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Note

Synthesis and characterization of some 2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4*H*-chromon-4-ones, 4-(2-hydroxyphenyl)-6-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)pyrimidine-2-(1*H*)-thione, 2-(5-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenol and 2-(2,3-dihydro-2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-benzo[*b*][1,4]thiazepin-4-yl)-phenol

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Oxidative cyclization of **1** with DMSO-I_2 yields 2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4*H*-chromon-4-one **2**. Compound **2** reacts with thiourea in the presence of potassium hydroxide to form 4(2-hydroxyphenyl)-6-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)pyrimidine-2-(1*H*)-thione **3**. Compound **2** is refluxed in ethanol with hydrazine hydrate and KOH to afford 2-(5-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenol **4**. Compound **1** when treated with 2-amino thiophenol affords 2-(2,3-dihydro-2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-benzo[b][1,4]thiazepin-4-yl)-phenol **5**.

Keywords: Thianyl pyrazoles, pyrazolyl chromones, pyrazolyl thiazepins and pyrazolyl pyrimidines

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The chemistry of chromones and its derivatives have been studied for over a century or more due to important biological activities[1]. Activities associated with this nucleus are antimicrobial[2], agrochemical fungicides[3] etc. Some chromones are also used as beta agonist in asthma[4]. Chromones with heterocyclic nucleus at 2- or 3- position are found to be associated with promising antibacterial and antifungal properties[5].

Pyrazoles are important class of heterocyclic compounds which are associated with important applications[6,7]. Like other heterocyclic compounds, pyrazoles also exhibit wide range of biological activities. The activities associated with this nucleus are antihyperglycemic[8], antibacterial[9], fungicidal[10], anticancer[11] and antiviral[12].

The chemistry of pyrimidines and its derivatives have been studied since past century due to their close pharmacological association with diverse pharmacological properties. Pyrimidines are associated with analgesic and anti-inflammatory activities[13]. Some thiopyrimidines have been reported to possess antiviral activities[14]. Some thiopyrimidine derivatives have shown anti-HIV activities[15].

1,4-Benzothiazepine derivatives are of considerable interest because of their biological activities as inhibitors of HIV-1 integrase, anti-tumor, antibiotics, enzyme inhibitors, muscle relaxant, anticonvulsant, sedatives and hypnotics[16]. Some dihydro benzothiazepines have excellent fungicidal activities[17]. Benzothiazepines are also associated with chemotherapeutic application such as antihypertension[18] and antibacterial activities[19]. Benzothiazepines have been reported as potent neuroleptic agents[20].

The various physiological and biological activities associated with chromone, pyrazole, thiopyrimidine, thiophene and 1,4-benzothiazepine nucleus prompted the synthesis of pyrazolyl substituted chromones, thiopyrimidines, 1,4-benzothiazepines, pyrazoles with thiophene moiety.

Results and Discussion

In the present work chalcones **1** were treated with I_2 / DMSO to afford corresponding 2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4*H*-chromon-4-one **2**. Formation of compounds **2** has been confirmed by IR, NMR and mass spectra. In IR, the peak at 3340 cm^{-1} disappears which is a significant peak in chalcones **1**. Compounds **2** shows another significant peak around 1645 cm^{-1}, which is characteristic of carbonyl group of chromones. NMR of compounds **2** shows signals at around δ 6.7 due to C_3-H. Formations of chromones were also confirmed by disappearance of signal due to –OH in chalcones, which appeared around δ 12 in **1**. Formation of **2** was also confirmed by mass spectra. The compound **2b** showed significant peaks in its mass spectrum as shown in **Figure A**.

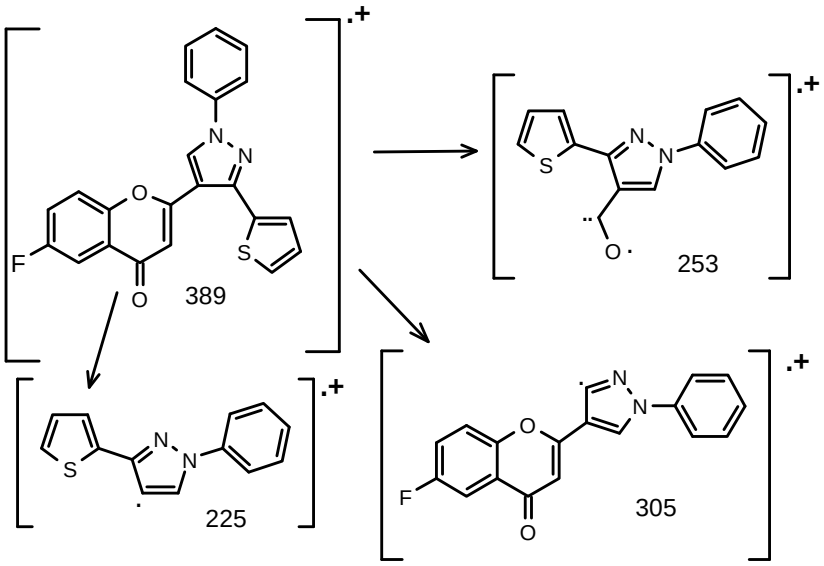


Figure A

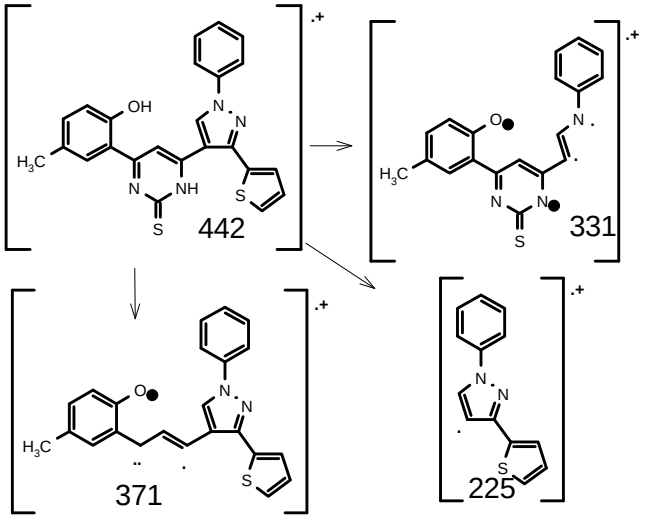


Figure B

Compounds **2** were then reacted with thiourea in the presence of KOH which resulted in 4-(2-hydroxyphenyl)-6-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)pyrimidine-2-(1*H*)-thione **3**. Formation of compounds **3** has been confirmed by IR, NMR and mass spectroscopy.

IR of compounds **3** shows band at around 3436 and 3117 cm^{-1} due to –OH and –NH, these bands are absent in compounds **2**, also the band at 1650 cm^{-1} gets disappeared indicates absence of >C=O group and new band appeared at 1268 cm^{-1} due to >C=S. NMR of compounds **3** shows all signals in between δ 7.0 to 9.5, the bands at 6.5 δ disappeared. Formation of compounds **2** is also confirmed by mass spectra of **3h**. The compound **3h** showed following significant peaks in its mass spectrum as shown in **Figure B.**

Compounds **2** were then refluxed in ethanol with hydrazine hydrate and KOH to afford 2-(5-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3yl)-phenol **4**. Formation of compounds **4** has been confirmed by IR, NMR and mass spectra. Compounds **4** shows IR bands around 3425 and 3125 cm^{-1} due to -OH and –NH groups which were absent in compounds **2**. NMR of compounds **4** shows all peaks

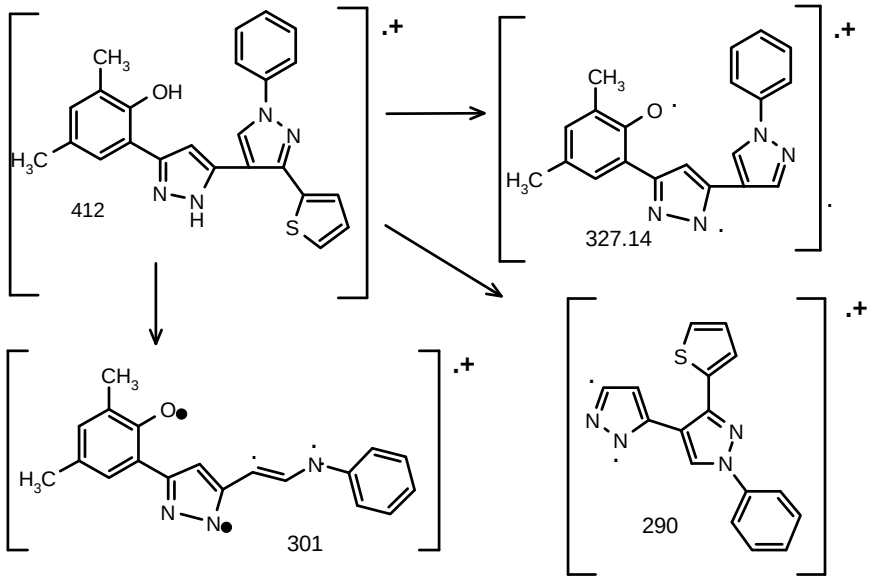


Figure C

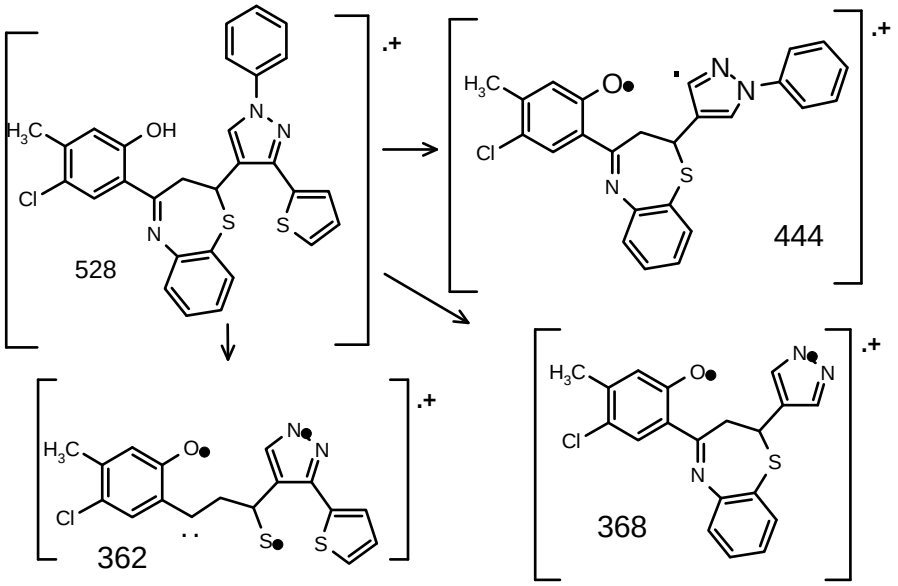


Figure D

in between δ 7.0 to 9.5, peaks around δ 6.5 gets disappeared. The compound **4d** showed significant peaks in its mass spectrum as shown in **Figure C**.

Compounds **1** when treated with 2-amino thiophenol affords 2-(2,3-dihydro-2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)benzo[b][1,4]thiazepin-4-yl)phenol **5**. All synthesized compounds **5** were characterized by IR, NMR and mass spectrometric techniques. IR of **5** shows disappearance of bands around 1680 cm^{-1} due to >C=O and new band appeared at 1597 cm^{-1} due to >C=N. NMR of compounds **5** shows characteristic peak around δ 3.0 (t, 1H), 3.7 (dd, 1H) and 5.5 (dd 1H), while other signals appears in between δ 7.0 to 8.5 due to aromatic protons, -OH showed singlet around δ 14. Structures of compounds **5** are also confirmed by mass spectra. The compound **5c** showed following significant peaks in its mass spectrum as shown in **Figure D**.

Experimental Section

General. Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. The reaction was monitored by TLC. Products were

purified by column chromatography using silica gel. IR spectra were recorded in nujol on a Perkin-Elmer 1605 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer in $CDCl_3$ or DMSO as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on a PEP-SCIUX-APIQ* Pulser (electron pre-ionization) mass spectrometer.

2-(1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4*H*-chromon-4-one 2. The compound **1** (0.001 mole) was dissolved in 15 mL DMSO. To this reaction mixture catalytic amount of I_2 was added. Contents were heated at 140°C for 1 hr and then the reaction mixture was left overnight. To the reaction mixture 100 mL of cold water was slowly added and the separated product was filtered and washed with cold water followed by dilute sodium thiosulphate solution several times, again it was washed with cold water. The product was crystallized from gl. acetic acid and further purified by column chromatography to afford compounds **2**. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table I** with their physical constants, percentage yield. Their structures has been confirmed by IR, NMR and mass spectral studies.

IR: **2i**: 3061, 1643, 1612, 1598, 1564, 754 cm^{-1}; ^{1}H NMR: **2i**: δ 6.74 (s,1H), 7.20 to 7.98 (m,11H), 9.37 (s,1H); Mass: **2b**: M^+ 389, 305, 253, 225.

4-(2-Hydroxyphenyl)-6-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)pyrimidine-2(1*H*)-thione 3. A mixture of **2** (0.001 mole) and (0.003 mole) of thiourea was dissolved in 10 mL ethanol. To this reaction mixture potassium hydroxide (0.005 mole) was added. Then reaction mixture was heated under reflux for 3 hr. After completion of heating, the reaction mixture was cooled to room temperature and then poured over crushed ice and neutralized with acetic acid. The resulting product was separated by filtration. The product was crystallized from gl. acetic acid and further purified by column chromatography to afford pure compounds **3** (**Scheme I**).

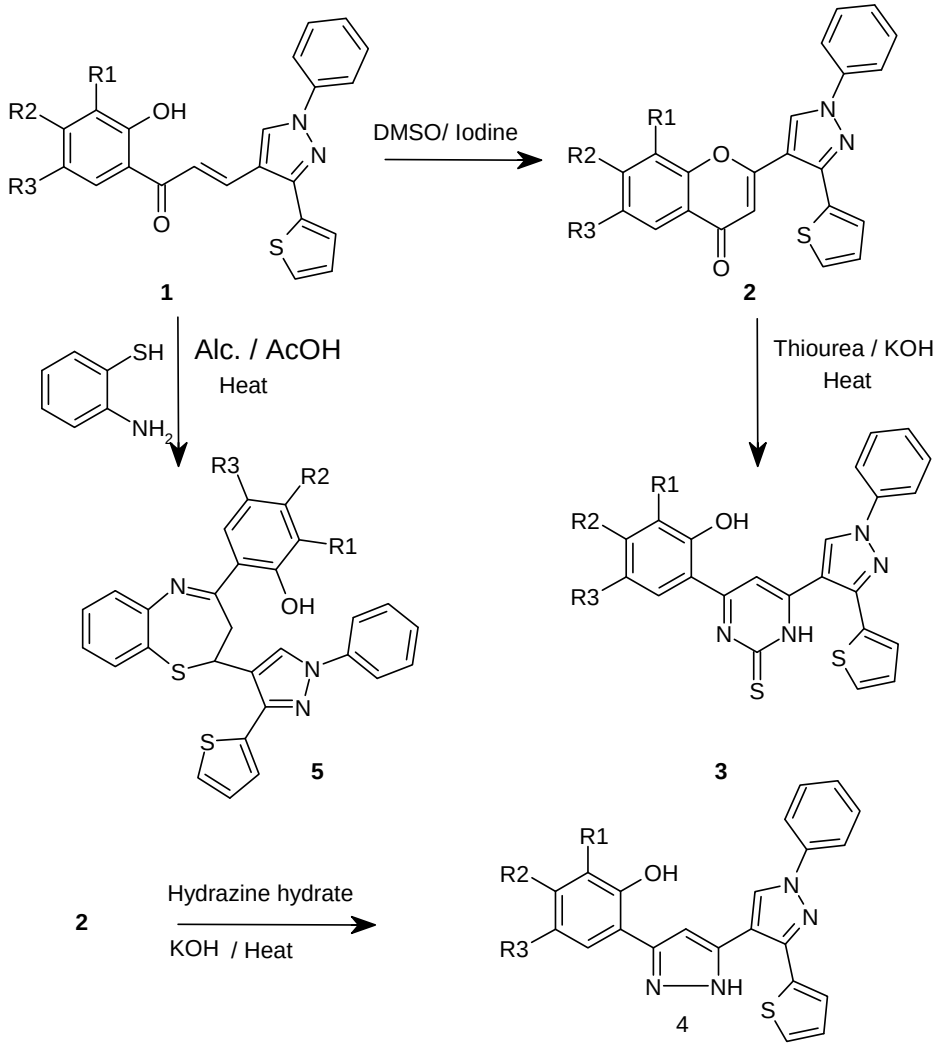
The compounds synthesized by above procedures are listed in **Table I** with their physical constants, percentage yield. Their structures have been confirmed by IR, NMR and mass spectral studies. IR: **3h**: 3436, 3117, 1674, 1596, 1573, 1517, 1268 cm^{-1}; ^{1}H NMR: **3h**: δ 2.54 (s, 3H), 7.14 to 8.21 (m, 14H), 9.41 (s, 1H); Mass: **3h**: M^+ 442, 331, 371, 225.

2-(5-(1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenol 4. A mixture of **2** (0.002 mole) and (0.005 mole) of hydrazine hydrate was dissolved in 10 mL ethanol with 0.5 g KOH. The reaction mixture was then refluxed for 3 hr. After completion of heating, the reaction mixture was cooled to room temperature and then poured over crushed ice and neutralized with acetic acid. The

Table I—Characterization data of the synthesized compounds

Compd	R_1	R_2	R_3	m.p. (°C)	Yield (%)	Solvents for Hexane(%)	Column EA(%)
2a	H	H	Br	229	80	40	60
2b	H	H	F	201-2	72	40	60
2c	H	CH_3	Cl	249	74	30	70
2d	CH_3	H	CH_3	218	73	40	60
2e	Cl	H	Cl	221	71	30	70
2f	H	H	C_2H_5	168	57	50	50
2g	H	CH_3	H	202	85	50	50
2h	H	H	CH_3	247	60	40	60
2i	H	H	Cl	227	64	40	60
3a	H	H	Br	180	51	50	50
3b	H	H	F	252	56	30	70
3c	H	CH_3	Cl	152	55	60	40
3d	CH_3	H	CH_3	185	53	50	50
3e	Cl	H	Cl	214	51	40	60
3f	H	H	C_2H_5	147	50	50	50
3g	H	CH_3	H	208	52	40	60
3h	H	H	CH_3	149	54	50	50
3i	H	H	Cl	148	52	40	60
4a	H	H	Br	182	45	35	65
4b	H	H	F	178	49	40	60
4c	H	CH_3	Cl	120	44	50	50
4d	CH_3	H	CH_3	144	46	40	60
4e	Cl	H	Cl	147	51	35	65
4f	H	H	C_2H_5	100	47	60	40
4g	H	CH_3	H	116	45	60	40
4h	H	H	CH_3	168	40	40	60
4i	H	H	Cl	144	44	50	50
5a	H	H	Br	167	82	40	60
5b	H	H	F	194	64	30	70
5c	H	CH_3	Cl	169	77	40	60
5d	CH_3	H	CH_3	261	78	30	70
5e	Cl	H	Cl	185	69	40	60
5f	H	H	C_2H_5	154	77	50	50
5g	H	CH_3	H	266	80	30	70
5h	H	H	CH_3	242	77	40	60
5i	H	H	Cl	181	72	35	65
5j	H	H	H	259	69	30	70

All compounds showed satisfactory elemental analysis.



Scheme I

resulting product was separated by filtration. The product was crystallized from ethanol and further purified by column chromatography to afford pure compounds **4**. The compounds synthesized by above procedures are listed in **Table I** with their physical constants, percentage yield. Their structures have been confirmed by IR, ^{1}H NMR and mass spectral studies. IR: **4h**: 3424, 3118, 1674, 1596, 1550, 1517 cm^{-1}; ^{1}H NMR **4h**: δ 2.57 (s, 3H), 7.14 to 8.21 (m, 14H), 9.41 (s,1H); Mass: **4d**: M$^+$ 412, 327, 301, 290.

2-(2,3-Dihydro-2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)benzo[b][1,4]thiazepin-4-yl)phenol 5. Compounds **1** (0.001 mole) and 2-amino thiophenol (0.001 mole) were taken in 100 mL RBF with 15 mL ethanol. The contents were heated under refluxed for 4 hr. Then to the reaction mixture, 2 mL gl. acetic acid was added and heating was continued for further 4 hr. After completion of heating, the contents were cooled to room temperature and poured over crushed ice. The solid thus obtained was separated by filtration. The resulting product was crystallized with alcohol and further purified by column chromatography to afford compounds **4**. Products obtained were identified with the help of spectral data. Their characterization data is given in the **Table I**. IR: **5i**: 3436, 1597, 1556, 1501, 763 cm^{-1}; ^{1}H NMR: **5i**: δ 3.11 (t, 1H), 3.71 (dd, 1H), 5.57 (dd, 1H), 7.02 to 8.03 (m, 15H), 8.52 (s, 1H), 14.20 (s, 1H); Mass: **5c**: M$^+$ 528, 444, 421, 368.

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