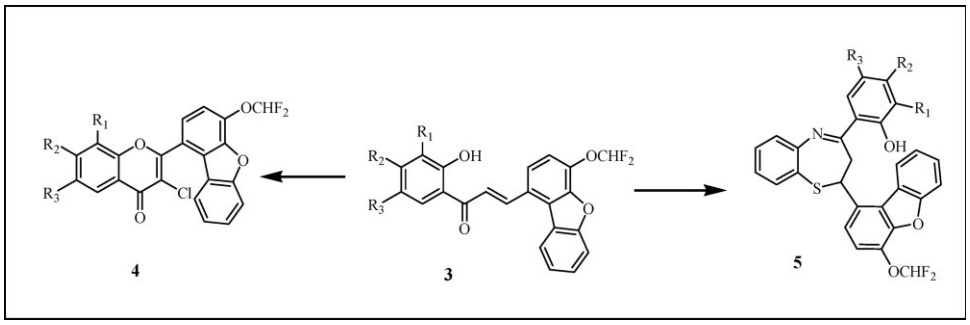
Synthesis and Biological Screening of Some Fluorinated Dibenzofuran Containing 3-Chlorochromones and Benzothiazepines

Pratibha Randhavane and Bhausaheb Karale*

Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar 414001, India
*E-mail: bkkarale@yahoo.com

Received July 3, 2008
DOI 10.1002/jhet.139
Published online 14 July 2009 in Wiley InterScience (www.interscience.wiley.com).



Variously substituted chalcones were synthesized from 4-difluoromethoxy-dibenzofuran-1-carboxaldehyde. These chalcones were converted into corresponding 3-chlorochromones and dihydro-benzothiazepines. Synthesized compounds were tested for their antifungal, antibacterial, antiviral and antioxidant activities.

J. Heterocyclic Chem., **46**, 732 (2009).

INTRODUCTION

In recent days, active research has been initiated on halogen containing heterocycles, particularly fluorine containing heterocycles. Incorporation of fluorine can alter the course of reaction as well as biological activities. Introduction of fluorine atom into an organic molecule largely enhances the pharmacological properties as compared with nonfluorinated analogues [1]. Despite the fact that fluorine has greater size than hydrogen, several studies have demonstrated that fluorine is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites [2].

Fluorine containing organic compounds are associated with antimicrobial [3], antibacterial [4], and anticancer [5] activities. They also act as selective inhibitors of biosynthesis of aminergic neurotransmitters [6].

Dibenzofurans are associated with biological activities like antifungal [7], antibacterial [8], anti-inflammatory, and antiallergic [9].

Chalcones are versatile synthones and can be cyclized to give chromones [10], chlorochromones, and benzothiazepines [11]. Chalcones can be converted into 3-chlorochromones by using DMSO+$CuCl_2$ system [11,12].

Chalcones possess a broad spectrum of biological activities including antibacterial, anthelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic, immunosuppressive, etc. [13,14].

Halogeno substituted chromones with heterocyclic substituent at 2-position are reported to have bronchodilatory [15], coronary spasmolytic [16], and antimicrobial properties [17,18].

1,4-Benzothiazepine derivatives are of considerable interest because of their biological activities as inhibitors of HIV-1 integrase [10], anti-tumor, antibiotics, enzyme inhibitors, muscle relaxant, anticonvulsant, sedatives, and hypnotics [19]. Some dihydrobenzothiazepines have excellent fungicidal activities [20]. Benzothiazepines are also associated with chemotherapeutic application such as antihypertension [21] and antibacterial activities [11,22]. Benzothiazepines have been reported as potent neuroleptic agents [23].

Biological activities associated with these molecules and importance of fluorine, prompted us to synthesize some fluorine containing chalcones, 3-chlorochromones and 1,4-benzothiazepines, and screen them for biological activities.

RESULT AND DISCUSSION

In this work, 2-hydroxy acetophenones **2** were treated with 4-difluoro-methoxy-dibenzofuran-1-carboxaldehyde **1** in presence of 40% KOH to afford corresponding 3-(4-(difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one **3**. Compound **3** on treatment with copper

Table 1

Antioxidant activity results with test concentration 125 μg/mL.

Compd.	R_1	R_2	R_3	% AO activity
3a	H	H	H	−2.96
3f	H	Cl	H	5.65
4a	H	H	H	−2.71
4e	Cl	H	Cl	−23.26
5a	H	H	H	4.58
5b	H	H	Br	1.62

chloride in DMSO gave 3-chlorochromone **4** and with 2-aminothiophenol in alcohol gave benzothiazepine **5**.

The structures of compounds **3**, **4**, and **5** are confirmed by spectral analysis (IR, ^{1}H-NMR, and MS). The IR spectrum of compound **3a** shows a strong absorption band (cm^{-1}) at 3305 for —OH and 1633 for α, β-unsaturated carbonyl groups. The IR spectrum of compound **4a** shows no absorption band for —OH, whereas the band at 1650 is for carbonyl group of chromone. The IR spectrum of compound **5a** shows the absorption band at 3397 for —OH, whereas the band for carbonyl group is absent.

The ^{1}H-NMR spectra of **3a** shows a doublet at 8.40 δ for one proton (J = 15 Hz) for transcoupled protons of α, β-unsaturated carbonyl group. In ^{1}H-NMR spectrum of **4a**, the presence of triplet for one proton at 6.80 δ (J = 72.94 Hz) indicates coupling of proton of —$OCHF_2$ group with two fluorine atoms. The ^{1}H-NMR spectrum of **5a** shows three doublet of doublets at 3.21, 3.47, and 5.97 δ, which are the characteristic peaks of dihydrobenzothiazepine moiety.

The structures of all compounds are also confirmed by mass spectral analysis. The mass spectra shows M^+ peaks at corresponding masses of respective molecules.

Antioxidant activity. The antioxidant activity of some of the synthesized compounds was determined by DPPH method using Trolox as a reference standard. Amongst, the compounds screened for antioxidant activity none of the compounds showed promising activity as shown in Table 1.

Antimicrobial activity. The antimicrobial activity of some compounds was assessed against 24 hr culture of some selected bacteria and fungi. The bacteria used were *Escherichia coli* and *Staphylococcus aureus*; the fungi used were *Candida albicans* and *Aspergillus fumigatus*.

The antimicrobial activity was performed by agar well diffusion method at 100 and 1000 μg/mL conc. in DMSO. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi, respectively.

Amphotericin B and Vancomycin were used as standards for comparison of antifungal and antibacterial activities respectively. The activity is reported by measuring the diameter of the zone of inhibition. All the screened compounds were found inactive as shown in Table 2.

Antiviral activity. The antiviral activity of some of the compounds was determined against *Herpes Simplex virus-2* by CPE inhibition assay. Vero cells (African green monkey kidney cell line-ATCC # CCL-81) were cultivated as monolayers in 5% carbon dioxide at 37°C, in Dulbecco's modified Eagle medium (MEM) with 5% fetal bovine serum (FBS).

The diluted extracts (100 μg/mL) were transferred to the aspirated Vero cell monolayers. Cultures were incubated at 37°C for 60 minutes. 100 μL of virus (100 $TCID_{50}$) was added to each well. The tray was transferred to an environmental chamber (37°C).

Cultures were inspected periodically for virus-induced cytopathic effect (viral CPE). Absence of CPE indicated

Table 2

Antimicrobial activity results.

					Antifungal test models		Antibacterial test models		
Compd.	R_1	R_2	R_3	Conc. (μg/ml)	*C. albicans* ATCC 14503	*A. fumigatus* ATCC 16424	*S. aureus* 209P	E. coli ATCC 25922	Remark
3a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
3f	H	Cl	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
4a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
4e	Cl	H	Cl	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
5a	H	H	H	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
5b	H	H	Br	100	–	–	–	–	inactive
				1000	–	–	–	–	inactive
Amphotericin B (20 μg/ml)					22	24	18	–	–

Table 3

Antiviral activity results with test concentration 50 μg/mL.

Compd.	R_1	R_2	R_3	% CPE inhibition
3a	H	H	H	–
3f	H	Cl	H	–
4a	H	H	H	–
4e	Cl	H	Cl	–
5a	H	H	H	–
5b	H	H	Br	–
Scoring	**−0–25%**			**++26–50%**
	+++51–75%			**++++76–100%**

complete inactivation of the virus. Partial inhibition was considered to be a negative result. All the screened compounds were found inactive as shown in Table 3.

EXPERIMENTAL

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H-NMR spectra were recorded on Varian 300 MHz spectrometer and Bruker Avance II 400 MHz spectrometer in DMSO or $CDCl_3$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were recorded on a Q-T micromass 5630 mass spectrometer.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (3a–f). Equimolar amount of compound **1** (0.02 mol) and **2** (0.02 mol) were dissolved in 25 mL of alcohol in conical flask. To this reaction mixture 40% KOH (10 mL) was added. The reaction mixture was stirred at room temperature for 48 hr. The contents were then poured into crushed ice and neutralized with acetic acid. The yellow solid thus obtained was filtered and crystallized from alcohol to afford compounds **3**. The compounds synthesized by above procedure are listed in Table 4.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(2-hydroxyphenyl)-prop-2-en-1-one (3a). IR (KBr): 3305, 1633, 1589 and 1501, 1115 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.75–8.22 (m, 12H, aromatic, olefinic, and —$OCHF_2$), 8.40 (d, 1H, J = 15.00 Hz, β to carbonyl), 12.61 (s, 1H, —OH); Mass: M^+ 380.

1-(5-Bromo-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3b). IR (KBr): 3308, 1635, 1598 and 1515, 1125 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.81–8.31 (m, 11H, aromatic, olefinic, and —$OCHF_2$), 8.43 (d, 1H, J = 15.10 Hz, β to carbonyl), 12.72 (s, 1H, —OH); Mass: M^+ 459.

3-(4-(Difluoromethoxy)dibenzofuran-1-yl)-1-(5-fluoro-2-hydroxyphenyl)prop-2-en-1-one (3c). IR (KBr): 3313, 1638, 1610 and 1519, 1177, 1130 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.87–7.91 (m, 7H, aromatic, olefinic, and —$OCHF_2$), 8.13–8.20 (m, 3H, aromatic), 8.40–8.44 (m, 1H, aromatic) 8.55 (d, 1H, J = 15.30 Hz, β to carbonyl), 12.87 (s, 1H, —OH); Mass: M^+ 398.

1-(5-Chloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3d). IR (KBr): 3311, 1636, 1601 and 1510, 1125, 1066 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.72–7.75 (m, 7H, aromatic, olefinic, and —$OCHF_2$), 7.98–8.42 (m, 4H, aromatic) 8.48 (d, 1H, J = 15.17 Hz, β to carbonyl), 12.77 (s, 1H, —OH); Mass: M^+ 414 with isotopic peaks.

1-(3,5-Dichloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl) prop-2-en-1-one (3e). IR (KBr): 3320, 1642, 1125, 1076 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.77–7.87 (m, 6H, aromatic, olefinic, and —$OCHF_2$), 7.98–8.42 (m, 3H, aromatic) 8.48–8.50 (m, 2H, aromatic, and β to carbonyl), 12.83 (s, 1H, —OH); Mass: M^+ 449 with isotopic peaks.

1-(4-Chloro-2-hydroxyphenyl)-3-(4-(difluoromethoxy)dibenzofuran-1-yl)prop-2-en-1-one (3f). IR (KBr): 3305, 1635, 1599 and 1496, 1125, 1063 cm^{-1}; ^{1}H-NMR (DMSO): δ 6.73–7.92 (m, 8H, aromatic, olefinic, and —$OCHF_2$), 8.21–8.42 (m, 4H, aromatic, and β to carbonyl), 12.97 (s, 1H, —OH); Mass: M^+ 414 with isotopic peaks.

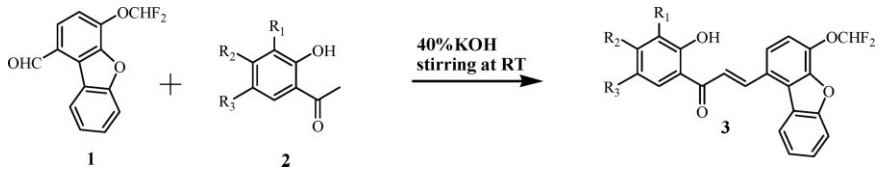
3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4*H*-chromon-4-one (4a–f). Compound **3** (0.001 mole) was dissolved in 15 mL DMSO. To this reaction mixture excess of $CuCl_2$ (2 gm) was added. The reaction mixture was heated under mild reflux for 3 hr and left overnight. Then 100 mL ice

Table 4

Physical and analytical data of synthesized compounds.

Compound	R_1	R_2	R_3	mp (°C)	Yield (%)	Elemental analysis Calcd. (Found) C	H
3a	H	H	H	157	66	69.47 (69.45)	3.71 (3.73)
3b	H	H	Br	188	67	57.54 (57.53)	2.85 (2.86)
3c	H	H	F	182	65	66.34 (66.33)	3.29 (3.31)
3d	H	H	Cl	201	67	63.70 (63.68)	3.16 (3.16)
3e	Cl	H	Cl	191	61	58.82 (58.79)	2.69 (2.71)
3f	H	Cl	H	174	68	63.70 (63.68)	3.16 (3.19)
4a	H	H	H	184	49	64.02 (64.00)	2.69 (2.71)
4b	H	H	Br	200	52	53.74 (53.73)	2.05 (2.08)
4c	H	H	F	193	51	61.34 (61.32)	2.34 (2.32)
4d	H	H	Cl	216	55	59.08 (59.05)	2.25 (2.27)
4e	Cl	H	Cl	205	50	54.86 (54.85)	1.88 (1.90)
4f	H	Cl	H	215	55	54.86 (54.85)	1.88 (1.90)
5a	H	H	H	205	51	68.98 (68.96)	3.93 (3.94)
5b	H	H	Br	217	53	59.37 (59.35)	3.20 (3.21)
5c	H	H	F	193	51	66.53 (66.51)	3.59 (3.60)
5d	H	H	Cl	185	55	64.43 (64.40)	3.48 (3.50)
5e	Cl	H	Cl	213	50	60.44 (60.43)	3.08 (3.10)
5f	H	Cl	H	215	51	64.43 (64.40)	3.48 (3.50)

Scheme 1



1 2 3

cold water was added in it. The solid thus obtained was filtered and washed with dil. HCl and again with water. The product was crystallized from acetic acid to afford compounds **4.** The compounds synthesized by above procedure are listed in Table 4.

3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4H-chromon-4-one (4a). IR (KBr): 1650, 1128, 1072 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.80 (t, 1H, J = 72.94 Hz, —$OCHF_2$), 7.15–8.13 (m, 10H, aromatic); Mass: M^+ 491 with isotopic peaks.

6-Bromo-3-chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4H-chromon-4-one (4b). IR (KBr): 1647, 1135, 1065 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.83 (t, 1H, J = 72.95 Hz, —$OCHF_2$) 7.25–7.77 (m, 8H, aromatic), 8.22 (d, 1H, aromatic); Mass: M^+ 491 with isotopic peaks.

3-Chloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-6-fluoro-4H-chromon-4-one (4c). IR (KBr): 1658, 1169, 1132, 1078 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.87 (t, 1H, J = 72.95 Hz, —$OCHF_2$) 7.35–7.92 (m, 8H, aromatic), 8.32 (m, 1H, aromatic); Mass: M^+ 430 with isotopic peaks.

3,6-Dichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4H-chromon-4-one (4d). IR (KBr): 1652, 1135, 1075 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.85 (t, 1H, J = 72.94 Hz, —$OCHF_2$), 7.25–7.74 (m, 8H, aromatic), 8.22(d, 1H, aromatic); Mass: M^+ 447 with isotopic peaks.

3,6,8-Trichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4H-chromon-4-one (4e). IR (KBr): 1662, 1134, 1107, 1072, 1052, 1015 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.97 (t, 1H, J = 72.96 Hz, —$OCHF_2$) 7.26–7.70 (m, 6H, aromatic), 7.81 (d, 1H, J = 2.48 Hz, aromatic), 8.26 (d, 1H, J = 2.48 Hz, aromatic); Mass: M^+ 481 with isotopic peaks.

3,7-Dichloro-2-(4-(difluoromethoxy)dibenzofuran-1-yl)-4H-chromon-4-one (4f). IR (KBr): 1655, 1125, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.88 (t, 1H, J = 72.93Hz, —$OCHF_2$), 7.23–7.80 (m, 9H, aromatic), Mass: M^+ 447 with isotopic peaks.

2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol (5a–f). Compound **3** (0.001 mol) and 2-aminothiophenol (0.001 mol) were dissolved in 15 mL ethanol in 100 mL RBF. The reaction mixture was heated under reflux for 4 hr. Then 5 mL glacial acetic acid was added and heating was continued for further 4 hr. After completion of reaction, the contents were cooled to room temperature and poured into crushed ice. The solid thus obtained was separated by filtration and crystallized with alcohol to afford compounds **5.** The compounds synthesized by above procedure are listed in Table 4.

2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol. (5a). IR (KBr): 3397, 1598 and 1499, 1123 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.21 (dd, 1H,) 3.47 (dd, 1H), 5.97 (dd, 1H), 6.81 (t, 1H, J = 72.97Hz, —$OCHF_2$), 6.99–7.90 (m, 14H, aromatic), 15.77 (s, 1H, —OH); Mass: M^+ 487.

4-Bromo-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol (5b). IR (KBr): 3395, 1595 and 1518, 1116 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.23 (dd, 1H), 3.49 (dd, 1H), 5.95 (dd, 1H), 6.84 (t, 1H, J = 72.95Hz, —$OCHF_2$), 7.02–7.85 (m, 13H, aromatic), 15.79(s, 1H, —OH); Mass: M^+ 566.

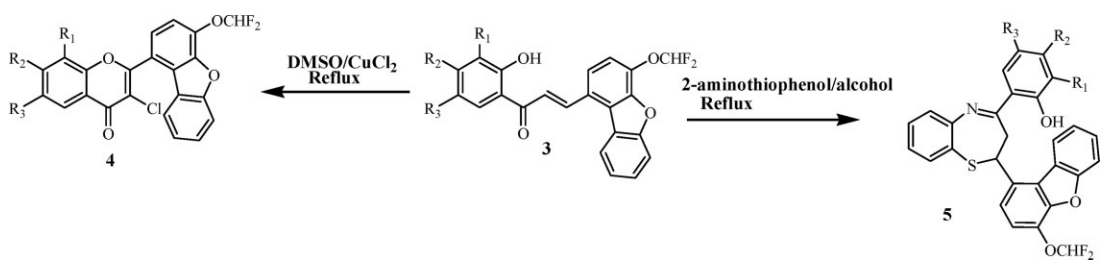
2-(2-(4-(Difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)-4-fluorophenol (5c). IR (KBr): 3398, 1170, 1145 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.24 (dd, 1H), 3.50 (dd, 1H), 5.95 (dd, 1H), 6.85 (t, 1H, J = 72.96Hz, —$OCHF_2$), 7.32–8.20 (m, 13H, aromatic), 15.82 (s, 1H, —OH); Mass: M^+ 505.

4-Chloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol. (5d). IR (KBr): 3390, 1590 and 1489, 1131, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.23 (dd, 1H), 3.58 (dd, 1H), 6.00 (dd, 1H), 6.82 (t, 1H, J = 72.95 Hz, —$OCHF_2$), 7.15–7.98 (m, 13H, aromatic), 15.77(s, 1H, —OH); Mass: M^+ 521 with isotopic peaks.

2,4-Dichloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b] [1,4]thiazepin-4-yl)phenol (5e). IR (KBr): 3409, 1125, 1072 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.29(dd, 1H), 3.47 (dd, 1H), 6.00 (dd, 1H), 6.85 (t, 1H, J = 72.96 Hz, —$OCHF_2$), 7.11–7.95 (m, 10H, aromatic),8.02 (d, 1H, aromatic), 8.23 (d, 1H, aromatic), 15.74 (s, 1H, —OH); Mass: M^+ 556 with isotopic peaks.

3-Chloro-2-(2-(4-(difluoromethoxy)dibenzofuran-1-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol. (5f). IR (KBr): 3395, 1592 and 1501, 1131 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.25 (dd, 1H), 3.49 (dd, 1H), 5.99 (dd, 1H), 6.82 (t, 1H, J = 72.95Hz, —$OCHF_2$), 7.21–8.06 (m, 13H, aromatic), 15.80 (s, 1H, —OH); Mass: M^+ 521 with isotopic peaks.

Scheme 2



4 3 5

Acknowledgments. Authors are highly thankful to Dr. Saji George, Nicholas Piramal Research Centre, Mumbai for providing the biological activities. Authors are also thankful to the Principal Dr. T. N. Gholap for providing the necessary facilities.

REFERENCES AND NOTES

[1] Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Pihuliac, E.; Maleczka, C. W.; Pernet, A. G. J Med Chem 1985, 28, 1558.

[2] Park, K. B.; Kitteringham, N. R.; O'Neill, P. M. Annu Rev Pharmacol Toxicol 2001, 41, 443.

[3] Shelke, S. N.; Dalvi, N. R.; Kale, S. B.; More, M. S.; Gill, C. H.; Karale, B. K. Indian J Chem 2007, 46B, 1174.

[4] Patel, V. M.; Desai, K. R. Indian J Chem 2005, 44B, 1084.

[5] Hammam, A. E. G.; El-Salam, O. I. A.; Mohammed, A. M.; Hafez, N. A. Indian J Chem 2005, 44B, 1887.

[6] Kollonitsh, J.; Patchet, A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D. Nature 1978, 274, 906.

[7] Qu, J.; Xie, C.; Guo, H.; Yu, W.; Lou, H. Phytochemistry 2007, 68, 1767.

[8] Purohit, N. V.; Sanghavi, T. Indian J Hetercycl Chem 2005, 14, 235.

[9] Balasubramanian, G.; Gharat, L. A.; Lakdawala, A. D.; Anupindi, R. R. PCT Int Appl W.O. 2004037805 A1 254, 6 May (2004). Chem Abstr 140, 391192 (2004).

[10] Joshi, N. S.; Shaikh, A. A.; Deshpande, A. P.; Karale, B. K.; Bhirud, S. B.; Gill, C. H. Indian J Chem 2005, 44B, 422.

[11] Karale, B. K.; Chavan, V. P.; Mane, A. S.; Hangarge, R. V.; Gill, C. H.; Shingare, M. S. Korean J Med Chem 2000, 10, 84.

[12] Sahasrabuddhe, A. S.; Ghiya, B. J. Indian J Chem 1990, 29B, 61.

[13] Chen, M.; Christensen, S. B.; Blom, J.; Lemmich, E. Nadelmann, L.; Fich, K.; Theander, T.G.; Kharazmi, A. Antimicrob Agents 1993, 37, 2550.

[14] Chen, M.; Theander, T. G.; Christensen, S. B.; Kharazmi, A. Antimicrob Agents Chemother 1994, 38, 1470.

[15] Wiley, P. F. J Am Chem Soc 1952, 74, 4329.

[16] (a) Jongerbreur, G. Arch Int Pharmacodyn 1952, 90, 384; (b) Schmtz, J.; Hirt, R.; Eichenberger, F. E.; Lavener, H. Helv Chim Acta 1953, 36, 620. (c) Wander, A. G. Brit. Pat., 27, 728, 768. (d) Koo, J. J Org Chem 1961, 26, 1635.

[17] Pawar, S. B.; Shelke, S. N.; Sonawane, S. M.; Gill, C. H.; Karale, B. K. Orient J Chem 2007, 23, 215.

[18] Halnor, V. B.; Joshi, N. S.; Karale, B. K.; Gill, C. H. Het Comm 2005, 11, 16.

[19] (a) Neamati, N.; Turpin, J. A.; Orr, A.; Rice, W. G.; Pommier, Y.; Garafalo, A.; Brizzi, A.; Campiani, G.; Fiorini, I.; Nacci, V. J Med Chem 1999, 42, 3334. (b) Garafelo, A.; Balconi, G.; Botta, M.; Corelli, F.; D' Incalci, M.; Fabrizi, G.; Lamba, D.; Nacci, V. Eur J Med Chem 1993, 28, 213. (c) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. J Med Chem 1996, 39, 3539. (d) Toshiyuki, H.; Takiharo, I.; Hisao, J.P. 7272107. Chem Abstr 1972, 77, 140187f.

[20] Singh, K. P.; Srivastava, V.; Singh and Siddiqui, J. Indian J Chem 2005, 44B, 2178.

[21] Inoue, H.; Konda, M.; Hashiyama, T.; Oskuka, H.; Watanbe, A.; Okamura, K.; Takida, M.; Date, T.; Narita, T.; Murata, S.; Odwara, A.; Sasaki, H.; Nagao, T. Chem Pharm Bull 1997, 45, 1008.

[22] Agarkar, S. V.; Gurav, V. M. Indian J Heterocycl Chem 2004, 13, 273.

[23] Bajaj, K.; Srivastava, V. K.; Kumar, A. Indian J Chem 2003, 42B, 1149.