### A Convenient Synthesis of Novel 7-Phosphonylbenzyl-2-Substituted Pyrazolo[4,3-*e*]-1,2,4-Triazolo[1,5-*c*]-Pyrimidine Derivatives

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ABSTRACT: A series of pyrazolo[4,3-e]-1,2,4triazolo-[1,5-c]pyrimidine derivatives, bearing phosphonylbenzyl chain in position 7, were conveniently synthesized in an attempt to obtain potent and selective antagonists for the  $A_{2A}$  adenosine receptor or potent pesticide lead compounds. Diethyl[(5-amino-4cyano-3-methylsulfanyl-pyrazol-1-yl)-benzyl]phosphonate (3), which was prepared by the cyclization of diethyl 1-hydrazinobenzylphosphonate (1) with 2-[bis(methylthio)methylene]malononitrile (2), reacted with triethyl orthoformate to afford diethyl (4-cyano-5-ethoxymethyleneamino-3-methylsulfanyl-pyrazol-1-yl)benzyl]phosphonate (4), which reacted with various acyl hydrazines in refluxing 2-methoxyethanol to give the target compounds **5a-h** in good yields. Their structures were confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS, and elemental analysis. The crystal structure of **5e** was determined by single crystal X-ray diffraction © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:634-638, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20478

### INTRODUCTION

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors that have been classified as  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and A<sub>3</sub> adenosine receptor subtypes [1,2]. Efforts made in medicinal chemistry over the last two decades have led to the discovery of a series of adenosine analogs that possess specific agonist properties at A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, or A<sub>3</sub> receptors [3,4]. As for adenosine receptor antagonists, a large number of xanthine derivatives have been synthesized in an attempt to improve both receptor subtype affinity and selectivity of the natural compounds caffeine and theophylline [3]. Recently, pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine derivatives, such as SCH 58261, SCH 63390, and 8FB-PTP, have been found to be potent adenosine A<sub>2A</sub> antagonists [5,6]. However, they are unselective, while being potent at  $A_1$  receptor as well. In recent years, it is found that 1-amino phosphonates act as the phosphorus analogues of natural amino acids and have received an increasing attention in medicinal chemistry and pesticide science [7,8] due to their wide biological activities such as enzyme inhibition [9], antibiotics [10], and haptens of catalytic antibodies [11], antifungal agents, herbicides, plant regulators, and plant virucides [12]. To find potent and selective antagonists for the A2A adenosine receptor or potent pesticide lead compounds, herein we report a convenient synthesis of pyrazolo[4,3-e]-1,2,

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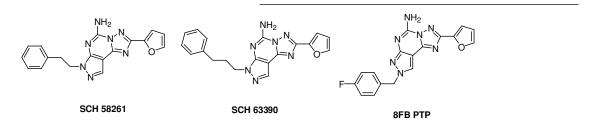
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4-triazolo-[1,5-*c*]pyrimidine derivatives, bearing a phosphonylbenzyl chain in position 7.

in one step (Scheme 1), without the isolation of 5-acylamino-4-imino-4,5-dihydropyrazolo[3,4-



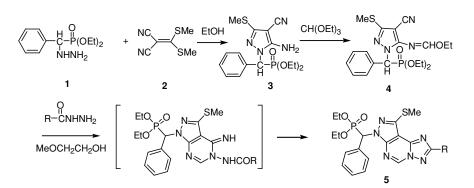
#### **RESULTS AND DISCUSSION**

The synthesis of diethyl 1-hydrazinobenzylphosphonate (1) has been reported by several methods [13]. It was synthesized by a modified procedure of Yuan's report [13a]. For converting benzaldehyde to diethyl 1-hydroxybenzyl phosphonate, an excess of catalyst (KF, four times) was used, which caused difficulty in stirring and incomplete reactivity. Instead, we used 1 equiv of catalyst (Et<sub>3</sub>N) in CH<sub>2</sub>Cl<sub>2</sub> to avoid these shortcomings and obtained it in a better yield (85%). 1 can be obtained in a better yield by the reaction of diethyl 1-hydroxybenzyl phosphonate with mesyl chloride, followed by the nucleophilic substitution with hydrazine in a one-pot reaction.

Cyclization of **1** with 2-[bis(methylthio)methylene]malononitrile (**2**) in mild conditions gave diethyl[(5-amino-4-cyano-3-methylsulfanyl-pyrazol-1-yl)-benzyl]phosphonate (**3**), which can be easily converted to diethyl[(4-cyano-5-ethoxymethyleneamino-3-methylsulfanyl-pyrazol-1-yl)-benzyl]phosphonate (**4**) by refluxing triethyl orthoformate. **4** reacted with various acyl hydrazines to yield the corresponding tricyclic target compounds **5a-h** conveniently in refluxing 2-methoxyethanol *d*]pyrimidine intermediates, contrary to the report by Baraldi et al. [14]. In Baraldi's report, analogous imidates reacted with acyl hydrazine in refluxing 2-methoxyethanol to provide 5-acylamino-4imino-4,5-dihydropyrazolo[3,4-*d*]pyrimidines. Whereas the ring closure of these imidates to the corresponding pyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*] pyrimidines thermally needed a higher boiling point solvent (260°C) like diphenyl ether.

To confirm the structure of the regioisomer of the cyclization and investigate its regioselectivity, a single crystal of the compound **5e** was obtained as colorless crystals from the mixture of petroleum ether and acetone (6:1 v/v) and its molecular structure was determined by X-ray diffraction (Fig. 1) [15].

In conclusion, we have developed an efficient and selective synthesis of pyrazolo[4,3-e]-1,2,4triazolo-[1,5-c]pyrimidine derivatives, bearing phosphonylbenzyl chain in position 7, via the directed ring closure of functionalized imidates with various acyl hydrazines. Owing to the easily accessible and versatile starting materials and straightforward product isolation, we think that this method has potential in the synthesis



R= methyl; *n*-propyl; phenyl; phenoxymethyl; 4-chlorophenoxymethyl; 2,4-dichlorophenoxymethyl;

4-tert-butylphenoxymethyl; 3-trifluoromethylphenoxymethyl

SCHEME 1

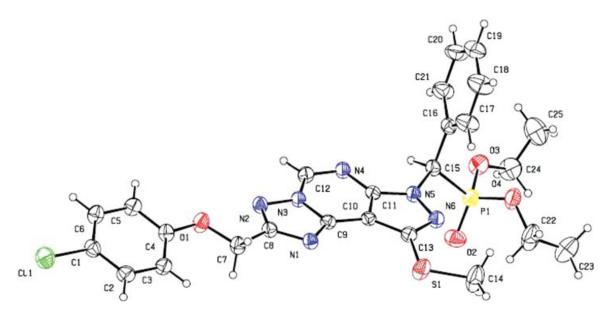


FIGURE 1 X-ray crystal structure of compound 5e.

of phosphonyl-substituted pyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine derivatives with biological and pharmaceutical activities.

#### EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Varian mercury-plus 400 spectrometer with TMS as the internal reference and CDCl<sub>3</sub> as the solvent, whereas mass spectra were obtained with a Finnigan TRACEMS 2000 spectrometer using the EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with an Elementar Vario ELIIICHNSO elementary analyzer. X-ray diffraction analysis was performed on a Bruker Smart 1000 CCD diffractometer. All of the solvents and materials were of high-reagent grade and were purified as required. Diethyl 1-hydrazinobenzylphosphonate (1), 2-[bis(methylthio)methylene]malononitrile (2), and acyl hydrazines were prepared according to the methods described in [13a], [16], and [17], respectively.

*Preparation of Diethyl[(5-amino-4-cyano-3-methylsulfanyl-pyrazol-1-yl)-benzyl]phosphonate* (**3**) [18]

A mixture of **1** (6.27 g, 24.3 mmol), **2** (3.89 g, 22.9 mmol), and ethanol (30 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and the residues

were recrystallized from ethyl acetate and petroleum (1:1, v/v) to give white crystals (5.58 g, 64% yield). mp 161–163°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  1.19–1.27 (m, 6H, 2CH<sub>3</sub>), 2.53 (s, 3H, SCH<sub>3</sub>), 4.01–4.16 (m, 4H, 2CH<sub>2</sub>), 5.54 (s, 2H, NH<sub>2</sub>), 5.75 (d, *J* = 24 Hz, 1H, PCH), 7.27–7.52 (m, 5H, Ar-H). Anal. Calcd for C<sub>16</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub>PS: C 50.52, H 5.56, N 14.73; Found: C 50.69, H 5.48, N 14.89.

### *Preparation of Diethyl[(4-cyano-5ethoxymethyleneamino-3-methylsulfanylpyrazol-1-yl)-benzyl]phosphonate (4)*

Compound **3** (2.28 g, 6 mmol) was dissolved in triethyl orthoformate (4 mL), and the mixture was refluxed for 2 h; after cooling, the solvent was removed under a reduced pressure, and the residues were purified on silica gel (EtOAc-light petroleum, 1:5, v/v) to afford **4** as a white solid (2.48 g, 95%). mp 64– 66°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.18–1.27 (m, 6H, 2CH<sub>3</sub>), 1.40 (t, *J* = 7 Hz, 3H, CH<sub>3</sub>), 2.62 (s, 3H, SCH<sub>3</sub>), 4.01–4.20 (m, 4H, 2CH<sub>2</sub>), 4.39 (t, *J* = 6.6 Hz, 2H, CH<sub>2</sub>), 5.90 (d, *J* = 22.8 Hz, 1H, PCH), 7.33–7.55 (m, 5H, Ar-H), 8.39 (s, 1H, =CH). Anal. Calcd for C<sub>19</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub>PS: C 52.28, H 5.77, N 12.84; Found: C 52.41, H 5.54, N 12.72.

Preparation of Diethyl{[9-(methylsulfanyl)-2substituted-7H-pyrazolo-[4,3-e]-1,2,4-triazolo-[1,5-c]-pyrimidin-7-yl]-benzyl}phosphonate (**5a-h**): General Procedure

A solution of 4 (0.65 g, 1.5 mmol) and acyl hydrazine (such as acetyl hydrazine, benzoyl hydrazine, and

substituted phenoxy acetyl hydrazine) (1 mmol) in methoxyethanol (20 mL) was refluxed for 3–5 h. After cooling, the solvent was removed under reduced pressure, and the residues were purified on silica gel (acetone and light petroleum, 1:6–7, v/v) to afford the corresponding target compounds **5a–h**.

### *Diethyl[(2-methyl-9-methylsulfanyl-pyrazolo [4,3-e]-1,2,4-triazolo[1,5-c]pyrimidin-7-yl)-benzyl]phosphonate (5a)*

Colorless crystals, yield, 75%, mp 95–96°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.17–1.27 (m, 6H, 2CH<sub>3</sub>), 2.64 (s, 3H, CH<sub>3</sub>), 2.83 (s, 3H, SCH<sub>3</sub>), 4.04–4.22 (m, 4H, 2CH<sub>2</sub>), 6.43 (d, *J* = 23 Hz, 1H, PCH), 7.27–7.72 (m, 5H, Ar-H), 8.97 (s, 1H, N=CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  166.1, 148.2, 147.9, 142.1, 138.7, 133.2, 129.0, 128.7, 128.5, 101.4, 63.8, 63.4, 63.3, 59.4, 57.8, 16.3, 14.7. Anal. Calcd for C<sub>19</sub>H<sub>23</sub>N<sub>6</sub>O<sub>3</sub>PS: C 51.11, H 5.19, N 18.82; Found: C 50.99, H 5.27, N 18.97.

# *Diethyl[(9-methylsulfanyl-2-propyl-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidin-7-yl)-benzyl]-phosphonate (5b)*

Colorless oil, yield, 69%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.02 (t, J = 6.8 Hz, 3H, CH<sub>3</sub>), 1.17–1.27 (m, 6H, 2CH<sub>3</sub>), 1.90 (q, J = 7.5 Hz, 2H, CH<sub>2</sub>), 2.82 (s, 3H, SCH<sub>3</sub>), 2.93 (t, J = 7.6 Hz, 2H, CH<sub>2</sub>), 4.02–4.22 (m, 4H, 2CH<sub>2</sub>), 6.43 (d, J = 23 Hz, 1H, PCH), 7.27–7.71 (m, 5H, Ar-H), 8.99 (s, 1H, N=CH); MS (70 eV) m/z(%): 476 (5.14), 474 (M<sup>+</sup>, 12.4), 337 (100), 291 (5.9), 262 (19.3), 109 (16.4), 91 (8.9), 81 (12.5). Anal. Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>6</sub>O<sub>3</sub>PS: C 53.15, H 5.74, N 17.71; Found C: 53.23, H 5.81, N 17.50.

## *Diethyl[(9-methylsulfanyl-2-phenyl-pyrazolo[4, 3-e]-1,2,4-triazolo[1,5-c]pyrimidin-7-yl)-benzyl phosphonate* (**5c**)

White crystals, yield, 88%, mp 111–113°C.<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.15–1.27 (m, 6H, 2CH<sub>3</sub>), 2.87 (s, 3H, SCH<sub>3</sub>), 4.03–4.25 (m, 4H, 2CH<sub>2</sub>), 6.46 (d, *J* = 23 Hz, 1H, PCH), 7.27–7.75 (m, 10H, Ar-H), 9.07 (s, 1H, N=CH); MS (70 eV) *m*/*z* (%): 508 (M<sup>+</sup>, 6), 371 (42), 261 (2), 109 (100). Anal. Calcd for C<sub>24</sub>H<sub>25</sub>N<sub>6</sub>O<sub>3</sub>PS: C 56.68, H 4.96, N 16.53; Found: C 56.40, H 5.03, N 16.75.

### *Diethyl[(9-methylsulfanyl-2-phenoxymethylpyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidin-7yl)-benzyl]phosphonate (5d)*

White crystals, yield, 86%, mp 130.3–131.8°C. IR (KBr, cm<sup>-1</sup>) v: 2982, 1497, 1245, 1027, 761, 694,

565; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  1.17–1.27 (m, 6H, 2CH<sub>3</sub>), 2.83 (s, 3H, SCH<sub>3</sub>), 4.04–4.22 (m, 4H, 2CH<sub>2</sub>), 5.41 (s, 2H, OCH<sub>2</sub>), 6.44 (d, *J* = 23 Hz, 1H, PCH), 7.05–7.73 (m, 10H, Ar-H), 9.07 (s, 1H, N=CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$ : 164.6, 158.0, 148.3, 147.7, 142.2, 139.0, 132.9, 129.3, 128.9, 128.6, 128.4, 121.3, 114.6, 101.5, 63.6, 63.4, 63.2, 59.3, 57.8, 16.2, 14.6. Anal. Calcd for C<sub>25</sub>H<sub>27</sub>N<sub>6</sub>O<sub>4</sub>PS: C 55.75, H 5.05, N 15.60; Found: C 55.93, H 5.11, N 15.74.

### *Diethyl{[2-(4-chlorophenoxy)methyl-9methylsulfanyl-pyrazolo[4,3-e]-1,2,4-triazolo[1, 5-c]pyrimidin-7-yl]-benzyl}phosphonate* (**5e**)

White crystals, yield, 91%, mp 159.1–160.0°C. IR (KBr, cm<sup>-1</sup>)  $\nu$ : 2983, 1493, 1248, 1050, 826, 563 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$ : 1.18–1.27 (m, 6H, 2CH<sub>3</sub>), 2.82 (s, 3H, SCH<sub>3</sub>), 4.00–4.24 (m, 4H, 2CH<sub>2</sub>), 5.38 (s, 2H, OCH<sub>2</sub>), 6.44 (d, *J* = 23 Hz, 1H, PCH), 6.96–7.73 (m, 9H, Ar-H), 9.06 (s, 1H, N=CH); MS (70 eV) *m*/*z* (%): 575 (6.5), 573.5 (10.5), 572 (M<sup>+</sup>, 24.6), 438 (14.3), 437.5 (25.7), 436.5 (74.0), 435 (100), 434 (69.9), 433 (36.5), 432.5 (16.9), 309 (9.2), 307 (12.1), 262 (12.7), 129 (5.0), 128 (5.9), 91 (5.4). Anal. Calcd for C<sub>25</sub>H<sub>26</sub>ClN<sub>6</sub>O<sub>4</sub>PS: C 52.40, H 4.57, N 14.67; Found: C 52.57, H 4.41, N 14.42.

### *Diethyl{[2-(2,4-dichlorophenoxy)methyl-9methylsulfanyl-pyrazolo[4,3-e]-1,2,4-triazolo[1, 5-c]pyrimidin-7-yl]-benzyl}phosphonate* (**5f**)

White crystals, yield, 92%, mp 109.6–111.3°C. IR (KBr, cm<sup>-1</sup>)  $\nu$ : 2968, 1511, 1250, 1019, 830, 805, 565; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.18–1.27 (m, 6H, 2CH<sub>3</sub>), 2.83 (s, 3H, SCH<sub>3</sub>), 4.05–4.22 (m, 4H, 2CH<sub>2</sub>), 5.46 (s, 2H, OCH<sub>2</sub>), 6.48 (d, J = 23 Hz, 1H, PCH), 7.01–7.71 (m, 8H, Ar-H), 9.06 (s, 1H, N=CH); MS (70 eV) m/z (%): 609 (10.3), 608 (31.2), 607 (14.6), 606 (M<sup>+</sup>, 42), 571 (11.4), 473 (16.1), 472 (20.3), 471 (74.5), 470 (29.2), 469 (100), 308 (17.4), 261 (8.8), 163 (23.0), 161 (37.3), 135 (20.0), 133 (32.7), 116 (14.3), 109 (36.2), 105 (14.0), 91 (40.6), 81 (41.2), 77 (35.1). Anal. Calcd for C<sub>25</sub>H<sub>25</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>4</sub>PS: C 49.43, H 4.15, N 13.83; Found: C 49.29, H 4.07, N 13.60.

### *Diethyl{[2-(4-t-butylphenoxy)methyl-9methylsulfanyl-pyrazolo[4,3-e]-1,2,4-triazolo[1, 5-c]pyrimidin-7-yl]-benzyl}phosphonate* (**5g**)

White crystals, yield, 84%, mp 121–122°C. IR (KBr, cm<sup>-1</sup>)  $\nu$ : 2960, 1514, 1251, 1017, 829, 697, 569; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.17–1.31 (m, 15H, CH<sub>3</sub>), 2.83 (s, 3H, SCH<sub>3</sub>), 4.06–4.22 (m, 4H, 2CH<sub>2</sub>), 5.40 (s, 2H, OCH<sub>2</sub>), 6.44 (d, *J* = 23 Hz, 1H, PCH), 6.98–7.73 (m, 9H, Ar-H), 9.08 (s, 1H, N=CH); <sup>13</sup>C NMR

 $(CDCl_3, 100 \text{ MHz}) \, \delta: \, 165.0, \, 155.8, \, 148.4, \, 147.9, \, 144.1, \\ 142.3, \, 139.0, \, 133.0, \, 129.0, \, 128.7, \, 128.5, \, 126.2, \, 114.2, \\ 101.6, \, 63.9, \, 63.7, \, 63.3, \, 59.4, \, 57.9, \, 34.0, \, 31.4, \, 16.3, \\ 14.7. \, Anal. \, Calcd \, for \, C_{29}H_{35}N_6O_4PS: C \, 58.57, \, H \, 5.93, \\ N \, 14.13; \, Found: C \, 58.69, \, H \, 6.08, \, N \, 14.00. \\ \end{cases}$ 

### Diethyl{[9-methylsulfanyl-2-(3trifluoromethylphenoxy)methyl-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidin-7-yl]-benzyl} phosphonate (**5h**)

Colorless oil, yield, 85%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$ : 1.18–1.27 (m, 6H, 2CH<sub>3</sub>), 2.83 (s, 3H, SCH<sub>3</sub>), 4.05– 4.22 (m, 4H, 2CH<sub>2</sub>), 5.44 (s, 2H, OCH<sub>2</sub>), 6.44 (d, J = 23 Hz, 1H, PCH), 7.21–7.72 (m, 9H, Ar-H), 9.07 (s, 1H, N=CH); MS (70 eV) m/z (%): 608 (10.6), 606 (M<sup>+</sup>, 23.0), 469 (100), 449 (4.6), 308 (6.0), 261 (6.1), 161 (9.7), 133 (11.9), 109 (21.3), 91 (17.5). Anal. Calcd for C<sub>26</sub>H<sub>26</sub>F<sub>3</sub>N<sub>6</sub>O<sub>4</sub>PS: C 51.48, H 4.32, N 13.86; Found: C 51.51, H 4.17, N 13.63.

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