New Antifungal 1,2,4-Triazoles with Difluoro(heteroaryl)methyl Moiety

Hiromichi ETO,* Yasushi KANEKO, and Takao SAKAMOTO[a]

Central Research Labs., SS Pharmaceutical Co., Ltd., 1143 Nanpeidai, Narita, Chiba 286–8511, Japan and Graduate School of Pharmaceutical Sciences, Tohoku University,[a] Aramaki-aza-Aoba, Aoba-ku, Sendai 980–8578, Japan.
Received January 12, 2000; accepted April 27, 2000

New 1,2,4-triazoles (1) having a difluoro(heteroaryl)methyl moiety were designed and synthesized *via* 1-aryl-2,2-difluoro-2-(heteroaryl)ethanones (2), which were prepared by two routes starting from the reaction of ethyl 2,2-difluoro(heteroaryl)acetate with phenyllithiums (Route A) and from the reaction of chlorodifluoro(heteroaryl)methane with benzaldehydes (Route B). The compounds 1 except for 1g show antifungal activities against yeasts and filamentous fungi *in vitro*, especially (+)-1f have equal or superior activities compared to those of itraconazole.

Key words antifungal; 1,2,4-triazole; difluoro(heteroaryl)methyl derivatives

The treatment of systemic mycoses have been a problem in the immunocompromised patient, and partly be due to the improved recognition and diagnosis of fungal infections. Another contributory factor are the prolonged survival of patients with global defects in their host defense mechanisms including patients with neoplastic diseases, organ transplant, diabetics and AIDS.

1,2,4-Triazole antifungals inhibit the biosynthesis of the cell membrane in fungi by direct interaction with cytochrome P-450 which acts on the 14-α-demethylation of lanosterol.[1] For the treatment of systemic mycoses such as candidosis and cryptococcosis in immunocompromised patients, 1,2,4-triazole antifungals such as fluconazole (FLCZ) and itraconazole (ITCZ) have been used.[2] However, FLCZ is not effective against aspergillosis, and ITCZ is not so efficacy *in vivo* because of its poor solubility and low bioavailability. And recently, the resistance to FLCZ in *Candida albicans* (*C. albicans*) has been reported.[3] Therefore more effective and safer drugs with broader spectra have been desired and many 1,2,4-triazole antifungals containing the heterocyclic moiety were developed, such as voriconazole,[4] SCH-56592,[5] ER-30346,[6] D-0870,[7] UR-9825,[8] and TAK-187.[9]

It is well known that the introduction of a fluorine atom into an organic molecule causes dramatic changes in its biological activities,[10] mainly due to the high electronegativity of fluorine, the strong carbon-fluorine bond, and increased solubility in lipids. Therefore, we designed the 1,2,4-triazole derivatives (**1**) with difluoro(heteroaryl)methyl moiety as shown in Chart 1. In this paper, we will describe the synthesis of **1** and their antifungal activities.

Chemistry The designed compounds **1** can be prepared from key intermediates, aryl difluoro(heteroaryl)methyl ketones (**2**), by the usual methods, which are prepared *via* Routes A and B. Route A consists of two reactions, namely the coupling reaction of heteroaryl halides with a copper-difluoroacetate complex, followed by the reaction of the cou-

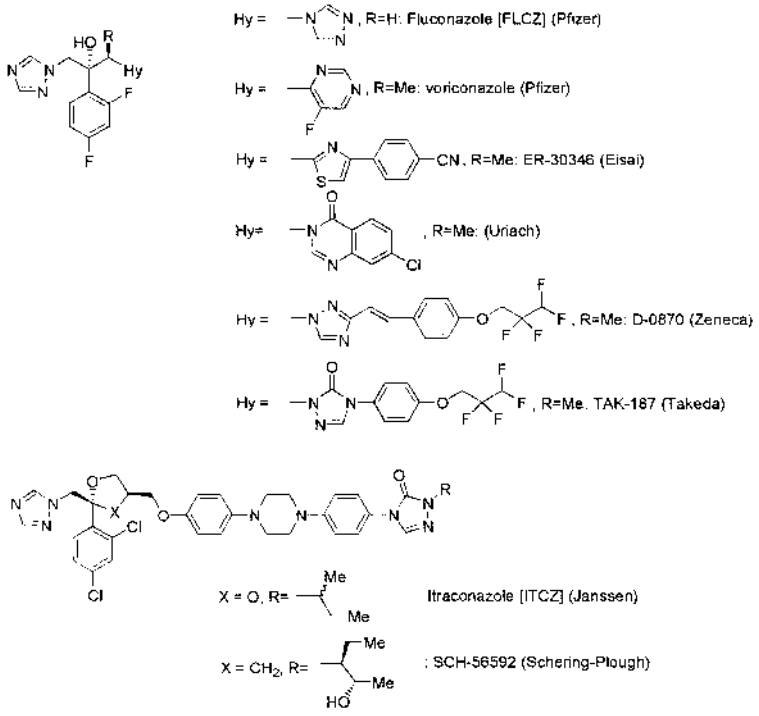

Fig. 1

* To whom correspondence should be addressed. e-mail: Hiromichi.Eto@ssp.co.jp

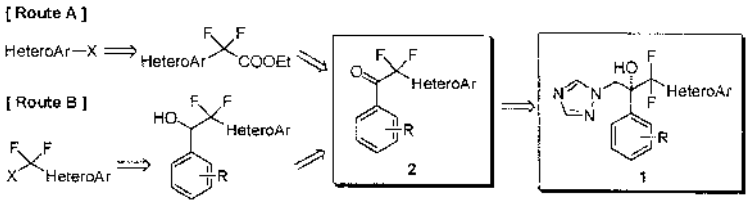

Chart 1

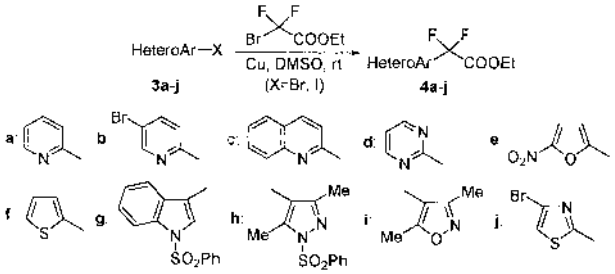

Chart 2

Table 1. Synthesis of Ethyl 2,2-Difluoro(heteroaryl)acetates (**4**) by the Reaction of Heteroaryl Halides (**3**) with Ethyl Bromodifluoroactate in the Presence of Copper in DMSO

Run	HeteroArX (**3**)	X	Product (**4**)	Yield (%)
1	**3a**	Br	**4a**	59.5
2	**3a**	Br	**4a**	—[a]
3	**3b**	Br	**4b**	62.4
4	**3c**	Br	**4c**	37.4
5	**3c**	I	**4c**	56.9[b]
6	**3d**	Cl	**4d**	—
7	**3d**	Br	**4d**	12.3[c]
8	**3e**	I	**4e**	71.7
9	**3f**	Br	**4f**	—
10	**3f**	Br	**4f**	3.8[c]
11	**3f**	I	**4f**	2.4[d]
12	**3f**	I	**4f**	74.4
13	**3f**	I	**4f**	52.4[e]
14	**3g**	I	**4g**	65.5
15	**3h**	I	**4h**	89.5
16	**3i**	I	**4i**	39.2
17	**3j**	I	**4j**	91.7

a) Reaction was carried out at 55 °C for 1 h using ethyl chlorodifluoroacetate. *b*) Reaction time is 5 h. *c*) CuI was added as an additive to the reaction. *d*) Reaction was carried out in DMF. *e*) Reaction was carried out in HMPA.

pling products, 2,2-difluoro(heteroaryl)acetates, with aryllithiums. Also Route B consists of two reactions, namely the reaction of benzaldehydes with Reformatsky reagents prepared from chlorodifluoro(heteroaryl)methanes followed by the oxidation reaction of the resulting alcohols.

The coupling reaction of the copper-difluoroacetate complex with heteroaryl halides has been reported by Kobayashi *et al.*[11] and recently by Kumadaki *et al.*[12] Kobayashi reported the coupling reaction of aliphatic, aromatic, and heteroaromatic halides with ethyl iododifluoroacetate, and Kumadaki reported the coupling reaction of aliphatic and aromatic iodides with commercially available ethyl bromodifluoroacetate. Therefore, we carried out the coupling reaction of various heteroaryl halides with the copper-difluoroacetate complex prepared from copper powder and commercially available ethyl bromodifluoroacetate.

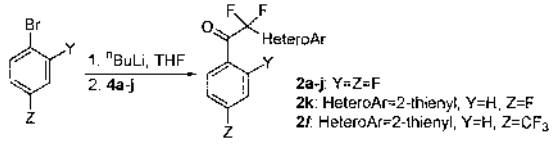

Chart 3

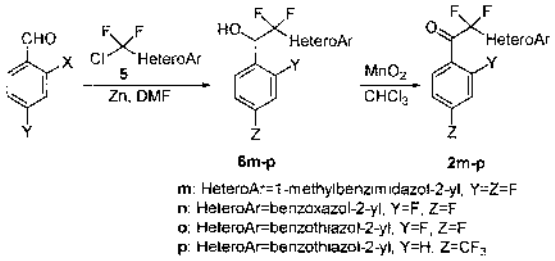

Chart 4

The results are summarized in Table 1. According to the Table 1, dimethyl sulfoxide (DMSO) (Run 12) is more preferred than *N*,*N*-dimethylformamide (DMF) (Run 11) and hexamethylphosphoramide (HMPA) (Run 13) as the solvent. The reactions using ethyl bromodifluoroacetate proceeded at room temperature, while the reaction using ethyl chlorodifluoroacetate did not proceed at 55 °C in DMSO (Run 2). The results in Table 1 show that most heteroaryl iodides produced products (**4**) in moderate to good yields while the bromides showed moderate yields. When the reactions did not proceed, the reaction slightly proceeded by the addition of copper(I) iodide (Run 10).

Prepared compounds (**4a**—**k**) were then allowed to react with 4- and 2,4-substituted phenyllithiums, which were derived from the corresponding bromides by the reaction with *n*-butyllithium in tetrahydrofuran (THF) at −78 °C, to give 1-aryl-2,2-difluoro-2-heteroarylethanones (**2a**—**l**).

In the reaction of ethyl 2-(5-bromo-2-pyridyl)-2,2-difluoroacetate (**4b**) with 2,4-difluorophenyllithium prepared from 2,4-difluorobromobenzene, the yield of 2-(5-bromo-2-pyridyl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanone (**2b**) was low owing to the formation of 2,6-difluorophenyllithium by autometallation of the aryllithium.[13] Namely, 2-(5-bromo-2-pyridyl)-2,2-difluoro-1-(2,6-difluorophenyl)-1-ethanone (**2b′**) was obtained as the major product (**2b** : **2b′** = 6 : 11) when THF was used as the solvent. However, the reaction in diethyl ether gave **2b** as the sole product in good yield without contamination of **2b′**.

Other 1-aryl-2,2-difluoro-2-heteroarenes (**2m**—**p**) were prepared by the oxidation of the corresponding alcohols (**6m**—**p**), which were synthesized from 2-(chlorodifluoromethyl)benzo-1,3-azoles (**5**)[14] and arylaldehydes using the

Reformatsky-type reaction.

Namely, Reformatsky-type reagents prepared from commercially available 2-(chlorodifluoromethyl)benzo-1,3-azoles (**5**) and zinc in DMF were allowed to react with 4- or 2,4-substituted benzaldehydes at 70 °C to give the 1-aryl-2,2-difluoro-2-heteroarylethanols (**6m**—**p**). Oxidation of the alcohols (**6m**—**p**) with activated manganese(IV) oxide in chloroform at room temperature for 15 h gave the corresponding ketones (**2m**—**p**). Other strong oxidants such as potassium permanganate, potassium dichromate, and pyridinium chlorochromate caused C–CF_2 bond cleavage of **6** to generate the corresponding benzaldehydes or benzoic acids without the formation of **2**.

Compounds **2a**—**p** were allowed to react with trimethylsulfoxonium iodide (TMSI) in the presence of sodium hydride in DMSO to give compounds **7a**—**p**. In the cases producing products (**7**) in low yields, the reaction of **2** with diazomethane is an alternative method, *e.g.*, the yields of **7e** and **7n** were significantly improved from 9% to 81.8% and from 22.8% to 85%, respectively.

Finally, compounds **7a**—**p** were allowed to react with 1,2,4-triazole in the presence of potassium carbonate in DMF to give the expected compounds (**1a**—**p**). **1b**, **1c**, **1f** and **1o**, which show strong antifungal activities, were optically resolved to (+)-**1** and (−)-**1** by chiral separation column chromatography.

For comparison, unfluorinated pyridylmethylene derivative (**8**)[15] was prepared from 2-methylpyridine and 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazole-1-yl)ethanone.[16]

Antifungal Activities and Discussion The synthesized 1,2,4-triazole derivatives (**1a**—**p**) containing the difluoro(heteroaryl)methyl moiety were screened for their *in vitro* activities against *C. albicans*, *Candida krusei* (*C. krusei*), *Aspergillus fumigatus* (*A. fumigatus*), *Aspergillus flavus* (*A. flavus*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Trichophyton rubrum* (*T. rubrum*) in comparison with those of FLCZ and ITCZ. The minimum inhibitory concentrations (MICs) are shown in Table 2.

Many of these compounds showed excellent *in vitro* antifungal activities. Their activities were generally and exceptionally high against *C. albicans* and *T. rubrum* and were good against the others. The introduction of fluorine atoms enhanced *in vitro* antifungal activities *A. fumigatus*, *A. flavus*, *T. mentagrophytes* and *T. mentagrophyte* (**1a** and **8**).

As phenyl substituents, the 2,4-difluoro derivative (**1f**) and

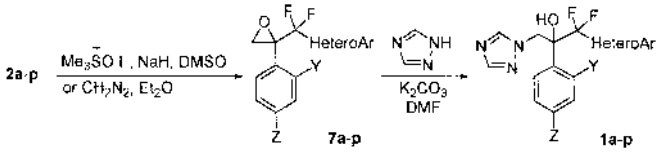

Chart 5

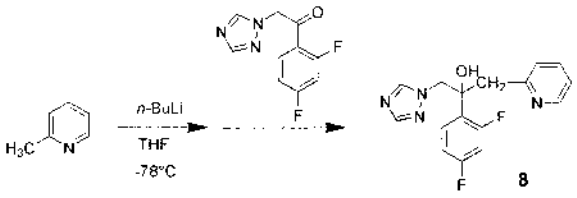

Chart 6

Table 2. *In Vitro* Antifungal Activities against Yeasts and Filamentous Fungi

	MIC (μg/ml)					
	C. albicans ATCC 90028	*C. krusei* ATCC 6258	*A. flavus* IFM 41935	*A. fumigatus* IFM 40808	*T. mentagrophytes* IFM 40769	*T. rubrum* IFO 6204
1a	≤0.125	1	2	1	0.25	0.25
1b	≤0.125	1	8	4	1	0.25
(−)-**1b**	0.25	>8	>8	>8	>8	>8
(+)-**1b**	0.031	0.25	1	0.5	0.25	0.063
1c	≤0.016	0.25	1	1	0.5	0.063
(−)-**1c**	>8	>8	>8	>8	>8	>8
(+)-**1c**	≤0.016	0.25	1	0.5	0.25	0.031
1d	0.5	>8	>8	>8	>8	>8
1e	0.125	4	>8	>8	4	0.25
1f	≤0.125	0.25	2	1	≤0.125	≤0.125
(−)-**1f**	0.125	1	8	4	0.5	0.063
(+)-**1f**	≤0.016	0.063	0.5	0.5	0.063	≤0.016
1g	>64	>64	>64	>64	>64	>64
1h	2	>8	>8	>8	>8	>8
1i	0.125	1	>8	>8	2	0.25
1j	≤0.125	0.5	2	2	0.5	≤0.125
1k	≤0.125	1	2	1	0.25	≤0.125
1l	≤0.125	2	>64	>64	64	8
1m	0.125	8	>8	>8	2	0.25
1n	0.25	1	>8	8	2	0.5
1o	≤0.016	0.25	2	2	0.25	0.063
(−)-**1o**	8	>8	>8	>8	>8	>8
(+)-**1o**	0.063	0.125	1	1	0.25	0.031
1p	≤0.016	0.25	4	4	2	0.25
8	0.125	1	>8	>8	4	2
FLCZ	0.5	64	>64	>64	64	64
ITCZ	0.063	0.5	0.5	0.5	0.5	0.25

4-fluoro derivative (**1k**) were superior over the 4-trifuoromethyl derivative (**1l**). As a heteroaromatic moiety, pyridine (**1a**, **b**), quinoline (**1c**), thiophene (**1f**), thiazole (**1j**), and the benzothiazole derivatives (**1o**) showed higher activities than pyrimidine (**1d**), furan (**1e**), pyrazole (**1h**), isoxazole (**1i**), benzimidazole (**1m**), and the benzoxazole derivatives (**1n**). On the other hand, the indole derivative (**1g**) did not show any antifungal activities.

The conformation of **1e**, **1g**, voriconazole and lanosterol were calculated by PM3.[17] We used *R* configuration in PM3 calculation, because *R* configuration of **1e** is well overlapped with voriconazole, whose absolute configuration is determined. The superimposition of **1e** and voriconazole (a), and that of **1e** and lanosterol (b) are shown in Fig. 2. We presume that the compounds **1** except for **1g** interact with cytochrome P-450 with this form and show antifungal activities.

In the lowest energy conformer of **1e**, the distance of fluorine atom of difluoromethylene group and oxygen atom of hydroxy group is 2.88 Å that suggests the existence of hydrogen bond. We presume that the hydrogen bond of these atoms contributes to the stabilization of the configuration. Similar contribution of hydrogen bond were observed in compound (**6**). For example, in the ^{1}H-NMR spectrum of **6o**, the different H–F coupling constants were observed (J=3 and 18 Hz) (Fig. 3).

On the other hand, a PM3 calculation of **1g**, mainly two conformations were calculated. One is an extended form, and the other is a folded form which has a 0.5 kcal/mol lower energy than extended form (Fig. 4). In the ^{1}H-NMR spectrum of **1g**, high magnetic field shifts of the phenyl protons were observed at δ 6.30—6.40 and 6.65—6.75 (each 1H, m), which were due to the shielding effect of an aromatic ring. The PM3 calculation and ^{1}H-NMR spectra suggest that **1g** take a folded conformation, and we presume that **1g** cannot enter into the cytochrome P-450 pocket by steric hindrance and did not show any antifungal activities.

Compounds (+)-**1b**, (+)-**1c**, (+)-**1f** and (+)-**1o** showed antifungal activities, but those of (−)-form showed no significant activities. Especially, (+)-**1f** showed activities superior to FLCZ and ITCZ against *C. albicans*, *C. krusei*, *T. mentagrophytes*, and *T. rubrum*, and activities equal to itraconazole against *A. fumigatus* and *A. flavus*.

Conclusion

We designed antifungal 1,2,4-triazoles (**1**) having a heteroaryl-*gem*-difluoromethylene moiety, which were synthesized using the coupling reaction of heteroaryl halides with an ethyl difluoroacetate–copper complex or the reaction of benzaldehydes with Reformatsky type reagents prepared from chlorodifluoro(heteroaryl)methanes and zinc, as the key

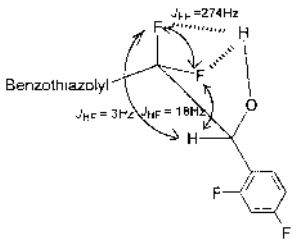

Fig. 3

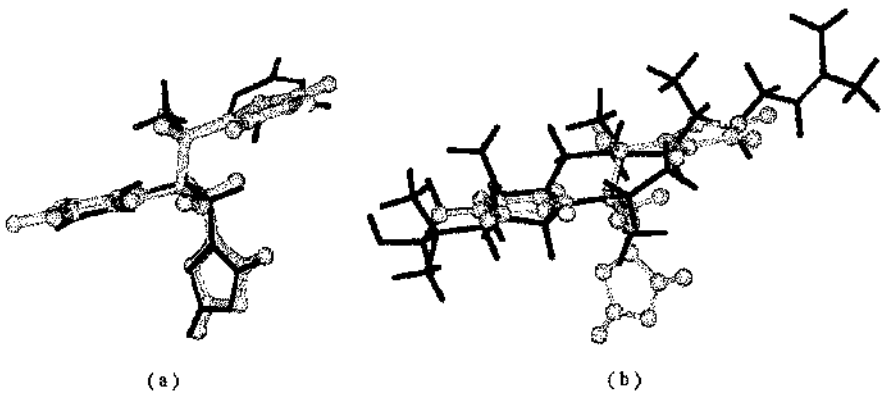

Fig. 2. Superimposition of **1e** and voriconazole (a), and that of **1e** and lanosterol (b)

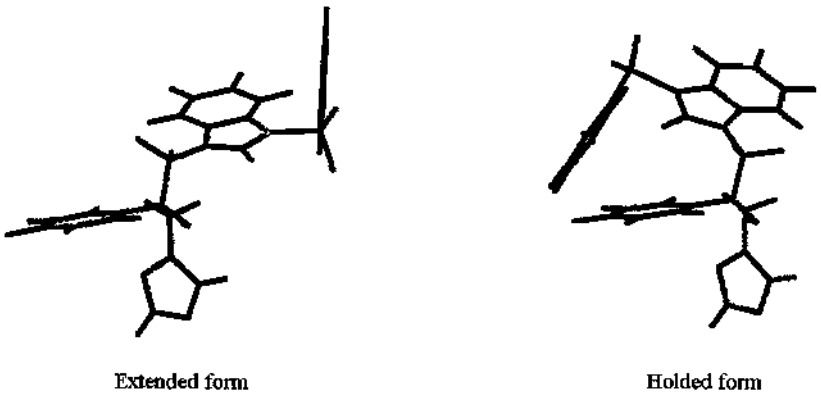

Fig. 4

reactions. The compounds **1** except for **1g** showed strong antifungal activities and especially (+)-**1f** showed activities equal or superior to ITCZ against yeasts and filamentous fungi.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus without correction. IR spectra measured on a Nihon-bunko IR-810 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi FT-NMR R-3000 or Varian Gemini 2000 spectrometer using tetramethylsilane as a respective internal standard. ^{19}F-NMR spectra were recorded on a JOEL JNM-EX400 FT-NMR spectrometer in $CDCl_3$ with trifluoroacetic acid as an external standard. The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, dt=double triplet, ddd=double double doublet, t=triplet, q=quartet, m=multiplet, br=broad. MS or high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DX303 or JEOL JMS-AX500 mass spectrometer. Optical rotations were determined on a Horiba SEPA-300 polarimeter. HPLC were performed on a Hitachi L-6000 pump equipped with a Hitachi L-4000 detector. Preparative HPLC were carried out on a Yamazen 800E pump equipped with an UV-10V detector. Column chromatography was carried out on a silica gel (BW-80S Fuji-sirial). Resolution of (±)-**1** was carried out by preparative HPLC on Chiralpak AS (2 cm I.D.×25 cm) with pre-column Chiralpak AS (2 cm I.D.×5 cm) (Daicell Chemical Industries, Ltd.) and optical yields were measured by HPLC using Chiralpack AS (4.6 mm I.D.×250 mm) with pre-column Chiralpak AS (4.6 mm I.D.× 50 mm) (Daicell Chemical Industries, Ltd.).

General Procedure for the Synthesis of Ethyl 2,2-Difluoro(heteroaryl)acetate (4) Ethyl bromodifluoroacetate (2 mmol) was added to a mixture of Cu powder (4 mmol) and DMSO (5 ml) at room temperature with stirring. After the mixture was stirred at the same temperature for 1 h, a heteroaryl halide (**3**) (1 mmol) was added to the solution at room temperature with stirring. The mixture was stirred at the same temperature for 15 h. After addition of aqueous NH_4Cl, the mixture was extracted with $CHCl_3$. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] to give **4**.

Ethyl 2,2-Difluoro-2-(2-pyridyl)acetate (**4a**): Colorless oil. Yield 59.5%. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz), 4.38 (2H, q, J=7.2 Hz), 7.40—7.45 (1H, dd, J=5.0, 7.7 Hz), 7.74 (1H, d, J=8.0 Hz), 7.87 (1H, dd, J=7.7, 8.0 Hz), 8.66 (1H, d, J=5.0 Hz). MS *m/z* (%): 201 (3, M^+), 129 (100), 128 (98). HRMS *m/z*: 201.0592 (Calcd for $C_9H_9F_2NO_2$: 201.0601). IR (neat) cm^{-1}: 1770.

Ethyl 2-(5-Bromo-2-pyridyl)-2,2-difluoroacetate (**4b**): Colorless oil. Yield 62.4%. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz), 4.38 (2H, q, J=7.2 Hz), 7.65 (1H, d, J=8.2 Hz), 8.01 (1H, dd, J=2.2, 8.2 Hz), 8.72 (1H, d, J=2.2 Hz). MS *m/z* (%): 278 (18, M^+), 206 (100). HRMS *m/z*: 278.9720 (Calcd for $C_9H_8BrF_2NO_2$: 278.9707). IR (neat) cm^{-1}: 1780.

Ethyl 2,2-Difluoro-2-(2-quinolinyl)acetate (**4c**): Colorless oil. Yield 56.9%. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 4.43 (2H, q, J=7.1 Hz), 7.63 (1H, dd, J=8.0, 7.1 Hz), 7.77 (1H, dd, J=7.1, 8.3 Hz), 7.81 (1H, d, J=7.1 Hz), 7.87 (1H, d, J=8.3 Hz), 8.14 (1H, d, J=8.5 Hz), 8.33 (1H, d, J=8.5 Hz). MS *m/z* (%): 251 (39, M^+), 178 (100). HRMS *m/z*: 251.0759 (Calcd for $C_{13}H_{11}F_2NO_2$: 251.0758). IR (neat) cm^{-1}: 1790.

Ethyl 2,2-Difluoro-2-(2-pyrimidinyl)acetate (**4d**): 2 mmol of CuI was added and other procedure was same as general procedure. Colorless oil. Yield 12.3%. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 7.49 (1H, t, J=4.9 Hz), 8.89 (2H, d, J=4.9 Hz). MS *m/z* (%): 202 (7, M^+), 129 (100). HRMS *m/z*: 202.0565 (Calcd for $C_8H_8F_2N_2O_2$: 202.0553). IR (neat) cm^{-1}: 1780.

Ethyl 2,2-Difluoro-2-(5-nitro-2-furanyl)acetate (**4e**): Colorless oil. Yield 71.7%. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.1 Hz), 4.43 (2H, q, J=7.1 Hz), 7.00 (1H, d, J=3.8 Hz), 7.35 (1H, d, J=3.8 Hz). MS *m/z* (%): 235 (16, M^+), 162 (87), 86 (100). HRMS *m/z*: 235.0292 (Calcd for $C_8H_7F_2NO_5$: 235.0292. IR (neat) cm^{-1}: 1770.

Ethyl 2,2-Difluoro-2-(2-thienyl)acetate (**4f**): Colorless oil. Yield 74.4%. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz), 4.37 (2H, q, J=7.1 Hz), 7.08 (1H, dd, J=3.6, 4.9 Hz), 7.40 (1H, dd, J=1.4, 3.6 Hz), 7.48 (1H, dd, J=1.4, 4.9 Hz). MS *m/z* (%): 206 (28, M^+), 133 (100). HRMS *m/z*: 206.0235 (Calcd for $C_8H_8F_2O_2S$: 206.0213). IR (neat) cm^{-1}: 1760.

Ethyl 2,2-Difluoro-2-[1-(phenylsulfonyl)-3-indolyl]acetate (**4g**): Colorless oil. Yield 65.6%. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.2 Hz), 4.32 (2H, q, J=7.2 Hz), 7.32 (1H, d, J=7.4, 7.7 Hz), 7.39 (1H, t, J=7.2 Hz), 7.49 (2H, t, J=7.2 Hz), 7.56 (1H, d, J=7.4, 8.2 Hz), 7.76 (1H, d, J=7.7 Hz), 7.92 (2H, d, J=7.2 Hz), 7.93 (1H, s), 7.98 (1H, d, J=8.2 Hz). MS *m/z* (%): 379 (49, M^+), 306 (100), 165 (15), 141 (47). HRMS *m/z*: 379. 0692 (Calcd for $C_{18}H_{15}F_2NO_4S$: 379.0690). IR (neat) cm^{-1}: 1770.

Ethyl 2-[3,5-Dimethyl-1-(phenylsulfonyl)-4-pyrazolyl]-2,2-difluoroacetate (**4h**): Colorless oil. Yield 89.5%. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz), 2.30 (3H, s), 2.63 (3H, s), 4.29 (2H, q, J=7.1 Hz), 7.55—7.60 (2H, m), 7.65—7.75 (1H, m), 7.95—8.05 (2H, m). MS *m/z* (%): 358 (6, M^+), 285 (100). HRMS *m/z*: Calcd for 358.0786 ($C_{15}H_{16}F_2N_2O_4S$: 358.0798). IR (neat) cm^{-1}: 1760.

Ethyl 2-(3,5-Dimethyl-4-isoxazolyl)-2,2-difluoroacetate (**4i**): Colorless oil. Yield 39.2%. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.1 Hz), 2.33 (3H, s), 2.5 (3H, s), 4.34 (2H, q, J=7.1 Hz). MS *m/z* (%): 219 (17, M^+), 146 (100). HRMS *m/z*: 219.0700 (Calcd for $C_9H_{11}F_2NO_3$: 219.0707). IR (neat) cm^{-1}: 1750.

Ethyl 2-(4-Bromo-2-thiazolyl)-2,2-difluoroacetate (**4j**): Colorless oil. Yield 91.7%. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 7.48 (1H, s). MS *m/z* (%): 285 (21, M^+), 214 (71), 212 (68), 162 (100). HRMS *m/z*: 284.9275 (Calcd for $C_7H_6BrF_2NO_2S$: 284.9272). IR (neat) cm^{-1}: 1780.

General Procedure for the Synthesis of 1-Aryl-2,2-difluoro-2-heteroarylethanone (2) from 4 A solution of *n*-BuLi (1.37 M solution in *n*-hexane; 10 mmol) was added to a solution of 2,4-difluorobromobenzene or 4-(trifluoromethyl)bromobenzene (10.4 mmol) in THF (45 ml) with stirring at −78 °C under Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h. A solution of **4** (10.4 mmol) in THF (5 ml) was added to the solution with stirring at −78 °C and stirred at the same temperature for 1 h and at room temperature for 1 h. After addition of aqueous NH_4Cl, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 8 (v/v)] to give **2**.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(2-pyridyl)ethanone (**2a**): Colorless oil. Yield 78.4%. ^{1}H-NMR ($CDCl_3$) δ: 6.75—6.85 (1H, m), 6.90—7.00 (1H, m), 7.40—7.50 (1H, d, J=4.7, 7.7 Hz), 7.83 (1H, d, J=8.0 Hz), 7.90—7.95 (1H, m), 8.07 (1H, dd, J=7.7, 8.0 Hz), 8.58 (1H, d, J=4.7 Hz). MS *m/z* (%): 269 (3, M^+), 141 (100), 128 (6). HRMS *m/z*: 269.0461 (Calcd for $C_{13}H_7F_4NO$: 269.0464). IR (neat) cm^{-1}: 1705.

2-(5-Bromo-2-pyridyl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanone (**2b**): Colorless oil. Yield 18.6% (in THF) and 87.4% (in Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 6.80—7.00 (2H, m), 7.40—7.50 (1H, m), 7.67 (1H, d, J=8.5 Hz), 8.02 (1H, dd, J=2.2, 8.5 Hz), 8.72 (1H, d, J=2.2 Hz). MS *m/z* (%): 346 (5, M^+), 206 (4), 141 (100). HRMS *m/z*: 346.9569 (Calcd for $C_{13}H_6BrF_4NO$: 346.9569). IR (neat) cm^{-1}: 1720.

2-(5-Bromo-2-pyridyl)-2,2-difluoro-1-(2,6-difluorophenyl)ethanone (**2b′**): Colorless oil. Yield 32.4%. ^{1}H-NMR ($CDCl_3$) δ: 6.90—7.00 (2H, m), 7.45—7.50 (1H, m), 7.67 (1H, d, J=8.5 Hz), 8.02 (1H, dd, J=2.2, 8.5 Hz), 8.72 (1H, d, J=2.2 Hz). MS *m/z* (%): 346 (5, M^+), 206 (4), 141 (100). HRMS *m/z*: 346.9557 (Calcd for $C_{13}H_6BrF_4NO$: 346.9569). IR (neat) cm^{-1}: 1720.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(2-quinolinyl)ethanone (**2c**): Colorless oil. Yield 67.1%. ^{1}H-NMR ($CDCl_3$) δ: 6.85—6.95 (1H, m), 6.95—7.10 (1H, m), 7.55—7.60 (1H, m), 7.65—7.75 (1H, m), 7.80—7.90 (2H, m), 7.99 (1H, d, J=8.5 Hz), 8.10—8.15 (1H, m), 8.34 (1H, d, J=8.5 Hz). MS *m/z* (%): 319 (5, M^+), 178 (28), 141 (100). HRMS *m/z*: 319.0620 (Calcd for $C_{17}H_9F_4NO$: 319.0610). IR (neat) cm^{-1}: 1720.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(2-pyrimidinyl)ethanone (**2d**): Colorless oil. Yield 64.1%. ^{1}H-NMR ($CDCl_3$) δ: 6.75—6.85 (1H, m), 7.00—7.05 (1H, m), 7.48 (1H, t, J=4.8 Hz), 8.05—8.15 (1H, m), 8.88 (2H, d, J=4.8 Hz). MS *m/z* (%): 270 (4, M^+), 141 (100). HRMS *m/z*: 270.0399 (Calcd for $C_{12}H_6F_4N_2O$: 270.0416). IR (neat) cm^{-1}: 1720.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(5-nitro-2-furanyl)ethanone (**2e**): Colorless oil. Yield 32.0%. ^{1}H-NMR ($CDCl_3$) δ: 7.02 (1H, d, J=3.8 Hz), 6.90—7.00 (2H, m), 7.38 (1H, d, J=3.8 Hz), 7.95—8.05 (1H, m). MS *m/z* (%): 141 (100, $M^+-C_5H_2F_2NO_3$). HRMS *m/z*: 141.0122 (Calcd for $C_7H_3F_2S$: 141.0151). IR (neat) cm^{-1}: 1710.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(2-thienyl)ethanone (**2f**): Colorless oil. Yield 67.2%. ^{1}H-NMR ($CDCl_3$) δ: 6.80—7.00 (2H, m), 7.07 (1H, d, J=3.6, 4.9 Hz), 7.37 (1H, dd, J=1.5, 3.6 Hz), 7.53 (1H, dd, J=1.5, 4.9 Hz), 7.80—7.90 (1H, m). MS *m/z* (%): 274 (4, M^+), 141 (100), 133 (34). HRMS *m/z*: 274.0048 (Calcd for $C_{12}H_6F_4OS$: 274.0079). IR (neat) cm^{-1}: 1710.

1-(2,4-Difluorophenyl)-2,2-difluoro-2-[1-(phenylsulfonyl)-3-indolyl] ethanone (**2g**): Colorless oil. Yield 84.8%. ^{1}H-NMR ($CDCl_3$) δ: 6.9—7.0 (2H, m), 7.29 (1H, d, J=7.2, 7.7 Hz), 7.38 (1H, t, J=7.3 Hz), 7.4—7.5 (1H, m), 7.47 (2H, t, J=7.3 Hz), 7.50 (1H, d, J=7.2, 8.4 Hz), 7.74 (1H, d,

J=7.7 Hz), 7.88 (2H, d, J=7.3 Hz), 7.89 (1H, s), 7.94 (1H, d, J=8.4 Hz). MS m/z (%): 447 (M^+, 14), 306 (100), 165 (9), 141 (50). HRMS m/z: 447.0553 (Calcd for $C_{22}H_{13}F_4NO_3S$ 447.0552). IR (neat) cm^{-1}: 1720.

1-(2,4-Difluorophenyl)-2-[3,5-dimethyl-1-(phenylsulfonyl)-4-pyrazolyl]-2,2-difluoroethanone (**2h**): Colorless oil. Yield: 85.1%. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 2.55 (3H, s), 6.85—7.0 (2H, m), 7.55—7.6 (2H, m), 7.65—7.7 (1H, m), 7.8—7.85 (1H, m), 7.95—8.0 (2H, m). MS m/z (%): 285 (100, $M^+-C_6H_5O_2S$), 141 (48). IR (neat) cm^{-1}: 1725.

1-(2,4-Difluorophenyl)-2-(3,5-dimethyl-4-isoxazolyl)-2,2-difluoroethanone (**2i**): Colorless oil. Yield 30.7%. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.45 (3H, s), 6.9—7.05 (2H, m), 7.85—7.95 (1H, m). MS m/z (%): 288 (M^++1, 0.2), 141 (100). HRMS m/z: 288.0644 (Calcd for $C_{13}H_{10}F_4NO_4$: 288.0648). IR (neat) cm^{-1}: 1710.

2-(4-Bromo-2-thiazolyl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanone (**2j**): Colorless oil. Yield 21.6%. ^{1}H-NMR ($CDCl_3$) δ: 6.85—6.95 (1H, m), 7.00—7.10 (1H, m), 7.50 (1H, s), 8.00—8.10 (1H, m). MS m/z (%): 353 (1, M^+), 141 (100). HRMS m/z: 352.9131 (Calcd for $C_{11}H_4BrF_4NOS$: 352.9133). IR (neat) cm^{-1}: 1720.

2,2-Difluoro-1-(4-fluorophenyl)-2-(2-thienyl)ethanone (**2k**): Colorless oil. Yield 69.3%. ^{1}H-NMR ($CDCl_3$) δ: 7.00—7.05 (3H, m), 7.35—7.40 (1H, m), 7.50—7.60 (2H, m), 7.70—7.80 (1H, m). MS m/z (%): 256 (2, M^+), 123 (100). HRMS m/z: 256.0150 (Calcd for $C_{12}H_7F_3OS$: 256.0169). IR (neat) cm^{-1}: 1715.

2,2-Difluoro-2-(2-thienyl)-1-[4-(trifluoromethyl)phenyl]ethanone (**2l**): Colorless oil. Yield 68.1%. ^{1}H-NMR ($CDCl_3$) δ: 7.05—7.10 (1H, m), 7.30—7.35 (1H, m), 7.55 (1H, dd, J=1.1, 4.9 Hz), 7.74 (2H, d, J=8.3 Hz), 8.18 (2H, d, J=8.3 Hz). MS m/z (%): 306 (6, M^+), 173 (100). HRMS m/z: 306.0173 (Calcd for $C_{13}H_7F_5OS$: 306.0137). IR (neat) cm^{-1}: 1710.

General Procedure for the Synthesis of 1-Aryl-2,2-difluoro-2-heteroarylethanol (6) A mixture of a (chlorodifluoromethyl)heteroarene (**5**) (11.4 mmol), Zn (2.6 g, 40 mmol), a benzaldehyde (20 mmol), and DMF (50 ml) was heated at 70 °C for 15 h. After addition of aqueous NH_4Cl, the precipitate was filtered and washed with AcOEt (50 ml×3). The filtrate was extracted with AcOEt. The combined AcOEt layer was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] to give **6**.

2,2-Difluoro-1-(2,4-difluorophenyl)-2-(1-methylbenzimidazol-2-yl)-ethanol (**6m**): Colorless powder. mp 195—197 °C. Yield 32.5%. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (1H, s), 3.91 (3H, s), 5.92 (1H, dd, $J_{H\text{-}F}$=3, 19 Hz), 6.80—6.90 (1H, m), 6.95—7.00 (1H, m), 7.38 (1H, t, J=7.7 Hz), 7.44 (1H, t, J=7.7 Hz), 7.45 (1H, d, J=7.7 Hz), 7.70—7.75 (1H, m), 7.82 (1H, d, J=7.7 Hz). MS m/z (%): 324 (23, M^+), 182 (100). HRMS m/z: 324.0927 (Calcd for $C_{16}H_{12}F_4N_2O$: 324.0875). IR (KBr) cm^{-1}: 3100.

2-(Benzoxazol-2-yl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanol (**6n**): Colorless powder. mp 146—147 °C. Yield 77.8%. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (1H, br), 5.85 (1H, dd, $J_{H\text{-}F}$=3, 18 Hz), 6.80—6.90 (1H, m), 6.95—7.00 (1H, m), 7.45 (1H, dd, J=7.4, 7.7 Hz), 7.51 (1H, dd, J=7.7, 8.0 Hz), 7.60—7.70 (1H, m), 7.66 (1H, d, J=8.0 Hz), 7.83 (1H, d, J=7.4 Hz). MS m/z (%): 311 (0.3, M^+), 169 (100). HRMS m/z: 311.0567 (Calcd for $C_{15}H_9F_4NO_2$: 311.0569). IR (KBr) cm^{-1}: 3100.

2-(Benzothiazol-2-yl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanol (**6o**): Colorless powder. mp 122—123 °C. Yield 57.7%. ^{1}H-NMR ($CDCl_3$) δ: 4.37 (1H, d, J=4.1 Hz), 5.88 (1H, ddd, J=4.1, $J_{H\text{-}F}$=3, 18 Hz), 6.80—6.90 (1H, m), 6.9—7.0 (1H, m), 7.56 (1H, dd, J=7.2, 8.0 Hz), 7.60—7.70 (1H, m), 7.62 (1H, dd, J=7.2, 8.0 Hz), 8.00 (1H, d, J=8.0 Hz), 8.16 (1H, d, J=8.0 Hz). ^{19}F-NMR δ: −21.4 (1F, ddd, J=3, 11, 274 Hz), −31.0 (1F, ddd, J=5, 18, 274 Hz), −33.3—−33.4 (1F, m), −37.4—−37.5 (1F, m). MS m/z (%): 328 (6, M^++1), 185 (100). HRMS m/z: 328.0387 (Calcd for $C_{15}H_{10}F_4NOS$: 328.0419). IR (KBr) cm^{-1}: 3300.

2-(Benzothiazol-2-yl)-2,2-difluoro-1-(4-fluorophenyl)ethanol (**6p**): Colorless powder. mp: 142—143 °C. Yield 11.7%. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (1H, br), 5.52 (1H, dd, $J_{H\text{-}F}$=6, 16 Hz), 7.50 (2H, t, J=8.8 Hz), 7.48 (1H, d, J=8.8 Hz), 7.49 (1H, d, J=8.8 Hz), 7.53 (1H, dd, J=7.2, 7.7 Hz), 7.59 (1H, dd, J=7.2, 8.0 Hz), 7.96 (1H, d, J=8.0 Hz), 8.13 (1H, d, J=7.7 Hz). MS m/z (%): 309 (2, M^+), 185 (100). HRMS m/z: 309.0469 (Calcd for $C_{15}H_{10}F_3NOS$: 309.0435). IR (KBr) cm^{-1}: 3140.

General Procedure for the Synthesis of 2m—p from 6 MnO_2 (2 g) was added to a solution of **6** (2.7 mmol) in $CHCl_3$ (10 ml) at room temperature with stirring for 15 h. The precipitate was filtered off, and the precipitate was washed with $CHCl_3$. The filtrate was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 9 (v/v)] to give **2**.

2-(1-Methylbenzimidazol-2-yl)-2,2-difluoro-1-(2,4-difluorophenyl)-ethanone (**2m**): Colorless powder. mp 110—112 °C. Yield 37.4%. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (3H, s), 6.75—6.85 (1H, m), 6.95—7.05 (1H, m), 7.33 (1H, t, J=8.2 Hz), 7.45 (1H, t, J=8.2 Hz), 7.47 (1H, d, J=8.2 Hz), 7.8 (1H, d, J=8.2 Hz), 8.10—8.20 (1H, m). MS m/z (%): 322 (2, M^+), 294 (48), 141 (100). HRMS m/z: 322.0705 (Calcd for $C_{16}H_{10}F_4N_2O$: 322.0729). IR (KBr) cm^{-1}: 1710.

2-(Benzoxazol-2-yl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanone (**2n**): Colorless powder. mp 71—72 °C. Yield: 43.1%. ^{1}H-NMR ($CDCl_3$) δ: 6.80—6.90 (1H, m), 7.00—7.10 (1H, m), 7.45 (1H, dd, J=7.7, 8.0 Hz), 7.50 (1H, dd, J=7.4, 8.0 Hz), 7.68 (1H, d, J=7.4 Hz) 7.82 (1H, d, J=7.7 Hz), 8.10—8.15 (1H, m). MS m/z (%): 309 (4, M^+), 141 (100). HRMS m/z: 309.0402 (Calcd for $C_{15}H_7F_4NO_2$: 309.0412). IR (KBr) cm^{-1}: 1705.

2-(Benzothiazol-2-yl)-2,2-difluoro-1-(2,4-difluorophenyl)ethanone (**2o**): Colorless powder. mp 61—62 °C. Yield: 46.9%. ^{1}H-NMR ($CDCl_3$) δ: 6.80—6.90 (1H, m), 6.95—7.05 (1H, m), 7.55—7.60 (1H, m), 7.55 (1H, dd, J=7.2, 7.7 Hz), 8.00 (1H, d, J=7.2 Hz), 8.08 (1H, d, J=8.0 Hz), 8.12 (1H, dd, J=7.7, 8.0 Hz). MS m/z (%): 325 (10, M^+), 141 (100). HRMS m/z: 325.0159 (Calcd for $C_{15}H_7F_4NOS$: 325.0184). IR (KBr) cm^{-1}: 1710.

2-(Benzothiazol-2-yl)-2,2-difluoro-1-(4-fluorophenyl)ethanone (**2p**): Colorless powder. mp 90—91 °C. Yield 95.4%. ^{1}H-NMR ($CDCl_3$) δ: 7.16 (2H, dd, J=8.6, 8.8 Hz), 7.52 (1H, dd, J=7.1, 7.7 Hz), 7.57 (1H, dd, J=7.1, 7.4 Hz), 7.99 (1H, d, J=7.7 Hz), 8.09 (1H, d, J=7.4 Hz), 8.19 (1H, d, J=8.6 Hz), 8.21 (1H, d, J=8.8 Hz). MS m/z (%): 307 (M^+, 6), 123 (100). HRMS m/z: 307.0296 (Calcd for $C_{15}H_8F_3NOS$: 307.0279). IR (KBr) cm^{-1}: 1705.

General Procedure for the Synthesis of 2-Aryl-2-[difluoro(heteroaryl) methyl]oxirane (7) from 2 with Trimethylsulfoxonium Iodide DMSO (10 ml) in THF (5 ml) was added to NaH (60% in oil; 64 mg, 1.6 mmol) washed twice with *n*-hexane. To the mixture, was added TMSI (349 mg, 1.6 mmol). After stirring at room temperature for 1 h, the mixture was added to **2** (1.57 mmol) in THF (5 ml) at 0 °C with stirring. The mixture was stirred at the same temperature for 1 h. After addition of aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel colum using *n*-hexane–AcOEt [9 : 1 (v/v)] to give **7**.

General Procedure for the Synthesis of 7 from 2 with Diazomethane Diazomethane (0.29 M in Et_2O; 10 ml) was added to a solution of **2e**, **n** (0.5 mmol) in Et_2O (10 ml) with stirring at 0 °C. The mixture was stirred at room temperature for 12 h, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 8 (v/v)] to give **7e**, **n**.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]pyridine (**7a**): Colorless oil. Yield 79.3%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.00 (1H, m), 3.45—3.50 (1H, m), 6.70—6.85 (2H, m), 7.38 (1H, dd, J=5.0, 8.0 Hz), 7.45—7.50 (1H, m), 7.57 (1H, d, J=7.7 Hz), 7.75 (1H, dd, J=7.7, 8.0 Hz), 8.67 (1H, d, J=5.0 Hz). MS m/z (%): 283 (17, M^+), 141 (10), 127 (100). HRMS m/z: 283.0647 (Calcd for $C_{14}H_9F_4NO$: 283.0620). IR (neat) cm^{-1}: 1240.

5-Bromo-2-[difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]pyridine (**7b**): Colorless oil. Yield 54.9%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.05 (1H, m), 3.40—3.45 (1H, m), 6.85—6.95 (2H, m), 7.30—7.40 (1H, m), 7.46 (1H, d, J=8.5 Hz), 7.92 (1H, dd, J=2.2, 8.5 Hz), 8.71 (1H, d, J=2.2 Hz). MS m/z (%): 360 (27, M^+), 206 (24), 155 (87), 127 (100). HRMS m/z: 360.9688 (Calcd for $C_{14}H_8BrF_4NO$: 360.9725). IR (neat) cm^{-1}: 1245.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]quinoline (**7c**): Colorless oil. Yield 89.8%. ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.05 (1H, m), 3.50—3.55 (1H, m), 6.70—6.85 (2H, m), 7.40—7.45 (1H, m), 7.59 (1H, d, J=8.5 Hz), 7.63 (1H, d, J=8.2 Hz), 7.77 (1H, dd, J=7.7, 8.5 Hz), 7.85 (1H, dd, J=7.7, 8.2 Hz), 8.17 (1H, d, J=8.5 Hz), 8.22 (1H, d, J=8.5 Hz). MS m/z (%): 333 (83, M^+), 178 (91), 127 (100). HRMS m/z: 333.0763 (Calcd for $C_{18}H_{11}F_4NO$: 333.0776). IR (neat) cm^{-1}: 1245.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]pyrimidine (**7d**): Colorless oil. Yield 48.8%. ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.05 (1H, m), 3.55—3.65 (1H, m), 6.70—6.75 (1H, m), 6.85—6.90 (1H, m), 7.42 (1H, t, J=4.9 Hz), 7.55—7.50 (1H, m), 8.85 (2H, d, J=4.9 Hz). MS m/z (%): 284 (12, M^+), 127 (100). HRMS m/z: 284.0545 (Calcd for $C_{13}H_8F_4N_2O$: 284.0572). IR (neat) cm^{-1}: 1240.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]-5-nitrofuran (**7e**): Colorless oil. Yield 9% (with TMSI) and 81.1% (with CH_2N_2). ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.05 (1H, m), 3.45—3.50 (1H, m), 6.78 (1H, d, J=4.0 Hz), 6.75—6.85 (1H, m), 6.90—6.95 (1H, m), 7.29 (1H, d, J=4.0 Hz), 7.40—7.50 (1H, m). MS m/z (%): 317 (1, M^+), 127 (100). HRMS m/z: 317.0288 (Calcd for $C_{13}H_7F_4NO_4$: 317.0311). IR (neat) cm^{-1}: 1250.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]thiophene (**7f**): Colorless oil. Yield 79.9%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.00 (1H, m), 3.20—3.25 (1H, m), 6.85—6.90 (2H, m), 7.03 (1H, dd, J=3.7, 5.1 Hz), 7.25 (1H, d, J=3.7 Hz), 7.30—7.40 (1H, m), 7.43 (1H, d, J=5.1 Hz). MS m/z (%): 288 (14, M^+), 155 (100). HRMS m/z: 288.0222 (Calcd for $C_{13}H_8F_4OS$: 288.0223). IR (neat) cm^{-1}: 1245.

3-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]-1-(phenylsulfonyl) indole (**7g**): Colorless oil. Yield 54.9%. ^{1}H-NMR ($CDCl_3$) δ: 2.90—2.95 (1H, m), 3.15—3.20 (1H, m), 6.80—6.90 (2H, m), 7.26 (1H, d, J=6.8, 7.2 Hz), 7.30—7.40 (1H, m), 7.37 (1H, t, J=7.2 Hz), 7.47 (2H, t, J=7.2 Hz), 7.55 (1H, dd, J=7.2, 8.8 Hz), 7.63 (1H, d, J=8.8 Hz), 7.76 (1H, s), 7.89 (2H, d, J=7.2 Hz), 7.97 (1H, d, J=8.8 Hz). MS m/z (%): 461 (53, M^+), 306 (100), 165 (11), 141 (39). HRMS m/z: 461.0738 (Calcd for $C_{23}H_{15}F_4NO_3S$: 461.0709). IR (neat) cm^{-1}: 1240.

4-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]-3,5-dimethyl-1-(phenylsulfonyl)pyrazole (**7h**): Colorless oil. Yield 54.3%. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.30 (3H, s), 2.85—2.80 (1H, m), 3.10—3.15 (1H, m), 6.55—6.60 (1H, m), 6.65—6.75 (1H, m), 7.10—7.15 (1H, m), 7.45—7.50 (2H, m), 7.60—7.65 (1H, m), 7.85—7.90 (2H, m). MS m/z (%): 440 (5, M^+), 285 (100). HRMS m/z: 440.0822 (Calcd for $C_{20}H_{16}F_4N_2O_3S$: 440.0818). IR (neat) cm^{-1}: 1240.

4-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]-3,5-dimethylisoxazole (**7i**): Colorless oil. Yield 59.8%. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.26 (3H, s), 2.95—3.00 (1H, m), 3.25—3.30 (1H, m), 6.80—6.95 (2H, m), 7.35—7.40 (1H, m). MS m/z (%): 301 (16, M^+), 155 (82), 127 (100). HRMS m/z: 301.0735 (Calcd for $C_{14}H_{11}F_4NO_2$: 301.0725). IR (neat) cm^{-1}: 1240.

4-Bromo-2-[difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]thiazole (**7j**): Colorless oil. Yield 42.3%. ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.05 (1H, m), 3.55—3.60 (1H, m), 6.80—6.90 (2H, m), 7.40—7.50 (2H, m). MS m/z (%): 369 (15, M^+), 367 (15), 155 (63), 141 (20), 127 (100). IR (neat) cm^{-1}: 1260.

2-[Difluoro[2-(4-fluorophenyl)-2-oxiranyl]methyl]thiophene (**7k**): Colorless oil. Yield 78.9%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.00 (1H, m), 3.35—3.40 (1H, m), 7.00—7.15 (3H, m), 7.15—7.20 (1H, m), 7.30—7.40 (2H, m), 7.40—7.45 (1H, m). MS m/z (%): 270 (35, M^+), 137 (100). HRMS m/z: 270.0301 (Calcd for $C_{13}H_9F_3OS$: 270.0326). IR (neat) cm^{-1}: 1250.

2-[Difluoro[2-(4-trifluoromethyl)phenyl]-2-oxiranyl]methyl]thiophene (**7l**): Colorless oil. Yield 55.2%. ^{1}H-NMR ($CDCl_3$) δ: 2.90—2.95 (1H, m), 3.40—3.45 (1H, m), 6.95—7.00 (1H, m), 7.15—7.20 (1H, m), 7.35—7.40 (1H, m), 7.50—7.60 (4H, m). MS m/z (%): 320 (33, M^+), 201 (80), 159 (43), 133 (100). HRMS m/z: 320.0273 (Calcd for $C_{14}H_9F_5OS$: 320.0295). IR (neat) cm^{-1}: 1250.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]-1-methylbenzimidazole (**7m**): Colorless powder. mp 123—125 °C. Yield 62.3%. ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.05 (1H, m), 3.25—3.30 (1H, m), 3.91 (3H, s), 6.80—6.90 (2H, m), 7.30—7.40 (3H, m), 7.55—7.60 (1H, m), 7.83 (1H, d, J=7.7 Hz). MS m/z (%): 336 (64, M^+), 182 (100), 141 (51). HRMS m/z: 336.0894 (Calcd for $C_{17}H_{12}F_4N_2O$: 336.0885). IR (KBr) cm^{-1}: 1255.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]benzoxazole (**7n**): Colorless powder. mp 91—92 °C. Yield 22.8% (with TMSI) and 85% (with CH_2N_2). ^{1}H-NMR ($CDCl_3$) δ: 3.05—3.10 (1H, m), 3.60—3.65 (1H, m), 6.75—6.80 (1H, m), 6.85—6.95 (1H, m), 7.44 (1H, dd, J=7.5, 7.7 Hz), 7.49 (1H, dd, J=7.2, 7.5 Hz), 7.50—7.60 (1H, m), 7.63 (1H, d, J=7.7 Hz), 7.83 (1H, d, J=7.2 Hz). MS m/z (%): 323 (43, M^+), 189 (96), 127 (100). HRMS m/z: 323.0617 (Calcd for $C_{16}H_9F_4NO_2$: 323.0665). IR (KBr) cm^{-1}: 1240.

2-[Difluoro[2-(2,4-difluorophenyl)-2-oxiranyl]methyl]benzothiazole (**7o**): Colorless powder. mp 107—108 °C. Yield 22.8%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.05 (1H, m), 3.60—3.65 (1H, m), 6.70—6.90 (2H, m), 7.46 (1H, dd, J=7.2, 7.7 Hz), 7.56 (1H, dd, J=7.2, 8.0 Hz), 7.50—7.60 (1H, m), 7.95 (1H, d, J=8.0 Hz), 8.16 (1H, d, J=7.7 Hz). MS m/z (%): 339 (77.5, M^+), 184 (64), 127 (100). HRMS m/z: 339.0333 (Calcd for $C_{16}H_9F_4NOS$: 339.0341). IR (KBr) cm^{+1}: 1250.

2-[Difluoro[2-(4-fluorophenyl)-2-oxiranyl]methyl]benzothiazole (**7p**): Colorless powder. mp 57—58 °C. Yield 21.2%. ^{1}H-NMR ($CDCl_3$) δ: 2.95—3.05 (1H, m), 3.60—3.65 (1H, m), 6.98 (2H, t, J=8.8 Hz), 7.48 (2H, d, J=8.8 Hz), 7.51 (1H, dd, J=7.2, 8.0 Hz), 7.56 (1H, dd, J=7.2, 8.5 Hz), 7.92 (1H, d, J=8.0 Hz), 8.15 (1H, d, J=8.5 Hz). MS m/z (%): 321 (3, M^+), 109 (100). HRMS m/z: 321.0422 (Calcd for $C_{16}H_{10}F_3NOS$: 321.0435). IR (KBr) cm^{-1}: 1240.

General Procedure for the Synthesis of 1,1-Difluoro-1-heteroaryl-3-(1,2,4-triazol-1-yl)-2-propanol (1) 1,2,4-Triazole (70 mg, 1 mmol) and K_2CO_3 (70 mg, 0.5 mmol) were added to a solution of **7** (0.93 mmol) in DMF (5 ml). The mixture was warmed at 65 °C for 5 h. After addition of aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH [98 : 2 (v/v)] as a mobile phase to give **1**.

Resolution of (±)-1 into (+)-1 and (−)-1 Compound (±)-**1** (50 mg) was subjected to preparative HPLC (Chiralpak AS with pre-column Chiralpak AS), using *n*-hexane–2-propanol [25 : 1 (v/v)] for **1b**, **c**, **o** and [19 : 1 (v/v)] for **1f** as a mobile phase. The more mobile isomer is (+)-**1** and the less mobile isomer is (−)-**1**. Their optical yields are measured by HPLC (Chiralpack AS with pre-column Chiralpak AS) using *n*-hexane–2-propanol [9 : 1 (v/v)] as a mobile phase (flow rate: 0.5 ml/min, column temperature: 21 °C).

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(2-pyridyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1a**): Colorless powder. mp 101—103 °C. Yield 63.8%. ^{1}H-NMR ($CDCl_3$) δ: 4.87 (1H, d, J=14.5 Hz), 5.36 (1H, d, J=14.5 Hz), 6.70—6.80 (2H, m), 6.86 (1H, s), 7.35—7.45 (1H, m), 7.45 (1H, dd, J=4.1, 7.7 Hz), 7.57 (1H, d, J=8.0 Hz), 7.69 (1H, s), 7.80 (1H, dd, J=7.7, 8.0 Hz), 8.32 (1H, s), 8.57 (1H, d, J=4.1 Hz). MS m/z (%): 353 (1, M^++1), 224 (47), 129 (100). HRMS m/z: 353.0980 (Calcd for $C_{16}H_{13}F_4N_4O$: 353.1025). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{16}H_{12}F_4N_4O$: C, 54.55; H, 3.43; N, 15.90. Found: C, 54.56; H, 3.57; N, 15.71.

1-(5-Bromo-2-pyridyl)-1,1-difluoro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1b**): Colorless powder. mp 142—143 °C. Yield 66.8%. ^{1}H-NMR ($CDCl_3$) δ: 4.73 (1H, d, J=14.3 Hz), 5.58 (1H, d, J=14.3 Hz), 5.75—5.85 (1H, m), 6.70—6.80 (2H, m), 7.15—7.25 (1H, m), 7.47 (1H, d, J=8.5 Hz), 7.75 (1H, s), 7.92 (1H, dd, J=2.2, 8.5 Hz), 8.24 (1H, s), 8.69 (1H, s). MS m/z (%): 433 (4, M^+), 431 (4), 224 (48), 207 (28), 182 (100). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{16}H_{11}BrF_4N_4O$: C, 44.57; H, 2.57; N, 12.99; Br, 18.53. Found: C, 44.83; H, 2.63; N, 12.95; Br, 18.43.

(−)-**1b**: Colorless oil. e.e. 100%. $[\alpha]_D^{24}$: −18.4 (c 0.1, MeOH). Retention time (min): 12.27.

(+)-**1b**: Colorless oil. e.e. 99.4%. $[\alpha]_D^{24}$: 17.6 (c 0.1, MeOH). Retention time (min): 15.06.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(2-quinolinyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1c**): Colorless powder. mp 136—138 °C. Yield 50.4%. ^{1}H-NMR ($CDCl_3$) δ: 4.95 (1H, d, J=14.4 Hz), 5.43 (1H, d, J=14.4 Hz), 6.60—6.80 (2H, m), 7.19 (1H, s), 7.40—7.50 (1H, m), 7.65 (1H, s), 7.60—7.70 (2H, m), 7.2 (1H, dd, J=8.2, 8.5 Hz), 7.88 (1H, d, J=8.2 Hz), 8.10 (1H, d, J=8.5 Hz), 8.19 (1H, s), 8.28 (1H, d, J=8.5 Hz). MS m/z (%): 403 (1, M^++1), 224 (22), 179 (100). HRMS m/z: 403.1133 (Calcd for $C_{20}H_{15}F_4N_4O$: 403.1182). IR (KBr) cm^{-1}: 3200. *Anal.* Calcd for $C_{20}H_{14}F_4N_4O$: C, 59.70; H, 3.51; N, 13.93. Found: C, 59.75; H, 3.55; N, 13.79.

(−)-**1c**: Colorless oil. e.e. 100%. $[\alpha]_D^{24}$: −7.14 (c 0.1, MeOH). Retention time (min): 20.63.

(+)-**1c**: Colorless oil. e.e. 99.2%. $[\alpha]_D^{24}$: 6.77 (c 0.1, MeOH). Retention time (min): 37.52.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(2-pyrimidinyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1d**): Colorless powder. mp 129—131 °C. Yield 14.6%. ^{1}H-NMR ($CDCl_3$) δ: 4.97 (1H, d, J=14.5 Hz), 5.42 (1H, d, J=14.5 Hz), 6.09 (1H, s), 6.70—6.80 (2H, m), 7.43 (1H, t, J=5.0 Hz), 7.60—7.65 (1H, m), 7.73 (1H, s), 8.15 (1H, s), 8.82 (2H, d, J=5.0 Hz). MS m/z (%): 354 (5, M^++1), 224 (51), 182(100). HRMS m/z: 354.0991 (Calcd for $C_{15}H_{12}F_4N_5O$: 354.0978). IR (KBr) cm^{-1}: 3200. *Anal.* Calcd for $C_{15}H_{11}F_4N_5O$: C, 51.00; H, 3.14; N, 19.82. Found: C, 51.01; H, 3.25; N,19.63.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(5-nitro-2-furanyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1e**): Colorless oil. Yield 49.2%. ^{1}H-NMR ($CDCl_3$) δ: 4.88 (1H, d, J=14.5 Hz), 5.39 (1H, d, J=14.5 Hz), 5.9 (1H, br), 6.73 (1H, d, J=3.7 Hz), 6.75—6.85 (2H, m), 7.26 (1H, d, J=3.7 Hz), 7.45—7.50 (1H, m), 7.84 (1H, s), 8.16 (1H, s). MS m/z (%): 368 (6, M^+), 224 (100). HRMS m/z: 368.0601 (Calcd for $C_{18}H_{10}F_4N_4O_4$: 386.0639). IR ($CHCl_3$) cm^{-1}: 3050.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(2-thienyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1f**): Colorless powder. mp 130—132 °C. Yield 67.3%. ^{1}H-NMR ($CDCl_3$) δ: 4.72 (1H, d, J=14.6 Hz), 5.40 (1H, d, J=14.6 Hz), 5.66 (1H, s), 6.65—6.80 (2H, m), 6.96 (1H, dd, J=3.5, 4.9 Hz), 7.10 (1H, d, J=1.5, 3.5 Hz), 7.35—7.45 (1H, m), 7.40 (1H, dd, J=1.5, 4.9 Hz) 7.81 (1H, s), 8.10 (1H, s). MS m/z: 358 (2, M^++1), 224 (100). HRMS m/z: 358.0646 (Calcd for $C_{15}H_{12}F_4N_3OS$: 358.0637). IR (KBr) cm^{-1}: 3150. *Anal.* Calcd for $C_{15}H_{11}F_4N_3OS$: C, 50.42; H, 3.10; N, 11.76; S, 8.97. Found: C, 50.57; H, 3.12; N, 11.48; S, 8.72.

(−)-**1f**: Colorless powder. mp 99—100 °C. e.e. 100%. $[\alpha]_D^{24}$: −8.21 (c 0.1, MeOH). Retention time (min): 15.33.

(+)-**1f**: Colorless powder. mp 97—98 °C. e.e. 95.2%. $[\alpha]_D^{24}$: 7.99 (c 0.1, MeOH). Retention time (min): 16.99.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-[1-(phenylsulfonyl)-3-indolyl]-3-(1,2,4-triazol-1-yl)-2-propanol (**1g**): Colorless powder. mp 136—138 °C.

Yield 17.0%. ^{1}H-NMR ($CDCl_3$) δ: 4.78 (1H, d, J=14.5 Hz), 5.47 (1H, d, J=14.5 Hz), 5.60 (1H, s), 6.30—6.40 (1H, m), 6.65—6.75 (1H, m), 6.95—7.05 (1H, m), 7.18 (1H, t, J=7.2 Hz), 7.31 (1H, dd, J=7.1, 7.4 Hz), 7.48 (1H, s), 7.50 (2H, t, J=7.2 Hz), 7.50 (1H, dd, J=7.1, 8.5 Hz), 7.60 (1H, d, J=7.4 Hz), 7.80 (1H, s), 7.84 (2H, d, J=7.2 Hz), 7.94 (1H, d, J=8.5 Hz), 8.13 (1H, s). MS *m/z* (%): 530 (2, M^+), 306 (24), 224 (100). HRMS *m/z*: 530.1069 (Calcd for $C_{25}H_{18}F_4N_4O_3S$: 530.1036). IR (KBr) cm^{-1}: 3400.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-[3,5-dimethyl-1-(phenylsulfonyl)-4-pyrazolyl]-3-(1,2,4-triazol-1-yl)-2-propanol (**1h**): Colorless powder. mp 175—176 °C. Yield 22.8%. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, br), 2.14 (3H, br), 4.78 (1H, d, J=14.6 Hz), 5.47 (1H, d, J=14.6 Hz), 5.61 (1H, br), 6.40—6.50 (1H, m), 6.65—6.75 (1H, m), 6.90—7.00 (1H, m), 7.50—7.60 (2H, m), 7.65—7.75 (1H, m), 7.78 (1H, s), 7.90—7.95 (2H, m), 8.13 (1H, s). MS *m/z* (%): 510 (0.2, M^++1), 285 (65), 224 (95), 145 (100). HRMS *m/z*: 510.1232 (Calcd for $C_{22}H_{20}F_2N_5O_3S$: 510.1223). IR ($CHCl_3$) cm^{-1}: 3100. *Anal.* Calcd for $C_{22}H_{19}F_4N_5O_3S$: C, 51.86; H, 3.77; N, 13.75; S, 6.30. Found: C, 51.86; H, 3.76; N, 13.75; S, 6.29.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(3,5-dimethyl-4-lisoxazolyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1i**): Colorless powder. mp 188—189 °C. Yield 79.0%. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s), 2.01 (3H, s), 4.82 (1H, d, J=14.5 Hz), 5.51 (1H, d, J=14.5 Hz), 5.67 (1H, s), 6.70—6.80 (2H, m), 7.20—7.25 (1H, m), 7.8 (1H, s), 8.15 (1H, s). MS *m/z* (%): 370 (0.4, M^+), 224 (100). HRMS *m/z*: 370.1025 (Calcd for $C_{16}H_{14}F_4N_4O_2$: 370.1053). IR (KBr) cm^{-1}: 3150. *Anal.* Calcd for $C_{16}H_{14}F_4N_4O_2$: C, 51.90; H, 3.81; N, 15.13. Found: C, 52.03; H, 3.89; N, 15.09.

1-(4-Bromo-2-thiazolyl)-1,1-difluoro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1j**): Colorless powder. mp 91—93 °C. Yield 38.6%. ^{1}H-NMR ($CDCl_3$) δ: 4.92 (1H, d, J=14.3 Hz), 5.46 (1H, d, J=14.3 Hz), 5.92 (1H, s), 6.70—6.85 (2H, m), 7.44 (1H, s), 7.50—7.60 (1H, m), 7.78 (1H, s), 8.14 (1H, s). MS *m/z* (%): 437 (0.6, M^++1), 224 (71), 182(100). HRMS *m/z*: 436.9675 (Calcd for $C_{14}H_{10}BrF_4N_4OS$: 436.9695). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{14}H_9BrF_4N_4OS$: C, 38.46; H, 2.07; Br, 18.28; N, 12.81; S, 7.33. Found: C, 38.50; H, 2.18; N, 13.06; Br, 18.44; S, 7.51.

1,1-Difluoro-2-(4-fluorophenyl)-1-(2-thienyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1k**): Colorless powder. mp 110—112 °C. Yield 88.3%. ^{1}H-NMR ($CDCl_3$) δ: 4.73 (1H, d, J=14.3 Hz), 5.45 (1H, d, J=14.3 Hz), 5.68 (1H, s), 6.90—7.00 (3H, m), 7.05—7.10 (1H, m), 7.20—7.25 (1H, m), 7.35—7.40 (2H, m), 7.75 (1H, s), 8.10 (1H, s). MS *m/z*: 340 (0.6, M^++1), 206 (100). HRMS *m/z*: 340.0767 (Calcd for $C_{15}H_{13}F_3N_3OS$: 340.0732). IR (KBr) cm^{-1}: 3200. *Anal.* Calcd for $C_{15}H_{12}F_3N_3OS$: C, 53.09; H, 3.56; N, 12.38; S, 9.45. Found: C, 53.06; H, 3.49; N, 12.19; S, 9.47.

1,1-Difluoro-1-(2-thienyl)-3-(1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl) phenyl]-2-propanol (**1l**): Colorless powder. mp 117—118 °C. Yield 34.3%. ^{1}H-NMR ($CDCl_3$) δ: 4.89 (1H, d, J=14.5 Hz), 4.96 (1H, d, J=14.5 Hz), 5.6 (1H, s), 6.85—6.90 (1H, m), 6.95—7.00 (1H, m), 7.32 (1H, m), 7.52 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz) 7.94 (1H, s), 7.84 (1H, s). MS *m/z* (%): 390 (5, M^++1), 256 (100). HRMS *m/z*: 390.0681 (Calcd for $C_{16}H_{13}F_5N_3OS$: 390.0699). IR (KBr) cm^{-1}: 3200. *Anal.* Calcd for $C_{16}H_{12}F_5N_3OS$: C, 49.36; H, 3.11; N, 10.79; S, 8.24. Found: C, 49.41; H, 3.15; N, 10.71; S, 8.27.

1,1-Difluoro-2-(2,4-difluorophenyl)-1-(1-methylbenzimidazol-2-yl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1m**): Colorless powder. mp 73—75 °C. Yield 50.4%. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s), 4.95 (1H, d, J=14.5 Hz), 5.48 (1H, d, J=14.5 Hz), 6.75—6.85 (2H, m), 6.86 (1H, s), 7.35—7.40 (1H, m), 7.40—7.45 (2H, m), 7.68 (1H, s), 7.65—7.75 (1H, m), 7.80 (1H, d, J=8.3 Hz), 8.18 (1H, s). MS *m/z* (%): 405 (5, M^+), 236 (85), 182 (100). HRMS *m/z*: 405.1218 (Calcd for $C_{19}H_{15}F_4N_5O$: 405.1213). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{19}H_{15}F_4N_5O$ 2/3H_2O: C, 54.68; H, 3.94; N, 16.78. Found: C, 54.44; H, 4.08; N, 16.61.

1-(Benzoxazol-2-yl)-1,1-difluoro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1n**): Colorless powder. mp 147—148 °C. Yield 22.0%. ^{1}H-NMR ($CDCl_3$) δ: 4.98 (1H, d, J=14.5 Hz), 5.13 (1H, d, J=14.5 Hz), 5.88 (1H, s), 6.75—6.85 (2H, m), 7.46 (1H, dd, J=7.4, 7.7 Hz), 7.49 (1H, dd, J=7.7, 8.0 Hz), 7.55—7.65 (1H, m), 7.61 (1H, d, J=8.0 Hz), 7.78 (1H, s), 7.82 (1H, d, J=7.4 Hz), 8.15 (1H, s). MS *m/z* (%): 392 (3, M^+), 224 (100). HRMS *m/z*: 392.0891 (Calcd for $C_{18}H_{12}F_4N_4O_2$: 392.0897). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{18}H_{12}F_4N_4O_2$: C, 55.11; H, 3.08; N, 14.28. Found: C, 55.29; H, 3.31; N, 14.17.

1-(Benzothiazol-2-yl)-1,1-difluoro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1o**): Colorless powder. mp 123—125 °C. Yield 82.9%. ^{1}H-NMR ($CDCl_3$) δ: 5.00 (1H, d, J=14.5 Hz), 5.51 (1H, d, J=14.5 Hz), 6.15 (1H, s), 6.70—6.80 (2H, m), 7.5—7.6 (1H, m), 7.51 (1H, dd, J=7.2, 7.7 Hz), 7.57 (1H, t, J=7.7 Hz), 7.73 (1H, s), 7.95 (1H, d, J=7.2 Hz), 8.11 (1H, d, J=7.7 Hz), 8.16 (1H, s). MS *m/z* (%): 408 (1, M^+), 224 (96), 141 (100). HRMS *m/z*: 408.0678 (Calcd for $C_{18}H_{12}F_4N_4OS$: 408.0668). IR (KBr) cm^{-1}: 3400. *Anal.* Calcd for $C_{18}H_{12}F_4N_4OS$: C, 52.94; H, 2.96; N, 13.72; S, 7.85. Found: C, 53.20; H, 3.09; N, 13.44; S, 8.04.

(−)-**1o**: Colorless powder. mp 56—57 °C. e.e. 100%. $[\alpha]_D^{24}$: −20.3 (*c* 0.1, MeOH). Retention time (min): 15.56.

(+)-**1o**: Colorless powder. mp 55—56 °C. e.e. 99.7%. $[\alpha]_D^{24}$: 20.1 (*c* 0.1, MeOH). Retention time (min): 17.39.

1-(Benzothiazol-2-yl)-1,1-difluoro-2-(4-fluorophenyl)-3-(1,2,4-triazol-1-yl)-2-propanol (**1p**): Colorless powder. mp 122—123 °C. Yield 56.4%. ^{1}H-NMR ($CDCl_3$) δ: 4.98 (1H, d, J=14.5 Hz), 5.13 (1H, d, J=14.5 Hz), 6.15 (1H, s), 6.94 (2H, t, J=8.2 Hz), 7.45—7.60 (4H, m), 7.89 (1H, s), 7.90 (1H, d, J=7.7 Hz), 8.08 (1H, d, J=7.8 Hz), 8.09 (1H, s). MS *m/z* (%): 390 (3, M+), 306 (82), 123 (100). HRMS *m/z*: 390.0782 (Calcd for $C_{18}H_{13}F_3N_4OS$: 390.0762). IR (KBr) cm^{-1}: 3450. *Anal.* Calcd for $C_{18}H_{13}F_3N_4OS$: C, 55.38; H, 3.36; N, 14.35; S, 8.21. Found: C, 55.43; H, 3.56; N, 14.42; S. 8.02.

Preparation of 2-(2,4-difluorophenyl)-1-(2-pyridyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (8) A solution of *n*-BuLi (1.37 M solution in *n*-hexane; 10 mmol) was added to a solution of 2-methylpyridine (10.4 mmol) in THF (50 ml) with stirring at −78 °C under Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h. A solution of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (10 mmol) in THF (5 ml) was added to the solution with stirring at −78 °C and stirred at the same temperature for 1 h and at room temperature for 1 h. After addition of aqueous NH_4Cl, the mixture was extracted with AcOEt. The organic extract was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using AcOEt–*n*-hexane [1 : 8 (v/v)] to give 1.03 g of **8** (yield 32.5%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.07 (1H, d, J=14.7 Hz), 3.55 (1H, d, J=14.7 Hz), 4.52 (1H, d, J=14.2 Hz), 4.67 (1H, d, J=14.2 Hz), 6.64—6.75 (2H, s), 7.01 (1H, d, J=7.8 Hz), 7.07 (1H, dd, J=4.4, 7.3 Hz), 7.35—7.45 (1H, m), 7.50 (1H, dd, J=7.3, 7.8 Hz), 7.81 (1H, s), 8.28 (1H, s), 8.34 (1H, d, J=4.4 Hz). MS *m/z* (%): 316 (0.3, M^+), 234 (55), 141 (61), 93 (100). HRMS *m/z*: 316.1165 (Calcd for $C_{16}H_{15}F_2N_4O$: 316.1136). IR (KBr) cm^{-1}: 3300.

Antifungal *in Vitro* Activities of 1 The minimum inhibitory concentrations (MICs) of the compounds were determined by the National Committee for Clinical Laboratory Standards (NCCLS) M27-A broth microdilution method for yeasts and by the NCCLS M38-P for filamentous fungi. The compounds dissolved in DMSO (final concentration: 1%) were tested at different concentrations (from 64 to 0.016 μg/ml). *C. albicans* (ATCC 90028) and *C. krusei* (ATCC 6258) for yeast strains, and *A. flavus* (IFM 41935), *A. fumigatus* (IFM 40808), *T. mentagrophytes* (IFM 40769), and *T. rubrum* (IFO 6204) for filamentous fungi strains were used. The MICs were measured after 48 h (72 h for *Trichophyton* species) incubation at 35 °C (at 27 °C for *Trichophyton* species).

Acknowledgement We would like to thank M. Matsumoto, K. Maebash, and K. Ishida of SS Pharmaceutical Co., Ltd. Central Research Labs. for screening against yeasts and filamentous fungi.

References and Notes

1) *a*) Aoyama Y., Yoshida Y., Sato R., *J. Biol. Chem*., **259**, 1661—1666 (1984), *b*) Hitchcock C. A., Dickinson K., Brown S. B., Evans E. G., Adams D. J., *Biochem. J*., **266**, 475—480 (1990).
2) Lyman C. A., Walsh T. J., *Drugs*, **44**, 9—35 (1992).
3) Odds F. C., *J. Antimicrob. Agents Chemother*., **31**, 463—471 (1993).
4) Fromiyling Robert A., Castaner J., *Drugs Future*, **21**, 266—271 (1996).
5) Fromiyling Robert A., Castaner J., *Drugs Future*, **21**, 160—166 (1995).
6) Naito T., Hata K., Tsuruoka A., *Drugs Future*, **21**, 20—24 (1996).
7) Yamada H., Tsuda T., Watanabe T., Ohashi M., Murakami K., Mochizuki H., *Antimicrob. Agents Chemother*., **37**, 2412—2417 (1993).
8) Bartroli J., Yurmo E., Alguero M., Boncompte E., Vericat M. L., Conte L., Ramis J., Merlos M., Garcia-Rafanell J., Forn J., *J. Med. Chem*., **41**, 1869—1882 (1998).
9) Tasaka A., Hayashi R., Kitazaki T., Tamura N., Tsutimori N., Matsusita Y., Hayashi R., Okonogi K., Itoh K., *Chem. Pharm. Bull*., **45**, 321—326 (1997).
10) Filler R., Kobayashi Y., "Biomedicinal Aspects of Fluorine Chemistry," Kodansha Ltd., Tokyo, Elsvier Biomedical Press, 1982.
11) Taguchi T., Kitagawa O., Morikawa T., Nishiwaki T., Uehara H., Endo H., Kobayashi Y., *Tetrahedron Lett*., **27**, 6103—6106 (1986).
12) Sato K., Kawata R., Ama F., Omote M., Ando A., Kumadaki I., *Chem.*

Pharm. Bull., **47**, 1013—1016 (1999).
13) *a*) Bridges A. J., Patt W. C., Stickney T. M., *J. Org. Chem*., **55**, 773—775 (1990). *b*) Coe P. L., Waring A. J., Yawood T. D., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2729—2737.
14) Tsukiyama T., Sato K., Japan Kokai Tokkyo Koho, JP 10-45735, Feb. 17, 1998; [*Chem. Abst*., **128**, 140695 (1998)].
15) Richardson K., Brit. U. K. Patent Appl. GB 2099818, Dec. 15,1982; [*Chem. Abst*., **99**, 38467*q* (1983)].
16) Roger P., Andrew B., Christopher H., Subramaniyan N., Stephen R., Kenneth R., Peter T., *Bioorg. Med. Chem. Lett*., **6**, 2031—2036 (1996).
17) PM3 calculation was performed using MOPAC on a Macintosh CAChe system: Stewart J. J. P., *J. Comput. Chem*., **10**, 209—220 (1989).