Novel Trifluoromethylcoumarinyl Urea Derivatives: Synthesis, Characterization, Fluorescence, and Bioactivity

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Abstract: A series of novel trifluoromethylcoumarinyl urea derivatives were designed, synthesized, and characterized by ^{1}H-NMR, ^{13}C-NMR, and HR-ESI-MS. The fluorescence spectra of the target compounds were recorded. The spectra show that most of the title compounds glow green with λ_{max}^{em} of 500–517 nm, while compounds **5r**, **5s**, **5u**, and **5l** (compounds named by authors) glow violet with λ_{max}^{em} of 381–443 nm. Moreover, the herbicidal and antifungal activities of the synthesized compounds were evaluated for their potential use as pesticides. The results indicate that compound **5f** against the caulis of *Amaranthus retroflexus* and compounds **5j** and **5l** against the taproot of *Digitaria sanguinalis* are equivalent to the commercial herbicide Acetochlor. Nine of the title compounds are more antifungal than commercial fungicide Carbendazim against *Botrytis cinerea*.

Keywords: trifluoromethylcoumarinyl urea; synthesis; fluorescence; herbicidal activity; antifungal activity

1. Introduction

Ureas are very important compounds in organic chemistry because of their extensive applications in medicine and agriculture. The substituted ureas exhibit diversified medicinal activities such as antimicrobial [1], antiviral [2], anti-HIV [3], anti-AIDS [4], anti-malaria [5], anti-proliferative [6], antitumor [7], anticancer [8], anti-inflammatory [9], anti-ulcerogenic [10], anticonvulsant [11], anti-nociceptive [12], antihypertensive [9], antidepressant [13], complement inhibition [14], HDL-elevating [15], and inhibition of nitric oxide [16]. Urea compounds also possess a broad spectrum of pesticidal activities, such as benzoylurea type insecticides (Diflubenzuron, Chlorbenzuron, etc.) [17], fungicides (Triclocarban, Pencycuron, etc.) [18], sulfonylurea type herbicides (Chlorsulfuron, Nicosulfuron, etc.), and urea herbicides (Benzthiazuron, Siduron, etc.) [19], as well as plant growth regulators (Thidiazuron, Forchlorfenuron, etc.) [20].

On the other hand, coumarin is a subunit of many natural products and a wide range of synthetic compounds, constituting an important class of heterocycles. These kinds of compounds are widely used in the food, cosmetic, and perfume industries. Coumarins are also an important class of fluorescents and are used as laser dyes, brighteners, fluorescent labels, and other organic optical materials, such as emission layers of organic light-emitting diodes (OLED) [21–24]. Additionally, they are sometimes used as probes to monitor certain physiological process and trace harmful substances in environment [25–27]. It has been noted that the photophysical and spectroscopic properties of coumarin can be easily adjusted by the introduction of different substituents into the core, which leads them to be more flexible and fit well in various applications [28]. It is reported that the electron-withdrawing groups on 3- or 4-position and electron-releasing groups on 6- or 7-position of the coumarin skeleton could enhance the band intensity of fluorescence [29]. Moreover, coumarins have been extensively

studied for their use as biological agents with anti-depressant, anticoagulant, anti-inflammatory, antibacterial, antifungal, antimalarial, moluscicidal, and anthelmintic activities [30–36]. Much research has been focused on coumarin derivatives for their pesticidal activities too. One of the representative compounds is 7-hydroxyl-4-methylcoumarin, which exhibited interesting pesticidal activities of allelopathy and antifungal, and it is reported that the C7 hydroxyl group and C4 methyl substitution contributed significantly to the activity [37,38]. Moreover, brominated derivatives of the compound showed remarkable larvicidal and ovicidal activities against vector mosquitoes [39]. Derivatives of 7-hydroxyl-4-methylcoumarin are also reported to show anthelmintic and acaricidal activities [40,41].

In addition, fluorine is the most electronegative of all elements, which endows it with unique properties. Indeed, it is commonly accepted that introducing a fluorine-containing group onto the molecule scaffold often leads to improvement of the molecular chemical, physical, and biological properties [42]. To date, the trifluoromethyl (CF_3) group has appeared as the archetypal and most sought-after fluorine-containing group, and there have been reported a huge and ever-increasing number of trifluoromethylated compounds in the literature [43,44]. The CF_3 group is very important in medicinal chemistry [45] due to its high lipophilicity, easy transportation, and hard degradation in vivo [46,47]. Thus, the introduction of a CF_3 group into bioactive molecules has become a preferable approach in pharmaceutical studies [48,49]. However, the literature about CF_3-substituted coumarins is limited, and the reports about these compounds are mainly focused on their use as substrate probes to detect the physiology [50–52]. Also, in view of these observations and in continuation of our research program on the synthesis of fluorinated coumarins [53], we herein report the synthesis and characterization of some novel 4-trifluoromethyl-6-substituted-ureido-7-methoxylcoumarins, whose fluorescent properties and antifungal and herbicidal activities are also evaluated.
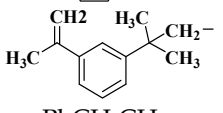
2. Results and Discussion

2.1. Chemistry

The synthesis of target compounds was carried out according to Scheme 1. Compound **1** was prepared from the reaction of resorcinol with ethyl trifluoroacetoacetate catalyzed by Con. (concentrated) H_2SO_4. Compound **2** was synthesized by methylation of compound **1** with dimethyl sulfate using anhydrous K_2CO_3 as catalyst in acetone. Compound **3** was synthesized by nitration of compound **2** with guanidine nitrate in Con. H_2SO_4. Compound **4** was obtained by reduction of compound **3** with Fe powder in aqueous solution of NH_4Cl. The target compounds **5a–5u** were furnished by addition of compounds **4** to a series of isocyanates catalyzed by triethylamine in CH_2Cl_2 (DCM). The structures of all target compounds were well characterized by ^{1}H-NMR, ^{13}C-NMR, and HR-ESI-MS. The spectrograms were listed in the supplementary materials.

2.2. UV Absorption and Fluorescence Characteristics

The λ_{max}^{ab} (maximum absorption wavelength), ε_{max} (molar absorptivity), λ_{max}^{em} (maximum emission wavelength), $\Delta\lambda$ (Stokes shift) and Φ_f (fluorescence quantum yield) of the title compounds are listed in Table 1. The λ_{max}^{ab} of all the title compounds are 360–374 nm, and the ε_{max} are 5.24–7.67×10^3 L·mol^{-1}·cm^{-1}. Most of the title compounds glow green fluorescence with λ_{max}^{em} of 500–517 nm when illuminated by ultraviolet light, while compounds **5r**, **5s**, **5u**, and **5l** glow violet fluorescence with λ_{max}^{em} of 381–443 nm (Figure 1). However compounds **5o** and **5t** do not fluoresce at the concentration. The values of Φ_f indicate that all the title compounds are weaker fluorescent compare to the standard reference compound quinine sulfate. Table 1 shows that alkyl substituted compounds **5a–5i** have higher fluorescence quantum yield than the phenyl substituted compounds **5k–5p** and **5r–5u**, but compounds **5j** and **5q** with high Φ_f were the exceptions. From the phenomenon, it can be concluded that electron-donating groups may favor the fluorescence of the compounds.

Scheme 1. Synthetic route of title compounds.
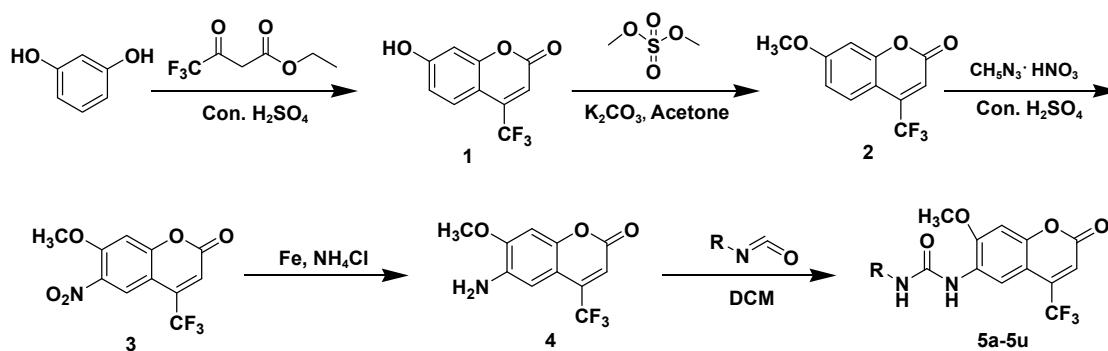
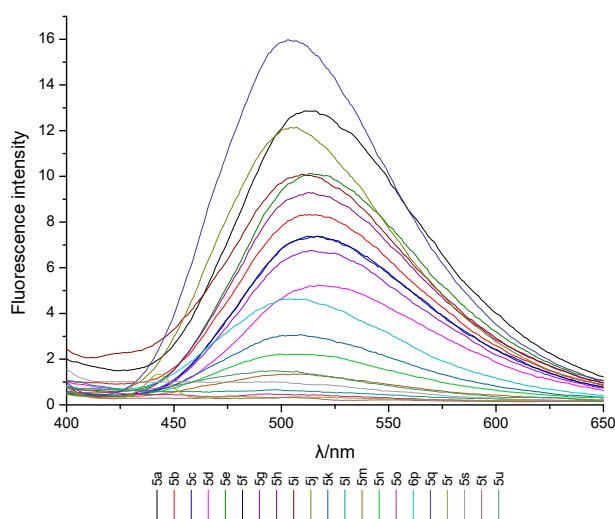| Compd.	R	Compd.	R
5a	CH₃CH₂-	**5k**	3-ClPh-
5b	CH₃CH₂CH₂-	**5l**	4-ClPh-
5c	(CH₃)₂CH-	**5m**	3-FPh-
5d	(CH₃)₃C-	**5n**	2,4-F₂Ph-
5e	CH₃(CH₂)₄CH₂-	**5o**	3-CH₃Ph-
5f		**5p**	3-CF₃Ph-
5g		**5q**	4-CF₃Ph-
5h		**5r**	2-CH₃OPh-
		5s	3-CH₃OPh-
5i	PhCH₂CH₂-	**5t**	4-CH₃OPh-
5j	2-ClPh-	**5u**	4-CF₃OPh-

**Figure 1.** Fluorescence spectrum of title compounds.

Table 1. Properties of UV absorption and fluorescence of title compounds.

Compd.	λ_{max}^{ab} (nm)	A	$\varepsilon_{max} \times 10^3$ (L·mol^{-1}·cm^{-1})	λ_{max}^{em} (nm)	$\Delta\lambda$ (nm)	Φ_f
5a	369	0.216	7.13	512	143	0.114
5b	369	0.186	6.40	511	142	0.110
5c	374	0.180	6.19	516	143	0.065
5d	373	0.188	6.73	517	145	0.044
5e	360	0.189	7.30	513	154	0.087
5f	369	0.160	5.92	512	144	0.064
5g	370	0.154	5.92	513	143	0.053
5h	370	0.150	6.90	512	142	0.070
5i	366	0.129	5.24	510	144	0.082
5j	367	0.182	7.50	507	141	0.098
5k	367	0.171	7.05	509	143	0.024
5l	369	0.174	7.17	381	12	0.028
5m	363	0.162	6.71	506	143	0.013
5n	367	0.183	7.25	500	134	0.020
5o	367	0.164	6.43	-	-	-
5p	363	0.166	7.40	504	141	0.041
5q	367	0.134	5.98	503	137	0.115
5r	372	0.143	5.84	443	72	0.005
5s	363	0.134	5.47	396	33	0.013
5t	365	0.136	5.55	-	-	-
5u	367	0.166	7.67	387	21	0.013

- no fluorescence was detected.

2.3. Herbicidal Activities

The herbicidal activities of the 21 title compounds of 20 mg·L^{-1} and 100 mg·L^{-1} against the taproot and caulis growth of dicotyledonous weed *A. retroflexus* and monocotyledonous weed *D. sanguinalis* were assayed. The inhibition of the compounds with effectiveness of greater than 50% to at least one organ of the test weeds at 100 mg·L^{-1} are displayed in Figure 2. It indicates that compounds **5j** and **5s** show medium inhibition against the taproot growth of *A. retroflexus*, and compounds **5f**, **5s**, **5k** and **5n** show medium to high inhibition against the caulis growth of *A. retroflexus*. Moreover, compounds **5j** and **5l** show medium inhibition against the taproot growth of *D. sanguinalis*, and compounds **5f**, **5q**, and **5r** show medium inhibition against the caulis growth of *D. sanguinalis*. Furthermore, the herbicidal activities of **5f** against the caulis of *A. retroflexus*, **5j** and **5l** against the taproot of *D. sanguinalis* are equivalent to the commercial herbicide Acetochlor. It also shows that only compounds **5j** and **5s** are both active to the two test herbs; the other compounds display certain selectivity between the test herbs. Contrary to the fluorescence, the phenyl substituted compounds show higher herbicidal activity than the alkyl substituted compounds except compound **5f** substituted by cyclopentyl. All the compounds substituted by phenyls with chlorine (**5j**–**5l**) exhibit better activity. Compounds **5o** (3-CH$_3$Ph-), **5r** (2-CH$_3$OPh-) and **5s** (3-CH$_3$OPh-) substituted by phenyls with electron donating groups are more active.
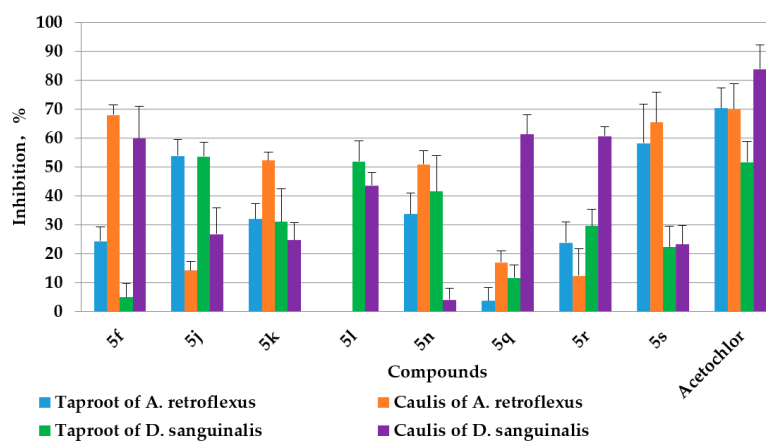
Figure 2. Herbicidal activities of title compounds.

2.4. Antifungal Activities

The in vitro antifungal activities of the title compounds of 20 mg·L^{-1} and 100 mg·L^{-1} against the mycelium growth of the phytopathogens *Valsa mali*, *B. cinerea*, *Colletotrichum glecosporioides*, and *Fusarium oxysporum* were assayed. The inhibition of the synthesized compounds with effectiveness of greater than 50% at 100 mg·L^{-1} are exhibited in Figure 3. This indicates that more compounds exhibit stronger inhibition against *B. cinerea* than the other three plant disease fungi (the inhibitory rates of all the title compounds against *F. oxysporum* are less than 50%, and they do not appear in Figure 3). There are only four title compounds showing medium inhibition against *V. mali*, and only one compound having an inhibitory rate of more than 50% to *C. glecosporioides*. Meanwhile, 12 of the title compounds exhibit medium to high activity against *B. cinerea*, and nine of them are more antifungal than the commercial fungicide Carbendazim. Based on the above description, it seems that the phenyl substitutes are of more benefit to the antifungal activity. Compounds **5j**, **5l**, and **5o–5t** with substitutes of –Cl, –CH$_3$, –CF$_3$, or –OCH$_3$ on phenyls have more potential.
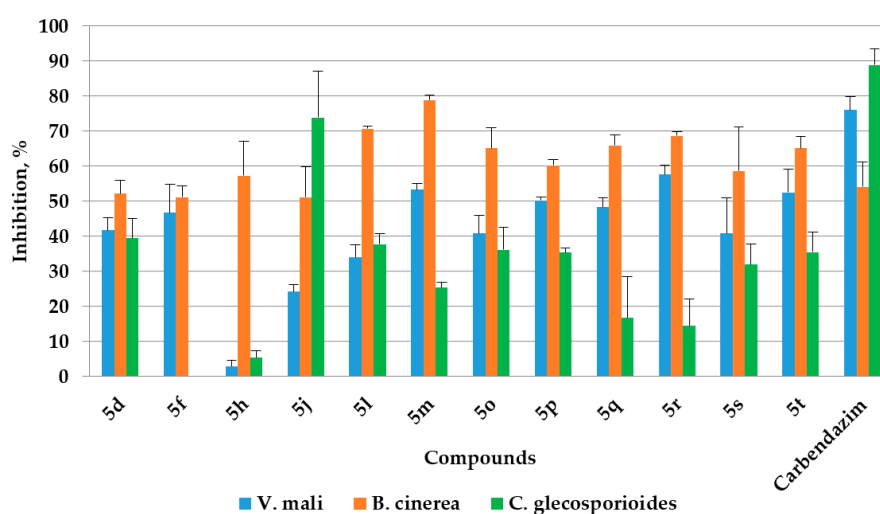

Figure 3. Antifungal activities of title compounds.

3. Experimental Section

3.1. Chemistry

3.1.1. General Procedures

All chemicals were obtained from commercial sources and used without further purification. Glass plates pre-coated with silica gel 60 GF$_{254}$ (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China) were used for analytical thin layer chromatography (TLC). An uncorrected WRS-1B digital melting-point apparatus (Shanghai Precision Optical Instrument Co., Ltd., Shanghai, China) was used to determine the melting points. A Bruker Avance III HD 500 MHz nuclear magnetic resonance instrument (Bruker, Fällanden, Switzerland) was used to record the ^{1}H- and ^{13}C-NMR spectra in CDCl$_3$ or DMSO-d_6 (^{1}H at 500 MHz and ^{13}C at 126 MHz) using tetramethylsilane (TMS) as the internal standard. A maXis Q-TOF high-resolution mass spectra instrument (Bruker, Karlsruhe, Germany) was used to measure the HR-ESI-MS. An F-4600 fluorescence spectrophotometer (Hitachi, Tokyo, Japan) was used to record the fluorescence.

3.1.2. Synthesis of 4-Trifluoromethyl-7-hydroxycoumarin (**1**)

Concentrated sulfuric acid (2 mL) and trifluoroacetoacetate (3.7 g, 10 mmol) were added dropwise in turn to the solution of resorcinol (2.2 g, 10 mmol) in ethanol (4 mL) with stirring. Then the mixture

was heated to maintain at 80 °C until the end of the reaction was detected by TLC. The resulted thick magenta liquid was dripped into 10 mL of cold water with rigorous stirring. The precipitate was filtered and dried to give compound **1**. Yield 88.9%, m.p. (melting point) 175–176 °C [lit. (literature) 178–179 °C] [54].

3.1.3. Synthesis of 4-Trifluoromethyl-7-methoxycoumarin (**2**)

Dimethyl sulfate (2.5 g, 20 mmol) was added dropwise to the suspension of compound **1** (5.8 g, 25 mmol) and anhydrous K_2CO_3 (4.1 g, 30 mmol) in 66 mL of acetone with stirring. Then the mixture was heated to reflux for 8 h. After K_2CO_3 was filtered out, the filtrate was rotary evaporated to 1/3 of the total volume. Then the residue was allowed to cool to room temperature until a white solid precipitated. The solid product was filtered out and washed with cold water to neutral pH to get compound **2**. Yield 97.8%, m.p. 110–112 °C (lit. 111–112 °C) [55].

3.1.4. Synthesis of 4-Trifluoromethyl-6-nitro-7-methoxycoumarin (**3**)

Guanidine nitrate (1.4 g, 11.6 mmol) was added batch-wise to the solution of **2** (2.6 g, 10.7 mmol) in 16 mL Conc. H_2SO_4 with stirring at 0–5 °C. The mixture was stirred at room temperature for 3 h until the end of the reaction. Then the reaction mixture was poured into 40 mL of ice water with stirring to obtain a pale yellow solid. The solid product was filtered and dried to give compound **3**. Yield 97.7%, m.p. 118–119 °C (as reported) [53].

3.1.5. Synthesis of 4-Trifluoromethyl-6-amino-7-methoxycoumarin (**4**)

The mixture of compound **3** (2.9 g, 10 mmol), iron powder (5.0 g, 90 mmol), NH_4Cl (1.1 g, 20 mmol) and 50 mL water was mechanically stirred at room temperature until the end of the reaction. The mixture was extracted with ethyl acetate (50 mL × 3). The extract was dried over anhydrous sodium sulfate, then filtered and rotary evaporated to get a dark yellow crystal of compound **4**. Yield 70%, m.p. 179–180 °C (as reported) [53]. The compound is unstable and needs to be used as soon as possible for the next step.

3.1.6. General Procedure for Synthesis of 4-Trifluoromethyl-6-amino-7-methoxycoumarinyl Urea Derivatives (**5a**–**5u**)

To a cool suspension of **4** (0.65 g, 2.5 mmol) in 3.5 mL of anhydrous dichloromethane, isocyanate (3 mmol) was added dropwise with stirring. The mixture was allowed to return to room temperature until the end of the reaction. The solid produced was filtered and chromatographed on a flash silica gel column (ethyl acetate/petroleum ether = 1:3) to give the target compounds **5a**–**5u**. The yield, appearance, m.p., NMR and HR-ESI-MS (MS) date of the synthesized compounds are listed below.

1-Ethyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5a**). Light yellow solid; yield: 42.8%; m.p. 232–233 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.68 (s, 1H), 8.14 (s, 1H), 7.23 (s, 1H), 6.95 (t, *J* = 5.3 Hz, 1H), 6.83 (s, 1H), 4.01 (s, 3H), 3.20–3.09 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.46, 155.39, 152.17, 150.33, 140.41 (q, *J* = 31.5 Hz), 127.99, 122.27 (q, *J* = 275.94 Hz), 113.47 (q, *J* = 6.3 Hz), 111.52 (q, *J* = 1.26Hz), 106.07, 100.16, 57.24, 34.31, 15.72.; HR-ESI-MS *m/z*: 353.0712 [M + Na]$^+$ (calculated for $C_{14}H_{13}F_3N_2NaO_4$, 353.0725).

1-Propyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5b**). White solid; yield: 31.1%; m.p. 229 °C. ^{1}H-NMR (500 MHz, DMSO) δ: 8.68 (s, 1H), 8.16 (s, 1H), 7.22 (s, 1H), 6.97 (t, *J* = 5.3 Hz, 1H), 6.82 (s, 1H), 4.00 (s, 3H), 3.06 (q, *J* = 5 Hz, 2H), 1.52–1.38 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (126MHz, DMSO) δ: 159.47, 155.50, 152.16, 150.32, 140.41 (q, *J* = 31.5 Hz), 128.03, 122.27 (q, *J* = 275.94 Hz), 113.49 (q, *J* = 6.3 Hz), 111.48, 106.09, 100.18, 57.26, 41.24, 23.31, 11.83; HR-ESI-MS *m/z*: 367.0882 [M + Na]$^+$ (calculated for $C_{15}H_{15}F_3N_2NaO_4$, 367.0882).

1-Isopropyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5c**). Light yellow solid; yield: 54.2%; m.p. 224 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.66 (s, 1H), 8.07 (s, 1H), 7.20 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.80 (s, 1H), 3.99 (s, 3H), 3.82–3.72 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 6H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.45, 154.74, 152.11, 150.28, 140.42 (q, *J* = 31.5 Hz), 128.03, 122.16 (q, *J* = 275.94 Hz), 113.43 (q, *J* = 5.0 Hz), 111.36 (q, *J* = 2.52 Hz), 106.06, 100.11, 57.22, 41.36, 23.41; ESI-MS *m/z*: 345.30 [M + Na]$^+$ (calculated for $C_{15}H_{16}F_3N_2O_4$, 345.21).

1-(tert-Butyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5d**). yellow solid; Yield: 31.1%; m.p. 237 °C; ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 8.54 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.64 (s, 1H), 4.90 (s, 1H), 3.93 (s, 3H), 1.40 (s, 9H); ^{13}C-NMR (126 MHz, CDCl$_3$) δ: 159.76 (q, *J* = 6.2 Hz), 152.2 (q, *J* = 22.68 Hz), 151.92 (q, *J* = 5.5 Hz), 150.76 (q, *J* = 7.3 Hz), 142.11 (q, *J* = 32.76 Hz), 127.15 (q, *J* = 12.2 Hz), 121.57 (q, *J* = 275.94 Hz), 113.46 (q, *J* = 2.52 Hz), 112.58 (q, *J* =5.04 Hz), 106.85, 98.98 (q, *J* = 6.2 Hz), 56.33, 51.03, 29.31; HR-ESI-MS *m/z*: 381.1038 [M + Na]$^+$ (calculated for $C_{16}H_{17}F_3N_2NaO_4$, 381.1038).

1-Hexyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5e**). Light yellow solid; yield: 31.2%; m.p. 143 °C; ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 8.68 (s, 1H), 7.29 (s, 1H), 6.82 (s, 1H), 6.63 (s, 1H), 5.47 (t, *J* = 5.0 Hz, 1H), 3.89 (s, 3H), 3.28 (q, *J* = 5 Hz, 2H), 1.58–1.48 (m, 2H), 1.38–1.20 (m, 6H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (126 MHz, CDCl$_3$) δ: 159.73, 154.77, 151.80, 150.85, 142.13 (q, *J* = 32.76 Hz), 126.90, 122.63 (q, *J* = 122.37 Hz), 113.61 (q, *J* = 1.26 Hz), 112.66 (q, *J* = 5.04 Hz), 106.90, 98.98, 56.38, 40.53, 31.50, 29.99, 26.56, 22.57, 14.00; HR-ESI-MS *m/z*: 409.1346 [M + Na]$^+$ (calculated for $C_{18}H_{21}F_3N_2NaO_4$, 409.1351).

1-Cyclopentyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5f**). Light yellow solid; yield: 43.6%; m.p. 225 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.68 (s, 1H), 8.07 (s, 1H), 7.21 (s, 1H), 7.01 (d, *J* = 6.9 Hz, 1H), 6.81 (s, 1H), 4.00 (s, 3H), 3.97-3.91 (m, 1H), 1.90–1.81 (m, 2H), 1.72–1.48 (m, 4H), 1.45–1.31 (m, 2H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.49, 155.02, 152.10, 150.30, 140.42 (q, *J* = 32.76 Hz), 128.04, 122.29(q, *J* = 273.42 Hz),113.52 (q, *J* = 1.26 Hz), 111.34 (q, *J* = 2.52 Hz), 106.10, 100.18, 57.27, 51.28, 33.30, 23.59; HR-ESI-MS *m/z*: 393.1033 [M + Na]$^+$ (calculated for $C_{17}H_{17}F_3N_2NaO_4$, 393.1038).

1-Cyclohexyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5g**). Light yellow solid; yield 48.9%; m.p. 265 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.68 (s, 1H), 8.13 (s, 1H), 7.23 (s, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.82 (s, 1H), 3.99 (s, 3H), 3.54–3.45 (m, 1H),1.86–1.76 (m, 2H), 1.72–1.63 (m, 2H), 1.37–1.11 (m, 6H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.48, 154.70, 152.14, 150.29, 140.42 (q, *J* = 31.5 Hz), 128.06, 122.28(q, *J* = 275.94 Hz), 113.49(q, *J* = 6.3 Hz), 111.40 (q, *J* = 2.52 Hz), 106.09, 100.18, 57.27, 48.02, 33.35, 25.70, 24.71; HR-ESI-MS *m/z*: 407.1191 [M + Na]$^+$ (calculated for $C_{18}H_{19}F_3N_2NaO_4$, 407.1195).

1-(2-(3-(Prop-1-en-2-yl)phenyl)propan-2-yl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5h**). Light yellow solid; yield: 20.0%; m.p. 228–229 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.52 (s, 1H), 8.29 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.39–7.29 (m, 3H), 7.22 (s, 1H), 6.79 (s, 1H), 5.38 (s, 1H), 5.08 (s, 1H), 4.01 (s, 3H), 2.11 (s, 3H), 1.62 (s, 6H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.43, 154.39, 152.20, 150.33, 148.72, 143.45, 140.62, 140.34 (q, *J* = 31.5 Hz), 128.54, 128.04, 124.66, 123.56, 122.22 (q, *J* = 275.94 Hz), 122.21, 113.47 (q, *J* = 6.3 Hz), 112.89, 111.22, 106.03, 100.21, 57.29, 55.01, 30.25, 22.01; HR-ESI-MS *m/z*: 483.1504 [M + Na]$^+$ (calculated for $C_{24}H_{23}F_3N_2NaO_4$, 483.1508).

1-Phenethyl-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5i**). Light yellow solid; yield: 41.7%; m.p. 222 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 8.68 (s, 1H), 8.22 (s, 1H), 7.36–7.29 (m, 2H), 7.27–7.24 (m, 2H), 7.23–7.18 (m, 2H), 6.99 (t, *J* = 5.1 Hz, 1H), 6.82 (s, 1H), 3.98 (s, 3H), 3.38 (q, *J* = 6.6 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.46, 155.48, 152.21, 150.38, 140.40 (q, *J* = 31.5 Hz), 139.96, 129.17, 128.84, 127.96, 126.57, 122.28 (q, *J* = 275.94 Hz), 113.53 (q, *J* = 6.3Hz), 111.57 (q, *J* = 1.26 Hz), 106.09, 100.21, 57.25, 40.92, 36.20; HR-ESI-MS *m/z*: 429.1038 [M + Na]$^+$ (calculated for $C_{20}H_{17}F_3N_2NaO_4$, 429.1038).

1-(2-Chlorophenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5j**). Yellow solid; yield: 45.0%; m.p. 231 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.76 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 7.96 (s, 1H), 7.68–7.44 (m, 2H), 7.33 (d, *J* = 6.2 Hz, 1H), 7.27 (s, 1H), 6.83 (s, 1H), 4.03 (s, 3H); ^{13}C-NMR

(126 MHz, DMSO) δ: 159.34, 152.77, 152.54, 151.06, 140.72, 140.24 (q, *J* = 32.76 Hz), 130.54, 130.08 (q, *J* = 31.5 Hz), 126.78, 122.25 (q, *J* =274.68 Hz), 122.16, 118.80 (q, *J* = 3.6 Hz), 114.32 (q, *J* = 4.0 Hz), 113.83 (q, *J* = 5.2 Hz), 112.27, 106.13, 100.50, 57.44; HR-ESI-MS *m/z*: 435.0328, 437.0298 [M + Na]$^+$ (calculated for $C_{18}H_{12}ClF_3N_2NaO_4$, 435.0335, 437.0306).

1-(3-Chlorophenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5k**). Yellow solid; yield: 41.5%; m.p. 241 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.57 (s, 1H), 8.62 (s, 1H), 8.50 (s, 1H), 7.69 (s, 1H), 7.32–7.25 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 4.01 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.36, 152.70, 152.54, 151.04, 141.38, 140.24 (q, *J* = 31.2 Hz), 133.77, 131.00, 126.83, 122.27(q, *J* = 275.94 Hz), 122.21, 117.87, 117.03, 113.91 (q, *J* = 6.3 Hz), 112.28 (q, *J* = 1.6 Hz), 106.15, 100.54, 57.47; HR-ESI-MS *m/z*: 435.0323, 437.0294 [M + Na]$^+$ (calculated for $C_{18}H_{12}ClF_3N_2NaO_4$, 435.0335, 437.0306).

1-(4-Chlorophenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5l**). White solid; yield: 44.8%; m.p. 243 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.52 (s, 1H), 8.67 (s, 1H), 8.51 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.39–7.27 (m, 3H), 6.87 (s, 1H), 4.04 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.39, 152.75, 152.52, 150.97, 140.34 (q, *J* = 52.92 Hz), 138.85, 129.22, 126.97, 126.06, 122.29 (q, *J* = 287.28 Hz), 120.11, 113.92 (q, *J* = 2.52 Hz), 112.22 (q, *J* = 2.2 Hz), 106.17, 100.53, 57.48; HR-ESI-MS *m/z*: 435.0323, 437.0294 [M + Na]$^+$ (calculated for $C_{18}H_{12}ClF_3N_2NaO_4$, 435.0335, 437.0306).

1-(3-Fluorophenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5m**). Yellow solid; yield: 53.8%; m.p. 292 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.62 (s, 1H), 8.66 (s, 1H), 8.55 (s, 1H), 7.48 (d, *J* = 11.8 Hz, 1H), 7.38–7.27 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.87 (s, 1H), 6.81 (t, *J* = 8.4 Hz, 1H), 4.04 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 162.90 (d, *J* = 240 Hz), 159.37, 152.71, 152.53, 151.01, 141.69 (d, *J* = 11.3 Hz), 140.25 (q, *J* = 32.76 Hz), 130.92 (d, *J* = 9.8 Hz), 126.86, 122.26 (q, *J* = 275.94 Hz), 114.33 (d, *J* = 2.3 Hz), 113.85 (q, *J* = 6.3 Hz), 112.26, 108.90 (d, *J* = 21.42 Hz), 106.14, 105.28 (d, *J* = 26.46 Hz), 100.50, 57.45; HR-ESI-MS *m/z*: 419.0620 [M + Na]$^+$ (calculated for $C_{18}H_{12}F_4N_2NaO_4$, 419.0631).

1-(2,4-Difluorophenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5n**). Light yellow solid; yield: 47.6%; m.p. 240 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.28 (s, 1H), 8.95 (s, 1H), 8.67 (s, 1H), 8.13 (q, *J* = 10, 1H), 7.35–7.26 (m, 2H), 7.05 (t, *J* = 8.6 Hz, 1H), 6.85 (s, 1H), 4.04 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.38, 157.39 (dd, J_1 =240 Hz, J_2 =11.25 Hz), 152.86, 152.68 (dd, J_1 = 243.75 Hz, J_2 = 12.5 Hz), 152.64, 151.01, 140.27 (q, *J* = 31.5 Hz), 126.96, 124.24 (dd, J_1 = 7.5 Hz, J_2 = 3.75 Hz), 122.69 (dd, J_1 = 6.25 Hz, J_2 = 2.5 Hz), 122.25 (q, *J* = 273.75 Hz), 113.82 (q, *J* = 6.3 Hz), 112.40 (q, *J* = 2.0 Hz), 111.52 (dd, J_1 = 21.25 Hz, J_2 = 3.75 Hz), 106.12, 104.25 (dd, J_1 = 22.5 Hz, J_2 = 3.75 Hz), 100.51, 57.42; HR-ESI-MS *m/z*: 437.0527 [M + Na]$^+$ (calculated for $C_{18}H_{11}F_5N_2NaO_4$, 437.0537).

1-(m-Tolyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5o**). Yellow solid, yield: 24.7%; m.p. 217–218 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.33 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 4.04 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.39, 152.83, 152.47, 150.84, 140.30 (q, *J* = 31.5 Hz), 139.80, 138.56, 129.19, 127.22, 123.31, 122.29 (q, *J* = 275.94 Hz), 119.07, 115.82, 113.78 (q, *J* = 5.04 Hz), 112.03 (q, *J* = 1.6 Hz), 106.15, 100.46, 57.44, 21.70; HR-ESI-MS *m/z*: 415.0874 [M + Na]$^+$ (calculated for $C_{19}H_{15}f_3n_2nao_4$, 415.0882).

1-(3-(Trifluoromethyl)phenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5p**). Light yellow solid; yield 39.0%; m.p. 219 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.24 (s, 1H), 9.06 (s, 1H), 8.66 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.35–7.28 (m, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.86 (s, 1H), 4.05 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.40, 152.95, 151.10, 140.26(q, *J* = 31.5 Hz), 136.13, 129.76, 127.98, 126.94, 124.36, 123.32, 123.17, 122.27 (q, *J* = 275.94 Hz), 118.98, 113.84 (q, *J* = 6.3 Hz), 112.99, 106.11, 100.56, 57.43; HR-ESI-MS *m/z*: 469.0593 [M + Na]$^+$ (calculated for $C_{19}H_{12}F_6N_2NaO_4$, 469.0599).

1-(4-(Trifluoromethyl)phenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5q**). Yellow solid; yield: 16.9%; m.p. 212–213 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.80 (s, 1H), 8.67 (s, 1H), 8.59 (s, 1H), 7.66

(q, *J* = 9.0 Hz, 4H), 7.29 (s, 1H), 6.86 (s, 1H), 4.04 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ : 159.35, 152.62, 152.56, 151.08, 143.58, 140.24 (q, *J* = 32.76 Hz), 126.74, 126.65 (q, *J* = 3.78 Hz), 125.00 (q, *J* = 270 Hz), 122.47 (q, *J* = 31.5 Hz), 122.26 (q, *J* = 275.94 Hz), 118.28, 113.88 (q, *J* = 6.3 Hz), 112.34, 106.14, 100.54, 57.47; HR-ESI-MS *m/z*: 469.0593 [M + Na]+ (calculated for $C_{19}H_{12}F_6N_2NaO_4$, 469.0599).

1-(2-Methoxyphenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5r**). Light yellow solid; yield: 30.9%; m.p. 152 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.15 (s, 1H), 9.01 (s, 1H), 8.69 (s, 1H), 8.09 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 7.27 (s, 1H), 7.06–6.95 (m, 2H), 6.93–6.87 (m, 1H), 6.84 (s, 1H), 4.03 (s, 3H), 3.88 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.42, 153.15, 152.90, 150.89, 148.76, 140.35 (q, *J* = 32.76 Hz), 128.81, 127.36, 122.77, 122.28 (q, *J* = 275.94 Hz), 120.94, 119.89, 113.65 (q, *J* = 6.3 Hz), 112.69 (q, *J* = 1.9 Hz), 111.34, 106.08, 100.40, 57.28, 56.17; HR-ESI-MS *m/z*: 431.0826 [M + Na]+ (calculated for $C_{19}H_{15}F_3N_2NaO_5$, 431.0831).

1-(3-Methoxyphenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5s**). Yellow solid; yield: 37.8%; m.p. 196 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.40 (s, 1H), 8.67 (s, 1H), 8.47 (s, 1H), 7.29 (s, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 2.1 Hz, 1H), 6.98 (dd, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 6.86 (s, 1H), 6.58 (dd, J_1 = 8.2 Hz, J_2 =2.3 Hz, 1H), 4.04 (s, 3H), 3.75 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 160.21, 159.39, 152.78, 152.52, 150.90, 141.06, 140.29(q, *J* = 32.76 Hz), 130.16, 127.12, 122.29 (q, *J* = 275.94 Hz), 113.82 (q, *J* = 6.3Hz) 112.13 (q, *J* = 1.9 Hz), 111.00, 107.86, 106.16, 104.50, 100.49, 57.45, 55.46; HR-ESI-MS *m/z*: 431.0829 [M + Na]+ (calculated for $C_{19}H_{15}F_3N_2NaO_5$, 431.0831).

1-(4-Methoxyphenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5t**). Light yellow solid; yield: 37.7%; m.p. 212–213 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.21 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.28 (s, 1H), 6.91–6.83 (m, 3H), 4.03 (s, 3H), 3.72 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.43, 155.10, 153.01, 152.42, 150.75, 140.32 (q, *J* = 31.5 Hz), 132.85, 127.36, 122.28 (q, *J* = 275.94 Hz), 120.42, 114.55, 113.76 (q, *J* = 5.04 Hz), 111.94 (q, *J* = 1.1 Hz), 106.16, 100.42, 57.43, 55.66; HR-ESI-MS *m/z*: 431.0826 [M + Na]+ (calculated for $C_{19}H_{15}F_3N_2NaO_5$, 431.0831).

1-(4-(Trifluoromethoxy) phenyl)-3-(7-methoxy-2-oxo-4-(trifluoromethyl)-2H-chromen-6-yl) urea (**5u**). Light yellow solid; yield: 43.7%; m.p. 209 °C; ^{1}H-NMR (500 MHz, DMSO) δ: 9.61 (s, 1H), 8.70 (s, 1H), 8.54 (s, 1H), 7.62–7.56 (m, 2H), 7.39–7.29 (m, 3H), 6.88 (s, 1H), 4.07 (s, 3H); ^{13}C-NMR (126 MHz, DMSO) δ: 159.37, 152.79, 152.52, 150.98, 143.24 (q, *J* = 2.52 Hz), 140.28 (q, *J* = 31.5 Hz), 139.12, 126.95, 122.29, 122.27 (q, *J* = 273.75 Hz), 120.67 (q, *J* = 273.75 Hz), 119.84, 113.86 (q, *J* = 5.04 Hz), 112.25, 106.16, 100.52, 57.47; HR-ESI-MS *m/z*: 463.3020 [M + Na]+ (calculated for $C_{19}H_{13}F_6N_2O_5$, 463.3024).

3.2. Determination of UV Absorption and Fluorescence Spectrum

The title compounds were dissolved in methanol to prepare 1 and 10 μg·mL^{-1} solutions, and the same concentrations of the reference compound, quinine sulfate, were obtained using 0.1 mol·L^{-1} H_2SO_4 aqueous solution as the solvent. The 10 μg·mL^{-1} solutions of all the compounds were used to record UV absorption spectra. The intersection point wavelength of UV spectrums of title compound and quinine sulfate that lay between 300 to 400 nm was selected as the excitation wavelength to record the fluorescence spectrum. The 1 μg·mL^{-1} solutions were used to determine the fluorescence to ensure the absorbance was less than 0.05. The refraction indexes (n) of the 1 μg·mL^{-1} solutions were also measured to calculate the Φ_f. Δλ and Φ_f were calculated according to the following formulas [56]:

$$\Delta\lambda = \lambda_{max}{}^{em} - \lambda_{max}{}^{ab} \tag{1}$$

$$\Phi_f = (n^2{}_x \cdot D_x \cdot \Phi_{fstd})/(n^2{}_{std} \cdot D_{std}), \tag{2}$$

where n_x, n_{std}—refraction index of title compound and reference compound, respectively; D_x, D_{std}—fluorescence peak area of title compound and reference compound, respectively; Φ_{fstd}—fluorescence quantum efficiency of reference compound with value of 0.55.

3.3. Procedures for Activities Evaluation

3.3.1. Herbicidal Activity

The inhibition of the title compounds against the taproot and caulis growth of dicotyledonous weed *A. retroflexus* and monocotyledonous weed *D. sanguinalis* were determined in vitro [57]. Two-milligram and 10-mg portions of the title compounds were dissolved in 1 mL of acetone to give 2 and 10 g·L^{-1} of stock solutions, respectively. A suspension of 0.3 g agar powder in 60 mL distilled water was microwave heated to melt. Then 0.6 mL of the stock solution was added to 60 mL of the melting agar of about 50 °C to achieve the required concentration. Then, 10 mL of the compound–agar medium was poured into a small beaker (10 mL) and cooled to room temperature. After that, 10 just-germinated weed seeds were planted onto the surface of the medium. Then the beaker was sealed with a piece of plastic wrap with several small holes made in it by a needle. Finally, cultivation was achieved in an illumination incubator (28 ± 1 °C, 50–55% relative humidity, 12 h L: 12 h D) for seven days. Acetone was used as a blank control, and Acetochlor was used as a positive control. Each treatment was repeated three times. After cultivation, the taproot and caulis lengths of the weed seedlings were measured, and the growth inhibitory rate of the treatment to the untreated control was determined.

3.3.2. Antifungal Activity

The in vitro antifungal activities of the title compounds against the mycelium growth of four phytopathogenic fungi, *V. mali*, *B. cinerea*, *F. oxysporium*, and *C. glecosporioides*, were tested [57]. The stock solutions of the title compounds were prepared according to the procedures in Section 3.3.1. Then 1 mL of the stock solutions was added to 100 mL portions of melted (~50 °C) potato dextrose agar (PDA), and the mixtures were fully shaken to obtain the required concentrations of compound mixed medium. Then 5 mL portions of the mixed medium were poured into 6 cm petri dishes and allowed to cool to ambient temperature to form solid plates. After that, one 4 mm activated mycelium disk was inoculated on each of the PDA plates and incubated at 28 °C in the dark for a sufficient period. Acetone was used as a blank control, and Carbendazim was used as a positive control. Each treatment was repeated three times. The radius (mm) of the fungus mycelium settlements was measured and the growth inhibition rate relative to the untreated control was calculated.

4. Conclusions

In conclusion, 21 novel trifluoromethylcoumarinyl urea derivatives have been designed and synthesized according to the principle of bioactive substructure combination. The fluorescence spectrums of the title compounds showed that most of them glow green with λ_{max}^{em} of 500–517 nm when illuminated by ultraviolet light, while compounds **5r**, **5s**, **5u**, and **5l** glow violet with a λ_{max}^{em} of 381–443 nm. However, the fluorescent intensity of all the title compounds is weaker than the standard reference compound, quinine sulfate. Moreover, the pesticidal activities evaluation of the title compounds indicated that compound **5f** against the caulis of *A. retroflexus* and compounds **5j** and **5l** against the taproot of *D. sanguinalis* are equivalent to the commercial herbicide Acetochlor. Nine of the title compounds are more antifungal than commercial fungicide Carbendazim against *B. cinerea*.

Author Contributions: S.H. conceived and designed the experiments; L.Q. performed the experiments and analyzed the data; S.H. wrote the paper.

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