International Journal of Modern Organic Chemistry, 2018, 5(1): 12-20

Modern Scientific Press

International Journal of Modern Organic Chemistry **ISSN: 2166-0174**

Journal homepage: www.ModernScientificPress.com/Journals/IJOrgChem.aspx *Florida, USA*

Article

An Efficient Synthesis of Novel Thiazolyl-pyrazolyl-chromen-2-ones by Multicomponent Approach and Evaluation of Their Antioxidant Activities

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Article history: Received 18 September 2018, Revised 15 October 2018, Accepted 23 October 2018, Published 1 November 2018.

Abstract: A new series of thiazolyl-pyrazole-chromen-2-ones **3a-f** and **5a-c** have been efficiently designed and synthesized under facile reaction conditions *via* one-pot multicomponent approach of 3-bromoacetylcoumarin, thiosemicarbazide and various chalcones or 1,3-diketones in ethanol. Some of the synthesized targets were evaluated for the antioxidant screening and compound **5a** displayed promising activity.

Keywords: 3-Bromoacetylcoumarin; thiazolyl-pyrazole-chromen-2-ones; thiosemicarbazide; chalcones; antioxidant activity

1. Introduction

Coumarin is one of the most important heterocycles found in a wide variety of pharmacologically and biologically active compounds especially with antibacterial, antifungal [1-3], antitumor [4, 5], anti-inflammatory [6], antioxidant [7], anticancer and anti-HIV [8]. On the other hand, multifunctionalized Pyrazole derivatives are important class of compounds with pharmacological or biological activities. They are serving as antidepressants, antiamoebies, antioxidants and analgesics [9-13]. In addition, the thiazole moiety is remarkable medicinal value and attracted much attention because of its applications as hypotonic

[14], pesticidal [15], antimicrobial [16-18], antifungal [19, 20], antiparasitic [21], antiviral [22] and anticancer [23] properties. Keeping in mind these motivating pharmacological countenance and in resumption of an ongoing research endeavor at finding novel heterocyclic compounds leads with promising chemotherapeutic effectiveness [24-27], we decided to plan a molecular skeleton by incorporation of these worthy pharmacophores in a compact structure aiming to have compounds of antioxidants activity. Thus, **e**co-friendly one pot synthesis for a series of novel thiazolyl-pyrazole-chromen-2-ones **3a-f** and **5a-c** is achieved from 3-bromoacetylcoumarin, thiosemicarbazide and various chalcones or 1,3-diketones in ethanol.

2. Materials and Methods

All melting points were measured in degree Celsius on an electrothermal Gallenkamp (Germany) apparatus. The infrared spectra υ cm^{-1} (KBr) were determined on a Mattson 5000 FTIR Spectrometer (USA). The ^{1}H-NMR and ^{13}C-NMR spectra were run on a Bruker Avance III spectrophotometer at 400 and 100 MHz, respectively. The mass measurements were recorded on Kratos MS (Kratos Analytical Instrument, Ramsey, NJ) apparatus by EI mode with ionizing voltage 70 eV. Elemental (C, H, and N) analyses were measured on Perkin-Elmer 2400 (PerkinElmer Instruments, Shelton, CT).

2.1. General Procedure for the synthesis of thiazolyl-pyrazolyl-chromen-2-ones 3a-f:

A mixture of thiosemicarbazide (5 mmol), the appropriate chalcones **1a-f** and 3-bromoacetylcoumarin **2** (5 mmol) in ethanol (25 ml) and acetic acid (four drops) was heated on a water bath. A precipitate was formed within 1 hr. After accomplishment of the reaction (monitored by TLC), the products were filtered off and hot ethanol was used for washing and for recrystallization.

3-(2-(5-(4-Methoxyphenyl)-3-methyl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (3a).

Yellow crystals; yield 41%; mp 200-202^{o}C. IR (KBr) ν_{max}/cm^{-1}: 2926 (CH, str.), 1707 (C=O, lactone), 1604 (C=N), 1558 (C=C), 1355 (C-S), 1055 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.57 (s, 1H, thiazole-H5), 7.81 (s, 1H, coumarin-H4), 7.83-6.79 (m, 8H, Ar-H), 6.75 (s, 1H, pyrazole-H4), 3.82 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3). MS: (*m/z*, %): 414.82 (M^+, 5.1), 334.87 (100.0, base peak). Anal. Calcd. for $C_{23}H_{17}N_3O_3S$ (415.47): C, 66.49; H, 4.12; N, 10.11. Found: C, 66.52; H, 4.14; N, 10.14%.

3-(2-(3,5-Diphenyl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (3b).

Yellow crystals; yield 38%; mp 244-246^{o}C. IR (KBr) ν_{max}/cm^{-1}: 1712 (C=O, lactone), 1610 (C=N), 1576 (C=C), 1365 (C-S), 1070 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.18 (s, 1H, thiazole-H5), 7.79 (s, 1H, coumarin-H4), 8.00-7.21 (m, 14H, Ar-H), 7.08 (s, 1H, pyrazole-H4). MS: (*m/z*, %): 447.11 (M^+, 5.17), 88.97 (100.0, base peak). Anal. Calcd. for $C_{27}H_{17}N_3O_2S$ (447.51): C, 72.47; H, 3.83; N, 9.39. Found: C,

72.49; H, 3.85; N, 9.43%.

3-(2-(5-(4-Nitrophenyl)-3-phenyl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (3c).

Yellow crystals; yield 25%; mp 220-222ºC. IR (KBr) ν_{max}/cm^{-1}: 1751 (C=O, lactone), 1597 (C=N), 1556 (C=C), 1375 (C-S), 1080 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.53 (s, 1H, thiazole-H5), 8.16 (s, 1H, coumarin-H4), 8.14-7.37 (m, 13H, Ar-H), 6.37 (s, 1H, pyrazole-H4). MS: (*m/z*, %): 492.04 (M$^+$, 52.66), 76.98 (100.0, base peak). Anal. Calcd. for $C_{27}H_{16}N_4O_4S$ (492.51): C, 65.85; H, 3.27; N, 11.38. Found: C, 65.84; H, 3.25; N, 11.34%.

3-(2-(5-(4-Fluorophenyl)-3-phenyl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (3d).

Yellow crystals; yield 17%; mp 140-142ºC. IR (KBr) ν_{max}/cm^{-1}: 1791 (C=O, lactone), 1603 (C=N), 1561 (C=C), 1363 (C-S), 1098 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.59 (s, 1H, thiazole-H5), 8.53 (s, 1H, coumarin-H4), 8.19-7.14 (m, 13H, Ar-H), 6.36 (s, 1H, pyrazole-H4). MS: (*m/z*, %): 465.36 (M$^+$, 5.07), 303.68 (100.0, base peak). Anal. Calcd. for $C_{27}H_{16}FN_3O_2S$ (465.50): C, 69.67; H, 3.46; N, 9.03. Found: C, 69.70; H, 3.47; N, 9.05%.

3-(2-(5-(4-Acetylphenyl)-3-phenyl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (3e).

Pale yellow crystals; yield 33%; mp 250-252ºC. IR (KBr) ν_{max}/cm^{-1}: 2929 (CH, str.), 1711 (C=O, lactone), 1607 (C=N), 1546 (C=C), 1375 (C-S), 1085 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.32 (s, 1H, thiazole-H5), 8.07 (s, 1H, coumarin-H4), 7.83-7.36 (m, 13H, Ar-H), 6.98 (s, 1H, pyrazole-H4), 2.51 (s, 3H, CH_3). MS: (*m/z*, %): 489.14 (M$^+$, 30.15), 277.13 (100.0, base peak). Anal. Calcd. for $C_{29}H_{19}N_3O_3S$ (489.55): C, 71.15; H, 3.91; N, 8.58. Found: C, 71.17; H, 3.89; N, 8.60%.

3-(2-(7-Benzylidene-3-phenyl-4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazol-4-yl)-2H-chromen-2-one (3f).

Yellow crystals; yield 38%; mp 285-287ºC. IR (KBr) ν_{max}/cm^{-1}: 2921 (CH, str.), 1719 (C=O, lactone), 1604 (C=N), 1545 (C=C), 1365 (C-S), 1070 (C-N). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.91 (s, 1H, thiazole-H5), 8.71 (s, 1H, coumarin-H4), 8.18-7.24 (m, 14H, Ar-H), 6.34 (s, 1H, =CH), 2.30 (t, 2H, CH_2), 1.80–1.77 (m, 4H, 2CH_2). MS: (*m/z*, %): 513.70 (M$^+$, 21.66), 149.92 (100.0, base peak). Anal. Calcd. for $C_{32}H_{23}N_3O_2S$ (513.62): C, 74.83; H, 4.51; N, 8.18. Found: C, 74.85; H, 4.22; N, 8.21%.

2.2. General procedure for the synthesis of thiazolyl-pyrazolyl-chromen-2-ones 5a-c.

3-Bromoacetylcoumarin **2** (2 mmol), thiosemicarbazide (2 mmol) and 1,3-diketones **4a-c** (2 mmol) in ethanol (20 ml) was refluxed. The obtained products have been collected by filtration, dried then boiled in ethanol to take off all the traces of the reactants.

3-(2-(3-Methyl-5-(phenylamino)-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (5a).

Reaction time: 30 min., yellow crystals; yield 85%; mp 190-192ºC. IR (KBr) ν_{max}/cm^{-1}: 3267 (NH),

1712 (C=O, lactone), 1646 (C=N), 1600 (C=N), 1590 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.74 (s, 1H, NH), 8.59 (s, 1H, thiazole-H5), 8.26 (s, 1H, coumarin-H4), 7.82-6.98 (m, 9H, Ar-H), 6.95 (s, 1H, pyrazole-H4), 2.11 (s, 3H, CH_3). MS: (*m/z*, %): 400.37 (M^+, 46.08), 170.62 (100.0, base peak). Anal. Calcd. for $C_{22}H_{16}N_4O_2S$ (400.46): C, 65.99; H, 4.03; N, 13.99. Found: C, 65.95; H, 4.02; N, 13.97%.

3-(2-(3-Methyl-5-(thiazol-2-ylamino)-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (5b).

Reaction time: 4 h, yellow crystals; yield 54%; mp 270-272°C. IR (KBr) ν_{max}/cm^{-1}: 3411(NH), 1712 (C=O, lactone), 1606 (C=N), 1596 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.67 (s, 1H, thiazole-H5), 8.20 (s, 1H, coumarin-H4), 8.06 (s, 1H, NH), 7.66-7.06 (m, 6H, Ar-H), 6.95 (s, 1H, pyrazole-H4), 2.30 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ_{ppm}: 161.00 (C=O), 150.11 (pyrazole-C5), 147.01 (coumarin-C4), 140.17 (pyrazole-C3), 154.66, 153.78, 152.99, 144.00, 130.52, 129.12, 128.98, 125.29, 123.37, 122.26, 118.62, 116.00, 112.00 (Ar-C), 80.23 (pyrazole-C4), 15.00 (CH_3). MS: (*m/z*, %): 407.00 (M^+, 33.17), 144.94 (100.0, base peak). Anal. Calcd. for $C_{19}H_{13}N_5O_2S_2$ (407.47): C, 56.01; H, 3.22; N, 17.19. Found: C, 56.10; H, 3.22; N, 17.21%.

1,5-Dimethyl-4-((3-methyl-1-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)-1H-pyrazol-5-yl)amino)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (5c).

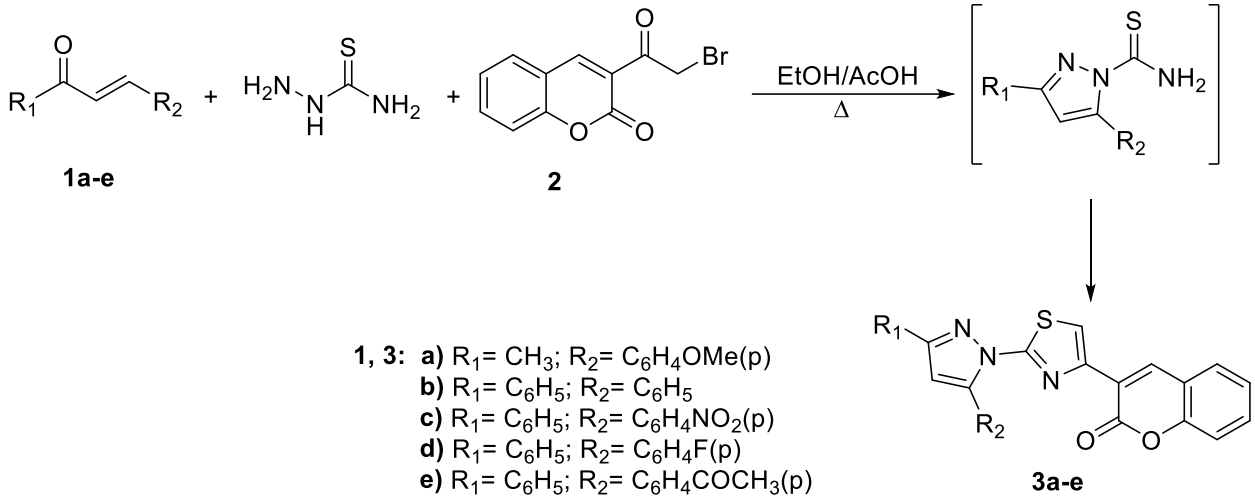
Reaction time: 8 h, yellow crystals; yield 33%; mp 200-202°C. IR (KBr) ν_{max}/cm^{-1}: 3441(NH), 1721 (C=O, lactone), 1640 (C=O, amidic), 1615 (C=N), 1604 (C=C). ^{1}H-NMR (DMSO-d_6) δ_{ppm}: 8.79 (s, 1H, thiazole-H5), 8.72 (s, 1H, coumarin-H4), 8.06 (s, 1H, NH), 8.13-7.35 (m, 9H, Ar-H), 7.26 (s, 1H, pyrazole-H4), 3.11 (s, 3H, NCH_3), 2.30 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). MS: (*m/z*, %): 510.00 (M^+, 18.56), 161.00 (100.0, base peak). Anal. Calcd. for $C_{27}H_{22}N_6O_3S$ (510.57): C, 63.52; H, 4.34; N, 16.46. Found: C, 63.55; H, 4.35; N, 16.48%.

3. Results and Discussion

3.1. Synthetic Chemistry

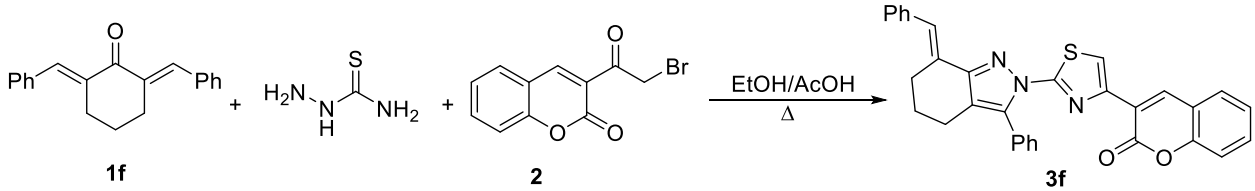
Previously, a series of thiazolyl-pyrazole-chromen-2-ones have been achieved and screened for their antioxidant activities [28]. It has been reported that the coumarin nucleus plays vital role in enhancing the antioxidant activities of compounds [29]. So, the interesting pharmacological properties of coumarin compounds has motivated us to synthesize novel thiazolyl-pyrazole-chromen-2-ones **3a-e**, in reasonable yields, *via* reaction of chalcones **1a-e** [30, 31], thiosemicarbazide and 3-bromoacetylcoumarin **2** [7] in refluxing ethanol and glacial acetic acid as a catalytic amount (Scheme 1). Addition of thiosemicarbazide to chalcones **1a-e** is considered as regioselective reaction preceding through addition of the NH_2 group to the carbonyl of chalcone, and then intramolecular cycloaddition of NH to the olefinic bond to give *in-situ* pyrazolethioamide as intermediate compound. Formation of the latter is put up with the Hantzsch thiazole

synthesis *via* nucleophilic substitution reaction of the Br of 3-bromoacetylcoumarin by *S*-atom of the thioamide to generate the isothiourea, which followed by cyclocondensation and water elimination to afford the thiazole derivative **3a-e**. The IR spectra of compounds **3a-e** in general discover the presence of a lactone carbonyl at 1791-1707 cm^{-1} and C=N group at 1610-1597 cm^{-1}. Peaks in the part 1375-1355 cm^{-1} and 1098-1055 cm^{-1} elucidate the presence of C-S and C-N functions. In the ^{1}H-NMR spectra, the aromatic protons show in the part 7.83-6.79 ppm. Besides, three singlet signals at δ 8.18, 7.79 and 6.36 ppm specific to thiazole-H5, chromenone-H4 and pyrazole-H4, respectively. The molecular ion peaks of compounds **3a-e** in the mass spectra were in endorsement with the molecular formula of these compounds.



Scheme 1

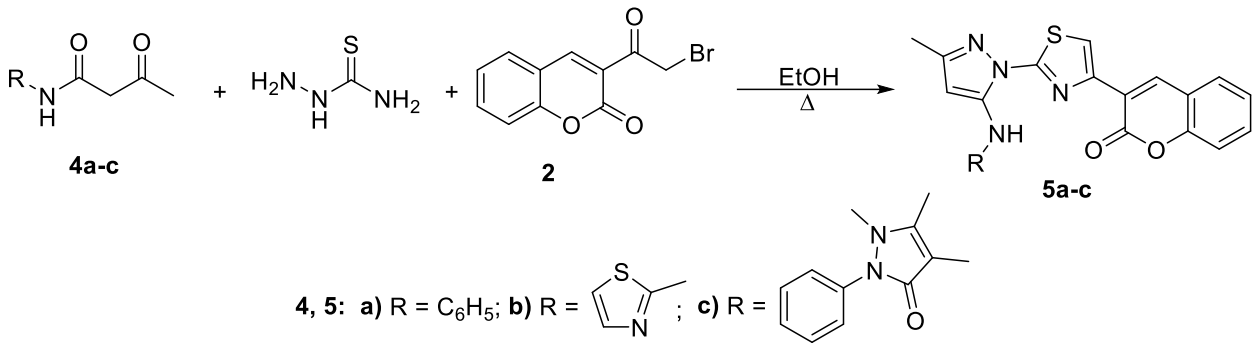
The foregoing results promoted us to prolonged our protocol to the synthesis of 3-(2-(7-benzylidene-3-phenyl-4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazol-4-yl)-2H-chromen-2-one **(3f)** using 2,6-di(benzylidene)cyclohexan-1-one **(1f)**, thiosemicarbazide and 3-bromoacetylcoumarin **2** under the same conditions (Scheme 2). The reaction performed in a smooth manner and afforded 38% yield of the product in short time without the consistence of any by-products.



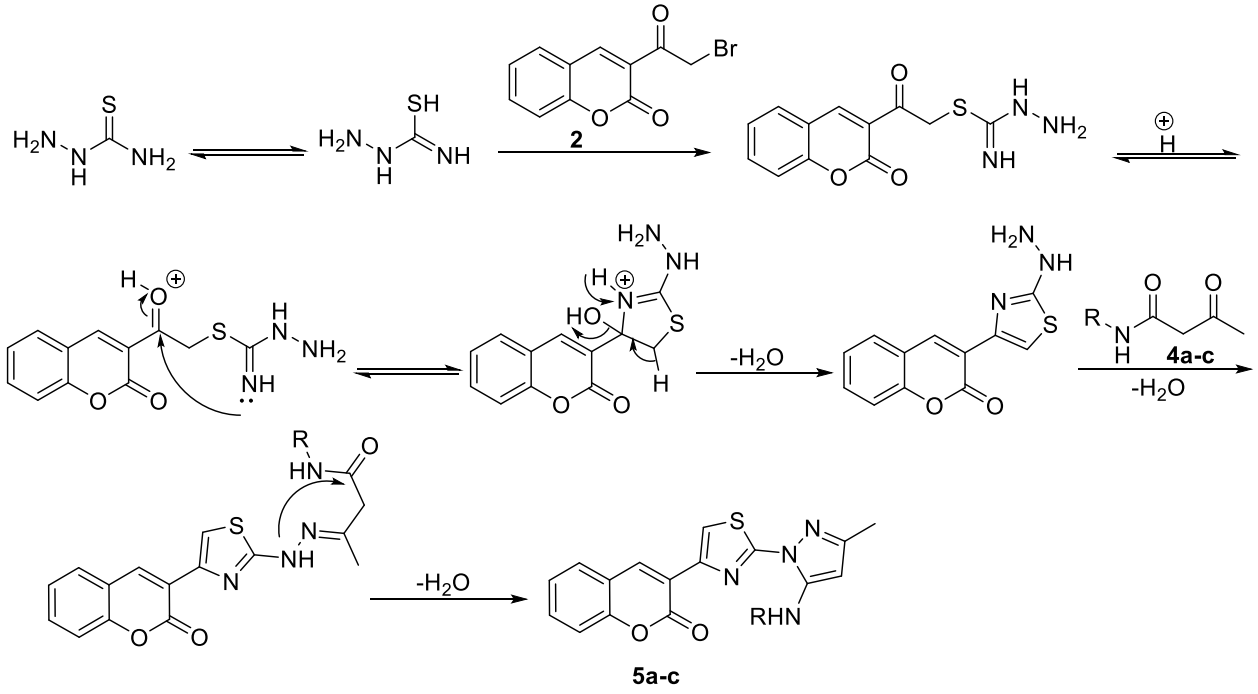
Scheme 2

Shifting to Scheme 3, another efficient synthesis to thiazolyl-pyrazole-chromen-2-ones **5a-c** *via* Hantzsch thiazole and Knorr pyrazole MCRS, respectively, including 1,3-diketones **4a-c** combined with 3-bromoacetylcoumarin **2** and thiosemicarbazide as dinucleophilic coupling center. Compounds **5a-c** were

efficiently designed and synthesized in ethanol by reflux. Scheme 4 showed a sensible mechanism for the formation of **5a-c**. The latter structures **5a-c** were inspected with spectral studies and elemental analysis. The IR spectra of **5b**, for example, disclose the presence of bands at 3411, 1712, 1606 and 1596 cm^{-1} due to NH, a lactone carbonyl, C=N and C=C groups, respectively. The ^{1}H-NMR spectrum of this compound exhibited five singlet signals at δ = 8.67, 8.20, 8.06, 6.95 and 2.30 ppm which were easily specific to the thiazole-H5, coumarin-H4, NH, pyrazole-H4 and CH_3, respectively. ^{13}C-NMR analysis likewise assured the structure **5b**, with signals observed at δ = 161.00, 150.11, 147.01, 140.17, 80.23 and 15.00 ppm due to C=O, pyrazole-C5, coumarin-C4, pyrazole-C3, pyrazole-C4 and CH_3, respectively, besides the other expected signals. A distinguishing peak was observed in the mass spectrum of **5b** at *m/z* = 407.00 (M^+, 33.17) corresponding to the proposed molecular formula.



Scheme 3



Scheme 4

3.2. Pharmacology

3.2.1. Antioxidant Activity

The antioxidant effectiveness of some synthetic targets contrasted to Ascorbic acid as standard was achieved as describe in the literature method [32]. **Table 1** showed that the tested synthetic compounds disclosed changeable inhibitory effects. Compound **5a** was found to be more effective with percentage inhibition 85.4%, compounds **3a**, **5b** and **5c** appeared a sensible inhibition range of 33.1-54.1%, while compounds **3c** and **3d** displayed weakened antioxidant effectiveness with percentage inhibition 17.4 and 25.3%, respectively.

Table 1. Antioxidant activity screening for some of the synthetic compounds.

Compound No.	Absorbance of samples	% Inhibition
Control of ABTS	0.562	0.0
Ascorbic acid	0.063	88.8
3a	0.328	41.6
3c	0.464	17.4
3d	0.420	25.3
5a	0.082	85.4
5b	0.258	54.1
5c	0.376	33.1

In the opinion of structure activity relationships (SAR), high antioxidant effectiveness can be connected with low electron density of ring systems. In this view, compound **5a** was more potent antioxidant activity than **5b** and **5c**. Also, it is interesting to point out that thiazolyl-pyrazolyl-chromen-2-ones **3a** and **3d** having electron donating groups such as OMe or F gave high efficiency while thiazolyl-pyrazolyl-chromen-2-one **3c** having electron withdrawing group (NO_2) unfortunately produced weak antioxidant efficiency.

4. Conclusion

In summary, we have described an easy and effective one-pot multicomponent synthesis for the formation of thiazolyl-pyrazole-chromen-2-one derivatives **3a-f** and **5a-c**. Some of the synthesized targets were measured for the antioxidant activity and compound **5a** proved to the most strenuous member in this research with distinctive efficiency.

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