Novel C-Acylated Triazole Derivatives of Ravuconazole, an Azole Antifungal Agent

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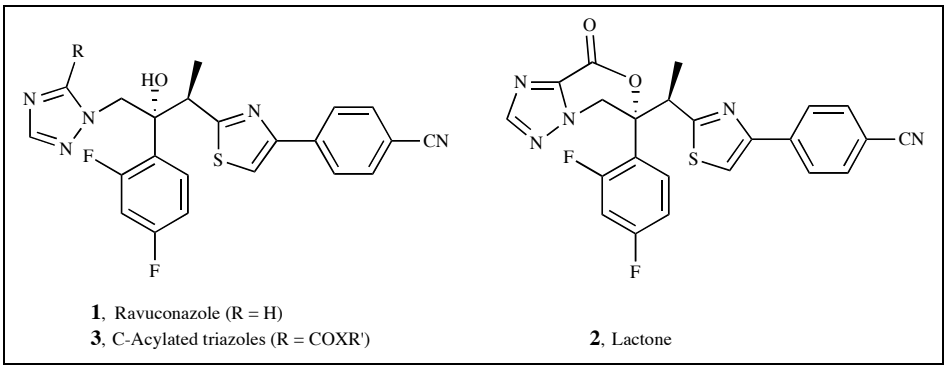

1, Ravuconazole (R = H)
3, C-Acylated triazoles (R = COXR')

2, Lactone

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.

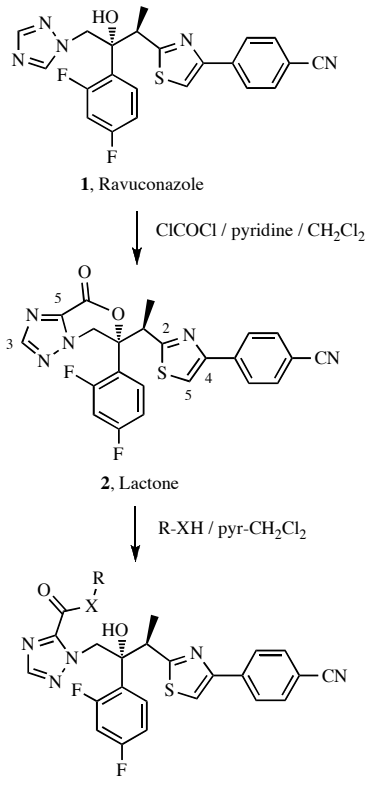
During our investigation to functionalize the hydroxy group of **1**, leading to a potential water-soluble prodrug, useful for the development as an iv drug [2], we found unusual chemistry, resulting in formation of a bicyclic triazole lactone. This lactone served as a synthetic intermediate for a variety 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-phenylcarbamate 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 CH_2Cl_2 proceeded with exceptional ease, producing a white amorphous powder which was characterized as a bicyclic triazole-lactone **2** [4]. Its ^1H NMR spectrum ($CDCl_3$) 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).

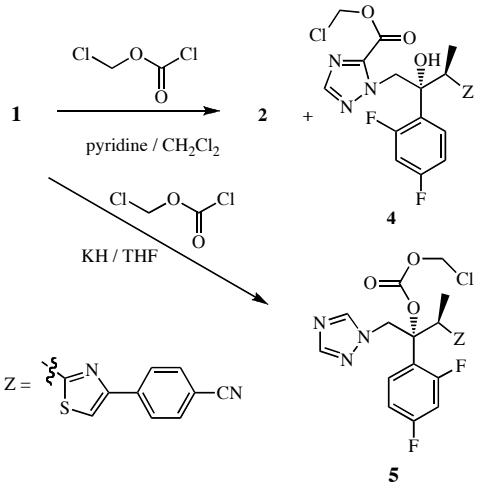
The lactone **2** reacted readily with various amines, and methanol to produce novel triazole C-acylated amide derivatives, and methyl ester of ravuconazole, **3**, respectively in good to modest yield, as illustrated in Scheme 1. This lactone was also readily hydrolyzed with aqueous sodium bicarbonate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

Although C-acyaltion 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].

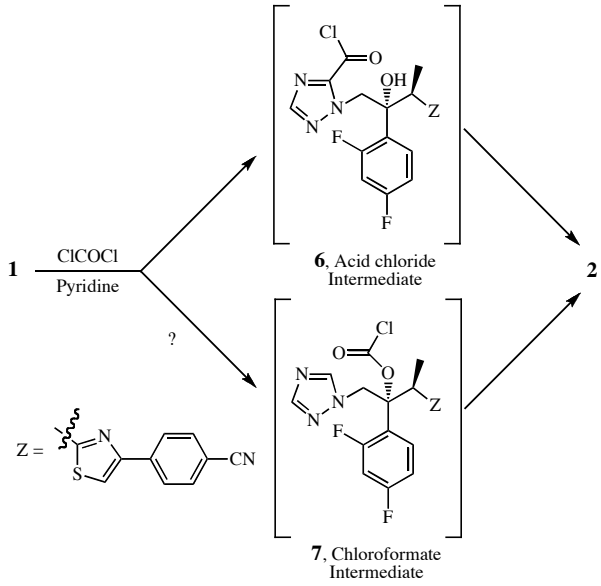
However, we were curious about how the lactone **2** was formed, and investigated other acylating agents under similar conditions. Methyl chloroformate [10] did not react to form the C-acylated ravuconazole, recovering only the starting ravuconazole. Although C-acylation was reported in the reaction 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 μg/mL. For comparison, the reference compound ravuconazole (**1**) had an MIC of 0.015 μg/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] *Candida albicans* (μg/mL)
1	Ravuconazole	-	5.72 (OH) 7.63 (thiazole-5) 7.66 (triazole-3) 7.83 (triazole-5)	0.015
2	lactone	22 (from **1**)	7.60 (thiazole-5) 7.90 (triazole-3)	ND
3a	-$NHCH_2CH_2NHAc$	65	6.03 (OH) 7.51 (triazole-3) 7.63 (thiazole-5)	4
3b	-$NHCH_2CH_2OH$	61	6.04 (OH) 7.49 (triazole-3) 7.63 (thiazole-5)	>16
3c	-$NHCH_2CH_2NMe_2$	89	6.17 (OH) 7.50 (triazole-3) 7.63 (thiazole-5)	>16
3d	-$N(CH_3)_2$	92	6.26 (OH) 7.57 (triazole-3) 7.62 (thiazole-5)	ND
3e	-OCH_3	45	5.88 (OH) 7.63 (triazole-3) 7.63 (thiazole-5)	ND
3f	-O^-Na^+ (carboxylate)	67	~7.34 (triazole-3) 7.95 (thiazole-5) (CD_3OD)	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 ^{1}H and ^{13}C 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. ^{1}H-^{1}H COSY (Correlation Spectroscopy), DEPT (Distortionless Enhancement by Polarization Transfer), ^{1}H-^{13}C HMQC (Heteronuclear Multiple Quantum Coherence) and ^{1}H-^{13}C 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-5*H*-[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 CH_2Cl_2 (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/CH_2Cl_2) to obtain **2** in about 22 % yield as a white amorphous powder after trituration in hexanes, ^{1}H NMR ($CDCl_3$) δppm 1.46 (3H, d, J = 7.3 Hz, CH_3), 4.23 (1H, q, J = 7.0 Hz, *CH*-Me), 5.09 (1H, d, J = 14.7 Hz, NCH_2), 5.33 (1H, d, J = 14.7 Hz, NCH_2), 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); ^{13}C NMR ($CDCl_3$) δppm 16.3 (CH_3), 45.3 (d, J = 2.9 Hz, *CH*-Me), 51.2 (d, J = 8.6 Hz, NCH_2), 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 (triazole-5-C), 153.0 (lactone-C=O), 153.2 (triazole-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]-2*H*-[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; ^{1}H 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 ($CDCl_3$) δppm 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 $C_{27}H_{25}F_2N_7O_3S$ •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-((2*R*,3*R*)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-*N*-(2-hydroxyethyl)-2*H*-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, ^{1}H 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 $C_{25}H_{22}F_2N_6O_3S$• 0.18 C_6H_{14}•0.3H_2O: C, 587.42; 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-((2*R*,3*R*)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-*N*-(2-(dimethylamino)ethyl)-2*H*-1,2,4-triazole-3-carboxamide (**3c**). This compound was obtained as a beige amorphous powder after trituration of the crude in hexanes, ^{1}H 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 ($CDCl_3$) δppm 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 $C_{27}H_{27}F_2N_7O_2S$•0.28 C_6H_{14}: C, 59.89; H, 5.32; N, 17.05. Found: C, 59.51; H, 5.24; N, 16.72.

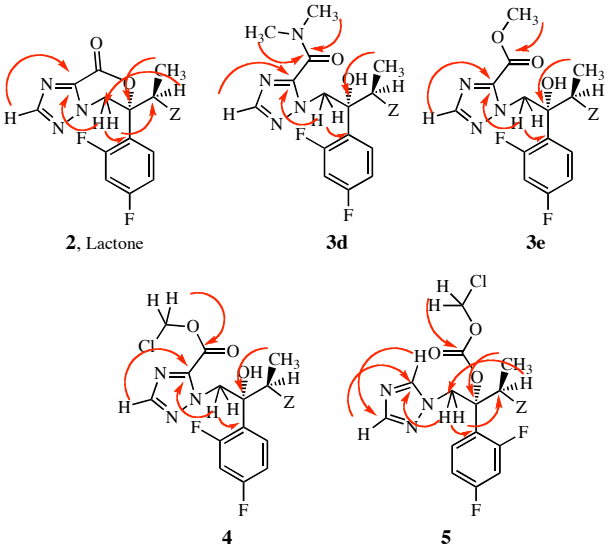
2-((2*R*,3*R*)-3-(4-(4-Cyanophenyl)thiazol-2-yl)-2-(2,4-difluorophenyl)-2-hydroxybutyl)-*N*,*N*-dimethyl-2*H*-1,2,4-triazole-3-carboxamide (**3d**). This compound was obtained as off-white crystals after crystallization from diethyl ether, mp 202°C; ^{1}H NMR ($CDCl_3$) δ ppm 1.18 (3H, d, J = 7.0 Hz, 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 ($CDCl_3$) δppm 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; ^{1}H NMR ($CDCl_3$) δ ppm 1.20 (3H, d, J = 7.3 Hz, CH_3), 3.85 (3H, s, OCH_3), 4.20 (1H, q, J = 7.0 Hz, *CH*-Me), 4.93 (1H, d, J = 14.0 Hz, NCH_2), 5.17 (1H, d, J = 14.0 Hz, NCH_2), 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); ^{13}C NMR ($CDCl_3$) δppm 17.9 (CH_3), 44.3 (d, J = 5.8 Hz, CH), 53.0 (OCH_3), 57.0 (d, J = 3.8 Hz, NCH_2), 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 (triazole-5-C), 150.2 (triazole-3-CH), 153.2 (CN/Ph-4-C), 158.8 (triazole-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 $C_{24}H_{20}F_2N_5O_3S$ (M+H) 496.1255, found 496.1274 (δ +3.8 ppm). *Anal.* Calcd. for $C_{24}H_{19}F_2N_5O_3S$: 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, ^{1}H NMR (CD_3OD) δ ppm 1.06 (3H, d, J = 6.7 Hz, CH_3), 4.18 (1H, q, J = 7.0 Hz, *CH*-Me), 4.78 - 4.86 (1H, m, NCH_2), 4.95 (1H, d, J = 13.4 Hz, NCH_2), 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); ^{13}C NMR ($CDCl_3$) δppm 16.9 (CH_3), 46.0 (d, J = 5.8 Hz, CH), 56.8 (NCH_2), 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 (triazole-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 $C_{23}H_{16}F_2N_5O_3S$ (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 CH_2Cl_2 (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 CH_2Cl_2 (1 mL). The mixture was stirred at ambient temperature overnight. The mixture diluted with CH_2Cl_2 (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, ^{1}H NMR ($CDCl_3$) δppm 1.19 (3H, d, J = 7.0 Hz; CH_3), 4.14 (1H, q, J = 7.1 Hz; *CH*-Me), 4.97 (1H, d, J = 13.7 Hz, NCH_2), 5.08 (1H, d, J = 13.7 Hz; NCH_2), 5.73 (1H, d, J = 6.1 Hz, OCH_2), 5.88 (1H, d, J = 6.1 Hz, OCH_2), 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; ^{13}C NMR ($CDCl_3$) δppm 18.0 (CH_3), 42.7 (d, J = 5.8 Hz, CH), 57.3 (d, J = 3.8 Hz, NCH_2), 69.5 (OCH_2), 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 (triazole-5-C), 150.3 (triazole-3-CH), 153.5 (CN/Ph-4-C), 156.9 (triazole-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 $C_{24}H_{19}F_2N_5O_3S$ (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, ^{1}H NMR ($CDCl_3$) δppm 1.53 (3H, d, J = 7.0 Hz; CH_3), 4.35 (1H, q, J = 6.7 Hz; *CH*-Me), 5.47 (1H, d, J = 15 Hz; NCH_2), 5.61 (1H, d, J = 15 Hz, NCH_2), 5.69 (1H, d, J = 6.1 Hz, OCH_2), 5.74 (1H, d, J = 6.5 Hz, OCH_2), 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 ($CDCl_3$) δppm 15.9 (CH_3), 44.3 (CH), 50.3 (d, J = 11.5 Hz, NCH_2), 72.4 (OCH_2), 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 (triazole-5-CH), 151.1 (OC=O), 152.1 (triazole-3-CH), 152.9 (CN/Ph-4-C), 159.3 (dd, J = 249, 11.5 Hz, F/Ph-2-CF), 163.1 (dd, J = 253, 13.0 Hz, F/Ph-4-CF), 168.7 (thiazole-2-C). Peaks corresponding to ravuconazole (**1**) were also observed. HRMS (ESI) Calcd. for $C_{24}H_{19}F_2N_5O_3S$ (M+H) 530.0865, found 530.0887 (δ + 4.1 ppm).

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[4] We originally thought O-carbonates or O-carbamates which contain a water-soluble functionality, prepared by the reaction of ravuconazole with phosgene followed by amines or alcohols containing a water-soluble group could serve as potential prodrugs since those can be hydrolyzed in vivo by esterases or carbamidases [5].

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[6] 2D NMR correlation of the representative compounds, **2**, **3d**, **3e**, **4**, and **5** by HMBC is shown in Figure 1. It is interesting to note the absence of connectivity between the N*CH*$_2$ and the *CH*-Me in the C-acylated derivatives, such as compound **3d**, **3e** and **4**.

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