A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (8) 202412282

Multi-component reactions for the synthesis of current spiro-quinoxaline pyrrolizidine carboxylates *via* [3+2] cycloaddition reactions

Sundar S. Shinde,[a] Dipak B. Deokar,[a] Soumi Laha,*[b] S. Uday Bhaskar,[b] B. Sridhar,[c] and Pravin R. Likhar*[a]

[a]*Catalysis and Fine Chemicals Department, CSIR- Indian Institute of Chemical Technology, Uppal Road, Tarnaka Hyderabad-500007, India*

[b]*Malla Reddy Engineering College (Autonomous), Maisammaguda, Secundrabad, Hyderabad, Telengana-500010*

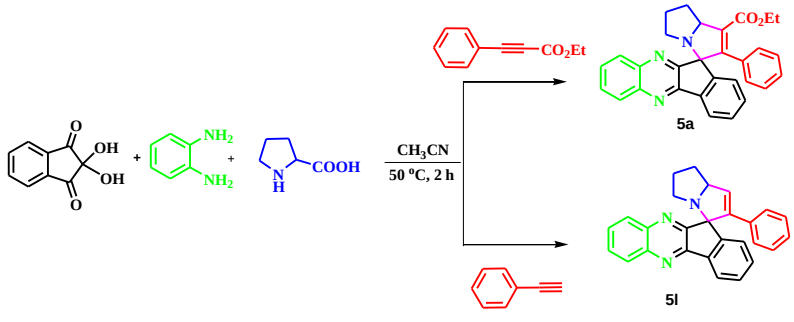
[c]*X-Ray Crystallography Centre, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India*

Email: soumilaha@gmail.com

Received 09-03-2024 **Accepted** 11-21-2024 **Published on line** 12-11-2024

Abstract

A novel series of multi-component reactions (MCRs) has been devised for the synthesis of spiro-quinoxaline pyrrolizine compounds using ninhydrin, *o*-phenylenediamine, proline, and propiolate esters via a [3+2] cycloaddition process. This efficient one-pot sequential four-component synthesis demonstrates high performance in acetonitrile, yielding spiro-quinoxaline pyrrolizine derivatives with remarkable efficiency. Spiro-quinoxaline pyrrolizine structures represent versatile molecular frameworks with potential applications in drug discovery, showcasing intriguing features for scaffold diversification.



Keywords: Ninhydrin, *o*-phenylenediamine, L-proline, alkynes

Cite as *Arkivoc* **2024** (8) 202412282

DOI: https://doi.org/10.24820/ark.5550190.p012.282

Introduction

The discovery of spiro-compounds has garnered significant interest owing to their presence in numerous bioactive molecules with diverse properties, including antibacterial,[1-3] anti-convulsant,[4,5] anti-tuberculosis,[6] anti-microbial,[7] anti-Alzheimer's,[8] anti-dermatitis,[9] and pain relief agents.[10] The effective utilization of N-heterocycles as foundational structures extends across various pharmacological domains, ranging from vitamins and herbicides to anti-cancer agents.[11] The continuous advancement of synthetic methodologies remains a focal point of research efforts.[12-18] Recently, there has been notable attention towards spiro-quinoxaline pyrrolizine and their derivatives due to their distinctive core structures and significant biological activities, particularly their acetylcholinesterase (AChE) inhibitory properties.[19]

Pyrrolizine alkaloids[20] have been subjected to clinical trials for their potential antitumor activities.[21-23] In recent years, ninhydrin-based multi-component reactions have had increased attention due to their rapid and systematic generation of novel scaffolds. Typically, the condensation of reactive ninhydrin, *o*-phenylenediamine, and proline yields azomethine ylides, which are subsequently reacted with various 1,2-dipoles to yield densely functionalized heterocycles. In the realm of multi-component synthesis of spiro molecules, Trivedi and colleagues have described a domino approach for synthesizing spiro polycyclic compounds via [3+2]-cycloaddition between (*Z*)-1-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)pyrrolidin-1-ium-2-ide and nitro styrene.Therefore, the azomethine ylide, which is formed in situ from ninhydrin and proline [Scheme 1, equation (1)],[19] was utilized by our research group in a multi-component reaction to synthesize pyrrolizine derivatives through a [3+2]-cycloaddition between the azomethine ylide and maleimide [Scheme 1, equation (2)].[24-27]

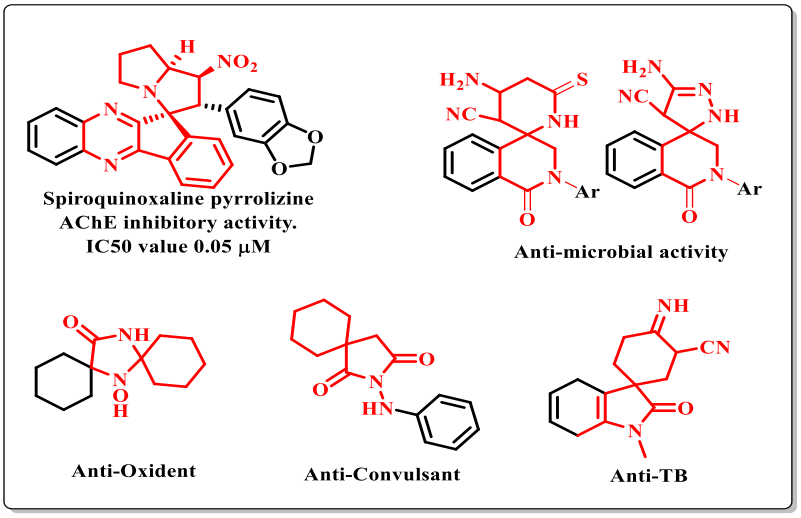
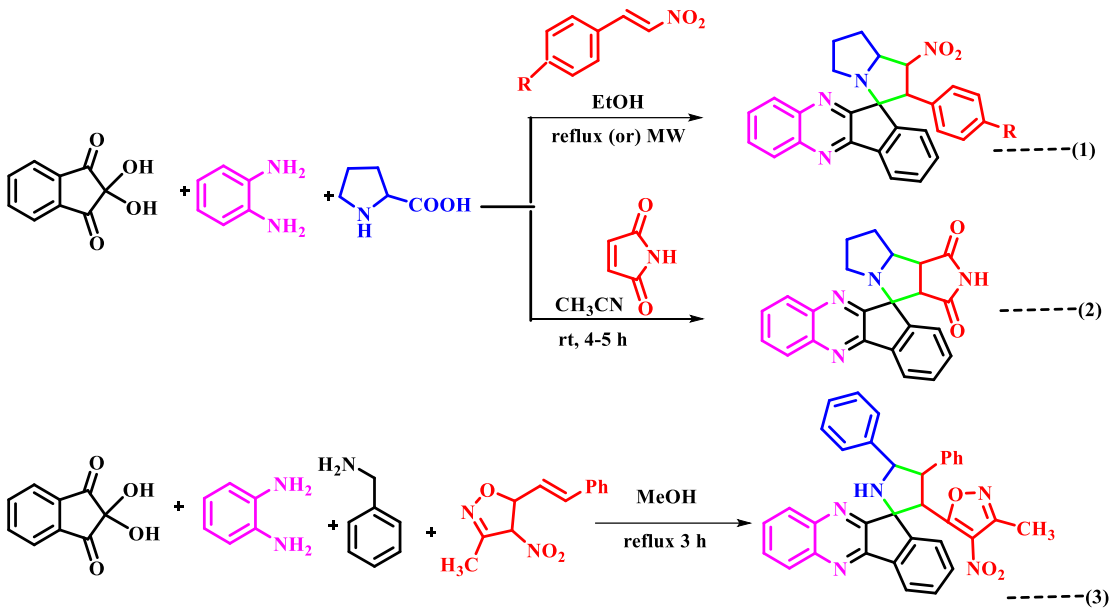


Figure 1. Some examples of bioactive spirocyclic compounds.

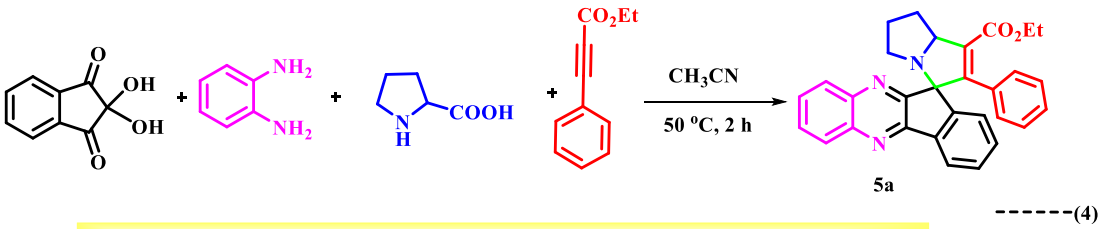
Soon after M. S. Reddy et al. reported the synthesis of a spiro compound from azomethine ylide and substituted alkenes [(Scheme 1, eqn (3)][28], significant advancements have been made in this area.

Previous work:



Herein, we present a mild and efficient approach for the synthesis of spiro-quinoxalines via [3+2]-cycloaddition reactions between alkynes and previously prepared azomethine ylides. Importantly, this method enables the synthesis of fused spiro-quinoxalines pyrrolizine carbohydrates through [3+2]-cycloaddition reactions between alkynes and azomethine ylides, which are generated in situ from proline and ninhydrin [Scheme 1, eqn (4)]

Present work:



- Transition metal, reagent and additive free conditions
- Under air atmosphere
- In situ generation of precedented azomethine ylide
- Formation of three new C-N bonds two C-C bonds in a single pot
- Formation of three new rings

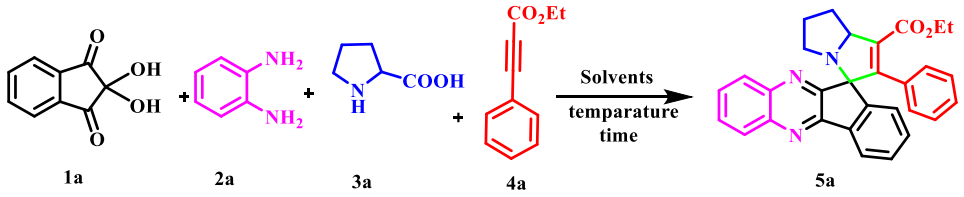
Scheme 1. [3+2]-cycloaddition between alkynes and *in situ* generated azomethine ylide from ninhydrin, *o*-phenylenediamine and proline.

Results and Discussion

In order to determine the optimal conditions, hydrated ninhydrin (**1a**), *o*-phenylenediamine (**2a**), L-proline (**3a**), and ethyl phenylpropiolate (**4a**) were initially selected as model substrates. It was discovered that the

reaction, which produced the new product (**5a**) in very low yield, was successful when hydrated ninhydrin (**1a**), *o*-phenylenediamine (**2a**), proline (**3a**), and ethyl phenylpropiolate (**4a**) were treated in acetonitrile solvent at room temperature under air, for half an hour (Table 1, entry 1).

Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CH_3CN	rt	1/2	22
2	CH_3CN	rt	1	40
3	CH_3CN	35	1	70
4	CH_3CN	50	2	90
5	methanol	50	4	50
6	Ethanol	50	1	62
7	DCM	40	4	trace
8	DCE	50	4	trace
9	DMF	50	4	trace
10	DMSO	50	4	trace
11	toluene	50	4	NR
12	1,4-dioxane	50	4	NR
13	THF	50	4	NR
14	water	50	4	NR

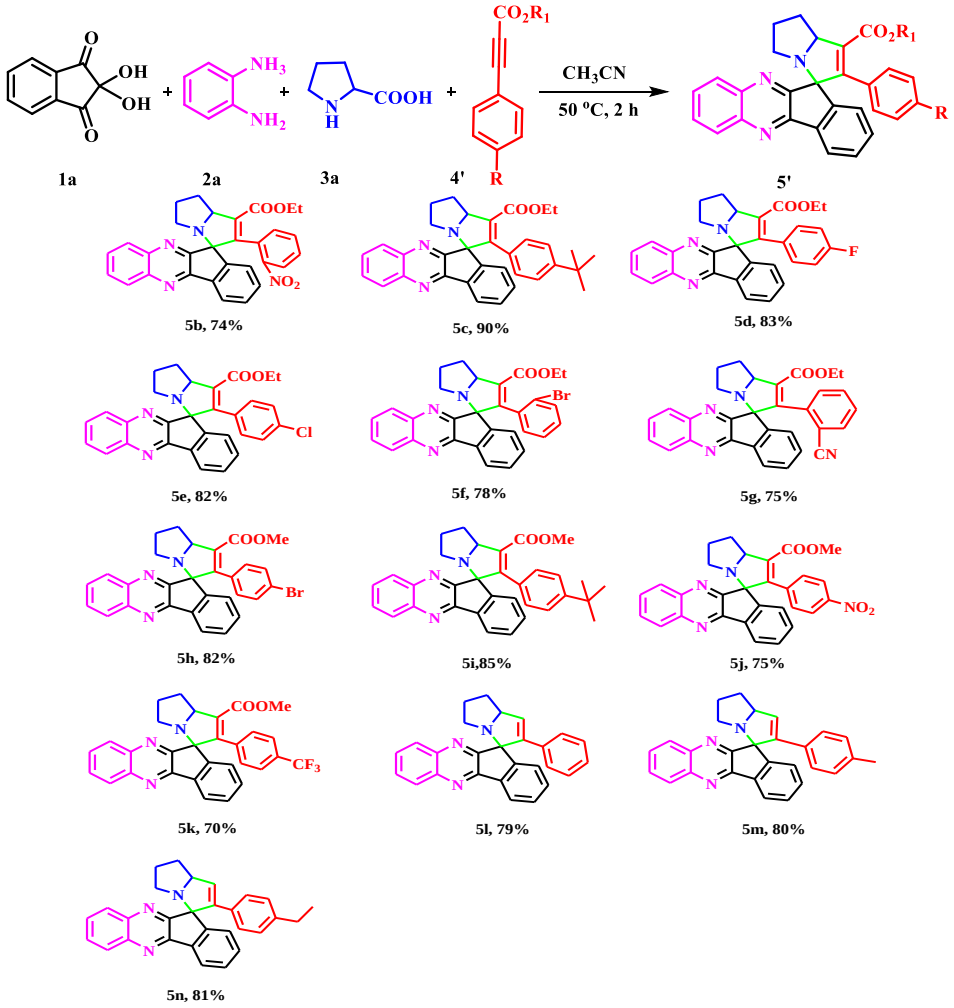
[a]Reaction conditions: Ninhydrin (**1a**, 1.0 mmol), *o*-phenylenediamine (**2a**, 1.0 mmol), l-proline (**3a**, 1.0 mmol), and ethyl phenylpropiolate (**4a**, 1.0 mmol) in Solvent (5.0 mL) in air. [b]Yields of the isolated product.

Table 1 provides a summary of the main findings. At room temperature the reaction duration was increased from 30 minutes (Table 1, entry 1) to one hour in an effort to increase the yield of the intended product (**5a**) (Table 1, entry 2). Subsequently, the reaction temperature was raised to 35 °C to increase the yield of (**5a**), (Table 1, entry 3). Gratifyingly, when the reaction was performed at 50 °C for a duration of two hours, an excellent yield (90%) of the desired product (**5a**) was achieved (Table 1, entry 4). The impact of various other solvents on the product yield—including methanol, ethanol, dichloromethane, dichloroethane, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), toluene, 1,4-dioxane, tetrahydrofuran (THF), and water were examined (Table 1, entries 5-14). Moderate yields of the product **(5a)** were obtained in protic solvents like methanol and ethanol (Table 1, entries 5 and 6). Furthermore, even with longer reaction duration, the intended product was only formed in trace amounts in the chlorinated solvents, such as dichloromethane and dichloroethane (Table 1, entries 7 and 8), and in the polar solvents, such as DMF and DMSO (Table 1, entries 9 and 10). Solvents including toluene, 1, 4-dioxane, THF and water failed to produce

the product **5a** (Table 1, entries 11–14). Hence, in terms of product yield, it was found that acetonitrile is the ideal solvent and the optimal condition for the synthesis of desired product (**5a**) were finalized at 50 °C temperature for two-hour reaction duration using acetonitrile as the solvent and in air (Table 1, entry 4).

To explore the scope of the methodology, after determining the optimal reaction conditions (Table 1, entry 4), we evaluated the substrate scope of the current methodology for various substituted alkynes and terminal alkynes (Table 2). Various derivatives of ethyl phenylpropiolates such as ring substituted with functional groups such as nitro, *tert*-butyl, fluoro, chloro, bromo and cyano, tolerated the reaction conditions well and produced the desired products with good to excellent yields and selectivity (Table 2, products **5b-5g**). Substituted Methyl phenylpropiolates containing different functional groups such as bromo, nitro, trifluoro methane and tertiary butyl groups furnished densely functionalized pyrrolizine derivatives with good to excellent yields (Table 2, products **5h-5k**). Phenylacetylene and substituted phenylacetylenes underwent the [3+2]-cycloaddition reaction with efficiency as the desired pyrrolizine derivatives were obtained in moderate to good yields (Table 2, products **5l-5n**).

Table 2. Investigation of substrate scope



[a]Reaction conditions: Ninhydrin (**1a**, 1.0 mmol), *o*-phenylenediamine (**2a**, 1.0 mmol), L-proline (**3a**, 1.0 mmol), and ethyl 3-phenylpropiolate (**4a-4m**, 1.0 mmol) in CH_3CN (5.0 mL) under air atmosphere.

The structures and regiochemistry of all the spiro adducts (Table 2) were verified using spectroscopic data. In the ^1H NMR spectrum of **5c**, a triplet at 0.97 ppm (0.97 t, J = 7.1 Hz, 3H) indiçâtes the ester CH_3 protons. A

singlet at 1.06 ppm (1.06 s, 9H) confirms the presence of a *tert*-butyl group. A doublet of doublet at 5.11 ppm (dd, *J* 9.3, 6.3 Hz, 1H) was observed which resulted from the coupling of neighbouring N atom of pyrrolidine. The ester ethyl CH2 protons appeared at 4.05 ppm (q, *J* = 7.1 Hz, 2H), corroborating the regiochemistry of **5c**. Additionally, 12 protons from the indenoquinoxaline ring (8 protons) and the 4-*tert*-butylphenyl ring (4 protons) were identified.

In the ^{13}C NMR spectrum, the spiro carbon of **5c** resonated at 84.30 ppm, with other carbons showing appropriate chemical shifts consistent with the proposed structure. The high-resolution mass spectrometry (HRMS) confirmed the product with an observed mass of *m/z* 516.1237 (found: 516.1234 [M+H]+). The molecular structure of **5e** was further confirmed by single-crystal X-ray diffraction (Figure 3). Crystals were grown by the slow diffusion of hexane into a saturated dichloromethane solution, and were found to be orthorhombic.

X-ray crystallography:

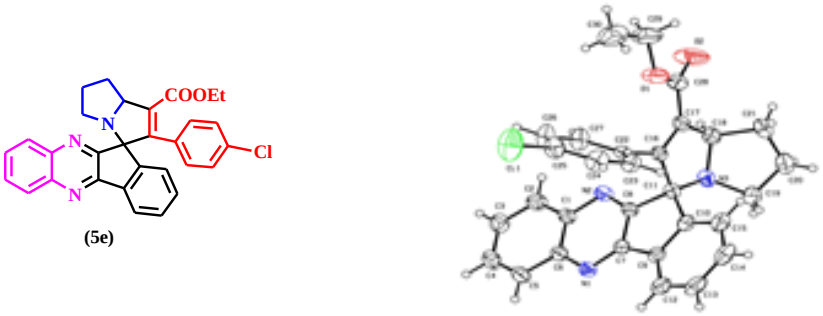
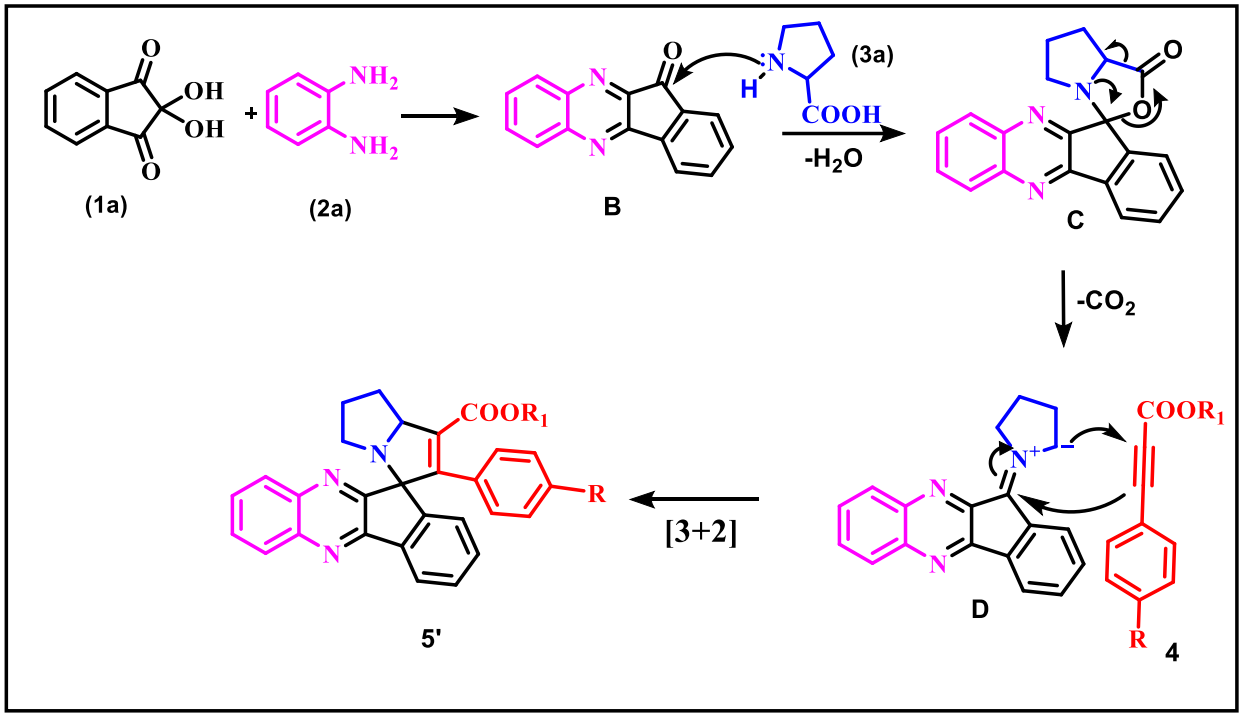


Figure 3. X-ray ORTEP diagram of compound **(5e).**

Based on our findings and relevant literature reports,[29] we propose a plausible reaction mechanism for the multicomponent reaction. First, ninhydrin **1a** reacts with *o*-phenylenediamine **2a** to form intermediate **B**. In the next step, nitrogen lone pair of L-proline **3a** attacks the carbonyl carbon of intermediate **B** to produce imine. Subsequently, carboxylic acid of **3a** attack on the carbon atom of the imine resulting in the formation of intermediate **C**. The intermediate **C**, subsequently undergoes decarboxylation to form the intermediate **D**. The negative charge on intermediate **D** can be stabilized by the adjacent nitrogen of pyrrolidine. The intermediate **D** then participates in a [3+2]-cycloaddition reaction with alkynes **4**, yielding the product **5a** (Scheme 2).



Scheme 2. Plausible mechanistic pathway.

Conclusions

In summary, we have demonstrated an efficient one-pot tandem protocol for broadening the synthesis scope of various spiro-quinoxaline pyrrolizine derivatives in acetonitrile. The reactive intermediate, an azomethine ylide, undergoes a [3+2]-cycloaddition with both activated and inactivated alkynes, facilitating the synthesis of densely functionalized pyrrolizine derivatives. This multicomponent reaction facilitated the formation of three new C-N and two C-C bonds in a single operation. Detailed mechanistic studies are currently ongoing in our laboratory, and we look forward to sharing our findings in due course.

Experimental Section

General. All substrates and reagents were readily and commercially available. TLC analysis was performed using pre-coated glass plates. Column chromatography was conducted using silica gel (60-120 mesh). All ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) on Advance 300 or 400 or Avance 500 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ (^{1}H: δ 7.26 (ppm), ^{13}C: δ 77.00 (ppm) as an internal reference. Coupling constants (J) are reported in (Hz). Peak multiplicities are indicated as: s-singlet, t-triplet, q-quartet, m-multiplate and dd-doublet of doublet. Mass spectra were recorded by using 70 Ev spectrometer. High resolution mass spectra (HRMS) were recorded using Applied Bio-sciences HRMS spectrometer at the national center for mass spectroscopy. Ninhydrin, *o*-phenylenediamine, L-proline, and ethyl 3-phenyl propiolate and substituted ethyl 3-phenyl propiolate were purchased from Sigma-Aldrich and used as such. Acetonitrile and other solvents were purchased from local sources and dried before use.

Synthesis of spiro-quinoxaline pyrrolizine compounds. Ninhydrin (**1a**, 1.0 mmol), *o*-phenylenediamine (**2a**, 1.0 mmol), L-proline (**3a**, 1.0 mmol), and ethyl phenylpropiolate (**4a**, 1.0 mmol) were placed in a round bottom flask containing acetonitrile solvent (5.0 mL) under air and stirred for 2 h at 50 °C. The excess acetonitrile was removed through rotary evaporator in vacuo. The reaction mixture was purified by column chromatography with hexane : ethyl acetate (7:3) mixture to obtain the desired product **5a** as a solid.

Ethyl 2'-phenyl-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5a). Compound was purified by column chromatography with hexane : ethyl acetate (7:3), white solid ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.24 (m, 1H), 8.05 (d, *J* 7.6 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.59 – 7.48 (m, 4H), 6.92 (d, *J* 7.4 Hz, 1H), 6.82 (t, *J* 7.6 Hz, 2H), 6.52 (d, *J* 7.3 Hz, 2H), 5.15 (dd, *J* 9.2, 6.4 Hz, 1H), 4.07 (dt, *J* 10.9, 3.7 Hz, 2H), 2.84 – 2.70 (m, 2H), 2.53 – 2.44 (m, 1H), 2.09 – 1.97 (m, 2H), 1.91 – 1.84 (m, 1H), 1.02 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.05, 153.18, 143.72, 142.70, 142.36, 138.25, 134.84, 133.42, 130.90, 130.12, 130.02, 129.70, 128.97, 128.88, 128.42, 127.86, 127.78, 127.51, 127.15, 122.75, 84.43, 73.03, 60.29, 48.41, 32.92, 27.85, 14.15, 13.79.

Ethyl 2'-(2-nitrophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5b). Yield 74% (373 mg) purified by column chromatography with hexane : ethyl acetate (6:4) White solid. mp: 185-187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* 8.0, 1.5 Hz, 1H), 8.12 (dd, *J* 8.1, 1.5 Hz, 1H), 8.07 – 8.04 (m, 1H), 7.83 (dd, *J* 8.2, 1.0 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.48 – 7.40 (m, 2H), 7.17 – 7.12 (m, 1H), 6.96 (td, *J* 7.7, 1.1 Hz, 1H), 6.26 (dd, *J* 7.8, 1.2 Hz, 1H), 5.29 (t, *J* 7.3 Hz, 1H), 4.14 – 4.03 (m, 2H), 3.32 (td, *J* 9.7, 5.5 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.48 (dt, *J* 12.5, 7.5 Hz, 1H), 2.09 – 2.00 (m, 2H), 1.91 (ddd, *J* 17.1, 12.0, 5.1 Hz, 1H), 1.05 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.49, 163.37, 153.09, 148.22, 146.20, 142.98, 142.25, 142.00, 138.47, 138.16, 132.42, 131.27, 130.19, 130.11, 129.97, 129.71, 129.09, 12*9.09, 128.95, 128.45, 128.41, 124.47, 122.40, 83.55, 71.34, 60.64, 50.47, 31.21, 26.43, 13.73.* HRMS: (ESI) *m/z* for $C_{30}H_{24}N_4O_4$ $[M+H]^+$: calcd: 505.1394, found: 505.1385.

Ethyl 2'-(4-(*tert*-butyl)phenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5c). Yield 90% (464 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid. mp: 166-168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.81 (s, 1H), 7.54 – 7.47 (m, 3H), 6.85 – 6.81 (m, 2H), 6.47 – 6.43 (m, 2H), 5.11 (dd, *J* 9.3, 6.3 Hz, 1H), 4.10 – 4.00 (m, 2H), 2.72 (ddt, *J* 13.4, 10.5, 6.5 Hz, 2H), 2.48 (t, 3H), 2.08 – 1.82 (m, 3H), 1.06 (s, 9H), 0.97 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.19, 164.09, 153.32, 152.80, 150.33, 144.01, 142.69, 142.42, 138.29, 134.88, 130.93, 130.30, 130.20, 129.98, 129.67, 128.89, 128.83, 128.36, 127.80, 127.58, 124.90, 124.09, 122.72, 84.30, 72.96, 60.20, 48.41, 34.30, 32.88, 31.07, 29.73, 27.77, 22.72, 13.68. HRMS: (ESI) *m/z* for $C_{34}H_{23}N_3O_2$ $[M+H]^+$: calcd: 516.1237, found: 516.1234.

Ethyl 2'-(4-fluorophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5d). Yield 83% (396 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid. mp: 134-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.22 (m, 1H), 8.11 – 8.05 (m, 2H), 7.75 – 7.69 (m, 2H), 7.54 (ddd, *J* 10.1, 7.9, 5.4 Hz, 3H), 6.56 – 6.48 (m, 4H), 4.09 (dddd, *J* 18.0, 14.2, 7.1, 3.8 Hz, 2H), 3.48 (q, *J* 7.0 Hz, 1H), 2.84 – 2.78 (m, 1H), 2.72 (ddd, *J* 10.6, 8.0, 3.0 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.12 – 1.98 (m, 2H), 1.85 (ddd, *J* 19.0, 6.6, 4.1 Hz, 1H), 1.06 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.68, 163.07, 161.11, 153.09, 152.00, 143.58, 142.74, 142.34, 138.27, 135.25, 130.99, 130.07, 129.83, 129.74, 129.67, 129.03, 128.99, 127.64, 122.86, 114.40, 114.22, 84.41, 73.03, 65.88, 60.41, 48.34, 32.92, 27.87, 15.30, 13.86 . HRMS: (ESI) *m/z* for $C_{30}H_{24}FN_3O_2$ $[M+H]^+$: calcd: 478.2169, found: 478.2160.

Ethyl 2'-(4-chlorophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5e). Yield 82% (405 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid. mp: 174-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.23 (m, 1H), 8.10 – 8.04 (m, 2H), 7.75 – 7.70

(m, 2H), 7.60 – 7.50 (m, 3H), 6.84 – 6.79 (m, 2H), 6.49 – 6.44 (m, 2H), 5.13 (dd, *J* 9.5, 6.3 Hz, 1H), 4.09 (dddd, *J* 18.0, 10.9, 7.1, 3.7 Hz, 2H), 2.79 (dd, *J* 9.0, 7.4 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.52 – 2.45 (m, 1H), 2.13 – 1.98 (m, 2H), 1.90 – 1.80 (m, 1H), 1.07 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.58, 153.06, 151.86, 143.43, 142.74, 142.31, 138.23, 135.33, 133.62, 131.88, 131.04, 130.23, 130.07, 129.89, 129.27, 129.04, 127.64, 127.53, 127.61, 127.60, 127.62, 122.92, 122.93, 84.34, 73.08, 60.50, 48.33, 32.94, 27.91, 13.89. HRMS: (ESI) *m/z* for $C_{30}H_{24}ClN_3O_2$ $[M+H]^+$: calcd: 494.1649, found: 494.1640.

Ethyl 2'-(2-bromophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5f). Yield 78% (419 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid. mp: 189-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.22 (m, 1H), 8.07 (ddd, *J* 10.0, 4.2, 1.8 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.61 – 7.47 (m, 4H), 7.00 – 6.94 (m, 2H), 6.45 – 6.37 (m, 2H), 5.13 (dd, *J* 9.5, 6.3 Hz, 1H), 4.09 (dddd, *J* 18.0, 10.9, 7.1, 3.7 Hz, 2H), 2.84 – 2.68 (m, 2H), 2.53 – 2.44 (m, 1H), 2.13 – 1.97 (m, 2H), 1.90 – 1.81 (m, 1H), 1.08 (t, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.04, 163.55, 153.03, 152.16, 143.37, 142.76, 142.31, 138.27, 134.96, 132.18, 131.31, 131.03, 130.54, 130.25, 130.05, 129.88, 129.47, 129.05, 128.82, 127.60, 126.48, 122.94, 122.09, 84.23, 73.01, 51.63, 48.37, 32.87, 29.72, 27.82. HRMS: (ESI) *m/z* for $C_{30}H_{24}BrN_3O_2$ $[M+H]^+$: calcd: 538.1394, found: 538.1385.

Ethyl 2'-(2-cyanophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5g). Yield 75% (363 mg) purified by column chromatography with hexane : ethyl acetate (6:4) White solid. mp: 180-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.26 (m, 1H), 8.15 – 8.10 (m, 1H), 8.01 (d, *J* 7.5 Hz, 1H), 7.83 – 7.74 (m, 3H), 7.54 (t, *J* 7.3 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.07 (t, *J* 7.6 Hz, 1H), 6.93 (t, *J* 7.6 Hz, 1H), 6.22 (d, *J* 7.8 Hz, 1H), 5.20 (t, *J* 7.4 Hz, 1H), 4.22 – 4.11 (m, 2H), 3.03 – 2.94 (m, 1H), 2.77 – 2.70 (m, 1H), 2.54 (dt, *J* 10.3, 7.1 Hz, 1H), 2.14 – 1.96 (m, 3H), 1.10 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.66, 162.86, 153.37, 147.21, 142.98, 142.34, 142.29, 138.90, 137.73, 137.36, 132.22, 131.79, 131.25, 130.25, 130.16, 130.09, 129.16, 129.12, 128.74, 127.96, 126.77, 122.49, 118.41, 113.53, 84.33, 72.68, 60.81, 49.38, 32.69, 27.22, 13.80. HRMS**:** (ESI) *m/z* for $C_{31}H_{24}N_4O_2$ $[M+H]^+$: calcd: 485.1394, found: 485.1385.

Methyl 2'-(4-bromophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5h). Yield 82%, (429 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid, mp: 154-156°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.21 (m, 1H), 8.10 – 8.05 (m, 2H), 7.75 – 7.69 (m, 2H), 7.61 – 7.47 (m, 4H), 6.99 – 6.96 (m, 2H), 6.42 – 6.39 (m, 2H), 5.13 (dd, *J* 9.5, 6.3 Hz, 1H), 3.65 (s, 3H), 2.84 – 2.77 (m, 1H), 2.73 – 2.68 (m, 1H), 2.51 – 2.43 (m, 1H), 2.14 – 2.05 (m, 1H), 2.04 – 1.97 (m, 1H), 1.89 – 1.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.04, 163.55, 153.03, 152.17, 143.36, 142.76, 142.31, 138.27, 134.95, 132.18, 131.04, 130.54, 130.26, 130.05, 129.89, 129.48, 129.06, 127.61, 122.95, 122.10, 84.23, 73.02, 51.64, 48.38, 32.88, 27.82. HRMS: (ESI) *m/z* for $C_{29}H_{22}BrN_3O_2$ $[M+H]^+$: calcd: 524.1494, found: 524.1485.

Methyl 2'-(4-tert-butylphenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5i). Yield 85% (426 mg) purified by column chromatography with hexane:ethyl acetate (7:3) White solid. mp: 170-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.81 (s, 1H), 7.55 – 7.47 (m, 3H), 6.84 – 6.81 (m, 2H), 6.47 – 6.43 (m, 2H), 5.11 (dd, *J* 9.3, 6.3 Hz, 1H), 4.09 – 4.01 (m, 1H), 2.78 – 2.74 (m, 1H), 2.71 – 2.65 (m, 1H), 2.49 (q, 3H), 2.48 (s, 2H), 2.08 – 1.96 (m, 1H), 1.86 – 1.81 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.13, 163.18, 153.11, 152.42, 150.21, 143.74, 141.45, 141.26, 140.01, 139.18, 138.60, 134.70, 130.44, 129.83, 129.46, 128.16, 127.69, 127.57, 127.57, 124.02, 124.02, 122.39, 84.30, 72.93, 60.15, 48.36, 34.28, 32.91, 31.08, 27.78, 20.32, 20.28, 13.68. HRMS: (ESI) *m/z* for $C_{33}H_{32}N_3O_2$ $[M+H]^+$: calcd: 502.1294, found: 502.1285.

Methyl 2'-(4-nitrophenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate (5j). Yield 75% (368 mg) purified by column chromatography with hexane : ethyl acetate (6:4) White solid. mp: 203-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 8.10 – 8.04 (m, 2H), 7.76 – 7.70

(m, 4H), 7.63 – 7.52 (m, 3H), 6.75 – 6.70 (m, 2H), 3.65 (d, *J* 5.0 Hz, 3H), 3.48 (q, *J* 7.0 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.73 (ddd, *J* 10.6, 7.9, 3.1 Hz, 1H), 2.50 (ddd, *J* 8.9, 6.6, 3.4 Hz, 1H), 2.08 (dddd, *J* 15.7, 10.8, 5.8, 2.6 Hz, 2H), 1.88 (ddd, *J* 14.8, 10.8, 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.62, 163.02, 152.80, 151.22, 147.13, 142.83, 142.28, 140.37, 138.24, 135.96, 131.18, 130.54, 130.13, 130.00, 130.10, 129.28, 129.13, 128.97, 128.97, 127.54, 123.09, 123.09, 122.58, 84.24, 73.12, 51.82, 48.38, 32.85, 27.88. HRMS: (ESI) *m/z* for $C_{29}H_{23}N_4O_4$ $[M+H]^+$: calcd: 491.1260, found: 491.1250.

Methyl 2'-(4-(trifluoromethyl)phenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1'-carboxylate(5k). Yield 70% (359 mg) purified by column chromatography with hexane : ethyl acetate (7:3) White solid. mp: 190-194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 – 8.23 (m, 1H), 8.07 (ddd, *J* 8.7, 5.5, 3.2 Hz, 2H), 7.72 (ddd, *J* 8.6, 5.0, 2.2 Hz, 2H), 7.60 – 7.52 (m, 3H), 7.11 (d, *J* 8.3 Hz, 2H), 6.67 (d, *J* 8.1 Hz, 2H), 5.16 (dd, *J* 9.5, 6.3 Hz, 1H), 3.64 (s, 3H), 2.84 – 2.78 (m, 1H), 2.72 (ddd, *J* 10.6, 8.0, 3.0 Hz, 1H), 2.52 – 2.46 (m, 1H), 2.14 – 2.07 (m, 1H), 2.03 – 1.98 (m, 1H), 1.91 – 1.83 (m, 1H). ^{13}C NMR (101 MHz) δ 163.87, 163.37, 152.98, 151.90, 143.16, 142.79, 142.32, 138.25, 137.08, 135.48, 131.06, 130.35, 130.06, 129.96, 129.78, 129.46, 129.11, 129.08, 128.27, 127.59, 124.29, 124.26, 122.98, 84.27, 73.03, 51.69, 48.37, 32.87, 27.84, 14.22. 130.6 (1C, q, $J^{13}C$-^{19}F =3.9 Hz) HRMS: (ESI) *m/z* for $C_{30}H_{23}O_2N_3F_3$ $[M+H]^+$: calcd: 514.1748, found: 514.1736.

2'-phenyl-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine] (5l). Yield 79% (383 mg) purified by column chromatography with hexane : ethyl acetate (8:2) White solid. mp: 145-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* 7.3 Hz, 1H), 8.13 (ddd, *J* 11.5, 8.0, 1.0 Hz, 2H), 7.68 (ddt, *J* 8.2, 6.9, 5.4 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.36 (d, *J* 7.5 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.75 (d, *J* 2.0 Hz, 1H), 6.71 – 6.67 (m, 2H), 4.90 (t, *J* 7.0 Hz, 1H), 2.72 (dd, *J* 8.7, 7.0 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.21 (ddd, *J* 14.4, 7.0, 3.5 Hz, 1H), 1.97 – 1.88 (m, 2H), 1.83 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.21, 153.32, 145.38, 142.75, 142.45, 141.56, 138.15, 133.62, 132.84, 131.16, 130.17, 129.81, 129.46, 128.91, 128.74, 128.07, 128.07, 127.58, 127.33, 126.43, 126.43, 122.79, 80.83, 71.62, 49.00, 32.00, 27.49. HRMS**:** (ESI) *m/z* for $C_{27}H_{21}N_3$ $[M+H]^+$: calcd: 388.1394, found: 388.1385.

2'-(p-tolyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine] (5m). Yield 80% (321 mg) purified by column chromatography with hexane:ethyl acetate (8:2) White solid. mp: 160-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* 7.1 Hz, 1H), 8.13 (td, *J* 8.2, 1.1 Hz, 2H), 7.73 – 7.62 (m, 2H), 7.50 (dtd, *J* 20.7, 7.3, 1.1 Hz, 2H), 7.36 (d, *J* 7.3 Hz, 1H), 6.73 – 6.69 (m, 2H), 6.58 (d, *J* 8.2 Hz, 2H), 4.88 (t, *J* 6.9 Hz, 1H), 2.71 (dd, *J* 16.4, 9.3 Hz, 1H), 2.58 (ddd, *J* 10.5, 7.1, 3.7 Hz, 1H), 2.27 – 2.15 (m, 1H), 2.08 (s, 3H), 1.93 (ddd, *J* 18.4, 11.0, 6.0 Hz, 2H), 1.70 (dd, *J* 20.5, 9.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.35, 153.35, 145.58, 142.74, 142.48, 141.41, 138.14, 137.11, 131.91, 131.17, 130.70, 130.20, 129.77, 129.42, 128.89, 128.80, 128.80, 128.70, 127.58, 126.29, 126.29, 122.76, 80.84, 71.65, 48.95, 32.10, 27.54, 20.95. HRMS: (ESI) *m/z* for $C_{28}H_{23}N_3$ $[M+H]^+$: calcd: 402.1394, found: 402.1385.

2'-(4-ethylphenyl)-5',6',7',7a'-tetrahydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine] (5n). Yield 81% (336 mg) purified by column chromatography with hexane :ethyl acetate (8:2) White solid. mp: 137-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* 7.5 Hz, 1H), 8.15 – 8.11 (m, 2H), 7.67 (ddd, *J* 7.8, 7.1, 1.0 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.49 – 7.45 (m, 1H), 7.37 (d, *J* 7.5 Hz, 1H), 6.72 (d, *J* 2.1 Hz, 2H), 6.61 (d, *J* 8.3 Hz, 2H), 4.97 – 4.86 (m, 1H), 2.72 (dd, *J* 16.5, 9.3 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.41 – 2.34 (m, 2H), 2.20 (ddd, *J* 14.5, 7.0, 3.5 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.72 (dt, *J* 17.7, 8.0 Hz, 1H), 1.20 (d, *J* 7.6 Hz, 1H), 1.02 (t, *J* 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.33, 145.55, 144.23, 143.41, 142.74, 142.46, 141.31, 138.17, 136.70, 131.91, 131.19, 130.20, 129.82, 129.45, 128.90, 128.72, 127.60, 127.60, 126.31, 126.31, 122.81, 80.78, 71.59, 48.99, 32.05, 29.73, 28.28, 15.08. HRMS: (ESI) *m/z* for $C_{29}H_{25}N_3$ $[M+H]^+$: calcd: 416.1394, found: 416.1385.

X-ray crystallography study. X-ray data for the compound was collected at room temperature on a Bruker D8 QUEST instrument with an IμS Mo microsource (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames of **5h** were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms of were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and U_{iso}(H) = 1.5U_{eq}(C) for methyl H or 1.2U_{eq}(C) for other H atoms].
Crystal structure determination of 5e. Crystal Data for $C_{30}H_{24}N_3O_2Cl$ (*M* =493.97 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 19.6937(15) Å, *b* = 13.4393(9) Å, *c* = 9.6001(7) Å, *β* = 98.102(2)°, *V* = 2515.5(3) Å^3, *Z* = 4, *T* = 294.15 K, μ(MoKα) = 0.185 mm^{-1}, *Dcalc* = 1.304 g/cm^3, 33466 reflections measured (5.162° ≤ 2Θ ≤ 50°), 4432 unique (R_{int} = 0.0678, R_{sigma} = 0.0412) which were used in all calculations. The final R_1 was 0.0604 (I > 2σ(I)) and wR_2 was 0.1693 (all data). CCDC 2049616 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

Acknowledgements

Sundar S. Shinde thanks CSIR-UGC India for the fellowship New Delhi for the financial support and AcSIR for all academic activities. The authors are grateful to the Director, CSIR-IICT for providing the necessary infrastructure. IICT/Pubs./2020/330.

Supplementary Material

Copies of all ^{1}H and ^{13}C NMR and Mass spectra along with X-ray crystallography study details are available in the Supplementary Material related to this article.

References

1. Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanvelkar, R. R.; Vaidya R. B.; Ajaykumar, K. B. *Eur. J. Med. Chem.* **2005**, *40*, 1143. https://doi.org/10.1016/j.ejmech.2005.06.004
2. Park, H. B.; Jo, N. H.; Hong, J. H.; Chei, J. H.; Cho, J. H.; Yoo K. H.; Oh, C. H. *Arch. Pharm. Chem. Life Sci.* **2007,** *340,* 530. https://doi.org/10.1002/ardp.200700060
3. Vithiya, M. ; Indumati B. ; Prasad T, A. A. *Der Pharma Chemica.* **2012**, *4*, 1906 .
4. Obniska, J. ; Kaminski, K. *Acta Poloniae Farmaceutica.* **2006**, *63*, 101.
5. Kaminski, K. ; Obniska, J. ; Dybala, M. *Eur. J. Med. Chem.* **2008**, *43*, 53. https://doi.org/10.1016/j.ejmech.2007.02.024
6. Youssef, M. M. ; Amin, M. A. *Molecules* **2010**, *15*, 8827. https://doi.org/10.3390/molecules15128827

7. Thadhaney, B. ; Sain, D. ; Pemawat, G. ; Talesara G. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **2010**, *49*, 368.
8. Masakazu, F. ; Kenji H. ; Jiro K. *Int. Pat. WO*/066546, **2001**.
9. Nakao, K. ; Ekeda, K. ; kurokawa, T. ; Togashi, Y. ; Umeuchi, H. ; Honda, T. ; Okano, K. ; Mochizuki, H. ; *Nihon Shinkei Seishin Yakurigaku Zasshi.* **2008**, *28*,75.
10. Frank, R. ; Reich, M. ; Justock, R. ; Bahrenberg, G. ; Schick, H. ; Henkel, B. ; Sonnenschein, H. *US. Pat.* 20080269271, **2008** .
11. Chin, Y. W. ; Salim, A. A. ; Su, B. N. ; Mi, Q. ; Chai, H. B. ; Riswan, S. ; Cardono, L. B. S. ; Ruskandi, A. ; Farnsworth, N. R. ; Swanson, S. M. ; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 390. https://doi.org/10.1021/np070584j.
12. Hu, H. ; Guo, H. ; Li, E. ; Liu, X. ; Zhou Y. ; Che, Y. *J. Nat. Prod.* **2006**, *69*, 1672. https://doi.org/10.1021/np0603830
13. Lindell, S. ; Sanft U. ; Thonessen, M-Th. *Int. Pat. WO*/011968, **2001**.
14. Kreudar, W. ; Yu N. ; Salbeck, J. *Int. Pat. WO*/040655, **1999**.
15. Lupo, D. ; Selbeck, J. ; Schenk, H. ; Stehlin, T. ; Stern R. ; Wolf, A. *US Pat*. 5840217, **2008**.
16. Shimakawa, S. ; Yoshida, Y. ; Niki E. *Lipids.* **2003**, *38*, 225. https://doi.org/10.1007/s11745-003-1055-3
17. Youssef, M. M. ; Amin, M. A. *Molecules* **2010**, *15,* 8827. https://doi.org/10.3390/molecules15128827
18. Sarma, B. K. ; Manna, D. ; Minoura, M. ; Mugesh, G. *J. Am. Chem. Soc.* **2010**, *132*, 5364. https://doi.org/10.1021/ja908080u
19. Akondi, A. M. ; Mekala, S. ; Kantam, M. L. ; Trivedi, R. ; Chowhan, L. R. ; Das, A. *New. J. Chem.* **2017**, *41*, 873. https://doi.org/10.1039/C6NJ02869A
20. Ikeda, Y. ; Nonaka, H. ; Furumai, T. ; Igarashi, Y. *J. Nat. Prod.* **2005**, *68*, 572. https://doi.org/10.1021/np050091j
21. Niwa, H. ; Ogawa, T. ; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4985. https://doi.org/10.1016/S0040- 4039(01)80561-X
22. Belal, A. ; Dien B. E. ; Gendy, E. *Bioorg. Med. Chem.* **2014**, *22*, 4653.
23. Bradner, W. T. *Cancer Treat. Rev.* **2001**, *27*, 35. https://doi.org/10.1053/ctrv.2000.0202
24. Mali, P. R. ; Khomane, N. B. ; Sridhar, B. ; Meshram, H. M. ; Likhar, P. R. *New. J. Chem.* **2018**, *42*, 13819. https://doi.org/10.1039/C8NJ02127A
25. Shinde, S. S. ; Laha, S. ; Tiwari, D. K. ; Sridhar, B. ; Likhar, P. R. *Org. Biomol. Chem.* **2019**, *17*, 4121. https://doi.org/10.1039/C9OB00560A
26. Kumar, A. ; Shinde, S. S. ; Tiwari, D. K. ; Sridhar, B. ; Likhar, P. R. *RSC Adv.* **2016**, *6*, 43638. https://doi.org/10.1039/C6RA06755G
27. Karkhelikar, M. V. ; Rao, V. V. ; Shinde, S. S. ; Likhar, P. R. *Tetrahedron Lett.* **2016**, *57*, 4803. https://doi.org/10.1016/j.tetlet.2016.09.044
28. Reddy, M. S. ; Chowhan, L. R. ; Kumar, N. S. ; Ramesh, P. ; Mukkamala, S. B. *Tetrahedron Lett.* **2018**, *59*, 1366. https://doi.org/10.1016/j.tetlet.2018.02.044
29. *Karsalary, A. A., Mohammadizadeh, M. R., Hasaninejad, A. R., Mohammadi, A. A. ; Karimi, A. R. Iran. Chem. Soc., **2010**, 7, 45.*

https://doi.org/10.1007/BF03245858