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Phosphine-Catalyzed [3+2] and [4+3]Annulation Reactions of C,N-Cyclic Azomethine Imines with Allenoates

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Abstract

Phosphine-catalyzed [3+2] and [4+3]annulation reactions of C,N-cyclic azomethine imines with allenoates have been developed to give a variety of pharmaceutically attractive tetrahydroisoquinoline derivatives in moderate to excellent yields. The two distinct reaction pathways, [3+2] and [4+3]cyclization, depend on the nature of the nucleophilic phosphine and the allenoate. Generally, for α-alkylallenoates, the reactions always proceed with [3 +2]cyclization as the major pathway no matter what phosphine was used; for α-$ArCH_2$-substituted allenoates, the reaction pathway was controlled by the phosphine catalyst used.

Keywords

allenoates; annulation; azomethine imines; catalysis; phosphines

Introduction

Tetrahydroisoquinoline derivatives are structural motifs often occurring in natural products and pharmacologically important agents exhibiting a wide range of biological activities such as antitumor, antibiotic, antivirus, anti-inflammatory, anticoagulation, and bronchodilation.[1] Therefore, the synthesis of tetrahydroisoquinoline derivatives has attracted much attention.[2] Although some synthetic methods have been developed,[2] novel procedures applicable for their synthesis would still be highly desirable.

The nucleophilic phosphine-catalyzed intermolecular cycloaddition reaction has been developed as one of the most powerful tools for the convergent synthesis of a variety of

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carbo- and heterocycles from simpler precursors.[3] In these cycloaddition reactions, activated allenes have been used as a versatile reaction substrate and exhibited super diverse reactivity towards electrophilic reagents. These allenes act as one, two-, three- or four-carbon synthons to react with various electrophilic coupling partners including aldehydes, activated alkenes, imines or aziridines to render all kinds of annulation reactions.[4–11] Such a diverse pattern of reactivity of the allene as one of the reaction substrates is often induced by its electrophilic coupling partners. Consequently, searching for a new electrophilic substrate with a proper reactivity that can effectively be utilized in the synthesis of heterocycles with new skeletons or structural features constitutes a major challenge for the formation of diverse cycloaddition products from the nucleophilic phosphine catalysis of allenes. Recently, a new type of electrophilic coupling reagent, N,N′-cyclic azomethine imines (**1**), has been used as an N′N′C trio-of-atoms synthon in the phosphine-catalyzed [3+2]annulation with α-substituted allenoates to produce biologically active tetrahydropyrazolopyrazolones (Scheme 1).[12] This work prompted us to investigate whether the catalytic process can be used in the reactions of another noteworthy class of azomethine imines, C,N-cyclic imines, to synthesize pharmaceutically attractive tetrahydroisoquinoline derivatives. In addition, while the [4+2] and [3+2]cycloadditions are widely explored in phosphine-catalyzed annulation reactions of allenoates, only two examples of the phosphine-catalyzed [4+3]annulation reactions of allenes were reported so far.[8,12] Thus, we conceived to use an α-substituted allenoate as a 1,4-dipole to develop a novel [4+3]cycloaddition.

N,N′-Cyclic azomethine imines **1** have recently been employed as efficient 1,3-dipoles in various metal-catalyzed or organocatalytic cycloadditions.[13] However, catalytic cycloaddition reactions of C,N-cyclic azomethine imines have rarely been studied. Only three examples involving C,N-cyclic substrates have been reported so far.[14] In 2008, Charette and co-workers reported an $Ni(ClO_4)_2$-catalyzed [3 + 3] cycloaddition of C,N-cyclic aromatic azomethine imines with 1,1-cyclopropane diesters, giving access to unique tricyclic dihydroquinoline derivatives.[14a] In 2010, Maruoka and co-workers developed the BINOL-Ti-catalyzed enantioselective [3+2]cycloaddition of C,N-cyclic azomethine imines with α,β-unsaturated aldehydes, providing derivatives of 1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinoline;[14b] in 2011, Maruoka's group further developed an axially chiral dicarboxylic acid-catalyzed asymmetric inverse-electron-demand 1,3-dipolar cycloaddition of the above azomethine imines with vinyl ether or vinylogous aza-enamines, affording 1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinoline derivatives.[14c] Herein, we report the first example of phosphine-catalyzed cycloaddition of C,N-cyclic azomethine imines with allenoates. The novel [3+2] and [4+3]annulation reactions were achieved depending on the number of carbon atoms that the allenoates contribute to the final cyclic products, furnishing 1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinoline derivatives and 1,4,5,7,8,12b-hexahydro-[1,2]diazepino-[7,1-*a*]isoquinoline derivatives, respectively (Scheme 1).

Results and Discussion

We initiated our study and screened the reaction conditions by evaluating the reactions of azomethine imine **2a** and allenoate **3f** (Table 1). Considering that the direct cycloadditions

of azomethine imines with allenoates often occur,[15] the reaction of **2a** with **3f** was first carried out in dichloromethane at room temperature in the absence of phosphines, no new spot was observed on the TLC (entry 1), therefore, the background reaction resulting from possible direct [3+2]cycloaddition of azomethine imine and allenoate in dichloromethane at room temperature could be excluded. However, once the temperature is above 30°C, the thermal cycloaddition product would be observed. In order to avoid the background reaction, when the following reactions were performed, the reaction temperature was strictly controlled at room temperature (25°C). Since the efficiency of nucleophilic phosphine catalysis often depends on the nature of the tertiary phosphine catalyst, several phosphines with different nucleophilicity have been screened (entries 2–6). When PMe_3 was used, a 66% yield of [3+2]cyclization product and <5%yield of [4+3]cyclization product were achieved (entry 2). In contrast, with PBu_3 as the catalyst, < 5%yield of [3 + 2]cyclization product and 90%yield of [4+3]product were obtained (entry 3). The structures of the new [3+2]annulation product (**4**) and [4+3]product (**5**) were confirmed by NMR spectra and subsequently by the X-ray crystallography of **4ef** and **5df** (see Table 3 below). Notably, a single diastereomer (**5af**) of [4+ 3]cyclization product was obtained, and other diastereomer was not observed. When phosphines Me_2PPh, $EtPPh_2$ and PPh_3 were utilized as catalysts, the reactions were somewhat sluggish and both overall yield and chemoselectivity were unsatisfactory (entries 4–6). On the basis of these results, PBu_3 and PMe_3 were established as the optimal catalysts in terms of both yield and chemoselectivity.

With 20 mol% of PBu_3 or PMe_3 as catalyst, the annulation reactions of C,N-cyclic azomethine imine **2a** with various allenoates were performed in dichloromethane at room temperature for 24 h to provide the corresponding products in moderate to excellent yields (Table 2).[16] Especially, with either PBu_3 or PMe_3 as the catalyst, α-alkylallenoates (**3a**–**3e**) underwent the reactions to afford the [3+2]products, 1,2,3,5,6,10b-hexahydropyrazolo-[5,1-*a*]isoquinoline derivatives, as the major products (entries 1–5, 14–18). Those reactions demonstrated excellent chemoselectivity towards the [3+2]products in most cases, giving only very small amounts (<1%) of the [4+ 3]products (entries 2–5, 14–18), except that the reaction of α-methylallenoate (**3a**) exhibited a moderate chemoselectivity to deliver [3+2] and [4+3]products in 62% and 7% yields, respectively (entry 1).

When β′-arylallenoate was used as substrate, PBu_3 and Me_3P displayed quite different catalytic behaviors. Using PBu_3 as the catalyst, contrary to chemoselectivity of α-alkylallenoates (**3a**–**3e**), all β′-arylallenoates examined (**3f**–**3m**) preferably gave a single diasteoreomer of the [4+3]cyclization product, 1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline derivatives, as the major product in moderate to excellent yields, together with small amounts of [3+ 2]product (entries 6–13). A broad range of aryl groups with electron-donating or electron-withdrawing substituents on the benzene ring could be tolerated in the process. In general, allenoates bearing electron-withdrawing groups on the benzene ring provided somewhat higher yields of the [4+3]cyclization products than did those bearing electron-donating groups (entries 10–13 and 7–9). Particularly, with β′-(4-BrC_6H_4)-substituted allenoate (**3m**) as substrate, the desired [4+3]product was produced in up to 93% yield (entry 13). With PMe_3 as the catalyst, however, the [4+3]products were

obtained as the major product in only three cases (entries 23, 24, 26). In another five cases (entries 19—22, 25), the [3+2]products were produced as the major products.

The generality of this reaction was explored with several azomethine imines bearing different substituents on the benzene rings. α-Benzylallenoate (**3f**) and α-ethylallenoate (**3b**) were used as the standard allenoates. The reaction is tolerant of a wide range of azomethine imines (**2b**–**2f**), providing a series of the corresponding products in moderate to excellent yields with moderate to excellent chemoselectivity (Table 3). In the presence of 20 mol% of PBu_3, the reactions of azomethine imines (**2b**–**2f**) with α-benzylallenoate (**3f**) afforded the [4+3]products as the major products in 61–73% yield, and the [3+2]products as the minor products in 23–34% yield (entries 1–5). In contrast, using 20 mol% of PMe_3 as the catalyst, the reactions of azomethine imines with α-benzylallenoate (**3f**) demonstrated excellent chemoselectivity, giving the [3+2]products as major product in 40–92% yield and [4+3]product in <1% yield (entries 6–10). In these cases, a significant electronic effect was observed. Electron-donating alkyl-substituted azomethine imines provided lower yields than those with electron-withdrawing groups (entries 6, 7 *vs.* entries 8–10). When α-ethylallenoate (**3b**) was employed as the substrate, under the catalysis of 20 mol% PBu_3, the [3 + 2]cycloaddition products were acquired in uniformly high yields with excellent chemoselectivity (entries 11–15). The X-ray crystallographic structures of **4ef** and **5df** are shown in the Figure 1 and Figure 2.[17]

Asymmetric variants of these cyclizations had been investigated too. Unfortunately, a variety of commercial available chiral phosphines such as DiPAMP, BINAP, Me-DuPhos, TangPhos, Et-BINEPINE, *t*-Bu-BINEPINE, FerroPHANE, SITCP and Et-BPE were not active in the reactions and afforded very small amounts of [3+2]cyclization products (<10% yield and <10% *ee*) and no [4+3]cyclization product.

The transformations of [3+2] and [4+3]cyclization products have been demonstrated in several reports for the synthesis of tetrahydroisoquinoline derivatives and other useful compounds. For example, the 1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinoline derivatives **4** could further be transformed to 1,3-diamine derivatives *via* N′N bond cleavage with samarium iodide (SmI_2),[14b,18] reduced with SmI_2[12] and oxidation[12] to give biologically important compounds or building blocks for bioactive compounds.

On the basis of the reported mechanistic studies of nucleophilic phosphine-catalyzed reactions,[3] as shown in Scheme 2, a plausible mechanism has been outlined. The zwitterionic intermediate **A**, which was formed from the addition of PBu_3 to the β-carbon of allenoate, attacks the azomethine imine **2a** *via* γ-carbon atom of **A** to provide the intermediate **B**. The intramolecular conjugate addition of **B** accomplishes the [3+2]cyclization to form β-phosphonium enoate **C**, which undergoes facile β-elimination to regenerate the catalyst, affording the final [3+2]product **4**. When R is a hydrogen atom or aryl, the intermediate **B** isomerizes into another amide species **F** due to the more acidic nature of the γ-proton. The ylide **G** formed from the 7-*endo* cyclization of **F**, expels the catalyst PBu_3 through the ylide-to-enoate conversion to furnish the [4+3]product **5**. Compared with PBu_3, when PMe_3 is used as the catalyst, conjugate addition of the amide to

the β-phosphonium enoates in **B** is the major reaction pathway in most cases, resulting in the [3+2]product due to decreased steric congestion at the β-carbon atom.

Conclusions

In summary, phosphine-catalyzed [3+2] and [4+ 3]cycloaddition reactions of C,N-cyclic azomethine imines with allenoates have successfully been developed, providing the 1,2,3,5,6,10b-hexahydropyrazolo-[5,1-*a*]isoquinoline derivatives and 1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline derivatives, respectively, in high yields. Particularly, the novel [4+3]cycloaddition represents one of the few examples of phosphine-catalyzed [4+3]cycloaddition of the allenoates.

Experimental Section

General Procedures

All reactions were performed under an argon atmosphere in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Dichloromethane employed in the reactions was freshly distilled from CaH_2. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Reactions were monitored through thin-layer chromatography (TLC) on silica gel-precoated glass plates. Chromatograms were visualized by fluorescence quenching under UV light at 254 nm. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (200–300 mesh). Infrared spectra were recorded using a Bruker Optics TENSOR 27 instrument. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker 300M spectrometer, as indicated. Accurate mass measurements were performed using an Agilent instrument with the ESI-MS technique. X-ray crystallographic data were collected using a Bruker SMART CCD-based diffractometer equipped with a low-temperature apparatus operated at 100 K.

Preparation of C,N-Cyclic Azomethine Imines (2)

All C,N-cyclic azomethine imines (**2**) were prepared by the reported procedure.[14b,19]

General Procedure for the [3+2] and [4+3]Cyclo-addition Reactions of Azomethine Imines and Allenoate

An oven-dried, 15-mL Schlenk tube was charged with azomethine imine (0.125 mmol), 5 mL of CH_2Cl_2 and allenoate (0.15 mmol) at room temperature. Then, phosphine (0.025 mmol) was added to the above solution and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and the residue was purified by flash column (ethyl acetate/petroleum ether) to afford the corresponding cycloaddition product.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-propanoate (4aa)—Yield: 79% (Table 2, entry 14); a yellow solid. TLC (EtOAc/petroleum ether 1/5): $R_f = 0.52$; IR (film): $\nu_{max} = 2965, 2929, 2849, 1703, 1644, 1600, 1580, 1493, 1446, 1368, 1281, 1222, 1104, 1041, 911, 866, 789, 762, 730, 677, 647$ $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H), 1.94 (t, $J = 1.9$ Hz, 3H),

2.77 (dd, *J*=15.5, 2.4 Hz, 1H), 2.94–3.10 (m, 2H), 3.14–3.23 (m, 1H), 3.37–3.41 (m, 1H), 3.71 (ddd, *J*=18.7, 8.4, 1.9 Hz, 1H), 4.21 (q, *J*=7.1 Hz, 2H), 4.31 (apparent t, 1H), 7.02–7.17 (m, 4H), 7.37–7.49 (m, 3H), 7.71–7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.4, 16.7, 29.1, 40.2, 47.8, 60.5, 61.6, 117.9, 118.1, 126.4, 126.8, 127.1, 127.7, 128.3, 128.5, 131.1, 132.3, 135.22, 135.24, 148.5, 167.6, 170.7; HR-MS (ESI): *m/z*=377.1858, calcd. for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$: 377.1860.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-butanoate (4ab)—Yield: 91% (Table 2, entry 15); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.56; IR (film): ν_{max} = 2926, 2853, 1704, 1638, 1581, 1493, 1455, 1368, 1299, 1240, 1220, 1142, 1106, 1062, 1028, 973, 909, 865, 786, 736, 695, 678, 648 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.12 (t, *J* = 7.4 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 2.34–2.47 (m, 2H), 2.73–2.79 (m, 1H), 2.91–3.16 (m, 3H), 3.35–3.40 (m, 1H), 3.68 (dd, *J*=18.6, 8.5 Hz, 1H), 4.18–4.28 (m, 3H), 7.00–7.16 (m, 4H), 7.35–7.48 (m, 3H), 7.70–7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 12.7, 14.3, 23.8, 29.1, 40.0, 47.6, 60.3, 61.2, 124.6, 126.3, 126.7, 127.1, 127.6, 128.2, 128.5, 131.0, 132.3, 135.25, 135.31, 147.1, 167.4, 171.5; HR-MS (ESI): *m/z*=391.2016, calcd. for $C_{24}H_{27}N_2O_3^+$ $[M+H]^+$: 391.2016.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo-[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-pentanoate (4ac)—Yield: 93% (Table 2, entry 16); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.58; IR (film): ν_{max} = 2925, 2853, 1704, 1637, 1541, 1491, 1456, 1291, 1141, 1110, 1033, 910, 863, 789, 747, 695, 677 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.91 (t, *J* = 7.4 Hz, 3H) 1.30 (t, *J*=7.1 Hz, 3H), 1.39–1.73 (m, 2H), 2.23–2.33 (m, 1H), 2.45 (ddd, *J*=14.0, 9.2, 5.0 Hz, 1H), 2.69–2.81 (m, 1H), 2.93–3.22 (m, 3H), 3.33–3.44 (m, 1H), 3.65 (dd, *J*=18.7, 8.5 Hz, 1H), 4.16–4.28 (m, 3H), 6.99–7.15 (m, 4H), 7.36–7.49 (m, 3H), 7.70–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2, 21.4, 29.1, 29.6, 32.4, 40.0, 47.6, 60.3, 61.2, 123.1, 126.3, 126.7, 127.1, 127.6, 128.2, 128.4, 131.0, 132.3, 135.3, 147.5, 167.6, 171.4; HR-MS (ESI): *m/z*=405.2177, calcd. for $C_{25}H_{29}N_2O_3^+$ $[M+H]^+$: 405.2173.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-4-methylpentanoate (4ad)—Yield: 92% (Table 2, entry 17); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.58; IR (film): ν_{max} = 2957, 2867, 1704, 1644, 1600, 1581, 1493, 1456, 1367, 1297, 1217, 1115, 1063, 1028, 973, 910, 863, 790, 763, 730, 696, 677, 647 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85 (d, *J*=6.5 Hz, 3H), 0.93 (d, *J*=6.6 Hz, 3H), 1.30 (t, *J*=7.1 Hz, 3H), 1.83–1.96 (m, 1H), 2.04 (dd, *J*=13.9, 9.5 Hz, 1H), 2.51–2.57 (m, 1H), 2.71–2.82 (m, 1H), 2.97–3.09 (m, 2H), 3.23–3.41 (m, 2H), 3.60 (ddd, *J*=18.7, 8.3, 1.4 Hz, 1H), 4.12–4.29 (m, 3H), 6.99–7.16 (m, 4H), 7.36–7.49 (m, 3H), 7.69–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2, 22.0, 23.4, 27.6, 29.2, 39.3, 40.0, 47.7, 60.2, 61.3, 122.1, 126.3, 126.7, 127.1, 127.6, 128.2, 128.4, 131.1, 132.3, 135.3, 135.4, 147.9, 167.7, 171.3; HR-MS (ESI): *m/z*=419.2319, calcd. for $C_{26}H_{31}N_2O_3^+$ $[M+ H]^+$: 419.2329.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-4,4-dimethylpentanoate (4ae)—Yield: 74% (Table 2, entry 5); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.60; IR (film): ν_{max} = 2953, 1705, 1682, 1541,

1508, 1456, 1364, 1294, 1165, 1094, 1067, 1026, 789, 762, 695, 677 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 9H), 1.31 (t, *J*=7.1 Hz, 3H), 2.27 (d, *J*=14.1 Hz, 1H), 2.64 (d, *J*=14.1 Hz, 1H), 2.77 (d, *J*=15.5 Hz, 1H), 3.06 (dtd, *J*=17.0, 12.4, 4.0 Hz, 2H), 3.38–3.45 (m, 3H), 4.16–4.23 (m, 3H), 6.98–7.14 (m, 4H), 7.36–7.49 (m, 3H), 7.67–7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2, 29.3, 29.9, 32.9, 40.3, 42.3, 47.6, 60.3, 61.4, 120.9, 126.3, 126.8, 127.1, 127.7, 128.25, 128.32, 131.1, 132.4, 135.3, 135.7, 147.6, 168.9, 171.7; HR-MS (ESI): *m/z*=433.2495, calcd. for $C_{27}H_{33}N_2O_3^+$ $[M+H]^+$: 433.2486.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-phenylpropanoate (4af)—Yield: 66% (Table 2, entry 19); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.51; IR (film): ν_{max} = 2929, 1703, 1541, 1508, 1493, 1455, 1368, 1298, 1219, 1095, 1030. 770, 699, 677 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H), 2.62–2.78 (m, 2H), 2.84–2.97 (m, 2H), 3.25 (dd, *J*=18.9, 10.1 Hz, 1H), 3.58–3.76 (m, 2H), 3.98 (d, *J*= 15.8 Hz, 1H), 4.08–4.27 (m, 3H), 6.99–7.04 (m, 2H), 7.07–7.13 (m, 2H), 7.16–7.23 (m, 5H), 7.27–7.39 (m, 2H), 7.41–7.47 (m, 1H), 7.51–7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1, 29.1, 35.4, 40.5, 47.4, 60.6, 61.0, 122.0, 125.8, 126.3, 126.8, 127.1, 127.6, 128.1, 128.2, 128.4, 128.6, 131.0, 132.3, 135.1, 135.2, 140.7, 149.3, 167.4, 170.8; HRMS (ESI): *m/z*=453.2165, calcd. for $C_{29}H_{29}N_2O_3^+$ $[M+H]^+$: 453.2173.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(*o*-tolyl)propanoate (4ag)—Yield: 18% (Table 2, entry 20); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.50; IR (film): ν_{max} = 3062, 3023, 2976, 2932, 2848, 1706, 1682, 1601, 1581, 1493, 1447, 1368, 1299,1272, 1219, 1095, 968, 909, 788, 761, 740, 716, 699, 678, 648 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=1.17 (t, *J*= 7.1 Hz, 3H), 2.27 (s, 3H), 2.66–2.98 (m, 4H), 3.34 (dd, *J*= 18.8, 10.0 Hz, 1H), 3.61–3.74 (m, 2H), 3.99 (d, *J*=16.3 Hz, 1H), 4.08–4.18 (m, 2H), 4.22–4.28 (m, 1H), 7.00–7.17 (m, 8H), 7.33–7.38 (m, 2H), 7.42–7.47 (m, 1H), 7.53–7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.8, 29.1, 33.4, 40.3, 47.4, 60.5, 61.1, 121.3, 125.5, 125.9, 126.3, 126.8, 127.1, 127.6, 128.2, 128.4, 128.9, 130.0, 131.0, 132.4, 135.1, 136.2, 138.6, 148.9, 162.3, 167.3, 171.1; HR-MS (ESI): *m/z*= 467.2335, calcd. for $C_{30}H_{31}N_2O_3$ $[M + H]^+$: 467.2329.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(*m*-tolyl)propanoate (4ah)—Yield: 55% (Table 2, entry 21); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.48; IR (film): ν_{max} = 2927, 2851, 1697, 1493, 1447, 1369, 1298, 1199, 1097, 1031, 969, 866, 766, 703, 678 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 2.25 (s, 3H), 2.62–2.93 (m, 4H), 3.24 (dd, *J*= 18.8, 10.1 Hz, 1H), 3.60–3.76 (m, 2H), 3.97 (d, *J*=15.9 Hz, 1H), 4.12–4.27(m, 3H), 6.94–7.04 (m, 5H), 7.07–7.14 (m, 3H), 7.31–7.37 (m, 2H), 7.40–7.46 (m, 1H), δ7.47–7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.3, 29.1, 35.2, 40.5, 47.4, 60.6, 61.0, 77.2, 122.1, 125.6, 126.3, 126.5, 126.8, 127.1, 127.6, 128.0, 128.2, 128.4, 129.6, 131.0, 132.4, 135.1, 135.2, 137.5, 140.6, 149.2, 167.5, 170.7; HR-MS (ESI): *m/z*= 467.2328, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(*p*-tolyl)propanoate (4ai)—Yield: 92% (Table 2, entry 22); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.48; IR (film): ν_{max} = 2924, 2853, 1704, 1580, 1514, 1494, 1455, 1369, 1293, 1198, 1095, 1030, 968, 909, 866, 787, 763, 677, 647 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3H), 2.33 (s, 3H), 2.66–3.00 (m, 4H), 3.26 (dd, *J*=18.8, 10.0 Hz, 1H), 3.62–3.76 (m, 2H), 3.91 (d, *J*=15.8 Hz, 1H), 4.08–4.34 (m, 3H), 7.00–7.15 (m, 8H), 7.34–7.59 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.0, 29.1, 35.1, 40.4, 47.4, 60.5, 61.1, 122.1, 126.3, 126.8, 127.1, 127.6, 128.2, 128.4, 128.5, 128.7, 131.1, 132.4, 135.20, 135.21, 137.5, 148.9, 167.4, 170.9; HR-MS (ESI): *m/z*= 467.2323, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(4-fluorophenyl)propanoate (4aj)—Yield: 18% (Table 2, entry 23); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.48; IR (film): ν_{max} = 2930, 1714, 1650, 1602, 1507, 1455, 1369, 1310, 1240, 1158, 1097, 1059, 1026, 912, 958, 825, 733, 700, 672 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H), 2.72 (ddd, *J*=18.7, 13.2, 3.5 Hz, 2H), 2.89–3.00 (m, 2H), 3.23 (dd, *J*= 18.7, 10.2 Hz, 1H), 3.62–3.77 (m, 2H), 3.92 (d, *J*=15.8 Hz, 1H), 4.07–4.33 (m, 3H), 6.86–7.18 (m, 8H), 7.33–7.58 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 29.1, 34.7, 40.5, 47.5, 60.6, 61.1, 114.9, 121.9, 126.4, 126.8, 127.1, 127.7, 128.3, 128.4, 129.9, 130.0, 131.1, 132.3, 135.0, 136.28, 136.32, 149.4, 159.7, 162.9, 167.3, 170.9; HR-MS (ESI): *m/z*=471.2068, calcd. for $C_{29}H_{28}FN_2O_3^+$ $[M+H]^+$: 471.2078.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(3-chlorophenyl)propanoate (4ak)—Yield: 28% (Table 2, entry 24); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.52; IR (film): ν_{max} = 2979, 1701, 1598, 1474, 1429, 1368, 1297, 1200, 1096, 1030, 865, 767, 697 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (d, *J*=7.1 Hz, 3H), 2.66–2.79 (m, 2H), 2.86–2.96 (m, 2H), 3.24 (dd, *J*=18.8, 10.1 Hz, 1H), 3.62–3.78 (m, 2H), 3.96 (d, *J*= 15.7 Hz, 1H), 4.10–4.33 (m, 3H), 7.01–7.08 (m, 3H), 7.10–7.18 (m, 5H), 7.33–7.38 (m, 2H), 7.42–7.47 (m, 1H), 7.50– 7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 29.1, 35.1, 40,6, 47.5, 60.7, 61.0, 121.3, 126.0, 126.4, 126.8, 126.9, 127.1, 127.7, 128.2, 128.3, 128.7, 129.3, 131.1, 132.3, 133.9, 135.0, 142.8, 150.0, 167.2, 170.9; HR-MS (ESI): *m/z*= 487.1772, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(4-chlorophenyl)propanoate (4al)—Yield: 40% (Table 2, entry 25); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.50; IR (film) ν_{max} = 2927, 2853, 1697, 1600, 1541, 1490, 1455, 1368, 1276, 1199, 1095, 1015, 910, 866, 804, 763, 740, 696, 678 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, *J*=7.1 Hz, 3H), 2.67–2.84 (m, 2H), 2.91–3.00 (m, 2H), 3.25 (dd, *J*=18.8, 10.1 Hz, 1H), 3.48–3.78 (m, 2H), 3.93 (d, *J*=15.8 Hz, 1H), 4.11–4.34 (m, 3H), 7.00–7.25 (m, 8H), 7.32–7.58 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 29.1, 35.0, 40.5, 47.5, 60.7, 61.1, 67.1, 119.5, 121.4, 126.4, 126.9, 127.1, 127.4, 127.7, 127.8, 128.3, 128.4, 130.3, 131.1, 131.2, 131.5, 132.3, 132.7, 135.0, 139.7, 149.7, 167.2, 171.0; HR-MS (ESI): *m/z*=487.1776, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

(*E*)-Ethyl 2-[3-benzoyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-(4-bromophenyl)propanoate (4am)—Yield: 30% (Table 2, entry 26); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.48; IR (film): ν_{max} = 2926, 2850, 1704, 1541, 1487, 1446, 1301, 1241, 1200, 1099, 1011, 909, 788, 762, 736, 696, 677 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=1.20 (t, *J*=7.1 Hz, 3H), 2.53–3.00 (m, 4H), 3.13–3.29 (m, 1H), 3.57–3.77 (m, 2H), 3.90 (d, *J*=15.8 Hz, 1H), 4.00–4.33 (m, 3H), 7.00–7.24 (m, 6H), 7.30–7.56 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 29.1, 35.0, 40.5, 47.5, 60.7, 61.1, 119.5, 121.4, 126.4, 126.9, 127.1, 127.4, 127.7, 127.8, 128.3, 128.4, 130.3, 131.1, 131.2, 131.5, 132.3, 132.7, 135.0, 139.7, 149.7, 167.2, 171.0; HR-MS (ESI): *m/z*= 531.1254, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

(*E*)-Ethyl 2-[3-benzoyl-7-methyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]butanoate (4bb)—Yield: 95% (Table 3, entry 11); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.52; IR (film): ν_{max} = 3059, 2974, 2934, 1941, 1704, 1639, 1599, 1447, 1369, 1299, 1252, 1234, 1211, 1175, 1143, 1110, 1046, 1027, 935, 921, 866, 785, 758, 713, 696, 678, 648, 617, 545, 517 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.4 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.20 (s, 3H), 2.40–2.44 (m, 2H), 2.78–2.83 (m, 1H), 2.92–3.01 (m, 2H), 3.15 (dd, *J*=18.7, 10.0 Hz, 1H), 3.41–3.45 (m, 1H), 3.69 (dd, *J*=18.6, 8.5 Hz, 1H), 4.19–4.26 (m, 3H), 6.86 (s, 1H), 6.90–7.09 (m, 2H), 7.39–7.46 (m, 3H), 7.71–7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 14.3, 19.2, 23.8, 26.6, 39.9, 47.4, 60.3, 61.3, 124.7, 124.9, 126.2, 127.6, 128.0, 128.4, 130.9, 131.0, 135.1, 135.3, 135.8, 147.0, 167.4, 171.5; HR-MS (ESI): *m/z*=405.2138, calcd. for $C_{25}H_{29}N_2O_3^+$ $[M+ H]^+$: 405.2173.

(*E*)-Ethyl 2-[3-benzoyl-9-methyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]butanoate (4cb)—Yield: 97% (Table 3, entry 12); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.53; IR (film): ν_{max} = 3055, 2975, 2933, 1895, 1765, 1679, 1638, 1600, 1581, 1505, 1463, 1446, 1429, 1365, 1299, 1276, 1239, 1214, 1195, 1175, 1142, 1107, 1063, 1028, 977, 921, 880, 866, 843, 785, 734, 711, 695, 677, 641, 617, 550, 517, 460 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, *J*=7.4 Hz, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 2.25 (s, 3H), 2.37–2.47 (m, 2H), 2.66–2.77 (m, 1H), 2.89–3.01 (m, 2H), 3.11 (dd, *J*=18.6, 9.9 Hz, 1H), 3.35–3.38 (m, 1H), 3.67 (dd, *J*=18.6, 8.5 Hz, 1H), 4.18–4.26 (m, 3H), 6.83 (s, 1H), 6.91–6.97 (m, 2H), 7.36–7.46 (m, 3H), 7.70–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 14.3, 20.9, 23.7, 28.6, 40.0, 47.7, 60.3, 61.1, 124.5, 127.51, 127.58, 127.60, 128.0, 128.4, 129.1, 131.0, 135.1, 135.3, 135.8, 147.2, 167.4, 171.5; HR-MS (ESI): *m/z*=405.2164, calcd. for $C_{25}H_{29}N_2O_3^+$ $[M+H]^+$: 405.2173.

(*E*)-Ethyl 2-[3-benzoyl-8-bromo-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]butanoate (4db)—Yield: 87% (Table 3, entry 13); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.47; IR (film): ν_{max} = 3058, 2974, 2934, 1891, 1704, 1638, 1599, 1580, 1466, 1446, 1425, 1369, 1299, 1252, 1211, 1175, 1143, 1110, 1046, 1027, 935, 921, 866, 784, 758, 713, 696, 678, 649, 617, 522 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.4 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.20 (s, 3H), 2.35–2.43 (m, 2H), 2.69–2.74 (m, 1H), 2.87–3.11 (m, 3H), 3.35–3.39 (m, 1H), 3.66 (dd, *J*= 18.6, 8.5 Hz, 1H), 4.15–4.25 (m, 3H), 6.87 (d, *J*=8.2 Hz, 1H), 7.21–7.26 (m, 2H), 7.37–7.47

(m, 3H),7.69–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 12.7, 14.2, 23.7, 28.8, 39.8, 47.2, 60.3, 60.8, 120.4, 124.8, 127.7, 128.4, 128.6, 129.4, 131.0, 131.1, 134.3, 134.6, 135.1, 146.6, 167.3, 171.4; HR-MS (ESI): *m/z*=469.1113, calcd. for $C_{24}H_{26}BrN_2O_3^+$ $[M+H]^+$: 469.1121.

(*E*)-Ethyl 2-[3-benzoyl-9-bromo-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]butanoate (4eb)—Yield: 96% (Table 3, entry 14); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.50; IR (film): ν_{max} = 3057, 2975, 2934, 2850, 1891, 1704, 1680, 1597, 1579, 1486, 1464, 1446, 1427, 1412, 1365, 1330, 1299, 1268, 1254, 1240, 1217, 1189, 1177, 1142, 1107, 1077, 1063, 1027, 974, 924, 867, 800, 785, 769, 725, 710, 696, 677, 656, 639, 611, 533 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.12 (t, *J* = 7.4 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 2.35–2.44 (m, 2H), 2.68–2.73 (m, 1H), 2.90–2.97 (m, 2H), 3.10 (dd, *J*=18.6, 9.9 Hz, 1H), 3.35–3.39 (m, 1H), 3.65 (dd, *J*=18.6, 8.6 Hz, 1H), 4.16–4.26 (m, 3H), 6.92 (d, *J*=8.2 Hz, 1H), 7.14–7.24 (m, 2H), 7.39–7.41 (m, 3H), 7.69–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.7, 14.3, 23.7, 28.6, 39.8, 47.4, 60.4, 60.7, 119.9, 124.8, 127.7, 128.4, 129.85, 129.88, 129.89, 131.1, 131.3, 135.1, 137.5, 146.5, 167.4, 171.4; HR-MS (ESI): *m/z*=469.1123, calcd. for $C_{24}H_{26}BrN_2O_3^+$ $[M+H]^+$: 469.1121.

(*E*)-Ethyl 2-[3-benzoyl-9-chloro-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]butanoate (4fd)—Yield: 95% (Table 3, entry 15); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.51; IR (film): ν_{max} = 3057, 2975, 2934, 2850, 1891, 1704, 1681, 1640, 1600, 1579, 1489, 1464, 1446, 1427, 1365, 1299, 1268, 1254, 1239, 1216, 1192, 1176, 1142, 1107, 1063, 1027, 975, 867, 801, 785, 725, 711, 695, 677, 630, 539 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.12 (t, *J* = 7.4 Hz, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 2.35–2.44 (m, 2H), 2.70–2.75 (m, 1H), 2.92–3.15 (m, 3H), 3.37–3.39 (m, 1H), 3.66 (dd, *J*=18.6, 8.6 Hz, 1H), 4.16–4.26 (m, 3H), 6.97–7.10 (m, 3H), 7.39–7.47 (m, 3H),7.69–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 12.7, 14.3, 23.7, 28.6, 39.8, 47.4, 60.4, 60.8, 124.9, 126.9, 127.0, 127.7, 128.4, 129.6, 130.8, 131.1, 132.0, 135.1, 137.1, 146.5, 167.4, 171.4; HR-MS (ESI): *m/z*= 425.1599, calcd. for $C_{24}H_{26}ClN_2O_3^+$ $[M+H]^+$: 425.1626.

(*E*)-Ethyl 2-[3-benzoyl-7-methyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-phenylpropanoate (4bf)—Yield: 40% (Table 3, entry 6); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.51; IR (film): ν_{max} = 3060, 3026, 2926, 2852, 1705, 1674, 1600, 1494, 1469, 1446, 1369, 1299, 1236, 1210, 1140, 1093, 1052, 1029, 979, 921, 885, 866, 845, 812, 783, 699, 677, 552 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.21 (t, *J* = 7.1 Hz, 3H), 2.17 (s, 3H), 2.66–2.89 (m, 4H), 3.28 (dd, *J*=18.9, 10.1 Hz, 1H), 3.66–3.77 (m, 2H), 3.99 (d, *J*=15.8 Hz, 1H), 4.12–4.25 (m, 3H), 6.85–7.24 (m, 8H), 7.33–7.55 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.1, 19.2, 26.6, 35.4, 40.4, 47.2, 60.6, 61.2, 122.1, 124.9, 125.8, 126.2, 127.6, 128.04, 128.08, 128.4, 128.6, 131.0, 134.9, 135.2, 135.9, 140.7, 149.3, 167.4, 170.8; HR-MS (ESI): *m/z*=467.2322, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

(*E*)-Ethyl 2-[3-benzoyl-9-methyl-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3H)-ylidene]-3-phenylpropanoate (4cf)—Yield: 46% (Table 3, entry 7); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.53; IR (film): ν_{max} = 3059, 3026,

2925, 2851, 1766, 1601, 1581, 1505, 1494, 1447, 1428, 1365, 1298, 1274, 1251, 1216, 1136, 1095, 1077, 1030, 975, 867, 814, 788, 734, 699, 678, 561, 465 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 2.59–2.88 (m, 4H), 4.13–4.24 (m, 3H), 3.26 (dd, J=18.9, 10.1 Hz, 1H), 3.67–3.77 (m, 2H), 3.99 (d, J=15.7 Hz, 1H), 6.82 (s, 1H), 6.93 (d, J=1.0 Hz, 2H), 7.16–7.25 (m, 5H), 7.33–7.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1, 20.9, 28.6, 35.4, 40.5, 47.5, 60.5, 61.0, 121.9, 125.8, 127.51, 127.55, 127.64, 128.0, 128.3, 128.5, 128.6, 129.2, 130.9, 134.9, 135.2, 135.9, 140.7, 149.4, 167.4, 170.84; HR-MS (ESI): *m/z*=467.2326, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

(*E*)-Ethyl 2-[3-benzoyl-8-bromo-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-phenylpropanoate (4df)—Yield: 73% (Table 3, entry 8); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.46; IR (film): ν_{max} = 3057, 3018, 2981, 2928, 2849, 1703, 1676, 1599, 1580, 1493, 1483, 1447, 1426, 1368, 1300, 1266, 1241, 1204, 1188, 1138, 1075, 1029, 998, 969, 908, 889, 866, 854, 839, 817, 781, 738, 702, 679, 650, 545 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, J=7.1 Hz, 3H), 2.60–2.73 (m, 2H), 2.83–2.87 (m, 2H), 3.21 (dd, J=18.8, 10.1 Hz, 1H), 3.63–3.75 (m, 2H), 3.98 (d, J=15.7 Hz, 1H), 4.12–4.22 (m, 3H), 6.88 (d, J= 8.2 Hz, 1H), 7.14–7.23 (m, 7H), 7.33–7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 28.9, 35.4, 40.3, 46.9, 60.6, 60.7, 120.5, 122.2, 125.9, 127.7, 128.1, 128.4, 128.6, 128.7, 129.5, 131.08, 131.12, 134.15, 134.7, 135.0, 140.6, 148.9, 167.4, 170.7; HR-MS (ESI): *m/z*=531.1261, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

(*E*)-Ethyl 2-[3-benzoyl-9-bromo-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-phenylpropanoate (4ef)—Yield: 92% (Table 3, entry 9); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.52; IR (film): ν_{max} = 3059, 3026, 2977, 2930, 2849, 1705, 1677, 1599, 1578, 1485, 1446, 1426, 1365, 1298, 1270, 1240, 1201, 1131, 1096, 1077, 1030, 968, 917, 867, 810, 785, 736, 700, 678, 610, 558 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (t, J= 7.1 Hz, 3H), 2.58–2.88 (m, 4H), 3.24 (dd, J=18.8, 10.1 Hz, 1H), 3.64–3.74 (m, 2H), 3.99 (d, J=15.9 Hz, 1H), 4.13–4.23 (m, 3H), 6.90 (d, J=8.2 Hz, 1H), 7.14–7.25 (m, 7H), 7.33–7.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2, 28.6, 35.4, 40.3, 47.1, 60.58, 60.65, 119.9, 122.3, 125.9, 127.6, 128.1, 128.3, 128.6, 129.9, 131.1, 131.4, 135.0, 137.3, 140.6, 148.7, 167.4, 170.7; HR-MS (ESI): *m/z*=531.1253, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

(*E*)-Ethyl 2-[3-benzoyl-9-chloro-1,5,6,10b-tetrahydropyrazolo[5,1-*a*]isoquinolin-2(3*H*)-ylidene]-3-phenylpropanoate (4ff)—Yield: 80% (Table 3, entry 10); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.52; IR (film): ν_{max} = 3060, 3027, 2929, 2852, 1706, 1681, 1601, 1578, 1489, 1447, 1426, 1366, 1296, 1269, 1240, 1201, 1130, 1094, 1030, 969, 932, 868, 839, 813, 785, 699, 678, 630, 563 $cm^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, J=7.1 Hz, 3H), 2.60–2.72 (m, 2H), 2.80–2.88 (m, 2H), 3.23 (dd, J=18.8, 10.1 Hz, 1H), 3.63–3.75 (m, 2H), 3.98 (d, J=15.8 Hz, 1H), 4.13–4.22 (m, 3H), 6.94–7.23 (m, 8H), 7.33–7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 28.6, 35.4, 40.3, 47.2, 60.6, 60.7, 122.3, 125.9, 126.95, 127.03, 127.6, 128.1, 128.4, 128.6, 129.6, 130.9, 131.1, 132.0, 135.0, 136.9, 140.6, 148.7, 167.4, 170.7; HR-MS (ESI): *m/z*=487.1766, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

Ethyl 5-benzoyl-4-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino[7,1-*a*]isoquinoline-3-carboxylate (5af)—Yield: 90% (Table 2, entry 6); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.38; IR (film): ν_{max} = 2929, 1708, 1649, 1541, 1491, 1454, 1368, 1311, 1240, 1058, 1028, 912, 744, 699 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=0.95 (t, *J*=7.1 Hz, 3H), 2.31–2.46 (m, 2H), 2.63–2.84 (m, 2H), 3.05–3.14 (m, 1H), 3.88–3.96 (m, 3H), 4.08–4.33 (m, 1H), 5.13 (dd, *J*=7.7, 4.9 Hz, 1H), 6.00 (s, 1H), 7.03–7.05 (m, 1H), 7.10–7.19 (m, 3H), 7.22–7.25 (m, 3H), 7.32–7.37 (m, 2H), 7.47–7.72 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 30.6, 38.0, 49.1, 59.5, 60.7, 65.2, 125.9, 126.0, 126.06, 126.09, 127.7, 128.0, 128.4, 128.6, 128.7, 129.6, 133.9, 134.8, 136.9, 138.0, 138.2, 141.5, 165.9, 170.7; HR-MS (ESI): *m/z*=453.2166, calcd. for $C_{29}H_{29}N_2O_3^+$ $[M+H]^+$: 453.2173.

Ethyl 5-benzoyl-4-(*o*-tolyl)-1,4,5,7,8,12b-hexahydro[1,2]diazepino[7,1-*a*]isoquinoline-3-carboxylate (5ag)—Yield: 42% (Table 2, entry 7); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.33; IR (film): ν_{max} = 2920, 1716, 1647, 1541, 1488, 1456, 1410, 1362, 1339, 1260, 735 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.1 Hz, 3H), 2.01 (s, 3H), 2.19–2.39 (m, 2H), 2.56–2.90 (m, 2H), 3.16 (dt, *J*=18.1, 5.2 Hz, 1H), 3.86–4.05 (m, 3H), 4.11–4.33 (m, 1H), 5.08 (dd, *J*=8.1, 5.0 Hz, 1H), 6.11 (s, 1H), 7.02–7.10 (m, 3H), 7.12–7.22 (m, 4H), 7.41–7.47 (m, 4H), 7.49–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.3, 30.5, 38.7, 49.1, 59.3, 60.7, 62.4, 125.2, 125.9, 126.1, 126.3, 126.5, 127.8, 128.3, 128.6, 129.6, 130.0, 130.1, 134.7, 134.8, 135.4, 136.3, 136.6, 138.4, 141.7, 165.9, 170.6; HR-MS (ESI): *m/z*=467.2338, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

Ethyl 5-benzoyl-4-(*m*-tolyl)-1,4,5,7,8,12b-hexahydro[1,2]-diazepino[7,1-*a*]isoquinoline-3-carboxylate (5ah)—Yield: 55% (Table 2, entry 8); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.34; IR (film): ν_{max} = 2930, 1714, 1651, 1491, 1446, 1368, 1313, 1243, 1157, 1096, 1059, 1038, 778, 734, 701, 677 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J*=7.1 Hz, 3H), 2.31 (s, 3H), 2.44–2.49 (m, 2H), 2.67–2.85 (m, 2H), 3.05–3.15 (m, 1H), 3.92–3.97 (m, 3H), 4.17–4.34 (m, 1H), 5.11–5.15 (m, 1H), 5.97 (s, 1H), 7.04–7.09 (m, 4H), 7.12–7.20 (m, 4H), 7.30–7.39 (m, 1H), δ7.48–7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.4, 30.6, 38.0, 49.1, 59.5, 60.7, 65.2, 125.6, 125.9, 126.1, 127.8, 128.4, 128.6, 128.7, 129.1, 129.6, 133.9, 134.8, 137.0, 137.4, 137.9, 138.3, 141.3, 166.0, 170.7; HR-MS (ESI): *m/z*=467.2425, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

Ethyl 5-benzoyl-1-(*p*-tolyl)-1,4,5,7,8,12b-hexahydro[1,2]-diazepino[7,1-*a*]isoquinoline-2-carboxylate (5ai)—Yield: 71% (Table 2, entry 9); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.34; IR (film): ν_{max} = 2927, 1714, 1650, 1541, 1509, 1491, 1370, 1311, 1240, 1096, 1025, 911, 855, 788, 732, 700, 674 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.1 Hz, 3H), 2.34 (s, 3H), 2.47 (d, *J*=13.7 Hz, 2H), 2.69–2.85 (m, 2H), 2.99–3.24 (m, 1H), 3.86–4.01 (m, 3H), 4.25 (d, *J*=45.9 Hz, 1H), 5.07–5.26 (m, 1H), 5.97 (s, 1H), 7.05–7.20 (m, 8H), 7.31–7.39 (m, 2H), 7.48–7.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.1, 30.6, 38.1, 49.0, 59.5, 60.7, 64.9, 125.9, 126.0, 126.1, 128.4, 128.6, 128.7, 129.6, 134.1, 134.8, 135.0, 137.0, 137.3, 138.3, 141.1, 166.0, 170.7; HR-MS (ESI): *m/z*=467.2320, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

Ethyl 5-benzoyl-4-(4-fluorophenyl)-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5aj)—Yield: 92 (Table 2, entry 10); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.34; IR (film): ν_{max} = 2924, 2853, 1714, 1650, 1602, 1541, 1507, 1456, 1369, 1310, 1239, 1157, 1097, 1026, 911, 825, 735, 700, 670 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, *J*=7.0 Hz, 3H), 2.39–2.51 (m, 2H), 2.66–2.84 (m, 2H), 3.06–3.15 (m, 1H), 3.90–3.98 (m, 3H), 4.15–4.33 (m, 1H), 5.11–5.16 (m, 1H), 5.96 (s, 1H), 6.94–7.07 (m, 4H), 7.13–7.23 (m, 5H), 7.31–7.39 (m, 1H), 7.47–7.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 30.6, 37.8, 49.1, 59.6, 60.8, 64.5, 114.8, 115.1, 125.97, 126.03, 126.2, 128.7, 128.8, 129.8, 130.1, 130.2, 133.7, 134.0, 134.6, 136.8, 138.2, 141.5, 165.8, 170.6; HR-MS (ESI): *m/z*=471.2070, calcd. for $C_{29}H_{28}FN_2O_3^+$ $[M+H]^+$: 471.2078.

Ethyl 5-benzoyl-4-(3-chlorophenyl)-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5ak)—Yield: 75% (Table 2, entry 11); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.36; IR (film): ν_{max} = 3062, 2980, 1714, 1651, 1596, 1575, 1493, 1475, 1446, 1429, 1368, 1311, 1242, 1189, 1059, 1026, 787, 752, 701 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, *J*=7.1 Hz, 3H), 2.45–2.53 (m, 2H), 2.71–2.85 (m, 2H), 3.06–3.16 (m, 1H), 3.91–4.00 (m, 3H), 4.17–4.34 (m, 1H), 5.12–5.16 (m, 1H), 5.97 (m, 1H), 7.07–7.22 (m, 7H), 7.36–7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 30.5, 38.0, 49.2, 59.6, 60.8, 64.7, 126.0, 126.2, 126.7, 127.9, 128.5, 128.7, 128.8, 129.3, 129.8, 133.2, 133.8, 134.6, 136.7, 138.1, 140.2, 165.6, 170.7; HR-MS (ESI): *m/z*=487.1819, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

Ethyl 5-benzoyl-4-(4-chlorophenyl)-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5al)—Yield: 84% (Table 2, entry 12); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.36; IR (film): ν_{max} = 2924, 2854, 1714, 1650, 1541, 1489, 1456, 1368, 1309, 1241, 1091, 1015, 912, 852, 748, 709, 670 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=0.99 (t, *J*=7.1 Hz, 3H), 2.43–2.52 (m, 2H), 2.68–2.84 (m, 2H), 3.05–3.15 (m, 1H), 3.89–3.98 (m, 3H), 4.16–4.33 (m, 1H), 5.11–5.15 (m, 1H), 5.95 (s, 1H), 7.05–7.19 (m, 6H), 7.24–7.25 (m, 1H), 7.27 (s, 1H), 7.33–7.36 (m, 1H), 7.47 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 30.6, 37.8, 49.2, 59.6, 60.8, 64.6, 125.9, 126.0, 126.2, 128.2, 128.7, 128.8, 129.8, 133.5, 133.6, 134.6, 136.7, 138.1, 141.8, 165.7, 170.7; HR-MS (ESI): *m/z*=487.1775, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

Ethyl 5-benzoyl-4-(4-bromophenyl)-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5am)—Yield: 93% (Table 2, entry 13); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.33; IR (film): ν_{max} = 2930, 1713, 1650, 1540, 1487, 1445, 1368, 1308, 1241, 1158, 1071, 910, 851, 803, 734, 704, 647, 503 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=0.99 (t, *J*=7.1 Hz, 3H), 2.44–2.53 (m, 2H), 2.68–2.84 (m, 2H), 3.05–3.13 (m, 1H), 3.89–3.98 (m, 3H), 4.16–4.33 (m, 1H), 5.11–5.15 (m, 1H), 5.93 (s, 1H), 7.05–7.20 (m, 6H), 7.33–7.42 (m, 4H), 7.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 30.6, 37.8, 49.2, 59.7, 60.8, 64.6, 121.8, 125.96, 126.03, 126.3, 128.7, 128.8, 129.8, 130.2, 131.2, 133.4, 134.6, 136.7, 137.3, 138.1, 141.8, 165.7, 170.7; HR-MS (ESI): *m/z*=531.1258, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

Ethyl 5-benzoyl-9-methyl-4-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5bf)—Yield: 73% (Table 3, entry 1); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.36; IR (film): ν_{max} = 3060, 3028, 2978, 2926, 2855, 1955, 1710, 1648, 1600, 1534, 1492, 1465, 1452, 1388, 1368, 1310, 1240, 1191, 1159, 1096, 1074, 1060, 1028, 1092, 977, 904, 875, 857, 844, 783, 735, 700, 674, 648, 625, 567, 505, 467 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.34 (m, 5H), 7.32–7.11 (m, 5H), 7.09–7.00 (m, 3H), 5.98 (s, 1H), 5.17 (t, *J*=8.9 Hz, 1H), 4.29–4.15 (m, 1H), 3.94–3.87 (m, 3H), 3.14–3.04 (m, 1H), 2.84–2.74 (m, 1H), 2.46–2.44 (m, 3H), 2.19 (t, *J*=7.1 Hz, 3H), 0.95 (t, *J*= 8.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 165.9, 141.4, 138.2, 137.0, 136.0, 133.8, 133.4, 129.7, 128.8, 128.4, 128.0, 127.7, 127.6, 126.0, 125.7, 123.8, 65.3, 60.6, 59.7, 49.0, 37.5, 27.6, 19.4, 13.8; HR-MS (ESI): *m/z*=467.2332, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

Ethyl 5-benzoyl-11-methyl-4-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5cf)—Yield: 68% (Table 3, entry 2); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.38; IR (film): ν_{max} = 3058, 3028, 2979, 2927, 2866, 1891, 1710, 1649, 1601, 1578, 1536, 1504, 1493, 1452, 1393, 1368, 1311, 1240, 1186, 1158, 1097, 1075, 1039, 1059, 1027, 972, 960, 942, 909, 876, 844, 815, 736, 700, 677, 649, 678, 560, 536, 470, 457 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.49 (m, 5H), 7.38–7.27 (m, 5H), 6.99–6.96 (m, 3H), 6.01 (s, 1H), 5.12–5.08 (m, 1H), 4.31–4.17 (m, 1H), 3.96–3.88 (m, 3H), 3.13–3.03 (m, 1H), 2.85–2.77 (m, 1H), 2.75–2.77 (m, 1H), 2.41–2.39 (m, 2H), 2.34 (s, 3H), 0.97 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 165.9, 141.6, 138.0, 137.0, 135.3, 133.8, 131.7, 129.6, 128.7, 128.4, 128.0, 127.6, 127.0, 126.6, 126.0, 65.2, 60.6, 59.5, 49.2, 38.0, 30.1, 21.1, 13.8; HR-MS (ESI): *m/z*=467.2324, calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$: 467.2329.

Ethyl 5-benzoyl-10-bromo-4-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5df)—Yield: 61 (Table 3, entry 3); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.32; IR (film): ν_{max} = 2922, 2851, 1709, 1647, 1482, 1452, 1368, 1309, 1239, 1058, 1026, 851, 729, 699 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.48 (m, 5H), 7.35–7.25 (m, 5H), 7.23–7.03 (m, 3H), 6.01 (s, 1H), 5.09 (s, 1H), 4.26–4.16 (m, 1H), 3.96–3.87 (m, 3H), 3.11–3.03 (m, 1H), 2.81–2.60 (m, 2H), 2.44–2.39 (m, 2H), 2.34 (s, 3H), 0.96 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8, 165.8, 140.9, 138.0, 137.2, 136.7, 134.0, 131.4, 129.8, 129.0, 128.8, 128.4, 128.1, 127.8, 126.0, 120.0, 65.2, 60.8, 59.3, 48.8, 37.5, 30.3, 13.8; HR-MS (ESI): *m/z*=531.1254, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

Ethyl 5-benzoyl-11-bromo-4-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-3-carboxylate (5ef)—Yield: 62% (Table 3, entry 4); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.38; IR (film): ν_{max} = 3059, 3028, 2927, 2852, 1709, 1649, 1600, 1484, 1452, 1392, 1368, 1310, 1189, 1158, 1127, 1097, 1077, 1059, 1038, 1026, 973, 954, 912, 855, 843, 810, 735, 699, 678, 648, 531 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.48 (m, 5H), 7.35–7.25 (m, 5H), 7.23–6.91 (m, 3H), 6.00 (s, 1H), 5.10–5.05 (m, 1H), 4.26–4.16 (m, 1H), 3.96–3.85 (m, 3H), 3.13–3.03 (m, 1H), 2.83–2.57 (m, 2H), 2.43–2.39 (m, 2H), 0.96 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8,

165.8, 140.8, 140.4, 138.1, 136.7, 134.0, 133.9, 130.4, 129.8, 129.3, 129.0, 128.8, 128.4, 128.1, 127.8, 126.1, 119.6, 65.3, 60.8, 59.3, 48.9, 37.3, 30.1, 13.8; HRMS (ESI): *m/z*=531.1255, calcd. for $C_{29}H_{28}BrN_2O_3^+$ $[M+H]^+$: 531.1278.

Ethyl 5-benzoyl-11-chloro-1-phenyl-1,4,5,7,8,12b-hexahydro[1,2]diazepino [7,1-*a*]isoquinoline-2-carboxylate (5ff)—Yield: 62% (Table 3, entry 5); yellow solid. TLC (EtOAc/petroleum ether 1/5): R_f = 0.38; IR (film): ν_{max} = 3059, 3018, 2927, 2852, 1709, 1648, 1650, 1484, 1452, 1392, 1368, 1310, 1241, 1159, 1158, 1097, 1077, 1059, 1038, 1026, 973, 924, 912, 855, 843, 810, 735, 699, 678, 648, 531 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.48 (m, 5H), 7.35–7.31 (m, 3H), 7.23–6.97 (m, 3H), 6.00 (s, 1H), 5.10–5.05 (m, 1H), 4.29–4.16 (m, 1H), 3.96–3.86 (m, 3H), 3.13–3.04 (m, 1H), 2.83–2.59 (m, 2H), 2.44–2.40 (m, 2H), 0.96 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8, 165.8, 140.8, 140.0, 138.0, 136.7, 134.0, 133.4, 131.6, 130.1, 129.8, 128.8, 128.4, 128.1, 127.8, 126.4, 126.1, 65.3, 60.8, 59.4, 49.0, 37.3, 30.0, 13.8; HR-MS (ESI): *m/z*=487.1763, calcd. for $C_{29}H_{28}ClN_2O_3^+$ $[M+H]^+$: 487.1783.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. An unknown side-product in each case was observed in < 5% yield.
17. Crystallographic data for **4ef** and **5df** have been deposited with the Cambridge Crystallographic Data Centre under the numbers CCDC 838502 and CCDC 838503. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336033.
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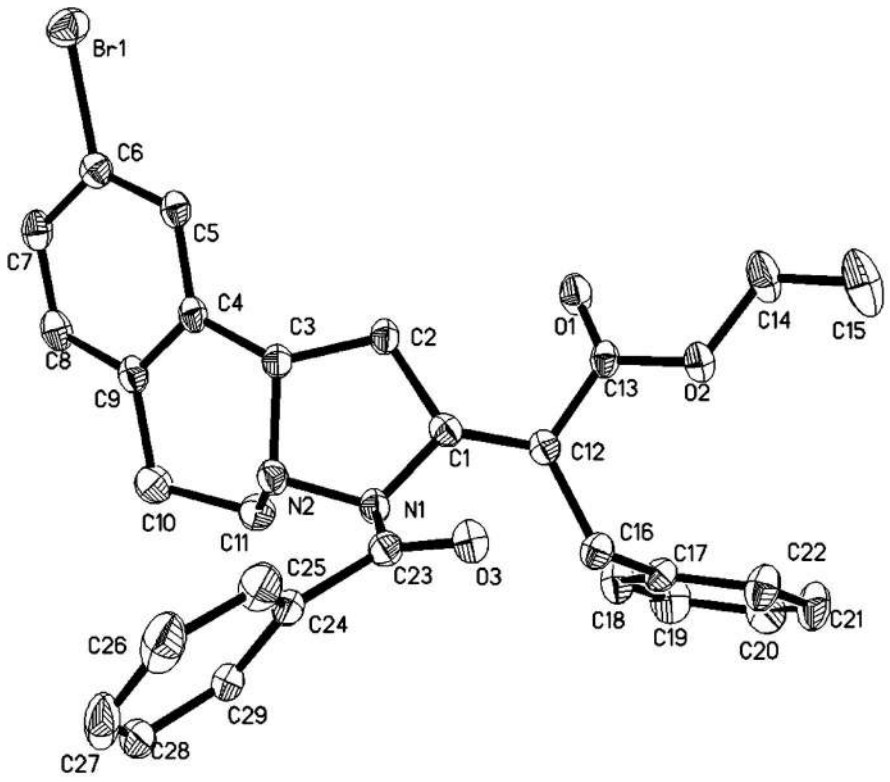


Figure 1.
ORTEP view of compound **4ef**. The hydrogen atoms have been omitted for clarity.

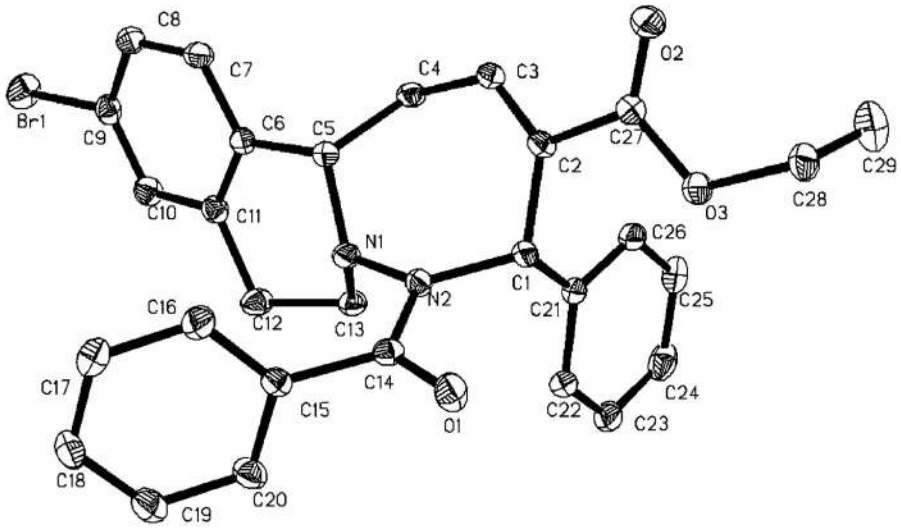
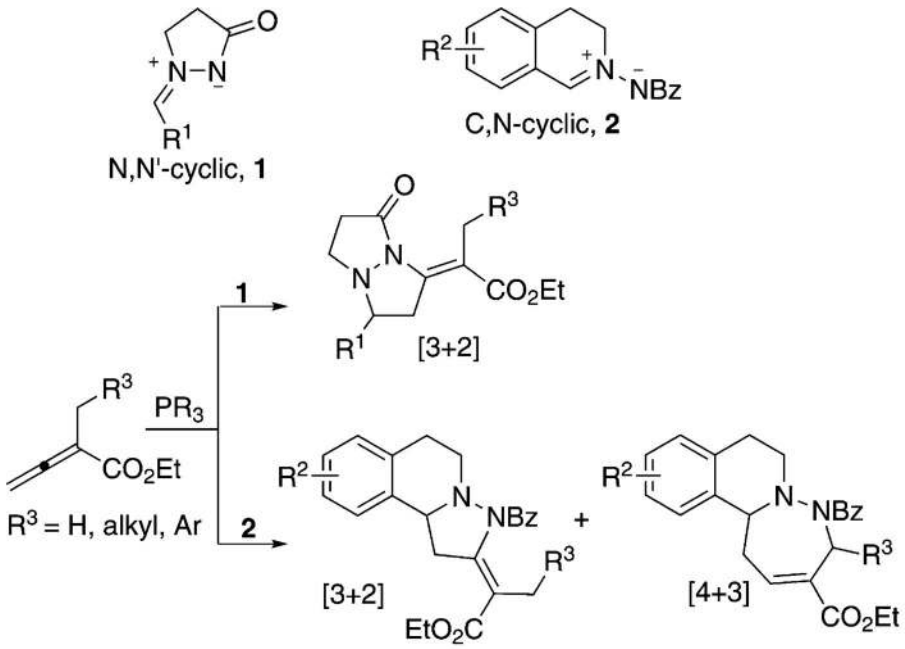
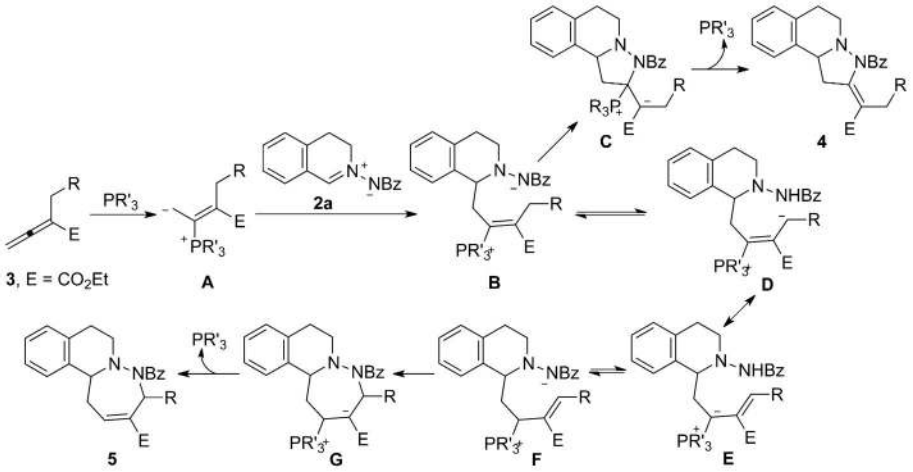


Figure 2.
ORTEP view of compound **5df**. The hydrogen atoms have been omitted for clarity.



Scheme 1.
Phosphine-catalyzed annulations of azomethine imines with allenoates.

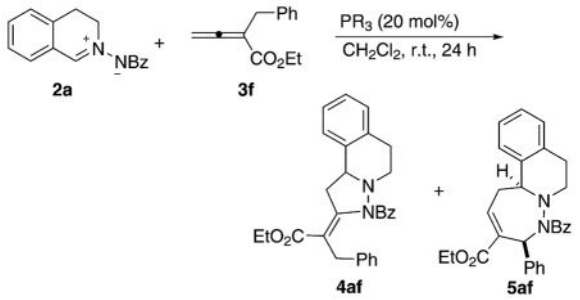


Scheme 2.

A plausible reaction mechanism for the phosphine-catalyzed cycloaddtion of azomethine imines with allenoates.

Table 1

Screening of phosphine catalysts for annulations of azomethine imines with allenoates.[a]



Entry	PR_3	4af, Yield [%][b]	5af, Yield [%][b]
1	–	0[c]	0[c]
2	PMe_3	66	<5
3	PBu_3	<5	90
4	Me_2PPh	23	15
5	$EtPPh_2$	18	33
6	PPh_3	20	<5

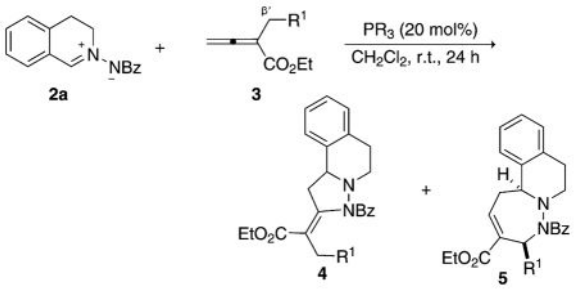
[a] 1.2 equiv. of allenoate was used.

[b] Isolated yields, unless otherwise indicated.

[c] Without phosphine catalyst.

Table 2

Phosphine-catalyzed cycloaddition of azomethine imine (**2a**) with allenoates.[a]



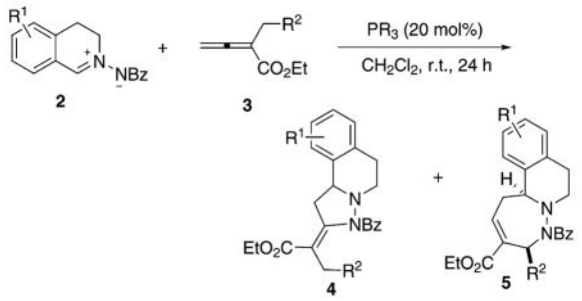
Entry	R^1	PR_3	4, Yield [%][b]	5, Yield [%][b]
1	H (**3a**)	PBu_3	**4aa**, 62	**5aa**, 7
2	Me (**3b**)	PBu_3	**4ab**, 89	**5ab**, <1
3	Et (**3c**)	PBu_3	**4ac**, 87	**5ac**, <1
4	*i*-Pr (**3d**)	PBu_3	**4ad**, 79	**5ad**, <1
5	*t*-Bu (**3e**)	PBu_3	**4ae**, 74	**5ae**, <1
6	Ph (**3f**)	PBu_3	**4af**, <5	**5af**, 90
7	2-MeC_6H_4 (**3g**)	PBu_3	**4ag**, <2	**5ag**, 42
8	3-MeC_6H_4 (**3h**)	PBu_3	**4ah**, <5	**5ah**, 55
9	4-MeC_6H_4 (**3i**)	PBu_3	**4ai**, 16	**5ai**, 71
10	4-FC_6H_4 (**3j**)	PBu_3	**4aj**, <5	**5aj**, 92
11	3-ClC_6H_4 (**3k**)	PBu_3	**4ak**, <5	**5ak**, 75
12	4-ClC_6H_4 (**3l**)	PBu_3	**4al**, <5	**5al**, 84
13	4-BrC_6H_4 (**3m**)	PBu_3	**4am**, <5	**5am**, 93
14	H (**3a**)	PMe_3	**4aa**, 79	**5aa**, <1
15	Me (**3b**)	PMe_3	**4ab**, 91	**5ab**, <1
16	Et (**3c**)	PMe_3	**4ac**, 93	**5ac**, <1
17	*i*-Pr (**3d**)	PMe_3	**4ad**, 92	**5ad**, <1
18	*t*-Bu (**3e**)	PMe_3	**4ae**, 60	**5ae**, <1
19	Ph (**3f**)	PMe_3	**4af**, 66	**5af**, <1
20	2-MeC_6H_4 (**3g**)	PMe_3	**4ag**, 18	**5ag**, <5
21	3-MeC_6H_4 (**3h**)	PMe_3	**4ah**, 55	**5ah**, 11
22	4-MeC_6H_4 (**3i**)	PMe_3	**4ai**, 92	**5ai**, <5
23	4-FC_6H_4 (**3j**)	PMe_3	**4aj**, 18	**5aj**, 27
24	3-ClC_6H_4 (**3k**)	PMe_3	**4ak**, 28	**5ak**, 36
25	4-ClC_6H_4 (**3l**)	PMe_3	**4al**, 40	**5al**, <5
26	4-BrC_6H_4 (**3m**)	PMe_3	**4am**, 30	**5am**, 35

[a] 1.2 equiv. of allenoate was used.

[b] Isolated yields, unless otherwise indicated.

Table 3

Phosphine-catalyzed cycloaddition of azomethine imines (**2**) with allenoates.[a]



Entry	R^1	R^2	PR_3	4, Yield [%][b]	5, Yield [%][b]
1	5-Me (**2b**)	Ph (**3f**)	PBu_3	**4bf**, 24	**5bf**, 73
2	7-Me (**2c**)	Ph (**3f**)	PBu_3	**4cf**, 23	**5cf**, 68
3	6-Br (**2d**)	Ph (**3f**)	PBu_3	**4df**, 34	**5df**, 61
4	7-Br (**2e**)	Ph (**3f**)	PBu_3	**4ef**, 23	**5ef**, 62
5	7-Cl (**2f**)	Ph (**3f**)	PBu_3	**4ff**, 27	**5ff**, 62
6	5-Me (**2b**)	Ph (**3f**)	PMe_3	**4bf**, 40	**5bf**, <1
7	7-Me (**2c**)	Ph (**3f**)	PMe_3	**4cf**, 46	**5cf**, <1
8	6-Br (**2d**)	Ph (**3f**)	PMe_3	**4df**, 73	**5df**, <1
9	7-Br (**2e**)	Ph (**3f**)	PMe_3	**4ef**, 92	**5ef**, <1
10	7-Cl (**2f**)	Ph (**3f**)	PMe_3	**4ff**, 80	**5ff**, <1
11	5-Me (**2b**)	Et (**3c**)	PBu_3	**4bc**, 95	**5bc**, <1
12	7-Me (**2c**)	Et (**3c**)	PBu_3	**4cc**, 97	**5cc**, <1
13	6-Br (**2d**)	Et (**3c**)	PBu_3	**4dc**, 87	**5dc**, <1
14	7-Br (**2e**)	Et (**3c**)	PBu_3	**4ec**, 96	**5ec**, <1
15	7-Cl (**2f**)	Et (**3c**)	PBu_3	**4fc**, 95	**5fc**, <1

[a] 1.2 equiv. of allenoate was used.

[b] Isolated yields, unless otherwise indicated.