Facile synthesis of novel monocyclic trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams

Aman Bhalla, Shamsher S. Bari, Shiwani Berry, Jitender Bhalla, Sunil Vats, Sanjay Mandal, and Sadhika Khullar

Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160014, India

Indian Institute of Science Education and Research (IISER), Mohali 160062, India

E-mail: amanbhalla@pu.ac.in

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.172

Abstract

A facile synthesis of novel monocyclic trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6) is described. The reaction of 2-methoxy/phenoxy/benzyl/phenylthio/seleno ethanoic acids or acetoxyacetyl chloride 4 with pyrazolyl substituted Schiff’s bases 3a-d using POCl₃ and Et₃N in refluxing toluene furnished β-lactams (5, 6). These synthesized β-lactams have been characterized by spectroscopic techniques viz. NMR (¹H, ¹³C and ⁷⁷Se), FT-IR, mass spectrometry (EI-MS and HRMS) and elemental analysis. Single crystal X-ray crystallographic study of trans-1-(4’-methoxyphenyl)-3-methoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)azetidin-2-one 5p has confirmed the molecular structure and the stereochemical outcome. The cis or trans configuration of β-lactams (5, 6) was assigned with respect to position of C3-H and C4-H.

Keywords: β-Lactams, pyrazole derivatives, trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams, X-ray crystal structure

Introduction

β-Lactam heterocyclic compounds have been reported as synthons for the synthesis of amino acids, alkaloids and taxoids¹ and successfully used for medicinal applications, such as cholesterol acyl transferase inhibitors, thrombin inhibitors, human cytomegalovirus protease inhibitors, matrix-metallo protease inhibitors, human leukocyte elastase inhibitors, cysteine protease inhibitors, apoptosis inducers, gene activators, and β-turn nucleators.² The biological activity usually associated with the nature of the groups linked to N-1, C-3 and C-4 of the β-lactam molecules. Therefore, the construction of novel pyrazole substituted β-lactams with control of
functionality, stereochemistry and regioselectivity has remained a great challenge for the synthetic organic chemist in order to enhance their spectrum of biological activity, potency and specificity.

Pyrazole substituted heterocycles have a wide range of applications in agrochemicals, medicine and the pharmaceutical industry. 3,4-Disubstituted pyrazole derivatives have been shown to exhibit cyclin dependent kinase inhibitory activity and inhibited \textit{in vitro} cellular proliferation in various human cells.\textsuperscript{3} A series of pyrazole derivatives have been showing high antiproliferative and antiangiogenic activities against human breast (MCF-7) and cervical carcinoma cells.\textsuperscript{4-6} Identification of antitumor activity of pyrazole oxime ethers has been well documented.\textsuperscript{7} Bonesi \textit{et al.}\textsuperscript{8} synthesized a substituted pyrazole and investigated their potential activity as inhibitors of angiotensin converting enzyme (ACE). In literature, several reports have demonstrated substituted pyrazole and their derivatives as inhibitors of GSK3\(\beta\) Glycogen synthase kinase,\textsuperscript{9} VEGFR2 kinase,\textsuperscript{10} tyrosinase,\textsuperscript{11} phagocytosis of opsonized blood cells\textsuperscript{12} and aryamine N-acetyltransferase.\textsuperscript{13}

Bondock \textit{et al.},\textsuperscript{14} Radi \textit{et al.},\textsuperscript{15} Sahu \textit{et al.},\textsuperscript{16} Barsoum \textit{et al.}\textsuperscript{17} and Burguete \textit{et al.}\textsuperscript{18} have synthesized a series of substituted pyrazole and their derivatives possess antifungal, antimicrobial, antibacterial and anti-inflammatory activities. 4,5-Disubstituted pyrazoles have been shown to exhibit potent antiviral activity against a broad panel of viruses in different cell cultures (HEL Cell cultures) including hepatitis A virus and Herpes simplex virus type-1.\textsuperscript{19,20} Antidepressant and anticonvulsant activity of pyrazole derivatives has been reported by Abdel Aziz \textit{et al.}\textsuperscript{21} The recent success of pyrazole derivatives as acyclonucleoside analogues,\textsuperscript{15} blockers of divalent metal transporter 1 (DMT1)\textsuperscript{22} and COX-2 inhibitors\textsuperscript{23} has further highlighted the importance of this heterocyclic ring.

3-Methoxy-\(\beta\)-lactams have been found to have apoptotic activity against human leukemia, breast, prostate and head-neck cancer cells, thus exhibiting antitumor activity.\textsuperscript{24} 3-Acetoxy/phenoxyl-\(\beta\)-lactams serve as the precursors to taxol, taxotere (highly promising anticancer drugs).\textsuperscript{25} 3-Benzyl/phenylthio/seleno-\(\beta\)-lactams have been reported to be synthons of biologically important heterocycles.\textsuperscript{26} Encouraged by the broad spectrum of biological activity of pyrazole derivatives and \(\beta\)-lactams, it was planned to incorporate the pyrazolyl moiety into suitably substituted \(\beta\)-lactams to furnish novel pyrazole substituted \(\beta\)-lactam heterocycles.

In literature, very few reports are available for the synthesis of such type of molecules. Buttero \textit{et al.}\textsuperscript{27} have prepared 4-(pyrazol-4/5-yl)carbonyl-2-azetidinones \textit{via} nitrilimine cycloaddition. Parmar \textit{et al.}\textsuperscript{28} have prepared \(\beta\)-lactams based on \(N\)-phenyl-3-phenyl-4-formyl pyrazole (PEP). Banik \textit{et al.}\textsuperscript{29} have recently reported the iodine/bismuth catalyzed synthesis of pyrrole substituted \(N\)-polyaromatic-\(\beta\)-lactams. Therefore, our present studies have been directed towards the synthesis of novel monocyclic \textit{trans}- and \textit{cis}-3-oxy/thio/seleno-4-pyrazolyl-\(\beta\)-lactams.

In previous studies we have demonstrated the synthesis of selenoalkanoic acids useful as \(\beta\)-lactam precursors,\textsuperscript{30,31} novel 3-thio/seleno-\(\beta\)-lactams and their Lewis acid mediated functionalization,\textsuperscript{32-38} stereoselective synthesis of \textit{cis}- and \textit{trans}-3-alkoxy-\(\beta\)-lactams,\textsuperscript{39} spirocyclic-\(\beta\)-lactams,\textsuperscript{2,34,40} \((Z)\)- and \((E)\)-3-allylidene-\(\beta\)-lactams,\textsuperscript{41} 3-keto-\(\beta\)-lactams\textsuperscript{42} and
bicyclic-β-lactams. Herein, we report the synthesis of novel monocyclic trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6).

Results and Discussion

The study began with the chloropyrazolecarbaldehyde 2, prepared from the pyrazolinone 1 following a literature procedure (Scheme 1). The pyrazole-substituted Schiff’s bases 3a-d were prepared by stirring equivalent amounts of an appropriate primary amine with the aldehyde 2 using molecular sieves (4Å) in dichloromethane (Scheme 1, Table 1). The structures of the novel Schiff’s bases 3a-d were confirmed on the basis of their NMR spectra (1H, 13C) and CHN elemental analysis.

Table 1. Pyrazolyl substituted Schiff's bases 3a-d

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Schiff’s base 3</th>
<th>Yielda,b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>4-OCH3C6H4</td>
<td>3b</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>CH2C6H5</td>
<td>3c</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>4-ClC6H4</td>
<td>3d</td>
<td>87</td>
</tr>
</tbody>
</table>

a Yields quoted for pure, isolated products. b Isolated products characterized by NMR (1H, 13C) and elemental analysis.

The synthesis of novel trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams 5-6 has been achieved via Staudinger cycloaddition between the Schiff’s bases 3a-d and a ketene generated from 2-substituted ethanoic acids or acid chloride 4, respectively (Scheme 2).

Initially, 2-(phenylthio)ethanoic acid was reacted with Schiff’s base 3a using phosphorus oxychloride (POCl3) and triethylamine (Et3N) in dry methylene chloride at 0 °C, but this reaction did not afford the desired product. However, when the reaction was performed in refluxing dry toluene and the progress of the reaction was monitored by thin-layer chromatography (TLC), it resulted in the exclusive formation of trans-3-phenylthio-4-pyrazolyl-β-lactam 5a in excellent
yield (Scheme 2, Table 2, Entry 1). The target product 5a was purified by column chromatography on silica gel using ethyl acetate–hexane (10:90) as eluant and was identified as trans-1-(4’-methoxyphenyl)-3-phenylthio-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)azetidin-2-one on the basis of 1H NMR spectroscopy.

![Scheme 2](image)

Scheme 2. Synthesis of 3-acetoxy/methoxy/phenoxy/benzyl/phenylthio/seleno substituted 4-pyrazolyl-β-lactams 5a-m,o-r and 6n-q,s.

To understand the nature of the substituted ethanoic acids or acetoxyacetyl chloride 4 and the pyrazole substituted Schiff’s bases 3a-d towards Staudinger cycloaddition, the reaction was performed by altering the R, X and R1 substituents i.e. R = C6H5, C6H5CH2, CH3, CH2CO; X = O, S, Se; R1 = C6H5, 4-OCH3C6H4, CH2C6H5, 4-ClC6H4 (Scheme 2, Table 2, Entries 1-19). A successful attempt has also been made towards the synthesis of cis-3-phenoxy/acyloxy-4-pyrazolyl-β-lactams 6n, 6s when the nitrogen atom in the Schiff’s base 3 was substituted with a benzyl group (3c) instead of a p-methoxyphenyl or phenyl group (Scheme 2 and Table 2, entry 14, 19). However, 2-methoxyethanoic acid on treatment with Schiff’s bases 3a-c furnished trans-β-lactams 5o-q as the major isomers along with cis-β-lactams 6o-q as the minor isomers, respectively (Scheme 2, Table 2, Entry 15-17).

All these newly synthesized monocyclic trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6) were purified by column chromatography on silica gel using ethyl acetate-hexane (10:90) as the eluant.

The structures of these trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6) were established on the basis of various spectroscopic techniques viz., FTIR, NMR (1H, 13C, 77Se), mass spectrometry (EI-MS and HRMS) and their elemental analysis (solid β-lactams only). The IR absorption band in the range 1724-1755 cm⁻¹ for the C=O of the β-lactam ring supported the formation of pyrazolyl-β-lactams 5, 6. The spatial juxtaposition of the C3-H and C4-H was assigned trans and cis in products 5, 6 on the basis of coupling constant values (J = 1.2-2.7 Hz and J = 4.5-5.1 Hz C3-H and C4-H), respectively in the 1H NMR spectra.35,39
stereochemistry at C-3 and C-4 of \(\beta\)-lactams 5, 6 was established through single crystal X-ray crystallographic studies of 5p (Figure 1). In the EIMS spectrum of \textit{trans}-3-methoxy-4-pyrazolyl-\(\beta\)-lactam 5p, a peak corresponding to the fragment [M+Na]\(^+\) with low intensity confirmed the formation of the target product. The base peak does not correspond to the molecular ion peak and appears at \(m/z\) 420.2 (100) [M+Na]\(^+\), while the spectra display the molecular ion peak [M+H]\(^+\) at \(m/z\) 398.2 (61), respectively. The other prominent peaks which are present at \(m/z\) 362.2 (28) and \(m/z\) 271.1 (10.87) corresponds to [C\(_2\)H\(_{20}\)N\(_3\)O\(_3\)]\(^+\) and [C\(_{13}\)H\(_{12}\)ClN\(_2\)NaO]\(^+\) respectively. CHN elemental analysis of the solid \(\beta\)-lactams (5d, 5f, 5l, 5m, 6n, 6p, 6s) and the HRMS analysis of \(\beta\)-lactams (5a, 5b, 5c, 5e, 5g, 5h, 5i, 5j, 5k, 5o, 5q, 5r, 6o and 6q) further confirmed the formation of the target products.

### Table 2. 3-Oxy/thio/seleno-4-pyrazolyl-\(\beta\)-lactams 5a-m,o-r and 6n-q,s (Scheme 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>R¹</th>
<th>Yield (^a) (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_6)H(_5)S</td>
<td>C(_6)H(_5)</td>
<td>5a (79)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>2</td>
<td>C(_6)H(_5)S</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5b (74)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>3</td>
<td>C(_6)H(_5)S</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>5c (69)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>4</td>
<td>C(_6)H(_5)S</td>
<td>4-ClC(_6)H(_4)</td>
<td>5d (52)(^d)</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>C(_6)H(_5)CH(_2)S</td>
<td>C(_6)H(_5)</td>
<td>5e (63)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>6</td>
<td>C(_6)H(_5)CH(_2)S</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5f (68)(^d)</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>C(_6)H(_5)CH(_2)S</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>5g (56)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>8</td>
<td>C(_6)H(_5)Se</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5h (75)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>9</td>
<td>C(_6)H(_5)Se</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>5i (68)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>10</td>
<td>C(_6)H(_5)CH(_2)Se</td>
<td>C(_6)H(_5)</td>
<td>5j (71)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>11</td>
<td>C(_6)H(_5)CH(_2)Se</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5k (66)(^c)</td>
<td>Oil</td>
</tr>
<tr>
<td>12</td>
<td>C(_6)H(_5)O</td>
<td>C(_6)H(_5)</td>
<td>5l (62)(^d)</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>C(_6)H(_5)O</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5m (57)(^d)</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>C(_6)H(_5)O</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>–</td>
<td>6n (61)(^d)</td>
</tr>
<tr>
<td>15</td>
<td>CH(_3)O</td>
<td>C(_6)H(_5)</td>
<td>5o (63)(^c)</td>
<td>6o (20)(^c)</td>
</tr>
<tr>
<td>16</td>
<td>CH(_3)O</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5p (65)(^b,c)</td>
<td>6p (22)(^d)</td>
</tr>
<tr>
<td>17</td>
<td>CH(_3)O</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>5q (55)(^c)</td>
<td>6q (28)(^c)</td>
</tr>
<tr>
<td>18</td>
<td>CH(_3)COO</td>
<td>4-CH(_3)OC(_6)H(_4)</td>
<td>5r (64)(^c)</td>
<td>–</td>
</tr>
<tr>
<td>19</td>
<td>CH(_3)COO</td>
<td>CH(_2)C(_6)H(_5)</td>
<td>–</td>
<td>6s (69)(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Yields quoted are for the isolated products characterized by FT-IR, NMR (\(^1\)H, \(^13\)C, \(^77\)Se). \(^b\) The structure of this molecule was also established from single crystal X-ray data (Figure 1). \(^c\) The
mass of the products were analyzed on the basis of EI-MS and HRMS (oily compounds). The products were characterized on the basis of CHN elemental analysis (solid compounds).

The trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams 5, 6 are air- and moisture-stable, soluble in solvents such as dichloromethane, chloroform, acetone, toluene and ethyl acetate. trans-4-Pyrazolyl-β-lactams 5d, 5f, 5l, 5m, 5p and cis-4-pyrazolyl-β-lactams 6n, 6p, 6s were obtained as stable solids while the rest were obtained as yellowish brown oils.

Scheme 3. Plausible mechanism for synthesis of 3-oxy/thio/seleno-4-pyrazolyl-β-lactams 5, 6.
All these cycloaddition reactions were found to be highly stereoselective and indicate that the presence of different groups in the substrate moieties effect the stereochemical outcome of the desired pyrazolyl-β-lactams. The plausible mechanism for the formation of trans- and cis-β-lactams having a variety of substitutions at the C-3 position is depicted in Scheme 3. The synthesis of pyrazolyl-β-lactams proceeds with the generation of ketene A by treatment of 2-methoxy-phenoxo/benzyl/phenylthio/phenylseleno ethanoic acids or acetoxyacetyl chloride 4 with phosphorus oxychloride and triethylamine in refluxing toluene. Further, the nucleophilic attack of the imino nitrogen of the E-imine on the face of the ketene A (RX = C₆H₅O, C₆H₅S, C₆H₂Se, C₆H₅CH₂S, C₆H₅CH₂Se CH₃O, CH₃COO) generating the zwitterionic intermediate B and C respectively, which on direct ring closure or conrotatory electrocyclicization afforded the stereoselective trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6).

The plausible mechanism included above is in accordance with our earlier publication of stereoselective synthesis of cis- and trans-3-alkoxy-β-lactams, where mechanistic aspects were discussed in detail with relevance to reports available in the literature. In the present work, all the 2-benzyl/phenylthio/seleno ethanoic acids (Moore ketenes having S/Se-alkyl or aryl groups) on treatment with pyrazolyl substituted imines gives trans-β-lactams as suggested in the literature. Whereas, the Bose-Evans ketenes (having O-alkyl or O-aryl groups) should give cis-β-lactams, which have been achieved in the synthesis of cis-3-methoxy/acetoxy-β-lactams with low yield. However, this cycloaddition did not afford the targeted products at lower temperature, therefore high temperature selectively favors the formation of predominantly trans-β-lactams. Further, competition between the rate of isomerisation and direct ring closure, temperature and substituents plays an important role towards the stereoselectivity of these Staudinger cycloadditions which is well documented in literature.

The crystal structure of trans-1-(4′-methoxyphenyl)-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)azetidin-2-one 5p was established by X-ray crystallographic analysis (Figure 1). It was crystallized from dichloromethane-hexane (3:1) as a colorless crystalline solid suitable for single crystal X-ray diffraction. A perspective view of the molecular structure with atom numbering has been given in Figure 1.
A single crystal unit of β-lactam 5p exhibit intermolecular hydrogen bonding interactions with two crystal units. The methoxy oxygen of [O(2)] of one crystal unit is showing hydrogen bonding with C4–H [H(6A)] of the other crystal unit. Whereas, carbonyl oxygen of the same
crystal unit [O(3)] shows hydrogen bonding with the phenyl hydrogen of the pyrazole ring [H(3A)] of the other crystal unit respectively (Figure 2, Table 3). In comparison to hydrogen bonding, quite weak intermolecular C–H interactions are also present.

Representatives of all these new trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (5, 6) have been submitted for Molecular Docking studies to examine their binding affinities/interactions which will be followed by in vitro screening of the best fit molecules for their bioactivities such as antibacterial, antitumor, antiviral and antimicrobial activity. Further elaboration of the pyrazole substituted β-lactams (5, 6) to potential spirocyclic and bicyclic-β-lactams is underway in our laboratory.

Conclusions

In conclusion, a successful attempt has been made towards the synthesis of novel monocyclic trans- and cis-3-oxy/thio/seleno-4-pyrazolyl-β-lactams. Substrate scope was also investigated by varying the R, R₁ and X groups R = C₆H₅, C₆H₄CH₂, CH₃, CH₃CO; X = O, S, Se; R₁ = C₆H₅, CH₂C₆H₅, 4-OCH₃C₆H₄, 4-ClC₆H₄. The X-ray crystallographic analysis of compound 5p allowed the stereochemistry at C-3 of trans-β-lactams 5 to be established.

Experimental Section

General. Melting points were determined in an open capillary on melting point apparatus Perfit GSI-MP-3. Fourier transform infrared spectra were recorded on a Thermo Scientific Nicolet iS50 (FTIR) spectrophotometer (ν max in cm⁻¹). ¹H (300 MHz), ¹³C (75 MHz) and ⁷⁷Se (57 MHz) NMR spectra were recorded on JEOL AL 300 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to Me₄Si as an internal standard (δ = 0 ppm) for ¹H NMR, CDCl₃ (δ = 77.0 ppm) for ¹³C NMR spectra and Me₂Se (δ = 0 ppm) for ⁷⁷Se NMR spectra. The mass spectra (EI-MS and HRMS) were obtained using a Waters Q-TOF Micromass (YB361) spectrometer (permissible % error = 5-10 ppm). The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer. Column chromatography was performed using Merck silica gel (60-120 mesh) using ethyl acetate-hexanes (10:90) as eluant system. Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck silica gel G using ethyl acetate-hexanes (10:90) as an eluant system. For visualization, TLC plates were stained with iodine vapors or observed under UV light.

The reactions for the preparation of pyrazole substituted β-lactams were carried out under dry and deoxygenated nitrogen atmosphere. Phosphorus oxychloride (Merck), triethylamine (Qualigen), ethyl acetoacetate (Merck), phenylhydrazine (Hi-media) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dimethylformamide and dichloromethane were dried and distilled over
anhydrous calcium chloride (CaCl₂) and phosphorus pentoxide (P₂O₅) respectively. Toluene was distilled under N₂ from sodium-benzophenone immediately before use.

Starting materials pyrazolone 1 and pyrazolecarbaldehyde 2 were prepared following the methods described in literature. The IR, NMR, mass and elemental analysis for 1 [127-128 °C (literature m.p. 128-130 °C)] and 2 [138-139 °C (literature m.p. 140-141 °C)] are as given in the cited reference.

Typical procedure for the preparation of Schiff’s bases 3a-d. A solution of the appropriate primary amine (1 mmol) and 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (1 mmol) in the presence of molecular sieves (4 Å) in dry methylene chloride (15 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered to remove the molecular sieves and the solvent was evaporated under vacuum to yield the imine, which was recrystallized from methylene chloride: hexane to afford a crystalline solid.

N-[(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)methylene]benzenamine (3a). Yellow crystalline solid; yield 85%; mp 102-103 °C; ¹H NMR (300 MHz, CDCl₃): δH 2.54 (3H, s, CH₃), 6.94-7.47 (10H, m, ArH), 8.29 (1H, s, –N=CH–); ¹³C NMR (75 MHz, CDCl₃): δC 14.7, 114.8, 115.8, 118.3, 120.7, 124.8, 125.4, 128.1, 128.9, 129.0, 137.7, 150.4, 151.0, 152.8; Anal. Calcd. for C₁₇H₁₄ClN₃: C 69.03, H 4.77, N 14.21%. Found: C 68.87, H 4.73, N 14.13%.

N-[(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)methylene]-4-methoxybenzenamine (3b). Yellow crystalline solid; yield: 82%; mp 117-119 °C; ¹H NMR (300 MHz, CDCl₃): δH 2.54 (3H, s, CH₃), 3.70 (3H, s, OCH₃), 6.75-7.49 (9H, m, ArH), 8.31 (1H, s, –N=CH–); ¹³C NMR (75 MHz, CDCl₃): δC 14.7, 55.2, 114.2, 116.0, 121.8, 124.8, 128.2, 128.5, 129.1, 137.8, 145.7, 149.2, 149.3, 150.3, 158.0; Anal. Calcd. for C₁₈H₁₆ClN₃O: C 66.36, H 4.95, N 12.90%. Found: C 66.20, H 4.73, N 14.13%.

N-[(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)methylene](phenyl)methanamine (3c). Yellow crystalline solid; yield 79%; mp 129-131 °C; ¹H NMR (300 MHz, CDCl₃): δH 2.54 (3H, s, CH₃), 4.75 (2H, s, CH₂), 7.21-7.53 (10H, m, ArH), 8.35 (1H, s, –N=CH–); ¹³C NMR (75 MHz, CDCl₃): δC 14.7, 65.9, 115.3, 124.8, 126.7, 127.4, 127.5, 127.9, 128.1, 128.3, 128.4, 128.9, 137.8, 139.7, 150.3, 152.7, 152.8; Anal. Calcd. for C₁₈H₁₆ClN₃: C 69.79, H 5.21, N 13.56%. Found: C 69.61, H 15.18, N 13.69%.

4-Chloro-N-[(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)methylene]benzenamine (3d). Yellow crystalline solid; yield 87%; mp 153-154 °C; ¹H NMR (300 MHz, CDCl₃): δH 2.79 (3H, s, CH₃), 7.16-7.39 (9H, m, ArH), 7.50 (1H, s, N=CH); ¹³C NMR (75 MHz, CDCl₃): δC 12.8, 108.7, 120.2, 123.7, 126.4, 129.4, 130.2, 132.8, 133.0, 139.7, 147.3, 149.5, 160.3; Anal. Calcd. for C₁₇H₁₅Cl₂N₁: C 61.83, H 3.94, N 12.73%. Found: C 61.65, H 3.89, N 12.68%.

Typical procedure for preparation of β-lactams 5, 6. Phosphorus oxychloride (POCl₃, 0.69 mmol, 1.5 equiv.) was added dropwise to a solution of 2-substituted ethanoic acid (0.55 mmol, 1.2 equiv.), Schiff’s base (0.46 mmol, 1 equiv.) and triethylamine (1.38 mmol, 3 equiv.) under nitrogen atmosphere, at reflu xing temperature, with constant stirring. The reaction mixture was...
refluenced for 3-4 h. The solvent was evaporated and the crude product was extracted with CH$_2$Cl$_2$. The organic layer was washed with water (3 × 10 ml), 1N HCl (3 × 10 ml), 5% NaHCO$_3$ (3 × 10 ml) and brine (3 × 10 ml), then dried (Na$_2$SO$_4$) and concentrated. The residue was purified by silica gel column chromatography with hexane/EtOAc (90:10) as eluant to afford pure products.

1-Phenyl-3-phenylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5a).

Yellowish brown oil; yield 79%; IR (ν$_{max}$ cm$^{-1}$): 1741 (C=O); $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.21 (3H, s, CH$_3$), 4.45 (1H, d, $^3$J$_{HH}$ 2.4 Hz, C4–H), 4.74 (1H, d, $^3$J$_{HH}$ 2.7 Hz, C3–H), 6.94-7.48 (15H, m, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 13.0, 54.4, 58.9, 111.7, 116.7, 119.8, 124.5, 124.7, 125.1, 126.1, 127.0, 128.2, 128.3, 129.0, 129.2, 129.4, 131.8, 132.6, 137.2, 137.8, 148.0, 162.6; HRMS (EI): m/z [M+H] Calcd. for C$_{25}$H$_{22}$ClN$_3$OS: 446.1093. Found: 446.1058.

trans-1-(4′-Methoxyphenyl)-3-phenylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5b).

Yellowish brown oil; yield 74%; IR (ν$_{max}$ cm$^{-1}$): 1737 (C=O); $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.19 (3H, s, CH$_3$), 3.64 (3H, s, OCH$_3$), 4.42 (1H, d, $^3$J$_{HH}$ 2.4 Hz, C4–H), 4.69 (1H, d, $^3$J$_{HH}$ 2.4 Hz, C3–H), 6.64-7.43 (14H, m, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 12.9, 29.6, 54.2, 55.0, 55.1, 58.7, 111.7, 114.3, 114.4, 118.0, 124.5, 124.6, 126.0, 128.0, 128.1, 128.8, 129.1, 130.5, 130.6, 131.8, 131.9, 132.5, 137.7, 147.9, 156.3, 161.8; HRMS (EI): m/z [M+H] Calcd. for C$_{26}$H$_{23}$ClN$_3$O$_2$: 476.1199. Found: 476.1131.

1-Benzyl-3-phenylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5c).

Yellowish brown oil; yield 69%; IR (ν$_{max}$ cm$^{-1}$): 1752 (C=O); $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.07 (3H, s, CH$_3$), 3.65 (1H, d, $^3$J$_{HH}$ 15 Hz, CH$_2$), 4.10 (1H, d, $^3$J$_{HH}$ 2.4 Hz, C4–H), 4.38 (1H, d, $^3$J$_{HH}$ 1.8 Hz, C3–H), 4.62 (1H, d, $^3$J$_{HH}$ 15 Hz, CH$_2$), 6.67-7.48 (15H, m, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 12.6, 44.9, 52.9, 58.4, 111.2, 124.8, 126.2, 127.6, 128.2, 128.5, 128.7, 129.0, 129.2, 131.0, 134.2, 134.3, 137.9, 148.6, 164.9; HRMS (EI): m/z [M+H] Calcd. for C$_{26}$H$_{22}$ClN$_3$OS: 460.1250. Found: 460.1236.

1-(4′-chlorophenyl)-3-phenylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5d).

White crystalline solid; yield 52%; mp 164-165 °C; IR (ν$_{max}$ cm$^{-1}$): 1726 (C=O); $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.20 (3H, s, CH$_3$), 4.90 (1H, d, $^3$J$_{HH}$ 1.8 Hz, C3–H), 5.29 (1H, d, $^3$J$_{HH}$ 1.8 Hz, C4–H), 6.82-7.46 (14H, m, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 13.0, 55.7, 85.7, 110.8, 114.6, 114.8, 115.5, 118.2, 121.1, 122.5, 124.7, 126.1, 128.4, 129.0, 129.5, 129.7, 129.9, 130.0, 135.5, 137.7, 148.0, 156.9, 161.4; Anal. Calcd for C$_{23}$H$_{19}$ClN$_3$OS: C, 62.50; H, 3.99; N, 8.75; S, 6.67%. Found: C, 62.32; H, 3.91; N, 8.67; S, 6.61%.

trans-1-Phenyl-3-benzylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5e).

Yellowish brown oil; yield 63%; IR (ν$_{max}$ cm$^{-1}$): 1740 (C=O); $^1$H NMR (300 MHz, CDCl$_3$): δ$_H$ 2.08 (3H, s, CH$_3$), 3.82-3.93 (2H, m, $^3$J$_{HH}$ 13.5 Hz, CH$_2$S), 4.15 (1H, d, $^3$J$_{HH}$ 2.7 Hz, C4–H), 4.46 (1H, d, $^3$J$_{HH}$ 2.7 Hz, C3–H), 6.96-7.45 (15H, m, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ$_C$ 12.9, 29.7, 35.3, 54.8, 56.0, 111.7, 116.8, 124.4, 124.6, 124.7, 125.1, 126.0, 127.3, 128.2, 128.6, 128.9, 129.0, 129.1, 129.2, 137.2, 137.5, 137.7, 147.9, 162.9; HRMS (EI): m/z [M+H] Calcd. for C$_{23}$H$_{22}$ClN$_3$OS: 460.1250. Found: 460.1289.

trans-1-(4′-Methoxyphenyl)-3-benzylthio-4-(5′-chboro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5f).

Yellowish solid; yield: 68%; mp 39-40 °C; IR (ν$_{max}$ cm$^{-1}$): 1743 (C=O);
trans-1-Benzyl-3-benzylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5g). Yellowish brown oil; yield 56%; IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1756 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>): δH 1.92 (3H, s, CH₃), 3.66 (1H, d, ³J<sub>NN</sub> 13.2 Hz, CH₂S), 3.79 (1H, d, ³J<sub>NN</sub> 14.7 Hz, CH₂N), 3.85 (1H, d, ³J<sub>NN</sub> 13.5 Hz, CH₂S), 3.99 (1H, d, ³J<sub>NN</sub> 2.4 Hz, C₄–H), 4.07 (1H, d, ³J<sub>NN</sub> 2.4 Hz, C₃–H), 4.52 (1H, d, ³J<sub>NN</sub> 14.7 Hz, CH₃N), 7.04-7.47 (15H, m, ArH); ¹³C NMR (75 MHz, CDCl<sub>3</sub>): δC 12.6, 35.1, 45.2, 54.2, 55.1, 111.4, 124.7, 126.0, 126.2, 128.8, 129.0, 129.3, 130.9, 135.6, 143.7, 150.3, 151.1, 156.4, 162.6, 164.6, 172.4, 174.0; ⁷⁷Se NMR: δ<sub>Se</sub> 350.5; HRMS (EI): m/z [M+H] Calcd. for C<sub>₆</sub>H<sub>₂</sub>ClN<sub>₃</sub>O₂Se: 474.1406. Found: 474.1375.
	rans-1-(4′-Methoxyphenyl)-3-phenylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5h). Yellowish brown oil; yield 75%; IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1735 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>): δH 2.15 (3H, s, CH₃), 3.65 (3H, s, OCH₃), 4.43 (1H, d, ³J<sub>NN</sub> 2.4 Hz, C₄-H), 4.65 (1H, d, ³J<sub>NN</sub> 2.1 Hz, C₃-H), 6.64-7.62 (14H, m, ArH); ¹³C NMR (75 MHz, CDCl<sub>3</sub>): δC 13.1, 23.5, 29.3, 29.8, 37.0, 43.6, 43.7, 48.4, 50.5, 52.1, 54.5, 55.1, 71.2, 108.0, 112.2, 114.5, 118.0, 124.7, 126.0, 126.2, 128.8, 129.0, 129.3, 130.9, 135.6, 138.0, 148.0, 156.4, 162.6, 164.6, 172.4, 174.0; ³Se NMR: δ<sub>Se</sub> 350.5; HRMS (EI): m/z [M+H] Calcd. for C<sub>₂₆</sub>H<sub>₂</sub>ClN<sub>₃</sub>NaOSe: 524.0644. Found: 524.0699.

1-Benzyl-3-phenylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5i). Yellowish brown oil; yield 68%; IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1724 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>): δH 2.02 (3H, s, CH₃), 3.63 (1H, d, ³J<sub>NN</sub> 14.7 Hz, CH₂Ph), 4.08 (1H, d, ³J<sub>NN</sub> 2.1 Hz, C₄–H), 4.39 (1H, d, ³J<sub>NN</sub> 2.1 Hz, C₃–H), 4.53 (1H, d, ³J<sub>NN</sub> 14.7 Hz, CH₂Ph), 6.61-7.60 (15H, m, ArH); ¹³C NMR (75 MHz, CDCl<sub>3</sub>): δC 12.6, 29.8, 32.0, 44.1, 45.1, 50.1, 53.3, 81.2, 111.5, 124.8, 126.1, 127.2, 127.6, 127.7, 128.2, 128.3, 128.6, 128.9, 129.0, 129.4, 129.5, 132.1, 134.4, 136.6, 150.3, 160.3, 164.1; HRMS (EI): m/z [M+Na] Calcd. for C<sub>₆</sub>H<sub>₁₂</sub>ClN<sub>₄</sub>NaOSe: 530.0514. Found: 530.0625.

1-Phenyl-3-benzylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5j). Yellowish brown oil; yield 71%; mp 118-119 °C; IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1741 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>): δH 2.10 (3H, s, CH₃), 3.93-4.03 (2H, q, ³J<sub>NN</sub> 12 Hz, CH₂), 4.24 (1H, d, ³J<sub>NN</sub> 2.4 Hz, C₄–H), 4.52 (1H, d, ³J<sub>NN</sub> 2.4 Hz, C₃–H), 6.96-7.43 (15H, m, ArH); ¹³C NMR (75 MHz, CDCl<sub>3</sub>): δC 13.4, 14.6, 23.2, 27.9, 29.8, 29.9, 30.2, 32.4, 47.5, 50.8, 54.8, 54.9, 55.5, 112.5, 117.1, 117.2, 124.7, 125.1, 125.2, 126.5, 127.5, 128.7, 129.0, 129.2, 129.4, 129.6, 129.8, 136.0, 137.7, 137.9, 138.3, 138.6, 148.4, 148.5, 163.8, 164.0; HRMS (EI): m/z [M+H] Calcd. for C<sub>₆</sub>H<sub>₁₂</sub>ClN<sub>₃</sub>OSe: 508.0694. Found: 508.0660.

trans-1-(4′-Methoxyphenyl)-3-benzylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5k). Yellowish brown oil; yield 66%; IR (ν<sub>max</sub>, cm<sup>-1</sup>): 1748 (C=O); ¹H NMR (300 MHz, CDCl<sub>3</sub>): δH 2.04 (3H, s, CH₃), 3.59 (3H, s, OCH₃), 3.86-3.95 (2H, dd, ³J<sub>NN</sub> 15.6, 15.9
1-Phenyl-3-phenoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5i). White crystalline solid; yield 62%; IR (νmax, cm−1): 1767 (C=O); 1H NMR (300 MHz, CDCl3): δH 2.25 (3H, s, CH3), 4.98 (1H, d, 3JHH 1.8 Hz, C4–H), 5.37 (1H, d, 3JHH 1.8 Hz, C3–H), 6.86-7.50 (15H, m, ArH); 13C NMR (75 MHz, CDCl3): δC 13.0, 55.6, 85.2, 110.9, 114.8, 115.3, 117.2, 120.1, 122.5, 124.8, 124.9, 126.5, 128.5, 129.1, 129.3, 129.9, 136.7, 137.6, 148.3, 156.9, 157.1, 162.0, 166.2; Anal. Calcd. for C27H25ClN2O2Se: C, 67.72; H, 4.77; N, 9.06%. Found: C, 69.69; H, 4.63; N, 9.68%.

trans-1-(4′-Methoxyphenyl)-3-phenoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5m). White crystalline solid; yield 57%; mp 145-146 °C; IR (νmax, cm−1): 1739 (C=O); 1H NMR (300 MHz, CDCl3): δH 2.19 (3H, s, CH3), 3.53 (3H, s, OCH3), 4.64 (1H, d, 3JHH 1.8 Hz, C4–H), 4.81 (1H, d, 3JHH 1.8 Hz, C3–H), 6.97-7.49 (10H, m, ArH); 13C NMR (75 MHz, CDCl3): δC 11.2, 40.4, 55.2, 86.8, 114.1, 114.4, 119.0, 120.2, 120.4, 122.6, 126.4, 128.0, 129.0, 129.4, 134.2, 139.7, 147.6, 156.3, 157.5, 165.0; Anal. Calcd. for C26H21ClN2O2: C, 69.70; H, 4.82; N, 9.14%. Found: C, 67.72; H, 4.77; N, 9.06%.

1-Benzyl-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1H-pyrazol-4′-yl)-azetidin-2-one (5q). Yellowish brown oil; yield 55%; IR (νmax, cm−1): 1739 (C=O); 1H NMR (300 MHz, CDCl3): δH 2.07 (3H, s, CH3), 3.45 (3H, s, OCH3), 3.78 (1H, d, 3JHH 14.7 Hz, CH2), 4.19 (1H, d, 3JHH 1.8 Hz, C4–H), 4.63 (1H, d, 3JHH 1.8 Hz, C3–H), 4.70 (1H, d, 3JHH 14.7 Hz, CH2), 7.07-7.44 (10H, m, ArH); 13C NMR (75 MHz, CDCl3): δC 13.6, 30.6, 32.0, 45.5, 54.5, 58.6, 89.3, 125.6, 128.8, 129.6, 129.7, 129.8, 158.1, 166.5; HRMS (EI): m/z [M+Na]+ Calcd. for C21H21ClN2O2: 382.1322. Found: 382.1306.
trans-1-(4’-Methoxyphenyl)-3-acetoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (5r). Yellowish brown oil; yield 64%; IR (ν_max, cm⁻¹): 1743 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.09 (3H, s, CH₃), 2.21 (3H, s, CH₃), 3.68 (3H, s, OCH₃), 4.80 (1H, d, J_HH 1.8 Hz, C4-H), 5.88 (1H, d, J_HH 1.8 Hz, C3-H), 6.71-7.46 (15H, m, ArH); ¹³C NMR (75 MHz, CDCl₃): δ_C 12.9, 20.4, 29.7, 55.7, 60.8, 80.6, 111.0, 114.6, 118.5, 124.9, 126.3, 128.3, 128.9, 130.2, 137.8, 148.2, 156.8, 160.3, 169.2, 169.7, 171.4; HRMS (EI): m/z [M+Na] Calcd. for C₂₂H₂₀ClN₃NaO₄: 448.0940. Found: 448.0980.

1-Benzyl-3-phenoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (6n). White crystalline solid; yield 61%; mp 109-110 °C; IR (ν_max, cm⁻¹): 1733 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.29 (3H, s, CH₃), 3.92 (1H, d, J_HH 14.4Hz, CH₂), 4.78 (1H, d, J_HH 4.8 Hz, C4-H), 4.85 (1H, d, J_HH 14.4 Hz, CH₂), 5.40 (1H, d, J_HH 4.8 Hz, C3–H), 6.77-7.43 (15H, m, ArH); ¹³C NMR (75 MHz, CDCl₃): δ_C 13.7, 29.8, 44.6, 53.1, 81.8, 109.0, 114.5, 115.0, 121.4, 122.0, 124.8, 127.1, 128.1, 128.7, 128.8, 128.9, 129.2, 129.5, 134.5, 138.0, 149.5, 156.7, 164.4; Anal. Calcd. for C₂₆H₂₅ClN₂O₂: C, 70.34; H, 5.00; N, 9.47%. Found: C, 70.19; H, 4.98; N, 9.39%.

1-Phenyl-3-methoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (6o). Yellowish brown oil; yield 20%; IR (ν_max, cm⁻¹): 1742 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.19 (3H, s, CH₃), 3.41 (3H, s, OCH₃), 4.74 (1H, d, J_HH 5.1 Hz, C4–H), 5.18 (1H, d, J_HH 3.6 Hz, C3–H), 6.97-7.52 (10H, m, ArH); ¹³C NMR (75 MHz, CDCl₃): δ_C 13.2, 13.6, 22.2, 28.8, 28.9, 29.1, 29.6, 53.0, 58.5, 58.7, 84.0, 114.9, 116.2, 116.6, 123.9, 124.2, 124.3, 124.6, 127.4, 127.7, 128.3, 128.5, 128.7, 129.1, 157.5; HRMS (EI): m/z [M+Na] Calcd. for C₂₀H₁₅ClN₃NaO₂: 390.0985. Found: 390.0936.

cis-1-(4’-Methoxyphenyl)-3-methoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (6p). Colorless crystalline solid; yield 22%; mp 154-155 °C; IR (ν_max, cm⁻¹): 1749 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.21 (3H, s, CH₃), 3.45 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 4.79 (1H, d, J_HH 4.8 Hz, C4–H), 5.20 (1H, d, J_HH 4.8 Hz, C3–H), 6.77-7.57 (9H, m ArH); ¹³C NMR (75 MHz, CDCl₃): δ_C 13.9, 53.6, 55.2, 58.7, 84.7, 109.9, 114.5, 118.1, 124.7, 128.0, 128.9, 130.8, 138.2, 156.5, 163.2; Anal. Calcd. for C₂₁H₂₀ClN₂O₃: C, 63.40; H, 5.07; N, 10.56%. Found: C, 63.30; H, 5.02; N, 10.49%.

1-Benzyl-3-methoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (6q). Yellowish brown oil; yield 28%; IR (ν_max, cm⁻¹): 1755 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.20 (3H, s, CH₃), 3.32 (3H, s, OCH₃), 3.78 (1H, d, J_HH 14.4 Hz, CH₂), 4.52 (1H, d, J_HH 4.5 Hz, C4–H), 4.57 (1H, d, J_HH 4.5 Hz, C3–H), 4.71 (1H, d, J_HH 14.7 Hz, CH₂), 7.07-7.48 (10H, m, ArH); ¹³C NMR (75 MHz, CDCl₃): δ_C 13.9, 44.3, 52.7, 58.5, 85.5, 109.7, 124.7, 126.9, 128.0, 128.7, 128.9, 134.8, 138.2, 149.9, 166.1; HRMS (EI): m/z [M+H] Calcd. for C₂₁H₂₁ClN₃O₂: 382.1322. Found: 382.1306.

1-Benzyl-3-acetoxy-4-(5’-chloro-3’-methyl-1’-phenyl-1H-pyrazol-4’-yl)-azetidin-2-one (6s). White crystalline solid; yield 69%; mp 123-124 °C; IR (ν_max, cm⁻¹): 1731 (C=O); ¹H NMR (300 MHz, CDCl₃): δ_H 2.08 (3H, s, CH₃), 3.85 (1H, d, J_HH 14.7 Hz, CH₂N), 4.68 (1H, d, J_HH 4.8 Hz, C4–H), 4.82 (1H, d, J_HH 14.7 Hz, CH₂N), 5.68 (1H, d, J_HH 4.8 Hz, C3–H), 7.04-7.27 (10H, m,
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$C 19.6, 44.7, 60.2, 60.9, 70.1, 128.1, 128.3, 128.7, 128.9, 132.3, 134.2, 165.0, 168.8, 170.1, 172.1; Anal. Calcd. for C$_{22}$H$_{20}$ClN$_3$O$_3$: C, 64.47; H, 4.92; N, 10.25%. Found: C, 64.32; H, 4.87; N, 10.13%.

**Acknowledgements**


**Supporting Information**

$^1$H and $^{13}$C NMR spectra of some of representative β-lactams 5b, 5f, 5h, 5k, 5p, 5r and 6p. EIMS spectra of 5p and HRMS spectra of 5a, 5b, 5c, 5e, 5g, 5h, 5j, 5k, 5o, 5q, 5r.

**References and Notes**


http://dx.doi.org/10.1016/j.bmcl.2005.03.082

http://dx.doi.org/10.1016/j.bmcl.2010.01.113

http://dx.doi.org/10.1016/j.bmcl.2010.01.072

http://dx.doi.org/10.1016/j.bmc.2013.01.074

http://dx.doi.org/10.1016/j.bmc.2012.12.053

http://dx.doi.org/10.1016/j.bmcl.2013.02.064

http://dx.doi.org/10.1016/j.bmcl.2013.02.052

http://dx.doi.org/10.1016/j.ejmech.2010.05.018


http://dx.doi.org/10.1016/j.ejmech.2008.10.020

http://dx.doi.org/10.1016/j.bmcl.2007.10.002

http://dx.doi.org/10.1016/j.ejmech.2009.03.038

http://dx.doi.org/10.1016/j.bmc.2008.06.054

http://dx.doi.org/10.1016/j.bmcl.2011.11.069

http://dx.doi.org/10.3906/kim-1110-8


http://dx.doi.org/10.1021/jm00038a001

PII: S 0 0 4 0 - 4 0 3 9 ( 0 2 ) 0 2 8 7 4 - 5


http://dx.doi.org/10.1016/j.tet.2012.06.009

http://dx.doi.org/10.1080/00397910601133540

http://dx.doi.org/10.1016/j.jorganchem.2008.10.020

http://dx.doi.org/10.1016/j.tet.2006.03.050

http://dx.doi.org/10.1016/j.tetlet.2006.05.160

http://dx.doi.org/10.1016/j.tet.2007.02.001

http://dx.doi.org/10.1016/j.tet.2009.09.086

http://dx.doi.org/10.1016/j.jorganchem.2010.05.005


   http://dx.doi.org/10.1016/j.tet.2006.06.062


   http://dx.doi.org/10.1016/j.tetlet.2010.01.085

   http://dx.doi.org/10.1007/s00706-010-0346-9

   http://dx.doi.org/10.1016/j.tetlet.2010.01.085

   http://dx.doi.org/10.1007/s10870-011-0178-4

45. Crystal data for 5p: monoclinic, P 1 21/c 1, a = 11.0168(8) Å; b = 12.0862(8) Å; c = 15.2820(11) Å; α = 90°; β = 101.541(4)°; γ = 90°; V = 1993.7(2) Å³; Z = 4, ρCalcd = 1.325 Mg/cm³, μ(Mo-Kα) = 0.71073 Å, T = 296(2) K, full matrix least-square on F²; R₁ = 0.0478, wR²=0.1073 for 3534 [R(int.) = 0.0504] observed reflections [I>2σ(I)] and R₁=0.1060, wR²=0.1324 for all 12183 reflections. Single crystals were mounted on glass capillaries of Bruker AXS KAPPA APEX II diffractometer using graphite-monochromated Mo Kα radiation at room temperature. The data integration and reduction were processed with Bruker SAINT Software package. The crystal structures of 5p was solved by direct methods using Bruker SHELXS-97 and refined by full-matrix least squares method. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the ideal position with fixed isotropic U values and were riding. The empirical absorption corrections for these compounds were performed using SADBAD program. CCDC 963963 (5p) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

46. Sheldrick GM. SHELX-97 (Sheldrick 2008), programme for the solution and refinement of crystal structure. Goettingen, Germany; 1997.

47. Sheldrick, G. M. Sadbas, Programme for empirical absorption of area detector data. University of Goettingen, Germany, 1996.

   http://dx.doi.org/10.3998/ark.5550190.0010.903

   http://dx.doi.org/10.1021/ja00015a036