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

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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 $POCl_3$ and Et_3N in refluxing toluene furnished β-lactams (**5**, **6**). These synthesized β-lactams have been characterized by spectroscopic techniques viz. NMR (^1H, ^{13}C and ^{77}Se), 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-1*H*-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 taxoids[1] 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 inductors, 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

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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 *in vitro* cellular proliferation in various human cells.[3] A series of pyrazole derivatives have been showing high antiproliferative and antiangiogenic activities against human breast (MCF-7) and cervical carcinoma cells.[4-6] Identification of antitumor activity of pyrazole oxime ethers has been well documented.[7] Bonesi *et al.*[8] synthesized a substituted pyrazole and investigated their potential activity as inhibitors of angiotensin coverting enzyme (ACE). In literature, several reports have demonstrated substituted pyrazole and their derivatives as inhibitors of GSK3β Glycogen synthase kinase,[9] VEGFR2 kinase,[10] tyrosinase,[11] phagocytosis of opsonized blood cells[12] and arylamine N-acetyltransferase.[13]

Bondock *et al.*,[14] Radi *et al.*,[15] Sahu *et al.*,[16] Barsoum *et al.*[17] and Burguete *et al.*[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-I.[19,20] Antidepressant and anticonvulsant activity of pyrazole derivatives has been reported by Abdel Aziz *et al.*[21] The recent success of pyrazole derivatives as acyclonucleoside analogues,[15] blockers of divalent metal transporter 1 (DMT1)[22] and COX-2 inhibitors[23] has further highlighted the importance of this heterocyclic ring.

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

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

In previous studies we have demonstrated the synthesis of selenoalkanoic acids useful as β-lactam precursors,[30,31] novel 3-thio/seleno-β-lactams and their Lewis acid mediated functionalization,[32-38] stereoselective synthesis of *cis*- and *trans*-3-alkoxy-β-lactams,[39] spirocyclic-β-lactams,[2,34,40] (*Z*)- and (*E*)-3-allylidene-β-lactams,[41] 3-keto-β-lactams[42] and

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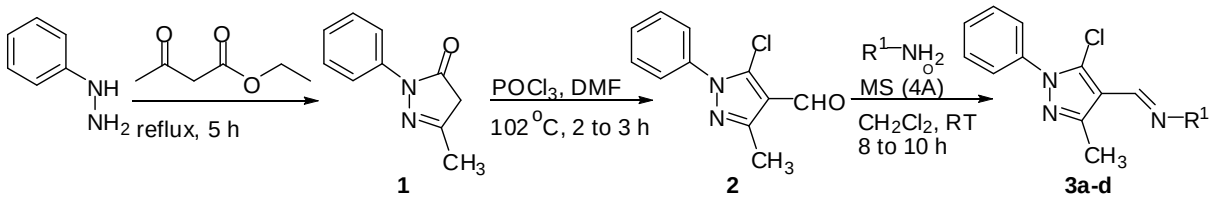
bicyclic-β-lactams.[43] Herein, we report the synthesis of novel monocyclic *trans*- and *cis*-3-oxy/thio/seleno-4-pyrazolyl-β-lactams (**5, 6**).

Results and Discussion

The study began with the chloropyrazolecarbaldehyde **2**, prepared from the pyrazolinone **1** following a literature procedure [44] (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 (^{1}H, ^{13}C) and CHN elemental analysis.



R^1 = C_6H_5, 4-$OCH_3C_6H_4$, $CH_2C_6H_5$, 4-ClC_6H_4

Scheme 1. Synthesis of pyrazolyl substituted Schiff′s bases **3a-d.**

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

Entry	R^1	Schiff′s base **3**[b]	Yield[a,b] (%)
1	C_6H_5	**3a**	85
2	4-$OCH_3C_6H_4$	**3b**	82
3	$CH_2C_6H_5$	**3c**	79
4	4-ClC_6H_4	**3d**	87

[a] Yields quoted for pure, isolated products. [b] Isolated products characterized by NMR (^{1}H, ^{13}C) 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 ($POCl_3$) and triethylamine (Et_3N) 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

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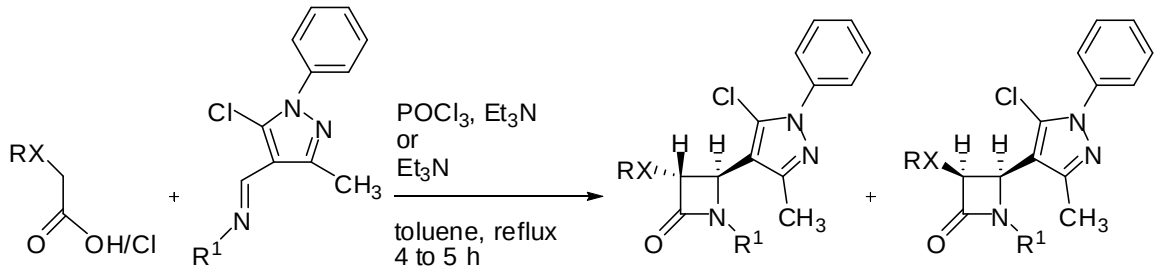
yield (Scheme 2, Table 2, Entry 1). The target product **5a** was purified by column chromatography on silica gel using ethyl acetate–hexane (10:90) as eluant and was identified as *trans*-1-(4′-methoxyphenyl)-3-phenylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)azetidin-2-one on the basis of ^{1}H NMR spectroscopy.



4 **3** **5(a-m, o-r)** *trans*-β-Lactams **6(n-q, s)** *cis*-β-Lactams

X = O, S, Se
R = CH_3CO, CH_3, C_6H_5, $C_6H_5CH_2$
R^1 = C_6H_5, 4-$OCH_3C_6H_4$, $CH_2C_6H_5$, 4-ClC_6H_4

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 R^1 substituents i.e. R = C_6H_5, $C_6H_5CH_2$, CH_3, CH_3CO; X = O, S, Se; R^1 = C_6H_5, $CH_2C_6H_5$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4 (Scheme 2, Table 2, Entries 1-19). A successful attempt has also been made towards the synthesis of *cis*-3-phenoxy/acetoxy-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 (^{1}H, ^{13}C, ^{77}Se), 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 ^{1}H NMR spectra.[35,39] The

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stereochemistry at C-3 and C-4 of β-lactams **5, 6** was established through single crystal X-ray crystallographic studies of **5p** (Figure 1).[45] In the EIMS spectrum of *trans*-3-methoxy-4-pyrazolyl-β-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 $[C_{21}H_{20}N_3O_3]^+$ and $[C_{13}H_{13}ClN_2NaO]^+$ respectively. CHN elemental analysis of the solid β-lactams (**5d**, **5f**, **5l**, **5m**, **6n**, **6p**, **6s**) and the HRMS analysis of β-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-β-lactams **5a-m,o-r** and **6n-q,s** (Scheme 2)

Entry	RX	R^1	Yield [a] (%)		Mp (°C)
			trans-β-lactams **5**	*cis*-β-lactams **6**	
1	C_6H_5S	C_6H_5	**5a** (79)[c]	–	Oil
2	C_6H_5S	4-$CH_3OC_6H_4$	**5b** (74)[c]	–	Oil
3	C_6H_5S	$CH_2C_6H_5$	**5c** (69)[c]	–	Oil
4	C_6H_5S	4-ClC_6H_4	**5d** (52)[d]	–	164-165
5	$C_6H_5CH_2S$	C_6H_5	**5e** (63)[c]	–	Oil
6	$C_6H_5CH_2S$	4-$CH_3OC_6H_4$	**5f** (68)[d]	–	39-40
7	$C_6H_5CH_2S$	$CH_2C_6H_5$	**5g** (56)[c]	–	Oil
8	C_6H_5Se	4-$CH_3OC_6H_4$	**5h** (75)[c]	–	Oil
9	C_6H_5Se	$CH_2C_6H_5$	**5i** (68)[c]	–	Oil
10	$C_6H_5CH_2Se$	C_6H_5	**5j** (71)[c]	–	Oil
11	$C_6H_5CH_2Se$	4-$CH_3OC_6H_4$	**5k** (66)[c]	–	Oil
12	C_6H_5O	C_6H_5	**5l** (62)[d]	–	118-119
13	C_6H_5O	4-$CH_3OC_6H_4$	**5m** (57)[d]	–	145-146
14	C_6H_5O	$CH_2C_6H_5$	–	**6n** (61)[d]	109-110
15	CH_3O	C_6H_5	**5o** (63)[c]	**6o** (20)[c]	Oil
16	CH_3O	4-$CH_3OC_6H_4$	**5p** (65)[b,c]	**6p** (22)[d]	84-85/154-155
17	CH_3O	$CH_2C_6H_5$	**5q** (55)[c]	**6q** (28)[c]	Oil
18	CH_3COO	4-$CH_3OC_6H_4$	**5r** (64)[c]	–	Oil
19	CH_3COO	$CH_2C_6H_5$	–	**6s** (69)[d]	123-124

[a] Yields quoted are for the isolated products characterized by FT-IR, NMR (^1H, ^{13}C, ^{77}Se). [b] The structure of this molecule was also established from single crystal X-ray data (Figure 1). [c] The

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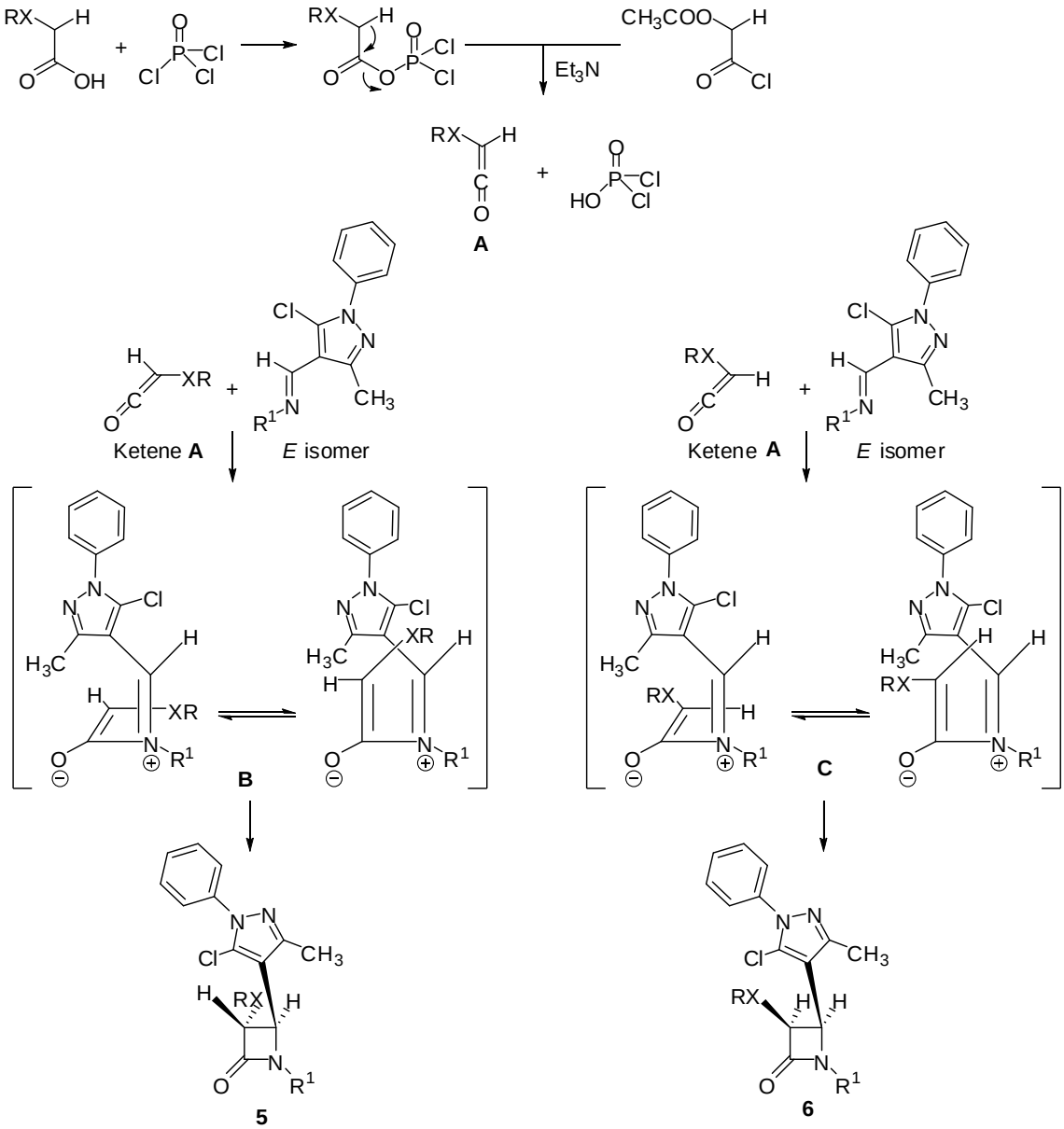
mass of the products were analyzed on the basis of EI-MS and HRMS (oily compounds). [d] The products were characterized on the basis of CHN elemental analysis (solid compounds).

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.**

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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-/phenoxy/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 = C_6H_5O, C_6H_5S, C_6H_5Se, $C_6H_5CH_2S$, $C_6H_5CH_2Se$ CH_3O, CH_3COO) generating the zwitterionic intermediate **B** and **C** respectively, which on direct ring closure or conrotatory electrocyclization 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,[39] where mechanistic aspects were discussed in detail with relevance to reports available in the literature.[48-50] 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.[48-50] 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.[39,48-50]

The crystal structure of *trans*-1-(4′-methoxyphenyl)-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)azetidin-2-one **5p** was established by X-ray crystallographic analysis (Figure 1).[45] 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.

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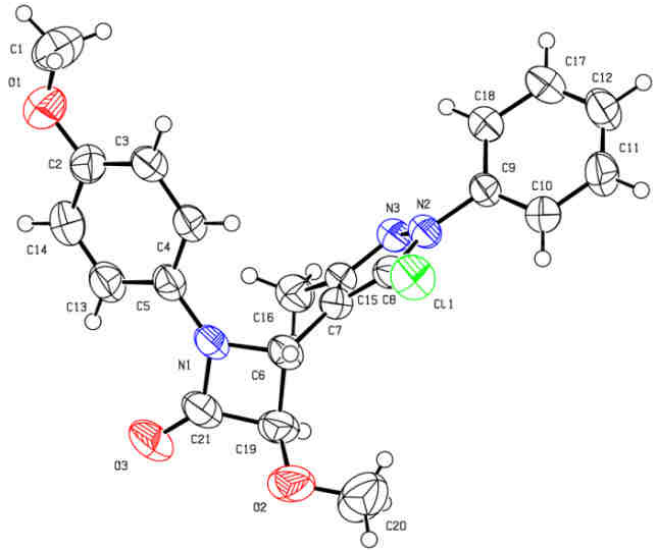

Figure 1. X-ray crystal structure of **5p.**

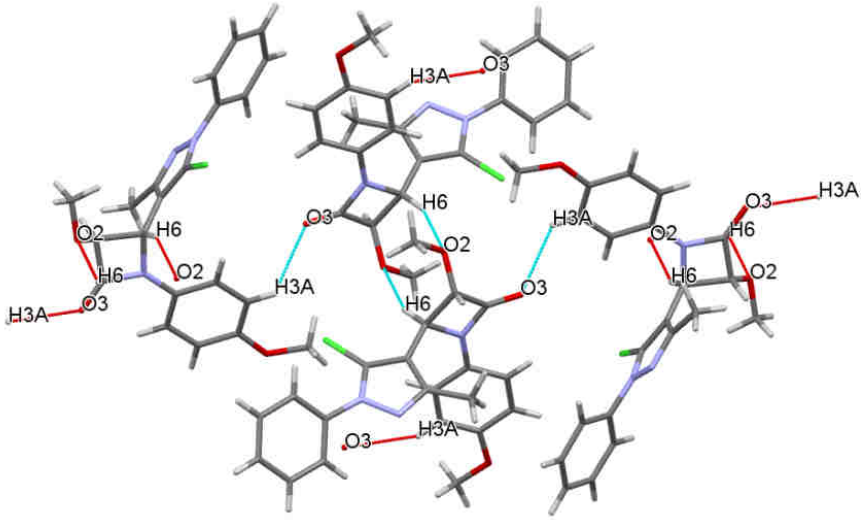

Figure 2. Hydrogen bonding interactions in **5p.**

Table 3. Hydrogen bonding interactions for compound **5p**

Entry	Intermolecular hydrogen bond (Å)	Bond Length (Å)
1.	O(2).....H(6)	2.505
2.	O(3).....H(3A)	2.612

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

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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, R^1 and X groups R = C_6H_5, $C_6H_5CH_2$, CH_3, CH_3CO; X = O, S, Se; R^1 = C_6H_5, $CH_2C_6H_5$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4. 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), ^{13}C (75 MHz) and ^{77}Se (57 MHz) NMR spectra were recorded on JEOL AL 300 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to Me_4Si as an internal standard (δ = 0 ppm) for ^1H NMR, $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra and Me_2Se (δ = 0 ppm) for ^{77}Se 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

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anhydrous calcium chloride ($CaCl_2$) and phosphorus pentoxide (P_2O_5) respectively. Toluene was distilled under N_2 from sodium-benzophenone immediately before use.

Starting materials pyrazolone **1** and pyrazolecarbaldehyde **2** were prepared following the methods described in literature.[44] The IR, NMR, mass and elemental analysis for **1** [127-128 °C (literature[44] m.p. 128-130 °C)] and **2** [138-139 °C (literature[44] 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-1*H*-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-1*H*-pyrazol-4′-yl)methylene]benzenamine (3a).** Yellow crystalline solid; yield 85%; mp 102-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.54 (3H, s, CH_3), 6.94-7.47 (10H, m, ArH), 8.29 (1H, s, –N=CH–); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{17}H_{14}ClN_3$: 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-1*H*-pyrazol-4′-yl)methylene]-4-methoxybenzenamine (3b).** Yellow crystalline solid; yield: 82%; mp 117-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.54 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 6.75-7.49 (9H, m, ArH), 8.31 (1H, s, -N=CH-); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{18}H_{16}ClN_3O$: C 66.36, H 4.95, N 12.90%. Found: C 66.20, H 4.92, N 12.85%.

***N*-[(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)methylene](phenyl)methanamine (3c).** Yellow crystalline solid; yield 79%; mp 129-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.54 (3H, s, CH_3), 4.75 (2H, s, CH_2), 7.21-7.53 (10H, m, ArH), 8.35 (1H, s, –N=CH–); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{18}H_{16}ClN_3$: C 69.79, H 5.21, N 13.56%. Found: C 69.61, H 5.18, N 13.49%.

4-Chloro-*N*-[(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)methylene]benzenamine (3d). Yellow crystalline solid; yield 87%; mp 153-154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.79 (3H, s, CH_3), 7.16-7.39 (9H, m, ArH), 7.50 (1H, s, N=CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{17}H_{13}Cl_2N_3$: 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 ($POCl_3$, 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 refluxing temperature, with constant stirring. The reaction mixture was

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refluxed for 3-4 h. The solvent was evaporated and the crude product was extracted with CH_2Cl_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_2SO_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′-chloro-3′-methyl-1′-phenyl-1*H*-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, $^3J_{HH}$ 2.4 Hz, C4–H), 4.74 (1H, d, $^3J_{HH}$ 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 $C_{25}H_{21}ClN_3OS$: 446.1093. Found: 446.1058.

***trans*-1-(4′-Methoxyphenyl)-3-phenylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-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, $^3J_{HH}$ 2.4 Hz, C4-H), 4.69 (1H, d, $^3J_{HH}$ 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 $C_{26}H_{23}ClN_3O_2S$: 476.1199. Found: 476.1131.

1-Benzyl-3-phenylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-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, $^3J_{HH}$ 15 Hz, CH_2), 4.10 (1H, d, $^3J_{HH}$ 2.4 Hz, C4–H), 4.38 (1H, d, $^3J_{HH}$ 1.8 Hz, C3–H), 4.62 (1H, d, $^3J_{HH}$ 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 $C_{26}H_{23}ClN_3OS$: 460.1250. Found: 460.1236.

1-(4′-chlorophenyl)-3-phenylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-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, $^3J_{HH}$ 1.8 Hz, C3–H), 5.29 (1H, d, $^3J_{HH}$ 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 $C_{25}H_{19}Cl_2N_3OS$: 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′-chloro-3′-methyl-1′-phenyl-1*H*-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, $^3J_{HH}$ 13.5 Hz, CH_2S), 4.15 (1H, d, $^3J_{HH}$ 2.7 Hz, C4–H), 4.46 (1H, d, $^3J_{HH}$ 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 $C_{26}H_{23}ClN_3OS$: 460.1250. Found: 460.1289.

***trans*-1-(4′-Methoxyphenyl)-3-benzylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5f).** Yellowish solid; yield: 68%; mp 39-40 °C; IR (ν_{max}, cm^{-1}): 1743 (C=O);

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^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.05 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 3.79-3.90 (2H, dd, $^3J_{HH}$ 19.2 Hz, CH_2S), 4.09 (1H, d, $^3J_{HH}$ 2.4 Hz, C4-H), 4.37 (1H, d, $^3J_{HH}$ 2.4 Hz, C3-H), 6.66-7.40 (14H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.8, 35.2, 54.6, 55.0, 56.0, 111.8, 114.3, 118.0, 124.5, 125.7, 127.2, 128.0, 128.5, 128.8, 129.0, 130.7, 137.6, 137.8, 147.8, 156.3, 161.8; Anal. Calcd. for $C_{27}H_{24}ClN_3O_2S$: C, 66.18; H, 4.94; N, 8.58%. Found: C, 65.97; H, 4.87; N, 8.47%.

***trans*-1-Benzyl-3-benzylthio-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5g).** Yellowish brown oil; yield 56%; IR (ν_{max}, cm^{-1}): 1756 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.92 (3H, s, CH_3), 3.66 (1H, d, $^3J_{HH}$ 13.2 Hz, CH_2S), 3.79 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2N), 3.85 (1H, d, $^3J_{HH}$ 13.5 Hz, CH_2S), 3.99 (1H, d, $^3J_{HH}$ 2.4 Hz, C4–H), 4.07 (1H, d, $^3J_{HH}$ 2.4 Hz, C3–H), 4.52 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2N), 7.04-7.47 (15H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.6, 35.1, 45.2, 54.2, 55.1, 111.4, 124.7, 126.0, 127.2, 127.9, 128.1, 128.5, 128.7, 128.9, 134.8, 134.8, 137.5, 137.9, 148.3, 165.1; HRMS (EI): *m/z* [M+H] Calcd. for $C_{27}H_{25}ClN_3OS$: 474.1406. Found: 474.1375.

***trans*-1-(4′-Methoxyphenyl)-3-phenylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5h).** Yellowish brown oil; yield 75%; IR (ν_{max}, cm^{-1}): 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.15 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 4.43 (1H, d, $^3J_{HH}$ 2.4 Hz, C4-H), 4.65 (1H, d, $^3J_{HH}$ 2.1 Hz, C3-H), 6.64-7.62 (14H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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, 128.2, 128.8, 129.0, 129.3, 130.9, 135.6, 138.0, 148.0, 156.4, 162.6,164.6, 172.4, 174.0; ^{77}Se NMR: δ_{Se} 350.5; HRMS (EI): *m/z* [M+H] Calcd. for $C_{26}H_{23}ClN_3O_2Se$: 524.0644. Found: 524.0699.

1-Benzyl-3-phenylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5i). Yellowish brown oil; yield 68%; IR (ν_{max}, cm^{-1}): 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.02 (3H, s, CH_3), 3.63 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2Ph), 4.08 (1H, d, $^3J_{HH}$ 2.1 Hz, C4–H), 4.39 (1H, d, $^3J_{HH}$ 2.1 Hz, C3–H), 4.53 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2Ph), 6.61-7.60 (15H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{26}H_{22}ClN_3NaOSe$: 530.0514. Found: 530.0625.

1-Phenyl-3-benzylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5j). Yellowish brown oil; yield 71%; mp 118-119 °C; IR (ν_{max}, cm^{-1}): 1741 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.10 (3H, s, CH_3), 3.93-4.03 (2H, q, $^3J_{HH}$ 12 Hz, CH_2), 4.24 (1H, d, $^3J_{HH}$ 2.4 Hz, C4–H), 4.52 (1H, d, $^3J_{HH}$ 2.4 Hz, C3–H), 6.96-7.43 (15H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{26}H_{23}ClN_3OSe$: 508.0694. Found: 508.0660.

***trans*-1-(4′-Methoxyphenyl)-3-benzylseleno-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5k).** Yellowish brown oil; yield 66%; IR (ν_{max}, cm^{-1}): 1748 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.04 (3H, s, CH_3), 3.59 (3H, s, OCH_3), 3.86-3.95 (2H, dd, $^3J_{HH}$ 15.6, 15.9

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Hz, CH_2Se), 4.20 (1H, d, $^3J_{HH}$ 2.1 Hz, C4-H), 4.46 (1H, d, $^3J_{HH}$ 2.7 Hz, C3-H), 6.65-7.38 (14H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.7, 27.2, 29.5, 39.0, 55.1, 111.8, 114.3, 117.9, 124.4, 125.8, 126.8, 128.0, 128.4, 128.8, 128.9, 130.7, 137.6, 138.1, 147.8, 156.2, 162.8.; ^{77}Se NMR: δ_{Se} 330.1; HRMS (EI): *m/z* [M+H] Calcd. for $C_{27}H_{25}ClN_3O_2Se$: 538.0800. Found: 538.0756.

1-Phenyl-3-phenoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5l). White crystalline solid; yield 62%; IR (ν_{max}, cm^{-1}): 1767 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.25 (3H, s, CH_3), 4.98 (1H, d, $^3J_{HH}$ 1.8 Hz, C4–H), 5.37 (1H, d, $^3J_{HH}$ 1.8 Hz, C3–H), 6.86-7.50 (15H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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, 129.7, 129.9, 136.7, 137.6, 148.3, 156.9, 157.1, 162.0, 166.2; Anal. Calcd. for $C_{25}H_{20}ClN_3O_2$: C, 69.85; H, 4.69; N, 9.77%. Found: C, 69.69; H, 4.63; N, 9.68%.

***trans*-1-(4′-Methoxyphenyl)-3-phenoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5m).** White crystalline solid; yield 57%; mp 145-146 °C; IR (ν_{max}, cm^{-1}): 1726 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.07 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 4.42 (1H, d, $^3J_{HH}$ 2.4 Hz, C4-H), 4.69 (1H, d, $^3J_{HH}$ 2.4 Hz, C3-H), 6.48-7.49 (14H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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 $C_{26}H_{22}ClN_3O_3$: C, 67.90; H, 4.82; N, 9.14%. Found: C, 67.72; H, 4.77; N, 9.06%.

1-Phenyl-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5o). Yellowish brown oil; yield 63%; IR (ν_{max}, cm^{-1}): 1731 (C=O);. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.18 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 4.64 (1H, d, $^3J_{HH}$ 1.8 Hz, C4–H), 4.81 (1H, d, $^3J_{HH}$ 1.8 Hz, C3–H, 6.97-7.45 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.0, 54.6, 57.9, 88.7, 88.8, 111.8, 116.9, 124.4, 124.6, 125.6, 128.1, 128.9, 129.2, 137.1, 137.8, 147.8, 163.2; HRMS (EI): *m/z* [M+Na] Calcd. for $C_{20}H_{18}ClN_3NaO_2$: 390.0985. Found: 390.0936.

***trans*-1-(4′-Methoxyphenyl)-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5p).** Colorless crystalline solid; yield 65%; mp 84-85 °C; IR (ν_{max}, cm^{-1}): 1745 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.19 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 4.64 (1H, d, $^3J_{HH}$ 1.2 Hz, C4-H), 4.79 (1H, d, $^3J_{HH}$ 1.2 Hz, C3-H), 6.72-7.47 (9H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.1, 53.6, 54.8, 55.2, 58.0, 58.7, 84.7, 88.9, 111.9, 114.5, 118.1, 118.3, 124.7, 125.8, 128.0, 128.2, 128.9, 129.0, 130.7, 130.8, 137.9, 148.0, 156.5, 162.8, 163.2; MS-EI (*m/z*): 420 (100, $[M+Na]^+$), 398 (61, $[M+H]^+$), 362 (28, $[C_{21}H_{20}N_3O_3]^+$), 249 (4, $[C_{13}H_{13}ClN_2O]^+$). Anal. Calcd. for $C_{21}H_{20}ClN_3O_3$: C, 63.40; H, 5.07; N, 10.56%. Found: C, 63.33; H, 5.07; N, 10.81%.

1-Benzyl-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5q). Yellowish brown oil; yield 55%; IR (ν_{max}, cm^{-1}): 1739 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.07 (3H, s, CH_3), 3.45 (3H, s, OCH_3), 3.78 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2), 4.19 (1H, d, $^3J_{HH}$ 1.8 Hz, C4–H), 4.63 (1H, d, $^3J_{HH}$ 1.8 Hz, C3–H), 4.70 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2), 7.07-7.44 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 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+H] Calcd. for $C_{21}H_{21}ClN_3O_2$: 382.1322. Found: 382.1306.

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***trans*-1-(4′-Methoxyphenyl)-3-acetoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (5r).** Yellowish brown oil; yield 64%; IR (ν_{max}, cm^{-1}): 1743 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.09 (3H, s, CH_3), 2.21 (3H, s, CH_3), 3.68 (3H, s, OCH_3), 4.80 (1H, d, $^3J_{HH}$ 1.8 Hz, C4-H), 5.58 (1H, d, $^3J_{HH}$ 1.8 Hz, C3-H),6.71-7.46 (15H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{22}H_{20}ClN_3NaO_4$: 448.1040. Found: 448.0980.

1-Benzyl-3-phenoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (6n). White crystalline solid; yield 61%; mp 109-110 °C; IR (ν_{max}, cm^{-1}): 1733 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.29 (3H, s, CH_3), 3.92 (1H, d, $^3J_{HH}$ 14.4Hz, CH_2), 4.78 (1H, d, $^3J_{HH}$ 4.8 Hz, C4–H), 4.85 (1H, d, $^3J_{HH}$ 14.4 Hz, CH_2), 5.40 (1H, d, $^3J_{HH}$ 4.8 Hz, C3–H), 6.77-7.43 (15H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{22}ClN_3O_2$: 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-1*H*-pyrazol-4′-yl)-azetidin-2-one (6o). Yellowish brown oil; yield 20%; IR (ν_{max}, cm^{-1}): 1742 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.19 (3H, s, CH_3), 3.41 (3H, s, OCH_3), 4.74 (1H, d, $^3J_{HH}$ 5.1 Hz, C4–H), 5.18 (1H, d, $^3J_{HH}$ 3.6 Hz, C3–H), 6.97-7.52 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{20}H_{18}ClN_3NaO_2$: 390.0985. Found: 390.0936.

***cis*-1-(4′-Methoxyphenyl)-3-methoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (6p).** Colorless crystalline solid; yield 22%; mp 154-155 °C; IR (ν_{max}, cm^{-1}): 1749 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.21 (3H, s, CH_3), 3.45 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.79 (1H, d, $^3J_{HH}$ 4.8 Hz, C4-H), 5.20 (1H, d, $^3J_{HH}$ 4.8 Hz, C3-H), 6.77-7.57 (9H, m ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{20}ClN_3O_3$: 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-1*H*-pyrazol-4′-yl)-azetidin-2-one (6q). Yellowish brown oil; yield 28%; IR (ν_{max}, cm^{-1}): 1755 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.20 (3H, s, CH_3), 3.32 (3H, s, OCH_3), 3.78 (1H, d, $^3J_{HH}$ 14.4 Hz, CH_2), 4.52 (1H, d, $^3J_{HH}$ 4.5 Hz, C4–H), 4.57 (1H, d, $^3J_{HH}$ 4.5 Hz, C3–H), 4.71 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2), 7.07-7.48 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{21}ClN_3O_2$: 382.1322. Found: 382.1306.

1-Benzyl-3-acetoxy-4-(5′-chloro-3′-methyl-1′-phenyl-1*H*-pyrazol-4′-yl)-azetidin-2-one (6s). White crystalline solid; yield 69%; mp 123-124 °C; IR (ν_{max}, cm^{-1}): 1731 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.08 (3H, s, CH_3), 3.85 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2N), 4.68 (1H, d, $^3J_{HH}$ 4.8 Hz, C4–H), 4.82 (1H, d, $^3J_{HH}$ 14.7 Hz, CH_2N), 5.68 (1H, d, $^3J_{HH}$ 4.8 Hz, C3–H), 7.04-7.27 (10H, m,

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ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_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 $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25%. Found: C, 64.32; H, 4.87; N, 10.13%.

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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**, **5i**, **5j**, **5k**, **5o**, **5q**, **5r**.

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