Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 524–529
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

# Efficient microwave enhanced solvent-free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused β-lactam derivatives

Anshu Dandia *, Ruby Singh, Sarita Khaturia

*Department of Chemistry, University of Rajasthan, Jaipur, India*

Received 28 August 2006; received in revised form 30 December 2006; accepted 6 January 2007
Available online 13 January 2007

**Abstract**

A microwave enhanced, facile cycloaddition has been developed for the synthesis of fluorine containing azeto[2,1-d][1,5]benzothiazepine derivatives (**Va–m**) on the surface of potassium carbonate ($K_2CO_3$). Microwave enhanced solvent-free improved synthesis of required 1,5-benzothiazepines is also developed using montmorillonite clay. The synthesized compounds have been screened '*in vitro*' for antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici*. Most of the compounds have shown good activity against these pathogens.

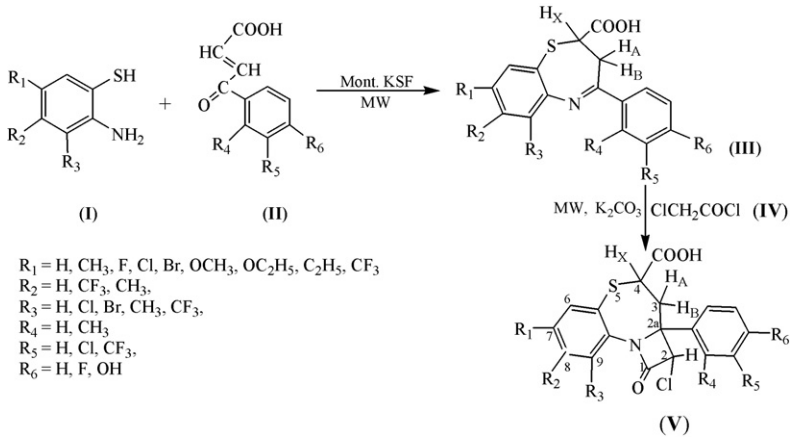

*Keywords:* Azeto[2,1-d][1,5]benzothiazepine; Microwaves; Antifungal activity

## 1. Introduction

Owing to their well known bioactivities, the 1,5-benzothiazepine is especially important nitrogen and sulfur containing heterocyclic compounds in drug research [1]. Thiazesim [2] and diltiazem [3] are well known drugs having the 1,5-benzothiazepine skeletons. While carrying out drug design, it was found that an important number of fluorinated 1,4- and 1,5-benzodiazepines had been introduced as pharmacological and cardiovascular agents, such as *fluorodiazepam*, *triflubazam*, etc. Incorporation of fluorine atoms on 1,5-benzothiazepines or analogous nucleus enhances pharmacological properties by increasing the solubility in lipid materials and fat deposits in the body when compared to their non-fluorinated analogs [4]. The literature survey reveals that Cl, Me, $CF_3$, or a free COOH groups when present on different positions in the 1,5-benzothiazepine nucleus act as potential pharmacophores [5]. Further, since after the discovery of non-classical β-lactams antibiotics, the synthesis of compounds containing the β-lactam moiety has been a subject of intense study by a number of research groups [6]. More recently lactams have also been found to be versatile intermediates of non-protogenic amino acids, peptides, peptide turn mimetics [7], taxoid antitumour agents [8], and other types of heterocyclic compounds of biological interest [9]. Because of the growing resistance of bacteria and fungi against common antibiotics and the need for medicines with a more specific antibacterial and antifungal activity, it seemed necessary to synthesize some novel compounds with a fused β-lactam heterocyclic ring for bioassay of antimicrobial activity. The literature survey reveals that the most of the effective antibiotics possess the representative structure of a β-lactam fused to a five- and six-membered heterocyclic ring containing nitrogen and sulfur atom [10]. However, less attention has been paid on synthesis and bioactive evolution of β-lactam derivatives of benzothiazepine have been published [11]. Conventionally, the synthesis of β-lactam derivatives suffers from various drawbacks including long reactions times, low yield of products, difficult operational conditions and tedious work up. Thus, a simple general and efficient procedure for the synthesis of this important heterocyclic system is required. In recent years, our group has focused on the synthesis of numerous benzothiazepine derivatives due to their potential biological and pharmaceutical importance [12]. Hence, in this connection,

* Corresponding author. Tel.: +91 141 2520301; fax: +91-141-2719122.
*E-mail address:* dranshudandia@yahoo.co.in (A. Dandia).

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.01.003




Scheme 1.

and in view of our interest on the facile, economical and ecofriendly synthesis of biodynamic heterocycles [13] under microwaves. We report herein, for the first time, the synthesis of β-lactam fused benzothiazepines derivatives (**Va–m**) on potassium carbonate surface in few minutes without using any strong base. Potassium carbonate is a mild base, inexpensive and water-soluble which further eliminate the use of organic solvents required for washing the adducts from the solid surface. The reaction was also carried out conventionally in basic medium (triethylamine + dry benzene) and the product was obtained in lower yield (20%) after long reaction time (90 h). The desired starting material, 2,3-dihydro-1,5-benzothizepines were also synthesized by improved solvent-free procedure using montmorillonite KSF under microwaves (Table 1 and Scheme 1).

In conclusion, we have shown in the present study that facile synthesis of fused β-lactam benzothiazepine takes place on potassium carbonate surface under microwave irradiation. Compared to existing methods, main advantage of present procedure is shorter reaction times, solvent-free conditions, convenient work-up and present methodology may contribute to the dream of green technology (Table 2).

## 2. Result and discussion

Structures of all azeto[2,1-d][1,5]benzothiazepines (**Va–m**) have been elucidated by elemental analyses and spectral studies. The IR spectra of azeto[2,1-d][1,5]benzothiazepine showed a characteristic β-lactam carbonyl absorption at 1720–1738 $cm^{-1}$. Theoretically, compound **Va–m** having two chiral centers hence it can exist in two diastereomeric forms but the $^1H$ NMR spectra and chromatographic studies of isolated compounds indicated the formation of only one diastereomer. In $^1H$ NMR spectra of **Va–m** a characteristic singlet of the azetidinone ring proton is recorded at 4.95–5.08 ppm along with other three double doublets of benzothiazepine ring protons at $\delta$: 3.11–3.22 ($H_A$, dd, $J_{A-B}$ = 16.20–16.34 Hz, $J_{A-X}$ = 9.26–9.35 Hz), 3.68–3.77 ($H_B$, dd, $J_{A-B}$ = 16.20–16.34 Hz, $J_{B-X}$ = 8.36–8.42 Hz), 4.11–4.24 ($H_X$, dd, $J_{A-X}$ = 9.26–9.35 Hz, $J_{B-X}$ = 8.36–8.42 Hz).

Formation of the final compound was further confirmed on the basis of $^{13}C$ NMR and mass spectrum. In the $^{13}C$ NMR spectrum of **Va** signals were observed at $\delta$: 180.2, 178.81 (two C=O), 39.7 (C-3), 43.8 (C-4), 52.25 (Cl–CH), 114.5–141.99 (aromatic carbons). In the mass spectrum of **Va** the appearance of molecular ion peaks *m/z* ($M^+$) at 391 and ($M^+$ + 2) at 393 due

Table 1
Physical data of 2-carboxy-2,3-dihydro-1,5-benzothiazepines (**IIIa–m**)

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Time (min) | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| **IIIa** | $CH_3$ | H | H | H | H | F | 4 | 215[a] | 80 |
| **IIIb** | F | H | H | H | H | F | 3 | 201[a] | 82 |
| **IIIc** | Cl | H | H | H | H | F | 4 | 214[a] | 75 |
| **IIId** | Br | H | H | H | H | F | 5 | 227[a] | 81 |
| **IIIe** | $OCH_3$ | H | H | H | H | F | 4 | 185[a] | 70 |
| **IIIf** | $OC_2H_5$ | H | H | $CH_3$ | H | F | 4 | 211 | 73 |
| **IIIg** | $C_2H_5$ | H | H | $CH_3$ | H | F | 3 | 218 | 78 |
| **IIIh** | H | $CF_3$ | H | H | Cl | H | 5 | 222 | 80 |
| **IIIi** | H | H | Br | H | $CF_3$ | H | 4 | 230 | 76 |
| **IIIj** | $CF_3$ | H | H | H | H | OH | 6 | 225 | 75 |
| **IIIk** | H | H | Cl | H | Cl | F | 5 | 240 | 78 |
| **IIIl** | H | H | $CF_3$ | $CH_3$ | H | F | 3 | 252 | 82 |
| **IIIm** | H | $CH_3$ | $CH_3$ | H | $CF_3$ | H | 6 | 235 | 74 |

[a] Ref. [14].

Table 2
Physical data of azeto-[2,1-d][1,5]benzothiazepines (**Va–m**)

| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Time (min) | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Va** | $CH_3$ | H | H | H | H | F | 4 | 270 | 78 |
| **Vb** | F | H | H | H | H | F | 5 | 258 | 80 |
| **Vc** | Cl | H | H | H | H | F | 5 | 237 | 82 |
| **Vd** | Br | H | H | H | H | F | 3 | 263 | 85 |
| **Ve** | $OCH_3$ | H | H | H | H | F | 5 | 275 | 83 |
| **Vf** | $OC_2H_5$ | H | H | $CH_3$ | H | F | 4 | 269 | 85 |
| **Vg** | $C_2H_5$ | H | H | $CH_3$ | H | F | 4 | 248 | 76 |
| **Vh** | H | $CF_3$ | H | H | Cl | H | 6 | 260 | 75 |
| **Vi** | H | H | Br | H | $CF_3$ | H | 5 | 272 | 80 |
| **Vj** | $CF_3$ | H | H | H | H | OH | 4 | 280 | 84 |
| **Vk** | H | H | Cl | H | Cl | F | 3 | 250 | 75 |
| **Vl** | H | H | $CF_3$ | $CH_3$ | H | F | 6 | 230 | 85 |
| **Vm** | H | $CH_3$ | $CH_3$ | H | $CF_3$ | H | 5 | 268 | 82 |

to chlorine isotopic peak showed the formation of fused ring system azeto-1,5-benzothiazepine.

The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root rot of okra, *Fusarium oxysporum*, causing wilt of mustard and *Collectotrichum capsici* causing leaf spot and fruit rot of chilli and most of compounds shows good activity against these pathogens. In the pot trial experiment, it was found that compounds having alkoxy group (OR) and trifluoromethyl $CF_3$ showed maximum germination (76–80%) indicating that, it is most effective in controlling the growth of pathogen. ''Baynate'' and ''Thiram'' recommended as standard fungicide as seed dressers to control this disease are also having –N–C–S linkage, similar to the synthesized compounds, which is responsible for their antifungal activity.

## 3. Evaluation of antifungal activity: it was done by two methods

### 3.1. Poison plate technique [15]

The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations. Potato-dextrose-agar medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into petri-plates in three replication. A culture of test fungus was grown on PDA for 6–7 days. Small disc (4 mm) of the fungus culture was cut with a sterile corkborer and transferred ascetically, upside-down in centre of petridishes containing the medium and fungicides. Plates were incubated at 25 ± 1 °C for 6 days. Colony diameters were measured and data was statistically analysed (Table 3).

### 3.2. Pot trial method [16]

White seeded sorghum grains were soaked in water for about 12 h, 160 g of the soaked kernels were placed in 500 ml flasks and 20 ml of water was added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask and flasks were kept for 10 days at 25–27 °C. One hundred seeds of okra were taken for one treatment of each compound. Inoculum was added at 2 g/kg of soil, 3-day prior to sowing. Sowing was done after 3 days and germination data were recorded after 7, 15, 25 days of sowing. Suitable checks were maintained and the data was statistically analyzed (Table 4).

Table 4
Evaluation of azeto[2,1-d][1,5]benzothiazepines (**Va–m**) as seed dressers against *Rhizoctonia solani* causing root rot of okra (in Pot trial)

| Compound | Percent germination | Plant stand 25 DAS |
|---|---|---|
| **Va** | 68.00 | 46.00 |
| **Vb** | 52.00 | 46.00 |
| **Vc** | 55.00 | 47.00 |
| **Vd** | 60.00 | 51.00 |
| **Ve** | 76.00 | 68.00 |
| **Vf** | 72.00 | 61.00 |
| **Vg** | 80.00 | 70.00 |
| **Vh** | 74.00 | 66.00 |
| **Vi** | 78.00 | 65.00 |
| **Vj** | 66.00 | 56.00 |
| **Vk** | 58.00 | 62.00 |
| **Vl** | 64.00 | 52.00 |
| **Vm** | 69.00 | 66.00 |
| Baynate (0.2%) | 98.00 | 64.00 |
| Thiram (0.3%) | 79.00 | 68.00 |
| Check with inoculum | 10.00 | 6.00 |
| Check without inoculum | 90.00 | 81.00 |

DAS: days after sowing.

## 4. Experimental

Melting points were determined in open glass capillary and were uncorrected. IR spectra were recorded on a Perkin-Elmer (model-577) in KBr Pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and

Table 3
Effect of concentrations of different chemicals on the mean radial growth (cm) of different fungus in vitro

| Compound | *Rhizoctonia solani* | | *Fusarium oxysporum* | | *Collectotrichum capsici* | |
|---|---|---|---|---|---|---|
| | 1000 ppm | 500 ppm | 1000 ppm | 500 ppm | 1000 ppm | 500 ppm |
| **Va** | 1.96[b] | 3.95 | 1.85[a] | 2.10[a] | 2.22[b] | 3.20 |
| **Vb** | 2.52 | 3.68 | 3.10 | 5.48 | 1.68[a] | 2.88[b] |
| **Vc** | 1.88[b] | 3.92 | 2.66 | 3.67 | 2.39 | 3.79 |
| **Vd** | 2.48 | 4.62 | 3.69 | 4.75 | 3.28 | 4.66 |
| **Ve** | 1.45[a] | 1.95[a] | 2.10[b] | 3.61 | 1.82[b] | 1.96[a] |
| **Vf** | 1.92[b] | 2.82 | 1.98[b] | 2.85[b] | 3.10 | 4.68 |
| **Vg** | 1.62[b] | 2.56[b] | 1.92 | 2.95[b] | 2.10 | 4.02 |
| **Vh** | 1.98 | 3.66 | 2.86 | 2.98 | 3.59 | 2.96 |
| **Vi** | 1.63 | 2.85[b] | 3.12 | 2.12 | 2.76[b] | 3.15 |
| **Vj** | 1.89[b] | 3.30 | 2.78 | 3.27 | 3.68 | 3.22 |
| **Vk** | 1.97[b] | 3.16 | 3.14 | 4.22 | 3.22 | 2.92 |
| **Vl** | 2.22 | 2.88[b] | 2.98[b] | 3.18 | 2.67 | 3.58 |
| **Vm** | 2.16 | 3.28 | 3.33 | 3.58 | 3.26 | 3.94 |
| **Check** | 9.00 | 9.00 | 8.17 | 8.17 | 7.33 | 7.33 |
| **CD%** | 0.74 | 1.22 | 0.77 | 1.14 | 1.08 | 1.25 |

[a] Minimum value.
[b] At par with minimum values.

75.47, respectively. TMS was used as internal reference. Mass spectrum of representative compound was recorded on Kratos 50 mass spectrometer at 70 eV. Purity of all compounds was checked by TLC using silica Gel 'G' coated glass plates and benzene:ethyl acetate (8:2) as eluent. The microwave induced reactions were carried out in BMO-700T modified multimode oven fitted with a condenser and a magnetic stirrer. 5-Substituted-2-aminobenzenethiols [17] and 3-(substituted benzoyl)-2-propionic acid [18] was prepared by literature methods.

### 4.1. Synthesis of 2-carboxy-2,3-dihydro-1,5-benzothiazepines (*IIIa–m*)

An equimolar mixture of substituted aminobenzenethiol (**I**) (0.01 mol) and 3-(substituted benzoyl)-2-propionic acid (**II**) was introduced in a beaker and dissolved in acetone. Montmorillonite KSF (4 g) was then added and swirled for a while followed by removal of the solvent under gentle vacuum. The dry flowing powder thus obtained was irradiated under microwave oven. After completion of the reaction (monitored by TLC) the recyclable inorganic solid support was separated by filtration after eluting the product with methanol. The solvent was evaporated to give crystalline products (**IIIa–m**). Synthesized benzothiazepines (**IIIa–e**) are known and their authenticity was ensured on the basis of spectroscopic, analytical data and on comparison with authentic samples prepared conventionally [14]. While newly synthesized compounds **IIIf–m** are characterized on the basis of spectral and analytical data.

### 4.2. Synthesis of azeto[2,1-d][1,5]benzothiazepine (*Va–m*)

Synthesis of **Va** has been carried out by using two different methods: (1) conventional synthesis and (2) microwave assisted procedure.

#### 4.2.1. Conventional synthesis

2-Carboxy-2,3-dihydro-1,5-benzothiazepine (**III**) (2 mmol) and chloroacetyl chloride (**IV**) (2.5 mmol) were dissolved in anhydrous benzene and dried triethylamine (2 mmol) in anhydrous benzene was added drop wise into the solution over a period of 20 min. After addition of chloroacetyl chloride the mixture was stirred for 3 days. The precipitated triethylamine hydrochloride that had formed was removed by filtration, and the benzene solution was washed with water, saturated aqueous $NaHCO_3$, brine, and then dried over $Na_2SO_4$. The residue was passed through a silica gel column with a mixture of ethyl acetate and petroleum ether (1:15, v/v) as an eluent to give pure product. Yield = 20%; time = 90 h.

#### 4.2.2. Microwave-assisted synthesis

The substituted-1,5-benzothiazepine (**III**) (2 mmol) was adsorbed activated potassium carbonate (4 mmol) with the help of methanol. The solvent was removed under reduce pressure using a rotatory evaporator. To this, chloroacetyl chloride (**IV**) (2.5 mmol) was added and mixed thoroughly and resulting reaction mixture was taken in a conical flask and irradiated in the microwave oven. After completion of the reaction (monitored by TLC) the reaction mixture was cooled (r.t.), added to ice water and the supernatant aqueous layer decanted and filtered to yield desired product. Yield = 78%; time = 4 min.

All other azeto-[2,1-d][1,5]benzothiazepine (**Vb–m**) were similarly prepared under solvent-free conditions using $K_2CO_3$ under microwaves.

*4.2.2.1. Compound **IIIf**.* $^1$H NMR ($CDCl_3$), $\delta$: 1.21 (t, 3H, $OCH_2$–*$CH_3$*), 2.31 (s, 3H, $CH_3$), 3.12 (dd, 1H, $H_A$, $J_{A–B}$ = 16.27 Hz, $J_{A–X}$ = 9.21 Hz), 3.71 (dd, $H_B$, $J_{A–B}$ = 16.27 Hz, $J_{B–X}$ = 8.23 Hz), 3.34 (q, 2H, *$OCH_2$*–$CH_3$), 6.62–7.81 (m, 6H, Ar-H), 8.17 (bs, 1H, COOH). IR ($cm^{-1}$): 1688 (C=O), 3278 (bs-OH), 1142 (C–F). Anal. Calcd. for $C_{19}H_{18}FNO_3S$: C, 63.49; N, 3.90. Found: C, 63.61; N, 3.92.

*4.2.2.2. Compound **IIIg**.* $^1$H NMR ($CDCl_3$), $\delta$: 1.19 (t, 3H, –$CH_2$–*$CH_3$*), 2.41 (s, 3H, $CH_3$), 2.69 (q, 2H –*$CH_2$*–$CH_3$), 3.11 (dd, 1H, $H_A$, $J_{A–B}$ = 16.23 Hz, $J_{A–X}$ = 9.23 Hz), 3.77 (dd, $H_B$, $J_{A–B}$ = 16.23 Hz, $J_{B–X}$ = 8.22 Hz), 4.12 (dd, $H_X$, $J_{A–X}$ = 9.23 Hz, $J_{B–X}$ = 8.22 Hz), 6.63–7.82 (m, 6H, Ar-H), 8.19 (bs, 1H, COOH). IR ($cm^{-1}$): 1685 (C=O), 3275 (bs-OH), 1145 (C–F). Anal. Calcd. for $C_{19}H_{18}FNO_2S$: C, 66.45; N, 4.08. Found: C, 66.57; N, 4.06.

*4.2.2.3. Compound **IIIh**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.19 (dd, 1H, $H_A$, $J_{A–B}$ = 16.28 Hz, $J_{A–X}$ = 9.23 Hz), 3.72 (dd, $H_B$, $J_{A–B}$ = 16.28 Hz, $J_{B–X}$ = 8.20 Hz), 4.14 (dd, $H_X$, $J_{A–X}$ = 9.21 Hz, $J_{B–X}$ = 8.20 Hz), 6.63–7.82 (m, 7H, Ar-H), 8.18 (bs, 1H, COOH). IR ($cm^{-1}$): 1690 (C=O), 3277 (bs-OH), 1140 (C–F), 740 (C–Cl). Anal. Calcd. for $C_{17}H_{11}ClF_3NO_2S$: C, 52.93; N, 3.63. Found: C, 52.76; N, 3.62.

*4.2.2.4. Compound **IIIi**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.18 (dd, 1H, $H_A$, $J_{A–B}$ = 16.29 Hz, $J_{A–X}$ = 9.25 Hz), 3.71 (dd, $H_B$, $J_{A–B}$ = 16.29 Hz, $J_{B–X}$ = 8.38 Hz), 4.18 (dd, $H_X$, $J_{A–X}$ = 9.25 Hz, $J_{B–X}$ = 8.38 Hz), 6.69–7.81 (m, 7H, Ar-H), 8.19 (bs, 1H, COOH). IR ($cm^{-1}$): 1689 (C=O), 3275 (bs-OH), 1145 (C–F). Anal. Calcd. for $C_{17}H_{11}BrF_3NO_2S$: C, 47.76; N, 3.26. Found: C, 47.61; N, 3.27.

*4.2.2.5. Compound **IIIj**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.22 (dd, 1H, $H_A$, $J_{A–B}$ = 16.33 Hz, $J_{A–X}$ = 9.28 Hz), 3.78 (dd, $H_B$, $J_{A–B}$ = 16.33 Hz, $J_{B–X}$ = 8.37 Hz), 4.12 (dd, $H_X$, $J_{A–X}$ = 9.28 Hz, $J_{B–X}$ = 8.37 Hz), 6.68–7.82 (m, 7H, Ar-H), 8.21 (bs, 1H, COOH). IR ($cm^{-1}$): 1690 (C=O), 3278 (bs-OH), 1130 (C–F). Anal. Calcd. for $C_{17}H_{12}F_3NO_3S$: C, 55.58; N, 3.81. Found: C, 55.74; N, 3.80.

*4.2.2.6. Compound **IIIk**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.20 (dd, 1H, $H_A$, $J_{A–B}$ = 16.32 Hz, $J_{A–X}$ = 9.27 Hz), 3.72 (dd, $H_B$, $J_{A–B}$ = 16.32 Hz, $J_{B–X}$ = 8.36 Hz), 4.16 (dd, $H_X$, $J_{A–X}$ = 9.27 Hz, $J_{B–X}$ = 8.36 Hz), 6.67–7.80 (m, 7H, Ar-H), 8.20 (bs, 1H, COOH). IR ($cm^{-1}$): 1688 (C=O), 3277 (bs-OH), 1134 (C–F). Anal. Calcd. for $C_{16}H_{10}Cl_2FNO_2S$: C, 51.91; N, 3.78. Found: C, 51.74; N, 3.77.

*4.2.2.7. Compound **IIIl**.* $^1$H NMR ($CDCl_3$), $\delta$: 2.31 (s, 3H, $CH_3$), 3.21 (dd, 1H, $H_A$, $J_{A-B}$ = 16.34 Hz, $J_{A-X}$ = 9.28 Hz), 3.77 (dd, $H_B$, $J_{A-B}$ = 16.34 Hz, $J_{B-X}$ = 8.34 Hz), 4.18 (dd, $H_X$, $J_{A-X}$ = 9.28 Hz, $J_{B-X}$ = 8.34 Hz), 6.71–7.79 (m, 6H, Ar-H), 8.23 (bs, 1H, COOH). IR ($cm^{-1}$): 1680 (C=O), 3277 (bs-OH), 1128 (C–F). Anal. Calcd. for $C_{18}H_{13}F_4NO_2S$: C, 56.39; N, 3.65. Found: C, 56.56; N, 3.64.

*4.2.2.8. Compound **IIIm**.* $^1$H NMR ($CDCl_3$), $\delta$: 2.37 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 3.22 (dd, 1H, $H_A$, $J_{A-B}$ = 16.32 Hz, $J_{A-X}$ = 9.28 Hz), 3.78 (dd, $H_B$, $J_{A-B}$ = 16.32 Hz, $J_{B-X}$ = 8.32 Hz), 4.12 (dd, $H_X$, $J_{A-X}$ = 9.28 Hz, $J_{B-X}$ = 8.32 Hz), 6.71–7.79 (m, 6H, Ar-H), 8.26 (bs, 1H, COOH). IR ($cm^{-1}$): 1689 (C=O), 3278 (bs-OH), 1130 (C–F). Anal. Calcd. for $C_{19}H_{16}F_3NO_2S$: C, 60.15; N, 3.69. Found: C, 60.32; N, 3.70.

*4.2.2.9. Compound **Va**.* $^1$H NMR ($CDCl_3$), $\delta$: 2.31 (s, 3H, $CH_3$), 3.14 (dd, 1H, $H_A$, $J_{A-B}$ = 16.31 Hz, $J_{A-X}$ = 9.26 Hz), 3.76 (dd, $H_B$, $J_{A-B}$ = 16.31 Hz, $J_{B-X}$ = 8.41 Hz), 4.13 (dd, $H_X$, $J_{A-X}$ = 9.26 Hz, $J_{B-X}$ = 8.41 Hz), 4.98 (s, 1H, Cl–CH), 6.67–7.85 (m, 7H, Ar-H), 8.16 (bs, 1H, COOH). IR ($cm^{-1}$): 1680, 1738 (two C=O), 3270 (bs, OH), 1140 (C–F), 740 (C–Cl). Anal. Calcd. for $C_{19}H_{15}ClFNO_3S$: C, 58.24; N, 3.57. Found: C, 58.09; N, 3.58.

*4.2.2.10. Compound **Vb**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.18 (dd, 1H, $H_A$, $J_{A-B}$ = 16.32 Hz, $J_{A-X}$ = 9.27 Hz), 3.72 (dd, $H_B$, $J_{A-B}$ = 16.32 Hz, $J_{B-X}$ = 8.40 Hz), 4.12 (dd, $H_X$, $J_{A-X}$ = 9.27 Hz, $J_{B-X}$ = 8.40 Hz), 4.97 (s, 1H, Cl–CH), 6.68–7.84 (m, 7H, Ar-H), 8.15 (bs, 1H, COOH). IR ($cm^{-1}$): 1695, 1726 (two C=O), 3270 (bs, OH), 1146 (C–F), 735 (C–Cl). Anal. Calcd. for $C_{18}H_{12}ClF_2NO_3S$: C, 54.62; N, 3.54. Found: C, 54.80; N, 3.55.

*4.2.2.11. Compound **Vc**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.15 (dd, 1H, $H_A$, $J_{A-B}$ = 16.28 Hz, $J_{A-X}$ = 9.30 Hz), 3.75 (dd, $H_B$, $J_{A-B}$ = 16.28 Hz, $J_{B-X}$ = 8.42 Hz), 4.16 (dd, $H_X$, $J_{A-X}$ = 9.30 Hz, $J_{B-X}$ = 8.42 Hz), 5.01 (s, 1H, Cl–CH), 6.68–7.85 (m, 7H, Ar-H), 8.17 (bs, 1H, COOH). IR ($cm^{-1}$): 1690, 1725 (two C=O), 3275 (bs, OH), 1142 (C–F), 750 (C–Cl). Anal. Calcd. for $C_{18}H_{12}Cl_2NO_3S$: C, 52.44; N, 3.40. Found: C, 52.60; N, 3.42.

*4.2.2.12. Compound **Vd**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.16 (dd, 1H, $H_A$, $J_{A-B}$ = 16.30 Hz, $J_{A-X}$ = 9.33 Hz), 3.77 (dd, $H_B$, $J_{A-B}$ = 16.30 Hz, $J_{B-X}$ = 8.38 Hz), 4.19 (dd, $H_X$, $J_{A-X}$ = 9.33 Hz, $J_{B-X}$ = 8.38 Hz), 4.99 (s, 1H, Cl–CH), 6.65–7.80 (m, 7H, Ar-H), 8.15 (bs, 1H, COOH). IR ($cm^{-1}$): 1698, 1729 (two C=O), 3265 (bs, OH), 1148 (C–F), 735 (C–Cl). Anal. Calcd. for $C_{18}H_{12}BrClFNO_3S$: C, 47.34; N, 3.07. Found: C, 47.18; N, 3.08.

*4.2.2.13. Compound **Ve**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.19 (dd, 1H, $H_A$, $J_{A-B}$ = 16.33 Hz, $J_{A-X}$ = 9.35 Hz), 3.71 (dd, $H_B$, $J_{A-B}$ = 16.33 Hz, $J_{B-X}$ = 8.37 Hz), 3.73 (s, 3H, $OCH_3$), 4.20 (dd, $H_X$, $J_{A-X}$ = 9.35 Hz, $J_{B-X}$ = 8.37 Hz), 5.03 (s, 1H, Cl–CH), 6.67–7.83 (m, 7H, Ar-H), 8.22 (bs, 1H, COOH). IR ($cm^{-1}$): 1690, 1730 (two C=O), 3270 (bs-OH), 1140 (C–F), 740 (C–Cl). Anal. Calcd. for $C_{19}H_{15}ClFNO_4S$: C, 55.95; N, 3.43. Found: C, 55.76; N, 3.44.

*4.2.2.14. Compound **Vf**.* $^1$H NMR ($CDCl_3$), $\delta$: 1.18 (t, 3H, –O–$CH_2$–$CH_3$), 2.48 (s, 3H, $CH_3$), 3.11 (dd, 1H, $H_A$, $J_{A-B}$ = 16.31 Hz, $J_{A-X}$ = 9.31 Hz), 3.77 (dd, $H_B$, $J_{A-B}$ = 16.31 Hz, $J_{B-X}$ = 8.41 Hz), 4.01 (q, 2H, –O–$CH_2$–$CH_3$), 4.12 (dd, $H_X$, $J_{A-X}$ = 9.31 Hz, $J_{B-X}$ = 8.41 Hz), 4.98 (s, 1H, Cl–CH), 6.63–7.82 (m, 6H, Ar-H), 8.19 (bs, 1H, COOH). IR ($cm^{-1}$): 1685, 1728 (two C=O), 3275 (bs-OH), 1145 (C–F), 745 (C–Cl). Anal. Calcd. for $C_{21}H_{19}ClFNO_4S$: C, 57.86; N, 3.21. Found: C, 57.67; N, 3.22.

*4.2.2.15. Compound **Vg**.* $^1$H NMR ($CDCl_3$), $\delta$: 1.20 (t, 3H, –$CH_2$–$CH_3$), 2.35 (s, 3H, $CH_3$), 2.59 (q, 2H –$CH_2$–$CH_3$), 3.16 (dd, 1H, $H_A$, $J_{A-B}$ = 16.27 Hz, $J_{A-X}$ = 9.29 Hz), 3.71 (dd, $H_B$, $J_{A-B}$ = 16.27 Hz, $J_{B-X}$ = 8.42 Hz), 4.11 (dd, $H_X$, $J_{A-X}$ = 9.29 Hz, $J_{B-X}$ = 8.42 Hz), 4.95 (s, 1H, Cl–CH), 6.62–7.81 (m, 7H, Ar-H), 8.21 (bs, 1H, COOH). IR ($cm^{-1}$): 1688, 1725 (two C=O), 3278 (bs-OH), 1142 (C–F), 748 (C–Cl). Anal. Calcd. for $C_{19}H_{15}ClFNO_3S$: C, 55.95; N, 3.43. Found: C, 55.80; N, 3.42.

*4.2.2.16. Compound **Vh**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.18 (dd, 1H, $H_A$, $J_{A-B}$ = 16.32 Hz, $J_{A-X}$ = 9.31 Hz), 3.72 (dd, $H_B$, $J_{A-B}$ = 16.32 Hz, $J_{B-X}$ = 8.40 Hz), 4.18 (dd, $H_X$, $J_{A-X}$ = 9.31 Hz, $J_{B-X}$ = 8.40 Hz), 5.02 (s, 1H, Cl–CH), 6.62–7.84 (m, 7H, Ar-H), 8.18 (bs, 1H, COOH). IR ($cm^{-1}$): 1692, 1720 (two C=O), 3275 (bs-OH), 1135 (C–F), 742 (C–Cl). Anal. Calcd. for $C_{19}H_{12}Cl_2F_3NO_3S$: C, 49.37; N, 3.03. Found: C, 49.53; N, 3.02.

*4.2.2.17. Compound **Vi**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.22 (dd, 1H, $H_A$, $J_{A-B}$ = 16.30 Hz, $J_{A-X}$ = 9.28 Hz), 3.71 (dd, $H_B$, $J_{A-B}$ = 16.30 Hz, $J_{B-X}$ = 8.39 Hz), 4.20 (dd, $H_X$, $J_{A-X}$ = 9.28 Hz, $J_{B-X}$ = 8.39 Hz), 4.98 (s, 1H, Cl–CH), 6.65–7.82 (m, 7H, Ar-H), 8.12 (bs, 1H, COOH). IR ($cm^{-1}$): 1685, 1722 (two C=O), 3270 (bs-OH), 1142 (C–F), 740 (C–Cl). Anal. Calcd. for $C_{19}H_{12}BrClF_3NO_3S$: C, 45.04; N, 2.76. Found: C, 45.19; N, 2.75.

*4.2.2.18. Compound **Vj**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.18 (dd, 1H, $H_A$, $J_{A-B}$ = 16.34 Hz, $J_{A-X}$ = 9.26 Hz), 3.68 (dd, $H_B$, $J_{A-B}$ = 16.34 Hz, $J_{B-X}$ = 8.38 Hz), 4.24 (dd, $H_X$, $J_{A-X}$ = 9.26 Hz, $J_{B-X}$ = 8.38 Hz), 4.96 (s, 1H, Cl–CH), 6.62–7.81 (m, 7H, Ar-H), 8.08 (s, 1H, OH), 8.26 (bs, 1H, COOH). IR ($cm^{-1}$): 1670, 1728 (two C=O), 3265 (bs-OH), 1160 (C–O), 1120 (C–F), 730 (C–Cl). Anal. Calcd. for $C_{19}H_{13}ClF_3NO_4S$: C, 51.42; N, 3.16. Found: C, 51.59; N, 3.17.

*4.2.2.19. Compound **Vk**.* $^1$H NMR ($CDCl_3$), $\delta$: 3.21 (dd, 1H, $H_A$, $J_{A-B}$ = 16.27 Hz, $J_{A-X}$ = 9.29 Hz), 3.69 (dd, $H_B$, $J_{A-B}$ = 16.27 Hz, $J_{B-X}$ = 8.38 Hz), 4.16 (dd, $H_X$, $J_{A-X}$ = 9.29 Hz, $J_{B-X}$ = 8.38 Hz), 5.02 (s, 1H, Cl–CH), 6.66–7.86 (m, 6H, Ar-H), 8.16 (bs, 1H, COOH). IR ($cm^{-1}$): 1680, 1720 (two C=O), 3260 (bs-OH), 1125 (C–F), 740 (C–Cl). Anal. Calcd. for $C_{18}H_{11}Cl_3FNO_3S$: C, 48.40; N, 3.14. Found: C, 48.56; N, 3.15.

*4.2.2.20. Compound **Vl**.* $^1$H NMR ($CDCl_3$), $\delta$: 2.35 (s, 3H, $CH_3$), 3.20 (dd, 1H, $H_A$, $J_{A-B}$ = 16.20 Hz, $J_{A-X}$ = 9.33 Hz), 3.74 (dd, $H_B$, $J_{A-B}$ = 16.20 Hz, $J_{B-X}$ = 8.40 Hz), 4.22 (dd, $H_X$,

$J_{A-X}$ = 9.33 Hz, $J_{B-X}$ = 8.40 Hz), 5.08 (s, 1H, Cl–CH), 6.64–7.82 (m, 6H, Ar-H), 8.19 (bs, 1H, COOH). IR ($cm^{-1}$): 1682, 1726 (two C=O), 3270 (bs-OH), 1120 (C–F), 730 (C–Cl). Anal. Calcd. for $C_{20}H_{14}ClF_4NO_3S$: C, 52.24; N, 3.05. Found: C, 52.41; N, 3.04.

*4.2.2.21. Compound **Vm**.* $^1$H NMR ($CDCl_3$), $\delta$: 2.37 (s, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 3.22 (dd, 1H, $H_A$, $J_{A-B}$ = 16.22 Hz, $J_{A-X}$ = 9.27 Hz), 3.76 (dd, $H_B$, $J_{A-B}$ = 16.22 Hz, $J_{B-X}$ = 8.36 Hz), 4.18 (dd, $H_X$, $J_{A-X}$ = 9.27 Hz, $J_{B-X}$ = 8.36 Hz), 5.06 (s, 1H, Cl–CH), 6.58–6.79 (m, 6H, Ar-H), 8.22 (bs, 1H, COOH). IR ($cm^{-1}$): 1688, 1728 (two C=O), 3265 (bs-OH), 1125 (C–F), 720 (C–Cl). Anal. Calcd. for $C_{21}H_{17}ClF_3NO_3S$: C, 55.33; N, 3.07. Found: C, 55.50; N, 3.08.

## Acknowledgements

Financial assistance from CSIR (No. 01(1907)03/EMR-II) and UGC New Delhi is gratefully acknowledged. One of us (RS) is thankful to CSIR for the award of Research Associateship. We are also thankful to Department of Pathology, Agricultural Research Station, Durgapura, and Jaipur for antifungal screening and RSIC, CDRI, Lucknow, for the elemental and spectral analyses.

## References

[1] (a) A. Levai, Heterocycl. Commun. 8 (2002) 375–380;
(b) J. Slade, J.L. Stanton, D.S. Ben-David, G.C. Mazzenga, J. Med. Chem. 28 (1985) 1517–1521;
(c) T. Asano, T. Okumura, K. Hirano, T. Adachi, M. Sugiura, Chem. Pharm. Bull. 34 (1986) 4238–4243.

[2] S. Ohno, K. Mizukoshi, K. Izumi, M. Hori, Chem. Pharm. Bull. 36 (1988) 551–562.

[3] K. Weiss, A. Fitscha, A. Gazso, D. Gludovacz, H. Sinzinger, Prog. Clin. Biol. Res. 301 (1989) 353–357 (Chem. Abstr. 111 (1989) 70642v).

[4] R. Filler, Chem. Tech. 4 (1974) 752–756.

[5] (a) A. Odawara, T. Ikeo, Jpn. Kokai. Tokkyo. Koho JP.06 (1994) 183, 978 [94, 183, 978] (CI. A 61. K 31/55), Appl. 92/341, 753 (Chem. Abstr. 122 (1992) 96150c).
(b) K.S. Atwal, S.Z. Ahmed, D.M. Floyd, S. Moreland, A. Hedberg, Bioorg. Med. Chem. Lett. 3 (1993) 2797–2800;
(c) D.M. Floyd, S.D. Kimball, J. Krapcho, J. Das, C.F. Turk, R.V. Mosquin, M.W. Lago, K.J. Duff, V.G. Lee, R.E. White, J. Med. Chem. 35 (1992) 756–772;
(d) Y. Inada, M. Tanabe, K. Itoh, H. Sugihara, K. Nishikawa, Jpn. J. Pharmacol. 48 (1988) 323 (Chem. Abstr. 110 (1989) 539x).

[6] M. Gomez-Gallego, M.J. Mancheno, M.A. Sierra, Tetrahedron 56 (2000) 5743–5744.

[7] F. Fulop, Chem. Rev. 101 (2001) 2181–2204.

[8] S. Bacchi, A. Bongini, M. Panunzio, M. Villa, Synlett (1998) 843–844.

[9] (a) S.B. Rosenblum, T. Huynh, A. Afonso, H.R. Davis, N. Yumibe, J.W. Clader, D.A. Burnett, J. Med. Chem. 41 (1998) 973–980;
(b) P.R. Bonneau, F. Hasani, C. Plouffe, E. Malenfant, S.R. Laplante, I. Guse, W.W. Ogilvie, R. Plante, W.C. Davidson, J.L. Hopkins, M.M. Morelock, M.G. Cordingley, R. Deziel, J. Am. Chem. Soc. 121 (1999) 2965–2973;
(c) B.K. Banik, F.F. Becker, Tetrahedron Lett. 41 (2000) 6551–6554;
(d) F. Fulop, G. Bernath, K. Pihlaja, Adv. Heterocycl. Chem. 69 (1998) 349–354.

[10] (a) W. Duerckheimer, J. Blumbach, R. Lattrell, K.H. Scheunemann, Angew. Chem. Int. Ed. 97 (1985) 183–205;
(b) R.B. Morin, M. Gorman, Chemistry and biology of lactam antibiotics, Vols.1–3, Academic Press, New York, 1982.

[11] (a) Xu. Jiaxi, Mol. Divers. 9 (2005) 45–49;
(b) S. Pippich, H. Bartsch, T.J. Erker, Heterocycl. Chem. 34 (1997) 823–826;
(c) A. Szollosy, G. Kotovych, G. Toth, A. Levai, Can. J. Chem. 66 (1988) 279–282.

[12] (a) A. Dandia, M. Sati, K. Arya, P. Sarawagi, A. Loupy, Arkivoc (i) (2005) 105–113;
(b) A. Dandia, M. Sati, K. Arya, A. Loupy, J. Sulfur Chem. 25 (2004) 283–289;
(c) A. Dandia, M. Sati, K. Arya, A. Loupy, Heterocycles 3 (2003) 563–569;
(d) A. Dandia, M. Sati, K. Arya, R. Sharma, A. Loupy, Chem. Pharm. Bull. 50 (2003) 1137–1141;
(e) A. Dandia, M. Sati, K. Arya, A. Loupy, Green Chem. 4 (2002) 599–602.

[13] (a) A. Dandia, R. Singh, S. Khaturia, Bioorg. Med. Chem. 14 (2006) 1303–1308;
(b) A. Dandia, R. Singh, S. Khaturia, Bioorg. Med. Chem. 14 (2006) 2409–2417;
(c) A. Dandia, K. Arya, N. Dhaka, J. Chem. Res. (2006) 192–198;
(d) A. Dandia, K. Arya, M. Sati, S. Gautum, Tetrahedron 60 (2004) 5253–5258;
(e) A. Dandia, R. Singh, P. Sarawgi, J. Fluorine Chem. 125 (2004) 1835–1840;
(f) A. Dandia, R. Singh, K. Arya, Org. Prep. Proced. Int. 35 (4) (2003) 401–408.

[14] U.C. Pant, M. Upreti, S. Pant, A. Dandia, Phosphorus Sulfur Silicon 113 (1996) 165–171.

[15] Y.L. Nene, P.N. Thapliyal, Fungicides in Plant Disease Control, Oxford & IBH Publishing Co., New Delhi, 1993.

[16] M.D. Whitehead, Phytopathology 47 (1952) 550.

[17] V. Migrdichian, Org. Synthesis, Reinhold Publishing Corporation, New York, 1960.

[18] U.C. Pant, M. Upreti, S. Pant, A. Dandia, G.K. Patnaik, A.K. Goel, Phosphorus Sulfur Silicon 126 (1997) 193–199.