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# Structurally Designed Novel Furogamma Lactams as Inhibitors for Bacterial Propagations

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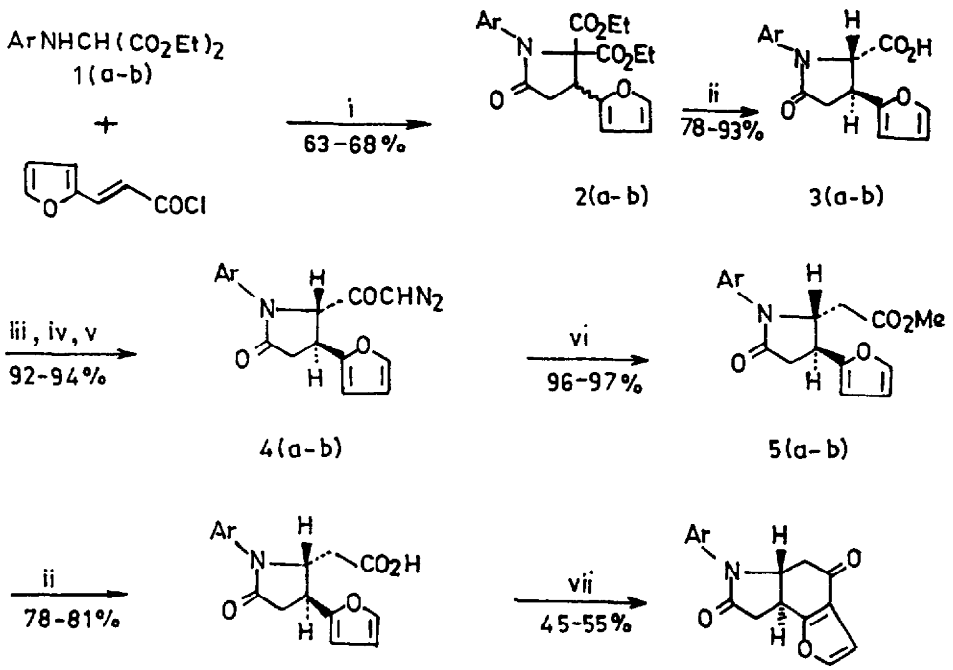
**Abstract**—Some novel furogamma lactams have been synthesised by one step condensation of arylaminomalonates with substituted furyl acryloyl chlorides. The annulation of substituted monocyclic gammalactams followed by cyclization produced novel tricyclic furogamma lactams. Some of these furogammalactams are found to exhibit Gram-positive and Gram-negative antibacterial activity at very high concentrations.

## Introduction

The resurgence of interest in the synthesis of non-β-lactam mimics of several β-lactam antibiotics[1] has led to the successful design and synthesis of many γ-lactam antibacterial derivatives.[2–4] Also, the isolation of many naturally occurring γ-lactam containing antibiotics[5–9] has questioned the classical concept that the presence of a β-lactam ring is a prerequisite for antibacterial activity. It is now believed that the bioactivity of the lactam compounds depends on the acylating ability of several proteins to inhibit the cross-linking of the bacterial cell wall,[10] which again is dependent on a suitably substituted and activated lactam ring.[11]

In connection with our studies towards the synthesis of novel γ-lactam analogues that could potentially serve as a biological surrogate for the β-lactam ring, we have recently reported the synthesis of some tricyclic γ-lactam derivative simulating the B-C-D rings of azasteroid.[12] Here we report the synthesis and bacterial propagation inhibitory property of some hitherto unknown furo-γ-lactams. The idea of introduction of the furan ring is based on its ability to behave as a masked 1,4-dicarbonyl system which can help in activating the γ-lactam ring.

Our synthetic approach is based on the construction of a γ-lactam ring having a furyl group (at the C-4 position of a γ-lactam moiety) and other necessary functionalities




**Reagents and Conditions:**
(i) benzene/$Et_3N$, reflux 6 h, (ii) KOH/EtOH–$H_2O$, reflux 4 h, (iii) NaOMe/MeOH, (iv) $(COCl)_2$/benzene; 0–60°C, 2 h, (v) diazomethane/$Et_2O$–$CH_2Cl_2$; 0°C–r.t., 15 h, (vi) $Ag_2O$/MeOH reflux 2 h, (vii) PPA/100°C, 30 min.

a, Ar = phenyl
b, Ar = p-chlorophenyl.

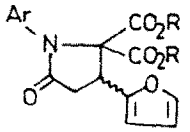
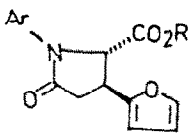
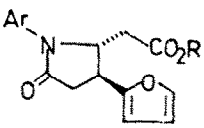
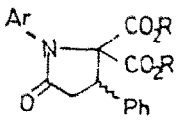
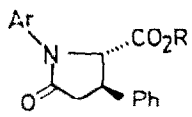
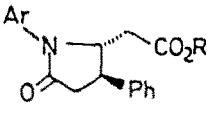
**Scheme I.**

that could be exploited in building up the desired polycyclic furo-γ-lactam framework. (Scheme I).

The arylaminomalonate (**1**) on reaction with 2-(2'-furyl) acryloyl chloride in the presence of triethylamine afforded the γ-lactam diester (**2**) in high yield through the intermolecular Michael addition followed by intramolecular amidification.[13] Compound **2** when hydrolysed with two-equivalents of KOH in refluxing water–ethanol mixture underwent *in situ* decarboxylation to produce the *trans* acid **3** exclusively. The *trans* geometry of the C-4 and C-5 substitutions was assigned from the coupling constant values of H-4 and H-5 which was approximately 3.2–3.3 Hz.

Homologation of the -COOH sidechain was achieved by sequential transformation of the carboxylic acid moiety → acid chloride → diazoketone → $CH_2CO_2Me$. Thus the sodium salt of compound **3** was converted to the acid chloride with the help of oxalylchloride, which

**Table 1.**

| Compound | Ar | R | Inhibition | |
|---|---|---|---|---|
| | | | *E. coli* ampicillin resistant | *S. aureus* amplicillin resistant |
|  | $C_6H_5$ | Et | Nil | Nil |
| | p-$ClC_6H_4$ | Et | Nil | Nil |
|  | $C_6H_5$ | Me | Nil | Nil |
| | p-$ClC_6H_4$ | Me | Nil | Nil |
| | $C_6H_5$ | H | 30–35% | 30–35% |
| | p-$ClC_6H_4$ | H | 35–40% | 35–40% |
|  | $C_6H_5$ | Me | Nil | Nil |
| | p-$ClC_6H_4$ | Me | Nil | Nil |
| | $C_6H_5$ | H | 10–12% | 10–12% |
| | p-$ClC_6H_4$ | H | 12–15% | 12–15% |
|  | $C_6H_5$ | Et | Nil | Nil |
| | m-$C_6H_4NO_2$ | Et | Nil | Nil |
| | p-$ClC_6H_4$ | Et | Nil | Nil |
|  | $C_6H_5$ | H | Nil | Nil |
| | m-$C_6H_4NO_2$ | H | Nil | Nil |
| | p-$ClC_6H_4$ | H | Nil | Nil |
|  | p-$ClC_6H_4$ | H | Nil | Nil |
| | m-$C_6H_4NO_2$ | H | Nil | Nil |

Concentration of γ-lactam derivative used = 1000 μg/0·02 mL.
% refers to zones of inhibition with respect to ampicillin.

on reaction with diazomethane afforded the diazoketone in excellent yield.

The diazoketone when subjected to reflux with $Ag_2O$ in MeOH produced the γ-lactam ester **5** in 96–97 % yield. Alkaline hydrolysis of **5** gave the acid **6** in excellent yield. Cyclization of the acid **6** with PPA/100 °C afforded the tricyclic furo-γ-lactam **7** in moderate to good yield. The final compounds as well as the intermediates, were characterized by usual spectroscopic methods as well as by analysis (see Experimental).

The antibacterial properties of furo-γ-lactams are not well reported. In our present study we have taken some of the above furo-γ-lactam derivatives as well as their 4-phenyl analogues for the detection of their antibacterial properties against the growth of *E. coli* resistant to ampicillin and *S. aureus* with lactamase producing strains. Interestingly, the presence of the furan ring was found to play some role in inhibiting the bacterial propagation. Some activity was observed for 1-aryl-4(2'-furyl)-pyrrolidine-2-one-5-carboxylic acid **3(a,b)** in both the strains while the 4-phenyl analogues of these compounds were found to be totally inactive. In compound **3**, replacement of the $-CO_2H$ sidechain at C-5 with $-CH_2CO_2H$ (as in **6**) resulted in reduced activity. However, weak activity was still observed for these compounds. Compound **2**, the methyl ester derivative of **3**, **5** and their 4-phenyl analogues show no bacterial growth inhibitory property at all (Table 1). Thus it is observed that the furan moiety clearly contributes to the activity of the γ-lactam unit in showing inhibitory properties. The minimum structural requirements, we observed is the presence of a furyl group at C-4 and a $-CO_2H$ group at C-5 in the 2-pyrrolidinone moiety. Studies are in progress to modify the N-aryl part with other suitable substituents which would permit greater diffusion rate and show enhanced activity.

It may be concluded, therefore, that this joint chemistry–biology researeh serves other purposes, such as providing vehicles for testing and developing new synthetic methods, providing a general way of preparing various analogues and testing how well these model compounds can be used towards assessing bioactivities.

## Experimental

All melting points are uncorrected and were checked in a one side open glass capillary using a $H_2SO_4$ bath. $^1$H-NMR spectra were recorded on 200 MHz (Brucker), 100 MHz (Jeol) and 90 MHz (Varian) machines using TMS as internal standard. IR spectra were recorded on a Perkin Elmer 800 spectrometer. Elemental analyses were performed by CDRI, Lucknow. Mass spectral data were obtained from RSIC, IIT, Madras and CDRI, Lucknow.

*General procedure for the preparation of 1-aryl-4-(2'-furyl)- 5,5-dicarbethoxypyrrolidin-2-one 2(a,b)*

To a stirred mixture of diethylarylaminomalonate (**1**) (20.9 mmol) and triethylamine (40 mmol) in 50 mL dry benzene, 3-(2'-furyl)-acryloyl chloride (20.9 mmol) in 25 mL dry benzene was added dropwise. The reaction mixture warmed up and a precipitate separated out. It was then refluxed on water bath, protecting from moisture, for 6 h. The reaction mixture was then cooled to room temperature, washed successively with $H_2O$, 2 N HCl, 5% $NaHCO_3$ solution and finally several times with $H_2O$. After drying the benzene layer ($Na_2SO_4$), solvent was stripped out at reduced pressure. The crude product thus obtained was recrystallized from isopropyl alcohol.

*Compound 2a.* Colourless solid; mp 95–96 °C; yield 63 %; IR (KBr) $\nu_{max}$ 1710, 1720, 1745 cm$^{-1}$; $^1$H NMR ($CDCl_3$) : δ 0.89 (t, 3H, $J$ = 7.3 Hz), 1.04 (t, 3H, $J$ = 7.2 Hz), 2.79–2.91 (dd, 1H, $J_{vic}$ = 8–7 Hz, $J_{gem}$ = 16.6 Hz), 3.00–3.14 (dd, 1H, $J$ = 11.6 Hz, $J_{gem}$ = 16.6 Hz), 3.75–4.12 (m,4H), 4.60–4.75 (dd, 1H, $J$ = 8.7 Hz & 11.6 Hz), 6.27–6.33 (m,2H), 7.22–7.36 (m, 6H). (Found C, 64.58; H, 5.42; N, 3.55, Calcd for $C_{20}H_{21}NO_6$ C, 64.69; H, 5.66; N, 3.77 %).

*Compound 2b.* Colourless solid; mp. 71–72 °C; yield 68 %; IR (KBr) $\nu_{max}$ 1725, 1740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) : δ 0.98 (t, 3H, $J$ = 7.2 Hz) 1.02 (t, 3H, $J$ = 7.3 Hz), 2.79–2.91 (dd, 1H, $J_{vic}$ = 8.8 Hz, $J_{gem}$ = 16.7 Hz), 2.97–3.11 (dd, 1H, $J_{vic}$ = 11.2 Hz, $J_{gem}$ = 16.7 Hz), 3.74–4.16(m, 4H), 4.57–4.67 (dd, 1H, $J$ = 8.8 & 11.2 Hz), 6.27–6.34 (m, 2H), 7.17–7.21 (d, 2H, $J$ = 8.7 Hz), 7.31–7.35 (d, 2H, $J$ = 8.7 Hz), 7.35–7.37 (m, 1H, $J$ = 0.8 Hz). (Found C, 59.15; H, 4.68; N, 3.25, Calcd for $C_{20}H_{20}NO_6Cl$ C, 59.18; H, 4.93; N, 3.45 %).

*General procedure for the preparation of 1-aryl-4-(2'-furyl)-pyrrolidin-2-one-5-carboxylic acid 3(a,b)*

To a solution of γ-lactam diester **2** (7.4 mmol) in 35 mL ethanol, a solution of KOH (15.7 mmol) in 10 mL $H_2O$ was added and refluxed for 4 h. EtOH was removed by distillation, the residue diluted by ice $H_2O$ and acidified with cold dil HCl. The solid separated was extracted with EtOAc, washed with $H_2O$, dried ($Na_2SO_4$) and solvent removed. The crude product thus obtained was recrystallized from a suitable solvent.

*Compound 3a.* Colourless solid; mp 171–172 °C (EtOAc–benzene); yield 78 %; IR (KBr) $\nu_{max}$ 1656, 1707 cm$^{-1}$; $^1$H NMR ($CDCl_3$) : δ 2·76–2·87 (dd, 1H, $J_{vic}$ = 4·1 Hz, $J_{gem}$ = 17.1 Hz), 3.05–3.19 (dd, 1H, $J_{vic}$ = 8.9 Hz, $J_{gem}$ = 17.1 Hz), 3.78–3.82 (m, 1H), 4.82 (d, 1H, $J$ = 3.3 Hz), 6.25 (d, 1H, $J$ = 3.2 Hz), 6.33–6.36 (dd, 1H, $J$ = 1. 9 Hz), 7.10–7.50 (m, 6H). (Found C, 70.38; H, 4.85; N, 5.27, Calcd for $C_{15}H_{13}NO_4$ C, 70.58; H, 5.09; N, 5.49 %).

*Compound 3b.* Shining colourless solid; mp 159–160 °C (EtOAc–petroleum ether 60–80 °C); yield 93 %; IR (KBr) $\nu_{max}$ 1588, 1659, 1748 cm$^{-1}$; $^1$H NMR ($CDCl_3$) : δ 2.75–2.84 (dd, 1H, $J_{vic}$ = 4·1 Hz, $J_{gem}$ = 13·9 Hz), 3.03–3.13 (dd, 1H, $J$ = 9.0 Hz & 13.9 Hz), 3.75- 3.85 (m, 1H), 4.78 (d, 1H, $J$ = 3.3 Hz), 6.23 (d, 1H, $J$ = 3.2 Hz), 6.36 (dd, 1H, $J$ = 1.8 Hz), 7.30–7.45 (m, 5H), MS (m/z) 307 [M+2], 306 [M+1], 305 [M]$^+$, 262, 261, 260, 220, 218, 107. (Found C, 58.7; H, 3.75; N, 4.47, Calcd for $C_{15}H_{12}NO_4Cl$ C, 58.92; H, 3.93; N, 4.58 %).

*General procedure for the preparation of 1-aryl-4(2'-furyl)-5-diazoacetylpyrrolidin-2-one **4(a,b)***

The acid **3** (6 mmol) was dissolved in dry MeOH (10 mL) and was converted to its sodium-salt by neutralizing with 2 % solution of NaOMe in MeOH using phenolphthalein as indicator. The solvent was removed under reduced pressure. The sodium salt thus obtained was dried by azeotropic distillation with dry benzene and finally dried *in vacuo* for 1 h. The sodium-salt was suspended in dry benzene (50 mL) containing a catalytic amount of anhydrous pyridine and cooled in an ice bath. Oxalyl chloride (8 mmol) was added to the reaction mixture with constant shaking. After 30 min in the ice bath, the reaction mixture was stirred at room temperature for 1 h and then for 30 min at 60 °C. The NaCl was filtered off and the filtrate concentrated *in vacuo*. The acid chloride [IR (KBr), $\nu_{max}$ 1704–1707 & 1795 $cm^{-1}$] obtained as an off-white solid was dissolved in dry $Et_2O$–$CH_2Cl_2$ mixture and added dropwise in about 30 min to an ice-cooled $Et_2O$ solution of $CH_2N_2$ (generated from 10 g of nitrosomethyl urea). The mixture was kept overnight at room temperature. Removal of solvent gave a yellowish brown oil. This was dissolved in dry $Et_2O$ and passed through a short column of neutral alumina. Evaporation of solvent gave the title compound as a yellow viscous oil which solidified on standing for a long time.

*Compound **4a**.* Colourless solid; mp 121–122 °C (ether, 0 °C); yield 92 %; IR (KBr) $\nu_{max}$ 1638 1708, 2107 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.65–2.96 (dd, 1H, $J$ = 5.5 Hz), 2.92–3.28 (dd, 1H, $J$ = 8.5 Hz), 3.65–3.85 (m, 1H), 4.72 (d, 1H, $J \approx$ 4.0 Hz), 5.40 (s, 1H), 6.24 (d, 1H, $J \approx$ 4.0 Hz), 6.26 (d, 1H, $J \approx$ 4.0 Hz), 6.32–6.40 (dd, 1H, $J \approx$ 2.0 Hz), 7.34–7.60 (m, 6H).

*Compound **4b**.* Colourless solid; mp 120–121 °C (ether, 0 °C); yield 94 %; IR (KBr) $\nu_{max}$ 1647, 1708, 2110 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.74–2.86 (dd, 1H, $J$ = 5.1 Hz), 3.00–3.13 (dd, 1H, $J$ = 9.0 Hz), 3.65–3.74 (m, 1H), 4.68 (d, 1H, $J$ = 3.8 Hz), 5.38 (s, 1H), 6.23 (d, 1H, $J$ = 3.4 Hz), 6.33–6.35 (dd, 1H, $J$ = 1.9 Hz), 7.26–7.43 (m, 5H).

*General procedure for the preparation of 1-aryl-4(2'-furyl)-5-carbomethoxymethyl pyrrolidin-2-one **5(a,b)***

To a stirred solution of diazoketone **4** (2.5 mmol) in 25–30 mL dry methanol at 50 °C, 1.5 g of freshly prepared $Ag_2O$ was added in two to three batches. Immediate evolution of $N_2$ took place. When the evolution of $N_2$ ceased, a further quantity of $Ag_2O$ (~1 g) was added and the mixture refluxed for 2 h on a water bath. Then it was filtered and solvent removed. The brownish yellow oil was purified by passing through a short column of neutral $Al_2O_3$. Elution with ether afforded the diazo compound **5** as a viscous oil.

*Compound **5a**.* Viscous yellow oil; yield 97 %; IR (KBr) $\nu_{max}$ 1706, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.50–2.68 (m, 2H), 2.76–3.18 (m, 2H), 3.40–3.68 (m, 1H), 3.52 (s, 1H), 4.50–4.70 (m, 1H), 6.20 (d, 1H, $J \approx$ 3.0 Hz), 6.30–6.40 (dd, 1H, $J \approx$ 2.0 Hz), 7.20–7.50 (m, 6H).

*Compound **5b**.* Viscous oil which solidified on standing for a long time; mp 60–61 °C; yield 96 %; IR (KBr) $\nu_{max}$ 1706, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.52–2.68 (m, 2H), 2.76–3.16 (dd, 2H, $J \approx$ 8.0 Hz), 3.40–3.68 (m, 1H), 3.52 (s, 3H), 4.50–4.80 (m, 1H), 6.20 (d, 1H, $J \approx$ 3.0 Hz), 6·28–6·36 (dd, 1H, $J \approx$ 2.0 Hz), 7.25–7.50 (m, 5H). (Found C, 61.04; H, 4·62; N, 4·16, Calcd for $C_{17}H_{16}NO_4Cl$ C, 61.16; H, 4.79; N, 4.19 %).

*General procedure for the preparation of 1-aryl-4(2'-furyl)-pyrrolidin-2-one-5-acetic acid 6(**a,b**)*

The γ-lactam ester **5** (2 mmol), in a mixture of 10 mL EtOH and 10 mL $H_2O$, was refluxed with 5 % KOH (aq.) solution (2·4–2·6 mL) for 4 h. The alcohol was removed as much as possible by distillation, diluted with $H_2O$ and extracted with $Et_2O$ to remove neutral matter if any. The aqueous layer was then cooled in an ice bath and acidified with ice-cooled dil HCl and extracted with EtOAc. After usual work-up it gave the title product as a viscous oil which solidified on standing.

*Compound **6a**.* Colourless solid; mp 147–148 °C; yield 81 %; IR (KBr) $\nu_{max}$ 1644, 1720, 3436 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.54–2.70 (m, 2H) 2·77–3·10 (m, 2H), 3.55–3.62 (m, 1H), 4.57–4.63 (m, 1H), 6.22 (d, 1H, $J$ = 2.8 Hz), 6.32 (d, 1H, $J$ = 2.8 Hz), 7.23–7.43 (m, 6H); MS (m/z) 287 [M+2], 286 [M+1], 285 $[M]^+$, 271, 241, 226, 225, 164, 163, 107, 104, 94.

*Compound **6b**.* Colourless solid; mp 166–167 °C; yield 78 % IR (KBr) $\nu_{max}$ 1589, 1650, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.55–2.69 (m, 2H), 2.76–3.09 (m, 2H), 3.55– 3.61 (m, 1H), 4.58–4.62 (m, 1H), 6.21 (d, 1H, $J$ = 2.8 Hz), 6.33 (d, 1H, $J$ = 2.8 Hz), 7.27–7.39 (m, 5H).

*General procedure for the preparation of 9-aryl-9-aza-3,8-dioxofuro[5,4-b]bicyclo[4.3.0]nonane 7(**a,b**)*

The acid **7** (0.9 mmol) was stirred with 8 g polyphosphoric acid at 100 °C for 30 min. After cooling it was decomposed with ice-$H_2O$ and extracted with $CHCl_3$. The $CHCl_3$ layer was then washed successively with $NaHCO_3$ solution, $H_2O$ and dried over anhydrous $Na_2SO_4$. Removal of solvent gave a light brown solid which was further purified by passing through a column of basic alumina (benzene:EtOAc, 8:2).

*Compound **7a**.* Colourless solid; mp 171–172 °C; yield 45 %; IR (KBr) $\nu_{max}$ 1692, 1701 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.60–2.80 (m, 2H), 2.85–3.10 (m, 2H), 3.80–4.05 (m, 1H), 4.80–4.90 (m, 1H), 6.70 (d, 1H, $J$ = 2.0 Hz), 7.10–7.60 (m,5H); MS (m/z) 257 $[M]^+$, 254, 211, 197, 169, 168, 167, 83, 77, 71, 57. (Found C, 71.73; H, 4.70; N, 5.08, Calcd for $C_{16}H_{13}NO_3$ C, 71.91; H, 4.87; N, 5.24 %).

*Compound **7b**.* Colourless solid; mp 140–141 °C; yield 55 %; IR (KBr) $\nu_{max}$ 1690, 1702 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ 2.73–2.80 (m, 2H), 2.85–3.15 (m, 2H), 3.84–3.99 (m, 1H, $J$ = 4.5 Hz), 4.80–4.89 (m, 1H, $J$ = 4.5 Hz), 6·68 (d, 1H, $J$ = 1.9 Hz), 7.10–7.45 (m, 4H), 7.52 (d, 1H, $J$ = 1.9 Hz). MS (m/z) 303 [M+2], 302 [M+1], 301 $[M]^+$, 272, 189, 180, 174, 148, 147, 121, 120, 111, 105, 91, 75, 65, 55.

(Found Cl, 63.51; H, 3.75; N, 4.39, Calc.d for $C_{16}H_{12}NO_3Cl$ C, 63.68; H, 3.98; N, 4.64 %).

*Bioassay of γ-lactams*

*E. coli* C 600 K-12 sensitive to ampicillin was collected from NCL, Pune, in addition to that the strain was mutated to ampicillin resistant, concentration up to 1000–2000 mg/mL. *Staphylococcus aureus* with lactamase producing activity was also used in this investigation. Mutations were followed according to the method (measuring of antibiotic activity by Oxford Cylinder Plate method) described by Sale[14] with some modifications.

The strains were grown on standard media containing nutrient borth purchased from HIMEDIA, India.

Nutrient (15 g/L) and agar–agar (15 g/L) were applied when solid agar Petri dishes were used. In these cases bacteria were grown for at least 12 h previously in an incubator at 37 °C with constant agitation. Then 5:20 ratios of 5 mL of bacterial culture $10^9$ cells/mL of total cells were mixed with 20 mL of molted agar at 50 °C and quickly poured into sterile and clean Petri dishes. After solidification, dishes were immediately preserved in a refrigerator at 10 °C to stop all further bacterial propagation.

Solidified Petri dishes with bacterial cells $10^{6-7}$/mL were grooved with one cork borer with absolute sterility. Alcohol burning was usually applied to sterile needles forceps and glasswares, against local contamination. However, major sterilization was mostly carried out in an autoclave. After making four individual grooves on each four inch diametric Petri dishes (plates) they were placed carefully under a laminar hood. Dissolved gamma-lactam (2000 μg/0.04 mL) in acetonitrile was added carefully with all precautions into each groove. After all solution diffused from the grooves the plates with γ-lactams and bacteria were incubated for 48 h at 37 °C. With respect to ampicillin, clean plaques were observed in the case of positive results.

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