



Research Article

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Synthesis and antimicrobial activity of Thiosemicarbazone induced Hydrazone of 2-Anilino-3-formylchromone

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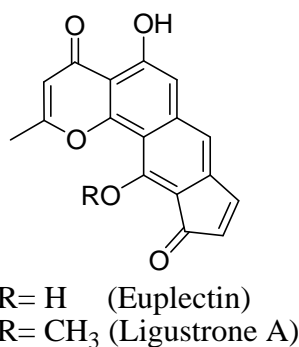
ABSTRACT

The present investigations provide an access to the synthesis of pure thiosemicarbazone derivatives in high yields under catalytic conditions, which do not require chromatographic separation. The newly synthesized compounds when screened for antibacterial activities, these show enhanced antimicrobial activities due to presences of additional binding site for receptors.

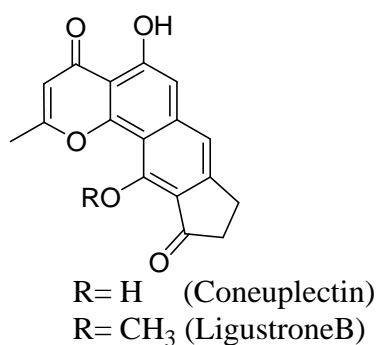
Keywords: 2-Anilino-3-formylchromone, Thiosemicarbazone, Zinc perchlorate, Chromone, Antibacterial.

INTRODUCTION

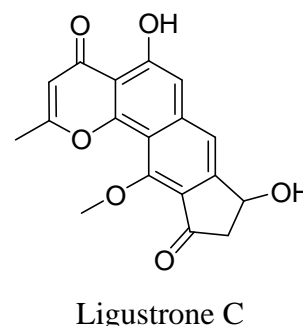
The chromone ring system is the core fragment in several flavonoids, such as flavones, flavonols and isoflavones. Chromone derivatives have been widely studied due to their significant biological activities such as anticancer, [1, 2] antitumor, [3 - 5]antiviral, [6-7] antibiotic,[8] antimicrobial, [9] antifungal, [10] antioxidant, analytical reagents for transition elements due to their ability to form metal chelates and DNA binding properties of chromone metal complexes [11], anti-HIV [12] and anti-inflammatory [13], antimycobacterial, anti-asthmatics, mushroom tyrosinase inhibition activities [14], plant growth inhibitors. Naturally occurring hydroxychromone fused with indenones **1-3** reported to exhibit cytotoxicity against the growth of murine P-815 mastocytoma cells.



1

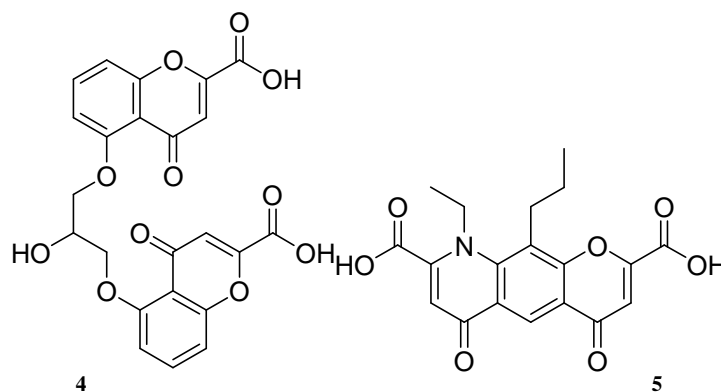


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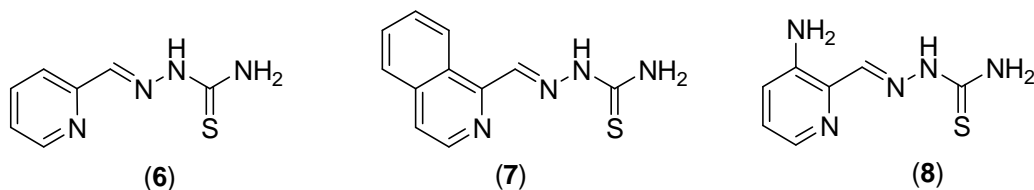
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Cromoglicic acid derivatives **4** of chromone exhibit significant antihistaminic properties, Nedocromil sodium **5** a chromone derivative have mast cell stabilizer activities which inhibits the degranulation of mast cells, and prevents release of histamine and tryptase.

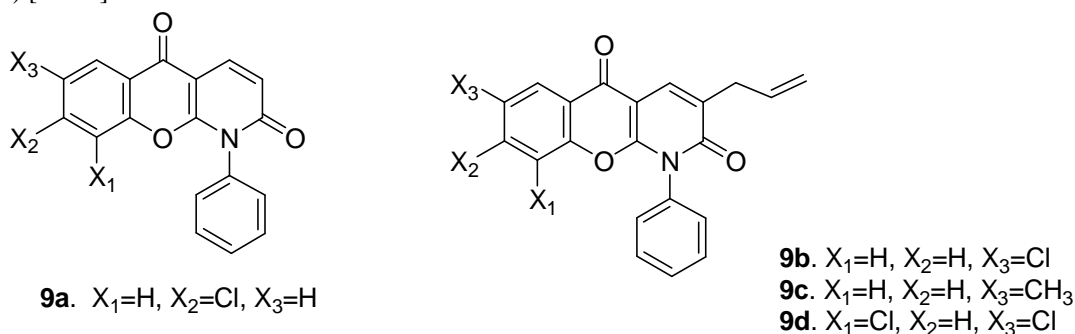


Important features of hydrazone is that these are an important class of chemical intermediate which can act both as electrophile and as nucleophile in mannish type reaction. Various types of hydrazones had also been used as a protecting group for carbonyl group. The hydrazones are used to couple with certain drugs which undergo lysis under highly acidic environment of lysosomes.

A semicarbazone is a derivative of an aldehyde or ketone formed by a condensation reaction between a ketone or aldehyde and semicarbazide. They display a broad spectrum of pharmacological properties such as antifungal, antibacterial, antiepileptic activities [15, 16]. Thiosemicarbazones are present in many bioactive heterocyclic compounds **6-8**. These compounds have various biological and clinical applications [17]. Thiosemicarbazones display a broad spectrum of pharmacological properties, including antitumor, antifungal, antibacterial, antiviral and antimalarial activities [18]. Much effort has been devoted to structural variations of the thiosemicarbazones for achieving the ultimate goal of medicinal applications [19 -22]. The antitumor activity of such thio-compounds was revealed in their ability to inhibit ribonucleotide reductase (RR), a necessary enzyme for DNA synthesis [23].



Recently chromeno-pyridone derivatives (**9a - d**) have been reported to show significant cytotoxic properties, chromone derivatives bearing electron withdrawing groups on chromone moiety were more active against cancer cells than compounds bearing electron donating groups and allylated chromeno-pyridones displayed good activity to various human cancer cell lines such as Prostate (PC-3), Breast (MCF-7), CNS (IMR-32), Cervix (Hela-) and Liver (Hep-G2) [24-26].



EXPERIMENTAL SECTION

Experimental Procedure

Starting materials and reagents were purchased from commercial suppliers and used after further purification (crystallization/distillation). IR spectra were recorded on Shimadzu 8400 S FT-IR spectrophotometer as KBr pellets. All melting points are uncorrected and measured in an open glass-capillaries.

General method for the synthesis

To a clear solution of thiosemicarbazide (1 moleq) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 min under anhydrous condition. To the stirred solution, 2-anilino-3-formylchromone (**10a-e**, 1.2 moleq) dissolved in methanol added and contents were stirred for completion of reaction at room temperature. Progress of reaction was monitored using TLC (Chloroform:Ethylacetate :: 1:1). After the completion of reaction (TLC), solvent was evaporated under reduced pressure and the product was obtained, which was further triturated with diethyl ether to afford pure desired product

Synthesis of 2-((4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)hydrazine-carboamide (11a) :

To a clear solution of thiosemicarbazide (103mg, 1.130×10^{-3} mole) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 minutes under anhydrous condition. To the stirred solution 2-anilino-3-formylchromone (**10a**, 200mg, 0.754×10^{-3} mole) and reaction was carried vide experimental to afford pure product (180mg, 71%). R_f value = 0.41 (Chloroform:Ethylacetate :: 1:1), melting point 245-247 °C. IR (KBr) $\nu_{cm^{-1}}$: 3341, 3311 (NH₂), 3178 (NH), 3032 (sp²Ar CH), 1647 (CO), other peak in the spectra showing the various vibrations in the molecule 1570, 1529, 1464, 1448, 1413, 1340, 1267, 1224, 1097.

Synthesis of 2-((6-methyl-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)-hydrazinecarboamide (11b):

To a clear solution of thiosemicarbazide (97mg, 1.064×10^{-3} mole) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 minutes under anhydrous condition. To the stirred solution 6-methyl-2-anilino-3-formylchromone (**10b**, 200mg, 0.716×10^{-3} mole) and reaction was carried vide experimental to afford pure product (200mg, 79%). R_f value = 0.37 (Chloroform:Ethylacetate :: 1:1), melting point 257-260 °C. IR (KBr) $\nu_{cm^{-1}}$: 3396, 3243 (NH₂), 3153 (NH), 3041 (sp²Ar CH), 1651 (CO), other peak in the spectra showing the other various vibrations in the molecule 1573, 1537, 1473, 1450, 1417, 1367, 1334, 1278, 1215.

Synthesis of 2-((6-fluoro-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene) hydrazinecarboamide (11c):

To a clear solution of thiosemicarbazide (96mg, 1.053×10^{-3} mole) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 minutes under anhydrous condition. To the stirred solution 6-fluoro-2-anilino-3-formylchromone (**10c**, 200mg, 0.703×10^{-3} mole) and reaction was carried vide experimental to afford pure product (200mg, 80%). R_f value = 0.40 (Chloroform:Ethylacetate :: 1:1), melting point 244-246 °C. IR (KBr) $\nu_{cm^{-1}}$: 3431, 3308 (NH₂), 3188 (NH), 3030 (sp²Ar CH), 1651 (CO), other peak in the spectra showing the other various vibrations in the molecule 1575, 1527, 1471, 1454, 1415, 1367, 1332, 1257, 1217, 1197, 1170, 1130.

Synthesis of 2-((6-chloro-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)-hydrazinecarboamide (11d):

To a clear solution of thiosemicarbazide (99mg, 0.998×10^{-3} mole) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 minutes under anhydrous condition. To the stirred solution 6-chloro-2-anilino-3-formylchromone (**10d**, 200mg, 0.667×10^{-3} mole) and reaction was carried vide experimental to afford pure product (185mg, 74%). R_f value = 0.37 (Chloroform:Ethylacetate :: 1:1), melting point 268-270 °C. IR (KBr) $\nu_{cm^{-1}}$: 3394, 3246 (NH₂), 3153 (NH), 3036 (sp²Ar CH), 1645 (CO), other peak in the spectra showing the other various vibrations in the molecule 1566, 1529, 1458, 1367, 1329, 1217, 1153, 1105, 1058.

Synthesis of 2-((6-bromo-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)-hydrazinecarboamide (11e):

To a clear solution of thiosemicarbazide (79mg, 0.866×10^{-3} mole) dissolved in methanol, taken in dry RBF, zincperchlorate (5mg) was added. Contents were stirred on magnetic stirrer for about 10 minutes under anhydrous condition. To the stirred solution 6-bromo-2-anilino-3-formylchromone (**20e**, 200mg, 0.581×10^{-3} mole) and reaction was carried vide experimental to afford pure product (145mg, 60%). R_f value = 0.33 (Chloroform:Ethylacetate :: 1:1), melting point 233-235 °C. IR (KBr) $\nu_{cm^{-1}}$: 3390, 3203 (NH₂), 3156 (NH), 3054 (sp²Ar CH), 1645 (CO), other peak in the spectra showing the other various vibrations in the molecule 1566, 1529, 1545, 1329, 1220, 1107.

RESULTS AND DISCUSSION

Initially reaction of variously substitute 2-anilino-3-formylchromone (**10 a-e**) was carried with an equimolar solution of thiosemicarbazide prepared in anhydrous methanol in presence of catalytic amount of zinc perchlorate with stirring at room temperature, after prolonged stirring reaction did not proceed to completion. However when the same reaction was carried with 1:1.2 molar equivalent of reactants reaction proceeded to completion and with shorter duration of time to afford the desired product, results of the reactions are summarized in scheme-1, and table-1.

Reactions of 2-anilino-3-formylchromone derivatives with thiosemicarbazide

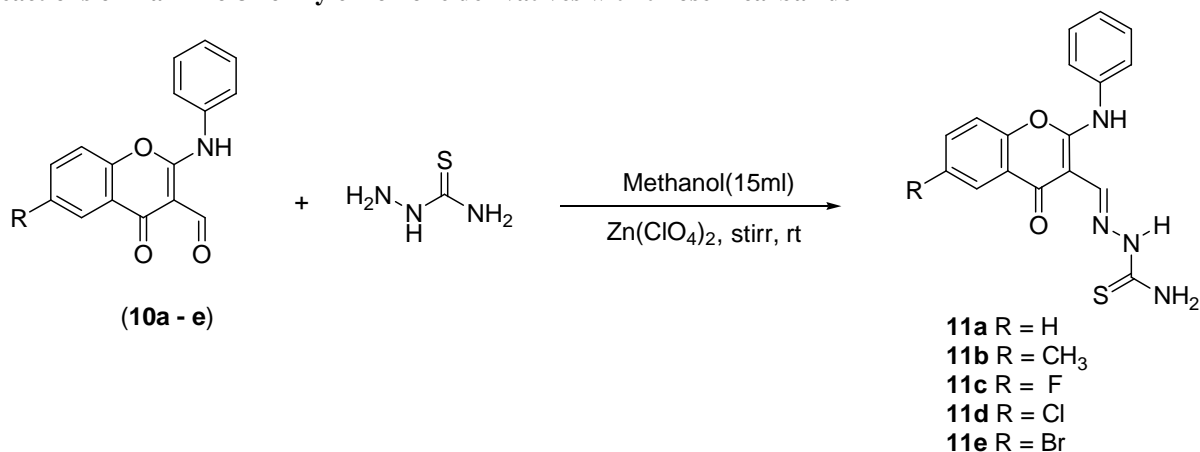


Table 1. Reaction time and %yield of various hydrazine (11a – e) obtained

Sr. No.	R	Reaction Time	Yield (%)
11a	H	80min	71%
11b	CH ₃	80min	79%
11c	F	90min	80%
11d	Cl	80min	74%
11e	Br	90min	60%

Antibacterial Activity

Due to anticipated antibacterial activity of chromone derivatives along with the thiosemicarbazide group, the newly synthesized compounds (**11a-e**) have been screened for their antibacterial activity. The solution of respective compounds in the DMSO provides significance activity by displaying zone of inhibition. Newly synthesized derivatives show enhanced activity as compared to respective 2-Anilino-3-formylchromone due to the presence of additional binding site for better receptor interaction and thereby inhibiting the cell growth mechanism of bacterial cell and act as significant antimicrobial agent. These compound exhibit a very low activity at 10 ppm concentration however with the increase of concentration to 50ppm all these compounds exhibit some activity. Similarly increasing the concentration to 100ppm these compound exhibit a significant activity against bacterial cell growth. Result of antibacterial against *E. coli* are summarized in Table 2, 3 and Figure 1,2.

Table 2. Antibacterial Activity of 2-Anilino-3-formylchromone derivatives 10(a-e) at 100ppm, 50ppm and 10ppm concentrations against *E. coli*

Sr. No.	Entry	Zone of Inhibition (cm)		
		100ppm	50ppm	10ppm
1	10a	1.98	1.28	0.7
2	10b	1.58	1.41	0.7
3	10c	1.28	0.78	0.68
4	10d	1.12	0.64	0.6
5	10e	1.75	1.55	1.21

Table 3. Antibacterial Activity of 2-((4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)hydrazine-carboamide derivatives 11(a-e) at 100ppm, 50ppm and 10ppm concentrations against *E. coli*

Sr. No.	Entry	Zone of Inhibition (cm)		
		100ppm	50ppm	10ppm
1	11a	2.18	1.32	0.7
2	11b	1.9	1.35	0.9
3	11c	2.85	2.0	0.73
4	11d	1.53	1.40	0.65
5	11e	1.42	1.38	1.15

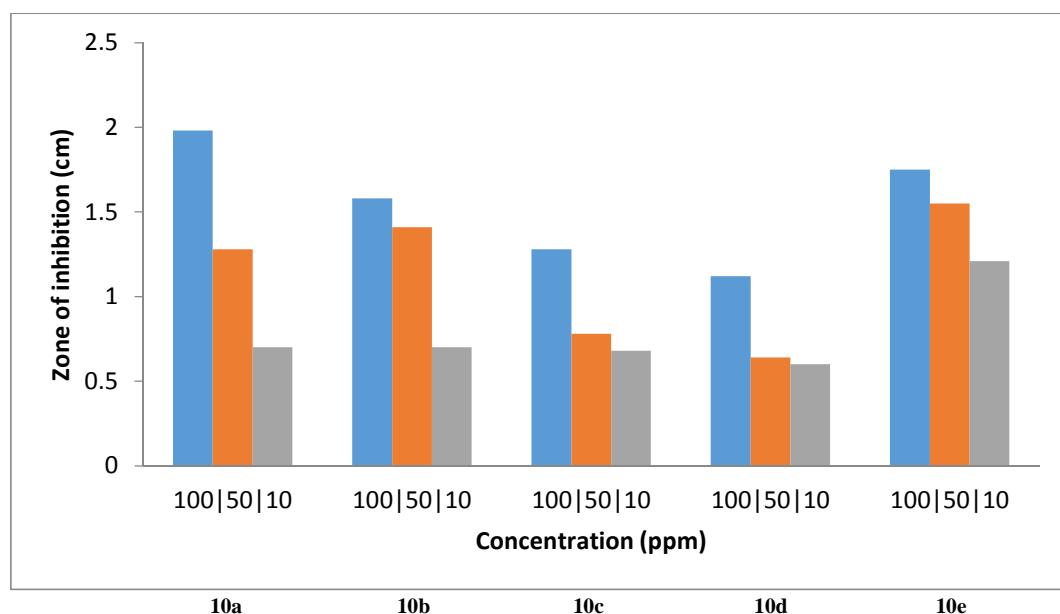


Figure1. Antibacterial Activity of 2-Anilino-3-formylchromone derivatives 10(a-e) at 100ppm, 50ppm and 10ppm concentrations against *E. coli*

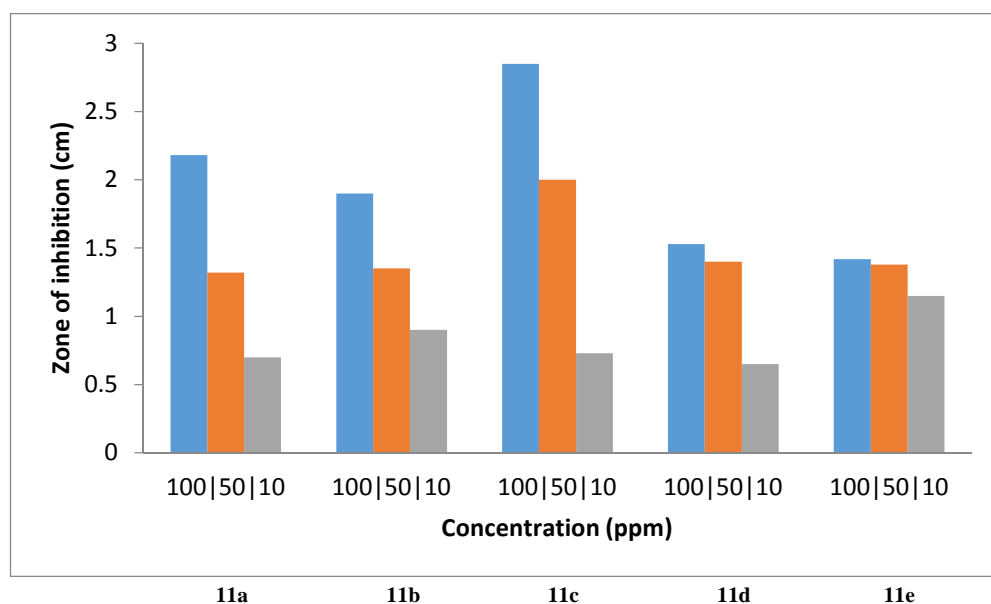
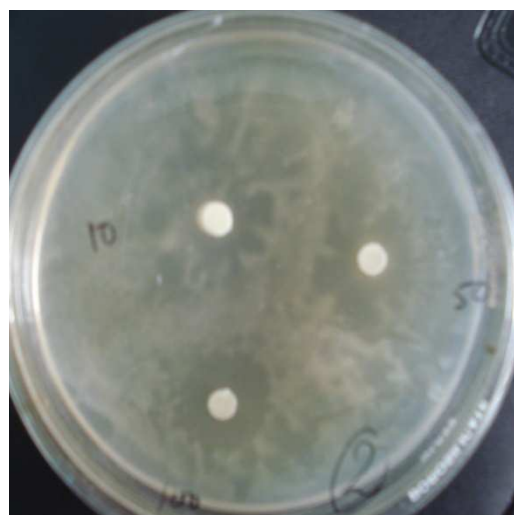


Figure2. Antibacterial Activity of 2-((4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)-hydrazinecarboamide derivative 11(a-e) at 100ppm, 50ppm and 10ppm concentrations against *E. coli*

Antimicrobial evaluation of the compound **10** (a-e) and **11** (a-e) shows very significant inhibition against microbial growth. In case of fluoro-derivative of (E)-2-((4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene) hydrazine carboamide (**11 c**) at the 100 ppm concentration a very high amount of inhibition activity was observed along with compounds **10(a, b, e)**, **11(a, b)** and compounds **10(e, d)** and **11(c, d)** display a significant activity against strain of *E. coli*.



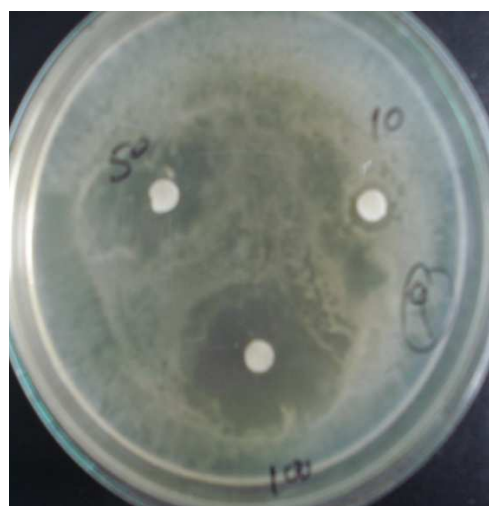
Inhibition by 2-Anilino-3-formyl-chromone (10a)



Inhibition by 6-Bromo-2-Anilino-3-formylchromone (10e)



Inhibition by 2-((6-methyl-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)hydrazinecarboamide derivative (11b)



Inhibition by 2-((6-fluoro-4-oxo-2-(phenylamino)-4H-chromone-3-yl)methylene)hydrazinecarboamide derivative (11c)

CONCLUSION

Present investigations provides an easy access to the synthesis of thiosemicarbazone based 2-anilino-3-formylchromone derivatives involving the use of zinc perchlorate as catalyst. The method provides an easy access for the synthesis in high yield along with the product with high purity, which does not require chromatographic separations. Compound so obtained were further investigated for their antibacterial activity against *E. coli* which show some significant results. The compound so obtained has certain characteristic features involving the presence of various functional groups for better receptor interaction along with presence of various heteroatom. This study provides some basic leads for the synthesis of new chromone based hydrazones which can be further developed to get better results as antimicrobials.

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