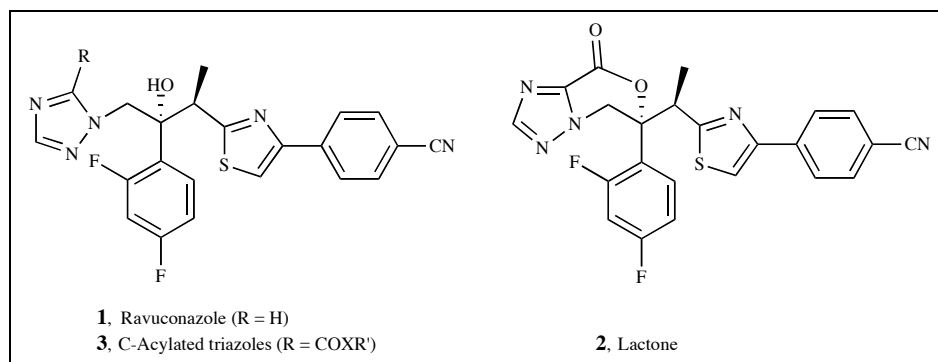


Oak Kim,[§] Yunhui Zhang, John Wichtowski,[†] Stella Huang, Joan Fung-Tomc, Joanne Bronson, and Yasutsugu Ueda*Bristol-Myers Squibb Company, Pharmaceutical Research Institute, Wallingford, CT 06492-7660, USA
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Novel C-acylated triazoles were synthesized from ravuconazole via bicyclic triazole lactone. The synthesis and antifungal activity of these C-acylated derivatives are described.

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INTRODUCTION

Ravuconazole **1** (BMS-207147, ER-30346) is a potent and broad spectrum antifungal agent [1], which was licensed to Bristol-Myers Squibb Co. from Eisai Co. and was undergoing clinical evaluation at BMS as an oral agent. Although an intravenous formulation is highly desirable for treatment of serious systemic fungal infections, ravuconazole's poor aqueous solubility makes it nearly impractical for the development as an intravenous agent.

During our investigation to functionalize the hydroxy group of **1**, leading to a potential water-soluble prodrug, useful for the development as an iv drug [2], we found unusual chemistry, resulting in formation of a bicyclic triazole lactone. This lactone served as a synthetic intermediate for a variety of novel C-acylated triazole derivatives of ravuconazole.

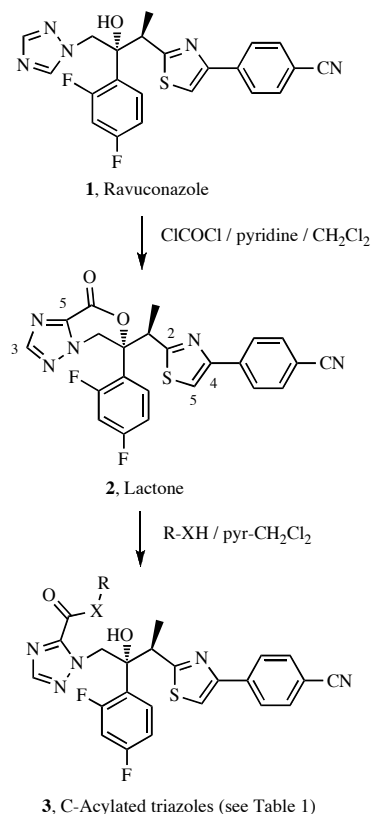
RESULTS AND DISCUSSION

We had previously encountered difficulty in derivatizing the hydroxyl group present in ravuconazole under the traditional acylating conditions, presumably because of the sterically hindered nature of this tertiary hydroxyl group. For example, O-acetate or O-phenyl-carbamate could not be obtained by conventional methods (e.g. AcCl/pyr or phenylisocyanate [3]).

In contrast to the above observation, reaction of ravuconazole with phosgene in the presence of excess pyridine in CH₂Cl₂ proceeded with exceptional ease, producing a white amorphous powder which was characterized as a bicyclic triazole-lactone **2** [4]. Its ¹H NMR spectrum (CDCl₃) showed two singlets (7.60 and 7.90 ppm) which were assigned to the protons attached to

the thiazole and the triazole ring, respectively, with a loss of one triazole proton. Its IR spectrum indicated the presence of a carbonyl absorption at 1770 cm⁻¹, which is typical of a γ -lactone. Its low resolution mass spectrum indicated an M+H ion at 464.

Scheme 1. Preparation of C-acylated triazoles **3** via lactone **2**.



These spectroscopic data, including other NMR data (H-COSY, ^{13}C , DEPT, HMQC and HMBC [6]), and its elemental analysis were consistent with the lactone structure shown in **2** (Scheme 1).

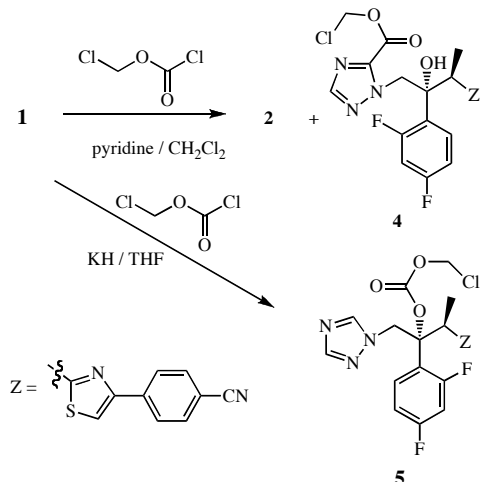
The lactone **2** reacted readily with various amines, and methanol to produce novel triazole C-acylated amide derivatives, and methyl ester of ravuconazole, **3**, respectively in good to modest yield, as illustrated in Scheme 1. This lactone was also readily hydrolyzed with aqueous sodium bicarbonate in CH_3CN to provide triazole-5-carboxylate **3** ($\text{XR} = \text{O}^- \text{Na}^+$). However, treatment of the sodium salt with dilute HCl to isolate the acid form caused decarboxylation, resulting in formation of ravuconazole.

Although C-acylation of N-substituted 1,2,4-triazoles *via* lithiation [7] or enol acylate rearrangement [8] are well documented, we believe the facile formation of C-acylated amides and esters *via* cyclic lactone **2** described here is unique.

The formation of the lactone **2** was not totally unexpected, since similar cyclic lactones were reported in a patent literature [9].

However, we were curious about how the lactone **2** was formed, and investigated other acylating agents under similar conditions. Methyl chloroformate [10] did not react to form the C-acylated ravuconazole, recovering only the starting ravuconazole. Although C-acylation was reported in the reaction of N-substituted 1,2,4-triazoles with alkyl chloroformate with TEA [10], these authors revised the condition in the later publication [7a], using lithiation followed by reaction with alkyl chloroformate to produce 5-acylated esters of N-substituted triazoles.

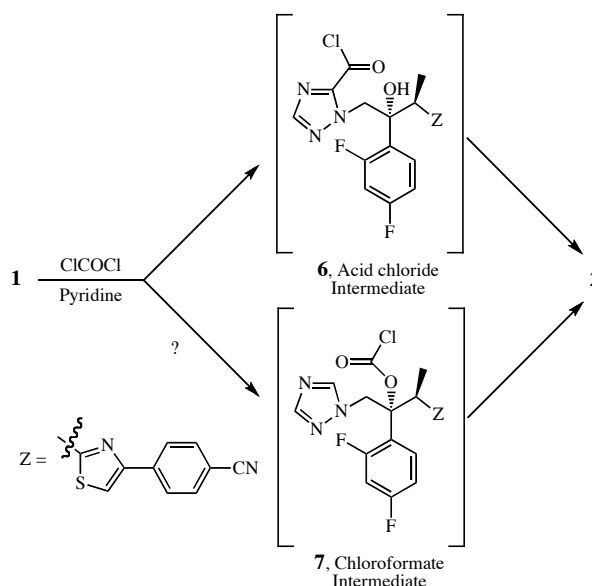
Scheme 2. Related reaction



Interestingly, when we used more activated chloromethyl chloroformate [11], C-acylated chloromethyl ester **4** was isolated as a crude product contaminated with the lactone **2**, as shown in the Scheme 2. Attempted purification of **4** by silica gel column or C-18 reverse

phase silica column resulted in a material contaminated with more of **2**, indicating the chloromethyl ester **4** cyclized during the column purification. Although C-acylated chloromethyl ester **4** was not isolated as a pure material, spectroscopic data of the crude material were consistent with the structure **4**. This indicates more activated acylating agents such as phosgene and chloromethyl chloroformate reacted with this 1,2,4-triazole to form acylated triazoles, but not non-activated methyl chloroformate. In a separate experiment, the reaction of ravuconazole with chloromethyl chloroformate, after generating the oxy-anion by potassium hydride in THF at room temperature provided O-acylated chloromethyl carbonate **5**, contaminated with ravuconazole (Scheme 2). Compound **5** was found to be unstable in methanol solution, being hydrolyzed to ravuconazole.

Scheme 3. Proposed mechanism to lactone **2**.



Based on these results, we believe the lactone **2** was formed *via* the intermediacy of acid chloride **6**, followed by the participation of the neighboring hydroxyl group, rather than *via* chloroformate **7**, followed by C-acylation (Scheme 3).

These novel C-acylated triazole derivatives were tested for their antifungal activity. As summarized in Table 1, none of these derivatives (**3a-3c**, **3f**) displayed any significant antifungal activity against *Candida albicans*, with MIC values being 4 - >16 $\mu\text{g/mL}$. For comparison, the reference compound ravuconazole (**1**) had an MIC of 0.015 $\mu\text{g/mL}$ [12].

The table also lists isolated yields of C-acylated triazoles **3** from lactone **2**, and the chemical shifts of their hydroxy proton and heteroaromatic protons in their ^1H NMR spectra.

Table 1
C-Acylated triazole derivatives of ravuconazole.

Compound	-XR in 3	Yields ^a (%)	¹ H NMR (CDCl ₃ , ppm)	MICs ^b <i>Candida albicans</i> (μg/mL)
1	Ravuconazole	-	5.72 (OH) 7.63 (thiazole-5) 7.66 (thiazole-3) 7.83 (thiazole-5)	0.015
2	lactone	22 (from 1)	7.60 (thiazole-5) 7.90 (thiazole-3)	ND
3a	-NHCH ₂ CH ₂ NHAc	65	6.03 (OH) 7.51 (thiazole-3) 7.63 (thiazole-5)	4
3b	-NHCH ₂ CH ₂ OH	61	6.04 (OH) 7.49 (thiazole-3) 7.63 (thiazole-5)	>16
3c	-NHCH ₂ CH ₂ NMe ₂	89	6.17 (OH) 7.50 (thiazole-3) 7.63 (thiazole-5)	>16
3d	-N(CH ₃) ₂	92	6.26 (OH) 7.57 (thiazole-3) 7.62 (thiazole-5)	ND
3e	-OCH ₃	45	5.88 (OH) 7.63 (thiazole-3) 7.63 (thiazole-5)	ND
3f	-O ⁻ Na ⁺ (carboxylate)	67	~7.34 (thiazole-3) 7.95 (thiazole-5) (CD ₃ OD)	16

^a Yields are not optimized; ^b MIC: minimum inhibitory concentration [11], ND: not determined.

In summary, novel C-acylated triazole derivatives were prepared by the reaction of ravuconazole with phosgene to form bicyclic lactone **2**, followed by addition of substituted amines, methanol, or sodium bicarbonate. Although these triazole carboxyamides and carboxylate were found to display no useful *in vitro* antifungal activity against *Candida albicans*, this is a unique way of introducing carboxyamides and carboxylates at the C-5 position of the 1,2,4-triazole in antifungal triazoles.

EXPERIMENTAL

Melting points were determined on an EZ-Melt automated melting point apparatus (Stanford Research Systems). The ¹H and ¹³C NMR spectra are recorded on a Bruker A500 spectrometer at 500 and 125.8 MHz, respectively. Electrospray ionization (ESI) high-resolution mass spectra (HRMS) were obtained on a Micromass LCT mass spectrometer. The IR measurement and elemental analysis were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. ¹H-¹H COSY (Correlation Spectroscopy), DEPT (Distortionless Enhancement by Polarization Transfer), ¹H-¹³C HMQC (Heteronuclear Multiple Quantum Coherence) and ¹H-¹³C HMBC [6] (Heteronuclear Multiple Bond Correlation) measurements obtained for the products were consistent with the assignments reported below.

4-(2-((R)-1-((R)-6-(2,4-Difluorophenyl)-8-oxo-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-6-yl)ethyl)thiazol-4-yl)-benzonitrile (2). To a cold solution of ravuconazole (**1**) (1.09 g, 2.5 mmol) in CH₂Cl₂ (40 mL) was added under anhydrous nitrogen atmosphere anhydrous pyridine (1.98 g, 25 mmol, 10 eq.). The mixture was stirred under ice cooling for 10 minutes. To this was added dropwise 20% phosgene solution in toluene (6.18 g, 12.5 mmol, 5 eq.). The mixture was stirred at ambient temperature overnight. The mixture was washed with water three times, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give 1.02 g (2.2 mmol, crude yield, 88%) of a dark brown powder. A portion of the crude product was purified by column chromatography (silica, 10% EtOAc/CH₂Cl₂) to obtain **2** in about 22 % yield as a white amorphous powder after trituration in hexanes, ¹H NMR (CDCl₃) δppm 1.46 (3H, d, J = 7.3 Hz, CH₃), 4.23 (1H, q, J = 7.0 Hz, CH-Me), 5.09 (1H, d, J = 14.7 Hz, NCH₂), 5.33 (1H, d, J = 14.7 Hz, NCH₂), 6.83-6.96 (2H, m, F/Ph-3,5-H), 7.41-7.52 (1H, m, F/Ph-6-H), 7.60 (1H, s, thiazole-5-H), 7.71 (2H, d, J = 7.9 Hz, CN/Ph-3,5-H), 7.90 (1H, s, triazole-3-H), 7.98 (2H, d, J = 8.2 Hz, CN/Ph-2,6-H); ¹³C NMR (CDCl₃) δppm 16.3 (CH₃), 45.3 (d, J = 2.9 Hz, CH-Me), 51.2 (d, J = 8.6 Hz, NCH₂), 85.9 (d, J = 4.8 Hz, OC), 105.9 (t, J = 26.5 Hz, F/Ph-3-CH), 111.9 (CN), 112.8 (dd, J = 21.1, 2.9 Hz, F/Ph-5-CH), 116.8 (thiazole-5-CH), 118.8 (CN/Ph-1-C), 121.1 (dd, J = 10.6, 3.8 Hz, F/Ph-1-C), 126.9 (CN/Ph-2,6-CH), 129.9 (dd, J = 9.6, 3.8 Hz, F/Ph-6-CH), 132.8 (CN/Ph-3,5-CH), 137.9 (thiazole-4-C), 141.3 (thiazole-5-C), 153.0 (lactone-C=O), 153.2 (thiazole-3-CH), 153.3 (CN/Ph-4-C), 158.8 (dd, J = 249.5, 12.5 Hz, F/Ph-2-C), 163.6 (dd, J = 253.4, 12.5 Hz, F/Ph-4-C), 169.2 (thiazole-2-C); MS (ES) *m/z* 464 [M+H]⁺; IR (KBr) ν_{max} 2226, 1770 cm⁻¹;

HRMS (ESI) Calcd. for $C_{23}H_{16}F_2N_5O_2S$ (M+H) 464.0993, found 464.1013 (δ +4.4 ppm). *Anal.* Calcd. for $C_{23}H_{15}F_2N_5O_2S$: C, 59.60; H, 3.26; N, 15.11. Found: C, 59.90; H, 3.53; N, 14.87.

General Procedure for the Reaction of Lactone 2 with Amine, Methanol, or Bicarbonate. For **3a–3d**, a solution of **2** and amine (3–4 equiv.) in anhydrous pyridine at room temperature or in THF (0.06–0.14 M solution of **2**) at 50°C was stirred for 1–3 hours. For **3e**, a mixture of lactone **2** (31 mg, 0.067 mmol), methanol (1 mL), and triethylamine (202 mg, 2 mmol) in THF (10 mL) was heated at reflux for 21 hours. For the work-up of the above reactions, the mixture was concentrated *in vacuo* to dryness and the residue was purified as indicated in each section. The sodium salt **3f** was obtained by treatment with aqueous sodium bicarbonate (1 eq.) in CH_3CN overnight, followed by concentration to dryness, and analyzed spectroscopically as such.

2-[3-[4-(4-Cyanophenyl)-thiazol-2-yl]-2-(2,4-difluorophenyl)-2-hydroxy-butyl]-2H-[1,2,4]triazole-3-carboxylic acid (2-acetylamino-ethyl)-amide (3a). This compound was obtained as pinkish crystals after purification by silica gel column (eluant: 10–60% EtOAc/ CH_2Cl_2), followed by crystallization from a mixture of diethyl ether and 95% EtOH (10:1), mp 113°C; 1H NMR ($CDCl_3$) δ ppm 1.20 (3H, d, J = 6.9 Hz, CH_3), 1.96 (3H, s, $COCH_3$), 3.38–3.46 (4H, m, NCH_2), 4.24 (1H, q, J = 7.0 Hz, $CH-Me$), 4.98 (1H, d, J = 14.0 Hz, NCH_2), 5.21 (1H, d, J = 14.0 Hz, NCH_2), 5.92 (1H, br.s, OH), 6.71–6.77 (1H, m, F/Ph-5-H), 6.80–6.88 (1H, m, F/Ph-3-H), 7.34–7.43 (1H, m, F/Ph-6-H), 7.56 (1H, s, triazole-3-H), 7.64 (1H, s, thiazole-5-H), 7.73 (2H, d, J = 8.5 Hz, CN/Ph-3,5-H), 7.94 (1H, br.s, CONH), 8.09 (2H, d, J = 8.5 Hz, CN/Ph-2,6-H); presence of a few amount of EtOH was detected; ^{13}C NMR ($CDCl_3$) δ ppm 17.6 (CH_3), 23.2 ($CO-CH_3$), 39.6 (NCH_2), 40.3 (NCH_2), 44.5 (d, J = 5.8 Hz, CH), 57.0 (d, J = 4.8 Hz, NCH_2), 77.5 (OC), 104.1 (t, J = 26.9 Hz, F/Ph-3-CH), 111.1 (dd, J = 20.6, 2.4 Hz, F/Ph-5-CH), 111.5 (CN), 116.1 (thiazole-5-CH), 119.0 (CN/Ph-1-C), 124.1 (dd, J = 12.0, 3.4 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.4 (dd, J = 8.6, 5.8 Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 138.5 (thiazole-4-C), 147.0 (triazole-5-C), 149.4 (triazole-3-CH), 152.7 (CN/Ph-4-C), 158.5 (triazole-5-C=O), 159.2 (dd, J = 247.1, 12.0 Hz, F/Ph-2-CF), 162.9 (dd, J = 249.0, 12.0 Hz, F/Ph-4-CF), 171.3 ($CH_3-C=O$), 172.8 (thiazole-2-C); HRMS (ESI) Calcd. for $C_{27}H_{26}F_2N_7O_3S$ (M+H) 566.1786, found 566.1803 (δ +3.0 ppm). *Anal.* Calcd. for $C_{27}H_{25}F_2N_7O_3S \cdot 0.6 C_2H_5OH$: C, 57.09; H, 4.86; N, 16.53. Found: C, 57.26; H, 4.65; N, 16.35.

2-((2R,3R)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-N-(2-hydroxyethyl)-2H-1,2,4-triazole-3-carboxamide (3b). This compound was obtained as a white foam after purification by silica gel column (eluant: 10–60% EtOAc/ CH_2Cl_2), followed by trituration in hexanes, 1H NMR ($CDCl_3$) δ ppm 1.19 (3H, d, J = 7.0 Hz, CH_3), 2.20 (1H, br, OH), 3.40–3.53 (2H, m, NCH_2), 3.70–3.80 (2H, m, NCH_2), 4.24 (1H, q, J = 7.2 Hz, $CH-Me$), 5.01 (1H, d, J = 14.0 Hz, NCH_2), 5.18 (1H, d, J = 14.0 Hz, NCH_2), 6.72 (1H, dt, J = 8.3, 2.5 Hz, F/Ph-5-CH), 6.83 (1H, ddd, J = 11.5, 8.5, 2.5 Hz, F/Ph-3-CH), 7.35–7.04 (1H, m, F/Ph-6-CH), 7.52 (1H, s, triazole-3-CH), 7.63 (1H, s, thiazole-5-CH), 7.66 (1H, t, J = 5.3 Hz, CONH), 7.72 (2H, d, J = 8.5 Hz, CN/Ph-3,5-CH), 8.09 (2H, d, J = 8.5 Hz, CN/Ph-2,6-CH), presence of a few amount of hexanes was detected; ^{13}C NMR ($CDCl_3$) δ ppm 17.6 (CH_3), 42.2 (NCH_2), 44.3 (d, J = 4.8 Hz, CH), 57.0 (d, J = 3.8 Hz, NCH_2), 61.3 (OCH_2), 77.5 (OC), 104.1 (t, J = 28 Hz, F/Ph-3-CH), 111.1

(dd, J = 20.6, 3.8 Hz, F/Ph-5-CH), 111.5 (CN), 116.1 (thiazole-5-CH), 119.0 (CN/Ph-1-C), 124.1 (dd, J = 12.5, 3.8 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.4 (dd, J = 9.6, 5.8 Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 138.4 (thiazole-4-C), 147.0 (triazole-5-C), 149.1 (triazole-3-CH), 152.8 (CN/Ph-4-C), 158.3 (triazole-5-C=O), 159.2 (dd, J = 248, 11.5 Hz, F/Ph-2-CF), 162.9 (dd, J = 249, 12 Hz, F/Ph-4-CF), 172.9 (thiazole-2-C); HRMS (ESI) Calcd. for $C_{25}H_{23}F_2N_6O_3S$ (M+H) 525.1520, found 525.1527 (δ +1.3 ppm). *Anal.* Calcd. for $C_{25}H_{22}F_2N_6O_3S \cdot 0.18 C_6H_{14} \cdot 0.3H_2O$: C, 58.74; H, 4.64; N, 15.41; H_2O , 0.99. Found: C, 57.44; H, 4.74; N, 15.08; H_2O , 1.28 (KF).

2-((2R,3R)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-N-(2-(dimethylamino)ethyl)-2H-1,2,4-triazole-3-carboxamide (3c). This compound was obtained as a beige amorphous powder after trituration of the crude in hexanes, 1H NMR ($CDCl_3$) δ ppm 1.19 (3H, d, J = 7.0 Hz, CH_3), 2.21 (6H, s, NCH_3), 2.36–2.49 (2H, m, NCH_2), 3.36 (2H, d, J = 4.9 Hz, NCH_2), 4.23 (1H, q, J = 7.0 Hz, $CH-Me$), 4.97 (1H, d, J = 14.0 Hz, NCH_2), 5.19 (1H, d, J = 14.0 Hz, NCH_2), 6.17 (1H, br.s, OH), 6.73 (1H, dt, J = 8.3, 2.4 Hz, F/Ph-5-CH), 6.83 (1H, ddd, J = 12, 8.5, 2.5 Hz, F/Ph-3-CH), 7.36–7.45 (1H, m, F/Ph-6-CH), 7.51 (1H, s, triazole-3-CH), 7.64 (1H, s, thiazole-5-CH), 7.71 (1H, br, CONH), 7.71 (2H, d, J = 8.2 Hz, CN/Ph-3,5-CH), 8.09 (2H, d, J = 8.2 Hz, CN/Ph-2,6-CH), presence of a few amount of hexanes was detected; ^{13}C NMR ($CDCl_3$) δ ppm 17.6 (CH_3), 37.0 (NCH_2), 44.6 (d, J = 5.8 Hz, CH), 45.2 (NCH_3), 57.0 (d, J = 4.8 Hz, NCH_2), 57.3 (NCH_2), 77.4 (OC), 104.0 (t, J = 27 Hz, F/Ph-3-CH), 111.1 (dd, J = 20.6, 3.4 Hz, F/Ph-5-CH), 111.4 (CN), 116.1 (thiazole-5-CH), 119.0 (CN/Ph-1-C), 124.2 (dd, J = 12.5, 3.8 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.4 (dd, J = 9.6, 5.8 Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 138.5 (thiazole-4-C), 147.2 (triazole-5-C), 149.3 (triazole-3-CH), 152.7 (CN/Ph-4-C), 157.8 (triazole-5-C=O), 159.3 (dd, J = 248.1, 12.0 Hz, F/Ph-2-CF), 162.9 (dd, J = 248.6, 12.5 Hz, F/Ph-4-CF), 172.8 (thiazole-2-C); HRMS (ESI) Calcd. for $C_{27}H_{28}F_2N_7O_2S$ (M+H) 552.1993, found 552.1979 (δ -2.6 ppm). *Anal.* Calcd. for $C_{27}H_{27}F_2N_7O_2S \cdot 0.28 C_6H_{14}$: C, 59.89; H, 5.32; N, 17.05. Found: C, 59.51; H, 5.24; N, 16.72.

2-((2R,3R)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-N,N-dimethyl-2H-1,2,4-triazole-3-carboxamide (3d). This compound was obtained as off-white crystals after crystallization from diethyl ether, mp 202°C; 1H NMR ($CDCl_3$) δ ppm 1.18 (3H, d, J = 7.0 Hz, CH_3), 2.99 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 4.15 (1H, q, J = 7.0 Hz, $CH-Me$), 4.70 (1H, d, J = 14.3 Hz, NCH_2), 5.10 (1H, d, J = 14.3 Hz, NCH_2), 6.26 (1H, br.s, OH), 6.75 (1H, t, J = 8.2 Hz, F/Ph-5-CH), 6.84 (1H, t, J = 10.2 Hz, F/Ph-3-CH), 7.39 (1H, q, J = 8.2 Hz, F/Ph-6-CH), 7.57 (1H, s, triazole-3-CH), 7.62 (1H, s, thiazole-5-CH), 7.73 (2H, d, J = 7.6 Hz, CN/Ph-3,5-CH), 8.08 (2H, d, J = 7.3 Hz, CN/Ph-2,6-CH); ^{13}C NMR ($CDCl_3$) δ ppm 17.7 (CH_3), 35.8 (NCH_3), 39.0 (NCH_3), 44.0 (d, J = 4.8 Hz, CH), 56.5 (d, J = 4.8 Hz, NCH_2), 77.7 (OC), 104.0 (t, J = 26.4 Hz, F/Ph-3-CH), 111.2 (d, J = 20.2 Hz, F/Ph-5-CH), 111.6 (CN), 116.0 (thiazole-5-CH), 119.0 (CN/Ph-1-C), 124.1 (dd, J = 12.5, 3.8 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.4 (dd, J = 8.6, 5.8 Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 138.4 (thiazole-4-C), 148.2 (triazole-5-C), 149.1 (triazole-3-CH), 152.8 (CN/Ph-4-C), 159.2 (dd, J = 247.6, 11.5 Hz, F/Ph-2-CF), 159.9 (triazole-5-C=O), 162.9 (dd, J = 249.5, 12.5 Hz, F/Ph-4-CF), 173.1 (thiazole-2-C); HRMS (ESI) Calcd. for $C_{25}H_{23}F_2N_6O_2S$ (M+H) 509.1571, found 509.1588 (δ +3.3 ppm). *Anal.* Calcd. for $C_{25}H_{22}F_2N_6O_2S$: C, 59.04; H, 4.36; N, 16.52. Found: C, 59.11; H, 4.42; N, 16.41.

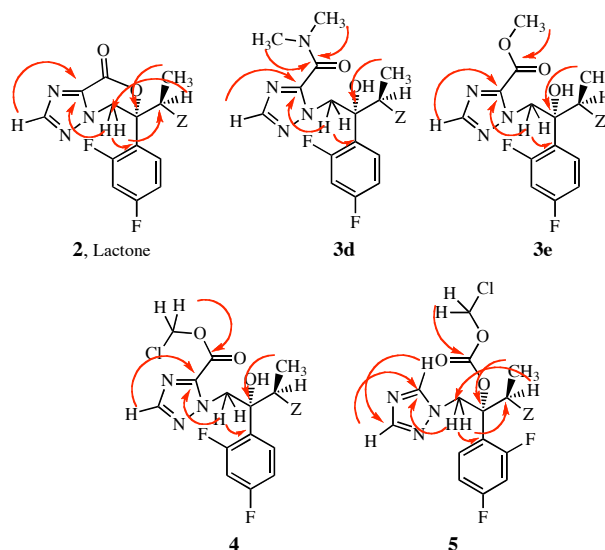
Methyl 2-((2*R*,3*R*)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-2*H*-1,2,4-triazole-3-carboxylate (3e). This compound was obtained as beige crystals after crystallization from a mixture of diethyl ether and methanol (2:1), mp 169°C; ¹H NMR (CDCl₃) δ ppm 1.20 (3H, d, J = 7.3 Hz, CH₃), 3.85 (3H, s, OCH₃), 4.20 (1H, q, J = 7.0 Hz, CH-Me), 4.93 (1H, d, J = 14.0 Hz, NCH₂), 5.17 (1H, d, J = 14.0 Hz, NCH₂), 6.79 – 6.87 (1H, m, F/Ph-5-CH), 6.79 – 6.87 (1H, m, F/Ph-3-CH), 7.33 – 7.41 (1H, m, F/Ph-6-CH), 7.63 (2H, s, triazole-3-CH and thiazole-5-CH), 7.74 (2H, d, J = 8.5 Hz, CN/Ph-3,5-CH), 8.09 (2H, d, J = 8.5 Hz, CN/Ph-2,6-CH); ¹³C NMR (CDCl₃) δ ppm 17.9 (CH₃), 44.3 (d, J = 5.8 Hz, CH), 53.0 (OCH₃), 57.0 (d, J = 3.8 Hz, NCH₂), 77.8 (d, J = 4.8 Hz, OC), 104.1 (t, J = 26.5 Hz, F/Ph-3-CH), 111.4 (dd, J = 20.2, 2.9 Hz, F/Ph-5-CH), 112.0 (CN), 115.5 (thiazole-5-CH), 118.8 (CN/Ph-1-C), 123.5 (dd, J = 12.5, 3.8 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.4 (dd, J = 9.6, 5.8 Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 137.9 (thiazole-4-C), 145.3 (thiazole-5-C), 150.2 (thiazole-3-CH), 153.2 (CN/Ph-4-C), 158.8 (thiazole-5-C=O), 159.1 (dd, J = 247.6, 12.5 Hz, F/Ph-2-CF), 163.0 (dd, J = 249.5, 12.5 Hz, F/Ph-4-CF), 173.1 (thiazole-2-C); HRMS (ESI) Calcd. for C₂₄H₂₀F₂N₅O₃S (M+H) 496.1255, found 496.1274 (δ +3.8 ppm). Anal. Calcd. for C₂₄H₁₉F₂N₅O₃S: C, 58.17; H, 3.86; N, 14.13. Found: C, 58.13; H, 3.81; N, 14.15.

Sodium 2-((2*R*,3*R*)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-2*H*-1,2,4-triazole-3-carboxylate (3f). This compound was obtained as an off-white powder, ¹H NMR (CD₃OD) δ ppm 1.06 (3H, d, J = 6.7 Hz, CH₃), 4.18 (1H, q, J = 7.0 Hz, CH-Me), 4.78 – 4.86 (1H, m, NCH₂), 4.95 (1H, d, J = 13.4 Hz, NCH₂), 6.68 (1H, br.s, F/Ph-5-CH), 6.84 (1H, t, J = 9.2 Hz, F/Ph-3-CH), 7.28 – 7.47 (2H, m, F/Ph-6-CH, and triazole-3-CH), 7.69 (2H, d, J = 7.6 Hz, CN/Ph-3,5-CH), 7.95 (1H, s, thiazole-5-CH), 8.07 (2H, d, J = 7.0 Hz, CN/Ph-2,6-CH); ¹³C NMR (CDCl₃) δ ppm 16.9 (CH₃), 46.0 (d, J = 5.8 Hz, CH), 56.8 (NCH₂), 77.0 (OC), 103.7 (t, J = 27 Hz, F/Ph-3-CH), 110.6 (dd, J = 21.1, 2.9 Hz, F/Ph-5-CH), 111.0 (CN), 118.0 (thiazole-5-CH), 118.9 (CN/Ph-1-C), 125.7 (dd, J = 13.0, 3.4 Hz, F/Ph-1-C), 127.1 (CN/Ph-2,6-CH), 130.8 (dd, J = 9.1, 6.2 Hz, F/Ph-6-CH), 132.8 (CN/Ph-3,5-CH), 139.3 (thiazole-4-C), 148.9 (thiazole-3-CH), 152.1 (CN/Ph-4-C), 159.9 (dd, J = 247.1, 12.0 Hz, F/Ph-2-CF), 163.2 (dd, J = 247.1, 13.0 Hz, F/Ph-4-CF), 173.5 (thiazole-2-C); HRMS (ESI) Calcd. for C₂₃H₁₆F₂N₅O₃S (M-H) 480.0942, found 480.0935 (δ -1.4 ppm).

2-[3-[4-(4-Cyanophenyl)-thiazol-2-yl]-2-(2,4-difluorophenyl)-2-hydroxy-butyl]-2*H*-[1,2,4]triazole-3-carboxylic acid chloromethyl ester (4). To a stirred solution of ravuconazole (1) (88 mg, 0.2 mmol) and anhydrous pyridine (158 mg, dried over KOH) in CH₂Cl₂ (1 mL; Sure Seal) was added in an ice-bath under anhydrous nitrogen atmosphere dropwise a solution of chloromethyl chloroformate (129 mg, 1.0 mmol; Fluka) in CH₂Cl₂ (1 mL). The mixture was stirred at ambient temperature overnight. The mixture diluted with CH₂Cl₂ (15 mL) was washed successively with water, 0.1 N HCl and brine. This was dried (sodium sulfate), and concentrated *in vacuo* to give the title compound 4 (95 mg, 0.18 mmol; Y. 90 %), contaminated with the lactone 2 as a crude film, ¹H NMR (CDCl₃) δ ppm 1.19 (3H, d, J = 7.0 Hz; CH₃), 4.14 (1H, q, J = 7.1 Hz; CH-Me), 4.97 (1H, d, J = 13.7 Hz, NCH₂), 5.08 (1H, d, J = 13.7 Hz; NCH₂), 5.73 (1H, d, J = 6.1 Hz, OCH₂), 5.88 (1H, d, J = 6.1 Hz, OCH₂), 5.98 (1H, br.s, OH), 6.74 (1H, dt, J = 8.3, 2.3 Hz, F/Ph-5-CH), 6.83 (1H, ddd, J = 12, 8.7, 2.5 Hz, F/Ph-3-CH), 7.34 (1H, dt, J = 8.9, 6.7 Hz, F/Ph-6-CH), 7.61 (1H, s, triazole-

3-CH or thiazole-5-CH), 7.63 (1H, s, thiazole-5-CH or triazole-3-CH), 7.76 (2H, d, J = 8.5 Hz, CN/Ph-3,5-CH), 8.11 (2H, d, J = 8.5 Hz, CN/Ph-2,6-CH). The presence of about 40 mol % of the lactone 2 was observed; ¹³C NMR (CDCl₃) δ ppm 18.0 (CH₃), 42.7 (d, J = 5.8 Hz, CH), 57.3 (d, J = 3.8 Hz, NCH₂), 69.5 (OCH₂), 77.9 (d, J = 4.8 Hz, OC), 104.1 (t, J = 26.5 Hz, F/Ph-3-CH), 111.5 (dd, J = 20.6, 3.4 Hz, F/Ph-5-CH), 111.9 (CN), 115.3 (thiazole-5-CH), 118.9 (CN/Ph-1-C), 123.2 (dd, J = 11.5, 3.8 Hz, F/Ph-1-C), 127.2 (CN/Ph-2,6-CH), 130.3 (dd, J = 9.1, 5.3 Hz, F/Ph-6-CH), 132.8 (CN/Ph-3,5-CH), 137.8 (thiazole-4-C), 144.3 (thiazole-5-C), 150.3 (thiazole-3-CH), 153.5 (CN/Ph-4-C), 156.9 (thiazole-5-C=O), 159.1 (dd, J = 247.6, 11.5 Hz, F/Ph-2-CF), 163.0 (dd, J = 250.5, 12.5 Hz, F/Ph-4-CF), 172.9 (thiazole-2-C). Peaks corresponding to the lactone 2 were also observed; HRMS (ESI) Calcd. for C₂₄H₁₉F₂N₅O₃S (M+H) 530.0865, found 530.0847 (δ -3.4 ppm).

Carbonic acid chloromethyl ester 2-[4-(4-cyanophenyl)-thiazol-2-yl]-1-(2,4-difluorophenyl)-1-[1,2,4]triazol-1-yl-methyl-propyl ester (5). To a stirred solution of ravuconazole (1) (88 mg, 0.20 mmol) in anhydrous THF (1 mL) was added a suspension of KH (35 mg, 30 % oil suspension) in THF (0.5 mL) at room temperature under anhydrous nitrogen atmosphere, and the mixture stirred for 15 minutes. To this mixture was added chloromethyl chloroformate (50 mg, 0.3 mmol; Fluka), and the mixture stirred for 1.5 hours. The reaction was quenched by addition of water, and the mixture diluted with EtOAc (~15 mL) was washed successively with water, 0.1 N HCl, and then with brine. The organic phase was dried (sodium sulfate), and concentrated *in vacuo* to obtain 75 mg (0.14 mmol, Y. 71 %) of the title compound 5, contaminated with about 35 mol % of ravuconazole (1) as an amber foam, ¹H NMR (CDCl₃) δ ppm 1.53 (3H, d, J = 7.0 Hz; CH₃), 4.35 (1H, q, J = 6.7 Hz; CH-Me), 5.47 (1H, d, J = 15 Hz; NCH₂), 5.61 (1H, d, J = 15 Hz, NCH₂), 5.69 (1H, d, J = 6.1 Hz, OCH₂), 5.74 (1H, d, J = 6.5 Hz, OCH₂), 6.70 (1H, t, J = 7.6 Hz, F/Ph-5-CH), 6.75-6.83 (1H, m, F/Ph-6-CH), 6.87 (1H, m, F/Ph-3-CH), 7.52 (1H, s, thiazole-5-CH), 7.65 (2H, d, J = 8.2 Hz, CN/Ph-3,5-CH), 7.85 (2H, d, J = 7.9 Hz,



a: The newly formed section of the each compound is shown. Red arrows indicate observed H-C connectivity.

Figure 1. 2D NMR Correlation of the representative compounds by HMBC^a

CN/Ph-2,6-CH), 7.88 (1H, s, triazole-3-CH), 8.04 (1H, s, triazole-5-CH). The presence of about 35 mol % of ravuconazole (**1**) was observed; ^{13}C NMR (CDCl_3) δ ppm 15.9 (CH_3), 44.3 (CH), 50.3 (d, $J = 11.5$ Hz, NCH_2), 72.4 (OCH_3), 87.4 (d, $J = 5.8$ Hz, OC), 105.0 (dd, $J = 28.3, 25.4$ Hz, F/Ph-3-CH), 111.5 (CN), 111.7 (dd, $J = 20.6, 3.4$ Hz, F/Ph-5-CH), 116.2 (thiazole-5-CH), 118.9 (CN/Ph-1-C), 119.1 (dd, $J = 10.6, 3.8$ Hz, F/Ph-1-C), 126.8 (CN/Ph-2,6-CH), 130.0 (dd, $J = 9.1, 5.3$ Hz, F/Ph-6-CH), 132.7 (CN/Ph-3,5-CH), 138.3 (thiazole-4-C), 144.9 (thiazole-5-CH), 151.1 ($\text{OC}=\text{O}$), 152.1 (thiazole-3-CH), 152.9 (CN/Ph-4-C), 159.3 (dd, $J = 24.9, 11.5$ Hz, F/Ph-2-CF), 163.1 (dd, $J = 25.3, 13.0$ Hz, F/Ph-4-CF), 168.7 (thiazole-2-C). Peaks corresponding to ravuconazole (**1**) were also observed. HRMS (ESI) Calcd. for $\text{C}_{24}\text{H}_{19}\text{F}_2\text{N}_5\text{O}_3\text{S}$ ($\text{M}+\text{H}$) 530.0865, found 530.0887 ($\delta + 4.1$ ppm).

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- [§] Present address: Paratek Pharmaceuticals Inc., 75 Kneeland St., Boston, MA 02111.
- [⊥] Present address: Pfizer Inc., MS 8260-1611, Eastern Point Road, Groton, CT 06340
- * Corresponding author. Fax: 203-677-7702, e-mail: Yasutsugu.Ueda@bms.com
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