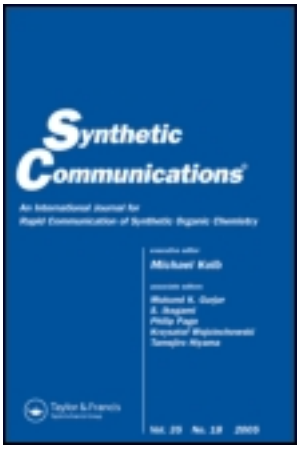

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N-ARYL MODIFICATION IN γ-LACTAM: DESIGN AND SYNTHESIS OF NOVEL MONOCYCLIC γ-LACTAM DERIVATIVES AS INHIBITOR FOR BACTERIAL PROPAGATION

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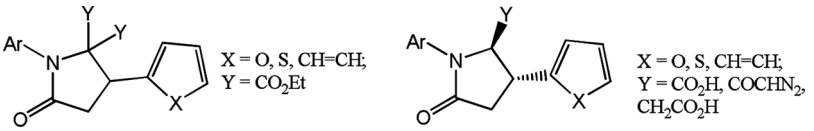
GRAPHICAL ABSTRACT



Abstract *In search of novel γ-lactam antibacterial agents as non-β-lactam mimics of some γ-lactam antibiotics, N-aryl modification in the γ-lactam ring has been made to synthesize compounds* ***4–8*** *in two to six steps. Compound* ***4*** *was synthesized using the intermolecular Michael addition of diethyl N-(6-coumarinyl)-2-aminomalonate and 3-aryl/(2-heteroaryl) acryloyl chloride followed by intramolecular amidification. Hydrolysis and stereoselective decarboxylation of* ***4*** *resulted in the formation of trans- γ-lactam carboxylic acids (****5****), which on side chain homologation followed by saponification of the intermediate γ-lactam monoester (****7****) afforded γ-lactam carboxylic derivatives* ***8****. Moderate to good bacterial growth inhibition was observed for some of the synthesized compounds against* E. coli *and* S. aureus.

Keywords Antibacterial activity; γ-lactam; Michael addition; *N*-aryl modification

INTRODUCTION

Several modifications on the tail and/or head of the penicillin antibiotics (Fig. 1) have led to the development of many clinically useful β-lactam antibacterial agents. However, untill the late 1980s, very limited efforts were taken to modify the β-lactam ring (i.e., the body of the molecule) as it was believed that presence of the β-lactam ring is necessary for showing the bioactivities of such compounds. After the middle of the 1970s, many groups of scientists began to raise questions about

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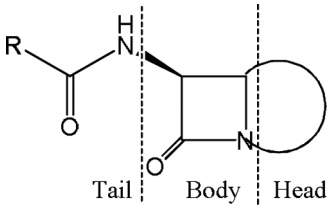


Figure 1. Tail, body, and head segments of bicyclic β-lactam antibiotics.

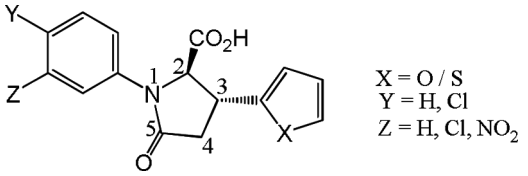
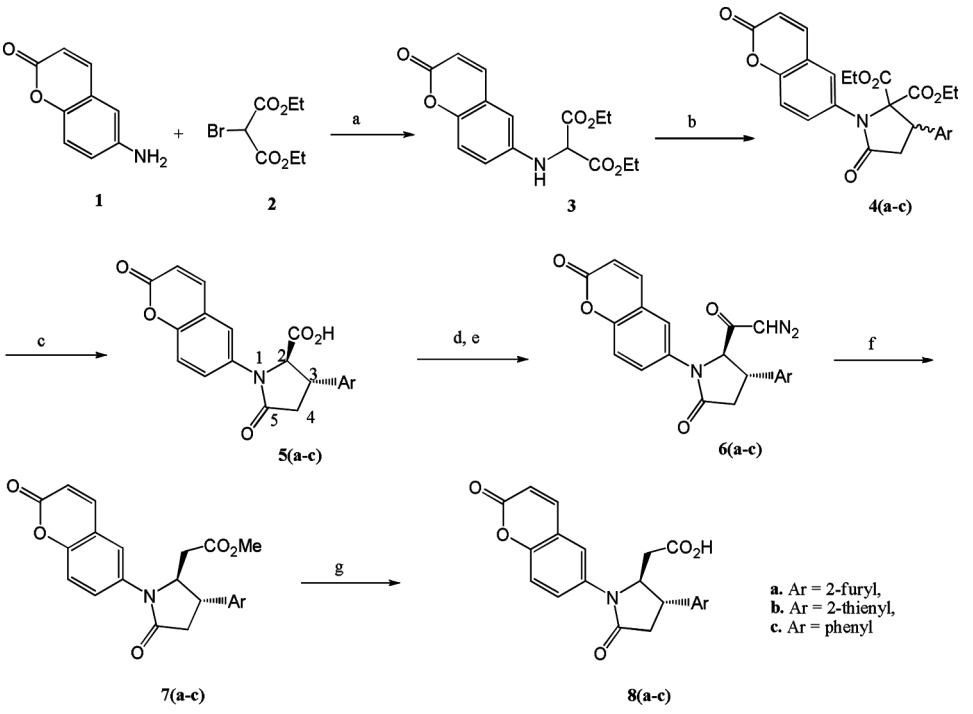


Figure 2. Monocyclic N-aryl γ-lactam carboxylic acids.



Scheme 1. Reagents and conditions: (a) 140 °C, 1 h, then at 125 °C, 2 h. (b) ArCH=CHCOCl, Et_3N, dry benzene, reflux, 7.5–8 h. (c) KOH (2.5 equiv.), EtOH, H_2O, reflux, 4–4.5 h. (d) $SOCl_2$, dry benzene, DMF (cat.), reflux 4–4.5 h. (e) CH_2N_2 (excess) in ether-CH_2Cl_2, 0 °C to r.t, overnight. (f) Ag_2O, dry MeOH, reflux, 2 h. (g) KOH (1.1 equiv.), EtOH, H_2O, rt, 1.5 h.

the theory that presence of the β-lactam ring is needed to display the bioactivities of β-lactam antibacterial agents, and in the search for biological surrogates of β-lactam rings, significant attention was given to the design of γ-lactam analogs by various groups. As a result of these research works, syntheses of large number of γ-lactam derivatives[1] have appeared in literature in the past few decades. Many of these γ-lactam derivatives showed moderate to high biological activity. The research toward the synthesis of novel γ-lactam antibacterials have been further stimulated by the isolation of many naturally occurring biologically active compounds such as lactivicin,[2] virgineone,[3] salinosporamide,[4] ergobalansine,[5] thyrotropine-releasing hormone (TRH),[6] and oleficine[7] bearing a γ-lactam moiety within the molecule. In the late 1990s, we have shown that the antibacterial activities of monocyclic *N*-aryl γ-lactam carboxylic acids[8] are dependent on the substituents present on the *N*-aryl group as well as on the nature of C_3-aryl group (Fig. 2). As an extension of this work in search of novel γ-lactam antibacterial agents, the present article describes the synthesis and biological evaluation of some novel γ-lactam carboxylic acid derivatives bearing 2-oxo-2*H*-chromen-6-yl functionality as the *N*-aryl part (Scheme 1). We expected that presence of the weakly electron-withdrawing coumarin moiety may enhance the reactivity of the γ-lactam carbonyl to facilate its binding with penicillin-binding proteins (PBP).

RESULTS AND DISCUSSION

The required starting material diethyl 2-(2-oxo-2*H*-chromen-6-yl-amino)-malonate (**3**) was prepared, in 70% yield, by heating a mixture of 6-aminocoumarin (**1**) and the bromomalonic ester (**2**) at 125–140 °C in a solvent-free condition. Diethyl 2-(2-oxo-2*H*-chromen-6-yl-amino)malonate (**3**) on intermolecular Michael addition followed by intramolecular amidification[9] with 2-(2′-furyl)acryloyl chloride in the presence of triethylamine produced the γ-lactam diester derivative (**4a**) in the 68% yield.

The diester derivative (**4a**) on hydrolysis with ~2 equivalents of KOH in refluxing aqueous ethanol underwent in situ decarboxylation to furnish the *trans* γ-lactam monocarboxylic acid derivative (**5a**) as a colorless solid in 75% yield (100% diastreoselectivity). The *trans* geometry was assigned from the coupling constant value of H_2 and H_3 protons ($J \sim 3.4$ Hz) as well as by analogy.[8,10] Homologation of the carboxylic side chain was achieved via Arndt–Eistert method. The γ-lactam carboxylic acid was converted to the acid chloride by treatment with thionyl chloride. The acid chloride on treatment with an excess of a solution of diazomethane in Et_2O afforded the diazoketone **(6a)** as a pale yellow viscous liquid, which solidified on standing. The diazoketone on refluxing with Ag_2O in anhydrous MeOH afforded **7a** in 56% yield. ^{1}HNMR and ^{13}CNMR spectra of **7a** are in good agreement with the assigned structure. The ester derivative (**7a**), when hydrolyzed with 1.1 equivalent of KOH in refluxing aqueous ethanol, produced the carboxylic acid **8a** in 70% yield.

Following a similar sequence of reactions, starting from diethyl 2-(2-oxo-2*H*-chromen-6-yl-amino)malonate (**2**) and 2-(2′-thienyl)acryloyl chloride or cinnamoyl chloride, the C_3-2-thienyl or C_3-phenyl analogs **4b, 4c, 5b, 5c** and **6b, 6c, 7b, 7c 8b, and 8c** were prepared.

The antibacterial properties of the γ-lactam acids **5(a–c)** as well as their methyl ester derivatives were then tested by the cylinder plate method, using reference standard ampicillin sodium solution, against the growth of *E. coli* (NCTC 9002), *S. aureus* (ATCC 29737), and *P. aureginosa* (ATCC 9027) with lactamase-producing strains. Both compounds **5a** and **5b** were found to inhibit the growth of bacterial propagation in moderate to good amounts, while the corresponding C_3-phenyl derivative **5c** was poorly active in inhibiting the growth. For the corresponding methyl ester derivatives of compound **5(a–b)**, bacterial growth inhibition was found to be lesser compared to the free acid derivatives **5a** or **5b**. Unlike the *N*-aryl-3-phenylpyrrolidine-2-carboxylic ester/acid derivatives,[8a] the *N*-coumarinyl-3-phenylpyrrolidine-2-carboxylic ester/acid derivatives displayed weak but positive activity in inhibiting the bacterial propagation. This may be due to the synergistic effect of the coumarin moiety. All the compounds, however, showed either no activity or poor activity in inhibiting the growth of *P. aureginosa.* The results are summarized in Table 1.

EXPERIMENTAL

All melting points are uncorrected and were checked with one-side-open glass capillary using a sulfuric acid bath. Solvents were dried following standard literature procedure. ^{1}HNMR spectra were recorded on Brucker 500-MHz (at Chemgen Pharma, Kolkata) and Brucker 200-MHz (at IIT Kharagpur) instruments. ^{13}CNMR spectra were recorded respectively in 50 or 125 MHz NMR spectrometer (Brucker) respectively. Electrospray ionization (ESI)-mass spectra were recorded on a Micro mass Q-TOF mass spectrometer (serial no. YA 263) at Indian Association for the Cultivation of Sciences (IACS), Kolkata. Infrared (IR) spectral data was obtained on a Jasco FT/IR680 Plus spectrometer.

2-(2-Oxo-2*H*-chromen-6-yl-amino)malonic Acid Diethyl Ester (3)

6-Aminocoumarin (**1**) (8.05 g, 0.05 mol) and 6.0 g (0.025 mol) of diethyl 2-bromomalonate (**2**) were taken in a 100-mL, round-bottomed flask fitted with a

Table 1. Zone of inhibition with standard solution of γ-lactam carboxylic acids **5(a–c)** and the corresponding methyl ester derivatives against *E coli*, *S. aureus*, and *P. aureginosa*

	Zone of inhibition (diameter in cm) (% with respect to ampicillin[a])		
γ-Lactam derivative	*E. coli* (NCTC 9002) (ampicillin resistant)	*S. aureus* (ATCC 29737) (ampicillin resistant)	*P. aureginosa* (ATCC 9027)
5a	0.2 (∼24%)	0.3 (∼25%)	Not significant
5b	0.3 (∼35%)	0.5 (∼42%)	0.1 (∼12%)
5c	0.1 (∼12%)	0.2 (∼17%)	Not significant
Methyl ester derivative of **5a**	0.2 (∼24%)	0.1 (∼8%)	Not significant
Methyl ester derivative of **5b**	0.1 (∼12%)	0.1 (∼8%)	0.1 (∼8%)
Methyl ester derivative of **5c**	Not significant	0.1 (∼8%)	Not significant

[a]Sample concentration and ampicillin concentration used: 100 μg/mL of acetonitrile.

two-way stopcock. It was then evacuated and the stopcock was closed. The mixture was then heated on an oil bath, first at 135–140 °C for 1 h and then at 125 °C for 2 h. After cooling to room temperature, the vacuum was released, and the dark brown residue was digested with dry benzene (toluene also can be used) and filtered to separate the 6-aminocoumarin hydrobromide salt. The filtrate was washed once with 5% diluted HCl and then thoroughly with water and dried (anhydrous Na_2SO_4). The benzene layer was treated with a little active charcoal and filtered. Removal of the solvent afforded the crude product, which was recrystallized from ethanol to furnish the title compound (**3**) as a pale yellow solid. Yield, 5.6 g (70%); mp 101–102 °C (EtOH). IR (KBr) ν_{max}: 1715, 1748 and 3411 cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 1.30 (t, 6H, $J = 7.0$ Hz), 4.29 (q, 4H, $J = 7.0$), 4.74 (d, 1H, $J = 7.5$ Hz), 4.91 (d, 1H, $J = 7.5$ Hz), 6.39 (d, 1H, $J = 9.5$ Hz), 6.65 (d, 1H, $J = 2.5$ Hz), 6.90 (dd, 1H, $J = 2.5$ and 9.0 Hz), 7.20 (d, 1H, $J = 9.0$ Hz), 7.59 (d, 1H, $J = 9.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$/125 MHz) δ: 14.05, 60.96, 62.62, 109.70, 117.08, 117.79, 118.68, 119.41, 142.27, 143.22, 147.60, 161.06, 167.32 ppm.

3-Aryl/heteroaryl-5-oxo-1-(2-oxo-2*H*-chromen-6-yl)pyrrolidine-2,2-dicarboxylic Acid Diethyl Ester 4(a–c)

A solution of 0.012–0.013 mol of 2-(2-furoyl/thienyl)acryloyl chloride or cinnamoyl chloride in 25 mL dry benzene was added drop wise to a stirred solution of compound **3** (3.19 g, 0.01 mol) and triethylamine (3.03 g or 4.2 mL, 0.03 mol) in 60 mL dry benzene. The reaction mixture warmed up and a white precipitate separated out. The mixture was then refluxed on water bath for 7–8 h with protection from moisture (completion of the reaction was monitored with thin-layer chromatography). It was then cooled to room temperature, and the reaction mixture was transferred to a separatory funnel. The mixture was successively washed with cold 5% HCl, 5% $NaHCO_3$ solution, and finally thoroughly with water. The organic layer was collected and dried (anhydrous Na_2SO_4), and removal of solvent furnished a highly viscous brownish yellow oil, which solidified on standing. It was further purified by recrystallization from EtOH or by column chromatography [silica gel; petroleum ether (60–80 °C)–EtAc mixture] to furnish the γ-lactam derivatives **4** in 66–72% yield.

Compound 4a. White solid; yield, 68%, mp 132–133 °C (EtOH). IR (KBr) ν_{max}: 1610, 1624, 1730 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 1.00 (t, 3H, $J = 7.0$ Hz), 1.05 (t, 3H, $J = 7.0$ Hz), 2.94 (dd, 1H, $J = 9.0$ & 17.0 Hz), 3.09 (dd, 1H, $J = 11.0$ & 17.0 Hz), 3.83 (m, 1H), 4.05 (m, 1H), 4.11 (m, 1H), 4.17 (m, 1H), 4.69 (dd, 1H, $J = 9.0$ and 11.0 Hz), 6.33 (d, 1H, $J = 3.0$ Hz), 6.38 (br t, 1H, $J \sim 2.5$ Hz), 6.46 (d, 1H, $J = 9.5$ Hz), 7.35 (d, 1H, $J = 8.5$ Hz), 7.41–7.42 (m, 2H), 7.52 (d, 1H, $J = 2.5$ Hz), 7.69 (d, 1H, $J = 9.5$ Hz) ppm.; ^{13}C NMR ($CDCl_3$/125 MHz) δ: 13.62, 33.21, 39.97, 62.63, 62.75, 109.15, 110.59, 117.17, 117.44, 119.07, 128.31, 132.26, 132.85, 142.69, 143.00, 149.39, 153.44, 160.28, 166.14, 167.19, 173.91 ppm. HRMS (ESI, 70 eV): $m/z = 440.1055$ ($M^+ + H$), 462.1004 ($M^+ + Na$) [calculated mass for $C_{23}H_{22}NO_8$ 440.1345 ($M^+ + H$), $C_{23}H_{21}NO_8Na$: 462.1165 ($M^+ + Na$)].

Compound 4b. White solid; yield, 66%, mp 163–164 °C (EtOH). IR (KBr) ν_{max}: 1622, 1693, 1720, 1751 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 0.91 (t, 3H, $J = 7.2$ Hz), 0.99 (t, 3H, $J = 7.2$ Hz), 3.06 (d, 1H, $J = 9.8$ Hz), 3.64–3.80 (m, 1H), 3.95–4.21 (m, 3H), 4.84 (t, 1H, $J = 9.8$ Hz), 6.44 (d, 1H, $J = 9.6$ Hz), 6.97–7.04 (m, 2H), 7.27–7.41 (m, 3H), 7.47 (d, 1H, $J \sim 2.5$ Hz), 7.60 (d, 1H, $J = 9.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$/125 MHz) δ: 13.39, 13.58, 35.89, 40.98, 62.54, 62.58, 78.80, 117.09, 117.38, 119.00, 125.55, 126.62, 126.83, 128.24, 132.17, 132.97, 138.35, 142.96, 153.35, 160.24, 166.16, 167.00, 173.90 ppm. HRMS (ESI, 70 eV): $m/z = 456.1054$ ($M^+ + H$) [calculated mass for $C_{23}H_{22}NO_7S$: 456.1117 ($M^+ + H$)].

Compound 4c. White solid; yield, 72%, mp 120–122 °C (cold EtOH, ~5 °C). IR (KBr) ν_{max}: 1626, 1696, 1731 (strong & broad), 1747 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 0.79 (t, 3H, $J = 7.2$ Hz), 0.99 (t, 3H, $J = 7.2$ Hz), 3.04 (d, 1H, $J = 9.2$ Hz), 3.51 (m, 1H), 3.86 (m, 1H), 4.00 (m, 1H), 4.17 (m, 1H), 4.60 (t, 1H, $J = 9.2$ Hz), 6.44 (d, 1H, $J = 9.6$ Hz), 7.33–7.34 (m, 6H), 7.40 (dd, 1H, $J = 2.1$ and 8.8 Hz), 7.52 (d, 1H, $J = 2.0$ Hz), 7.67 (d, 1H, $J = 9.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$/125 MHz) δ: 13.28, 13.63, 35.18, 45.18, 62.09, 62.50, 79.17, 117.12, 117.38, 119.03, 128.31, 128.39, 128.48, 128.57, 132.38, 133.15, 136.42, 142.99, 153.41, 160.28, 166.81, 167.13, 174.98 ppm. HRMS (ESI, 70 eV): $m/z =$ 450.2034 ($M^+ + H$), 472.2255 ($M^+ + Na$) [calculated mass for $C_{25}H_{24}NO_7$: 450.1553($M^+ + H$), $C_{25}H_{23}NO_8Na$: 472.1372 ($M^+ + Na$)].

3-Aryl/heteroaryl-5-oxo-1-(2-oxo-2*H*-chromen-6-yl)pyrrolidine-2-carboxylic Acid 5(a–c)

To a solution of the γ-lactam diester derivative (**4**) (5.0 mmol) in 20 mL EtOH, 20 mL of aqueous solution of KOH (700 mg, 12.5 mmol) was added. The mixture was refluxed on a water bath for 4.0–4.5 h. Excess ethanol was distilled out, and crushed ice was added to the residue and then acidified with concentrated HCl. The separated solid was filtered or extracted with ethyl acetate, washed with water, and dried (anhydrous Na_2SO_4), and the solvent was removed. The crude *trans* acid derivative thus obtained was redissolved in saturated aqueous $NaHCO_3$ solution and extracted with EtAc to remove the neutral part (if any). The aqueous part was treated with a pinch of active charcoal (if required) and filtered. The filtrate was cooled in ice and on acidification produced the carboxylic acid **5** as a white precipitate, which was filtered under suction to furnish the title compound **5** in 70–75% yield. An analytical sample was prepared by recrystallization from ethyl acetate–petroleum ether mixture. [NMR spectra/HRMS data of the samples were recorded as methyl ester derivative (prepared by treatment of the sample with diazomethane).]

Compound 5a. White solid; yield, 75%, mp 148–149 °C. IR (KBr) ν_{max}: 1730 (strong & broad), 3443 (broad) cm^{-1}; ^1H NMR of the methyl ester derivative ($CDCl_3$/200 MHz) δ: 2.82 (dd, 1H, $J = 4.4$ and 17.2 Hz), 3.12 (dd, 1H, $J = 8.8$ and 17.2 Hz), 3.77 (s, 3H), 3.78 (m, 1H), 4.83 (d, 1H, $J = 3.4$ Hz), 6.25 (d, 1H, $J = 3.4$ Hz), 6.36 (dd,1H, $J = 1.8$ and 3.4 Hz), 6.44 (d, 1H, $J = 9.6$ Hz), 7.32 (d, 1H, $J = 8.8$ Hz), 7.41 (dd, 1H, $J = 0.8$ and 1.8 Hz), 7.46 (dd, 1H, $J = 2.6$ and 8.8 Hz), 7.90 (d, 1H, $J = 9.6$ Hz), 8.0 (d, 1H, $J = 2.5$ Hz) ppm; ^{13}C NMR of the methyl ester derivative

($CDCl_3$/50 MHz) δ: 35.94, 36.17, 53.49, 66.83, 106.91, 110.99, 117.80, 117.96, 119.55, 122.26, 125.99, 134.54, 143.13, 143.51, 152.01, 153.37, 160.78, 171.25, 173.20 ppm; HRMS of the methyl ester derivative (ESI, 70 eV): $m/z = 353.9624$ ($M^+ + H$), 375.9337 ($M^+ + Na$) [calculated mass for $C_{19}H_{16}NO_6$ 354.0987 ($M^+ + H$), $C_{19}H_{15}$ NO_6Na: 376.0797 ($M^+ + Na$)].

Compound 5b. White solid; yield, 74%, mp 138–140 °C. IR (KBr) ν_{max}: 1609, 1730 (strong & broad) cm^{-1}; ^1H NMR of the methyl ester derivative ($CDCl_3$/500 MHz) δ: 2.79 (dd, 1H, $J = 3.7$ and 17.2 Hz), 3.23 (dd, 1H, $J = 8.8$ and 17.2 Hz), 3.78 (s, 3H), 4.00 (m, 1H), 4.75 (d, 1H, $J = 3.0$ Hz), 6.44 (d, 1H, $J = 9.6$ Hz), 6.98–7.0 (m, 2H), 7.25 (d, 1H, $J = 4.9$ Hz), 7.32 (d, 1H, $J = 8.9$ Hz), 7.49 (dd, 1H, $J = 2.5$ and 8.9 Hz), 7.69 (d, 1H, $J = 9.6$ Hz), 7.74 (d, 1H, $J = 2.0$ Hz) ppm; ^{13}C NMR of the methyl ester derivative ($CDCl_3$/125 MHz) δ: 37.96, 39.65, 53.51, 70.00, 117.81, 118.00, 119.58, 122.37, 125.03, 125.13, 126.11, 127.62, 134.48, 143.50, 144.67, 152.08, 160.75, 171.09, 173.07 ppm. HRMS of the methyl ester derivative (ESI, 70 eV): $m/z = 370.0054$ ($M^+ + H$), 392.0514 ($M^+ + Na$) [calculated mass for $C_{19}H_{16}NO_5S$ 370.0749 [($M^+ + H$), $C_{19}H_{15}$ NO_5SNa: 392.0569 ($M^+ + Na$)].

Compound 5c. White solid, yield 70%, m.p. 140–141 °C. IR (KBr) ν_{max}: 1610, 1649, 1731 (strong & broad) cm^{-1}; ^1H NMR of the methyl ester derivative ($CDCl_3$/200 MHz) δ: 2.76 (dd, 1H, $J = 4.0$ and 17.4 Hz), 3.21 (dd, 1H, $J = 9.0$ & 17.4 Hz), 3.66 (dt, 1H, $J = 3.6$ & 9.0 Hz), 3.76 (s, 3H), 4.70 (d, 1H, $J = 3.0$ Hz), 6.44 (d, 1H, $J = 9.6$ Hz), 6.26–7.40 (m, 6H), 7.44 (d, 1H, $J = 2.5$ & 9.0 Hz), 7.90 (d, 1H, $J = 9.6$ Hz), 8.0 (d, 1H, $J = 2.5$ Hz) ppm; HRMS of the methyl ester derivative (ESI, 70 eV): $m/z = 364.2425$ ($M^+ + H$) [calculated mass for $C_{21}H_{18}NO_5$, 364.1185($M^+ + H$)].

4-Aryl/heteroaryl-1-(2-oxo-2*H*-chromen-6-yl)-5-diazoacetylpyrrolidine-2-one 6(a–c)

To a solution of γ-lactam monocarboxylic acid (**4**) (3.8 mmol) in 60 ml of dry benzene, 570 mg (0.35 mL, 4.8 mmol) of $SOCl_2$ was added followed by addition of catalytic amount of dry dimethylformamide (DMF). The mixture was refluxed on a water bath for 4–4.5 h protecting from moisture. Removal of solvent and excess thionyl chloride afforded the crude acid chloride as viscous light yellow oil in almost quantitative yield. The crude acid chloride was immediately dissolved in a dry dichloromethane–ether mixture and was added dropwise with stirring to an ice-cold solution of diazomethane in ether (generated from 6.5 g of nitrosomethylurea). The mixture was left overnight at room temperature. Removal of the solvent left a brown oil. It was redissolved in anhydrous ether and filtered through a column of neutral alumina. Evaporation of the solvent afforded the diazoketone as a pale yellow viscous mass, which solidified on standing. Yield, 60–65%.

Compound 6a. White solid; yield, 65%, mp 151–152 °C (diethyl ether, 0–5 °C). IR (KBr) ν_{max}: 1632, 1713 (strong & broad), 2112 (strong) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.84 (dd, 1H, $J = 4.9$ and 17.3 Hz), 3.10 (dd, 1H, $J = 9.2$ and 17.3 Hz), 3.72 (m, 1H), 4.73 (d, 1H, $J = 2.5$ Hz), 5.40 (s, 1H), 6.26 (br

s, 1H), 6.37 (br s, 1H), 6.43 (d, 1H, $J = 10.0$ Hz), 7.32 (d, 1H, $J = 8.9$ Hz), 7.42 (br s, 1H), 7.48 (br d, 1H, $J = 8.7$ Hz), 7.68 (d, 1H, $J = 10.0$ Hz), 7.73 (br s, 1H) ppm.

Compound 6b. White solid; yield, 64%, mp 153–154 °C (diethyl ether, 0–5 °C). IR (KBr) ν_{max}: 1625, 1710 (strong & broad), 2108 (strong) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.77 (dd, 1H, $J = 4.6$ and 17.2 Hz), 3.20 (dd, 1H, $J = 8.8$ and 17.2 Hz), 3.92 (quin, 1H, $J = 4.3$ Hz), 4.61 (d, 1H, $J = 3.3$ Hz), 5.34 (s, 1H), 6.44 (d, 1H, $J = 9.6$ Hz), 6.96–6.98 (m, 2H), 7.23 (dd, 1H, $J = 1.7$ and 4.5 Hz), 7.32 (d, 1H, $J = 9.0$ Hz), 7.48 (dd, 1H, $J = 2.4$ and 9.0 Hz), 7.68 (d, 1H, $J = 9.6$ Hz), 7.74 (d, 1H, $J = 2.4$ Hz) ppm.

Compound 6c. White solid; yield, 60%, mp 156–157 °C. IR (KBr) ν_{max}: 1646, 1701 (strong), 1727 (strong), 2111 (strong) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.78 (dd, 1H, $J = 4.0$ and 17.5 Hz), 3.20 (dd, 1H, $J = 9.5$ and 17.5 Hz), 3.61 (t, 1H, $J = 4.0$ Hz), 4.62 (br s, 3H), 5.29 (s, 1H), 6.45 (d, 1H, $J = 9.5$ Hz), 7.29–7.39 (m, 6H), 7.52 (br d, 1H, $J = 8.5$ Hz), 7.69 (d, 1H, $J = 9.5$ Hz), 7.78 (br s, 1H) ppm.

trans-Methyl 2-[(3-Aryl)-5-oxo-1-(2-oxo-2*H*-chromen-6-yl)pyrrolidine-2yl]acetate 7(a–c)

To a stirred solution of the diazoketone (**6**) (4.3 mmol) in 15 mL of dry methanol at 50 °C, 0.5 g of Ag_2O was added in two to three batches. Immediate evolution of N_2 took place. When the nitrogen evolution ceased, a further quantity of Ag_2O (500 mg) was added, and the mixture was refluxed on a water bath for 2 h. It was then filtered, and the solvent was removed. The brownish yellow oil obtained on purification by column chromatography (silica gel, light petrol–EtAc mixture, 9:1) afforded the title compound as a pale semisolid mass. Yield, 56–58%.

Compound 7a. White solid; yield, 56%, mp 135–136 °C (diethyl ether, 0–5 °C). IR (KBr) ν_{max}: 1729 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.62 (dd, 1H, $J = 7.2$ and 15.7 Hz), 2.71 (dd, 1H, $J = 4.6$ and 15.7 Hz), 2.86 (dd, 1H, $J = 6.7$ and 17.3 Hz), 3.02 (dd, 1H, $J = 9.2$ and 17.3 Hz), 3.54 (s, 3H), 3.59 (m, 1H), 4.66 (m, 1H), 6.23 (d, 1H, $J = 3.2$ Hz), 6.35 (dd, 1H, $J = 1.9$ and 3.2 Hz), 6.46 (d, 1H, $J = 9.6$ Hz), 7.36 (d, 1H, $J = 8.9$ Hz), 7.41 (d, 1H, $J = 1.8$ Hz), 7.48 (dd, 1H, $J = 2.4$ and 8.9 Hz), 7.58 (d, 1H, $J = 2.4$ Hz), 7.69 (d, 1H, $J = 9.6$ Hz) ppm; HRMS (ESI, 70 eV): $m/z = 368.1574$ ($M^+ + H$), 390.1384 ($M^+ + Na$) [calculated mass for $C_{20}H_{18}NO_6$ 368.1134 [($M^+ + H$), $C_{20}H_{17}NO_6Na$: 390.0954 ($M^+ + Na$)].

Compound 7b. White solid; yield, 58%, mp 146–147 °C. IR (KBr) ν_{max}: 1622, 1693, 1715 (strong & broad), 1751 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.55 (dd, 1H, $J = 7.5$ and 15.8 Hz), 2.64 (dd, 1H, $J = 4.5$ and 15.8 Hz), 2.73 (dd, 1H, $J = 5.8$ and 17.4 Hz), 3.08 (dd, 1H, $J = 8.9$ and 17.4 Hz), 3.48 (s, 3H), 3.72 (m, 1H), 4.53 (m, 1H), 6.39 (d, 1H, $J = 9.6$ Hz), 6.92–6.94 (m, 2H), 7.18 (dd, 1H, $J = 1.9$ and 4.5 Hz), 7.29 (d, 1H, $J = 8.9$ Hz), 7.43 (dd, 1H, $J = 2.5$ and 8.9 Hz), 7.54 (d, 1H, $J = 2.5$ Hz), 7.61 (d, 1H, $J = 9.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$/125 MHz) δ: 37.60, 38.76, 43.06, 51.89, 64.45, 117.45, 117.69, 119.25, 123.51, 126.88, 127.46, 127.66, 129.21, 133.25, 141.91, 142.93, 151.90, 160.30, 170.35, 173.10 ppm; HRMS (ESI, 70 eV): $m/z = 384.2672$ ($M^+ + H$),

406.2572 ($M^+ + Na$) [calculated mass for $C_{20}H_{18}NO_5S$ 384.0906 [($M^+ + H$), $C_{20}H_{17}NO_5SNa$: 306.0725 ($M^+ + Na$)].

Compound 7c. White solid; yield, 58%, mp 122–123 °C.(diethyl ether, 0–5 °C). IR (KBr) ν_{max}: 1693 (strong & broad), 1715 (strong & broad), 1751 (strong & broad) cm^{-1}; ^1H NMR ($CDCl_3$/500 MHz) δ: 2.58 (dd, 1H, $J = 7.9$ and 15.6 Hz), 2.69 (dd, 1H, $J = 4.4$ and 15.6 Hz), 2.77 (dd, 1H, $J = 5.9$ and 17.6 Hz), 3.14 (dd, 1H, $J = 9.2$ and 17.6 Hz), 3.45 (m, 1H), 3.50 (s, 3H), 4.57 (m, 1H), 6.45 (d, 1H, $J = 9.6$ Hz), 7.27–7.40 (m, 6H), 7.51 (dd, 1H, $J = 2.5$ and 8.9 Hz), 7.62 (d, 1H, $J = 2.4$ Hz), 7.69 (d, 1H, $J = 9.6$ Hz) ppm; HRMS (ESI, 70 eV): $m/z = 378.0778$ ($M^+ + H$) [calculated mass for $C_{22}H_{20}NO_5$ 364.1341 ($M^+ + H$).

trans-Methyl 2-[(3-Aryl)-5-oxo-1-(2-oxo-2*H*-chromen-6-yl)pyrrolidine-2yl]acetic Acid 8(a–c)

A mixture of the ester derivative (**7**) (0.27 mmol), KOH (0.3 mmol), ethanol (5.0 ml), and water (5.0 mL) was refluxed on a water bath for 1.5 h. The solvent was removed as much as possible. The residue was the cooled to 0–5 °C and acidified with concentrated HCl. The residue was the extracted with ethyl acetate thoroughly. The organic layer was washed with saturated $NaHCO_3$ solution. The sodium bicarbonate layer was collected, cooled to 0–5 °C, and acidified with concentrated HCl. The white precipitate formed was extracted with ethyl acetate, washed with cold brine solution, and dried (anhydrous Na_2SO_4), and the solvent was removed. The carboxylic acid **8** was obtained as a white powder. Yield, 70–75%.

Compound 8a. White solid; yield, 70%, mp 140–142 °C. IR (KBr) ν_{max}: 1693, 1715, 1751 cm^{-1} (all are strong & broad). (Mp and ^1H NMR spectra of methyl ester derivative, prepared by treatment of the sample with diazomethane, were identical with those of **7a**.)

Compound 8b. White solid; yield, 72%, mp 148–150 °C. IR (KBr) ν_{max}: 1693, 1715, 1751 cm^{-1} (all are strong & broad). (Mp and ^1H NMR spectra of methyl ester derivative, prepared by treatment of the sample with diazomethane, were identical with those of **7b**.)

Compound 8c. White solid; yield, 75%, mp 131–132 °C. IR (KBr) ν_{max}: 1699, 1736 cm^{-1} (both strong & broad). (Mp and ^1H NMR spectra of methyl ester derivative, prepared by treatment of the sample with diazomethane, were identical with those of **7c**.)

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