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An Improved Synthesis of Natural Product Inspired Chromenopyrrolizines and Chromenoindolizines Scaffolds: Rapid Access to the Diverse Pyrrolizine Analogs of Aza-Medicarpin and Tetracyclic Isolamellarin Core through a General Base and Metal Free Strategy

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An Improved Synthesis of Natural Product Inspired Chromenopyrrolizines and Chromenoindolizines Scaffolds: Rapid Access to the Diverse Pyrrolizine Analogs of Aza-Medicarpin and Tetracyclic Isolamellarin Core through a General Base and Metal free Strategy

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Abstract

An improved synthesis for easy access to the natural product inspired chromenopyrrolizine and chromenoindolizine scaffolds is delineated. The strategy involves controlled thermal activation of diverse salicylaldehyde tethered dipolarophiles having the strategically stationed activating substituents with proline/pipecolic acid for the facile [3+2] cycloaddition of the in situ generated azomethine ylides and concomitant oxidation of the resulting cycloadducts to arrive at diverse chromenopyrrolizine or pyrrolizine analogs of aza-medicarpin and chromenoindolizines embodying the tetracyclic core isomeric to lamellarin alkaloids, in good yields under base and metal free condition.

1. Introduction

Natural products has been the source of inspiration of most of the currently used medicines and will continue to inspire many future drug molecules.[1-4] As a matter of fact an estimated 40% of all medicines are either natural products or their semisynthetic derivatives.[5] In quest for better therapeutic values the intricate molecular architecture of natural products are often tweaked for the diversity-oriented synthesis (DOS) of natural products.[6] In our endeavor towards the diversity oriented synthesis of natural products we chose the recently reported aza analog of medicarpin[7] which we are referring as aza-medicarpin and lamellarins[8] as the natural products to grapple with their scaffold. Aza-medicarpin which was isolated from the roots of Black Locust didn't show significant cytotoxicity against the human colon cancer cell lines, however it was the synthetic indole analog as depicted in **Figure 1** which infact served as a precursor during the synthesis of the natural product that was found to be fairly cytotoxic with an IC_{50} of 66.1 µM against the human colon cancer cell lines. [7] Similarly, lamellarins which represent a rich diverse class of marine pyrrole alkaloids, first reported by Andersen et. al. in 1985[8a] have also been gifted with remarkable bioactivity.[9] Although, most of the lamellarins alkaloids exhibit cytotoxicity but among all the members lamellarin D (**Figure 1)** has been found to be an extremely potent antiproliferative agent.[9] Also, its cytotoxic action is fully maintained in multi-drug resistant (MDR) cancerous cells.[9] And very recently its closely related structural sibling namely lamellarin N (**Figure 1**) has been reported to be having even better cytotoxicity profile in comparison to the D analog against certain cell lines.[10] But it is their poor solubility in aqueous medium that has thwarted their further development as anticancer agents but on the other hand sparked the inspiration for the synthesis of azalamellarin D and N analogs (**Figure 1**) which indeed renders them less lipophilicity without any compromise in the bioactivity.[11] Further, also the isolamellarins with transposed α-carboxyl

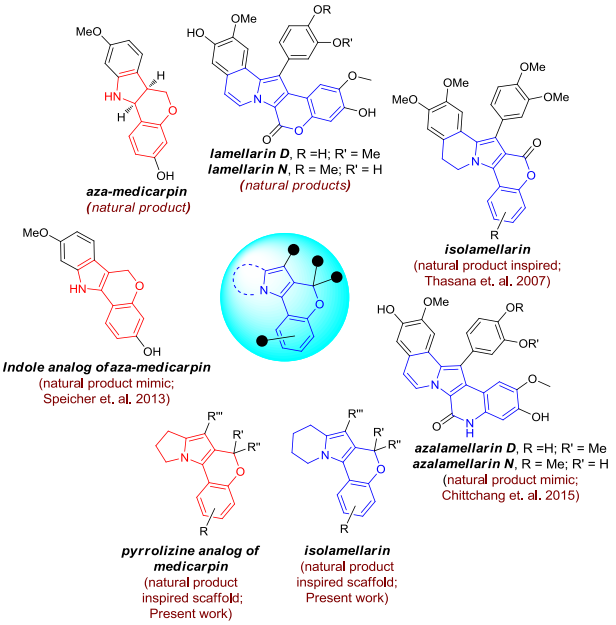
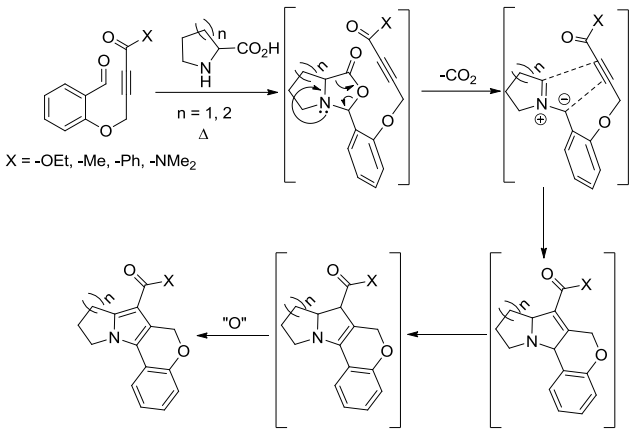


Figure 1. Natural products and natural products mimics featuring chromeno-indole/pyrrolizine/indolizine scaffolds.

group and the β-aryl group have been synthesized[12] but the influence of transposition on the bioactivity profile is not yet reported.

In view of the renewal of interest in natural products as source of inspiration for innovative future drug molecules, [13-16] we got interested in devising a general synthetic route for accessing the chromenopyrrolizines **1** (**Figure 1**) as aza-medicarpin inspired pyrrolizine analogs and chromenoindolizines **2** (**Figure 1**) as lamellarin inspired tetracyclic isolamellarin to study the effect of structural modification on the bioactivity. Although there are several approaches reported specifically for pyrrolizine[17] or indolizine scaffold[18] but the precedent on general approaches targeting both these motifs has been very scarce.[19-21] To the best of our knowledge there has been only one exploratory report describing the synthesis of chromenopyrrolizines and chromenoindolizines though with limited substrate scope.[20] Therefore, we believe there lies ample scope for the exploration of a general cum diversity oriented approach in context of these privileged scaffolds. Henceforth, in this article we disclose our efforts in this direction by disclosing an improved protocol over the reported ones that is acid/base as well as metal and oxidant free and which provides quick access to the diverse chromeno-annulated pyrrolizines and indolizines in a single pot operation.

In pursuit of step, atom and redox economical synthesis[22] we envisioned to access the chromenopyrrolizine and chromenoindolizine scaffold via a strategy as outlined in



Scheme 1. A tandem [3+2] cycloaddition/oxidation strategy towards chromenopyrrolizines and chromenoindolizines.

Scheme 1 which involves the intramolecular 1, 3-dipolar cycloaddition of the insitu generated azomethine ylide[23] resulting from the treatment of proline/pipecolic acid with salicylaldehyde tethered alkynes that are activated by electron withdrawing group. We presumed that the strategically stationed electron withdrawing functionality at the salicylaldehyde tethered alkyne would facilitate the intramolecular [3+2] cycloaddition reaction as well as the concomitant aromatization of the resultant cycloadduct under milder reaction condition and perhaps without the use of any conventional oxidizing agent.

2. Experimental

All the reagents were purchased from Sigma-Aldrich and other commercial suppliers and used without further purification. While most of the desired solvents supplied by commercial suppliers were dried using the standard drying procedures.[24] All nonaqueous reactions were executed under oxygen atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz Bruker spectrometer using TMS signal as an internal standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet/pentet, td = triplet of doublet, and m = multiplet. The chemical shifts are reported as δ values (ppm) and the coupling constants (J) values are reported in Hz. High Resolution Mass Spectra (HRMS) were obtained using electron spray ionisation (ESI) technique and as TOF mass analyzer. IR spectra were recorded on a Bruker FT/IR-460 Plus spectrometer. Reactions monitoring were done using precoated SiO_2-gel GF_{254} glass TLC plates while spot visualizations were done under UV light and spot developing stains like iodine, ninhydrin or $KMnO_4$. Purifications were done using column chromatography with 100-200 mesh size SiO_2-gel as the stationary phase. The known salicylaldehyde tethered ynoates **1a-h** were synthesized by earlier reported procedure[25] and using the same strategy the other unknown derivatives were synthesized. For synthesis of compound **1m** and **1o-q** please refer our supporting information.

General procedure for the synthesis of chromeno-annulated pyrrolizines/indolizines via tandem [3+2] cycloaddition/ oxid- ation reaction

In an oven dried round-bottom flask, salicylaldehyde tethered activated alkyne (0.1 mmol, 1 equiv.) and proline/pipecolic acid (0.125 mmol, 1.25 equiv.), were dissolved in dry 1, 4 Dioxane (2 mL) and allowed to stir at 90 °C in presence of powdered molecular sieves 4Å (~15mg), under oxygen atmosphere. The progress of reaction was monitored by TLC technique. Upon complete consumption of starting materials, the reaction was worked up by evaporating the dioxane solvent followed by subjection of the crude residue to SiO_2-gel column chromatography using petroleum ether/ethyl acetate as the eluent to arrive at diverse tetracyclic chromeno-annulated pyrrolizines/indolizines.

Ethyl 6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3a):

The title compound was prepared according to the general procedure. [TLC profile: R_f (1a) = 0.51, R_f (3a) = 0.74 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded 3a as a pale yellow solid; (19.6 mg, 69% yield); **IR** (neat): ν_{max} 2978 1694, 1564, 1554, 1374, 1275, 1105, 751 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H), 7.04 (td, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 6.90-6.86 (m, 2H) , 5.51 (s, 2H), 4.28-4.21 (m, 4H) , 3.10 (t, J = 7.6 Hz, 2H), 2.62 (p, J = 7.6 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.8, 152.5, 146.1, 127.0, 121.2, 120.1, 119.3, 119.2, 118.3, 116.8, 103.8, 66.0, 59.5, 47.3, 27.1, 25.1, 14.5; **HRMS** (ES) m/z calcd for $C_{17}H_{18}NO_3$ $(M+H)^+$: 284.1287; found: 284.1278.

Ethyl 6, 6-dimethyl-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3b):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1b**) = 0.58, R_f (**3b**) = 0.70 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3b** as a fluorescent green solid; (19.4 mg, 62% yield); **IR** (neat): ν_{max} 2976, 1687, 1502, 1247, 1179, 1116, 1100, 749 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (dd, J_1 = 6.8 Hz, J_2 = 1.8 Hz, 1H), 7.04 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H),6.88-6.84 (m, 2H) , 4.262 (Q, J = 7.2 Hz, 4H), 3.12 (t, J = 7.6 Hz, 2H), 2.60 (Q, J = 7.2 Hz, 2H), 1.78 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.4, 151.4, 147.1, 127.0, 126.9, 120.3, 119.4, 118.9, 117.1, 117.0, 103.4, 80.4, 59.4, 47.8, 28.5 (2C), 26.7, 26.2, 14.5; HRMS (ES) m/z calcd for $C_{19}H_{22}NO_3$ $(M+H)^+$: 312.1600; found:312.1594.

Ethyl 2-methyl-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3c):

The title compound was prepared according to the general procedure. [TLC profile: R_f (1c) = 0.56, R_f (3c) =0.67 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded 3c as a brown solid; (21.2 mg, 71% yield); IR (neat): ν_{max} 2976, 2924, 1698, 1509, 1432, 1257, 1107, 1000, 813 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.02 (d, J = 1.6 Hz, 1H), 6.85 (dd, J_1 = 8.6 Hz, J_2 = 1.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.46 (s, 2H), 4.27-4.21 (m, 4H) , 3.09 (t, J = 7.6 Hz, 2H), 2.61 (p, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 150.2, 146.0, 130.4, 127.4, 120.2, 119.8, 119.4, 118.1, 116.5, 103.7, 65.8, 59.4, 47.3, 27.0, 25.1, 20.9, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{20}NO_3$ $(M+H)^+$: 298.1443; found:298.1441.

Ethyl 2, 4-di-tert-butyl-6, 8, 9, 10-tetrahydrochromeno[3, 4-b]pyrrolizine-7-carboxylate (3d):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1d**) = 0.59, R_f (**3d**) =0.53 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using

petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3d** as a white solid; (28.9 mg, 73% yield); **IR** (neat): ν_{max} 2957, 1699, 1285, 1254, 1111, 1087 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 5.04 (s, 2H), 4.28-4.23 (m, 4H) , 3.12 (t, J = 7.6 Hz, 2H), 2.62 (p, J = 7.6 Hz, 2H), 1.40 (s, 9H), 1.32 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0, 148.4, 145.8, 143, 137.9, 121.7, 121.3, 119.3, 118.6, 114.4, 103.5, 64.7, 59.4, 47.3, 35.0, 34.4, 31.6 (3C), 29.8 (3C), 27.2, 25.2, 14.6; HRMS (ES) m/z calcd for $C_{25}H_{34}NO_3$ $(M+H)^+$: 396.2539; found: 396.2500.

Ethyl 2-methoxy-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3e):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1e**) = 0.50, R_f (**3e**) =0.50 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3e** as a pale yellow solid; (20.1 mg, 64% yield); **IR** (neat): ν_{max} 2930, 1697, 1488, 1276, 1260, 1108, 1067, 749 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 3.2 Hz, 1H), 6.57 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 5.43 (s, 2H), 4.27-4.20 (m, 4H) , 3.78 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 2.61 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.8, 154.1, 146.4, 146.2, 120.3, 120.1, 119.1, 117.0, 110.6, 106.2, 103.8, 65.8, 59.5, 55.7, 47.1, 27.1, 25.2, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{20}NO_4$ $(M+H)^+$: 314.1392; found: 314.1390.

Ethyl 3-methoxy-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3f):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1f**) = 0.52, R_f (**3f**) =0.71 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **3f** as a pale yellow solid; (29 mg, 93% yield); **IR** (neat): ν_{max} 2973, 1689, 1514, 1141, 1124, 1111 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 6.46 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H), 5.49 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.20 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.09 (t, J = 7.6 Hz, 2H), 2.61 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165, 159.1, 153.9, 145.2, 120.2, 119.8, 117, 111.6, 106.8, 103.5, 103, 66.3, 59.4, 55.4, 47.1, 27.2, 25.1, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{20}NO_4$ $(M+H)^+$: 314.1392; found:314.1358.

Ethyl 2-chloro-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3g):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1g**) = 0.58, R_f (**3g**) =0.77 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **3g** as a pale brown solid; (16.8 mg, 53% yield); **IR** (neat): ν_{max} 2980, 1728, 1670, 1470, 1442, 1286, 1269, 1077, 823 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.13 (d, J = 2.4 Hz, 1H), 6.96 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.48 (s, 2H), 4.27-4.19 (m, 4H), 3.10 (t, J = 7.6 Hz, 2H), 2.62 (p, J = 7.6 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.6, 150.8, 146.6, 126.4, 126, 120.1, 119.5, 119, 118.8, 117.9, 104, 66.2, 59.5, 47.3, 27.0, 25.1, 14.5; HRMS (ES) m/z calcd for $C_{17}H_{17}ClNO_3$ $(M+H)^+$: 318.0897; found:318.0891.

Ethyl 2, 4-dichloro-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3h):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1h**) = 0.70, R_f (**3h**) =0.50 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3h** as a dark brown solid; (19.2 mg, 55% yield); **IR** (neat): ν_{max} 2962, 1687, 1524, 1496, 1430, 1261, 1106, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.08 (d, J = 2.4 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.6 (s, 2H), 4.28-4.21 (m, 4H), 3.12 (t, J = 7.6 Hz, 2H), 2.66 (p, J = 7.6 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.4, 147.3, 146.7, 126.7, 125.8, 123.5, 122.4, 120.4, 118.3, 117.3, 104.1, 67, 59.7, 47.4, 27.0, 25.1, 14.5; HRMS (ES) m/z calcd for $C_{17}H_{16}Cl_2NO_3$ $(M+H)^+$: 352.0507; found:352.0502.

Ethyl 2-bromo-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3i):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1i**) = 0.40, R_f (**3i**) = 0.54 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3i** as a white solid; (19.5 mg, 54% yield); **IR** (neat): ν_{max} 2922, 1699, 1602, 1464, 1299, 1234, 1171, 1110, 1021 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 2 Hz, 1H), 7.10 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 4.28-4.20 (m, 4H), 3.10 (t, J = 7.6 Hz, 2H), 2.63 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.6, 151.4, 146.7, 129.4, 121.7, 120.1, 120.0, 118.8, 118.4, 113.3, 104.0, 66.2, 59.6, 47.3, 27.0, 25.2, 14.5; HRMS (ES) m/z calcd for $C_{17}H_{17}BrNO_3$ $(M+H)^+$: 362.0392; found: 362.0386.

Ethyl 2-fluoro-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3j):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1j**) = 0.54, R_f (**3j**) =0.73 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **3j** as a white solid; (14.4 mg, 48% yield); **IR** (neat): ν_{max} 2979, 1697, 1528, 1508, 1435, 1261, 1175, 1115, 1104 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.91 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.82 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 6.71 (td, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 5.47 (s, 2H), 4.28-4.19 (m, 4H), 3.15 (t, J = 7.6 Hz, 2H), 2.64 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.7, 157.5 (d, J_{CF} = 236 Hz, 1H), 148.2, 146.6, 120.4, 119.5, 119.1 (d, J_{CF} = 9 Hz, 1H), 117.5 (d, J_{CF} = 9 Hz, 1H), 112.6 (d, J_{CF} = 23 Hz, 1H), 106 (d, J_{CF} = 26 Hz, 1H), 104, 66, 59.6, 47.1, 27.1, 25.2, 14.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -122.4 ppm; HRMS (ES) m/z calcd for $C_{17}H_{17}FNO_3$ $(M+H)^+$: 302.1192; found: 302.1187.

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Ethyl 2-phenyl-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3k):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1k**) = 0.50, R_f (**3k**) = 0.71 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3k** as a brown solid; (23.7 mg, 66% yield); **IR** (neat): ν_{max} 2978, 1696, 1530, 1493, 1432, 1261, 1229, 1109, 762, 698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.44-7.40 (m, 3H), 7.34-7.30 (m, 1H), 7.26 (dd, J_1 = 8.4 Hz, J_2 = 2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.55 (s, 2H), 4.31-4.24 (m, 4H), 3.12 (t, J = 7.2 Hz, 2H), 2.64 (p, J = 7.6 Hz, 2H), 1.35 (t, J = 7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.8, 152.1, 146.2,

141.1, 134.4, 128.8 (2C), 126.8, 126.7 (2C) , 125.8, 119.9, 119.5, 118.5, 117.9, 117.0, 103.9, 66.2, 59.5, 47.4, 27.1, 25.2, 14.5; HRMS (ES) m/z calcd for $C_{23}H_{22}NO_3$ $(M+H)^+$: 360.1600 ; found: 360.1593.

Ethyl 2-(4-trifluoromethyl) phenyl-6, 8, 9, 10-tetrahydro chromeno[3, 4-b] pyrrolizine-7-carboxylate (3l):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1l**) = 0.55, R_f (**3l**) = 0.74 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ethyl acetate(8:2) as the eluent afforded **3l** as a white solid; (17.5 mg, 41% yield); **IR** (neat): ν_{max} 1687, 1236, 1266, 1165, 1111, 1072 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (q, J = 8.4 Hz, 4H), 7.41 (d, J = 2.4 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.57 (s, 2H), 4.32-4.24 (m, 4H), 3.13 (t, J = 7.6 Hz, 2H), 2.65 (p, J = 7.2 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.7, 152.8, 146.4, 144.5, 132.8, 128.9 (q, J = 33 Hz, 1C), 126.9 (2C), 125.9, 125.7 (q, J = 4 Hz, 2C) , 124.3 (q, J = 270 Hz, 1C) 119.6, 119.5, 118.8, 117.8, 117.2, 104, 66.3, 59.6, 47.4, 27.1, 25.2, 14.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.5 ppm HRMS (ES) m/z calcd for $C_{24}H_{21}F_3NO_3$ $(M+H)^+$: 428.1474; found:428.1468.

Ethyl 2-(furan-2-yl)-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxylate (3m):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1m**) = 0.48, R_f (**3m**) = 0.70 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ethyl acetate(8:2) as the eluent afforded **3m** as a white solid; (16.4 mg, 47% yield); **IR** (neat): ν_{max} 2924, 1695, 1532, 1456, 1260, 1231, 1109, 1012 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.33 (dd, J_1 = 8.4 Hz, J_2 = 2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 6.46 (dd, J_1 = 3.6 Hz, J_2 = 2 Hz, 1H), 5.54 (s, 2H), 4.33 (t, J = 7.2 Hz, 2H), 4.26 (q, J = 6.8 Hz, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.65 (p, J = 7.2 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.8, 154, 152, 146.3, 141.4, 124.4, 122.8, 119.7, 119.5, 118.4, 117, 114.7, 111.6, 103.8, 103.6, 66.2, 59.5, 47.4, 27.1, 25.2, 14.5; HRMS (ES) m/z calcd for $C_{21}H_{20}NO_4$ $(M+H)^+$: 350.1392; found: 350.1389.

Ethyl 2-(5-(ethyoxycarbonyl)thiophen-2-yl)phenyl)-6, 8, 9, 10-tetrahydrochromeno[3, 4-b]pyrrolizine-7-carboxylate (3n):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1n**) = 0.55, R_f (**3n**) =0.77 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ethyl acetate (8:2) as the eluent afforded **3n** as a fluorescent green solid; (21.4 mg, 49% yield); **IR** (neat): ν_{max} 2925, 1701, 1538, 1464, 1431, 1367, 1334, 1263, 1243, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, J = 4 Hz, 1H), 7.45 (d, J = 2 Hz, 1H), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 7.18 (d, J = 4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.56 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 4.32 (t, J = 7.2 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 2.67 (p, J = 7.2 Hz, 2H), 1.4 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.7, 162.4, 153.2, 151.2, 146.6, 134.3, 131.5, 126.6, 122.7, 119.7, 119.2, 118.7, 117.3, 117, 104, 66.5, 61.2, 59.6, 47.4, 29.7, 27.1, 25.2, 14.5, 14.4; HRMS (ES) m/z calcd for $C_{24}H_{24}NO_5S$ $(M+H)^+$: 438.1375; found: 438.1373.

1-(6, 8, 9, 10-tetrahydrochromeno[3, 4-b]pyrrolizine-7-yl) ethanone (3o):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1o**) = 0.62, R_f (**3o**) = 0.50 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **3o** as a pale yellow solid; (6.5 mg, 26 % yield); **IR** (neat): ν_{max} 2922, 1641, 1512, 1422, 1365,1313, 1256, 1119, 1036 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 7.05 (td, J_1 = 7.8 Hz, J_2 = 2 Hz, 1H), 6.90-6.86 (m, 2H), 5.57 (s, 2H), 4.26 (t, J = 7.2 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 2.68 (p, J = 7.2 Hz, 2H), 2.34 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193, 152.7, 145, 127.4, 121.1, 120.6, 119.4, 119.3, 118, 116.8, 114.6, 66.4, 47.2, 28.7, 27.1, 26.2; HRMS (ES) m/z calcd for $C_{16}H_{16}NO_2$ $(M+H)^+$: 254.1181; found: 254.1166.

Phenyl (6, 8, 9, 10-tetrahydrochromeno[3, 4-b]pyrrolizine-7-yl) methanone (3p):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1p**) = 0.43, R_f (**3p**) = 0.60 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **3p** as a pale yellow solid; (23 mg, 73% yield); **IR** (neat): ν_{max} 2923, 1620, 1503, 1419 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65-7.63 (m, 2H), 7.53-7.49 (m, 1H), 7.46-7.42 (m, 2H), 7.28-7.26 (m, 1H), 7.07 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 6.92-6.89 (m, 2H), 5.45 (s, 2H), 4.25 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.54 (p, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.8, 152.8, 146.1, 140.9, 131.1, 128.2, 127.9 (2C), 127.4 (2C), 121.2, 121.2, 119.9, 119.4, 118.1, 116.9, 113.7, 66.2, 47.3, 27.3, 26.0; HRMS (ES) m/z calcd for $C_{21}H_{18}NO_2$ $(M+H)^+$: 316.1338; found: 316.1315.

N, N-dimethyl-6, 8, 9, 10-tetrahydrochromeno[3, 4-b] pyrrolizine-7-carboxamide (3q):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1q**) = 0.38, R_f (**3q**) = 0.31 (petroleum ether/ethyl acetate 1:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (1:1) as the eluent afforded **3q** as a pale yellow solid (13 mg, 45% yield); **IR** (neat): ν_{max} 2932, 1608, 1526, 1504, 1455, 1393, 1225, 1117, 1091, 756, 732 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 6.4 Hz, 2H), 5.32 (s, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.07 (s, 6H), 2.93 (t, J = 7.2 Hz, 2H), 2.62 (p, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.6, 152.4, 140.0, 126.8, 121.3, 119.9, 119.3, 118.8, 118.5, 116.9, 107.3, 65.8, 46.8, 37.3 (2C), 27.7, 24.8; HRMS (ES) m/z calcd for $C_{17}H_{19}N_2O_2$ $(M+H)^+$: 283.1447; found: 283.1446.

Indolizine series:

Ethyl 8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5a):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1a**) = 0.51, R_f (**5a**) = 0.68 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5a** as a pale yellow solid (18 mg, 61% yield); **IR** (neat): ν_{max} 2940, 1694, 1513, 1500, 1259, 1171, 1130, 1106, 1063 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (dd, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 7.06 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 6.96-6.90 (m, 2H) , 5.44 (s, 2H), 4.29-4.21 (m, 4H) , 3.16 (t, J = 6.4 Hz, 2H), 2.04-1.98 (m, 2H), 1.90-1.84 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.1, 153.2, 138.8,

126.7, 122.9, 121.3, 120.5, 119, 117.2, 106.8, 65.7, 59.3, 46.1, 29.7, 24.4, 23.3, 19.3, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{20}NO_3$ $(M+H)^+$: 298.1443; found:298.1427.

Ethyl 6, 6-dimethyl-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b]indolizine-7-carboxylate (5b):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1b**) = 0.58, R_f (**5b**) = 0.68 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5b** as a fluorescent green solid; (15.4 mg, 47% yield); **IR** (neat): ν_{max} 2971, 1695, 1499, 1377, 1251, 1172, 1124, 1103, 1055 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (dd, J_1 = 8 Hz, J_2 = 1.4 Hz, 1H), 7.06 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 6.95-6.88 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.23 (t, J = 6 Hz, 2H), 3.09 (t, J = 6.4 Hz, 2H), 2.01-1.98 (m, 2H), 1.89-1.86 (m, 2H), 1.72 (s, 6H), 1.36 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 151.7, 138.4, 126.7, 124.7, 122.6, 120.7, 120.45, 118.0, 117.8, 107.3, 79.6, 59.6, 46.5, 27.4 (2C), 25, 23.2,19.6, 14.4; HRMS (ES) m/z calcd for $C_{20}H_{24}NO_3$ $(M+H)^+$: 326.1756; found:326.1734.

Ethyl 2-methyl-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5c):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1c**) = 0.56, R_f (**5c**) = 0.69 (petroleum ther/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5c** as a brown solid; (18.5 mg, 59% yield); **IR** (neat): ν_{max} 2925, 1695, 1517, 1446, 1425, 1260, 1175, 1131, 1113, 1064 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17(s, 1H), 6.89-6.84 (m, 2H), 5.39 (s, 2H), 4.28.-4.23 (m, 4H), 3.15 (t, J = 6.4 Hz, 2H), 2.30 (s, 3H), 2.05-1.99 (m, 2H), 1.90-1.84 (m, 2H), 1.35 (t, J = 7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 151, 138.7, 130.5, 127.1, 123.1, 121.2, 118.8, 117.3, 116.9, 65.6, 59.4, 46.1, 29.7, 24.4, 23.3, 21.1, 19.3, 14.5; HRMS (ES) m/z calcd for $C_{19}H_{22}NO_3$ $(M+H)^+$: 312.1600; found: 312.1594.

Ethyl 2, 4-di-tert-butyl-8, 9, 10, 11- tetrahydro-6H-chromeno[3, 4-b] indolizine -7- carboxy- late (5d):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1d**) = 0.59, R_f (**5d**) = 0.70 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5d** as a white solid; (36 mg, 88% yield); **IR** (neat): ν_{max} 2952, 1692, 1517, 1259, 1123, 1092 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 2 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 5.32 (s, 2H), 4.29.-4.22 (m, 4H), 3.17 (t, J = 6.4 Hz, 2H), 2.02-1.99 (m, 2H), 1.90-1.87 (m, 2H), 1.42 (s, 9H), 1.34 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.3, 149.1, 142.9, 138.6, 138.0, 124.3, 121.5, 119.2, 117.3, 116.0, 106.5, 64.4, 59.3, 46.1, 35.0, 34.5, 31.6 (3C), 29.9 (3C), 24.5, 23.5, 19.4, 14.6; HRMS (ES) m/z calcd for $C_{26}H_{36}NO_3$ $(M+H)^+$: 410.2695; found: 410.2693.

Ethyl 2-methoxy-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5e):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1e**) = 0.50, R_f (**5e**) = 0.57 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5e** as a pale yellow solid; (20.5 mg, 63% yield); **IR** (neat): ν_{max} 2947, 1694, 1515, 1427, 1331, 1269, 1174, 1131, 1111, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94 (d, J = 2.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.60 (dd, J_1 = 8.6 Hz, J_2 = 3 Hz, 1H), 5.36 (s, 2H), 4.28-4.20 (m, 4H) , 3.78 (s, 3H), 3.14 (t, J = 6.4 Hz, 2H), 2.02-1.99 (m, 2H), 1.88-1.85 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.1, 154.1, 147.1, 139, 123, 119.7, 118.1, 117.3, 110.0, 107.9, 106.9, 65.6, 59.4, 55.8, 46, 24.4, 23.2, 19.3, 14.5; HRMS (ES) m/z calcd for $C_{19}H_{22}NO_4$ $(M+H)^+$: 328.1549; found: 328.1536.

Ethyl 3-methoxy-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5f):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1f**) = 0.52, R_f (**5f**) = 0.66 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5f** as a pale yellow solid; (29.3 mg, 90% yield); **IR** (neat): ν_{max} 2938, 1693, 1589, 1556, 1509, 1423, 1245, 1132, 1063 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 6.49 (dd, J_1 = 8.4 Hz, J_2 = 2.5 Hz, 1H), 5.43 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.19 (t, J = 6 Hz, 2H), 3.79 (s, 3H), 3.14 (t, J = 6.4 Hz, 2H), 2.04-1.99 (m, 2H), 1.89-1.85 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 158.7, 154.6, 138, 123.1, 121.2, 114.8, 112.2, 106.9, 106.6, 103.3, 66.0, 59.3, 55.3, 46, 24.4, 23.3, 19.4, 14.5; HRMS (ES) m/z calcd for $C_{19}H_{22}NO_4$ $(M+H)^+$: 328.1549; found: 328.1496.

Ethyl 2-chloro-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5g):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1g**) = 0.58, R_f (**5g**) = 0.74 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5g** as a pale yellow solid; (15.6 mg, 47% yield); **IR** (neat): ν_{max} 2949, 1696, 1513, 1444, 1263, 1135, 1112, 1093, 815 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 2.4 Hz, 1H), 6.98 (dd, J_1 = 8.8 Hz, J_2 = 2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.19 (t, J = 6 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H), 2.05-1.99 (m, 2H), 1.90-1.84 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 151.6, 139.5, 126.2, 126.1, 121.9, 120.2, 118.2, 117.9, 107.0, 65.9, 59.5, 46.0, 29.7, 24.4, 23.1, 19.2, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{19}ClNO_3$ $(M+H)^+$: 332.1053; found: 332.1048.

Ethyl 2, 4-dichloro-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b]indolizine-7-carboxylate (5h):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1h**) = 0.70, R_f (**5h**) = 0.78 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5h** as a pale yellow solid; (28.5 mg, 78% yield); **IR** (neat): ν_{max} 2927, 1697, 1676, 1513, 1261, 1136, 1104, 1086 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 5.54 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 6 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H), 2.06-2.00 (m, 2H), 1.90-1.84 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.7,147.4, 140.2, 126.4, 125.9, 122.9, 121.3, 121.1, 118.6, 118.3, 107.1, 66.6, 59.6, 46.2, 24.4, 23.1, 19.1, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{18}Cl_2NO_3$ $(M+H)^+$: 366.0664; found: 366.0571.

Ethyl 2-bromo-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5i):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1i**) = 0.40, R_f (**5i**) = 0.49

(petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5i** as a white solid; (17.6 mg, 47% yield); **IR** (neat): ν_{max} 2949, 1693, 1493, 1468, 1331, 1136, 1114, 1064, 823 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (d, J = 2.4 Hz, 1H), 7.14 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.43 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.20 (t, J = 6 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 2.05-2.02 (m, 2H), 1.89-1.84 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 152.1, 139.5, 129.1, 123.0, 121.8, 120.7, 118.8, 117.9, 113.6, 107, 65.9, 59.5, 46.1, 24.4, 23.2, 19.2, 14.5; HRMS (ES) m/z calcd for $C_{18}H_{19}BrNO_3$ $(M+H)^+$: 376.0548; found: 376.0543.

Ethyl 2-fluoro-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5j):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1j**) = 0.54, R_f (**5j**) = 0.73 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5j** as a pale yellow solid; (23.4 mg, 75% yield); **IR** (neat): ν_{max} 2949, 1697, 1517, 1444, 1261, 1173, 1125, 1102, 1006, 810 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06 (dd, J_1 = 9.6 Hz, J_2 = 3 Hz, 1H), 6.88 (dd, J_1 = 9 Hz, J_2 = 5 Hz, 1H), 6.74 (td, J_1 = 9 Hz, J_2 = 3 Hz, 1H), 5.4 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 4.19 (t, J = 7.2 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 2.04-1.99 (m, 2H), 1.90-1.86 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 157.5 (d, J = 236 Hz, 1C), 148.9, 139.4, 122.4, 119.7 (d, J = 9 Hz, 1C), 118.2, 117.8 (d, J = 9 Hz, 1C) , 112.3 (d, J = 23 Hz, 1C), 107.4 (d, J = 26 Hz, 1C), 107, 65.8, 59.4, 45.9, 24.4, 23.2, 19.2, 14.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -121.8 ppm; HRMS (ES) m/z calcd for $C_{18}H_{19}FNO_3$ $(M+H)^+$: 316.1349; found: 316.1347.

Ethyl 2-phenyl-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxylate (5k):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1k**) = 0.50, R_f (**5k**) = 0.73 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5k** as a brown solid; (21 mg, 56% yield); **IR** (neat): ν_{max} 2927, 1695, 1519, 1491, 1261, 1174, 1135, 1114, 1025, 762 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56-7.54 (m, 3H), 7.46-7.42 (m, 2H), 7.36-7.32 (m, 1H), 7.29-7.26 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 5.48 (s, 2H), 4.31-4.25 (m, 4H), 3.17 (t, J = 6.4 Hz, 2H), 2.04-2.00 (m, 2H), 1.91-1.87 (m, 2H), 1.35 (t, J = 7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0, 152.8, 141.3, 139.0, 134.6, 128.8 (2C), 126.8 (3C), 125.5, 122.8, 119.4, 119.2, 117.4, 117.3, 106.9, 65.9, 59.4, 46.2, 24.5, 23.3, 19.3, 14.5; HRMS (ES) m/z calcd for $C_{24}H_{24}NO_3$ $(M+H)^+$: 374.1756; found: 374.1751.

Ethyl 2-(4-(trifluoromethyl)phenyl)-8, 9, 10, 11-tetrahydro -6H-chromeno[3, 4-b]indolizine-7-carboxylate (5l):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1l**) = 0.55, R_f (**5l**) = 0.80 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5l** as a brown solid (16 mg, 36% yield); **IR** (neat): ν_{max} 2949, 1696, 1512, 1325, 1261, 1167, 1113, 1071, 821 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (q, J = 8.4 Hz, 4H), 7.55 (d, J = 2.4 Hz, 1H), 7.28 (dd, J_1 = 8 Hz, J_2 = 2.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.49 (s, 2H), 4.30-4.25 (m, 4H), 3.18 (t, J = 6.4 Hz, 2H), 2.06-2.03 (m, 2H), 1.90-1.89 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165, 153.5, 144.8, 139.3, 133.0, 128.9 (q, J = 33 Hz, 1C), 127.0 (2C), 125.7 (q, J = 4 Hz, 2C), 125.6, 124.3 (q, J = 270 Hz, 1C), 122.4, 119.4, 119.3, 117.6, 117.5, 107.1, 66, 59.5, 46.2, 24.5, 23.3, 19.2, 14.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.3 ppm; HRMS (ES) m/z calcd for $C_{25}H_{23}F_3NO_3$ $(M+H)^+$: 442.1630; found: 442.1615.

Ethyl 2-(furan-2-yl)-8, 9, 10, 11-tetrahydro-6H-chromeno [3, 4-b]indolizine-7-carboxylate (5m):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1m**) = 0.48, R_f (**5m**) = 0.74 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5h** as a brown solid (24 mg, 66% yield); **IR** (neat): ν_{max} 2924, 1696, 1518, 1269, 1133, 1113, 1063, 1011 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, J = 2 Hz, 1H), 7.44 (dd, J_1 = 2 Hz, J_2 = 0.5 Hz, 1H), 7.34 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 6.52 (dd, J_1 = 3.2 Hz, J_2 = 0.5 Hz 1H), 6.46 (dd, J_1 = 3.2 Hz, J_2 = 2 Hz, 1H), 5.45 (s, 2H), 4.32-4.24 (m, 4H), 3.16 (t, J = 6.4 Hz, 2H), 2.05-2.02 (m, 2H), 1.92-1.87 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0, 154.1, 152.7, 141.4, 139.1, 124.5, 122.6, 122.5, 119.0, 117.33, 117.3 116, 111.6, 106.9, 103.6, 66, 59.4, 46.1, 24.5, 23.3, 19.3, 14.5; HRMS (ES) m/z calcd for $C_{22}H_{22}NO_4$ $(M+H)^+$: 364.1549; found: 364.1549.

Ethyl 2-(5-(ethoxycarbonyl)thiophen-2-yl)-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b]indolizine-7-carboxylate (5n):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1n**) = 0.55, R_f (**5n**) = 0.77 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5n** as a fluorescent green solid (26 mg, 57% yield); **IR** (neat): ν_{max} 2950, 1699, 1535, 1517, 1425, 1261, 1136, 1094, 1063 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (d, J = 4 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.32 (dd, J_1 = 8 Hz, J_2 = 2.4 Hz, 1H), 7.17 (d, J = 4 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 5.48 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 4.29-4.23 (m, 4H), 3.16 (t, J = 6.4 Hz, 2H), 2.07-2.02 (m, 2H), 1.92-1.88 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165, 162.4, 153.9, 151.4, 139.4, 134.3, 131.5, 126.8, 124.6, 122.7, 122.0, 119.4, 118.4, 117.6, 117.6, 107.3, 66.2, 61.2, 59.5, 46.2, 24.5, 23.3, 19.2, 14.5, 14.4; HRMS (ES) m/z calcd for $C_{25}H_{25}NO_5SNa$ $(M+-Na)^+$: 474.1351; found: 474.1353.

1-(8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b]indolizin-7-yl)ethanone (5o):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1o**) = 0.62, R_f (**5o**) = 0.62 (petroleum ether/ethyl acetate 8:2, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (8:2) as the eluent afforded **5o** as a pale yellow solid; (11.2 mg, 42% yield); **IR** (neat): ν_{max} 2947, 1638, 1501, 1416, 1364, 1265, 1131, 1040, 738 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.08 (td, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 6.98-6.93 (m, 2H) , 5.46 (s, 2H), 4.24 (t, J = 6 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 2.37 (s, 3H), 2.04-1.99 (m, 2H), 1.94-1.88 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.5, 153.2, 137.8, 127, 123.4, 121.4, 120.8, 118.7, 17.8, 117.2, 116.9, 66.0, 46.3, 30.7, 25.5, 23.0, 19.4; HRMS (ES) m/z calcd for $C_{17}H_{18}NO_2$ $(M+H)^+$: 268.1338; found: 268.1327.

Phenyl(8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizin-7-yl)methanone (5p):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1p**) = 0.43, R_f (**5p**) = 0.57 (petroleum ether/ethyl acetate 9:1, UV detection)]. Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ ethyl acetate (9:1) as the eluent afforded **5p** as a pale yellow solid; (17 mg, 52% yield); **IR** (neat): ν_{max} 2945, 1626, 1546, 1500, 1420, 1331, 1185, 1041, 980 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 2H), 7.53-7.49 (m, 1H), 7.44-7.41 (m, 3H), 7.08 (td, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 6.98-6.92 (m, 2H) , 4.86 (s, 2H), 4.28 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 2.06-2.02 (m, 2H), 1.87-1.82 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.1, 153.3, 141.7, 139.0, 131.3, 128.3 (2C), 128.2 (2C), 127.0, 123.7, 121.5, 121, 119.1, 117.3, 116.7, 116.5, 65.5, 46.1, 25.2, 23.2, 19.4; HRMS (ES) m/z calcd for $C_{22}H_{20}NO_2$ $(M+H)^+$: 330.1494 ; found: 330.1494.

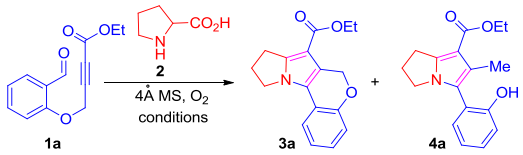
N, N-dimethyl-8, 9, 10, 11-tetrahydro-6H-chromeno[3, 4-b] indolizine-7-carboxamide (5q):

The title compound was prepared according to the general procedure. [TLC profile: R_f (**1q**) = 0.38, R_f (**5q**) = 0.42 (petroleum ether/ethyl acetate 1:1, UV detection)].Purification of the crude residue by SiO_2-gel column chromatography using petroleum ether/ethyl acetate (1:1) as the eluent afforded **5q** as a pale yellow solid; (18.4 mg, 62% yield); **IR** (neat): ν_{max} 2942, 1658, 1526, 1499, 1453, 1397, 1265, 1130 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (d, J = 6.8 Hz, 1H), 7.05-7.03 (m, 1H) , 6.96-6.94 (m, 2H) , 5.15 (s, 2H), 4.23 (t, J = 6.4 Hz, 2H), 3.04 (s, 6H), 2.88 (t, J = 6.4 Hz, 2H), 2.04-2.01 (m, 2H), 1.85-1.83 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168, 153, 132.1, 126.5, 122.4, 121.5, 120.6, 119.6, 117.2, 114.7, 110.9, 65.2, 45.8, 36.9 (2C), 23.6 (2C), 19.6; HRMS (ES) m/z calcd for $C_{18}H_{21}N_2O_2$ $(M+H)^+$: 297.1603 ; found: 297.1602.

3. Results and Discussion

Towards the realization of our hypothesis as outlined in **Scheme 1**, we commenced our foray with the exploration of the intramolecular cycloaddition of salicylaldehyde tethered dipolarophile **1a** activated by a carboethoxy group with proline **2** in the presence of 4Å MS in different solvent medium and at different temperature under oxygen blanket as captured in **Table 1**.

Table 1. Condition Optimization for the tandem [3+2] cycloaddition/oxidation reaction[a]



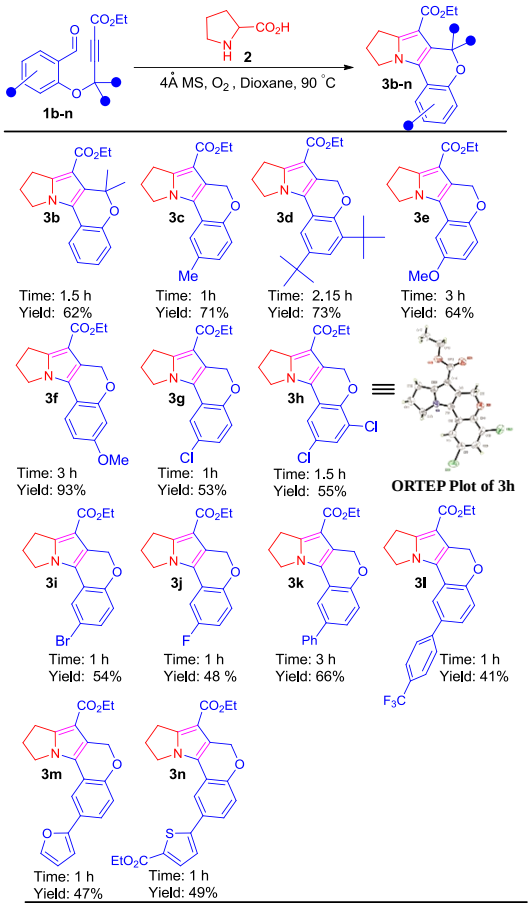
Entry	Solvent	Temp. (°C)	Time (h)	Yield: 3a/4a[b] (%)
1	**Dioxane**	**110**	**0.75**	**44/9**
2	**Dioxane**	**90**	**1**	**69/0**
3	**Benzene**	**90**	**2**	**33/0**
4	**Toluene**	**90**	**1**	**17/22**
5	**MeCN**	**90**	**1.5**	**23/13**
6	**DME**	**90**	**1**	**46/0**
7	**DMF**	**90**	**1**	**24/14**
8	**DMSO**	**90**	**1**	**17/13**
9	**1,2-DCE**	**90**	**1**	**28/0**
10	**$CHCl_3$**	**65**	**1**	**42/0**
11	**THF**	**65**	**4**	**52/0**
12	**Ethanol**	**90**	**2**	**0/0**

[a]Reaction condition: 1a (0.1 mmol), 2 (0.125 mmol) and solvent (2 ml). [b]Isolated yield.

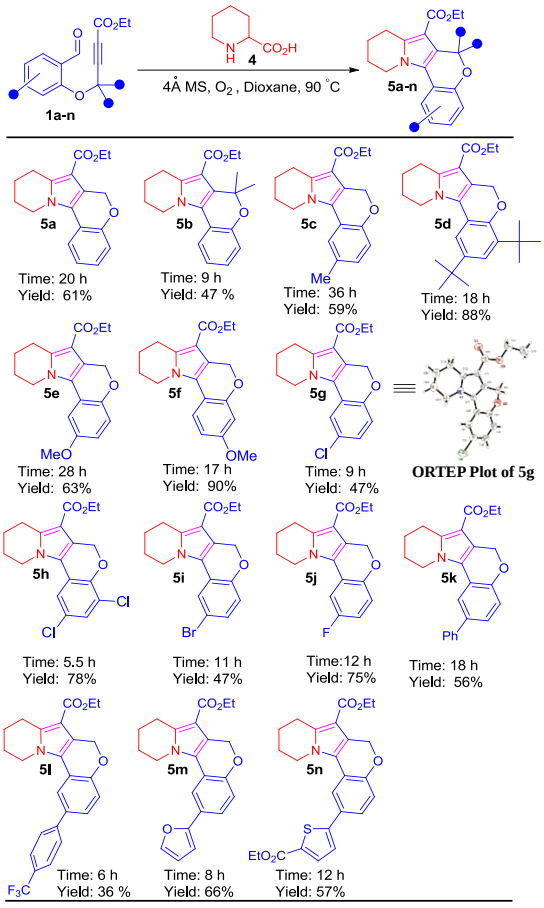
Indeed to our delight, as per our plan the thermal activation of the salicylaldheyde tethered ynoate (**1a**) with proline **2**, in refluxing dioxane afforded within 45 min. the expected chromenopyrrolizine **3a** although in moderate yields but along with a marginal amount of ring cleaved product **4a** (entry 1, **Table 1**). The formation of **4a** is attributed to the pyrano ring opening in the [3+2] cycloadduct during the concomitant aromatization stage.[26] Interestingly, lowering the reaction temperature to 90 °C using the same solvent with slight increase in the reaction time helped in suppressing the formation of **4a** together with substantial improvement in yield of the desired **3a** (entry 2, **Table 1**). Therefore considering 90 °C as the optimum temperature, the cycloaddition was further explored in other polar and nonpolar solvents at that temperature. But surprisingly, even at 90 °C in solvents like toluene, acetonitrile, DMF and DMSO in almost similar time period the formation of **4a** was observed along with **3a** (entry 4, 5, 7, 8, **Table 1**). Notably, the most significant yield of **4a** was observed in case where toluene was used as the solvent. Whereas, in case of benzene, DME and dichloroethane at same temperature and in similar time period only **3a** was obtained as the sole product although in poor to moderate yields (entry 3, 6, 9, **Table 1**). Further, lowering of temperature to 65 °C in case of THF as the reaction medium, increased the reaction time to 4 h but offered only **3a** as the single product and that too in moderate yields (entry 11, **Table 1**). On the other hand, neither **3a**/**4a** nor the starting materials were isolated in case of reactions executed in ethanol (entry 12, **Table 1**). Therefore, among all the investigated solvent, dioxane proved to be the ideal solvent with reaction temperature of 90 °C as the critical temperature to arrive at **3a** in good yields and in shorter reaction time. Certainly, the employment of salicylaldehyde tethered activated dipolarophiles in the present synthesis culminated in a reaction condition which holds an edge over the earlier reported one[20] in the sense it involves tandem cycloaddition/oxidation sequence in a single pot operation in a single go, compared to the reported stepwise sequence of cycloaddition and then oxidation in a single pot.[20] The present synthesis avoids the intermittent stopping of the reaction for careful analysis of completion of the [3+2] cycloaddition step as well as avoids addition of non-metal/metal based oxidants to trigger the aromatization step. Thereby, simplifying the reaction monitoring as well as the work-up for the synthesis and at the same time averting the use or generation of any hazardous waste material.

With the optimized condition in hand we next focused our attention towards demonstrating the substrate scope of the approach. In this context, various 3, 4 and 5-substituted salicylaldehyde tethered ynoates **1b-n** with both electron donating as well as electron withdrawing ability were synthesized using the earlier reported protocol[25] and a modified approach developed by us (refer Supporting Information) to couple with proline under the optimized condition. Through this exercise diverse functionally embellished chromeno-pyrrolizines **3b-n** (**Scheme 2**) were delivered with moderate to excellent yields in a single pot operation. As summarized in **Scheme 2**, on investigating the gem-dimethyl substituted salicylaldehyde tethered ynoates **1b**, **3b** was offered in slightly inferior yield compared to **3a**. While, substituents with weak electron donating ability viz. –Me, $–C(Me)_3$, –Ph as well as those with strong electron donating ability viz. –OMe, either at the 5th position or both 3rd and 5th of the salicylaldehyde tethered ynoates offered the corresponding chromeno-annulated pyrrolizines (**3c-e**) in yields ranging from 64-73% and same time period. Gratifyingly, **1f** with –OMe at the 4th position offered **3f** in the best yield of 93% among all the explored

Scheme 2. Access to diverse chromeno-annulated pyrrolizines via tandem [3+2] cycloaddition /oxidation reaction[a]



Scheme 3. Access to diverse chromeno-annulated indolizines via tandem [3+2] cycloaddition /oxidation reaction[a]



[a]Reaction condition: **1** (0.1 mmol), **2** (0.125 mmol) and solvent (2 ml).

substrate whereas the lowest yield was observed in case of **3l**. Further, a trend similar to the one observed in case of electron donating substituent was discerned in case of substituent with poor electron withdrawing ability as well. In almost similar timeframe (1-1.5 h), **1g**-**1j** delivered **3g**-**3j** in moderate yields of 48-55%. Lastly, we also investigated the feasibility of the reaction with heterocycle appendage at 5th position in the form of furan and thiophene rings to arrive at **3m** and **3n** in satisfactory yields.

After successful testing the versatility of the approach towards the construction of diverse functionalized chromenopyrrolizines we then decided to extend the scope of the strategy towards the chromenoindolizine analogs byreplacing proline with pipecolic acid **4** as the coupling partner in the intramolecular [3+2] cycloaddition. In this regard, initially the coupling of same salicylaldehyde tethered ynoate **1a** which was used earlier in reaction optimization was explored with **4** under the same optimized condition as that of pyrrolizine series (**Scheme 3**). To our joy, this time again the same reaction condition regime cleanly delivered the expected product **5a** without any side product albeit in comparatively slightly lower yield and over quite longer reaction time. Elevation of reaction temperature beyond 90 °C didn't help much in acceleration of the reaction but certainly resulted in formation of ring opened side product as that observed in case of pyrrolizine series. As captured in **Scheme 3**, in general comparatively longer reaction completion time was observed for all the investigated chromenoindolizine analogs compared to their pyrrolizine counterparts. While in terms of yields, reactions with electron donating substituents like –C(Me)$_3$ at 3rd, 5th position and –OMe at the 5th position of the

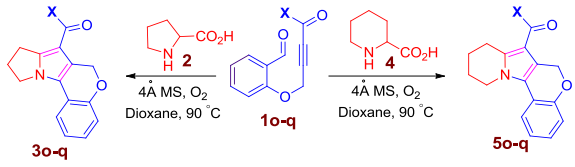
[a]Reaction condition: **1** (0.1 mmol), **4** (0.125 mmol) and solvent (2 ml).

salicylaldehyde tethered ynoates offered better yields than those with electron withdrawing substituents at similar positions. Further, the easy amenability of the dichloro and chloro derivatives in the pyrrolizine as well as indolizine series to X-ray crystallography motivated us to determine the X-ray crystal structure of angularly fused tetracyclic structure of **3h** and **5g**.[27]

Although, the carboethoxy group as per our expectation fared satisfactorily in the strategic one pot tandem [3+2] cycloaddition-oxidation reaction and also undoubtedly serve as a good handle for various other functional group manipulations. But next, we were impelled to check the tolerance of other activating functionalities at the salicylaldehyde tethered dipolarophile. In this connection, salicylaldehyde tethered ynones **1o, 1p** with acetyl and benzoyl group respectively and ynamide **1q** with dimethylcarbamide group stationed at the terminal position of the alkyne arm were synthesized and evaluated for their reactivity with proline and pipecolic acid. As highlighted in **Table 2**, under the similar crafted condition used earlier for **1a-n,** the reactions afforded the expected tetracyclic indolizines **3o-q** and pyrrolizines **5o-q** in comparable yields as that of **3a** and **5a**.

Some of the noteworthy advantages of the presently reported synthetic method includes (i) milder reaction conditions (ii) single pot operation (iii) no metal activation nor metal/non-metal based oxidants for the aromatization (iv) no aqueous work-up and more importantly (iv) flexibility in diversity creation both in the case of chromenopyrrolizine as well as indolizines.

Table 2. Functional Group tolerance at the activated alkyne for the tandem [3+2] cycloaddition/oxidation reaction[a]



Entry	Compound (1)	X	Yield[b] (%)[Time (h)]	
			3	5
1	1a	-OEt	69 [1]	57 [20]
2	1o	-Me	26 [1]	42 [12]
3	1p	-Ph	73 [3]	52 [24]
4	1q	-NMe_2	45 [1]	62 [54]

[a]Reaction condition: **1** (0.1 mmol), **2/4** (0.125 mmol) and solvent (2 ml). [b]Isolated yield.

4. Conclusion

In conclusion we have demonstrated an improved synthesis of diverse functionalized chromenopyrrolizines and chromenoindolizines in a single pot operation and metal free condition. The simple activation of the dipolarophile by electron withdrawing groups makes the reaction more facile and allows for the spontaneous aromatization of the cycloadducts thereby expediting the synthesis and making it an inexpensive, nontoxic and environmentally friendly synthetic strategy. The bioactivity profile screening for all the synthesized scaffolds is currently under progress. Also, efforts are channelized for the application of this approach in the synthesis of other natural products mimics.

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27. CCDC 1441955 and 1441950 contain the crystallographic information for **3h** and **5g**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at deposit@ccdc.cam.ac.uk

Graphical Abstract

An Improved Synthesis of Natural Product Inspired Chromenopyrrolizines and Chromenoindolizines Scaffolds: Rapid Access to the Diverse Pyrrolizine Analogs of Aza-Medicarpin and Tetracyclic Isolamellarin Core through a General, Base and Metal free Strategy

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A general and improved synthesis based on the intramolecular trapping of the dipolarophile activated by electron withdrawing group with the insitu generated azomethine ylide is described for easy access to chromenopyrrolizines as aza-medicarpin inspired pyrrolizine analogs and chromenoindolizines scaffolds as lamellarin alkaloids inspired tetracyclic isolamellarin core, under base and metal free condition.