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Intramolecular [3+2]-cycloaddition of salicylaldehydes-based cyclic azomethine imines to access novel tetrahydrochromeno[4,3-*c*]pyrazolo[1,2-*a*]pyrazol-9-ones

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ABSTRACT

An efficient intramolecular [3 + 2]-cycloaddition of *in situ*-formed salicylaldehyde-based *N,N′*-cyclic azomethine imines was successfully developed to access novel tetracyclic skeleton bearing three contiguous stereogenic centres. This established protocol features high functional-group tolerance, excellent chemical yields, good diastereoselectivities, and variable reaction conditions.

1. Introduction

Nitrogen-containing skeletons are widely encountered in marketed drugs and pharmaceuticals [1]. As such, rapid assembly of these privileged frameworks is of outmost importance for drug discovery. Up to now, enormous efforts have been made to construct nitrogen-containing heterocycles with structural complexity and diversity [2].Despite these impressive advances, new efficient methods to access diversified multicyclic nitrogen-containing skeletonsis still extremely attractive and urgent, allowing for broad exploitation of their medicinal potentials. Undoubtedly, cycloaddition reactions offer the most straightforward pathways for rapid construction of heterocycles· [3]. Among these methods, 1,3-dipolar [3 + 2]-cycloadditions is particularly powerful transformations to furnish a set of structurally significant five-membered nitrogen-containing heterocycles [4], including pyrroline [4a-4b], pyrrole [4c], oxazole [4d],*etc*. Since reported by Dorn and Otto in 1968 [5], *N,N′*-cyclic azomethine imines derived from pyrazolidin-3-ones have emerged as a stable, easily accessed and versatile building blocks for the construction of dinitrogen-fused heterocycles with various dipolarophiles (Scheme 1) [6]. For example, in 2003, an elegant asymmetric Cu-catalyzed [3 + 2]-cycloaddition of *N,N′*-cyclic azomethine imines with alkynes were established by Fu's group [7]. After that, a range of diverse dipolarophiles especially activated alkenes have been identified to be suitable counterparts in 1,3-dipolar cycloaddition reactions of *N,N′*-cyclic azomethine imines under transition metal- or organo-catalysis [8]. In addition to [3 + 2]-cycloadddition transformation, [3 + 3] [9] or [3 + 4] [10] cycloadditions of *N,N′*-cyclic azomethine imines have also been realized as well in recent years, affording six- or seven-membered dinitrogen-fused heterocycles. In 2019, Chen and co-authors documented a formal [5 + 3] cycloaddition reaction of *N,N′*-cyclic azomethine imines with unmodified Morita–Baylis–Hillman alcohols *via* double activation catalysis [11]. More recently, isatin *N,N′*-cyclic azomethine imine 1,3-dipolar cyclic azomethine imines were devised and employed in the construction of diversified spirooxindole cores by Wang's group [12]. Notably, almost all these reported transformations were restricted to the intermolecular type.

It was well accepted that intramolecular cycloaddition possesses unparalleled advantages in assembling challenging multicyclic ring systems. Despite intramolecular variant of [3 + 2] cycloaddition of

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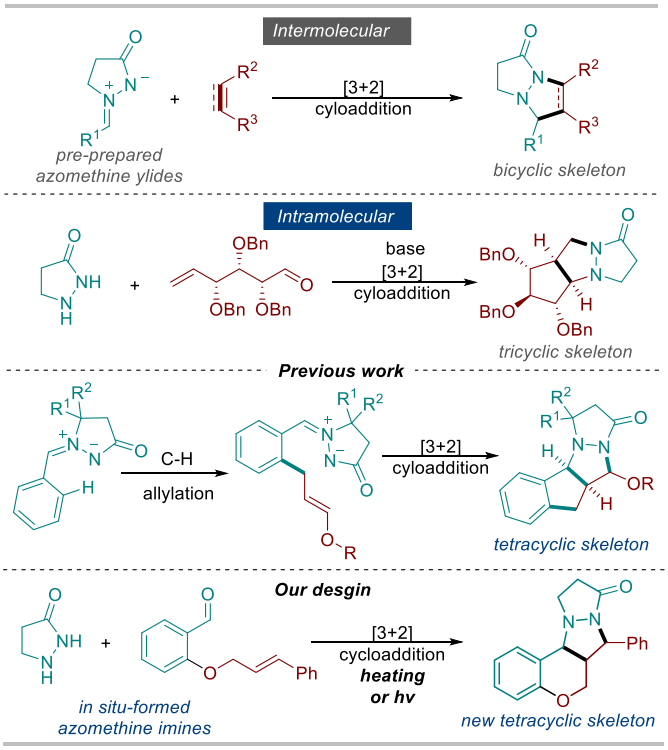
0040-4020/



Scheme 1. Profiles for [3 + 2] cycloaddition reaction of *N,N′*-cyclic azomethine imines.

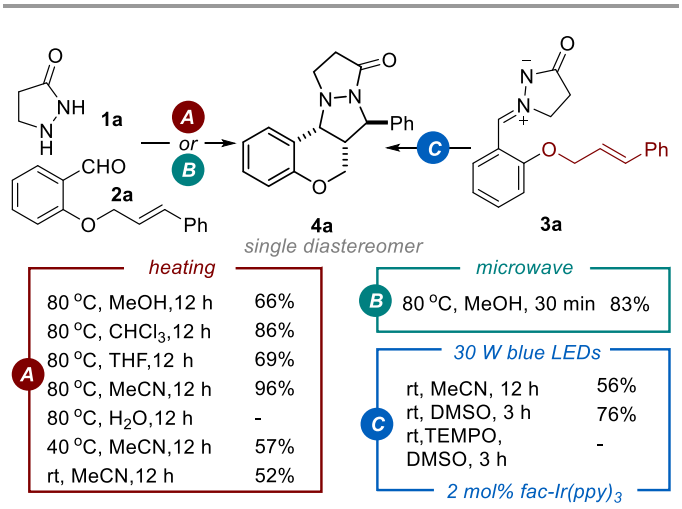
other azomethine imines, such as those directly derived from linear hydrazines [13] were well achieved, the intramolecular fashion of cycloaddition for *N,N′*-cyclic azomethine imines with dipolarophiles has been rarely realized ever since. Back to 2011, Li and Meng's group designed a intramolecular 1,3-dipolar cycloaddition of *N,N′*-cyclic azomethine imines that formed from sugar-derived hex-5-enal for the assembly of diaza-triquinane framework [14]. Very recently, Kim, Hong and co-authors reported a tandem C–H allylation and [3 + 2] dipolar cycloaddition of this type of cyclic azomethine imines, leading to a series of indenopyrazolopyrazolones [15] (Scheme 1). To achieve the intramolecular annulation reaction, a well-designed linker is crucial to facilitate the occurrence of this process. Following this rationale, we designed new precursors to merge the *N,N′*-cyclic azomethine imine moiety with olefin unit by using salicylaldehyde as the linker, in which the dipolar and dipolarophile moiety can be intentionally preinstalled on the salicylaldehyde scaffold. Practically, the designed precursors could be formed in *situ* during the reaction process. As part of our continued interest in construction of complex heterocycles [16], we herein disclose our success in diastereoselective assembly of unprecedented fused tetracyclic skeleton bearing three contiguous stereogenic centres from pyrazolidin-3-one and 2-(cinnamyloxy) benzaldehydes. As a result, a range of tetrahydrochromeno [4,3-*c*] pyrazolo [1,2-*a*]pyrazol-9-ones were easily prepared, which might demonstrate the synergistic effects of both chromane and pyrazoline scaffolds as a new class of heterocycles for medicinal studies.

2. Results and discussion

2.1. Optimization of the reaction conditions

At the outset of our study, optimization of the reaction conditions was carried out with pyrazolidin-3-one (**1a**) and 2-(cinnamyloxy)benzaldehyde (**2a**) as the substrates (Table 1). Pleasingly, the corresponding product **4a** was isolated as a single diastereoisomer in both protonic and aprotic solvents at 80 °C, while heating in oil bath (Table 1, conditions A). And CH_3CN was the optimal choice. However, no desired product **4a** was formed when using water as solvent. Lowering the reaction temperature resulted in the decrease in yield. To our delight, the reaction time could be shortened to 30 min by performing this intramolecular cycloaddition reaction under MW irradiation, albeit with a slightly lowered yield (Table 1, conditions B). Ultimately, inspired by our previous

Table 1
Investigation of reaction conditions[a].



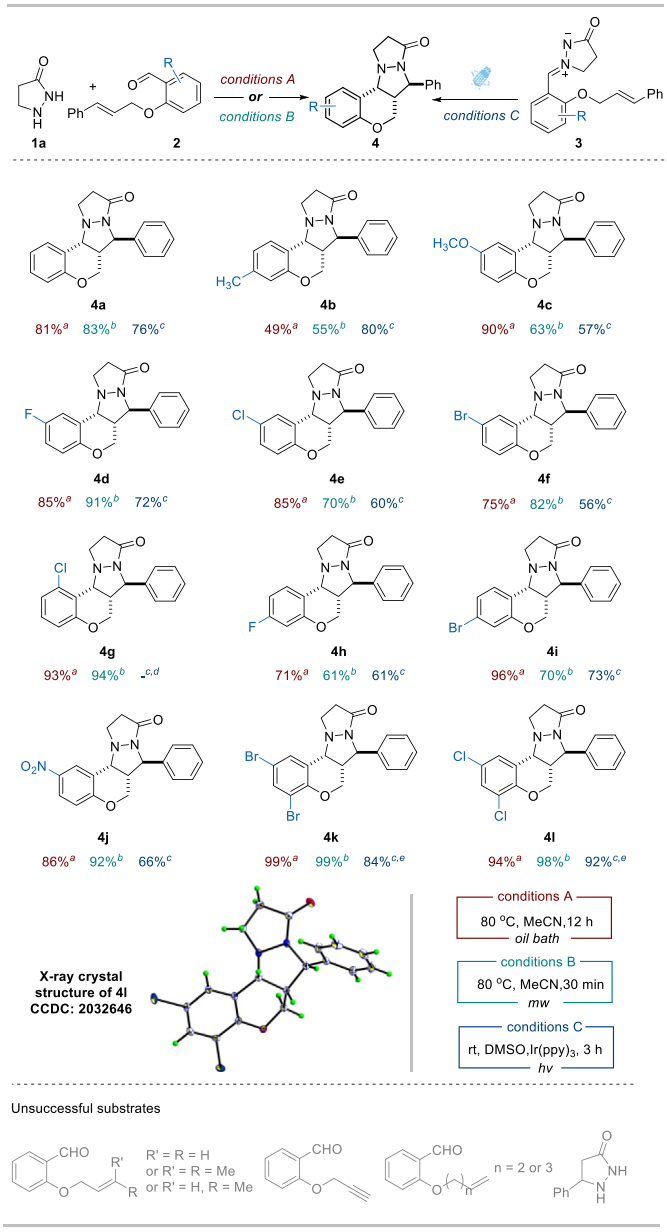
[a] Reagents and conditionsA and B:**1a** (0.6 mmol, 3 equiv.) and **2a** (0.2 mmol, 1 equiv.) in solvent (2 mL), isolated yield, >20:1 dr determined by crude ^{1}HNMR; Conditions C: **3a** (0.2 mmol, 1 equiv.) in solvent (2 mL), 2 mol% *fac*-Ir (ppy)$_3$, rt, isolated yield, >20:1 dr determined by crude ^{1}HNMR.

studies on the photochemical behavior of *N,N′*-cyclicazomethine imines under visible light [17], we were also curious that this transformation might be driven by photocatalytic conditions. Unfortunately, adding *fac*-Ir (ppy)$_3$ to the above reaction systems under irradiation of a blue light-emitting diode (LED) only rendered a fairly complex reaction, and the corresponding product were unable to be isolated. Interestingly, while the pre-prepared precursor **3a** was employed in the protocol, the desired product **4a** could be obtained albeit in lower yield (Table 1, conditions C). Considering the solubility of substrate **3a**, we slightly modified the solvent system to DMSO, leading to an increased chemical yield within a shorter reaction time. Compared to the thermally induced transformation, the photocatalytic reaction conditions offered a milder alternative pathway. When TEMPO was added into the photo-induced reaction, no desired product was detected. These results indicate that a radical pathway may be involved.

2.2. Scope and limitations of substrates

With these conditions in hand, we next shifted our attention to the scope of this new intramolecular [3 + 2]- cycloaddition, as well as the compatibility of the reaction conditions. A range of 2-(cinnamyloxy)benzaldehydes derived from commercially available salicylaldehydes were prepared and subjected to the corresponding photo- or thermal-reaction conditions (Table 2). Both electron-donating and electron-withdrawing substituents were well tolerated and the presence of electron-withdrawing groups usually gave slightly higher yields than electron-donating groups (**4a-4c** *vs* **4d-4l**). It is worth mentioning that the photocatalytic conditions generally gave inferior chemical yields. As for the thermal processes, these two different heating ways exhibited similar reaction efficacy. Specifically, substrates bearing NO_2 or dihalogenated groups could afford the desired products **4j-4l** successfully. The subsequent transformation of NO_2 or halogen groups would facilitate the expansion of the synthetic potentials for these functionalized heterocycles. However, the substituents on the olefin of side chain for compounds **2** were merely limited to aromatic ringat the current stage. Phenyl-substituted pyrazolidin-3-one was unsuitable for this transformation. The structure of product **4l** was unambiguously confirmed by X-ray crystallographic analysis.

Table 2
Exploration of substrate scope.



3. Conclusion

In summary, a new intramolecular [3 + 2]-cycloaddition by employing azomethineylides formed from 2-(cinnamyloxy)benzaldehyde and pyrazolidin-3-one was designed and successfully developed. This transformation occurred smoothly under photocatalytic and thermal reaction conditions, with wide scope and excellent diastereoselectivity. As such, a series of tetrahydrochromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-ones were facilely assembled, which would surely enrich the library of heterocycles and provide more options for drug screening in the future. Further biological studies of these privileged scaffolds are ongoing in our laboratory.

4. Experimental section

Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = quint, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Infrared spectra (IR) were measured by FT-IR apparatus. High resolution mass spectroscopy (HRMS) was recorded on TOF MS ES + mass spectrometer and acetonitrile was used to dissolve the sample. Column chromatography was carried out on silica gel (200–300 mesh). The starting materials **2** and **3** were prepared according to the previously described method [18,19].

4.1. General procedures for synthesis of *2a-2l*

To a solution of salicylaldehyde derivatives in DMF (2 mL) was added cinnamyl bromide (6 mmol, 1.2 equiv) and K_2CO_3 (6 mmol, 1.2 equiv). Subsequently, the reaction mixture was stirred at rt for

2 h. Then, the resulting mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (PE/EA = 95/5–80/20) to afford the corresponding products.

4.2. General procedures for synthesis of **4a-4l**

4.2.1. Conventional heating process

2-(Cinnamyloxy)benzaldehydes **2a-2l** (0.2 mmol, 1.0 equiv) was added to a solution of pyrazolidin-3-one **1a** (0.60 mmol, 3equiv.) in CH_3CN (2 mL). Then, the reaction mixture was stirred in the oil bath at 80 °C for 12 h. The crude product was purified by flash chromatography on silica gel (PE/EtOAc = 3/2).

4.2.2. Microwave process

2-(Cinnamyloxy)benzaldehyde **2** (0.2 mmol, 1.0 equiv) was added to a solution of pyrazolidin-3-one **1a** (0.60 mmol, 3equiv) in CH_3CN (2 mL). The resulting mixture in a sealed vial was irradiated in the 250 w microwave at 80 °C for 0.5 h. The crude product was purified by flash chromatography on silica gel (PE/EtOAc = 3:2).

4.2.3. Photo-induced process

2-(Cinnamyloxy)benzylidene-5-oxopyrazolidin-2-ium-1-ides **3** (0.2 mmol, 1.0 equiv), Ir $(ppy)_3$ (2.0 mmol%) were well mixed in DMSO (2 mL). Then the reaction mixture was stirred at room temperature for 3 h under irradiation of 30 W blue LEDs (distance app. 5 cm). The resulting mixture was purified by flash chromatography on silica gel (PE/EtOAc = 3:2).

Tetrahydrochromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4a**: yellow solid 49.6 mg (oil bath), 50.8 mg (mw), 46.5 mg (*hv*); m. p. 122–124 °C; IR (neat) *ν* 2908, 1680, 1386, 1222, 1018, 737 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40–7.18 (m, 7H), 6.97–6.92 (m, 2H), 4.54 (s, 1H), 4.34 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.27 (t, *J* = 10.9 Hz, 1H), 3.92 (d, *J* = 4.6 Hz, 1H), 3.70 (td, *J* = 8.2, 2.3 Hz, 1H), 3.34–3.27 (m, 1H), 2.91–2.83 (m, 1H), 2.79–2.65 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.9, 154.2, 137.3, 129.2, 129.0, 128.0, 127.1, 125.2, 120.1, 116.6, 64.3, 58.9, 56.7, 49.4, 48.9, 35.5; HRMS (ESI):$C_{19}H_{18}N_2O_2Na^+$ $[M+Na]^+$Calcd 329.1260, Found 329.1264.

3-Methyl-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4b**: yellow solid 31.4 mg (oil bath), 32.5 mg (mw), 51.2 mg (*hv*); m. p. 141–143 °C; IR (neat) *ν* 2919, 1688, 1405, 1042, 790, 680 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.41–7.25 (m, 5H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.78–6.75 (m, 2H), 4.54 (s, 1H), 4.30 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.21 (t, *J* = 10.8 Hz, 1H), 3.90 (d, *J* = 5.3 Hz, 1H), 3.69 (dd, *J* = 9.7, 7.2, 2.8 Hz, 1H), 3.28 (dt, *J* = 11.9, 9.1 Hz, 1H), 2.85 (dtd, *J* = 10.8, 5.4, 2.2 Hz, 1H), 2.72–2.63 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.1, 154.1, 139.3, 139.4, 128.9, 127.9, 127.0, 125.2, 121.2, 116.9, 113.7, 64.4, 58.7, 56.7, 49.2, 49.1, 35.4, 20.2; HRMS (ESI):$C_{20}H_{20}N_2O_2Na^+$ $[M+Na]^+$Calcd 343.1417, Found 343.1432.

6- Methoxy-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4c**: yellow solid 47.0 mg (oil bath), 42.3 mg (mw), 38.3 mg (*hv*); m. p. 177–179 °C; IR (neat) *ν* 2924, 1680, 1400, 1257, 1020, 696 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39–7.25 (m, 5H), 6.87–6.81 (m, 2H), 6.71–6.70 (m, 1H), 4.52 (s, 1H), 4.20 (dd, *J* = 10.7, 4.8 Hz, 1H), 4.08 (t, *J* = 10.8 Hz, 1H), 3.80 (d, *J* = 5.6 Hz, 1H), 3.76 (s, 3H), 3.73–3.69 (m, 1H), 3.27 (dt, *J* = 8.8, 8.8 Hz, 1H), 2.87–2.65 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.9, 152.8, 148.2, 137.3, 128.0, 127.1, 125.2, 117.3, 117.2, 114.7, 113.9, 64.5, 59.1, 56.6, 54.8, 49.5, 49.1, 35.4; HRMS (ESI):$C_{20}H_{20}N_2O_3Na^+$ $[M+Na]^+$Calcd 359.1366, Found 359.1374.

2-Fluoro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4d**: yellow solid 55.1 mg (oil bath), 59.0 mg (mw), 46.7 mg (*hv*); m. p. 154–156 °C; IR (neat) *ν* 2917, 1700, 1245, 1029, 712 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39–7.38 (m, 4H), 7.35–7.29 (m, 1H), 6.97 (dd, *J* = 9.2, 7.9, 2.9 Hz, 1H), 6.90–6.87 (m, 2H), 4.52 (s, 1H), 4.32 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.18 (t, *J* = 10.9 Hz, 1H), 3.86 (d, *J* = 5.6 Hz, 1H), 3.71 (td, *J* = 8.2, 2.1 Hz, 1H), 3.27 (dt, *J* = 12.3, 8.7 Hz, 1H), 2.87–2.67 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.7, 156.9 (d, $^1J_{C\text{-}F}$ = 240.3 Hz), 151.3 (d, $^4J_{C\text{-}F}$ = 2.1 Hz), 138.1, 129.0, 128.2, 126.2, 118.8 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 118.8 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 117.0 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 65.5, 59.8, 57.6, 50.5, 49.8, 36.5; HRMS (ESI):$C_{19}H_{17}FN_2O_2Na^+$ $[M+Na]^+$Calcd 347.1166, Found 347.1181.

2-Chloro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4e**: yellow solid 57.8 mg (oil bath), 47.6 mg (mw), 40.8 mg (*hv*); m. p. 165–167 °C; IR (neat) *ν* 2914, 1702, 1384, 1252, 678 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39–7.31 (m, 5H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.51 (s, 1H), 4.34 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.20 (t, *J* = 11.0 Hz, 1H), 3.84 (d, *J* = 5.6 Hz, 1H), 3.72 (td, *J* = 8.4, 1.9 Hz, 1H), 3.27 (dt, *J* = 12.5, 8.6 Hz, 1H), 2.86–2.68 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.6, 153.8, 138.0, 130.0, 129.7, 129.0, 128.2, 126.8, 125.8, 119.3, 119.0, 65.4, 59.6, 57.5, 50.6, 49.7, 36.6; HRMS (ESI):$C_{19}H_{17}ClN_2O_2Na^+$ $[M+Na]^+$Calcd 363.0871, Found 363.0885.

2-Bromo-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4f**: yellow solid 57.6 mg (oil bath), 63.0 mg (mw), 43.0 mg (*hv*); m.p. 170–172 °C; IR (neat) *ν* 2918, 1721, 1393, 1256, 1102, 703 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40–7.30 (m, 7H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.50 (s, 1H), 4.35 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.20 (t, *J* = 11.0 Hz, 1H), 3.84 (d, *J* = 5.4 Hz, 1H), 3.73 (td, *J* = 8.4, 1.8 Hz, 1H), 3.27 (dt, *J* = 12.5, 8.5 Hz, 1H), 2.86–2.77 (m, 2H), 2.77–7.69 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.5, 154.3, 137.9, 132.9, 132.7, 129.1, 128.3, 126.2, 119.8, 119.4, 113.0, 65.4, 59.5, 57.5, 50.7, 49.6, 36.7; HRMS (ESI):$C_{19}H_{17}BrN_2O_2K^+$ $[M+K]^+$Calcd 423.0105, Found 423.0126.

1-Chloro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4g**: yellow solid 63.2 mg (oil bath), 63.9 mg (mw), 49.0 mg (*hv*); m. p. 144–146 °C; IR (neat) *ν* 2919, 1704, 1408, 1257, 1047, 763 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.41–7.37 (m, 4H), 7.33–7.29 (m, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.01 (dd, *J* = 8.9, 1.3 Hz, 1H), 6.85 (d, *J* = 8.3, 1.3 Hz, 1H), 4.70 (s, 1H), 4.42 (d, *J* = 5.2 Hz, 1H), 4.37 (dd, *J* = 11.0, 5.0 Hz, 1H), 4.23 (t, *J* = 11.1 Hz, 1H), 3.56 (t, *J* = 7.9 Hz, 2H), 2.92–2.59 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.3, 155.4, 136.9, 134.7, 129.2, 128.0, 127.1, 125.0, 121.1, 115.2, 115.1, 64.1, 56.5, 54.6, 50.9, 47.6, 35.5; HRMS (ESI):$C_{19}H_{17}ClN_2O_2H^+$ $[M+H]^+$Calcd 341.1051, Found 341.1007.

3-Fluoro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4h**: yellow solid 46.0 mg (oil bath), 39.5 mg (mw), 39.5 mg (*hv*); m.p. 137–139 °C; IR (neat) *ν* 2909, 1680, 1380, 1226, 1020, 738 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40–7.39 (m, 4H), 7.35–7.30 (m, 1H), 7.14 (dd, *J* = 8.4, 6.3 Hz, 1H), 6.71–6.64 (m, 2H), 4.52 (s, 1H), 4.36 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.22 (t, *J* = 11.0 Hz, 1H), 3.87 (d, *J* = 5.5 Hz, 1H), 3.68 (td, *J* = 8.1, 2.0 Hz, 1H), 3.26 (dt, *J* = 12.4, 8.6 Hz, 1H), 2.85–2.68 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.6, 162.4 (d, $^1J_{C\text{-}F}$ = 247.6 Hz), 155.3 (d, $^3J_{C\text{-}F}$ = 12.2 Hz), 137.0, 130.3 (d, $^3J_{C\text{-}F}$ = 10.2 Hz), 127.9, 127.2, 125.2, 112.6, 107.7 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 103.8 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 64.4, 58.5, 56.6, 49.5, 48.6, 35.5; HRMS (ESI):$C_{19}H_{17}FN_2O_2Na^+$ $[M+Na]^+$Calcd 347.1166, Found 347.1177.

3-Bromo-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4i**: yellow solid 73.4 mg (oil bath), 53.8 mg (mw), 56.1 mg (*hv*); m. p. 150–152 °C; IR (neat) *ν* 2923, 1690, 1251, 1013, 695 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40–7.39 (m, 4H), 7.34–7.30 (m, 1H), 7.11–7.03 (m, 3H), 4.50 (s, 1H), 4.34 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.20 (t, *J* = 11.1 Hz, 1H), 3.83 (d, *J* = 5.3 Hz, 1H), 3.67 (td, *J* = 8.4, 1.9 Hz, 1H), 3.25 (td, *J* = 12.6, 8.5 Hz, 1H), 2.85–2.76 (m, 2H), 2.74–2.67 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.6, 155.8, 138.0, 131.3, 129.0, 128.3, 126.2, 124.4, 123.2, 120.8, 116.8, 65.4, 59.4, 57.5, 50.6, 49.6, 36.7; HRMS

(ESI):$C_{19}H_{17}BrN_2O_2Na^+$ $[M+Na]^+$Calcd 407.0366, Found 407.0377.

2-Nitro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4j**: yellow solid 60.4 mg (oil bath), 64.6 mg (mw), 46.3 mg (*hv*); m. p. 173–175 °C; IR (neat) ν 2924, 1678, 1237, 1027, 750 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.17–8.14 (m, 2H), 7.39 (s, 5H), 7.03 (d, J = 8.7 Hz, 1H), 4.52–4.49 (m, 2H), 4.33 (t, J = 11.3 Hz, 1H), 3.93 (d, J = 5.2 Hz, 1H), 3.75 (t, J = 8.1 Hz, 1H), 3.35 (dt, J = 12.9, 8.3 Hz, 1H), 2.93–2.84 (m, 2H), 2.77 (dd, J = 16.1, 7.8 Hz, 1H); 13C NMR (100 MHz, Chloroform-*d*) δ 164.0, 160.3, 141.4, 137.5, 129.1, 128.4, 126.5, 126.2, 125.8, 118.3, 118.1, 65.8, 59.3, 57.4, 50.8, 49.1, 36.8; HRMS (ESI):$C_{19}H_{17}N_3O_4Na^+$ $[M+Na]^+$ Calcd 374.1111, Found 374.1155.

2,4-Dibromo-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4k**: white solid 92.6 mg (oil bath), 92.7 mg (mw), 78.0 mg (*hv*); m. p. 194–196 °C; IR (neat) ν 2914, 1680, 1393, 1252, 1013, 681 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, J = 2.0 Hz, 1H), 7.40–7.33 (m, 5H), 7.26–7.25 (m, 1H), 4.50–4.46 (m, 2H), 4.26 (t, J = 11.2 Hz, 1H), 3.82 (d, J = 5.4 Hz, 1H), 3.69 (td, J = 8.3, 1.8 Hz, 1H), 3.24 (dt, J = 12.7, 8.3 Hz, 1H), 2.89–2.71 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.0, 150.1, 136.6, 134.7, 130.9, 128.0, 127.3, 125.1, 119.7, 111.8, 111.4, 65.0, 58.4, 56.3, 49.8, 48.4, 35.7; HRMS (ESI):$C_{19}H_{16}Br_2N_2O_2Na^+$ $[M+Na]^+$Calcd 484.9471, Found 484.9499.

2,4-Dichloro-7-phenyl-6a,10, 11, 12a-tetrahydro-6*H*,7*H*,9*H*-chromeno [4,3-*c*]pyrazolo [1,2-*a*]pyrazol-9-one **4l**: white solid 70.3 mg), 73.3 mg (mw), 68.8 mg (*hv*); m.p. 180–182 °C; IR (neat) ν 2918, 1702, 1413, 1255, 1126, 697 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.31 (m, 6H), 7.08 (s, 1H), 4.51–4.48 (m, 2H), 4.27 (t, J = 11.0 Hz, 1H), 3.84 (d, J = 5.5 Hz, 1H), 3.71 (d, J = 8.8 Hz, 1H), 3.22–3.29 (m, 1H), 2.90–2.71 (m, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.0, 148.7, 136.6, 129.2, 128.0, 127.3, 127.2, 125.2, 124.5, 122.3, 119.3, 64.9, 58.4, 56.4, 49.8, 48.4, 35.7; HRMS (ESI):$C_{19}H_{16}Cl_2N_2O_2Na^+$ $[M+Na]^+$Calcd 397.0481, Found 397.0493.

Declaration of competing interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

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