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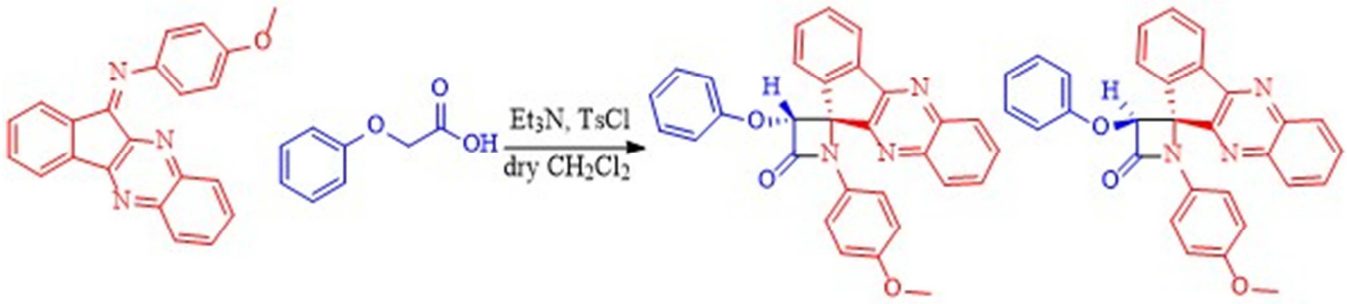

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Synthesis of some novel indeno[1,2-b]quinoxalin spiro-β-lactam conjugates

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ABSTRACT

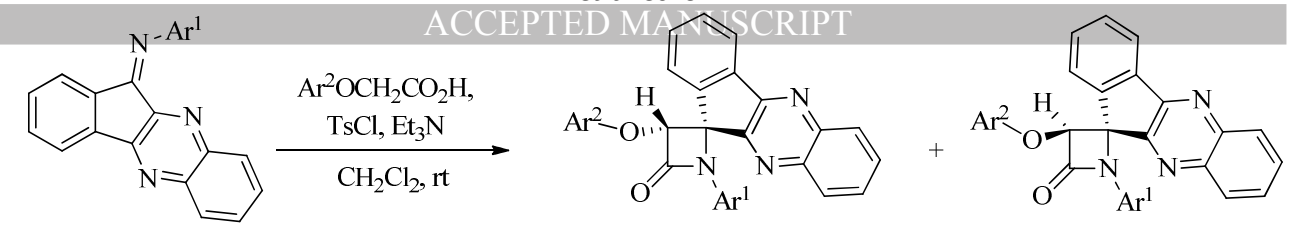
This article reports the synthesis of some new spiro-*β*-lactams bearing an indeno[1,2-b]quinoxaline ring system, prepared by a [2+2] cycloaddition of ketenes with imines derived from 11-H-indeno[1,2-b]quinoxalin-11-one. The structures of newly synthesized spiro-β-lactams **2a–i** and **3a-i** were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analyses. The relative stereochemistry of spiro-*β*-lactams **2a** and **3a** was determined unequivocally by X-ray crystallographic studies.

1. Introduction

The four-membered 2-azetidinone ring, commonly known as the β-lactam, is a privileged structural unit encountered in the most widely used antibiotics that include penicillins, cephalosporins, and carbapenems.[1] To counter deadly pathogenic microorganisms that have built up resistance against traditional antibiotic drugs, researchers continue to explore new β-lactam compounds with the objective of identifying variants having improved antibacterial capabilities.[2] In this respect, a variety of different methods have been reported for the synthesis of 2-azetidinones, including cyclization reactions, carbene insertion reactions, rearrangement of heterocyclic compounds, Reformatsky reaction, Ugi-4CR/ cyclization and [2+2] ketene-imine cycloaddition (Staudinger reaction).[3-9] The classical Staudinger reaction remains one of the most popular procedures for the synthesis of β-lactam ring systems,[10-12] including spiro-β-lactams,[13-14] which have shown a great variety of important biological properties such as antimalarial activity,[15] cholesterol absorption inhibition,[16] TRPV1 antagonism,[17] T-type calcium channel blocking,[18] and as β-turn mimics.[19] Jarrahpour et al have recently synthesized spiro-β-lactams having potent antimalarial capabilities.[20] Spiro-β-lactams also serve as synthetic intermediates to access α,α-disubstituted β-amino acids and peptide derivatives.[21]

Quinoxalines comprise another important class of heterocyclic compounds also having a diverse range of biological activities such as anti-hypertensive, [22] anti-tubercular,[23] convulsant,[24] anti-malarial,[25] anti-anti-HIV,[26] anti-depressant,[27] anti-diabetic,[28] anti-inflammatory,[29] antibacterial,[30] antimicrobial,[31] and anticancer.[32] The quinoxaline derivatives brimonidine and varenicline have been approved by the U.S. Food and Drug Administration for the treatment of glaucoma.[33] Tetracyclic indenoquinoxalines are also important types of heterocycles containing quinoxaline. Indenoquinoxalines are not only used as intermediates in the synthesis of several types of spiro compounds such as spiro-indenoquinoxaline pyrrolizidines, [34] and spiro-lactones,[35] but also as potent α-glucosidase inhibitor and antibacterial agents. [36]

To further capitalize on the unique properties of both β-lactams and quinoxalines, we have expanded upon our work on conjugated β-lactams[37] towards the syntheses of some interesting indenoquinoxaline-bearing spiro-β-lactams **2** and **3**, depicted in Scheme 1.



1a-d **2a-i** **3a-i**

Ar^1: a: 4-$MeOC_6H_4$ Ar^2: C_6H_5
b: 4-MeC_6H_4 4-ClC_6H_4
c: 4-IsopropylC_6H_4 2,4-$DiClC_6H_3$
d: 3,4-$DiMeOC_6H_3$

Scheme 1. Synthesis of indeno[1,2-b]quinoxaline spiro-β-lactams **2a-i** and **3a-i**

2. Results and Discussion

2.1. Synthesis of novel spiro-β-lactams bearing the 2,11'-indeno[1,2-b]quinoxalin moiety:

Spirocyclic indeno[1,2-b]quinoxaline β-lactams **2a-i** and **3a-i** were synthesized by a modified Staudinger reaction between N-phenyl-11H-indeno[1,2-b]quinoxalin-11-imine derivatives **1** and various phenoxyacetic acid derivatives. The reactions were carried out in the presence of triethylamine and tosyl chloride in anhydrous CH_2Cl_2 at room temperature, in molar ratios of 1:1.5:5:1.5, respectively. Purification of the reaction mixture by thick-layer silica gel chromatography confirmed the formation of diastereomers, **2a-i** and **3a-i,** in equal amounts and in isolated yields varying from 46-83%. The ratio of diastereomers **2** and **3** was determined by the integration of the proton H-3 of the β-lactam rings in the ^{1}H NMR spectrum.

X-ray crystallographic studies were done on diastereomers **2a** and **3a** (Figures 1 and 2). All bond lengths and bond angles appear to be normal and comparable with those reported for related compounds.[33-42] Intramolecular C-H···O hydrogen bonds stabilize the molecular conformations of **2a** and **3a**. In the crystals of both **2a** and **3a** exist evidence of C-H···π interactions, and in **3a**, additional O-H···N hydrogen bonds, forming a three-dimensional structure. The IR spectra of **2a** and **3a** showed the characteristic absorption of the β-lactam carbonyl at 1759 cm^{-1} and 1766 cm^{-1}, respectively. The ^{1}H NMR spectrum of **2a** exhibited the aryl methoxy protons as a singlet at 3.53 ppm, and at 3.84 ppm for **3a.** The β-lactam H-3 proton appeared to be highly deshielded for **2a** and **3a**, appearing downfield at 6.13 and 6.24, respectively. The ^{13}C NMR spectrum exhibited signals at 55.05 ppm and 55.07 ppm for the methyl carbon for **2a** and **3a**, respectively, 68.87 ppm for the C-3 and 84.85 ppm for the C-4 in **2a**, 86.89 ppm for the C-3 and 95.42 ppm for the C-4 in **3a**, the aromatic carbons at appropriate shifts, and the β-lactam carbonyl carbon at 161.0 ppm and 161.3 for **2a** and **3a**, respectively. The GC-MS analysis showed the expected parent ion at m/z 471 for both diastereomers.

The cycloaddition reaction between N-(4-methoxyphenyl)-11H-indeno [1,2-b]quinoxalin-11-imine (**1a**) and phenoxyacetyl chloride was then attempted in the presence of triethylamine in anhydrous CH_2Cl_2 and toluene at different temperatures (Scheme 2). To investigate the diastereoselectivity of the cycloaddition reaction under different reaction conditions, the same mixture with the same ratios of reagents was treated at room temperature, -10 °C or -83 °C in anhydrous CH_2Cl_2 or refluxed in toluene

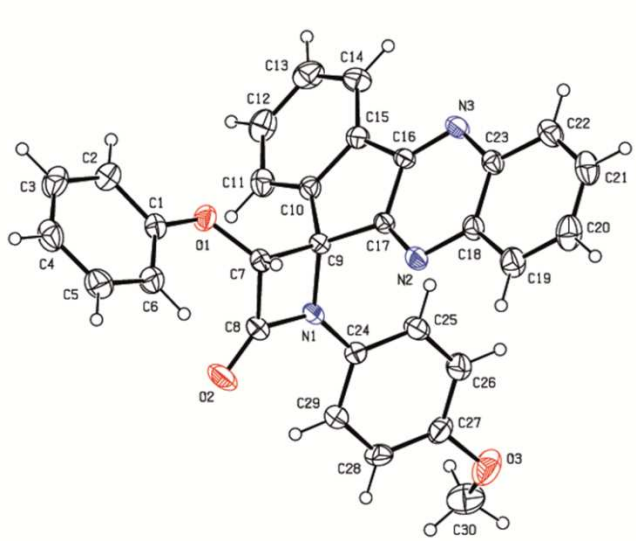


Figure 1. ORTEP diagram of diastereomer **2a**.

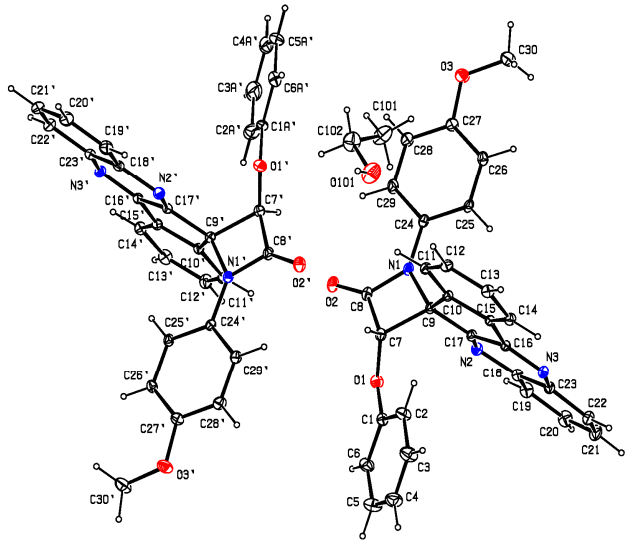
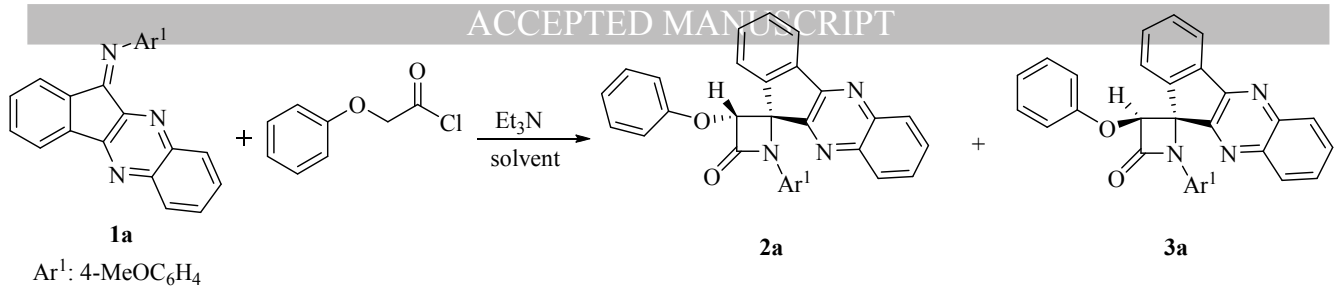


Figure 2. ORTEP diagram of diastereomer **3a**. A molecule of EtOH as a crystallizing solvent was trapped in the crystal structure (top left quadrant).



Scheme 2. Staudinger reaction of imine **1a** with phenoxyacetyl chloride

(Table 1). The isolated yields of the two products were drastically diminished at lower temperature, or when toluene was used as the solvent. It is noteworthy that the Staudinger reaction did not afford any cyclization product when using 4-methoxyphenylacetic acid, 4-hydroxyphenylacetic acid, 4-biphenylacetic acid, phthaloyl glycine, or methoxyacetic acid as the coupling partner with the imine.

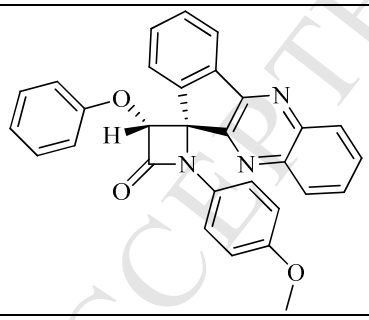
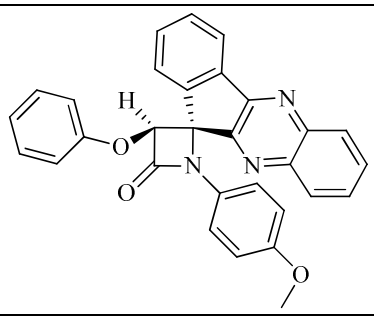
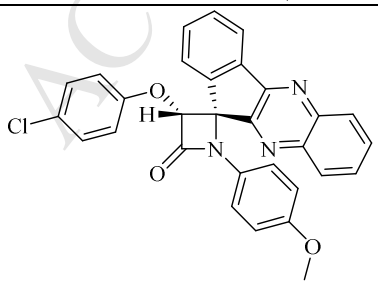
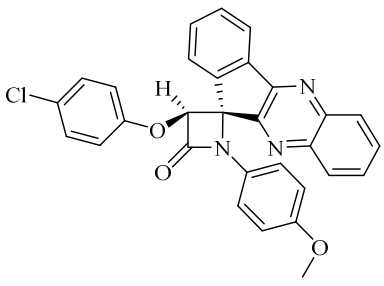
Table 1. Different conditions for the reaction of imine **1** and phenoxyacetic acid

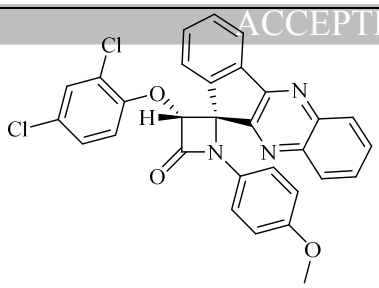
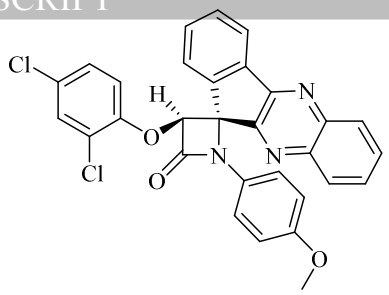
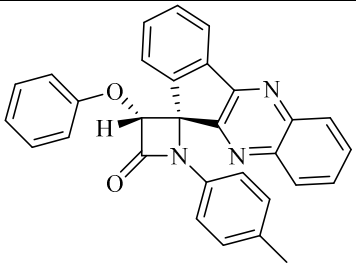
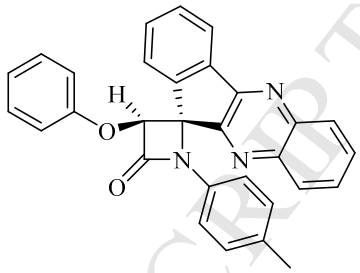
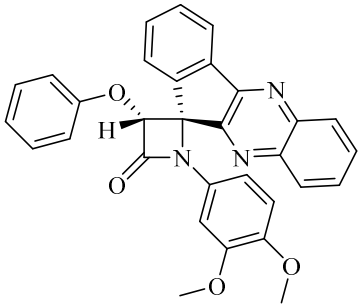
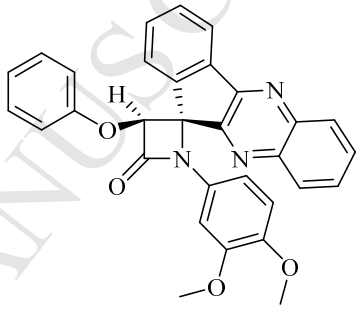
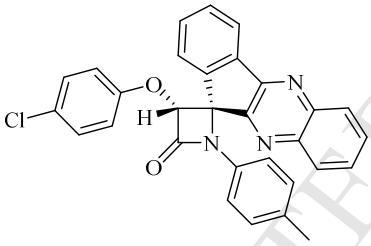
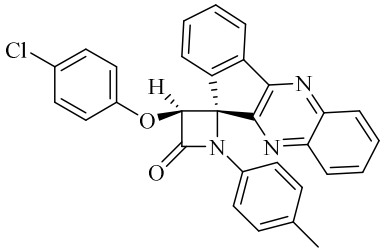
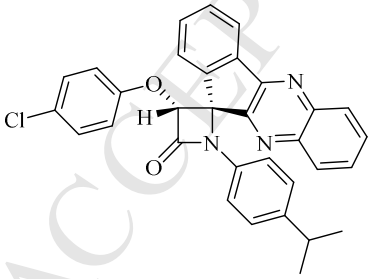
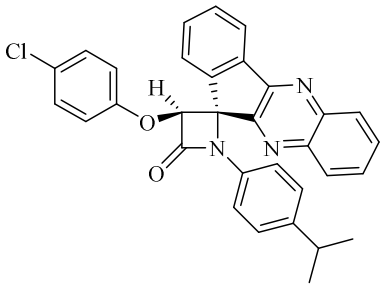
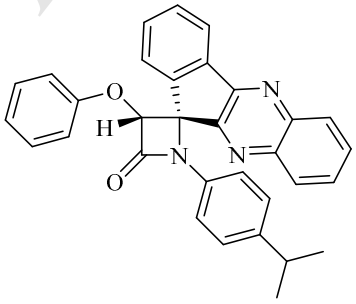
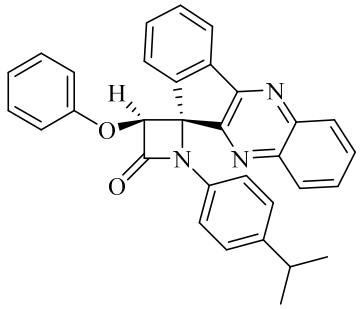
Entry	Solvent	Temperature °C	Yield
1	**CH_2Cl_2**	**rt**	**61%**
2	CH_2Cl_2	-10	Trace
3	CH_2Cl_2	-83	Trace
4	Toluene	Reflux	15%
5	Toluene	rt	No reaction

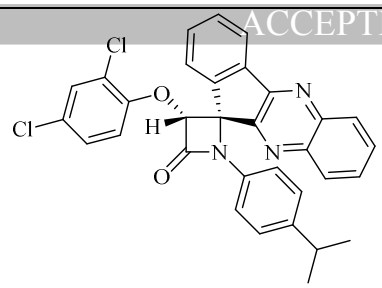
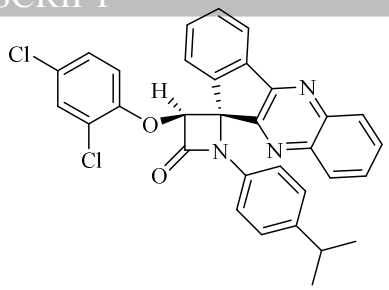
Then it was decided to evaluate the order of addition of the reactants on the diastereoselectivity and overall yield of the reaction of imine **1a** with phenoxyacetic acid. Two conditions were compared: the first was the dropwise addition of the acyl chloride to the mixture of imine and triethylamine at -83 °C, and the second was the same reaction at room temperature after addition of reactants at -83 °C. Next the order of addition was reversed and triethylamine was added dropwise to the mixture of phenoxyacetyl chloride and imine under both sets of reaction conditions. Although the diastereoselectivity of the cycloaddition reaction using the carboxylic acid and tosyl chloride was similar to that using the acid chloride, the former method proved to be more efficient.

Using these preferred reaction conditions, we synthesized 18 spiro-β-lactam derivatives **2a-i** and **3a-i** (Table 2).

Table 2. Structures of different diastereomeric spiro-β-lactam derivatives **2a–i** and **3a-i.**

β-lactam	Structure	β-lactam	Structure	Yield[a] (2+3) (%)
2a		**3a**		61
2b		**3b**		64

2c		**3c**		55
2d		**3d**		83
2e		**3e**		65
2f		**3f**		46
2g		**3g**		80
2h		**3h**		73

2i		**3i**		50

[a] Isolated yields.

3. Conclusion

In this study, a library of novel indeno[1,2-b]quinoxaline spiro-β-lactams has been synthesized. These β-lactams were prepared in good yields from N-phenyl-11H-indeno[1,2-b]quinoxalin-11-imines and different phenoxyacetic acids in the presence of triethylamine and p-toluenesulfonyl chloride. The structures of cycloadducts **2a-i** and **3a-i** were established by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analyses. The three-dimensional structures of β-lactams **2a** and **3a** were unambiguously determined by X-ray single crystal diffraction analysis, as a means to assign relative stereochemistry. Efforts to evaluate the potential biological properties of these new β-lactams-quinoxaline hybrids are underway.

4. Experimental Section

4.1. General:

All needed chemicals were purchased from Merck, Fluka and Acros chemical companies. and were used without further purification, All reagents and solvents were dried prior to use according to standard methods.[43] IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer using potassium bromide pellets (υ in cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded in dimethylsulfoxide-d_6 (DMSO-d_6) or chloroform-d ($CDCl_3$) using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane (TMS). The coupling constants (*J*) are reported in Hertz (Hz). ^{1}H NMR splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublet. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were obtained on a Buchi 510 melting point apparatus. X-ray data were collected on a Bruker APEX-II CCD diffractomer.

4.2. General procedure for preparation of Schiff bases **1a-d**:

A mixture of ninhydrin (5.00 mmol) and 1,2-phenylenediamine (5.0 mmol) were combined in absolute ethanol (20 mL) and then heated at reflux for 20 min to produce the corresponding aromatic ketone (not isolated), and after cooling the mixture to room temperature, the desired aniline derivative (5.5 mmol) and 3 drops of glacial AcOH were added. The reaction mixture was returned to reflux for several hours to produce the imine derivatives **1a-d** in high yield. The progress of the reaction was monitored by thin-layer silica gel chromatography (TLC). Evaporation of the solvent afforded the crude imine as a solid, which was used for the next step without further purification.

4.3. General procedure for the preparation of spiro-β-lactams **2** and **3** by a modified Staudinger reaction:

The appropriate aromatic imine (N-phenyl-11H-indeno[1,2-b]quinoxalin-11-imine) (1 mmol), triethylamine (5 mmol), phenoxyacetic acid (1.5 mmol) and tosyl chloride (1.5 mmol) were added to anhydrous CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 24 h (TLC control in a solvent system n-hexane: ethyl acetate = 10:3). The mixture was washed twice with 1N aqueous HCl solution (20 mL), and once with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed to yield the product as a crystal that was then purified by recrystallization from ethanol. Diastereomers were purified by silica gel chromatography.

4. 2. 1: 1-(4-Methoxyphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2a**):

Yellow crystals; Mp. 220-222 ºC; IR (KBr, cm^{-1}): 1759 (CO β-lactam),; ^{1}H NMR (250 MHz, DMSO-d_6): 3.53 (3H, s, C<u>H</u>$_3$), 6.12 (1H, s, <u>H</u>-3), 6.42 (2H, d, *J* 7.75 Hz, Ar<u>H</u>), 6.64-6.86 (5H, m, Ar<u>H</u>), 6.98 (2H, t, *J* 7.87 Hz, Ar<u>H</u>), 7.50-7.67 (2H, m, Ar<u>H</u>), 7.76-8.00 (3H, m, Ar<u>H</u>), 8.12 (1H, dd, *J* 5.50, 1.75 Hz, Ar<u>H</u>), 8.21 (2H, td, *J* 9.25, 1.50 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 161.0 (CO β-lactam), 142.6, 141.0, 139.8, 139.0, 138.7, 137.1, 131.9, 131.3, 131.0, 130.0, 129.5, 129.3, 129.2, 126.7, 122.4, 122.1, 118.4, 118.2, 114.7, 114.4, 114.4, 109.6 (aromatic carbons), 84.8 (C spiro β-lactam), 68.8 (C β-lactam), 55.0 (O-CH_3); GC-MS m/z = 471 [M^+]; Analysis calculated for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91%. Found: C, 75.12; H, 5.04; N, 8.22%.

4. 2. 2: 1-(4-Methoxyphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3a**):

White crystals; Mp. 180-181ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 3.84 (3H, s, C<u>H</u>$_3$), 6.52 (1H, s, <u>H</u>-3), 6.57 (2H, dd, *J* 7.75, 1.00 Hz, ArH), 6.88-7.05 (3H, m, Ar<u>H</u>), 7.08–7.22 (4H, m, Ar<u>H</u>), 7.95–8.17 (4H, m, Ar<u>H</u>), 8.28-8.57 (4H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 161.3 (CO β-lactam), 155.5, 142.0, 141.7, 140.6, 138.9, 136.2, 132.8, 131.4, 130.9, 129.9, 129.4, 129.3, 128.8, 128.8, 124.9, 122.7, 122.0, 121.5, 118.5, 118.4, 114.7, 114.1 (aromatic carbons), 95.4 (C spiro β-lactam), 86.8 (C β-lactam), 55.0 (O-CH_3); GC-MS m/z = 471[M^+]; Analysis calculated for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91%. Found: C, 77.08; H, 4.58; N, 9.15%.

4. 2. 3: 3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)spiro-[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one: (**2b**):

Yellow crystals; Mp. 200-201 ºC; IR (KBr, cm^{-1}): 1759 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 3.52 (3H, s, C<u>H</u>$_3$), 6.14 (1H, s, <u>H</u>-3), 6.48 (2H, d, *J* 7.50 Hz, Ar<u>H</u>), 6.70 (2H, d, *J* 7.75 Hz, Ar<u>H</u>), 6.79 (2H, d, *J* 8.75 Hz, Ar<u>H</u>), 7.03 (2H, d, *J* 8.75 Hz, Ar<u>H</u>), 7.52-7.65 (2H, m, Ar<u>H</u>), 7.75-7.96 (3H, m, Ar<u>H</u>), 8.07-8.27 (3H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 160.7 (CO β-lactam), 156.3, 154.4, 141.0, 138.6, 137.1, 131.9, 131.3, 131.0, 131.0, 130.0, 129.4, 129.2, 129.2, 129.1, 129.1, 126.7,

122.5, 118.4, 116.4, 116.3, 114.7, 112.8 (aromatic carbons), 98.0 (C spiro β-lactam), 84.7 (C β-lactam), 55.0 (O-CH_3); GC-MS m/z = 507 [M^+, ^{37}Cl], 505 [M^+, ^{35}Cl]; Analysis calculated for $C_{30}H_{20}ClN_3O_3$: C, 71.22; H, 3.98; N, 8.31%. Found: C, 72.05; H, 4.36; N, 8.57%.

4. 2. 4: 3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-spiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3b**):

White crystals; Mp. 210-212ºC; IR (KBr, cm-1): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 3.54 (3H, s, C<u>H</u>$_3$), 6.16 (1H, s, <u>H</u>-3), 6.34 (2H, dd, *J* 7.00, 2.25 Hz, Ar<u>H</u>), 6.50 (2H, dd, *J* 6.75, 2.25 Hz, Ar<u>H</u>), 6.69-6.75 (5H, m, Ar<u>H</u>), 6.78–6.85 (5H, m, Ar<u>H</u>), 6.95 (2H, dd, *J* 6.75, 2.25 Hz, Ar<u>H</u>), 7.05 (2H, dd, *J* 7.00, 2.25 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d6) δ 161.0 (CO β-lactam),156.3, 156.2, 154.3, 132.8, 131.4, 131.4, 131.0, 129.4, 129.2, 129.1, 128.9, 128.7, 125.8, 124.9, 122.8, 118.5, 118.4, 116.3, 116.0, 114.7, 114.7 (aromatic carbons), 86.7 (C spiro β-lactam), 68.7 (C β-lactam), 55.0 (O-CH_3); GC-MS m/z = 507 [M^+, ^{37}Cl], 505 [M^+, ^{35}Cl]; Analysis calculated for $C_{30}H_{20}ClN_3O_3$: C, 71.22; H, 3.98; N, 8.31%. Found: C, 70.65; H, 4.59; N, 8.61%.

4. 2. 5: 3-(2,4-dichlorophenoxy)-1-(4-methoxyphenyl)spiro-[azetidine- 2,11'-indeno[1,2-b]quinoxalin]-4-one (**2c**):

White crystals; Decompose 250 ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 3.51 (CH_3, s, 3H), 6.27 (H-3, s, 1H), 6.47 (ArH, d, 1H, J =8.75), 6.65-6.76 (ArH, m, 2H), 6.79 (ArH, d, 2H, J=9.00), 6.98 (1H, dd, *J* 9.00, 2.50 Hz, Ar<u>H</u>), 7.39-7.69 (3H, m, Ar<u>H</u>), 7.79-7.94 (3H, m, Ar<u>H</u>), 8.07-8.26 (3H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 165.6 (CO β-lactam), 156.3, 152.5, 142.7, 138.5, 137.1, 132.7, 131.9, 131.5, 131.4, 131.0, 130.0, 128.4, 129.4, 129.3, 129.2, 129.2, 128.6, 127.7, 126.6, 124.1, 122.4, 122.4, 118.5, 114.7 (aromatic carbons), 84.8 (C spiro β-lactam), 55.0 (C β-lactam), 54.6 (O-CH_3); GC-MS m/z = 541 [M^+, ^{37}Cl], 539 [M^+, ^{35}Cl]; Analysis calculated for $C_{30}H_{19}Cl_2N_3O_3$: C, 66.68; H, 3.54; N, 7.78%. Found: C, 67.54; H, 4.27; N, 8.54%.

4. 2. 6: 3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)spiro [azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3c**):

Gray crystals; Mp. 178-180ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 3.53 (3H, s, C<u>H</u>$_3$), 6.30 (1H, s, <u>H</u>-3), 6.50 (1H, d, *J* 7.00 Hz, Ar<u>H</u>), 6.72 (2H, dd, *J* 9.00, 1.75 Hz, Ar<u>H</u>), 6.82 (2H, dd, *J* 9.00, 2.25 Hz, Ar<u>H</u>), 6.98- 7.05 (1H, m, Ar<u>H</u>), 7.53-7.68 (2H, m, Ar<u>H</u>), 7.71-7.94 (4H, m, Ar<u>H</u>), 8.11-8.24 (3H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 161.4 (CO β-lactam), 158.4, 156.0, 153.4, 148.3, 148.3, 142.4, 141.0, 139.6, 136.6, 133.1, 131.8, 131.2, 130.3, 129.8, 129.7, 129.3, 129.3, 125.4, 132.1, 122.4, 119.1, 116.8, 114.5, 113.0, (aromatic carbons), 87.1 (C spiro β-lactam), 69.3 (C β-lactam), 40.3 (O-CH_3); GC-MS m/z = 541 [M^+, ^{37}Cl], 539 [M^+, ^{35}Cl]; Analysis calculated for $C_{30}H_{19}Cl_2N_3O_3$: C, 66.68; H, 3.54; N, 7.78%. Found: C, 67.59; H, 4.86; N, 8.73%.

4. 2. 7: 3-Phenoxy-1-(p-tolyl)spiro[azetidine-2,11'-indeno [1,2-b]quinoxalin]-4-one (**2d**):

White crystals; Mp. 258-260ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 2.06 (3H, s, C<u>H</u>$_3$), 4.15 (1H, s, <u>H</u>-3), 5.84 (1H, s, Ar<u>H</u>), 6.21-6.56 (2H, m, Ar<u>H</u>), 6.61-7.03 (6H, m, Ar<u>H</u>), 7.34-7.85 (5H, m, Ar<u>H</u>), 7.97-8.26 (3H, m, Ar<u>H</u>); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 163.0 (CO β-lactam), 153.2, 144.3, 131.8, 131.8, 131.0, 130.9, 130.8, 130.6, 130.0, 129.9, 129.7, 129.6, 129.5, 129.4, 129.3, 128.7, 127.0, 122.6, 122.3, 122.3, 117.4, 115.0 (aromatic carbons), 85.6 (C spiro β-lactam), 68.1 (C β-lactam), 29.6 (-CH_3); GC-MS m/z = 455 [M+], Analysis calculated for $C_{30}H_{21}N_3O_2$: C, 79.10; H, 4.65; N, 9.22%. Found: C, 81.68; H, 4.92; N, 10.14%.

4. 2. 8: 3-Phenoxy-1-(p-tolyl)spiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3d**):

Yellow crystals; Mp. 169-171ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 2.06 (3H, s, C<u>H</u>$_3$), 5.64 (1H, s, <u>H</u>-3), 5.84 (1H, s, Ar<u>H</u>), 6.21-6.56 (2H, m, Ar<u>H</u>), 6.61-7.03 (6H, m, Ar<u>H</u>), 7.34-7.85 (5H, m, Ar<u>H</u>), 7.97-8.26 (3H, m, Ar<u>H</u>), 6.30 (2H, dd, *J* 7.50, 1.25 Hz, Ar<u>H</u>), 6.63 (1H, d, *J* 7.50 Hz, Ar<u>H</u>), 6.77-6.93 (6H, m, Ar<u>H</u>), 7.54-7.72 (5H, m, Ar<u>H</u>), 7.99 (1H, d, *J* 7.50 Hz, Ar<u>H</u>), 8.06 (1H, d, *J* 7.50 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.7 (CO β-lactam), 142.5, 137.1, 134.7, 132.4, 131.2, 130.5, 130.4, 130.3, 130.2, 129.8, 129.6, 129.5, 129.4, 129.2, 129.1, 129.0, 123.6, 123.2, 122.2, 117.5, 114.9, 114.7 (aromatic carbons), 88.3 (C spiro β-lactam), 77.1 (C β-lactam), 20.8 (-CH_3); GC-MS m/z = 455 [M^+], Analysis calculated for $C_{30}H_{21}N_3O_2$: C, 79.10; H, 4.65; N, 9.22%. Found: C, 81.91; H, 5.02; N, 10.32%.

4. 2. 9: 1-(3,4-Dimethoxyphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2e**):

Yellow crystals; Mp. 170-171ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 3.66 (6H, s, 2C<u>H</u>$_3$), 5.93 (1H, s, <u>H</u>-3), 5.95-6.07 (1H, m, Ar<u>H</u>), 6.34-6.55 (4H, m, Ar<u>H</u>), 6.80 (1H, t, *J* 7.00 Hz, Ar<u>H</u>), 6.99 (1H, t, *J* 7.75 Hz, Ar<u>H</u>), 7.12 (1H, s, Ar<u>H</u>), 7.55 (3H, t, *J* 6.50 Hz, Ar<u>H</u>), 7.71-7.96 (4H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.8 (CO β-lactam), 134.2, 132.6, 131.8, 131.0, 130.8, 130.7, 129.9, 129.8, 129.7, 129.4, 128.2, 127.1, 125.3, 123.9, 122.6, 122.3, 119.9, 116.9, 115.0, 111.0, 108.6, 103.9, 102.8, 102.8 (aromatic carbons), 98.6 (C spiro β-lactam), 85.5 (C β-lactam), 55.8 (O-CH_3), 55.7 (O-CH_3); GC-MS m/z = 501 [M^+], Analysis calculated for $C_{31}H_{23}N_3O_4$: C, 74.24; H, 4.62; N, 8.38%. Found: C, 73.61; H, 5.42; N, 9.83%.

4. 2. 10: 1-(3,4-Dimethoxyphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3e**):

Yellow crystals; Mp. 175-177ºC; IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 3.66 (3H, s, C<u>H</u>$_3$), 3.67 (3H, s, C<u>H</u>$_3$), 5.07 (1H, s, <u>H</u>-3), 6.00 (1H, dd, *J* 8.5, 2.5 Hz, Ar<u>H</u>), 6.40 (2H, t, *J* 8.25 Hz, Ar<u>H</u>), 6.70 (1H, t, *J* 8.25 Hz, Ar<u>H</u>), 6.89 (2H, t, *J* 8.00 Hz, Ar<u>H</u>), 7.10-7.32 (2H, m, Ar<u>H</u>), 7.61-7.83 (5H, m, Ar<u>H</u>), 7.99-8.21 (2H, m, Ar<u>H</u>), 8.31 (1H, d, *J* 7.00 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.6 (CO β-lactam), 149.2, 146.3, 146.2, 142.7, 142.6, 141.6, 139.3, 132.4, 131.2, 130.8, 130.5, 130.2, 129.7, 129.4, 129.2, 129.0, 128.7, 123.7, 123.2, 122.2, 114.7, 111.0, 108.6, 102.9 (aromatic carbons), 88.2 (C spiro β-lactam), 77.2 (C β-lactam), 55.8 (O-CH_3), 55.7 (O-CH_3); GC-MS m/z = 501 [M^+], Analysis calculated for $C_{31}H_{23}N_3O_4$: C, 74.24; H, 4.62; N, 8.38%. Found: C, 75.83; H, 4.42; N, 8.91%.

4. 2. 11: 3-(4-Chlorophenoxy)-1-(p-tolyl)spiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2f**):

Gray crystals; Mp. 290 decompose ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, DMSO-d_6): 2.05 (3H, s, C<u>H</u>$_3$), 5.77 (1H, s, <u>H</u>-3), 6.32 (2H, d, *J* 9.00 Hz, Ar<u>H</u>), 6.78 (2H, d, *J* 6.25 Hz, Ar<u>H</u>), 6.86 (2H, d, *J* 9.00 Hz, Ar<u>H</u>), 7.38-7.56 (3H, m, Ar<u>H</u>), 7.62-7.80 (4H, m, Ar<u>H</u>), 8.04 (1H, d, *J* 8.00 Hz, Ar<u>H</u>), 8.14 (2H, d, *J* 7.75 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, DMSO-d_6) δ 162.9 (CO β-lactam), 155.9, 147.3, 142.6, 138.9, 137.6, 135.3, 131.8, 131.3, 131.2, 131.1, 130.9, 130.1, 129.3, 129.1, 127.5, 123.0, 123.0, 117.7, 114.7, 111.2, 104.3, 102.7, (aromatic carbons), 91.0 (C spiro β-lactam), 73.6 (C β-lactam), 23.5 (-CH_3); GC-MS m/z = 491 [M^+, ^{37}Cl], 489 [M^+, ^{35}Cl], Analysis calculated for $C_{30}H_{20}ClN_3O_2$: C, 73.54; H, 4.11; N, 8.58%. Found: C, 74.93; H, 5.25; N, 9.12%.

4. 2. 12: 3-(4-Chlorophenoxy)-1-(p-tolyl)spiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3f**):

White crystals; 250 decompose ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 1.54 (3H, s, C<u>H</u>$_3$), 5.64 (1H, s, <u>H</u>-3), 6.32 (2H, d, *J* 7.25 Hz, Ar<u>H</u>,), 7.19-7.30 (5H, m, Ar<u>H</u>), 7.57-7.92 (6H, m, Ar<u>H</u>), 8.10 (2H, t, *J* 8.00 Hz, Ar<u>H</u>), 8.31 (1H, t, *J* 7.00 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.0 (CO β-lactam), 158.6, 157.1, 149.2, 146.8, 145.9, 140.5, 138.4, 137.0, 132.4, 131.3, 130.6, 129.6, 129.5, 129.2, 129.1, 123.3, 120.7, 120.1, 118.0, 117.5, 116.0, 101.8 (aromatic carbons), 88.2 (C spiro β-lactam), 77.3 (C β-lactam), 20.8 (-CH_3); GC-MS m/z = 491 [M^+, ^{37}Cl], 489 [M^+, ^{35}Cl], Analysis calculated for $C_{30}H_{20}ClN_3O_2$: C, 73.54; H, 4.11; N, 8.58%. Found: C, 72.98; H, 4.35; N, 9.17%.

4. 2. 13: 3-(4-Chlorophenoxy)-1-(4-isopropylphenyl)spiro [azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2g**):

White crystals; Mp. 169-171ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 1.07 (6H, d, *J* 7.00 Hz, 2C<u>H</u>$_3$), 2.61-2.78 (1H, m, C<u>H</u>), 5.86 (1H, s, <u>H</u>-3), 6.41 (2H, dd, *J* 7.00, 2.25 Hz, Ar<u>H</u>), 6.87-6.98 (6H, m, Ar<u>H</u>), 7.45-7.62 (2H, m, Ar<u>H</u>), 7.72-7.81 (1H, m, Ar<u>H</u>), 7.85 (2H, d, *J* 7.00 Hz, Ar<u>H</u>,), 8.13 (1H, dd, *J* 8.25, 1.5 Hz, Ar<u>H</u>), 8.22 (2H, d, *J* 7.75 Hz, Ar<u>H</u>) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.6 (CO β-lactam), 155.0, 153.1, 145.7, 143.3, 141.7, 139.5, 137.6, 133.8, 131.8, 131.1, 130.7, 129.9, 129.7, 129.4, 129.3, 127.4, 127.1, 127.0, 127.0, 122.7, 117.5, 116.4 (aromatic carbons), 85.6 (C spiro β-lactam), 69.0 (C β-lactam), 33.4 (CH), 23.7 (CH_3); GC-MS m/z = 519 [M^+,^{37}Cl], 517 [M^+,^{35}Cl]; Analysis calculated for $C_{32}H_{24}ClN_3O_2$: C, 74.20; H, 4.67; N, 8.11%. Found: C, 73.13; H, 4.73; N, 7.91%.

4. 2. 14. 3-(4-Chlorophenoxy)-1-(4-isopropylphenyl)spiro [azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3g**):

Yellow crystals; Mp. 224-226ºC; IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$): 1.02 (3H, , s, C<u>H</u>$_3$), 1.05 (3H, s, C<u>H</u>$_3$), 2.60-2.81(1H, m, C<u>H</u>), 5.62 (1H, s, <u>H</u>-3), 6.30 (2H, d, *J* 6.75 Hz, Ar<u>H</u>), 6.79-7.09 (6H, m, Ar<u>H</u>), 7.22 (1H, s, Ar<u>H</u>), 7.59-7.88 (5H, m, Ar<u>H</u>), 8.09 (1H, t, *J* 8.25 Hz, Ar<u>H</u>), 8.30 (1H, d, *J* 7.00 Hz, Ar<u>H</u>) ; ^{13}C NMR (63 MHz, CDCl3) δ 161.3 (CO β-lactam), 153.1, 145.7, 142.7, 137.1, 135.1, 133.7, 132.5, 131.3, 130.6, 130.2, 129.5, 129.2, 129.1, 129.0, 127.3, 127.1, 123.7, 123.6, 123.3, 117.5, 116.1, 105.4 (aromatic carbons), 88.2 (C spiro β-lactam), 86.4 (C β-lactam), 33.5 (CH), 23.75 (CH3); GC-MS m/z = 519 [M^+,^{37}Cl], 517 [M^+,^{35}Cl];, Analysis calculated for $C_{32}H_{24}ClN_3O_2$: C, 74.20; H, 4.67; N, 8.11%. Found: C, 75.53; H, 5.78; N, 8.78%.

4. 2. 15: 1-(4-Isopropylphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2h**):

Yellow crystals; Mp. 180-181 ºC; IR (KBr, cm^{-1}): 1759 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 1.05-1.09 (6H, m, 2C<u>H</u>$_3$), 2.64-2.76 (1H, m, C<u>H</u>), 5.92 (1H, s, <u>H</u>-3), 6.46 (2H, d, *J* 8.75 Hz, Ar<u>H</u>); 6.79 (1H, d, *J* 7.75 Hz, Ar<u>H</u>), 6.91-6.93 (4H, m, Ar<u>H</u>), 6.98 (2H, d, *J* 7.75 Hz, Ar<u>H</u>), 7.46-7.61 (2H, m, Ar<u>H</u>), 7.70-7.90 (3H, m, Ar<u>H</u>), 8.11-8.25 (3H, m, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.0 (CO β-lactam), 156.7, 156.4, 153.2, 145.5, 144.5, 143.3, 141.7, 139.8, 139.8, 137.6, 133.9, 131.8, 130.9, 130.6, 129.9, 129.6, 129.3, 127.1, 122.6, 122.3, 117.5, 115.0 (aromatic carbons), 85.6 (C spiro β-lactam), 69.2 (C β-lactam), 33.4 (CH), 23.7 (CH_3); GC-MS m/z = 483 [M^+];, Analysis calculated for $C_{32}H_{25}N_3O_2$: C, 79.48; H, 5.21; N, 8.69%. Found: C, 77.93; H, 6.27; N, 9.18%.

4. 2. 16: 1-(4-Isopropylphenyl)-3-phenoxyspiro[azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3h**):

Yellow crystals; Mp. 190-191ºC; IR (KBr, cm^{-1}): 1751 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 1.04 (3H, s, C<u>H</u>$_3$), 1.07 (3H, s, CH_3), 2.59-2.85 (1H, m, CH), 5.71 (1H, s, <u>H</u>-3), 6.37 (2H, dd, *J* 7.50, 1.00 Hz, Ar<u>H</u>), 6.67 (2H, d, *J* 7.00 Hz, Ar<u>H</u>), 6.82-7.06 (6H, m, Ar<u>H</u>), 7.59-7.86 (5H, m, Ar<u>H</u>), 8.04-8.14 (2H, m, Ar<u>H</u>) 8.31 (1H, d, *J* 7.00 Hz, Ar<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.8 (CO β-lactam), 156.3, 154.4, 153.2, 145.6, 143.7, 142.6, 141.6, 137.1, 133.8, 132.4, 131.1, 130.4, 130.2, 129.4, 129.2, 129.0, 127.0, 123.7, 123.2, 122.2, 117.5, 114.8 (aromatic carbons), 88.3 (C spiro β-lactam), 69.3 (C β-lactam), 33.4 (CH), 23.7 (CH_3); GC-MS m/z = 483 [M^+]; Analysis calculated for $C_{32}H_{25}N_3O_2$: C, 79.48; H, 5.21; N, 8.69%. Found: C, 80.93; H, 5.27; N, 8.98%.

4. 2. 17: 3-(2,4-Dichlorophenoxy)-1-(4-isopropylphenyl)spiro [azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**2i**):

White crystals; Mp. 158-160ºC; IR (KBr, cm^{-1}): 1759 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 2.14 (6H, s, 2C<u>H</u>$_3$), 2.60-2.77 (1H, m, C<u>H</u>), 5.85 (1H, s, <u>H</u>-3), 6.48 (1H, d, *J* 8.75 Hz, Ar<u>H</u>), 6.87-6.97 (5H, m, Ar<u>H</u>), 7.24 (1H, s, Ar<u>H</u>), 7.51-7.64 (2H, m, Ar<u>H</u>), 7.69-7.83 (2H, m, Ar<u>H</u>), 7.92 (1H, dd, *J* 7.50, 1.25 Hz, Ar<u>H</u>), 8.21 (1H, dd, *J* 8.25, 1.75 Hz, Ar<u>H</u>), 8.21 (2H, t, *J* 7.00 Hz, Ar<u>H</u>,); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.3 (CO β-lactam),151.1, 145.7, 142.2, 141.7, 139.3, 137.6, 133.7, 132.8, 131.8, 131.2, 130.7, 130.1, 129.8, 129.7, 129.4, 127.4, 127.1, 124.7, 124.0, 122.6, 117.5, 116.7, 115.5, 106.9 (aromatic carbons), 85.8 (C spiro β-lactam), 77.21 (C β-lactam), 30.9 (CH), 23.7 (CH_3); GC-MS m/z = 553 [M^+,^{37}Cl], 551 [M^+,^{35}Cl];, Analysis calculated for $C_{32}H_{23}Cl_2N_3O_2$: C, 69.57; H, 4.20; N, 7.61%. Found: C, 70.83; H, 5.67; N, 8.91%.

4. 2. 18: 3-(2,4-Dichlorophenoxy)-1-(4-isopropylphenyl) spiro [azetidine-2,11'-indeno[1,2-b]quinoxalin]-4-one (**3i**):

Yellow crystals; Mp. 170-172ºC; IR (KBr, cm^{-1}): 1766 (CO β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$): 2.14 (6H, s, 2C<u>H</u>$_3$), 2.60-2.77 (1H, m, C<u>H</u>), 5.85 (1H, s, <u>H</u>-3), 6.48 (1H, d, *J* 8.75 Hz, Ar<u>H</u>), 6.87-6.97 (5H, m, Ar<u>H</u>), 7.24 (1H, s, Ar<u>H</u>), 7.51-7.64 (2H, m, Ar<u>H</u>), 7.69-7.83 (2H, m, Ar<u>H</u>), 7.92 (1H, dd, *J* 7.50, 1.25 Hz, ArH), 8.21 (1H, dd, *J* 8.25, 1.75 Hz, Ar<u>H</u>), 8.21 (2H, t, *J* 7.00 Hz, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.0 (CO β-lactam),157.3, 152.6, 144.9, 143.7, 140.1, 136.4, 136.1, 132.8, 129.8, 129.7, 129.3, 127.0, 126.7, 126.0, 123.2, 122.7, 120.9, 120.5, 120.4, 119.9, 119.8, 115.6, 108.1, 102.6 (aromatic carbons), 98.6 (C spiro β-lactam), 80.33 (C β-lactam), 45.16 (CH), 27.31 (CH_3); GC-MS m/z = 553 [M^+,^{37}Cl], 551 [M^+,^{35}Cl];, Analysis calculated for $C_{32}H_{23}Cl_2N_3O_2$: C, 69.57; H, 4.20; N, 7.61%. Found: C, 69.51; H, 4.37; N, 8.50%.

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Conflict of interest

The authors declare that they have no conflict of interest.

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