0 to 4 h after carrageenan injection. Paw edema volume was compared with vehicle control group and reduction percent was calculated as the following

$$\% \text{ reduction in edema} = (1 - \text{Vt Vc}) \times 100$$

Where Vt and Vc are the edema volume in the group treated with drug and control, respectively [38]. Results were expressed as mean ± standard deviation (SD). Differences between means were tested for significance using a one-way analysis of variance (ANOVA) followed by Duncan's test (Table 2).

Antioxidant screening

a. DPPH free radical scavenging assay was determined (4). Results were presented in Table 3 as IC $_{50}$ (μg/ml). Ascorbic acid was used as reference standard antioxidant.
b. Lipid peroxidation assay (**5** and **6**) was calculated as IC_{50} and recorded in Table 3.

The newly synthesized compounds exhibited a remarkable in vivo and in vitro anti-inflammatory activity. These results are in agreement with those obtained by other researchers [39]. They reported that some novel pyrimidine-pyridine hybrids inhibited cyclooxygenase enzyme and had a significant anti-inflammatory activity comparable to celecoxib as a standard drug. In this concern, other authors [40] reported an investigation of the efficacy of pyridine and pyrimidine analog of acetaminophen as peroxyl radical trapping antioxidants and inhibitors of enzyme catalyzed lipid peroxidation by cyclooxygenase and lipoxygenase. Compounds **3** and **4** exhibited antioxidant activity screening higher scavenging activity towards the DPPH radicals than that of ascorbic acid. Similar results were reported for new pyridine and triazolopyridine derivatives [41–45].

Table 2 Inhibition percent of rat paw edema after administration of newly synthesized compounds

Groups	0 h	1 h	2 h	3 h	4 h
Diclofenac sodium	0.49 ± 0.032^{a}	30.22 ± 1.27^{a}	33.85 ± 1.19^{a}	36.21 ± 0.93^{a}	41.10 ± 3.98^{a}
Compound **3** 5 mg/kg.b.wt	0.48 ± 0.027^{ab}	21.72 ± 0.79^{b}	22.79 ± 1.07^{d}	24.79 ± 0.49^{c}	28.41 ± 1.30^{c}
Compound **3** 10 mg/kg.b.wt	0.47 ± 0.04^{ab}	31.98 ± 9.35^{a}	29.93 ± 1.43^{b}	34.16 ± 0.61^{b}	41.15 ± 0.750^{a}
Compound **4** 5 mg/kg.b.wt	0.46 ± 0.03^{b}	18.91 ± 1.19^{bc}	20.07 ± 1.43^{e}	21.96 ± 1.25^{d}	27.38 ± 1.68^{c}
Compound **4** 10 mg/kg.b.wt	0.49 ± 0.01^{ab}	21.43 ± 0.96^{b}	26.27 ± 49^{e}	33.13 ± 2.64^{b}	37.15 ± 0.69^{b}
Compound **5** 5 mg/kg.b.wt	0.49 ± 0.01^{a}	11.62 ± 1.24^{de}	14.61 ± 1.81^{g}	18.41 ± 1^{e}	19.48 ± 0.89^{e}
Compound **5** 10 mg/kg.b.wt	0.48 ± 0.01^{ab}	15.41 ± 0.83^{cd}	18.83 ± 0.75^{ef}	24.19 ± 1.59^{c}	28.59 ± 2.26^{c}
Compound **6** 5 mg/kg.b.wt	0.50 ± 0.02^{a}	9.61 ± 1.12^{e}	12.28 ± 1.38^{h}	17.19 ± 1.26^{e}	18.51 ± 2.26^{e}
Compound **6** 10 mg/kg.b.wt	0.49 ± 0.01^{a}	13.75 ± 1.15^{de}	17.52 ± 1.13^{f}	20.43 ± 0.65^{d}	22.39 ± 1.16^{d}

Values are expressed as mean ± SD

Different superscript letters are significantly different at $P \leq 0.05$

Table 3 Showing antioxidant activities of the newly synthesized compounds

Groups	IC_{50} (μg/ml) for DPPH Scavenging	IC_{50} (μg/ml) for anti-lipid peroxidation
Compound **3**	10.72 ± 0.54	16.81 ± 2.71
Compound **4**	12.64 ± 0.41	22.53 ± 3.25
Compound **5**	14.61 ± 0.72	23.62 ± 2.31
Compound **6**	15.26 ± 0.44	22.67 ± 3.51
Ascorbic acid	13.71 ± 0.75	25.72 ± 1.23

Experimental

Chemistry

Melting points were measured using an Electrothermal IA 9100 equipment with open capillary tube and were kept uncorrected. All experiments were done using dry solvents. TLC was performed on Merck Silica Gel 60F254 with detection by way of UV Light. The formed compound has been purified using recrystallization. The IR spectra (KBr disc) were recorded using Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were measured by means of JEOL-JNM-LA 400 MHz spectrometer using DMSO-d_6 as a solvent. All chemical shifts had been expressed on the δ (ppm) scale using TMS as an internal well-known reference. The coupling constant (*J*) values are given in Hz. Analytical information was acquired from the Microanalysis center at Cairo University, Giza, Egypt.

(E)-1-(pyridin-3-yl)-3-(thiophen-2-yl) prop-2-en-1-one (3)

To a stirred mixture of thiophene-2-carbaldehyde **1** (100 mmol) and 3-acetylpyridine **2** (100 mmol) in 200 ml ethanol at room temperature, 40% NaOH aqueous solution was added portion-wise while stirring 2 h. The pale yellow precipitate formed was filtered and washed using 4% aqueous HCl, and crystallized from ethanol to give chalcone **3** in 82% yield, mp 256–258 °C. IR (KBr) cm^{-1}: 3336, 3255, 1678, 1645; ^{1}H NMR (300 MHz, DMSO-d6): 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.53 (d, 1H, *J* = 12.9 Hz, (C=O)(CH=C), 7.92 (d, 1H, *J* = 12.9 Hz (C=O) (C=CH), δ = 7.28(d, 1H, *J* = 3.6 Hz, thienyl-*C*$_3$′*H*), 7.94 (dd, 1H, thienyl-*C*$_4$′*H*), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-*C*$_5$′*H*).^{13}C NMR (DMSO-d_6, 150 MHz): δ = 200.18 (C1=O);153.3 (C4′-pyridine); 149.2 (C2′-pyridine); 147.4 (C3); 135.2 (C4′′); 134.9 (C6′-pyridine); 133.2 (C′′-pyridine); 132.8 (C2′′); 127.1(C2); 126.8 (C5′-pyridine);125.4 (C3′′);123.6(C1′′). Anal. Calcd for $C_{12}H_9NOS$ (215.27): C, 66.95; H, 4.21; N, 6.51; S, 14.90; Found C, 66.89; H, 4.19; N, 6.50; S, 14.79%.

4-(pyridin-3-yl)-6-(thiophen-2-yl) pyrimidine-2(1H)-thione (4)

Chalcone **3** (10 mmol) was added to sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and 50 ml of absolute ethanol] then thiourea (10 mmol) was added. The reaction mixture was refluxed for 16 h., left to cool and poured into crushed ice and neutralized with diluted hydrochloric acid, filtration, washed with ethanol and dried. Crystallization from EtOH afforded the pyrimidine derivatives **4**. Yellow powder, yield 74%, mp 220–225 °C; IR (KBr): 3433 (NH), 1270 (C=S) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-*C*$_3$′*H*), 7.94 (dd, 1H, thienyl-*C*$_4$′*H*), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-*C*$_5$′*H*), 8.82 (s, D_2O-exchangeable, 1H, pyrimidin NH). ^{13}CNMR (DMSO-d_6, 100 MHz) δ: 110.2, 123.9, 127.1, 128.2, 130.5, 136.6, 137.2, 151.5, 152.0, 157.164.6, 180.4. Anal. Calcd for $C_{13}H_9N_3S_2$ (271.36): C, 57.54; H, 3.34; N, 15.48; S, 23.63; Found: C, 57.49; H, 3.32; N, 15.49; S, 23.59%.

1-(4-(pyridin-3-yl)-6-(thiophen-2-yl)pyrimidin-2-yl)hydrazine (5)

The reaction of thiopyrimidinone **4** (10.0 mmol) with hydrazine hydrate (10.0 mmol) catalyzed by acetic acid (5 drops) in refluxing ethanol for 6 h. Evaporation of alcohol and recrystallization with ethanol gave compound **5** as pale brown crystals mp 180–182 °C, yield 85%. IR: νmax/cm^{-1}: 3212 (NH_2), 3184 (NH). ^{1}H NMR (DMSO-d_6): δ = 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), δ = 7.28(d, 1H, *J* = 3.6 Hz, thienyl-*C*$_3$′*H*), 7.53 (dd, 1H, thienyl-*C*$_4$′*H*), 7.89 (d, 1H, *J* = 5.2 Hz, thienyl-*C*$_5$′*H*) 0.7.94 (s, 1H, pyrimidin), 8.93–8.95 (brs, 3H, D_2O Exch., NH_2, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 98.4, 123.9, 127.1, 128.2, 130.5, 134.1, 137.2, 151.5, 152.0, 148.0, 149.1, 155.8, 157, 161.1. Anal.Calcd. For $C_{13}H_{11}N_5S$ (269.32): C, 57.97; H, 4.12; N, 26.00; S, 11.91; Found: C, 57.96; H, 4.09; N, 26.03%.

2-oxo-6-(pyridin-3-yl)-4-(thiophen-2-yl)-2H-pyran-3-carbonitrile (6)

To a stirred solution of chalcone **3** (10 mmol) and ethyl cyanoacetate (10 mmol) in 50 ml absolute ethanol, a sodium ethoxide solution prepared from 0.23 g sodium metal (10 mmol) and 10 ml absolute ethanol was added refluxing the reaction mixture for 8 h. The solid that formed after cooling was collected by filtration, washed with water, dried and finally crystallized from ethanol to afford compound **6** as pale yellow crystals in 72% yield, mp 210–212 °C; IR (KBr): 2222 (C≡N), 1688 (C=O)

cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ = 7.32 (s, 1H, C5), 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-$C_3'H$), 7.94 (dd, 1H, thienyl-$C_4'H$), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-$C_5'H$). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 98.8, 113.3, 115.9, 123.8, 127.1, 128.2, 130.5, 137.7, 136.6, 149.6, 157.4, 173.4. Anal. Calcd for $C_{15}H_8N_2O_2S$ (280.3): C, 64.27; H, 2.88; N, 9.99; S, 11.44; Found: C, 64.25; H, 2.84; N, 9.96; S, 11.42%.

1-amino-6-oxo-4-(thiophen-2-yl)-1,6-dihydro-[2,3′-bipyridine]-5-cabonitrile (7)

To a solution of the pyranone **6** (2 mmol) in 30 ml of ethanol, hydrazine hydrate (2 mmol) was added. The mixture was refluxed for 6 h. Left to cool, the formed solid product was filtered off, dried, and then crystallized from ethanol to give compounds **7**. Yellow powder, yield 70%, mp 250–252 °C; IR (KBr): 3320, 3190 (NH_2, NH), 2219 (C≡N), 1670 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.51(s, D_2O-exchangeable, 2H, NH_2), 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-$C_3'H$), 7.94 (dd, 1H, thienyl-$C_4'H$), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-$C_5'H$). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 110.8, 115.9, 121.3, 123.8, 127.1, 128.2, 130.5, 131.6, 136.8, 149.6, 150.0, 160.5, 169.4. Anal. Calcd for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04; S, 10.89; Found: C, 61.20; H, 3.40; N, 19.09; S, 10.90%.

3,4-dimethyl-1-(4-(pyridin-3-yl)-6-(thiophen-2-yl)pyrimidin-2-yl)pyrano[2,3-c]pyrazol-6(1H)-one (8)

Compound **5** (10 mmol) and ethyl acetoacetate in excess (30 ml) was heated at reflux temperature for 6 h. The mixture was poured into ice cold water and the obtained product washed with water, dried and recrystallized from ethanol to give pale brown crystals of the pyrazolone compound **8** mp 190–192 °C, yield 80% IR: νmax/cm^{-1} 3367 (NH), 1715 (C=O). ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.60 (s, 1H, pyranone), 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-$C_3'H$), 7.94 (dd, 1H, thienyl-$C_4'H$), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-$C_5'H$). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 11.9, 21.2, 101.5, 105, 118.5, 124.0, 125.5, 127.9, 33.1, 134.1, 141.7, 148.0, 149.1, 152.8, 155.6, 159.0, 160.9, 161.0. Anal. Calcd. For $C_{21}H_{15}N_5O_2S$ (401.44): C, 62.83; H, 3.77; N, 17.45; S, 7.99; Found: C, 62.79; H, 3.79; N, 17.47; S, 7.95%.

3-methyl-1-(4-(pyridin-3-yl)-6-(thiophen-2-yl) pyrimidin-2-yl)-1H-pyrazol-5(4H)-one (9)

Compound **5** (10 mmol) and ethyl acetoacetate (10 mmol) in acetic acid (30 ml) was heated at reflux temperature for 6 h. The mixture was poured into ice cold water and the obtained product washed with ice cold water, dried and recrystallized from ethanol to afford pale brown crystals of **9** mp 225–227 °C, yield 76% IR: νmax/cm^{-1}: 3216 (NH), 1718 (C=O). ^{1}H NMR (DMSO-d6): δ 1.20 (s, 3H, CH_3), 2.25 (s, 2H, CH_2, pyrazol), 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-$C_3'H$), 7.94 (dd, 1H, thienyl-$C_4'H$), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-$C_5'H$), 8.90 (s, 1H, pyrimidin).^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 24.6, 42.4, 99.9, 124.0, 125.5, 127.6, 133.1, 134.1, 140, 148.0, 149.1, 156.1, 160.2, 163.1, 159.5, 172.8. Anal. Calcd. For $C_{17}H_{13}N_5OS$ (335.38): C, 60.88; H, 3.91; N, 20.88; S, 9.56; Found: C, 60.90; H, 3.90; N, 20.86; S, 9.55%.

2-(3,5-dimethyl-1H-pyrazol-1-yl)-4-(pyridin-3-yl)-6-(thiophen-2-yl)pyrimidine (10)

A solution of compound **5** (10 mmol) in absolute ethanol and acetylacetone (10 mmol) was heated at reflux temperature for 5 h. the obtained product was recrystallized from ethanol to afford pale brown crystals of pyrazolo pyrimidine derivative **10**. mp 190–188 °C, yield 70% IR: νmax/cm^{-1} 3170 (NH), 1600 (C=N), 1574 (C=N). ^{1}H NMR (DMSO-d6): δ 2.3 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.99 (s, 1*H*, pyrazole), 6.93–6.96 (t, 1H, H5′-pyridine), 7.47–7.51 (dd, 1*H*, *H*3′-pyridine), 7.30–7.327(t, 1H, H4′-pyridine), 7.28(d, 1H, *J* = 3.6 Hz, thienyl-$C_3'H$), 7.94 (dd, 1H, thienyl-$C_4'H$), 8.11 (d, 1H, *J* = 5.2 Hz, thienyl-$C_5'H$), 8.94 (s, 1H, pyrimidine).^{13}C-NMR (DMSO-d6, 100 MHz) δ: 11.1, 18, 105, 125.5, 127.6, 133.1, 140, 144.3, 148.0, 149.1, 155.6, 159.0, 161.0. Anal. Calcd. For $C_{18}H_{15}N_5S$ (333.41): C, 64.84; H, 4.53; N, 21.01; S, 9.62; Found: C, 64.80; H, 4.52; N, 21.02, S, 9.60%.

Conclusions

We have reported the synthesis of (E)-1-(pyridin-3-yl)-3-(thiophen-2-yl) prop-2-en-1-one **3** and using to designing a polycyclic heterocyclic compounds containing five and/or six rings fused. Moreover, we concluded that compounds **3** and **4** showed a significant antioxidant activity regarding cyclooxygenase inhibitory activity, compound 3 presented the highest inhibitory activity in comparison to the standard reference drug [IC_{50} as 3.7 and 0.39 μM for COX-1 and COX-2, respectively compared to 5.47 and 0.86 for the standard celecoxib]. Compound **4** also

showed a potent inhibitory activity for COX-2 with IC_{50} 0.44. Compounds **5** and **6** showed inhibitory activity against COX-1 and COX-2 nearly like that of the standard drug. Compound 3 showed the highest inhibitory potential for 5-lipoxygenase with IC_{50} (4.71 μM) compared to (6.15 μM) of the standard anti-inflammatory drug meclofenamate sodium.

Abbreviations
EtOH: ethanol; NMR: nuclear magnetic resonance; IR: infrared radiation; DMSO: dimethyl sulfoxide; COX-1: cyclooxygenase-I; COX-2: cyclooxygenase-II; 5-LOX: 5-lipoxygenase; DPPH: 2, 2-diphenyl-1-picrylhydrazil.

Authors' contributions
WSS carried the literature and designed synthetic schemes (synthesis and purification). SMM contributed to study of anti-inflammatory activities both in vitro and in vivo and Antioxidant vitalities against α, α-diphenyl-β-picrylhydrazyl (DPPH) scavenging activity and lipid peroxidation. MHA records the ^{13}CNMR of all compounds. All authors read and approved the final manuscript.

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