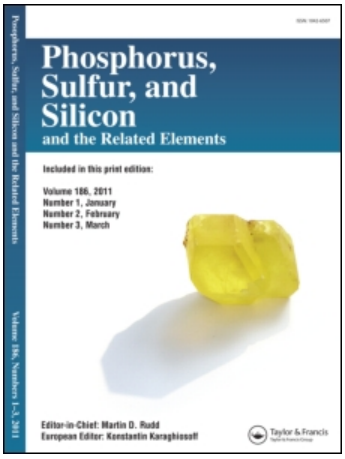

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SYNTHESIS OF NOVEL DERIVATIVES OF 2-CYANO-3-METHYLTHIO-3'-BENZYLAMINO ACRYLATES(ACRYLAMIDES) AND THEIR BIOLOGICAL ACTIVITY

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SYNTHESIS OF NOVEL DERIVATIVES OF 2-CYANO-3-METHYLTHIO-3′-BENZYLAMINO ACRYLATES(ACRYLAMIDES) AND THEIR BIOLOGICAL ACTIVITY

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A series of new substituted derivatives of 2-cyano-3-methvlthio-3′-aminoacrylates(acrylamides) have been designed and synthesized. Their structures were confirmed by ^{1}H NMR and elemental analysis. The bioassay test indicates that most of these new compounds show good Hill reaction inhibitory activity.

Keywords: photosystem II; acrylates(acrylamides); molecular design; Hill inhibitory activity

INTRODUCTION

Photosynthesis is important physiological and biochemical phenomenon for plants, and it is necessary to select photosynthesis as a herbicidal target in order to get nontoxic pesticides. Recently, Deisenhofer *et al* have successfully proved the dimensional structure of L protein of photosynthetic reaction center of *Rps. Viridis* with X-ray diffraction[1], and these important results make it possible to design new photosystem II (PS II)inhibitors based on the receptor structure.

A large number of inhibitors are known to block PS II by displacing plastoquinone from Q_B-binding niche of the D1 protein in the reaction

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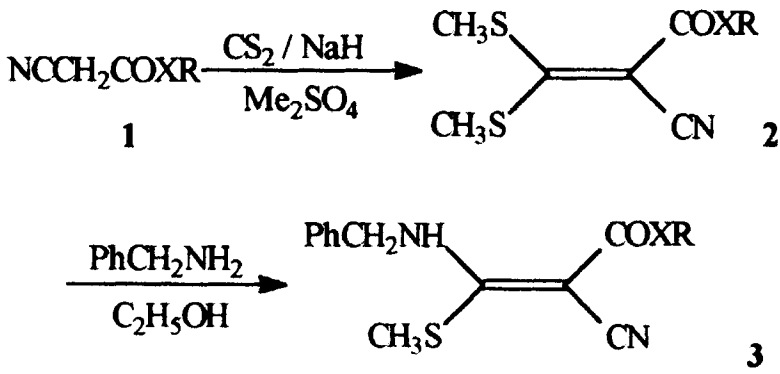
center[1,2]. Based on the above dimensional structure of L protein of the photosynthetic reaction center of *Rps. Viridis*, the 3D-structure of *Pisum sativum* 32Kdal(D1) was constructed by a homologous modeling method, and the properties, such as steric, hydrophobic, electrostatic properties of the active site region of the D1 protein were also characterized by the grid search method with probes of CH_3E, H_2O, NT and proton [3].

Acrylates (Scheme 1) are potent inhibitors of photosynthetic electron transport. A number of studies concerning the inhibition of photosynthetic electron flow in PS II with a series of acrylate inhibitors have shown that the potency of acrylates in blocking photosynthetic electron flow is extremely sensitive to minor structural variation[2,4]. It can be concluded that this class of inhibitors is useful as probes for determining the nature of the receptor topography.



SCHEME 1

RESULTS AND DISCUSSION

A. Design of the Title Compounds

Our previous studies[3] show that SER268 in D1 protein might be another important active site. In either side structure of the acrylates, a negative atom might bind to SER 268 with H-bond interaction, resulting in decrease of the energy of interaction between a small molecule and the receptor, and improving molecules' inhibitory activity. On the other side, the methylene

between the phenyl moiety and the amine group let the phenyl ring connect with a sp^3-hybridized carbon atom, and the phenyl ring can turn freely and easily, so that there will be fit interaction between the small molecule and the receptor, and these also can improve molecular inhibition activity. Based on the above studies, novel new substituted derivatives of acrylates(acrylamides) were designed and synthesized.

B. Synthesis of the Title Compounds

For synthesizing the title compounds, the following route shown in scheme 1 was selected.

Compounds **1** with different esters(amides) have different reactivity, so there should exist different conditions in order to produce good yield of compounds **2**. The detailed conditions are shown in Table I. It was found that those effect factors on the reaction are the base and the reaction temperature. For amides, the base KOH is better than sodium hydride to a lesser degree, because there is another active hydrogen in amides beside methylene. On the other hand, the temperature also has a great effect on the reaction. High temperature could lead to a lot of by-product. Only suitable temperature with little long reaction time can produce high yield **2**.

TABLE I Reaction condition and experimental data

No.	*Group XR*	*Base*	*Temperature (°C)*	*Time (h.)*	*Yield (%)*	*m.p. (°C) or n_D^{25}*
2a	$OCH_2CH_2OCH_3$	NaH	20	6.0	76	1.4956
2b	$NHCH_2CH_2OCH_3$	KOH	20	6.0	77	49~50
2c	$OCH_2CH_2OC_2H_5$	NaH	20	6.0	80	1.5128
2d	$NHCH_2CH_2CH_2OCH_3$	KOH	20	6.0	79	67~68
2e	OCH_2CH_2Cl	NaH	5	10.0	77	56~58
2f	$OCH_2CH_2C_6H_4(CH_3)$-*2*	NaH	10	7.0	75	45~46
2g	$OCH_2CH_2C_6H_3(CH_3)_2$-*3, 4*	NaH	10	7.0	74	78~80
2h	$OC_6H_4(OCH_3)$-*4*	NaH	10	7.0	78	84~86
2i	$OCH_2CH{=}CH_2$	NaH	5	11.0	74	67~69
2j	$OCH_2C{\equiv}CH$	NaH	5	10.5	73	79~81

The two methythio groups in compounds **2** have different reactivity. According to our previous study[5,6], the methylthio on the reverse side of the cyano group have higher reactivity, and thus produce compounds **3** shown as in Scheme 1.

All compounds **3** have been analyzed by ^1H NMR and elemental analysis (see Table II and III). Determination on a 200 M Hz NMR spectrometer in deuteriochloroform indicated that a single peak appeared around 4.7 ppm which should be $-CH_2N=$. For IR spectra, a strong absorption band around 2200 cm^{-1} and 1670 cm^{-1} may separately belong to C=N and C=O. The other could all be rationalized. The EI-MS spectra showed that compounds **3** could cleave to give fragment $C_6H_5CH_2$ as a base peak and the molecular ion peak could also be observed.

TABLE II Experimental data of title compounds

No.	*State**	*Yield(%)*	*m.p.(°C)*	*No.*	*State**	*Yield(%)*	*m.p.(°C)*
3a	W. S.	96	58~59	3f	W. S.	97	81~82
3b	W. S.	95	55~56	3g	W. S.	96	67~68
3c	W. S.	92	46~47	3h	W. S.	91	59~61
3d	W. S.	98	75~76	3i	W. S.	97	64~66
3e	Y. S.	98	56~58	3j	W. S.	97	77~78

* W = white, S = solid and Y = yellow.

C. Hill Inhibitory Activity

Compounds were assayed for Hill inhibitory activity using suspensions of chloroplasts isolated from the leaves of 20 day old plants of *Pisum sativum*. The experimental procedure was as described elsewhere[7]. The activity of a compound as a Hill inhibitor was expressed in terms of its pI_{50} value i. e. $-\lg IC_{50}$, where IC_{50} was the molar concentration required to decrease the rate of dye reduction under illumination of saturating intensity to 50% that obtained in the absence of the compound. All the Hill inhibitory activity of compounds **3** are recorded in Table IV. Results from bioassay test indicate that most of the designed and synthesized title compounds have good activity, especially, compound **3c** show high activity.

TABLE III Data of ^1H NMR and results from elemental analysis of Title Compounds

No.	*Formula*	*^1H NMR ($CDCl_3$, δ, ppm)*	*Elemental analysis(%)*		
			C	*H*	*N*
3a	$C_{15}H_{18}O_3N_2S$	2.65(s, 3H, SCH_3), 3.30(s, 3H, OCH_3), 3.60(t, 2H, OCH_2), 4.30(t, 2H, $OCOCH_2$), 4.65(d, 2H, CH_2N), 7.01~7.34(m, 5H, C_6H_5), 10.20(w, 1H, NH)	58.56 (58.80)	6.20 (5.92)	9.25 (9.14)
3b	$C_{15}H_{19}O_2N_3S$	2.54(s, 3H, SCH_3), 3.34(s, 3H,OCH_3), 3.43(m, 4H, CH_2CH_2), 4.74(d, 2H, CH_2N), 6.22(w, 1H, NH), 7. 10~7.45(m, 4H, C_6H_4), 11.25(w, 1H, NH)	58.96 (58.99)	6.25 (6.27)	13.46 (13.76)
3c	$C_{16}H_{20}O_3N_2S$	1.18(t, 3H, CH_3), 2.63(s, 3H, SCH_3), 3.55(dq, 2H, CH_2), 3.65(t, 2H, CH_2), 4.26(t, 2H, CH_2), 4.77(d, 2H, CH_2N), 7.23~7.31(m, 5H, C_6H_5), 10.24(w, 1H, NH)	59.84 (59.98)	6.32 (6.29)	8.83 (8.74)
3d	$C_{16}H_{21}O_2N_3S$	2.53(s, 3H, SCH_3), 3.34(m, 2H, CH_2), 3.37(s, 3H, OCH_3), 3.45(m, 4H, CH_2CH_2), 4.73(d, 2H, CH_2), 6.58(w, 1H, NH), 7.23~7.33(m, 5H, C_6H_5), 11.12(w, 1H, NH)	60.15 (60.16)	6.56 (6.63)	13.15 (13.16)
3e	$C_{14}H_{15}O_2N_2SCl$	2.66(s, 3H, CH_3S), 3.69(t, 2H, CH_2Cl), 4.37(t, 2H, OCH_2), 4.78(d, 2H, CH_2Ar), 7.20~7.42(m, 5H, C_6H_5), 10.24(w, 1H, NH)	54.18 (54.10)	5.01 (4.86)	8.99 (9.01)
3f	$C_{21}H_{22}O_2N_2S$	2.20(s, 3H, CH_3Ar), 2.68(s, 3H, CH_3S), 4.20(t, 2H, CH_2), 4.44(t, 2H, $COOCH_2$), 4.74(d, 2H, CH_2Ar), 6.80~7.32(m, 9H, C_6H_5 and C_6H_4), 10.32(w, 1H, NH)	68.08 (68.83)	5.89 (6.05)	7.31 (7.64)
3g	$C_{22}H_{24}O_2N_2S$	2.23(s, 3H, CH_3Ar), 2.25(s, 3H, CH_3Ar), 2.68(s, 3H, CH_3S), 4.20(t, 2H, CH_2), 4.48(t, 2H, $COOCH_2$), 4.78(d, 2H, CH_2Ar), 6.56~7.52 (m, 8H, C_6H_5 and C_6H_3), 10.30(w, 1H, NH)	69.44 (69.45)	6.23 (6.36)	7.22 (7.36)
3h	$C_{19}H_{18}O_3N_2S$	2.67(s, 3H, CH_3S), 3.78(s, 3H, OCH_3), 4.78(d, 2H, CH_2Ar), 6.80~7.38 (m, 9H, C_6H_5 and C_6H_4), 10.33(w, 1H, NH)	64.33 (64.39)	5.34 (5.12)	8.00 (7.90)
3i	$C_{15}H_{16}O_2N_2S$	2.67(s, 3H, SCH_3), 4.20(d, 2H, OCH_2), 4.30(d, 2H, $OCOCH_2$), 4.72(d, 2H, CH_2N), 5.32(m, 2H, CH_2C=), 5.99(m, 1h, CH=), 6.98~7.12(m, 5H, C_6H_5), 10.28(w, 1H, NH)	62.54 (62.48)	5.65 (5.59)	9.68 (9.71)
3j	$C_{15}H_{14}O_2N_2S$	2.48(s, 1H, CH), 2.68(s, 3H, SCH_3), 4.26(s, 2H, $OCH_2C\equiv$)4.30(s, 2H, $OCOCH_2$), 4.74(d, 2H, CH_2N), 7.01~7.23(m, 5H, C_6H_5), 10.29(w, 1H, NH)	63.00 (62.92)	4.99 (4.93)	9.81 (9.78)

TABLE IV Data of Hill Inhibitory Activity

Comp.	pI_{50}	*Comp.*	pI_{50}
3a	7.73	3f	7.33
3b	7.41	3g	6.35
3c	8.30	3h	7.47
3d	7.28	3i	7.20
3e	7.60	3j	7.11

EXPERIMENTAL

1. Apparatus and Reagents

Elemental analysis was carried out in CHN CORDER MT-3 elementary analyzer. 1H NMR was recorded with Bruker AC-P200 SPECTROMETER, TMS was used as an internal standard. The IR spectra were measured by using a Shimadzu-IR 435 instrument. The MS was performed with VG-7070E spectrometer using the EI method. Melting points were determined with Thomas-Hoover capillary melting point apparatus and uncorrected. Cyanoacrylates(acrylamides) **1** were prepared by the reaction of cyanoacetic acid with corresponding substituted acohols or amines. All reagents are commercial.

2. Synthesis of 2-cyano-3,3-dimethylthioacrylates(acrylamides) 2a~2d

The intermediates were prepared according to our previous paper[5,6] by corresponding intermediates including cyanoacetic methoxylethyl, cyanoacetic ethoxylethyl, cyanoacetamide methoxylethyl, cyanoacetamide methoxylpropyl reacted, respectively, with carbon disulfide and dimethyl sulfate, in the presence of sodium hydride, yield 76~80%.

Typical procedure

A mixture of 0.005 mol cyanoacetic methoxylethyl, 0.1 mol sodium hydride and anhydrous CH_3CN was stirred at 20 °C. After ten minutes, 0.05 mol carbon disulfide were added dropwise at 0 °C, and the mixture

was still stirred at 20 °C for half an hour, then 0.1 mol dimethyl sulfate was added dropwise. After the completion of the methylation reaction, the CH_3CN was removed under reduced pressure, and the residue was purified by column chromatography(silica gel H) to give 0.038 mol compound **2a**, n_D^{25}=1.4956, yield 76%. ^1H NMR (δ, ppm), 2.57(s, 3H, SCH_3), 2.73(s, 3H, SCH_3), 3.38(s, 3H, OCH_3), 3.66(t, 2H, OCH_2), 4.31[t, 2H, $C(O)OCH_2$].

3. Synthesis of 2-cyano-3-methylthio-3′-aminoacrylates(acrylamides) 3a~3u

Typical procedure

A mixture of 5 mmol **2a** (XR = $OCH_2CH_2OCH_3$), 5mmol benzyl amine and 8 ml anhydrous alcohol was stirred at room temperature or little heat until the TLC showed that the intermediate **2a** were almost disappeared, the white solid products 4.48 mmol were obtained and recrystallized from anhydrous alcohol, yield 96%, m.p. 58~59 °C.

IR (cm^{-1}), 2199(s, C≡N), 3170(s, N-H), 1672(s, C=O), 1241

MS (CI, m/e) 306(M+), 203, 155, 106, 91, 65, 39.

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