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N-Fluorinated phenyl-*N*′-pyrimidyl urea derivatives: Synthesis, biological evaluation and 3D-QSAR study

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ABSTRACT

With the increase of herbicide-resistant weeds, novel, more selective and even more potent herbicides to control weeds are needed. In this paper, a series of *N*-fluorinated phenyl-*N*′-pyrimidyl urea derivatives were synthesized and screened for their herbicidal activities against *Amaranthus retroflexus* (*AR*) and *Setaria viridis* (*SV*). Compound **25** (*N*-(3-trifluoromethylphenyl)-*N*′-(2-amino-4-chloro-6-methylpyrimidyl) urea) exhibited marked herbicidal activity against *SV* (IC_{50} = 11.67 mg/L) and is more potent than bensulfuron (IC_{50} = 27.45 mg/L), a commercially available herbicide. A statistically significant CoMFA model with high prediction abilities (q^2 = 0.869, r^2 = 0.989) was obtained.

1. Introduction

Pesticides have greatly benefited grain harvest by reducing harmful pests. The widespread use of herbicides in farming has led to annual increases in the dosage of herbicides used. Simultaneously, the problem of herbicide-resistance emerged and became more and more serious. The increasing of the amount of spraying has also caused a series of problems. For example, they have led to harm to human health, the degradation of water resource quality, and the reduction in the biodiversity of field communities [1–3]. Therefore, it is essential and urgent to develop novel, more selective, and even more potent herbicides to control weeds.

The urea group is an attractive structural unit due to its broad range of biological activities, and it can be widely found in natural products [4]. As such, urea derivatives have attracted a lot of attention for applications in herbicidal [5], antifungal [6], antibacterial [7], and plant growth regulator [8] chemicals. Pyrimidines are also considered important heterocyclic compounds for their wide range of biological activities. *N*-phenyl-*N*′-pyrimidyl urea derivatives are considered to be prospective compounds with high activity due to their containing both a carbamide bridge (NH–CO–NH) and a pyrimidyl group [9]. On the other hand, fluorine is a very important element for its high electronegativity and small volume. The high electronegativity of fluorine will affect the distribution of the electrons in the molecule. Biologically active molecules will have significantly improved lipophilicity if they contain fluorine atoms [10–15]. It was speculated that the introduction of a fluorine atom into the compound could improve the compound's physicochemical effects.

Inspired by these findings, we focused on designing and synthesizing a series of novel compound derivatives based on the essential fluorinated *N*-phenyl-*N*′-pyrimidyl urea scaffold. All the structures of the synthesized target compounds were thoroughly characterized by IR and ^{1}H NMR spectra. Then all the compounds were screened for their herbicidal activities against *Amaranthus retroflexus* (*AR*) and *Setaria viridis* (*SV*). The biological testing results showed that compound **25** (*N*-(3-trifluoromethylphenyl)-*N*′-(2-amino-4-chloro-6-methylpyrimidyl) urea) displayed the most potent biological activity against *SV* (IC_{50} = 11.67 mg/L), and was more potent than bensulfuron (IC_{50} = 27.45 mg/L), a commercially available herbicide. With this data, in this present study, we also performed quantitative structure–activity relationship (QSAR) studies, and a statistically significant CoMFA model with high predictive abilities (q^2 = 0.869, r^2 = 0.989) was obtained.

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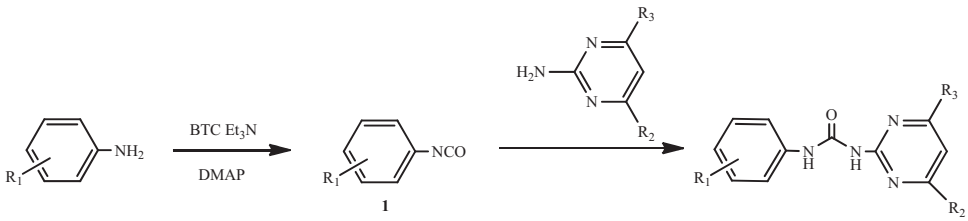

Scheme 1. Synthetic route for target compounds **3**–**47**.

2. Experimental

2.1. Chemistry

All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried and redistilled before use. Melting points were determined with a digital melting point apparatus and were uncorrected. IR spectra were recorded on a Thermo Nicolet FT-IR Avatar 330 instrument. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Mercury 600 spectrometer, and chemical shifts (δ) were given in ppm relative to tetramethylsilane. The progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel plates visualized with UV light.

2.1.1. General procedure for the synthesis of target compounds **3**–**47**

The synthetic route for *N*-fluorinated phenyl-*N*′-pyrimidyl urea derivatives is depicted in Scheme 1. At first, 40 mL toluene solution which contained 5 mmol fluorine-containing aniline was slowly dropped into another toluene solution which contained 2 mmol BTC (triphosgene) and a few drops Et_3N while mixing at 0 °C for about 1 h. The mixture was stirred at room temperature for 1 h and then heated to 80 °C until the white solid completely dissolved. The intermediate **1** was isolated and obtained by concentration under reduced pressure and flushing by nitrogen [16,17]. To obtain the final target compounds, the unpurified intermediate **1** was added into a series of substituted pyrimidinamine (5 mmol, as shown in Table 1) solutions which contained a little tetrabutylammonium bromide that was used as phase transfer catalyst. Then, the mixture was agitated at 80–100 °C for 6–9 h. The reaction was detected according to TLC. When the reaction was complete, the product was cooled to room temperature, filtered, and washed with 10% Na_2CO_3, water, and acetone. The final target compounds were purified by recrystallization (DMF/acetone).

2.1.2. Characterization data of some selected target compounds

N-(2, 4-Difluorophenyl)-*N*′-(2-amino-4-chloro-6-methoxypyrimidyl) urea (**10**): White crystal, yield 52.6%, mp 230–232 °C, IR (KBr, cm^{-1}): ν 3414 (N–H), 3032 (Ar–H), 1701 (C=O), 1236 (OCH3). ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.42 (s, 1H, NH), 8.17 (d, 1H, J = 6.6 Hz, ArH), 7.36 (t, 1H, J = 9.0 Hz, ArH), 7.07 (t, 1H, J = 7.8 Hz, ArH), 6.78 (s, 1H, pyrH), 3.96 (s, 3H, OMe).

N-(3-Trifluoromethylphenyl)-*N*′-(2-amino-4-chloro-6-methylpyrimidyl) urea (**25**): White crystal, yield 58.5%, mp 191–192 °C, IR (KBr, cm^{-1}): ν 3430 (N–H), 3141 (Ar–H), 1691 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.39 (s, 1H, NH), 10.43 (s, 1H, NH), 7.89 (d, 1H, J = 7.2 Hz, ArH), 7.74 (t, 1H, J = 8.4 Hz, ArH), 7.26 (m, 2H, J = 4.2 Hz, ArH), 6.90 (s, 1H, pyrH), 2.54 (s, 3H, CH_3).

N-(3-Fluorophenyl)-*N*′-(2-amino-4-hydroxy-6-methylpyrimidl) urea (**40**): White powder, yield 75.8%, mp 271–273 °C, IR (KBr, cm^{-1}): ν 3431 (N–H), 3223 (O–H), 3116 (Ar–H), 1707 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.13 (d, 1H, J = 5.4 Hz, ArH), 7.74 (m, 2H, J = 7.8 Hz, ArH), 7.37 (s, 1H, ArH), 5.97 (s, 1H, pyrH), 2.20 (s, 3H, Me).

Table 1
Structures and biological activities of the compounds used in the training and testing sets.

Compd.	R_1	R_2	R_3	IC_{50} (mg/L)	
				A.R (root)	*S.V* (root)
3	2-F	Cl	OMe	138.05	212.53
4	3-F	Cl	OMe	171.70	159.24
5	4-F	Cl	OMe	115.03	175.50
6^T	2-CF_3	Cl	OMe	225.41	660.12
7	3-CF_3	Cl	OMe	750.80	446.34
8	4-CF_3	Cl	OMe	315.73	112.77
9	2,6-di-F	Cl	OMe	409.70	210.15
10	2,4-di-F	Cl	OMe	83.83	42.33
11	2,5-di-F	Cl	OMe	124.80	51.87
12	2-F	H	H	198.79	256.32
13	3-F	H	H	150.20	161.25
14^T	4-F	H	H	108.57	255.31
15	2-CF_3	H	H	163.94	530.49
16	3-CF_3	H	H	132.60	67.56
17^T	4-CF_3	H	H	318.84	330.60
18	2,6-di-F	H	H	208.20	485.31
19	2,4-di-F	H	H	138.62	284.56
20	2,5-di-F	H	H	74.61	127.60
21	2-F	Me	Cl	415.20	115.22
22	3-F	Me	Cl	301.13	79.56
23	4-F	Me	Cl	190.11	92.13
24	2-CF_3	Me	Cl	341.74	190.01
25	3-CF_3	Me	Cl	222.47	11.67
26	4-CF_3	Me	Cl	413.53	221.56
27	2,6-di-F	Me	Cl	371.62	250.18
28^T	2,4-di-F	Me	Cl	165.40	140.24
29	2,5-di-F	Me	Cl	342.65	179.86
30	2-F	OMe	OMe	298.11	198.56
31	3-F	OMe	OMe	164.93	205.52
32	4-F	OMe	OMe	94.13	164.06
33	2-CF_3	OMe	OMe	193.30	585.88
34^T	3-CF_3	OMe	OMe	116.32	409.95
35	4-CF_3	OMe	OMe	196.50	604.66
36	2,6-di-F	OMe	OMe	222.79	125.77
37	2,4-di-F	OMe	OMe	58.51	74.33
38	2,5-di-F	OMe	OMe	443.43	115.14
39	2-F	OH	Me	54.55	56.94
40^T	3-F	OH	Me	61.47	34.15
41	4-F	OH	Me	35.13	39.40
42	2-CF_3	OH	Me	175.97	226.73
43	3-CF_3	OH	Me	196.13	92.66
44	4-CF_3	OH	Me	66.89	59.06
45^T	2,6-di-F	OH	Me	242.12	219.16
46	2,4-di-F	OH	Me	73.45	90.14
47	2,5-di-F	OH	Me	200.87	150.46
Bensulfuron				14.67	27.45

AR: *Amaranthus retroflexus*.
SV: *Setaria viridis*.
^{T} Testing set compounds.

N-(4-Fluorophenyl)-*N*′-(2-amino-4-hydroxy-6-methylpyrimidl) urea (**41**): White powder, yield 68.3%, mp 225–226 °C, IR (KBr, cm^{-1}): ν 3415 (N–H), 3230 (O–H), 3070 (Ar–H), 1712 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.54 (m, 2H, J = 5.4 Hz, ArH), 7.16 (m, 2H, J = 7.8 Hz, ArH), 5.92 (s, 1H, pyrH), 2.22 (s, 3H, Me).