Synthesis of novel [1,2,4]triazolo[4,3-*b*]pyridazines

Karmen Čuček and Bojan Verček*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana
E-mail: Bojan.Vercek@uni-lj.si

Dedicated to Professor Miha Tišler on the occasion of his 75th birthday

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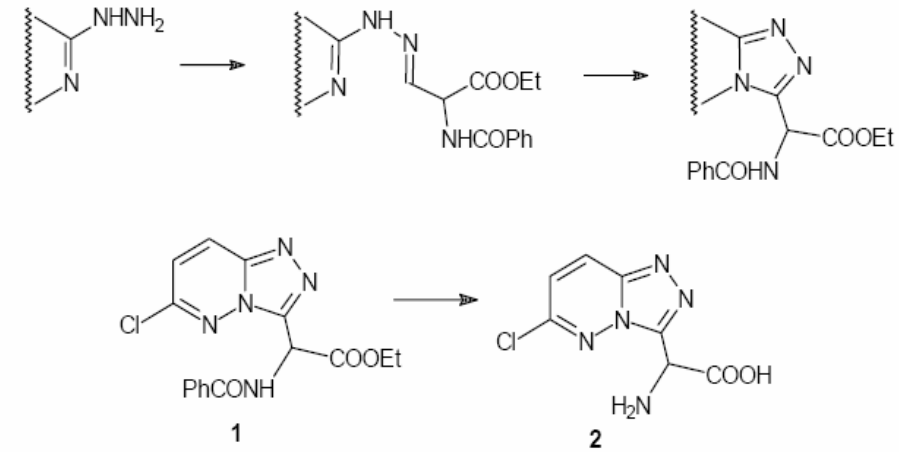
Abstract

The preparation of some derivatives of the [1,2,4]triazolo[4,3-*b*]pyridazine system from ethyl *N*-benzoyl-(6-chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)glycinate is reported.

Keywords: [1,2,4]Triazolo[4,3-*b*]pyridazines, amino acid derivatives

Introduction

Recently, we have elaborated a general approach to ethyl *N*-benzoyl-α-hetero-aryl-glycinates based on the annulation of the 1,2,4-triazole ring on the suitably substituted azine or fused azine derivative (Scheme 1).[1]

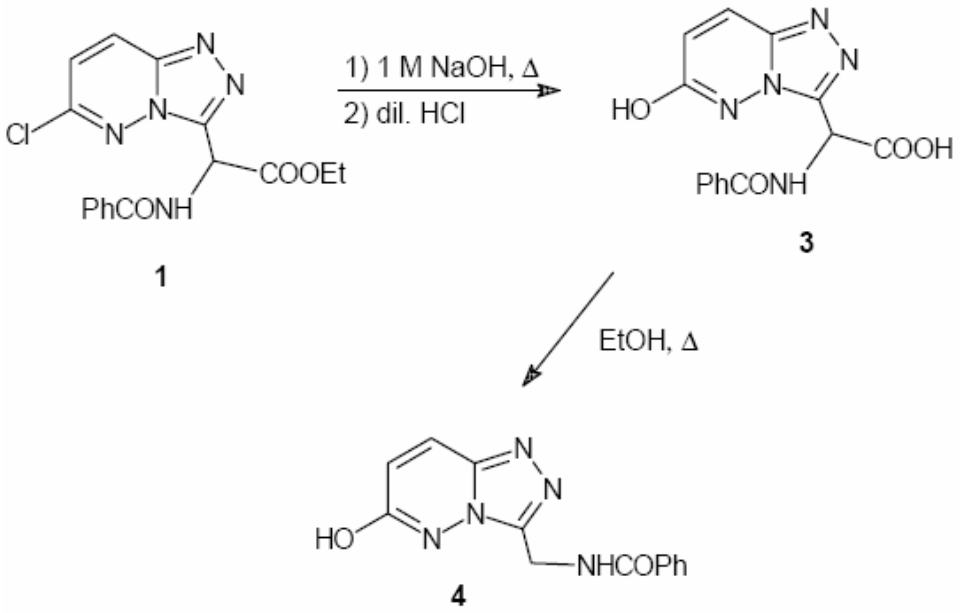


Scheme 1

Since the [1,2,4]triazolo[4,3-*b*]pyridazine system[2] has attracted great attention in the literature, it seemed worthwhile to explore synthetic utility of compound **1** in the preparation of some other derivatives of this system. In particular, we were interested in the preparation of the amino acid **2**. Herein we report on the results of these investigations.

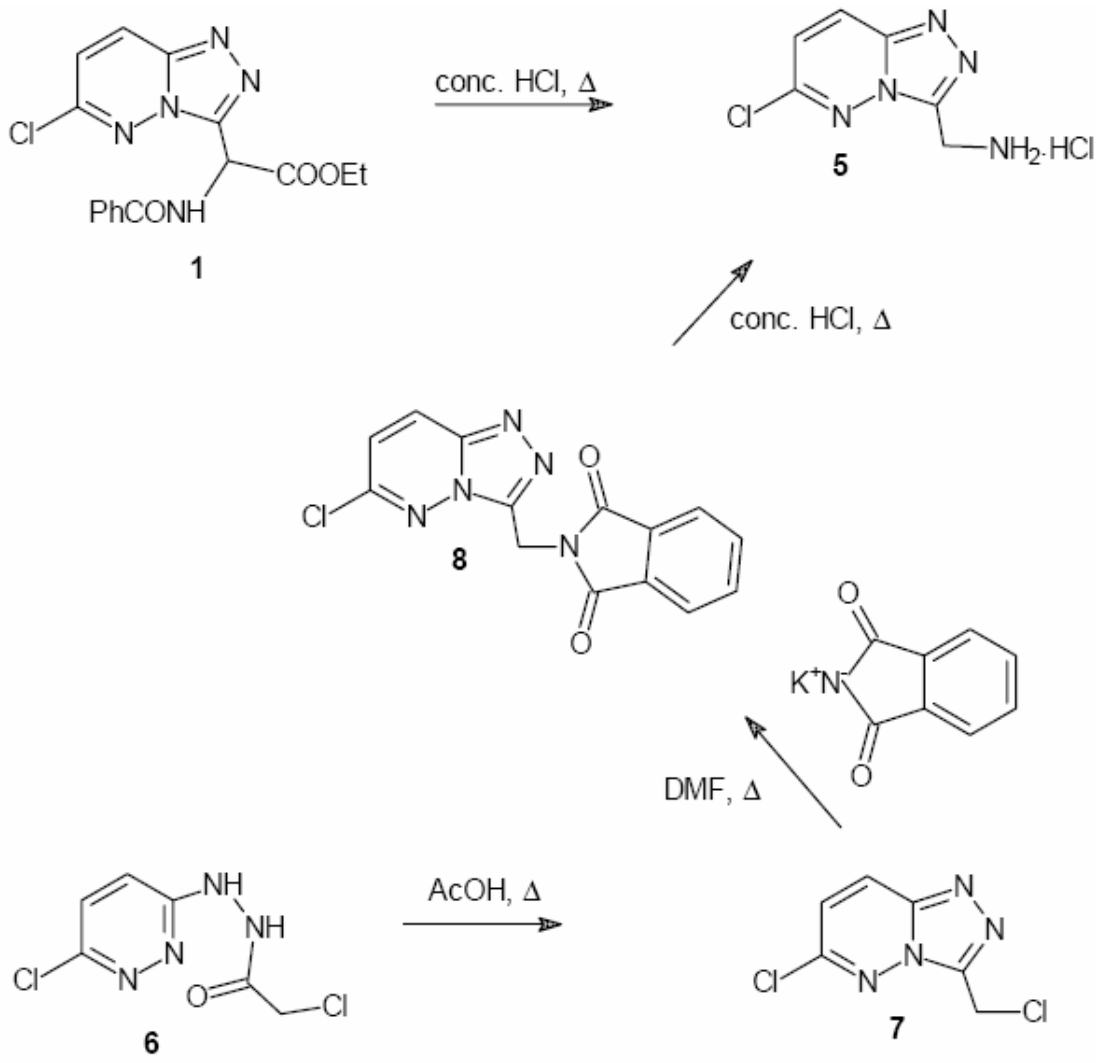
Results and Discussion

Reaction of **1** with hot 1 M sodium hydroxide solution took place on the ethoxycarbonyl group and at the position 6 of the triazolopyridazine system to give **3**, which underwent decarboxylation in hot ethanol affording benzamide **4** (Scheme 2).



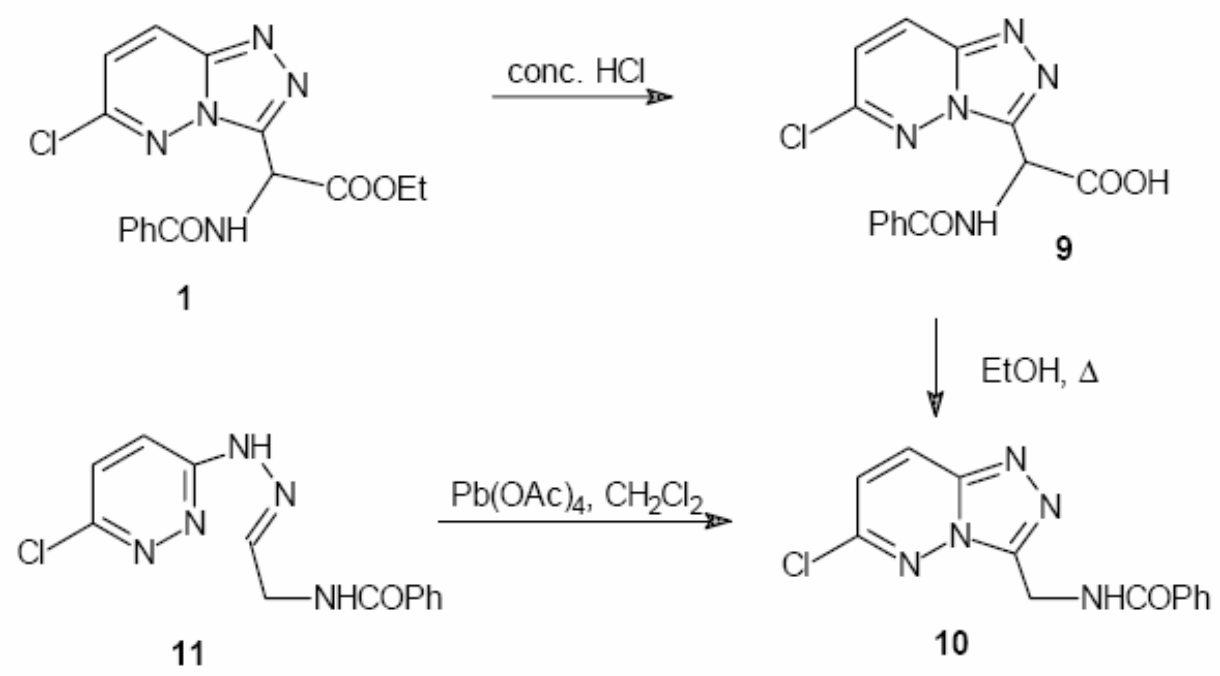
Scheme 2

Refluxing of **1** in diluted hydrochloric acid (1:1) for 4 h gave hydrochloride **5**. This compound was also prepared via a longer reaction sequence starting from hydrazide **6**,[3] which was firstly transformed by heating in acetic acid into the chloromethyl substituted triazolopyridazine **7**. Substitution of the chloro group with potassium phthalimide in hot *N*,*N*-dimethylformamide produced **8**, which hydrolyzed in hot hydrochloric acid to give **5** (Scheme 3).



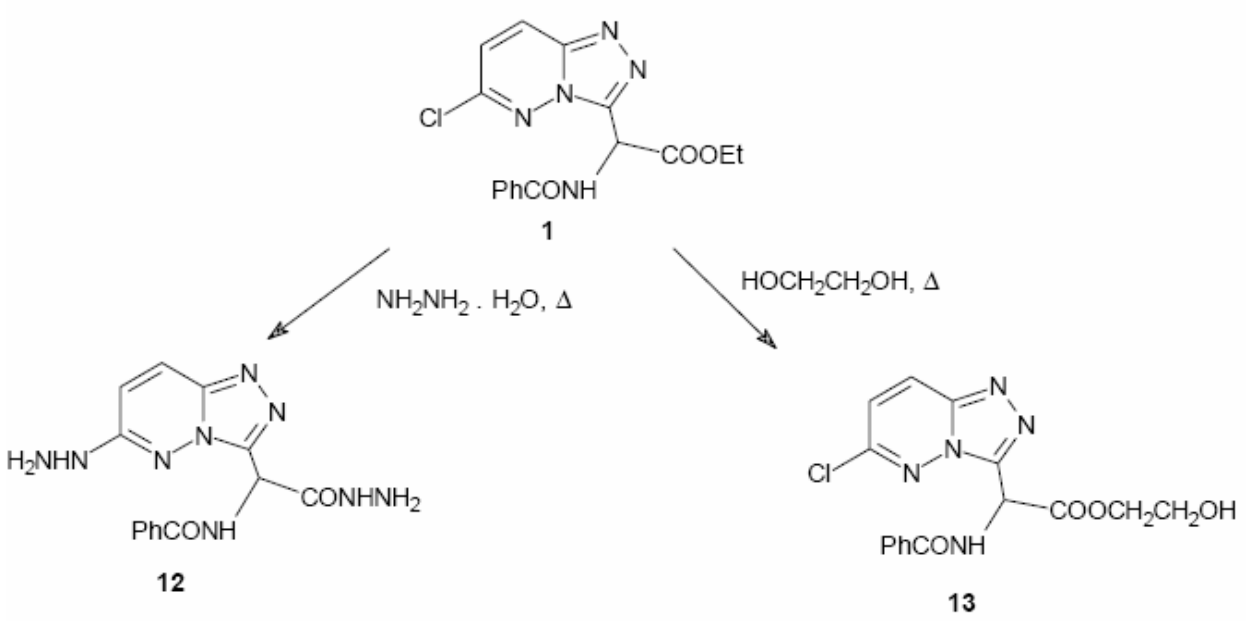
Scheme 3

On the other hand, treatment of **1** with concentrated hydrochloric acid at room temperature for 15 days yielded acid **9**, which similarly as **3** underwent decarboxylation by heating in ethanol giving benzamide **10**. The latter was also prepared by oxidative cyclization of hydrazone **11**.[4] Evidently, strong reaction conditions required for the elimination of the protective groups caused the decarboxylation of **9** making impossible the preparation of the acid **2** (Scheme 4).



Scheme 4

Stable triazolopyridazine were obtained in reactions of **1** with hydrazine hydrate and ethylene glycol. Reaction with hot 80% hydrazine hydrate proceeded similarly as with sodium hydroxide at two electron deficient carbons, carbon 6 and carbonyl group, giving hydrazide **12**, whereas treatment with hot ethylene glycol resulted in the formation of **13**. Both products might be suitable starting compounds for the preparation of some tricyclic systems, the former also for the peptide synthesis (Scheme 5).



Scheme 5

Experimental Section

General Procedures. Melting points were determined on a Kofler micro hot stage and are uncorrected. ^{1}H NMR spectra were recorded on Varian EM 360L (60 Hz) in DMSO-d_6 using TMS as internal standard. Elemental analyses for C, H, N were obtained on a Perkin-Elmer CHN Analyzer 2400. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Compounds **1**,[1] **6**,[3] and **11**,[4] were prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources.

***N*-Benzoyl-(6-hydroxy[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)glycine (3).** A mixture of 180 mg (0.5 mmol) of 1 and 3.6 mL of 1 M NaOH was heated under reflux for 25 min. The reaction mixture was then cooled to room temperature and acidified with diluted HCl (pH=1). The separated solid was then collected by filtration to give 127 mg (81%) of 3, which was for analysis washed with chloroform; mp 259-262°C. ^{1}H-NMR δ: 6.13 (d, 1H, J=7Hz, CH), 6.94 (d, 1H, J=9.5Hz, 7-H), 7.43 (m, 3H, Ph), 7.88 (m, 2H, Ph), 8.21 (d, 1H, J=9.5Hz, 8-H), 9.23 (d, 1H, J=7Hz, NH), 12.33 (broad, 1H, OH). *Anal*. Calc. for $C_{14}H_{11}N_5O_4$: C, 53.68; H, 3.54; N, 22.36. Found: C, 53.23; H, 3.22; N, 21.95.

***N*-(6-Hydroxy[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl benzamide (4).** A suspension of

313 mg (1 mmol) of **3** in 25 mL of ethanol was heated under reflux until it cleared up. Upon cooling, the separated solid was collected by filtration to give 202 mg (75%) of **4**; mp 292-294.5°C (methanol). ^{1}H-NMR δ: 4.88 (d, 2H, J=5Hz, CH2), 6.98 (d, 1H, J=9.5Hz, 7-H), 7.57 (m, 3H, Ph), 7.97 (m, 2H, Ph), 8.28 (d, 1H, J=9.5Hz, 8-H), 9.17 (t, 1H, J=5Hz, NH), 12.85 (broad, 1H, OH). *Anal*. Calc. for $C_{13}H_{11}N_5O_2$: C, 57.98; H, 4.12; N, 26.01. Found: C, 57.99; H, 3.93; N, 25.88.

***N*-(6-Chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methylamine hydrochloride (5).** (a) A suspension of 500 mg (1.4 mmol) of **1** in 5 mL of diluted HCl (1:1) was heated under reflux for 4 h. The reaction mixture was then poured on ice and the white separated solid was collected by filtration to give 126 mg (80%) of benzoic acid. The remaining filtrate was evaporated under reduced pressure and the residue was treated with 6 mL of ethanol (96%). The separated solid was collected by filtration to give 227 mg (74%) of **5**.

(b) A suspension of 352 mg (1 mmol) of **8** in 6 mL of concentrated HCl was heated under reflux for 3 h. After cooling, the reaction mixture was diluted with 6 mL of water. The separated solid was collected by filtration to give 87 mg (52%) of phthalic acid. The remaining filtrate was evaporated under reduced pressure and the residue was treated with 6 mL of ethanol (96%). The separated solid was collected by filtration to give 120 mg (54%) of **5**; mp over 360°C (ethanol/water). ^{1}H-NMR δ: 4.56 (s, 2H, CH_2), 7.62 (d, 1H, J=9.5Hz, 7-H), 8.58 (d, 1H, J=9.5Hz, 8-H), 9.08 (broad, 3H, NH_3^+). *Anal*. Calc. for $C_6H_7Cl_2N_5$: C, 32.75; H, 3.21; N, 31.82. Found: C, 33.09; H, 3.14; N, 32.28.

6-Chloro-3-(chloromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine (7). A suspension of 884 mg (4 mmol) of **6** in 3.2 mL of acetic acid was heated under reflux for 1 h. The reaction mixture was evaporated under reduced pressure, the oily residue was dissolved in methylene chloride, treated with charcoal, and filtered. After the addition of hexane to filtrate, the precipitated solid was filtered to give 111 mg (55%) of **7**; mp 132-134°C (methylene chloride/hexane). ^{1}H-NMR δ: 5.28 (s, 2H, CH_2), 7.63 (d, 1H, J=9.5Hz, 7-H), 8.58 (d, 1H, J=9.5Hz, 8-H). MS (EI, m/z): 202 (M^+). *Anal*. Calc. for $C_6H_4Cl_2N_4$: C, 35.46; H, 1.99; N, 27.60. Found: C, 35.20; H, 1.60; N, 27.51.

***N*-(6-Chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl phthalimide (8).** To a suspension of 609 mg (3 mmol) of **7** in 9 mL *N*,*N*-dimethylformamide, 556 mg (3 mmol) of potassium phthalimide was added. The reaction mixture was then heated on an oil bath at 120-130°C for 12 h, and poured into 90 mL of cold water. Upon cooling the separated solid was collected by filtration to give 547 mg (58%) of crude **8** which was for analysis purified by radial chromatography (chloroform); mp 264-266.5°C (chloroform/ethanol). ^{1}H-NMR δ: 5.41 (s, 2H, CH_2), 7.62 (d, 1H, J=9.5Hz, 7-H), 8.04 (s, 4H, Ar), 8.57 (d, 1H, J=9.5Hz, 8-H). *Anal*. Calc. for $C_{14}H_8Cl\ N_5O_2$: C, 53.60; H, 2.57; N, 22.33. Found: C, 53.43; H, 2.31; N, 22.50.

***N*-Benzoyl-(6-chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)glycine (9).** A suspension of 360 mg (1 mmol) of **1** in 2 mL of concentrated HCl was left at room temperature for 15 days. The reaction mixure was then poured on ice and the separated solid was collected by filtration to give 259 (78%) of **9**; mp 120.5-122°C. ^{1}H-NMR δ: 6.28 (d, 1H, J=7.5Hz, CH), 7.57 (m, 4H, three H of Ph, 7-H), 7.96 (m, 2H, Ph), 8.61 (d, 1H, J= 9.5Hz, 8-H), 9.44 (d, 1H, J=7.5Hz, NH).

***N*-(6-Chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl benzamide (10). (**a) A suspension of 166 mg (0.5 mmol) of 9 in 8 mL of ethanol was heated under reflux for 15 min. Upon cooling the separated solid was collected by filtration to give 124 mg (75%) of **10**.

(b) To a suspension of 290 mg (1 mmol) of **11** in 25 mL of methylene chloride, 570 mg (1.1 mmol) of lead tetraacetate (85%) was added. The reaction mixture was stirred at room temperature for 3 h. The solid was filtered, washed with methylene chloride (2x10 mL) and discarded. The filtrate was evaporated under reduced pressure, and treated with 2 mL of ethanol. Upon cooling, the separated solid was collected by filtration to give 69 mg (46%) of **10**; mp 195-196°C (ethanol). ^{1}H-NMR δ: 4.97 (d, 2H, J=5Hz, CH_2), 7.53 (m, 4H, three H of Ph, 7-H), 7.92 (m, 2H, Ph), 8.52 (d, 1H, J=9.5Hz, 8-H), 9.20 (t, 1H, J=5Hz, NH). *Anal*. Calc. for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.50; N, 24.34. Found: C, 54.10; H, 3.53; N, 24.30.

***N*-Benzoyl-(6-hydrazino[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)glycine hydrazide (12).** A mixture of 360 mg (1 mmol) of 1 and 4 mL of hydrazine hydrate (80%) was heated under reflux for 1.5 h. Upon cooling the separated white solid was collected by filtration to give 324 mg (95%) of 12; mp 238-240°C (ethanol/*N,N*-dimethylformamide). ^{1}H-NMR δ: 4.33 (broad, 4H, two NH_2), 6.23 (d, 1H, J=7.5Hz, CH), 6.90 (d, 1H, J=10Hz, 7-H), 7.53 (m, 3H, Ph), 7.98 (m, 3H, two H of Ph, 8-H), 8.61 (broad, 1H, NH), 9.06 (d, 1H, J=7.5Hz, NH), 9.57 (broad, 1H, NH). *Anal*. Calc. for $C_{14}H_{15}N_9O_2$: C, 49.26; H, 4.43; N, 36.93. Found: C, 48.81; H, 4.57; N, 37.43.

2-Hydroxyethyl *N*-benzoyl-(6-chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)glycinate (13). A suspension of 200 mg (0.56 mmol) of **1** in 1 mL of ethylene glycol was heated on an oil bath at 180°C for 3.5 h. Upon cooling the separated solid was collected by filtration to give 202 mg (97%) of **13**; mp 194-196°C (ethanol). ^{1}H-NMR δ: 3.63 (t, 2H, J=5Hz, CH_2), 4.27 (t, 2H, J=5Hz, CH_2), 6.43 (d, 1H, J=7Hz, CH), 7.62 (m, 4H, three H of Ph, 7-H), 7.98 (m, 2H, Ph), 8.64 (d, 1H, J=9.5Hz, 8-H), 9.57 (d, 1H, J=7Hz, NH). *Anal*. Calc. for $C_{16}H_{14}Cl\ N_5O_4$: C, 51.14; H, 3.76; N, 18.64. Found: C, 51.45; H, 3.87; N, 18.92.

Acknowledgements

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