

Design, Synthesis, and Insecticidal Evaluation of New Benzoylureas Containing Amide and Sulfonate Groups Based on the Sulfonylurea Receptor Protein Binding Site for Diflubenzuron and Glibenclamide

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ABSTRACT: On the basis of the sulfonylurea receptor (SUR) protein binding site for diflubenzuron and glibenclamide, 15 new benzoylphenylureas containing amide and sulfonate groups were designed and synthesized. Their structures were characterized by ^1H nuclear magnetic resonance (NMR) and elemental analysis [or high-resolution mass spectrometry (HRMS)]. The larvicidal activities of the new compounds against oriental armyworm and diamondback moth were evaluated. Compound **II-3** showed nearly the same level of insecticidal activity against oriental armyworm as commercial insecticide flucyclozuron and, thus, emerged as a new lead compound for the development of new benzoylurea insecticides.

KEYWORDS: Benzoylphenylureas, benzoylurea, amide, sulfonate, insecticidal activity, insect growth regulator

■ INTRODUCTION

Benzoylurea insecticides, which have been used for almost 40 years, have been very useful in many integrated pest management (IPM) programs because of their unique mode of action.^{1,2} The action mechanism research of benzoylureas has been under way since diflubenzuron (dimilin) was discovered in 1972.³ The initial study results showed that incorporation of uridine diphosphate-*N*-acetylglucosamine (UDP-NAGA) to chitin was clearly inhibited *in vivo* or *in situ* (isolated integument incubated in a tissue culture medium). However, all of the subsequent studies trying to prove some action of benzoylureas on any part of the chitin synthesis pathway in insects in cell-free systems (rather than *in vivo* and *in situ*) failed.^{4–9} In addition, benzoylureas showed no inhibitory actions on fungal systems *in vivo* as well as in cell-free systems, which have roughly equivalent chitin synthesis pathways as insects.⁴ Therefore, the action mechanism of benzoylureas remained unresolved.

Recently, Matsumura and co-workers reported that the benzoylurea insecticide diflubenzuron acted on the same target site on the sulfonylurea receptor (SUR) protein as a typical sulfonylurea, glibenclamide, in *Drosophila melanogaster* and *Blattella germanica*. Furthermore, such action by these chemicals is the cause of their inhibitory effect on chitin synthesis.^{10,11} It is a great discovery on the action mechanism research of benzoylurea insecticides.

On the basis of the SUR protein binding site for diflubenzuron and glibenclamide, we found that both chemicals have a urea fragment but glibenclamide has an amide fragment by comparing the chemical structure of diflubenzuron to glibenclamide (Figure 1). To find new chitin synthesis inhibitors, compound **I** was designed and synthesized according to combination principles. The results of bioevaluation showed that compound **I** did not exhibit good insecticidal activities against oriental armyworm and diamondback moth. Probably because compound **I** cannot pass smoothly through the stomach lining of the insect and reach the target site on the receptor protein because of the strong polarity and poor lipid solubility.

Bioisosterism is an effective way to design bioactive compounds.¹² A series of compounds **A** containing haloalkylsulfonyl groups reported by Takeda Chemical Industries, Ltd. (TCI) exhibited high insecticidal activity against pests of Lepidoptera.¹³ Consequently, compound **II** was designed according to bioisosterism and analogue synthesis to improve the lipid solubility and find new benzoylurea insecticides.

■ MATERIALS AND METHODS

Instruments. ^1H nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer or at 400 MHz using a Varian Mercury Plus 400 spectrometer in CDCl_3 or $\text{DMSO-}d_6$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million (ppm). Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer. High-resolution mass spectrometry (HRMS) data were obtained on a Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) instrument (Ionspec7.0T). The melting points were determined on a X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized.

General Synthesis. The reagents were all analytically or chemically pure. All anhydrous solvents were dried and purified by standard techniques prior to use. 2,6-Difluorobenzoyl isocyanate was prepared according to the literature method.¹⁴

General Synthetic Procedure for Target Compounds I-1–I-7 (Scheme 1). *Synthesis of N-tert-Butyl-4-nitrobenzamide (I-1a).* 4-Nitrobenzoic acid (1.48 g, 8.9 mmol) was added to thionyl chloride (30.0 g) and refluxed for 3 h. Then, excess thionyl chloride was removed under vacuum, and anhydrous dichloromethane (20 mL) was added. After the mixture was cooled to 0 °C, 2-methylpropan-2-amine (0.78 g, 10.7 mmol) and triethylamine (1.35 g, 13.4 mmol) in dichloromethane (10 mL) were added dropwise. The reaction stood at room temperature for 6 h. Then, the mixture was successively washed with 5%

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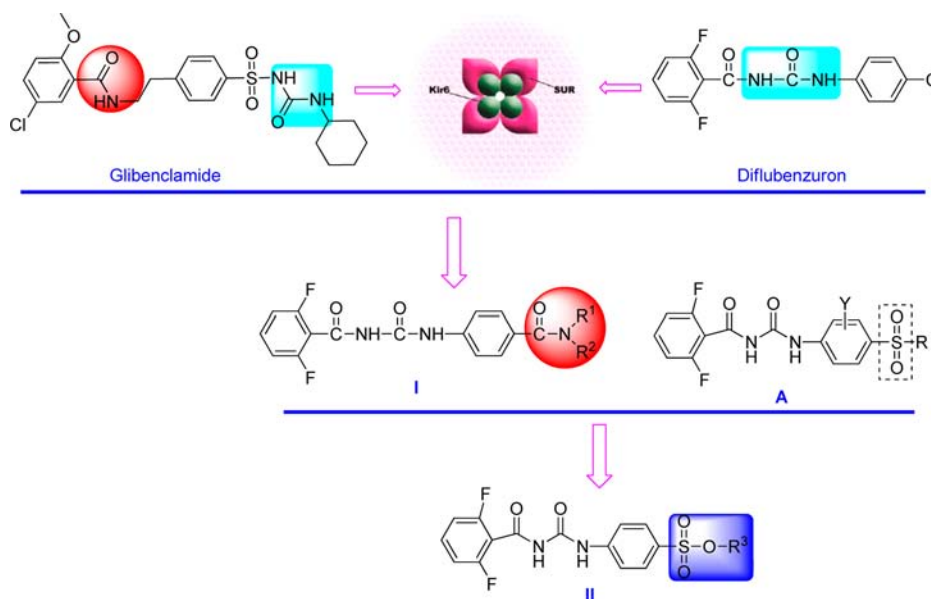
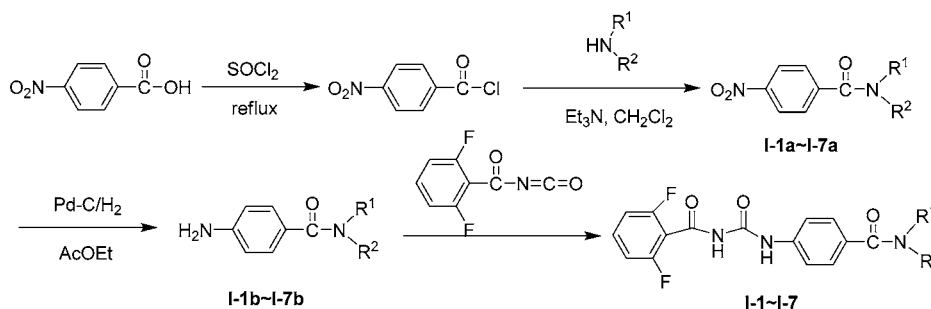


Figure 1. Design of compounds I and II.

Scheme 1. General Synthetic Procedure for Target Compounds I-1–I-7



aqueous HCl solution and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give a crude product. The product was purified by recrystallization from ethyl acetate and petroleum ether (60–90 °C) to give compound **I-1a** (1.05 g, 53.0%) as a white solid. melting point (mp) = 161–163 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.27 (d, 2H, *J* = 8.6 Hz, Ar–H), 7.87 (d, 2H, *J* = 8.7 Hz, Ar–H), 5.97 (brs, 1H, NH(CH₃)₃), 1.49 (s, 9H, NH(CH₃)₃).

Synthesis of 4-Amino-*N*-*tert*-butylbenzamide (I-1b). Compound **I-1a** (1.02 g, 4.6 mmol) was dissolved in ethyl acetate (35 mL), and 10% Pd/C (0.20 g, 53% moisture) was added. Hydrogen was bubbled at room temperature through the reaction solution for 9 h. Then, the mixture was filtered, and the filtrate was concentrated under reduced pressure to give compound **I-1b** as a colorless liquid without further purification in a nearly quantitative yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.56 (d, 2H, *J* = 8.4 Hz, Ar–H), 6.65 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.31 (d, 2H, *J* = 8.7 Hz, Ar–H), 5.82 (brs, 1H, NH(CH₃)₃), 3.94 (brs, 2H, NH₂), 1.45 (s, 9H, NH(CH₃)₃).

Synthesis of *N*-(4-(*tert*-Butylcarbamoyl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound I-1). A solution of 2,6-difluorobenzoyl isocyanate (0.84 g, 4.6 mmol) in dichloromethane (20 mL) was added dropwise to a solution of **I-1b** (0.88 g, 4.6 mmol) in dichloromethane (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h. Then, the mixture was filtered, and the crude product was purified by recrystallization from ethyl acetate and petroleum ether (60–90 °C) to give compound **I-1** (1.60 g, 93.0%) as a white solid. mp = 199–201 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.61 (s, 1H, CONHCO), 9.21 (brs, 1H, CONHAr), 7.69 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.52–7.60 (m, 3H, Ar–H), 7.06 (t, 2H, *J* = 8.3 Hz, Ar–H), 5.91 (s, 1H, NH(CH₃)₃), 1.48 (s, 9H, NH(CH₃)₃). Anal.

Calcd for C₁₉H₁₉F₂N₃O₃: C, 60.79; H, 5.10; N, 11.19. Found: C, 60.61; H, 4.98; N, 10.98.

Compounds **I-2a–I-7a**, **I-2b–I-7b**, and **I-2–I-7** were prepared using the similar method for compounds **I-1a**, **I-1b**, and **I-1**, respectively. The physical properties and ¹H NMR data of compounds **I-2a–I-7a** and **I-2b–I-7b** are listed in Table 2.

Data for *N*-(4-(Diisopropylcarbamoyl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound I-2). White solid. Yield = 98.6%. mp = 193–196 °C. ¹H NMR (400 MHz, CDCl₃) δ: 10.52 (brs, 1H, CONHCO), 9.47 (brs, 1H, CONHAr), 7.47–7.58 (m, 3H, Ar–H), 7.27 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.06 (t, *J* = 8.4 Hz, 2H, Ar–H), 3.48–3.90 (m, 2H, 2(CH(CH₃)₂)), 1.23–1.45 (m, 12H, 2(CH(CH₃)₂)). Anal. Calcd for C₂₁H₂₃F₂N₃O₃: C, 62.52; H, 5.75; N, 10.42. Found: C, 62.31; H, 5.86; N, 10.36.

Data for *N*-(4-(4-Chlorophenyl)(methyl)carbamoyl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound I-3). White solid. Yield = 59.7%. mp = 194–196 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.45 (brs, 1H, CONHCO), 10.20 (brs, 1H, CONHAr), 7.58–7.66 (m, 1H, Ar–H), 7.45 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.34 (t, *J* = 8.7 Hz, 2H, Ar–H), 7.19–7.27 (m, 6H, Ar–H), 3.35 (s, 3H, CH₃). Anal. Calcd for C₂₂H₁₆ClF₂N₃O₃: C, 59.54; H, 3.63; N, 9.47. Found: C, 59.41; H, 3.65; N, 9.32.

Data for *N*-(4-(4-Chlorophenylcarbamoyl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound I-4). White solid. Yield = 76.7%. mp > 300 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.52 (brs, 1H, CONHCO), 10.38 (brs, 1H, CONHAr), 10.30 (s, 1H, ArCONHAr), 7.94 (d, 2H, *J* = 8.2 Hz, Ar–H), 7.79 (d, *J* = 8.1 Hz, 2H, Ar–H), 7.71 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.59–7.66 (m, 1H, Ar–H), 7.39 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.25 (t, *J* = 8.3 Hz, 2H, Ar–H). Anal. Calcd for C₂₁H₁₄ClF₂N₃O₃: C, 58.68; H, 3.28; N, 9.78. Found: C, 58.65; H, 3.35; N, 9.77.

Table 1. Larvicidal Activities against Oriental Armyworm and Diamondback Moth of Compounds I-1–I-7, II-1–II-8, and Flucycloxuron

compd	Chemical structures	Toxicities against Oriental armyworm		Toxicities against diamondback moth	
		C ^a (mg L ⁻¹)	P ^a (%)	C ^a (mg L ⁻¹)	P ^a (%)
I-1		200	100	200	0
		100	100		
		50	50		
I-2		200	0	20	100
I-3		200	0	200	0
I-4		200	0	200	0
I-5		200	0	200	0
I-6		200	0	200	0
I-7		200	0	200	0
II-1		200	0	200	0
II-2		200	0	200	0
II-3		200	100	200	100
		100	100	20	100
		50	100	5	90
		20	100	2	40
		10	100		
II-4		200	100	200	20
		100	100		
II-5		200	100	200	30
		100	100		
II-6		200	0	200	60
				20	20
II-7		200	100	200	20
		100	100		
II-8		200	100	200	30
		100	100		
Flucycloxuron		5	90	LC ₅₀ = 72.92 mg·L ⁻¹	
		2.5	50		
		1.0	10		

^aC, concentration; P, larvicidal activity.

Data for *N*-(4-(Butylcarbamoyl)phenylcarbamoyl)-2,6-difluorobenzamide (Target Compound I-5). White solid. Yield = 92.6%. mp = 171–173 °C. ¹H NMR (400 MHz, CDCl₃) δ: 10.59 (brs, 1H,

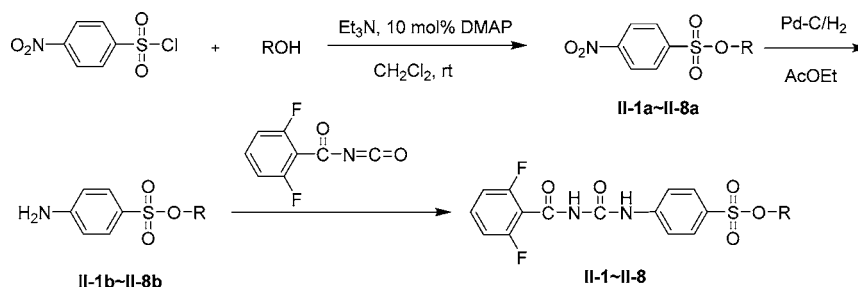
Table 2. Physical Properties and ¹H NMR Data of Compounds I-2a–I-7a and I-2b–I-7b

compd	R ¹	R ²	m.p. (°C)	¹ H NMR δ (ppm)	
				¹ H NMR (400 MHz, CDCl ₃)	¹ H NMR (400 MHz, CDCl ₃)
I-2a	CH(CH ₃) ₂	CH(CH ₃) ₂	white solid 146–147	¹ H NMR (400 MHz, CDCl ₃): 8.26 (d, 2H, J = 8.6 Hz, Ar-H), 7.47 (d, J = 8.6 Hz, 2H, Ar-H), 3.52–3.71 (m, 2H, 2(CH(CH ₃) ₂)), 1.57 (d, J = 16.3 Hz, 6H, CH(CH ₃) ₂), 1.15 (s, 6H, CH(CH ₃) ₂).	
				¹ H NMR (400 MHz, CDCl ₃): 7.15 (d, J = 8.2 Hz, 2H, Ar-H), 6.64 (d, J = 8.2 Hz, 2H, Ar-H), 3.78 (s, 4H, NH ₂ and 2(CH(CH ₃) ₂)), 1.32 (s, 12H, 2(CH(CH ₃) ₂)).	
I-2b	CH(CH ₃) ₂	CH(CH ₃) ₂	white solid	¹ H NMR (400 MHz, CDCl ₃): 8.07 (d, J = 8.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.2 Hz, 2H, Ar-H), 7.23 (d, J = 8.4 Hz, 2H, Ar-H), 6.97 (d, J = 8.0 Hz, 2H, Ar-H), 3.49 (s, 3H, CH ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.20 (d, J = 8.5 Hz, 2H, Ar-H), 7.12 (d, J = 8.3 Hz, 2H, Ar-H), 6.97 (d, J = 8.5 Hz, 2H, Ar-H), 6.43 (d, J = 8.4 Hz, 2H, Ar-H), 3.85 (brs, 2H, NH ₂), 3.43 (s, 3H, CH ₃).	
I-3a	CH ₃		white solid	¹ H NMR (400 MHz, CDCl ₃): 8.36 (d, 2H, J = 8.7 Hz, Ar-H), 8.04 (d, 2H, J = 8.6 Hz, Ar-H), 7.81 (brs, 1H, NHAr), 7.61 (d, 2H, J = 8.6 Hz, Ar-H), 7.37 (d, 2H, J = 8.7 Hz, Ar-H).	
				¹ H NMR (400 MHz, CDCl ₃): 7.70 (d, J = 8.5 Hz, 2H, Ar-H), 7.67 (brs, 1H, NHAr), 7.57 (d, J = 8.7 Hz, 2H, Ar-H), 7.31 (d, J = 8.7 Hz, 2H, Ar-H), 6.71 (d, 2H, J = 8.5 Hz, Ar-H), 4.05 (brs, 2H, NH ₂).	
I-3b	CH ₃		pale yellow solid	¹ H NMR (400 MHz, CDCl ₃): 8.29 (d, J = 8.1 Hz, 2H, Ar-H), 7.92 (d, J = 8.1 Hz, 2H, Ar-H), 6.21 (brs, 1H, NHCH ₃), 3.49 (q, J = 6.5 Hz, 2H, NHCH ₂ CH ₂), 1.60–1.67 (m, 2H, CH ₂ CH ₂ CH ₂), 1.39–1.48 (m, 2H, CH ₂ CH ₂ CH ₂), 0.98(t, J = 7.2 Hz, 3H, CH ₂ CH ₂ CH ₂).	
				¹ H NMR (400 MHz, CDCl ₃): 7.59 (d, J = 8.1 Hz, 2H, Ar-H), 6.66 (d, J = 8.0 Hz, 2H, Ar-H), 5.96 (brs, 1H, NHCH ₂), 3.94 (brs, 2H, NH ₂), 3.42 (q, J = 6.6 Hz, 2H, NHCH ₂ CH ₂), 1.54–1.62 (m, 2H, CH ₂ CH ₂ CH ₂), 1.36–1.45 (m, 2H, CH ₂ CH ₂ CH ₂), 0.95(t, J = 7.2 Hz, 3H, CH ₂ CH ₂ CH ₂).	
I-4a	H		pale yellow solid	¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.81 (s, 4H, CH ₂ OCH ₂), 3.64 (s, 2H, CH ₂ NCH ₂), 3.39 (s, 2H, CH ₂ NCH ₂).	
				¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.92 (brs, 2H, NH ₂), 3.64–3.69 (m, 8H, (CH ₂) ₄).	
I-4b	H		white solid	¹ H NMR (400 MHz, CDCl ₃): 8.28 (d, J = 8.2 Hz, 2H, Ar-H), 7.94 (d, J = 8.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.8 Hz, 2H, Ar-H), 7.30 (d, J = 7.7 Hz, 2H, Ar-H), 6.41 (s, 1H, NHCH ₂), 4.63 (d, J = 4.8 Hz, 2H, CONHCH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.3 Hz, 2H, Ar-H), 6.64 (d, J = 8.6 Hz, 2H, Ar-H), 6.22 (s, 1H, NHCH ₂), 4.59 (d, J = 5.5 Hz, 2H, CONHCH ₂), 3.96 (brs, 2H, NH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
I-5a	H	(CH ₂) ₃ CH ₃	white solid 104–106	¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.81 (s, 4H, CH ₂ OCH ₂), 3.64 (s, 2H, CH ₂ NCH ₂), 3.39 (s, 2H, CH ₂ NCH ₂).	
				¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.92 (brs, 2H, NH ₂), 3.64–3.69 (m, 8H, (CH ₂) ₄).	
I-5b	H	(CH ₂) ₃ CH ₃	white solid 99–101	¹ H NMR (400 MHz, CDCl ₃): 8.28 (d, J = 8.2 Hz, 2H, Ar-H), 7.94 (d, J = 8.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.8 Hz, 2H, Ar-H), 7.30 (d, J = 7.7 Hz, 2H, Ar-H), 6.41 (s, 1H, NHCH ₂), 4.63 (d, J = 4.8 Hz, 2H, CONHCH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.3 Hz, 2H, Ar-H), 6.64 (d, J = 8.6 Hz, 2H, Ar-H), 6.22 (s, 1H, NHCH ₂), 4.59 (d, J = 5.5 Hz, 2H, CONHCH ₂), 3.96 (brs, 2H, NH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
I-6a	H		white solid 107–109	¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.81 (s, 4H, CH ₂ OCH ₂), 3.64 (s, 2H, CH ₂ NCH ₂), 3.39 (s, 2H, CH ₂ NCH ₂).	
				¹ H NMR (400 MHz, CDCl ₃): 8.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.2 Hz, 2H, Ar-H), 3.92 (brs, 2H, NH ₂), 3.64–3.69 (m, 8H, (CH ₂) ₄).	
I-6b	H		pale yellow solid 137–139	¹ H NMR (400 MHz, CDCl ₃): 8.28 (d, J = 8.2 Hz, 2H, Ar-H), 7.94 (d, J = 8.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.8 Hz, 2H, Ar-H), 7.30 (d, J = 7.7 Hz, 2H, Ar-H), 6.41 (s, 1H, NHCH ₂), 4.63 (d, J = 4.8 Hz, 2H, CONHCH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.3 Hz, 2H, Ar-H), 6.64 (d, J = 8.6 Hz, 2H, Ar-H), 6.22 (s, 1H, NHCH ₂), 4.59 (d, J = 5.5 Hz, 2H, CONHCH ₂), 3.96 (brs, 2H, NH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
I-7a	H		white solid 147–149	¹ H NMR (400 MHz, CDCl ₃): 8.28 (d, J = 8.2 Hz, 2H, Ar-H), 7.94 (d, J = 8.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.8 Hz, 2H, Ar-H), 7.30 (d, J = 7.7 Hz, 2H, Ar-H), 6.41 (s, 1H, NHCH ₂), 4.63 (d, J = 4.8 Hz, 2H, CONHCH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.3 Hz, 2H, Ar-H), 6.64 (d, J = 8.6 Hz, 2H, Ar-H), 6.22 (s, 1H, NHCH ₂), 4.59 (d, J = 5.5 Hz, 2H, CONHCH ₂), 3.96 (brs, 2H, NH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
I-7b	H		pale yellow solid 194–196	¹ H NMR (400 MHz, CDCl ₃): 8.28 (d, J = 8.2 Hz, 2H, Ar-H), 7.94 (d, J = 8.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.8 Hz, 2H, Ar-H), 7.30 (d, J = 7.7 Hz, 2H, Ar-H), 6.41 (s, 1H, NHCH ₂), 4.63 (d, J = 4.8 Hz, 2H, CONHCH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	
				¹ H NMR (400 MHz, CDCl ₃): 7.62 (d, J = 8.6 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.3 Hz, 2H, Ar-H), 6.64 (d, J = 8.6 Hz, 2H, Ar-H), 6.22 (s, 1H, NHCH ₂), 4.59 (d, J = 5.5 Hz, 2H, CONHCH ₂), 3.96 (brs, 2H, NH ₂), 1.32 (s, 9H, C(CH ₃) ₃).	

CONHCO), 8.78 (brs, 1H, CONHAr), 7.74 (d, J = 7.9 Hz, 2H, Ar-H), 7.52–7.60 (m, 3H, Ar-H), 7.06 (t, 2H, J = 8.8 Hz, Ar-H), 6.07 (brs, 1H, NHCH₂), 3.42 (q, J = 6.2 Hz, 2H, NHCH₂CH₂), 1.58–1.65 (m, 2H, CH₂CH₂CH₂), 1.38–1.47 (m, 2H, CH₂CH₂CH₃), 0.97 (t, 3H, J = 7.2 Hz, CH₂CH₂CH₃). Anal. Calcd for C₁₉H₁₉F₂N₃O₃: C, 60.79; H, 5.10; N, 10.12. Found: C, 60.71; H, 5.10; N, 10.90.

Data for 2,6-Difluoro-N-(4-(morpholine-4-carbonyl)phenylcarbamoyl)benzamide (Target Compound I-6). White solid. Yield = 93.0%. mp = 198–200 °C. ¹H NMR (400 MHz, CDCl₃) δ: 10.57 (brs, 1H, CONHCO), 9.04 (brs, 1H, CONHAr), 7.51–7.57

Scheme 2. General Synthetic Procedure for Target Compounds II-1–II-8



(m, 3H, Ar–H), 7.40 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.06 (t, $J = 8.8$ Hz, 2H, Ar–H), 3.36–3.61 (m, 8H, $(\text{CH}_2)_4$). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_4$: C, 58.61; H, 4.40; N, 10.79. Found: C, 58.51; H, 4.65; N, 10.42.

Data for *N*-(4-(4-*tert*-Butylbenzylcarbamoyl)phenylcarbamoyl)-2,6-difluoro-benzamide (Target Compound I-7). White solid. Yield = 86.7%. mp = 204–206 °C. ^1H NMR (400 MHz, CDCl_3) δ : 10.62 (brs, 1H, CONHCO), 9.12 (brs, 1H, CONHAr), 7.76 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.51–7.57 (m, 3H, Ar–H), 7.40 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.31 (d, $J = 7.7$ Hz, 2H, Ar–H), 7.05 (t, 2H, $J = 8.8$ Hz, Ar–H), 6.33 (s, 1H, NHCH_2), 4.62 (d, $J = 4.8$ Hz, 2H, CONHCH_2), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$). Anal. Calcd for $\text{C}_{26}\text{H}_{25}\text{F}_2\text{N}_3\text{O}_3$: C, 67.09; H, 5.41; N, 9.03. Found: C, 67.05; H, 5.31; N, 9.18.

General Synthetic Procedure for Target Compounds II-1–II-8 (Scheme 2). **Synthesis of 4-Chlorophenyl 4-Nitrobenzenesulfonate (II-1a).** 4-Nitrobenzene-1-sulfonyl chloride (1.33 g, 6.0 mmol) and 4-chlorophenol (0.73 g, 6.0 mmol) were dissolved in dichloromethane (30 mL). Then, triethylamine (0.73 g, 7.2 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP, 0.07 g) in dichloromethane (10 mL) were added dropwise at room temperature. The mixture was stirred for 10 h and then successively washed with 5% aqueous HCl solution and saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give crude product. The product was purified by recrystallization from ethyl acetate and petroleum ether (60–90 °C) to give compound II-1a (1.57 g, 83.5%) as a yellow solid. mp = 123–125 °C. ^1H NMR (400 MHz, CDCl_3) δ : 8.39 (d, $J = 8.5$ Hz, 2H, Ar–H), 8.04 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.30 (d, $J = 8.6$ Hz, 2H, Ar–H), 6.95 (d, $J = 8.6$ Hz, 2H, Ar–H).

Synthesis of 4-Chlorophenyl 4-Aminobenzenesulfonate (II-1b). Compound II-1a (1.57 g, 5.0 mmol) was dissolved in ethyl acetate (40 mL), and 10% Pd/C (0.20 g, 53% moisture) was added. Then, hydrogen was bubbled at room temperature through the reaction for 8 h. Then, the mixture was filtered, and the filtrate was concentrated under reduced pressure to give compound II-1b as a white solid without further purification in 95.8% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.54 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.24 (d, $J = 8.8$ Hz, 2H, Ar–H), 6.92 (d, $J = 8.7$ Hz, 2H, Ar–H), 6.64 (d, $J = 8.6$ Hz, 2H, Ar–H), 4.27 (brs, 2H, NH_2).

Synthesis of 4-Chlorophenyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-1). A solution of 2,6-difluorobenzoyl isocyanate (0.84 g, 4.6 mmol) in dichloromethane (20 mL) was added dropwise to a solution of compound II-1b (1.30 g, 4.3 mmol) in dichloromethane (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. Then, the mixture was filtered, and the crude product was purified by recrystallization from ethyl acetate to give compound II-1 (1.75 g, 81.4%) as a white solid. mp = 207–214 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.56 (brs, 1H, CONHCO), 10.51 (brs, 1H, CONHAr), 7.90 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.78 (d, $J = 8.7$ Hz, 2H, Ar–H), 7.60–7.68 (m, 1H, Ar–H), 7.47 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.26 (t, $J = 8.3$ Hz, 2H, Ar–H), 7.06 (d, $J = 8.6$ Hz, 2H, Ar–H). Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{ClF}_2\text{N}_2\text{O}_5\text{S}$: C, 51.46; H, 2.81; N, 6.00. Found: C, 51.33; H, 2.81; N, 6.00.

Compounds II-2a–II-8a, II-2b–II-8b, and I-2–I-8 were prepared using the similar method for compounds II-1a, II-1b, and II-1. The physical properties and ^1H NMR data of compounds II-2a–II-8a and II-2b–II-8b are listed in Table 3.

Data for 2-Isopropyl-5-methylcyclohexyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-2). White solid. Yield = 81.6%. mp > 300 °C. ^1H NMR (400 MHz, CDCl_3) δ : 10.77 (brs, 1H, CONHCO), 8.99 (brs, 1H, CONHAr), 7.87 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.68 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.53–7.61 (m, 1H, Ar–H), 7.07 (t, $J = 8.7$ Hz, 2H, Ar–H), 4.30 (td, $J = 10.8, 4.5$ Hz, 1H, OCH), 2.15 (d, $J = 12.0$ Hz, 1H), 1.84–1.95 (m, 1H), 1.64–1.69 (m, 2H), 1.36–1.47 (m, 2H), 1.20 (m, 1H), 0.79–1.04 (m, 8H), 0.56 (d, $J = 6.9$ Hz, 3H). Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{F}_2\text{N}_2\text{O}_5\text{S}$: C, 58.29; H, 5.71; N, 5.66. Found: C, 58.19; H, 5.79; N, 5.78.

Data for 2,2,2-Trifluoroethyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-3). White solid. Yield = 90.7%. mp = 182–184 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.56 (brs, 1H, CONHCO), 10.51 (brs, 1H, CONHAr), 7.96 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.90 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.60–7.68 (m, 1H, Ar–H), 7.27 (t, $J = 8.4$ Hz, 2H, Ar–H), 4.88 (q, $J = 8.6$ Hz, 2H, OCH_2CF_3). Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{F}_5\text{N}_2\text{O}_5\text{S}$: C, 43.84; H, 2.53; N, 6.39. Found: C, 43.64; H, 2.73; N, 6.41.

Data for 2-Fluoroethyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-4). White solid. Yield = 71.4%. mp = 213–215 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.55 (brs, 1H, CONHCO), 10.50 (brs, 1H, CONHAr), 7.87–7.92 (m, 4H, Ar–H), 7.61–7.68 (m, 1H, Ar–H), 7.27 (t, $J = 8.2$ Hz, 2H, Ar–H), 4.66 (t, $J = 3.7$ Hz, 1H, CH_2F), 4.54 (t, $J = 3.7$ Hz, 1H, CH_2F), 4.33 (t, $J = 3.8$ Hz, 1H, OCH_2), 4.26 (t, $J = 3.8$ Hz, 1H, OCH_2). HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_5\text{S}$ ($\text{M} + \text{Na}$) $^+$, 425.0398; found, 425.0390.

Data for 2-Chloroethyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-5). White solid. Yield = 84.4%. mp = 206–209 °C. ^1H NMR (400 MHz, CDCl_3) δ : 10.81 (brs, 1H, CONHCO), 8.74 (brs, 1H, CONHAr), 7.90 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.74 (d, $J = 8.3$ Hz, 2H, Ar–H), 7.52–7.61 (m, 1H, Ar–H), 7.08 (t, $J = 8.7$ Hz, 2H, Ar–H), 4.27 (t, $J = 5.7$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{Cl}$), 3.68 (t, $J = 5.6$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{Cl}$). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{N}_2\text{O}_5\text{S}$: C, 45.89; H, 3.13; N, 6.69. Found: C, 45.74; H, 3.49; N, 6.72.

Data for 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-6). White solid. Yield = 90.7%. mp = 197–199 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.61 (brs, 1H, CONHCO), 10.60 (brs, 1H, CONHAr), 8.05 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.96 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.62–7.69 (m, 1H, Ar–H), 7.28 (t, $J = 8.3$ Hz, 2H, Ar–H), 6.78–6.85 (m, 1H, $\text{OCH}(\text{CF}_3)_2$). Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{F}_8\text{N}_2\text{O}_5\text{S}$: C, 40.33; H, 1.99; N, 5.53. Found: C, 40.36; H, 1.99; N, 5.53.

Data for 4-Chlorobutyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-7). White solid. Yield = 68.2%. mp = 175–177 °C. ^1H NMR (400 MHz, CDCl_3) δ : 10.79 (brs, 1H, CONHCO), 8.82 (brs, 1H, CONHAr), 7.87 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.72 (d, $J = 8.5$ Hz, 2H, Ar–H), 7.54–7.61 (m, 1H, Ar–H), 7.08 (t, $J = 8.6$ Hz, 2H, Ar–H), 4.10 (s, 2H, CH_2Cl), 3.53 (s, 2H, OCH_2), 1.84 (s, 4H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{ClF}_2\text{N}_2\text{O}_5\text{S}$: C, 48.38; H, 3.83; N, 6.27. Found: C, 48.11; H, 3.95; N, 6.24.

Data for Pentyl 4-(3-(2,6-Difluorobenzoyl)ureido)benzenesulfonate (Target Compound II-8). White solid. Yield = 87.9%. mp = 173–175 °C. ^1H NMR (400 MHz, CDCl_3) δ : 10.79 (brs, 1H, CONHCO), 9.07 (brs, 1H, CONHAr), 7.86 (d, $J = 8.6$ Hz, 2H,

Table 3. Physical Properties and ¹H NMR Data of Compounds II-2a–II-8a and II-2b–II-8b

compd	R	m.p. (°C)	¹ H NMR δ (ppm)
			a
			b
II-2a		pale yellow solid 71–73	¹ H NMR (400 MHz, CDCl ₃): 8.40 (d, <i>J</i> = 8.6 Hz, 2H, Ar-H), 8.12 (d, <i>J</i> = 8.6 Hz, 2H, Ar-H), 4.57 (td, <i>J</i> = 10.8, 4.5 Hz, 1H, OCH), 2.08 (d, <i>J</i> = 12.0 Hz, 1H), 1.80–1.91 (m, 1H), 1.65–1.74 (m, 2H), 1.33–1.52 (m, 2H), 1.14–1.27 (m, 2H), 0.94–1.06 (m, 1H), 0.81–0.91 (m, 6H), 0.60 (d, <i>J</i> = 6.9 Hz, 3H).
II-2b		white solid	¹ H NMR (400 MHz, CDCl ₃): 7.67 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 6.68 (d, <i>J</i> = 8.3 Hz, 2H, Ar-H), 4.30 (td, <i>J</i> = 10.5, 4.2 Hz, 1H, OCH), 3.96 (brs, 2H, NH ₂), 2.16 (d, <i>J</i> = 11.7 Hz, 1H), 1.58–1.65 (m, 2H), 1.09–1.45 (m, 4H), 0.82–1.02 (m, 8H), 0.53 (d, <i>J</i> = 6.8 Hz, 3H).
II-3a	CH ₂ CF ₃	yellow solid 123–125	¹ H NMR (400 MHz, CDCl ₃): 8.45 (d, <i>J</i> = 8.5 Hz, 2H, Ar-H), 8.15 (d, <i>J</i> = 8.5 Hz, 2H, Ar-H), 4.50 (q, <i>J</i> = 7.7 Hz, 2H, OCH ₂ CF ₃).
II-3b	CH ₂ CF ₃	white solid	¹ H NMR (400 MHz, CDCl ₃): 7.68 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 6.71 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 4.27–4.35 (m, 4H, NH ₂ and OCH ₂ CF ₃).
II-4a	CH ₂ CH ₂ F	yellow solid 119–120	¹ H NMR (400 MHz, CDCl ₃): 8.42 (d, <i>J</i> = 8.3 Hz, 2H, Ar-H), 8.14 (d, <i>J</i> = 8.4 Hz, 2H, Ar-H), 4.67 (d, <i>J</i> = 2.4 Hz, 1H, CH ₂ F), 4.55 (d, <i>J</i> = 2.5 Hz, 1H, CH ₂ F), 4.45 (d, <i>J</i> = 1.8 Hz, 1H, OCH ₂), 4.38 (d, <i>J</i> = 1.9 Hz, 1H, OCH ₂).
II-4b	CH ₂ CH ₂ F	yellow oil	¹ H NMR (400 MHz, CDCl ₃): 7.68 (d, <i>J</i> = 8.7 Hz, 2H, Ar-H), 6.70 (d, <i>J</i> = 8.7 Hz, 2H, Ar-H), 4.63 (t, <i>J</i> = 4.1 Hz, 1H, CH ₂ F), 4.51 (t, <i>J</i> = 4.1 Hz, 1H, CH ₂ F), 4.25 (t, <i>J</i> = 4.2 Hz, 3H, OCH and NH ₂), 4.18 (t, 1H, <i>J</i> = 4.2 Hz, 1H, OCH).
II-5a	CH ₂ CH ₂ Cl	white solid 107–109	¹ H NMR (400 MHz, CDCl ₃): 8.43 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 8.15 (d, <i>J</i> = 8.3 Hz, 2H, Ar-H), 4.38 (t, <i>J</i> = 5.5 Hz, 2H, OCH ₂ CH ₂ Cl), 3.71 (t, <i>J</i> = 5.4 Hz, 2H, OCH ₂ CH ₂ Cl).
II-5b	CH ₂ CH ₂ Cl	yellow solid	¹ H NMR (400 MHz, CDCl ₃): 7.68 (d, <i>J</i> = 8.7 Hz, 2H, Ar-H), 6.70 (d, <i>J</i> = 8.7 Hz, 2H, Ar-H), 4.27 (brs, 2H, NH ₂), 4.19 (t, <i>J</i> = 6.0 Hz, 2H, OCH ₂ CH ₂ Cl), 3.64 (t, <i>J</i> = 6.1 Hz, 2H, OCH ₂ CH ₂ Cl).
II-6a	CH(CF ₃) ₂	yellow solid 109–110	¹ H NMR (400 MHz, CDCl ₃): 8.47 (d, <i>J</i> = 8.4 Hz, 2H, Ar-H), 8.17 (d, <i>J</i> = 8.4 Hz, 2H, Ar-H), 5.30–5.38 (m, 1H, OCH(CF ₃) ₂).
II-6b	CH(CF ₃) ₂	pale yellow solid 97–99	¹ H NMR (400 MHz, CDCl ₃): 7.69 (d, <i>J</i> = 8.8 Hz, 2H, Ar-H), 6.71 (d, <i>J</i> = 8.8 Hz, 2H, Ar-H), 5.17–5.27 (m, 1H, OCH(CF ₃) ₂), 4.36 (brs, 2H, NH ₂).
II-7a	CH ₂ CH ₂ CH ₂ CH ₂ Cl	yellow solid 59–61	¹ H NMR (400 MHz, CDCl ₃): 8.42 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 8.12 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 4.19 (d, <i>J</i> = 5.6 Hz, 1H, CH ₂ Cl), 3.55 (d, <i>J</i> = 5.7 Hz, 1H, OCH ₂), 1.87 (s, 4H, OCH ₂ CH ₂ CH ₂ CH ₂ Cl).
II-7b	CH ₂ CH ₂ CH ₂ CH ₂ Cl	yellow oil	¹ H NMR (400 MHz, CDCl ₃): 7.67 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 6.70 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 4.03 (d, <i>J</i> = 4.8 Hz, 1H, CH ₂ Cl), 4.20 (brs, 2H, NH ₂), 3.50 (d, <i>J</i> = 5.4 Hz, 1H, OCH ₂), 1.82 (d, <i>J</i> = 2.5 Hz, 4H, OCH ₂ CH ₂ CH ₂ CH ₂ Cl).
II-8a	CH ₂ (CH ₂) ₃ CH ₃	yellow solid 57–58	¹ H NMR (400 MHz, CDCl ₃): 8.41 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 8.12 (d, <i>J</i> = 8.2 Hz, 2H, Ar-H), 4.14 (t, <i>J</i> = 6.5 Hz, 2H, OCH ₂ CH ₂), 1.69 (t, <i>J</i> = 6.1 Hz, 2H, OCH ₂ CH ₂ CH ₂), 1.20–1.36 (m, 4H, CH ₂ CH ₂ CH ₂ CH ₂), 0.89 (t, <i>J</i> = 8.2 Hz, 3H, CH ₂ CH ₃).
II-8b	CH ₂ (CH ₂) ₃ CH ₃	yellow oil	¹ H NMR (400 MHz, CDCl ₃): 7.67 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 6.70 (d, <i>J</i> = 8.1 Hz, 2H, Ar-H), 4.20 (brs, 2H, NH ₂), 3.98 (t, <i>J</i> = 6.5 Hz, 2H, OCH ₂ CH ₂), 1.57–1.65 (m, 2H, OCH ₂ CH ₂ CH ₂), 1.28 (s, 4H, CH ₂ CH ₂ CH ₂ CH ₂), 0.86 (t, <i>J</i> = 6.1 Hz, 3H, CH ₂ CH ₃).

Ar-H), 7.69 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.54–7.61 (m, 1H, Ar-H), 7.08 (t, *J* = 8.6 Hz, 2H, Ar-H), 4.04 (t, *J* = 6.5 Hz, 2H, OCH₂CH₂), 1.66 (t, *J* = 6.7 Hz, 2H, OCH₂CH₂CH₂), 1.22–1.37 (m, 4H, CH₂CH₂CH₂CH₂), 0.86 (t, *J* = 6.7 Hz, 3H, CH₂CH₃). Anal. Calcd for C₁₉H₂₀F₂N₂O₅S: C, 53.51; H, 4.73; N, 6.57. Found: C, 53.41; H, 4.86; N, 6.61.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.¹⁵ Evaluations are based on a percentage scale of 0–

100, in which 0 = no activity and 100 = total kill. The standard deviations of the tested biological values were ±5%. LC₅₀ values were calculated by probit analysis.¹⁶

Larvicidal Activities against Oriental Armyworm (*Mythimna separata*). The larvicidal activities of the target compounds I-1–I-7 and II-1–II-8 against oriental armyworm were evaluated by foliar application using the reported procedure.¹⁷ For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed 3 times. The biological data in Table 1 were the average value of the three tested values. For comparative purposes, flucycloxuron was tested under the same conditions.

Larvicidal Activities against Diamondback Moth (*Plutella xylostella*). The larvicidal activities of the target compounds I-1–I-7 and II-1–II-8 against diamondback moth were evaluated by the reported procedure.¹⁸ Compounds I-1–I-7 and II-1–II-8 were prepared to different concentrations by dissolving compounds I-1–I-7 and II-1–II-8 in dimethylformamide (DMF) and adding distilled water. Leaf discs (5 × 3 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf discs were placed individually into vertical tubes and the discs were infested with 10 s-instar diamondback moth larvae. Percentage mortalities were evaluated 4 days after treatment. The biological data in Table 1 were the average value of the three tested values. For comparative purposes, flucycloxuron was tested under the same conditions.

RESULTS AND DISCUSSION

Synthesis. The target compounds I-1–I-7 were synthesized from 4-nitrobenzoic acid, as shown in Scheme 1. 4-Nitrobenzoyl chloride was produced from 4-nitrobenzoic acid and thionyl chloride, and subsequent reaction with a primary or secondary amine yielded compounds I-1a–I-7a. Further reduction using hydrogen with 10% Pd/C as a catalyst provided compounds I-1b–I-7b, which were combined with 2,6-difluorobenzoyl isocyanate to afford compounds I-1–I-7.

The target compounds II-1–II-8 were synthesized from 4-nitrobenzene-1-sulfonyl chloride, as shown in Scheme 2. Compounds II-1a–II-8a were produced from 4-nitrobenzene-1-sulfonyl chloride and different alcohol or phenol, and further reduction using hydrogen with 10% Pd/C as a catalyst provided compounds II-1b–II-8b, which were combined with 2,6-difluorobenzoyl isocyanate to afford compounds II-1–II-8.

Bioassay. Table 1 shows the larvicidal activities of the target compounds I-1–I-7, II-1–II-8, and flucycloxuron against oriental armyworm and diamondback moth. The results indicated that benzoylureas containing amide groups did not have good larvicidal activities against oriental armyworm and diamondback moth, except compound I-1, which had 100% mortality against oriental armyworm at 100 mg L⁻¹. However, benzoylureas containing sulfonate groups exhibited much better larvicidal activities against oriental armyworm and diamondback moth than benzoylureas containing amide groups. In particular, compound II-3 had 100% mortality on oriental armyworm at 10 mg L⁻¹ and 90% mortality on diamondback moth at 5 mg L⁻¹, which exhibited comparable activity to commercial insecticide flucycloxuron. When R was 2–5 C straight-chain haloalkyl groups in the structure of compound II, new benzoylureas exhibited better larvicidal activities against oriental armyworm. For example, compounds II-3, II-4, and II-7 had 100% mortality at 100 mg L⁻¹, whereas compounds II-1, II-2, and II-6 with branched alkyl or aryl groups showed no larvicidal activities at 200 mg L⁻¹. Interestingly, among the sulfonates II, compound II-3 with a 2,2,2-trifluoroethyl group exhibited the best

larvicidal activities against oriental armyworm and diamondback moth; therefore, 2,2,2-trifluoroethyl group, which is proposed to interact with the target protein of tested insects, did play an important role in the insecticidal activity of benzoylureas containing sulfonate groups.

In summary, a series of new benzoylureas containing amide and the sulfonate groups were designed and synthesized. The results of the bioassay showed that benzoylureas containing sulfonate groups exhibited considerable larvicidal activities against oriental armyworm and diamondback moth, especially compound II-3, displaying comparable activity to commercial insecticide flucycloxuron; thereby, compound II-3 could be used as a lead compound for chemical modifications to find more active benzoylurea insecticides.

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Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Oberlander, H.; Silhacek, D. L. Mode of action of insect growth regulators in Lepidopteran tissue culture. *Pestic. Sci.* **1998**, *54*, 300–302.
- (2) Yang, X. L.; Wang, D. Q.; Chen, F. H. The synthesis and larvicidal activity of *N*-aroyl-*N'*-(*S*-aryl-2-furoyl)ureas. *Pestic. Sci.* **1998**, *52*, 282–286.
- (3) Post, L. C.; Vincent, W. R. A new insecticide inhibits chitin synthesis. *Naturwissenschaften* **1973**, *60*, 431–432.
- (4) Mayer, R. T.; Chen, A. C. Chitin synthesis inhibiting insect growth regulators do not inhibit chitin synthase. *Experientia* **1981**, *37*, 337–338.
- (5) Marks, E. P.; Leighton, T.; Leiehton, F. Modes of action of chitin synthesis inhibitors. In *Insecticide Mode of Action*; Coats, J. R., Eds.; Academic Press: New York, 1982; pp 281–313.
- (6) Cohen, E.; Casida, J. E. Inhibition of *Tribolium* gut chitin synthetase. *Pestic. Biochem. Physiol.* **1980**, *13*, 129–136.
- (7) Meola, S. M.; Mayer, R. T. Inhibition of cellular proliferation of imaginal epidermal cells by diflubenzuron in pupae of the stable fly. *Science* **1980**, *207*, 985–987.
- (8) DeLoach, J. R.; Meola, S. M.; Mayer, R. T.; Thompson, J. M. Inhibition of synthesis by diflubenzuron in pupae of the stable fly *Stomoxys calcitrans*. *Pestic. Biochem. Physiol.* **1981**, *15*, 172–180.
- (9) Ke, S. Y.; Liu, F. Y.; Wang, N.; Yang, Q.; Qian, X. H. 1,3,4-Oxadiazoline derivatives as novel potential inhibitors targeting chitin biosynthesis: Design, synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 332–335.
- (10) Abo-Elghar, G. E.; Fujiyoshi, P.; Matsumura, F. Significance of the sulfonylurea receptor (SUR) as the target of diflubenzuron in chitin synthesis inhibition in *Drosophila melanogaster* and *Blattella germanica*. *Insect Biochem. Mol. Biol.* **2004**, *34*, 743–752.
- (11) Matsumura, F. Studies on the action mechanism of benzoylurea insecticides to inhibit the process of chitin synthesis in insects: A review on the status of research activities in the past, the present and the future prospects. *Pestic. Biochem. Physiol.* **2010**, *97*, 133–139.
- (12) Lima, L. M. A.; Barreiro, E. J. Bioisosterism: A useful strategy for molecular modification and drug design. *Curr. Med. Chem.* **2005**, *12* (1), 23–49.
- (13) Hiroshi, N.; Yasuo, S. Benzoylureas, their production and use. U.S. Patent 4,843,100, 1989.
- (14) Weikert, R. J.; Emanuel, M. A. Synthesis and anthelmintic activity of 3'-benzoylurea derivatives of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole. *J. Med. Chem.* **1991**, *34*, 1630–1633.
- (15) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.
- (16) Raymond, M. Presentation d'un programme basic d'analyse log-probit pour micro-ordinateur. *Cah. ORSTOM, Ser. Ent. Med. Parasitol.* **1985**, *23*, 117–121.
- (17) Hsu, A. C.; Murphy, R. A.; Aller, H. E.; Hamp, D. W.; Weinstein, B. Insecticidal *N'*-substituted-*N,N'*-disubstitutedhydrazines. U.S. Patent 5,117,057, 1992.
- (18) Busvine, J. R. *FAO Plant Production and Protection Paper*; Food and Agriculture Organization (FAO): Rome, Italy, 1980; no. 21, pp 3–13, 119–122.