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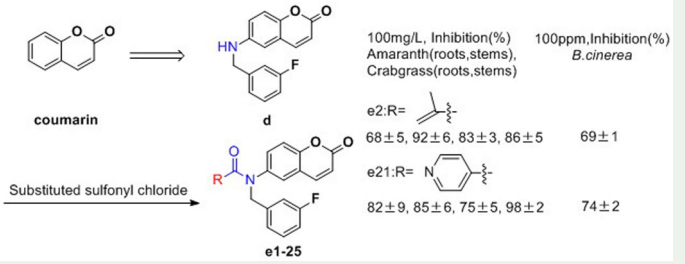
Design, synthesis and agricultural evaluation of derivatives of N-Acyl-N-(m-fluoro-benzyl)-6-amino-coumarin

Yan Jin[a], Yin-hao Ding[a], Jing-jing Dong[a], Yan Wei[b], Shuang-hong Hao[b] and Bai-cheng Feng[a]

[a]College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao, China; [b]College of Chemistry & Pharmacy, Research Center of Agro-bionic Engineering & Technology of Shandong Province, Qingdao Agricultural University, Qingdao, China

ABTRACT

This study aims to design and synthesize a series of N-Acyl-N-(m-fluoro- benzyl)-6- amino-coumarins through the principle of active substructure stitching, which are based on the core structure of N-(m-fluoro-benzyl)-6-amino-coumarin. The structures of target compounds **e1–e25** have been characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS and elemental analysis. Meanwhile, their agricultural activity have been evaluated in two weeds (*Amaranth* and *Crabgrass*) and four widespread noxious pathogens (*V.mali, B.cinerea, F.axysporium* and *C.bacteria*). The herbicidal activity results showed that almost all synthetic molecules have a greater impact on the stem system than on the root. Excellent inhibition rates were discovered from compounds **e2–e5** and **e20–e23** against *Amaranth* on stems, which were above 58%(20 mg/L), 68%(100 mg/L) respectively. Compounds **e2** and **e21** also exhibited striking inhibition on stems growth of both weeds. Anti-pathogenic activity showed that all the compounds exerted a better inhibitory activity on *B.cinerea* at 20 ppm compared to control carbendazim. All the heterocyclic substituted compounds (**e17–e24**, >57%) made a better influence than the control (54.1%) at the100 ppm. This research provides promising herbicidal and anti-pathogenic agents that have the better effects and can be potential for further development.



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CONTACT Bai-cheng Feng fbc515@163.com Shuang-hong Hao doublered@sina.com

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1. Introduction

Pesticides have been used at industrial-scale agriculture for a long time, which produces great benefits to agriculture. However, the large-scale use of pesticides on the environment has caused many negative effects, including possibly the emergence of pesticide-resistant pest species and easily the residue of pesticides in plants and groundwater (Andras et al. 2007). For the sake of the sustainable development of the agriculture, high efficiency, low toxicity, strong selectivity and easy degradation become the new direction of the pesticide development based on natural products. Many natural compounds have been reported to have herbicidal and antibacteria potential (Ncube et al. 2008; Dayan and Duke 2014).

Coumarin, a main secondary metabolite, is widely present in seeds, roots, and leaves of many plant species (Chon and Kim 2004; Pergo et al. 2008; Nazemi et al. 2015). It is well known as a versatile biodynamic agent for its benzene ring fused to á-pyrone ring structure, which possess a conjugated system with electron-rich and good charge-transport properties (Thakor and Savjani 2014; Hussain et al. 2018). Owing to the various structures of substitutions or pharmacophore in their basic nuclei, they are significant in showing effective and diverse of biological activity, including antimicrobial (Khidre et al. 2017), anti-inflammatory (Bansal et al. 2013), anticancer (Weng and Yuan 2017) and antioxidant properties (Al-Majedy et al. 2016).

Among the various coumarins, Some owning substitutes containing element N and its derivatives have been studied as anticancer, antimicrobial, antifungal, anti-inflammatory agent. For instance, C-7-aminocoumarins were effective as inhibitors against lung cancer cells hCA I and hCA XII (Carta et al. 2012). C-5 -NH_2- substituent derivatives were proved to have antimicrobial activities (Zhang et al. 2010). C-6 nitration substituted ramifications resulted the antifungal activities (de Araújo et al. 2013). C-6 amino substituted derivatives were also the most effective anticoagulation against MAO-A (Mattsson et al. 2014). Especially, when the coumarin substitute the 6-site of with CN, CHO, COOH, or NO_2 (electron-withdrawing group), the substituted analogues have been indicated to influence the TNF-αinhibitory effect of the inflammatory factors (Cheng et al. 2004).

Besides, application of coumarin analogues in agriculture is becoming more and more concerned, such as insecticidal weeds and other activities (Liu et al. 2016).

Along with coumarins, researches on amide derivatives have been a hot spot in the development of pesticides for their broad bioactivities, including insecticidal (Wu et al. 2012), herbicidal (Xu et al. 2008) and antifungal (Fu et al. 2010; Kim et al. 2010). Currently, some commercial pesticidal compounds have acylamino group in the molecules like Fluopyram, Mepronil and Flutolanil (Figure 1), which are having widely used on a large scale.

In modern drug designing, substructure splicing is routinely used as a common means. Many experiments showed that certain synergistic drug combinations may present a more potential version than a single drug (Liu et al. 2015). In our previous study (Wang et al. 2015), several 6-amino-coumarin derivatives with amide bond have been synthesized and showed excellent activity against *A. retroflexus*. So we believed that N-aceyl structure can be an essential part of the coumarin applying in the pesticidal activities.

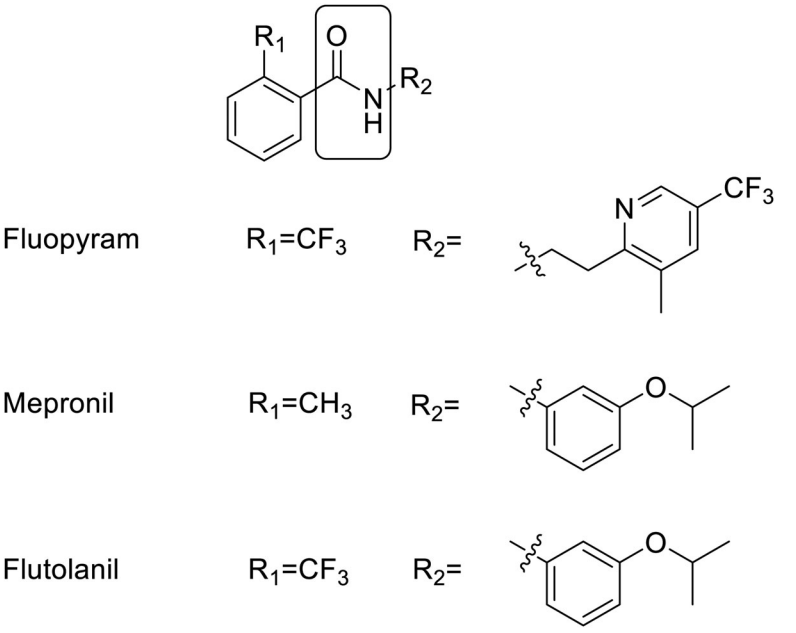


Figure 1. The structure of some commercial pesticidal compounds with acylamino group.

Through the principle of substructure splicing, this paper intends to carry out structural optimization research by stitching together the substituted alkanes and aromatic heterocycles with the modified coumarin **d**. To extend our research on developing novel amide coumarin derivatives as a herbicidal activity, 25 coumarin derivatives **e1-e25** have been synthesized and their pesticidal activity have been evaluated among two weeds and four widespread noxious pathogens.

2. Results and discussion

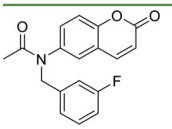
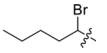
2.1. Chemistry

The target intermediate of N-(m-fluoro-benzyl)-6-amino-coumarin **d** was prepared as illustrated in Scheme 1. Preparation of 6-nitrocoumarin **a** was carried out through nitration reaction of coumarin and guanidine nitrate in presence of concentrated sulfuric acid as a catalyst. 6-aminocoumarin was obtained by reducing 6-nitrocoumarin **a** with 80% hydrazine hydrate, which using anhydrous ferric chloride and activated carbon as a catalyst. Schiff base compound **c** was synthesized by nucleophilic addition, rearrangement and elimination between 6-aminocoumarin **b** and m- fluorobenzaldehyde, and then N-(m-fluoro-benzyl)-6-amino- coumarin **d** was obtained by reduction reaction of schiff base compound **c** with sodium borohydride. The target compounds **e1-e25** (Scheme 1 and Table 1) were furnished by the acylation of compounds, respectively, with a series of acyl chlorides catalyzed by triethylamine.

2.2. Assay of herbicidal activity

As revealed from Table 2, comparing with the widely used herbicides and pesticides acetochlor(EC), most of the synthetic coumarin derivatives strongly affected the stems

Table 1. Structures of compound **e1–e25**.

Base Structure	Compd.	R	Compd.	R	Compd.	R
	**e1**		**e2**		**e3**	
	e4		**e5**		**e6**	
	e7		**e8**		**e9**	
	e10		**e11**		**e12**	
	e13		**e14**		**e15**	
	e16		**e17**		**e18**	
	e19		**e20**		**e21**	
	e22		**e23**		**e24**	
	e25					

of *Amaranth* and *Crabgrass*, and showed a dose-dependent inhibitory. Almost all the synthetic molecules strongly affected the stems system more than that of roots. For the stem of *Amaranth*, the inhibition of compounds **e2-e5** and **e20-e23** caused more than 58%(20 mg/L), 68%(100 mg/L) respectively, and this effect almost increased as their concentrations increased, all the above compounds showed excellent inhibition compared with the control EC(54.4%, 65.9%). It can be seen from this that the inhibitory rates of alkyl and heterocyclic substituted coumarin were greater than that of aryl substituted, which may be related to the electron-withdrawing effects of the heterocycle. Synchronously, these compounds on stems growth of *Crabgrass*(**e2**, **e4**, **e5** and **e21**) were discovered with excellent herbicidal activity at low and high concentration above 75.5% and 86.0% inhibition, which were also higher than the control. By comparison, most compounds showed no advantage effect beyong the control at high concentration on *Crabgrass*. Interestingly, compounds **e2** and **e21** exhibited striking inhibition on stems growth of both weeds. In accordance with these compounds on roots/stems inhibition of both weeds, the preliminary SAR was based on the following: when the carbon chain was longer, the activity was weaker, such as haloalkyl substituted **e5**>**e6**, **e7**>**e8**, and the trend was also observed in heterocyclic substituted coumarin **e17**>**e18**. When the carbon chain grows, the electron donating effect of the carbon chain increases, resulting in a decrease in the overall electron cloud density of the compound, thereby reducing the activity of the compound.

2.3. Assay of anti-pathogenic activity

Similarly to their herbicidal activity, the most of molecules showed certain inhibitory effects on *B.cinerea, V.mali, F.axysporium and C.bacteria* at concentration of 20 ppm

and 100 ppm. By comparing and analyzing these data, more abundant experimental data can be obtained, and the credibility of the experiment is also improved. As shown in Figure 2, all the synthetic molecules exerted a better inhibitory activity on *B.cinerea* than the other three pathogens compared to control carbendazim at two test concentrations. At the same time, according to the test results on the growth of four kinds of bacteria, most of these 25 compounds have better antibacterial effect at high concentration than at low concentration. It can be inferred that within a certain concentration range, the antibacterial effect of these compounds will increase with the increase of concentration. For the mycelium growth of *B.cinerea*, all the compounds showed significant activities beyond control at low concentration. More specifically, all the heterocyclic substituted compounds (**e17**–**e24**, >57%) made a great influence than control(54.1%) at the high concentration, which means that the spliced active substructure has a significant effect on the anti-pathogenic activity of the substance. The SAR was similar to herbicidal activities, including **e5**>**e6**, **e7**>**e8** and **e17**>**e18**, and so is the principle.

2.4. Crystal structure analysis

Further confirmation of the structure was obtained from X-rays single crystal diffraction, compound **e2** crystalline (CCDC 1838932, Figure 3) were grown by sublimation of the anhydrous powder at 303 K in ethanol/water solution. The crystals were cooled to 273 K and screened. The selected high-quality single crystal was placed on a Rigaku Raxis-Rapid X-ray diffractometer for single crystal X-ray diffraction analysis. Diffraction data were collected using graphite monochromated Mo kα rays ($\lambda = 0.71073$ Å) as the diffraction light source. Absorption correction was performed on all the diffraction data. The crystal structure was solved by the direct method in the SHELXS-97 program, and the structure was refined by the SHELXS-97 program. The data for this phase were collected at 273 K.

3. Experimental

All the experimental section is published as online-only supplemental materials in the single supplementary file.

4. Conclusions

In summary, a series of novel derivatives of N-Acyl-N-(m-fluoro-benzyl)-6-amino-coumarin (**e1**–**e25**) was synthesized. At the same time, their herbicidal activities (*Crabgrass* and *Amaranth*) and anti-pathogenic activities (*B.cinerea, V.mali, F.axysporium and C.bacteria*) were evaluated. Inhibitory analyses indicated that the substitution of the short carbon chain led to a more dramatical effect than that of long chain(**e5**>**e6, e7**>**e8** and **e17**>**e18**). In addition, heterocyclic substituted compounds showed excellent inhibitory activity against pathogen *B.cinerea* at 100 ppm. Particularly, compounds **e2** and **e21** may have potential and selective bioactivity on the two weeds and have

anti-pathogen (*B. cinerea*) activity, which were expected to be recognized as the most promising pesticide agents.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Al-Majedy Y, Al-Amiery A, Kadhum AA, BakarMohamad A. 2016. Coumarins: the antimicrobial agents. SRP. 8(1):24–30.

Andras P, Gwyther R, Madalinski AA, Lynden SJ, Andras A, Young MP. 2007. Ecological network analysis: an application to the evaluation of effects of pesticide use in an agricultural environment. Pest Manag Sci. 63(10):943–953.

Bansal Y, Sethi P, Bansal G. 2013. Coumarin: a potential nucleus for anti-inflammatory molecules. Med Chem Res. 22(7):3049–3060.

Carta F, Maresca A, Scozzafava A, Supuran CTB. 2012. Novel coumarins and 2-thioxo-coumarins as inhibitors of the tumor-associated carbonic anhydrases IX and XII. Bioorg Med Chem. 20(7): 2266–2273.

Cheng JF, Chen M, Wallace D, Tith S, Arrhenius T, Kashiwagi H, Ono Y, Ishikawa A, Sato H, Kozono T, et al. 2004. Discovery and structure-activity relationship of coumarin derivatives as TNF-alpha inhibitors. Bioorg Med Chem Lett. 14(10):2411–2415.

Chon SU, Kim YM. 2004. Herbicidal potential and quantification of suspected allelochemicals from four grass crop extracts. J Agron Crop Sci. 190(2):145–150.

Dayan FE, Duke SO. 2014. Natural compounds as next-generation herbicides. Plant Physiol. 166(3):1090–1105.

de Araújo RS, Guerra FQ, de O Lima E, de Simone CA, Tavares JF, Scotti L, Scotti MT, de Aquino TM, de Moura RO, Mendonça FJ, et al. 2013. Synthesis, structure–activity relationships (SAR) and in silico studies of coumarin derivatives with antifungal activity. Int J Mol Sci. 14(1): 1293–1309.

Fu J, Cheng K, Zhang ZM, Fang RQ, Zhu HLE. 2010. Synthesis, structure and structure–activity relationship analysis of caffeic acid amides as potential antimicrobials. Eur J Med Chem. 45(6): 2638–2643.

Hussain MI, Qamar Abbas S, Reigosa MJ. 2018. Acticities and novel applications of secondary metabolite coumarins. Planta Daninha. 36:1–13.

Khidre RE, El-Gogary SR, Mostafa MS. 2017. Design, synthesis, and antimicrobial evaluation of some novel pyridine, coumarin, and thiazole derivatives. J Heterocyclic Chem. 54(4): 2511–2519.

Kim BJ, Kim JA, Kim YK, Choi SY, Park Choo HY. 2010. Synthesis of benzoxazole amides as novel antifungal agents against Malassezia furfur. B Korean Chem Soc. 31(5):1270–1274.

Liu G, Hu Y, Chen XH, Wang GX, Ling F. 2016. Synthesis and anthelmintic activity of coumarin-imidazole hybrid derivatives against Dactylogyrus intermedius in goldfish. Bioorg Med Chem Lett. 26(20):5039–5043.

Liu TT, Ni Y, Zhong LK, Huang HY, Hu WQ, Xu TM, Tan CX. 2015. Synthesis and bactericidal activity of difluoromethyl substituted pyrazole amides. Chin J Org Chem. 35(2):422–427.

Mattsson C, Svensson P, Sonesson C. 2014. A novel series of 6-substituted 3-(pyrrolidin-1-ylmethyl)chromen-2-ones as selective monoamine oxidase (MAO) A inhibitors. Eur J Med Chem. 73:177–186.

Nazemi AH, Asadi GA, Ghorbani R. 2015. Herbicidal activity of coumarin when applied as a preplant incorporated into soil. Not Sci Biol. 7(2):239–243.

Ncube NS, Afolayan AJ, Okoh AL. 2008. Assessment techniques of antimicrobial properties of natural compounds of plant origin: current methods and future trends. Afr J Biotechnol. 7(12):1797–1806.

Pergo ÉM, Abrahim D, Soares Da Silva PC, Kern KA, Da Silva LJ, Voll E, Ishii-Iwamoto ELJ. 2008. Bidens pilosa L. Exhibits high sensitivity to coumarin in comparison with three other weed species. J Chem Ecol. 34(4):499–507.

Thakor T, Savjani J. 2014. Synthesis and cell line study of pyrazole substituted coumarin derivatives. Int J PharmTech Res. 4:1397–1406.

Wang D, Wei Y, Hao SH. 2015. Synthesis and herbicidal activity of N-acyl-N-m-fluorobenzyl-6-aminocoumarin. Chin J Org Chem. 35(8):1691–1699.

Weng KG, Yuan YL. 2017. Synthesis and evaluation of coumarin derivatives against human lung cancer cell lines. Braz. J Med Biol Res. 50:1–6.

Wu R, Zhu C, Du XJ, Xiong LX, Yu SJ, Liu XH, Li ZM, Zhao WG. 2012. Synthesis, crystal structure and larvicidal activity of novel diamide derivatives againstCulex pipiens. Chem Cent J. 6(1): 99–99.

Xu H, Hu XH, Zou XM, Liu B, Zhu YQ, Wang Y, Hu FZ, Yang HZ. 2008. Synthesis and herbicidal activities of novel 3-N-Substituted Amino-6-methyl-4-(3-trifluoromethylphenyl)pyridazine derivatives. J Agric Food Chem. 56(15):6567–6572.

Zhang BL, Fan CQ, Dong L, Wang FD, Yue JME. 2010. Structural modification of a specific antimicrobial lead against Helicobacter pylori discovered from traditional Chinese medicine and a structure-activity relationship study. Eur J Med Chem. 45(11):5258–5264.