Ionic Liquid Mediated Synthesis Of Novel Chromone-Pyrimidine Coupled Derivatives.

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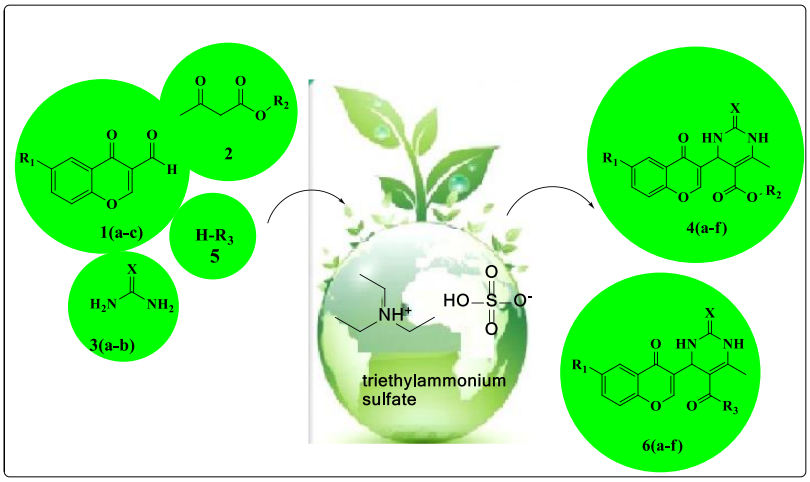
Abstract:

The work reports synthesis of twelve novel ethyl 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **4(a-f)** and 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2- thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide derivatives **6(a-f)**. The novel chromone-pyrimidine coupled derivatives were synthesized under solvent-free condition using Triethyl ammonium sulphate $[Et_3NH][HSO_4]$ as an efficient, eco-friendly and reusable catalyst. Compared to other methods, this new method consistently has advantages, including excellent yields, a short reaction time, mild reaction conditions and catalyst reusability. The heterocyclic compound Chromone, is associated with diverse biological activities of immense importance. The nitrogen containing heterocycle such as pyrimidine has attracted continuing interest because of its varied biological activities and its occurrence in natural medicinal plants. Pyrimidine and its derivatives are used as antifungal agents, antibacterial agents, anticancer agents, etc. Considering the importance of the two pharmacophores, promoted us to club both the pharmacophores in a single molecule using green protocol. The structures of the synthesized compounds were confirmed by spectral characterization such as IR, ^{1}H NMR, ^{13}CNMR and Mass spectral studies.

Keywords: Ionic Liquid; Chromone; Pyrimidine; Green protocol.

Graphical Abstract



1. Introduction

Coumarins, an elite class of naturally occurring compounds with promising therapeutic perspectives [1, 2]. This compound have become indispensable structural units that are useful in medicinal chemistry displaying profiles such as anticancer [3], antioxidant [4], antiplasmodial [5], antimalarial [6], antirhinovirus [7], antifungal [8] and antibacterial [9]. 4-Oxo-4H-chromen-3-carbaldehyde (3-formylchromone) a useful precursor for the synthesis of several biological active compounds owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3, and an electrophilic centre at C-2. Much research has been focused on the inhibition of bacterial growth by naturally occurring coumarins (xanthoxin, herniarin, umbelliferone, and scopoletin) and on the antifungal activity of umbelliferone, scopoletin, and coumarin itself [10].

The nitrogen containing heterocycle such as pyrimidine has attracted continuing interest because of its varied biological activities and its occurrence in natural medicinal plants. Pyrimidine and its derivatives are used as pesticides, herbicides and insecticides [11, 12]. Marketed antifungal drugs such as Flucytosine, Voriconazole and Albaconazole, also contain pyrimidine nucleus [13].

The molecular hybridization (MH) is a strategy of rational design of such ligands or prototypes based on the recognition of pharmacophoric sub-units in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-units, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates [14]. It is a new concept in drug design and development to produce a new hybrid compound with improved affinity, potency and efficacy, when compared to the parent drugs [25]. The selection of the two principles in the dual drugs is usually based on their observed (or anticipated) synergistic or additive pharmacological activities to enable the identification of highly active novel chemical entities. Hybrid drugs are basically designed to counterbalance the known side effects associated with the other hybrid part or to amplify its effect through action on another bio target or to interact with multiple targets as one single molecule [16, 17] lowering the risk of drug-drug interactions and minimizing the drug resistance [18]. The designing protocol of the synthesized derivatives is as shown in **Figure 1**.

Considering the focus on green synthesis in recent years, ionic liquid have attracted attention many of researchers. Ionic liquid have been referred as "designer solvents/ green solvents" because their physical and chemical properties can be adjusted by varying the cation and anion. Taking in consideration the above mentioned points we have carried out the synthesis of coumarin-pyrimidine coupled hybrid derivatives **4(a-f)** and **6(a-f)** using $[Et_3NH][HSO_4]$ as an solvent and easily recoverable Green catalyst (Scheme 1).

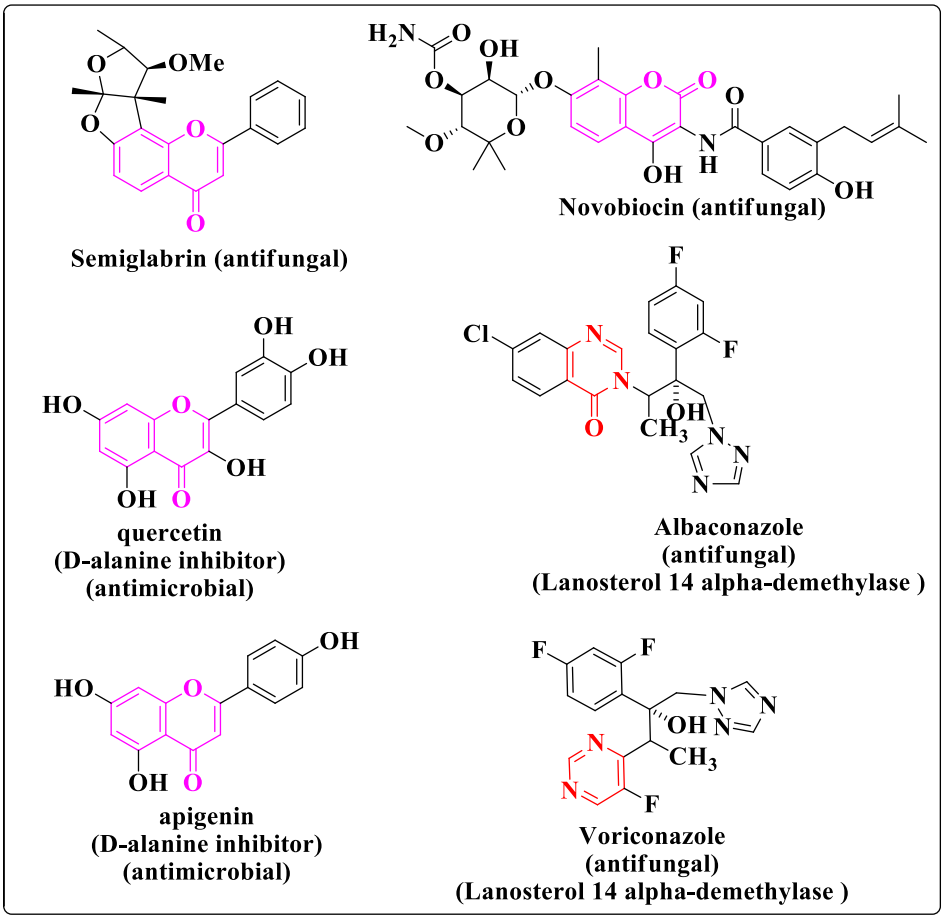


Figure 1. The designing protocol of the synthesized derivatives.

2. Result and Discussion

Chemistry

Herein, we describe the utility of $[Et_3NH][HSO_4]$ in molten state (Scheme 1), which is a low cost, mild, non-volatile and non-corrosive acidic ionic liquid, as an efficient Bronsted acid catalyst in solvent-free conditions for the Biginelli reaction.

We began our study with the model reaction of 4-oxo-4*H*-chromene-3-carbaldehydes, ethyl aceto-acetate and urea in $[Et_3NH][HSO_4]$ that was optimized by investigating various parameters such as mol percentage of catalyst at various temperatures. We screened the $[Et_3NH][HSO_4]$ ionic liquid as catalyst at various loads such as 5, 10, 15, 20 mol % and at various temperatures such as 80, 90, 100, 110 °C as shown in **Table 1**. When 5 mol % of the catalyst was used at 100 °C the product **4a** was obtained in 72 % yield in 150 min. Furthermore, the effect of the amount of catalyst was examined. We have studied the effect on various loads of catalyst such as 10, 15 and 20 mol % at 100 °C which gave the compound **4a** with 76 % in 105 min, 95 % in 60 min and 95 % in 60 min., respectively. Therefore, considering 15 mol % as an efficient amount the reaction was carried out at various temperatures like 80 °C, 90 °C, 100 °C and 110 °C. The use of 15 mol % catalyst at 100°C gave the compound **4a** with 95 % in 60 min. Therefore, 15 mol % of the $[Et_3NH][HSO_4]$ ionic liquid as catalyst and solvent was considered to ensure the best yield (95 %) in short reaction time (60 min) at 100 °C (Entry 3 of **Table 1**). These observations make the process under study more expeditious and economic, safe and eco-friendly. The recovery and reusability of the catalyst was investigated for the synthesis of compound **4a**. The findings are explained in **Table 2**; the recovered catalyst can be reused at least four additional times in subsequent reactions without a considerable decrease in its catalytic activity.

Total six novel ethyl 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **4(a-f)** were synthesized following this synthetic protocol. The reactions were completed in about 60-85 min (monitored by TLC). The yields of synthesized novel compounds were in the range of 86-95 %. Melting points were determined in open capillary tubes and are uncorrected. The physical data for the compounds are presented in **Table 3.** The formation of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral analysis and elemental analysis.

Table 1. Effect of different reaction conditions on $[Et_3NH][HSO_4]$ catalyzed synthesis of 4-(2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)pyrimidin-2(1H)-one **4a**.

Entry	Temperature (^{0}C)	Catalyst (mol %)	Time(min)	Yield (%)
1.	100	5	150	77
2.	100	10	105	76
3.	**100**	**15**	**60**	**95**
4.	100	20	60	95

5.	110	15	65	91
6.	90	15	80	70
7.	80	15	85	70

Table 2. Reusability of $[Et_3NH][HSO_4]$ catalyst for model reaction **4a**.

Entry	Run	Time	Yield
1.	1	60	95
2.	2	60	90
3.	3	60	88
4.	4	60	77

The synthesized derivatives **4(a-f)** (1mmol) was allowed to react with hydrazine hydrate (1.2 mmol) under solvent free condition using $[Et_3NH][HSO_4]$ as catalyst. The catalyst load and the temperature required for the synthesis of **6(a-f)** was also studied. We had screened the $[Et_3NH][HSO_4]$ ionic liquid as catalyst at various loads such as 5, 10, 15 mol % and at various temperatures such as 70, 80, 90 and 100 °C as shown in **Table 4**. When 5 mol % of the catalyst was used at 90 °C the product **6a** was obtained in 88 % yield in 30 min. Furthermore, the effect of the amount of catalyst was examined. We have studied the effect on various loads of catalyst such as 10 and 15 mol % at 90 °C which gave the compound **6a** with 87 % in 30 min and 85 % in 30 min., respectively. Therefore, considering 5 mol % as an efficient amount the reaction was carried out at various temperatures like 70 °C, 80 °C, 90 °C and 100 °C. The use of 5 mol % catalyst at 90°C gave the compound **6a** with 88 % in 30 min. Therefore, 5 mol % of the $[Et_3NH][HSO_4]$ ionic liquid as catalyst and solvent was considered to ensure the best yield (88 %) in short reaction time (30 min) at 90 °C (Entry 3 of **Table 4**). The recovery and reusability of the catalyst was investigated for the synthesis of compound **6a**. The findings are explained in **Table 5**; the recovered catalyst can be reused at least four additional times in subsequent reactions without a considerable decrease in its catalytic activity.

Total six 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2- thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **6(a-f)** were synthesized following this synthetic protocol. The reactions were completed in about 20-35 min (monitored by TLC). The yields of synthesized novel compounds were in the range of 80-95 %. Melting points were determined in open capillary tubes and are uncorrected. The physical data for the compounds are presented in

Table 3. The formation of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral analysis and elemental analysis.

Table 3. Time required for synthesis of **4(a-f)** and **6(a-f)** using $[Et_3NH][HSO_4]$ ionic liquid.

Compound	R_1	R_2	R_3	X	Molecular Formula	M.P. °C	Time (min)
4a	H	C_2H_5	-	O	$C_{17}H_{16}N_2O_5$	270-272	60
4b	H	C_2H_5	-	S	$C_{17}H_{16}N_2O_4S$	210-212	75
4c	F	C_2H_5	-	O	$C_{17}H_{15}FN_2O_5$	200-202	80
4d	OCH_3	C_2H_5	-	O	$C_{18}H_{18}N_2O_6$	230-232	82
4e	OCH_3	C_2H_5	-	S	$C_{18}H_{18}N_2O_5S$	222-224	85
4f	F	C_2H_5	-	S	$C_{17}H_{15}FN_2O_4S$	228-230	85
6a	H	-	$NHNH_2$	O	$C_{15}H_{14}N_4O_4$	256-258	30
6b	H	-	$NHNH_2$	S	$C_{15}H_{14}N_4O_3S$	198-200	28
6c	F	-	$NHNH_2$	O	$C_{15}H_{13}FN_4O_4$	210-212	20
6d	F	-	$NHNH_2$	S	$C_{15}H_{13}FN_4O_3S$	146-148	25
6e	OCH_3	-	$NHNH_2$	O	$C_{16}H_{16}N_4O_5$	208-210	30
6f	OCH_3	-	$NHNH_2$	S	$C_{16}H_{16}N_4O_4S$	158-160	35

M.P.: Melting point

Table 4. Effect of different reaction conditions on $[Et_3NH][HSO_4]$ catalyzed synthesis of 6-methyl-2-oxo-4-(4-oxo-4H-chromen-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **6a**.

Entry	Temperature (^{0}C)	Catalyst (mol %)	Time(min)	Yield (%)
1.	70	5	48	75
2.	80	5	42	80
3.	**90**	**5**	**30**	**88**
5.	100	5	30	85
6.	90	10	30	87
7.	90	15	30	85

Table 5. Reusability of $[Et_3NH][HSO_4]$ catalyst for model reaction **6a**.

Entry	Run	Time	Yield
1.	1	30	88
2.	2	30	86
3.	3	30	85
4.	4	30	80
5.	5	30	72

3. Materials and Methods

Chemistry

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. Infrared (IR) spectra were recorded on JASCO FTIR (PS 4000) using KBr pallet. Melting points were determined in open capillary tubes and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra of synthesized compounds were recorded on Bruker Advance II 400 NMR Spectrometer (Billerica, MA, USA) at 400 MHz Frequency in deuterated DMSO using TMS as internal standard (chemical shift δ in ppm). The chemical shifts are reported as NMR spectra δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), multiplet (m). Mass spectra were taken with WATERS, Q-TOF MICROMASS (E SI-MS).

Synthesis of $[Et_3NH][HSO_4]$ ionic liquid

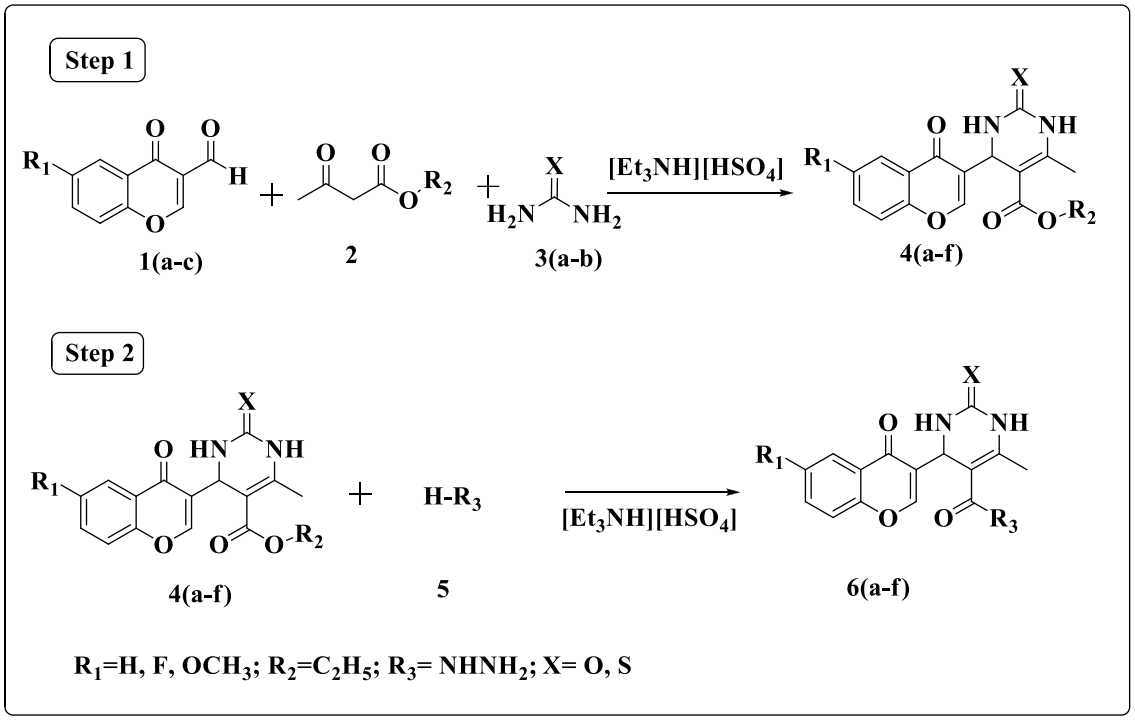
Sulfuric acid (1.96 g, 0.02 mol) 98 % solution in water was dropped into triethylamine (2.02 g, 0.02 mol) with stirring at 60 °C for 1 h. After the addition, the reaction mixture was stirred for another 1 h at 70 °C. The water molecule was removed by heating the residue at 80–90 °C under a high vacuum until the weight of the residue remained constant [19].

Synthesis of ethyl 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives 4(a-f).

A mixture of substituted 4-oxo-4*H*-chromene-3-carbaldehydes **1(a-c)** (1 mmol), 1,3-dicarbonyl compounds (1 mmol), urea (1 mmol) and $[Et_3NH][HSO_4]$ (15 mol %) under solvent-free conditions was heated to 100 °C for the required the time which was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and stirred for 5 min. The solid was filtered, washed with cold water and then recrystallized from ethanol to afford the pure product.

Synthesis of 4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2- thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide 6(a-f)

A mixture of ethyl4-(6-substituted-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivative **4(a-f)** (1 mmol), hydrazine hydrate **5** (1.2 mmol) and [Et3NH][HSO4] (5 mol %) under solvent-free conditions was heated to 90 °C for the required time which was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and stirred for 5 min. The solid was filtered, washed with cold water and then recrystallized from ethanol to afford the pure product.



Scheme 1. Synthesis of the target compounds **4(a-f)** and **6(a-f)**.

ethyl 6-methyl-2-oxo-4-(4-oxo-4H-chromen-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4a]

Yield 95 %; m.p.: 270-272 °C; IR (KBr ν_{max} in cm^{-1}): 3238 (N-H stretching), 3005 (C–H stretching), 2900 (-CH_3 stretching), 2815 (CH stretching of alkyl), 1746 (C=O stretching), 1601 (C=C stretching), 1454 (CH Bending of CH_2), 1356 (C-N stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.14 (t, *J*=7.10 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 4.05 (q, *J*=7.04 Hz, 2 H, CH_2), 4.72 (d, *J*=1.49 Hz, 1 H, CH), 7.41-7.59 (m, 3H, aromatic), 7.75 (s, 1 H, NH), 8.05 (s, 1 H, aromatic), 8.10 (d, *J*=1.44 Hz, 1 H, aromatic), 9.12 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.45, 18.51, 45.91, 61.37, 101.94, 118.07, 121.61, 123.87, 126.27,

126.68, 133.85, 149.33, 150.72, 155.65, 155.77, 167.37, 172.17; MS: m/z: 329.21 $[M+1]^+$; Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.20; H, 4.93; N, 8.50.

ethyl 6-methyl-4-(4-oxo-4H-chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4b]

Yield 87 %; m.p.: 210-212 °C; IR (KBr ν_{max} in cm^{-1}): 3235 (N-H stretching), 3005 (C–H stretching), 2905 (-CH_3 stretching), 2815 (CH stretching of alkyl), 1600 (C=C stretching), 1454 (CH Bending of CH_2), 1360 (C-N stretching), 1140 (C=S stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.17 (t, *J*=7.10 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.09 (q, *J*=7.04 Hz, 2 H, CH_2), 4.74 (d, *J*=1.49 Hz, 1 H, CH), 7.47-7.74 (m, 3H, aromatic), 8.03 (s, 1 H, NH), 8.06 (s, 1 H, aromatic), 8.12 (d, *J*=1.44 Hz, 1 H, aromatic), 8.89 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.50, 18.44, 50.62, 61.77, 106.24, 118.71, 121.32, 123.99, 126.12, 133.91, 150.11, 155.60, 160.39, 167.33, 171.94, 177.89; MS: m/z: 345.01 $[M+1]^+$; Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.31; H, 4.69; N, 8.10.

ethyl 4-(6-fluoro-4-oxo-4H-chromen-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4c]

Yield 92 %; m.p.: 200-202 °C; IR (KBr ν_{max} in cm^{-1}): 3230 (N-H stretching), 3000 (C–H stretching), 2900 (-CH_3 stretching), 2815 (CH stretching of alkyl), 1745 (C=O stretching), 1600 (C=C stretching), 1454 (CH Bending of CH_2), 1364 (C-N stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.15 (t, *J*=7.10 Hz, 3 H, CH_3), 2.29 (s, *J*=2.11 Hz, 3 H, CH_3), 4.09 (q, *J*=7.04 Hz, 2 H, CH_2), 4.74 (d, *J*=1.51 Hz, 1 H, CH), 6.91-7.11 (m, 2 H, aromatic), 7.43 (s, 1 H, NH), 7.74 (d, *J*=2.93 Hz, 1 H, aromatic) 8.06 (s, 1 H, aromatic), 9.13 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.22, 18.11, 45.51, 61.70, 101.99, 111.52, 118.71, 119.23, 122.00, 126.88, 149.14, 150.79, 155.13, 156.11, 164.19, 167.19, 172.10; MS: m/z: 347.11 $[M+1]^+$; Anal. Calcd. for $C_{17}H_{15}FN_2O_5$: C, 58.96; H, 4.37; N, 8.09. Found: C, 58.99; H, 4.39; N, 8.04.

ethyl 4-(6-methoxy-4-oxo-4H-chromen-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4d]

Yield 88 %; m.p.: 230-232 °C; IR (KBr ν_{max} in cm^{-1}): 3238 (N-H stretching), 3005 (C–H stretching), 2900 (-CH_3 stretching), 2845 (-OCH_3 stretching), 2815 (CH stretching of alkyl), 1742 (C=O stretching), 1600 (C=C stretching), 1454 (CH Bending of CH_2), 1362 (C-N stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.17 (t, *J*=7.10 Hz, 3 H, CH_3), 2.29 (s, *J*=2.11 Hz, 3 H, CH_3), 3.80 (s, 3 H, O CH_3), 4.10 (q, *J*=7.04 Hz, 2 H, CH_2) 4.74 (d, *J*=1.51 Hz, 1 H, CH), 7.37 (d, *J*=8.90 Hz, 1 H), 7.42 (s, 1 H, NH), 7.48 - 7.52 (m, 2 H), 8.06 (s, 1 H, aromatic), 9.13 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.45, 18.51, 45.91, 55.08, 61.37, 101.94, 107.44, 117.98, 119.35, 122.42, 149.33, 150.72, 152.63, 155.65, 156.18, 167.37, 171.94; MS: m/z: 359.91 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.35; H, 5.09; N, 7.80.

ethyl 4-(6-methoxy-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4e]

Yield 86 %; m.p.: 222-224 °C; IR (KBr ν_{max} in cm^{-1}): 3235 (N-H stretching), 3008 (C–H stretching), 2908 (-CH_3 stretching), 2845 (-OCH_3 stretching), 2813 (CH stretching of alkyl), 1740 (C=O stretching), 1600 (C=C stretching), 1454 (CH Bending of CH_2), 1360 (C-N stretching), 1148 (C=S stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.17 (t, *J*=7.10 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 3.80 (s, 3 H, O CH_3), 4.11 (q, *J*=7.04 Hz, 2 H, CH_2), 4.73 (d, *J*=1.49 Hz, 1 H), 7.37 (d, *J*=8.90 Hz, 1 H), 7.36 (s, 1 H, NH), 7.48 - 8.08 (m, 3 H), 8.89 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.45, 18.51, 49.08, 55.80, 61.37, 104.43, 107.44, 117.98, 119.35, 122.42, 126.68, 149.33, 152.63, 154.52, 156.18, 167.37, 171.94, 177.89; MS: m/z: 375.17 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.77; H, 4.86; N, 7.46.

ethyl 4-(6-fluoro-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate [4f]

Yield 92 %; m.p.: 228-230 °C; IR (KBr ν_{max} in cm^{-1}): 3230 (N-H stretching), 3000 (C–H stretching), 2910 (-CH_3 stretching), 2810 (CH stretching of alkyl), 1742 (C=O stretching), 1605 (C=C stretching), 1450 (CH Bending of CH_2), 1360 (C-N stretching), 1140 (C=S stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 1.15 (t, *J*=7.10 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.11 (q, *J*=7.04 Hz, 2 H, CH_2), 4.73 (d, *J*=1.49 Hz, 1 H, CH), 6.91-7.74 (m, 3 H,

aromatic), 7.76 (s, 1 H, NH), 8.08 (s, 1 H, aromatic), 8.89 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 14.44, 18.46, 50.66, 61.79, 106.33, 111.50, 118.73, 119.31, 122.18, 126.89, 149.15, 152.36, 160.19, 162.58, 167.79, 171.96, 177.88; MS: m/z: 363.15 $[M+1]^+$; Anal. Calcd. for $C_{17}H_{15}FN_2O_4S$: C, 56.35; H, 4.17; N, 7.73. Found: C, 56.37; H, 4.19; N, 7.70.

6-methyl-2-oxo-4-(4-oxo-4H-chromen-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6a]

Yield 88 %; m.p.: 256-258 °C; IR (KBr ν_{max} in cm^{-1}): 3520 (NH_2 stretching), 3450 (N-H stretching), 3000 (C–H stretching), 2900 (-CH_3 stretching), 1742 (C=O stretching), 1605 (C=C stretching), 1368 (C-N stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.03 (s, 3 H, CH_3), 3.13 (s, 2 H, NH_2), 4.74 (d, *J*=1.51 Hz, 1 H, CH), 7.08 (s, 1 H, NH), 7.42 (s, 1 H, NH), 7.47-8.13 (m, 5 H, aromatic), 9.39 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.49, 46.11, 102.31, 118.71, 121.61, 123.44, 126.23, 126.85, 133.88, 149.45, 150.71, 155.36, 159.17, 168.62, 172.49; MS: m/z: 315.25 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.32; H, 4.49; N, 17.83.

6-methyl-4-(4-oxo-4H-chromen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6b]

Yield 88 %; m.p.: 198-200 °C; IR (KBr ν_{max} in cm^{-1}): 3515 (NH_2 stretching), 3450 (N-H stretching), 3000 (C–H stretching), 2908 (-CH_3 stretching), 1742 (C=O stretching), 1600 (C=C stretching), 1360 (C-N stretching), 1145 (C=S stretching), 1002 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.26 (s, 3 H, CH_3), 3.13 (s, 2 H, NH_2), 4.74 (d, *J*=1.49 Hz, 1 H, CH), 7.08 (s, 1 H, NH), 7.47 (s, 1 H, NH), 7.59-8.13 (m, 5 H, aromatic), 8.89 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.97, 51.16, 106.11, 118.23, 121.14, 123.43, 126.28, 126.81, 133.69, 150.11, 155.49, 160.19, 168.66, 172.32, 177.80; MS: m/z: 331.29 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96. Found: C, 54.55; H, 4.29; N, 16.93.

4-(6-fluoro-4-oxo-4H-chromen-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6c]

Yield 95 %; m.p.: 210-212 °C; IR (KBr ν_{max} in cm^{-1}): 3510 (NH_2 stretching), 3455 (N-H stretching), 3000 (C–H stretching), 2910 (-CH_3 stretching), 1742 (C=O stretching), 1605 (C=C

stretching), 1365 (C-N stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.03 (s, 3 H, CH_3), 3.13 (s, 2 H, NH_2), 4.74 (d, *J*=1.51 Hz, 1 H, CH), 6.91 (d, *J*=8.93 Hz, 1 H), 7.08 (s, 1H, NH), 7.10-8.06 (m, 4 H, aromatic), 9.39 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.26, 46.83, 106.12, 109.11, 118.36, 121.33, 123.39, 126.10, 147.77, 150.18, 155.60, 155.99, 162.45, 168.20, 172.45; MS: m/z: 333.55 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{13}FN_4O_4$: C, 54.22; H, 3.94; N, 16.86. Found: C, 54.25; H, 3.96; N, 16.83.

4-(6-fluoro-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6d]

Yield 90 %; m.p.: 146-148 °C; IR (KBr ν_{max} in cm^{-1}): 3512 (NH_2 stretching), 3458 (N-H stretching), 3000 (C–H stretching), 2912 (-CH_3 stretching), 1742 (C=O stretching), 1605 (C=C stretching), 1360 (C-N stretching), 1140 (C=S stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.27 (s, 3 H, CH_3), 3.14 (s, 2 H, NH_2), 4.74 (d, *J*=1.49 Hz, 1 H, CH), 6.92 (d, *J*=8.93 Hz, 1 H), 7.09 (s, 1 H, NH), 7.11-8.09 (m, 4 H, aromatic), 8.90 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.10, 52.61, 106.21, 109.14, 118.24, 121.39, 123.41, 126.52, 150.19, 155.62, 160.41, 162.56, 168.21, 171.96, 177.81; MS: m/z: 349.72 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{13}FN_4O_3S$: C, 54.22; H, 3.94; N, 16.86. Found: C, 54.27; H, 3.99; N, 16.80.

4-(6-methoxy-4-oxo-4H-chromen-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6e]

Yield 82 %; m.p.: 208-210 °C; IR (KBr ν_{max} in cm^{-1}): 3520 (NH_2 stretching), 3452 (N-H stretching), 3000 (C–H stretching), 2905 (-CH_3 stretching), 2845 (-OCH_3 stretching), 1742 (C=O stretching), 1605 (C=C stretching), 1362 (C-N stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.03 (s, 3 H, CH_3), 3.13 (s, 2 H, NH_2), 3.80 (s, 3 H, OCH_3), 4.74 (d, *J*=1.51 Hz, 1 H), 7.08 (s, 1 H, NH), 7.37-8.06 (m, 5 H, aromatic), 9.39 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.92, 46.48, 56.82, 106.66, 109.11, 118.24, 121.48, 123.49, 125.76, 147.41, 150.62, 155.12, 156.30, 168.61, 172.27; MS: m/z: 345.02 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.84; H, 4.69; N, 16.25.

4-(6-methoxy-4-oxo-4H-chromen-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide [6f]

Yield 80 %; m.p.: 158-160 °C; IR (KBr ν_{max} in cm^{-1}): 3522 (NH_2 stretching), 3455 (N-H stretching), 3000 (C–H stretching), 2910 (-CH_3 stretching), 2845 (-OCH_3 stretching), 1742 (C=O stretching), 1605 (C=C stretching), 1360 (C-N stretching), 1146 (C=S stretching), 1005 (-O- stretching); ^{1}H NMR (400 MHz, DMSO, δ_H ppm): 2.26 (s, 3 H, CH_3), 3.13 (s, 2 H, NH_2), 3.80 (s, 3 H, OCH_3), 4.74 (d, *J*=1.49 Hz, 1 H), 7.08 (s, 1 H, NH), 7.37-8.08 (m, 5 H, aromatic), 8.89 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO, δ_C ppm): 18.90, 51.50, 105.66, 106.41, 118.90, 121.71, 123.44, 126.47, 150.53, 150.66, 156.30, 160.31, 168.22, 171.96, 177.98; MS: m/z: 361.10 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.47; N, 15.55. Found: C, 53.35; H, 4.49; N, 15.51.

4. Conclusion

In this study, a suite of novel chromone-pyrimidine coupled hybrid derivatives **4(a-f)** and **6(a-f)** has been synthesized using Green protocol. Use of green method, i.e. use of ionic liquid helped us in the synthesis of excepted derivatives in good yield and proving its advantage by avoiding pollution in the environment caused by hazardous chemicals. The mild reaction conditions, excellent yields in shorter reaction time and evasion of cumbersome work-up procedures make this process economically lucrative for industrial application with the advantage of reusability of catalyst.

5. References

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